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Aspects of the chemistry of 8-azabicyclo[3.2.1]octanes

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Abstract—Mesylation and elimination from dimethyl 3-hydroxy-8-azabicyclo[3.2.1]octane-2,8-dicarboxylate gave a conjugated alkenyl ester. Reduction of the mesyloxy ester by di-isobutylaluminium hydride was also accompanied by elimination giving an unsaturated aldehyde. Treatment of the mesylate of the corresponding monoprotected diol with potassium *tert*-butoxide gave a 2-unsubstituted alkene via a Grob fragmentation but a different alkene was obtained using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in acetonitrile. Epoxidation of both the protected hydroxy-alkene and the free hydroxy-alkene was stereoselective in favour of epoxidation from the *exo*-face, and ring-opening of the hydroxy-epoxide using hydrogen bromide gave the diaxial bromohydrin. Treatment of a 2-iodomethyl-3-oxo-8-azabicyclo[3.2.1]octane with *tert*-butyllithium gave a cyclopropane, whereas the corresponding iodo-alcohol gave the 1-azatricyclo[5.3.0.0^{4,10}]decan-2-one as the major product.

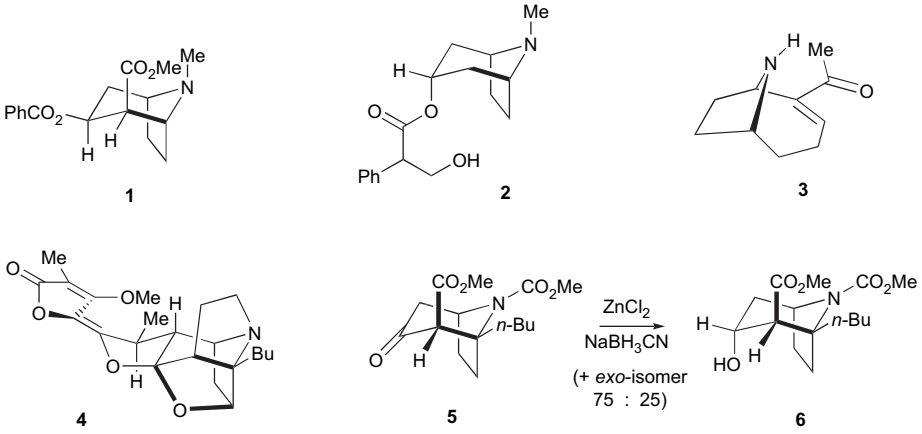
1. Introduction

Many 8-azabicyclo[3.2.1]octanes and related compounds show pronounced biological activity. Examples include the tropane alkaloids, e.g., cocaine **1** and atropine **2**, and the related anatoxin *a* **3**, which has the 9-azabicyclo[4.2.1]nonane skeleton.[1,2] Recently during studies of an approach to a synthesis of stemofoline **4**,[3–5] the 8-azabicyclo[3.2.1]octane-8-carboxylate **5** was prepared by a Mannich reaction and reduced to give the axial alcohol **6**.[6,7] In view of the interest in 8-azabicyclo[3.2.1]octanes, we report further aspects of the chemistry of the alcohol **6** and related compounds, including regioselective dehydration and the synthesis of tricyclic derivatives.

2. Results and discussion

An anti-dehydration of the hydroxy-ester **6** would be expected to give the corresponding non-conjugated unsaturated ester, but conversion to the mesylate **7** and treatment of the mesylate with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) gave the conjugated alkenyl ester **8**. Indeed reduction of the mesylate **7** with di-isobutylaluminium hydride (DIBAL–H) was also accompanied by elimination and gave the conjugated unsaturated aldehyde **9**, see Scheme 1.

Regioselective elimination from a 2-substituted 3-mesyloxy-8-azabicyclo[3.2.0]octane-8-carboxylate to give an 8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate with a disubstituted



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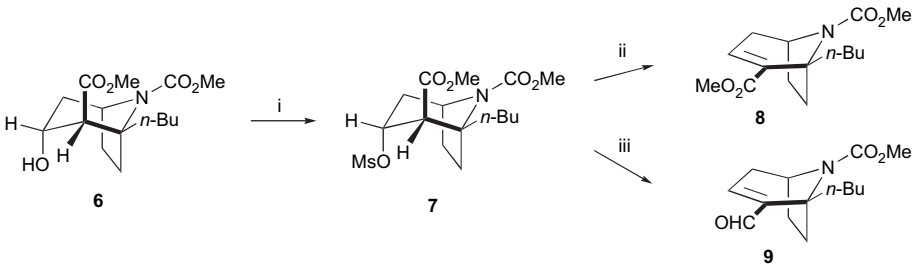
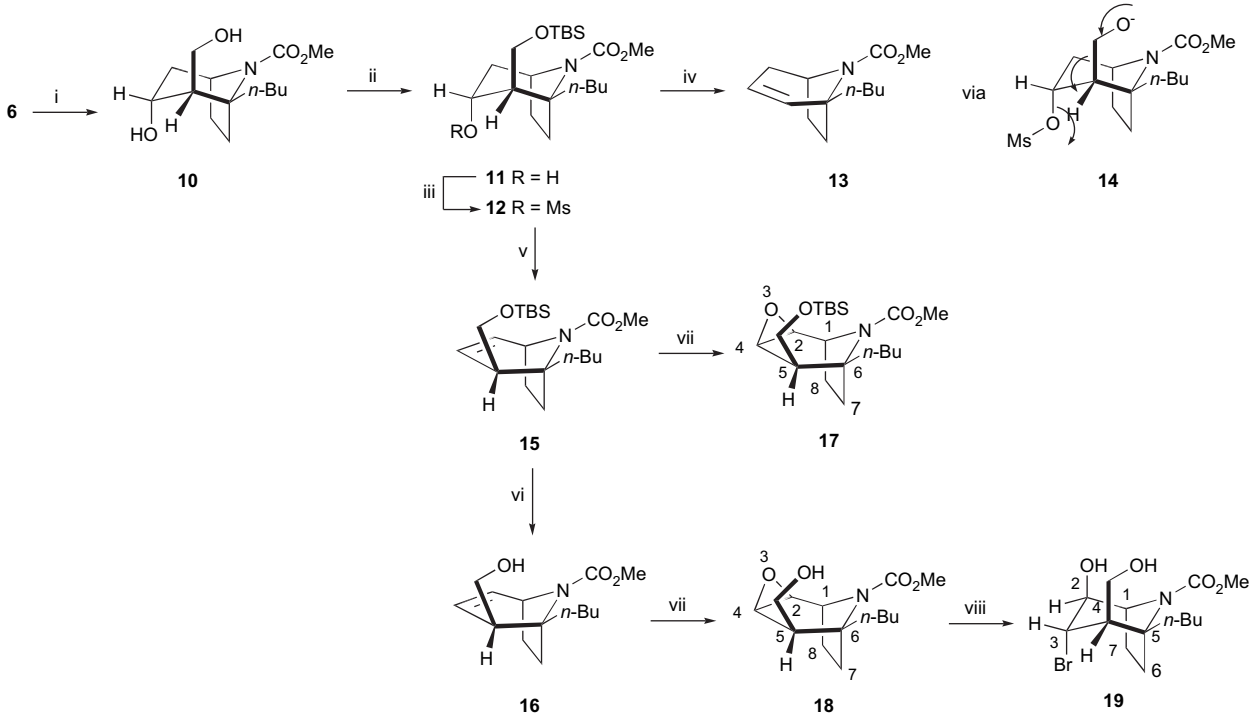


Scheme 1. Reagents and conditions: (i) MsCl, Et_3N, CH_2Cl_2 (87%); (ii) DBU, THF, heat (67%); (iii) DIBAL–H, hexane, −78 °C (68%).

double-bond, was achieved as outlined in Scheme 2. Following reduction of the ester **6**, the diol **10** so obtained was selectively monoprotected to give the silyl ether **11**, which was converted into the mesylate **12**. Attempts to eliminate the mesylate using DBU in tetrahydrofuran, alumina, sodium methoxide or potasium *tert*-butoxide in tetrahydrofuran gave recovered starting material, and the use of potassium *tert*-butoxide in dimethyl sulfoxide gave the 2-unsubstituted 1-butyl-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate **13**, presumably by a base-induced, Grob-type of fragmentation,[8] see **14**. However, elimination of the mesylate from **12** was achieved using DBU in acetonitrile at 100 °C and gave the disubstituted alkene **15**, which on desilylation, using tetra-*n*-butylammonium fluoride (TBAF), was converted into the alkenol **16**.

Epoxidation of both of the alkenes **15** and **16** using *meta*-chloroperoxybenzoic acid took place from the *exo*-face to give the epoxides **17** and **18** with the epoxidation of the 4-hydroxymethyl alkene **16** being significantly faster perhaps because of hydrogen bonding to the incoming per-acid.[9] The stereoselectivity of epoxidation of the silyl ether **15** was confirmed by ^1H NMR spectroscopy with strong NOEs being observed for the epoxide **17**, for H-2 and H-5 on irradiation of H-4, and for H-1 and H-4 on irradiation of H-2, but not for the 5-CH_2 in either case. Ring-opening of the epoxide **18** on reaction with hydrogen bromide was regioselective with the diaxial ring-opened product **19** being obtained. In the bromohydrin **19**, the hydroxyl group at C2 was assigned the axial stereochemistry as shown because H-1 was observed as a doublet, coupling only to H-7$_{exo}$, and H-3 was observed as a broadened singlet.[10]

In our approach to stemofoline **4**, alkyllithium intermediates generated from 2-iodomethyl-8-azabicyclo[3.2.1]octane-8-carboxylates, were shown to react with the 8-methoxycarbonyl substituents to form tricyclo[5.3.0.0^{4,10}]decan-2-ones.[6,7] It was of interest to investigate the compatibility of this chemistry with other functionality in the 8-azabicyclo[3.2.1]octane. Oxidation of the monoprotected diol **11** gave ketone **20** (Scheme 3). Desilylation of this using TBAF gave a mixture of the axial and equatorial hydroxymethylketones **21** and **22**, ratio ca. 2:1, but the use of acidic amberlite resin avoided epimerisation and gave the axial 2-hydroxymethyl ketone **21** with little epimerisation. The



Scheme 2. Reagents and conditions: (i) DIBAL–H, CH_2Cl_2, −78 °C, then $NaBH_4$, EtOH (63%); (ii) TBSOTf, 2,6-lutidine, CH_2Cl_2 (94%); (iii) MsCl, Et_3N, CH_2Cl_2 (71%); (iv) KO*t*-Bu, DMSO (78%); (v) DBU, CH_3CN, 100 °C (84%); (vi) TBAF, THF (100%); (vii) MCPBA, K_2CO_3, CH_2Cl_2 (**17**, 47%; **18**, 75%); (viii) HBr (83%).