

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

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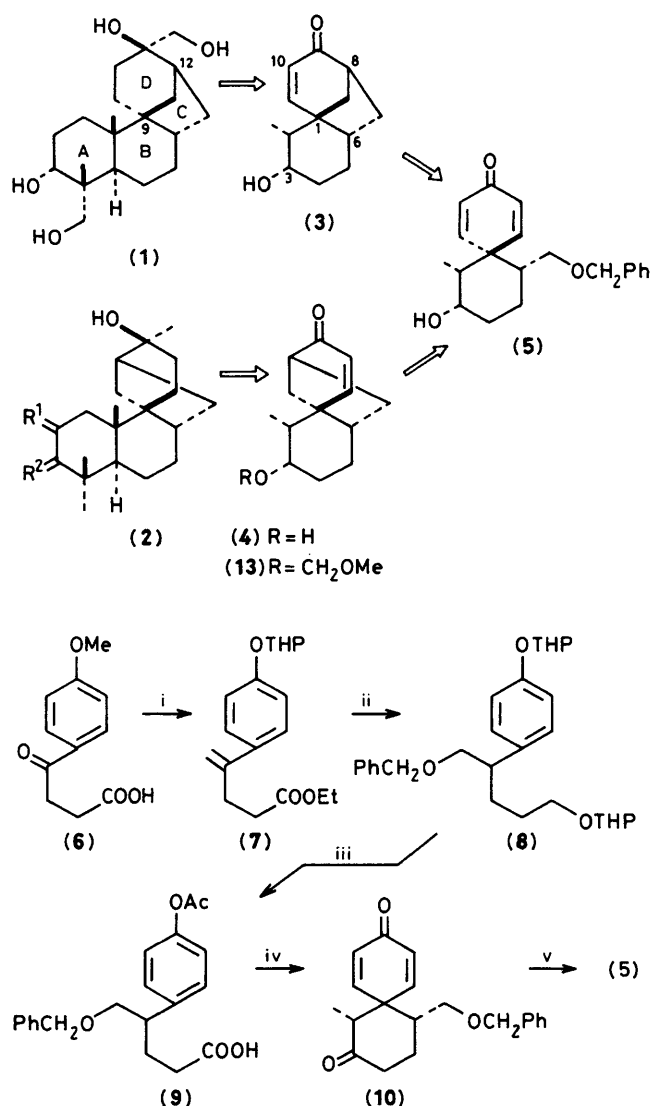
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Diastereoisomeric tricyclo[6.3.1.0^{1,6}]dodecane derivatives (**3**) and (**4**), which correspond to the B/C/D ring systems of aphidicolane and stemodane diterpenes, were selectively prepared from the common spirodienone (**5**) by means of facile 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 spirodi-

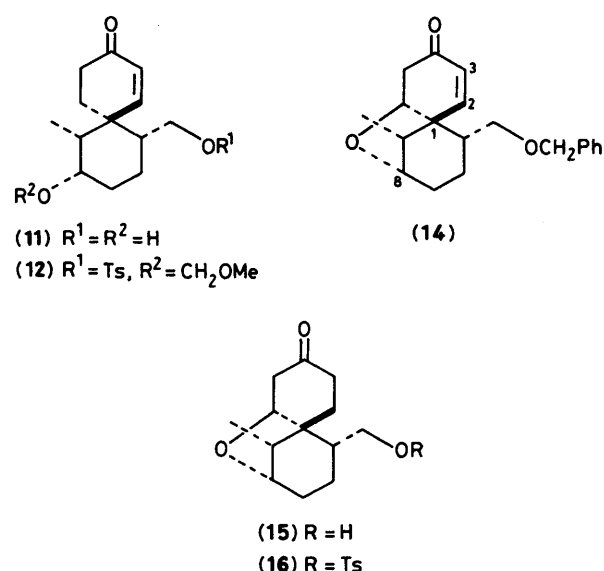
enone moiety (B/D rings), subsequent stereoselective construction of the ring C, and a final annelation (A ring). We now report the highly stereoselective synthesis of the tricyclic intermediates (**3**) and (**4**), which would serve as potential key compounds for aphidicolane and stemodane diterpene synthesis.

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



Scheme 1. Reagents: i $\text{HI}-\text{AcOH}$, $\text{HCl}-\text{EtOH}$, dihydropyran(DHP)- H^+ , $\text{Ph}_3\text{P}=\text{CH}_2$; ii LiAlH_4 , DHP- H^+ , B_2H_6 then $\text{H}_2\text{O}_2-\text{NaOH}$, $\text{PhCH}_2\text{Br}-\text{NaH}-\text{Bu}_4\text{NI}$ -hexamethylphosphoramide; iii $\text{TsOH}-\text{MeOH}$, $\text{Ac}_2\text{O}-\text{NaOH}$, PCC, Jones oxidation; iv $(\text{COCl})_2$, MeCHN_2 , aqueous $\text{Na}_2\text{CO}_3-\text{NaHCO}_3$, $\text{CuCl}_2-\text{CHCl}_3$; 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 chlorochromate (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) chloride⁷ to give the spirodienone (10) [38% from (9)], $\nu_{\text{max.}}(\text{CHCl}_3)$ 1710, 1660, and 1620 cm^{-1} ; $\delta(\text{CDCl}_3)$ 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, $-\text{CH}_2\text{OCH}_2\text{Ph}$), 3.34 (1 H, dd, J 10, 4 Hz, $-\text{CH}_2\text{OCH}_2\text{Ph}$), 4.32 (2 H, s, OCH_2Ph), and 6.30–6.57 (4 H, AA'BB', olefinic H); $\lambda_{\text{max.}}$ 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. $98-99^\circ\text{C}$, $\nu_{\text{max.}}(\text{CHCl}_3)$ 3600, 3430, 1660, and 1618 cm^{-1} ; $\delta(\text{CDCl}_3)$ 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); $\lambda_{\text{max.}}$ 248 nm (ϵ 9300); $M^+ m/z$ 312.[†]

Treatment of (5) with lithium (5 equiv.) in liquid ammonia⁷ at -78°C stereoselectively afforded the dihydroxyenone (11) (70%), $\nu_{\text{max.}}(\text{CHCl}_3)$ 3600, 3430, and 1670 cm^{-1} ; $\delta(\text{CDCl}_3)$ 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); $\lambda_{\text{max.}}$ 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. $102.5-103.5^\circ\text{C}$, $\nu_{\text{max.}}(\text{CHCl}_3)$ 3600, 3440, and 1670 cm^{-1} ; $\delta(\text{CDCl}_3)$ 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); $\lambda_{\text{max.}}$ 234 nm (ϵ 8800); $M^+ m/z$ 206.

Alternatively, treatment of the dienone-alcohol (5) with sodium amide in liquid ammonia⁷ at -78°C afforded the tricyclic ether (14) (84%), $\nu_{\text{max.}}(\text{CCl}_4)$ 1690 cm^{-1} ; $\delta(\text{CCl}_4)$ 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, $-\text{CH}_2\text{OCH}_2\text{Ph}$), 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); $\lambda_{\text{max.}}$ 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 Et₃N 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, $\nu_{\max}$ (CHCl₃) 3610, 3450, and 1675 cm^{–1}; δ (CDCl₃) 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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