Enantiocontrolled Synthesis of Physiologically Active Natural Products

THESIS PRESENTED
BY

ADEL SHABAN EL-AZAB

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SUPERVISED
BY

Dr. KUNIO OGASAWARA
PROFESSOR OF ORGANIC
CHEMISTERY FACULTY OF PHARMACY
TOHOKU UNIVERSITY

Dr. HAMDY M. RAGAB
PROFESSOR OF ORGANIC
CHEMISTERY FACULTY OF PHARMACY
CAIRO UNIVERSITY

Dr. FATHY M. SALAMA
PROFESSOR OF ANALYTICALCHEMISTERY
FACULTY OF PHARMACY AL-AZHAR UNIVERSITY

Faculty of Pharmacy
Al-Azhar University, [Cairo]

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ABBREVIATIONS

AIBAN	2,2'-azobisisobutyronitrile
Bn	benzyl
BnBr	benzyl bromide
$(Boc)_2O$	(di-*t*-butyl dicarbonate
Boc	*t*-butoxycarbonyl
Bu_3SnH	tin-tributyline hydride
Bz	benzoyl
CAN	cerric ammonium nitrate
Cbz or Z	benzyloxycarbonyl or carbobenzoxy
DIBAL-H	diisbutylaluminium hydride
DHP	dihydropyrane
DMAC	N,N-dimethylacetamide
DMAP	4-(*N*,*N*-dimethylamino) pyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
DPPA	diphenylphosphoryl azide
HMPA	hexamethlyphosphoric triamide
LAH	lithium aluminium hydride
LDA	lithium diisopropyl amide
LHMDS	lithium hexamethyldisilazide
m-CPBA	meta-chloroperbenzoic acid
MOM	methoxymethyl
ms	molecular sieve
Ms	methansulfonyl
NAP	2-naphthyl methyl
NBS	*N*-bromosuccinimide
NMO	*N*-methylmorpholine *N*-oxide
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
PMP	1,2,2,6,6,pentamethylpipridine
PPTS	pyridinium *p*-toluensulfonate
TBAF	tetrabutylammonium flouride
TBDPS	*tert*-butyldiphenylsilyl
TBSCl	*tert*-butyldimethyl chlorosilane
TFA	triflouroacetic acid
TFMSA	trifluoromethansulfonic acid
THP	tetrahydropyranyl

TIPS	triisopropylsilyl
TPAP	tetra-*n*-propylammonium perruthenate(VII)
p-Ts	*p*-toluenesulfonyl
p-TsCl	*p*-toluenesulfonyl chloride
p-TsOH	*p*-toluenesulfonic acid
PPA	polyphosphoric acid

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Adel S. El-Azab

CONTENTS

Abstract

The present study involves a comprehensive survey on the methods reported for the synthesis of Calabar bean alkaloids, [(-)- physovenine and (-)-physostigmine] and fresh water blue-green algae alkaloid, (-)-aphanorphine. It also comprises a new expedient route to (-)-physovenine and (-)-physostigmine alkaloids, and earnest attempt to synthesis of (-)-aphanorphine alkaloid.

The synthesis of (-)-physovenine and (-)-physostigmine in the present study is depending on the use of enantiopure 6,8-dioxabicyclo [3.2.1]-oct-3-en-2-one as chiral building blocks obtained from furfural via multistep-synthesis involving lipase-mediated kinetic resolution method as new strategy for enantiocontrolled synthesis that allow large scale preparation.

The present investigation involves new attempts to synthesize (-)-aphanorphine using the same chiral building block.

The thesis involves the synthesis of enantiopure levoglucosenone obtained from furfural via multistep-synthesis involving lipase-mediated kinetic resolution method as new strategy for enantiocontrolled synthesis.

Also, it includes a comprehensive study in the use of montmorillonite k-10 clay in selective deprotection of tetrahydropyranyl group (THP) in the presence of another sensitive protecting group e.g. epoxide, Bn, TBS or MOM.

The present investigation comprises the synthesis of the following compounds that are not easily accessible.

1)- 2-Vinylfuran (3).

2)- (-)- Levoglucosenone (2).

3)- (+)-Levoglucosenone (2).

4)- Ethyl (E) -3- (2-furfuryl) acrylate.

5)- (E) -3- (2-Furfuryl) prop-2-en-1-ol.

6)- (E) -3- (2-Furfuryl) prop-2-enyl (2-naphthylmethyl) Ether (8a).

7)- (-) - (*1S, 5S, 7R*) -7-(2-Naphthylmethyloxymethyl)-6,8dioxabicyclo-

[3.2.1] oct-3-en-2-one [(-) 11a].

8)- (+) - (*1R, 5R, 7S*) -7-(2-Naphthylmethyloxymethyl)-6,8dioxabicyclo-[3.2.1] oct-3-en-2-one [(-) 11a].

9)- (-) - (*2a R,3a S*)-5-Methoxy-3a, 8-dimethyl-3,3a,8,8a-tetrahydro-2H-furo- [2,3-b] indol (26).

10)- (-)-(*2aS ,3aS*)-5-Methoxy-1,3a,8-trimethyl-1,2,3,3a, 8,8a-hexahydro-pyrolo[2,3-b] indole (32).

11)- (+) - (*R*) -(7-Methoxymethyl-1, 2-dihydronaphthalen-1-yl) carbamic acid methyl ester (50).

12)- (+)- (R)-7- Methoxy-1-methyl-1, 2-dihydronaphthalen-1-ylmethyl)-methylamine (51).

In addition, the present investigation involves the synthesis of the following new compounds:

1)- 1-(2-Furyl) ethane-1, 2-diol [(±)-4].

2)- (±) - Isolevoglucosenone [(±)-2].

3)- (±) 7,8 -Dioxabicyclo [3.2.1] oct-3-en-2-ol [(±)-6].

4)- (±) -7,8 –Dioxabicyclo [3.2.1] oct-3-en-2-yl acetate [(±)-7].

5)- [(+) - (*1S, 4S, 5S*)] - 7,8 -Dioxabicyclo [3.2.1] oct-3-en-2-ol [6].

6)- (-) - (*1R, 4R, 5R*)- 7,8 –Dioxabicyclo [3.2.1] oct-3-en-2-yl acetate [7].

7)- (-) - (*1R, 4R, 5R*) -7,8 -Dioxabicyclo [3.2.1] oct-3-en-2-ol [6].

8)- (+) - (*1S, 4S ,5S*) -7,8 –Dioxabicyclo [3.2.1] oct-3-en-2-yl acetate [7].

9)- Benzyl (E) -3- (2-Furyl) prop-2-enyl Ether (8b).

10)- *Tert*-Butyldimethylsillyl (E) -3- (2-furyl) prop-2-enylether (8c).

11)- (±) - (*1RS, 2SR*) -1- (2-Furyl) -3- (2-naphthylmethyloxy)-Propane-1,2-diol [(±)-9a].

12)- (±) - (*1RS, 2SR*) -3- Benzyloxy-1- (2-furyl)-Propane-1, 2-diol [(±)-9b].

13)- (±) - (*1RS, 2SR*) -3- *tert*-Butyldimethylsilyloxy-1- (2-furyl)-Propane-1,2-diol [(±)-9c].

14) - (±) -7- (2-Naphthylmethyloxymethyl)-6,8-dioxabicyclo [3.2.1] oct-3-enone [(±)-11a].

15)- (±) - 7-Benzyloxymethyl-6, 8-dioxabicyclo- [3.2.1] oct-3-en-2-one [(±)-11b].

16)- (±) - 7-*tert*-butyldimethylsiloxy-6, 8-dioxabicyclo-[3.2.1] oct-3-en-2-one [(±)-11c].

17)- (±) - (*1RS, 2SR, 5SR, 7RS*) -7- (2-Naphthylmethyloxymehyl)-6,8-dioxabicyclo-[3.2.1] oct-3-en-2-ol. [(±)-12a].

18)- (±) - (*1RS, 2SR, 5SR, 7RS*) -7- Benzyloxymethyl-6, 8-dioxabicyclo-[3.2.1] oct-3-3n-2-ol. [(±)-12b].

19)- 6,8-dioxabicyclo (±) - (*1RS, 2SR, 5SR, 7RS*) -7- *tert*-Butyldimethylsil-oxymethyl-6,8-dioxabicyclo[3.2.1] oct-3-en-2-ol [(±)-12c].

20)- (±) - (*1RS, 2SR, 5SR, 7RS*) -2-Acetoxy-7-(2- naphthylmethyloxyme-

thyl)-6,8-dioxabicyclo [3.2.1] oct-3-ene [(±)-13a].

21)- (±) - (*1RS, 2SR, 5SR, 7RS*) -2-Acetoxy-7-benzyloxymethyl-6,8-dioxabicyclo [3.2.1] oct-3-ene [(±)-13b].

22)- (±) - (*1RS, 2SR, 5SR, 7RS*) -2-Acetoxy-7-*tert*-butyldimethylsiloxy-methyl-6,8-dioxabicyclo-[3.2.1] oct-3-en-2-one [(±)-13c].

23)- (+) - (*1R, 2S, 5S, 7R*) -7-(2-Naphthylmethyloxymethyl-6,8-dioxabicyclo [3.2.1] oct-3-en-2-ol [(+)-12a].

24)- (-) - (*1S, 2R, 5R, 7S*) -2-Acetoxy-7-(2-naphthylmethyloxymethyl)-6,8-dioxabicyclo- [3.2.1] oct-3-ene [(-)-13a].

25)- (+) - (*1R, 2S, 5S, 7R*) -7-benzyloxymethyl-6,8-dioxabicyclo [3.2.1] oct-3-en-2-ol [(+)-12b].

26)- (-) - (*1S, 2R, 5R, 7S*) -2-Acetoxy-7-benzyloxymethyl-6,8-dioxabicyclo- [3.2.1] 0ct-3-ene [(-)-13b].

27)- (+) - (*1R, 2S, 5S, 7R*)-7-*tert*-butydimethylsiloxymethyl-6,8-dioxabicyclo-[3.2.1] oct-3-en-ol [(+)-12c).

28)- (-) - (*1S, 2R, 5R, 7S*) -2-Acetoxy-7-*tert*-butyldimethylsiloxymethyl-6,8-dioxabicyclo-[3.2.1] oct-3-ene [(-)-13c].

29)- (-) - (*1S, 2R, 5R ,7S*) -7-(2-Naphthylmethyloxymethyl)-6,8-dioxabicyclo [3.2.1] oct-3-en-2-ol [(-)-12a].

30) - (+) - (*1R, 2S, 5S, 7R*) -2-Acetoxy-7-(2naphthylmethyloxymethyl) -6,8-dioxabicyclo-[3.2.1]-oct-3-ene [(+)-13a].

31)- (-) - (*1S, 2R, 5R, 7S*) -7-Benzyloxymethyl-6,8-dioxabicyclo [3.2.1] -oct-3-en-2-ol [(-)-12b].

32)- (+) - (*1R, 2S, 5S, 7R*) -2-Acetoxy-2-benzyloxymethyl-6,8-dioxabicyclo [3.2.1] oct-3-ene [(+)-13b].

33)-(-) - (*1S, 2R, 5R, 7S*) -7-*tert*-Butyldimethylsiloxymwthyl-6,8-dioxabicyclo [3.2.1] oct-3-en-2-ol [(-)-12c].

34)- (+) -(*1R, 2R, 5S, 7R*) -2-Acetoxy-7-*tert*-butyldimethylsiloxymethyl – 6,8-dioxabicyclo [3.2.1] -oct-3-ene [(+)-13c].

35)- (-) - (*1S ,5S, 7R*) -7-Benzyloxymethyl-6,8-dioxabicyclo [3.2.1] oct-3-one [(-)-11b].

36)- (-) - (*1S, 5S, 7R*) -7-*tert*-Butyldimethoxymwthyl-6,8-dioxabicyclo [3.2.1] oct-3-en-2-one [(-)-11c].

37)- (+) - (*1S, 5R, 7S*) -7-*tert*-Butyldimethylsiloxymethyl-6,8-dioxabicyclo [3.2.1] octa-2-one (16).

38)- (+) - (*1S,3R,5R,7S*)-7-*tert*-Butyldimethylsiloxymethyl-3-methyl-6,8-dioxabicyclo[3.2.1]octa-2-one (16a).

39)- (-) - (*1S, 2R, 3S, 5R, 7S*) -7-*tert*-Butyldimethylsiloxymethyl-3-methyl-6,8-dioxabicyclo [3.2.1] octan-[2,3,b] -5-methoxyindol-2-ol (17).

40)- (+) - (*1S ,2R, 3S, 5R, 7S*) -7-*tert* -Butyldimethylsiloxy-methyl-3-methyl-6,8-dioxabicyclo [3.2.1] octan-[2,3,b]-5-methoxyindol-1-carboxylicacid benzyl ester (18).

41)- (+) - (*1S, 2R, 3S, 5R, 7S*) -7-Hydroxymethyl-3-methyl-6,8-dioxabicyclo [3.2.1]-octan [2,3,b] 5-methoxyindol-1-carboxylic acid benzyl ester (19).

42)- (+) - (*1S, 2R, 3S, 5R, 7S*) -7-Methylsulfonyloxymethyl-3-methyl-6,8-dioxabicyclo-[3.2.1]-octan [2,3,b] 5-methoxyindol-1-carboxylic acid benzyl ester (20).

43)- (-) - (*1S, 2R, 3S, 5R, 7S*) -7-Iodomethyl-3-methyl-6,8-dioxabicyclo [3.2.1] octan [2,3,b] 5-methoxyindol-1-carboxylic acid benzyl ester (21).

44)- (-) - (*1S, 2R, 3S ,5R, 7S*) -3-Hydroxy-6-methoxy-4a-methyl-1-vinyl-1,3,4,4a,9a-tetrahydro-1-H-pyrano [3,4-b]-indol-9-carboxylic acid benzyl ester (22).

45)- (+) - (*2S, 3S*) -2-(I-Hydroxyallyl)-3-(2-hydroxyethyl)-5-methoxy-3-methyl-2,3-dihydroindole-1-carboxylic acid benzyl ester (23).

46)- (-) - (*2aR, 3aS*) -5-methoxy-3a-methyl-2,3,3a,8a-tetrahydrofuro [2,3-b] indole-8-carboxylic acid benzyl ester (24).

47)- (-) - (*2aR, 3a S*) -5-Methoxy-3a-methyl-3,3a,8,8a-tetrahydro-2H-furo [2,3-b] indole (25).

48)- (+) - (*2S, 3S*) -2-(1-Hydroxyallyl)-5-methoxy-3-methyl-3-(2-methylaminoethyl)-2,3-dihydroindole-1-carboxylic acid benzyl ester (28).

49)- (+) -(*2S, 3S*)-3-[2-(*tert*-Butoxycarbonylmethylamino)-ethyl]-2-(1-hydroxyallyl)-5-methoxy-3-methyl-2,3-dihydroindole-1-carboxylic acid benzyl ester (29).

50)- (+) - (*2S, 3S*) -5-Methoxy-1,3a-dimethyl-2,3,3a,8a-tetrahydro-1H-pyrolo- [2,3-b] indole-8-carboxylic acid benzyl ester (31).

51)- (+) - (*1S, 5R, 7S*) -7-benzyloxymethyl-6,8-dioxabicyclo [3.2.1] octa-2-one (33).

52)- (+)-(*1S,3R,5R,7S*)-7-benzyloxymethyl-3-methyl-6,8-dioxabicyclo-[3.2.1]octa-2-one (34).

53)- (-) - (*1S, 2R, 3S, 5R, 7S*) -7-Benzyloxymethyl-3-methyl-6,8-dioxabicyclo [3.2.1] octan-[2,3,b] -5-methoxyindol-2-ol (36).

54)- (-) - (*1S, 2R, 3S, 5R, 7S*) -7-Benzyloxymethyl-3-(3-methoxyphenyl)-3-methyl-6,8-dioxabicyclo [3.2.1] octan-2-one (37).

55)- (+) - (*1S, 2R, 3S, 5R, 7S*) -7-Benzyloxymethyl-3-(3-methoxyphenyl)-3-methyl-6,8-dioxabicyclo [3,21] octan-2-ol (38).

56)- (+) - (*1S, 2R, 3S, 5R, 7S*) -Dithiocarbonic acid O-[7-benzyloxymethyl-3-(3-methoxyphenyl)-3-methyl-6,8-dioxabicyclo [3.2.1]oct-2-yl]ester-S-methyl ester (39).

57)- (+) - (*1S, 2R, 3R, 5R, 7S*) -7-Benzyloxymethyl-3-(3-methoxyphenyl)-3-methyl-6,8-dioxabicyclo [3.2.1] octane (40).

58)- (+) - (*1S, 2R, 3R, 5R, 7S*) - [3-(3-Methoxyphenyl)-3-methyl-6,8-dioxabicyclo [3.2.1] oct-7-yl]-methanol (41).

59)- (+) - (*1S, 2R, 3R, 5R, 7R*) - Methanesulfonic acid 3-(3-methoxyphenyl)-3-methyl-6,8-dioxabicyclo [3.2.1] oct-7-ylmethyl ester (42).

60)- (+) - (*1S ,2R, 3R, 5R, 7R*) -7-Iodomethyl-3-(3-methoxyphenyl)-3-methyl-6,8-dioxabicyclo [3.2.1] octane (43).

61)*2R,4R*)6-Allyl-4-(3-methoxyphenyl)-4-methyl-tetrahydropyran-2-ol (44).

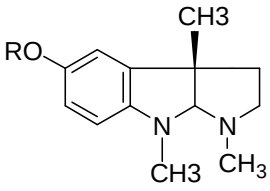
62)- (+) - (*4R*) -6-Allyl-4-(3-methoxyphenyl)-4-methyl-tetrahydropyran-2-one (45).

63)- (*4R, 6S*) -4-(3-Methoxyphenyl)-4-methyl-6-oxo-tetrahydropyran-2-carbaldehyde (47).

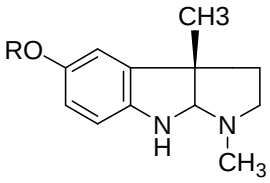
64)- *1R*)-(7-Methoxy-1-methyl-1,2-dihydronaphthalen-1-yl)-acetic acid (48).

1. Introduction

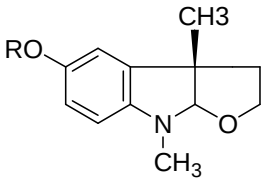
Physostigmine, norphysostigmine, physovenine, geneserine and eseramine are alkaloids that have been isolated from the African Calabar beans (*Physostigma venenosum*). They have interesting physiological effects such as cholinergic and miotic activities [1,2].



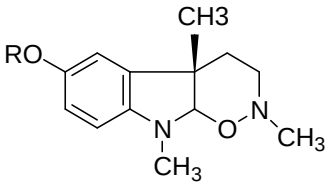
physostigmine



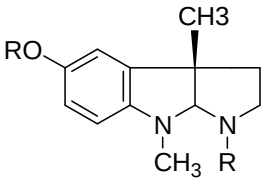
norphysostigmine



physovenine

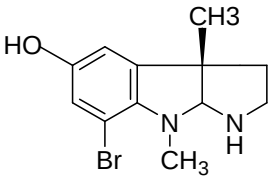


geneserine

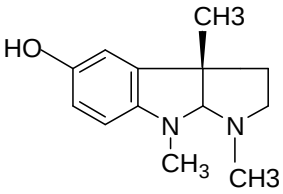


eseramine

R=CONHMe



bromoeseroline



eseroline

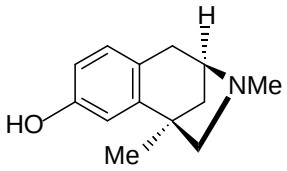
(-)- Physostigmine is used clinically in the treatment of glaucoma, myasthenia gravis and protection against organophosphate poisoning. These pharmacological effects of (-)- physostigmine are mainly based on its inhibition of acetylcholinesterase [3]. It has been reported that oral and intravenous administration of physostigmine significantly improved memory in patients with Alzheimer's disease [4].

Brossi and co-workers [5,6] investigated the anticholinestrase activity of (-)-N^1-norphysostigmine, eseramine, and other N^1- substituted analog of (-)-physostigmine and they found that (-)-N^1-norphysostigmine was potent as (-) -physostigmine. In addition, eseroline the major metabolite of (-)-

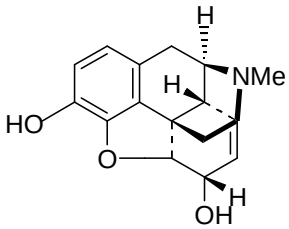
physostigmine was found to be an analgesic with potency similar to that of natural morphine [4]. Both enantiomers of eseroline were found bind to opiate receptors as inhibitors of adenylcyclase in vivo. It was confirmed that only (-)- eseroline showed potent narcotic activity enantiospicifically similar to that of morphine but neither (+)-eseroline nor natural forms of both N^1-noreseroline showed analgesic effect [5,7].

Moreover, (-)- bromoeseroline prepared from physostigmine by sequential bromination with NBS and alkaline hydrolysis, was reported to be a potent centrally acting analgesic superior to morphine in its antinoceptive effect in rodents with significantly reduced side effect [8].

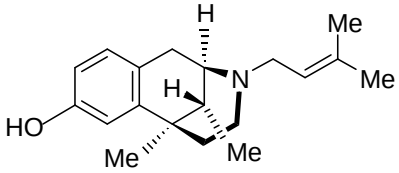
On the other hand, (-)- aphanorphine is a natural product with potential analgesic [9] and anesthetic [10] activity isolated in 1988 from the fresh water blue green-algae [11] *Aphanizomenon flos-aquae.* It possesses an interesting 3-benzazepine framework closely related to natural narcotic alkaloids as (-)-morphine and synthetic analgesic benzomorphans [48] such as ((-)-pentazocine and eptazocine. The absolute configuration of the natural product is (1*R*, 4*R*) [12]



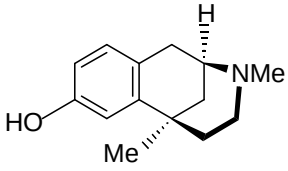
aphanorphine



morphine



pentazocine



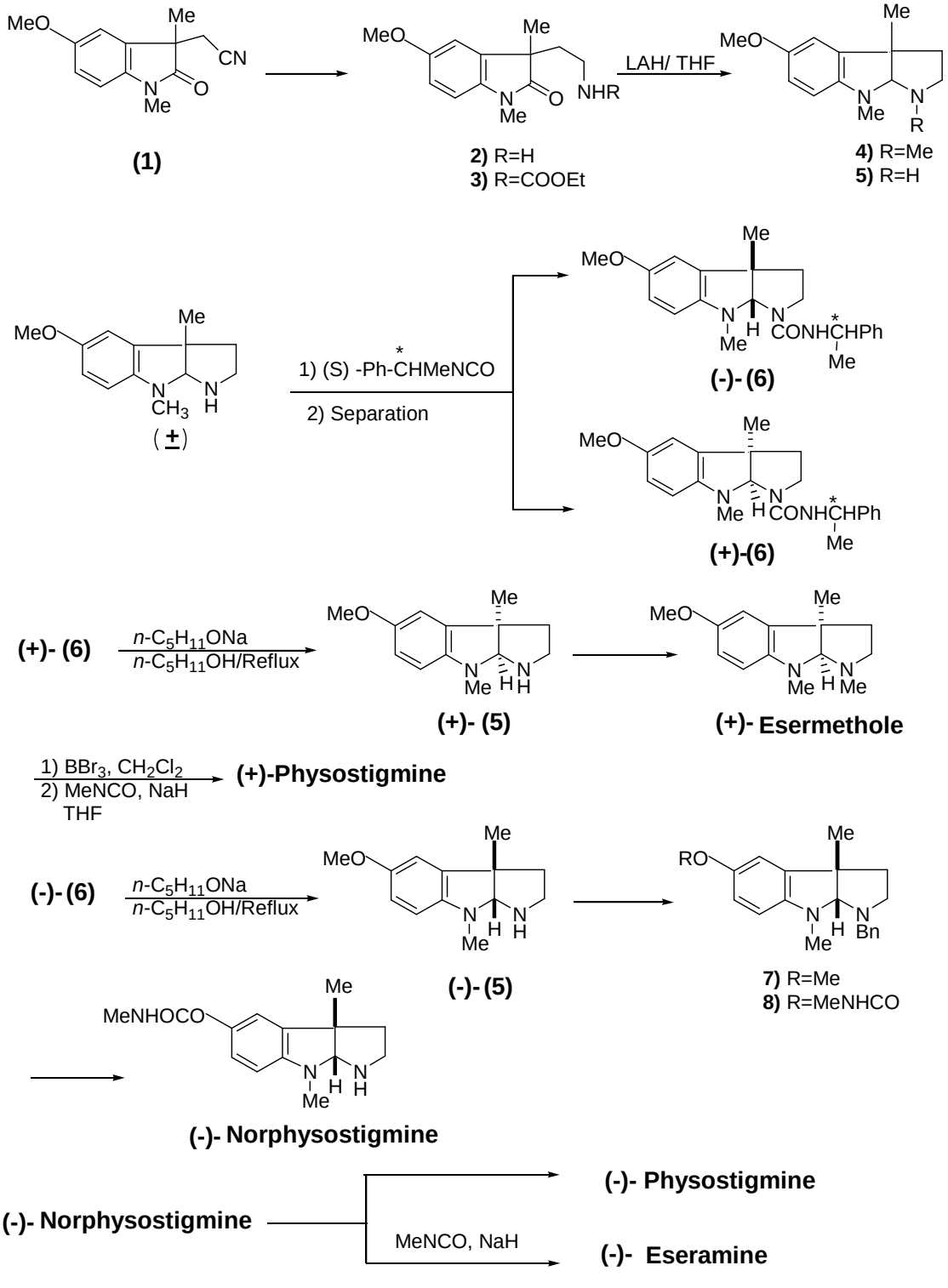
eptazocine

1.1. Synthesis of Calabar bean alkaloids

1.1.1. Synthesis of (-) and (+)- physostigmine

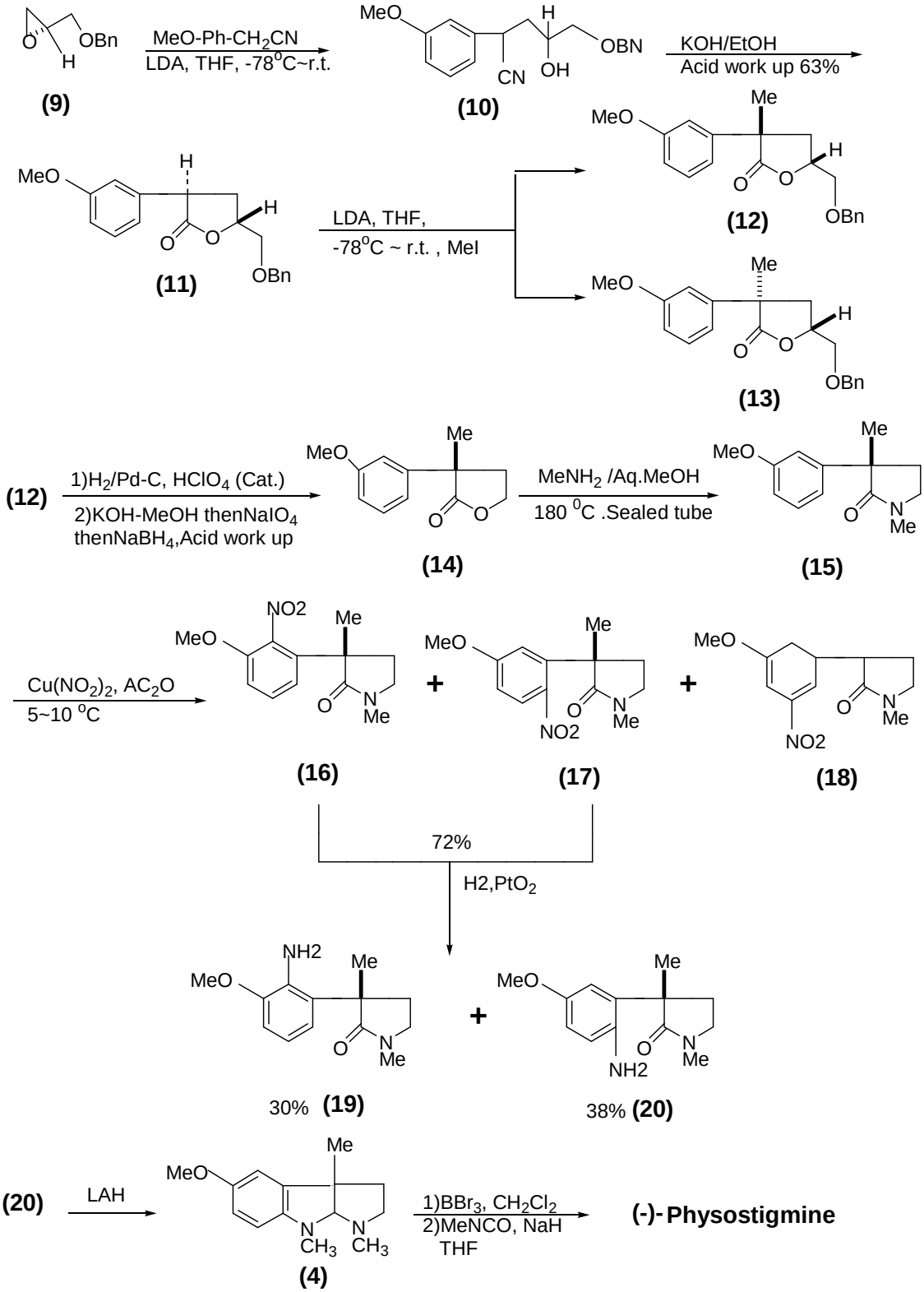
Julian and Pikl [13] reported the first synthesis of racemic physostigmine. Physovenine and geneserine were latter prepared from physostigmine [14-16] Since (-)- physostigmine [17-20] is the naturally occurring and the only biologically active enantiomer of these alkaloids, the enantiocontrolled synthesis is a critical process in the preparation of such biologically active alkaloid.

Schonenberger and Brossi [21] developed an efficient method for separation of racemic N^1-noresermethole obtained by Julian and Pickl [6] and its modification by Yu and Brossi. [22] The method involved catalytic reduction of methoxycyanooxindole (1) to afford the amine (2), which was converted to the corresponding carbamate (3) in quantitative yield. Reductive cyclization of the latter compound afforded racemic esermethole (4). Similarly, direct conversion of the cyanide (1) to N^1-noresermethole (5) was also achieved in 80% yield. The reaction of compound (5) with (-) (S)-(1-methylphenyl) isocyanate afforded the less polar (+)-urea (6) and more polar (-)-urea (6) in 37% and 40% yield respectively. The ureas (+)- (6) and (-)- (6) were decomposed easily by refluxing in 1 M sodium pentoxide in *n*-pentyl alcohol to afford (+) and (-)- N^1-noresermethole which were isolated as oxalate salts. Thus both enantiomers of physostigmine became readily available. The fumarate salt of (+)- N^1- noresermethole (6) underwent reductive methylation on treatment with formaline and triethylamine followed by sodium borohydride to afford (+)- esermethole. The fumarate salt of (-)- N^1-esermethole when treated with benzyl bromide in the presence of sodium bicarbonate gave (-)- N^1-benzyl-1-noresermethole (7), which was converted to N^1-benzylnorphysostigmine (8). The latter compound underwent hydrolytic debenzylation by palladium hydroxide on carbon to give (-)- N^1-norphysostigmine, which on reductive methylation with formaline and sodiumborohydride afforded physostigmine. The natural (-)-eseramine was also obtained in 98% yield on carbamoylation of (-)-norphysostigmine with methylisocyanate in the presence of sodium hydride.


MeO
Me
CN
N
Me
O
(1)
NHR
2) R=H
3) R=COOEt
LAH/ THF
4) R=Me
5) R=H
CH3
H
(±)
1) (S) -Ph-CHMeNCO
2) Separation
CONHCHPh
(-)-(6)
(+)-(6)
(+)- (6)
n-C5H11ONa
n-C5H11OH/Reflux
(+)- (5)
(+)- Esermethole
1) BBr3, CH2Cl2
2) MeNCO, NaH
THF
(+)-Physostigmine
(-)- (6)
(-)- (5)
RO
Bn
7) R=Me
8) R=MeNHCO
MeNHOCO
(-)- Norphysostigmine
(-)- Physostigmine
(-)- Eseramine
MeNCO, NaH

1.1.2. Synthesis of Natural (-)- Physostigmine by Enantiocontrolling Routes.

The first synthesis of natural (-)-enantiomer of physostigmine was achieved by Takano and co-workers [(23) in] 1982. Thus treatment of (-)-(S)-O-benzyl-2, 3-epoxypropyl ether (9) with carbanion prepared *in-situ* from 3-methoxybenzyl cyanide and lithium diisopropylamide (LDA) in THF afforded compound (10). Alkaline hydrolysis of (10) afforded γ-lactone (11) in 63% overall yield as 1:1 epimeric mixture. Alkylation of compound (11) with methyl iodide in the presence of LDA in THF lead to sterioselective introduction of a methyl group via the less hindered face of the molecule to give the desired compound (12) in 80% yield in addition to 11% of undesired epimer (13). Compound (12) was converted to the lactone (14) in 96% overall via multistep-reaction involving hydrogenolysis, hydrolysis with methanolic potassium hydroxide, oxidative cleavage with sodium periodate and reduction with sodium borohydride followed by acidic work-up. The lactone (14) was converted to the lactame (15) in 78% yield, which was treated with cupric nitrite in acetic anhydride to yield a mixture of three regioisomers (18), (16), and (17), from which the required amine (20) could be isolated in pure form in 38% yield after catalytic hydrogenation. When compound (20) was treated with LAH, it afforded tricyclic aminal which underwent reductive methylation to afford (-)- esermethole (4). The latter compound was easily converted to physostigmine via hydrolysis with borontribromide followed by carbamylation with methylisocyanate in the presence of sodium hydride.


MeO-Ph-CH2CN
LDA, THF, -78°C~r.t.
KOH/EtOH
Acid work up 63%
(9)
(10)
(11)
(12)
(13)
LDA, THF,
-78°C ~ r.t. , MeI
1)H2/Pd-C, HClO4 (Cat.)
2)KOH-MeOH thenNaIO4
thenNaBH4,Acid work up
MeNH2 /Aq.MeOH
180 °C .Sealed tube
(14)
(15)
Cu(NO2)2, AC2O
5~10 °C
(16)
(17)
(18)
72%
H2,PtO2
30% (19)
38% (20)
LAH
1)BBr3, CH2Cl2
2)MeNCO, NaH
THF
(4)
(-)-Physostigmine

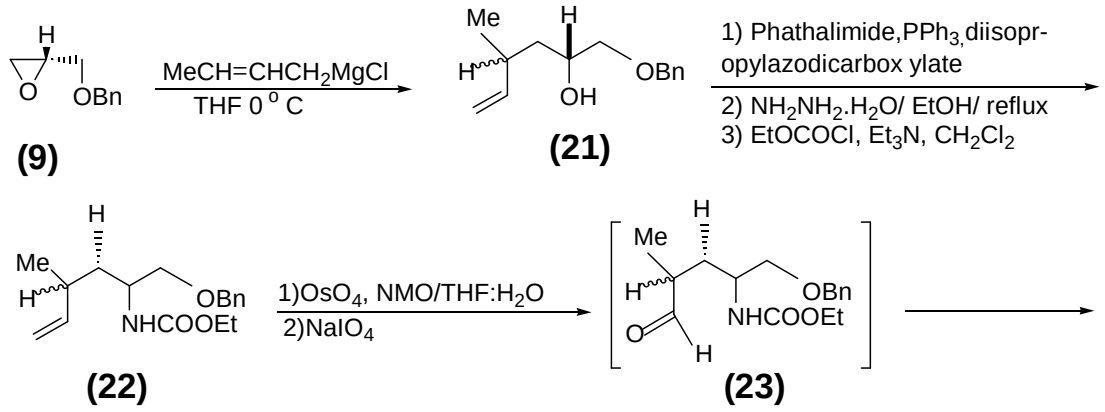
In 1990, Takano and co-worker [24] reported the synthesis of the key intermediate esermethole in its both enantiomeric forms.

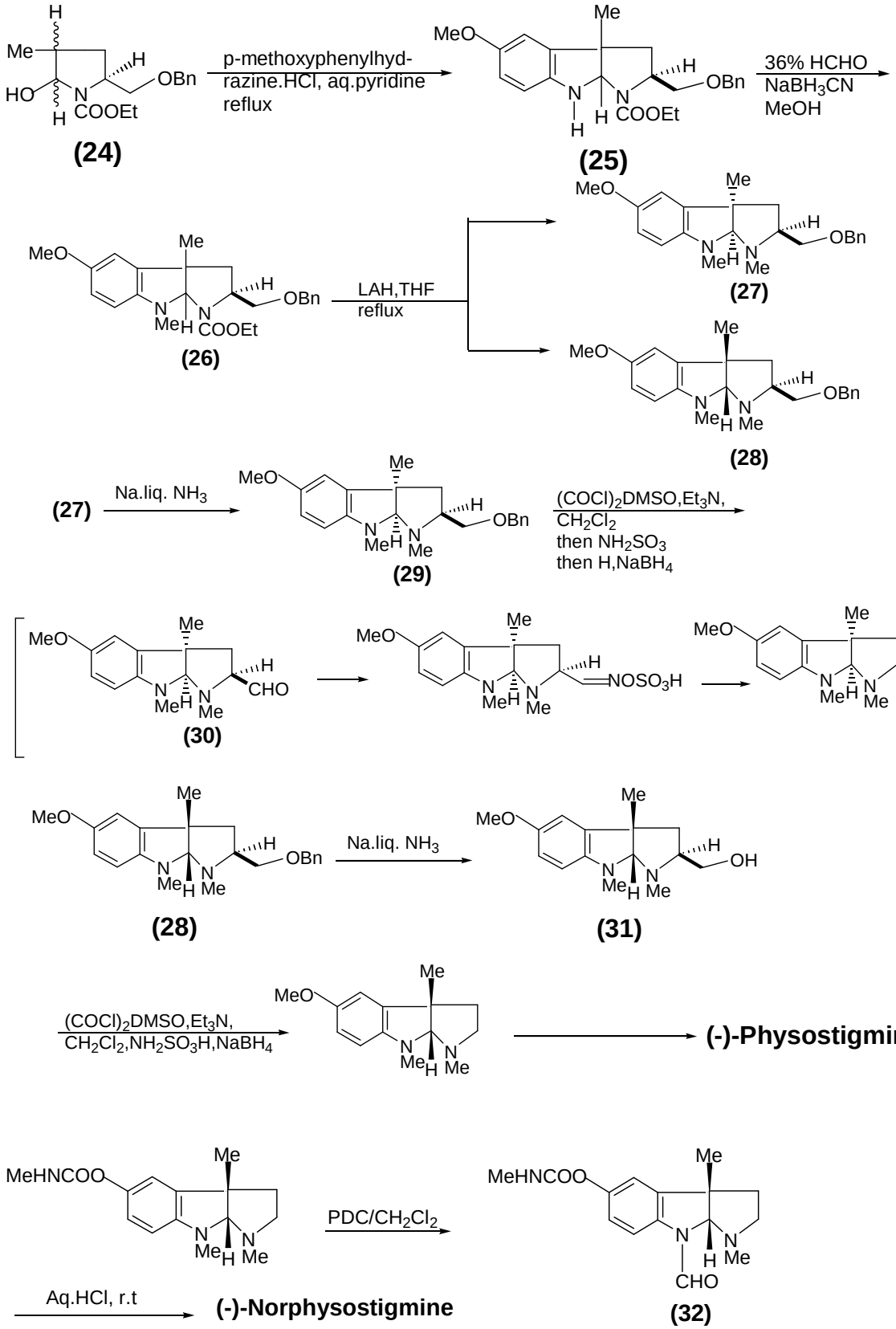
Hence, reaction of (s)-O-benzylglycidole (9) with crotylmagnesium chloride afforded the terminal olefin (21) in 90% yield. When the latter compound was subjected to Mitsunobu [25] reaction condition followed by sequential deacylation and carbomylation furnished the carbamate (22) in 72% overall yield. Treatment of (22) with a catalytic amount of osmium tetroxide in the presence of NMO followed by sodium periodate allowed cleavage at the terminal olefin to give the aldehyde intermediate (23) which underwent cyclodehydration to yield the pyrolidine derivative (24).

Upon Fischer indolization of (24) with 4-methoxyphenylhydrazine hydrochloride in aqueous pyridine, it furnished inseparable 2: 1 mixture of product (25) in 95% yield. The product was a mixture of the major unnatural isomer and the minor natural isomer. Fortunately the*N,N*- dimethylated derivatives obtained from the mixture of (25) by sequential *N*-methylation and reduction were separated by silica gel chromatography to afford unnatural and natural amines (27) and (28) in 53% and 29% respectively.

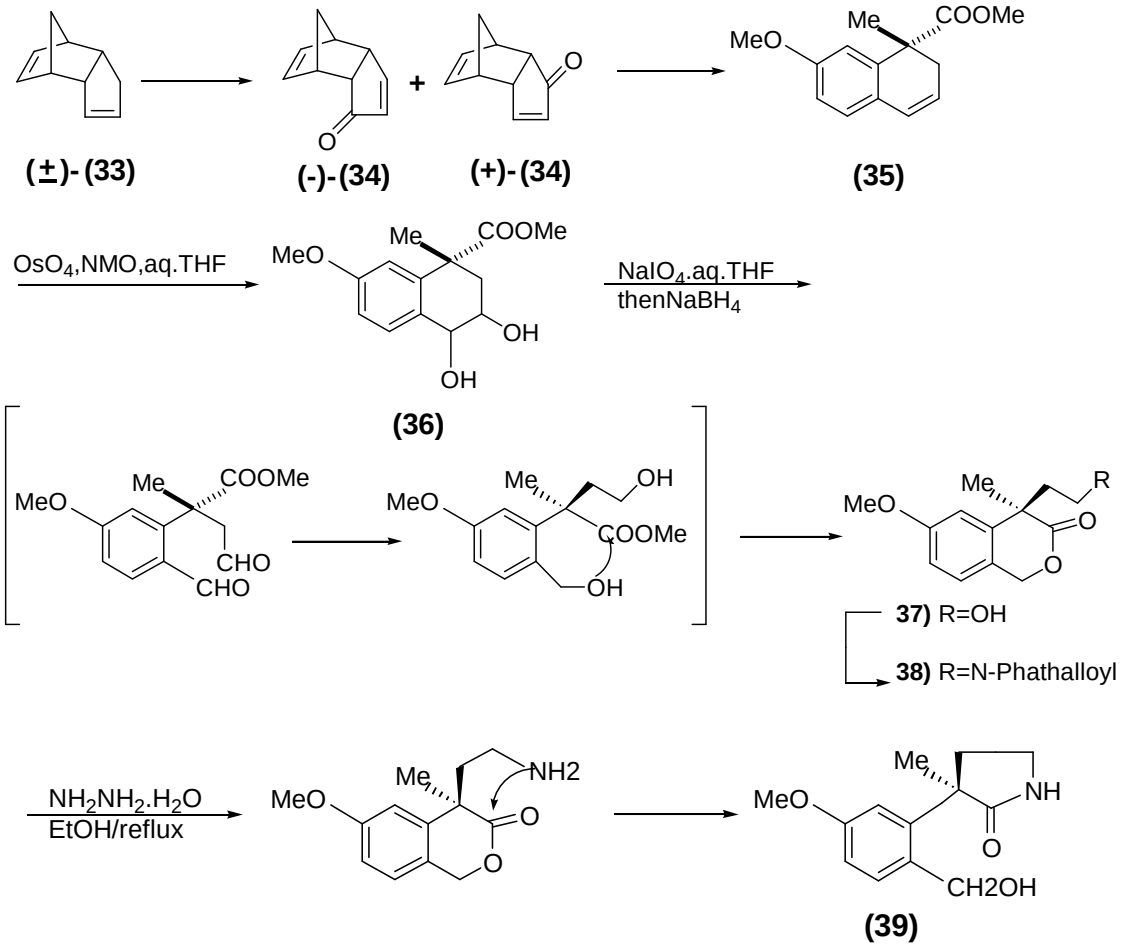
The major isomer (27) was debenzylated under Birch [26] condition to give the primary alcohol (29) quantitatively. The aldehyde (30) was obtained from (29) by Swern [27] oxidation and the mixture was successively treated with hydroxylamine-O-sulfonic acid and sodium borohydride to give the unnatural (+) esermethole in 22% yield.

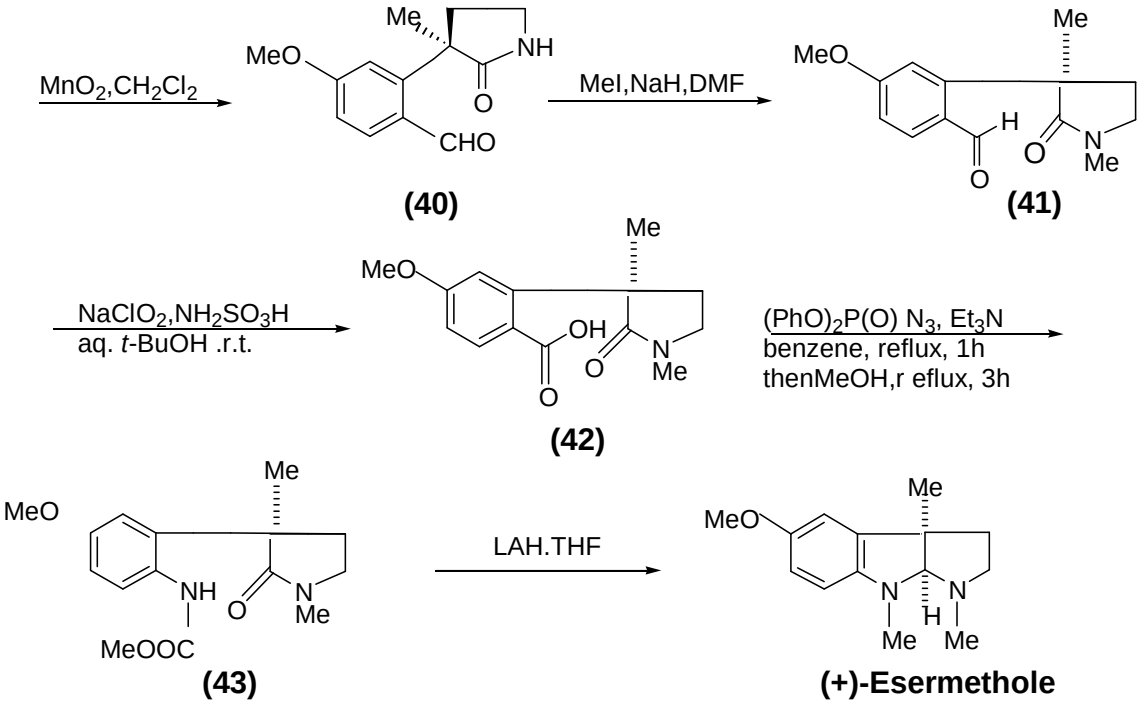
The isomeric alcohol (31) was obtained in 92% yield from (28) and afforded the natural (-)- esermethole in 25% yield. During oxidation of alcohol (29) to aldehyde (30) it was observed that *N* [8]-formyl derivative was generated in 25% yield, which underwent oxidation with pyridinium dichromate. The formamide (32) underwent hydrolysis with dilute hydrochloric acid to give (-)- norphysostigmine.




p-methoxyphenylhyd-
razine.HCl, aq.pyridine
reflux
36% HCHO
NaBH3CN
MeOH
(24)
(25)
LAH,THF
reflux
(26)
(27)
(28)
Na.liq. NH3
(29)
(COCl)2DMSO,Et3N,
CH2Cl2
then NH2SO3
then H,NaBH4
(30)
(28)
Na.liq. NH3
(31)
(COCl)2DMSO,Et3N,
CH2Cl2,NH2SO3H,NaBH4
(-)-Physostigmine
PDC/CH2Cl2
Aq.HCl, r.t
(-)-Norphysostigmine
(32)

The unnatural physostigmine was obtained by Takano and co-workers [28] via lipase mediated asymmetric hydrolysis of the dihydronaphthalene derivative (35) obtained from either enantiomers of dienone (34) that have been obtained from racemic dicyclopentadiene (33) [29]. Treatment of (35) with catalytic amount of osmium tetraoxide (OsO_4) in the presence of 2 equivalent of NMO afforded the glycol (36), which was treated with sodium periodate followed by sodium borohydride to give γ-lactone (37). When the γ-lactone was subjected to Mitsunobu [25] reaction condition afforded the corresponding phathalimide (38). Refluxing the latter compound (38) with hydrazine hydrate afforded lactame (39), which on sequential oxidation; *N*-alkylation and oxidation gave the carboxylic acid (42). By application of Shioiri [30,31] modification of Curtius reaction, the acid (42) gave the lactam carbamate (43) which when reduced with LAH afforded (+)- esermethole.

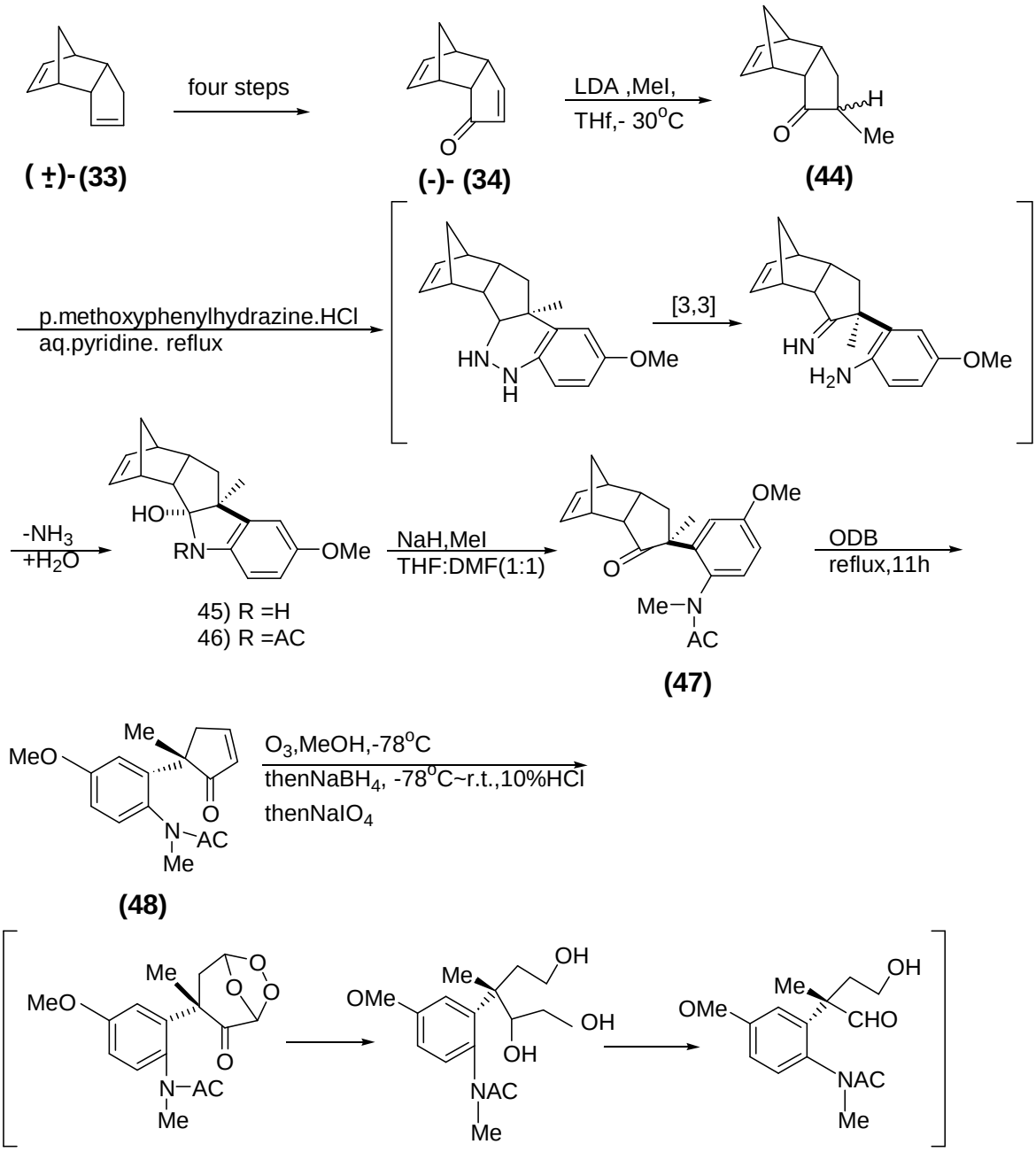


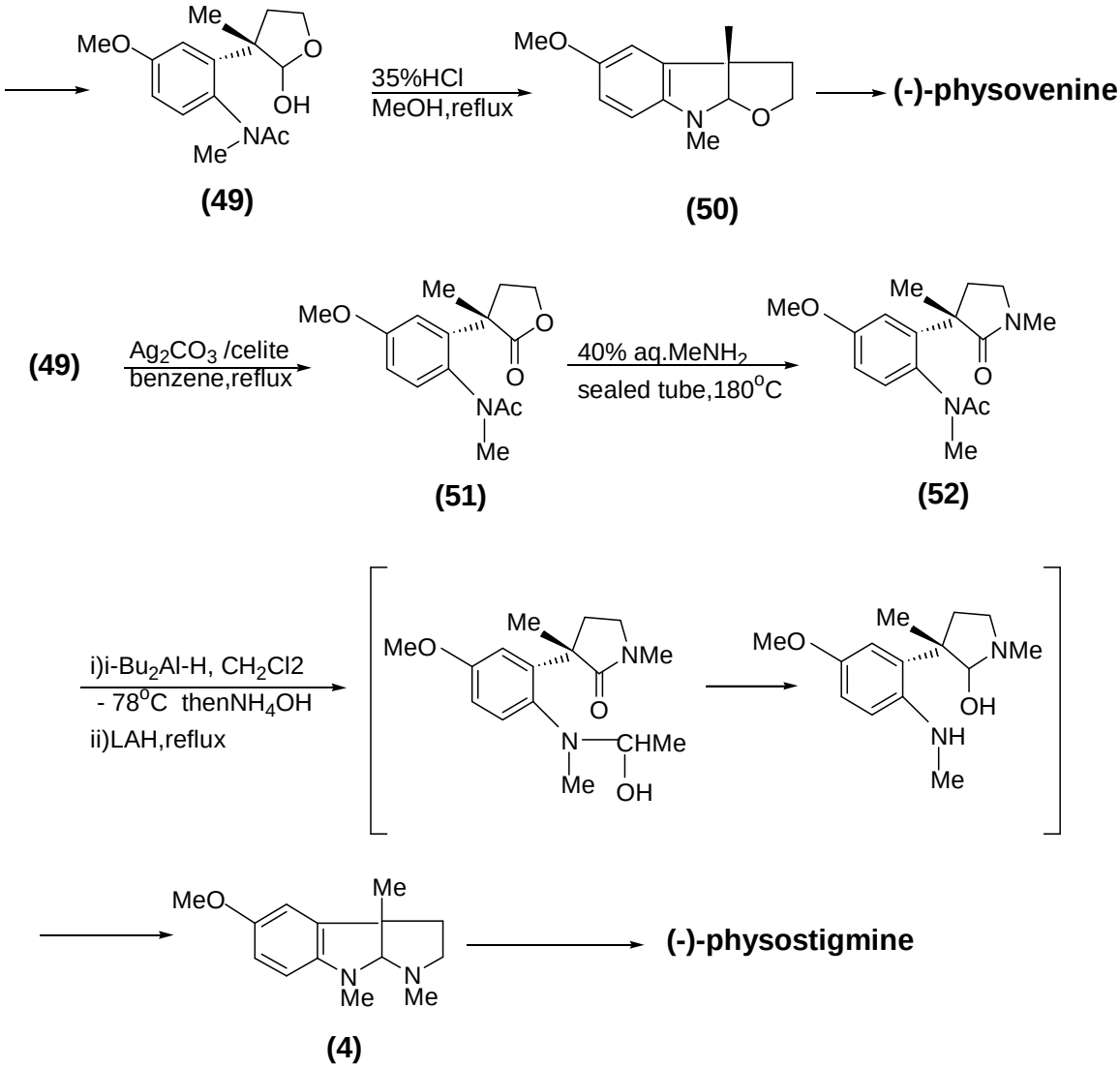


Enantiocontrolled total synthesis of (-)- physovenine and (-)- physostigmine has been achieved by by Takano and co-workers [32] in 1991 starting from optically active tricyclic enone (34) by employing Fischer indolization under non acidic conditions.

The alkylation of optically active (-)- tricyclic enone (34), prepared from racemic dicyclopentadiene in four steps sequence of reactions including lipase mediated resolution [31], afforded the monomethyl ketone (44) in 86%yield. When this compound was refluxed with 4-methoxyphenyl-hydrazine hydrochloride in aq. pyridine, it afforded carbinolamine (45). The reaction proceeded via [3,3]- sigmatropic rearrangement of diaza-1, 5-diene intermediate to afford the imine, which on hydrolysis under the reaction conditions gave (45)[33]. The latter compound underwent acetylation followed by methylation to afford a tertiary amide (47) in 86% overall yield. Refluxing (47) in 2-dichlorobenzene initiated *retro*-Diels-Alder reaction and gave the cyclopentanone (48). On sequential one flask ozonolysis of (48) followed by borohydrid reduction and periodate cleavage, it furnished the hemiacetal (49) in 62% yield. Refluxing (49) in methanol containing a trace of hydrochloric acid caused concomitant deacylation and cyclization to give tricyclic aminoacetal (50) in 71% yield. Treatment of (50) with boron tribromide followed by carbomylation of the resulting phenol afforded (-)-physovenine.

On the other hand, oxidation of lactole (49) by silver carbonate on celite gave the lactone (51) in 88% yield, which was then transformed to the lactam (52) in 76% yield by heating in aqueous methylamine in sealed tube. The latter compound (52) was allowed to react with diisobutylaluminium hydride at - 78°C followed by refluxing in THF with LAH to afford (-)-esermethole (4), which could be converted to (-)- physostigmine.

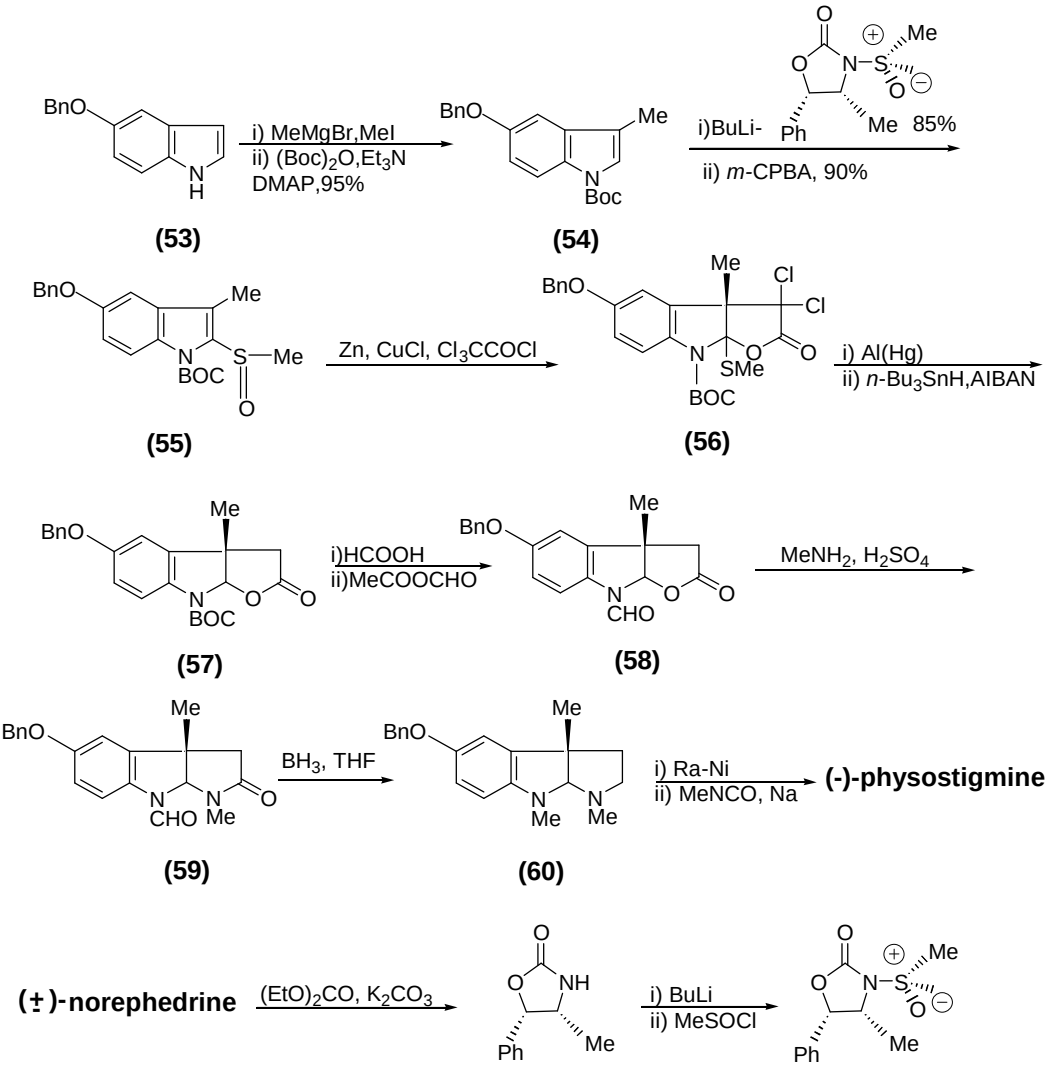




In1992, Marino et. al. [34] synthesized (-)- physostigmine through asymmetric induction of chirality from optically active 2-(alkylsulfinyl) indole to indoline butyrolactone bearing two chiral centers.

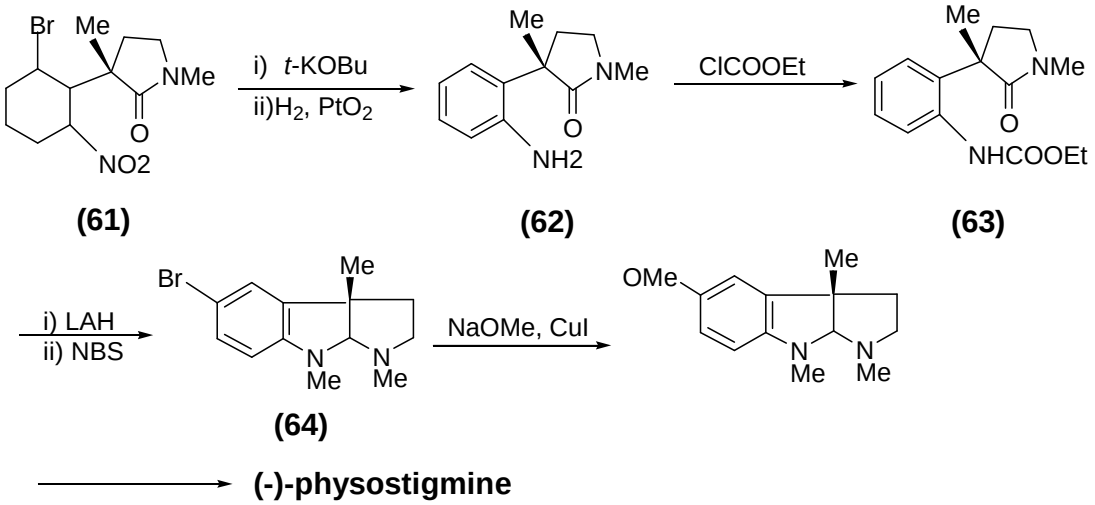
The reaction of 5-benzyloxyindole (53) with methylmagnesium bromide and methyl iodide afforded 5-benzyloxy-3-methylindole followed by protection of secondary amine with $(Boc)_2O$ to produce compound (54). Treatment of (54) with chiral dimethyl sulfide [(*N*-methylsulfinyl) oxazolidinone] produced 2-(methylsulfenyl)-indole derivative, which was easily oxidized with *m*-CPBA to afford chiral sulfoxide (55). The latter compound underwent lactonization when treated with excess trichloroac-etylchloride in the presence of Zinc-Cupper couple to afforded compound (56) which was desulfonated and dechlorinated through treatment with

aluminum amalgam and tributyline hydride respectively to afford the lactone (57). This lactone was converted to the lactame (59) by treatment with excess methylamine in the presence of sulfuric acid as a catalyst. Borane in THF reduced both lactame and formamide to afford O-benzyleseroline (60) in 70% yield. The benzyl group was cleaved with Raney nickel to afford a phenol which was immediately treated with methylisocyanate in the presence of sodium as catalyst to afford (-)- physostigmine.



In 1991, Node et al. [35] synthesized the natural (-)- physostigmine starting with chiral bromonitroolefenic lactones (61) which was converted to aniline derivative (62) by treatment with potassium tertiary butoxide followed by hydrogenolysis of the nitro group.

Thus, reaction of (62) with ethylchlorocarbonate afforded the corresponding carbamate (63), which when reduced with LAH and brominated with NBS gave tricyclic amine (64). The latter compound (64) was converted to (-)- esermethole by reaction with sodium methoxide and cuprous iodide.



(61) **(62)** **(63)**

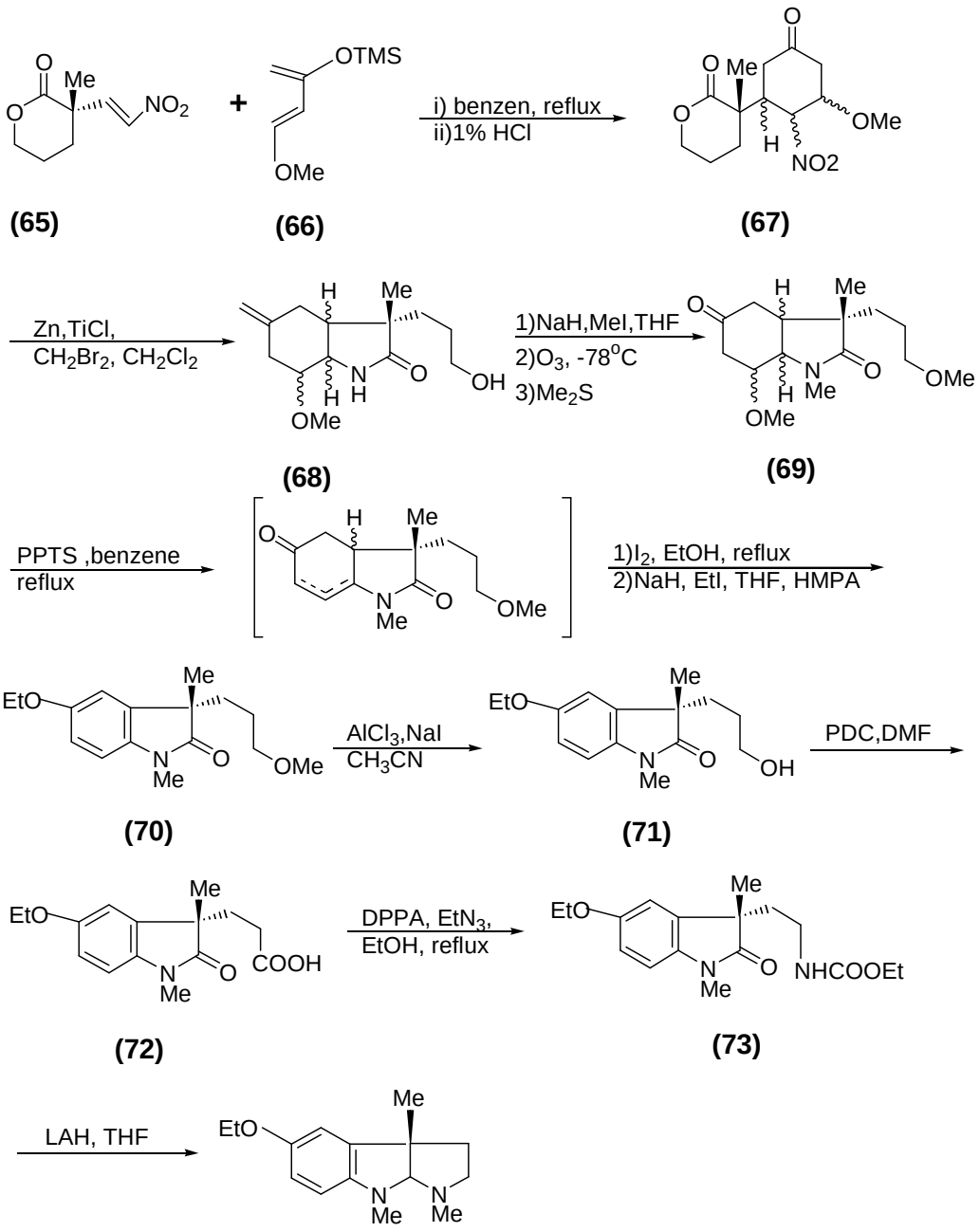
(64)

(-)-physostigmine

Node and co-workers, [36,37] in 1991, synthesized physostigmine using Deils-Alder reaction of (-)- nitroolefine [38,39] (65) with Dnishfsky's diene (66) followed by protonation to afford pentanolid (67) as four diastreomers in 95% yield.

Reaction of compound (67) with Nozaki [40] reagent (Zn-TiCl,CH_2Br_2) in dichloromethane afforded the desired lactam (68). Methylation of the latter compound followed by ozonoloysis gave the cyclic ketone (69), which underwent elimination of methanol to give a mixture of the conjugated and unconjugated cyclic ketone. Subsequent oxidation with iodine and ethylation with ethyl iodide gave single aromatized compound (70), which underwent selective bond cleavage of methyl ether with combination reagent system of aluminum chloride and sodium iodide to give the alcohol (71). Oxidation of such alcohol with pyridinium dichromate yielded the corresponding carboxylic acid (72), which was transformed to the carbamate (73) via modified Curtius [41] degradation with diphenylphosphorylazide.

The carbamate (73) underwent reductive cyclization with LAH to give the desired (-)- esermethole.



(65) **(66)** **(67)**

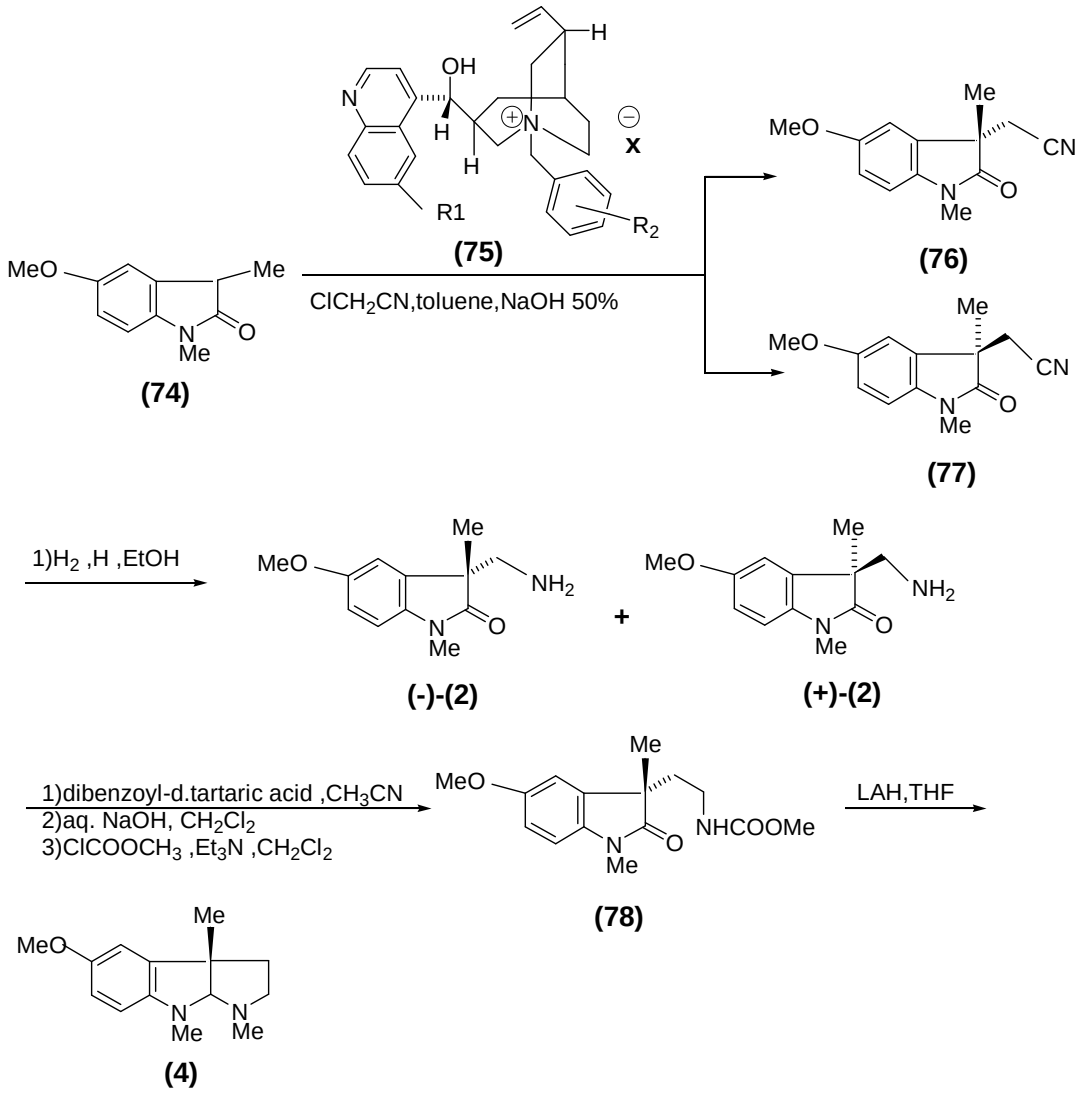
(68) **(69)**

(70) **(71)**

(72) **(73)**

In 1991, Wrong and co-workers [42] synthesized (-)-physostigmine through asymmetric alkylayion of oxindole by phase transfer catalysis using chiral catalyst (75).

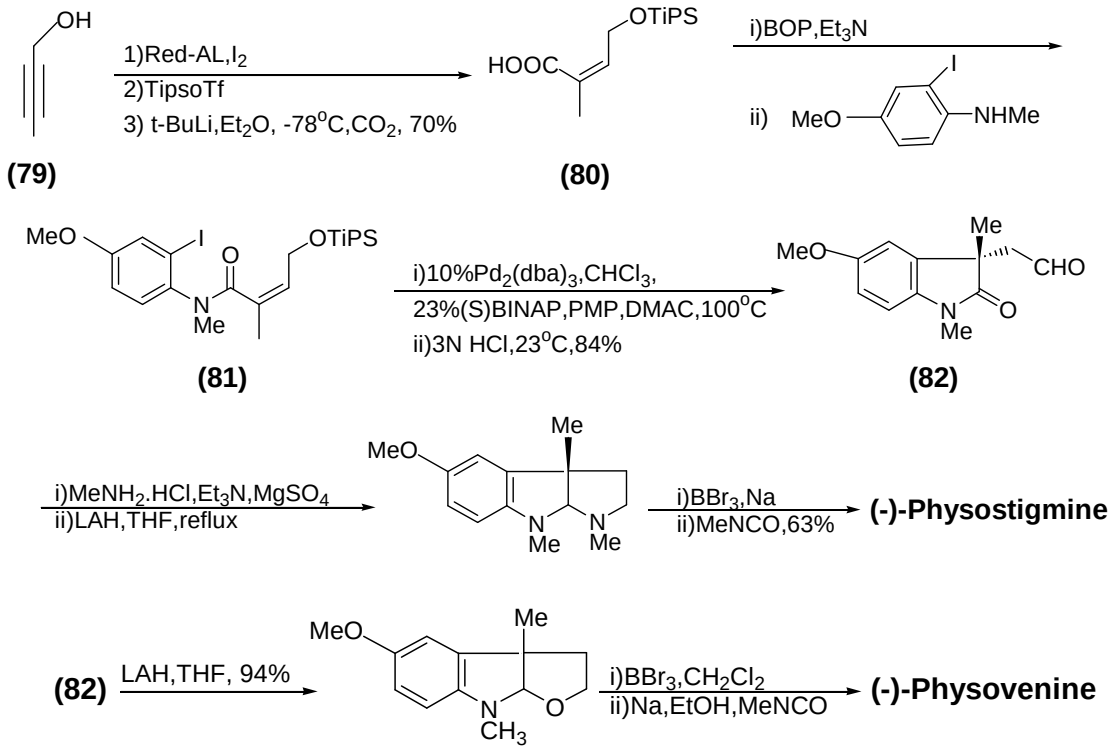
Alkylation of oxindole (74) with chloroacetonitrile followed by catalytic reduction yielded the corresponding primary amine (2) as optically enriched mixture. Treatment of amine with dibenzoyl-D-tartaric acid in acetonitrile offered optically pure salt that was finally converted to carbamate (78). Reductive cyclization of compound (78) gave (-)- esermethole.



The synthesis of (-)-physostigmine from z-butenanilide through asymmetric Heck [43,44] cyclization reaction was achieved by Overman and co-workers [45,46]. Starting from commercially available 2-butyn-1-ol (79). Hence, compound (79) was reduced with sodium bis (2-methoxyethoxy) aluminum hydride (Red-Al)) and the resulting vinylalanate was iodinated to give (z)-3-iodo-2-buten-1-ol. This latter intermediate was then protected and carboxylated to afford the (Z) acid (80) in 70% yield. Coupling of the latter compound in dichloromethane with benzotriazol-1-yloxytris (dimethylamino) phosphonium hexafluorophosphate (BOP) followed by heating the resulting activated ester with 2-iodo-*N*-methyl-*p*-anisidine (prepared from commercially available *N*-methyl-*p*-anisidine) [47] at 60°C afforded compound (81) in 76% yield. [44,48] Asymmetric Heck cyclization of (81) with 20% Pd-s-BINAP (formed *in-situ* from 10 % Pd $(dba)_3.CHCl_3$ and 23% (s)-

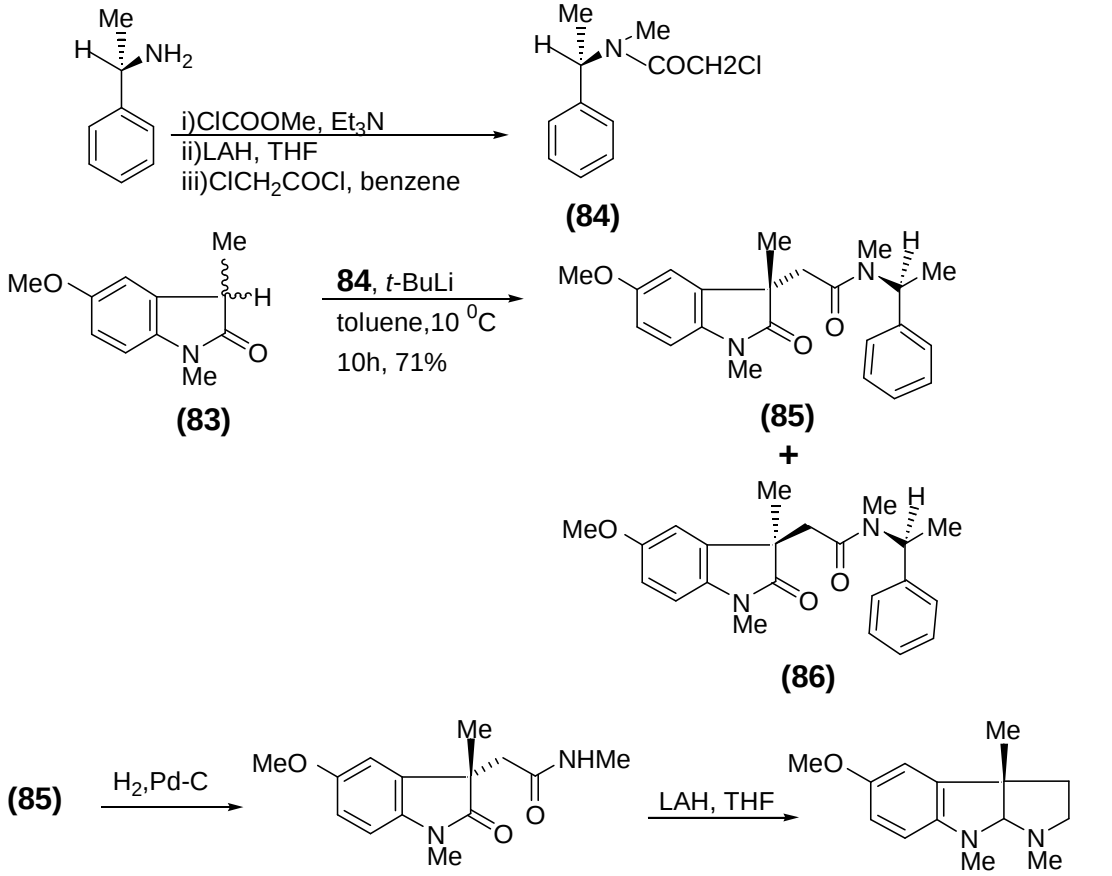
(BINAP) followed by hydrolysis gave (s)-oxindole aldehyde (82). Treatment of the aldehyde (82) with methylamine and LAH afforded (-)-esermethole, which was converted to (-)- physostigmine.

Heck cyclization of (Z)-butenanilide (81) with Pd-(R)-BINAP in the presence of PMP followed by acid hydrolysis and recrystalization provided enantio pure (R)-(82), which was converted to enantiopure (+)- physovenine and (+)- physostigmine.



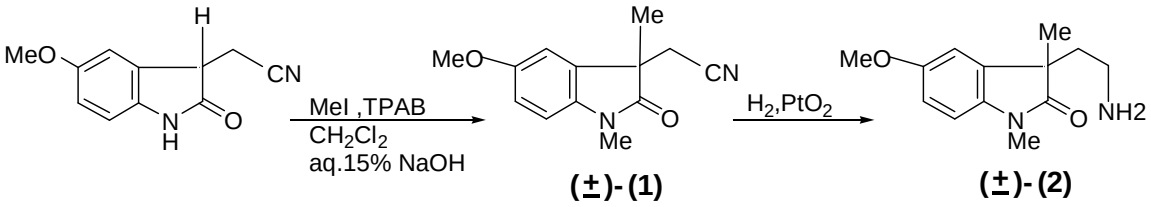
In 1994, Pallavicine and co-workers [49] reported a new synthesis of esermethole (4). The synthesis was based on asymmetric alkylation at C-3 of racemic 1,3-dimethyl-5-methoxy-2-oxindolone (83) with chloroacetyl derivative of (s)-*N*-methyl-1-phenylethyl-amine (84) as chiral alkylating agent in the presence of butyl lithium to afford (3s, 1s)-*N*-methyl-*N*- (1′-phenylethyl)-1,3-dimethyl-5-methoxy-2-oxindole-3-ilactamide (85) and its isomer (86).

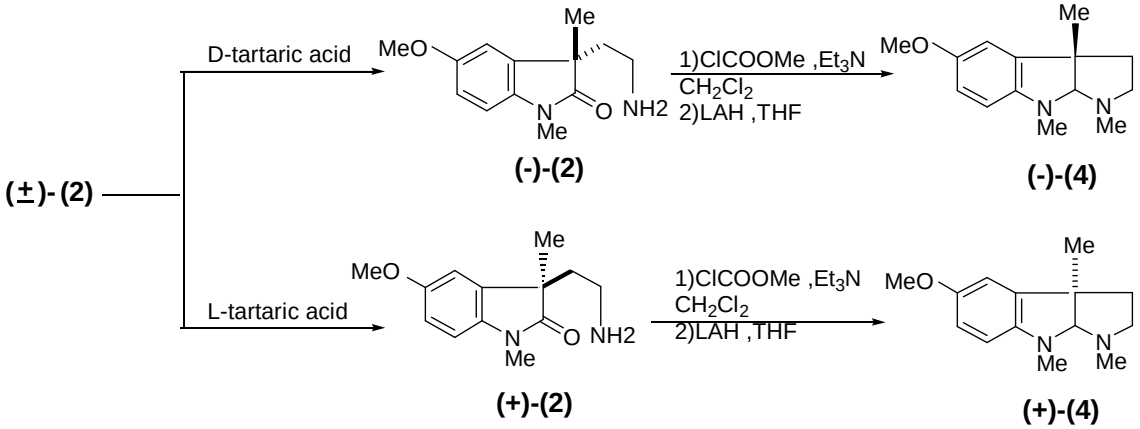
This chiral alkylating agent (84) was obtained from 1-phenylethylamine via condensation with methyl chloroformate followed by reduction with LAH and then condensation with chloroacetyl chloride. Compound (85) was converted to (-)- esermethole via hydrogenolysis and reductive cyclization.



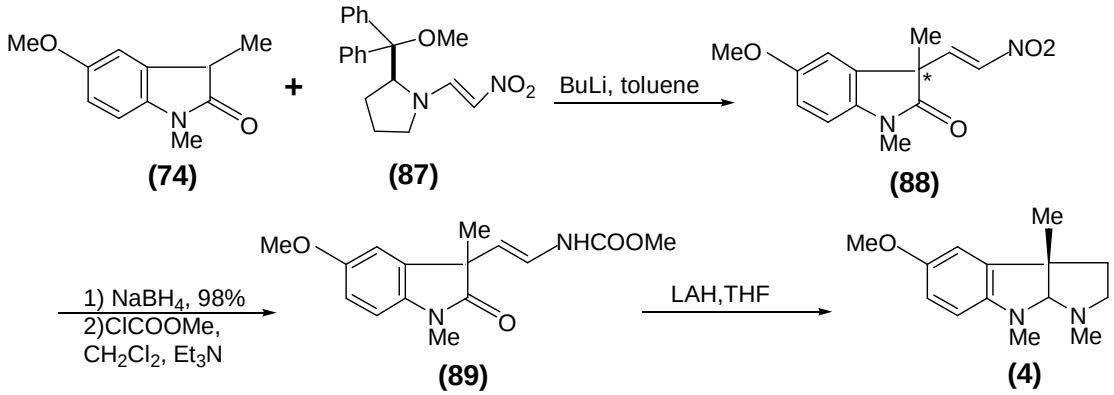
The synthesis of (-) and (+)-esermethole by chemical resolution of 1,3-dimethyl-3- (2-aminoethyl)-5-methoxy-2-oxindole (2) by Valoti and co-workers. [50]

Thus, dimethylation of 3-cyanomethyl-5-methoxy-2-oxindole and successive hydrogenation of the cyano group afforded 1,3-dimethyl-3- (2-aminoethyl)-5-methoxy-2-oxindole (2), which was efficiently resolved with optically active tartaric acid. Subsequent treatment with methyl chloroformate and reductive cyclization of the produced carbamate afforded (+) and (-)- esermethole.



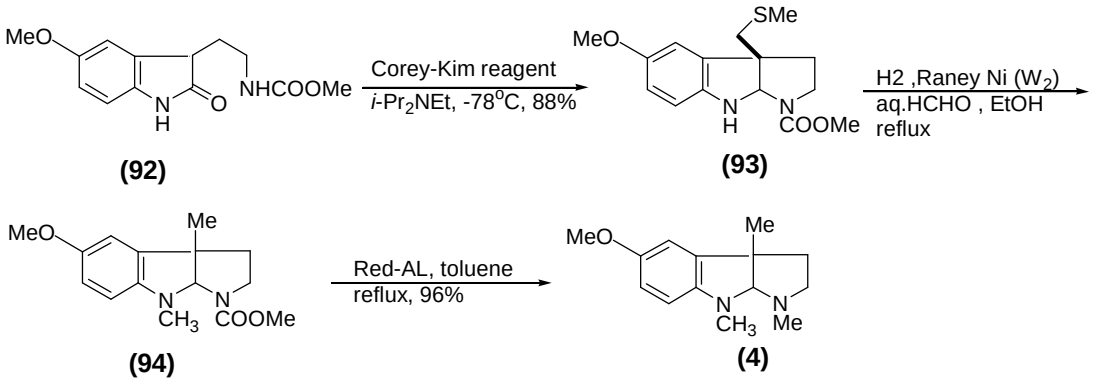


Fuji et al. [51] in 1998, reported the synthesis of (-)-physostigmine through nitroolefination of 1,3-methyl-5-methoxy-2-oxindoles (74) with nitro-enamine (87) followed by treatment with butyllithium in toluene to give compound (88). The latter compound was reduced by sodium borohydride to the corresponding amine, which was converted to the carbamate (89). Reductive cyclization of (89) by LAH afforded (-)- esermethole, which was converted to (-)- physostigmine.



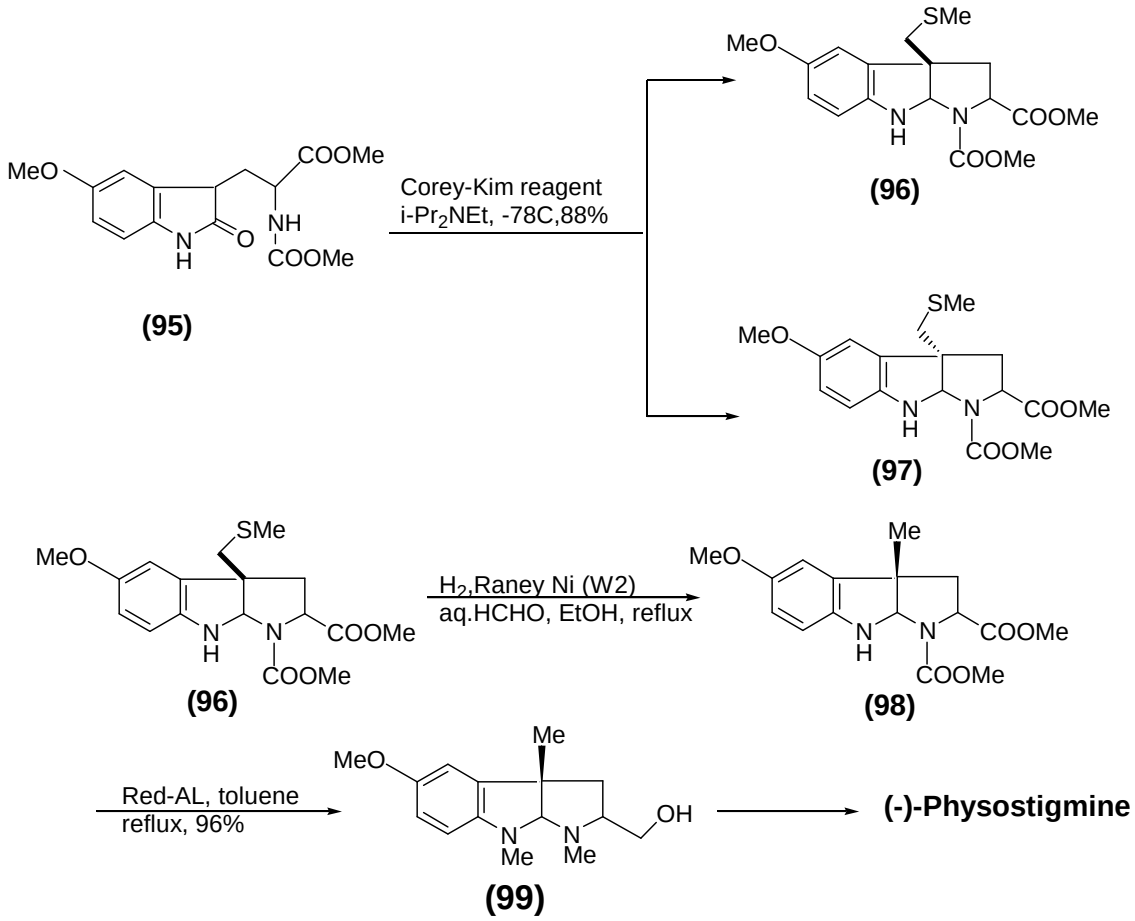
In 2000 a new efficient synthetic route for (-)-physostigmine was described by Nakagawa and co-workers [52] via reaction of Corey-Kim reagent with tryptamine or tryptophane carbamate to give 3-(methylthio) methyl-hexahydropyrolo-[2,3-b]-indole skeleton, which was converted to racemic physostigmine in excellent yield.

Thus alkylative cyclization reaction of 5-methoxy-*N*- (methyloxycarbonyl) tryptamine (92) with Corey-Kim [53] reagent afforded the corresponding pyroloindole (93) in 88% yield. The latter compound underwent reductive methylation and simultaneous desulfurization with Raney nickel (W2) under hydrogen atmosphere in the presence of formalin to afford (94), which was reduced with Red-Al to afford racemic esermethole.

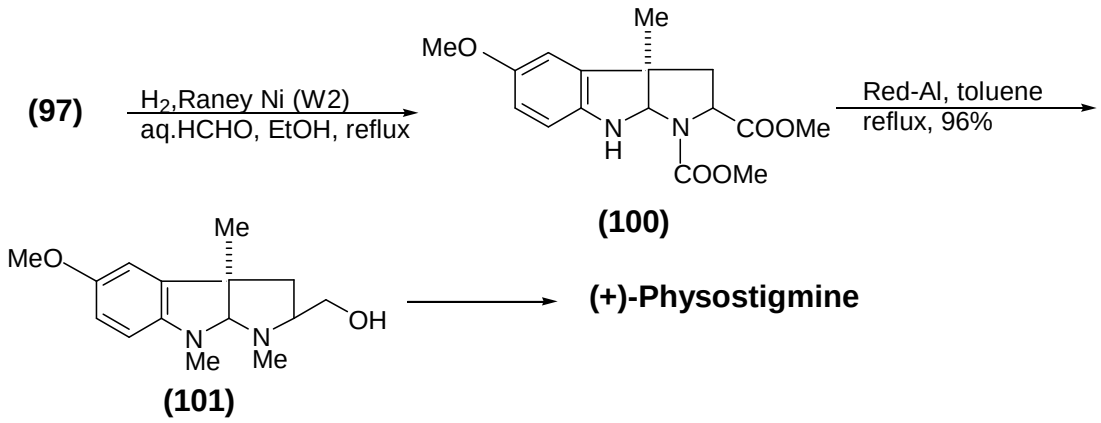


(92) **(93)** **(94)** **(4)**

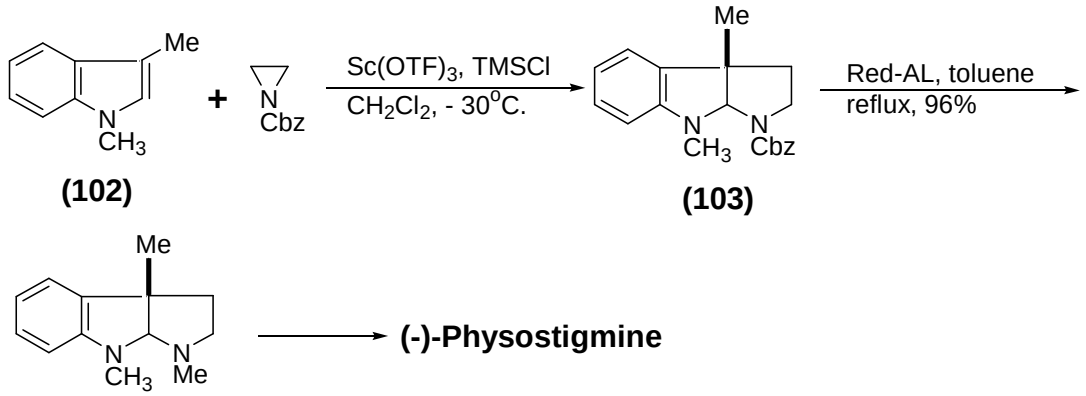
The same strategy was used to synthesis the optically active esermethole from tryptophane derivatives. Hence 5-methoxy-*N*-methoxycarbonyl-L-tryptophane methyl ester (95) was treated with Corey-Kim reagent in the presence of *i*-Pr_2NEt to give the pyrroloindole (96) and (97) as diastereo-isomers (1:1), which were readily separated by silica gel. Reductive methylation and desulfurization of (96) and (97) converted them to (98) and (100). Upon reduction the chiral compounds (99) and (101), were afforded and then converted to (-) and (+)-esermethole respectively. [24]



(95) **(96)** **(97)** **(96)** **(98)** **(99)**

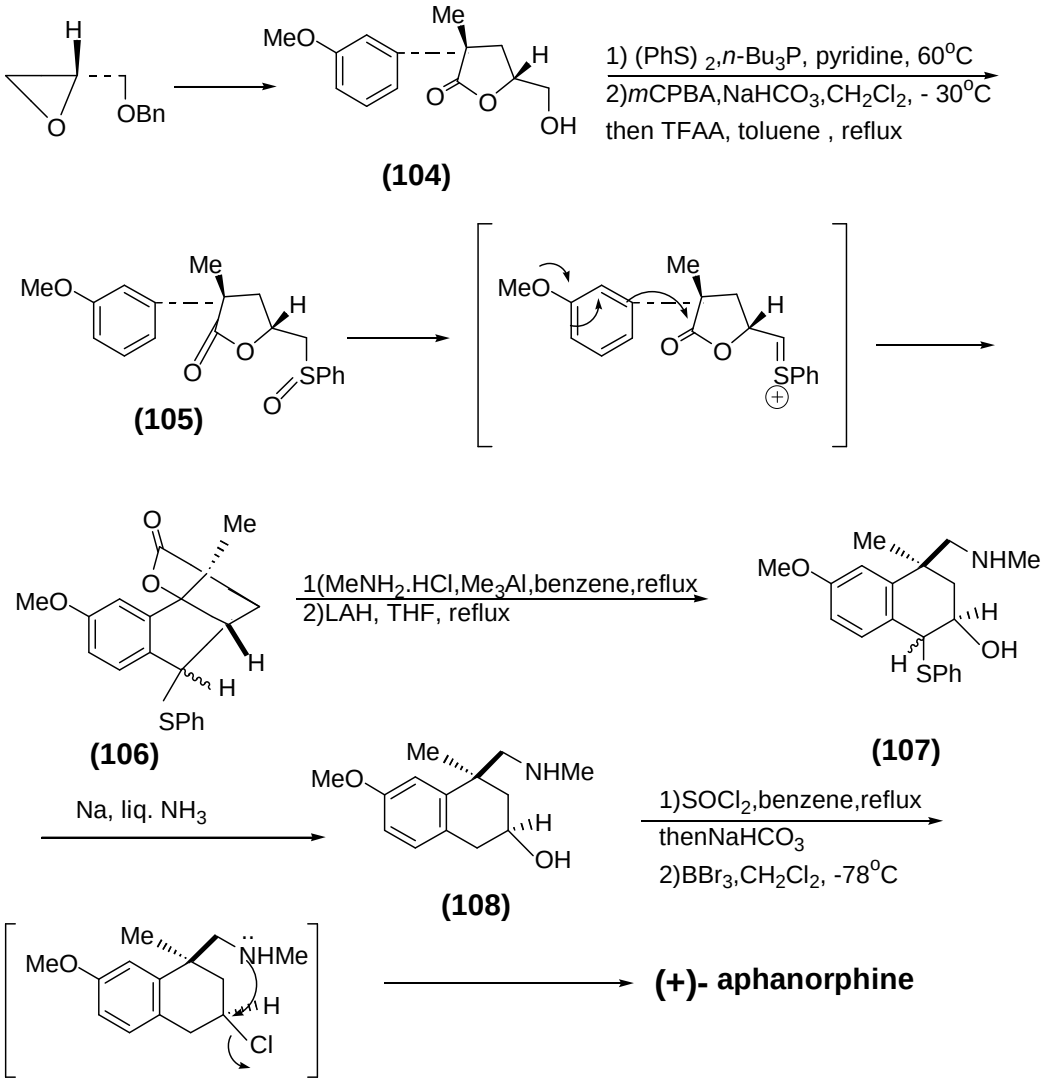


Nakagawa [54] reported a concise synthesis of physostigmine through alkylative cyclization of 1,3-dimethylindole (102) with (z)-aziridine catalyzed by SC (OTf) $_3$ and TMSCl in dichloromethane as key step to give (103) in 90% yield, which can readily be converted to physostigmine. [35] The optimum condition for this reaction was achieved by use of (2 equ.) of Sc $(OTf)_3$ and (1 equ.) of TMSCl.



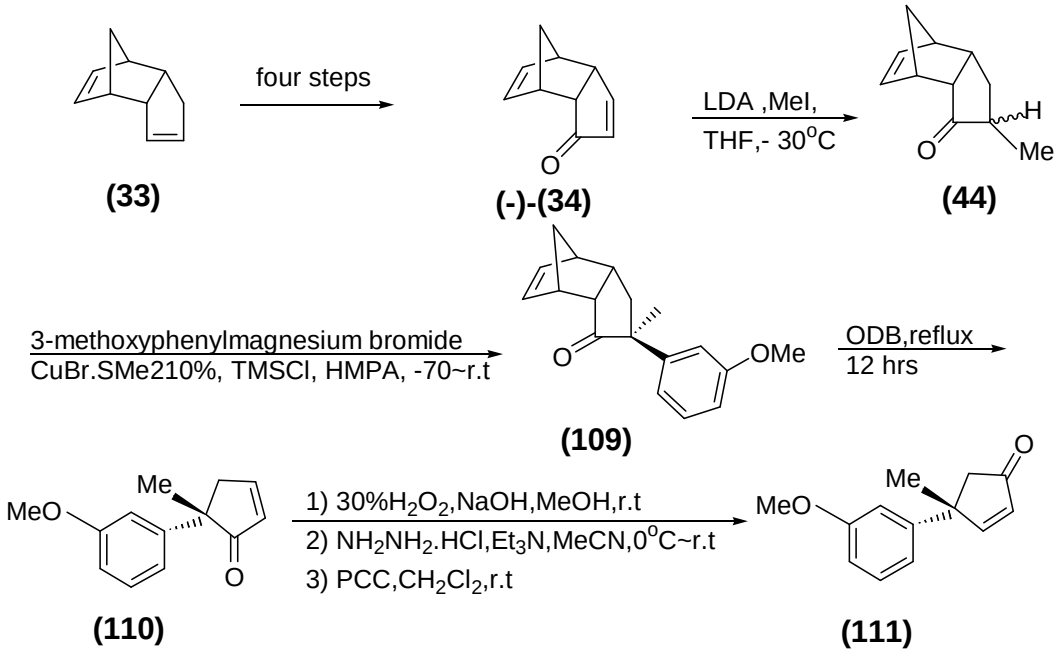
1.2. Synthesis of (-)-Aphanorphine.

In 1989, Takano and co-workers [55] synthesized aphanorphine in antipodal form starting from (*R*)- O-benzylglycidole, which was converted to the γ-lactone (**104**) [24]. Treatment of (**104**) with biphenyl disulfide and tri-*n*-butylphosphine afforded the sulfide (**105**), which on oxidation with *m*-chloroperbenzoic acid and treatment with trifluoroacetic anhydride (TFAA) in refluxing toluene furnished the tricyclic lactone (**106**) as mixture of epimers (3:1) in 88% yield. The lactone (**106**) was treated with a complex generated from methylamine hydrochloride and trimethylaluminium in benzene [56] and then reduced by LAH to give the secondary amine (**107**) as two epimers. Treatment of (107) with sodium in liquid ammonia afforded single aminoalcohol (**108**) which was cyclized by treatment with thionyl chloride in benzene followed by treatment with boron tribromide to afford (+)-aphanorphine.

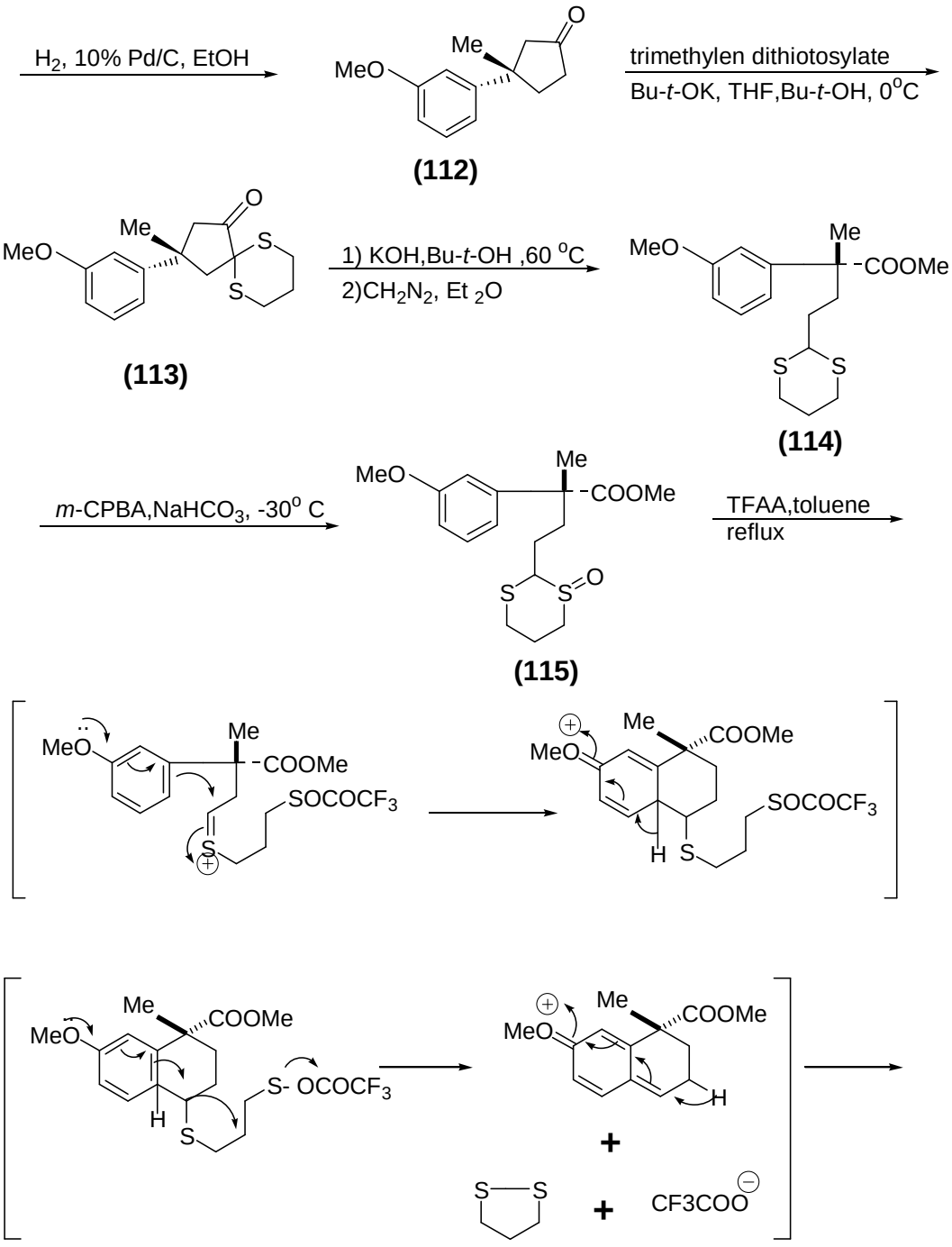


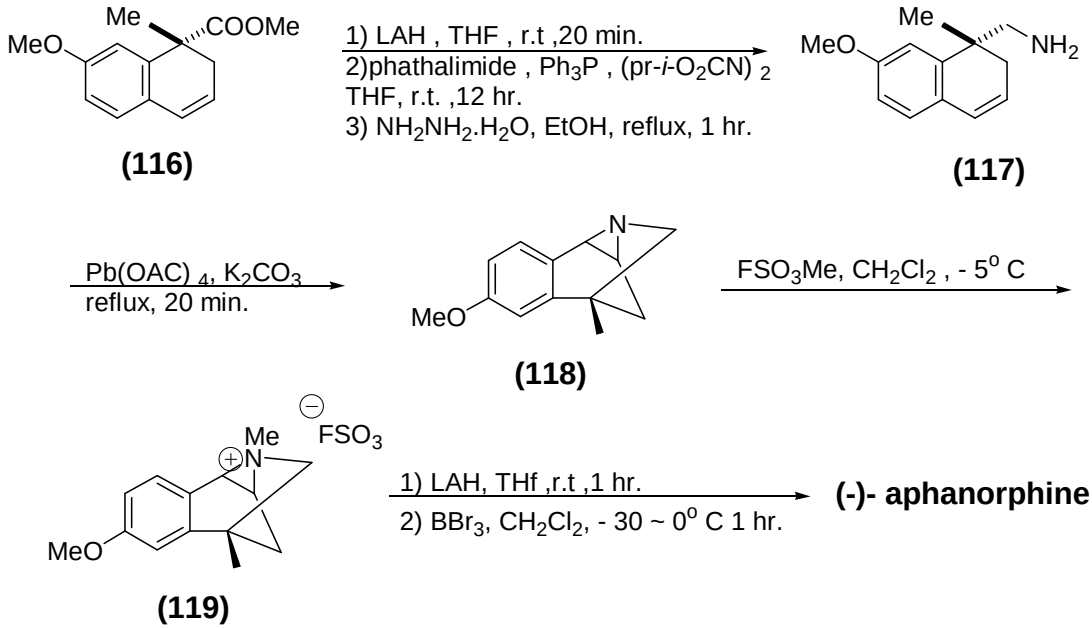
In another work, [29] the (-)-aphanorphine was synthesized starting from a known optically active dienone [31,57] (34). Thus treatment of (+)-enone (44) with 3-methoxyphenylmagnesium bromide in the presence of cupper (I) bromide and trimethylsilyl chloride gave a single 1,4- adduct (**109**), which on thermolysis in *O*-dichlorobenzene afforded the enone **(110)** by *retro*-Diels-Alder reaction followed by isomerization of **(110)** via whartorn [58] reaction yielded (111). The later underwent hydrogenation to give the ketone **(112)** that was transformed into the α-diketone monothioketal (**113**) in 53% yield by treatment with methylene dithiotosylate and potassium-*t*-butoxide. Treatment of compound (**113**) with potassium hydroxide in hot *t*-BuOH afforded the acid whose ester (**114**) was converted to mono-sulphoxide (**115**) as a mixture of diastereoisomers when reacted with *m*-chloroperbenzoic acid. The latter compound underwent facile cyclization to furnish the dihydronaphthalene derivative (**116**) in 55% yield as single regioisomer upon brief treatment with triflouroacetic anhydride in refluxing toluene. The ester (**116**) was reduced and allowed to undergo Mitsunbu [25] reaction to give the primary amine (**117**).

The amine (**117**) underwent Nagata [59] reaction to the aziridine (**118**) as unstable oil, that was immediately exposed to methylflourosulphonate to afford the ammonium salt (**119**). Treatment of the later with LAH followed by boron tribromide afforded (-) aphanorphine.

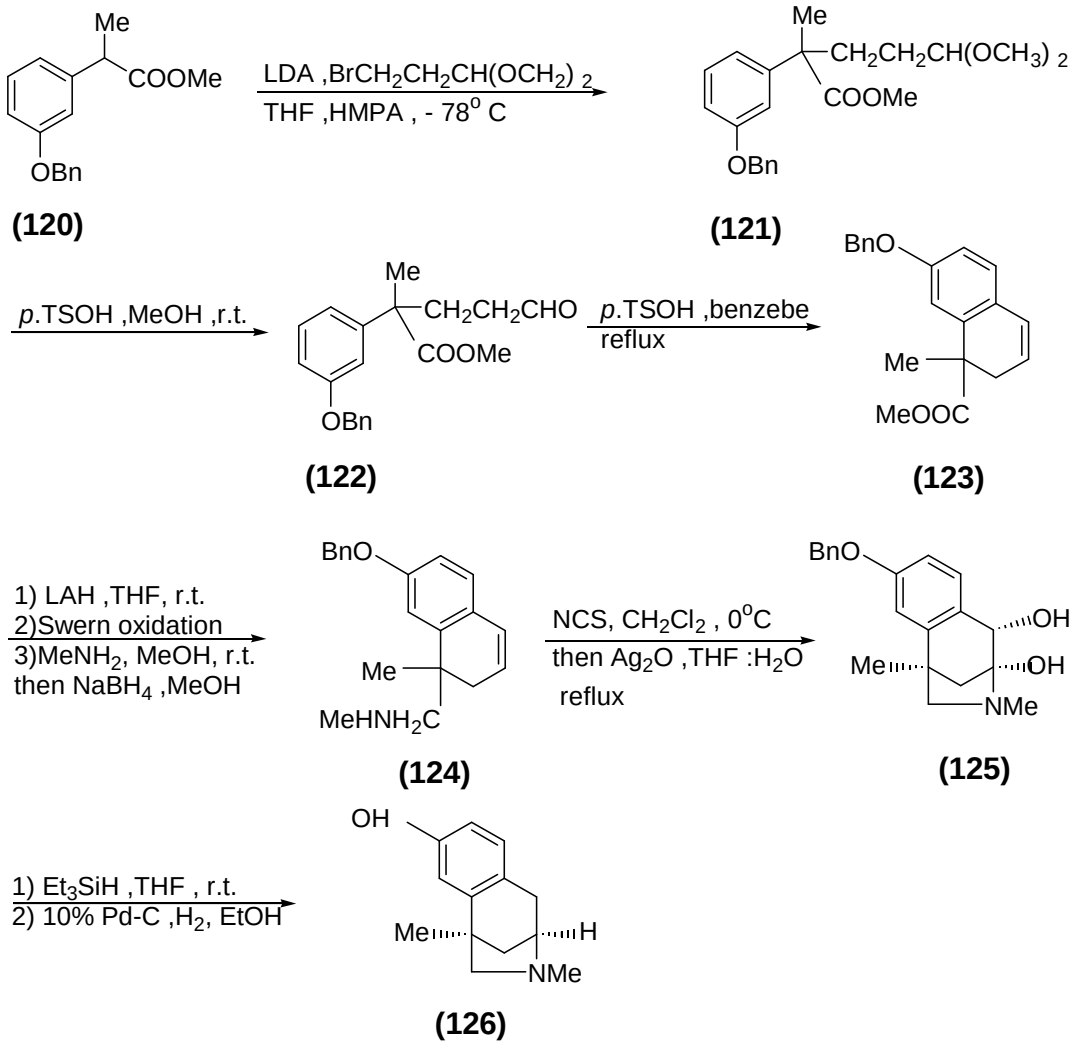


(33) **(-)-(34)** **(44)** **(109)** **(110)** **(111)**


H2, 10% Pd/C, EtOH
MeO
Me
O
trimethylen dithiotosylate
Bu-t-OK, THF,Bu-t-OH, 0°C
(112)
MeO
Me
O
S
S
(113)
1) KOH,Bu-t-OH ,60 °C
2)CH2N2, Et 2O
MeO
Me
COOMe
S
S
(114)
m-CPBA,NaHCO3, -30° C
MeO
Me
COOMe
S
S
O
(115)
TFAA,toluene
reflux
MeO
Me
COOMe
SOCOCF3
S
H
S
SOCOCF3
MeO
Me
COOMe
S- OCOCF3
H
S
MeO
Me
COOMe
H
+
S
S
+
CF3COO



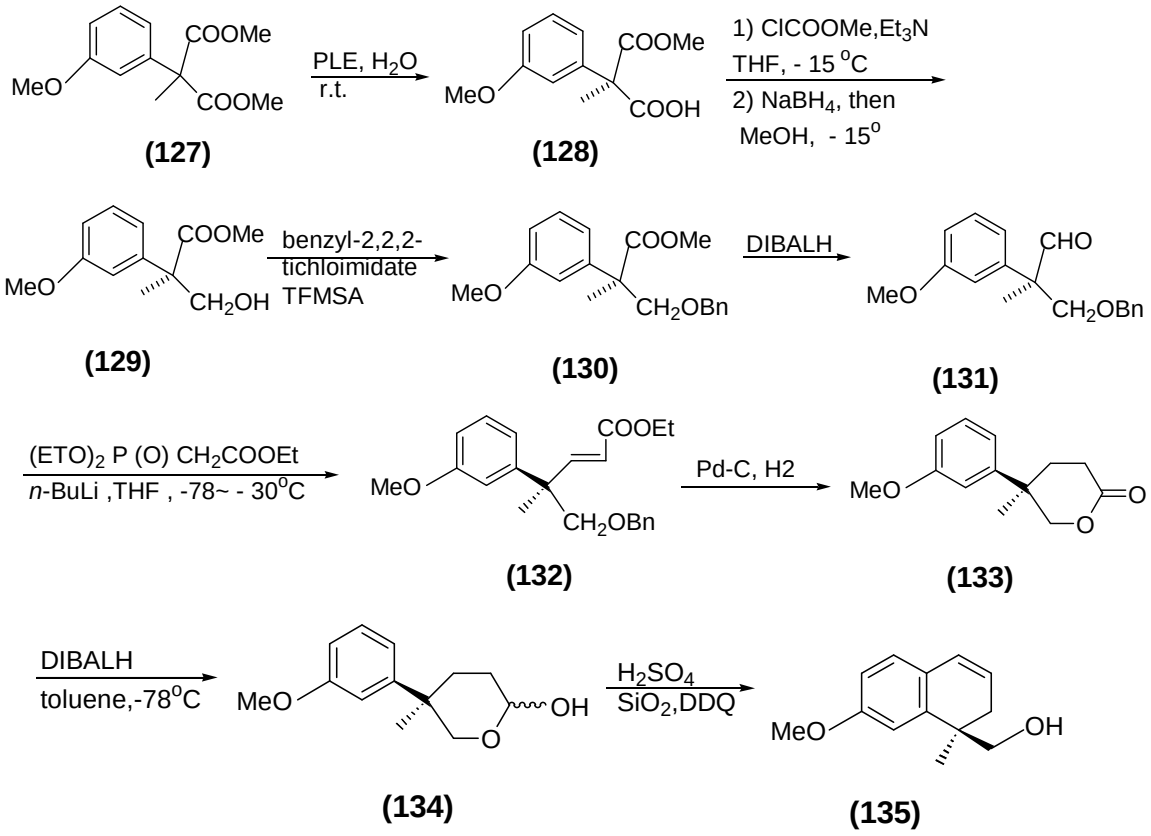
In 1992, Honda and co-workers [9] synthesized the racemic aphanorphine via the ester (**120**) that was treated with 2-(2-bromoethyl)-1,3-dioxolane and LDA in THF, HMPA to afford dioxolane (**121**) in 92% yield. Exposure of compound (**121**) to *p*-toluensulfonic acid in methanol gave the aldehyde (**122**), which underwent dehydration reaction on treatment with a catalytic amount of *p*-TsOH to give the ester (**123**). Reduction of (123) with LAH followed by Swern oxidation [27] and condensation with methylamine in methanol followed by reduction with sodium borohydride afforded the amine (124). Reaction of the amine (**124**) with *N*-chlorosuccinimide in dichloromethane followed by refluxing the resulting *N*-chloro compound with silver oxide in aqueous THF provided the target compound (**125**) in 83% yield as single isomer. The latter compound underwent reduction with triethylsilane in trifluoroacetic acid followed by debenzylation of benzylaphanorphine over 10% palladium carbon under hydrogen atmosphere to give aphanorphine in quantitative yield.



(120) **(121)** **(122)** **(123)** **(124)** **(125)** **(126)**

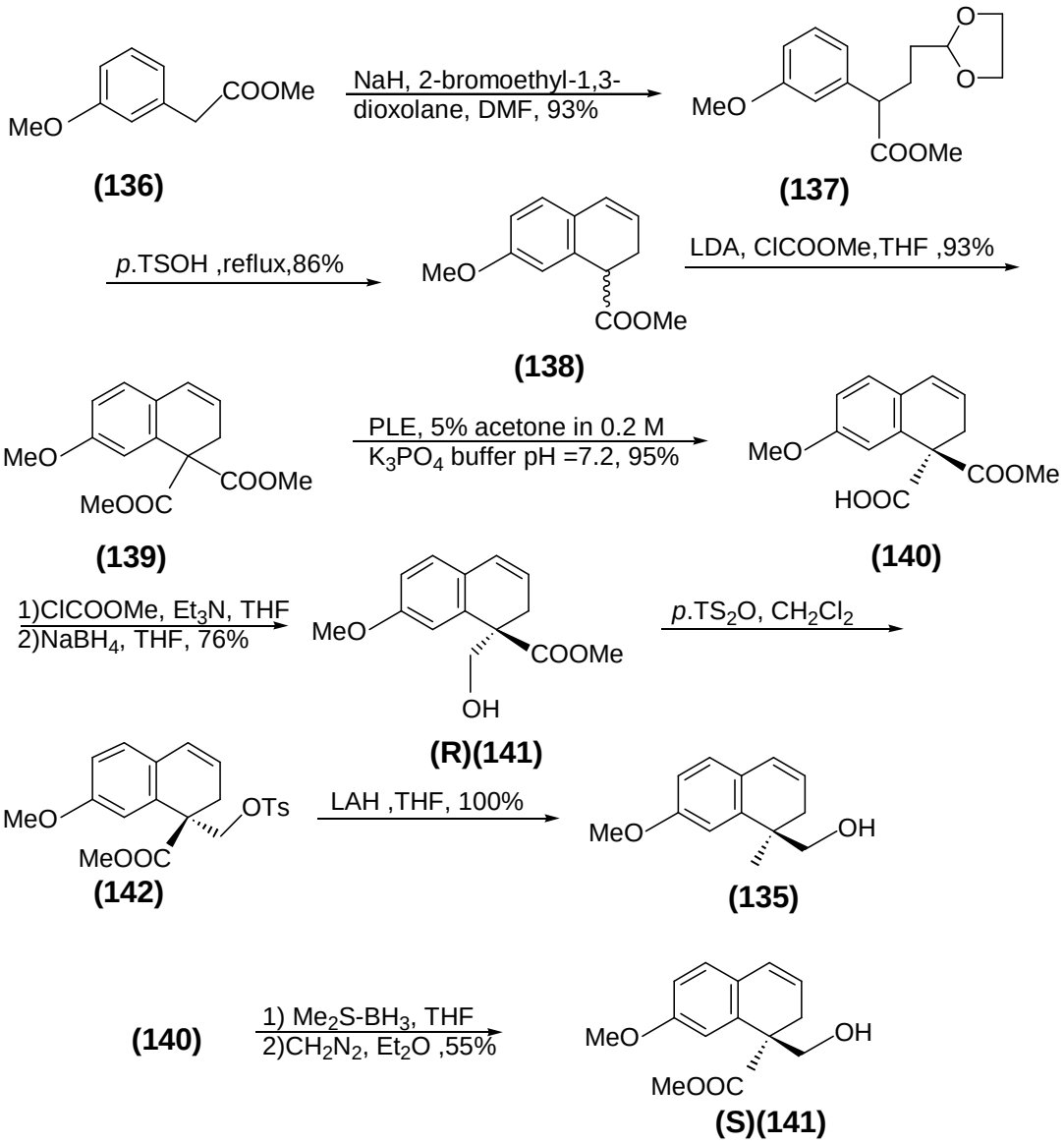
In 1995, Fadel and co-workers [60] synthesized (+)-enantiomerically pure dihydronaphthalen **(135)** as precursor of (-)- aphanorphine.Thus the prochiral dimethylmalonate (**127**) underwent enantioselective enzymatic hydrolysis by pig liver esterase (PLE) to provide the acid ester (R) (+) (**128**). Reaction of the latter compound with chloroformate in the presence of triethylamine gave mixed anhydride, which upon reduction with sodium borohydride gave the β-hydroxy ester (*R*) (+) (**129**) in 84%. The hydroxy ester **(129)** was found to be the key intermediate for the preparation of dihydronaphthalene (**135**). Application of Witting-Horner reaction on compound (**131**) afforded pure trans (+) (**132**) which on hydrogenolysis in the presence of 20% Pd $(OH)_2$-C and acidic cyclization furnished the expected lactone (**133**) in 85% yield. Reduction of the lactone with DIBALH in toluene at –78 °C led to diastereo-isomeric mixture of the lactol

(**134**). Treatment of lactol with catalytic amount of sulfuric acid and dichlorocyanobenzoquinone on silica gel furnished (**135**) in 85% yield.



In addition, Honda and co-workers [61] reported the synthesis of dihydronaphthalene **(135)** as key intermediate for (-)- aphanorphine synthesis. The methyl ester (**136**) was prepared from commercial 3-methoxy-phenylacetic acid. The ester **(136)** was treated with NaH and 2-(2-bromoeth-yl)-1,3-dioxolane to give the dioxolane (**137**), which was refluxed with catalytic amount of *p*-tolunsulfonic acid to give the dihydronaphthyl ester (**138**). The ester (**138**) was converted to (**139**) which on enzymatic hydrolysis by pig liver esterase (PLE) in 5% acetone and phosphate buffer gave (*R*) acid-ester (**140**). Treatment of **(140)** with methyl chloroformate and triethylamine followed by reduction with $NaBH_4$ afforded the alcohol ester (R)-**(141)** that was converted to tosylate (142). Reduction of the latter tosylate with LAH yielded the alcohol (135).

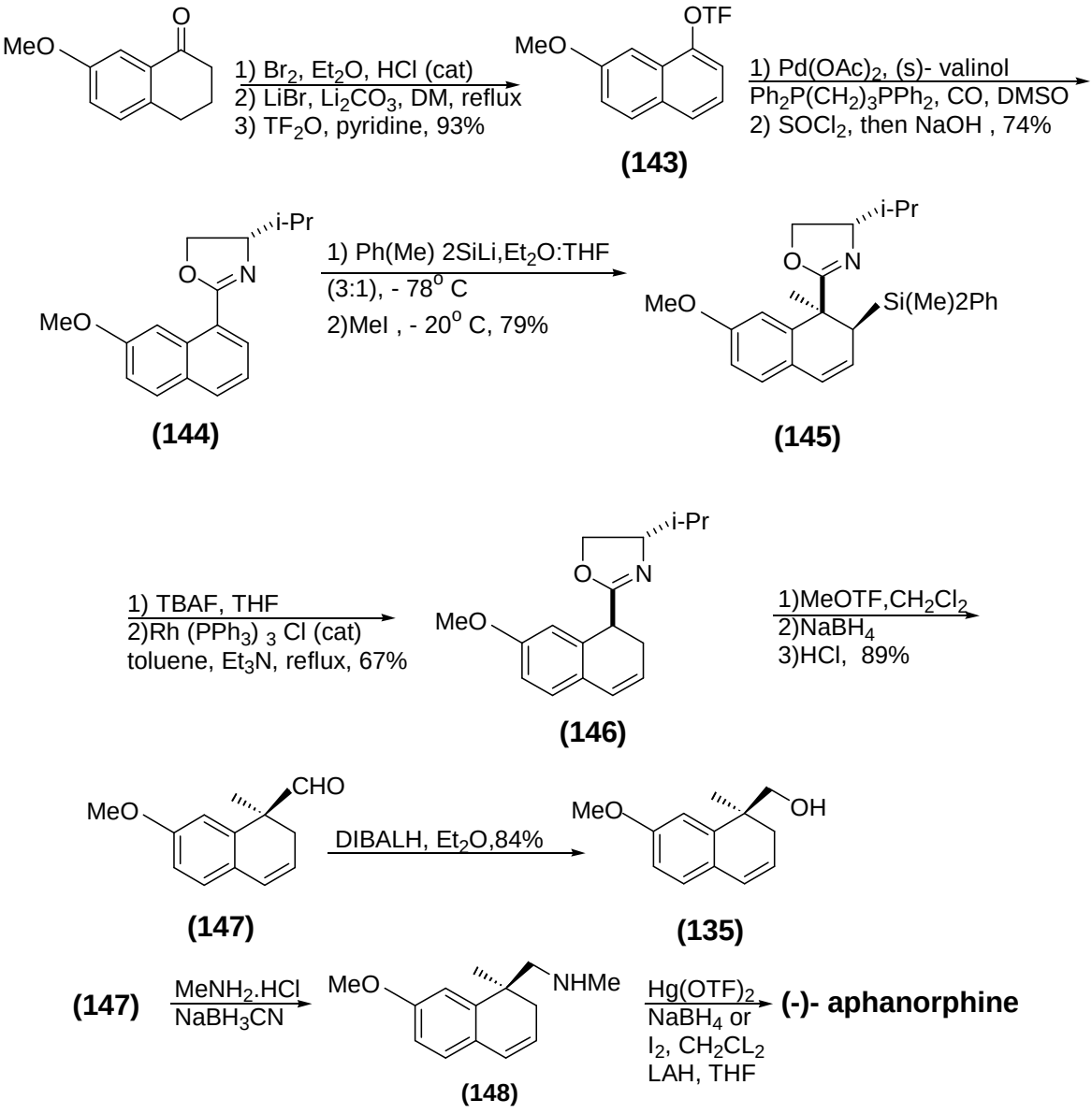
Furthermore, the (s)-enantiomer was prepared via boran-methylsulfide complex (Me_2S-BH_3) reduction and diazomethan esterification of the acid ester (S)-(140) to afford the alcohol (S)-(141).



In 1995, Meyers and co-workers [62] synthesized (-)-aphanorphine starting from the commercially available 7-methoxy-1-tetralone via bromination and dehydrobromination followed by protection of the formed alcohol to give the triflate (**143**). Treatment of DMSO solution of triflate (**143**) with carbon monoxide and valinol in the presence of palladium catalyst [generated from palladium (II) acetate and 1,3-bis- (diphenylphosphino) propane] followed by reaction with thionyl chloride and basic work-up afforded the naphthyloxazoline **(144)** in 63% overall yield. Application of asymmetric tandem addition reaction of lithiodimethylphenyl silane with **(144)** followed by electrophilic quench with iodomethane afforded sillyl derivative (**145**) which underwent protodesilation with tetrabutylammonium fluoride to give

a mixture of Δ^2& Δ^3 isomers of (**146**). The mixture was isomerized to Δ^3 isomer using Wilkinson's catalyst (Rh $(PPH_3)_3Cl$) in refluxing toluene.

Hydrolysis of oxazoline (**146**) gave the unsaturated aldehyde **(147)** [63] that was reduced to the alcohol (**135**) as key intermediate of (-)-aphanorphine. In addition the aldehyde (**147**) could also undergoes reductive amination to afford aminotetraline (**148**). Iodine induced activation of the double bond followed by selective removal of iodine [64,65] or aminmercuration with Hg $(TFA)_2$ and subsequent reduction with sodium borohydride followed by treatment with boron tribromide are two alternative routes to (-)-aphanorphine synthesis.



In 1996, Node and co-workers [66] utilized asymmetric nitroolefination reaction of α-methyl-δ-valerolactone to synthesize the alcohol **(149)** which is a precursor of (-)-aphanorphine. Thus nitroolefin lactone **(65)** [38,39] was subjected to Diels-Alder reaction with Danishfesky's diene to give the adduct (**67**) which on aromatization reaction in the presence of a catalytic amount of *p*-toluensulfonic acid gave the alcohol (**149**). The latter compound was oxidized to the corresponding aldehyde (**150**)[27] and subjected to intermolecular Friedel-Crafts cyclization using boron trifluoride etherate as a Lewis acid to give the ester (**116**) as intermediate for (-)-aphanorphine synthesis.

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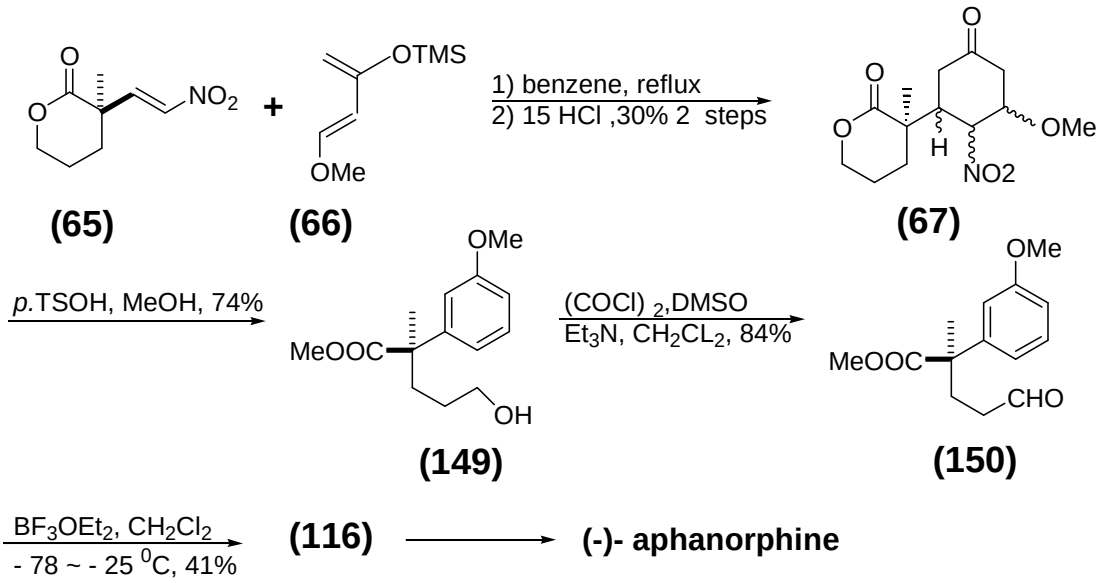
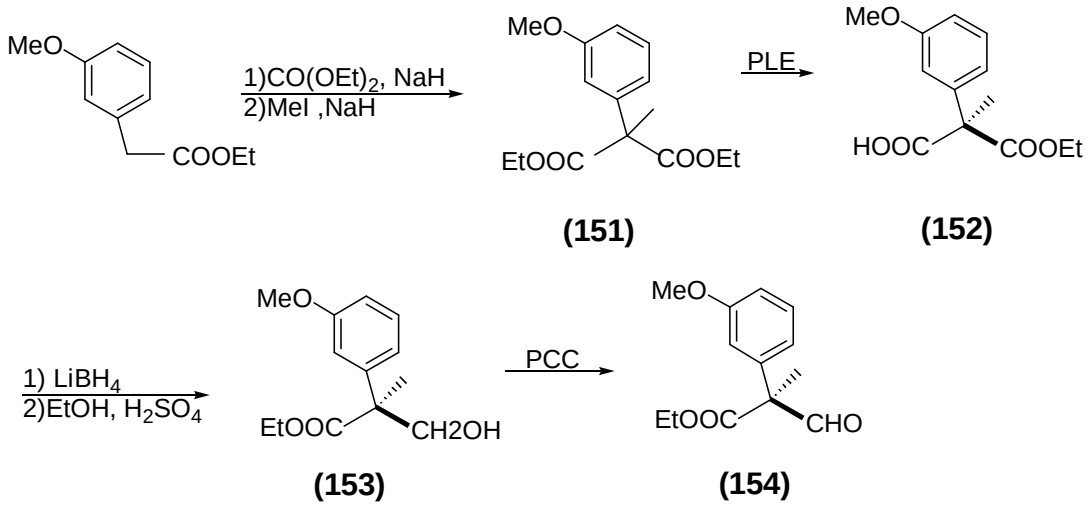
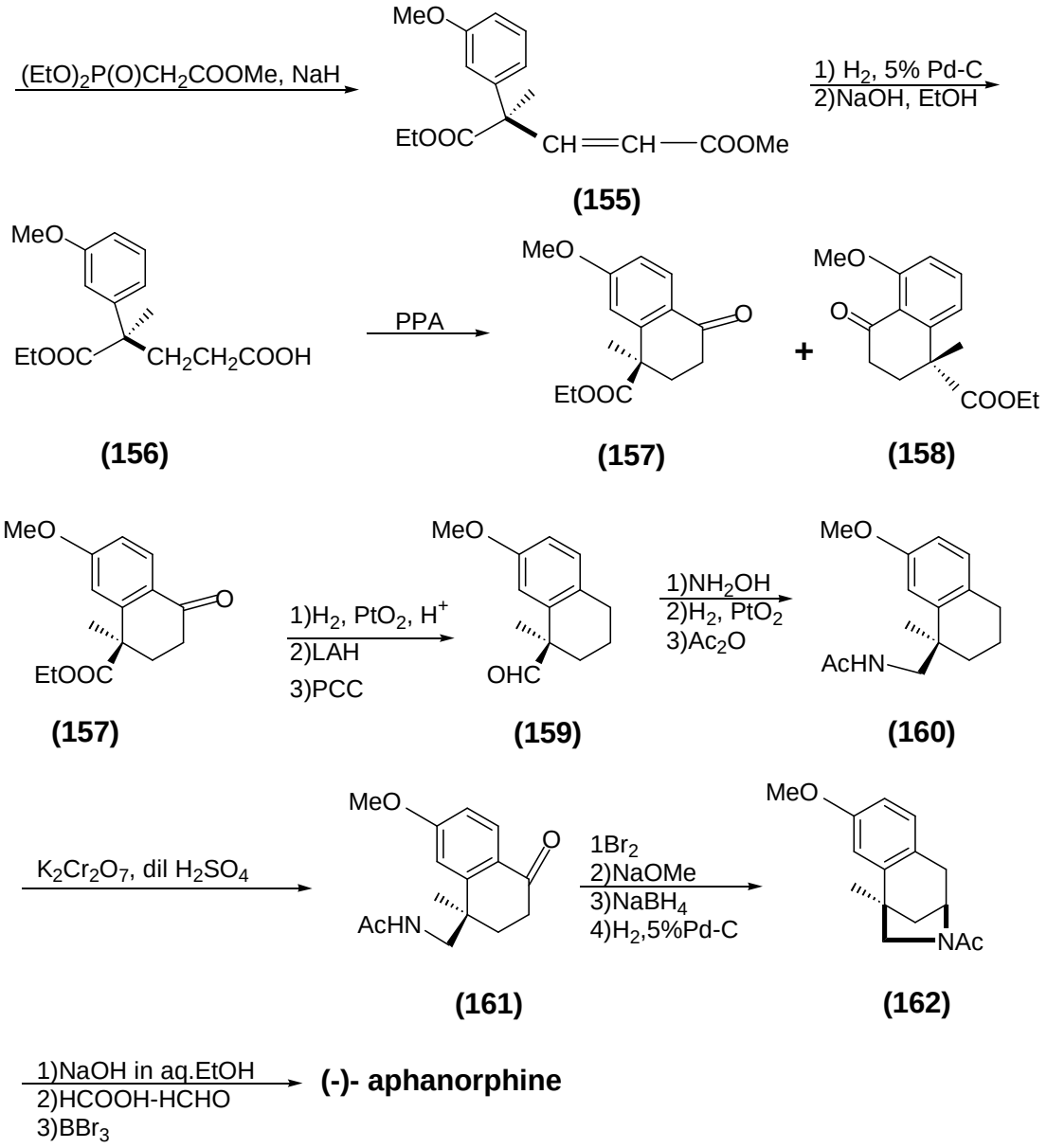


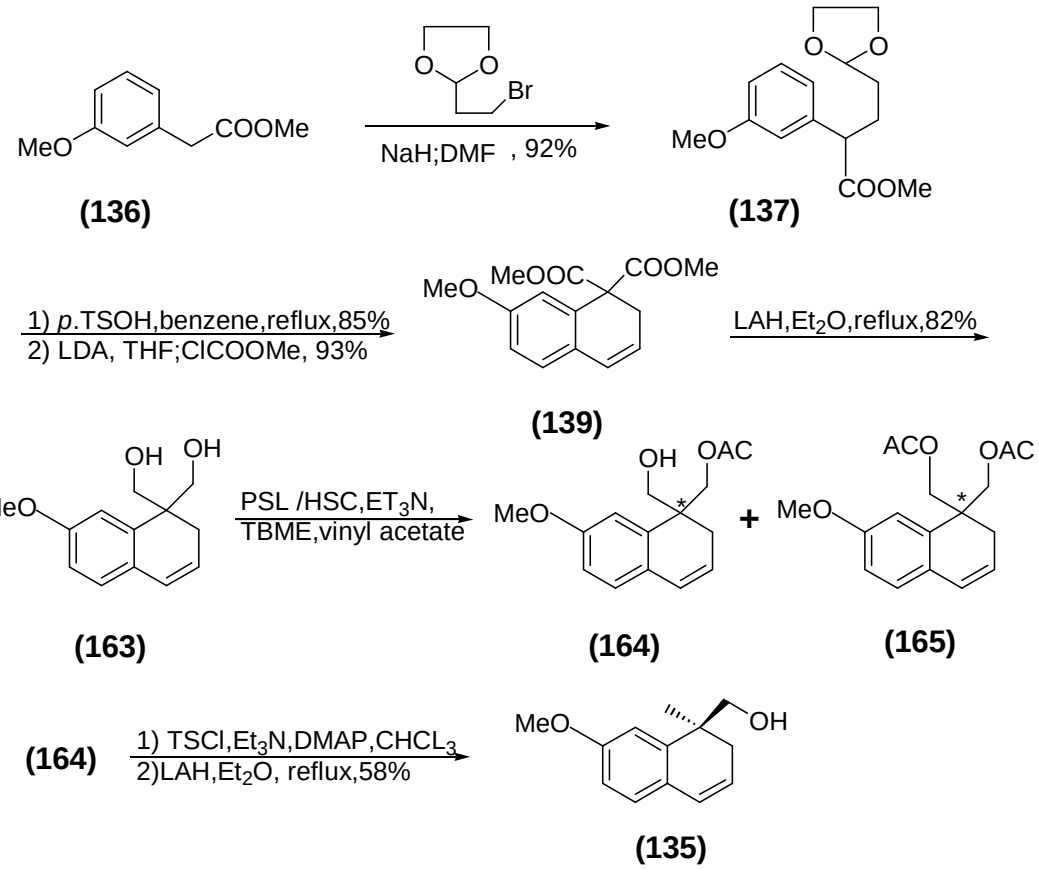
1996, Shiotani and co-workers [67] synthesized (-)-aphanorphine starting with ethyl *m*-methoxyphenylacetate which underwent ethoxycarbonylation via treatment with diethylcarbonate, sodium hydride and subsequent methylation with iodomethane and sodium hydride to afford the malonate ester **(151)**. The diester (**151**) was hydrolyzed with PLE in phosphate buffer solution to give the chiral monoester (**152**) which on reduction with LAH in THF and subsequent esterification afforded the hydroxymethyl carboxylic acid ester (**153**). The later was converted to the aldehyde (**154**) through oxidation with pyridinium chlorochromate (PPC). Application of Witting-Horner reaction on **(154)** using methyl diethylphosphate afforded α,β -unsaturated ester (**155**), which on hydrogenation over 5% palladium-carbon and subsequent alkaline hydrolysis of the methoxycarbonyl group at room temperature produced the monoester (**156**). Cyclization of **(156)** with polyphosphoric acid (PPA) afforded a mixture of 7-methoxytetralone (**157**) and 5-methoxy isomer **(158)** (4:1) which were easily separated by column chromatography. Compound (**157**) underwent hydrogenation over platinum oxide containing small amount of hydrochloric acid followed by reduction with LAH and then oxidation with PCC to give the aldehyde (**159**). Oxidation of (159) followed by catalytic reduction and acetylation afforded the acetamide (160) that was oxidized with $K_2Cr_2O_7$ to give the tetralone (161). The latter tetralone was brominated, treated with sodium methoxide and then reduced with sodium borohydride followed by catalytic hydrogenation to produced the tricyclic (162). The (-)-aphanprphine was obtained from (162) via hydrolysis, N-methylation and treatment with boron tribromide.



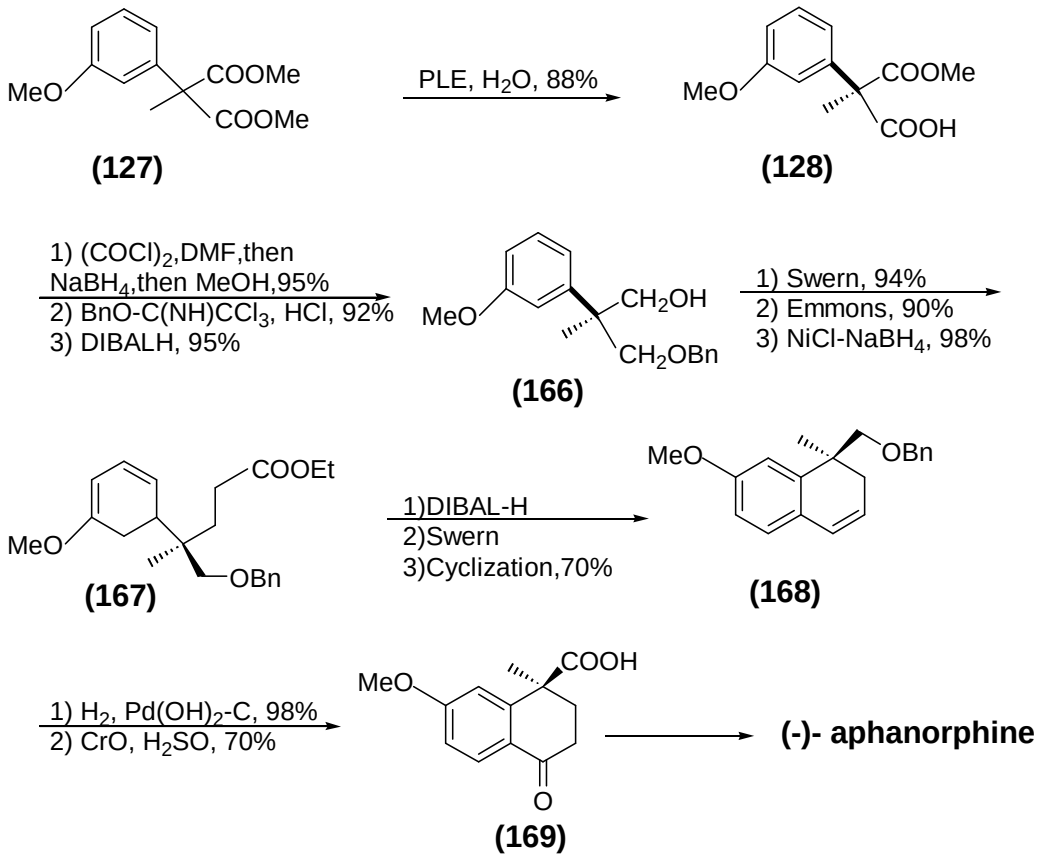


In 1997, Fadel and Arzel [68] synthesize (-)-aphanorphine via treatment of sodium enolate of ester (136) in DMF with 2-(2-bromoethyl)-1,3-dioxolane followed by cyclization and alkylation to afford the methyl diester (**139**) which was reduced with LAH in hot ether to give the prochiral diol (**163**).
The prochiral diol (**163**) was converted to monoester (**164**) and diester (**165**) by transesterificatin by lipase (PSL /HSC) from *Pseudomonas cepacia* immobilized on Hyflo supper cell in the presence of triethylamine and vinylacetate in *t*-butylmethyl ether (TBME). The monoester (-) (**164**) was

converted to alcohol (**135**) through tosylation followed by reduction with LAH. The alcohol (135) could be converted to (-)- aphanorphine [29]



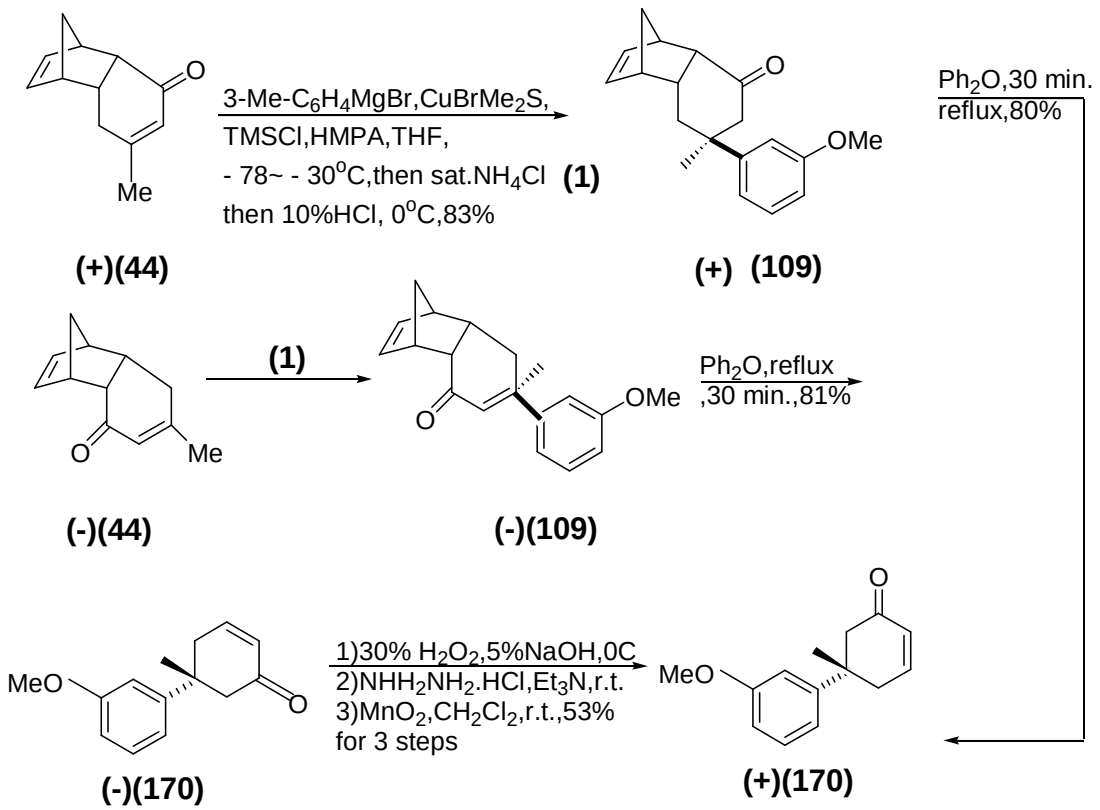
It is reported that enantioselective enzymatic hydrolysis of prochiral malonate (**127**) using PLE afforded the monoester (*R*) (**128**) [69] which was subjected to reduction, protection and further reduction to afford the alcohol (**166**). The protected alcohol (**166**) was subjected to Swern's oxidation and subsequent Emmon's reaction under Masamune's [70] condition [$(EtO)_2$ P (O) CH_2COOEt, DBU, LiCl] followed by reduction without affecting the ester group by the use of nickel bromide [71] generated *in-situ* ($NaBH_4NiCl.6H_2O$) to afford the ester (*R*) (+) (**167**). Reduction of the latter compound with DIBALH then Swern's oxidation followed by one-pot acidic Friedel-Crafts cyclization and dehydration furnished dihydronaphthalene (**168**).
Hydrogenolysis of the dihydronaphthalene (**168**) followed by oxidation produced the ketoacid (**169**), which was transformed to (-)-aphanorphine [55].



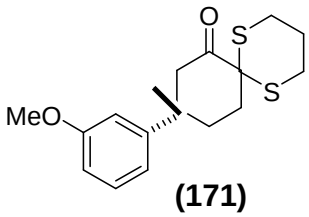
In 1998, Ogasawara and co-workers [72] synthesized (-)-aphanorphine employing an enantioconvergent tactic that allowed enantioconvergent transformation of both enantiomers of starting material into a single chiral target molecule. Hence the **[(+)-(44)]** and **[(-)-(44)]** enones were treated respectively with 3-methoxyphenyl magnesium bromide in the presence of chlorotrimethylsilane and a catalytic amount of copper (I) bromide-dimethylsulfide complex in THF containing hexamethylphosphoric triamide (HMPA) to yield the corresponding enantiomeric ketones (**109**) that underwent *retro* Diels-Alder reaction to afford (+) and (-)- 5,5-disubstituted cyclohexanones (**170**).

So as to make the synthesis enantioconvergent chirality, inversion of (-)-enone **(170)** was carried out by employing Wharton's [58,73] rearrangement. Thus (-) (**170**) was first treated with alkaline hydrogen peroxide then treated with hydrazine hydrate hydrochloride in the presence of triethylamine under sonication followed by oxidation with manganese (IV) dioxide in dichloromethane to afford the single enone (+)-(**170**). Compound [(+)-(**170**)] was transformed into thioketal (**171**) by sequential catalytic

hydrogenation and α-thioketalization. Alkaline cleavage of compound (**171**) followed by esterification gave the dithian (**172**), which was converted to methylacetal (**173**) via reaction with bis- (trifluoroacetoxy) iodobenzene in methanol. The latter compound **(173)** underwent intramolecular cyclization to afford dihydronaphtalene (**116**). The ester (**116**) was converted into carbamate [74] (**173**). After saponification of the carbamate (**173**), the resulting primary amine was exposed to lead tetraacetate in benzene in the presence of potassium carbonate to yield the unstable aziridine (**118**), which was immediately treated with methyl trifluoromethansulfonate in dichloro-methane to give the ammoniumtriflate (**174**). Further treatment of (174) with LAH in THF it gave (-)- aphanorphine methyl ether which was treated with boron tribromide in dichloromethane to afford (-)- aphanorphine.

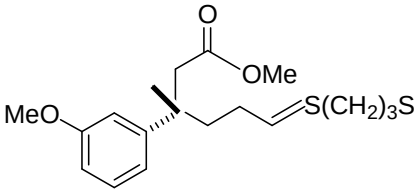


(+)-(170) → 1)H_2,10% Pd-C,MeOH,99%; 2)$CH_2(CH_2STS)_2$,*t*-BuOK, *t*-BuOH:THF (2:7), - 30^{o}C,54%



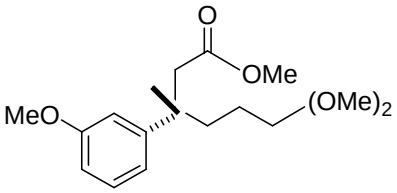
(171)

→ KOH,*t*-BuOH,reflux; then acid work-up, CH_2N_2,CH_2Cl_2,73%



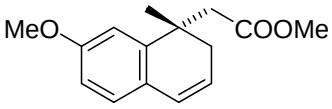
(172)

→ $PhI(OCOCF_3)_2$, MeOH,r.t,89%



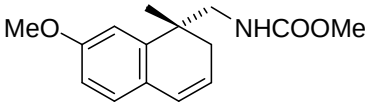
(173)

→ 2N HCl,THF, r.t. 92%



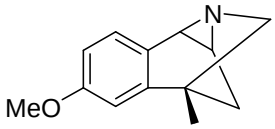
(116)

→ 1)KOH,50% MeOH,reflux; 2) (PhO)2P(O)N3,Et3N,benzene reflux,then MeOH reflux,79%



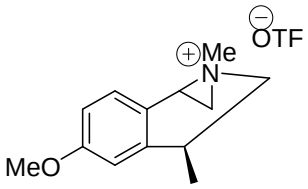
(173)

→ 1) 50% aq.KOH-MeOH(1:1),reflux; 2) $Pb(OAC)_4$,K_2CO_3,benzene,reflux



(118)

→ $MeOTF,CH_2Cl_2$, - 15^{o}C



(174)

→ LAH, THF, - 30 ^{0}C, 47% from 173 **(-)- aphanorphine**

2. Research Objectives.

The high and diverse biological activity of most alkaloids besides their few side effects have oriented the synthetic researchs to develop new procedures for production of such natural products. For instance the African Calabar bean alkaloids, (-)- physovenine and (-)- physostigmine are widely used medicinally as cholinergic and miotics. It is useful in the treatment of glaucoma and myasthenia gravis and as antidote for organophosphate poisoning. Physostigmine can sufficiently improve the memory of the Alzheimer's patients. In addition (-)- aphanorphine alkaloid isolated from fresh water blue -green algae *Aphanizomenon flos-aquae,* possesses narcotic analgesic and anaesthetic activity.

Such alkaloids occur in nature in one enantiomeric form, i.e. (-)-physostigmine, (-)- physovenine and (-)- aphanorphine which are the only forms having biological activity. Thus, the enantiocontrolled synthesis is a critical process in obtaining of the biologically active physostigmine, physovenine and aphanorphine.

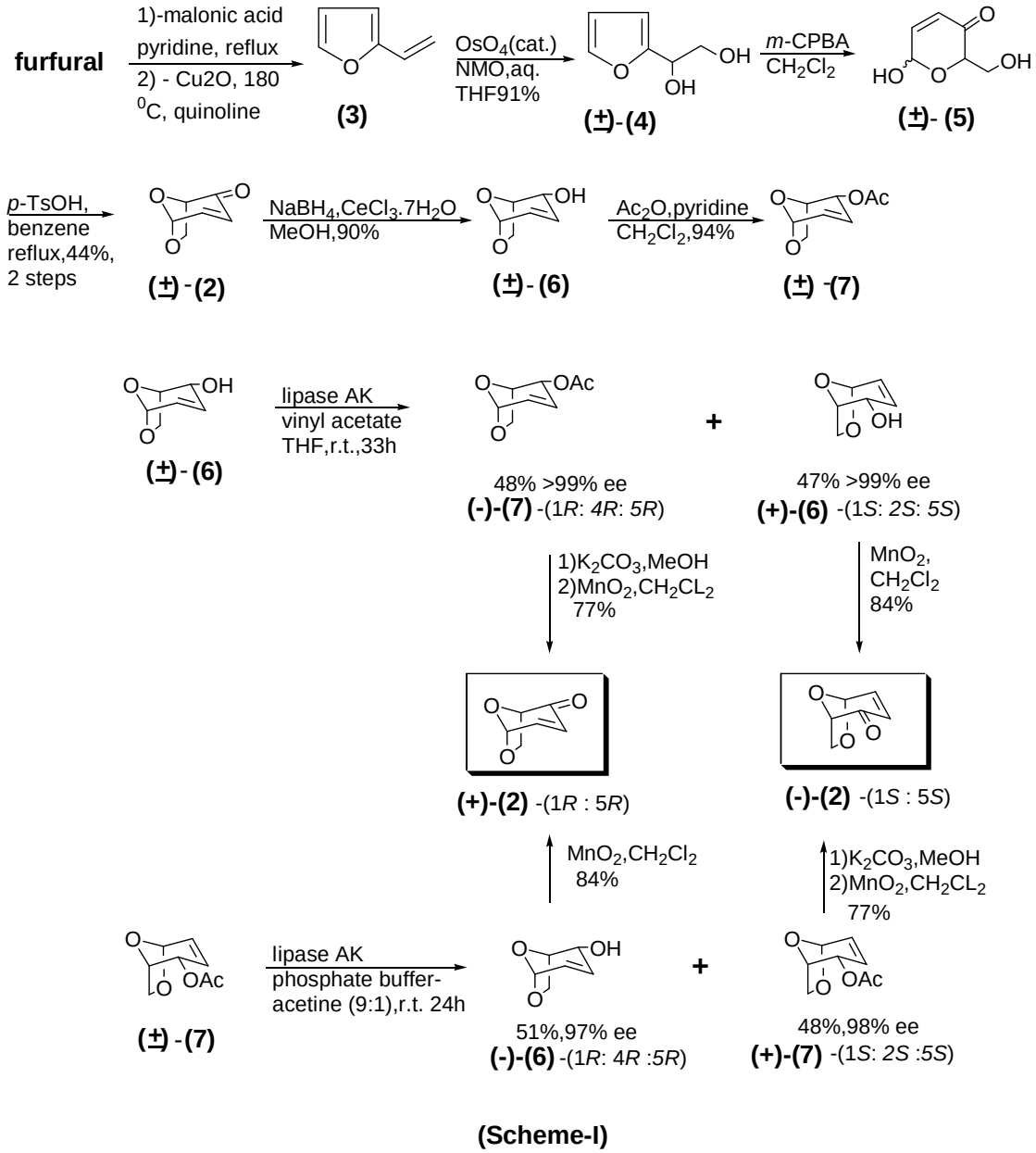
Despite all advances that have been developed to synthesize enantiopure (-)-physovenine, (-)- physostigmine and (-)- aphanorphine as shown in the aforementioned literature survey, a discovery of more enantioselective and enantiocontrolled methods for the total synthesis of such alkaloids is still being need. This in turn necessitates suitably designed chiral building blocks that can be used in such enantiocontrolled synthesis.

In this approach, levoglucosenone [76] seemed to be suitable chiral building block [77,78]. The synthesis of levoglucosenone was reported to be achieved starting from furfural via AD mix reaction [81,82]. During this synthesis, there are two major problems, one of them is the incomplete enantioselectivity in the AD mix reaction and the second is the low efficiency in the conversion of isolevoglucosenone into levoglucosenone [83].

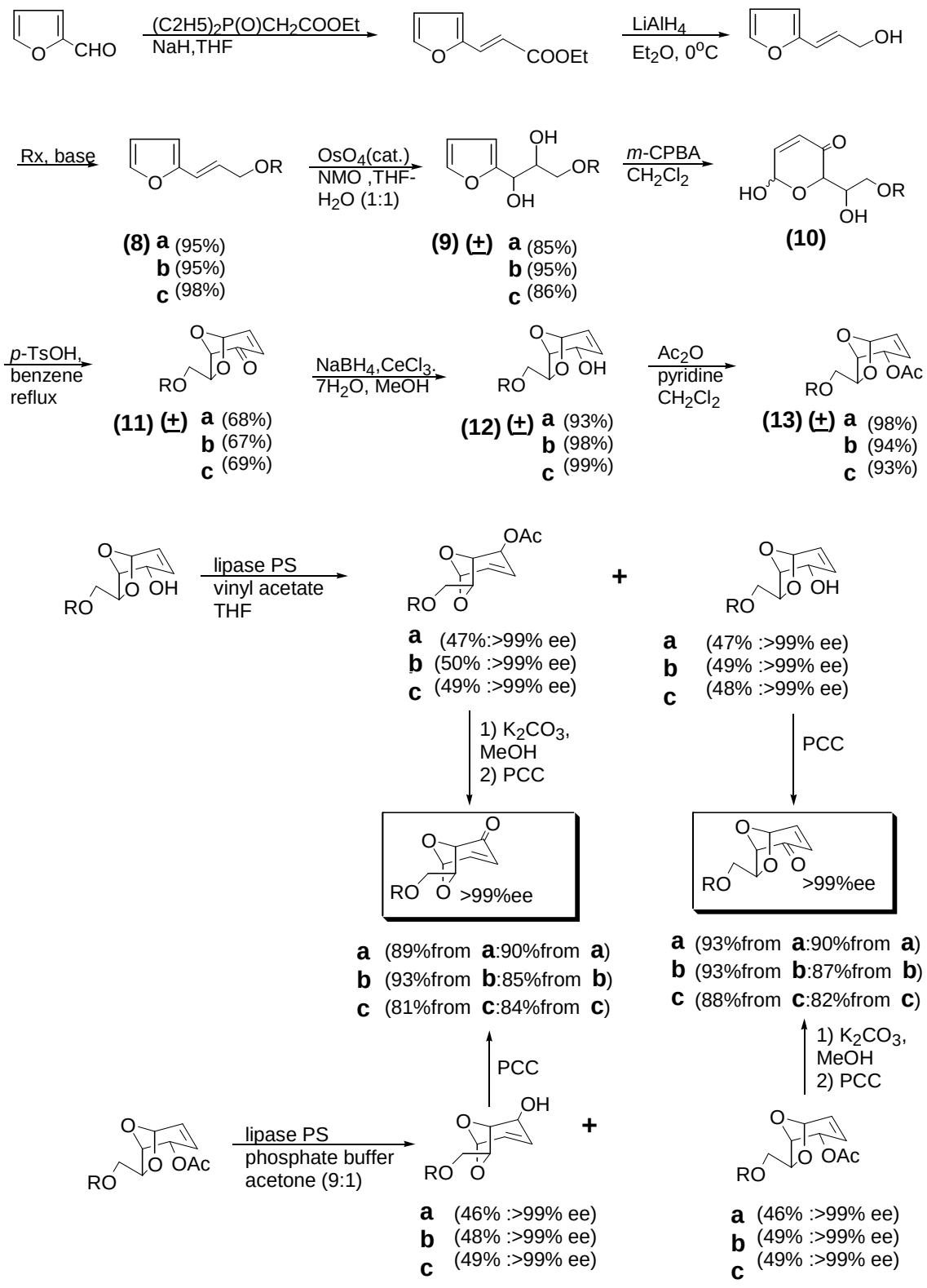
Accordingly, it seemed most interesting to design a new method capable of producing enantiopure isolevoglucosenone in both enantiomeric pure forms via lipase mediated resolution method (Scheme-I).

In addition the dioxabicyclooctane derivative can be used as chiral building block having levoglucosenone chromophore and different protective groups in both enantiomeric pure forms in order to synthesis the desired alkaloids. Such chiral building block can be prepared in large scale via lipase-mediated resolution method, without using expensive AD mix reagent (Scheme-II).

The chiral building block was adapted in the synthesis of the (-)-physovenine (scheme-IV), (-)- physostigmine (scheme-V) and (-)-aphanorphine (scheme-VI and VII).

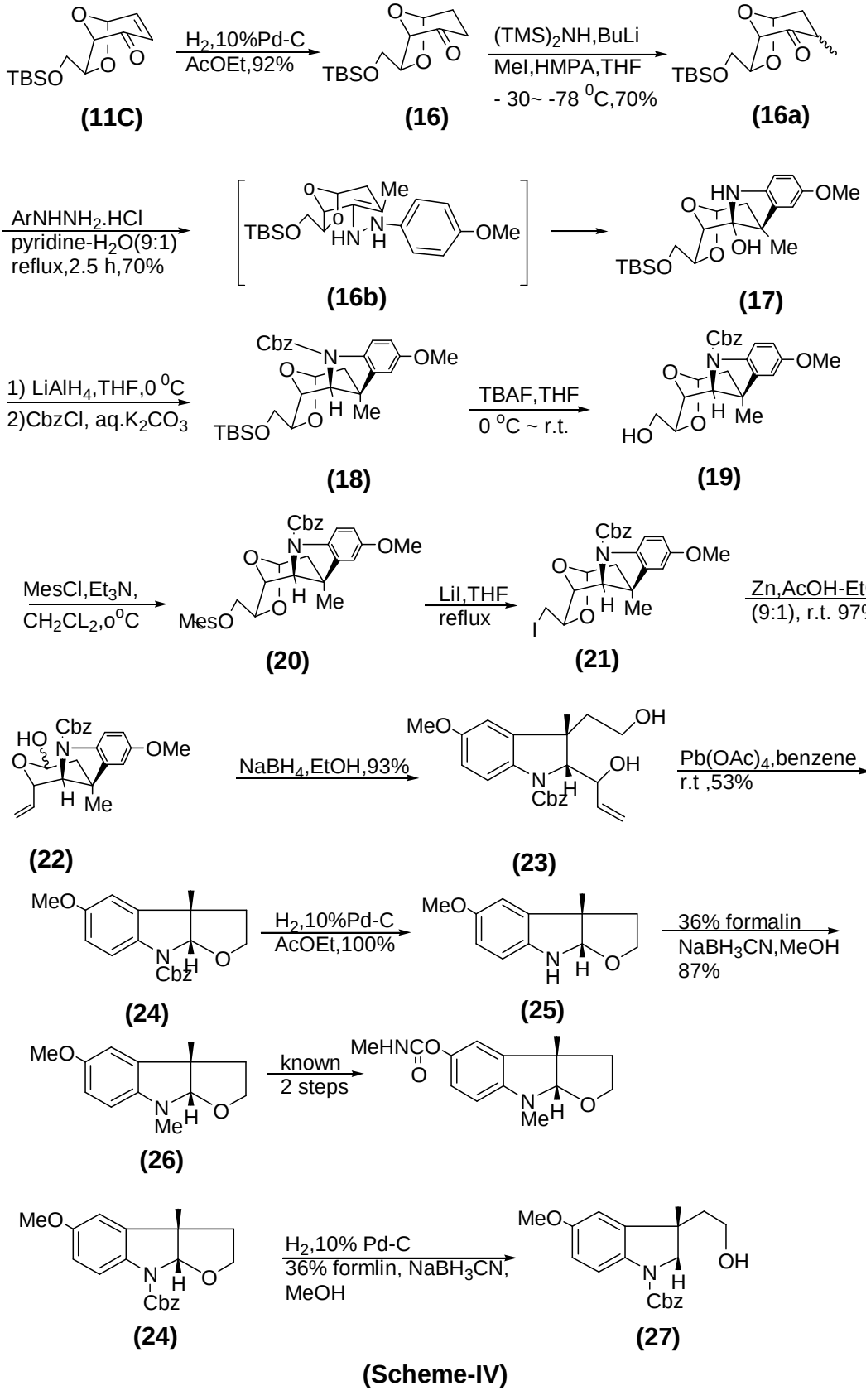


(Scheme-I)

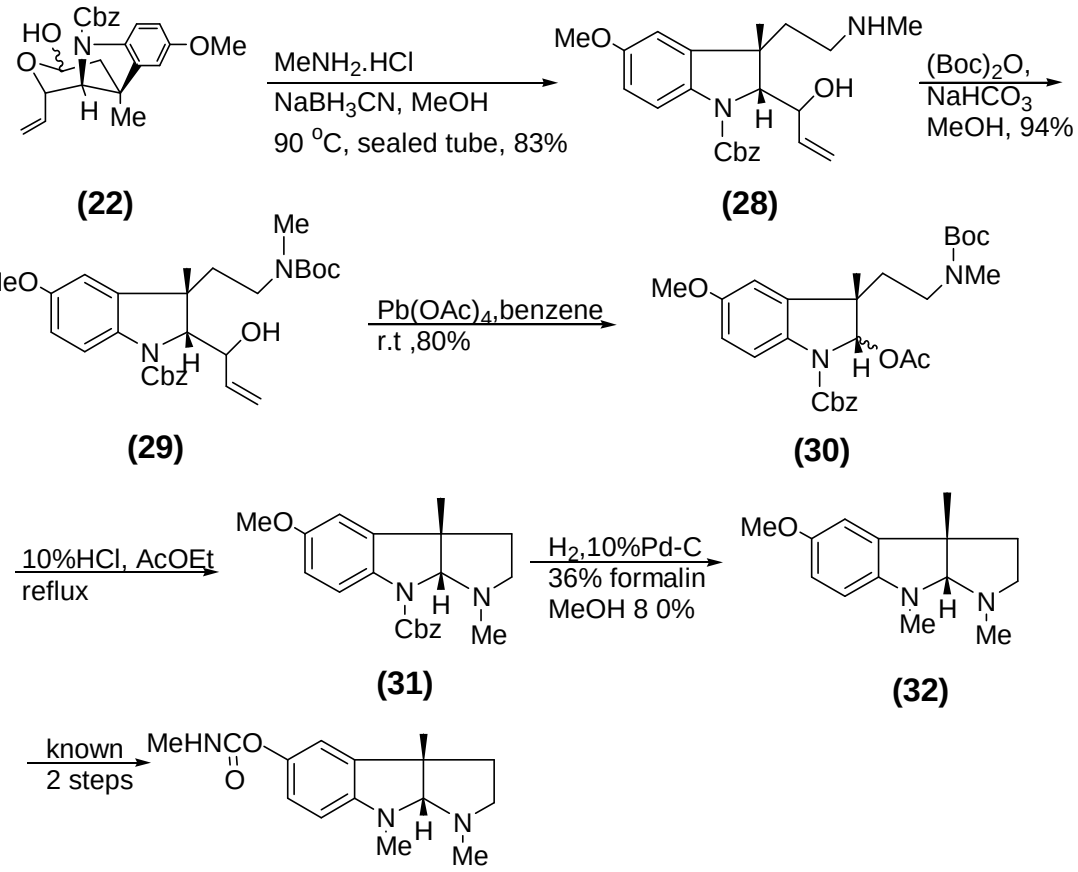


a = NAP **b** = Bn **c** = TBS

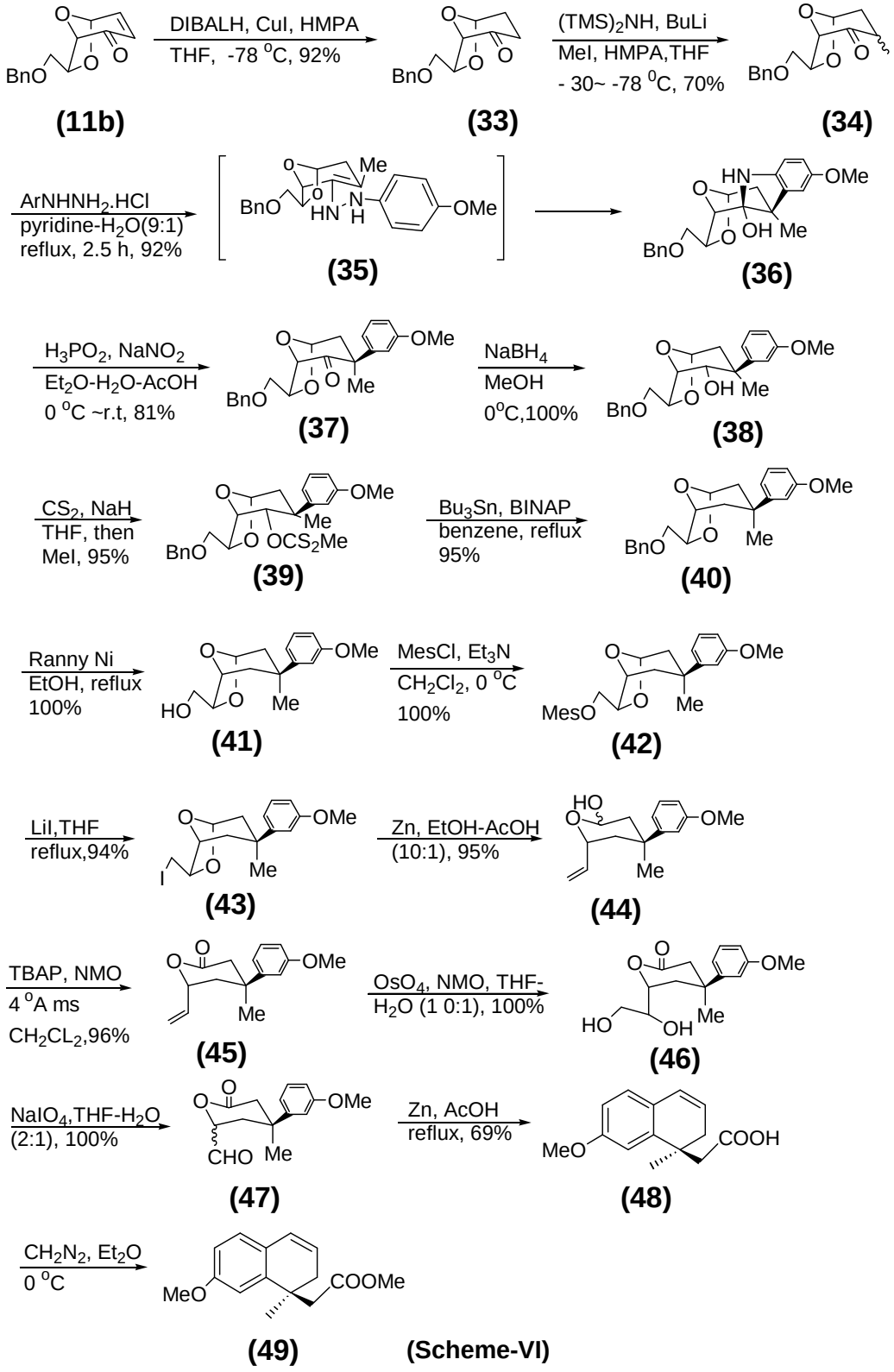
(Scheme-5)


H2,10%Pd-C
AcOEt,92%
(TMS)2NH,BuLi
MeI,HMPA,THF
- 30~ -78 0C,70%
(11C)
(16)
(16a)
ArNHNH2.HCl
pyridine-H2O(9:1)
reflux,2.5 h,70%
(16b)
(17)
1) LiAlH4,THF,0 0C
2)CbzCl, aq.K2CO3
TBAF,THF
0 0C ~ r.t.
(18)
(19)
MesCl,Et3N,
CH2CL2,o0C
LiI,THF
reflux
Zn,AcOH-EtOH
(9:1), r.t. 97%
(20)
(21)
NaBH4,EtOH,93%
Pb(OAc)4,benzene
r.t ,53%
(22)
(23)
H2,10%Pd-C
AcOEt,100%
36% formalin
NaBH3CN,MeOH
87%
(24)
(25)
known
2 steps
(26)
H2,10% Pd-C
36% formlin, NaBH3CN,
MeOH
(24)
(27)

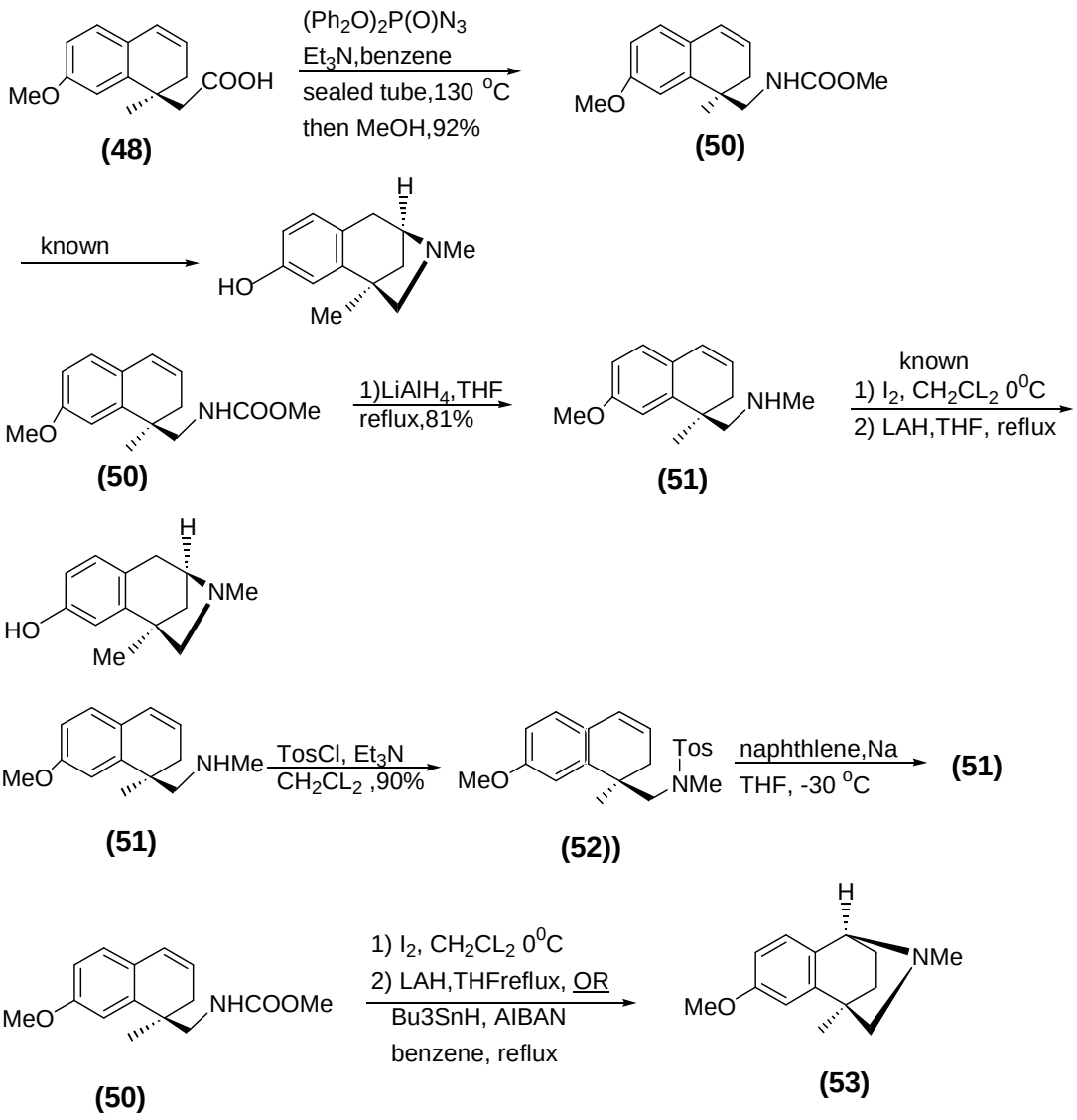
(Scheme-IV)


HO
Cbz
N
OMe
O
H
Me
MeNH2.HCl
NaBH3CN, MeOH
90 °C, sealed tube, 83%
MeO
NHMe
OH
N
H
Cbz
(Boc)2O,
NaHCO3
MeOH, 94%
(22)
(28)
Me
NBoc
MeO
OH
N
H
Cbz
Pb(OAc)4,benzene
r.t ,80%
Boc
NMe
MeO
N
H
OAc
Cbz
(29)
(30)
10%HCl, AcOEt
reflux
MeO
N
H
N
Cbz
Me
H2,10%Pd-C
36% formalin
MeOH 8 0%
MeO
N
H
N
Me
Me
(31)
(32)
known
2 steps
MeHNCO
O
N
H
N
Me
Me

(Scheme-V)


DIBALH, CuI, HMPA
THF, -78 °C, 92%
(TMS)2NH, BuLi
MeI, HMPA,THF
- 30~ -78 °C, 70%
(11b)
(33)
(34)
ArNHNH2.HCl
pyridine-H2O(9:1)
reflux, 2.5 h, 92%
(35)
(36)
H3PO2, NaNO2
Et2O-H2O-AcOH
0 °C ~r.t, 81%
(37)
NaBH4
MeOH
0°C,100%
(38)
CS2, NaH
THF, then
MeI, 95%
(39)
Bu3Sn, BINAP
benzene, reflux
95%
(40)
Ranny Ni
EtOH, reflux
100%
(41)
MesCl, Et3N
CH2Cl2, 0 °C
100%
(42)
LiI,THF
reflux,94%
(43)
Zn, EtOH-AcOH
(10:1), 95%
(44)
TBAP, NMO
4 °A ms
CH2CL2,96%
(45)
OsO4, NMO, THF-
H2O (1 0:1), 100%
(46)
NaIO4,THF-H2O
(2:1), 100%
(47)
Zn, AcOH
reflux, 69%
(48)
CH2N2, Et2O
0 °C
(49)

(Scheme-VI)


MeO
COOH
(48)
(Ph2O)2P(O)N3
Et3N,benzene
sealed tube,130 °C
then MeOH,92%
NHCOOMe
(50)
known
H
NMe
HO
Me
1)LiAlH4,THF
reflux,81%
NHMe
(51)
known
1) I2, CH2CL2 0°C
2) LAH,THF, reflux
TosCl, Et3N
CH2CL2 ,90%
Tos
(52))
naphthlene,Na
THF, -30 °C
1) I2, CH2CL2 0°C
2) LAH,THFreflux, OR
Bu3SnH, AIBAN
benzene, reflux
(53)

(Scheme-VII)

3. Theoretical Discussion.

3.1. A New Expedient Route to the Synthesis of Calabar Bean Alkaloids and Aphanorphine Alkaloid.

The chiral natural products used in medicine occur generally in one of their enantiomeric forms, that shows the biological activity. So the enantio-controlling process is an important factor in the synthesis of natural products.

In this investigation the Calabar bean alkaloids, [(-)-physovenine, (-)- physostigmine] and (-)-aphanorphine alkaloid were synthesized starting from furfural which was converted to versatile chiral building blocks, levoglucosenone and dioxabicyclooctenone, via a lipase-mediated kinetic resolution method as a new strategy for enantiocontrolled synthesis viz.

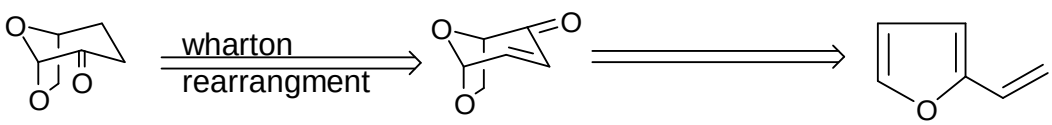
3.2. Lipase Mediated Synthesis of Enantiopure Isolevo-glucosenone.

Levoglucosenone **[(-)-1]**[75] is an acid-catalyzed pyrolysis product of cellulose and is used as versatile chiral building block [76,77] owing to its high functionality confined within a 6,8-dioxabicyclo [3.2.1] octane framework.

The reaction around the enone functionality occurs diasterioselectively from the convex face of molecules, which allows enantio and diastreocontrolled construction of a variety of natural products [78]. However its acquisition was not efficient and limited to (-)- enantiomers [79,80].

Recently the first enantiocontrolled synthesis of both enantiomers of levoglucosenone **[(-)-(1)]** from 2-vinylfuran (**3**) via isolevoglucosene [81] **[(+)- (2)]** was achieved by employing the sharpless asymmetric dihydroxylation (AD) reaction as key step [82].

During the synthesis there are two difficulties viz.; incomplete enantio-selectivity in the AD reaction in addition to lower efficiency in the conversion of isolevoglucosenone into levoglucosenone involving the Wharton rearrangement [83,84] as shown in following retro synthesis.



(-)-(1)
levoglucosenone

(+)-(2)
isolevoglucosenone

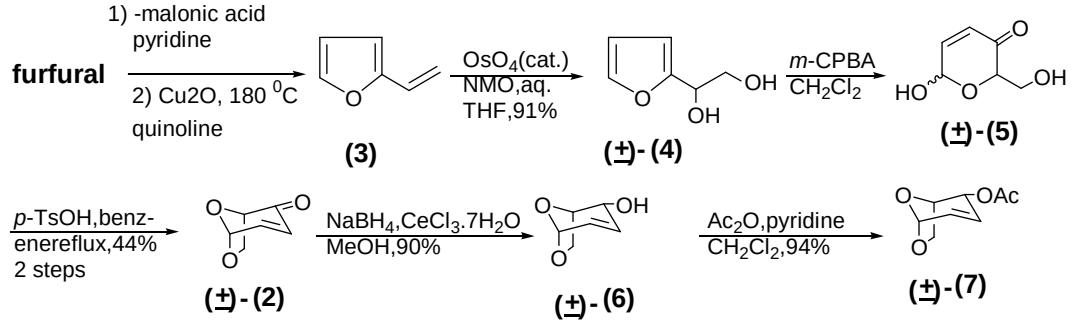
(3)

(Scheme-1)

Consequently, we explored a new procedure capable of producing *enantiopure* isolevoglucosenone in *both enantiomeric forms* by using lipase-mediated reaction.

2-Vinylfuran (**3**) [85,86] was first treated under catalytic dihydroxylation conditions with osmium tetraoxide and N-methylmorpholine N-oxide (NMO) to give the racemic 1,2-diol (±)-**(4)**. The racemate (±) - **(4)** was treated with *m*-chloroperbenzoic acid (*m*-CPBA) to give the 3-pyranone mixture **(5)** which was immediately refluxed in benzene with removal of water in the presence of *p*-toluene-sulfonic acid to give racemic isolevoglucosenone [(±)-**2**] in 44% yield.

In order to carry out enzymatic transesterification and hydrolysis, (±)-(**2)** obtained was reduced diastereoselectively from the convex face under Luche [87,88] conditions to give the *endo*-alcohol (±)- **(6)** which was used as the substrate for the lipase-mediated transesterification. Moreover, the racemic alcohol (±)- **(6)** was acetylated to give the *endo*-acetate (±)- **(7)** which was used as the substrate for the lipase-mediated hydrolysis (Scheme- 2).

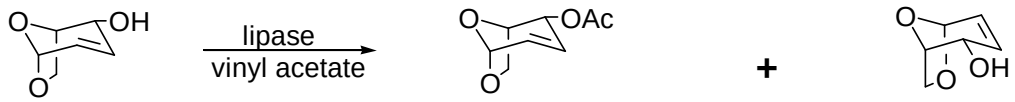


(Scheme-2)

We first examined the lipase-mediated kinetic transesterification with vinyl acetate in organic solvent using immobilized lipase. (Table-1).

Among the tested lipase, Lipase AK (Pseudomonas sp., Amano) exhibited the best result which afforded the enantiopure acetate (-)- (1*R*, 4*R*, 5*R*)- (**7)** in 48% yield, with the enantiopure alcohol (+)- (1*S*, 4*S*, 5*S*)-(**6)** in 47% recovery yield. Optical purity of the products was determined by HPLC equipped with a column with a chiral stationary phase (CHIRALCEL OD) after transformation into the benzoate having the corresponding chirality.

The absolute configuration of the products was determined by the respective transformation into isolevoglucosenone [81] (**2**) each having the corresponding chirality. Thus, the acetate (-)-(1*R*, 4*R*, 5*R*)- (**7)** furnished isolevoglucosenone [(+)- (1*R*, 5*R*)-] by sequential methanolysis and oxidation via the alcohol [89,90] (-)- (1*R*, 4*R*, 5*R*)- (**6**) while the alcohol (+)- (1*S*, 4*S*, 5*S*)- (**6**) yielded the enantiomeric non-racemic isolevoglucosenone [(-)-(1*S*,5*S*)-**2**] on oxidation.



(±) **(-)** **(+)**

Table 1: Lipase-mediated Kinetic Resolution of Allyl Alcohol

Entry	Lipase	Solvent	Time (h)	Acetate [%, (%ee*)]	Alcohol [%, (%ee*)]
1	PS	THF	86	44(91)	55(80)
2	PS	Hexane	22	51(86)	45(>99)
3	PS	^{t}BuOMe	19	49(85)	47(>99)
4	LIP	THF	24	43(74)	53(81)
5	NOV	THF	72	49(76)	47(66)
6	AK	Hexane	11	52(65)	48(97)
7	AK	^{t}BuOMe	24	46(64)	43(98)
8	AK	THF	33	48(>99)	47(>99)

On the other hand, kinetic hydrolysis of the reacemic acetate (±)- (**7)**, also proceeded well in the presence of lipase AK. Thus, stirring (±)- (**7)** with lipase AK in a 9:1 mixture of 0.1 M phosphate buffer and acetone at room temperature afforded enantiocomplem-entarily the alcohol (-)-(1*R*, 4*R*, 5*R*)- (**6)** in 51% yield having 97% ee, with the acetate (+)-(1*S*, 4*S*, 5*S*) – (**7)** having 98% ee in 48% recovery yield. Both of the products were transformed into isolevoglucosenone (**2**) having the corresponding chirality (Scheme 3).

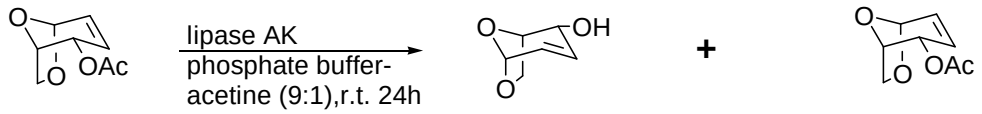
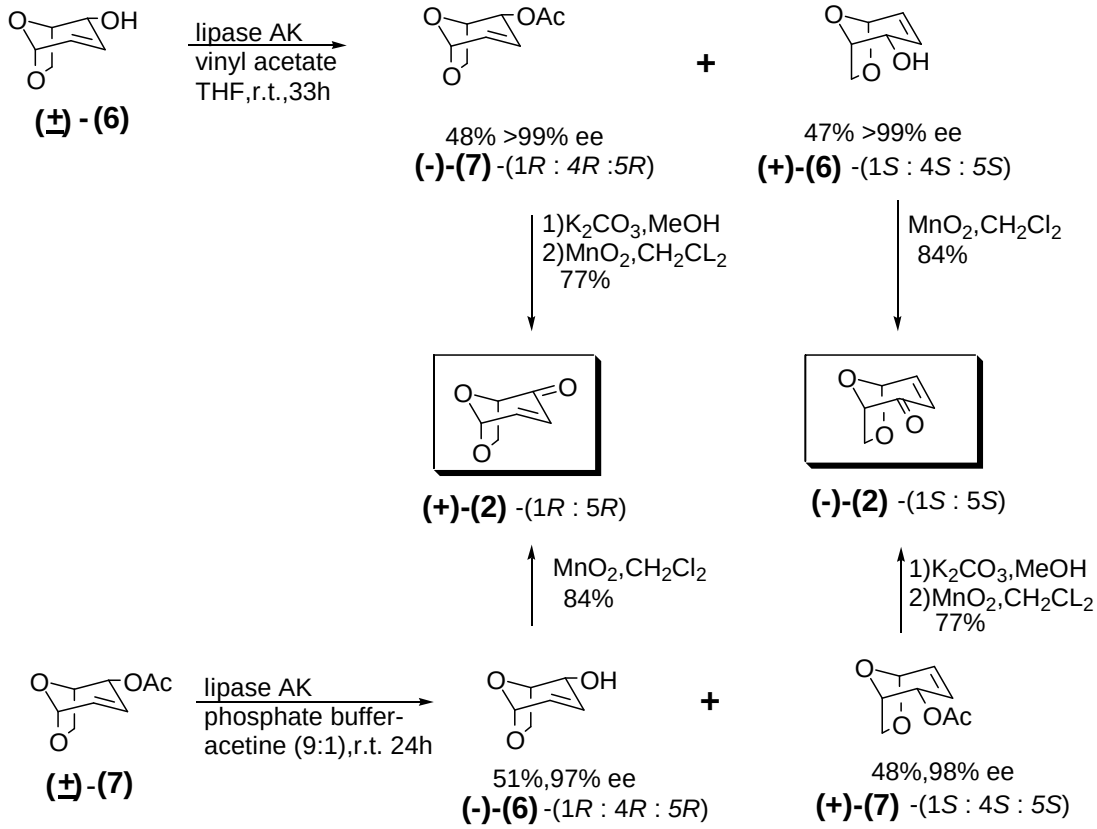


Table 2: Lipase-mediated Kinetic Resolution of Acetate.

Entry	Lipase	Tim (h)	Acetat [%, (% ee*)]	Al cohol [%, (% ee*)]
1	PS	24	49 (98)	51 (97)
2	AK	32.5	45 (> 99)	48 (95)



(Scheme-3)

3.3. Lipase-Mediated Synthesis of 6,8-Dioxabicyclo [3.2.1] oct-3-en-2-one as Chiral Building Blocks.

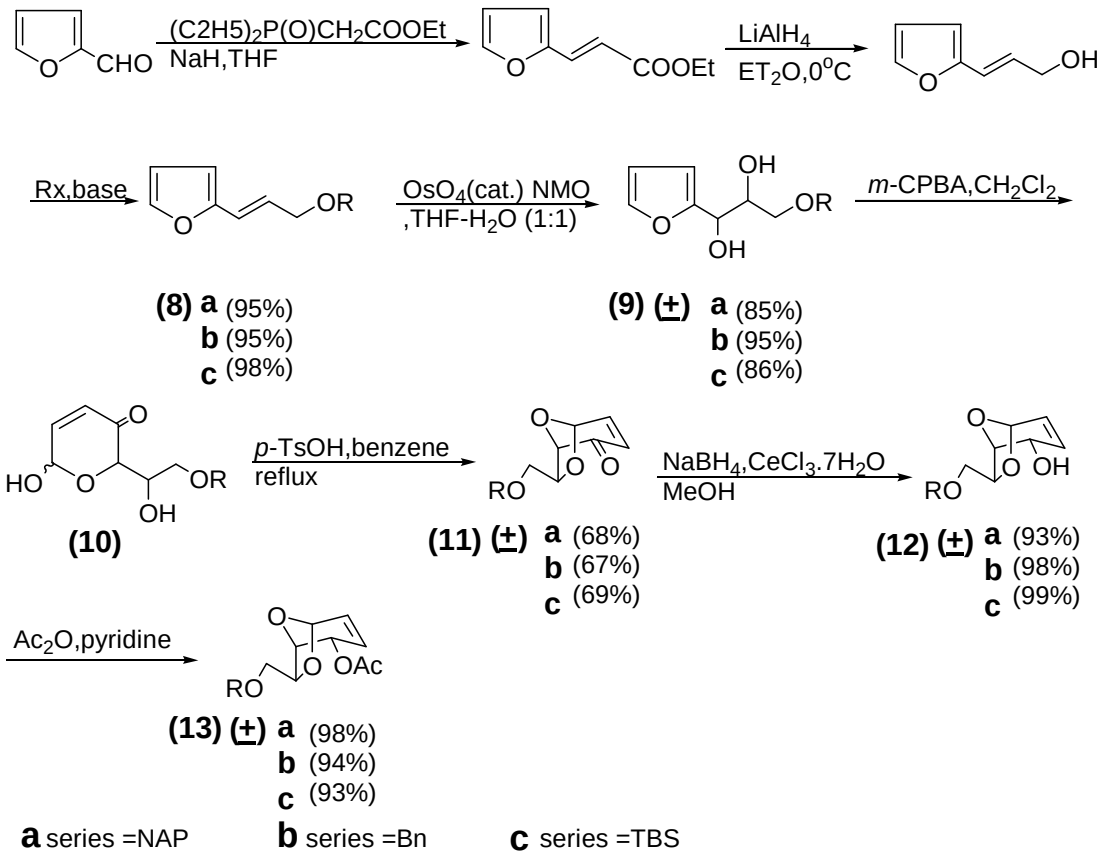
The asymmetric synthesis of the chiral building block (11a) in both enantiometrically pure forms and having the levoglucosenone chromophor was prepared from furfural, via employing Sharpless asymmetric [91] hydroxylation, followed by oxidative ring expansion (Achmatowicz [92] rearrangement, acid catalyzed cyclization). Although the synthesis allowed the generation of the enantiomerically pure enone [93] in satisfactory yield, we developed an alternative synthetic procedure which was carried out on a *large scale* without using the rather *expensive* AD-mix reagents used in Sharpless asymmetric dihyroxylation, with different protective groups (11a-c) utilizing lipase-mediated kinetic transesterification or hydrolysis reaction as key step. This chiral building block is used in the synthesis of many natural products like, (-)-physovenin, (-)-physostigmine [94], hexoses [95], (-)- aphanorphine [96], (+)- noviose [97], (+)- fibrifugine [98], FK506 C_{28-34} segment [99] and shikmic acid.[100]

The racemic dioxabicyclooctenone **[(±)- (11a)]** was first prepared from 2-(2-furfurydene) ethyl 2-naphthylmethyl ether **(8)** via a sequential osmate glycolysis, the peracid-mediated Achmatowicz [92] rearrangement and acidic cyclization via glycol **[(±)-(9)]** and the 3-pyrone (**10**).

Employing the same procedure, O-benzyl enone **[(±)- (11b)]** and O-TBS enone **[(±)- (11c)]** were prepared in comparable yields from the corresponding furfurydenethyl ether **(8b)** and **(8c)** respectively.

The enone **[(±)- (11a)]** was then reduced with sodium borohydride-cerium (III) chloride to give diastereoselectively the *endo*-alcohol [87,88] **[(±)-(12a)]** in 93% yield, serving as the substrate for the lipase-mediated kinetic transesterification. The alcohol **[(±)- (12a)]** thus obtained was further transformed into the acetate **[(±)- (13a)],** for subsequent lipase-mediated kinetic hydrolysis in 98% yield under standard conditions.

Employing the same procedure, both O-benzyl enone **[(±)- (11b)]** and the O-TBS **[(±)- (11c)]** were transformed to the corresponding enols, **[±)- (12b)]** and **[(±)- (12c)],** and the acetate, [(±)- **(13b)]** and **[(±)- (13c)]** respectively, in comparable yields. (Scheme-4).



(Scheme-4)

Among the lipase examined, lipase PS (*Pseudomonas* sp., Amano) brought about the best results under both transestrification and hydrolysis conditions. Thus, when the alcohol **[(±)-12a]** was stirred with vinyl acetate in THF for 24 hours at room temperature in the presence of lipase PS, a clear-cut enantiomeric discrimination occurred to afford enantiomerically pure acetate **[(-)-13a]** and the enantiomerically pure alcohol **[(+)-12a]** in yields of 47 and 47% with E value of > 1057. [101] [E value was calculated by estimating enantiomeric purities of the products as 99% ee.]

Absolute configuration of the products was determined after their transformation into the enone **(11a).** The acetate **[(-) -13a],** on alkaline methonolysis, gave quantitatively the alcohol **[(-)-12a]** which, on oxidation with pyridinium chlorochromate (PCC) in dichloromethane, gave the enone **[(+)-11a]**[93]**,** in 89% overall yield. The alcohol **[(+)-12a]** afforded the enantiomeric enone **[(-)-11a],** in 93% yield on PCC oxidation (scheme-5).

Enantiomeric purities of the resolution products were determined as the acetate, **[(-)-13a]** from **[(-)-12a]** and **[(+)-13a]** from **[(+)-12a]**, and found to be > 99% ee, respectively, by HPLC using a coulmn with a chiral stationary phase.

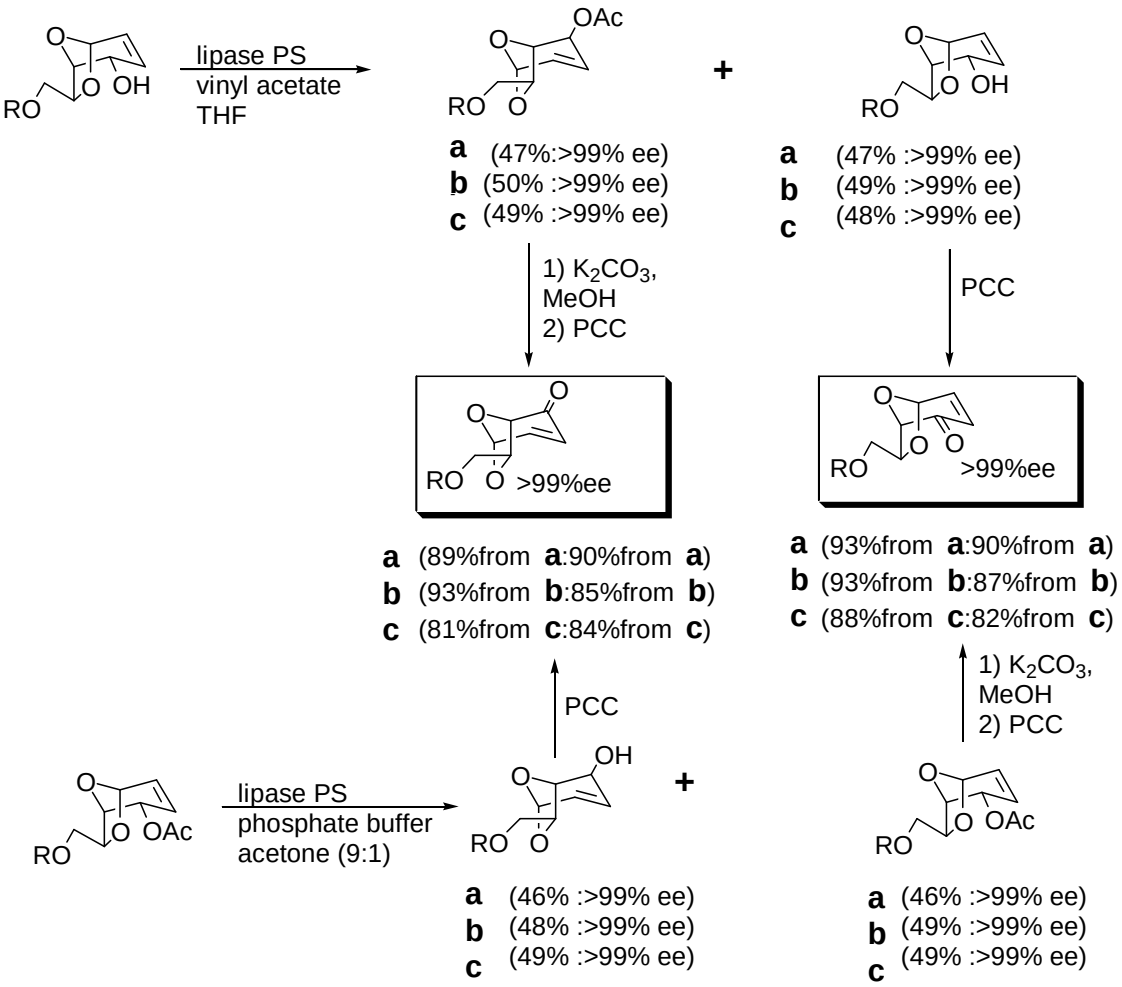
On the other hand, when the racemic acetate **[(±)-13a]** was stirred in a mixture of phosphate buffer and acetone (9:1 v/v) in the presence of lipase PS, a clear cut enantiomeric discrimination also occurs to give the enantiomerically pure alcohol **[(-)-12a]** and the acetate **[(+)-13a]** in yields of 46 and 46% with E value of >1057[(101)] [E value was calculated by estimating enantiomeric purities of the products as 99% ee.]

Enantiomeric purities were determined by HPLC using a column with a chiral stationary phase and were shown to be > 99% ee. The enzymatic reactions occurred in an enantiocomplementary way under the transesterification conditions and the hydrolysis conditions as expected.

Quite similarly, both the enones **(11b)** and **(11c)** having a different protecting group were obtained both in >99% ee with E values of >1057 [(101)]. Similarly the racemic alcohol **[(±)-12b]** and **(12c)** and the racemic acetates and **(13c)** were obtained in an enantiocomplementary way via the same lipase-mediated transesterification and hydrolysis conditions, respectively. (Scheme-5).

Finally we have developed an alternative procedure for the preparation of the chiral building block **(11a)** along with its two analogues **(11b)** and **(11c)** employing a lipase-mediated enantiocomplementary kinetic resolution procedure which exhibited comparable synthetic efficiency to Sharpless asymmetric hydroxylation.

The present *lipase-mediated* procedure allowed *facile (large-scale)* preparation of highly functionalized bicyclic enones in *both enantiomeric* forms in *enantiomerically pure* states without using expensive AD-mix reagents; the enones thus obtained are more *widely used* as versatile chiral building blocks.


lipase PS
vinyl acetate
THF
OAc
OH
RO
a (47%:>99% ee)
b (50% :>99% ee)
c (49% :>99% ee)
+
a (47% :>99% ee)
b (49% :>99% ee)
c (48% :>99% ee)
1) K2CO3, MeOH
2) PCC
PCC
>99%ee
a (89%from a:90%from a)
b (93%from b:85%from b)
c (81%from c:84%from c)
a (93%from a:90%from a)
b (93%from b:87%from b)
c (88%from c:82%from c)
lipase PS
phosphate buffer
acetone (9:1)
a (46% :>99% ee)
b (48% :>99% ee)
c (49% :>99% ee)
a (46% :>99% ee)
b (49% :>99% ee)
c (49% :>99% ee)

(Scheme-5)

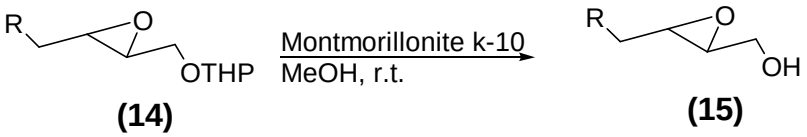
3.4. Deprotection of Tetrahydropyranyl Ether with Montmorillonite k-10 Clay in Methanol.

During our on going project we encountered a difficulty in deprotection the tetahydropyranyl (THP) group from the THP ether carrying epoxy functionality, such as **(14)** to give the epoxy alcohol **(15)** without affecting of the epoxy functionality. Among the condition, that were reported for the deprotection of this group is the use of dilute perchloric acid [102], *p*-toluensulfonic acid-MeOH [103], aqueous acetic acid [104], pyridinium *p*-toluenesulfonate (PPTS)-MeOH [105], carbon tetrabromide-MeOH [106] and cerric ammonium nitrate (CAN)-aqueous acetonitrile [107,108]. The only method that allows the deprotection of **(14a)** without affecting the epoxy functionality to give the alcohol **(15a)** is the use of CAN method in 74% yield [109]. However this method could not be used for **(14b)** having 4-methoxyphenoxy (PMPO) functionality since such group was removed concurrently under the reaction condition [110].

Therefore, another alternative deprotecting method in which the methanolysis of THP ether **(14)** in the presence of Montmorillonite **K-10** clay allowed smooth removal of the THP functionality. Thus, on stirring with the same weight of montmorillonite **K-10** clay in methanol at room temperature for 1 h, The THP ether **(14a-c)** afforded the corresponding epoxy alcohol in 77%, 76% and 73% yield respectively.

Rather surprisingly, although, **K-10** was used as catalyst in the formation of THP ether [111,112], in the present study it has been used for removal of THP protecting group from THP ether.

We investigated the deprotection of a variety of THP ethers employing **K-10** clay-mediated methanolysis condition to extend its general synthetic utility. Accordingly the methanolysis of a series of simple primary, secondary, tertiary alkyl, aralykyl and aryl THP ethers was tried. The reaction was carried out by stirring the ethers in methanol (5% w/v) with the same amount of **K-10** clay at room temperature. The reaction was completed within 2 h to give the corresponding alcohol in excellent yield. The β-naphthyl THP ether was the only stable derivative under prolonged stirring or even under refluxing conditions (Table-1).

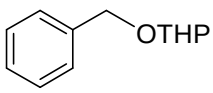
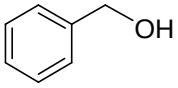
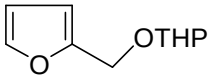
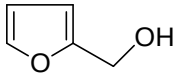
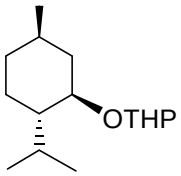
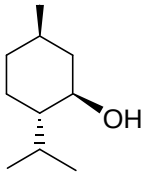
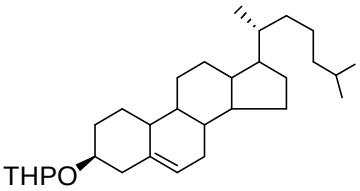
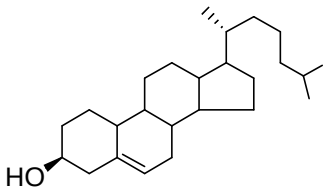
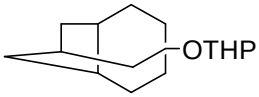
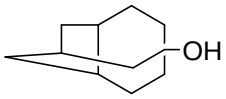
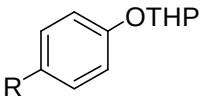
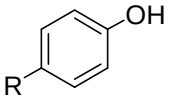
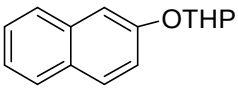
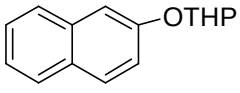


(14) **(15)**

a: R= BnO, (77%)
b: R= $MeOC_6H_4O$, (76%)
c: R= 2-NaphthylCH_2O, (73%)

(Scheme- 6)

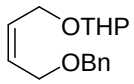
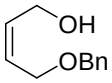
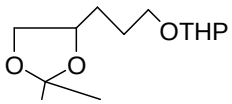
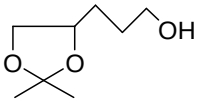
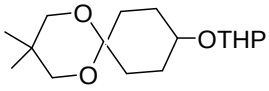
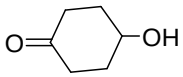
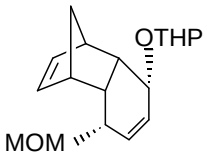
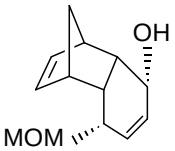
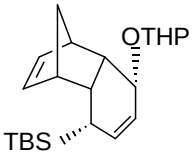
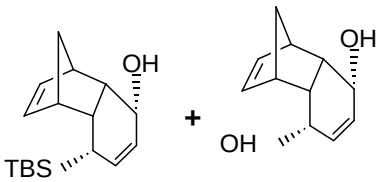
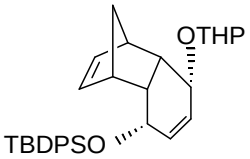
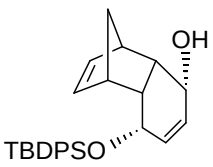
Table 3: K-10 Clay-Mediated Deprotection of Simple THP Ethers.

Entry	Substrate	Product	Yield %
1			91
2			95
3	$Me(CH_2)_5CH_2OTHP$	$Me(CH_2)_5CH_2OH$	97
4			86
5			80
6			90
			
7	**R=H**	**R=H**	98
8	**R=NO2**	**R=NO2**	83
9	**R=OMe**	**R=OMe**	99
10			0

Furthermore, we investigated the same reaction using the THP ethers carrying additional O-functional groups in their molecules. The THP protecting group was removed smoothly from the substrates carrying benzyloxy, allyloxy, methoxymethoxy, acetoxy, benzoyloxy, or *tert*-butyldiphenylsiloxy (TBDPSO), functional groups to give the corresponding alcohol in good to excellent yields.

On the other hand the THP ether carrying *tert*-butyldimethylsiloxy (TBSO), β, β, β, -trichloroethylimidoxy and ketal functionalities were unstable under these conditions.

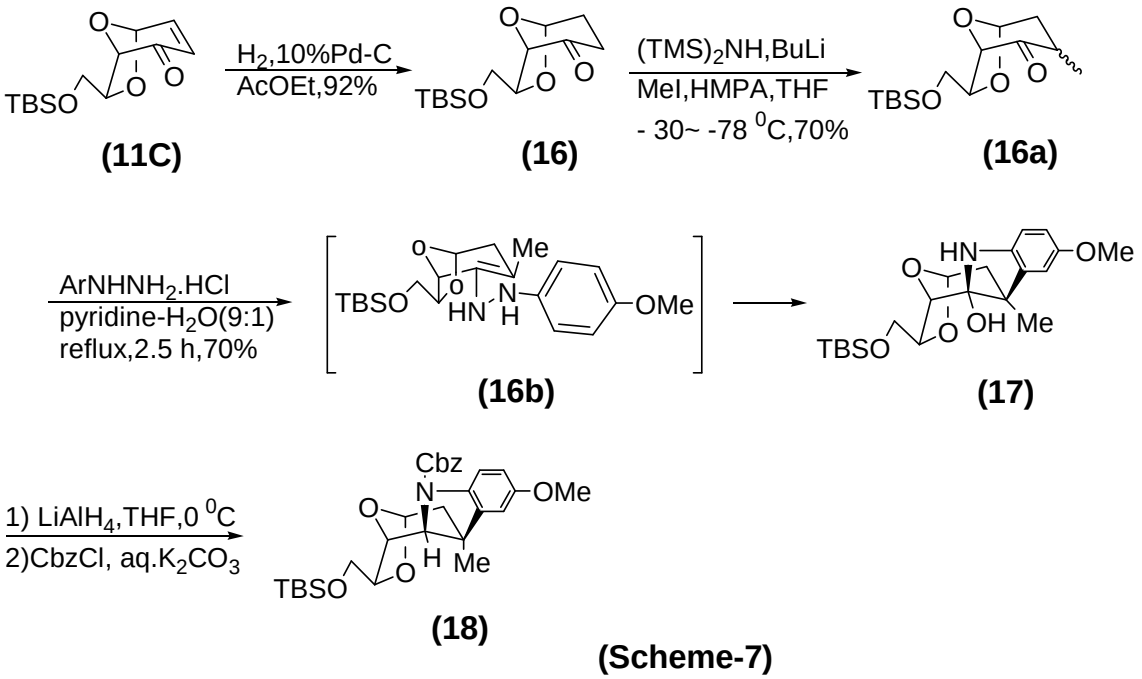
Table 4: K-10 Clay-Mediated Deprotection of Functionalized THP Ethers.

Entry	Substrate	Product	Yield %
	$RO(CH_2)_4OTHP$	$RO(CH_2)_4OH$	
1	R=Bn	R=Bn	92
2	R=allyl	R=allyl	82
3	$R=MeOCH_2$	$R=MeOCH_2$	98
4	$R={}^tBuMe_2Si$	$R={}^tBuMe_2Si$	25
5	$R={}^tBuPh_2Si$	$R={}^tBuPh_2Si$	82
6	R=MeCO	R=MeCO	92
7	R=PhCO	R=PhCO	97
8	$R=CCl_3C(=NH)$	R= OTHP	61
9			94
10			32
11			85
12			93
13			48
14			99

3.5. Synthesis of (-)-Physovenine.

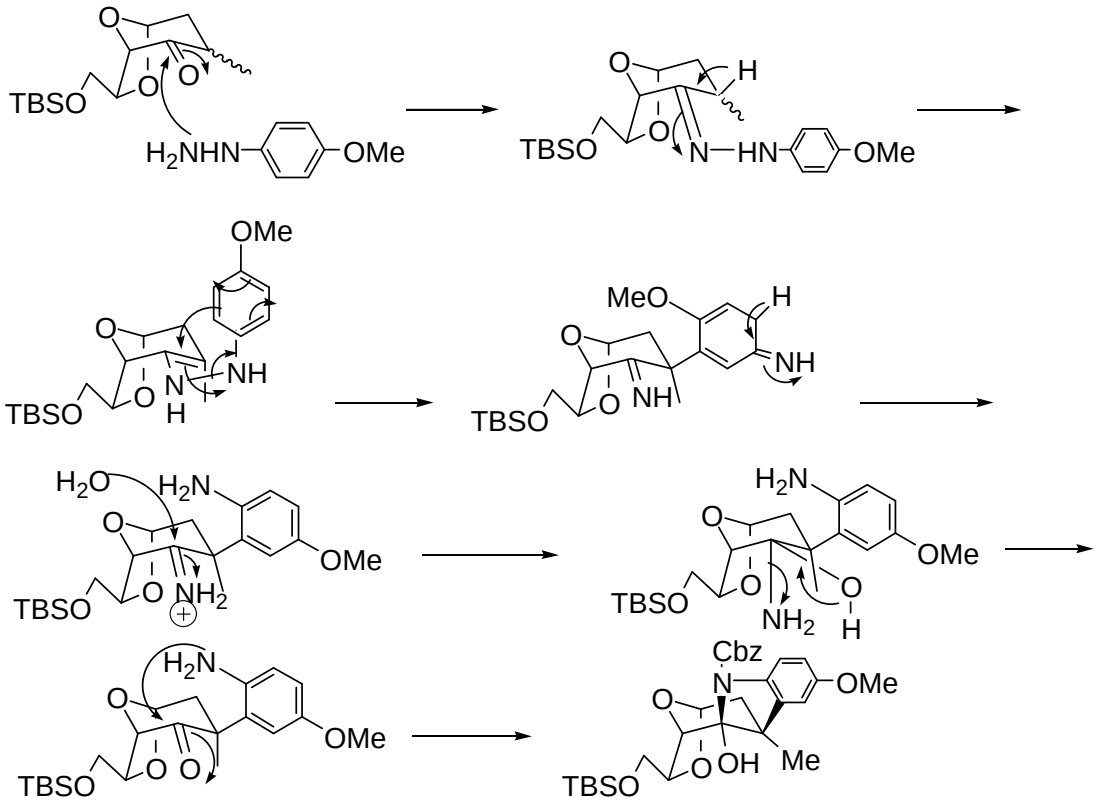
Accordingly, **[(-)- 11c]** [113] was first converted into ketone **(16)** by catalytic hydrogenolysis in ethyl acetate containing 10% palladium-carbon in 92 % yield. Monomethylation of ketone **(16)** was carried out with iodomethane in the presence of lithium hexamethyldisilazide (LHMDS) in THF containing hexamethylphosphoric triamide (HMPA) at -78 °C to -30 °C to give 2-methylketone **(16a)** as an epimeric (5:2) mixture in 70% yield. Refluxing the mixture **(16a)** with 4-methoxyphenylhydrazine hydrochloride in 90% aqueous pyridine [44,45] led to diastereoselective formation of the single carbinolamine **(17)** in 70% yield without affecting the siloxy-protecting group.

The carbinolamine **(17)** underwent reduction with lithium aluminum hydride followed by alkaline work up in the presence of carbobenzoxy chloride to afford the indoline *N*-carbamate **(18)** as a single diastereomer in quantitative yield as shown in scheme-7.



(Scheme-7)

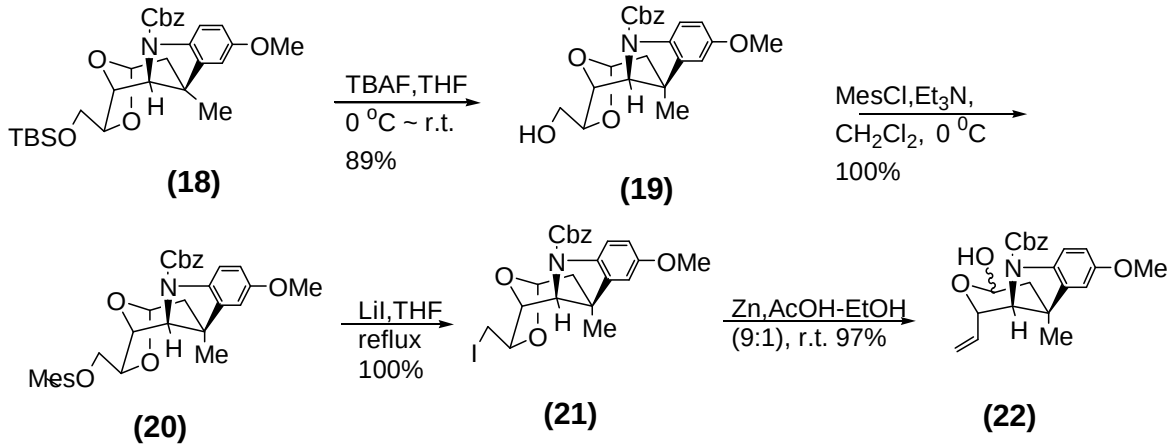
The mechanism involved in conversion of ketone (16a) to the carbinol-amine (17) could be outlined in scheme-7.



(Scheme-8)

Although the stereochemistery of compound (18) was not determined, the key Fischer indolization sequence involving a [3,3]-sigmatropic rearrangement was confirmed to proceed diastereoselectively from the convex face through diaza-1, 5-diene intermediate **(16b)** by acquistion of the known tricyclic aminoacetal **[(-)-25]** at the later stage.

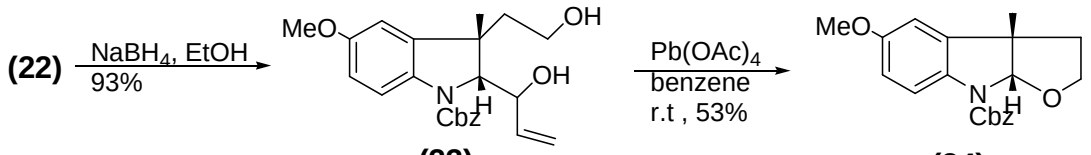
Compound **(18)** was desilated by TBAF in THF to afford the alcohol **(19)**. The latter alcohol was converted to mesylate **(20)** through reaction with methansulfonyl chloride in CH_2CL_2 containing Et_3N. Refluxing mesylate **(20)** with lithium iodide in THF afforded the corresponding iodide **(21)** which was exposed to zinc in hot ethanol containing acetic acid to initiate reductive cleavage of of the internal acetal linkage to afford the vinyl-hemiacetal **(22)** as an epimeric mixture as shown in scheme- 9. The overall yield of **(22)** from **(18)** was 86%. The mixture **(22)** was used as a common intermediate for both (-)- physovenine and (-)- physostigmine synthesis.



(18) **(19)** **(20)** **(21)** **(22)**

(Scheme-9)

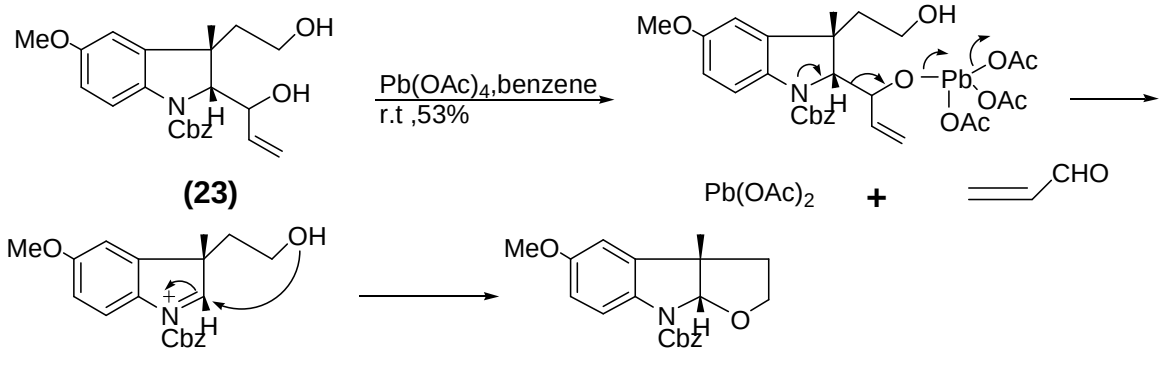
Vinylhemiacetal **(22)** was first reduced with sodium borohydride to give the diol **(23)**. After extensive investigation it was found that the removal of extra three-carbon chain (i.e. the allylic alcohol moiety) from **(23)** was best carried out in one step via oxidative cyclization utilizing with lead (IV) acetat [(114)]. Thus treatment of (23) with lead (IV) acetate in benzene at room temperature afforded the tricyclic compound **(24)** in 53% yield (Scheme-10).



(23) **(24)**

(Scheme-10)

The oxidative removal of the allylic alcohol moiety of (23) followed by cyclization to (24) could most probably proceed via the mechanism illustrated in scheme-11.

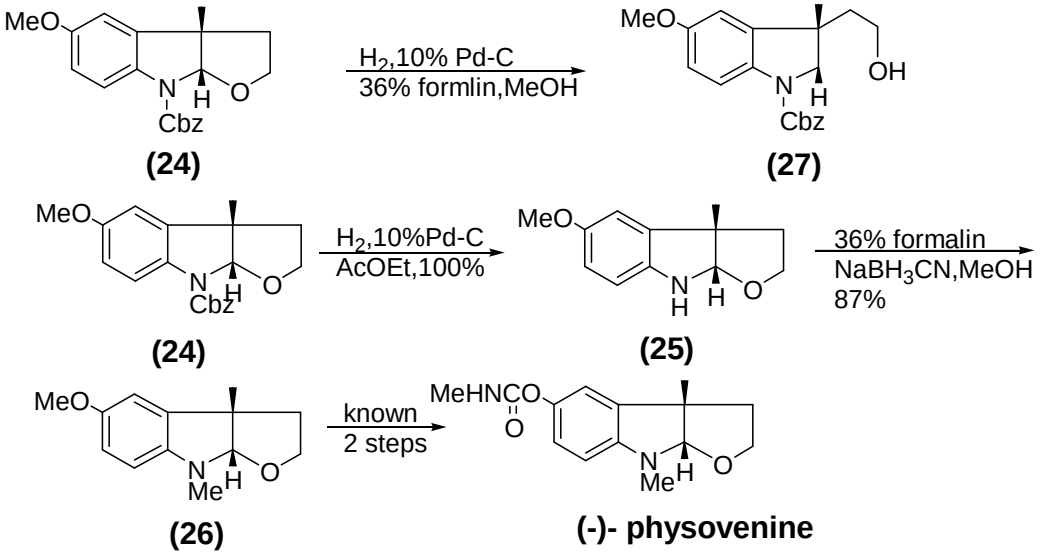


(23) **(24)**

(Scheme-11)

Several attempts were made to convert the tricyclic carbamate **(24)** to the known tricyclic N-methyl derivative **(26)**[44] through one-step reaction involving catalytic hydrogenolysis in the presence of formalin [115]. Unfortanatly, the alcohol **(27)** was the product in such case.

Accordingly, step-wise conversion of **(24)** to **(26)** was attempted. Hence, the tricyclic carbamate **(24)** was converted into the secondary amine **(25)** under standard palladium-catalyzed hydrogenolysis conditions. Compound (25) then underwent reductive methylation on treating with formalin in the presence of sodium cyanoborohydride to afford the tricyclic *N*-methyl aminoacetal **(26).** Through two step reaction, the *N*- methyl aminoacetal (26) was converted to (-)- physosvenine as shown in scheme-12.



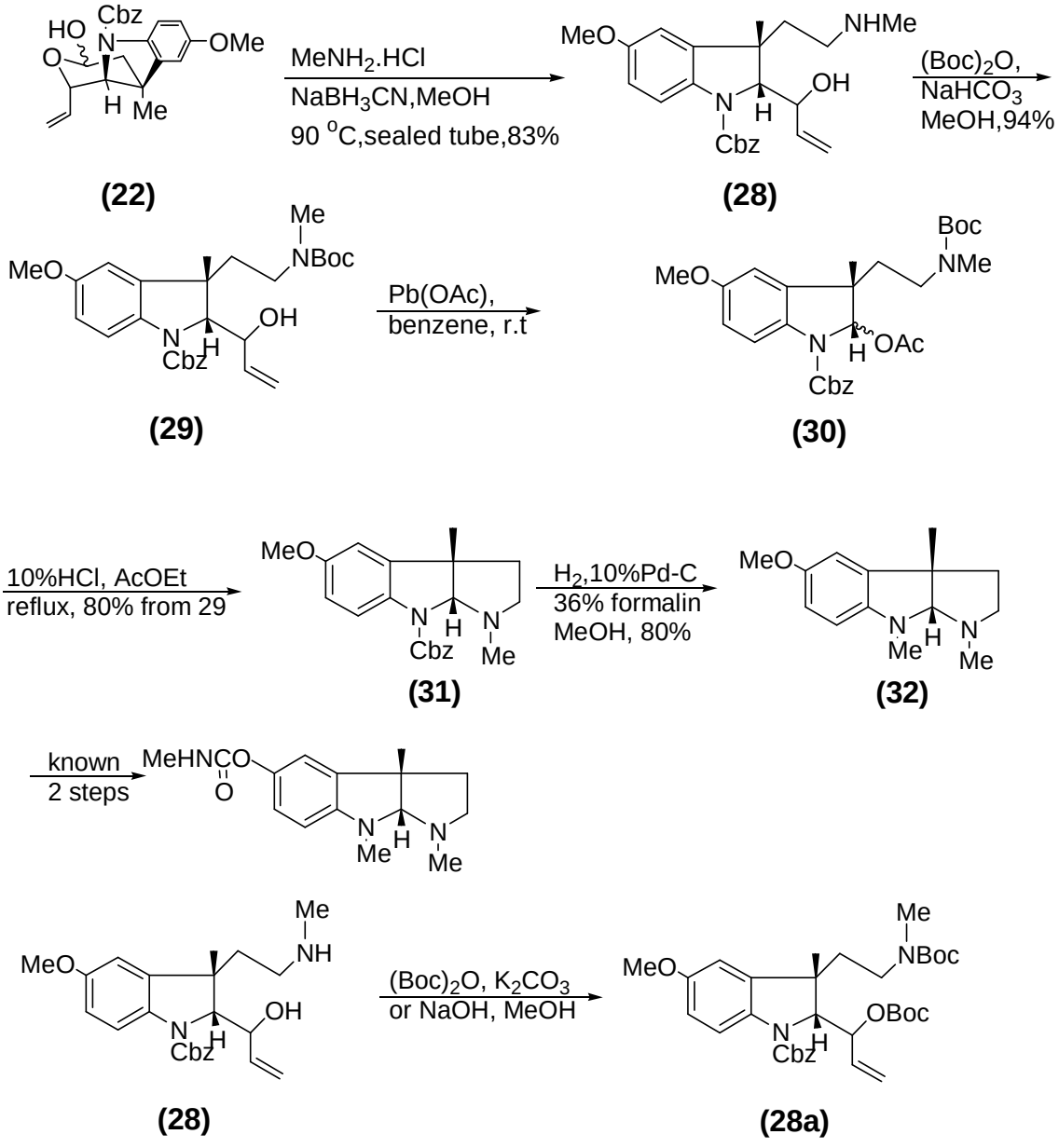
(Scheme-12)

3.6. Synthesis of (-)- Physostigmine.

In the present investigation, (-)- physostigmine was prepared starting from furfural which was transformed via standard procedure to vinylhemiacetal (22). Vinylhemiacetal **(22)** was then heated with methylamine hydrochloride in methanol in a sealed tube in the presence of sodium cyanoborohydride at 90 °C for 12 h to afford the *N*-methylaminoalcohol **(28)**, which was converted into the bis-carbamate **(29)** on treating with di-*tert*-butyl dicarbonate [$(Boc)_2O$] in MeOH in the presence of sodium bicarbonate in 94% yield as selective protection of secondary amine. When the reactions were done in the presence of K_2CO_3 or NaOH as base it afforded compound 28a.

Removal of the allylic alcohol moiety was carried out by treating the bis-carbamate **(29)** with lead (IV) acetate [114] in benzene to give crude acetate **(30)**, which was refluxed with 10% hydrochloric acid in hot ethyl acetate [116] to afford tricyclic carbamate **(31)** by concurrent chemoselective decarbamylation, deacetoxylation and internal aminalization.

The tricyclic carbamate (31) underwent reductive *N*-methylation under catalytic hydrogenolysis conditions in the presence of formalin [115] to afford the *N*, *N*-dimethylaminal esermethol (**32**), which was converted to (-)-physostigmine as shown in scheme-13.

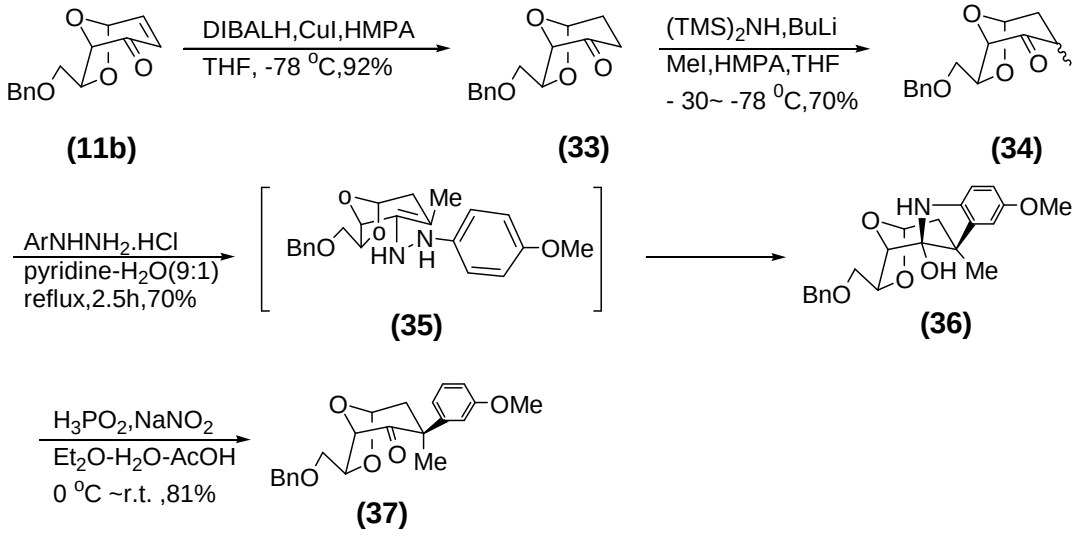


(Scheme-13)

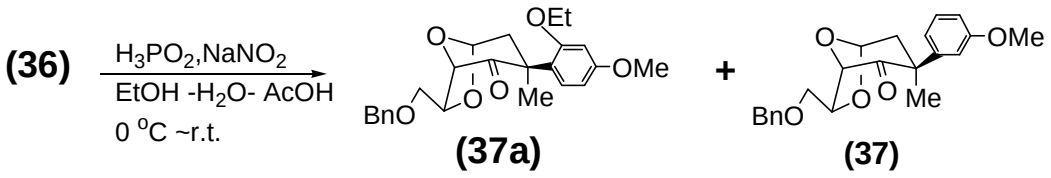
3.7. Synthesis of (-)- Aphanorphine.

Enantiopure protected enone **[(-) 11b]** [113] was first subjected to 1,4 addition reaction by treatment with DIBALH in the presence of CuI and hexamethylphosphoric triamide (HMPA) in THF at –78 °C to afford the ketone **(33)** in 92% yield. Monomethylation was carried out with iodomethane in the presence of lithium hexamethyldisilazide (LHMDS) in THF containing hexamethylphosphoric triamide (HMPA) to afford two α-methylketone **(34)** as an epimeric mixture (7:3) in 70% yield.

Refluxing this mixture with 4-methoxyphenylhydrazine hydrochloride in 90% aqueous pyridine led to the diastereoselective formation of single carbinolamine **(36)** [44,45] in 92% yield. Compound (36) was converted to the ketone (37) via deamination reaction under the effect of sodium nitrite in the presence of hypophosphorous acid. The reaction proceeded most probably through formation of an unstable diazonium salt [117]. The product of latter reaction was found to depend on the condition of deamination. When the reaction was done in a mixture of ether-acetic acid-water (10: 0.5: 0.5), the keton (37) was obtained in 81% yield (scheme-14). Replacement of ether with ethanol made the reaction to produce a mixture of (37) and its ethoxy derivative (37a) scheme-15.

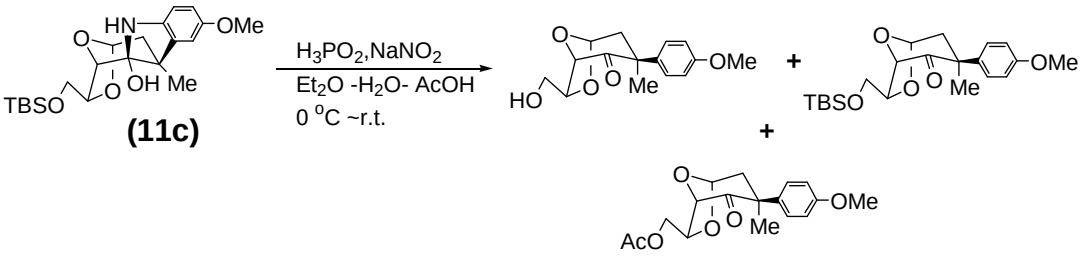


(Scheme-14)



(Scheme- 15)

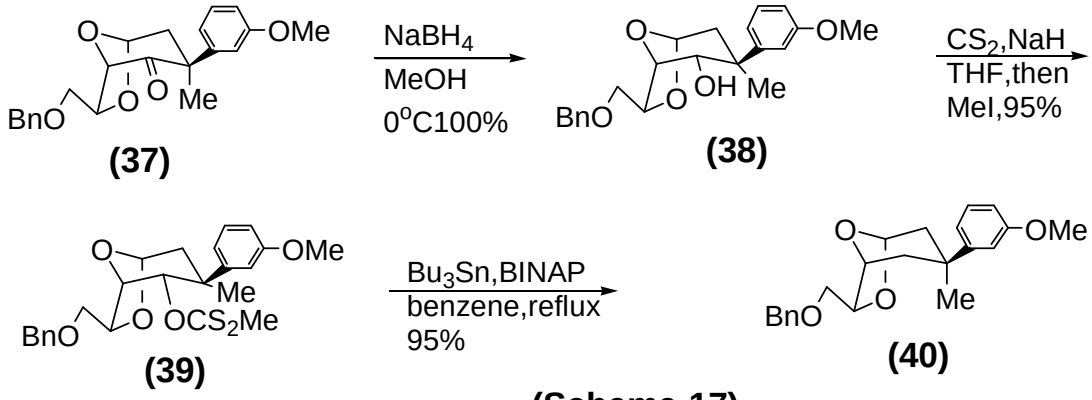
In addition when compound (11c) subjected to the deamination reaction it afforded a mixture of the free alcohol, TBS and the acetyl derivatives (Scheme-16).



(Scheme- 16)

It was found that the best method to convert the ketone **(37)** to dioxabicyclooctane derivative **(40)** involved reduction of **(37)** with sodium borohydride to the corresponding alcohol **(38)**, which was treated with carbon disulfide and sodium hydride followed by methylation with methyl iodide to produce the o-thiomethyl ester **(39)**.

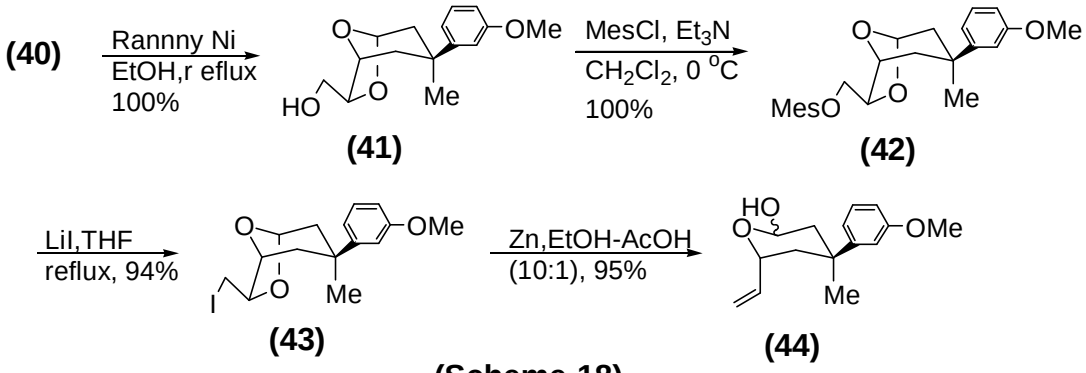
Removal of O-thiomethylester group was achieved by radical mechanism through the reaction with tributylinehydride (Bu_3SnH) in the presence of 2,2- azobisisobutylonitrile (AIBAN) in refluxing benzene to afford compound **(40) in** 95% yield (Shceme-17).



(Scheme-17)

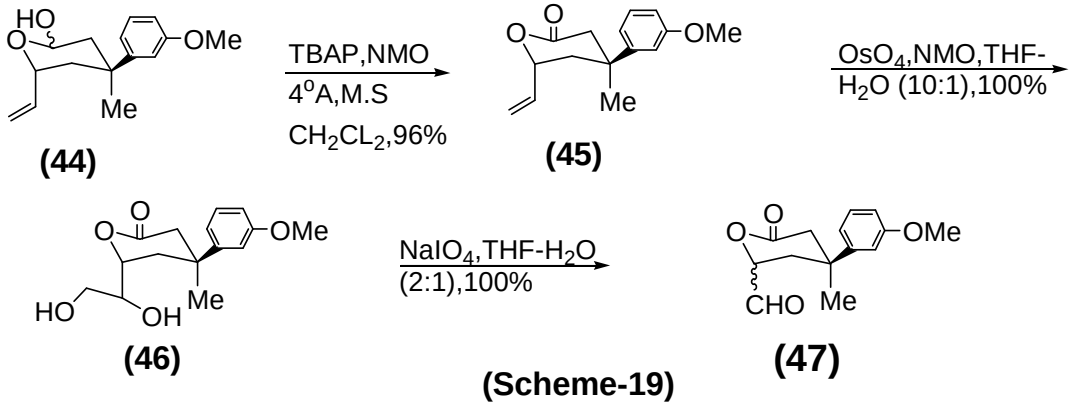
The acetal functionality of **(40)** was cleaved in sequence of four reactions in 90% overall yield. [94] Thus **(40)** was refluxed with Ranny Nickel in ethanol to afford the corresponding alcohol **(41)**, which was reacted with methansulfonyl chloride in the presence of triethylamine in dichloromethane to afford the corresponding mesylate (**42**) quantitatively.

The mesylate **(42)** was stirred with lithium iodide in refluxing THF and the resulting iodide **(43)** was exposed to zinc in ethanol containing acetic acid to initiate reductive cleavage of the internal acetal linkage to furnish vinylhemiacetal **(44)** as epimeric mixture in 95% yield (Scheme-18).



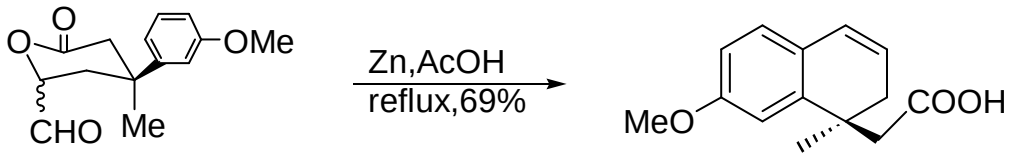
(Scheme-18)

The vinylhemiacetal **(44)** was oxidized to the corresponding ketone **(45)** in 96% yield by reaction with tetrapropylammonium perruthenate [118] (VII) in the presence of (NMO) and 4°A ms in dichloromethane at r.t. The vinyl moiety of the ketone **(45)** was converted to the aldehyde through reaction with osmium tetraoxide (OsO4) in the presence of (NMO) in aqueous THF to afford the diol **(46),** which was in-turn oxidatively cleaved by reaction with sodium periodate ($NaIO_4$) in aqueous THF at r.t. to afford qualitatively the corresponding aldehyde **(47)** (Scheme-19). When this reaction were done via ozonolysis or one-put OsO4/NaIO4 afforded the aldehyde in 10% and 41% yield respectively.



(Scheme-19)

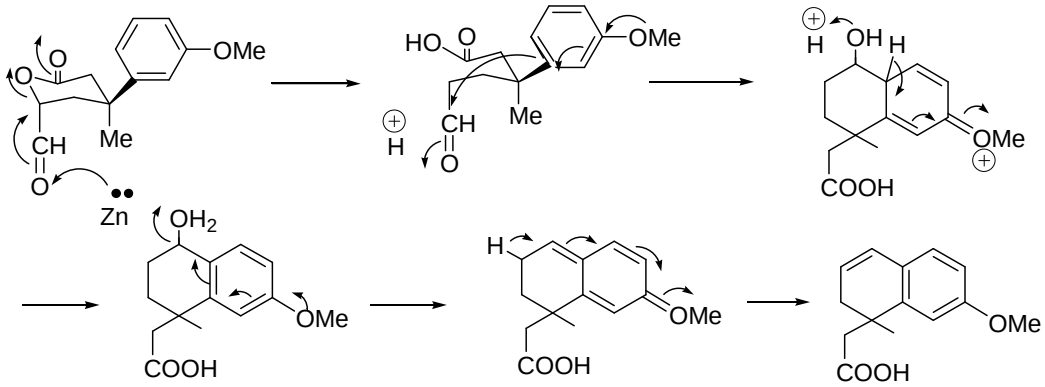
Overnight reflux of the aldehyde **(47)** with acetic acid in the presence of activated zinc facilitated its cyclization to afford dihydronaphthalene **(48)** in 69% yield, as shown in scheme-20.



(47) **(48)**

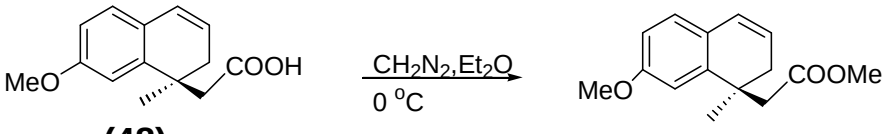
(Scheme-20)

Scheme-21 represent the most probable mechanism involved in such cyclization.



(Scheme-21)

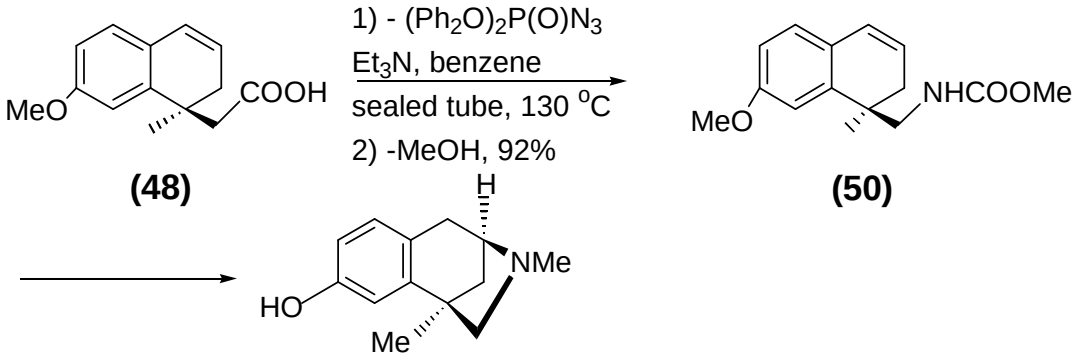
To justify the formation of the dihydronaphthalene **(48)** it was converted to the ester **(49)** by reaction with diazomethane (CH_2N_2) in Et_2O at 0 °C (Scheme-22).



(48) **(49)**

(Sheme-22)

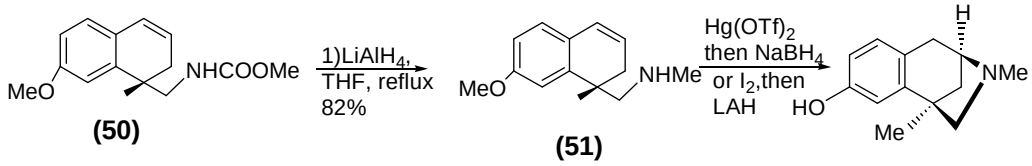
Treatment of (48) with diphenylphosphoryl azide in benzene containing Et_3N followed by addition of MeOH in sealed tube initiated the Curtius [119] rearrangement to afford the carbamate (50) in 92% yield. The latter carbamate (50) was converted to (-)- aphanorphine as shown in scheme-23.



(48) **(50)**

(Scheme-23)

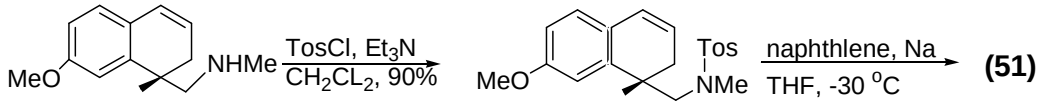
Furthermore, refluxing the carbamate **(50)** with lithium aluminum hydride in THF afforded the corresponding *N*-methylamine derivative **(51)** in 82% yield, which was converted to aphanorphine by aminomercuration or by iodination [63] (Scheme-24).



(50) **(51)**

(Scheme-24)

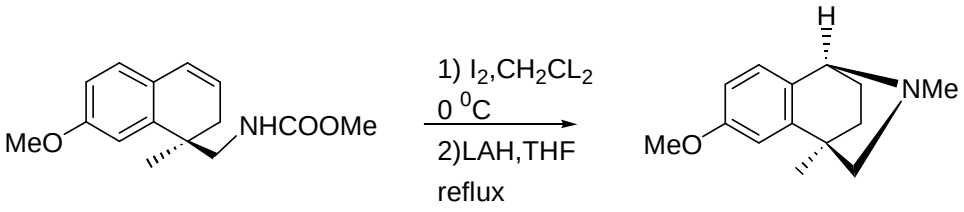
On the other hand, treatment of the *N*-methylamine derivative (**51**) with *p*-toluensulfonyl chloride in the presence of triethylamine in dichloromethane afforded the corresponding tosylate (**52**) in 90% yield. Cleavage and radical cyclization of **(52)** to (-)- aphanorphine under the effect of sodium naphthalenide [generated *in-situ*] [104] in THF at –30 °C, unfortunately did not achieved the reaction and afforded compound (**51**) (Scheme-25).



(51) **(52)**

(Scheme-25)

When the carbamate (**50**) was treated with iodine in dichloromethane at 0 °C and then refluxed with LAH in THF it afforded compound (**53**) (Scheme -26).



(50) **(53)**

(Scheme-26)

4. Experimental.

IR spectra were recorded on a JASCO-IR-700 spectrometer.
^{1}HNMR spectra were recorded on a Gemini 2000 (300MHz) spectrometer.

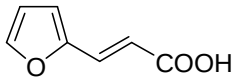
Mass spectra were recorded on a Jeol JMS-DX 303 instrument. Optical rotations were measured with a Jasco-DIP-370 digitalpolar-imeter.

Optical purity was determined by HPLC on a Gilson Model-307 instrument equipped with a column with a chiral stationary phase.

Elemental analysis was carried out on CHN analyzer by the Pharmacy Institute, Tohoku University, Japan.

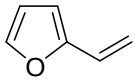
Melting points were determined on a Griffin apparatus and were uncorrected.

3- Furan-2-yl- acrylic acid [85,86].



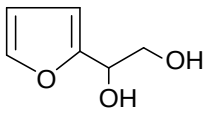
A mixture of furfural (100 g, 1040.0 mmol), malonic acid ((108.1 g, 1040.0 mmol) and pyridine (67.3 mL, 832.5 mmol) was refluxed for 3 h, then cooled to r.t. Neutralize with ammonia solution, acidify with 10% HCl, filter, wash the precipitate with H2O and dry. Spectral data were identical with the reported material.

2- Vinylfuran.



A suspension of Cu_2O (3.3 g, 21.7 mmol) in quinoline (24 mL) was heated at 180 ~ 190 ^{0} C. The carboxylic acid (30g, 217.2 mmol) in quinoline (36 mL) was added dropwise at the same temperature through dropping funnel and the product was distillate at the same temperature.
Spectral data were identical with the reported material. [85,86]

1-(2-Furyl) ethane-1, 2-diol [(±)-4].



To a stirred solution of 2- vinylfuran (**3**) (13 g, 142 mmol) and *N*-methyl-morpholine-*N*-oxide (20 g, 171 mmol) in aq. THF (15:1 v/v 284 mL) OsO_4

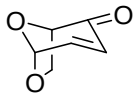
in THF (0.198 M, 0.8 mL, 0.158 mmol) was added at 0 °C and the mixture was stirred at r.t. for 48 h.

The solvent was evaporated under reduced pressure. The residue was extracted with EtOAc and the organic layer was washed with brine, dried over anhydrous $MgSO_4$, evaporated under reduced pressure, and chromatographed (SiO_2, 100 g, elution with EtOAc-hexane, 3: 2 v/v) to give the diol (±)-**4** (16.5 g, 91 %) as a pale yellow oil. Spectral data were identical with those of the optically active material [81]

IR (film): ν = 3359 cm^{-1} .^{1}H NMR (300 MHz, $CDCl_3$): δ =7.40 (1 H, dd, *J* =1.9. 0.8 Hz), 6.37 (1 H, dd, *J* = 3.3, 1.9 Hz), 6.33 (1 H, br d, *J* = 3.3 Hz), 4.82 (1 H, dd, *J* = 10.4, 4.9 Hz), 3.89 (2H, t, *J* = 4.9 Hz), 2.95 (1 H, br d, *J* = 4.9 Hz), 2.13 (1 H, m).

HRMS: *m/z* calcd for $C_6H_8O_3$: 128.0473, found: 128.0472.

(±) - Isolevoglucosenone [(±)-2].



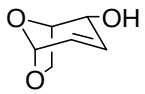
To a stirred solution of **[(±)-4]** (3.06 g, 28.1 mmol) in CH_2Cl_2 (70 mL) *m*-CPBA (70%, 7.62 g, 30.9 mmol) was added at 0 °C and the mixture was stirred at r.t. for 3 h, the mixture was filterd through a Celite-pad; the filtrate was evaporated under reduced pressure to give the crude pyrone (**5**).

The pyrone was dissolved in benzene (94 mL) and refluxed with *p*-TsOH.H_2O (53 mg, 0.28 mmol) for 3 h with removal of water using Dean-Stark apparatus, cooled to rt., the mixture was extracted with EtOAc, the organic layer was washed with Saturated $NaHCO_3$, brine, dried over anhydrous $MgSO_4$, evaporated under reduced pressure, and chromato-graphed (SiO_2, 80 g elution with Et_2O-pentane, 1: 5 v/v) to give **[(±)-2]** (1.56 g, 44%) as a colorless oil.

IR (film); ν = 1714 cm^{-1} · ^{1}H NMR (300 MHz, CDCl3): δ = 7.14 (1 H, dd, *J* = 9.9, 3.3 Hz), 6.11 (1H, dt, *J* = 9.9, 1.1 Hz), 5.82 (1 H, dd, *J* = 3.3, 0.5 Hz), 4.79 (1H, dt, *J* = 6.3, 1.4 Hz), 4.12 (1H,dd, *J* = 8.2, 6.3 Hz), 3.66 (1H, dd, *J* = 8.2, 1.4 Hz).

Mass: *m/z* =126. HRMS: *m/z* calcd for $C_6H_6O_3$: 126.0316, found: 126.0309.

(±) 7,8 -Dioxabicyclo [3.2.1] oct-2-en-4-ol [(±)-6].



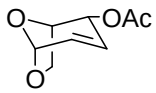
To a stirred solution of **[(±)-2]** (1.1 g, 8.73 mmol) and $CeCl_3.7H_2O$ (3.90 g, 10.5 mmol) in MeOH (30 mL) $NaBH_4$ (395 mg, 10.5 mmol) was added at 0 °C, the mixture was stirred for 10 min at the same temperature.

The mixture was evaporated under reduced pressure and the residue was dissolved in EtOAc (50 mL). The solution was washed with H_2O and brine, the organic layer was dried over anhydrous $MgSO_4$, evaporated under reduced pressure, and chromatographed (SiO_2, 30 g, elution with Et_2O - hexane, 1: 2 v/v) to give **[(±)-6]** (1.01g, 90%) as a colorless oil.

IR (film): ν = 3433 cm^{-1}.^{1}HNMR (300 MHz, $CDCl_3$): δ =5.90 (1 H, ddd, *J* = 9.9, 3.0, 1.6 Hz), 5.72 (1H, dt, *J* = 9.6, 1.4 Hz), 5.52 (1H, d, *J* = 3.0 Hz), 4.85 - 4.80 (1H, m), 4.56-5.51 (1H, m), 4.20 (1H, dd, *J* = 8.2, 1.9 Hz), 3.95 - 3.90 (1H, m), 1.77 (1H, br d, *J* = 5.8 Hz).

HRMS: *m/z* calcd for $C_6H_8O_3$: 128.0473, found: 128.0490.
Anal. Calcd for $C_6H_8O_3$: C 56.24 H 6.29, found: C 55.97 H 6.36.

(±) -7,8 –Dioxabicyclo [3.2.1] oct-2-en-4-yl acetate [(±)-7].



To a stirred solution of **[(±)-6]** (400 mg, 3.12 mmol) and pyridine (758 μL, 9.36 mmol) in CH_2Cl_2 (20 mL), Ac_2O (885 μL, 9.36 mmol) was added at r.t, the mixture was stirred for 12 h. The mixture was diluted with Et_2O, washed successively with 10% HCl, water and brine, the organic layer was dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed (SiO_2 15 g, elution with Et_2O/ hexane, 1:3 v/v) to give the acetate **[(±)-7]** (500 mg, 94%) as a pale yellow oil.

IR (film): ν = 1738 $cm^{-1.}$ ^{1}H NMR (300 MHz, $CDCL_3$): δ = 5.98 (1H, ddd, J= 9.6, 3.0, 1.6 Hz), 5.77 - 5.75 (1H, m), 5.69 (1H, dt, *J* = 9.6, 1.9 Hz), 5.55 (1H, d, *J* = 3.0 Hz), 4.69-4.65 (1H, m), 4.16 (1H, dd, *J* = 8.0, 1.9 Hz), 3.96-3.91 (1H, m), 2.10 (3 H, s).

HRMS: m/z calcd for $C_8H_{10}O_4$: 170.0578, found: 170.0571.
Anal. Calcd for $C_8H_{10}O_4$: C 56.47 H 5.92, found: C 56.51 H 5.86.

Kinetic transesterification of the racemic alcohol [(±)-6].

A solution of **[(±)-6]** (700 mg, 5.46 mmol) and vinyl acetate (5.03 mL, 54.6 mmol) in THF (11 mL) was stirred with Lipase AK (immobilized on Celite,

Pseudomonas sp., Amano) (350 mg) at r.t. for 33h. The mixture was filtrated through a Celite-Pad, the filtrate was evaporated under reduced pressure and chromatographed (SiO_2, 30 g, elution with Et_2O-Hexane, 1.3 - 1.1 v/v) gave the acetate **[**(-) -(*1R, 4R, 5R*)- **(7)]**, (445 mg, 48%), as pale yellow oil, $[\alpha]_D^{32}$ – 49.0 (*c* 1.12 $CHCl_3$).

The alcohol **[**(+) - (*1S, 4S, 5S*)- **(6)]**, (328 mg, 47%), $[\alpha]_D^{30}$ + 18.1 (*c* 1.08, $CHCl_3$), was obtained as a colorless solid. Optical purity of the product was determined by HPLC using a column with chiral stationary phase [CHIRALCEL OD, elution with *i*-PrOH-Hexane (3:97, v/v) (0.5 mL / min), retention time 18.8 for **[(+)-6]** and 22.8 min for **[(-)-6]** both having > 99% ee after transformation into the benzoate.

Kinetic hydrolysis of the racemic acetate [(±) –7].

A mixture of **[(±)-7]** (880 mg, 5.17 mmol) and Lipase AK (immobilized on Celite, Pseudomonas sp., Amano) (880 mg) in 0.1 M phosphate buffer solution (pH 7.2, 18 mL) and acetone (2 mL) was stirred at r.t. for 24 h.

The mixture was filtered through a Celite-pad, the filtrate was evaporated and chromatographed (SiO2, 40 g, elution with Et_2O - Hexane, 1.3 -1.1 v/v) gave the alcohol **[**(-) -(*1R, 4R, 5R*) - **(6)]**, (339 mg, 51%), $[\alpha]_D^{31}$ – 18.4 (*c* 1.00, $CHCl_3$), as a colorless solid and the acetate **[**(+)-(*1S, 4S ,5S*) - **(7)]** (425 mg, 48%), as a pale yellow oil, $[\alpha]_D^{29}$ + 50.0 (*c* 1.20, $CHCl_3$).

Optical purity of the products was determined by HPLC using a column with chiral stationary phase (CHIRALCEL OD elution with *i*-prOH-Hexne (3: 97 v/v) **[**(-)-(*1R, 4R, 5R*) - **(6)]** as 97% ee and [(+) - (*1S, 4S, 5S*) - **(7)**] as 98%ee, respectively.

Conversion of [(-) - (*1R, 4R, 5R*) - (7)] into [(-) - (*1R, 4R, 5R*) - (6)].

A solution of **[**(-)- (*1R, 4R, 5R*) –**(7)**] (360 mg, 2.12 mmol) in MeOH (12 mL) was stirred with K_2CO_3 (1.47 g, 10.6 mmol) at r.t. for 10 min.

The mixture was diluted with H_2O and extracted with Et_2O, the organic layer was washed with brine, dried over anhydrous ($MgSO_4$), evaporated under reduced pressure, and chromatographed (SiO_2, 10 g, elution with Et_2O-hexane, 1:2 v/v) gave **[**(-)- (*1R, 4R, 5R*)- **(6)]** (250 mg, 92%) as a colorless oil.

Conversion of [(+)- (*1S, 4S, 5S*)- (7)] into [(+)- (*1S, 4S, 5S*)- (6)].

A solution of **[**(+)-(*1S, 4S, 5S*)-**(7)]** (420 mg, 2.47 mmol) in MeOH (15 mL) was stirred with K_2CO_3 (1.71gm, 12.4 mmol) at r.t. for 10 min. The mixture was diluted with H_2O and extracted with Et_2O, the organic layer was washed with brine, dried over anhydrous ($MgSO_4$), evaporated under reduced pressure, and chromatographed (SiO_2, 10 g, elution with Et_2O-hexane, 1:2 v/v) gave **[**(+)- (*1S, 4S, 5S*)- **(6)]** (291 mg, 92%) as a colorless oil.

[(-)- (*1S, 5S*)] - Isolevoglucosenone from [(+)- (*1S, 4S, 5S*)- (6)].

To a stirred solution of **[**(+)- (*1S, 4S, 5S*)- **(6)]** (250 mg, 1.95 mmol) in CH_2Cl_2 (15 mL) MnO_2 (3.39 g, 39.0 mmol) was added, the mixture was stirred at r.t. for 2 h.

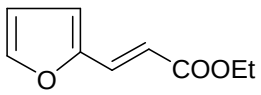
The mixture was filtrated through a Celite-pad, the filtrate was evaporated under reduced pressure and chromatographed (SiO_2, 10 g, elution with Et_2O-pentane, 1 :5 v/v) gave **[**(-)- (*1S, 5S*)-**(2)],** (206 mg, 84%), as a colorless oil, $[\alpha]_D^{30}$ - 428.0 (*c* 1.10, $CHCl_3$). [Lit. [69] $[\alpha]_D^{30}$ – 312.0 (*c* 1.0, $CHCl_3$, 93% ee).

(+) - (*1R, 5R*)] - Isolevoglucosenone from [(-)- (*1R, 4R, 5R*)- (6)].

To a stirred solution of [(-)- (*1R, 4R, 5R*)- **(6)**] (330 mg, 2.48 mmol) in CH_2Cl_2 (15 mL) MnO_2 (4.48 g, 51.6 mmol) was added at r.t, the mixture was stirred at for 2 h.

The mixture was filtered through a Celite-pad, the filtrate was evaporated under reduced pressure and chromatographed (SiO_2, 10 gm, elution with Et_2O-pentane, 1:5 v/v) gave [(+)- (*1R, 5R*)- **(6)**], (266 mg, 82%) as a colorless oil, $[\alpha]_D^{31}$ + 425.0 (*c* 1.10, $CHCl_3$). [Lit. [69] $[\alpha]_D^{31}$ + 321.0 (*c* 1.1, $CHCl_3$, 90% ee).

Ethyl (E) -3- (2-furfuryl) acrylate.



To a stirred suspension of NaH (60% in oil, 12.5 g, 0.3 mol) in THF (450 mL), triethylphosphone acetate (72 mL, 0.36 mol) was added at 0 ^oC and the mixture was stirred for 30 min.

The furfural (25 g, 0.26 mol) in THF (50 mL) was added dropwise at the same temperature, the mixture was stirred at r.t. for 30 min, diluted with Et_2O and H_2O .

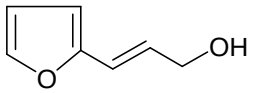
The organic layer was separated, washed with brine and dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and chromatographed (SiO_2 , 500 g, elution with AcOEt-hexane 1:10v/v) afforded pure (E) acrylate (42.1 g, 97%) as pale yellow oil.

IR (film) ν =1716, 1640 cm^{-1}.^{1}HNMR ($CDCL_3$, 500MHz); δ = 7.46 (d, 1H, *J* = 1.8 Hz), 7.42 (d, 1H, *J* = 15.3 Hz), 6.59 (d, 1H, *J* = 3.7 Hz), 6.45 (dd, 1H, *J* = 3.7, 1.8,Hz), 6.3(d, 1H, *J* = 15.3 Hz), 3.77 (s, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): 166.9, 150.9, 144.6, 130.8, 115.8, 114.5, 112.1, 60.1, and 14.0.

HRMS calcd for $C_8H_8O_3$ [M^+] 165.9925, found 165.9921.

(E) -3- (2-Furfyryl) prop-2-en-1-ol.

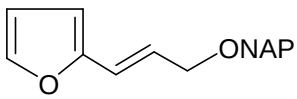


To a stirred solution of of LAH (3.7 g, 96.4 mmol) in Et_2O (400 mL) the acrylate (20 g, 120.4mmol) was added at 0 ^{o}C and the mixture was stirred at the same temperature for 1 h.

The excess hydride was quenched with by addition of 28% NH_4OH and filtered through Celite pad after 2 h, the filtrate was evaporated under reduced pressure and chromatographed (SiO2 400 g, elution with AcOEt-hexane 1:1) to afford (14.8 g, 97%) as pale yellow oil.

IR (film): ν =3328$cm^{-1.}$ ^{1}HNMR ($CDCl_3$, 300MHz): δ = 7.35 (d, 1H, *J* = 1.5 Hz), 6.45 (dt, 1H, *J* = 15.9, 1.2 Hz), 6.37 (dd, 1H, *J* = 3.3, 1.5 Hz), 6.30 (dt, *J* = 15.9, 5.7 Hz), 6.25 (d, 1H, *J* = 3.3 Hz), 4.30 (d, 2H, *J* = 5.7 Hz), 1.49 (br d, 1H). HRMS calcd for C_7 H_8O_2 [M^+] 124.0524. found 124.0482.

(E) -3- (2-Furyl) prop-2-enyl (2-naphthylmethyl) Ether (8a).



To a stirred solution of (E)-3-(2-furyl) prop-2-en-1-ol (8.74 g, 70.48 mmol) in THF (150 mL), NaH (60% in oil, 4.2 g, 105.72 mmol) was added at 0 ^{o}C. After the H_2 gas evolution had ceased, 2-bromomethylnaphthalene (25 g, 112.77 mmol) and Bu_4NI (2.6 g, 70.48 mmol) were added to the mixture at the same temperature and stirred for 8 h at r.t.

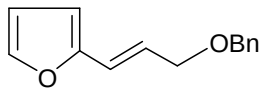
The mixture was then diluted with Et_2O and H_2O, extract the mixture with EtOAc (100 mL). The organic layer was washed with H_2O and brine, dried over anhydrous $MgSO_4$, evaporated under reduced pressure and chromatographed on silica gel column (200 g, eluion with EtOAc-hexane, 1: 200 then 1: 30) gave **(8a)** (6.1 g, 95%) as pale yellow oil.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.68-7.78 (m, 4H), 7.50-7.43 (m, 3H), 7.35 (br d, 1H, *J* = 1.7 Hz), 6.48 (d, 1H, *J* = 15.9 Hz), 6.36 (dd, 1H, *J* = 3.3, 1.7 Hz), 6.28 (dt, 1H, *J* = 15.9, 5.8 Hz), 6.24 (d, 1H, *J* = 3.3 Hz), 4.72 (s, 2H), 4.20 (dd, 2H, *J* = 5.8, 1.4 Hz).

HRMS: m/z calcd for $C_{18}H_{16}O_2$ [M^+] 264.1150. found 264.1132.

.

Benzyl (E) -3- (2-Furyl) prop-2-enyl Ether (8b).



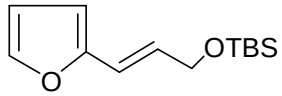
To a stirred solution of (E)-3-(2-furyl) prop-2-en-1-ol (3.70 g, 30 mmol) in THF (70 mL), NaH (60% in oil, 1.5 g, 36 mmol) was added at 0 ^{o}C. After the H_2 gas evolution has ceased, benzyl bromide (4.7 mL, 39 mmol), the mixture at the same temperature and stirred for 5 h at r.t.

The mixture was then diluted with Et_2O and H_2O, extract the mixture with EtOAc (100 mL). The organic layer was washed with H_2O and brine, dried over anhydrous $MgSO_4$, evaporated under reduced pressure and chromatographed on silica gel column (100g, eluion with EtOAC-hexane, 1: 200 then 1:30) gave **(8b)** (6.1 g, 95%) as a colorless oil.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.3 - 7.28 (m, 6H), 6.46 (br d, 1H, *J* =15.8 Hz), 6.36 (dd, 1H, *J* = 3.3, 1.8 Hz), 6.25 (dt, 1H, *J* = 15.8, 5.9 Hz), 6.24 (d, 1H, *J* = 3.3 Hz), 4.57 (s, 2H), 4.17 (dd, 2H, *J* = 5.9, 1.1 Hz).

HRMS: m/z calcd for $C_{14}H_{14}O_2$ [M^+] 214.0993. found 214.0992.
Anal. Calcd for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59 found: C, 78.39; H, 6.36.

Tert-**Butyldimethylsillyl (E) -3- (2-furyl) prop-2-enylether (8c).**



A mixture of (E)-3-(2-furyl) prop-2-en-1-ol (1.03 g, 8.34 mmol), Et_3N ((1.47 mL, 12.5 mmol), *tert*-butyldimethylchlorosilane (1.51 g, 10 mmol) and 4-(*N*,*N*-dimethylamino) pyridine (DMAP) in CH_2CL_2 (20 mL) was stirred at r.t. for 4 h.

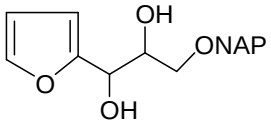
Extract the mixture with AcOEt, the organic layer was washed with H_2O and brine, dried over anhydrous $MgSO_4$, evaporated under reduced pressure and chromatographed on silica gel column (30 g, eluion with EtOAc-hexane, 1: 100) gave **(8c)** (1.95 g, 98%) as yellow oil.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.33 (d, 1H, *J* =1.8 Hz), 6.43 (dt, 1H, *J* =15.7, 1.8 Hz), 6.36 (dd, 1H, *J*=3.2, 1.8 Hz), 6.23 (dt, 1H, *J*= 15.7, 4.6 Hz), 6.21 (d, 1H, *J*= 3.2 Hz), 4.33 (dd, 2H, *J* = 4.6, 1.8 Hz), 0.93 (s, 9H), 0.10 (s, 6H),

^{13}C NMR (CDCl3), 75 MHz): δ =153.1, 141.8, 128.1, 117.8, 113, 107.3, 63.3, 52.9, 18.4, -5.3.

HRMS: m/z calcd for $C_{14}H_{14}O_2Si$ [M^+] 238.1389. found 238.1381.

(±) - (*1RS, 2SR*) -1- (2-Furyl) –3-(2-naphthylmethyloxy)-Propane-1, 2-diol [(±)-9a].



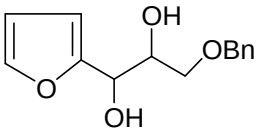
To a stirred solution of **(8a)** (1.8g, 6.8 mmol) and *N*-methylmorpholine *N*-oxide (NMO) (985 mg, 8.2 mmol) in THF-H2O (1:1 v/v, 30 mL), OsO_4 (0.2 M in THF, 350 µL, 70 mmol) was added at 0 ^{o}C, the mixture was stirred at r.t. for 10 h, the mixture was diluted with Saturated aqueous Na_2SO_3 (10 mL) and stirred for 10 min.The mixture was extracted with EtOAc, the extract was washed with H_2O and brine, dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The residue was chromatographed on a silica gel column (100 g, elution with hexane-EtOAc, 3:1 v/v) gave the diol **[**(±)-**9a]** (1.73 g, 85%) as colorless needles; mp 83-85 ^{o}C (EtOAc).

IR (nujol): *v* = 3379 cm-^{1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.85-7.81 (m, 3H), 7.75 (s, 1H), 7.52 - 7.43 (m, 3H), 7.36 (t, 1H, *J* = 1.1Hz), 6.34 - 6.31 (m, 2H), 4.78 (d, 1H, *J* = 4.7 Hz), 4.74 (d, 1H, *J* = 11.7 Hz), 4.74 (d, 1H, *J* = 11.7 Hz), 4.16 - 4.09 (m, 1H), 3.62 (dd, 1H, *J* = 9.8, 3.8 Hz), 3.53 (dd, 1H, *J* = 9.8, 5.5 Hz), 2.95 (d, 1H, *J* = 4.7 Hz), 2.76 (d, 1H, *J* = 5.2Hz).

HRMS: *m/z* calcd for $C_{18}H_{18}O_4$ [M^+] 298.1205 found. 298.1206.

Anal, calcd for $C_{18}H_{18}O_4$: C, 72.47; 6.08. found C, 72.57; H, 6.36.

(±) - (*1RS, 2SR*) -3- Benzyloxy-1- (2-furyl)-Propane-1, 2-diol [(±)-9b].

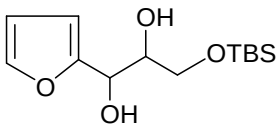


The ether **(8b)** (40g, 1.87 mmol) was treated with OsO_4 (0.2 M in THF, 9.5 mL, 1.87 mmol) in the presence of NMO (26.2 g) in THF-H2O (1:1 v/v. 600 mL) at 0 ^{o}C and the mixture was stirred at r.t. for 15 h. The mixture was diluted with Saturated aqueous Na_2SO_3 (10 mL) and stirred for 10 min.

The mixture was extracted with EtOAc, the extract was washed with H_2O and brine, dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The residue was chromatographed on a silica gel column (500 g, elution with hexane-EtOAc, 2:1 v/v) gave the diol **[(±)-9b]** (43.9g, 95%) as colorless needles; mp 37.0-38.0 ^oC (EtOAc).

IR (nujol): ν = 3406 cm^{-1} ^1H NMR ($CDCl_3$, 300 MHz): δ = 7. - 7.27 (m, 6H), 6.35 - 6.32 (m, 2H), 4.75 (dd, 1H, *J* = 5.5, 4.8 Hz), 4.57 (d, 1H, *J* = 11.7 Hz), 4.51(d, 1H, *J* = 11.7 Hz), 4.13 - 4.06 (m, 1H), 3.38 (dd, 1H, *J* = 9.9, 3.7 Hz), 3.94 (dd, 1H, *J* = 9.9, 5.5 Hz), 2.97 (d, 1H, *J* = 4.4 Hz), 2.75 (d, 1H, *J* = 5.5 Hz).

HRM*: m/z* calcd for $C_{14}H_{16}O_4$ [M^+] 248.1048. found 248.1033.
Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. found C, 67.54; H,6.65



(±) - (*1RS, 2SR*) -3- *tert*-Butyldimethylsilyloxy-1-(2-furyl)-Propane-1, 2, -diol [(±)-9c].

The ether **(8c)** (18 g, 75.6 mmol) was treated with OsO_4, (0.2 M in THF, 3.8 mL, 756 mmol) and NMO (10.6 g, 90.7 mmol) in THF-H2O (1:1 v/v, 360 mL) at 0 ^oC and the mixture was stirred at r.t. for 18 h. The mixture was diluted with Saturated aqueous Na_2SO_3 (10 mL) and stirred for 10 min.

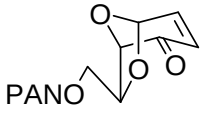
The mixture was extracted with EtOAc, the extract was washed with H_2O and brine, dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The residue was chromatographed on a silica gel column (400 g, elution with hexane-EtOAc, 2.5: 1 v/v) gave the diol **[(±)-9c]** (17.8g, 86%) as colorless oil.

IR (film): ν =3404 cm^{-1}. ^1H NMR ($CDCL_3$, 300 MHz): δ = 7.40 (t, 1H, *J* = 1.4 Hz), 6.36 (d, 2H, *J* = 1.4 Hz), 4.74 (dd, 1H, *J* = 5.5, 4.1 Hz), 3.98 - 3.92 (m, 1H), 3.72 (dd, 1H,*J* = 10.4 Hz), 3.61 (dd, 1H, *J* = 10.4, 4.9 Hz), 3.16 (d, 1H, *J* = 4.1 Hz), 2.72 (d, 1H, *J* = 6.3 Hz), 0.91 (s, 9H), 0.07 (s, 6H).

$^{13}CNMR$ ($CDCl_3$, 75 MHz): δ =153.9, 142.3, 128.1, 110.3, 107.6, 73.1, 68.2, 63.9, 25.7, and 18.1, -5.7.

HRMS: *m/z* calcd for $C_{13}H_{23}O_3Si$ [M - OH] 255.1417. Found 255.1418.
Anal. Calcd for $C_{13}H_{24}O_4Si$: C, 57.32; H, 8.89. Found C, 57.34; H, 8.88.

(±) -7- (2-Naphthylmethyloxymethyl)-6,8-dioxabicyclo [3.2.1] oct-3-en-one. [(±)-11a].



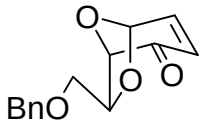
To a stirred solution of **[(±)-9a]** (4.61 g, 15.47 mmol) in CH_2Cl_2 (100 mL), *m*-CPBA (70%, 4.19 g, 17.01 mmol) was added at 0 ^oC and the mixture was stirred at r.t. for 3 h.

The mixture was filtered through a Celite pad and evaporated under reduced pressure to give the crude pyranone **(10a)**. Without purification, the crude **(10a)** was then refluxed in benzene (100 mL) in the presence of *p*-TsOH (29 mg, 0.15 mmol) for 10 h, cooled to r.t, the mixture was extracted with EtOAc (100 mL), the organic layer was washed with Saturated aqueous $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on a silica gel column (100 g, elution with hexane-EtOAc, 8:1 v/v) gave the bicyclic enone **[(±)-11a]** (3.11 g, 68%) as colorless prisms; m.p 80 - 83 ^oC (hexane-EtOAC).

IR (film): ν =1700 cm^{-1} ^1H NMR ($CDCL_3$, 300 MHz): δ = 7.68 - 7.82 (3H, m), 7.77 (1H, s), 7.52 - 7.45 (3H, m), 7.12 (1H, dd, *J* = 9.9, 3.2 Hz), 6.09 (d, 1H, *J* = 9.9 Hz), 5.83 (d, 1H, *J* = 3.2 Hz), 4.67 (s, 2H), 4.62 (t, 1H, *J* = 1.2 Hz), 4.04 (dt, *J* = 5.5, 1.4 Hz), 3.76 (dd, 1H, *J* = 10.0, 5.6 Hz), 3.57 (dd, 1H, *J* = 10.0, 6.6 Hz).

HRMS calcd for $C_{18}H_{16}O_4$ [M^+] 296.1048, found 296.1027.

(±) - 7-Benzyloxymethyl-6, 8-dioxabicyclo-[3.2.1]-oct-3-en-2-one. [(±)-11b].



The diol **[(±)-9b]** (20 g, 80.6 mmol) was treated with *m*-CPBA (70%, 30g, 120.9 mmol) in CH_2Cl_2 (400 mL)) at 0 ^oC and the mixture was stirred at r.t. for 2 h.

The mixture was filtered through a Celite pad and evaporated under reduced pressure to give the crude pyranone **(10b)**. Without purification, the crude **(10b)** was then refluxed in benzene (400 mL) in the presence of *p*-TsOH (200 mg, 1.05 mmol) for 18 h, cooled to r.t, the mixture was extracted with EtOAc (200 mL) and the organic phase was washed with Saturated aqueous $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on a silica gel column (400 g, elution with hexane-EtOAc, 5:1 v/v) gave the bicyclic enone **[(±)-11b]** (13.3 g, 67%) as as colorless prisms; m.p 56 - 58 0 ^oC (hexane-EtOAC).

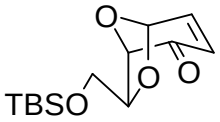
IR (film): ν =1721, 1690 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ =7.3 - 7.19 (m, 5H), 7.05 (dd, 1H, *J* = 9.8, 3.1 Hz), 6.01 (d, 1H, *J* = 9.8 Hz), 5.75 (d, 1H, *J* = 3.1 Hz), 4.52 (s, 2H), 3.96 - 3.93 (m, 1H), 3.56 (dd, 1H, *J* = 9.8, 6.1 Hz), 3.46 (dd, 1H, *J* = 9.8, 6.8 Hz).

^{13}C ($CDCl_3$, 125 MHz): δ =194.0, 147.3, 137.6, 128.5, 127.9, 127.8, 126.6, 81.8, 73.5, 73.0, and 69.8.

FABMS: *m/z* = 245 [M^+-1].

Anal. Calcd for $C_{14}H_{14}O_4$: C, 68.28; H; 5.73. Found C, 67.96; H, 5.93.

(±) - 7-*tert*-butyldimethylsiloxymethyl-6, 8-dioxabicyclo[3.2.1] oct-3-en-2-one. [(±)-11c].

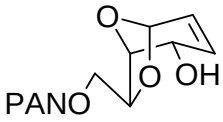


The diol **[(±)-9c]** (3.61 g, 13.2 mmol) was treated with *m*-CPBA (70%, 3.59 g, 14.6 mmol) in CH_2Cl_2 (80 mL) at 0 ^oC and the mixture was stirred at r.t. for 2 h. The mixture was filtered through a Celite pad and evaporated under reduced pressure to give the crude pyranose **(10c)**. Without purification, the crude **(10c)** was then refluxed in benzene (100 mL) in the presence of *p*-TsOH (25 mg, 0.13 mmol) for 6h, cooled to r.t, the mixture was extracted with EtOAc (100 mL) and the organic layer was washed with Saturated aqueous $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure and the residue was chromatographed on a silica gel column (100 g, elution with hexane-EtOAc, 10:1 v/v) gave the bicyclic enone **[(±)-11c]** (2.47 g, 69%) as pale yellow oil.

IR (film) *v* = 1701 $cm^{-1.}$ ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.12 (1H, dd, *J* = 9.8, 3.2 Hz), 6.08 (dd, 1H, *J* = 9.8, 1.1 Hz), 5.79 (d, 1H, *J* = 3.2 Hz), 4.61 (t, 1H, *J* = 1.1 Hz), 3.88 (m, 2H), 3.58 (1H, dd, *J* = 9.9, 7.1 Hz), 0.9 (s, 9H), 0.08 (s, 6H).

HRMS calcd for $C_{12}H_{19}O_4Si$ [M - CH_3] 255.1053, found 255.1008.

(±) - (*1RS, 2SR, 5SR, 7RS*) -7- (2-Naphthylmethyloxymehyl) -6,8-dioxabicyclo [3.2.1] oct-3-en-2-ol. [(±)-12a].



To a stirred solution of **[(±)-11a]** (595 mg, 2 mmol) and $CeCl_3.7H_2O$ (899 mg, 2.4 mmol) in MeOH (12 mL), $NaBH_4$ (91 mg, 2.4 mmol) was added at 0 ^oC and the mixture was stirred for 15 min at the same temperature.

The solvent was evaporated under reduced pressure, the residue was dissolved in EtOAc (60 mL) and the organic layer was washed with H_2O and brine, dried over anhydrous $MgSO_4$, and evaporated under reduced pressure.

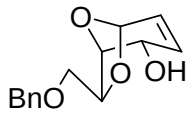
The residue was chromatogr-aphed on a silica gel column (60 g, elution with hexane-EtOAc, 4: 1 v/v) gave the alcohol) **[(±)-12a]** (555 mg, 93%) as colorless needles; m.p 80 - 81 ^oC (hexane/EtOAc).

IR (nujol): *v* = 3274 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.85 - 7.82 (m, 3H), 7.78 (s, 1H), 7.51 - 7.44 (m, 3H), 5.90 (ddd, 1H, *J* = 9.9, 3.0, 1.9

Hz), 5.70 (dt, 1H, *J* = 9.9, 1.9 Hz), 5.54 (d, 1H, *J* = 3.0 Hz), 4.80 - 4.72 (m, 3H), 4.54 (ddd, 1H, *J* = 6.0,5.8,1.6 Hz), 4.28 (dt, 1H, *J* = 4.7, 1.6Hz). 3.63 (dd, 1H, *J* = 9.9,5.8 Hz), 3.55 (dd, 1H, *J* = 9.9,6.0 Hz), 1.91 (d, 1H, *J* = 5.5 Hz). HRMS: *m/z* clacd for $C_{18}H_{18}O_4$ [M^+] 298.1205. Found 298.1208.

Anal. Calcd for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08. Found C 72.53; H, 6.19.

(±) - (*1RS, 2SR, 5SR, 7RS*) -7- Benzyloxymethyl-6, 8-dioxabicyclo [3.2.1] oct-3-3n-2-ol. [(±)-12b].



The enone **[(±)-11b]** (1.0 g, 4.1 mmol) was treated with $NaBH_4$ (184 mg, 4.9 mmol) in the presence of $CeCl_3.7H_2O$ (1.8 g, 4.9 mmol) in MeOH (20 mL) at 0^o Cand the mixture was stirred for 15 min at the same temperature.

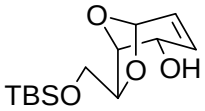
The solvent was evaporated under reduced pressure, the residue was dissolved in EtOAc (60 mL) and the organic layer was washed with H_2O and brine, dried over anhydrous $MgSO_4$, and evaporated under reduced pressure.

The residue was chromatogr-aphed on a silica gel column (80 g, elution with hexane-EtOAc, 6: 1 v/v) gave the alcohol) **[(±)-(12b)]** (984 mg, 98%).

Ir (film): *v* = 3420 cm^{-1} 1H NMR ($CDCl_3$, 300 MHz): δ = 7.38 - 7.26 (m, 5H), 5.91 (ddd, 1H, *J* = 9.6, 3.0, 1.6 Hz), 5.71 (m, 1H), 5.53 (d, 1H, *J* = 3.0 Hz), 4.77 (m, 1H), 4.60 (s, 2H), 4.60 - 4.46 (m, 2H), 4.28 (dt, 1H, *J* = 4.7, 1.9 Hz), 3.95 (dd, 1H, *J* = 9.9, 4.4 Hz) 3.52 (dd, 1H, *J* = 9.9, 6.3 Hz).

HRMS*: m/z* calcd for $C_{14}H_{16}O_4$ [M^+] 248.1049. Found 248.1024.
Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.71; H, 6.49. Found C, 67,43; H, 6.38.

6,8-dioxabicyclo (±) - (*1RS, 2SR, 5SR, 7RS*) -7- *tert*-Butydimethylsiloxymethyl [3.2.1] oct-3-en-2-ol [(±)12c].



The enone **[(±)-11c]** (658 mg, 2.44 mmol) was treated with $NaBH_4$ (411 mg, 2.92 mmol) in the presence of $CeCl_3.7H_2O$ (1.09 g, 2.92 mmol) in MeOH (25 mL) at 0 ^oC and the mixture was stirred for 10 min at the same temperature. The solvent under reduced pressure, the residue was dissolved in EtOAc (60 mL) and the organic layer was washed with H_2O and brine, dried over anhydrous $MgSO_4$, and evaporated under reduced pressure.

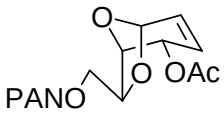
The residue was chromatographed on a silica gel column (60 g, elution with hexane-EtOAc, 10: 1 v/v) gave the alcohol) **[(±)-(12c)]** (654 mg, 99%) as colorless oil.

IR (film) *v* = 3456 $cm^{-1.}$ ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 5.91 (ddd, 1H, *J* = 9.7, 3.2, 1.8 Hz), 5.72 (1H, dtd, *J* = 9.7, 2.0, 0.8 Hz), 5.49 (d, 1H, *J* = 3.2

Hz), 4.80 - 4.75 (m, 1H), 4.32 (ddd, 1H, *J* = 7.1, 5.2, 1.6 Hz), 4.27 (dt, 1H, *J* = 4.7, 1.6 Hz), 3.74 (dd, 1H, *J* = 10.4, 5.2 Hz), 3.58 (dd, 1H, *J* = 10.4, 7.1 Hz), 1.75 (br d, 1H, *J* = 6.0 Hz), 0.89 (s, 9H), 0.07 (s, 6H).

HRMS*: m/z* calcd for $C_9H_{15}O_4$ Si [M^+ - C_4H_9] 215.0740. Found 215.0713.

(±) - (*1RS, 2SR, 5SR, 7RS*) -2-Acetoxy-7-(2-naphthylmethyl-oxymethyl)-6,8- dioxabicyclo [3.2.1] oct-3-ene [(±)-13a].

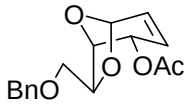


To a mixture of **(12a)** (1.55 g, 5.2 mmol) and pyridine (630 µL, 7.8 mmol) in CH_2Cl_2 (20 mL) Ac_2O (590 µl, 6.2 mmol) was added at r.t and the mixture was stirred for 12 h. The mixture was extracted with EtOAc (120 mL) and the solution was washed with 10% HCl, H_2O and brine, dried over anhydrous $MgSO_4$, evaporated under reduced pres-sure, and the residue was chromatographed on a silica gel column (130 g, elution with hexane-EtOAc, 6:1 v/v) to give the acetate **[(±)-13a]** (1.73 g, 98%) as a pale yellow oil.

IR (film): *v* = 1741 cm^{-1} . ^1H NMR ($CDCl_3$, 300 MHZ): δ = 7.85 - 7.82 (m, 3H), 7.77 (s, 1H), 7.49 - 7.44 (m, 3H), 6.01 (ddd, 1H, *J* = 9.6,3.0, 1.6 Hz), 5.75 - 5.68 (m, 2H), 5.57 (d, 1H, *J* = 3.0 Hz), 4.76 (d, 1H, *J* = 13.7 Hz), 4.71 (d, 1 H, *J* = 13.7 Hz), 4.53 - 4.48 (m, 2 H), 3.65 (dd, 1H, *J* = 9.6, 5.4 Hz), 3.51 (dd, 1H, *J* = 13.7 Hz), 4.53 - 4.48 (m, 2H), 3.65 (dd, 1H, *J* = 9.6, 5.4 Hz), 3.51 (dd, 1H, *J* = 9.6, 6.9 Hz), 2.00 (s, 3 H).

HRMS: *m/z* calcd for $C_{20}H_{20}O_5$: [M^+] 340.1259 found 340.1302.
Anal. Calcd. For $C_{20}H_{20}O_5$ C, 70.57; H, 5.92. Found C, 70.60; H, 5.92.

(±) - (*1RS, 2SR, 5SR, 7RS*) -2-Acetoxy-7-benzyloxymethyl-6,8-dioxabicyclo [3.2.1] oct-3-ene [(±)-13b].



The alcohol **[(±)-12b]** (1.0 g, 4.0 mmol) was treated with Ac_2O (431µl, 4.8 mmol) and pyridine (485 µl, 6.0 mmol) in CH_2Cl_2 (20 mL) at r.t and the mixture was stirred for 12 h.

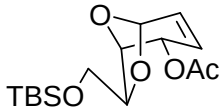
The mixture was extracted with EtOAc (120 mL) and the organic layer was washed with 10% HCL, H_2O and brine, dried over anhydrous $MgSO_4$, evaporated under reduced pressure, and the residue was chromatographed on a silica gel column (100 g, elution with hexane-EtOAC, 5:1 v/v) to give the acetate **[(±)-13b]** (1.1 g, 94%) as a colorless oil.

IR (film): *v* = 1743 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHZ): δ = 7.38 - 7.20 (m, 5H), 6.00 (ddd, 1H, *J* = 9.3, 3.3,1.4 Hz), 5.73 (m, 1H), 5.73 (d, 1H, *J* = 2.2 Hz), 5.56 (d, 1H, *J* = 3.3 Hz), 4.59 (d, 1H, *J* = 12.1 Hz), 4.55 (d, 1H , *J* =

12.1 Hz), 4.50 - 4.44 (m, 2H), 3.61 (dd, 1H, *J* = 9.6, 5.5 Hz), 3.45 (dd, 1H, *J* = 9.6,6.9 Hz), 3.01 (s, 3H).

HRMS: *m/z* calcd for $C_{16}H_{18}O5$ [M^+] 290.1153. Found 290.1177.
Anal. calcd for $C_{16}H_{18}O_5$: C, 66.18; H, 6.35. Found C, 66.38; H, 6.55.

(±) - (*1RS, 2SR, 5SR, 7RS*) -2-Acetoxy-7-*tert*-butyldimethylsiloxymethyl-6,8-dioxabicyclo-[3.2.1] oct-3-en-2-one [(±)-13c].



The alcohol **[(±)-12c]** (700 mg, 2.57 mmol) was treated with Ac_2O (323µL, 3.10 mmol) in the presence of pyridine (312 µL, 3.86 mmol) in CH_2Cl_2 (10 mL) at r.t and the mixture was stirred for 12 h .

The mixture was extracted with EtOAc (120 mL) and the solution was washed with 10% HCL, H_2O and brine, dried over anhydrous $MgSO_4$, evaporated under reduced pressure, and the residue was chromatographed on a silica gel column (80 g, elution with hexane-EtOAc, 6:1 v/v) gave the acetate **[(±)-13c]** (750 mg, 93%) as a colorless oil.

IR (film): ν = 1749 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 6.02 (ddd, 1H, *J* = 9.6, 3.0, 1.6 Hz), 5.73 (m, 1H), 5.68 (m, 1H), 5.52 (d, 1H, *J* = 3.0 Hz) , 4.46 (dt, 1H, *J* = 4.7, 1.6 Hz), 4.31 (m, 1H), 3.72 (dd, 1 H, *J* = 9.9, 4.9 Hz), 3.48 (dd, 1H, *J* = 9.9, 8.5 Hz), 2.06 (s, 3H), 0.89 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H). HRMS: *m/z* calcd for $C_{11}H_{17}O_5$ Si [M^+ - C_4H_{10}] 257.0844. Found 257.0847.

Anal. cald $C_{15}H_{28}O_5$ Si: C, 57.11; H, 8.63. Found C, 57.38; H, 8.55.

(-) - (*1S, 2R, 5R, 7S*) -2-Acetoxy-7-(2-naphthylmethyloxymethyl)-6,8-dioxabicyclo- [3.2.1] oct-3-ene. [(-)-13a] *and* (+) - (*1R, 2S, 5S, 7R*) -7-(2-Naphthylmethyloxymethyl -6,8-dioxabicyclo [3.2.1] oct-3-en-2ol. [(+)-12a] *from* the Racemic alcohol [(±)-12a].

To a stirred solution of the racemic alcohol **[(±)-12a]** (370 mg, 1.24 mmol) in THF (9 mL) and vinyl acetate (1.1 mL, 12.4 mmol), lipase Ps (370 mg) was added at r.t and the suspension was stirred for 24 h.

The mixture was filtered through a Celite pad, the filtrate was evaporated under reduced pressure, and the residue was chromatographed on a silica gel column (25 g, elution with hexane-EtOAc, 5 : 1 v/v) to give the acetate **[(-)-13a]** as an oil (175 mg, 47%); $[\alpha]_D^{29}$ - 24.9 (*c* =1.0, $CHCl_3$);

The alcohol **[(+)-12a]** was obtained as colorless needles (153 mg, 47%); $[\alpha]_D^{29}$ + 6.76 (*c* = 1.0, $CHCl_3$); m.p 80-81 ^oC (hexane-EtOAc).

Enantiomeric purities of the products were determined as >99% ee as the acetate **13a** by HPLC using a column with a chiral stationary phase (CHIRALCEL OD, elution with 3% *i*-PrOH-hexane, retntion time: 32.1 min for **[(-)-13a]** and 36.4 min for **[(+)-13a]** (after transformation to acetate) at 0.5 mL/min.).
Spectral data were identical with those of **[(±)-12a]** and **[(±)-13a].**

(-) - (*1S, 2R, 5R, 7S*) -2-Acetoxy-7-benzyloxymethyl-6,8-dioxabicyclo [3.2.1] 0ct-3-ene [(-)-13b]. *and* (+) - (*1R, 2S, 5S, 7R*) -7-benzyloxymethyl-6,8-dioxabicyclo [3.2.1] oct-3-en-2-ol [(+)-12b]. *from* the Racemic Alcohol [(±)-12b].

The racemic alcohol **[(±)-12b]** (1.0 g, 4.0 mmol) was treated with lipase Ps (1.0 g) in THF (20 mL) in the presence of vinyl acetate (3.7 mL, 40 mmol) at r.t and the suspension was stirred for 24 h.

The mixture was filtrated through a Celite pad, the filtrate was evaporated under reduced pressure, and the residue was chromatographed on a silica gel column (40 g, elution with hexane-EtOAc, 5:1 v/v) to give the acetate **[(-)-13b]** as an oil (590 mg, 50%); $[\alpha]_D^{26}$ - 24.8 (*c* =1.1, $CHCl_3$);

The alcohol **[(+)-12b]** was obtained as colorless oil (450 mg, 49%); $[\alpha]_D^{27}$ + 5.4 (*c* = 1.1, $CHCl_3$); Enantiomeric purities of the products were determined as > 99% ee as the acetate **(13b)** by HPLC using a column with a chiral stationary phase (CHIRALCEL OD, elution with 3% *i*-PrOH-hexane, retention time: 24.7min for **[(-)-13b]** and 42.4 min for **[(+)-13b]** (after transformation to acetate) at 0.5 mL/min.). spectral data of the product were identical with those of the racemates.

(-) - (*1S, 2R, 5R, 7S*) -2-Acetoxy-7-*tert*-butyldimethylsiloxymethyl-6,8-dioxabicyclo- [3.2.1] oct-3-ene [(-)-13c]. *and* (+) - (*1R, 2S, 5S, 7R*)-7-*tert*-butydimethylsiloxymethyl - 6,8-dioxabicyclo-[3.2.1] oct-3-en-ol [(+)-12c]. *from* the Racemic Alcohol [(±)-12c].

The racemic alcohol **[(±)-12c]** (200 mg, 0.73 mmol) in THF (4 mL) was treated with lipase PS (200 mg) in the presence of vinyl acetate (677 ML, 7.3 mmol) at r.t and the suspension was stirred for 24 h.

The mixture was filtered through a Celite pad, the filtrate was evaporated under reduced pressure, and the residue was chromatographed on a silica gel column (30g, elution with hexane-EtOAc, 10 : 1 v/v) to give the acetate **[(-)-13c]** as colorless needles; m.p 44 - 46 ^oC (114 mg, 49%); $[\alpha]_D^{26}$ – 16.5 (*c* =1.0, $CHCl_3$); the alcohol **[(+)-12c]** as colorless needles (96 mg, 49%); $[\alpha]_D^{26}$ + 2.6 (*c* = 1.0, $CHCl_3$); m.p 48 - 50 ^oC (hexane-EtOAc). Enantiomeric

purities of the products were determined as >99% ee as the acetate **(13c)** by HPLC using a column with a chiral stationary phase (CHIRALCEL OD, elution with 1% *i*-PrOH-hexane, retntion time: 11.5 min for **[(-)-13c]** and 22.7 min for **[(+)-13c]** (after transform-ation to benzoate) at 0.5 mL/min.

Spectral data of the product were identical with those of the racemates.

(-) - (*1S, 2R, 5R ,7S*) -7-(2-Naphthylmethyloxymethyl)-6,8-dioxabicyclo [3.2.1] oct-3-en-2-ol [(-)-12a]. *and* (+) - (*1R, 2S, 5S, 7R*) -2-Acetoxy-7-(2naphthylmethyloxymeth-yl)-6,8-dioxabicyclo-[3.2.1]-oct-3-ene[(+)13a]. *from* the Racemic Acetate [(±)-13a].

To a stirred solution of the racemic acetate **[(±)-13a]** (360 mg, 1.18 mmol) in 0.1 M phosphate buffer (pH 7.0, 8.1 mL) and acetone (0.9 mL) lipase Ps (360 mg) was added at r.t and the suspension was stirred for 24 h.

The mixture was filtrated through a Celite pad, the filtrate was extracted with EtOAc (50 mL). The extract was washed with H_2O and brine, dried ($MgSO_4$), and evaporated under reduced pressure, and the residue was chromatographed on a silica gel column (40 g, elution with hexane-EtOAc, 5:1 v/v) to give the acetate **[(+)-13a]** as an oil (166 mg, 46%); $[\alpha]_D^{30}$ + 23.9 (*c* =1.0,$CHCl_3$);

The alcohol **[(-)-12a]** was obtained as colorless needles (145 mg, 46%); $[\alpha]_D^{28}$ - 6.15 (*c* 0.8, $CHCl_3$); m.p 79 - 81^oC (hexane-EtOAc).

Enantiomeric purities of the products were determined as > 99% ee as the acetate **(13a)** by HPLC using a column with a stationary phase (CHIRALCEL OD, elution with 3% *i*-PrOH-hexane). Spectral data of both products were idential with those of **[(±)-12a]** and **[(±)-13a].**

(-) - (*1S, 2R, 5R, 7S*) -7-Benzyloxymethyl-6,8-dioxabicyclo [3.2.1]-oct-3-en-2-ol[(-)-12b] *and* (+) (*1R, 2S, 5S, 7R*) -2-Acetoxy-2-benzyloxymethyl-6,8-dioxabicyclo- [3.2.1] oct-3-ene [(+)-13b]. *from* the Racemic Acetate [(±)-13b].

The racemic acetate **[(±)-13b]** (500 mg, 1.7 mmol) in a mixture of 0.1 M phosphate buffer (pH 7.0, 9mL) and acetone (1 mL) was treated with lipase PS (500 mg)) at r.t and the suspension was stirred for 24 h.

The mixture was filtrated through a Celite pad, the filtrate was extracted with EtOAc (50 mL), and the extract was washed with H_2O and brine, dried over anhydrous $MgSO_4$, and evaporated under reduced pressure.The residue was chromatographed on a silica gel column (30 g, elution with hexane-EtOAc, 5:1 v/v) to give the acetate **[(+)-13b]** as an oil (245 mg, 49%); $[\alpha]_D^{26}$

+ 25.1 (*c* =1.0, $CHCl_3$); The alcohol **[(-)-12b]** as colorless oil (205 mg, 46%); $[\alpha]_D^{24}$ - 5.6 (*c* 1.0, $CHCl_3$); Enantiomeric purities of the products were determined as > 99% ee as the acetate **(13a)** and alcohol **(12b)** (after transformation to acetate) by HPLC using a column with a stationary phase (CHIRALCEL OD, elution with 3% *i*-PrOH-hexane). Spectral data of both proiducts were idential with those of **[(±)-12b]** and **[(±)-13b].**

(-) - (*1S, 2R, 5R, 7S*) -7-*tert*-Butyldimethylsiloxymwthyl-6,8-dioxabicyclo [3.2.1] oct-3-en-2-ol [(-)-12c] *and* (+) -(*1R, 2R, 5S, 7R*) -2-Acetoxy-7-*tert*-butyldimethylsiloxy-methyl -6,8-dioxabicyclo [3.2.1] -oct-3-ene [(+)-13c] *from* the Racemic Acetate [(±)-13c].

A mixture of the racemic acetate **[(±)-13c]** (150 mg, 0.48 mmol), 0.1 M phosphate buffer (pH 7.0, 2.7 mL) and acetone (0.3 mL) was treated with lipase PS (150 mg) at r.t and the suspension was stirred for 24 h.

The mixture was filtrated through a Celite pad, the filtrate was extracted with EtOAc (50 mL), and the extract was washed with H_2O and brine, dried over anhydrous $MgSO_4$, and evaporated under reduced pressure. Te residue was chromatographed on a silica gel column (20 g, elution with hexane-EtOAc, 10:1 v/v) to give the acetate **[(+)-13c]** as an needeles (73 mg, 49%); $[\alpha]_D^{28}$ + 15.5 (*c* =1.0, $CHCl_3$); m.p; 36 - 38(hexane-AtOAc) .

The alcohol **[(-)-12c]** was obtained as colorless needeles (63 mg, 49%); $[\alpha]_D^{24}$ - 2.8 (*c* 1.1, $CHCl_3$); Enantiomeric purities of the products were determined as > 99% ee as benzoate **(13c)** and alcohol **(12c)** (after transformation to benzoate) by HPLC using a column with a stationary phase (CHIRALCEL OD, elution with 1% *i*-PrOH-hexane). Spectral data of both products were idential with those of **[(±)-12c]** and **[(±)-13c].**

(-) - (*1S, 2R, 5R, 7S*) -7-(2-Naphthylmethyloxymethyl)-6,8-dioxabicyclo [3.2.1] oct-3-en-2-ol [(-)-12a]. *from* (-)-(*1S,2R,5R,7S*)-2-Acetoxy-7-(2-naphthylmethyloxymethyl)-6,8-dioxabicyclo [3.2.1] oct-3-ene [(-)-13a].

To a stirred solution of the acetate **[(-)-13a]** (150 mg, 0.44 mmol) in MeOH (2 mL), K_2CO_3 (61 mg, 0.44 mmol) was added at r.t and the mixture was stirred for 10 min.

The mixture was diluted with H_2O (3 mL), extracted with AcOEt (10 mL), and the extract was washed with H_2O and brine, dried $MgSO_4$, evaporated under reduced pressure to give the alcohol **[(-)-12a]** (130 mg, 99%); m.p 83 - 85 ^oC (EtOAc); $[\alpha]_D^{28}$ - 6.68 (*c* = 0.7, $CHCl_3$).

Spectral data were identical with those of **[(+)-12a]**.

In a similar manner, the enantiomeric **[(+)-13a]** was converted to the (+)-alcohol **[(+)-12a]**; m.p; 83 - 85C (EtOAC); $[\alpha]_D^{26}$ + 6.31 (*c* =1.0, $CHCl_3$) in 99% yiled.

(-) - (*1S, 2R, 5R, 7S*) - (2-Benzyllmethyloxymethyl)-6,8-dioxabicyclo [3.2.1] oct-3-en-2-ol [(-)-12b]. *from* (-) - (*1S, 2R5R, 7S*) -2-Acetoxy-7-(2-Benzylmethyloxymethyl)-6,8-dioxabicyclo [3.2.1] oct-3-ene [(-)-13b].

To a stirred solution of the acetate **[(-)-13b]** (220 mg, 0.75 mmol) in MeOH (3 mL), K_2CO_3 (105 mg, 0.75 mmol)) was added at r.t and the mixture was stirred for 10 min.

The mixture was diluted with H_2O (3 mL), extracted with AcOEt (10 mL), and the extract was washed with H_2O and brine, dried over anhydrous ($MgSO_4$), evaporated under reduced pressure to give the alcohol **[(-)-12b]** (180 mg, 96%); $[\alpha]_D^{28}$ - 5.6 (*c* = 1.0, $CHCl_3$).

Spectral data were identical with those of **[(+)-12b].**

In a similar manner, the enantiomeric **[(+)-13b]** was converted to the (+)-alcohol **[(+)-12b]**; $[\alpha]_D^{26}$ + 5.4 (*c* =1.0, $CHCl_3$) in 99% yield.

(-) - (1*S*, 2*R*, 5*R*, 7*S*) -7-*tert*-Butyldimethylsiloxymethyl-6,8-dioxabicyclo [3.2.1] oct-3-en-2-ol [(-)-12c] *from* (-) -(1*S*, 2*R*, 5*R*, 7*S*) -2-Acetoxy-7-tert-butyldimethylsiloxy-methyl-6,8-dioxabicyclo [3.2.1] oct-3-ene [(-)-13c].

To a stirred solution of the acetate **[(-)-13c]** (150 mg, 0.47 mmol) in MeOH (2 mL), K_2CO_3 (66 mg, 0.47 mmol)) was added at r.t and the mixture was stirred for 10 min. The mixture was diluted with H_2O (3 mL), extracted with AcOEt (10 mL) and the extract was washed with H_2O and brine, dried over anhydrous ($MgSO_4$), evaporated under reduced pressure to give the alcohol **[(-)-12c]** (128 mg, 99%); $[\alpha]_D^{28}$ - 2.8 (*c* = 1.0, $CHCl_3$). Spectral data were identical with those of **[(+)-12c].**

In a similar manner, the enantiomeric **[(+)-13c]** was converted to the (+)-alchol **[(+)-12c]**; m.p; $[\alpha]_D^{26}$ + 2.9 (*c* =1.0, $CHCl_3$) in 99% yiled.

(-) - (*1S, 5S, 7R*) -7-(2-Naphthylmethyloxymethyl)-6,8dioxabicyclo [3.2.1] oct-3-en-2-one [(-)11a] *from* (+) -(*1R, 2S, 5S, 7R*) -7-(2-Naphthyl-methyloxymthyl)-6,8-dioxabicyclo-[3.2.1] oct-3-en-2-ol [(+)-12a].

To a stirred suspension of **[(+)-12a]** (100 mg, 0.34 mmol), NaOAc (55 mg, 0.67 mmol) and molecular sieves (4^oA, 165 mg) in CH_2Cl_2 (5 mL), pyridinium chlorochr-omate (110 mg, 0.51 mmol)) was added at r.t. and the

mixture was stirred at for 3 h. The mixture was filtered through a Celite pad, the filtrate was eveporated under reduced pressure and chromatographed on a silica gel column (8 g, elution with hexane-EtOAc, 10 : 1 v/v) to give the enone **[(-)-11a]** (92 mg, 93%) as colorless prisms; m.p 80 - 83 c (hexane-EtOAc); $[\alpha]_D^{29}$ - 156.5 (*c* = 0.6, $CHCl_3$).

Spectral data were identical with those of **[(±)-11a].**

In a similar way, the enantiomeric **[(-)-12a]** gave the enone **[(+)-11a]**, m.p 80 - 83 ^oC (hexane-EtOAc); $[\alpha]_D^{29}$ + 148.3 (*c* = 0.6, $CHCl_3$), in 90% yiled.

(-) - (*1S ,5S, 7R*) -7-Benzyloxymethyl-6,8-dioxabicyclo [3.2.1] oct-3-one [(-)-11b]. *from* (+) - (*1R, 2S, 5S, 7R*) -7-Benzyloxymethyl-6,8-dioxabicyclo [3.2.1] oct-3-en-2-ol. [(+)-12b]

A stirred suspension of alcohol **[(+)-12b]** (200 mg, 0.81 mmol) was treated with PCC (259 mg, 1.22 mmol) in CH_2Cl_2 (10 mL) in the presence of NaOAc (131 mg, 1.62 mmol) and ms (4^oA 390 mg) and the mixture was stirred at r.t. for 3 h.

The mixture was filtered through a Celite pad, the filtrate was eveporated under reduced pressure and chromatographed on a silica gel column (15 g, elution with hexane-EtOAc, 5:1 v/v) to give the enone **[(-)-11b]** (185 mg, 93%) as colorless prisms, m.p 66-68 C (hexane-EtOAc); $[\alpha]_D^{27}$ – 187.7 (*c* =1.1, $CHCl_3$). Spectral data were identical with those of **[(±)-11b]**.

On similar treatment, the (-)-alcohol **[(-)-12b]** afforded the enantiomeric enone **[(+)-11b]**; m.p 64 - 66 ^oC (hexane-EtOAc); $[\alpha]_D^{25}$ + 191.8 (*c* =1.4, $CHCl_3$), in 96% yield.

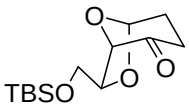
(-) - (*1S, 5S, 7R*) -7-*tert*-Butyldimethoxymthyl-6,8-dioxabicyclo [3.2.1] oct-3-en-2-one [(-)-11c] *from* (+) - (*1R, 2S, 5S, 7R*) -7-*tert*-Butyldimethylsiloxymethyl-6,8-dioxabicyclo [3.2.1] oct-3-en-2-ol [(+)-12c].

A stirred suspension of alcohol **[(+)-12c]** (180 mg, 0.66 mmol) was treated with PCC (213 mg, 0.99 mmol) in CH_2Cl_2 (5 mL) in the presence of NaOAc (108 mg, 1.32 mmol) and ms ($4A^0$ 320 mg) and the mixture was stirred at the r.t. for 3 h.

The mixture was filtered through a Celite pad, the filtrate was eveporated under reduced pressure and chromatographed on a silica gel column (20 g, elution with hexane-EtOAc, 10:1 v/v) to give the enone **[(-)-11c]** (145 mg, 81%) as a colorless oil; $[\alpha]_D^{27}$ - 184.6 (*c* = 1.1, $CHCl_3$).

Spectral data were identical with those of **[(±)-11c]**. In a similar way, the alcohol **[(-)-12c]** afforded the enantiomeric enone **([+)-11c]** in 88% yield; $[\alpha]_D^{25}$ + 187.0 (*c* = 1.4, CHCl3).

(+) - (*1S, 5R, 7S*) -7-*tert*-Butyldimethylsiloxymethyl-6,8-dioxabicyclo [3.2.1] octa-2-one (16).



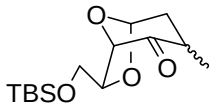
A suspension of **(11c)** (1.285 mg, 4.72 mmol) and10%Pd-C in AcOEt (35mL) was stirred under hydrogen atmosphere at r.t. for 2 h.

The suspension was filtered through Celite pad, the filtrate was evaporated under reduced pressure and chromatographed (SiO_2, 50 g, elution with hexane-AcOEt, 3 : 1v/v) to afford **(16)** (1.185 mg, 92%) as colorless oil, $[\alpha]_D^{24}$ + 20.9 (*c* 1.232, $CHCl_3$).

IR (film): ν = 1735 cm^{-1}. ^{1}HNMR (300 MHZ, $CDCl_3$): δ = 0.07(6H ,s), 0.88 (9H, s), 2.15-2.04 (2H, m), 2.49 (2H, dd, *J* = 8.2, 6.1 Hz) , 3.45 (1H, dd, *J* = 8.2, 0.5 Hz), 3.62 (1H, dd, *J* = 4.6, 0.5 Hz), 4.08 (1H, dd, *J* = 8.0, 5.2 Hz), 4.37 (1H, s), 5.71 (1H, d,
J = 2.4 Hz).

(Mass:*m/z* = 389 [M – C_4H_9]. HRMS: calcd.for C_{13} $H_{24}O_4Si$ = 215.0738. Found: 215.0714.

(+) - (*1S,3R,5R,7S*)-7-*tert*-Butyldimethylsiloxymethyl-3-methyl-6,8-dioxabicyclo[3.2.1]octa-2-one (16a).



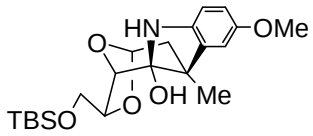
A solution of $(TMS)_2NH$ (1.2mL, 5.66 mmol) in THF and *n*-BuLi (1.54 M in hexane, 2.86ml, 4.40 mmol) was stirred for 30 min. at 0 °C. The HMPA (1.3mL, 4.40 mmol) and ketone **(16)** (1.185 g, 4.35 mmol) in THF (20mL) were added and the mixture was stirred at –78 °C for 1 h. MeI (0.3 ml, 4.87 mmol) was added at the same temperature, the mixure was stirred at –30 °C for 50 min, diluted with Et_2O (10mL) and H_2O (2mL), stirred at r.t. for 1 h and extracted with ether.

The extract was washed with brine, dried over anhydrous $MgSO_4$ and chromatographed (SiO_2, 50 g,elution with hexane-AcOEt,15:1v/v) to give methylketone **(16a)** (872 mg, 70%) as pale yellow oil.

IR (film): ν = 1730 cm^{-1}. ^{1}HNMR (300 MHZ, $CDCl_3$): δ = 0.05 (6H, s), 0.88 (3H, s), 0.89 (6H, s), 1.10 (3H, dd, *J* =8.2, 6.6 Hz), 1.77 - 1.69 (1H, m), 2.38 - 2.30 (1H, m), 2.70 - 2.36 (1H, m), 3.47 - 3.40 (1H, m), 3.64 - 3.56 (1H, m), 4.11 (1H, dd, *J* =8.2, 5.49 Hz), 4.33 (0.7H, s), 4.45 (0.3H, s), 5.64

(0.7H, s), 5.70 (0.3H, s). (Mass:*m/z* = 287 [M^+- 1]. HRMS: calcd.for $C_{14}H_{26}O_4Si$ = 287.1519. Found: 287.1648.

(-) - (*1S, 2R, 3S, 5R, 7S*) -7-*tert*Butyldimethylsiloxymethyl-3-methyl-6,8-dioxabicyclo [3.2.1] octan-[2,3,b]-5-methoxy-indol-2-ol (17).

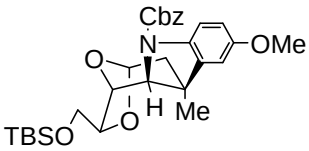


A mixture of **(15)** (600 mg, 2.09 mmol) and *p*-methoxyphenylhydrazine hydrochloride (403 mg, 2.30 mmol) in aqueous pyridine (10 : 1 v/v, 11 mL) was refluxed [19] [19a] for 2h, cooled to r.t. The mixture was evaporated under reduced pressure and the residue was extracted with ethyl acetate.

The extract was washed successively with 10% HCl and brine, dried over anhydrous $MgSO_4$, evaporated under reduced pressure,andchromatographed (SiO_2, 60 g, elution eith hexane-AcOEt 5 : 1 v/v); to afford **(17)**, (597 mg, 70%), as pale red oil: $[\alpha]_D^{29}$ – 104.1 (*c* 0.7, $CHCl_3$).

IR (film): ν = 3185 cm^{-1}. ^{1}HNMR (300 MHZ, $CDCl_3$): δ = 0.09 (3H, s), 0.1(3H, s), 0.91 (9H, s), 1.23 (br s,1H), 1.53 (3H, s), 1.83 (1H, dd, *J* =13.5, 1.4 Hz), 2.53 (1H, dd *J* = 13.5, 1.1 Hz), 3.57 (1H, dd, *J* = 9.9, 8.8 Hz), 3.69 (1H, dd, *J* = 9.9, 4.9 Hz), 3.76 (1H, br s), 6.81 (3H, s), 4.45 (1H, dd, *J* = 8.8, 4.9 Hz), 5.15 (1H, br s), 5.62 (1H, br s), 6.81 (1H, d, *J* = 2.5 Hz), 6.87 (1H, dd, *J* = 8.5, 2.5 Hz) , 7.57 (1H, d, *J* = 8.5 Hz). Mass:*m/z* = 389 [M^+- OH]. HRMS: calcd. for $C_{21}H_{31}NO_5Si$ = 389.2021. Found: 389.2040.

(+) - (*1S ,2R, 3S, 5R, 7S*) -7-*tert* -Butyldimethylsiloxy-methyl-3-methyl-6,8-dioxabicyclo [3.2.1] oct [2,3,b]-5-methoxyindol-1-carboxylicacid benzyl ester (18).



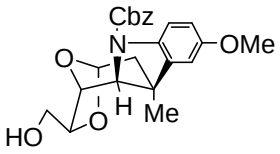
To a stirred mixture of **(17)** (515 mg, 1.26 mmol) in THF (10mL), $LiAlH_4$ (144mg, 3.79mmol) was added at 0 °C and the mixture was stirred for 5 min. The mixture was diluted with ether (5mL) followed by ammonia solution (1mL) and stirred for 30 min. at r.t, then treated with K_2CO_3 (874 mg, 6.32 mmol) followed by carbobenzoxy chloride (0.27 mL, 1.89 mmol) and stirred for 10 min.

The mixture was extracted with ethyl acetate, and the extract was washed successively with water and brine, dried over anhydrous $MgSO_4$, evaporated under reduced pressure, and chromatographed (SiO_2, 60 g, elution with hexane-AcOEt, 8 : 1 v/v) to afford **(18)** (664 mg, 100%) as pale yellow oil, $[\alpha]_D^{26}$ + 1.5 (*c* 1.2, $CHCl_3$).

IR (film): ν = 1700 cm^{-1}. ^{1}HNMR (300 MHZ, $CDCl_3$): δ = 0.08 (6H, s), 0.91 (9H, s), 1.48 (s, 1H), 1.93 (1H, d, *J* =14.6 Hz), 2.08 (1H, d, *J* =14.6 Hz) , 3.49 (1H, m), 3.58 (1H ,m), 3.76 (3H, s), 3.95 (1H, s), 3.95 (1H, s), 4.10 (1H, br t, *J* = 4.4 Hz), 4.92 (1H, br s), 5.28 (1H, d, *J* =12.4 Hz), 5.33 (1H, d, *J* =12.4 Hz), 5.52 (1H, br d, *J* =3.68 Hz), 6.58 (1H, d, *J* = 2.2 Hz), 6.68 (1H ,br d, *J* = 8.2 Hz), 7.45 - 7.32 (6H, m).

Mass:*m/z* = 525 [M^+]. HRMS: calcd. for C_{29} H_{39} NO_6Si = 525.2544. Found: 525.2527.

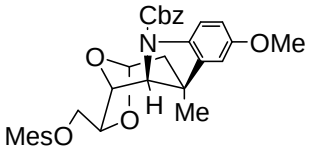
(+) - (*1S, 2R, 3S, 5R, 7S*) -7-Hydroxymethyl-3-methyl-6,8-dioxabicyclo [3.2.1] octan [2,3,b] 5-methoxy-indol-1-carboxylicacid benzyl ester (19).



To a stirred solution of **(18)** (620 mg, 1.18 mmol) in THF (12 mL), TBAF (1.0M in THF, 1.77 mL, 1.77 mmol) was added at 0 °C and stirred for 1 h. at r.t. The mixture was diluted with water (3mL), extracted with ethyl acetate, the extract was washed successively with water and brine, dried over anhydrous $MgSO_4$, evaporated under reduced pressure, and chromatographed (SiO_2, 30 g, elution with hexane-AcOEt, 1 : 1 v/v) to afford **(19)** (432 mg, 89%) as colorless solid m.p 43 - 45 ^oC (hexan-Et_2O), $[\alpha]_D^{26}$ + 22.9 (*c* 1.0, $CHCl_3$).

IR (film): ν = 3452, 1700 cm^{-1}. ^{1}HNMR (300 MHZ, $CDCl_3$): δ = 1.46 (3H, s), 1.75 (1H, br s), 1.92 (1H, d, *J* =15.4 Hz), 2.18 (1H, br s), 3.62 - 3.38 (2H, m), 3.76 (3H, s), 3.95 (1H, s) 4.14 (1H, m), 4.81 (1H, br s), 5.23 (1H, br s), 5.35 (1H, d, *J* = 12.1Hz), 5.55 (1H, d, *J* = 4.1 Hz), 6.59 (1H, d, *J* = 2.8 Hz), 6.68 (1H ,br d, *J* = 7.1 Hz), 7.33 - 7.44 (6H, m). Mass:*m/z* = 411[M^+]. HRMS: calcd. for C_{23} H_{25} NO_6 = 411.1680. Found: 411.1689.

(+) - (*1S, 2R, 3S, 5R, 7S*)-7-Methylsulfonyloxymethyl-3-methyl-6,8-dioxabicyclo [3.2.1] octan [2,3,b] 5-methoxyindol-1-carboxylicacid benzyl ester (20).



To stirred solution of **(19)** (432 mg, 1.04 mmol) in CH_2Cl_2 (10 mL),Et_3N (0.3 mL, 2.1 mmol) and MesCl (0.1 mL, 1.26 mmol) were added at 0 °C and the mixture was stirred for 10 min.

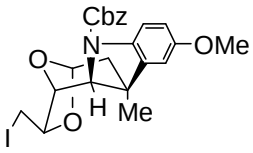
The mixture was diluted with water, extracted with ethyl acetate, and the extract was washed successively with water and brine, dried over anhydrous

$MgSO_4$, evaporated under reduced pressure, and chromatographed (SiO_2, 40 g,elution with hexane-AcOEt, 3 : 1 v/v) to afford **(20)** (514 mg, 100%) as colorless solid m.p 43 - 45 ^oC (hexan-Et_2O), $[\alpha]_D^{26}$ + 12.7 (*c* 1.1, $CHCl_3$).

IR (film): *v* = 1702 cm^{-1}. ^{1}HNMR (300 MHZ, $CDCl_3$): δ =1.48 (3H, s), 1.95 (1H, d, *J* =14.8 Hz), 2.08 (1H, m), 3.03 (1H, br s), 3.77 (3H, s), 3.96 (1H, br s), 4.21 - 4.02 (2H, m) ,4.34 (1H, br s), 4.95 (1H, br s), 5.28 (1H, br d, *J* = 12.1 Hz), 5.36 (1H, d, *J* = 12.1 Hz), 5.59 (1H, d, *J* = 3.0 Hz), 6.59 (1H, d, *J* = 2.5 Hz), 6.69 (1H, br d, *J* = 8.2 Hz), 7.36 - 7.46 (6H, m).

Mass: *m/z* = 489 [M^+]. HRMS: calcd. for C_{24} H_{27} NO_8S = 489.1455 Found: 489.1449.

(-) - (*1S, 2R, 3S, 5R, 7S*) -7-Iodomethyl-3-methyl-6,8-dioxabicyclo [3.2.1] octan [2,3,b] 5-methoxyindol-1-carboxylic acid benzyl ester (21).

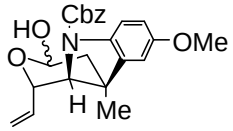


A solution of **(20)** (514 mg, 1.05 mmol) and LiI (1.41g, 10.5 mmol) in THF (20mL) was refluxed for 10h. The mixture was diluted with water (5mL), extracted with ethyl acetate, the extract was washed successively with water and brine, dried over anhydrous $MgSO_4$, evaporated under reduced pressure, and chromatographed (SiO_2, 20 g, elution with hexane-AcOEt, 8 : 1 v/v) to afford **(21)** (547 mg, 100%) as colorless solid, m.p 45 - 47 ^oC (hexan-Et_2O), $[\alpha]_D^{25}$ – 45.8 (*c* 1.0, $CHCl_3$).

IR (film): *v* = 1704 cm^{-1}. ^{1}HNMR (300 MHZ, $CDCl_3$): δ = 1.48 (3H, s), 1.91 (1H, d, *J* = 14.3 Hz), 2.02 (1H, br d, *J* = 14.3 Hz), 3.11 (2H, br s), 3.76 (3H, s), 3.94 (1H, s), 4.32 (1H, br, s), 5.05 (1H, br s), 5.29 (1H, d, *J* = 12.9), 5.35 (1H, d, *J* = 12.9 Hz), 5.61 (1H, d, *J* = 2.5 Hz), 6.58 (1H, d, *J* = 2.5 Hz), 6.68 (1H, br, d, *J* = 8.5 Hz), 7.31 - 7.47 (6H, m).

Mass: *m/z* = 521 [M^+]. HRMS: calcd. for C_{23} H_{24} NO_5I = 521.0696. Found: 521.0670.

(-) - (*1S, 2R, 3S ,5R, 7S*) -3-Hydroxy-6-methoxy-4a-methyl-1-vinyl-1,3,4,4a,9a-tetrahydro-1-H-pyrano [3,4-b]-indol-9-carboxylic acid benzyl ester (22).

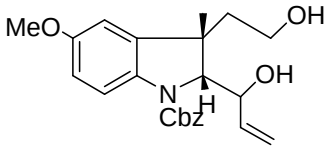


A suspension of **(21)** (481 mg, 0.92 mmol) and activated zinc (3.0 g, 46 mmol) in a mixture of EtOH and AcOH (9 : 1 v/v 20 ml) was stirred at r.t. for 5 min. The mixture was filtered through Celite pad, neutralized by addition of saturated $NaHCO_3$ and evaporated under reduced pressure .

The residue was diluted with water (5 ml), extracted with ethyl acetate, the extract was washed successively with water and brine, dried over anhydrous $MgSO_4$, evaporated under reduced pressure, and chromatographed (SiO_2, 20 g, elution with hexane-AcOEt, 3 : 1 v/v) to afford **(22)** (354 mg, 97%) as colorless solid, m.p 42 - 44 ^oC (Et_2O).

IR (film): ν = 3422,1701 cm^{-1}. ^{1}HNMR (300 MHZ, $CDCl_3$): δ = 1.19 (3H, s), 1.82 (1H, m), 2.41 (1H, m), 3.52 (1H, br s), 3.65 (1H, m), 3.78 (1.9H, s), 3.79 (1.1H, s), 3.98 (0.4H, d, *J* = 8.8 Hz), 4.10 ((0.6H, m), 4.74 (1H, br d, *J* = 8.8 Hz), 4.96 - 5.49 (4H, m), 6.85 (0.6H, m), 6.05 (0.4H, m), 6.70 (1H, d, *J* = 2.2Hz), 6.78 (1H, d, *J* = 6.9 Hz), 7.32 - 7.39 (5.4H, m), 7.71 (0.6H, d, *J* =8.5 Hz). Mass: *m/z* = 395 [M^+]. HRMS: calcd. for C_{23} H_{25} NO_5 = 395.1731. Found: 395.1725.

(+) - (*2S, 3S*) -2-(I-Hydroxyallyl)-3-(2-hydroxyethyl) -5-methoxy-3-methyl-2,3-dihydroindole-1-carboxylic acid benzyl ester (23).



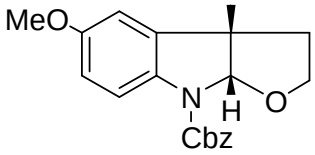
To a stirred solution of **(22)** (160 mg, 0.4 mmol) in EtOH (6 mL), $NaBH_4$ (46 mg, 1.21 mmol) was added at 0°C and the mixture was stirred at r.t. for 15 h. The mixture was evaporated under reduced pressure, diluted with water (2 mL) and extracted with ethyl acetate.

The extract was washed successively with water and brine, dried over anhydrous $MgSO_4$, evaporated under reduced pressure, and chromatographed (SiO_2, 7 g, elution with hexane-AcOEt, 1 : 1 v/v) to afford **(23)** (153 mg, 93%) as colorless oil, $[\alpha]_D^{30}$ + 28.5 (*c* 0.4, $CHCl_3$).

IR (film): ν = 3376,1700 cm^{-1}. ^{1}HNMR (300 MHZ, $CDCl_3$): δ = 1.24 (3H, s), 2.05 (1H, m), 2.22 (1H, br s), 3.77 (3H, s), 3.89 - 3.97 (2H, m), 4.31 - 4.42 (2H, br s), 4.92 (1H, d, *J* = 10.2 Hz), 5.05 (1H, br s), 5.20 - 5.38 (2H, m), 5.68 (1H, m), 6.62 - 6.65 (2H, m), 7.27 - 7.42 (6H, m).

Mass: *m/z* = 397 [M^+]. HRMS: calcd. for C_{23} H_{27} NO_5 = 397.1887. Found: 397.1875.

(-) - (*2aR, 3aS*) -5-methoxy-3a-methyl-2,3,3a,8a-tetrahydro-furo [2,3-b] indole-8-carboxylic acid benzyl ester (24).



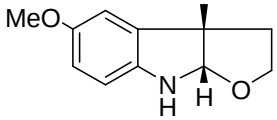
A solution of **(23)** (150 mg, 0.37 mmol) and $Pb(OAc)_4$ (419mg, 0.94 mmol) in benzene (6 mL) was stirred at r.t. for 24 h.

The mixture was extracted with ethyl acetate, washed successively with water and brine, dried over anhdrous $MgSO_4$, evaporated under reduced pressure, and chromato-graphed (SiO_2, 7 g, elution with hexane-AcOEt, 10 : 1v/v) to afford **(24)** (68 mg, 53%) as colorless oil, $[\alpha]_D^{24}$ – 45.2 (*c* 0.4, $CHCl_3$).

IR (film): *v* =1711 cm^{-1}. ^{1}HNMR (300 MHZ, $CDCl_3$): δ =1.49 (3H, s), 2.08 - 2.23 (2H, m), 3.51 (1H, m), 3.79 (3H, s), 4.00 (1H, t, *J* = 7.7 Hz), 5.24 (1H, br d, *J* = 12.6 Hz), 5.37 (1H, d, *J* = 12.6 Hz), 5.76 (1H, br s), 6.73 (1H, d, *J* = 2.5 Hz), 6.76 (1H, m), 7.32 - 7.78 (6H, m).

Mass: *m/z* = 339 [M^+]. HRMS: calcd. for C_{20} H_{21} NO_4 = 339.1469. Found: 339.1471.

(-) - (*2aR, 3a S*) -5-Methoxy-3a-methyl-3,3a,8,8a-tetrahydro-2H-furo [2,3-b] indole (25).

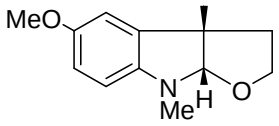


A suspension of **(24)** (68 mg, 0.20 mmol) and 10%Pd-C in AcOEt (5 mL) was stirred under hydrogen atmosphere at r.t. for 20 min. The suspension was filtered through Celite pad, the filtrate was evaporated under reduced pressure and chromatographed (SiO_2, 5 g, elution with hexane-AcOEt, 3 : 1v/v) to afford **(25)** (41 mg, 100%) as colorless oil, $[\alpha]_D^{24}$ – 120.7 (*c* 0.4, $CHCl_3$).

IR (film): *v* = 3366 cm^{-1}. ^{1}HNMR (300 MHZ, $CDCl_3$): δ = 1.47 (3H, s), 2.07 (1H, ddd, *J* =11.8, 11.8, 6.9 Hz), 2.17 (1H, ddd, *J* =11.0, 5.5, 1.9 Hz), 3.56 (1H, ddd, *J* = 11.0, 8.5, 5.2 Hz), 3.76 (3H, s), 3.94 (1H, m), 4.37 (1H, br s), 5.27 (1H, s), 6.53 (1H, d, *J* = 8.2Hz), 6.63 (1H, dd, *J* = 8.2, 2.5 Hz), 6.70 (1H, d, *J* = 2.5 Hz).

Mass: *m/z* = 205 [M^+]. HRMS: calcd. for C_{12} H_{15} NO_2 = 205.1101. Found: 205.1099.

(-) - (*2a R,3a S*)-5-Methoxy-3a,8-dimethyl-3,3a,8,8a-tetrahydro-2H-furo [2,3-b] indole (26).



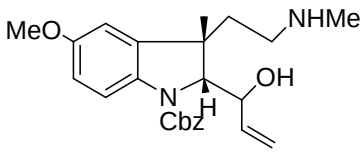
A solution of the amine **(25)** (40 mg, 0.19 mmol) in MeOH (2 mL) was stirred with 36% formaldhyde solution (0.15 mL, 1.95mmol) and $NaBH_3CN$ (61 mg, 0.97 mmol) at r.t. for 20 h.

The mixture was extracted with ethyl acetate, washed successively with water and brine, dried over anhydrous $MgSO_4$, evaporated under reduced pressure, and chromato-graphed (SiO_2, 5 g, elution with hexane-AcOEt, 8 : 1 v/v) to afford **(26)** (37 mg, 87%) as colorless oil. $[\alpha]_D^{32}$ – 94.9 (*c* 0.4, $CHCl_3$). [lit.[19] $[\alpha]_D^{24}$ – 96 (*c* 0.35, $CHCl_3$)].

^{1}HNMR (300 MHZ, $CDCl_3$): δ = 1.45 (3H, s), 2.15 - 1.97 (2H, m), 2.88 (3H, s), 3.60 – 3.33 (1H, m), 3.75 (3H, s), 4.05 – 3.81 (1H, m), 5.04 (1H, m), 6.28 (1H, d, *J* = 10 Hz), 6.70 – 6.60 (3H, m).

Mass: *m/z* = 219 [M^+]. HRMS: calcd. for C_{13} H_{17} NO_2 = 219.1258. Found: 219.1247.

(+) - (*2S, 3S*) -2-(1-Hydroxyallyl)-5-methoxy-3-methyl-3-(2-methylaminoethyl)-2,3-dihydro-indole-1-carboxylic acid benzyl ester (28).



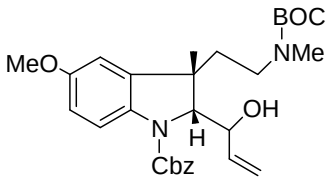
A solution of **(22)** (215 mg, 0.56 mmol), $MeNH_3Cl$ (381 mg, 5.64 mmol), and $NaBH_3CN$ (177 mg, 2.82 mmol) in MeOH (7 mL) was heated at 90 °C in a sealed tube for 15 h.

The solvent was evaporated under reduced pressure and the residue was chromatographed (SiO_2,10 g, elution with $CHCL_3$-MeOH,10 : 1 v/v) to afford **(28)** (185 mg, 83%) as colorless oil. $[\alpha]_D^{26}$ + 10.5 (*c* 0.5, $CHCl_3$).

IR (film): *v* = 3444, 1701 cm^{-1}. ^{1}HNMR (300 MHZ, $CDCl_3$): δ = 1.21 (3H, s), 1.98 (1H, m), 2.14 (1H, m), 2.47 (3H, s), 2.77 - 2.98 (2H, m), 3.77 (3H, s), 4.25 (2H, br s), 4.92 (1H, d, *J* =10.2 Hz), 5.08 (1H br s), 5.23 (1H, d, *J* = 12.1, Hz), 5.30 (1H br s), 5.67 (1H br s), 6.64 (1H, d, *J* = 2.5 Hz), 6.68 (1H, br d, *J* = 8.0Hz), 7.27 - 7.46 (6H, m).

Mass (FAB):*m/z* = 411 [M^+ + 1].

(+) - (*2S, 3S*)-3-[2-(*tert*-Butoxycarbonylmethyl amino)-ethyl]-2-(1-Hydroxyallyl)-5-methoxy-3-methyl-2,3-dihydro-indole-1-carboxylic acid benzyl ester (29).

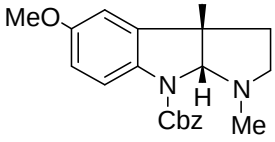


To a stirred Solution of amine **(28)** (165 mg, 0.4 mmol) in MeOH (5 mL) $NaHCO_3$ (68 mg, 0.8 mmol) and $(BOC)_2O$ (0.1 mL, 0.48 mmol) were added at r.t and the mixture was srirred for 15 min.

The mixture was diluted with water, extracted with ethyl acetate, the extract washed successively with water and brine, dried over anhydrous $MgSO_4$, evaporated under reduced pressure, and chromatographed (SiO_2,10 g, elution with hexane-AcOEt, 3 : 1 v/v) to afford **(29)** (192 mg, 94%) as colorless oil, $[\alpha]_D^{26}$ + 25.5 (*c* 0.6, $CHCl_3$).

IR (film): *v* = 3428,1700 cm^{-1}. ^{1}HNMR (300 MHZ, $CDCl_3$): δ = 1.23 (3H, s), 1.47 (9H, s) 1.85 - 2.18 (2H, m), 2.92 (3H, s), 3.49 (2H, br s), 3.78 (3H, s), 4.23 - 4.62 (3H, m), 4.93 (1H, d, *J* = 11 Hz), 5.10 - 5.50 (3H, m), 6.60 - 6.70 (2H, m), 7.43 - 7.34 (6H, m). Mass: *m/z* = 510 [M^+]. HRMS: calcd. for C_{29} H_{28} N_2O_6 = 510.2727. Found: 510.2746.

(+) - (*2S, 3S*) -5-Methoxy-1,3a-dimethyl-2,3,3a,8a-tetrahydro-1H-pyrolo [2,3-b] indole-8-carboxylic acid benzyl ester (31).



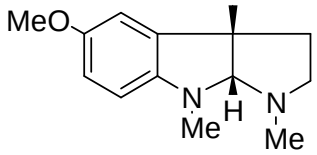
A solution of **(29)** (170 mg, 0.37 mmol) and Pb $(OAc)_4$ (825 mg, 1.86 mmol) in benzene (7 mL) was stirred at 60 °C for 15 h.

The mixture was extracted with ethyl acetate, the extract was washed successively with water and brine, dried over anhydrous $MgSO_4$, evaporated under reduced pressure to give the crude acetate **(30)**.

The residue was dissolved in AcOEt (7 mL) and refluxed with 10% HCl (3 mL) for 2 h, cooled to r.t, the organic layer was separated and washed successively with water and brine, dried over anhydrous $MgSO_4$, evaporated under reduced pressure, and chromatog-raphed (SiO_2, 10 g, elution with hexane-AcOEt, 3 : 2 v/v) to afforded **(31)** (94 mg, 80%) as colorless oil. $[\alpha]_D^{29}$ – 7.7 (*c* 0.3, $CHCl_3$).

IR (film): *v* =1703 cm^{-1}. ^{1}HNMR (300 MHZ, $CDCl_3$): δ = 1.28 (3H, s), 1.98 - 2.06 (2H, m), 2.50 (3H, br s), 2.60 - 2.70 (2H, m), 3.78 (3H, s), 4.90 (1H, br s), 5.28 (2H, br s), 6.68 (1H, d, *J* = 2.2 Hz), 6.72 (1H, m), 7.45 - 7.34 (6H, m) Mass: *m/z* = 352 [M^+]. HRMS: calcd. for C_{21} H_{24} N_2O_3 = 352.1785. Found: 352.1806.

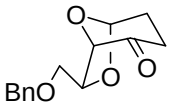
(-)-(*2aS ,3aS*)-5-Methoxy-1,3a,8-trimethyl - 1,2,3,3a,8,8a-hexahydro-pyrolo[2,3-b]indole (32).



A solution of **(31)** (80 mg, 0.22 mmol) in MeOH (5 mL) was stirred with 36% formaldhyde solution (0.17 mL, 2.27 mmol) and 10% Pd-C (10 mg) undr hydrogem atmospher at r.t. for 14 h.

The suspension was filtered through Celite pad, the filtrate was evaporated under reduced pressure, and chromatographed (SiO_2, 5 g, elution with Et_2o-MeOH, 20 : 1 v/v) to afforded **(32)** (42 mg, 80%) as colorless oil, $[\alpha]_D^{26}$ –129.5 (*c* 0.2, benzebe). [lit.[19] $[\alpha]_D^{34}$ – 134 (*c* 0.41, benzene)].

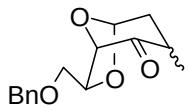
(+) - (*1S, 5R, 7S*) -7-benzyloxymethyl-6,8-dioxabicyclo [3.2.1] octa-2-one (33).



To a stirred suspension of [CuI, 6.47gm, 33.97 mmol] in THF - HMPA (4:1), (50mL) at –78 °C DIBAL-H (1.0 M in toluene, 30.88 mL, 30.88 mmol) was added and the mixture was stirred at – 78 ^{0}C for 1 h. The enone [96] **(11b)**, (3.8 gm, 15.44 mmol) in THF - HMPA (4 : 1), (25 mL) was added at the same temperature and the mixture was stirred for 1 h, the mixture was diluted with Et_2O (10 mL) and H_2O (5 mL) and stirred at r.t. for 1 h. The mixture was filterd thrugh Celite pad, washed successively with H_2O and brine, dried over anhydrous $MgSO_4$, evaporated under reduced pressure, and chromatographed (SiO_2, 120 g, elution with hexane-AcOEt, 4 : 1 v/v) to afford **(33),** (3.5 g, 92%) as pale yellow oil. $[\alpha]_D^{30}$ + 37.3 (*c* 1.08, CHCl)

IR (film): ν = 1729 cm^{-1}. ^{1}HNMR (300 MHZ, $CDCl_3$): δ = 2.18 - 1.93 (2H, m), 2.44 - 2.32 (2H, m), 3.32 (1H, dd, *J* = 9.6, 7.1 Hz), 3.42 (1H, dd, *J* = 9.6, 6.0 Hz), 4.17 (1H, t, *J* = 6.3), 4.29 (1H, s), 4.47 (2H, d, *J* = 2.1), 5.67 (1H, d, *J* = 1.6), 7.31 - 7.19 (5H, m), Mass: *m/z* = 248 [M^+]. HRMS: calcd. for C_{14} H_{16} O_4 = 248.1047. Found:248.1036.

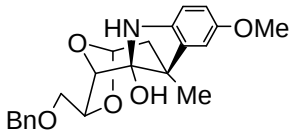
(+)-(*1S,3R,5R,7S*)-7-benzyloxymethyl-3-methyl-6,8-dioxabicyclo[3.2.1]octa-2-one (34).



A mixture of $(TMS)_2NH$ (1.85 ml, 8.80 mmol) in THF and BuLi (1.54 M in hexane, 5.27 ml, 8.1 mmol) was stirred for 30min. at 0 °C. The HMPA (1.8 ml, 8.1 mmol) and ketone **(33)** (1.68 g, 6.77 mmol) in THF (20 mL) were added and the mixture was stirred at – 78 °C for 1 h. MeI (0.45 ml, 7.44 mmol) was added at the same temperature and the mixure was stirred at – 30 °C for 40min. The mixture was diluted with Et_2O (10 mL) and H_2O (2 mL), stirred at r.t. for 1 h, and extract with ether, the extract washed with brine, dried over anhydrous $MgSO_4$ and chromatographed (SiO_2, 50 g, elution with hexane-AcOEt, 10 : 1 v/v) to afford methylketone **(34)**, (1.242 g, 70%) as pale yellow oil.

IR (film): ν = 1729 cm^{-1}. ^{1}HNMR (300 MHZ, $CDCl_3$): δ = 1.12 (3H, dd, *J* = 11.2.2, 4.3 Hz), 1.74 - 1.78 (1H, m), 2.68 - 2.34 (2H, m), 3.51 - 3.35 (2H, m), 4.17 (0.4H, t, *J* = 6.3 Hz), 4.31 (0.6H, t, *J* = 6.3 Hz), 4.33 (0.6H, s), 4.45 (0.4H, s), 4.55 (2H, s), 5.68 (0.6H, s), 5.75 (0.4H, s), 7.27 - 7.34 (5H, m). (Mass:*m/z* = 262 [M^+]. HRMS: calcd. for C_{15} $H_{18}O_4$ = 262.1204. Found 262.1212.

(-) - (*1S, 2R, 3S, 5R, 7S*) -7-Benzyloxymethyl-3-methyl-6,8-dioxabicyclo [3.2.1]octan-[2,3,b] -5-methoxy-indol-2-ol (36).



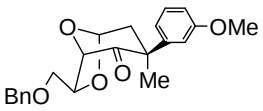
A mixture of **(34)** (1.1 g, 4.19 mmol) and *p*-methoxyphenylhydrazine hydrochloride (953 mg, 5.45 mmol) in aqueous pyridine (10:1 v/v, 25mL) was refluxed [19] [19a] for 1h, cooled to r.t, evaporated under reduced pressure and the residue was extracted with ethyl acetate after dilution with water.

The extract was washed successively with 10% HCl and brine, dried over anhydrous $MgSO_4$, evaporated under reduced pressure, and chromatographed (SiO_2, 60 g, elution eith hexane-AcOEt 3 : 1 v/v), to afforded **,** (1.48 g, 92%), as pale red oil, $[\alpha]_D^{29}$ – 88.6 (*c* 1.04, $CHCl_3$)

IR (film): ν = 3374 cm^{-1}. ^{1}HNMR (300 MHZ, $CDCl_3$): δ = 1.51 (3H, s), 1.83 (1H, d, *J* = 13.4 Hz), 2.53 (1H,d, *J* = 13.4Hz), 3.62 - 3.48 (2H, m), 3.82 (3H, s), 4.64 - 4.59 (3H, m), 5.16 (1H, s), 5.64 (1H, s), 6.88 - 6.89 (2H, m), 7.37 - 7.25 (5H, m), 7.55 (1H, d, *J* = 8.5 Hz).

Mass:*m/z* =365 [M^+- OH]. HRMS: calcd. For C_{22} H_{25} NO_5 = 365.1626 Found: 365.1648.

(-) - (*1S, 3S, 5R, 7S*) -7-Benzyloxymethyl-3-(-methoxyphenyl)-3-methyl-6,8-dioxabicyclo-[3,21] octan-2-one (37).



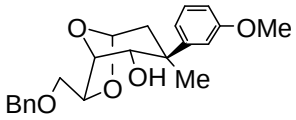
To a stirred solution of **(36)** (1.0 g, 2.60 mmol) in Et2O-AcOH (10 : 0.5) (21 mL) at 0 °C, H_3PO_2 50% (0.8 mL, 7.82 mmol) and $NaNO_2$ solution (540 mg, 7.28 mmol) (1 mL) were added, the mixture was srirred for 2 h and the stirring was continued for 10 h at r.t.

The mixture was diluted with water, extracted with EtOAc, the extract was washed successively with water and brine, dried over anhydrous $MgSO_4$, evaporated under reduced pressure, and chromatographed (SiO_2, 50 g, elution with hexane-AcOEt, 8 : 1 v/v) to afforded **(37)** (778 mg, 81%) as yellow oil, $[\alpha]_D^{26}$ – 31.8 (*c* 1.03, $CHCl_3$).

IR (film): *v* = 1729 Cm^{-1} .^{1}HNMR (300 MHZ, $CDCl_3$): δ =1.45 (3H, s), 1.91 (2H, d, *J* = 15.1 Hz), 2.96 (1H, dd, *J* = 15.1 ,4.9 Hz), 3.49 - 3.36 (2H, m), 3.79 (3H, s), 4.2 (1H, t, *J* = 6.3 Hz), 4.60 - 4.49 (2H, m), 5.79 (1H, d, *J* = 4.9 Hz), 6.88 - 6.75 (3H, m), 7.34 - 7.23 (6H m).

Mass: *m/z* = 368 [M^+]. HRMS: calcd. for C_{22} H_{24} O_5 = 368.1622. Found: 368.1648.

(+) - (*1S, 2R, 3S, 5R, 7S*) -7-Benzyloxymethyl-3-(-methoxyphenyl)-3-methyl-6,8-dioxabicyclo [3.2.1] octan-2-ol (38).

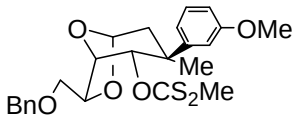


To a stirred solution of **(37)** (450 mg, 1.14 mmol) in MeOH (10 mL), $NaBH_4$ (87 mg, 2.29 mmol) was added at 0 °C and the mixture was stirred for 10 min. The mixture was evaporated under reduced pressure and the residue was dissolved in EtOAc (50 mL), the solution was washed with H_2O and brine, dried over anhydrous $MgSO_4$, evaporated under reduced pressure, and chromatogaphed (SiO_2, 30 g, elution with hexane-AcOEt, 6 : 1 v/v) to give **(38)** (452 mg, 100%) as a colorless oil, $[\alpha]_D^{29}$ + 7.1 (*c* 0.35, $CHCl_3$).

IR (film): *v* = 3460 Cm^{-1} .^{1}HNMR (300 MHZ, $CDCl_3$): δ = 1.55 (3H, s), 2.089 (3H, ddd, *J* = 6.8, 3.0, 1.6 Hz), 3.49 - 3.34 (2H, m), 3.79 (3H, s), 4.28 - 4.20 (2H, m), 4.60 - 4.50 (3H, m), 5.60 (1H, t, *J* = 1.9 Hz), 6.75 - 6.71 (1H, d t, *J* = 2.7, 1.9 Hz), 7.02 - 6.99 (2H, m), 7.34 - 7.20 (6H m).

Mass: m/z = 370 [M^+]. HRMS: calcd. for C_{22} H_{26} O_5 = 370.1778. Found: 370.1800.

(+) - (*1S, 2R, 3S, 5R, 7S*) -Dithiocarbonic acid O-[7-benzyloxymethyl-3-(3-methoxyphenyl)-3-methyl-6,8-dioxabicyclo [3.2.1]oct-2-yl] ester S-methyl ester (39).



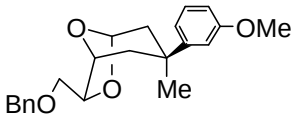
To a stirred solution of **(38)** (430 mg, 1.16 mmol) in THF (20 mL), NaH (233 mg, 5.80 mmol) was added at 0 °C, the suspension was stirred at the r.t. for 1 h, CS_2 (0.88 ml, 11.61 mmol) was added and the mixture was stirred for 2 h. MeI (0.7 mL, 11.61 mmol) was added and the mixture was stirred at the same temperature for 1.5 h.

The mixture was diluted with Et_2O and NH_4Cl and stirred for 1 h, extracted with AcOEt, washed with H_2O and brine, dried over anhydrous $MgSO_4$, evaporated under reduced pressure, and chromatogaphed (SiO_2, 60 g, elution with hexane-AcOEt, 30 : 1 v/v) to give **(39)** (510 mg, 96%) as a pale yellow oil. $[\alpha]_D^{28}$ + 32.1 (*c* 1.028 ,$CHCl_3$).

IR (film): *v* = 1601 Cm^{-1} .^{1}HNMR (300 MHZ, $CDCl_3$): δ = 1.71 (3H, s), 2.24 (2H, s), 2.56 (3H, s), 3.36 (1H, dd, *J* = 7.6 ,1.9 Hz), 3.50 (1H, dd, *J* = 5.7, 3.8 Hz) 3.76 (3H, s), 4.61 - 4.49 (3H, m), 4.70 (1H, d ,*J* = 4.9 Hz) 5.66 (1H, t, *J* = 1.9 Hz), 6.27 (1H, d, *J* = 4.6 Hz), 7.72 (1H, dd, *J* = 5.4, 2.4 Hz), 6.84 - 6.79 (2H, m), 7.36 - 7.18 (6H, m).

Mass: *m/z* = 460 [M^+. HRMS: calcd. for C_{24} H_{28} O_5 S_2 = 460.1376. Found: 460.1396.

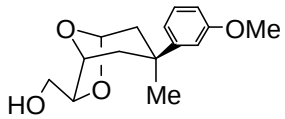
(+) - (*1S, 3R, 5R, 7S*) -7-Benzyloxymethyl-3-(3-methoxyphenyl)-3-methyl-6,8-dioxa-bicyclo [3.2.1] octane (40).



To a stirred solution of **(39)** (510 mg,1.10 mmol) in benzene (60 mL), AIBAN (19 g, 0.11 mmol) was added, the mixture was heated to 80 °C, Bu_3SnH (0.36 mL, 1.33 mmol) was added and the mixture was refluxed for 30min, cooled to r.t, evaporated under reduced pressure and chromato-graphed (SiO_2, 60 g, elution with hexane-AcOEt, 30 : 1 v/v) to give **(40)** (374 mg, 95%) as a pale yellow oil. $[\alpha]_D^{30}$ + 36.1 (*c* 1.016, $CHCl_3$).

^{1}HNMR (300 MHZ, $CDCl_3$): δ = 1.46 (3H, s), 1.64 (1H, s), 1.91 (1H,d , *J* = 14.5Hz), 2.0 (1H, d, *J* = 6.8 Hz), 2.32 (1H, dd, *J* = 9.6, 4.6 Hz), 3.30 (1H, d, *J* = 8.2 Hz), 3.40 - 3.37 (1H, m), 3.72 (3H, s), 4.37 - 4.27 (2H, m), 4.47 (2H, dd, *J* = 6.8, 1.6 Hz), 5.59 (1H, s), 6.63 (1H, dd, *J* = 7.9, 2.4 Hz), 6.97 - 6.71 (2H, m), 7.29 - 7.10 (6H m). Mass: *m/z* = 354 [M^+]. HRMS: calcd. for C_{22} H_{26} O_4 = 354.1829. Found: 354.1801.

(+) - (*1S, 3R, 5R, 7S*) - [3-(3-Methoxyphenyl)-3-methyl-6,8-dioxabicyclo [3.2.1] oct-7-yl]-methanol(41).



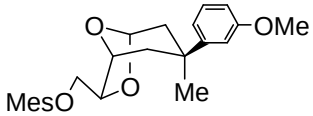
A solution of **(40)** (374 mg,1.05 mmol) in EtOH (20 mL) was refluxed with Ranny Ni (W2) for 30 min.

The mixture was filtered through Cellite pad, evaporated under reduced pressure and chromatographed (SiO_2, 20 g, elution with hexane-AcOEt, 2 : 1 v/v) to give **(41)** (279 mg, 100%) as acolorless oil. $[\alpha]_D^{29}$ + 66.2 (*c* 1.132, $CHCl_3$).

IR (film): *v* = 3460 $Cm^{-1.}$ ^{1}HNMR (300 MHZ, $CDCl_3$): δ = 1.56 (3H, s), 1.98 (2H, br s), 2.35 (1H, br s), 2.42 (1H,d, *J* = 4.6 Hz), 3.59 (2H, d, *J* = 5.7 Hz), 3.80 (3H, s), 4.34 (1H, t, *J* = 6.0 Hz), 4.41 (1H, d, *J* = 3.2 Hz), 5.73 (1H, s), 6.72 (1H, dd, *J* = 8.2, 1.9 Hz), 6.80 (1H, t , *J* = 2.1 Hz), 6.85 (1H, d, *J* = 8.5 Hz), 7.22 (1H, d, *J* = 7.9 Hz),

Mass: *m/z* = 264 [M^+]. HRMS: calcd. for C_{15} H_{20} O_4 = 264.1360. Found: 264.1386.

(+) - (*1S, 3R, 5R, 7R*) - Methanesulfonic acid 3-(3-methoxyphenyl)-3-methyl-6,8-dioxabicyclo [3.2.1] oct-7-ylmethyl ester (42).



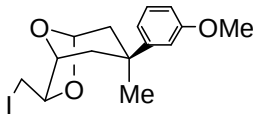
To a stirred solution of **(41)** (279 mg, 1.05 mmol) in CH_2Cl_2 (10 mL), Et_3N (0.3 mL, 2.11 mmol) and MesCl (0.1 mL, 1.26 mmol) were added at 0 °C and the mixture was stirred for 10 min.

The mixture was diluted with water and extracted with EtOAc, the extract was washed successively with water and brine, dried over anhydrous $MgSO_4$, evaporated under red-uced pressure, chromatographed (SiO_2, 40 g, elution with hexane-AcOEt, 3 : 1 v/v) to afford **(42)** (361 mg, 100%) as colorless oil, (hexan-Et_2O), $[\alpha]_D^{31}$ + 41.4 (*c* 1.05, $CHCl_3$).

^{1}HNMR (300 MHZ, $CDCl_3$): δ = 1.54 (3H, s), 2.00 (1H, br s), 2.05 (1H, br s), 2.10 (1H,d, *J* = 6.0 Hz), 2.44 (1H, dd, *J* = 14.5, 4.9 Hz), 3.06 (3H, s), 3.80 (3H, s), 4.19 - 4.06 (2H, m), 4.50 - 4.42 (2H, m), 5.72 (1H, s), 7.21 - 6.71 (3H, m), 7.23 (1H, d ,*J* = 4.9 Hz).

Mass: *m/z* = 342 [M^+]. HRMS: calcd. for C_{16} H_{22} O_6 S = 342.1135. Found: 342.1127.

(+) - (*1S , 3R, 5R, 7R*) -7-Iodomethyl-3-(3-methoxyphenyl)-3-methyl-6,8-dioxabicyclo [3.2.1] octane (43).



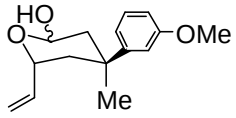
A solution of **(42)** (361 mg, 1.05 mmol) and LiI (7.0 g, 52.76 mmol) in THF (50 mL) was refluxed for 15 h.

The mixture was diluted with water (10 mL) and extracted with EtOAc, the extract was washed successively with water and brine, dried over anhydrous $MgSO_4$, evaporated under reduced pressure, and chromatographed (SiO_2, 20 g, elution with hexane-AcOEt, 20 : 1 v/v) to afford **(43)** (371 mg, 94%) as colorless oil. $[\alpha]_D^{30}$ + 2.7 (*c* 1.086, $CHCl_3$).

^{1}HNMR (300 MHZ, $CDCl_3$): δ = 1.53 (3H, s), 1.99 (1H, br s), 2.04 (1H, br s), 2.07 (1H, s), 2.42 (1H, dd, *J* = 14.5, 4.9 Hz), 3.10 (1H, d, *J* = 9.6 Hz), 3.16 (1H, d , *J* = 3.0 Hz), 3.80 (3H, s), 4.57 - 4.44 (2H, m), 5.77 (1H, s), 6.73 (1H, dd, *J* = 7.9, 2.4 Hz), 6.80 (1H, t , *J* = 7.9 Hz), 6.85 - 6.84 (1H, m), 7.24 (1H, m).

Mass: *m/z* = 374 [M^+]. HRMS: calcd. for C_{15} H_{19} O_3 I = 374.0376. Found: 374.0383.

(*2R, 4R, 6R*) -6-Vinyl-4-(3-methoxyphenyl)-4-methyl-tetrahydro-pyran-2-ol (44).

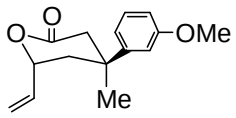


A suspension of **(43)** (471mg, 0.99 mmol) and activated zinc (3.24 g, 49.59 mmol) in a mixture of EtOH and AcOH (9:1 v/v 20 mL) was stirred at r.t. for 15 min. The mixture was filtred through Ccelite pad, neutralized by addition of saturated $NaHCO_3$, evaporated under reduced pressure and extracted with EtOAc. The extract was washed successively with water and brine, dried over anhydrous $MgSO_4$, evaporated under reduced pressure, and chromatographed (SiO_2, 20 g, elution with hexane-AcOEt, 3 : 1 v/v) to afford **(44)** (234 mg, 95%) as colorless oil.

IR (film): *v* = 3408,1581 Cm^{-1}. ^{1}HNMR (300 MHZ, $CDCl_3$): δ = 1.19 (3H, s), 1.53 - 1.43 (2H, m), 2.26 (0.6H, t, *J* = 2.1 Hz), 2.30 (.4H, t, *J* = 2.1 Hz), 2.55 (0.6H, t, *J* = 2.1 Hz), 2.59 (0.4H, t, *J* =2 .1 Hz), 3.28 (1H, br s), 3.79 (1.2H, s), 3.81 (1.8H, s), 3.99 - 3.92 (1H, m), 4.80 (1H, d, *J* = 9.0 Hz), 5.18 - 5.11 (1H, m), 5.34 - 5.22 (1H, m), 5.93-5.82 (1H, m), 6.76 (1H, dd, *J* = 8.2, 2.4 Hz), 6.98 - 6.87 (2H, m), 7.31 - 7.25 (1H, m).

Mass: *m/z* = 248 [M^+]. HRMS: calcd. for C_{15} H_{20} O_3 = 248.1141. Found: 248.1414.

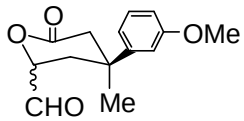
(+) - (4R, *6R*) -6-Vinyl-4-(3-methoxyphenyl)-4-methyl-tetrahydro-pyran-2-one (45).



A suspension of **(44)** (230 mg, 0.92 mmol), 4A°ms (345 mg), NMO (218 mg, 1.85 mmol) and TPAP (33 mg, 0.09 mmol) in CH_2Cl_2 was stirred at room temperature for 5 min. The mixture was filtered through Celite pad, evaporated under reduced pressure and chromatographed. (SiO_2, 25 g, elution with hexane-AcOEt, 4:1 v/v) to afford **(45)** (220 mg, 96%) as colorless oil, $[\alpha]_D^{30}$ + 35.6 (*c* 1.086, $CHCl_3$).

IR (film): *v* = 1732,1603 Cm^{-1}. ^{1}HNMR (300 MHZ, $CDCl_3$): δ = 1.40 (3H, s), 1.82 (1H, t, *J* = 2.3 Hz), 2.37 - 2.27 (1H, m), 2.46 (1H, d, *J* = 17.0 Hz), 3.14 (1H, dd, *J* = 17.0, 2.1 Hz), 3.81 (3H, s), 4.37 - 4.32 (1H, m), 5.29 - 5.15 (2H, m), 5.87 - 5.76 (1H, m), 6.88 - 6.74 (3H, m), 7.31 (1H, d, *J* = 7.6 Hz). Mass: *m/z* = 246[M^+]. HRMS: calcd. for C_{15} H_{18} O_3 = 246.1254. Found: 246.1264.

(*4R, 6S*) -4-(3-Methoxyphenyl)-4-methyl-6-oxo-tetrahydro-pyran-2-carbaldehyde (47).

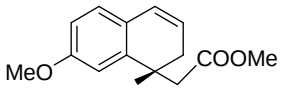


To a stirred solution of **(45)** (220 mg, 0.89 mmol) and NMO (210 mg, 1.78 mmol) in aq THF (10 : 1 v/v 11 mL), OsO_4 in THF (0.198 M, 0.45 mL, 0.089 mmol) was added at 0 °C and the mixture was stirred at r.t. for 48 h.

The solvent was evaporated under reduced pressure, the residue was extracted with EtOAc and the extract was washed with brine, dried over anhydrous $MgSO_4$, evaporated under reduced pressure to afford diol **(46)**, which without separation was dissolved in aq. THF ((2 : 1) (15 mL), $NaIO_4$ (956 mg, 4.46 mmol) was added at r.t and the mixture was stirred for 20 min. The mixture was extacted with AcOEt, washed with H_2O and brine, dried over anhy-drous $MgSO_4$ and chromatographed (SiO_2, 20 g, elution with EtOAc-hexane, 1 : 1 v/v) to give the aldehyde **(47)** (221 mg, 100 %) as colorless oil.

IR (film): *v* = 1734, Cm^{-1}. ^{1}HNMR (300 MHZ, $CDCl_3$): δ = 1.39 (1H, s), 1.42 (2H, s), 2.56 - 2.34 (2H, m), 3.22 - 3.10 (2H, m), 3.79 (1H, s), 3.81 (2H, s), 4.25 (1H, dd, *J* = 12.0, 4.1 Hz), 6.89 - 6.77 (3H, m), 7.33 - 7.25 (1H, m), 9.70 (0.7H, s), 9.79 (0.3H, s). Mass: *m/z* = 248 [M^+]. HRMS: calcd. for C_{14} H_{16} O_4 = 248.1647. Found: 248.1016.

(*1R*) - (7-Methoxy-1-methyl-1,2-dihydro-naphthalen-1-yl) - acetic acid methyl ester (48).

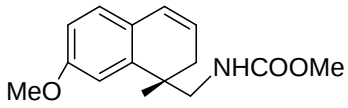


A mixture of **(47)** (220 mg, 0.88 mmol) and activated zinc (5.8 g, 88.65 mmol) was refluxed in AcOH (30 mL) for 20 h. The mixture was filtrated through Celite pad, neutralized by addition of saturated aqueous $NaHCO_3$ and evaporated under reduced pressure. The residue was diluted with water (5mL) and extracted with EtOAc, the extract was washed successively with water and brine, dried over anhydrous $MgSO_4$, evaporated under reduced pressure, and chromatographed (SiO_2, 15 g, elution with hexane-AcOEt, 3 : 1 v/v) to afford **(48)** (142 mg, 69%) as colorless oil. To identify the acid **(48)** it was transformed to the ester **(49)** by reaction with CH_2N_2 in Et_2O at 0°C .

IR (film): *v* = 1729, Cm^{-1}. ^{1}HNMR (300 MHZ, $CDCl_3$): δ = 1.45(3H, s), 2.23 (1H, td, *J* =17.3, 3.0 Hz), 2.45 (1H, d, *J* = 13.5 Hz),), 2.46 (1H, br. D, *J* = 17.0 Hz), 2.56 (1H, d, *J* = 13.5 Hz), 3.57 (3H, s), 3.80 (3H, s), 5.83 (1H, ddd, *J* = 9.4, 5.7, 3.5 Hz), 6.44 (1H, dd, *J* = 9.6, 2.5 Hz), 6.70 (1H, dd, *J* = 8.4, 2.6 Hz), 6.85 (1H, d, *J* = 2.5 Hz), 7.00 (1H, d, *J* = 8.2 Hz),

Mass: *m/z* = 246 [M^+]. HRMS: calcd. for C_{15} H_{18} O_3 = 246.1256. Found: 246.1252.

(+) - (1*R*) -(7-Methoxy1-methyl-1,2-dihydro-naphthalen-1-yl) carbamic acid methyl ester (50)



To a stirred mixture of acid **(48)** (90 mg, 0.38 mmol), Et_3N (0.8 ml,0.58 mmol), $(Ph_2O)_2$ P(O) N_3 (0.125 ml, o.58 mmol) in benzene (5 ml) was heated in a sealed tube at 130 °C for 1h, cooled to r.t, (2mL) MeOH were added and heated again at the same temperature for 5 h, cooled to r.t.

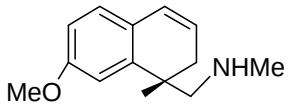
The solvent was evaporated under reduced pressure and chromatographed(SiO_2, 20 g, elution with hexane-AcOEt, 6 : 1 v/v) to afford **(50)** (95 mg, 92%) as colorless oil.

$[\alpha]_D^{28}$ + 6.6 (*c* 1.07, $CHCl_3$).). [lit.[62] $[\alpha]_D^{30}$ + 6.85 (*c* 0.90, $CHCl_3$)].

IR (film): *v* = 3336, 1729, Cm^{-1}. ^{1}HNMR (300 MHZ, $CDCl_3$): δ = 1.26 (3H, s), 2.35 –2.18 (2H, m), 3.39 –3.25 (2H, m), 3.63 (3H, s), 3.81 (3H, s), 5.30 (1H, br.s), 5.79 (1H, td, *J* = 9.3, 4.5 Hz), 6.38 (1H, d, *J* = 9.6 Hz), 6.71 (1H, dd, *J* = 8.4, 2.6 Hz), 6.81 (1H, d, *J* = 2.4 Hz), 7.00 (1H, d, *J* = 8.2 Hz).

Mass: *m/z* = 261 [M^+]. HRMS: calcd. for C_{15} H_{19} O_3 N = 261.1364. Found: 261.1411.

(+)- (1R)-7- Methoxy-1-methyl-1,2-dihydro-naphthalen-1-ylmethyl)-methylamine (51).



To a stirred solution of the carbamate **(50)** (90 mg, 0.34 mmol) in THF (5 mL), $LiAlH_4$ (40 mg, 1.03 mmol) was added at 0 °C, stirred for 5 min. and the mixture was refluxed for 25 min, cooled to r.t, diluted with ether (1mL) followed by ammonia solution (1mL) and stirred for 30 min. at r.t.

The mixture was filtered through Celite pad, washed with water and brine, dried over anhydrous MgSO4, evaporated under reduced pressure, and chromatographed (SiO_2, 10 g, elution with $CHCl_3$ & NH_4OH-MeOH, 50: 1 v/v) to afford **(51)** (62 mg, 83%) as pale yellow oil,

IR (film): ν = 3334, 1605 Cm^{-1}. ^{1}HNMR (300 MHZ, $CDCl_3$): δ = 1.29 (3H, s), 2.19 –2.14 (1H, m), 2.38 (3H, br. s), 2.53 – 2.44 (1H, m), 2.68 – 2.63 (2H, m), 3.80 (3H, s), 5.84 – 5.77 (1H, m), 6.36 (1H, d, *J* = 9.0 Hz), 6.69 (1H, dd, *J* = 8.24, 2.47 Hz), 6.83 (1H, d, *J* = 2.47 Hz), 6.98 (1H, d, *J* = 8.24Hz). Mass: *m/z* = 217 [M^+]. HRMS: calcd. for C_{14} H_{19} N O = 217.1465. Found: 217.1474.

General procedure for deprotection of THP group.

THP ether (500mg) in methanol (10mL) was stirred with Montmorillonite **k**-10 (500mg) at r.t. for 2 h.

The mixture was filtrated through Celite-pad, the filtrate was evaporated under reduced pressure and the residue was chromatographed on silica gel column (AcOEt-hexane) to give the corresponding alcohol as a colorless oil, (table-3 & 4).

Table 5: Spectral data.

Compounds	H^1NMR, IR &Mass
Table-2, 1	δ = 7.33 (5H, m), 3.65 (2H, dd, *J* =11.8, 5.7 Hz), 3.52 (2H, t), 1.74~1.65 (4H, m). IR (film): *v* =3400 cm^{-1} HRMS: *m/z* calcd for C_{11} H_{16} O_2 [M^+] 180.1239, found 180.1143.
Table-2, 9	δ = 7.35~7.25 (5H, m), 5.83~5.70 (2H, m), 4.52 (2H, s), 4.15 (2H, d, *J* =6.4 Hz), 4.09 2H, d, *J*= 5.7 Hz), 2.12 (1H,s). IR (film): *v* =3416 cm^{-1}

N.B: all the THP ethers were prepared by reaction of the alcohol with DHP in CH_2Cl_2 in the presence of *p*-TsOH at r.t. *and* reaction of the THP ethers with ather protective group in the suitable solvent and suitable base.

Table 3: K-10 Clay-Mediated Deprotection of Simple THP Ethers.

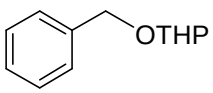
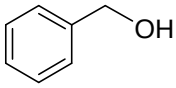
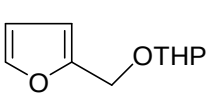
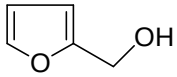
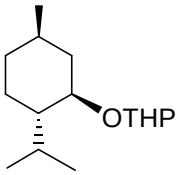
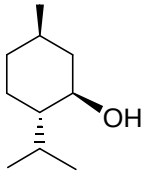
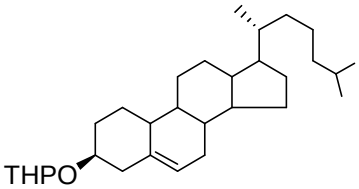
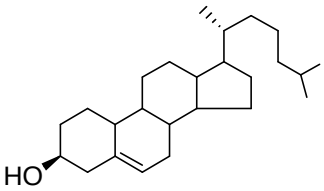
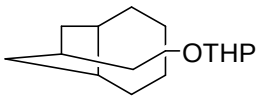
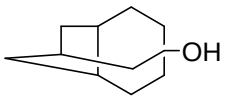
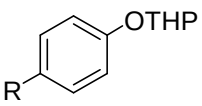
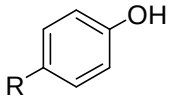
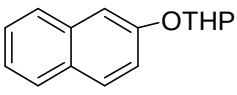
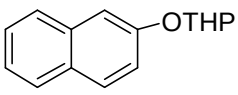
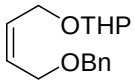
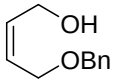
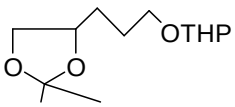
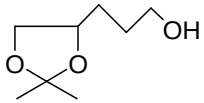
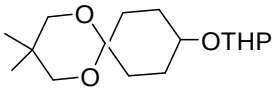
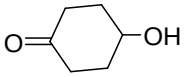
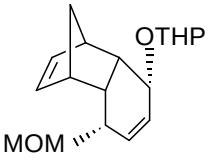
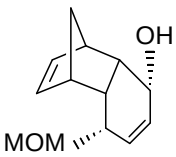
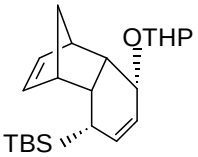
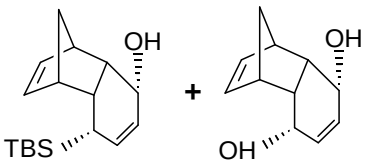
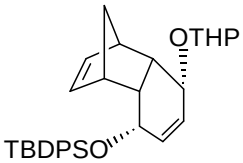
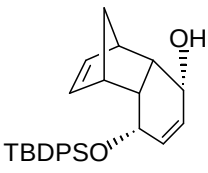
Entry	Substrate	Product	Yield %
1			91
2			95
3	$Me(CH_2)_5CH_2OTHP$	$Me(CH_2)_5CH_2OH$	97
4			86
5			80
6			90
			
7	**R=H**	**R=H**	98
8	**R=NO2**	**R=NO2**	83
9	**R=OMe**	**R=OMe**	99
10			0

Table 4: K-10 Clay-Mediated Deprotection of Functionalized THP Ethers.

Entry	Substrate	**Product**	**Yield %**
	$RO(CH_2)_4OTHP$	$RO(CH_2)_4OH$	
1	R=Bn	R=Bn	92
2	R=allyl	R=allyl	82
3	$R=MeOCH_2$	$R=MeOCH_2$	98
4	$R={}^tBuMe_2Si$	$R={}^tBuMe_2Si$	25
5	$R={}^tBuPh_2Si$	$R={}^tBuPh_2Si$	82
6	R=MeCO	R=MeCO	92
7	R=PhCO	R=PhCO	97
8	$R=CCl_3C(=NH)$	R=OTHP	61
9			94
10			32
11			85
12			93
13			48
14			99

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