Stereoselective Synthesis of the B/C/D Ring Systems of Aphidicolane and Stemodane Diterpenes

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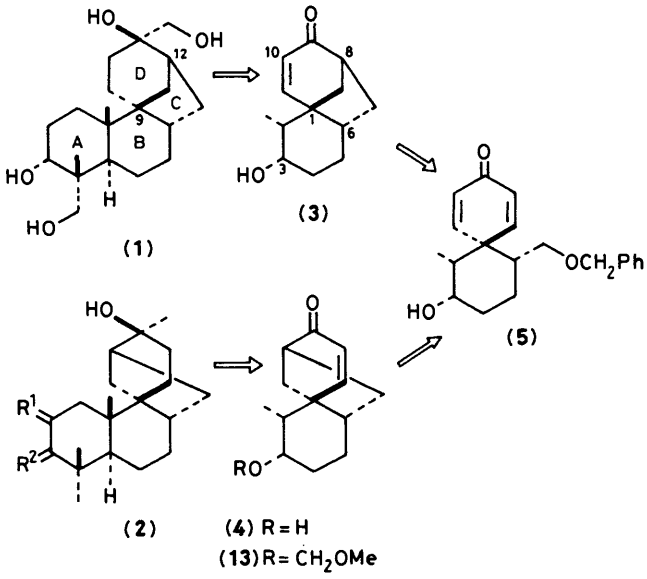
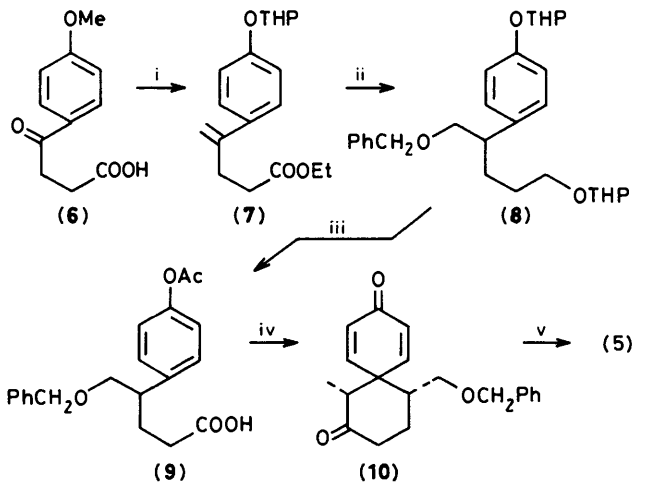
Diastereoisomeric tricyclo[6.3.1.$0^{1,6}$]dodecane derivatives (**3**) and (**4**), which correspond to the B/C/D ring systems of aphidicolane and stemodane diterpenes, were selectively prepared from the common spirodienone (**5**) by means of facile regioselective C–C bond formation mediated by the neighbouring hydroxy group participation.

Aphidicolane (**1**)[1] and stemodane (**2**)[2] diterpenes, epimeric at C-9 and C-12, attract much attention biologically and structurally, and have been the targets of many syntheses.[3] In connection with our continuing synthetic studies on naturally occurring spirocyclic compounds, we have designed a new and stereoselective route to these diterpenes. Our strategy consists of an initial preparation of the suitably substituted spirodienone moiety (B/D rings), subsequent stereoselective construction of the ring C, and a final annelation (A ring). We now report the highly stereoselective synthesis of the tricyclic intermediates (**3**) and (**4**), which would serve as potential key compounds for aphidicolane and stemodane diterpene synthesis.

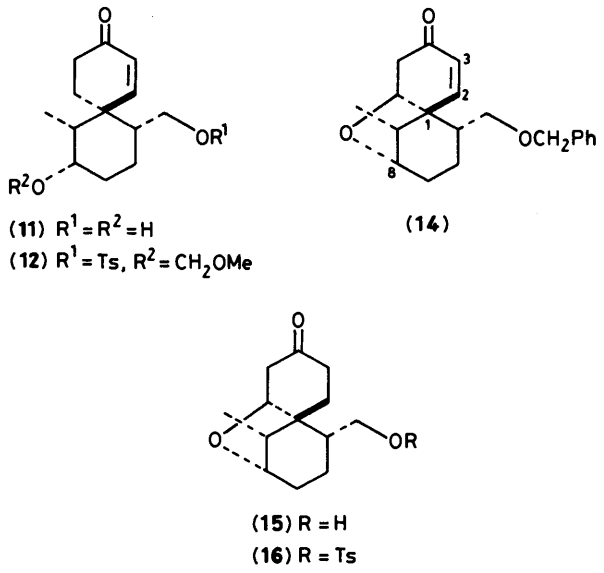
The spirodienone-alcohol (**5**) was synthesized as follows:





Scheme 1. *Reagents:* i HI–AcOH, HCl–EtOH, dihydropyran(DHP)–H^+, $Ph_3P{=}CH_2$; ii $LiAlH_4$, DHP–H^+, B_2H_6 then H_2O_2–NaOH, $PhCH_2Br$–NaH–Bu^t_4NI–hexamethylphosphoramide; iii TsOH–MeOH, Ac_2O–NaOH, PCC, Jones oxidation; iv $(COCl)_2$, $MeCHN_2$, aqueous Na_2CO_3–$NaHCO_3$, $CuCl_2$–$CHCl_3$; v $NaBH_4$, MeOH.

4-(4-Methoxyphenyl)-4-oxobutanoic acid (**6**)[4] gave the olefinic ester (**7**) (82%) by demethylation, esterification, tetrahydropyranylation, and Wittig reaction,[5] which was converted into the benzylbistetrahydropyranyl ether (**8**) (73%) by lithium aluminium hydride reduction, tetrahydropyranylation, hydroboration–oxidation, and benzylation.[6] Compound (**8**) afforded the acetoxycarboxylic acid (**9**) (87%) by de-tetrahydropyranylation, acetylation, and pyridinium chloro-chromate (PCC) oxidation followed by Jones oxidation, which was converted into the diazoketone (using diazoethane) *via* the acid chloride. After the diazoketone had been hydrolysed with buffered alkali, the resulting phenolic α-diazoketone was refluxed in chloroform containing copper(II) chloride[7] to give the spirodienone (**10**) [38% from (**9**)], $\nu_{max.}(CHCl_3)$ 1710, 1660, and 1620 cm^{-1}; δ ($CDCl_3$) 0.75 (3 H, d, *J* 8 Hz, C-7-Me), 2.36 (1 H, m, C-11-H), 2.68 (1 H, q, *J* 8 Hz, C-7-H), 3.06 (1 H, dd, *J* 10, 8 Hz, $-CH_2OCH_2Ph$), 3.34 (1 H, dd, *J* 10, 4 Hz, $-CH_2OCH_2Ph$), 4.32 (2 H, s, OCH_2Ph), and 6.30—6.57 (4 H, AA'BB', olefinic H); $\lambda_{max.}$ 240 nm (ε 13 200); M^+ *m/z* 310. Compound (**10**) was selectively reduced with sodium borohydride in methanol at −30 °C to give the hydroxyspirodienone (**5**) (76%), m.p. 98—99 °C, $\nu_{max.}(CHCl_3)$ 3600, 3430, 1660, and 1618 cm^{-1}; δ($CDCl_3$) 0.74 (3 H, d, *J* 7 Hz, C-7-Me), 2.90—3.30 (2 H, m, C-11-CH_2O), 3.93 (1 H, m, $w_{1/2}$ 8 Hz, C-8-H), 4.27 (2 H, s, OCH_2Ph), 6.28 (2 H, br. d, *J* 11 Hz, C-2- and C-4-H), 6.55, 7.41 (2 H, dd, *J* 11, 3 Hz, C-1- and C-5-H), and 7.15 (5 H, s, aromatic H); $\lambda_{max.}$ 248 nm (ε 9300); M^+ *m/z* 312.†



Treatment of (**5**) with lithium (5 equiv.) in liquid ammonia[7] at −78 °C stereoselectively afforded the dihydroxyenone (**11**) (70%), $\nu_{max.}(CHCl_3)$ 3600, 3430, and 1670 cm^{-1}; δ($CDCl_3$) 1.01 (3 H, d, *J* 7 Hz, C-7-Me), 3.38—3.82 (2 H, m, C-11-CH_2O), 3.92 (1 H, m, $w_{1/2}$ 8 Hz, C-8-H), and 6.00—6.30 (2 H, d, *J* 11 Hz, C-1- and C-2-H); $\lambda_{max.}$ 236 nm (ε 13 000); M^+ *m/z* 224. Tosylation (73%) of the primary hydroxy group of (**11**) with toluene-*p*-sulphonyl chloride (TsCl) in the presence of 4-dimethylaminopyridine (DMAP) and triethylamine in chloroform, followed by the methoxymethylation (81%) of the secondary hydroxy group with methoxymethyl chloride (MOMCl) and Hünig base,[8] gave the enone (**12**), M^+ *m/z* 422. Compound (**12**) afforded the tricyclic compound (**13**) (96%) on treatment with potassium t-butoxide in tetrahydrofuran (THF), and finally compound (**13**) was deprotected with acid (10% HCl in acetone) to give the tricyclo[6.3.1.$0^{1,6}$]dodecane derivative (**4**), (91%), m.p. 102.5—103.5 °C, $\nu_{max.}(CHCl_3)$ 3600, 3440, and 1670 cm^{-1}; δ ($CDCl_3$) 1.05 (3 H, d, *J* 8 Hz, C-2-Me), 2.27 (1 H, ddd, *J* 12, 5, 2 Hz, C-12-H), 2.78 (1 H, m, C-8-H), 3.90 (1 H, m, $w_{1/2}$ 6 Hz, C-3-H), 5.72 (1 H, dd, *J* 9, 2 Hz, C-10-H), and 6.72 (1 H, dd, *J* 9, 2 Hz, C-11-H); $\lambda_{max.}$ 234 nm (ε 8800); M^+ *m/z* 206.

Alternatively, treatment of the dienone-alcohol (**5**) with sodium amide in liquid ammonia[7] at −78 °C afforded the tricyclic ether (**14**) (84%), $\nu_{max.}(CCl_4)$ 1690 cm^{-1}; δ(CCl_4) 1.04 (3 H, d, *J* 7 Hz, C-12-Me), 2.35 (1 H, dd, *J* 16, 10 Hz, C-5-H), 2.76 (1 H, dd, *J* 16, 8 Hz, C-5-H), 3.16 (2 H, d-like, *J* 6 Hz, $-CH_2OCH_2Ph$), 4.02 (1 H, d-like, *J* 4 Hz, C-8-H), 4.25 (2 H, s, OCH_2Ph), 4.38 (1 H, dd, *J* 10, 8 Hz, C-6-H), 5.87 (1 H, d, *J* 10 Hz, C-3-H), 6.51 (1 H, d, *J* 10 Hz, C-2-H), and 7.12 (5 H, s, aromatic H); $\lambda_{max.}$ 234 nm (ε 8400); M^+ *m/z* 312.

† Compound (**5**) was obtained with its epimer regarding the configuration of the C-8-hydroxy group in the ratio of 15 : 1. The half width ($w_{1/2}$) of the C-8-H signal in the epimer is 20 Hz. Accordingly, the major product is the desired axial alcohol.

Compound (**14**) was hydrogenated in the presence of 10% palladium on carbon in ethanol–ethyl acetate (1 : 1) to give the tricyclic keto-alcohol (**15**) (92%), which was tosylated with TsCl, DMAP, and Et_3N to give compound (**16**) (85%). Treatment of (**16**) with Bu^tOK in THF at −10 °C gave the tricyclic enone (**3**) (59%), m.p. 99.5—101.0 °C, $\nu_{max.}(CHCl_3)$ 3610, 3450, and 1675 cm^{-1}; $\delta(CDCl_3)$ 1.13 (3 H, d, *J* 7 Hz, C-2-Me), 2.80 (1 H, m, C-8-H), 4.02 (1 H, m, $w_{1/2}$ 6 Hz, C-3-H), 5.85 (1 H, dd, *J* 10, 2 Hz, C-10-H), and 7.81 (1 H, dd, *J* 10, 2 Hz, C-11-H); $\lambda_{max.}$ 233 nm (ε 8700); M^+ *m/z* 206.

We have now engaged in the synthesis of aphidicolane and stemodane diterpenes *via* the tricyclic compounds (**3**) and (**4**), respectively.

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