

Novel Synthesis of a Key Intermediate for (\pm)-Atisine

Kozo Shishido,^a Kou Hiroya,^a Keiichiro Fukumoto,^{a*} and Tetsuji Kametani^b

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

^b Institute of Medicinal Chemistry, Hoshi University, Ebara 2-4-41, Shinagawa-ku, Tokyo 142, Japan

A novel synthesis of Nagata's tetracyclic intermediate (**2**) for (\pm)-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 target² because of its interesting chemical features and complex structure. In the context of our studies of the development of new methodology using benzocyclobutenes and of a novel route for the total synthesis of diterpene alkaloids,³ we have defined and explored the competitive electrocyclic reaction of *o*-quinodimethane⁴ 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 (\pm)-atisine.

The benzocyclobutenyl enol carbonate (**3**) was prepared in 82% overall yield by sequential alkylation [lithium di-isopropylamide (LDA), MeI, hexamethylphosphoramide (HMPA), tetrahydrofuran (THF)], methylation⁷ [MeI, Li, ultrasound, Et₂O], and enol carbonate formation⁸ (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 procedure¹⁰ 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 -triphenylphosphoranylidene-propionate, 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

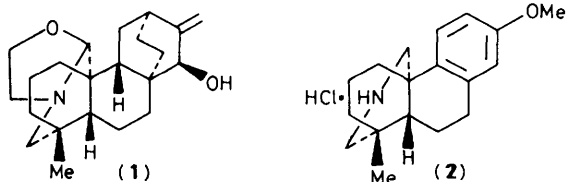
[†] Spectral data for (**6**): i.r. (CHCl₃, cm⁻¹) 2225, 1740; δ_{H} (90 MHz, CDCl₃) 3.68, 3.81 (3H each, s), 5.95 (1H, d, *J* 0.6 Hz), 6.21 (1H, d, *J* 0.6 Hz); *m/z* 245(*M*⁺).

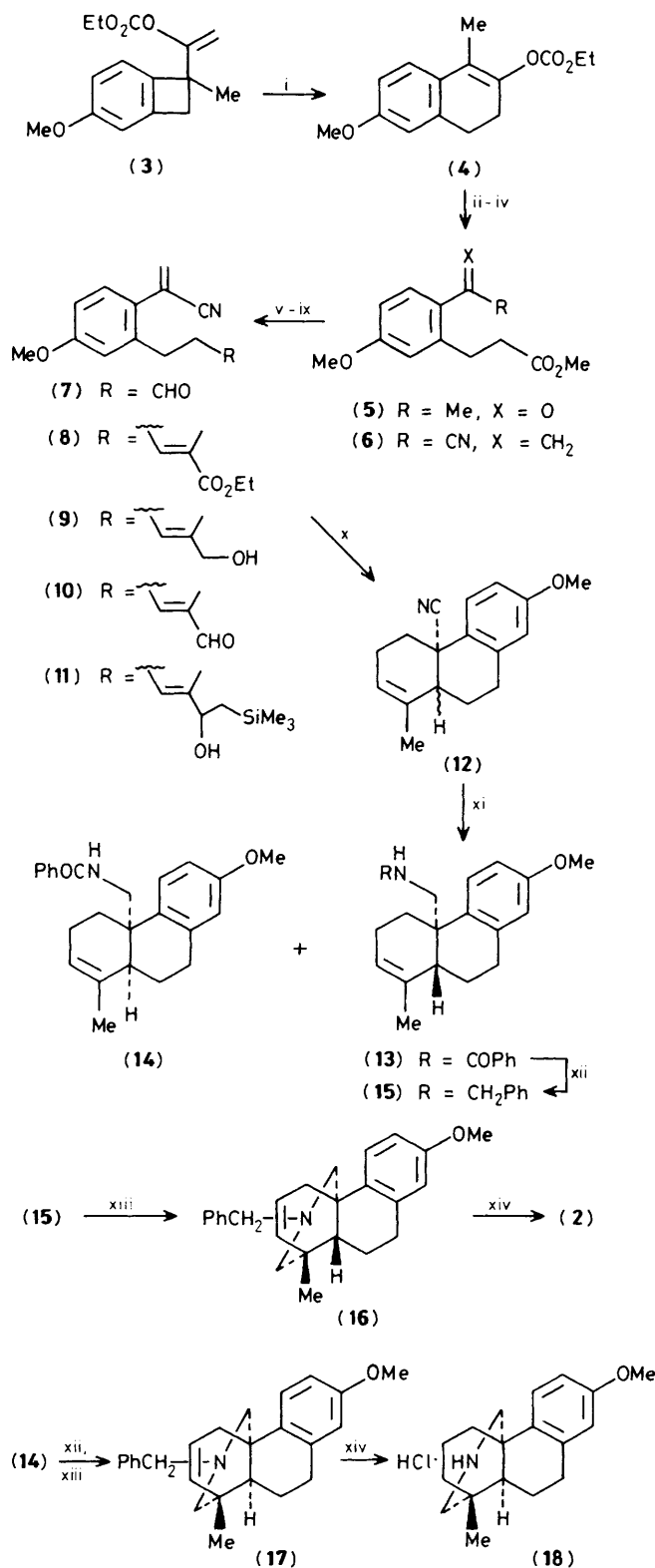
(**13**): i.r. (CHCl₃, cm⁻¹) 3450, 1650; δ_{H} (500 MHz, CDCl₃) 1.75 (3H, s), 3.21 (1H, dd, *J* 3.7 and 13.3 Hz), 3.80 (3H, s), 4.04 (1H, dd, *J* 8.7 and 13.3 Hz), 5.55 (1H, s), 5.78 (1H, br. s); *m/z* 361(*M*⁺).

(**14**): i.r. (CHCl₃, cm⁻¹) 3440, 1650; δ_{H} (500 MHz, CDCl₃) 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, CDCl₃) 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, CDCl₃) 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 , $\text{MeC}_6\text{H}_4\text{SO}_3\text{H}$; iv, Me_3SiCN , ZnI_2 then POCl_3 , pyridine; v, DIBAL-H; vi, $\text{Ph}_3\text{P}=\text{C}(\text{Me})\text{CO}_2\text{Et}$, benzene; vii, DIBAL-H, THF; viii, PDC, CH_2Cl_2 ; ix, $\text{Me}_3\text{SiCH}_2\text{MgCl}$, 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 group¹² ($\text{Me}_3\text{Si}-\text{CH}_2\text{MgCl}$, Et_2O) gave the alcohol (11) in 71% yield. Mesylation¹³ 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 benzylation in a one-pot procedure¹⁴ 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.

Received, 5th March 1987; Com. 277

References

- For a recent review, see S. W. Pelletier and N. V. Mody, 'The Alkaloids,' eds. R. H. F. Manske and R. G. A. Rodrigo, Academic Press Inc., New York, 1981, vol. 13, p. 122.
- (a) W. Nagata, T. Sugawara, M. Narisada, T. Wakabayashi, and Y. Hayase, *J. Am. Chem. Soc.*, 1963, **85**, 2342; (b) S. Masamune, *ibid.*, 1964, **86**, 291; (c) P. W. Guthrie, Z. Valenta, and K. Wiesner, *Tetrahedron Lett.*, 1966, 4645.
- For a review, see ref. 1, p. 99.
- K. Shishido, A. Yamashita, K. Hiroya, K. Fukumoto, and T. Kametani, unpublished results.
- K. Shishido, K. Hiroya, K. Fukumoto, and T. Kametani, *Tetrahedron Lett.*, 1986, **27**, 1167.
- T. Kametani, Y. Kato, T. Honda, and K. Fukumoto, *J. Am. Chem. Soc.*, 1976, **98**, 8185.
- K. Shishido, M. Ito, S. Shimada, K. Fukumoto, and T. Kametani, *Chem. Lett.*, 1984, 1943.
- R. A. Olofson, J. Cuomo, and B. A. Bauman, *J. Org. Chem.*, 1978, **43**, 2073.
- M. Oda, A. Yamamoto, and T. Watabe, *Chem. Lett.*, 1979, 1427.
- J. Ukai, Y. Ikeda, N. Ikeda, and H. Yamamoto, *Tetrahedron Lett.*, 1983, **24**, 4029.
- M. P. Savage and S. Trippett, *J. Chem. Soc. (C)*, 1966, 1842.
- P. A. Brown, P. R. Jenkins, J. Fawcett, and D. R. Russell, *J. Chem. Soc., Chem. Commun.*, 1984, 253.
- P. F. Hudrlík and D. Peterson, *Tetrahedron Lett.*, 1974, 1133.
- K. E. Harding and S. R. Burks, *J. Org. Chem.*, 1981, **46**, 3920.
- T. Cohen and A. Onopchenko, *J. Org. Chem.*, 1983, **48**, 4531.

[†] The relative stereochemistry shown for (13) was determined from its eventual transformation into (2).

[§] The conversions (15) \rightarrow (16) and (14) \rightarrow (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.