Effect of stereochemistry of the B/C ring juncture on the acid-catalyzed reactions of 9α,11α-epoxyfernane and 9α,11α-epoxyisoarborinyl acetate with $BF_3.Et_2O$ 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

9α,11α-Epoxyfernane possessing a *cis*-fused B/C rings derived from fern-9(11)-ene isolated from *Drynaria quercifolia* on treatment with $BF_3.Et_2O$ in nonpolar solvent like benzene afforded fern-7(8),9(11)-diene as the sole product. On the other hand, 9α,11α-epoxyisoarborinyl acetate having a *trans*-fused B/C rings gave earlier, besides only traces of the corresponding 7(8),9(11)-diene and 11α-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*, 9α,11α-epoxyfernane, $BF_3.Et_2O$, fern-7(8),9(11)-diene

Introduction

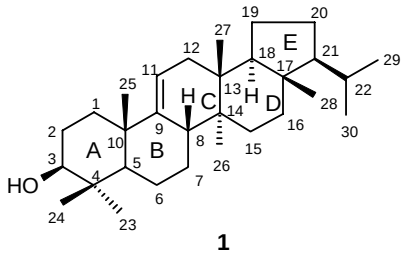
Acid-catalyzed reactions of triterpenoids of various skeletal types bearing an epoxide function at different sites of their molecules have uncovered a large volume of fascinating chemistry[1-9] involving, in some cases, interesting backbone rearrangements. The course of these reactions were found to 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 9α,11α-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 treated[1] with $HClO_4$/HOAc. On the other hand, reaction of the same epoxy derivative **2** earlier carried out[9] by us with $BF_3.Et_2O$ 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 9α,11α-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 9α,11α-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 cycloeucaneol[12] (**8**), respectively, indicating their respective identity. The third compound containing a terminal methylene group associated with the moiety $-C(CH_3)=CH_2$ [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 ^{13}C 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 CH_2Cl_2 at 0 ºC in the molar ratio of 1:1.2 for 24 h gave the corresponding epoxy derivative, $C_{30}H_{50}O$ (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 9α,11α-epoxyfernane (**9**) by its ^{13}C 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 ^{13}C 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**.



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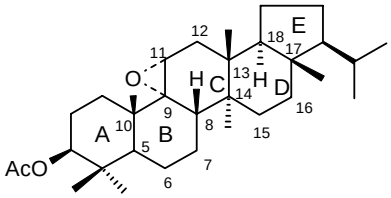

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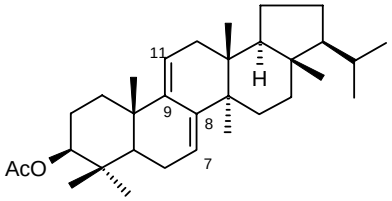

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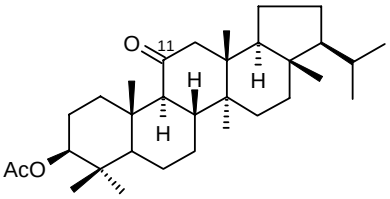

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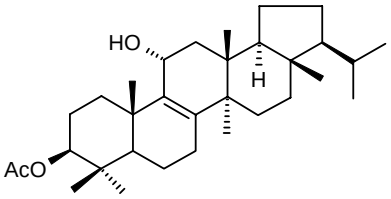

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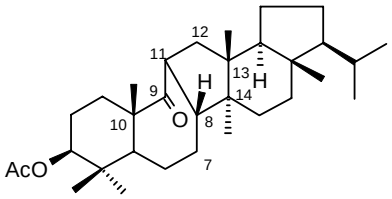

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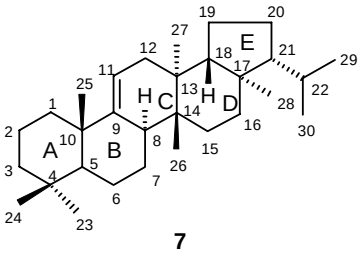

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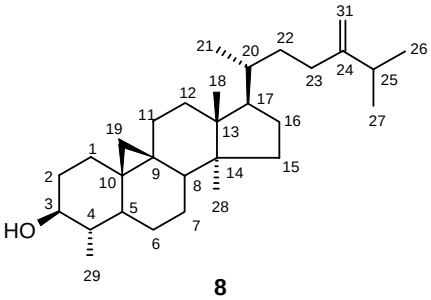

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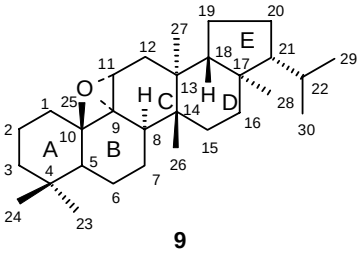

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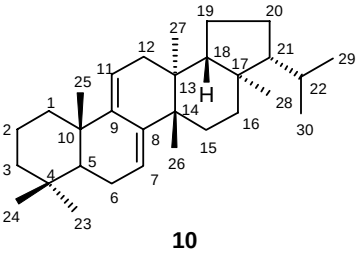


10

Treatment of **9** with $BF_3.Et_2O$ in dry benzene at room temperature for 3 hr afforded a single compound which analyzed for $C_{30}H_{48}$ (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 ε 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

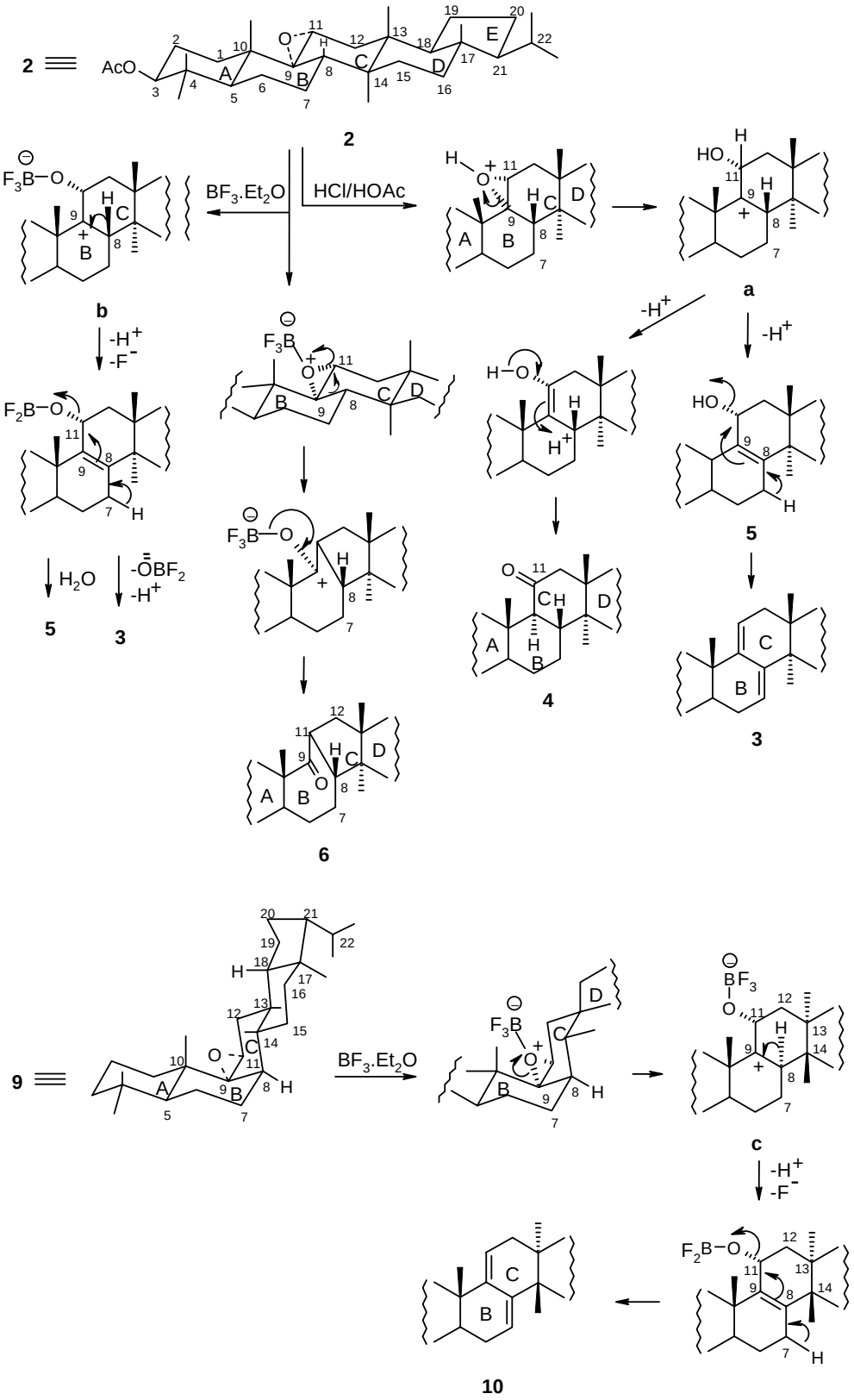
resonances of **10** were assigned by comparison with the δ_C values of structurally similar compounds like **3**[9] and **2**[9] and those of **7** and **9** (Table 1).

Table 1. ^{13}C 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 $CDCl_3$.
Chemical shifts were measured with $\delta_{(TMS)} = \delta_{(CDCl3)} + 76.9$ ppm.
Degree of protonation of each carbon atom was determined by DEPT experiment.

It is interesting to note that while 9α,11α-epoxyisoarborinyl acetate (**2**) having *trans*-fused B/C rings on treatment with $BF_3.Et_2O$ 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**, 9α,11α-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 C_9-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 $BF_3.Et_2O$ 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 C_{11}-O- bond being antiperiplanar (*trans*) with the C_8-C_9 bond the reaction of the compound with $BF_3.Et_2O$ in benzene proceeds through a concerted mechanism involving the cleavage of the C_{11}-O- bond with concomitant migration of the C_8-C_9 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**, C_{11}-O- bond is not antiperiplanar with the C_8-C_9 bond. As a result, similar concerted reaction involving the cleavage of the C_{11}-O- bond and migration of the C_8-C_9 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 $BF_3.Et_2O$ in benzene proceeds through the higher energy alternative pathway involving the intermediacy of a discrete carbocation **c** through the cleavage of the C_9-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 $BF_3.Et_2O$ 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 spectrta in KBr discs. ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, in $CDCl_3$ 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 P_2O_5 for 24 h in vacuo and were tested for purity by TLC and MS. Petrol used had bp 60-80 ºC. Anhydrous Na_2SO_4 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 Et_2O, 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-$CHCl_3$ (9:1), mp 172 ºC, $[\alpha]_D$-17º ($CHCl_3$). ^{1}H NMR : δ_H 0.73, 0.76, 0.82, 0.85, 0.89 and 1.05 (each 3H, s); 6x C-C*H*$_3$), 0.88 (3H, d, J = 6.07 Hz; CH-C*H*$_3$), 0.89 (3H, d, J = 6.36 Hz; CH-C*H*$_3$) 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 ºC.

Conversion of fern-9(11)-ene (7) to 9α, 11α-epoxyfernane (9). To a solution of *m*-chloroperbenzoic acid (0.15 g) in CH_2Cl_2 (25 ml) cooled in an ice-bath was added 0.3 g of **7** in 15 ml CH_2Cl_2 for a period of 30 min with stirring. The mixture was kept overnight at room temperature. The mixture was then washed twice with 10% $NaHCO_3$ solution and then with H_2O, 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 ºC. (Found: C, 84.39; H, 11.39. $C_{30}H_{50}O$ requires: C, 84.42; H, 11.82%). IR ν_{max} cm^{-1} : 2946, 2867, 1460, 1382, 962, 923, 867 and 776; ^{1}H NMR: δ_H 0.74, 0.82, 0.88, 0.92, 1.04 and 1.08 (each 3H, s; 6x C-C*H*$_3$), 0.81 (3H, d, J = 6.20 Hz; CH-C*H*$_3$), 0.86 (3H, d, J = 6.57 Hz; CH-C*H*$_3$) 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 BF_3.Et_2O (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 Et_2O, 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 ºC. (Found: C, 88.09; H, 11.80. $C_{30}H_{48}$ requires: C, 88.15; H, 11.84%). UV : λ_{max}^{ErOH} 239 nm (log ε 4.30); IR ν_{max} cm^{-1} : 1624 and 1000 (heteroannular diene), 2930, 1460, 1375, 1140, 815, 675 and 529; ^{1}H NMR : δ_H 0.71, 0.76, 0.86 and 1.25 (each 3H, s; 4x C-C*H*$_3$), 0.92 (6H,s ; 2x C-C*H*$_3$), 0.84 (3H, d, J = 6.5 Hz; CH-C*H*$_3$), 0.92 (3H, d, J = 6.4 Hz; CH-C*H*$_3$) 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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