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**Review Article**

# Application of chiral building blocks to the synthesis of drugs

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## Introduction

A number of piperidines and indolizidines bearing carbonaceous substituents at both α and α' positions have been isolated from natural sources (1, 2), and many of them have received much attention due to a variety of biological activities. 3-Piperidinol alkaloids having appendages at both α and α' positions also have been isolated from plants (3). These 3-piperidinol alkaloids also exhibit a variety of pharmacological properties such as anesthetic, analgesic and antibiotic activities. Recently, the alkaloids containing this ring system were isolated from marine species and all of them showed substantial cytotoxic activity against human solid tumor cell lines (4-6). On the other hand, construction of a versatile chiral building block for biologically active natural compounds would provide us with powerful tools for the synthesis of target natural products. In addition, it is very important for the evaluation of the biological activities of synthetic compounds that both enantiomers of the chiral building blocks be available in a similar manner. Accordingly, we designed two chiral building blocks (**1**, **2**) for the synthesis of biologically interesting alkaloids. This review describes the synthesis of the chiral building blocks (**1**, **2**) and its application to the stereodivergent synthesis of 3-piperidinol alkaloids, the flexible route to the dart-poison frog alkaloids and the synthesis of cytotoxic marine alkaloids.

## Design and synthesis of chiral building blocks

First, we designed the piperidinol (**1**) as the chiral building block for the synthesis of 3-piperidinol alkaloids. As mentioned above, it is very important that both enantiomers of the chiral building block be synthesised in a similar manner. To this end, we examined the chemo-enzymatic differentiation of azabicyclic *meso* glycol (**3**) and its acetate (**4**) as shown in Figure 1.

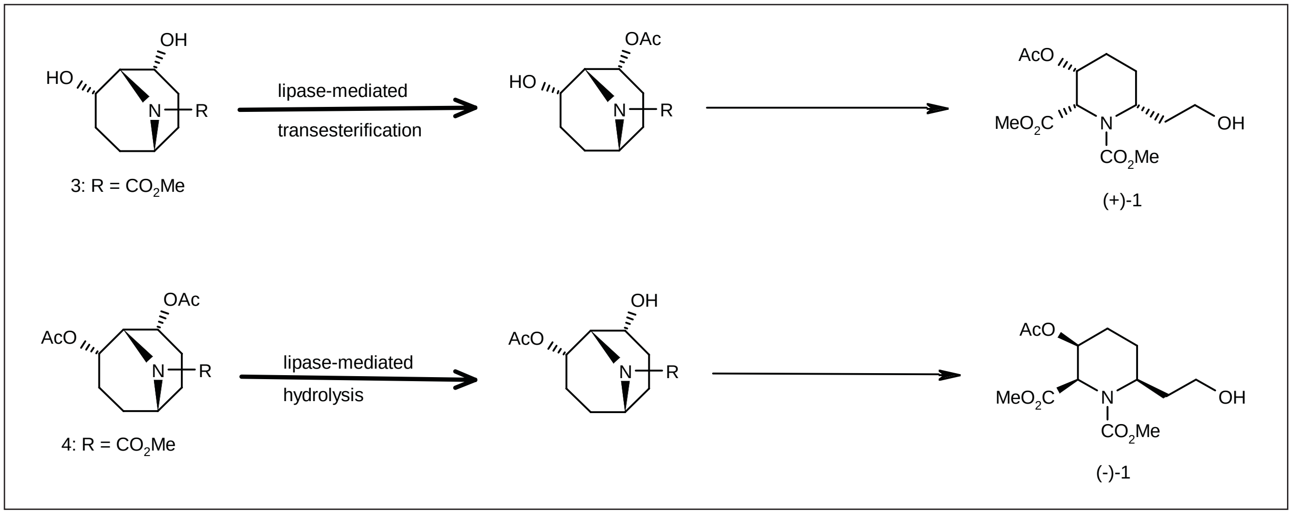
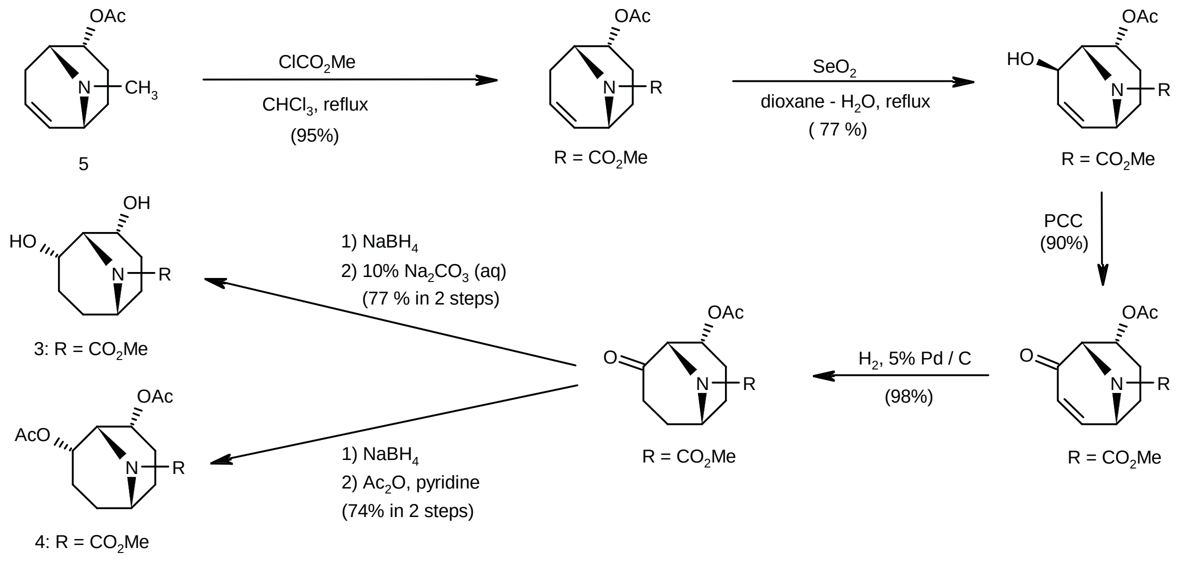


Fig. 1.

**Scheme 1**

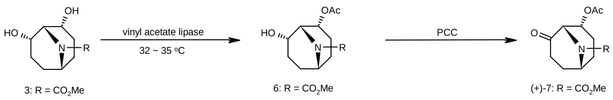


The substrates (**3**, **4**) for the lipase-mediated differentiation reaction were prepared from a known bicyclic amine (**5**) (7) as depicted in Scheme 1.

With the requisite **3** and **4** in hand, we focused our attention on the lipase-mediated enantioselective transesterification of **3** and hydrolysis of **4**. As shown in Tables I and II, the use of lipase CE gave the best results in both cases, and recrystallization of the enantiomeric ketone (**7**) derived from oxidation of the enantiomeric monoacetate (**6**) with PCC furnished an enantiomerically pure ketone (+)-(**7**) or (–)-(**7**) in 74% or 65% yield, respectively, from **3** or **4**.

The ketone (+)-(**7**) was converted to the desired building block (+)-(**1**) by the oxidative cleavage of the piperi-

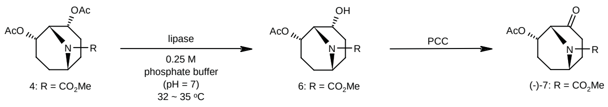
*Table I:*[a]



| Lipase[b] | Solvent | t/h | Yield (%)[c] | (% ee)[d] |
|---|---|---|---|---|
| CE | $C_6H_6$ | 98 | 38 (99) | 32 |
| CE | $i$-$Pr_2O$ | 109 | 85 (99) | 90 (>99) |
| AY | $i$-$Pr_2O$ | 87 | 33 (99) | 56 |
| CCL | $i$-$Pr_2O$ | 91 | 15 (94) | 54 |

[a] All runs were conducted with substrate (0.23 mmol), lipase (100 mg) and vinyl acetate (2 equiv.) in the organic solvent (10 ml). [b] Lipase CE (from *Humicola lanuginosa*) and AY (from *Candida rugosa*) were supplied by the Amano Pharmaceutical Co., Ltd. [c] Yields for the isolated monoacetates; yields in parentheses are those based on the conversion rate. [d] Optical yields were determined by HPLC analyses by using a column packed with Chiralpak AD (EtOH-hexane, 9:1) after oxidation of the monoacetate with PCC. Optical yield in parentheses is based on a sample after single recrystallization from $i$-$Pr_2O$.

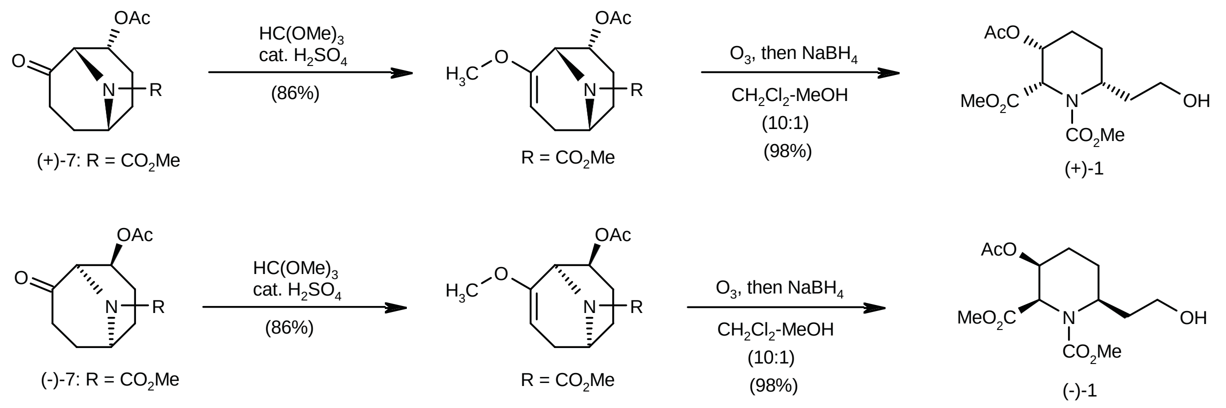
*Table II:*[a]

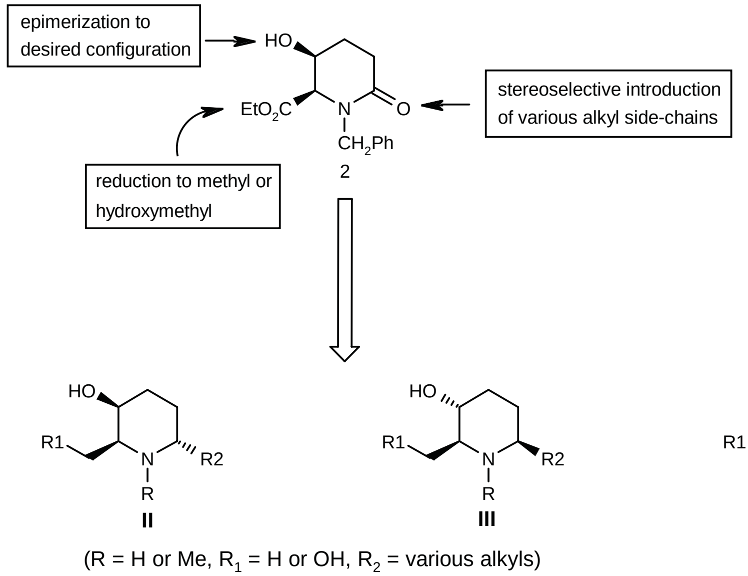


| Lipase[b] | t/h | Yield (%)[c] | (% ee)[d] |
|---|---|---|---|
| CE | 23 | 84 (99) | 80 (>99) |
| AY | 35 | 42 (76) | 78 |
| CCL | 66 | 23 (70) | 58 |
| PPL | 84 | 14 (45) | 48 |
| PLE | 48 | 39 (76) | 75 |

[a] All runs were conducted with substrate (0.17 mmol), lipase (100 mg) and phosphate buffer in the solvent (6 ml). [b] PLE (pig liver esterase) was supplied by the Amano Pharmaceutical Co., Ltd. and PPL (porcine pancreas lipase) was purchased from the Sigma Chemical Co., Ltd. [c] Yields for the isolated monoacetates; yields in parentheses are those based on the conversion rate. [d] Determined for (–)-**6** as in the transesterification of **3**. Optical yield in parentheses is based on a sample after recrystallization twice from $i$-$Pr_2O$.

**Scheme 2**

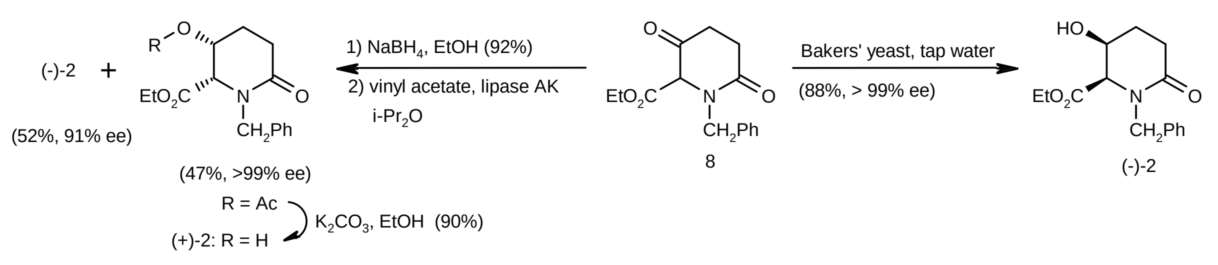




(R = H or Me, R$_1$ = H or OH, R$_2$ = various alkyls)

Fig. 2

**Scheme 3**

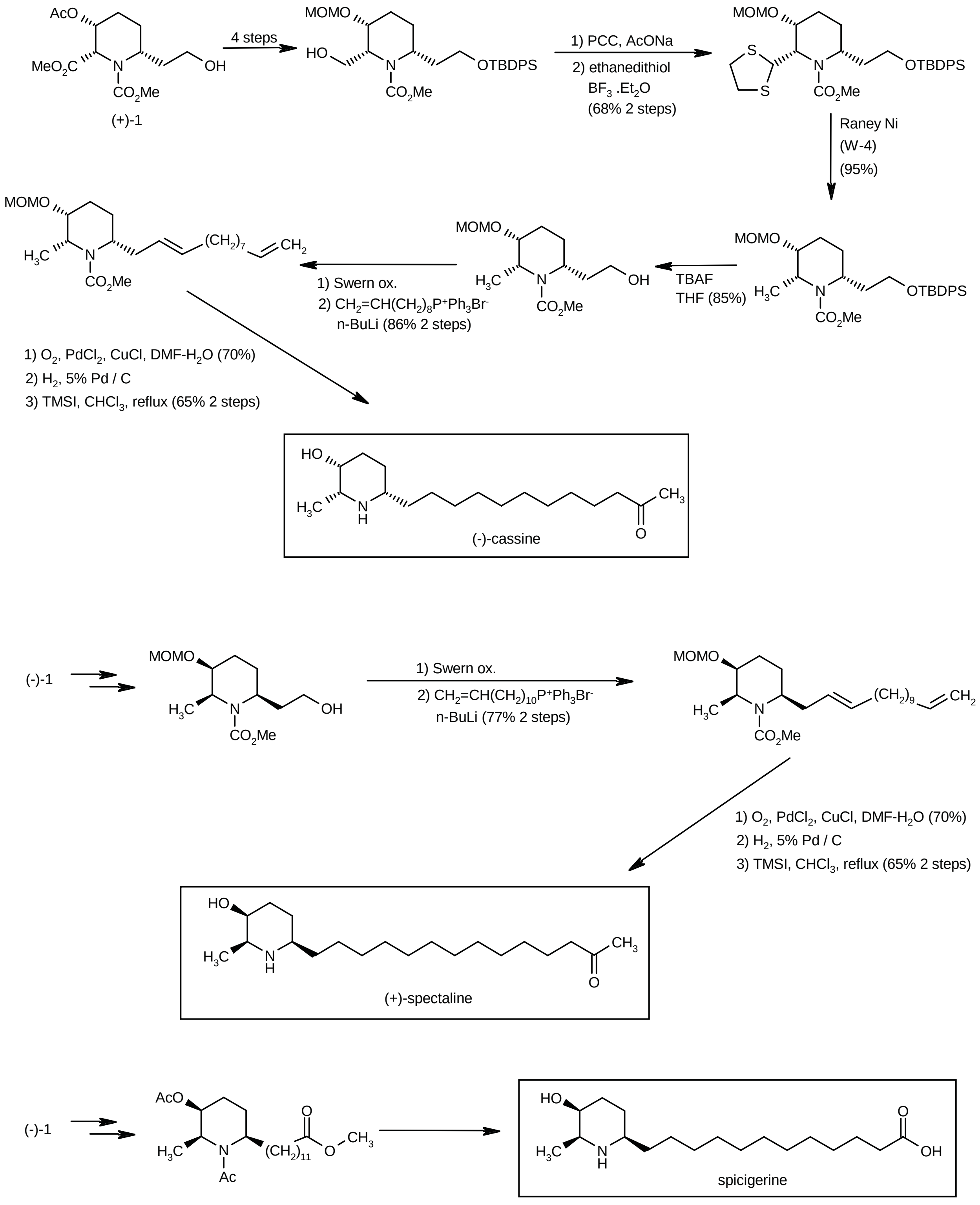


done ring in **7**. Similarly, (–)-**7** was transformed into (–)-**1** as shown in Scheme 2 (8, 9).

Next, we designed the 2-piperidone (**2**) as the more flexible chiral building block for the synthesis of 3-piperidinol alkaloids. The basic strategy we used to prepare all four stereoisomers of α,α'-disubstituted 3-piperidinol building blocks from **2** is presented in Figure 2.

Thus, we examined the preparation of both enantiomers of **2**, and prepared them from the known β-keto ester (**8**) (10) using bakers' yeast reduction of **8** or

**Scheme 4**


AcO
MeO2C
N
CO2Me
OH
(+)-1
4 steps
MOMO
HO
N
CO2Me
OTBDPS
1) PCC, AcONa
2) ethanedithiol
BF3 .Et2O
(68% 2 steps)
S
S
Raney Ni
(W-4)
(95%)
TBAF
THF (85%)
H3C
1) Swern ox.
2) CH2=CH(CH2)8P+Ph3Br-
n-BuLi (86% 2 steps)
(CH2)7
CH2
1) O2, PdCl2, CuCl, DMF-H2O (70%)
2) H2, 5% Pd / C
3) TMSI, CHCl3, reflux (65% 2 steps)
HO
CH3
O
NH
(-)-cassine
(-)-1
1) Swern ox.
2) CH2=CH(CH2)10P+Ph3Br-
n-BuLi (77% 2 steps)
(CH2)9
1) O2, PdCl2, CuCl, DMF-H2O (70%)
2) H2, 5% Pd / C
3) TMSI, CHCl3, reflux (65% 2 steps)
(+)-spectaline
(-)-1
Ac
(CH2)11
O
OH
spicigerine

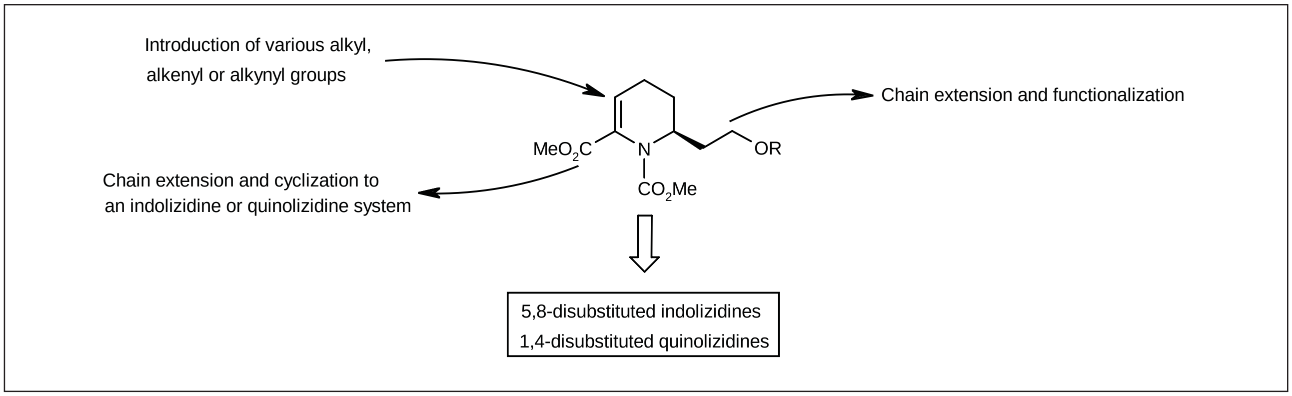
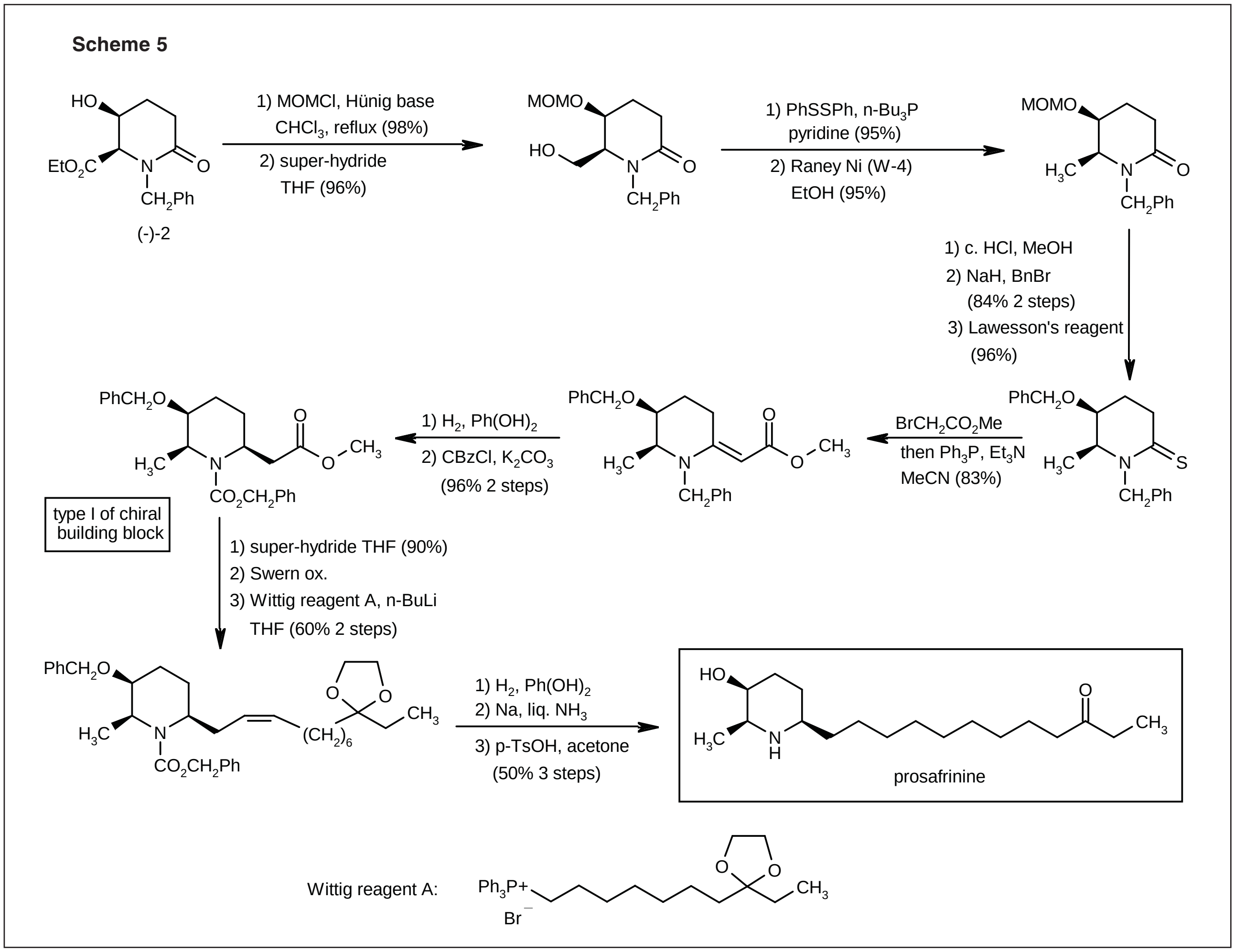


Fig. 3



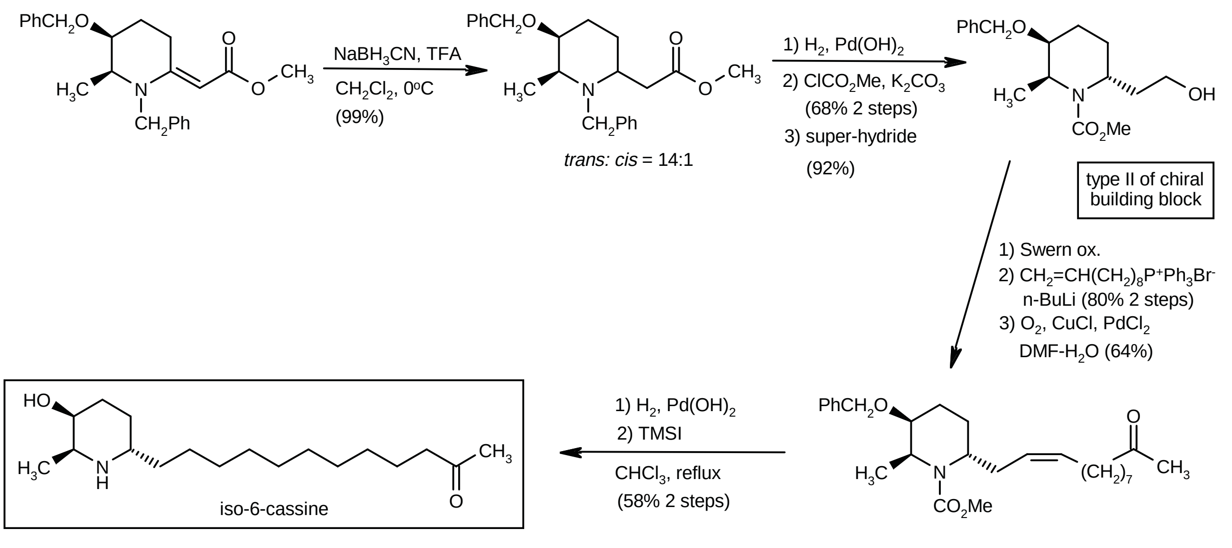
lipase-mediated kinetic resolution of the corresponding racemic **2** (11) (Scheme 3).

## Synthesis of 3-piperidinol alkaloids

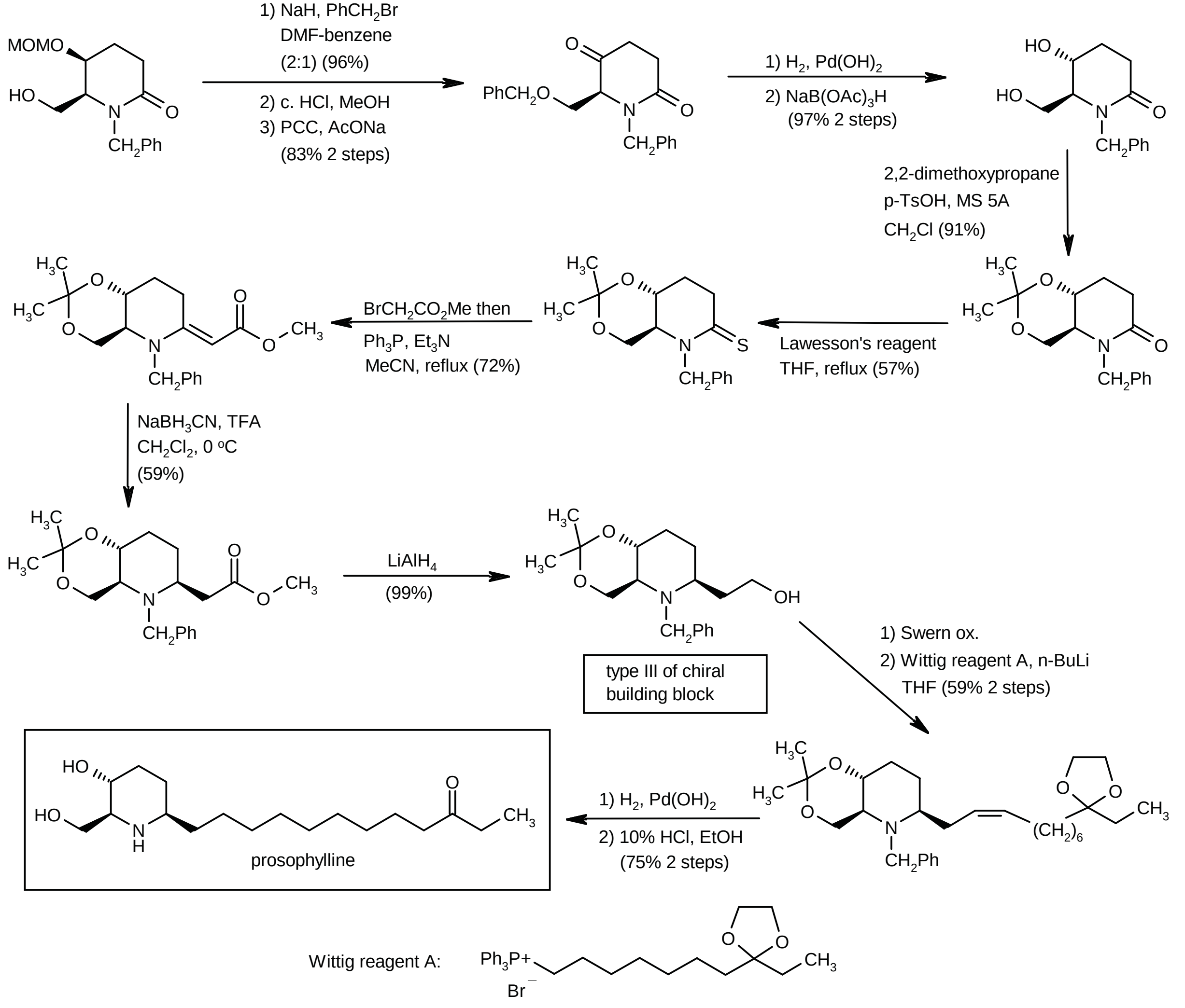
The synthetic utility of (+)- and (–)-**1** has been demonstrated by the first total synthesis of (–)-cassine, (+)-spectaline, (12) and methyl *N*,*O*-diacetylspicigerinate (13) as shown in Scheme 4. The absolute configuration of natural cassine, spectaline and spicigerine was unambiguously determined by the above chiral synthesis.

More efficiently, we synthesized the chiral building blocks (I, II, III and IV as shown in Figure 3) starting from (–)-2 and achieved the stereodivergent synthesis of the 3-piperidinol alkaloids prosafrinine, iso-6-cassine, prosophylline and prosopinine, respectively (14) (Schemes 5-8).

**Scheme 6**



**Scheme 7**



**Scheme 8**

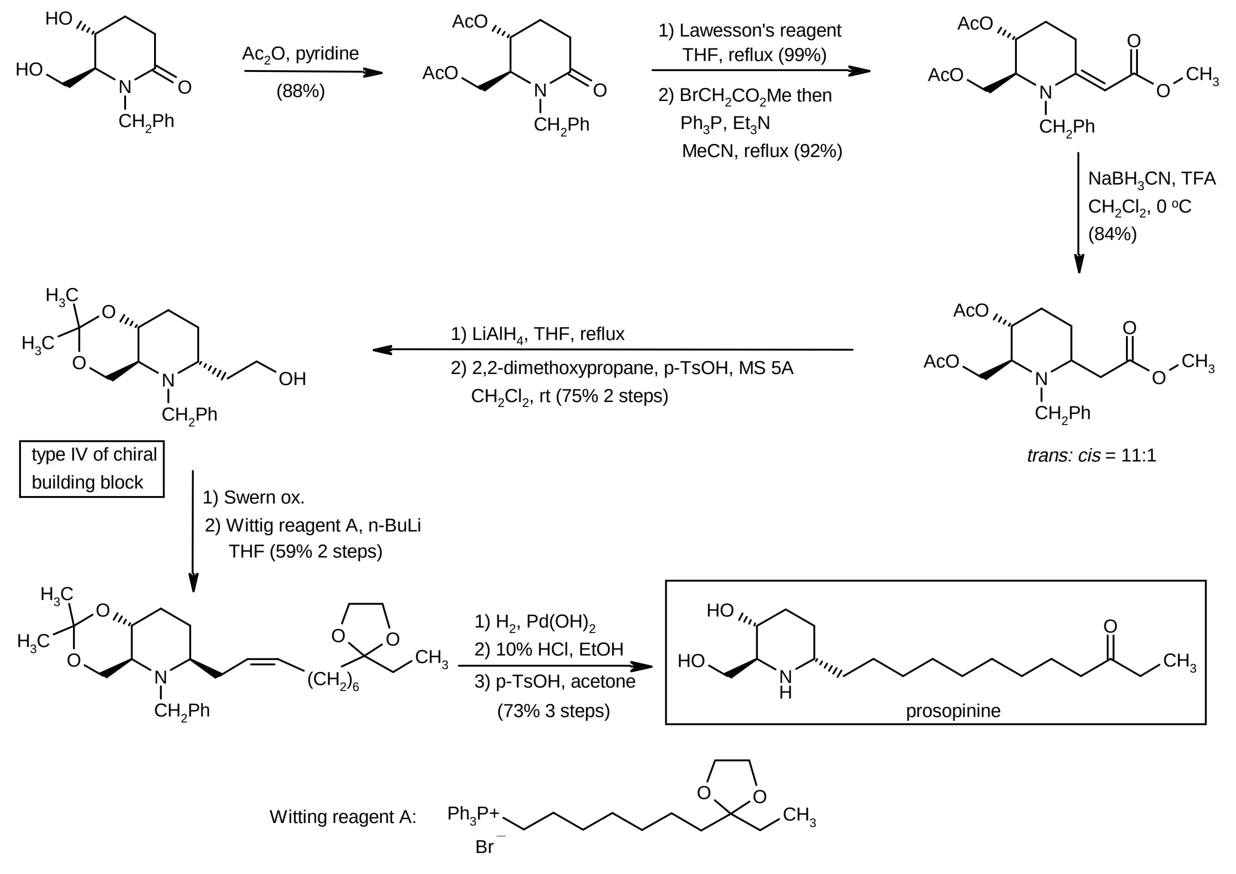
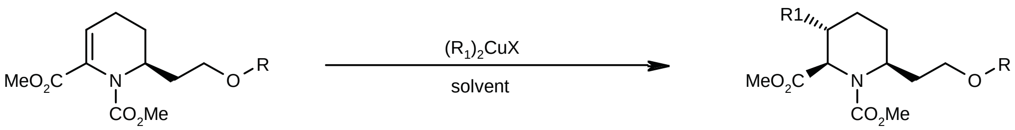


*Table III:*



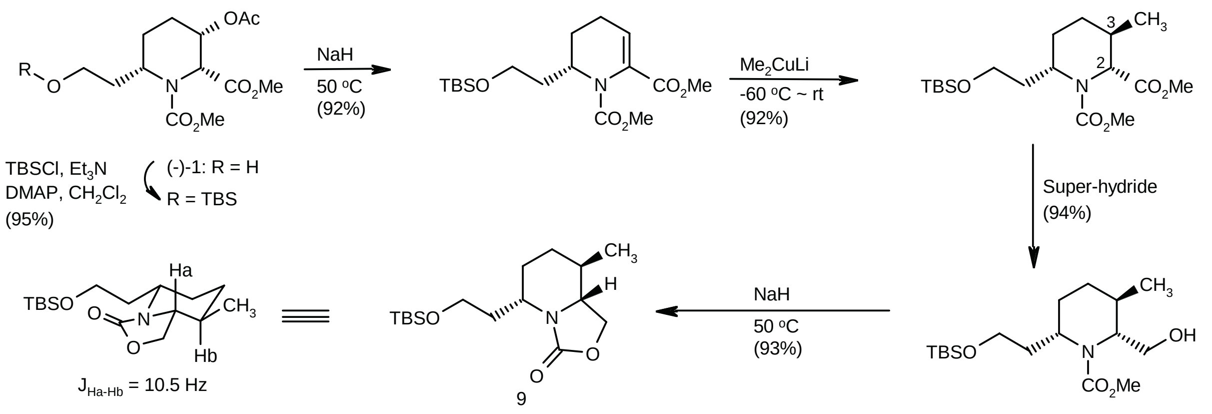
| R¹ | X | R | Solvent | Yield (%) |
|---|---|---|---|---|
| Et | MgBr | TBS | THF | 96 |
| Vinyl | Li | MOM | $Et_2O$ | 91 |
| Allyl | MgBr | MOM | THF | 80 |
| *n*-Bu | Li | TBS | $Et_2O$ | 94 |

## Synthesis of dart-poison frog alkaloids

Another application of building block (–)-**1** to the synthesis of natural alkaloids was accomplished by the flexible synthesis of 5,8-disubstituted indolizidine and 1,4-disubstituted quinolizidine types of Dendrobates alkaloids as shown in Figure 3.

The above synthetic strategy involved the highly stereoselective Michael reaction of the cyclic enaminoester to give rise to 2,3,6-trisubstituted piperidine ring systems, which were suitable intermediates for the synthsis of the above Dendrobates alkaloids. The results are summarized in Table III.

**Scheme 9**



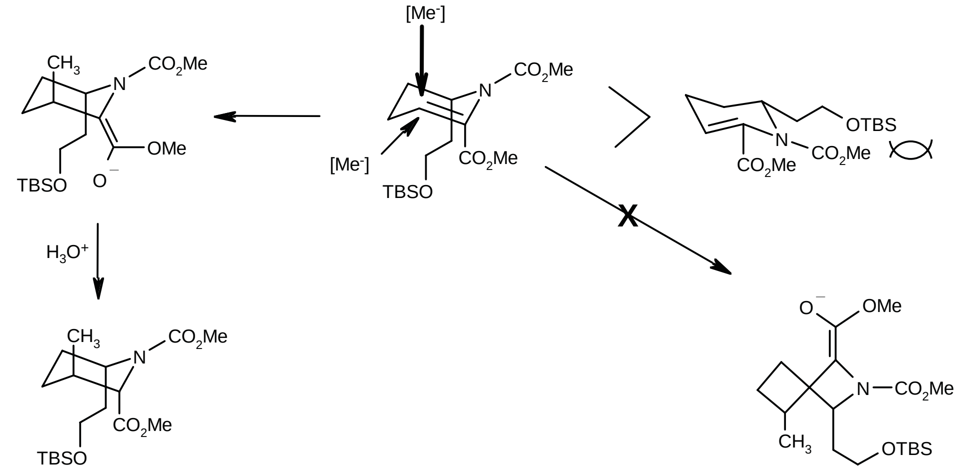


Fig. 4

Analysis of the coupling patterns of the methine proton at C-2 and the methyleme protons at C-7 in the NMR spectrum of the oxazolizinone (**9**) suggested that the stereochemistry of **9** could be assigned as depicted in Scheme 9, by assuming that all the ring appendages lie in equatorial orientation.

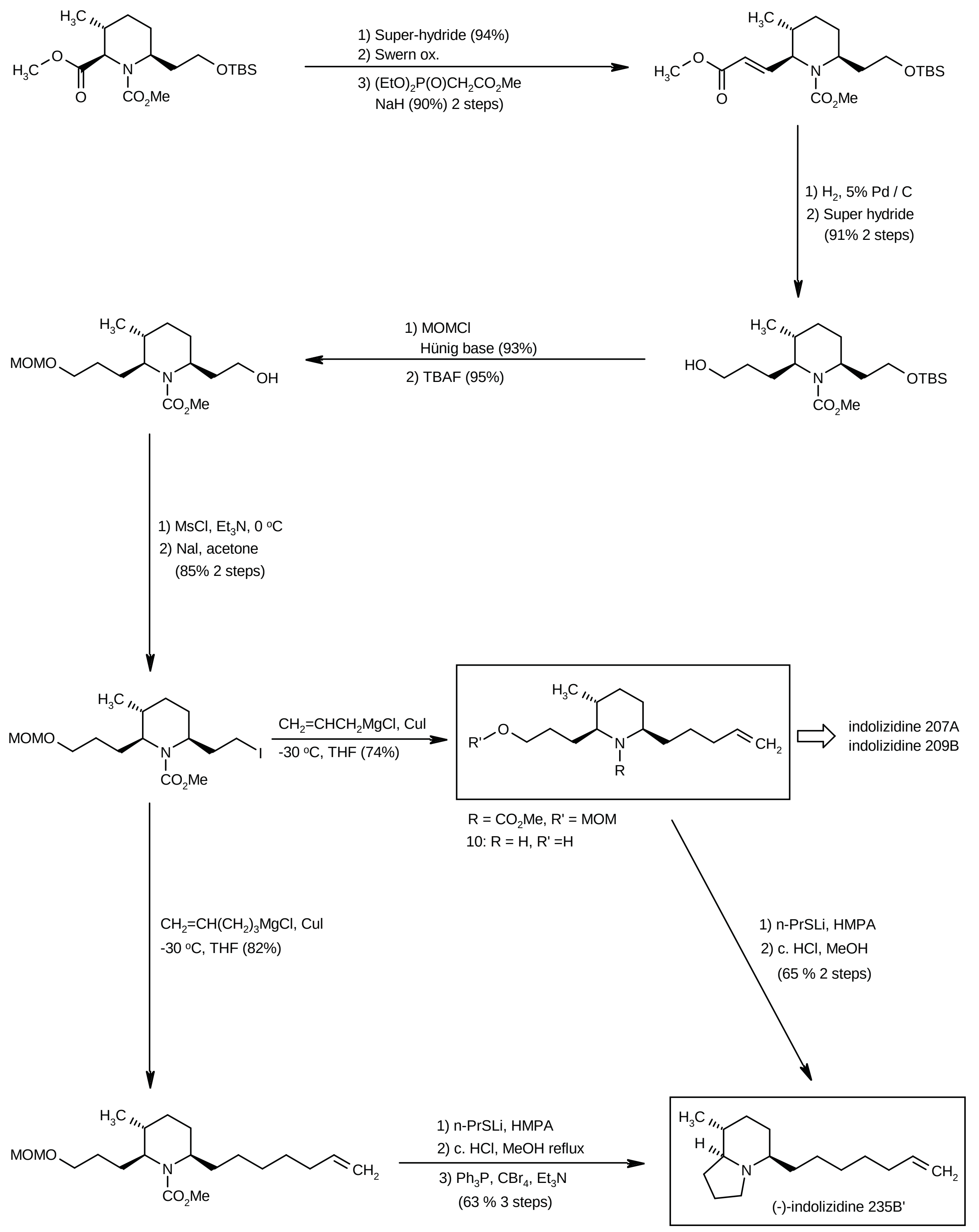
The stereoselectivity of this key Michael reaction results from the preferred $\alpha$-axial attack, leading not to boatlike transition state **B** but to chairlike transition state **A** where the C-6 side chain occupies the quasiaxial orientation owing to $A^{(1,3)}$ strain (Fig. 4).

As a result, we achieved the enantioselective formal synthesis of indolizidines 207A and 209B from the amino alcohol (**10**) (15, 16), and total synthesis of indolizidines 235B' and 223J and C1-epimer of quinolizidine 2071 (17) (Schemes 10, 11).

### Synthesis of marine alkaloids

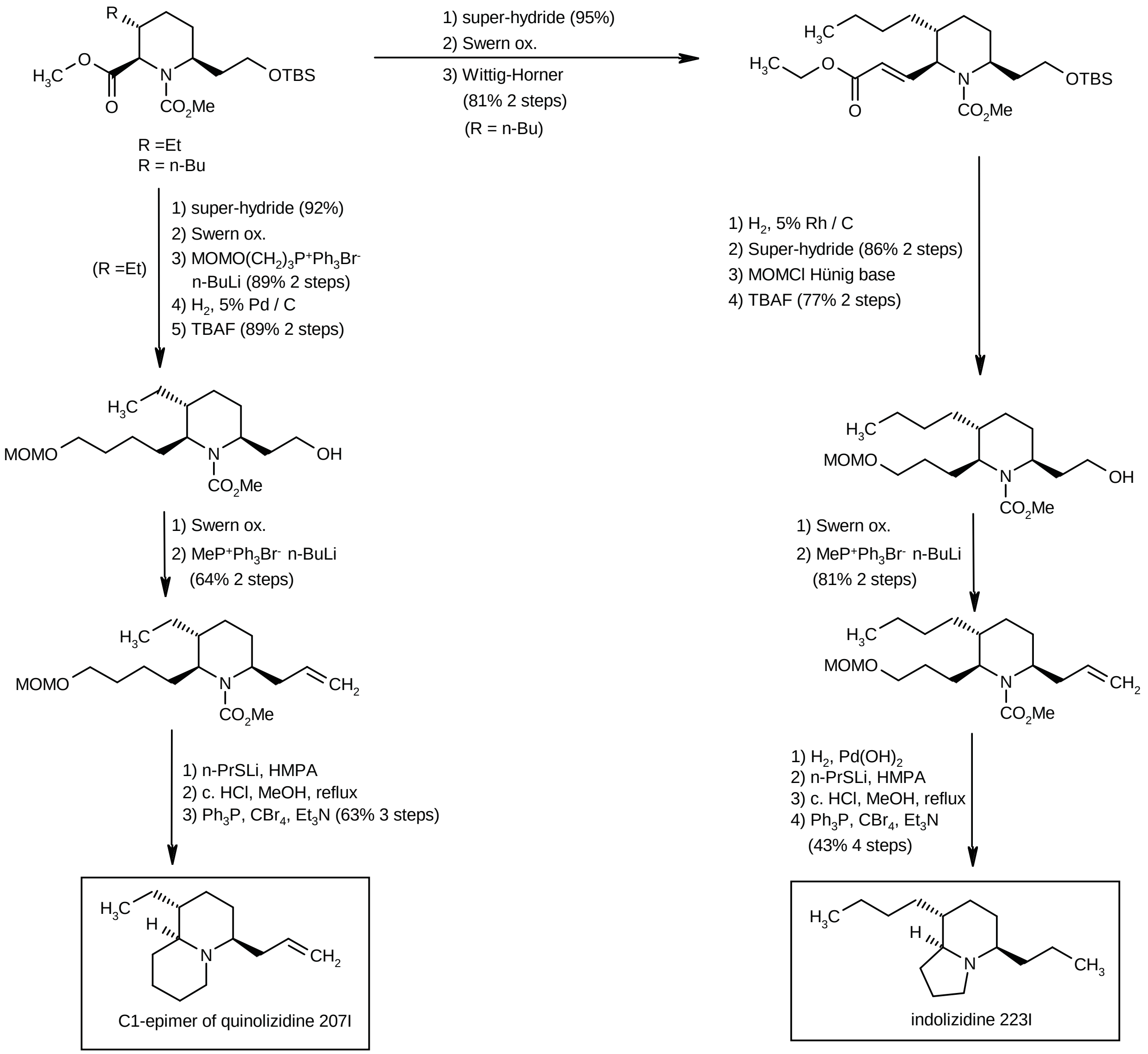
Cardellina's group reported the isolation of the quinolizidine alkaloids clavepictines A and B from the tunicate *Clavelina picta*, which are the first quinolizidine alkaloids from a tunicate. In the same year, Faulkner *et al.* isolated pictamine from the same marine species and its gross structure was determined to be a bis-nor analog of clavepictine A. Furthermore, lepadins A, B and C were isolated from the tunicate *Clavelina lepadiformis* by Steffan and Andesen *et al.* These marine alkaloids involved the 3-piperidinol nuclei and showed significant cytotoxic activity against a variety of murine and human cancer cell lines. Although their relative stereochemistry had been determined by extensive NMR studies of an X-ray diffraction analysis, the absolute stereochemistry

**Scheme 10**

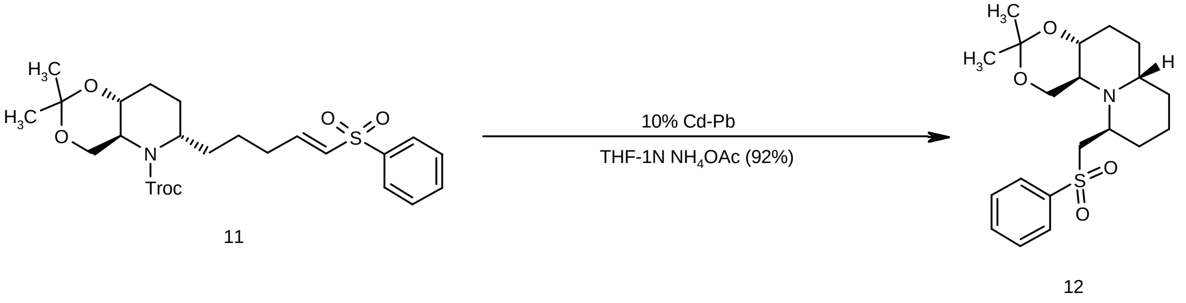


$H_3C$
$H_3C$
O
O
N
$CO_2Me$
OTBS
1) Super-hydride (94%)
2) Swern ox.
3) $(EtO)_2P(O)CH_2CO_2Me$
NaH (90%) 2 steps)
$H_3C$
$H_3C$
O
O
N
$CO_2Me$
OTBS
1) $H_2$, 5% Pd / C
2) Super hydride
(91% 2 steps)
$H_3C$
MOMO
N
$CO_2Me$
OH
1) MOMCl
Hünig base (93%)
2) TBAF (95%)
$H_3C$
HO
N
$CO_2Me$
OTBS
1) MsCl, $Et_3N$, 0 °C
2) NaI, acetone
(85% 2 steps)
$H_3C$
MOMO
N
$CO_2Me$
I
$CH_2=CHCH_2MgCl$, CuI
-30 °C, THF (74%)
$H_3C$
R'
O
N
R
$CH_2$
indolizidine 207A
indolizidine 209B
R = $CO_2Me$, R' = MOM
10: R = H, R' =H
$CH_2=CH(CH_2)_3MgCl$, CuI
-30 °C, THF (82%)
1) n-PrSLi, HMPA
2) c. HCl, MeOH
(65 % 2 steps)
$H_3C$
MOMO
N
$CO_2Me$
$CH_2$
1) n-PrSLi, HMPA
2) c. HCl, MeOH reflux
3) $Ph_3P$, $CBr_4$, $Et_3N$
(63 % 3 steps)
$H_3C$
H
N
$CH_2$
(-)-indolizidine 235B'

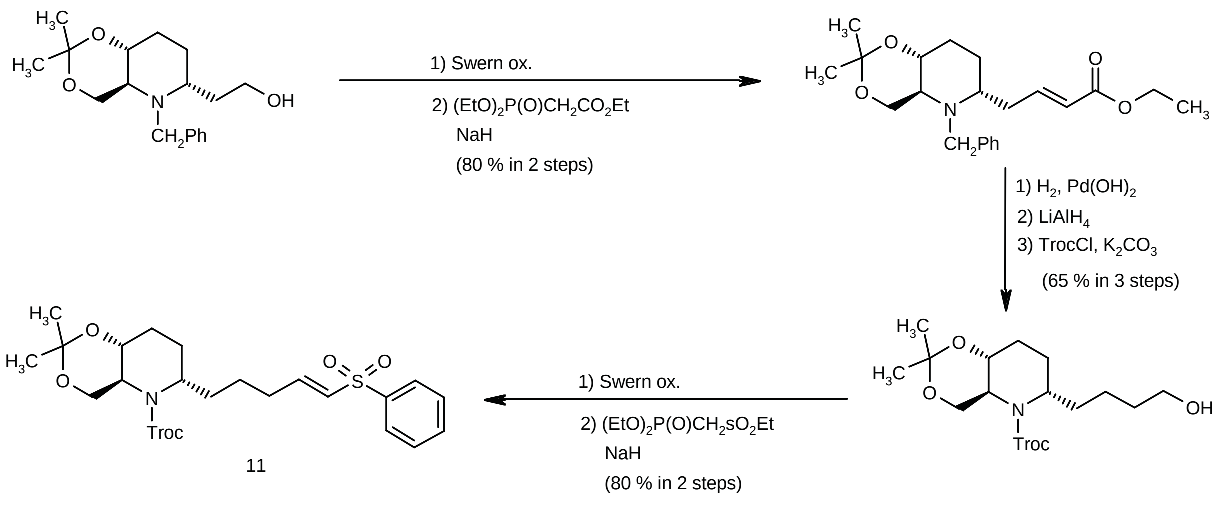
**Scheme 11**



**Scheme 12**



**Scheme 13**



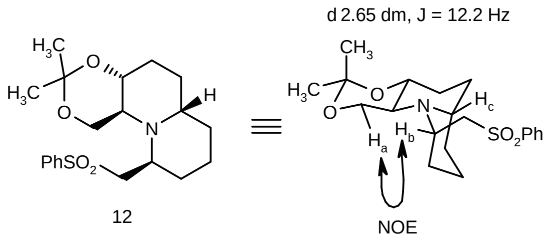


Fig. 5

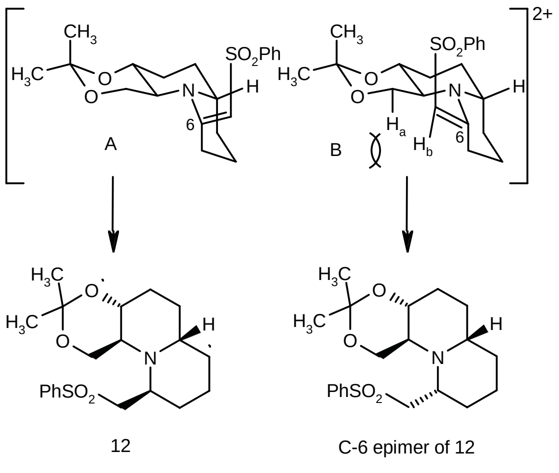
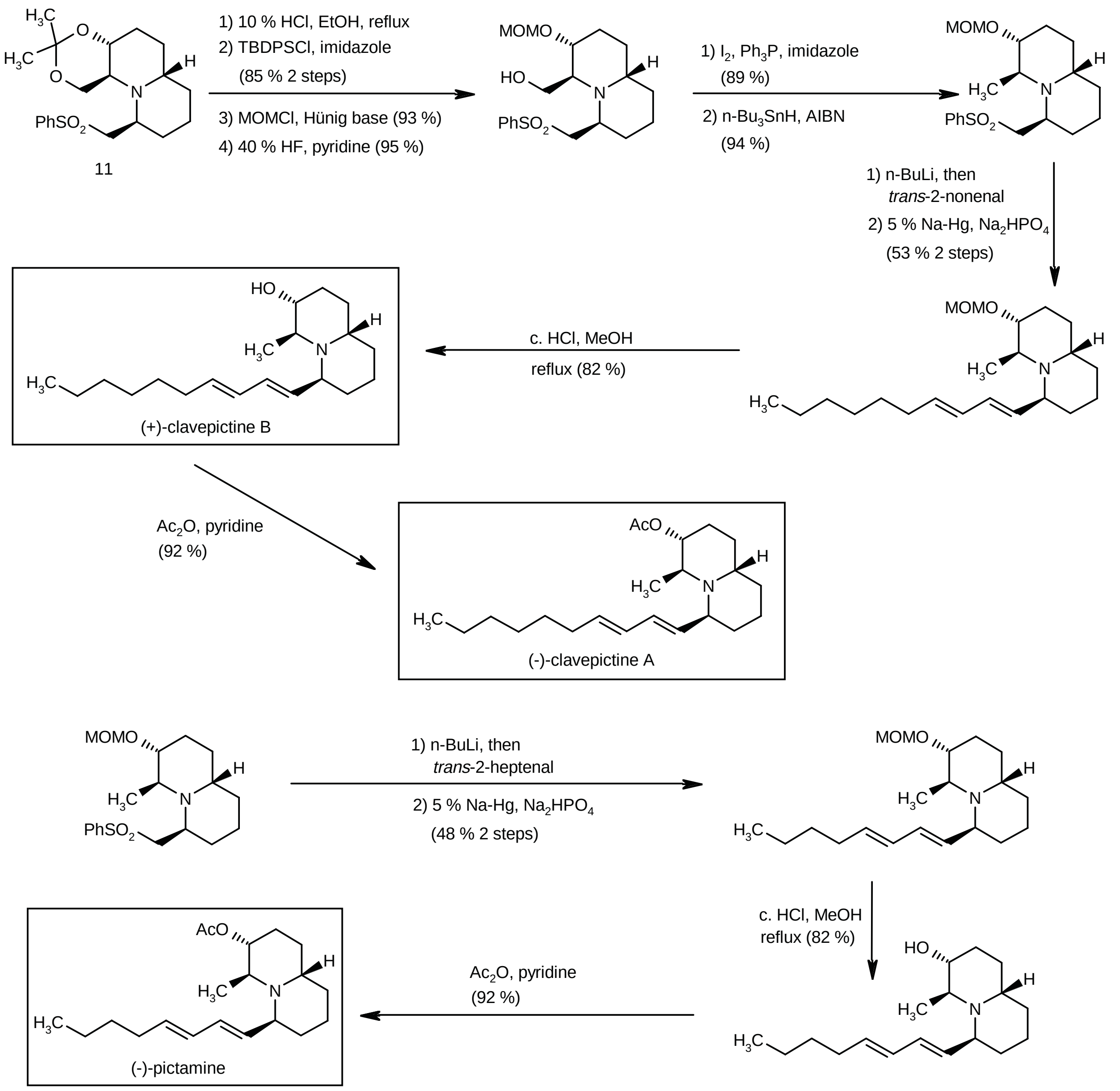


Fig. 6

**Scheme 14**



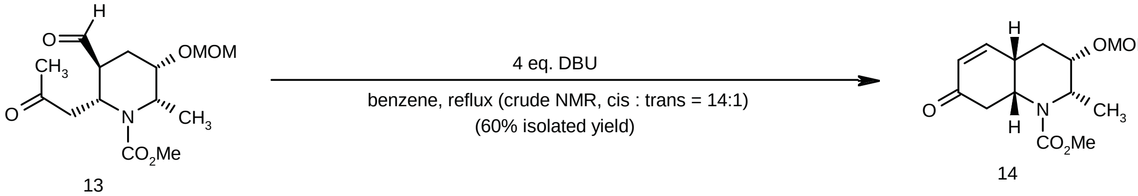
was unknown. We achieved the first enantioselective total synthesis of clavepictines A and B, pictamine and lepadin B starting from chiral building block (**2**). The synthetic strategy for clavepictines and pictamine involved the highly stereoselective quinolizidine ring closure as the key step (Scheme 12).

The key intermediate (**11**) for the above Michael type of quinolizidine ring closure reaction was synthesised as shown in Scheme 13.

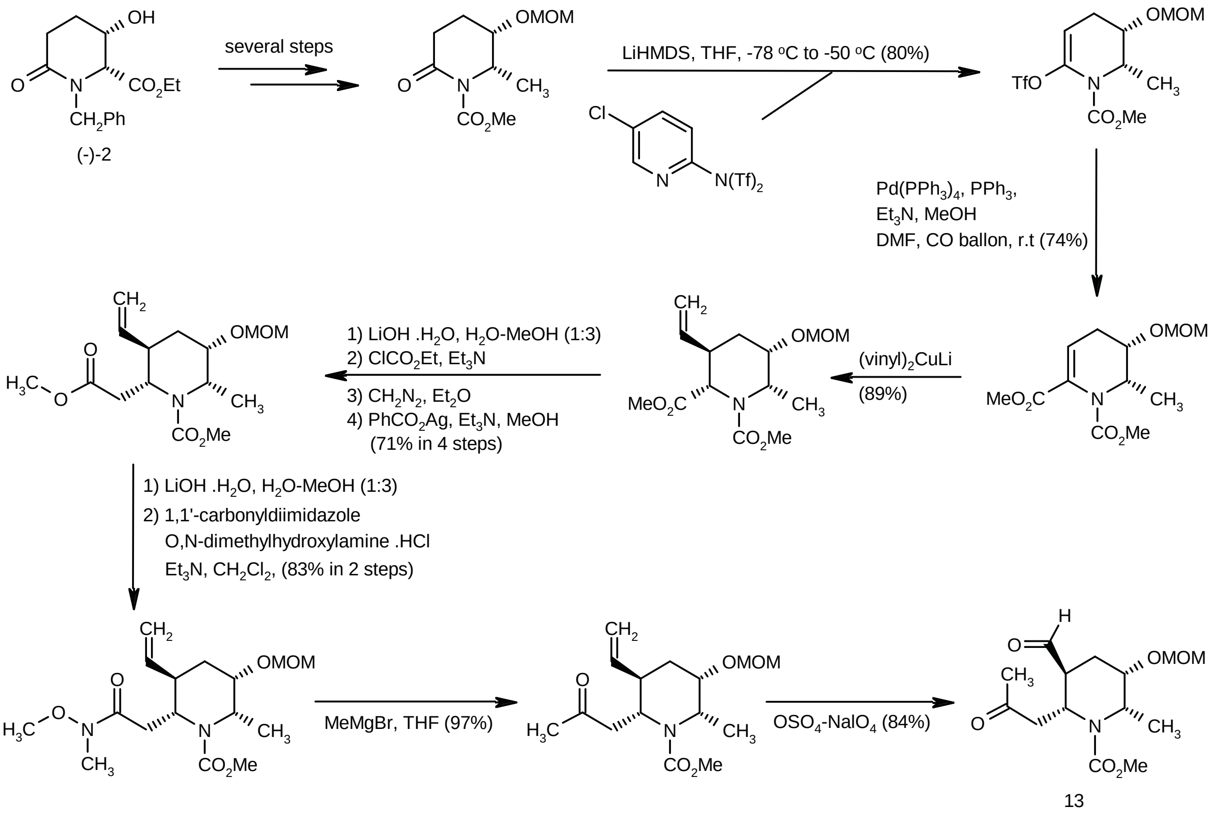
Treatment of (**11**) with Cd-Pb gave the quinolizidine (**12**) as the only cyclized product in excellent yield. The stereochemistry of (**12**) was initially assigned on the basis of the following NOE and coupling constant, and this assignment was confirmed by X-ray analysis (Fig. 5).

This high-kinetic stereoselectivity can be rationalized as shown in Figure 6. Comparison of two kinds of folded chairlike transition states (**A** and **B**) leading to (**12**) and C-6 epimer, respectively, reveals a potential steric repul-

**Scheme 15**



**Scheme 16**



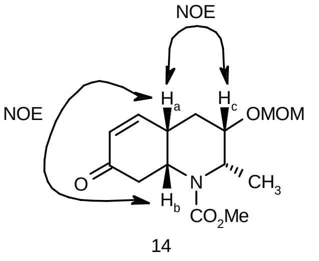


Fig. 7

sion involving the Ha and Hb protons for B. Therefore, the cyclization occurs via the transition state **A** to give rise to the desired product (**12**).

Completion of the total synthesis of clavepictines A, B and pictamine is depicted in Scheme 14. Thus, we achieved the first enantioselective total synthesis of clavepictines A, B and pictamine, and the absolute stereochemistry of these interesting alkaloids was determined by the present synthesis (18, 19).

Furthermore, we adopted the intramolecular aldol type of cyclization reaction of **13** to construct the hexahydroquinolinone ring system (**14**) for the synthesis of lepadin B as the key step as shown in Scheme 15.

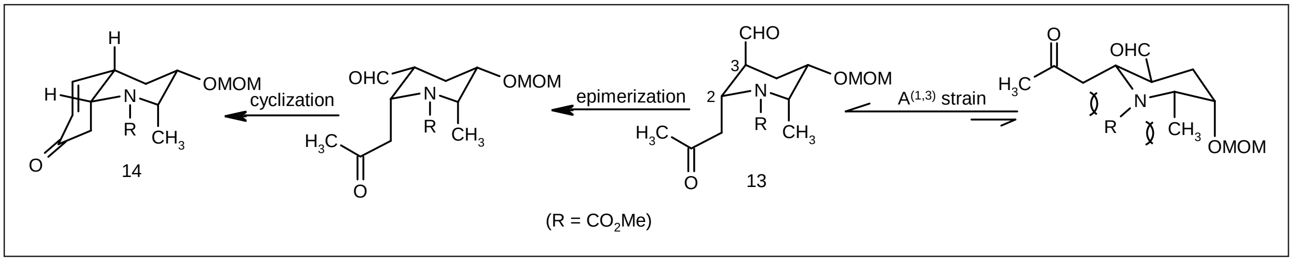
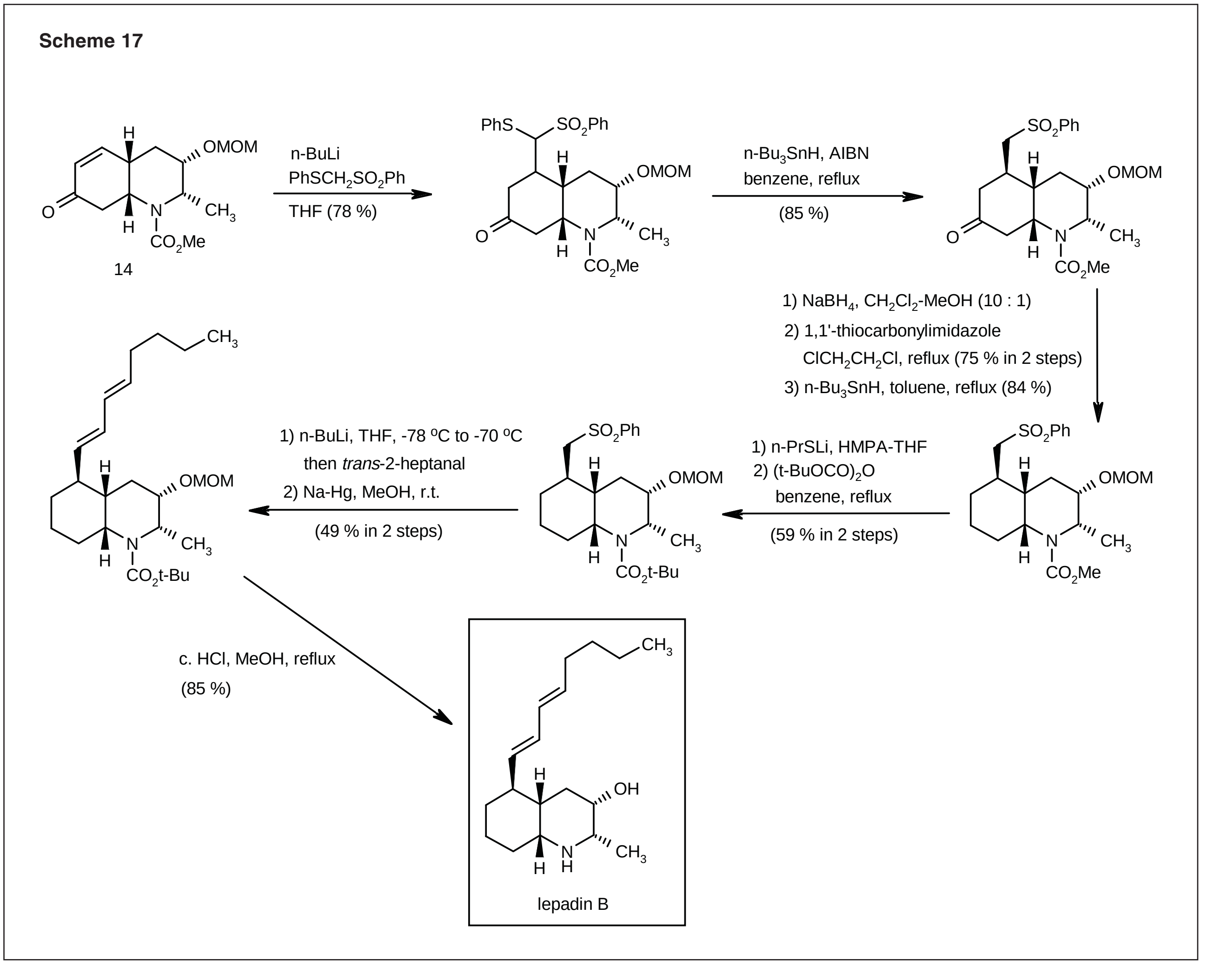


Fig. 8



The key intermediate (**13**) for the above cyclization was synthesized as shown in Scheme 16.

Treatment of (**13**) with 4 equiv. of DBU in refluxing benzene afforded the cyclized product in a ratio of 14:1, and the major product was isolated in 60% yield. The stereochemistry of the major product was determined to be that of the desired *cis*hexahydroquinolinone (**14**) on the basis of the observation of NOEs between Ha and Hb, Ha and Hc on the NOESY experiment (Fig. 7).

The conformation of **13** is restricted to conformer **A** because of the A$^{(1,3)}$ strain and because the appendages on C-2 and C-3 in A lie in a noncyclizable trans diaxial relationship.

Consequently, epimerization at the C-3 position will first give **A'**, which will cyclize easily to afford the desired 4a,8a-*cis*-hexahydroquinolinone **14** (Fig. 8).

Completion of the total synthesis of lepadin B is depicted in Scheme 17. Thus, we achieved the first enan-

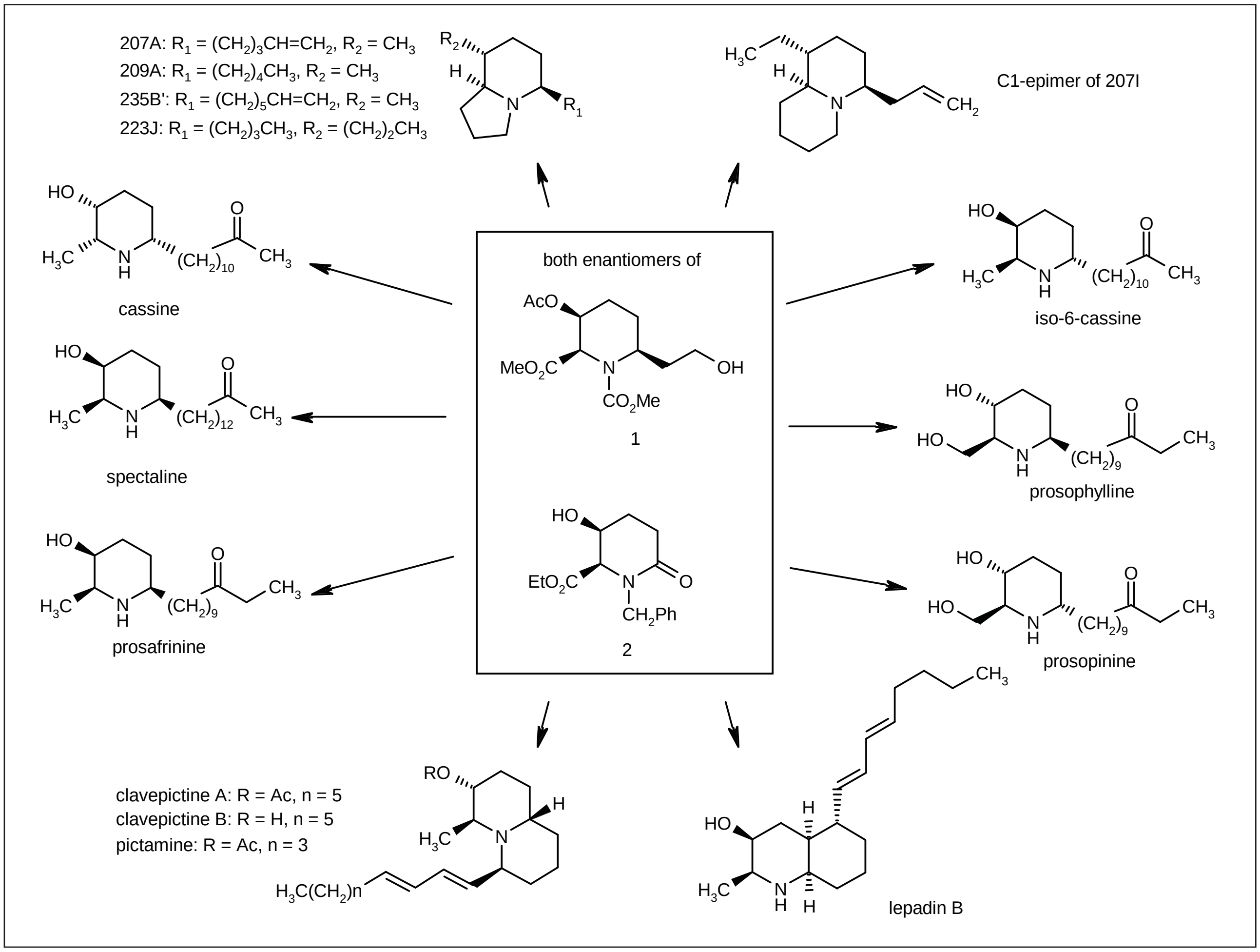


Fig. 9.

tioselective total synthesis of lepadin B, and the absolute stereochemistry of these interesting alkaloids was determined by the present synthesis (20, 21).

## Conclusions

We have demonstrated the efficient synthesis of the two enantiomers of versatile chiral building blocks (**1**, **2**) and its application to the synthesis of biologically active natural products. As a result, we accomplished the first chiral synthesis of the 3-piperidinol alkaloids cassine and spectaline starting from the chiral building block **1**, stereodivergent process for all four stereoisomers of 3-piperidinol chiral building block and its application to the stereodivergent synthesis of the 3-piperidinol alkaloids prosafrinine, iso-6-cassine, prosophylline and prosopinine. Furthermore, we achieved the first enantioselective total synthesis of the marine alkaloids clavepictines A and B, pictamine and lepadin B starting from the chiral building block **2** using the highly stereocontrolled Michael type of quinolizidine ring closure reaction and the intramolecular aldol type of cyclization reaction as the key steps, respectively. These results are summarized in Figure 9.

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