Monatshefte für Chemie 126, 1011–1019 (1995)

Monatshefte für Chemie
Chemical Monthly
© Springer-Verlag 1995
Printed in Austria

Synthesis and Stereochemistry of 8-Methyl-5-nitro-1-octalones

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Summary. Base catalyzed *Michael* addition of 5-nitropentan-2-one ethylene ketal (**1**) and cyclohex-2-enone (**2**), subsequent deprotection, and intramolecular aldol condensation yields the 8-methyl-5-nitro-1-octalone isomers (**5a, b**). The structure, relative configuration, and conformation of **5a** and **5b** were elucidated utilizing the results of ^{1}H and ^{13}C NMR investigations

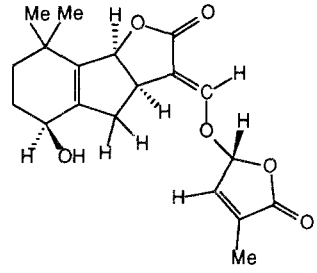
Keywords. Precursors of strigol analogues; *Michael* reaction; NMR; Molecular modelling.

Synthese und Stereochemie von 8-Methyl-5-nitro-octalonen

Zusammenfassung. Basenkatalysierte *Michael*-Addition von 5-Nitropentan-2-on-ethylenketal (**1**) und Cyclohex-2-enon (**2**), anschließende Entfernung der Schutzgruppe und darauffolgende Aldolkondensation liefert isomer 8-Methyl-5-nitro-1-octalone (**5a, b**). Struktur, relative Konfiguration und Konformation von **5a** und **5b** wurden mittels ^{1}H- und ^{13}C-NMR-Spektroskopie aufgeklärt.

Introduction

Recently, we have presented a reasonable synthetic route for the preparation of 1-oxohydrindene acetic acid which serves as a precursor to the germination stimulant strigol [1, 2] (Scheme 1), making use of the one-pot cyclization of 5-nitro-



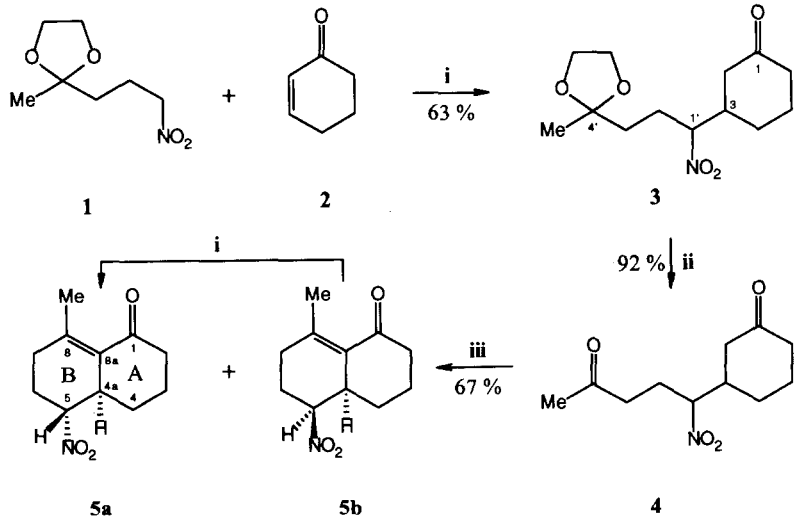
Scheme 1. Strigol

pentan-2-one and 5,5-disubstituted cyclopent-2-enone derivatives [3]. With the aim to extend the method toward strigol analogues, we were interested in the nitropentanone annulation with cyclohex-2-enone derivatives. In this paper we report the results of the model reaction with cyclohex-2-enone. The stereochemistry of the products thus prepared is also discussed.

Results and Discussion

Synthesis

The base catalyzed (*t*BuOK, *t*BuOH) *Michael* reaction of 5-nitro-pentane-2-one and the subsequent intramolecular aldol condensation of the adduct gave the desired products (**5a,b**) in moderate yield. The reaction can be carried out with a rather improved result if a protected nitropentane derivative (**1**) is applied (Scheme 2). Thereby we obtained **5a,b** as a mixture of *trans* and *cis* isomers (ratio 3:2) in three steps, however, with a better overall yield. The stereogenic centers are formed in the first step of the reaction and epimerization takes place only to a negligible degree during the acidic conditions applied. Thus, the diastereomeric ratio of the *Michael* adduct (**3**) can be deduced from the diastereomeric ratio of the final products (**5**). To prove this, the separated crystallic nitro-ketal **3** was deprotected. On the basis of the NMR spectra, we found that no epimerization occurs during this reaction step. Subsequently, the ring closure was carried out, the *cis* nitro-octalone was obtained as a product with 85% isomeric purity (NMR spectra). It can be concluded that the starting *Michael* adduct has the relative configuration 4a*R**,5*S**. This means that the *Michael* addition does not afford any stereoselectivity. Otherwise, the nitro-octalone isomeric mixture can be transformed into the thermodynamically more stable *trans* isomer (4a*R**,5*R**) in the presence of base (*t*BuOK, *t*BuOH) which is the best procedure to prepare *trans* nitro-octalone (**5a**) selectively. The structure and relative configuration of the products were elucidated by NMR studies.



Scheme 2. Reaction route

Stereochemical analysis

Characteristic ^1H chemical shifts of isomers **5a** and **5b** are summarized in Table 1. In order to differentiate the isomers of **5**, the protons of ring B were assigned α and β symbols, indicating their positions below and above the reference plane of the rings, respectively. Although the compounds are racemates, the structural formulae show only one enantiomeric series in each case (with H-4a in α position, *i.e.* C-4a is *R**). The determination of the isomers is rendered more difficult by the conformational flexibility of the $\Delta^{8(8a)}$-octalone skeleton. Therefore, different conformational equilibria should be taken into account (Scheme 3). The conformational analysis is based mainly on the vicinal proton–proton coupling constants which are obtained from the 500 MHz NMR spectra by a first-order approach (Table 2). In the case of both isomers of **5**, similarly to the previously examined 2,2-disubstituted analogous compounds [4], the predominance of the chair conformer for ring A is proven by $^3J = 11.5–13.0$ Hz of the trans positioned vicinal protons (H_{ax}-2,H_{ax}-3; H_{ax}-3,H_{ax}-4; H_{ax}-4,H-4a). A further support of the chair conformation follows from the appearance of an allylic coupling of 2 Hz between the diequatorial H-2 and H-4 protons. On the basis of these data, the conformation of compound **5** can be characterized by an equilibrium envelope-1⇌envelope-2⇌boat. It should be mentioned that the envelope conformation, which requires five coplanar atoms, is merely an approximation, as suggested by molecular models and semiempirical calculations. The introduction of the previously mentioned α, β notations for the B ring is especially required by the fact that inversion of this ring interconverts the axial and equatorial positions.

For **5a**, $J_{H\text{-}5,H_\alpha\text{-}6} = 12.4$ Hz suggests an antiperiplanar arrangement of these two protons; this can only be achieved in the envelope-1 conformer. In the envelope-2, the corresponding dihedral angle would amount to *ca.* 60°, whereas in the boat conformer a dihedral angle of 120° is to be expected. In both cases a coupling constant of 3–5 Hz would be required. Considering the small value of $J_{H_\beta\text{-}6,H_\alpha\text{-}7}$ (3.0 Hz), we can conclude that the envelope-2 as well as the boat

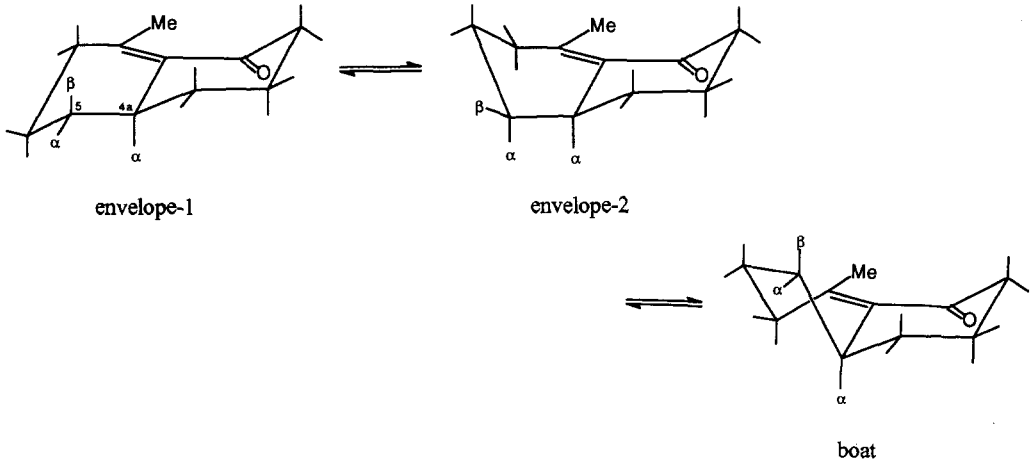
Table 1. ^1H chemical shifts of compounds **5**

	5a	**5b**
H_{ax}-2	2.32	2.35
H_{eq}-2	2.55	2.53
H_{ax}-3	1.76	1.80
H_{eq}-3	2.05	2.02
H_{ax}-4	1.49	1.61
H_{eq}-4	2.00	1.77
H-4a	3.01	2.94
H-5	4.45	4.81
H_α-6	2.13	2.08
H_β-6	2.25	2.21
H_2-7	2.32–2.42	2.24–2.35
CH_3-8	1.91	1.95

Table 2. $J_{H,H}$ and dihedral angles of compounds **5**

	5a			**5b**
	J(Hz)	Φ^1(°)	Φ^2(°)	J(Hz)
$^2J_{H_2\text{-}2}$	15.5			15.6
$^2J_{H_2\text{-}3}$	12.8			11.5
$^2J_{H_2\text{-}4}$	12.8			11.5
$^2J_{H_2\text{-}6}$	12.4			13.5
$^3J_{H_{ax}\text{-}2,H_{ax}\text{-}3}$	12.8	194	189	11.5
$^3J_{H_{ax}\text{-}2,H_{eq}\text{-}3}$	6.3	316	307	6.1
$^3J_{H_{eq}\text{-}2,H_{ax}\text{-}3}$	4.6	52	52	4.5
$^3J_{H_{eq}\text{-}2,H_{eq}\text{-}3}$	3.0	60	65	4.5
$^3J_{H_{ax}\text{-}3,H_{ax}\text{-}4}$	12.8	169	176	11.5
$^3J_{H_{ax}\text{-}3,H_{eq}\text{-}4}$	3.5	57	58	4.5
$^3J_{H_{eq}\text{-}3,H_{ax}\text{-}4}$	3.5	57	58	4.5
$^3J_{H_{eq}\text{-}3,H_{eq}\text{-}4}$	3.5	303	300	4.5
$^3J_{H_{ax}\text{-}4,H\text{-}4a}$	12.8	180	184	13.0
$^3J_{H_{eq}\text{-}4,H\text{-}4a}$	4.0	303	301	4.5
$^3J_{H\text{-}4a,H\text{-}5}$	9.8	155	164	5.8
$^3J_{H\text{-}5,H_\alpha\text{-}6}$	12.4	180	181	3.9
$^3J_{H\text{-}5,H_\beta\text{-}6}$	3.4	305	298	7.8
$^3J_{H_\alpha\text{-}6,H_\alpha\text{-}7}$	6.8	41	51	6.5
$^3J_{H_\alpha\text{-}6,H_\beta\text{-}7}$	10.8	152	169	6.5
$^3J_{H_\beta\text{-}6,H_\alpha\text{-}7}$	3.0	300	293	7.8
$^3J_{H_\beta\text{-}6,H_\beta\text{-}7}$	6.0	45	50	6.0
$^4J_{H_{eq}\text{-}2,H_{eq}\text{-}4}$	2.0			1.5
$^5J_{H\text{-}4a,CH_3\text{-}8}$	2.2			2.1

Φ^1: dihedral angles from AM1 calculations; Φ^2: dihedral angles calculated from the coupling constants applying the modified *Karplus* equation



Scheme 3. Conformational equilibrium

conformers can be neglected because of the *trans* diaxial arrangement of these two protons. The α position of the NO_2 group and the predominance of envelope-1 in **5a** are also in accordance with the value of $J_{H\text{-}4a,H\text{-}5}$ (9.8 Hz). A characteristic homoallylic coupling of 2 Hz between CH_3-8 and H-4a was observed for both **5a** and **5b**.

In the *cis* isomer (**5b**, with the nitro group in β position), the splitting pattern of H-5 ($J_{H\text{-}5,H_\beta\text{-}6} = 7.8$ Hz, $J_{H\text{-}5,H_\alpha\text{-}6} = 3.9$ Hz, and $J_{H\text{-}4a,H\text{-}5} = 5.8$ Hz) suggests that the envelope-2 conformer appears in a significant quantity beside envelope-1. Thus, H-5 and H_β-6 are in diaxial arrangement in the former conformer, increasing the average value of the coupling constant to 7.8 Hz, characteristic for the conformational equilibrium. In the boat conformer, H-5 and H_α-6 are eclipsed and show a coupling constant of *ca.* 10 Hz. AM1 (Mopac-6, version 1990) [5] calculations on the conformations of **5a** showed that the envelope-1 conformer is by 2.4 kcal/mol more stable than envelope-2. The dihedral angles of envelope-1 obtained from the semiempirical calculations are in accordance with those calculated from the coupling constants by applying the modified *Karplus* equation [6] (Table 2). AM1 calculations of **5b** revealed that envelope-1 and envelope-2 differ by 0.1 kcal/mol. Using the *Karplus* equation to calculate $J_{H\text{-}5,H_\beta\text{-}6}$ in envelope-1 and envelope-2 yields 3.4 Hz and 11.7 Hz, respectively. Therefore, the population of the two conformers should be nearly equal in the conformational equilibrium.

The chemical shift and the multiplicity of H-5 allowed an easy distinction of the two isomers. In the case of **5a**, the H-5 signal is shifted upfield by *ca.* 0.4 ppm.

The ^1H and ^{13}C signal assignments (Table 3) were corroborated by 2D TOCSY [7] (Fig. 1), 1D NOE [8] (Table 4), and HMQC [9] (Fig. 2) experiments. TOCSY measurements with a short mixing time (20 msec) were used, showing correlations for geminal and vicinal protons only. In the case of **5b**, the signal assignment of H_α-6 was also supported by a 1D NOE experiment which revealed the steric proximity of H-4a and H_α-6.

In the ^{13}C NMR spectra of isomers **5a** and **5b**, the chemical shifts C-5 differ considerably (88.3 and 83.7, respectively). In the latter isomer, a significant

Table 3. ^{13}C chemical shifts of compounds **5**

	5a	5b
C-1	201.5	202.5
C-2	42.0	41.7
C-3	22.2	22.3
C-4	28.9	26.1
C-4a	42.1	39.9
C-5	88.3	83.7
C-6	26.9	23.2
C-7	31.6	30.2
C-8	142.8	141.8
C-8a	130.2	130.3
CH_3-8	21.2	20.9

Table 4. Results of 1D NOE measurements for compounds **5**

	Irradiated proton	Observed NOE (%)
5a[a]	H-4a	H_{eq}-4 (2.5); H-5 (1.6)
	H-5	H_{ax}-4 (3.7); H-4a (4.0); H_{γ}-6 (1.2); H_{β}-6 (4.9); H_{α}-7 (1.6)
5b	H-4a	H_{ax}-3 ($\sim$1.5); H_{eq}-4 ($\sim$3.0); H-5 (4.6); H_{α}-6 (2.0)

[a] Measured at 250 MHz

deshielding appears with the signals assigned to the carbon atoms in β and γ position to the nitro group.

For both isomers, δ(C-1) = 202 ppm refers to a moderate conjugation. In the case of the previously examined 2,2-disubstituted analogous compounds [4], δ(C-1) amounted to 198 ppm, corresponding to an increased conjugation due to ring

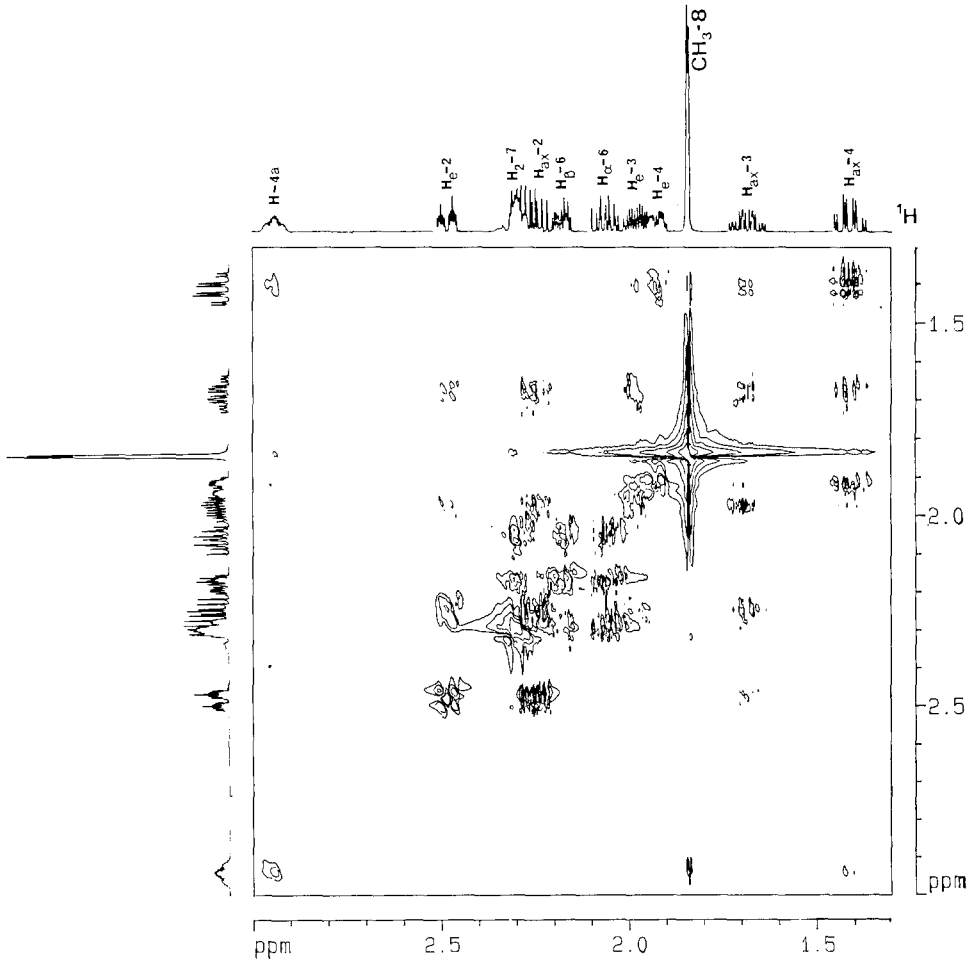


Fig. 1. 2D TOCSY spectrum of **5a**

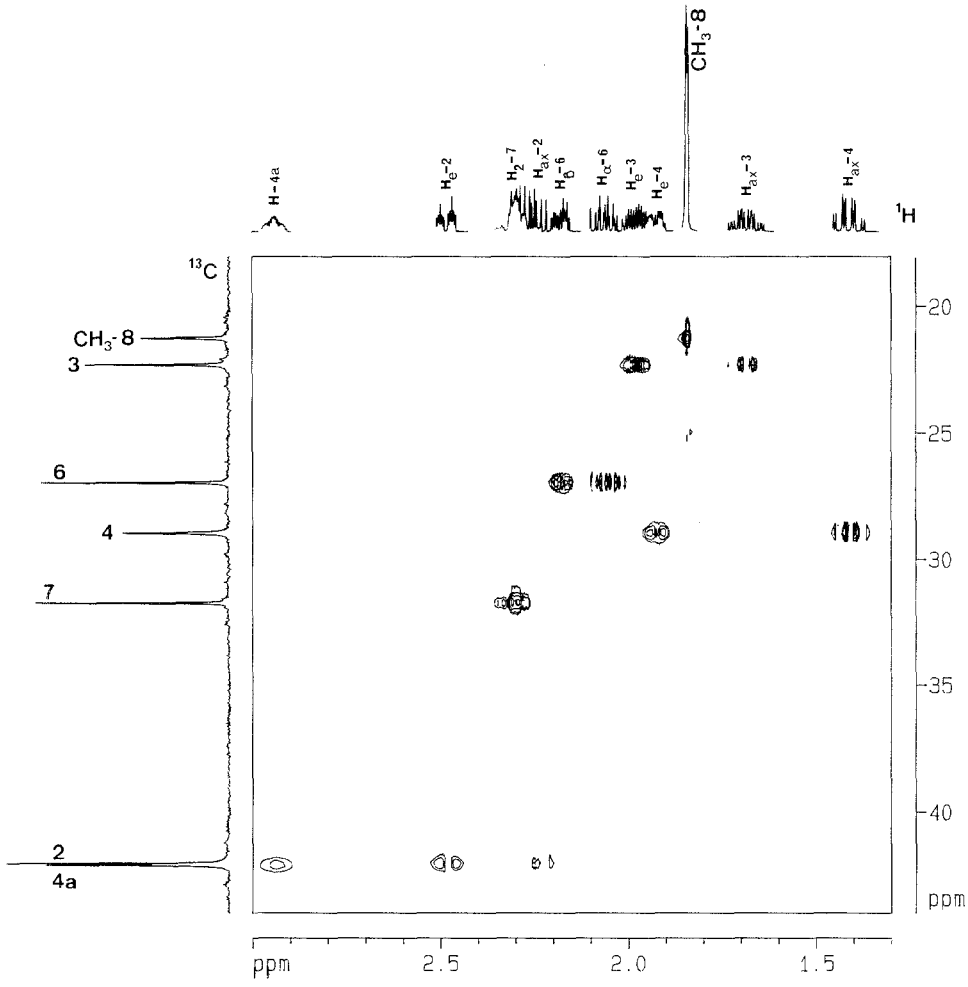


Fig. 2. HMQC spectrum of **5a**

flattening caused by the axial C-2 substituent. In the ^{13}C NMR spectra of **5**, the above mentioned decrease of δ(C-1) does not occur.

The nearly coplanar arrangement of C=C and C=O double bonds in the boat conformer (Scheme 3) should result in an extended conjugation and an upfield shift of C-1. This was not observed for compounds **5a** and **5b**. The downfield shift of protons located in the plane of the C=O group as a result of the anisotropy of the carbonyl group is well known [10]. Considering the similar chemical shifts of CH_3 in both isomers, we can conclude that the ratio of the boat conformer in **5b** is also negligible.

Experimental

Synthesis

3-(4,4-Ethylenedioxy-1-nitro-pent-1-yl)-cyclohexan-1-one (**3**)

A solution of 5-nitropentan-2-one ethylene ketal (**1**, 7 g, 40 mmol) and cyclohex-2-enone (**2**, 3.8 g, 40 mmol) in *t*BuOH (40 ml) was treated with *t*BuOK (0.45 g, 4 mmol) in *t*BuOH (20 ml). The mixture

was stirred at 60 °C in a nitrogen atmosphere for 6 h. Then it was cooled, diluted with ether (60 ml) and washed successively with 0.1 *M* HCl and satd. NaCl solution. The aqueous washings were extracted twice with ether and the collected organic layers were dried over $MgSO_4$. The solvents were evaporated in vacuum to give the *Michael* adduct **3** as a dense yellow oil which was purified by column chromatography over silica gel (eluent hexane:ethyl acetate 1:3). Yield 6.8 g (25.2 mmol, 63%).

From the diastereomeric mixture, one isomer (**3b**) was obtained pure on trituration with cold ether. M.p.: 74–76 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.15 (3H, s, CH_3) 3.91 (4H, m, $(OCH_2)_2$), 4.35 (1H, m, H-1′), 0.96–2.52 (13H, m, all other protons); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 22.4 (C-2′), 24.5 (C-5), 27.5 (C-4), 30.0 (CH_3), 34.6 (C-3′), 37.4 (C-6), 39.1 (C-2), 39.2 (C-3), 64.3 ($(OCH_2)_2$), 92.4 (C-1′), 108.2 (C-4′), 206.4 (C-1); IR (KBr): ν = 1724, 1560, 1460, 1385, 1265, 1240, 1065 cm^{-1}.

3-(1-Nitro-4-oxo-pent-1-yl)-cyclohexan-1-one (**4**)

The Michael adduct **3** (6.7 g, 25 mmol) was dissolved in a mixture of *THF* (100 ml) and 5% aq. HCl (50 ml); the resulting solution was stirred at ambient temperature for 24 h. Removal of *THF* gave two layers which were separated. The aqueous phase was then thoroughly extracted with ether. The collected ethereal phases were dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel (eluent hexane-ethyl acetate (1:1)) to yield diketone **4** (5.2 g, 23.2 mmol, 92%). Starting from the crystalline diastereomer **3b**, we obtained the pure diastereomer **4b**. ^{1}H NMR (100 MHz, $CDCl_3$): δ = 2.16 (3H, s, CH_3), 4.44 (1H, m, H-1′), 2.00–2.60 (13H, m, all other protons); ^{13}C NMR (25 MHz, $CDCl_3$): δ = 23.8 (C-5), 26.8 (C-4), 29.5 (CH_3), 38.4 (C-3′), 40.3 (C-6), 40.8 (C-2), 41.4 (C-3), 91.3 (C-1′), 205.9 (C-1), 208.0 (C-4′); IR (film): ν = 1725, 1560, 1380 cm^{-1}; MS (EI): *m/z* (%) = 227 (1.3, M^+), 181 (28), 123 (72), 95 (14), 67 (20), 55 (28), 43 (100), 41 (32), 38 (14).

8-Methyl-5-nitro-1-oxo-1,2,3,4,4a,5,6,7-octahydronaphthaline (**5**)

Diketone **4** (4.08 g, 17.97 mmol) was dissolved in toluene (120 ml). The mixture was refluxed in the presence of *p*-toluenesulfonic acid (0.3 g) for 4 h, water being removed with a *Dean-Stark* trap. Then it was washed with satd. NaCl solution, dried over $MgSO_4$, concentrated, and chromatographed on silica gel (eluent hexane-ether (1:9)). From the collected fractions 0.97 g of the crystalline *trans* isomer (**5a**), 0.35 g of the oily *cis* isomer (**5b**), and 1.21 g of a *ca.* 1:1 mixture were obtained. Yield: 2.53 g (12.09 mmol, 67.3%).

5a: M.p.: 54–56 °C; R_f = 0.53 (eluent hexane:ether 1:9); MS (EI): *m/z* (%) = 209 (31, M^+), 163 (25), 162 (100), 147 (35), 105 (19), 91 (34), 79 (18), 77 (18); IR (KBr): ν = 1678, 1605, 1544, 1371, 1275, 1126 cm^{-1}.

5b: R_f = 0.45 (eluent hexane:ether 1:9); IR (film): ν = 1680, 1610, 1540, 1440, 1420, 1370, 1250 cm^{-1}.

Isomerization of **5b** *to* **5a**

A diastereomeric mixture of **5** (0.36 g) in *t*BuOH (5 ml) was treated with *t*-BuOK (0.1 g) and refluxed for 3 h. Usual aqueous work-up afforded the pure *trans* isomer (0.29 g) which was crystallized from cold ether.

Spectra

NMR spectra were measured on Bruker AMX-500, AC-250 and Jeol Fx-100 spectrometers, respectively, at room temperature in $CDCl_3$. Chemical shift are given in ppm (^{1}H NMR: internal *TMS*; ^{13}C NMR: solvent resonance ($\delta(CDCl_3)$ = 77.0 ppm)). In the 1D measurements, 64k data points were used for the FID. In the case of the NOE measurements, an irradiation time of 3 s and a repetition time of 5 s were applied. For the 2D TOCSY and HMQC measurements, 4k × 512 data matrices were accumulated. IR spectra were measured on Specord 75 IR and Nicolet FT-IR instruments. Mass spectra were taken on a VG TRIO-2 spectrometer (EI model, 70 eV).

Acknowledgements

The authors are grateful to the *Hungarian Research Foundation* (OTKA Grant Ns. 1639 and F 7502) for financial support. They are also grateful to Prof. *H. Kessler* for helpful discussions. *G. T.* gratefully acknowledges a two months visiting fellowship of DAAD (Germany). *J. H.*, *G. A.*, and *K. M.* thank the *J. Varga Foundation* (Budapest, Hungary) for a fellowship.

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Received February 10, 1995. Accepted February 20, 1995