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

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The reaction of (4*R*,5*R*)-1-acetoxy-4-(1,2-epoxy-1-methylethyl)-5-methylcyclohex-1-ene 8 with BF_3·Et_2O 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 BF_3·Et_2O-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.

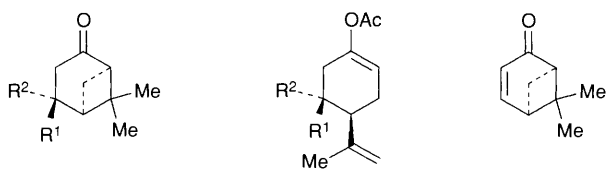
Enol acetate **6** was prepared as follows. We have previously reported the useful laboratory scale preparation of (+)-apoverbenone **7** from **1**.[2c,3] The stereoselective conjugate addition of lithium dimethylcuprate to the enone **7** according to the published procedure[4] provided (1*R*,4*R*,5*R*)-4-methylnopinone **3** in 95% yield. BF_3-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 (CH_2Cl_2, 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 CH_2Cl_2 or to add $NaHCO_3$ and $ZnCl_2$ 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 BF_3·OEt_2 (0.2 equiv.) in CH_2Cl_2 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 ^{1}H 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 $J_{1-7endo}$ 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 rearrangement[7] when treated with BF_3·Et_2O to give the aldehyde **10**, which could be intramolecularly cyclised by either of two routes; aldol-type condensation (route A) or ene reaction[8] 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.

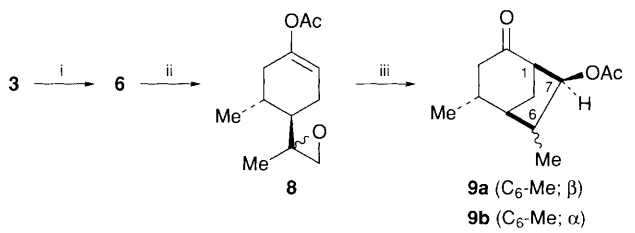
As part of the enantioselective synthesis of cyclopentanoids possessing vicinal asymmetric carbon centres on their cyclopetane rings and side chains, which are widely found in terpenoids and steroids,[9] a few chemical transformations of **9a,b** were performed. Treatment of **9a,b** with methyl Grignard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



1 $R^1 = R^2 = H$
2 R^1 = Me, R^2 = $CH{=}CH_2$
3 $R^1 = H$, R^2 = Me

4 $R^1 = R^2 = H$
5 R^1 = Me, R^2 = $CH{=}CH_2$
6 $R^1 = H$, R^2 = Me

7



9a (C_6-Me; β)
9b (C_6-Me; α)

Scheme 1 *Reagents and conditions*: i, BF_3·OEt_2, $Zn(OAc)_2$, Ac_2O, room temp., 1 d, 87%; ii, MCPBA, CH_2Cl_2, 0 °C, 64%; iii, BF_3·OEt_2, CH_2Cl_2, 0 °C, 30 min, 91%

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 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.

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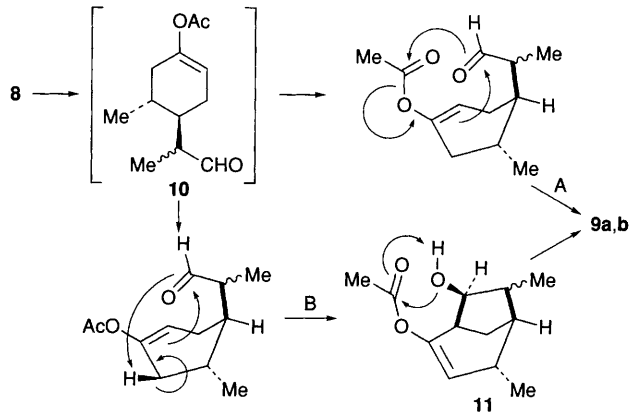
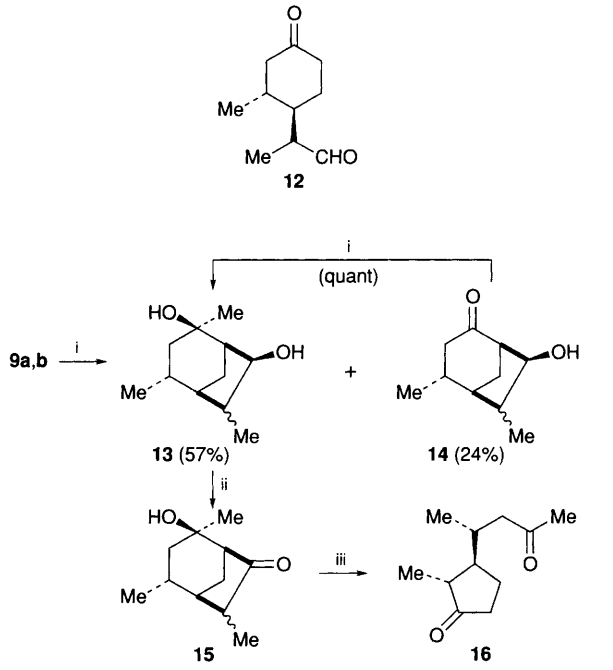


Scheme 2



Scheme 3 *Reagents and conditions*: i, MeMgBr (5 equiv.), Et_2O, 0 °C; ii, $(COCl)_2$, Me_2SO, CH_2Cl_2, −55 °C, then Et_3N, 10 h, 71%; iii, NaH, THF, 0 °C, 30 min, 75%

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**.

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