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Synthesis of the Pseudoguaianolide and Guaianolide Skeleton by Cleavage of the Ether Bridge of 8-Oxabicyclo[3.2.1]octan-3-one Derivatives†

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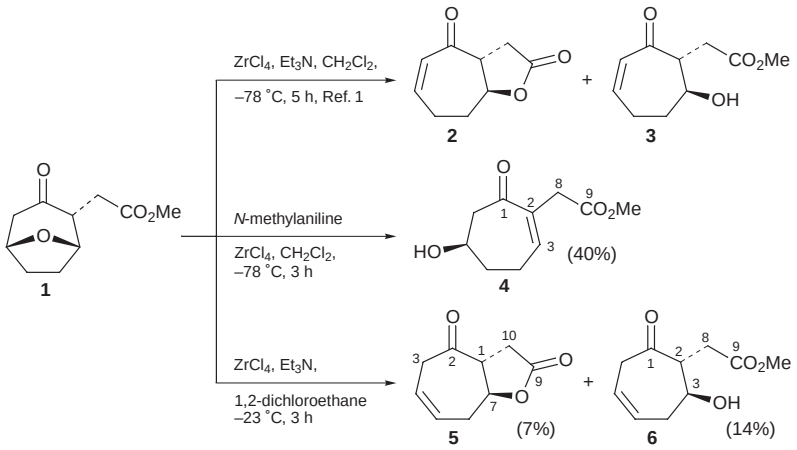
The synthesis of three new polysubstituted cycloheptenones by cleavage of the ether bridge of 8-oxabicyclo[3.2.1]octan-3-one derivatives is described, together with the application of this methodology in the construction of the guaianolide and pseudoguaianolide skeleton.

Derivatives of 8-oxabicycle[3.2.1]octan-3-one are important intermediates in the synthesis of natural products. Their synthetic utility can be extended by cleavage of the ether bridge, generating polysubstituted cycloheptenones. We have previously described[1] the synthesis of cycloheptenones **2** and **3** (Scheme 1) from oxabicyclic compounds, using $ZrCl_4$ and triethylamine in CH_2Cl_2. Here we describe new results from the application of this methodology, including the synthesis of three novel cycloheptenones and the construction of the basic skeleton of guaianolides and pseudoguaianolides, from 2α-methoxycarbonyl-methyl-8-oxabicyclo[3.2.1]octan-3-one **1**.[2]

1,2-dichloroethane at −23 °C (instead of dichloromethane at −78 °C) gave the non-conjugated unsaturated lactone **5** and keto alcohol **6** in low yield (Scheme 1).

As reported earlier, compound **2** could be obtained from **1** either by treatment with zirconium tetrachloride and triethylamine (Scheme 1) or with lithium diisopropylamide and trimethylsilyl triflate.[1] As an application of this methodology, the lactone **2** was converted into the two tricyclic compounds **8** and **9** *via* a Michael aldol route[4,5] (Scheme 3): a copper catalysed conjugate addition of a Grignard reagent to an α,β-unsaturated ketone followed by acid catalysed Aldol condensation.

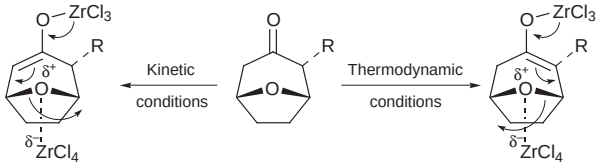


Scheme 1

Results and discussion

When compound **1** was treated with $ZrCl_4$ and *N*-methylaniline in CH_2Cl_2 at −78 °C, the cycloheptenane **4** was obtained (Scheme 1). Several other amines gave the kinetic product under these conditions.[1,3] This result indicates that *N*-methylaniline is a weak enough base to allow an equilibrium to take place and thence the formation of the most stable enolate. The ring is opened in sequence and the zirconium alkoxide is hydrolyzed to give the hydroxylated compound after the aqueous work-up (Scheme 2).

The reactions with zirconium tetrachloride were very sensitive to any change in the conditions applied. For example, zirconium tetrachloride and triethylamine in



Scheme 2

One major isomer of the adduct **7** was obtained, but although only one spot was observed in TLC some signals of much smaller intensity could be seen in the ^{1}H NMR spectrum, indicating that possibly another isomer was also formed as a secondary product. The relative stereochemistry at C4 was tentatively assigned by comparison with similar results published earlier.[6,7]

The aldol step had failed when attempted with a similar compound containing methyl groups at positions 1 and 3, with the starting acetal resisting for more than one

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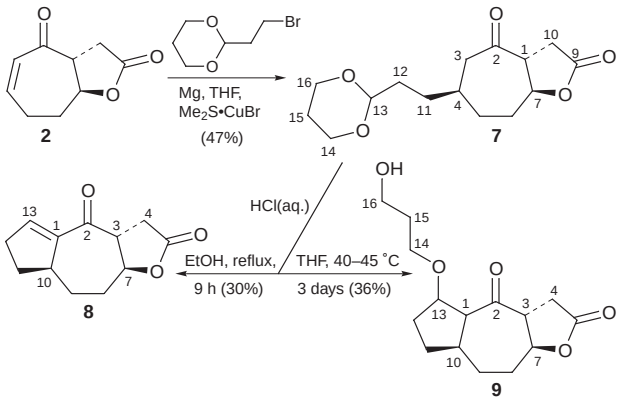

Scheme 3

day at 100 °C, together with the formation of a large number of products in small quantities.[8] Upon treatment of compound **7** with aqueous HCl, the acetal was hydrolysed. The resultant aldehyde reacted intramolecularly to give compound **8** or **9** depending on the solvent and the reaction temperature.

Although the relative stereochemistry at C1 and C10 in compound **9** was not defined it is clear that a major isomer was formed. It is probable that a *β-cis* fused ring product was formed, in analogy to the study carried out by Heathcock *et al.*[7]

Compounds **8** and **9** possess the same skeleton of the guaianolides and pseudoguaianolides, and we hope to prepare a range of novel compounds from these key intermediates.

Experimental

Compounds **1** and **2** were prepared according to the procedures described in the literature.[1,2] All products were purified by flash chromatography on silica gel with light petroleum (bp 40–60 °C) and ethyl acetate or diethyl ether. The proposed structures for compounds **4–9** were confirmed by IR, ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz) and mass spectrometry. All the NMR analyses ($CDCl_3$) were supported by DEPT, COSY and HETCOR data. The reaction yields were not optimised.

Polysubstituted Cycloheptenones **4–6**.—To a suspension of $ZrCl_4$ (3 equiv.) in the appropriate dry solvent at −78 °C or −23 °C (Scheme 1), under a N_2 atmosphere, was added the amine (3 equiv.). A solution of compound **1** (1 equiv.) in the same solvent was added and the mixture stirred for 3 to 7 h. A solution of NH_4Cl(sat.) was added and extractions with CH_2Cl_2 (for **4**) or ethyl acetate (for **5** and **6**) were performed. The organic extracts were dried over $MgSO_4$, concentrated and purified to yield compound **4** [yellow oil; ν_{max}/cm^{-1} 3218 (OH), 1737 (C=O, ester), 1672 S (C=O, unsat. ketone); $[M+H]^+$ m/z = 199.0970; ^{13}C NMR 24.7 (C4), 35.8 (C5), 38.5 (C8), 51.4 (C7), 52.0 (OMe), 66.6 (C6), 137.4 (C2), 146.0 (C3), 172.2 (C9), 199.8 (C1); ^{1}H NMR δ 1.64 (br s, 1H, OH), 1.82–1.89 (m, 1H, H5), 2.08–2.11 (m, 1H, H5′), 2.35–2.42 (m, 1H, H4), 2.56–2.64 (m, 1H, H4′), 2.92 (dd, 1H, J = 6.7, 13.0, H7′), 3.00 (dd, 1H, J = 5.1, 13.0, H7), 3.29 (d, 2H, J = 2.9, H8, 8′), 3.67 (s, 3H, OMe), 4.33 (br t, 1H, *J ca.* 6, H6), 6.70 (br t, 1H, *J ca.* 6 Hz, H3)], or compounds **5** [yellow solid; ν_{max}/cm^{-1} 1784 (C=O lactone), 1713 (C=O, sat. ketone), 1676 (C=C)]; M^+ m/z = 166.0631; ^{13}C NMR δ 30.0 (C10), 36.2 (C6), 42.8 (C3), 54.3 (C1), 77.0 (C7), 121.1 (C4), 125.4 (C5), 174.6 (C9), 203.6 (C2); ^{1}H NMR δ 2.54–2.69 (m/dd, 2H, *J ca.* 9, 18, H6, 10), 3.01–3.17 (m/dd, 2H, J = 11.4, 18.0 Hz, H6′, 10′), 3.17–3.32 (m, 2H, H3, 3′), 3.50–3.59 (m, 1H, H1), 4.53–4.60 (m, 1H, H7), 5.54–5.61 (m, 1H, H4), 5.76–5.80 (m, 1H, H5)] and **6** [yellow oil; ν_{max}/cm^{-1} 3447 (OH), 1736 (C=O, ester),1708 (C=O sat. ketone), 1646 (C=C); $[M+H]^+$ m/z = 199; ^{13}C NMR δ 33.0 (C8), 34.7(C4), 44.4 (C7), 51.9 (OMe), 54.7 (C2), 73.4 (C3), 125.3 (C6), 127.6 (C5), 173.7 (C9), 207.7 (C1); ^{1}H NMR δ 2.2–3.0 (br s, *ca.* 1H, OH), 2.43 (br b, 2H, J = 5.5, H4, 4′), 2.71 (dd, 1H, J = 4.8, 17.2, H8), 2.93 (dd, 1H, J = 8.8, 17.2 H8′), 3.16 (br dd, 1H, *J ca.* 3,18, H7), 3.25 (dd, 1H, J = 6.4, 17.8, H7′), 3.37 (td, 1H, J = 4.8, 8.6 Hz, H2), 3.66 (s, 3H, OMe), 3.77–3.82 (m, 1H, H3), 5.82–5.88 (m, 1H, H6), 5.90–5.96 (m, 1H, H5)].

Michael–Aldol Route.—The Grignard reagent (2.9 mmol) prepared from 2-(2-bromoethyl)-1,3-dioxane and magnesium was added to a solution of copper(I) bromide–dimethylsulfide complex (1.3 mmol) in dry THF at −78 °C under a N_2 atmosphere. The suspension was stirred at −78 °C for 10 min and at −25 °C for 20 min prior to the addition of a solution of compound **2** (1.2 mmol) in dry THF. After stirring at −25 °C for 35 min and at room temperature for 30 min the reaction mixture was poured into a mixture of 2:3 ammonia buffer [NH_4Cl(sat.)–NH_3(conc.) 4:1] and diethyl ether. The organic layer was washed with ammonia buffer and brine, dried over $MgSO_4$, concentrated and purified to yield **7** [Colourless oil; $[M+NH_4^+]$ m/z = 300.1811; ^{13}C NMR δ 25.7 (C15), 28.0 (C11), 29.1 (C5), 30.0 (C6), 30.8 (C10), 32.8 (C4), 33.0 (C12), 49.6 (C3), 54.9 (C1), 66.9 (C14 and C16), 79.6 (C7), 101.6 (C13), 174.6 (C9), 205.5 (C2); ^{1}H NMR δ 1.35 (dm, 1H, J = 13.6, H15),1.54–1.66 (m/dd, 4H, *J ca.* 6, 15, H11, 11′, 12, 12′), 1.77–1.85 (m, 1H, H5), 1.85–1.95 (m, 1H, H4), 1.95–2.08 (m, 3H, H6, 5′, 15′), 2.35–2.42 (m, 1H, H6′), 2.56 (d, 2H, J = 5.5, H3, 3′), 2.59 (dd, 1H, J = 8.4, 18.0, H10), 2.96 (ddd, 1H, J = 0.73, 11.7, 18.0, H10′), 3.36 (ddd, 1H, J = 8.4, 11.7, 11.4, H1), 3.75 (tm, 2H, *J ca.* 11, H14, 16), 4.09 (br dd, 2H, J = 4.8, 11.4 Hz, H14′, 16′), 4.26 (td, 1H, *J ca.* 4.4, 11 Hz, H7), 4.51–4.52 (m, 1H, H13)]. To a solution of **7** (*ca.* 0.5 mmol) in ethanol or THF (Scheme 3) were added *ca.* 0.5 mL of a HCl aqueous solution (10% for compound **8** or 0.1 mol L^{-1} for **9**). The mixture was stirred at the appropriate temperature till the consumption of the starting material. Then it was poured into a mixture of diethyl ether and water. Extractions with diethyl ether were performed. The organic extract was washed with brine and $NaHCO_3$ (sat.), dried over $MgSO_4$, concentrated and purified to yield **8** [colourless oil; M^+ m/z = 206.0943; ^{13}C NMR δ 29.9 (C4), 31.3 (C12), 32.4 (C9), 32.5 (C11), 35.1 (C8), 44.3 (C10), 55.4 (C3), 80.8 (C7), 145.9 (C13), 146.1 (C1), 174.8 (C5), 192.8 (C2); ^{1}H NMR δ 1.39–1.49 (m, 1H, H9), 1.57–1.66 (m, 2H, H11, 11′), 1.85–1.91 (m, 1H, H8), 2.02–2.07 (m, 1H, H9′), 2.33–2.57 (m/dd, 4H, J = 7.7, 18.0, H4, H8′, 12, 12′), 3.00–3.08 (m, 1H, H10), 3.20 (td, 1H, J = 11.7, 18.0, H4′), 3.39 (ddd, 1H, J = 7.7, 11.7, 11.5, H3), 4.10 (dd, 1H, *J ca.* 3, 11, H7), 6.99 (dd, 1H, J = 2.6, 4.8 Hz, H13)] or **9** [colourless oil; ν_{max}/cm^{-1} 3516 (OH); 1779 (C=O lactone), 1708 (C=O ketone); ^{13}C NMR δ 25.7 (C9), 28.2 (C4), 28.5 (C11), 28.7 (C8), 29.5 (C15), 32.7 (C12), 33.0 (C10), 46.5 (C16), 49.3 (C3), 66.9 (C14 and C1), 78.5 (C7), 101.9 (C13), 175.0 (C5), 206.2 (C2); ^{1}H NMR δ 1.25–1.52 (m, 4H, H9, 11, 15, 15′), 1.58–1.68 (m, 3H, H8, 12, 12′), 1.83–1.92 (m, 1H, H11′), 2.01–2.12 (m, 3H, H8′, 9′, 10), 2.31 (dd, 1H, J = 10.6, 16.3, H16), 2.51–2.60 (dd/m, 2H, J = 10.3, 18.7, H4, 16′), 3.21 (dd, 1H, J = 4.4, 18.7, H4′), 3.66–3.79 (m, 3H, H3, H14, 14′), 4.07–4.11 (dd/m, 1H, *J ca.* 5, 8, H1), 4.52 (t, 1H, J = 5.0, H13), 4.87 (ddd, 1H, J = 2.9, 8.9, 11.6 Hz, H7)].

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References

1 L. C. A. Barbosa, M. M. M. Rubinger, J. Mann and H. L. Mansell, *Tetrahedron*, 1996, **52**, 11927.
2 M. M. M. Rubinger, J. Mann and M. G. B. Drew, *Tetrahedron*, 1995, **51**, 11295.
3 I. Stoher and H. M. R. Hoffmann, *Tetrahedron*, 1992, **48**, 6021.
4 A. Marfat and P. Helquist, *Tetrahedron Lett.*, 1978, **44**, 4217.
5 A. Marfat, S. A. Bal and P. Helquist, *J. Org. Chem.*, 1982, **47**, 5045.
6 W. J. M. Cummings, G. B. Drew, J. Mann and A. J. Markson, *Tetrahedron*, 1988, **44**, 5151.
7 C. H. Heathcock, T. C. Germroth and S. L. Graham, *J. Org. Chem.*, 1979, **44, 4481.**
8 L. C. A. Barbosa and J. Mann, *J. Chem. Soc., Perkin Trans. 1*, 1990, 177.