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LANTHANIDE NMR SHIFT REAGENTS AND STEREOCHEMICAL ASSIGNMENTS

STEREOCHEMISTRY IN THE REDUCTION OF 6-DICYANOMETHYLIDENE AND 6-(1-CYANOETHYLIDENE) DERIVATIVES OF THE *cis*-8a-METHYL-1-DECALONE

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Abstract—Condensation of *cis*-decalone **3** with malononitrile and 2-diethylphosphonopropionitrile gives the corresponding 6-dicyanomethylidene and 6-(1-cyanoethylidene) derivatives (**4** and **7**), which upon reduction afford mixtures of diastereoisomeric products. The stereochemical assignments were made on the basis of NMR shift studies in the presence of Eu(FOD)$_3$.

INTRODUCTION

It has been reported that selective ketalization at the saturated CO group of the Wieland–Miescher ketone (**1**→**2**), followed by catalytic hydrogenation at atmospheric pressure over PdC, gives selectively the *cis*-decalone **3** (Scheme 1). Assignment of the *cis* stereochemistry to the product was based either upon NMR studies on the line width at half-height[1] or upon the solvent effect $\Delta^{CCl_4}_{C_6D_6}$ of the angular methyl resonance.[2]

In the present paper we report our results—which are of interest in connection with a new stereoselective synthesis of patchouli alcohol—on the reduction of 6-dicyanomethylidene and 6-(1-cyanoethylidene) derivatives of the *cis*-decalone **3** and the unequivocal stereochemical assignment of the resulting diastereoisomeric products by means of lanthanide NMR shift reagents:[3] namely, Eu(FOD)$_3$ in deuteriochloroform solution.

Condensation of the *cis*-decalone **3** with malononitrile gives the 6-dicyanomethylidene derivative **4**, m.p. 127-128°, which upon reduction can afford two diastereoisomeric products, **5** and **6** (Scheme 2).

On the other hand, condensation of **3** with 2-diethylphosphonopropionitrile, according to a Wittig–Horner reaction,[4] gives an $E+Z$ mixture of the two 6-(1-cyanoethylidene) derivatives **7**, m.p. 96–98°, which upon reduction should afford four diastereoisomeric products, **8**, **9**, **10** and **11** (Scheme 2).

Hydrolysis of these ketals should give the corresponding ketones, in which the lone electron pair of the CO group could effectively interact with the europium atom and affect differentially the resonance of the surrounding protons and, accordingly, give valuable information about their mutual spatial relationships.

Reduction of the 6-dicyanomethylidene derivative 4

In the reduction of ketal **4** (in the preferred or stabilized conformation A) with hydrides, the attack would be expected to proceed from the convex face of the *cis*-decalin system to produce **6**, in which the dicyanomethyl side-chain is in the α position (opposite to the angular Me group). In fact, in the reduction with sodium borohydride only one product, m.p. 67–71°, was isolated in 66% yield, from which a pure ketone **6a**, m.p. 93.5–95.5°, was obtained. The same product, but with lower yields, was isolated in the reduction of ketal **4** with aluminum amalgam.

All attempts to hydrogenate the ketal **4** at atmospheric pressure over PdC, in a variety of solvents, failed. However, the corresponding ketone **4a**, m.p. 100–104°, was catalytically hydrogenated (PdC), in methanol solution, to give, after purification by TLC on silica-gel, a 10:1 mixture of two epimers, the minor component being identical with ketone **6a** and, therefore, the predominant one, m.p. 132.5–135.5°, should have the dicyanomethyl side-chain in the β position (**5a**).[a] On the other hand, controlled reduction of the free ketone **4a** with sodium borohydride in ethanol gives a 3:1 mixture of the α and β isomers (**6a** and **5a**) as the result of no preferred conformation in the ketone **4a** in contrast to the ketal **4**.

Accepting that the dicyanomethyl groups are equatorially disposed and assuming that the coordination distance of the Eu atom to the oxygen of the CO group is 300 pm[5] and that it remains in the axis of the C=O bond, examination of the molecular models of the complexes of ketone **5a** and **6a** with europium shows that the angular Me protons of the β isomer (**5a**) are nearer to the

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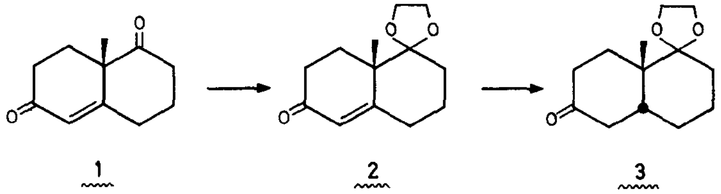
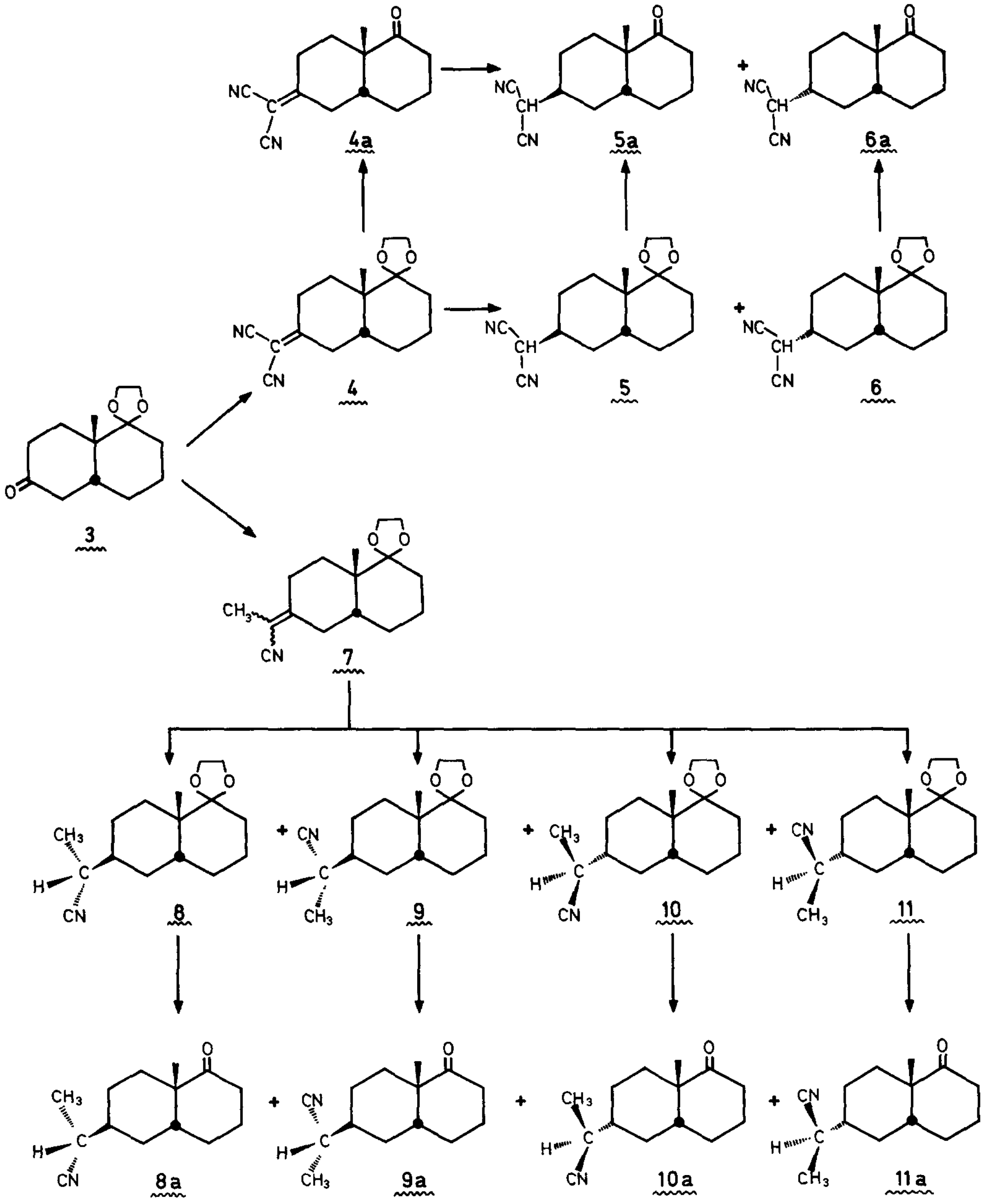
[a] The original crude reduction mixture contains, however, the β and α isomers in the proportion 2.5:1, together with other products (spectral evidence).

Owing to the fact that the β isomer (**5a**) has the carbonyl group more accessible to intermolecular attack than the α isomer (**6a**), it could be isolated by selective conversion to ketal **5**, m.p. 92–94°, chromatography on alumina and hydrolysis back to the free ketone **5a**.



Scheme 1.



Scheme 2.

europium atom than in the α isomer (**6a**) and, therefore, their NMR chemical shifts should be much more sensitive to the effects of the lanthanide shift reagent.

In agreement with our expectations, the plot of the induced shifts ($\Delta\delta$) on the angular Me protons vs equivalents of Eu(FOD)$_3$ added to the deuteriochloroform solution, gives straight lines which slopes (ρ_{CH_3}) are greater in the β isomer (**5a**) than in the α isomer (**6a**), 0.95 and 0.31 respectively (Table 1). Similarly, the proton of the methine group is also more affected in the β isomer than in the α isomer, as shown by the slopes (ρ_{CH}) of the corresponding straight lines (0.25 and 0.14 respectively).

Table 1. Slopes of the straight lines from the plot of $\Delta\delta$ vs equiv. of $Eu(FOD)_3$ added to the deuteriochloroform solution

	Slope (ρ)		
Ketone	Angular methyl (s)	Side-chain methine (d)	Side-chain methyl (d)
5a	0.95	0.25	—
6a	0.31	0.14	—
8a + 9a	1.02	—	0.24
10a	0.63	—	0.18
11a	0.47	—	0.17

Reduction of the 6-(1-*cyanoethylidene*) *derivative* 7

The reduction of the 6-(1-cyanoethylidene) derivative 7 could be efficiently accomplished by the method of Corey and Watt[4,6] with magnesium in methanol. Hydrolysis of the reaction mixture with hydrochloric acid affords, in 83% yield, a mixture of all four possible diastereoisomeric ketones **8a**, **9a**, **10a** and **11a**. However, hydrolysis with ammonium chloride leads to a mixture of the corresponding ketals **8**, **9**, **10** and **11**.

Although the NMR spectrum of the mixture of diastereoisomeric ketones is quite complex, addition of $Eu(FOD)_3$ to the deuteriochloroform solution resolves it partially (Fig. 1) and the peaks of the angular Me group (singlet) and the Me group of the side-chain (doublet) of each of the four diastereoisomers are apparent, the estimated proportion of ketones **8a**, **9a**, **10a** and **11a** being, approximately, 1 : 1 : 1.4 : 1.1.[b] Even a provisional assignment of structures could be made at this stage.

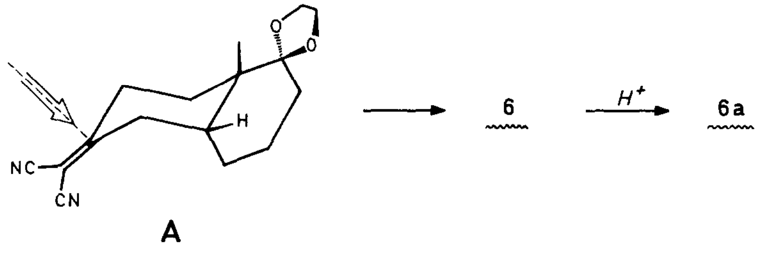
Owing to the different polarity of the diastereoisomeric ketones (a fact clearly related to the differential lanthanide induced NMR chemical shifts), chromatographic separation of the mixture on silica-gel led to two solid ketones, m.p. 66–68.5° and 81–83° (most probably the α isomers), followed by a mixture of the two other ketones (probably the β isomers).

Configurational assignments to these substances could be made on the basis of the previous studies done with the 6-dicyanomethyl derivatives, **5a** and **6a**, and $Eu(FOD)_3$ in deuteriochloroform solution.

The plot of the induced shifts ($\Delta\delta$) on the angular Me group and the side-chain Me group vs equivalents of $Eu(FOD)_3$ added, gives straight lines, the slopes of which (Table 1) allow to assign configuration **10a** to the ketone m.p. 66–68.5°, and configuration **11a** to the ketone m.p. 81–83°, the unresolved mixture being the two possible β isomers, **8a** and **9a**.[c]

EXPERIMENTAL

M.ps have been determined with a Kofler hot-stage and are uncorrected. IR spectra were recorded on a Perkin-Elmer Spectrophotometer, Model 720, and NMR spectra on a Perkin-Elmer Spectrometer, Model R-12A. Chemical shifts are given in ppm relative to TMS (δ scale).



Scheme 3.

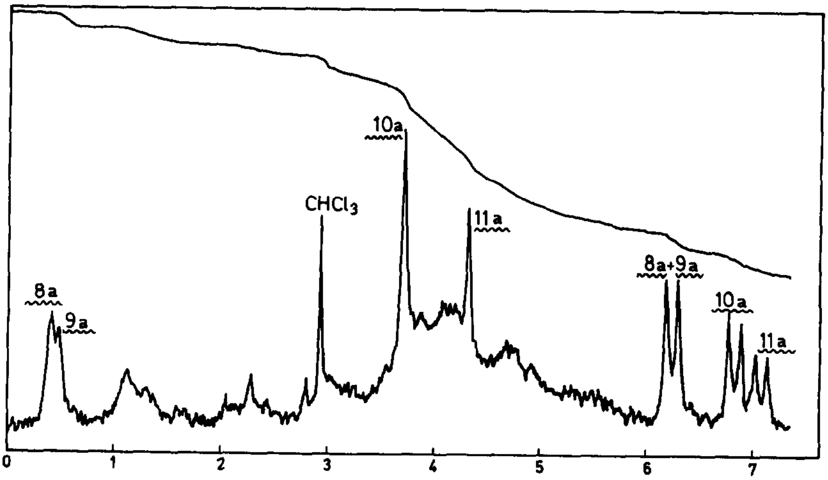


Fig. 1. 60 MHz NMR spectrum of the crude mixture of diastereoisomeric ketones **8a**, **9a**, **10a** and **11a** in the presence of 0.87 equiv $Eu(FOD)_3$, in deuteriochloroform solution.

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[b] Although the 6-(1-cyanoethylidene) derivative 7 is actually a mixture of *E* and *Z* isomers, notice that the final proportion of the four reduced diastereoisomeric ketones is independent of the original proportion of isomers.

[c] Although the distinction between ketone **10a** and **11a** from the shift data is not strictly unequivocal, examination of the molecular models shows that the methyl group of the side-chain of ketone **10a** is—on the average of all possible rotational isomers—closer to the Eu complex than in the isomeric ketone **11a**, and therefore the induced shift (Fig. 1) and the slope of the corresponding line (Table 1) should be greater in the former product.

6 - *Dicyanomethylidene* - 1,1 - *ethylenedioxy* - 8a - *methyl* - cis - *perhydronaphthalene*, 4

To a soln of 3[1,2] (2.24 g; 10 mmol) and malononitrile (0.66 g; 10 mmol) in 10 ml CH_2Cl_2, 8 drops of piperidine were added and the mixture refluxed for 18 hr. The mixture was then diluted with CH_2Cl_2, washed with water and sat. $NaHCO_3$aq, and dried. Elimination of the solvent under vacuum gave 2.66 g of an oily product that crystallized on standing. Recrystallization from EtOH gave 2.28 g (80% yield) of 4, m.p. 127–128°; IR (CCl_4), 2270 and 1590 cm^{-1}; NMR ($CDCl_3$), 1.03 (s) (3H, angular Me) and 3.74 (s) (4H, ethylenedioxy) (Found: C, 70.54; H, 7.68; N, 10.07. $C_{16}H_{20}N_2O_2$ requires: C, 70.56; H, 7.40; N, 10.29%).

6 - *Dicyanomethylidene* - 8a - *methyl* - 1 - *oxo* - cis - *perhydronaphthalene*, 4a

To a soln of 4 (1.92 g; 7 mmol) in 12 ml hot MeOH, 35 ml water and a trace of *p*-toluenesulfonic acid were added. The mixutre was refluxed for 4 hr and then extracted with chloroform. The combined chloroform extracts were washed with water, dried and the solvent removed under vacuum. The oily residue crystallized from EtOH to give 1.32 (81% yield) of 4a, m.p. 100–104°; IR (CCl_4), 2270, 1705 and 1600 cm^{-1}; NMR ($CDCl_3$), 1.38 (s) (3H, angular Me) (Found: C, 73.52; H, 7.28; N, 12.31. $C_{13}H_{16}N_2O$ requires: C, 73.66; H, 7.06; N, 12.27%).

Reduction of 6 - *dicyanomethylidene* - 1,1 - *ethylenedioxy* - 8a - *methyl* - cis - *perhydronaphthalene to* 6α - *dicyanomethyl* - 1,1 - *ethylenedioxy* - 8aβ - *methyl* - cis - *perhydronaphthalene*, 6

(A) *With sodium borohydride.* To a stirred, ice-cooled, suspension of 4, (541 mg; 2 mmol) in 30 ml abs. EtOH, $NaBH_4$ (22.8 mg) was added in small portions. The mixture was cooled and stirred for a further 1 hr, until all products were dissolved. The EtOH was removed under vacuum and the residue treated with sat. NH_4Claq. The aqueous soln was extracted with ether, the combined ether extracts washed with water, dried and the solvent removed under vacuum. The resulting oily residue (537 mg) was chromatographed over alumina and eluted with CH_2Cl_2 to give 359 mg (66% yield) of 6 as a colorless oil which crystallized from cold hexane, m.p. 67–71°. Alternatively, the oily product could be evaporatively distilled at 200°/1 Torr; IR (CCl_4), the C≡N st band is not apparent; NMR (CCl_4), 1.08 (s) (3H, angular Me), 3.54 (d, J = 4 Hz) (1H, methine) and 3.80 (s) (4H, ethylenedioxy) (Found: C, 70.26; H, 8.41; N, 10.44. $C_{16}H_{22}N_2O_2$ requires: C, 70.04; H, 8.08; N, 10.21%).

(B) *With aluminum amalgam.* To a stirred suspension of Al amalgam (prepared from 1 g Al, according to Ref. 7) in 25 ml wet ether, 4 (385 mg; 1.4 mmol) was added. After stirring for a further 2 hr, a few drops of water were added and the mixture stirred until all the metal was consumed. The soln was filtered, the ppt washed with ether and the ether soln dried. Elimination of the solvent gave a residue (383 mg) which was partially dissolved in hexane and chromatographed through alumina to give 90 mg of the α isomer (spectral evidence) as a colorless oil, from which 38 mg of crystals, m.p. 62–64°, were separated, identical with the product obtained from the sodium borohydride reduction.

6α - *Dicyanomethyl* - 8aβ - *methyl* - 1 - *oxo* - cis - *perhydronaphthalene*, 6a

To a soln of 6 (1.84 g; 6.7 mmol) in 30 ml MeOH, 100 ml 0.1N HCl was added and the mixture refluxed for 5 hr. The mixture was diluted with ether, the aqueous layer was separated and extracted with ether. The combined ether extracts were washed with water and $NaHCO_3$ aq, dried and the solvent removed under vacuum. The residue (1.4 g, 89.5% yield) was recrystallized from CCl_4 to give 6a, m.p. 93.5–95.5°. Alternatively, the product was purified by evaporative distillation at 250°/1 Torr; IR (CCl_4), 2280 and 1710 cm^{-1}; NMR ($CDCl_3$), 1.27 (s) (3H, angular methyl) and 3.55 (d, J = 6 Hz) (1H, methine) (Found: C, 73.07; H, 8.12; N, 12.26. $C_{14}H_{18}N_2O$ requires: C, 73.01; H, 7.88; N, 12.16%).

Reduction of 6 - *dicyanomethylidene* - 8a - *methyl* - 1 - *oxo* - cis - *perhydronaphthalene to* 6β - *and* 6α - *dicyanomethyl* - 8aβ - *methyl* - 1 - *oxo* - cis - *perhydronaphthalane*, 5a *and* 6a

(A) *With solium borohydride.* To a stirred, ice-cooled, soln of 4 (100 mg; 0.44 mmol) in 7 ml abs. EtOH, $NaBH_4$ (4.4 mg) was added and the mixture stirred for 1 hr. The solvent was removed under vacuum, the residue neutralized with sat. NH_4Cl aq and the aqueous soln extracted with chloroform. Elimination of the solvent under vacuum gave a 3:1 mixture of α and β isomers, together with starting material (spectral evidence), which was purified and partially enriched by TLC on silica-gel to a 3:2 mixture of isomers (35 mg).

(B) *Catalytic hydrogenation with* Pd–C (10%). To a soln of 4a (255 mg; 1.18 mmol) in 35 ml MeOH, 10% PdC (33.75 mg) was added and the mixture hydrogenated at atmospheric pressure until 20% excess (34.5 ml) of H_2 was absorbed.

The crude hydrogenation product was identified by spectroscopic techniques as a 2.5:1 mixture of the β and α isomers, which was then purified by TLC on silica-gel to give 75 mg of a 10:1 mixture of the isomers (5a and 6a).

The pure β isomer was isolated by ketalization of the mixture with MED, purification by chromatography and recrystallization, and hydrolysis back to the free ketone as described below.

The 10:1 mixture of isomer (258 mg; 1.12 mmol), from several batches, was shaken overnight at room temp. with 774 mg of MED and a trace of *p*-toluenesulfonic acid. After the usual work up the crude product was chromatographed on alumina and eluted with CH_2Cl_2. The first fraction, 149 mg, was recrystallized four times from hexane to give 5, m.p. 92–94°; NMR (CCl_4), 0.98 (s) (3H, angular methyl), 3.41 (d, J = 5.3 Hz) (1H, methine) and 3.86 (s) (4H, ethylenedioxy) (Found: C, 70.28; H, 7.88; N, 10.55. $C_{16}H_{22}N_2O_2$ requires : C, 70.04; H, 8.08; N, 10.21%).

The ketal 5 (60 mg; 0.22 mmol) was refluxed for 5 hr with 3.5 ml of 0.1N HCl and a few drops of MeOH. After the usual work up, the residue (50 mg, 100% yield) was recrystallized twice from CCl_4 to give 5a, m.p. 132.5–135.5°; IR (CCl_4), 2300 and 1710 cm^{-1}; NMR ($CDCl_3$), 1.23 (s) (3H, angular Me) and 3.68 (d, J = 5.3 Hz) (1H, methine) (Found: C, 72.26; H, 8.20; N, 11.48. $C_{14}H_{18}N_2O$ requires: C, 73.01; H, 7.88; N, 12.16%).

(E) - *and* (Z) - 6 - (1 - *cyanoethylidene*) - 1,1 - *ethylenedioxy* - 8a - *methyl* - *cis* - *perhydronaphthalene*, 7

To NaH (1.68 g; 70 mmol) in 65 ml anhyd. DME, a soln of 2 - diethylphosphonopropionitrile[8] (13.42 g; 70 mmol) in 65 ml anhydrous DME was slowly added. After stirring the mixture for 1 hr, the formation of the white phosphonate salt was judged complete by the absence of gas evolution, and 3 (5.23 g; 23 mmol) in 50 ml anhyd. DME was added. The mixture was stirred for 25 hr at room temp. during which time the precipitated phosphonate slowly dissolved. The product was poured into 900 ml water and extracted with ether, The combined ethereal extracts were washed successively with water and sat. NH_4Cl aq, and dried. The solvents were evaporated to afford an oily residue that crystallized spontaneously, and it was then recrystallized from EtOH to give 5 (4.28 g; 71% yield) as a mixture of *E* and *Z* isomers, m.p. 96–98°; IR (CCl_4), 2230 and 1637 cm^{-1}; NMR ($CDCl_3$), 1.10 (s) (3H, angular Me), 1.90 (s) (broad) (3H, side-chain methyl), and 3.93 (s) (4H, ethylenedioxy) (Found: C, 73.49; H, 8.77; N, 5.39. $C_{16}H_{23}NO_2$ requires: C, 73.52; H, 8.87; N, 5.36%).

Reduction of (E) - *and* (Z) - 6 - (1 - *cyanoethylidene*) - 1,1 - *ethylenedioxy* - 8a - *methyl* - cis - *perhydronaphthalene*[4,6]

To a stirred soln of 7 (105 mg; 0.42 mmol) as a mixture of *E* and *Z* isomers in 6 ml anhyd. MeOH, Mg (410 gm; 16.88 g-atoms) was added. After an induction period of approximately 1 hr a vigorous reaction followed which required frequent cooling in an ice bath. The mixture was stirred overnight during which time most of the Mg was consumed, and a gelatinous white ppt was formed.

The mixture was then treated with 10 ml 5N HCl[d] and the aqueous soln extracted with ether. The combined ethereal extracts were successively washed with water and $NaHCO_3$ aq, and dried. The solvents were evaporated to afford 73 mg (83% yield) of an

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[d] Hydrolysis with a solution of ammonium chloride led to a mixture of the corresponding ketals.

oily mixture of four diastereoisomeric ketones **8a**, **9a**, **10a** and **11a** in the proportion 1:1:1.4:1.1 (Fig. 1); IR (CCl_4), 2275 and 1708 cm^{-1}.

Chromatography on silica-gel of 738 mg of the diastereoisomeric mixture (from several batches) and elution with a 3:2 mixture of hexane:ether, and re-chromatography of the middle fractions, gave:

(1) 171 mg of ketones **10a**, m.p. 66–68.5° (from hexane): IR (CCl_4), 2275 and 1710 cm^{-1}; NMR ($CDCl_3$), 1.26 (s) (3H, angular Me) and 1.30 (d, $J = 6.7$ Hz) (3H, side-chain methyl) (Found: C, 76.73; H, 9.43; N, 6.48. $C_{14}H_{21}NO$ requires: C, 76.67; H, 9.65; N, 6.39%).

(2) 57.1 mg of ketone **11a**, m.p. 81–83° (from hexane); IR (CCl_4), 2275 and 1710 cm^{-1}; NMR ($CDCl_3$), 1.21 (s) (3H, angular Me) and 1.23 (d, $J = 6.7$ Hz) (3H, side-chain methyl) (Found: C, 76.76; H, 9.30; N, 6.69. $C_{14}H_{21}NO$ requires: C, 76.67; H, 9.65; N, 6.39%).

(3) 125 mg of ketones **8a** and **9a**, evaporatively distilled at 190°/0.3 Torr; IR (CCl_4), 2250 and 1710 cm^{-1}; NMR ($CDCl_3$), 1.16 (s) (3H, angular Me) and 1.28 (d, $J = 6.7$ Hz) (3H, side-chain methyl) (Found: C, 76.52; H, 9.31; N, 6.38. $C_{14}H_{21}NO$ requires: C, 76.67; H, 9.65; N, 6.39%).

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