Syntheses of Both Diastereoisomers of 2,8-Dioxabicyclo[3.2.1]octane Derivatives: Degradation Products of Daphniphyllum Alkaloids

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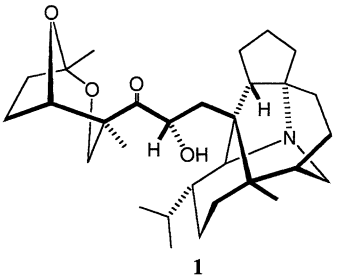
Both diastereoisomers of 1,4-dimethyl-2,8-dioxabicyclo[3.2.1]octane-4-caboxylic acid ester (**3, 4**) and the 4-hydroxy methyl analogues (**5, 6**) were synthesised from ethyl acetoacetate and diethyl malonate respectively. The key step of these process involved intramolecular cyclisation using palladium chloride as catalyst.

Certain Daphniphyllum alkaloids contain a 2,8-dioxabicyclo[3.2.1] octane structure moiety.[1-11] Oxidation of daphniphylline (**1**) gave the acetal acid (**2**).[2-7] The structure of **2** was determined by spectroscopic studies[2,3] and also by an X-ray single crystal structure analysis of the parent alkaloid.[2]



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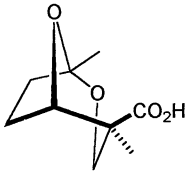

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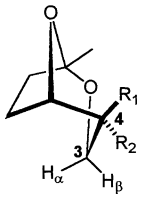
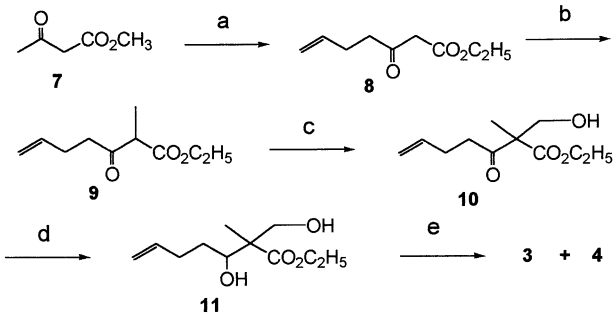


3 $R_1 = CO_2C_2H_5$; $R_2 = CH_3$; **4** $R_1 = CH_3$; $R_2 = CO_2C_2H_5$
5 $R_1 = CH_2OH$; $R_2 = CH_3$; **6** $R_1 = CH_3$; $R_2 = CH_2OH$

In continuation of our studies on the application of palladium catalysed cyclisation of alkenyldiols for the synthesis of natural products[12-16] we now report the synthesis of the ethyl ester of **2** and it's diastereoisomer (**4**) and the hydroxy analogues (**5, 6**) which is outlined in Scheme 1 and 2. The relative stereochemistry of **3** and **4** was determined by NMR studies.

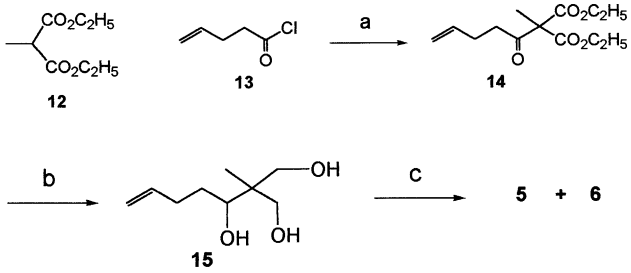
Akylation of the di-anion of acetoacetic ester (**7**) with allyl bromide gave the keto ester (**8**) which was subsequently methylated to afford keto ester (**9**) in 80% yield. Treatment of **9** with sodium hydrogencarbonate in formaldehyde solution gave **10** in 66% yield. Sodium borohydride reduction of **10** resulted in the diol (**11**) in 81% yield which was cyclised directly to give an isomeric mixture of the more stable chair conformer **3** and **4** in a 3:4 ratio (64% yield) using palladium chloride as catalyst in dry dimethoxyethane with copper(II) chloride as reoxidant for palladium. The ratio of isomeric products was determined by GC/MS and the mixture was separated by preparative GLC (Carbowax 20 M column). The products (**3**) and (**4**) were characterised by their NMR spectra.[17,18] Marked differences in the spectra can be interpreted in terms of the different stereochemistry at C-4. The C4-Me group of **3** resonated at δ 0.95 and gave n.O.e. enhancement to $H_{3\alpha}$ and $H_{3\beta}$ whereas C4-Me of **4** resonated at δ 1.45 and gave a selective n.O.e. to $H_{3\beta}$.



Scheme 1. Reagents and conditions: a) NaH, THF, 0 °C, n-BuLi, allyl bromide; b) C_2H_5ONa then CH_3I; c) $NaHCO_3$, CH_2O solution, RT; d) $NaBH_4$, CH_3OH, RT; e) $PdCl_2$, $CuCl_2$, O_2, DME, 65 °C.

The NMR spectrum of **3** is in agreement with that of the acetal acid (**2**) which was obtained from natural sources or by synthesis.[3,22]

Acetal alcohols (**5, 6**), reduction products of acetal acids (**3, 4**) were also synthesised by this method.



Scheme 2. Reagents and conditions : a) NaH, ether, RT, 15 min; b) $LiAlH_4$, ether, RT, 16 h. c) $PdCl_2$, $CuCl_2$, O_2, DME, 65 °C.

The trihydroxy olefin (**15**) was prepared in 60% yield from the reaction of acid chloride (**13**) and methylated diethyl methylmalonate (**12**), followed by reduction. This triol (**15**) was cyclised regioselectively to the isomeric products (**5**) and (**6**) in 58%. The glc analysis (SE 30 column, 100 °C) showed that it consisted of two isomers (**5**) and (**6**) in the ratio of 5:1. The isomeric products were separated by preparative HPLC and were characterised by their NMR spectra.[19,20] No evidence of the ring formation from both primary alcohols was obtained.

The NMR spectrum of **5** is in agreement with that of the acetal alcohol which was obtained from natural sources or by synthesis.[21,22]

References and Notes

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17 Compound (**3**) ^{1}H-NMR (400 MHz) ($CDCl_3$) δ 0.95 (s, 3H), 1.29 (t, J = 7.2 Hz, 3H), 1.45 (s, 3H), 1.84-1.96 and 2.01-2.16 (m, 4H), 3.47 (d, J = 12 Hz, 1H), 4.25 (q, J = 7.2 Hz, 2H), 4.30 (dd, J = 12 Hz, 2 Hz, 1H), 4.72 (m, 1H). MS. m/e : 214 ($M^{+\cdot}$, 0.12), 196 (0.04), 184 (0.05), 169 (0.29), 155 (0.05), 115 (18.50), 69 (25), 43 (100). Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.97; H, 8.61%. Found: C, 61.67; H, 8.47%.

18 Compound (**4**) ^{1}H-NMR, (400 MHz) ($CDCl_3$) δ 1.25 (t, 7.2 Hz, 3H), 1.48 (s, 3H), 1.51 (s, 3H), 1.71-1.83 and 2.02-2.16 (m, 4H), 3.62 (dd, J = 12 Hz, 1.8 Hz, 1H), 4.04 (d, J = 12 Hz, 1H), 4.14 (q, J = 7.2 Hz, 1H), 4.39 (m, 1H). 214 ($M^{+\cdot}$, 0.01), 196 (0.006), 184 (0.008), 169 (0.04), 155 (0.008), 141 (0.02), 115 (19.00), 69 (30.70), 43 (100). Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.97; H, 8.61%. Found: C, 61.86; H, 8.58%.

19 Compound (**5**) ^{1}H-nmr (400 MHz) ($CDCl_3$) δ 0.74 (s, 3H, CH_3), 1.47 (s, 3H, O-C-CH_3), 1.83 and 2.01(m, 4H, CH_2CH_2), 2.67(s,1H, OH),3.51 (d, J = 11.6 Hz, 1H, OC$\underline{H}H_{ax}$), 3.59 (dd, J = 11.6 Hz, 1.7 Hz, 1H, OC$\underline{H}H_{eq}$), 3.77 and 3.87 (d, J = 11.7 Hz, 1H each), 4.21 (m, 1H, CH). ^{13}C NMR.($CDCl_3$) δ 104.93, 80.45, 66.66, 65.51, 37.53, 33.20, 24.97, 23.83, 17.19. MS. m/e : 172 ($M^{+\cdot}$, 1.62), 154 (3.21), 124 (13.37), 101 (98), 85 (13.37), 83 (56.68), 57 (34.76), 43 (100). Anal. Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36%. Found: C, 62.68; H, 9.17%.

20 Compound (**6**) ^{1}H-nmr (400 MHz) ($CDCl_3$) δ 1.34 (s, 3H, CH_3), 1.50 (s, 3H, O-C-$C\underline{H}_3$), 1.80 and 2.02(m, 4H, CH_2CH_2), 3.33 and 3.39 (d, J = 11.7 Hz, 1H each), 3.42 (dd, J = 11.6 Hz, 1.7 Hz, 1H, OC$\underline{H}H_{eq}$), 3.61 (d, J =11.7 Hz, 1H, OC$\underline{H}H_{ax}$), 4.11 (m, 1H, CH). ^{13}C NMR.($CDCl_3$) δ 105.15, 81.18, 67.39, 66.64, 37.80, 33.36, 25.13, 23.92, 19.47. MS. m/e 172 ($M^{+\cdot}$ 1.45), 154 (3.01), 124 (15.00), 101 (97), 85 (12.89), 83 (54.98), 57 (33.35), 43 (100). Anal. Calcd for $C_9H_{16}O_3$: C, 62.77 ; H, 9.36%. Found: C, 62.71, H, 9.27%.

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