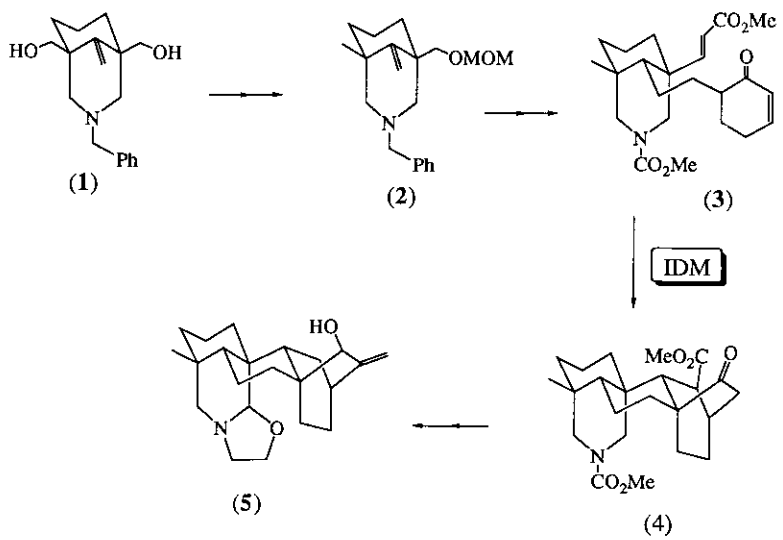
CHIRAL SYNTHESIS OF THE INTERMEDIATE OF ATISINE+

Masataka Ihara, Makoto Suzuki, and Keiichiro Fukumoto*

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

Abstract —The chiral key intermediate, (+)-(1R,5R)-3-benzyl-1-methoxymethyloxymethyl-5-methyl-9-methylene-3-azabicyclo[3.3.1]nonane (**2**), for the synthesis of atisine (**5**) was prepared from dimethyl 3-benzyl-3-azabicyclo[3.3.1]nonan-9-one-1,5-dicarboxylate (**6**) by a chemical methodology.

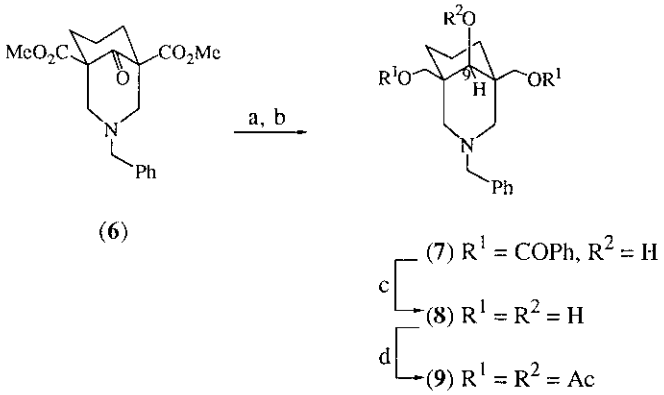
Recently we have developed an efficient route to a diterpene alkaloid, atisine (**5**), via the intramolecular double Michael reaction (IDM) of the enone-ester (**3**).[1] Furthermore the optically active methoxymethyl ether (**2**) was prepared by way of lipase-catalyzed acylation of the diol (**1**) and transformed into the naturally occurring enantiomeric form of atisine (**5**).[2] Simultaneous study by chemical means led us to find out an alternative route to the chiral intermediate (**2**) as follows.



Scheme 1

Reduction of dimethyl 3-benzyl-3-azabicyclo[3.3.1]nonan-9-one-1,5-dicarboxylate (**6**)[1] with lithium triethylborohydride in ether, followed by benzoylation, gave, in 91% yield, a mixture of two stereoisomers in a ratio of 7 : 1. The major isomer (**7**),† mp 138 - 140 °C, was readily isolated by flash chromatography on silica gel. Hydrolysis of the dibenzoate (**7**) afforded quantitatively the triol (**8**), mp 127 - 129 °C, whose stereostructure was determined on the basis of ^{1}H nmr nOe experiments of the corresponding triacetate (**9**).† Namely, 8% nOe effects were observed between the hydrogen at the C-9 position and $N(CH_2)_2$ of the triacetate (**9**).

+ This paper is dedicated to the memory of Professor Tetsuji Kametani.



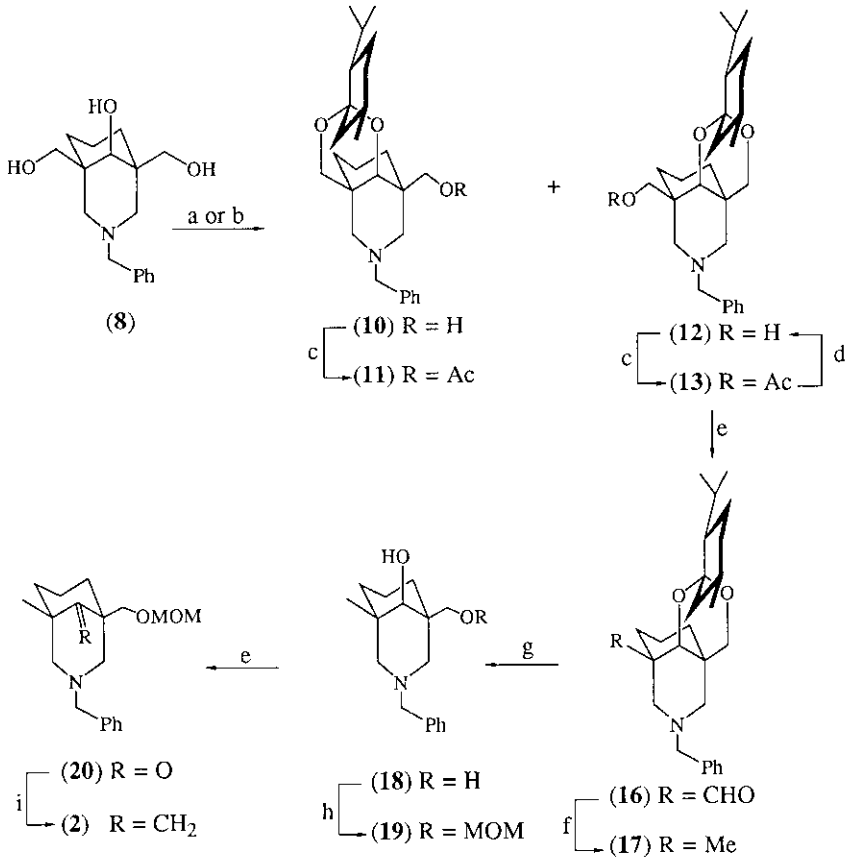
Reagents : (a) $LiBEt_3H$. (b) $PhCOCl$, Et_3N, DMAP.
(c) KOH, EtOH. (d) Ac_2O, Et_3N, DMAP.

Scheme 2

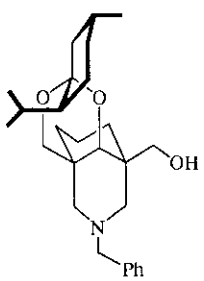
Heating a mixture of the triol (**8**) and l-menthone in the presence of (+)-10-camphorsulfonic acid in benzene furnished a mixture of two stereoisomers (**10** and **12**) in a ratio of 1.2 : 1 in 92% yield. On the other hand, trimethylsilylation of the triol (**8**), followed by treatment of the resulting tris-silyl ether with l-menthone in the presence of trimethylsilyl trifluoromethanesulfonate[3,4] and a successive treatment with tetrabutylammonium fluoride, produced, in 94% yield, a mixture of the two stereoisomers (**10** and **12**) in a ratio of 2.1 : 1. Although two isomers (**10** and **12**) were inseparable at this stage, separation of two isomers was easily achieved by flash chromatography after conversion to the acetates (**11**)† and (**13**)† (100% yield). It was considered that two other possible stereoisomers (**14**) and (**15**) were not formed because of severe non-bonded interactions. It was assumed from the inspection using Dreiding molecular models that the diastereoisomer (**12**) would have a more hindered molecular structure comparing with the other isomer (**10**). The component having the desired stereostructure was hydrolized, in 97% yield, to the alcohol (**12**),† which was then oxidized to the aldehyde (**16**)† in 96% yield. On Wolff-Kishner reduction of **16**, the methyl derivative (**17**)† was obtained in 68% yield. Removal of the chiral auxiliary of **17** was carried out by action of hydrochloric acid to form the diol (**18**)‡ in 92% yield. Reaction of the diol (**18**) with methoxymethyl chloride in the presence of diisopropylethylamine at 0 °C provided the secondary alcohol (**19**)† in 84% yield. Swern oxidation of **19**, followed by Wittig reaction of the resulting ketone (**20**)† (54% yield), furnished the olefin (**2**),† $[\alpha]_D^{26}$ + 8.14° (c = 0.27, $CHCl_3$), in 71% yield. The all physical properties of the olefin (**2**) including specific rotation were identical with those of the authentic compound, $[\alpha]_D^{27}$ + 8.10° (c = 2.02, $CHCl_3$), which had been correlated to atisine (**5**).[2]

ACKNOWLEDGEMENT

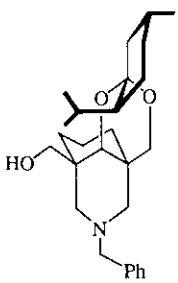
We are grateful to financial support from the Sendai Institute of Heterocyclic Chemistry.



Reagents : (a) l-menthone, CSA, heat. (b) (1) TMSCl, Et_3N, (2) l-menthone, TMSOTf, (3) $^nBu_4NF$. (c) Ac_2O, Et_3N, DMAP. (d) KOH, EtOH. (e) DMSO, $(COCl)_2$; Et_3N. (f) $NH_2NH_2 \cdot H_2O$, NaOH, triethylene glycol. (g) conc. HCl, MeOH. (h) MOMCl, $^iPr_2NEt$. (i) Ph_3PMeBr, ^nBuLi.



(14)



(15)

Scheme 3

REFERENCES AND NOTES

1. M. Ihara, M. Suzuki, K. Fukumoto, and T. Kametani, *J. Am. Chem. Soc.*, 1988, **110**, 1963.

2. M. Ihara, M. Suzuki, and K. Fukumoto, *J. Am. Chem. Soc.*, in the press.

3. T. Tsunoda, M. Suzuki, and R. Noyori, *Tetrahedron Lett.*, 1980, **21**, 1357.

4. T. Harada, T. Hayashiya, I. Wada, N. Iwa-ake, and A. Oku, *J. Am. Chem. Soc.*, 1987, **109**, 527.

† Ir ($CHCl_3$) and nmr ($CDCl_3$) data : (**7**) Ir, 3500 (OH) and 1715 cm^{-1} (C=O); nmr, δ 3.38 (2H, s, NCH_2), 3.87 and 4.40 (each 2H, each d, each *J* 11 Hz, 2 x OCH_2), and 7.10 - 8.10 (15H, m, 3 x Ph). (**9**) Ir, 1730 cm^{-1} (C=O); nmr, δ 2.03 (6H, s, 2 x Ac), 2.05 (3H, s, Ac), 2.27 and 2.82 [each 2H, each d, each *J* 10 Hz, $N(CH_2)_2$], 3.42 (2H, s, NCH_2Ph), 3.49 and 3.88 (each 2H, each d, each *J* 10 Hz, 2 x OCH_2), 4.98 (1H, s, *CH*OAc), and 7.20 - 7.40 (5H, m, Ph). (**11**) Nmr, δ 0.80 - 1.00 (9H, m, 3 x Me), 2.04 (3H, s, Ac), 3.17 and 3.70 (each 1H, each d, each *J* 11Hz, NCH_2), 3.29 and 3.46 (each 1H, each d, each *J* 14Hz, OCH_2), 3.60 (1H, s, OCH), 3.71 and 3.86 (each 1H, each d, each *J* 11Hz, CH_2 OAc), and 7.20 - 7.40 (5H, m, Ph). (**12**) Nmr, δ 0.90 (9H, d, *J* 6Hz, 3 x Me), 3.79 (1H, s, CHO), and 7.25 (5H, br s, Ph). (**13**) Nmr, δ 0.88, 0.89, and 0.91 (each 3H, each d, each *J* 7Hz, 3 x Me), 2.06 (3H, s, Ac), 3.10 and 3.46 (each 1H, each d, each *J* 11Hz, NCH_2), 3.28 and 3.47 (each 1H, each d, each *J* 13Hz, OCH_2), 3.66 (1H, s, OCH), 3.79 and 3.82 (each 1H, each d, each *J* 11Hz, CH_2 OAc), and 7.20 - 7.35 (5H, m, Ph). (**16**) Nmr, δ 0.83, 0.89, and 0.94 (each 3H, each d, each *J* 7Hz, 3 x Me), 3.37 (2H, br s, NCH_2), 4.00 (1H, br s, CH), 7.22 (5H, br s, Ph), and 9.42 (1H, s, CHO). (**17**) Nmr, δ 0.72 (3H, s, Me), 0.84, 0.89, and 0.96 (each 3H, each d, each *J* 7 Hz, 3 x Me), 3.31 (2H, br s, NCH_2), and 7.24 (5H, s, Ph). (**18**) Nmr, δ 0.85 (3H, s, Me) and 7.23 (5H, br s, Ph). (**19**) Ir, 3500 cm^{-1} (OH); nmr, δ 0.83 (3H, s, Me), 2.51 - 2.80 (4H, m, 2 x NCH_2), 3.28 (2H, s, OCH_2), 3.32 (2H, s, NCH_2Ph), 3.34 (3H, s, OMe), 4.57 (2H, s, OCH_2O), and 7.28 (5H, br s, Ph). (***20***) Nmr, δ 0.88 (3H, s, Me), 3.31 (3H, s, OMe), 3.45 (2H, s, NCH_2Ph), 4.56 (2H, s, OCH_2O), and 7.28 (5H, br s, Ph).

Received, 6th September, 1989