

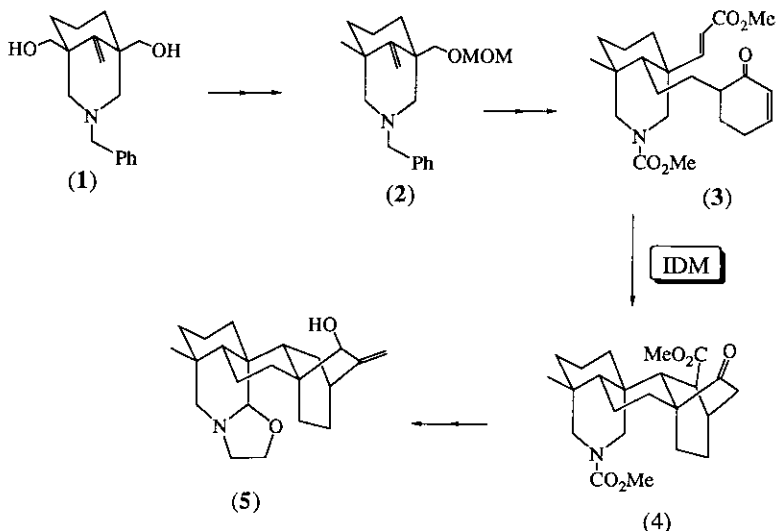
CHIRAL SYNTHESIS OF THE INTERMEDIATE OF ATISINE⁺

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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.

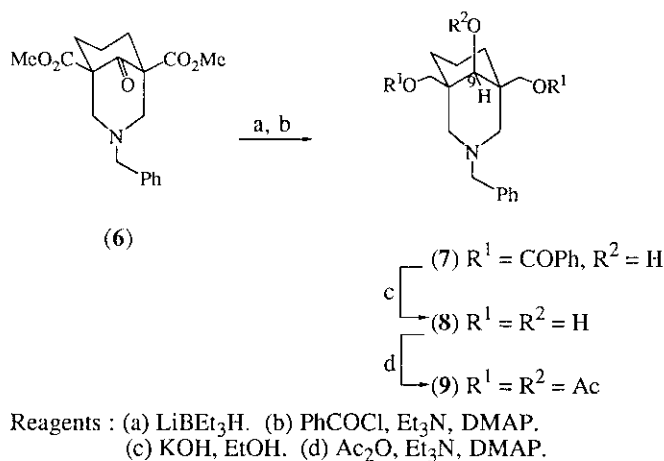
Recently we have developed an efficient route to a diterpene alkaloid, atisine (5), via the intramolecular double Michael reaction (IDM) of the enone-ester (3).¹ Furthermore the optically active methoxymethyl ether (2) was prepared by way of lipase-catalyzed acylation of the diol (1) and transformed 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 ¹H nmr nOe experiments of the corresponding triacetate (9).[†] Namely, 8% nOe effects were observed between the hydrogen at the C-9 position and N(CH₂)₂ of the triacetate (9).

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

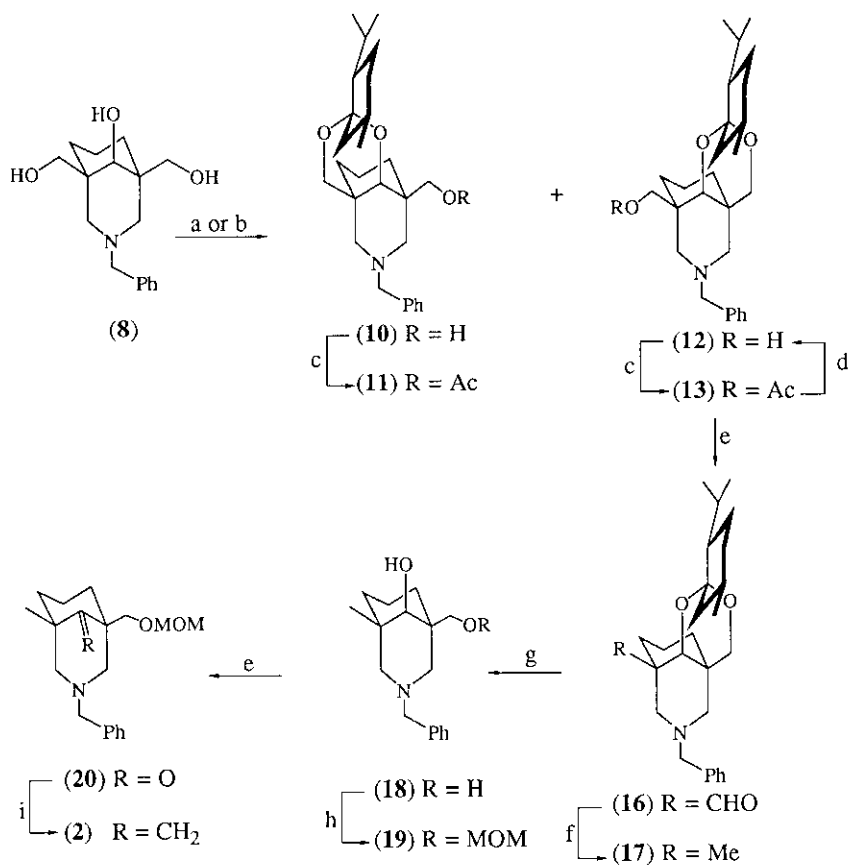


Scheme 2

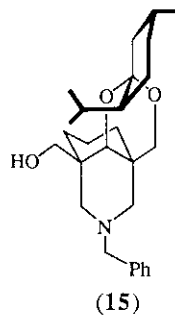
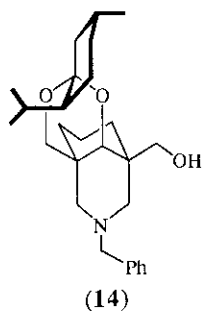
Heating a mixture of the triol (8) and l-menthone in the presence of (+)-10-camphorsulfonic acid in benzene furnished a mixture of two stereoisomers (10 and 12) in a ratio of 1.2 : 1 in 92% yield. On the other hand, trimethylsilylation of the triol (8), followed by treatment of the resulting tris-silyl 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 hydrolyzed, 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),[†] [α]_D²⁶ + 8.14° (c = 0.27, CHCl₃), in 71% yield. The all physical properties of the olefin (2) including specific rotation were identical with those of the authentic compound, [α]_D²⁷ + 8.10° (c = 2.02, CHCl₃), which had been correlated to aüsine (5).²

ACKNOWLEDGEMENT

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Reagents : (a) l-menthone, CSA, heat. (b) (1) TMSCl, Et₃N, (2) l-menthone, TMSOTf, (3) ⁿBu₄NF. (c) Ac₂O, Et₃N, DMAP. (d) KOH, EtOH. (e) DMSO, (COCl)₂; Et₃N. (f) NH₂NH₂·H₂O, NaOH, triethylene glycol. (g) conc. HCl, MeOH. (h) MOMCl, ⁱPr₂NEt. (i) Ph₃PMeBr, ⁿBuLi.



Scheme 3

REFERENCES AND NOTES

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† Ir (CHCl₃) and nmr (CDCl₃) data : (7) Ir, 3500 (OH) and 1715 cm⁻¹ (C=O); nmr, δ 3.38 (2H, s, NCH₂), 3.87 and 4.40 (each 2H, each d, each *J* 11 Hz, 2 x OCH₂), 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(CH₂)₂], 3.42 (2H, s, NCH₂Ph), 3.49 and 3.88 (each 2H, each d, each *J* 10 Hz, 2 x OCH₂), 4.98 (1H, s, CHOAc), 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, NCH₂), 3.29 and 3.46 (each 1H, each d, each *J* 14Hz, OCH₂), 3.60 (1H, s, OCH), 3.71 and 3.86 (each 1H, each d, each *J* 11Hz, CH₂ 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, NCH₂), 3.28 and 3.47 (each 1H, each d, each *J* 13Hz, OCH₂), 3.66 (1H, s, OCH), 3.79 and 3.82 (each 1H, each d, each *J* 11Hz, CH₂ 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, NCH₂), 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, NCH₂), 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 NCH₂), 3.28 (2H, s, OCH₂), 3.32 (2H, s, NCH₂Ph), 3.34 (3H, s, OMe), 4.57 (2H, s, OCH₂O), and 7.28 (5H, br s, Ph). (20) Nmr, δ 0.88 (3H, s, Me), 3.31 (3H, s, OMe), 3.45 (2H, s, NCH₂Ph), 4.56 (2H, s, OCH₂O), and 7.28 (5H, br s, Ph).

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