Tetrahedron Letters, Vol.31, No.40, pp 5795-5798, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

Partial Synthesis of 7-ß-hydroxyeudesmanolides

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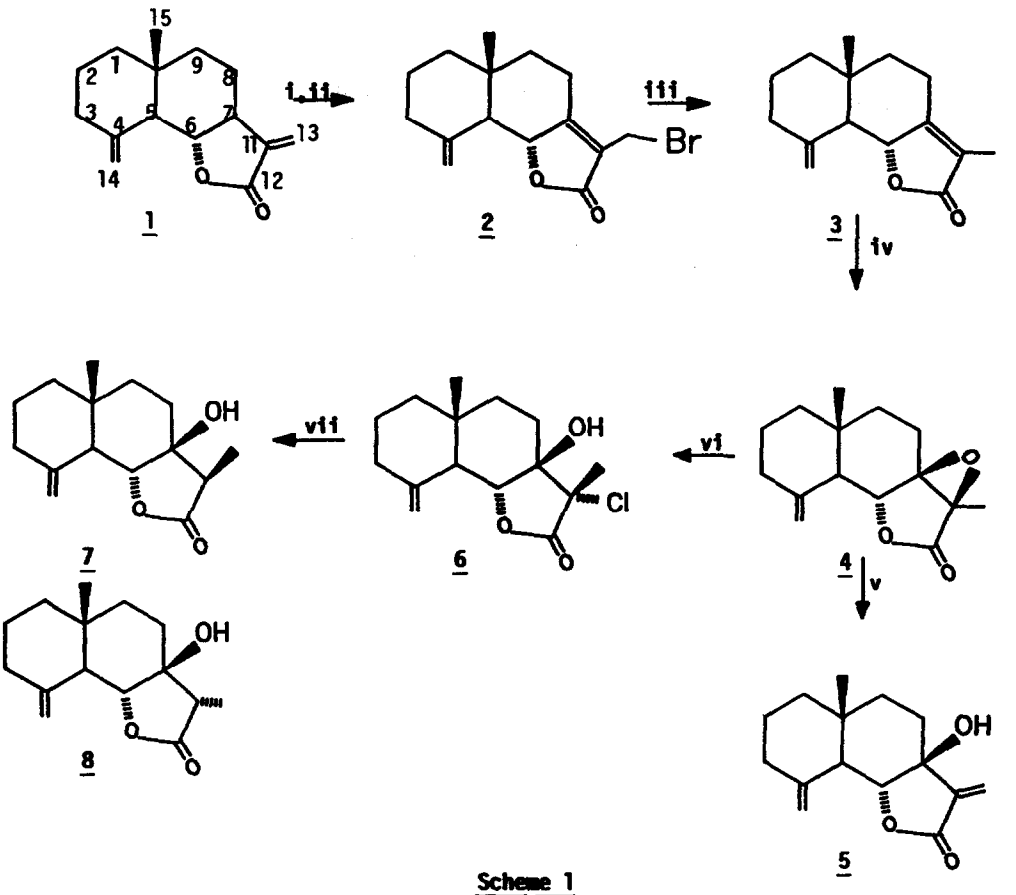
Summary:
ß-cyclocostunolide has been efficiently transformed into 7-ß-hydroxy-ß-cyclocostunolide. The key step in the conversion was the rearrangement of the 7ß,11ß-epoxy derivative with t-BuO⁻K⁺/THF. This synthesis supports the biogenetic routes of 7-hydroxyeudesmanolides.

In the last years a relative high number of 7-hydroxy sesquiterpene lactones have been isolated from natural sources[1-8] and it has been reported[9] that the molluscicidal activity of these compounds could be related with the functionalization on C-7.

In a previous paper[10] we comunicated a selective addition of bromine on double bond C11-C13 in eudesmanolides, using phenyltrimethylammonium perbromide as bromination reagent. We indicated that this reaction provides a facile way of obtaining sesquiterpene lactones functionalized on the lactone ring.

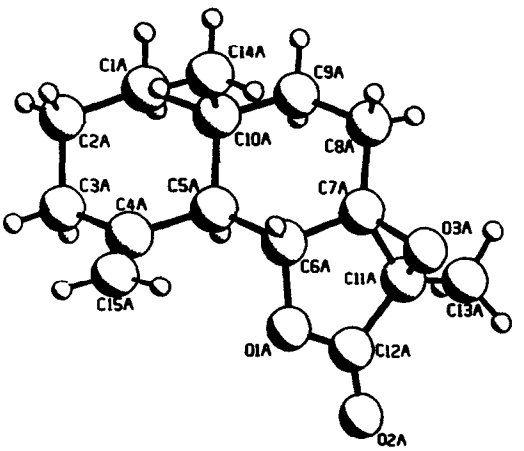
Continuing with our research programme directed towards the partial synthesis of biologically active sesquiterpene lactones, we show, in this paper, the applicability of above mentioned reaction and report the first synthesis of 7-hydroxyeudesmanolides from (1), via rearrangement of the epoxycompound (4). This strategy supports the biogenetic route proposed by Mabry et al[6].

The transformation of ß-cyclocostunolide (1) to the target derivative is outlined in scheme 1. The 13-bromo-7,11-ene-ß-cyclocostunolide was prepared from (1) as described previously[10], via bromination with TMPAP in dioxane (52%) following of dehydrobromination with $LiBr/Li_2CO_3$ in DMF (97%).



Scheme 1

Reagents: i) TMPAP/Dioxane ; ii) LiBr/Li_2CO_3 ; iii) nBu_3SnH; iv) H_2O_2/NaOH; v) $tBuO^-K^+$/THF ;vi) $CaCl_2$/Bencene; vii) nBu_3SnH



X Ray molecular structure compound (4)

Debromination of (2) (nBu_3SnH, toluene) gave (3) (90%), which was converted into the 7ß,11ß-epoxide (4) (85%) by regioselective epoxidation with H_2O_2/NaOH.

The presence of ß oxirane ring and was deduced from ^1H NMR* (4.64 (d, 1H, J= 10.8 Hz, H-6), 1,77 (d br, J= 10.8 Hz, H-5), 1,55 (s, 3H, H-13) and it was confirmed by single cristal X-ray diffraction[11].

In general two different strategies have been utilized to effect the rearrangement of epoxides to allylic alcohols[12],a) treatment with a strong base to abstract a ß-proton and epoxide opening to give the desired allylic alcohol;b) epoxide opening with a nucleophilic agent ElNu following of elimination of HNu to generate the double bond to yield allylic alcohol.

The most well-known method to isomerize epoxides to allylic alcohols involves the use of strong, non nucleophilic bases such as the lithium dialkylamides.

Attemps to rearrange 4 to the 7-hydroxy-ß-cyclocostunolide (5) using LDA, HMPT and $(iProp)_3Al$ were unsuccessfull, obtaining the starting material inalterate. When $tBuO^-K^+$/tBuOH, was used an intractable mixture was obtained.However the rearrangement was achieved when 4 was treated under reflux with $tBuO^-K^+$/THF.After 3h only one blue spot was observed in TLC. The structure of compound 5 was inferred from its IR and ^1H NMR(*). The ß orientation of hydroxy group on C-7 was confirmed by comparison of signals corresponding to protons H-13, H-13' and H-6 with those described in the literature[6] for 7α-hydroxyeudesmanolides.

In order to open the oxirane ring, compound 4 was treated with different reagents (NaH, NaMeO, $CaCl_2$). Successful result was obtained with $CaCl_2$/Bencene yielding 6* (70 %). Subsequent treatment with nBu_3SnH gave 7* (82 %) and 8* (15%) . Further works are in progress to synthetize 7-α-hydroxyeudesmanolides in order to carry out a comparative study of their bioactivity.

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*.- ^{1}HNMR ($CDCl_3$), 200 MHz. Compound 4, 4,56(d, 1H, J=10.6 Hz, H-6);2.27(ddd, 1H, J= 5, 13 Hz, H-8'); 1.48(s, 3H, H-13, H-13'); 4.90(s br, 1H, H-14); 4.69(s br,1H,H-14'); 0.82(s, 3H, H-15).Compound 5. 1.56 (d br, 1H, J=10.7 Hz, H-5); 4.57 (d, 1H, J= 10.7 Hz,H-6); 2.10 (m, 2H, H-8, H-8'); 6.31 (s, 1H, H-13); 5.74(s, 1H, H-13'); 4.90(s br, 1H, H-14); 4.72(s br, 1H, H-14');0.78 (s, 3H, H-15). Compound 6. 1.85(d, 1H, J= 11.4, H-5); 4.57(d, 1H, J= 11.4, H-6); 2.4(m, 2H, H-8, H-8'); 1.67(s, 3H,H-13); 4.92(s br, 1H, H-14); 4.71(s br, 1H, H-14'); 0.80(s, 3H, H-15). Compound 7. 4.52(d, 1H, J=11.1, H-6); 2.1(m,2H, H-8, H-8'); 1.33(d, 3H, J= 8 Hz, H-13); 4.92 (s br, 1H, H-14); 4.72 (s br, 1H, H-14'); 0.80(s, 3H, H-15); 2.52 (q, 1H, J= 8 Hz, H-11); Compound 8. 4.51(d, 1H, J= 11.0, H-6); 1.9-2.1(m, 2H, H-8, H-8');1.18 (d, 3H, J= 7 Hz, H-13); 4.94(s br, 1H, H-14); 4.76 (s br, 1H, H-14'); 0.83(s, 3H, H-15); 2.74 (q, 1H, J= 7 Hz, H-11).

Acknowledgement: This research was supported by grants from DGICYT, PB 87-0965, PB 88-0570 and by fellowship (to J. G. M.) from Junta de Andalucia (Spain).

(Received in UK 27 July 1990)