Novel Synthesis of a Key Intermediate for (±)-Atisine

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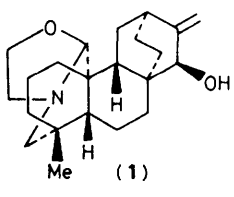
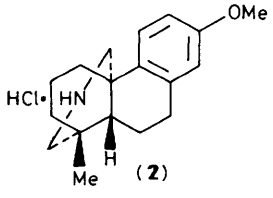
A novel synthesis of Nagata's tetracyclic intermediate (**2**) for (±)-atisine (**1**) has been accomplished from the benzocyclobutene (**3**) *via* two newly developed methodologies.

Atisine (**1**),[1] the principal alkaloid of *Aconitum heterophyllum*, continues to attract attention as a synthetic target[2] because of its interesting chemical features and complex structure. In the context of our studies of the development of new methodology using benzocylobutenes and of a novel route for the total synthesis of diterpene alkaloids,[3] we have defined and explored the competitive electrocylic reaction of *o*-quinodimethane[4] and the intramolecular Mannich type cyclisation.[5] We describe here an application of these methodologies to a novel synthesis of Nagata's intermediate (**2**)[2a,6] for (±)-atisine.

The benzocyclobutenyl enol carbonate (**3**) was prepared in 82% overall yield by sequential alkylation [lithium di-isopropylamide (LDA), MeI, hexamethylphosphoramide (HMPA), tetrahydrofuran (THF)], methylation[7] [MeI, Li, ultrasound, Et_2O], and enol carbonate formation[8] (LDA, ethyl chlorocarbonate, HMPA, THF) of 1-cyano-4-methoxybenzocyclobutene.[6] Thermolysis of (**3**) in *o*-dichlorobenzene at 180 °C for 2 h provided the dihydronaphthalene (**4**) in 94% yield *via* a selective electrocyclic process. Oxidative cleavage of the double bond in (**4**) followed by esterification afforded the keto ester (**5**) in 65% yield. Introduction of the dienophile portion for an intramolecular Diels–Alder reaction was achieved in 79% yield, affording (**6**),† by exposure of (**5**) to the conditions described by Oda.[9] To construct the diene group, we attempted to use a one-step procedure[10] involving treatment of the aldehyde (**7**), prepared by selective reduction of the ester moiety in (**6**) with di-isobutylaluminium hydride (DIBAL-H), with 1-methylallyldiphenylphosphine oxide.[11] However, satisfactory results were not obtained. After considerable effort, we found that the transformation and subsequent cycloaddition could best be achieved by the following sequence: Wittig reaction of (**7**) with the stable ylide, ethyl α-triphenylphosphoranylidenepropionate, stereoselectively provided the unsaturated ester (**8**), which was then chemoselectively reduced with DIBAL-H to afford the alcohol (**9**) in 74% yield from (**6**). Subsequent treatment



(**1**)



(**2**)

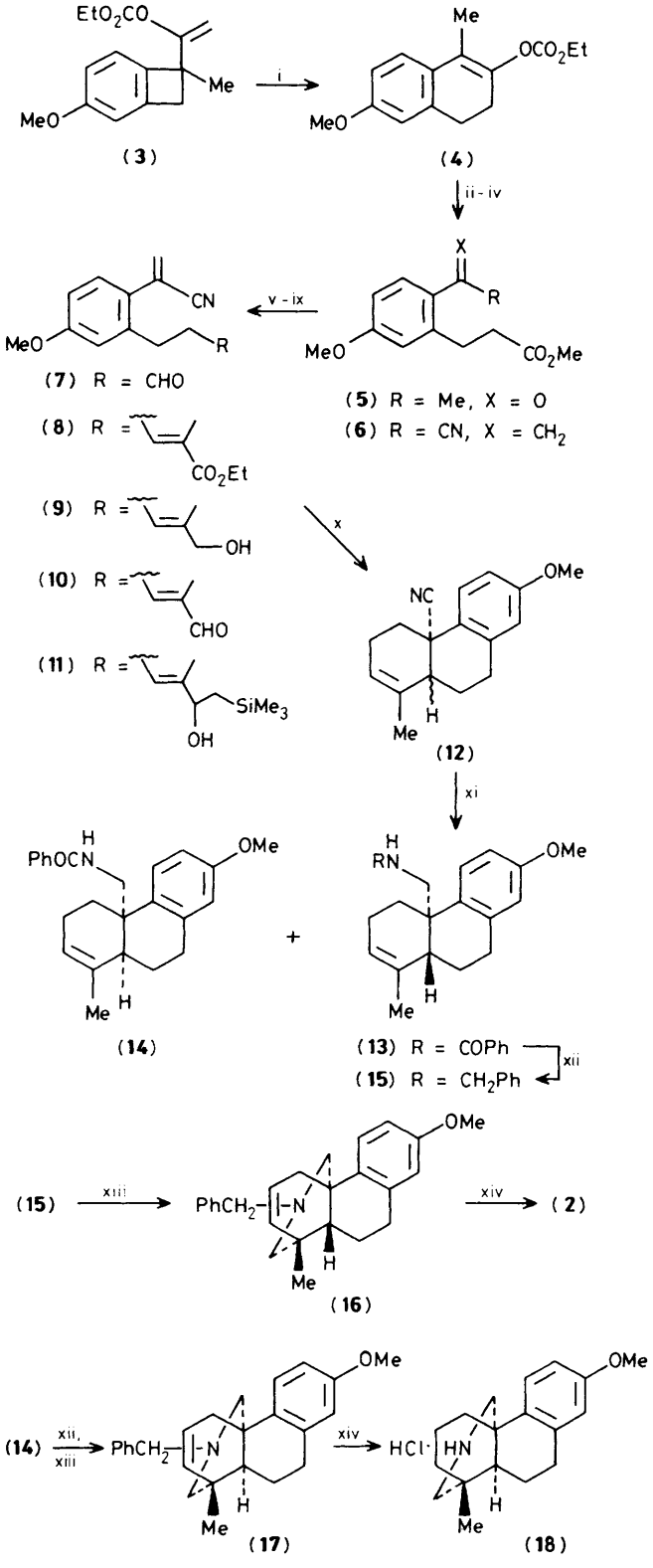
† *Spectral data* for (**6**): i.r. ($CHCl_3$, cm^{-1}) 2225, 1740; δ_H (90 MHz, $CDCl_3$) 3.68, 3.81 (3H each, s), 5.95 (1H, d, *J* 0.6 Hz), 6.21 (1H, d, *J* 0.6 Hz); *m/z* 245(M^+).

(**13**): i.r. ($CHCl_3$, cm^{-1}) 3450, 1650; δ_H (500 MHz, $CDCl_3$) 1.75 (3H, s), 3.21 (1H, dd, *J* 3.7 and 13.3 Hz), 3.80 (3H, s), 4.04 (1H, dd, *J* 8.7 and 13.3 Hz), 5.55 (1H, s), 5.78 (1H, br. s); *m/z* 361(M^+).

(**14**): i.r. ($CHCl_3$, cm^{-1}) 3440, 1650: δ_H (500 MHz, $CDCl_3$) 1.75 (3H, s), 3.42 (1H, dd, *J* 3.0 and 13.8 Hz), 3.80 (3H, s), 4.17 (1H, dd, *J* 3.0 and 13.8 Hz), 5.50 (1H, s), 5.64 (1H, br. s); *m/z* 361(M^+).

(**16**): δ_H(500 MHz, $CDCl_3$) 5.89 (1H, dt, *J* 9.2 and 3.4 Hz), 5.51 (1H, dt, *J* 9.2 and 2.1 Hz), 3.51 (1H, d, *J* 14.0 Hz), 3.47 (1H, d, *J* 14.0 Hz), 2.53 (1H, d, *J* 11.6 Hz), 2.40 (1H, d, *J* 11.6 Hz), 2.26 (1H, d, *J* 11.0 Hz), 2.08 (1H, d, *J* 11.0 Hz), 1.01 (3H, s); *m/z* 359 (M^+, 18%), 134(100%).

(**17**): m.p. 101—102 °C; δ_H (500 MHz, $CDCl_3$) 5.82 (1H, dt, *J* 9.8 and 3.4 Hz), 5.36 (1H, dd, *J* 9.8 and 1.2 Hz), 3.60 (1H, d, *J* 14.0 Hz), 3.56 (1H, d, *J* 14.0 Hz), 3.32 (1H, d, *J* 10.4 Hz), 2.52 (1H, d, *J* 10.4 Hz), 2.06 (1H, d, *J* 10.4 Hz), 1.86 (1H, d, *J* 10.4 Hz), 0.99 (3H, s): *m/z* 359 (M^+, 20%), 134(100%).



Scheme 1. *Reagents:* i, 180 °C, *o*-dichlorobenzene; ii, OsO_4(cat.), $NaIO_4$, Et_2O, H_2O; iii, MeOH, $MeC_6H_4SO_3H$; iv, Me_3SiCN, ZnI_2 then $POCl_3$, pyridine; v, DIBAL-H; vi, $Ph_3P{=}C(Me)CO_2Et$, benzene; vii, DIBAL-H, THF; viii, PDC, CH_2Cl_2; ix, Me_3SiCH_2MgCl, Et_2O; x, $MeSO_2Cl$, NEt_3, CH_2Cl_2; xi, $LiAlH_4$, THF, Et_2O then PhCOCl, K_2CO_3; xii, $LiAlH_4$, THF; xiii, for the hydrochloride of (**15**), 37% aq. HCHO, AcOH, 150 °C; xiv, for the hydrochloride of (**16**) or (**17**), H_2, 10% Pd–C, MeOH, 6.5 kg/cm^2.

with pyridinium dichromate (PDC) yielded the aldehyde (**10**) and addition of the trimethylsilylmethyl group[12] (Me_3SiCH_2MgCl, Et_2O) gave the alcohol (**11**) in 71% yield. Mesylation[13] of (**11**) with methanesulphonyl chloride and triethylamine in methylene dichloride at −78 °C to room temperature provided the tricyclic adduct (**12**) in 86% yield as an inseparable diastereoisomeric mixture, presumably *via* triene formation and spontaneous intramolecular Diels–Alder reaction under the reaction conditions. Separation of the two diastereoisomers could be achieved easily by the following conversion. Reduction of (**12**) with lithium aluminium hydride (LAH) followed by benzoylation in a one-pot procedure[14] afforded a chromatographically separable mixture of the desired *trans*-benzoate (**13**)†‡ and the *cis*-isomer (**14**)† in 97% yield, in a ratio of 1 : 1.2. The crucial intramolecular Mannich type cyclization[5]§ of the enamine hydrochloride (**15**) [m.p. 244—244.5 °C, prepared by reduction of (**13**) with $LiAlH_4$ and subsequent treatment with hydrochloric acid in ether], was effected uneventfully by heating with 37% aqueous formaldehyde in acetic acid in a sealed tube at 150 °C for 1 h, to give the tetracyclic enamine (**16**) as a free base in 98% yield.† Finally, the hydrochloride of (**16**) was hydrogenated over 10% Pd–C under hydrogen in methanol to furnish (**2**) quantitatively, m.p. 274—276 °C (lit.,[2a,6] 274—275 °C). The *cis*-isomer (**14**) could also be converted into the amine hydrochloride (**18**) *via* (**17**),† by the same procedure as used to obtain (**2**) in 86% overall yield.

It is evident that the methodology described here can be generally applied to the synthesis of the other kinds of diterpene alkaloids.

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‡ The relative stereochemistry shown for (**13**) was determined from its eventual transformation into (**2**).

§ The conversions (**15**) → (**16**) and (**14**) → (**17**) might be thought of as an unprecedented concerted pericyclic process, the iminium-ene reaction;[15] the reaction proceeds quite cleanly and quantitatively in a completely regioselective manner at 150 °C. Further examples of the cyclisation and mechanistic discussions will be reported in due course.