Pergamon

Tetrahedron Letters, Vol. 38, No. 26, pp. 4709-4712, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01004-6

Concomitant Bromination and Lactolisation of Unsaturated Diols with Sodium Bromite in Aqueous Acetic Acid

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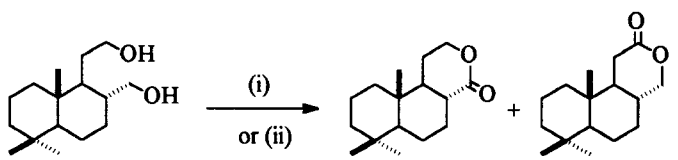
Abstract: The attempted lactonisation of unsaturated diols **8**, **13**, and **15** using sodium bromite in aqueous acetic acid gave the bromo lactols **9**, **16**, and **18** respectively. The bromo lactols were converted to their corresponding lactones **10**, **17**, and **19** using Jones reagent.

A key step in the synthesis of lactones which bear structural similarities to perfumery components and intermediates such as ambreinolide[2] and nor-ambreinolide[3] is the lactonisation of their appropriate diol precursors. The lactonisation step is usually achieved using Fetizons reagent.[4] An alternative general lactonisation procedure, reported by Kageyama,[5] uses sodium bromite in aqueous acetic acid. Under the conditions described a series of 1,ω-diols were lactonised in moderate to excellent yields (54 - 95 %). Bromite has previously been reported as an oxidising agent,[6-11] and has been shown to undergo addition reactions with alkenes[7] which can be interpreted as the addition of Br^+.

Initially attempts were made to lactonise the saturated 1,5-diol **1**. Treatment with sodium bromite in aqueous acetic acid gave a mixture of regioisomeric lactones **2** and **3** in 79% combined yield and in a ratio of 1:1 by ^1H NMR. This particular reaction lacked the regioselectivity of Fetizon's reagent which gave exclusively lactone **3** (72%) (Scheme 1).

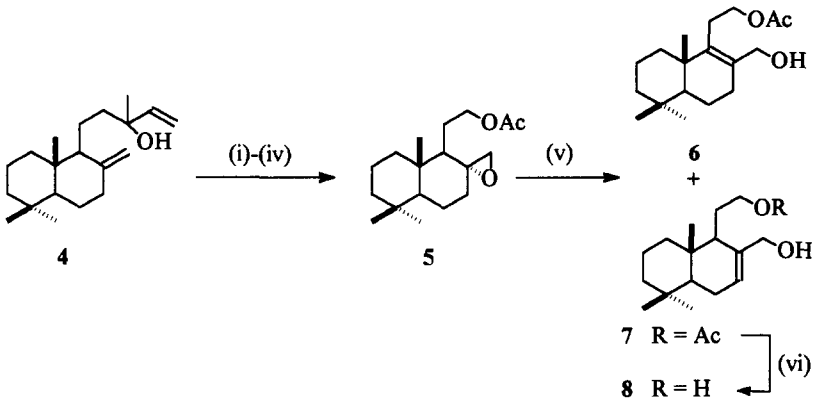


1 **2** **3**

Scheme 1: (i) $NaBrO_2$, aq. HOAc, r.t., 79%. (ii) Fetizons reagent, toluene, reflux, 72%.

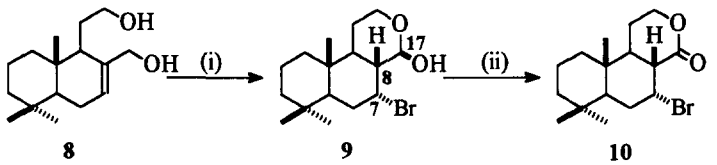
We next considered the lactonisation of unsaturated 1,5-diol **8** with sodium bromite in aqueous acetic acid. Unsaturated diol **8**[12a] was synthesised from manool **4**, in six steps, a key reaction being the treatment of the epoxy acetate **5**[13] with methanesulfonyl chloride in refluxing pyridine (Scheme 2). This gave a mixture of two allylic alcohols

6 and 7, from which the desired unsaturated alcohol 7 was isolated in moderate yield (27%) after careful chromatography. Reduction of compound 7 to unsaturated diol 8 was achieved quantitatively using $LiAlH_4$.



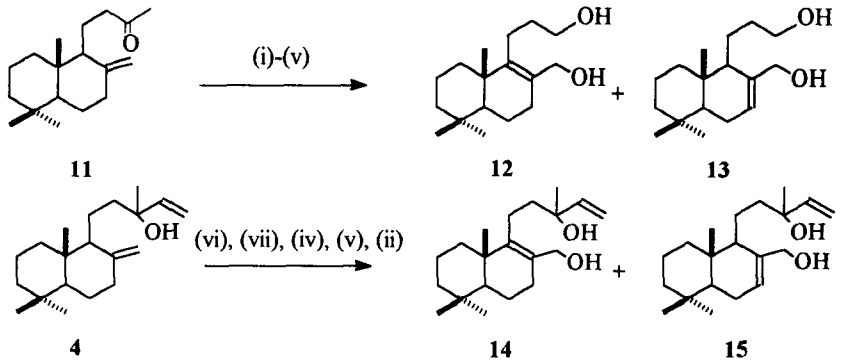
Scheme 2: (i) $VO(acac)_2$, *t*-BuOOH, Et_2O, reflux. (ii) $LiAlH_4$, Et_2O, reflux. (iii) $Pb(OAc)_4$, benzene, r.t. (iv) mCPBA, r.t. (v) MsCl, pyridine, reflux. (vi) $LiAlH_4$, Et_2O, r.t.

Reaction of the unsaturated diol **8** with sodium bromite in aqueous acetic acid gave the bromo lactol **9**[14] (53%) which decomposed on standing (Scheme 3). The stereochemistries of carbons 7, 8, and 17 were assigned with the aid of a combination of NMR spectral analysis and the oxidation of compound **9** to bromo lactone **10**. The ^1H NMR spectrum of **10**[15] showed a downfield shift of the H-8 signal to a clear region of the spectrum. The large coupling constant (J 12.2 Hz) established the configuration of H-8 as β.



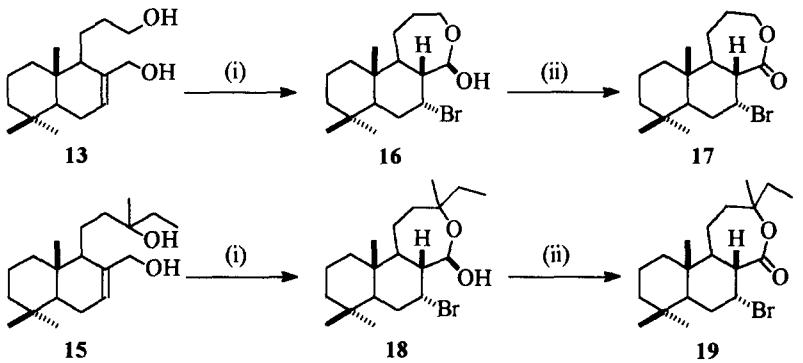
Scheme 3: (i) $NaBrO_2$, $HOAc/H_2O$, r.t., 53%. (ii) CrO_3, H_2SO_4, acetone, r.t., 55%.

The same series of reactions were repeated on two unsaturated 1,6-diols **13**[12a,b] and **15**[12a,b] (Scheme 4). Unsaturated diol **13** was prepared via methylene ketone **11**.[16] Unsaturated diol **15** was prepared from manool **4** in five steps.



Scheme 4: (i) Br_2, NaOH, dioxan, r.t. (ii) $LiAlH_4$, Et_2O, reflux. (iii) Ac_2O, pyridine, r.t. (iv) mCPBA, r.t. (v) MsCl, pyridine, reflux. (vi) PtO_2, MeOH, $H_2(g)$, r.t. (vii) Isopropenyl acetate, p-TsOH, r.t.

The unsaturated 1,6-diols, **13** and **15** were treated with sodium bromite in aqueous acetic acid and gave bromo-lactols **16** (55%) and **18** (57%) respectively (Scheme 5). These were then oxidised to their more stable bromo lactones **17** (55%) and **19** (85%) using Jones reagent. The stereochemistry in compounds **16** to **19** was assigned via the aid of NMR[17-20]spectral analysis and analogy with compounds **9** and **10**.



Scheme 5: (i) $NaBrO_2$, H_2O/HOAc, r.t. (ii) Jones reagent, acetone, r.t.

This reagent ($NaBrO_2$/aq. HOAc) has demonstrated ability in a one-pot procedure for the regioselective lactolisation of 1,5- and 1,6-diols while undergoing concomitant mono-bromination of an allylic olefin.

ACKNOWLEDGEMENTS

We are grateful for financial support for GBE from the University Grants Committee.

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12(a) This structure is consistent with ^{1}H and ^{13}C NMR, IR, and MS data. (b) This compound gave satisfactory elemental analysis.

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14. ^{1}H NMR **9**: methyls at δ 0.83, 0.86, 0.88; H_A3.98, H_B3.45, 2H, J_{AB}11.5, J_{AX}4.2, J_{AY}2.1, J_{BX}11.5, J_{BY}3.4 Hz, H-12; 4.64, 1H, d, J 7.4 Hz, H-17; 4.90, 1H, q, J 3.0 Hz, H-7. ^{13}C NMR **9**: 14.3 (C20), 18.7 (C2), 22.3 (C19), 23.8 (C11), 31.2 (C6), 32.6 (C4), 32.9 (C18), 36.8 (C10), 38.3 (C1), 41.8 (C3), 45.4 (C5), 45.5 (C8), 47.8 (C9), 57.4 (C7), 65.2 (C12), 99.3 (C17).
15. ^{1}H n.m.r. **10**: methyls at δ 0.84, 0.87, 0.89; 2.64, 1H, dd, J_{aa}12.2, J_{ae}2.9 Hz, H-8β; H_A4.41, H_B4.23, 2H, J_{AB}11.2, J_{AX}4.8, J_{AY}2.1, J_{BX}11.2, J_{BY}3.2Hz, H-12; 5.16, 1H, q, J2.9Hz, H-7. ^{13}C NMR **10**: 13.9 (C20), 18.6 (C2), 22.0 (C19), 22.1 (C11), 31.0 (C6), 32.7 (C4), 32.7 (C18), 36.9 (C10), 37.8 (C1), 41.7 (C3), 45.0 (C9), 47.5 (C8), 47.8 (C5), 53.7 (C7), 69.6 (C12), 170.3 (C17).
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17. ^{1}H n.m.r. **16**: methyls at δ 0.82, 0.86, 0.86; 2.90, 1H, s, OH; H_A3.93, H_B3.67, 2H, J_{AB}11.3, J_{AX}8.3, J_{AY}1.8, J_{BX}11.3, J_{BY}7.6Hz, H-12; 4.71, 1H, brd, J6.9Hz, H17, 4.99, 1H, q, J3.0Hz, H-7. ^{13}C NMR **16**: 14.6 (C20), 19.1 (C2), 20.6 (C11), 22.1 (C19), 28.7 (C12), 31.5 (C6), 32.9 (C4), 32.9 (C18), 38.5 (C10), 38.5 (C1), 41.9 (C3), 48.4 (C9), 49.9 (C8), 50.3 (C5), 60.4 (C7), 65.5 (C13), 99.6 (C17).
18. ^{1}H n.m.r. **17**: methyls at δ 0.84, 0.87, 0.89; 2.65 1H, dd, J_{aa}12.2, J_{ae}2.9 Hz, H-8β; H_A4.42, H_B4.23, 2H, J_{AB}11.1, J_{AX}4.8, J_{AY}2.1, J_{BX}11.1, J_{BY}3.2Hz, H-12; 5.16, 1H, q, J3.0Hz, H-7. ^{13}C NMR **17**: 13.8 (C20), 18.6 (C2), 20.9 (C11), 21.8 (C19), 27.1 (C6), 32.7 (C18), 32.8 (C4), 32.8 (C12), 37.5 (C1), 38.1 (C10), 41.9 (C3), 44.3 (C9), 48.4 (C5), 56.2 (C8), 57.7 (C7), 64.3 (C13), 173.7 (C17).
19. ^{1}H n.m.r. **18**: methyls at δ 0.82, 0.85, 0.86, 0.92 (t, J7.5Hz), 1.08; 4.74, 1H, d, J7.3Hz, H17, 4.97, 1H, q, J3.0Hz, H-7. ^{13}C NMR **18**: 8.6 (C15), 14.1 (C20), 19.1 (C2), 19.2 (C11), 22.2 (C19), 24.5 (C16), 31.5 (C14), 31.5 (C6), 32.5 (C4), 32.9 (C18), 38.3 (C10), 38.5 (C1), 39.6 (C12), 41.8 (C3), 48.4 (C9), 50.0 (C8), 50.4 (C5), 60.4 (C7), 76.7 (C13), 93.7 (C17).
20. ^{1}H n.m.r. **19**: methyls at δ 0.82, 0.84, 0.87, 0.97 (t, J7.4Hz), 1.26; 2.67, 1H, dd, J_{aa}11.4, J_{ae}3.2Hz, H-8β; 4.99, 1H, q, J3.0Hz, H-7. ^{13}C NMR **19**: 8.3 (C15), 14.0 (C20), 18.7 (C2), 22.2 (C11), 22.2 (C19), 24.3 (C16), 31.5 (C14), 32.8 (C4), 32.8 (C18), 34.8 (C6), 38.1 (C10), 38.2 (C12), 38.3 (C1), 41.7 (C3), 46.1 (C9), 47.6 (C5), 53.9 (C8), 57.7 (C7), 86.0 (C13), 178.4, (C17).

(*Received in UK* 14 *April* 1997; *revised* 20 *May* 1997; *accepted* 23 *May* 1997)