

Effect of stereochemistry of the B/C ring juncture on the acid-catalyzed reactions of 9 α ,11 α -epoxyfernane and 9 α ,11 α -epoxyisoarborinyl acetate with BF₃.Et₂O in benzene

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Dedicated to Professor (Mrs.) Asima Chatterjee on the occasion of her 85th birth anniversary
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Abstract

9 α ,11 α -Epoxyfernane possessing a *cis*-fused B/C rings derived from fern-9(11)-ene isolated from *Drynaria quercifolia* on treatment with BF₃.Et₂O in nonpolar solvent like benzene afforded fern-7(8),9(11)-diene as the sole product. On the other hand, 9 α ,11 α -epoxyisoarborinyl acetate having a *trans*-fused B/C rings gave earlier, besides only traces of the corresponding 7(8),9(11)-diene and 11 α -hydroxy-8(9)-ene, a unique rearranged product, in which ring B has expanded to a 7-membered ring containing a keto carbonyl function at C-9 with concomitant contraction of ring C to a 5-membered ring by migration of 8,9-bond to C-11. The observed differences in the products profile in the two reactions were rationalized in terms of the different stereochemistry of the B/C ring juncture of the two oxirane derivatives.

Keywords: Fern-9(11)-ene, triterpenoid, *Drynaria quercifolia*, 9 α ,11 α -epoxyfernane, BF₃.Et₂O, fern-7(8),9(11)-diene

Introduction

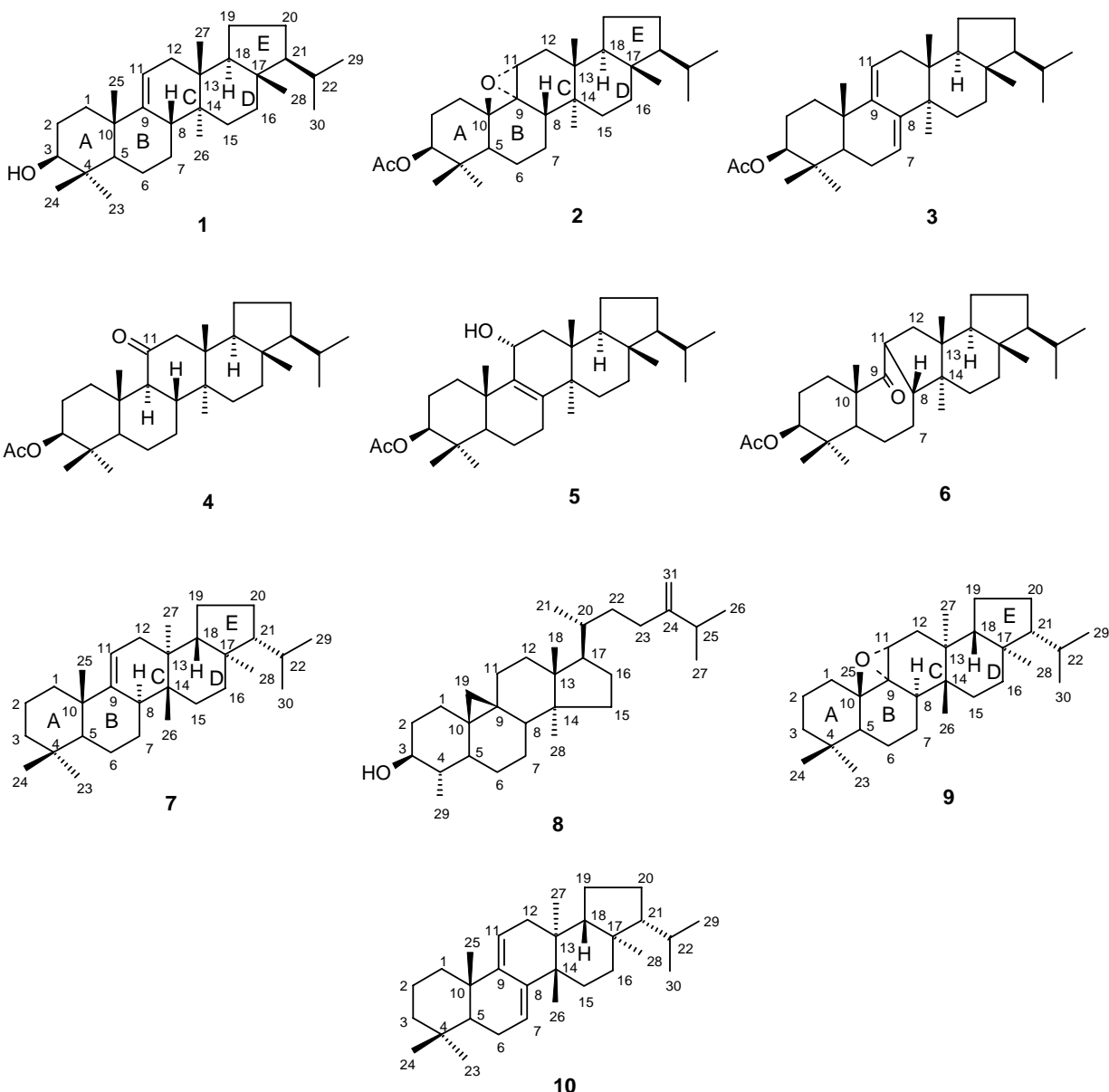
Acid-catalyzed reactions of triterpenoids of various skeletal types bearing an epoxide function at different sites of their molecules have uncovered a large volume of fascinating chemistry¹⁻⁹ involving, in some cases, interesting backbone rearrangements. The course of these reactions were found to be highly sensitive to (i) structures and stereochemistry of the epoxy derivatives, (ii) nature of the acidic reagents and (iii) the polarity of the solvent used. An interesting example was provided by the reactions of 9 α ,11 α -epoxyisoarborinyl acetate (**2**) having *trans*-fused B/C rings, derived from isoarborinol (**1**) under various reaction conditions^{1,9}. Thus, treatment of **2** with conc. HCl/HOAc afforded^{1,9} the heteroannular diene **3** and the 11-keto derivative **4** in the

ratio of 2:1. Similar results were observed when **2** was treated¹ with HClO₄/HOAc. On the other hand, reaction of the same epoxy derivative **2** earlier carried out⁹ by us with BF₃.Et₂O in nonpolar solvent like benzene gave only traces of the heteroannular diene **3** and the allylic alcohol **5**, but no 11-keto derivative **4**. The major product obtained in the above reaction was a unique rearranged product **6**. In the formation of **6**, the polarity of the solvent and the stereochemistry of the B/C ring juncture of **2** were assumed to play a vital role. We were, therefore, looking for a triterpenoid containing a 9 α ,11 α -epoxy function having *cis*-fused B/C rings to study the effect of stereochemistry on the course of the above reaction. This has now been possible by the isolation of fern-9(11)-ene (**7**) from the rhizomes of the fern *Drynaria quercifolia*, which was converted to 9 α ,11 α -epoxyfernane (**9**) having a *cis*-fused B/C rings. In the present paper we report the results of this reaction on **9** and the mechanistic rationale of the formation of the products obtained from both **2** and **9**.

Results and Discussion

Systematic chemical investigation of the fresh rhizomes of the fern *Drynaria quercifolia* afforded three triterpenoids. The physical constants and the spectral data of two of them were strikingly similar to those reported for fern-9(11)-ene^{10,11} (**7**) and cycloeucaneol¹² (**8**), respectively, indicating their respective identity. The third compound containing a terminal methylene group associated with the moiety $-\text{C}(\text{CH}_3)=\text{CH}_2$ [δ_{H} 4.78 (2H, br. signal), 1.63 (3H, s); δ_{C} 148.7 and 110] could not be separated from **7** due to their very close polarity and was assumed to be fern-22(29)-ene from a comparison of the ¹H and ¹³C NMR spectra of the mixture of this compound and **7** with those of pure **7**.

Compound **7** containing a trisubstituted double bond at 9,11-position [δ_{H} 5.29 (1H, m); δ_{C} 115.5 and 151.6] on treatment with *m*-chloroperbenzoic acid in CH₂Cl₂ at 0 °C in the molar ratio of 1:1.2 for 24 h gave the corresponding epoxy derivative, C₃₀H₅₀O (M⁺ 426). The ¹H NMR spectrum of the compound was devoid of the olefinic proton signal at δ_{H} 5.29 of **7**, and, instead, showed a one-proton signal at δ_{H} 3.05 (br. signal) for the epoxide methine proton at C-11. The chemical shift and the splitting pattern of the signal of this proton indicated an α -orientation of the oxirane moiety generated in the compound, which seemed to be more likely in view of the greater steric crowding of the β -face of the olefinic double bond of **7** than the α -side. The structure of the compound was finally confirmed as 9 α ,11 α -epoxyfernane (**9**) by its ¹³C NMR spectral data (Table 1). The appearance of the signals for a methine carbon at δ_{C} 55.9 (C-11) and a nonprotonated carbon at δ_{C} 66.8 (C-9) in the ¹³C NMR spectrum of **9** in place of the corresponding carbon resonances at δ_{C} 115.5 (C-11) and 151.6 (C-9) of **7** confirmed the generation of an epoxide ring at 9,11-position of **9**.



Treatment of **9** with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ in dry benzene at room temperature for 3 hr afforded a single compound which analyzed for $\text{C}_{30}\text{H}_{48}$ (M^+ 408). The ^1H NMR spectrum of the compound showed, besides the signals for 8 methyl groups attached to Sp^3 carbon atoms, two ill-resolved multiplet at δ_{H} 5.41 and 5.16 for two olefinic protons associated with a diene system. The compound exhibited UV absorptions, λ_{max} 239 nm ($\log \epsilon$ 4.30) which indicated it to be a heteroannular diene. The structure of the compound was finally established as fern-7(8),9(11)-diene (**10**) from its ^{13}C NMR spectral data (Table 1). Thus, the appearance of two protonated Sp^2 carbon signals at δ_{C} 117.4 (C-11) and 113.2 (C-7) and two nonprotonated Sp^2 carbon resonances at δ_{C} 146.9 (C-9) and 141.1 (C-8) in the ^{13}C NMR spectrum of **10** confirmed the generation of a diene system at 7(8),9(11)-positions in the compound. Other carbon

resonances of **10** were assigned by comparison with the δ_C values of structurally similar compounds like **3**⁹ and **2**⁹ and those of **7** and **9** (Table 1).

Table 1. ¹³C NMR spectral data of **7**, **9** and **10**

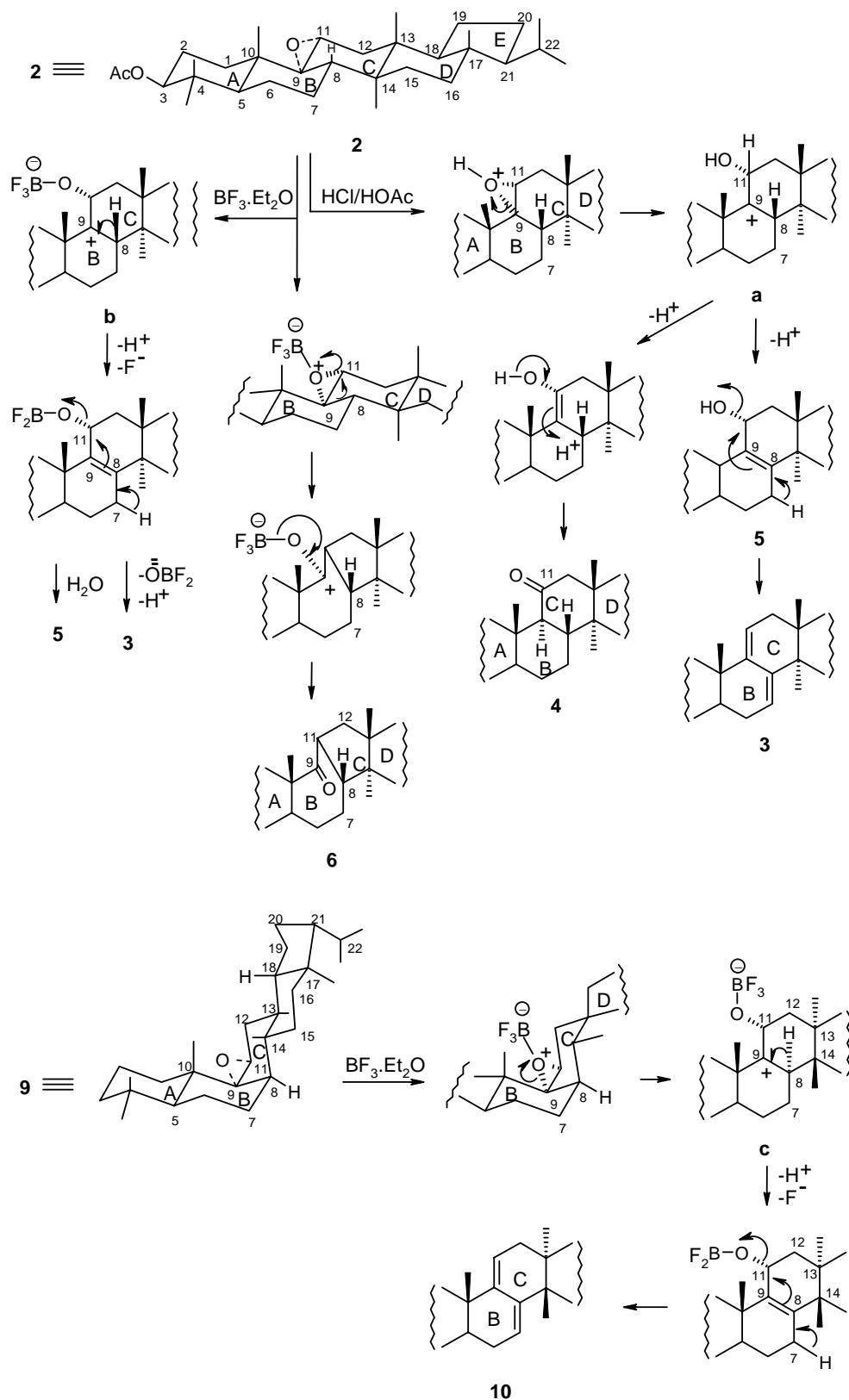
C	Chemical shifts (δ ppm)			C	Chemical shifts (δ ppm)		
	7	9	10		7	9	10
1	41.4	34.0	37.6	16	36.1	36.2	36.2
2	19.5	20.1	19.1	17	42.9	42.8	43.1
3	42.3	42.0	42.5	18	51.9	53.1	52.4
4	33.5	34.1	33.3	19	20.9	20.0	20.1
5	44.8	43.9	48.6	20	28.1	28.1	28.2
6	19.4	18.2	24.2	21	59.6	59.8	59.7
7	17.8	18.0	113.2	22	30.7	30.8	30.6
8	39.9	40.8	141.1	23	32.7	31.9	32.7
9	151.6	66.8	146.9	24	21.6	21.3	20.8
10	38.0	38.6	40.2	25	24.9	21.3	22.0
11	115.5	55.9	117.4	26	15.7	17.7	20.3
12	36.7	31.3	37.5	27	15.3	16.0	16.0
13	36.6	36.9	36.6	28	13.9	14.0	14.0
14	37.6	37.6	36.9	29	22.0	22.0	22.1
15	29.2	29.0	29.6	30	22.9	22.8	22.8

Spectra were run in CDCl₃.

Chemical shifts were measured with $\delta_{(TMS)} = \delta_{(CDCl_3)} + 76.9$ ppm.

Degree of protonation of each carbon atom was determined by DEPT experiment.

It is interesting to note that while 9 α ,11 α -epoxyisoarborinyl acetate (**2**) having *trans*-fused B/C rings on treatment with BF₃.Et₂O in benzene gave the rearranged ketone **6** as the major product along with only traces of the heteroannular diene **3** and the allylic alcohol **5**, 9 α ,11 α -epoxyfernane (**9**) with B/C rings *cis*-fused under the same reaction condition afforded the heteroannular diene **10** as the sole product. The observed differences in the products profile in the two cases may, therefore, be attributed to the different stereochemistry of the B/C ring juncture of the two oxiranes **2** and **9**, while the role of the solvent benzene remaining the same, viz. unfavourable for stabilizing the formation of a discrete carbocation. The formation of different products from **2** and **9** as stated above may be explained by an examination of the conformational structures of the two epoxide derivatives (Scheme 1). In polar solvent like HCl/HOAc the reaction of **2** was assumed to be initiated by the cleavage of the C₉-O- bond to give a discrete carbocation **a** which could be adequately stabilized by solvation. Collapse of this carbocation by loss of H⁺ from C-11 or C-8 gave **4**, **5** and **3** (Scheme 1). But with nonpolar solvent like benzene initiation of the reactions of both **2** and **9** with BF₃.Et₂O through discrete



Scheme 1. Mechanism of formation **3**, **4**, **5**, and **6** from **2** and that of **10** from **9**.

carbocations like **b** and **c** would be energetically unfavourable because of the absence of necessary stabilizing effect (through solvation) by the nonpolar solvent benzene. So the reaction tends to proceed through a concerted mechanism. In compound **2**, the C₁₁-O- bond being antiperiplanar (*trans*) with the C₈-C₉ bond the reaction of the compound with BF₃.Et₂O in benzene proceeds through a concerted mechanism involving the cleavage of the C₁₁-O- bond with concomitant migration of the C₈-C₉ bond to C-11 to give the unique rearranged product **6** (Scheme 1). Formation of traces of the diene **3** and the allylic alcohol **5** may be explained through the intermediacy of the discrete carbocation **b** generated to a small extent. But in the epoxide **9**, C₁₁-O- bond is not antiperiplanar with the C₈-C₉ bond. As a result, similar concerted reaction involving the cleavage of the C₁₁-O- bond and migration of the C₈-C₉ bond to C-11 to give a rearranged ketone similar to that obtained from **2** is not possible with **9**. But there is an inherent strain in **9** because of its *cis*-fused B/C rings, which tends to get released. Consequently, the reaction of **9** with BF₃.Et₂O in benzene proceeds through the higher energy alternative pathway involving the intermediacy of a discrete carbocation **c** through the cleavage of the C₉-O- bond to give the heteroannular diene **10** (Scheme 1), the driving force being the release of the steric strain in **9**. The conversion of **9** to **10** in benzene was thus found to be relatively slow because of the inability of nonpolar benzene to stabilize the intermediate carbocation **c** adequately through solvation.

The reactions of **2** and **9** with BF₃.Et₂O in benzene are thus two unique examples to demonstrate how a simple change in stereochemistry in the vicinity of the oxirane moiety in triterpenoids completely alters the course of their reactions.

Experimental Section

General Procedures. Mps were uncorrected. Silica gel (100-200 mesh) was used for column chromatography and silica gel G for TLC. UV spectra were run in 95% aldehyde-free EtOH and the IR spectra in KBr discs. ¹H and ¹³C NMR spectra were recorded at 300 and 75 MHz, respectively, in CDCl₃ using TMS as the internal standard. Chemical shifts were expressed in δ (ppm). Mass spectra were measured at 70 eV using a direct inlet system. All analytical samples were routinely dried over P₂O₅ for 24 h in vacuo and were tested for purity by TLC and MS. Petrol used had bp 60-80 °C. Anhydrous Na₂SO₄ was used for drying organic solvents.

Isolation of the triterpenoids from the rhizome of *Drynaria quercifolia*. Fresh rhizomes of *D. quercifolia* (2 kg) cut into small pieces were churned with EtOH (500 ml) in a grinder and the pasty macerated mass was kept soaked with more EtOH (2.5 L) for 3 weeks. The EtOH extract was then concentrated under reduced pressure to about 100 ml, diluted with water and extracted with Et₂O, dried and the solvent removed. The residue was chromatographed.

The petrol-EtOAc (90:1) eluate afforded a mixture of **7** and another triterpenoid as a glassy mass. Because of their highly nonpolar character and of very close polarity they could not be

separated even on repeated chromatography. However, **7** was finally obtained in the pure state (yield 0.02%) by repeated crystallization from MeOH-CHCl₃ (9:1), mp 172 °C, [α]_D-17° (CHCl₃). ¹H NMR : δ_{H} 0.73, 0.76, 0.82, 0.85, 0.89 and 1.05 (each 3H, s); 6x C-CH₃, 0.88 (3H, d, J = 6.07 Hz; CH-CH₃), 0.89 (3H, d, J = 6.36 Hz; CH-CH₃) and 5.29 (1H, m; H-11).

The combined mother liquor after separation of **7** contained a mixture of **7** and the other triterpenoid in about 2:3 ratio from which the latter could not be obtained in the pure state.

Further elution of the column with petrol-EtOAc (20:1) gave **8** (yield 0.005%), crystallized from MeOH, mp 137 °C.

Conversion of fern-9(11)-ene (7) to 9 α , 11 α -epoxyfernane (9). To a solution of *m*-chloroperbenzoic acid (0.15 g) in CH₂Cl₂ (25 ml) cooled in an ice-bath was added 0.3 g of **7** in 15 ml CH₂Cl₂ for a period of 30 min with stirring. The mixture was kept overnight at room temperature. The mixture was then washed twice with 10% NaHCO₃ solution and then with H₂O, dried and the solvent removed. The residue was chromatographed. The petrol-EtOAc (30:1) eluate afforded **9** (0.28 g), crystallized from petrol-EtOAc, mp 163 °C. (Found: C, 84.39; H, 11.39. C₃₀H₅₀O requires: C, 84.42; H, 11.82%). IR ν_{max} cm⁻¹ : 2946, 2867, 1460, 1382, 962, 923, 867 and 776; ¹H NMR: δ_{H} 0.74, 0.82, 0.88, 0.92, 1.04 and 1.08 (each 3H, s; 6x C-CH₃), 0.81 (3H, d, J = 6.20 Hz; CH-CH₃), 0.86 (3H, d, J = 6.57 Hz; CH-CH₃) and 3.05 (1H, br. signal; H-11); MS *m/z* (relative intensity) : 426 [M⁺] (45), 301 (23), 204 (37), 189 (28) and 123 (38).

Conversion of 9 to the heteroannular diene 10. A solution of **9** (0.25 g) in dry benzene was treated with freshly distilled BF₃.Et₂O (2 ml). The mixture was stirred at room temperature for 3 h and then poured into ice-cold water and kept overnight. The product was extracted with Et₂O, dried and the solvent removed. The residue was chromatographed. The petrol-EtOAc (50:1) eluate afforded **10** (0.215 g), crystallized from petrol-EtOAc, mp 206 °C. (Found: C, 88.09; H, 11.80. C₃₀H₄₈ requires: C, 88.15; H, 11.84%). UV : $\lambda_{\text{max}}^{\text{EtOH}}$ 239 nm (log ϵ 4.30); IR ν_{max} cm⁻¹ : 1624 and 1000 (heteroannular diene), 2930, 1460, 1375, 1140, 815, 675 and 529; ¹H NMR : δ_{H} 0.71, 0.76, 0.86 and 1.25 (each 3H, s; 4x C-CH₃), 0.92 (6H,s ; 2x C-CH₃), 0.84 (3H, d, J = 6.5 Hz; CH-CH₃), 0.92 (3H, d, J = 6.4 Hz; CH-CH₃) and 5.16 and 5.41 (each 1H, ill-resolved m; H-7 and H-11); molecular weight 408, established by FAB MS.

Acknowledgements

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