

A facile and efficient route to the bicyclo[3.2.1]octane system. Application to the enantioselective approach to cyclopentanoids

Hiroshi Kosugi, Junichiro Sugiura and Michiharu Kato*

Institute for Chemical Reaction Science, Tohoku University, Katahira, Aoba-ku, Sendai 980-77, Japan

The reaction of (4*R*,5*R*)-1-acetoxy-4-(1,2-epoxy-1-methyl-ethyl)-5-methylcyclohex-1-ene **8** with BF₃·Et₂O provides, in one chemical operation, (1*R*,4*R*,5*R*,7*S*)-7-acetoxy-4,6-dimethylbicyclo[3.2.1]octan-2-ones **9a,b** which are then transformed to (2*R*,3*R*)-2-methyl-3-[(*R*)-1-methyl-3-oxobutyl]-cyclopentanone **16** with the same absolute configuration as that of the steroid D ring.

We have been studying the utility of (+)-nopinone **1**, readily obtainable from (–)-β-pinene by ozonolysis, as a chiral source for the enantioselective synthesis of natural products, wherein we have demonstrated that BF₃·Et₂O-promoted cyclobutane opening of **1**¹ and its 4,4-dialkyl derivatives **2**² provides in high yields the enol acetates **4** and **5**, respectively, with little loss of stereochemical integrity. We now show an efficient chemical transformation of the enol acetate **6** derived from the cyclobutane opening of (1*R*,4*R*,5*R*)-4-methylnopinone **3** to bicyclo[3.2.1]octan-2-ones **9** via the epoxide **8**. In addition, elaboration of **9** directed toward enantioselective synthesis of cyclopentanoids such as steroid D ring synthons is described.

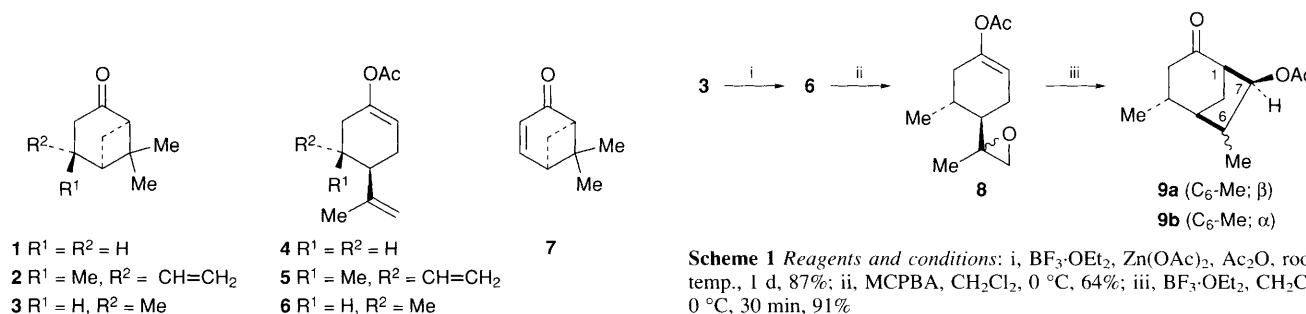
Enol acetate **6** was prepared as follows. We have previously reported the useful laboratory scale preparation of (+)-apoverbenone **7** from **1**.^{2c,3} The stereoselective conjugate addition of lithium dimethylcuprate to the enone **7** according to the published procedure⁴ provided (1*R*,4*R*,5*R*)-4-methylnopinone **3** in 95% yield. BF₃-promoted cyclobutane opening of the latter under our standard reaction conditions^{1,2} gave the requisite enol acetate **6** in 86% yield (Scheme 1).

Epoxidation of **6** with an equimolecular amount of MCPBA (CH₂Cl₂, 0 °C) proceeded in a regioselective fashion at the double bond of the prop-2-en-2-yl side chain, giving epoxide **8** as a diastereomeric mixture (a 3 : 1 ratio) in 64% isolated yield. It is well known that enol ethers are readily epoxidised with MCPBA to give epoxy ethers owing to the electronic effect.⁵ Considering that the electronic effect of enol acetates is less than that of enol ethers, and that epoxidation of limonene provides limonene-1,2-epoxide regioselectively,⁶ it is worthwhile mentioning that the present epoxidation reaction should go preferentially at the prop-2-en-2-yl double bond owing to the steric effect of the acetoxy group. In this epoxidation, attempts to use THF and diethyl ether in place of CH₂Cl₂ or to add NaHCO₃ and ZnCl₂ as additives proved to be fruitless due to low yields of the product **8** and contamination with the epoxide derived from epoxidation of the enol acetate function.

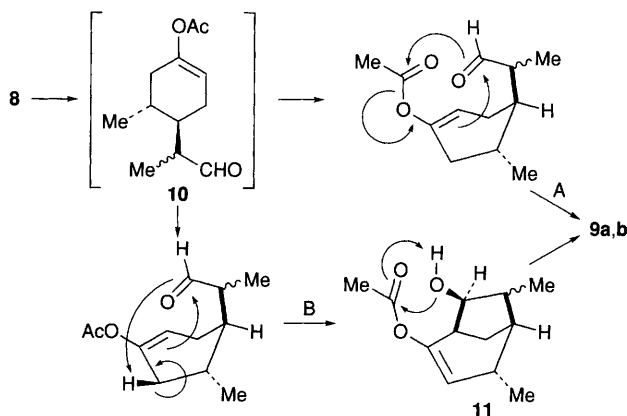
Reaction of **8** with BF₃·OEt₂ (0.2 equiv.) in CH₂Cl₂ at 0 °C proceeded smoothly to give the bicyclo[3.2.1]octan-2-ones **9a,b** as a separable diastereomeric mixture (2 : 1 ratio) in 91% yield. In the 400 MHz ¹H NMR spectroscopic analyses, the resonances due to the protons at the C(7) position of the major isomer **9a** and the minor isomer **9b** exhibit a double doublet (*J* 6.4 and 3.8 Hz) at δ 4.87 and a double doublet (*J* 7.0 and 3.5 Hz) at δ 5.47, respectively. The findings indicate that the configuration of the acetoxy group in **9a,b** is *endo* (*S*), since the vicinal protons H(1) and *endo*-H(7) are at approximate right angles as measured on Drieding models, suggesting that *J*_{1-7*endo*} is almost zero, so that the products **9a,b** are diastereomers with regard to the methyl group in the 5-membered ring. In addition, comparison of the chemical shifts of the methyl group in the 5-membered ring (δ 1.27 for **9a** and δ 1.05 for **9b**) is indicative of the stereochemical assignment of the methyl group; the *cis* relationship between the methyl and acetoxy groups in **9a** causes the methyl protons to shift downfield by 0.22 ppm, so that the stereostructures of **9a,b** are assigned as depicted.[†]

The proposed mechanism for the formation of **9a,b** from **8** in one chemical operation is shown in Scheme 2. The epoxide **8** initially undergoes epoxide rearrangement⁷ when treated with BF₃·Et₂O to give the aldehyde **10**, which could be intramolecularly cyclised by either of two routes; aldol-type condensation (route A) or ene reaction⁸ to form alcohol **11**, followed by the transfer of an acetyl group by neighbouring group participation (route B), thus producing **9a,b**. Judging from the fact that the ene reaction product **11** was not detected in spite of careful inspection of reaction products, route A may be most feasible. To the best of our knowledge, the one-pot synthesis of the bicyclo[3.2.1]octane system by Lewis acid promoted cyclisation between the enol acetate and aldehyde functions generated *in situ* from the epoxide has not been exploited. The present cyclisation corresponds almost exactly to the intramolecular aldol condensation of the keto aldehyde **12**. The successful realisation of the present sequence may be reliant upon not only regioselective cyclisation by the enol acetate function, but also the trapping of the aldol condensation product as its acetate.

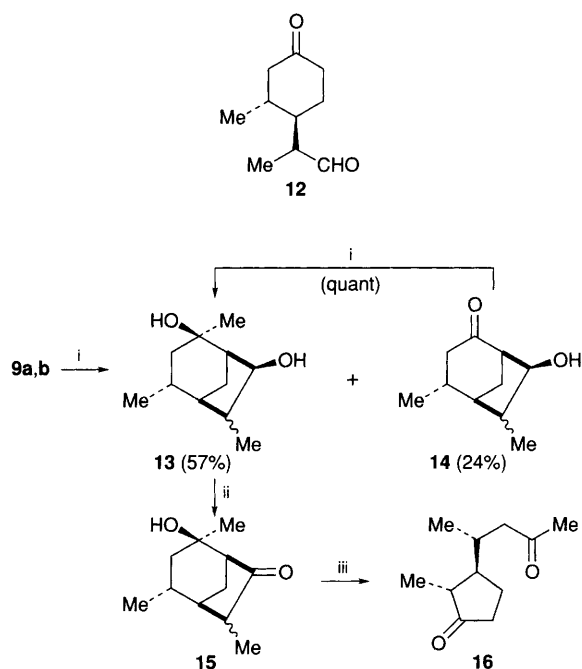
As part of the enantioselective synthesis of cyclopentanoids possessing vicinal asymmetric carbon centres on their cyclopentane rings and side chains, which are widely found in terpenoids and steroids,⁹ a few chemical transformations of **9a,b** were performed. Treatment of **9a,b** with methyl Grignard reagent (5



equiv.) in diethyl ether gave a mixture of diol **13** and ketol **14** in 57 and 24% yields, respectively (Scheme 3). The latter was converted to the former by repetition of this procedure. Swern oxidation of **13** provided the ketone **15**, whose exposure with sodium hydride in THF proceeded smoothly in retro-aldol condensation followed by isomerisation of the ring methyl



Scheme 2



Scheme 3 Reagents and conditions: i, MeMgBr (5 equiv.), Et₂O, 0 °C; ii, (COCl)₂, Me₂SO, CH₂Cl₂, -55 °C, then Et₃N, 10 h, 71%; iii, NaH, THF, 0 °C, 30 min, 75%

group, giving (2*R*,3*R*)-2-methyl-3-[(*R*)-1-methyl-3-oxobutyl]-cyclopentanone **16** as the homogeneous and sole product in over 50% yield from **13**. Judging from the fact that the absolute configuration of both the secondary methyl group (*R*) in the side chain and the side chain itself (*R*) in **16** are in agreement with those at C(17) and C(20) of steroidal substrates, and that preparation of hydrindenones, the C/D ring synthon for the steroid synthesis, from correctly substituted cyclopentanones has been well-studied,¹⁰ the C(1)–C(2) bond cleavage of this type in the bicyclo[3.2.1]octane system could be used as an entry for the construction of steroid D ring synthons, especially possessing a functionalised side-chain.

Further studies on the synthesis of steroidal natural products are in progress.

We are grateful to the Tokyo Ohka Foundation for the Promotion of Science and Technology (1995) for financial support.

Footnote

† It was confirmed that a rearrangement of this type occurred in good yields starting with epoxides regioselectively derived from the compounds **4** and **5**.

References

- 1 M. Kato, V. P. Kamat, Y. Tooyama and A. Yoshikoshi, *J. Org. Chem.*, 1989, **54**, 1536.
- 2 (a) M. Kato, F. Kido, M. Watanabe, Y. Masuda and B. Z. Awen, *J. Chem. Soc., Perkin Trans. 1*, 1993, 2831; (b) M. Kato, M. Watanabe and B. Z. Awen, *J. Org. Chem.*, 1993, **58**, 5145; (c) M. Watanabe, B. Z. Awen and M. Kato, *J. Org. Chem.*, 1993, **58**, 3923; (d) M. Kato, M. Watanabe, Y. Tooyama, B. Vogler and A. Yoshikoshi, *Synthesis*, 1992, 1055; (e) M. Kato, F. Kido, Y. Masuda and M. Watanabe, *J. Chem. Soc., Chem. Commun.*, 1992, 697; (f) M. Kato, M. Watanabe, B. Vogler, B. Z. Awen, Y. Masuda, Y. Tooyama and A. Yoshikoshi, *J. Org. Chem.*, 1991, **56**, 7071.
- 3 Preparation by bromination–dehydrobromination: P. D. Hobbs and P. D. Magnus, *J. Chem. Soc., Perkin Trans. 1*, 1973, 2879.
- 4 J. P. Konopelski, P. Sundaraman, G. Barth and C. Djerassi, *J. Am. Chem. Soc.*, 1980, **102**, 2737; C. Nishino and H. Takayanagi, *Agric. Biol. Chem.*, 1979, **43**, 1967.
- 5 H. O. House, *Modern Synthetic Reactions*, 2nd edn., W. A. Benjamin Inc., California, 1972, pp. 296–321.
- 6 J. C. Leffingwell and E. E. Royals, *Tetrahedron Lett.*, 1965, 3829; E. E. Royals and J. C. Leffingwell, *J. Org. Chem.*, 1966, **31**, 1973.
- 7 B. Rickborn, *Comprehensive Organic Synthesis*, ed. B. M. Trost and I. Fleming, Pergamon Press, New York, 1991, vol. 3, pp. 733–755.
- 8 Analogous reaction: I. Kitagawa, S. Tsujii, F. Nishikawa and H. Shibuya, *Chem. Pharm. Bull.*, 1983, **31**, 2639.
- 9 K. Nakanishi, T. Goto, S. Natori and S. Nozoe, *Natural Products Chemistry*, Kodansha Scientific, Tokyo, 1974, vol. 1.
- 10 K. Nagasawa, N. Matsuda, Y. Noguchi, M. Yamanashi, Y. Zako and I. Shimizu, *J. Org. Chem.*, 1993, **58**, 1483 and references cited therein; B. Lythgoe, *Chem. Soc. Rev.*, 1980, **9**, 449; A. A. Akhrem and Y. A. Titov, *Total Steroid Synthesis*, Plenum Press, New York, London, 1970.

Received, 12th August 1996; Com. 6/05612A