Pergamon

Tetrahedron Letters, Vol. 38, No. 11, pp. 2005-2006, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00216-5

A Biogenetically Patterned First Total Synthesis of (±)-6-Epijunicedranol (or Junicedran-11-ol)

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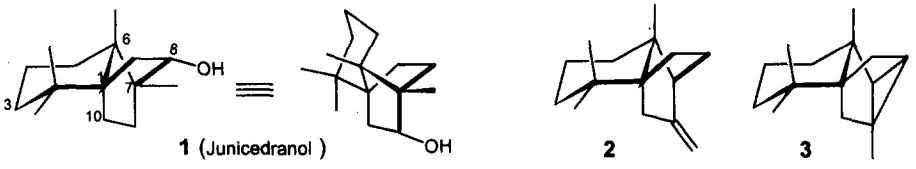
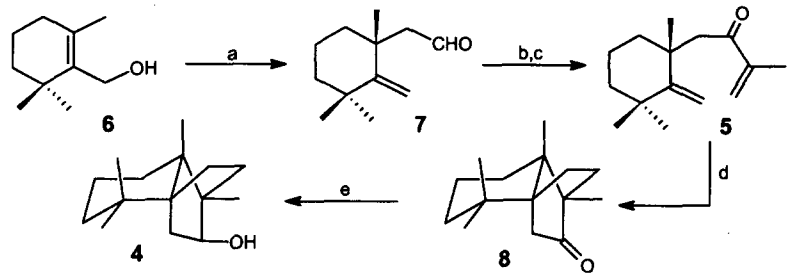
Abstract: The first total synthesis of (±)-6-epijunicedranol (**4**), employing a biogenetically patterned carbonium ion mediated cyclisation and rearrangement of an enone for the efficient generation of four contiguous quaternary carbon atoms, is described.

Junicedranol (**1**), a novel tricyclic sesquiterpene alcohol, recently isolated from *Juniperus oxycedrus* ssp. *macrocarpa* by Barrero and coworkers,[1] contains a unique carbon framework, 2,2,6,7-tetramethyltricyclo[5.2.2.0^{1,6}]undecane, incorporating four contiguous quaternary carbon atoms (C-1,2,6 and 7). It is worth noting that a very close isomeric carbon framework, 2,2,6,8-tetramethyltricyclo[5.2.2.0^{1,6}]undecane with three contiguous quaternary carbon atoms, is present in myltaylene (**2**) and cyclomyltaylene (**3**) sesquiterpenes.[2] The presence of the novel tricyclic structure incorporating the four contiguous quaternary carbon centers made junicedranol (**1**) an interesting and challenging synthetic target. The suggested biogenetic origin of junicedranol (**1**) from the chamigrenyl carbonium ion intrigued us, as based on molecular models, it is logical to think that the cyclisation of the chamigrenyl carbonium ion should lead to the alcohol **4**, a C-6 epimer of junicedranol (**1**). To substantiate our claim, herein we report a biogenetically patterned first total synthesis[3] of (±)-**4** (6-epijunicedranol or junicedran-11-ol).



1 (Junicedranol) **2** **3**

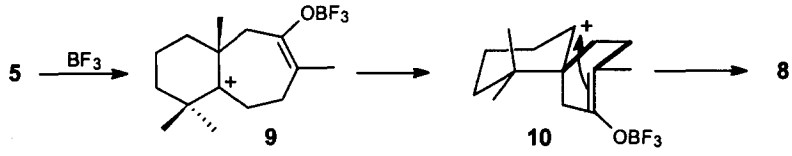
The synthetic sequence is depicted in Scheme 1. The key intermediate of the sequence, the dienone **5** was prepared from cyclogeraniol (**6**)[4] in three steps. Thus, one pot Claisen rearrangement of **6** using ethyl vinyl ether and mercuric acetate generated the ene-aldehyde **7**.[5] Addition of isopropenylmagnesium bromide to the ene-aldehyde **7** followed by oxidation of the resulting allyl alcohol with pyridinium chlorochromate (PCC) furnished the dienone **5** in 40% overall yield. The construction of the carbon framework of junicedrane was achieved *via* a Lewis acid mediated cyclisation and rearrangement of the dienone **5**. Thus, treatment of the dienone **5** with a catalytic amount of boron trifluoride etherate in methylene chloride furnished the tricyclic ketone **8** (a junicedranone) in 77% yield, creating the four contiguous quaternary centres. The structure of the ketone **8** was deduced from its spectral data[6] and established by comparison with that of the precursor[2e] of myltaylene. Finally, the ketone **8** was reduced to the thermodynamically favoured *endo* alcohol by lithium in liquid ammonia to furnish 6-epijunicedranol (**4**), which exhibited spectral data[6] very similar to that of junicedranol (**1**).



***Scheme 1**: Reagents and Conditions: (a) CH_2=CH-OEt, $Hg(OAc)_2$, 170°C, 30 h, 76%; (b) 2-Bromopropene, Mg, THF, 8 h; (c) PCC, molecular sieves, CH_2Cl_2, 40 min, 40% (from 7); (d) BF_3-OEt_2, CH_2Cl_2, 0°C→rt, 30 min, 77%; (e) Li, liq. NH_3, THF, 10 min, 80%.*

The formation of the tricyclic ketone **8** from the dienone **5** can be readily rationalised as depicted in Scheme 2. Acid catalysed cyclisation of the dienone **5** generates the bicyclic *tertiary* carbonium ion **9**, which rearranges to chamigrenyl carbonium ion **10**. Reketonisation of **10** *via* cyclisation furnishes the tricyclic ketone **8** with the C-6 methyl group *anti* to carbonyl group.

SCHEME 2



In conclusion, we have achieved the first total synthesis of (±)-6-epijunicedranol (**4**) employing a biogenetically patterned acid catalysed carbonium ion mediated cyclisation and rearrangement of a dienone as the key step, in which the requisite four contiguous quaternary carbons were efficiently generated.

***Acknowledgements:** We thank Professor A.F. Barrero, Universidad de Granada, for providing the copies of the NMR spectra of authentic Junicedranol, and the C.S.I.R., New Delhi for the award of a research fellowship to PPK.*

References

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6. All the compounds exhibited spectral data consistant with the structures. Selected spectral data for the ketone **8**: IR (neat) ν_{max} 1740, 1455, 1380 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.843 (3 H, s), 0.890 (3 H, s), 1.00 (3 H, s) and 1.061 (3 H, s) [4 x *tert*-CH_3], 0.9-2.0 (10 H, m), 1.811 (1 H, d, *J* 18.6 Hz, H-9 exo), 2.44 (1 H, dd, *J* 18.6 and 3.5 Hz, H-9 endo). ^{13}C NMR (100 MHz, $CDCl_3$, SEFT): δ 218.5 (C=O), 60.9 (C), 52.5 (C), 48.1 (C) and 33.7 (C) [4 x quaternary carbons], 45.4 (CH_2, CH_2-C=O), 36.1 (CH_2), 30.1 (CH_2), 28.9 (CH_2), 27.4 (CH_2), 18.8 (CH_2), 28.8 (CH_3), 23.5 (CH_3), 16.4 (CH_3) and 9.3 (CH_3) [4 x CH_3]. HRMS: Found 220.1816. $C_{15}H_{24}O$ requires 220.1827. For 6-epijunicedranol (**4**): IR (neat) ν_{max}: 3360 cm^{-1}. 1H NMR (400 MHz, $CDCl_3$): δ 0.76 (3 H, s), 0.82 (3 H, s), 0.91 (3 H, d, *J* 0.9 Hz) and 0.96 (3 H, s) [4 x *tert*-CH_3], 0.7-1.7 (10 H, m),1.88 (1 H, ddd, *J* 13.4, 9.0 and 4.4 Hz), 2.39 (1 H, ddd, *J* 14.0, 10.3 and 4.1 Hz), 3.945 (1 H, ddd, *J* 10.3, 4.0, 2.0 Hz, *CH*OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 75.6 (CHOH), 53.3, 52.1, 49.0, 41.7, 36.3, 33.9, 28.5 (2C), 27.5, 25.5, 23.7, 19.2, 17.5; 13.7. HRMS: Found, 222.1999; $C_{15}H_{26}O$ requires 222.1985.

(*Received in UK* 10 *December* 1996; *revised* 28 *January* 1997; *accepted* 31 *January* 1997)