The stereochemistry of the Grignard reaction of some boat ring ketones in the diterpenoids

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The stereochemistry of the addition of methylmagnesium bromide to boat ring B C-6 and C-7 ketones of the rosane and to C-16 of the beyerane diterpenoids has been shown to take place from the less-hindered face of the molecule.

Keywords: diterpenoids, boat ring ketones, Grignard reaction

The factors which affect the stereochemistry of the Grignard adducts to cyclic ketones have been thoroughly studied using alkylated cyclohexanones such as 4-t-butylcyclohexanone.[1] These substrates exist preferentially in the chair conformation. The results have been rationalised in terms of a balance between steric factors which tend to direct the incoming alkyl substituent to the less-hindered, usually equatorial position and other electronic and torsional factors which in some instances can favour an axial approach of the alkyl group. The electronic factors include a possible contribution from the adjacent axial C–H σ-bond to the developing σ^* orbital between the alkyl group and the carbonyl carbon.[2] Whilst there is a substantial body of information with chair rings, there is a paucity of information with boat rings. Cyclic ketones with rigid boat rings are relatively rare. When the carbonyl group is at the 'side' of the boat, as opposed to the 'prow', the adjacent axial C-H bonds may make equivalent contributions to each face of the carbonyl group. In the bornane series in which the bridge serves to lock the cyclohexanone into a boat, there is a complete change in stereoselectivity between camphor [100% endo (axial) attack] and norbornanone [100% exo (equatorial) attack][3] indicating a major steric influence by the methyl groups of the bridge on the Grignard reaction.

Rosenonolactone **1**[4] and rosololactone **3**[5] are two diterpenoid lactones in which the presence of a β-oriented 19-10 γ-lactone and a C-9β methyl group constrains ring B to adopt a boat conformation.[6] Treatment of the C-7 ketone **1** with methylmagnesium bromide gave a good yield of a single crystalline tertiary alcohol. The stereochemistry of this alcohol **2** was established by X-ray crystallography (see Fig. 1). In this product the methyl group occupies the 7α (axial) configuration with ring B adopting a twisted boat conformation. The formation of the 7β-hydroxy-7α-methylrosenonolactone **2** parallels the stereochemistry of the reduction of rosenonolactone **1** by sodium borohydride which gives the 7β-alcohol.[7]

Oxidation of the C-6 alcohol rosololactone **3** with chromium trioxide in sulfuric acid gave the known[5] C-6 ketone, rosonolactone **4**. Treatment of this ketone with methylmagnesium bromide gave a gummy C-6 hydroxy-methyl rosane. The stereochemistry **5** of this compound was established by nuclear Overhauser effect experiments. In addition to the rosane methyl groups (δ_H 0.97, 1,15 and 1.35; *cf*. rosololactone δ_H 0.96, 1.18 and 1.26), this product showed an extra C-methyl resonance at δ_H 1.42. On irradiation of the signal at δ_H 0.97 there were signifcant enhancements of the alkene resonances at δ_H 4.89 (3.1%) and 5.76 (2.5%) and hence the signal at δ_H 0.97 was assigned to H-17. Irradiation of the methyl group signals at δ_H 1.35 and 1.42 both enhanced a singlet (H-5α) at δ_H 1.72 (7.4 and 2.0% respectively). Hence, both these methyl groups are α-oriented. The signal at δ_H 1.42 was assigned to H-21 since irradiation of this methyl group signal and that at δ_H 1.15 (H-20) both enhanced a signal at δ_H 1.56 (2.5% and 9.2% respectively). This signal disappeared when the sample was treated with [$^2H_4$]-methanol and was therefore assigned to the 6β-hydroxyl hydrogen. Hence, the adduct has the 6β-hydroxyl-6α-methyl (equatorial methyl) configuration. The stereochemistry of this Grignard reaction again parallels that of the sodium borohydride reduction which regenerates 6β-hydroxyl of rosololactone.

When rosenonolactone **1** is treated with base epimerisation takes place at C-8 and isorosenonolactone (**1** 8β–H) is formed.[8] This compound retains ring B in a boat form. However the C-7 ketone did not react with methylmagnesium bromide and the starting material was recovered despite prolonged reaction conditions. In this compound approach to the C-7 carbonyl is hindered on both faces of the molecule.

The presence of a C-9β hydrogen and the C-14β methylene bridge constrains the cycloheptanone of rings C and D in ent-16-oxobeyeran-19-oic acid (isosteviol) **6**[9] to adopt a boat conformation. This ketone reacted with methylmagnesium bromide to give a single methylcarbinol **7**. The stereochemistry of this product was established by X-ray

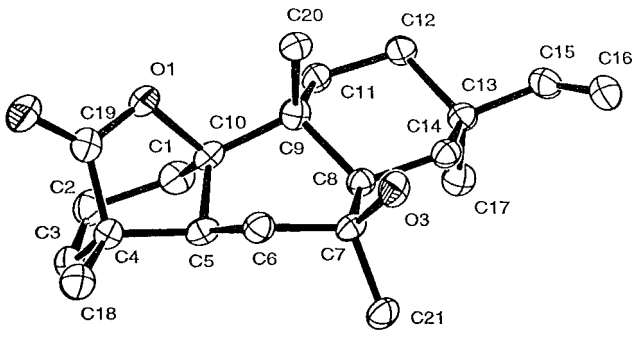


Fig. 1 X-ray crystal structure of compound **2**.

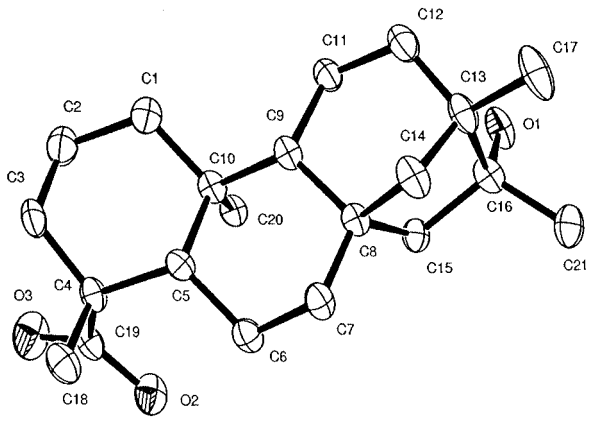
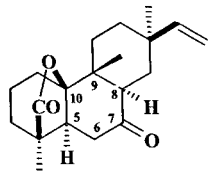


Fig. 2 X-ray crystal structure of compound **7**.

* Correspondence.



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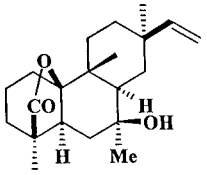

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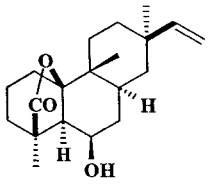

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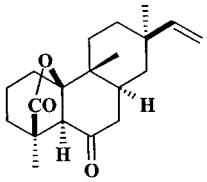

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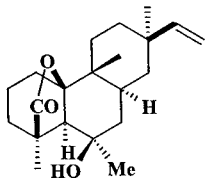

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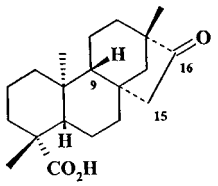
crystallography and is shown in Fig. 2. Addition of the methyl group has taken place from the exo-face of the ketone. In methyl gibberate **8** the hydrogen atom at C-9 has the α-configuration and the cycloheptanone ring then adopts a chair conformation. Since a sample of methyl 17-hydroxygibberate **9**[10] was available, it was also treated with methylmagnesium bromide. The product, **10**, was a gum and its stereochemistry was established by nOe experiments. The ^{1}H NMR spectrum of **10** was fully assigned (see experimental section) based on prior work.[11] In particular the H-14 and H-15 resonances were identified at δ_H 1.39 and 0.82 (H-14) and 2.03 and 2.32 (H-15). The 2D NOESY spectrum revealed a correlation between H-9 (δ_H 3.09) and the H-15 signal at δ_H 2.03 which was therefore assigned to the endo-proton. On the five-membered ring, there is a **W**-type long-range coupling (J=2.3Hz) between the endo-proton at H-15 (δ_H 2.03) and the H-14 proton signal at δ_H 1.39.leading to the assignment of this proton. The 2D-NOESY correlation spectrum showed a correlation between the two H-14 resonances (δ_H 0.82 and 1.39). There were also correlations between the H-14 resonance at δ_H 0.82 and the exo H-15 signal at δ_H 2.32 and the H-17 signal (δ_H 3.68). This led to the assignment of the resonances on the five-membered ring. The 2D-NOESY spectrum revealed a significant correlation between the methyl group signal at δ_H 1.41 and the exo-proton resonance at H-15 (δ_H 2.32). Hence the methyl group has taken up the exo configuration as in **10**.

In these diterpenoids the stereochemical determining feature is the approach of the Grignard reagent from the less-hindered face of the molecule. In the case of the C(7)rosanes this leads to tertiary alcohols with an axial methyl group and it contrasts with the generalization that in the steroid series there is a 'very pronounced preference for formation of the tertiary alcohol with an equatorial methyl group.'[12]

Experimental

Silica for chromatography was Merck 9385. Light petroleum refers to the fraction, b.p. 60–80°C. ^{1}H NMR spectra were determined at 300 MHz for solutions in deuteriochloroform; nOe measurements were made at 500 MHz. IR spectra were determined as nujol mulls. High resolution mass spectra were determined on a Fisons Autospec or a Bruker Daltonics Apex III Electrospray mass spectrometer. Extracts were dried over sodium sulfate. Rosenonolactone **1** and rosololactone



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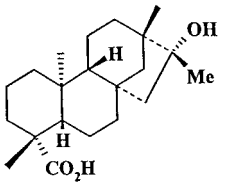

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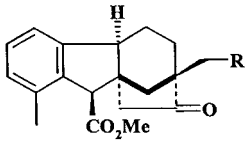
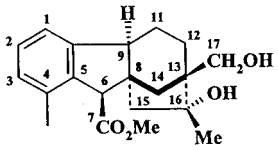


8 R=H

9 R=OH



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3 were obtained from *Trichothecium roseum*. Isorosenonolactone was prepared by the literature method[8] from rosenonolactone and had m.p. 135–137°C, (lit.,[8] 140–142°C), δ_H 0.86 (3H, s, H-17), 1.13 (3H, s, H-20), 1.25 (3H, s, H-18), 0.90–1.90 (12H, overlapping multiplets), 2.18 (2H, multiplet) 2.38 (1H, t, J=7.1 Hz), 2.60 (1H, dd, J=7.8 and 16.6 Hz), 4.85 (1H, d, J=10.6 Hz), 4.93 (1H, d, J=17.5 Hz), 5.78 (1H, dd, J=10.6 and 17.5 Hz). Isosteviol **6** was prepared from stevioside by treatment with cold hydrobromic acid[13] and methyl 17-hydroxygibberate was prepared from methyl 16, 17-epoxyallogibberate by reaction with tetracyanoethylene.[10]

Grignard reaction of rosenonolactone: A solution of methylmagnesium bromide (3M in ether)(1 cm^3) was added to tetrahydrofuran (15 cm^3) at 0°C under nitrogen. Rosenonolactone **1** (500 mg) in tetrahydrofuran (25 cm^3) was added dropwise and the mixture was stirred overnight. Aqueous ammonium chloride was added and the solution was extracted with dichloromethane. The extract was dried and the solvent evaporated to give 7β-hydroxy-7α-methylrosenonolactone **2** (490 mg) which crystallised from ethyl acetate as plates, m.p. 194–196°C (Found M$^+$ 332.235 $C_{21}H_{32}O_3$ requires 332.235), ν_{max}/cm^{-1} 3407, 1759, 1670; δ_H 0.96 (3H, s, H-17), 1.09 (3H, s, H-20), 1.11 (3H, s, H-18), 1.20 (3H, s, H-21), 0.7–2.2 (16H, overlapping multiplets), 4.87 (1H, d, J=17.5 Hz, H-16), 4.93 (1H, d, J=10.6 Hz, H-16), 5.82 (1H, dd, J=10.6 and 17.5 Hz, H-15). Under similar conditions and also after treatment for 96 hours, isorosenonolactone gave only the starting material.

Preparation of rosonolactone: A solution of rosololactone **3** (500 mg) in acetone (50 cm^3) was treated with the Jones' reagent until the orange colour persisted. The excess reagent was destroyed with methanol. The solution was concentrated *in vacuo*, diluted with water and extracted with ethyl acetate. The extract was washed with water, brine and dried. The solvent was evaporated and the residue was chromatographed on silica. Elution with 15% ethyl acetate:light petroleum gave rosonolactone **4** (450 mg), m.p. 123°C (lit.,[5] 126°C), ν_{max}/cm^{-1} 1730, 1710, 1671; δ_H 0.82 (3H, s, H-17), 1.03 (3H, s, H-20), 1.28 (3H, s, H-18), 0.7–2.5 (16H overlapping multiplets), 4.85 (1H, d, J=17.2 Hz, H-16), 4.93 (1H, d, J=10.6 Hz, H-16), 5.77 (1H, dd, J=10.6 and 17.2 Hz, H-15).

Grignard reaction of rosonolactone: A solution of methylmagnesium bromide (3M in ether) (0.5 cm^3) was diluted with tetrahydrofuran (10 cm^3) at 0°C under nitrogen. A solution of rosonolactone **4** (250 mg) in tetrahydrofuran (15 cm^3) was added dropwise and the mixture was left at room temperature overnight. Aqueous ammonium chloride was added and the solution was extracted with dichloromethane. The extract was washed with water, dried and the solvent evaporated. The residue was chromatographed on silica. Elution with 20% ethyl acetate: light petroleum gave 6α-methylrosololactone **5** (240 mg) as an oil, (Found M$^+$ 332.235 $C_{21}H_{32}O_3$ requires 332.235), ν_{max}/cm^{-1} 3453, 1760, 1673; δ_H 0.95 (3H, s, H-17), 1.13 (3H, s, H-20), 1.33 (3H, s, H-18), 1.40 (3H, s, H-21), 0.7–2.2 (17H, overlapping multiplets), 4.86 (1H, d, J=17.5 Hz, H-16), 4.93 (1H, d, J=10.6 Hz, H-16), 5.74 (1H, dd, J=10.6 and 17.5 Hz, H-15).

Reduction of rosonolactone: Rosonolactone **4** (150 mg) in methanol (15 cm^3) was treated with sodium borohydride (200 mg) at 0°C for 2.5 h. Acetic acid (2 drops) was added and the solution was concentrated *in vacuo*. Water was added and the solution was extracted with ethyl acetate. The extract was washed with water, dried and the solvent evaporated. The residue (135 mg) crystallised from

ethyl acetate:light petroleum as needles of rosololactone **3**, m.p. 182° (lit.,[5] 186°), identified by its ^{1}H NMR spectrum.

Grignard reaction of isosteviol: A solution of ent-16-oxobeyeran-19-oic acid (isosteviol)[9] **6** (500 mg) in dry tetrahydrofuran (15 cm^3) was treated with a solution of methylmagnesium bromide (3M in ether) (2 cm^3) diluted with tetrahydrofuran (10 cm^3). The solution was left at room temperature overnight. Aqueous ammonium chloride was added and the solution was acidified with dilute hydrochloric acid and extracted with dichloromethane. The extract was washed with water, dried and the solvent evaporated to give *ent*-16-hydroxy-16-methylbeyeran-19-oic acid **7** (483 mg) which crystallised from aqueous methanol as needles, m.p. 240–242°C, (Found: C, 73.1; H, 10.3; M$^+$ 691.495. $C_{21}H_{34}O_3.0.5H_2O$ requires C,73.4; H,10.2%; $(C_{21}H_{34}O_3)_2Na^+$ requires 691.491), ν_{max}/cm^{-1} 3403, 1693; δ_H (pyridine-d$_5$) 0.95 (3H,s,H-20), 1.16 (3H,s,H-17), 1.34 (3H,s, H-18), 1.37 (3H,s, Me-16). 0.90–2.00 (20H, overlapping multiplets). The methyl ester, prepared with diazomethane, had m.p. 168–169°C, (Found: C, 75.5; H, 10.3. $C_{22}H_{36}O_3$ requires C, 75.8; H, 10.4%), ν_{max}/cm^{-1} 3583,1705; δ_H (pyridine-d$_5$) 0.88 (3H,s, H-20), 0.98 (3H,s, H-17), 1.21 (3H,s, H-19), 1.38 (3H,s, Me-16), 0.90–2.00 (21H overlapping multiplets), 3.61 (3H,s, OMe).

Grignard reaction of methyl 17-hydroxygibberate: A solution of methyl 17-hydroxygibberate[10] **9** (100 mg) in dry tetrahydrofuran (10 cm^3) was treated with a solution of methylmagnesium bromide (3M in ether) (1 cm^3) diluted with tetrahydrofuran (5 cm^3). The solution was left at room temperature overnight. Aqueous ammonium chloride was added and the solution was acidified with dilute hydrochloric acid and extracted with dichloromethane. The extract was washed with water, dried and the solvent evaporated to give methyl 16,17-dihydroxy-16-methylgibberate **10** (82 mg) as an oil, (Found: M$^+$ 353.172. $C_{20}H_{26}O_4Na^+$ requires 353.172), ν_{max}/cm^{-1} 3410, 1730; δ_H ($CDCl_3$) 0.82 (1H,d, *J*=12.1 Hz, H-14), 1.39 (1H,dd, *J*=12.1 and 2.3 Hz,H-14), 1.41 (3H,s,Me-16), 1.60 and 2.25 (each 2H, m, H-11 and H-12), 2.03 (1H,dd, *J*=13.9 and 2.3Hz, H-15), 2.13 (3H, s, H-18), 2.32 (1H,d, *J*=13.9 Hz, H-15) 3.04 (1H,t, *J*=8.0 Hz, H-9), 3.49 and 3.68 (each 1H,d, *J*=10.1 Hz, H-17), 3.76 (3H,s, OMe), 4.00 (1H,s, H-6), 6.98 (1H,d, *J*=8.4 Hz, H-1), 7.00 (1H,d, *J*=8.4 Hz, H-3), 7.18 (1H,t, *J*=8.4 Hz, H-2). Irradiation at δ_H 2.13 gave nOe enhancements at δ_H 4.00 (2.8%) and 7.00 (6.8%) and irradiation at δ_H 6.98 gave an nOe enhancement to δ_H 3.04 (0.9%).

X-Ray crystallographic data and structure determinations: Compound **2**, $C_{21}H_{32}O_3$, M$_r$ 332.47, monoclinic, space group $P2_1$ (No. 14), *a* = 9.01835(5), *b* = 12.3809(8), *c* = 16.3086(8) Å, $\alpha = \gamma = 90°$, $\beta = 90.710(3)°$, *V* = 1820.79(18)Å^3, *Z* = 4, D_{calc} = 1.21 g cm^{-3}, μ= 0.08 mm^{-1}, F(000) 728. Data were collected from a crystal of size 0.40 × 0.20 × 0.05 mm^3 A total of 7370 reflections were collected for $3.73 < \theta < 23.00°$ and $-9 \le h \le 9$, $-13 \le k \le 13$, $-17 \le l \le 17$. There were 4514 independent reflections and 3756 reflections with $I > 2\sigma(I)$ were used in the refinement. No absorption correction was applied. The structure was solved by direct methods using SHELXL-97 and refined by full matrix least squares on F^2 The final *R* indices were [$I > 2\sigma(I)$] R_1 = 0.051, wR_2 = 0.119 and (all data) R_1 = 0.066, wR_2 = 0.1284. The goodness-of-fit on F_2 was 1.024 and the largest difference peak and hole was 0.22 and –0.22 eÅ^{-3}. There were two essentially identical independent molecules in the unit cell.

Compound **7**, $C_{21}H_{34}O_3$ 0.5H_2O, M$_r$ 343.49, monoclinic, space group C2 (No. 5), *a* = 30.0438(6), *b* = 7.3846(2), *c* = 21.8711(8) Å, $\alpha = \gamma = 90°$, $\beta = 129.313(1)°$, *V* = 3754.25(16)Å^3, *Z* = 8, D_{calc} = 1.22 g cm^{-3}, μ= 0.08 mm^{-1}, F(000) 1512. Data were collected from a crystal of size 0.20 × 0.05 × 0.02 mm^3 A total of 19566 reflections were collected for $3.77 < \theta < 25.04°$ and $-35 \le h \le 35$, $-8 \le k \le 8$, $-25 \le l \le 23$. There were 6515 independent reflections and 4520 reflections with $I > 2\sigma(I)$ were used in the refinement. No absorption correction was applied. The structure was solved by direct methods using SHELXL-97 and refined by full matrix least squares on F_2 The final *R* indices were [$I > 2\sigma(I)$] R_1 = 0.085, wR_2 = 0.172 and (all data) R_1 = 0.131, wR_2 = 0.197. The goodness-of-fit on F_2 was 1.084 and the largest difference peak and hole was 0.31 and –0.31 e.Å^{-3}. The asymmetric unit contains two essentially identical molecules and one water molecule. The crystallographic data will be deposited at the Cambridge Crystallographic Data Centre.

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