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A stereocontrolled total synthesis of methyl (±)-*O*-methylpodocarpate

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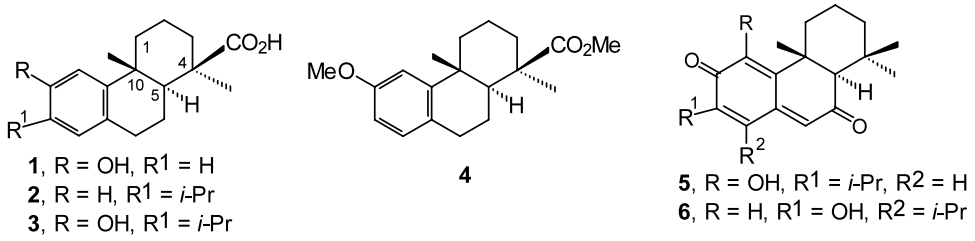
Abstract—A stereocontrolled total synthesis of methyl (±)-*O*-methyl podocarpate (**4**) has been successfully accomplished using the *trans*-fused diester **21** as a key intermediate. Intramolecular Michael reaction of the enone-diester **18** afforded the *cis*-fused keto-diester **19** in high yield which was stereoselectively converted into **21** via the enone **20**.

Naturally occurring ring C aromatic diterpene acids podocarpic acid (**1**),[1] callitrisic acid (**2**)[2] and lambertic acid (**3**)[3] incorporate an octahydrophenanthrene ring system as the basic carbocyclic framework and were isolated from *Podocarpus cupressium*, *Callitris columelaris* and *Podocarpus lambertius*, respectively. The diterpene acids **1**–**3** (Fig. 1) have common structural features in rings A and B; they have *trans*-stereochemistry at the A/B ring junction, an axially oriented carboxyl group at C-4, an axial methyl group at the angular position C-10, and an equatorial methyl group at C-4. Podocarpic acid (**1**) has been converted via methyl *O*-methylpodocarpate (**4**) into the bioactive diterpene quinones taxodione (**5**)[4] and maytenoquinone (**6**)[5] (Fig. 1) which possess tumour-inhibiting activity. Also, podocarpic acid derivatives have been reported[6] to possess hormonal and anti-inflammatory properties and a wide variety of biological activities such as inhibition of plant cell growth and antileukemic activity. Widespread interest in podocarpic acid is reflected in a number of diverse synthetic approaches reported in the literature[7] over the last few decades. The total synthesis of the diterpene acids **1**–**3** is associated with the difficulty in the generation of three contiguous asymmetric centres and an appropriately substituted aromatic ring in an octahydrophenanthrene nucleus. Starting from commercially available 7-methoxy-1-tetralone (**7**), we have successfully accomplished a stereocontrolled total synthesis of methyl (±)-*O*-methylpodocarpate (**4**) as shown in Scheme 1. Since **4** has been converted into **1**,[7] **2**[8] and **3**,[7] the present work constitutes the formal total synthesis of (±)-podocarpic acid, (±)-callitrisic acid and (±)-lambertic acid. The salient features of our synthesis are (i) facile conversion of the tetralone **7** into the enone-diester **18** (Scheme 1), (ii) intramolecular Michael reaction of **18** in the presence of base to afford the *cis*-fused keto-diester **19** as the sole product in high yield, (iii) stereoselective conversion of **19** into the *trans*-fused



1, R = OH, R1 = H
2, R = H, R1 = *i*-Pr
3, R = OH, R1 = *i*-Pr

4

5, R = OH, R1 = *i*-Pr, R2 = H
6, R = H, R1 = OH, R2 = *i*-Pr

Figure 1.

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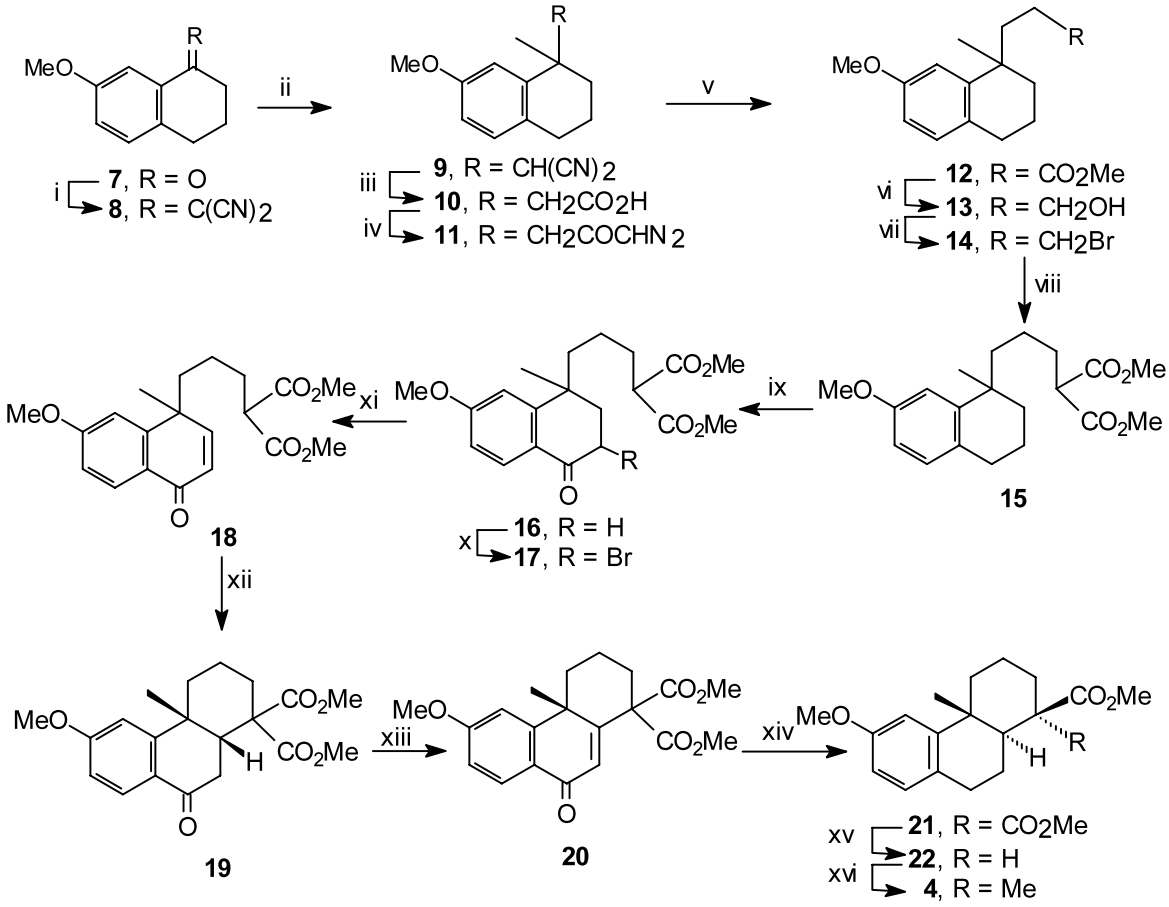

Scheme 1. *Reagents and conditions*: (i) $CH_2(CN)_2$, NH_4OAc, AcOH, C_6H_6, reflux; (ii) $LiMe_2Cu$, Et_2O, THF, 0–20°C; (iii) KOH, $HOCH_2CH_2OH$, H_2O, reflux, then H_3O^+; heat (190°C); (iv) $(COCl)_2$, C_6H_6, 60°C then CH_2N_2, Et_2O, 0–20°C; (v) $C_6H_5CO_2Ag$, MeOH, Et_3N, rt; (vi) $LiAlH_4$, Et_2O, reflux; (vii) PBr_3, C_6H_6, 0–70°C; (viii) $NaCH(CO_2Me)_2$, C_6H_6, DMF, reflux; (ix) CrO_3, AcOH, H_2O, 0°C to rt; (x) Br_2, Et_2O, 10°C to rt; (xi) LiBr, Li_2CO_3, DMF, 115°C; (xii) *t*-BuOK, *t*-BuOH, 25°C; (xiii) PhSeCl, CH_3CO_2Me, HCl (trace), rt then H_2O_2, CH_3CO_2Me, THF, AcOH, 5°C to rt; (xiv) H_2, 10% Pd–C, CH_3CO_2Me, rt; (xv) DMSO, NaCl, H_2O, 180°C; (xvi) LDA, HMPA, THF, 0°C; MeI, 0°C.

diester **21** via the enone-diester **20**, and (iv) stereocontrolled transformation of **21** into methyl (±)-*O*-methylpodocarpate (**4**).

Our synthesis of **4** from **7** is outlined in Scheme 1. The tetralone **7** was condensed with malononitrile to provide the unsaturated dinitrile **8**[9] in near quantitative yield. Conjugate addition of $LiMe_2Cu$ to **8** afforded **9** (89%) which on hydrolysis and decarboxylation furnished the acid **10** in 84% yield. The corresponding diazomethyl ketone **11** was treated[10] with silver benzoate in MeOH in the presence of Et_3N to give the methyl ester **12** (85%). Reduction of **12** with $LiAlH_4$ afforded the primary alcohol **13** (95%) which was treated with PBr_3 to furnish the bromoether **14** (74%). Condensation of **14** with dimethyl sodiomalonate afforded the diester **15** in 85% yield.

Oxidation of **15** with CrO_3 gave the keto-diester **16** (76%). Bromination of **16** in ether[11] followed by dehydrobromination of the resulting bromoketone **17** with LiBr and Li_2CO_3 in DMF at 115°C furnished the enone-diester **18**[12] in 76% overall yield. An intramolecular Michael reaction of **18** was effected by treatment with *t*-BuOK (0.5 equiv.) in *t*-BuOH at 25°C for 10 h to give the tricyclic keto-diester **19**[12] in 84% yield. The *cis*-stereochemistry of the A/B ring junction of **19** was conclusively established by single-crystal X-ray crystallography. In the ^1H NMR spectrum of **19**, the signals due to the ester methyl groups at C-4 appeared at δ 3.14 and 3.68 ppm for the axial and equatorial -CO_2Me groups respectively. Shielding of the axial substituent at C-4 by the aromatic C ring is a characteristic feature[13,14] for the *cis*-fused octahydrophenanthrenes.

The keto-diester **19** is suitably functionalised for conversion to **4** requiring introduction of the Δ^5 double bond in ring B followed by catalytic hydrogenation, decarbomethoxylation, and alkylation at C-4 with CH_3I. In order to generate the required Δ^5 double bond in ring B, the ketone **19** was treated[15] with PhSeCl followed by H_2O_2[16] to give the enone-diester **20**[12] in 64% yield. Catalytic hydrogenation of **20** proceeded stereoselectively with uptake of three moles of hydrogen to furnish the *trans*-diester **21**[12] in 95% yield. Catalytic hydrogenation of similar hexahydrophenanthrenones by Matsumoto and co-workers had

generated[17,18] exclusively *trans*-stereochemistry at the A/B ring junction. The stereostructure **21** of the diester was confirmed by X-ray crystallographic analysis.[19] Decarbomethoxylation of the diester **21** followed by alkylation of the resulting monoester **22** with MeI in the presence of LDA (1.6 equiv.) and HMPA (2 equiv.) at 0°C furnished methyl (±)-*O*-methylpodocarpate (**4**)[12] in 68% yield. Stereoselective methylation of similar ester enolate anions to generate equatorially methylated esters in cyclohexane rings has been reported recently by Theodorakis and co-workers.[20] The identity of synthetic **4** was secured through single-crystal X-ray crystallography.[19] The spectral data of **4** also agreed very well with those reported in the literature.

In conclusion, methyl (±)-*O*-methylpodocarpate has been successfully synthesised involving a few stereoselective steps. The present synthesis constitutes the formal total synthesis of the diterpene acids (±)-podocarpic acid, (±)-callitrisic acid and (±)-lambertic acid.

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