First Total Synthesis of (±)-Myltayl-4(12)-ene and Single-crystal X-ray Structure of *exo*-12-Normyltaylan-4-yl 4-Nitrobenzoate

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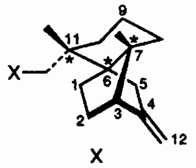
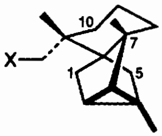
The total synthesis of the unusual sesquiterpene (±)-myltayl-4(12)-ene **3** starting from the readily available cyclogeraniol **5** and the single-crystal X-ray structure of the 4-nitrobenzoate **12** of the noralcohol **11** are described.

Recently, Matsuo and coworkers have reported the isolation of novel, irregular sesquiterpene alcohols, myltaylenol **1**[1] and cyclomyltaylenol **2**[2] from the liverwort *Mylia taylorii* (Hook, S. Gray) and identified the new carbon frameworks present in them as myltaylane and cyclomyltaylanes. Later Wu and Chang isolated[3] cyclomyltaylene **4** from the Taiwanese liverwort *Bazzania tridens*. A characteristic of the structure of myltaylane is the presence of a unique 2,4,4,7a-tetramethylperhydro-1,3a-ethanoindene carbon framework (cyclohexane fused to C-1, C-7 bond of norbornane) incorporating three contiguous quaternary carbon atoms (*), making it a challenging synthetic target. In continuation of our interest in the synthesis of sesquiterpenes containing multiple contiguous quaternary carbons,[4] herein we describe the first total synthesis of myltayl-4(12)-ene **3** employing biogenetically patterned cation mediated cyclisation and rearrangements as key operations.

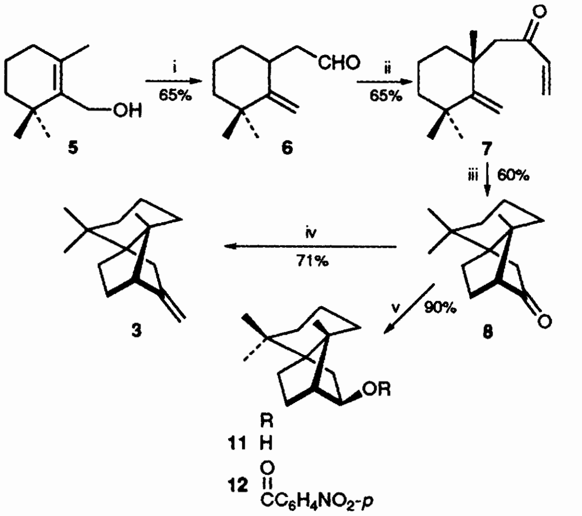


X
1 OH
3 H

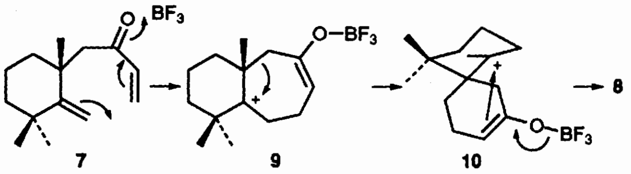


X
2 OH
4 H

The synthetic sequence starting from cyclogeraniol is depicted in Scheme 1. The starting material cyclogeraniol **5** was obtained[4b] by selective ozonation of the commercially available β-ionone followed by direct reduction of ozonide with sodium borohydride. One-pot Claisen rearrangement of cyclogeraniol **5** using ethyl vinyl ether and mercuric acetate at 170 °C for 36 hours (sealed tube) furnished the enal **6**[5] in 65% yield. Addition of vinylmagnesium bromide to the aldehyde followed by oxidation of the resultant allyl alcohol with buffered (NaOAc) pyridinium chlorochromate (PCC) in methylene chloride transformed the enal **6** into the key intermediate of the sequence, dienone **7**, in 65% overall yield. Treatment of the dienone **7** with a catalytic amount of boron trifluoride etherate in methylene chloride furnished the normyltayl-4-one **8** (2,4-DNP derivative mp 166–168 °C), in



Scheme 1 *Reagents and conditions*: i, $CH_2{=}CH{-}OEt$, $Hg(OAc)_2$, toluene, sealed tube, 170 °C, 36 h; ii, $CH_2{=}CH{-}MgBr$, THF, room temp., 1 h, then PCC, NaOAc, CH_2Cl_2, room temp., 0.5 h; iii, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C, 20 min; iv, $Ph_3P^+Me\ {}^-Br$, $K^+\ {}^-O{-}Amy^t$, $Amy^t{-}OH$, C_6H_6, room temp., 10 h; v, $NaBH_4$, MeOH, room temp., 45 min, then $4{-}NO_2C_6H_4COCl$, Py, CH_2Cl_2, DMAP, room temp., 5 h



Scheme 2

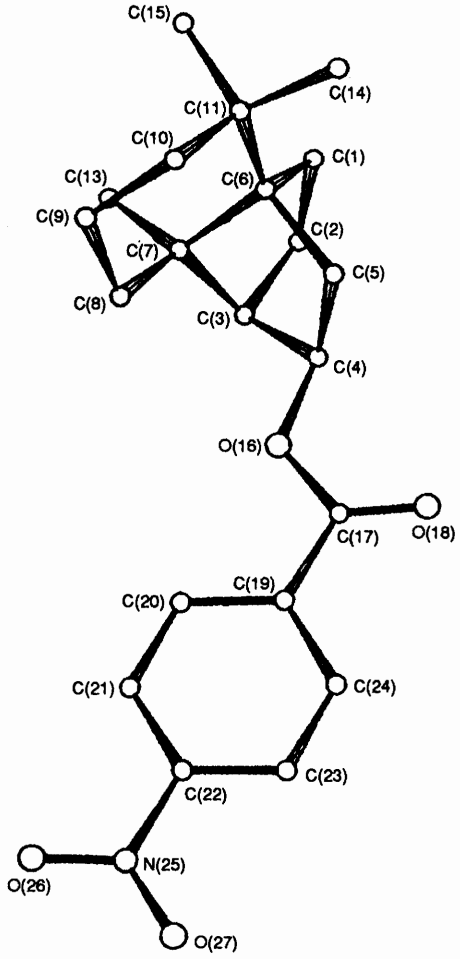


Fig. 1 X-Ray crystal structure of the *p*-nitrobenzoate **12**

60% yield, whose structure was derived from the spectral data† in comparison with that of myltaylenol,[1] and mechanistic rationale. Finally Wittig methylenation (methyltriphenylphosphonium bromide and potassium *tert*-amylate (KOAmy) in benzene–*tert*-amyl alcohol) of norketone **8** furnished the myltayl-4(12)-ene **3**† in 71% yield. The formation of the norketone **8** from the dienone **7** can be rationalised as depicted in Scheme 2, which also explains the stereochemical outcome at carbon C-7. First acid catalysed cyclisation of the dienone **7** generates the bicyclic tertiary carbonium ion **9**, which rearranges to the spiro system **10**. Reketonisation *via* cyclisation from the α-face of the carbonium ion centre furnishes the norketone **8** with β-methyl at C-7.

Since alternative pathways exist for the carbonium ions **9** and **10** for further rearrangements and cyclisation leading to different tricyclic systems, a single-crystal X-ray structure determination was undertaken to unambiguously establish the structure of the norketone **8**. Thus stereospecific reduction of the norketone **8** with sodium borohydride furnished the *exo* alcohol **11**, mp 123–25 °C, which was converted into the corresponding 4-nitrophenyl ester **12**, mp 156–57 °C. Repeated crystallisation of the *p*-nitrobenzoate **12** from methylene chloride–hexane (1:10) afforded suitable crystals.‡

In conclusion we have achieved the first total synthesis of (±)-myltayl-4(12)-ene **3** starting from the readily available cyclogeraniol **5**. The X-ray crystal structure of the *p*-nitrobenzoate **12** confirms the structure of the norketone **8** and hence the myltayl-4(12)-ene **3**.

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Footnotes

† All the compounds exhibited spectral data consistent with their structures. Selected spectral data for **8**: ν_{max}/cm^{-1} (neat) 1745: δ_H (400 MHz, CDCl$_3$) 2.49 (1 H, dd, *J* 18.6, 3.3 Hz, H-5 *exo*), 1.77 (1 H, d, *J* 18.6 Hz. H-5 *endo*), 1.3–2.2 (11 H, m), 1.08 (3 H, s), 1.03 (3 H, s), 0.84 (3 H, s); δ_C (22.5 MHz, CDCl$_3$) 216.3 (s, C=O), 61.8 (d, C-3), 52.7 (s), 46.1 (2 C, s and t, ?), 35.8 (t), 33.5 (s), 30.2 (t), 28.6 (q), 26.7 (t), 23.0 (q), 22.3 (t), 18.7 (2 C, t and q). For **3**: ν_{max}/cm^{-1} (neat) 3070, 1660, 870; δ_H (90 MHz, CDCl$_3$) 4.71 (1 H, q, *J* 2 Hz) and 4.53 (1 H, q, *J* 2 Hz) (C=CH$_2$), 2.54 (1 H, d, *J* 16.5 Hz), 1.1–2.1 (12 H, m), 1.01 (3 H, s), 0.96 (3 H, s), 0.81 (3 H, s); δ_C (100 MHz, CDCl$_3$) 154.7 (*C*=CH$_2$), 101.3 (C=*C*H$_2$), 52.8, 46.9 and 33.6 (3 × quaternary C), 57.7, 40.4, 36.5, 30.2, 28.7, 27.9, 27.6, 23.2, 19.2, 19.1.

‡ *Crystal data*: $C_{21}H_{27}NO_4$; *M* = 357.449, triclinic, space group $P\bar{1}$, $a = 7.058(5)$, $b = 7.655(4)$, $c = 18.435(9)$ Å, $\alpha = 90.15(4)$, $\beta = 95.39(5)$, $\gamma = 107.62(5)°$. $V = 945(1)$ Å^3, $Z = 2$, $D_c = 1.2567$ g cm^{-3}, $F(000) = 384$, $T = 291$ K, Mo-Kα ($\lambda = 0.7107$ Å). Intensity data were collected on an Enraf-Nonius CAD-4 diffractometer using a transparent colourless crystal of dimensions 0.4 × 0.35 × 0.3 mm in the ω–2θ mode. A total of 3620 measured, 3177 unique and 2417 observed reflections with $|F_o| > 5.0\sigma(F_o)$ were collected. The structure was solved by direct methods[6] and full-matrix least-squares refinement[7] with the non-hydrogen atoms anisotropic and hydrogen atoms isotropic, and converged at $R = 0.071$. The structure of the *p*-nitrobenzoate **12** thus determined is shown in Fig. 1. Atomic coordinates, bond lengths and angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

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