168. Deoxy-nitrosugars

5th Communication[1])

The Anomeric Effect of the Nitro Group

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Summary

The 1-deoxy-1-nitro-D-*manno*-pyranose **4** was transformed into the nitroolefin **5** and hence into the anomeric 1,2-dideoxy-1-nitro-3,4,6-tri-*O*-benzyl-D-*arabino*-hexopyranoses (**3a** and **3b**; *cf.* the *Scheme*). Conformational analysis of 1-benzyloxy-2-nitroethane (**6**) by ^{1}H-NMR spectroscopy *(Fig. 2)* showed the synclinal conformation to be more stable than the antiperiplanar one by about 1.4 kcal/mol (attractive *gauche*-effect). This *gauche*-effect favours the 1-deoxy-1-nitro-2,3,4,6-tetra-*O*-benzyl-*β*-D-*manno*-hexopyranose (**1b**) possessing an equatorial nitro group, which is, however, qualitatively the less stable anomer. The relative concentrations of the anomers of **1** and **3**, respectively, were determined by ^{1}H-NMR spectroscopy after base catalyzed equilibration at 37° in $CHCl_3$-solution *(Table)*. Anomeric effects for the nitro group of approximately 2.4 kcal/mol in **3** and of approximately 3.4 kcal/mol in **1** were calculated.

Introduction. – Protected and partially protected 1-nitro-1-deoxyaldoses are readily available and preparatively useful new sugar derivatives [1–3]. They anomerize under slightly acidic or basic conditions to yield predominantly the anomer with an axial nitro group [2], qualitatively indicating a normal anomeric effect (*cf.* [4–7]) of this group. We report now the first determination of the anomeric effect of the nitro group in the tetrabenzyl-*manno*-pyranoses **1** and in the corresponding 2-deoxypyranoses **3**[2]). The anomeric 1,2-dideoxy-1-nitropyranoses **3** were prepared by $NaBH_4$-reduction [8] of the 1-nitroglycal **5**, which was easily obtained by methanesulfonation of the known 2-hydroxy nitro-ether **4** [1] followed by *β*-elimination. Since the '*A*-value' (*cf.* [5] [9]) of the nitro group is known [17], the determination of the equilibrium between the anomers of **3** leads to the anomeric

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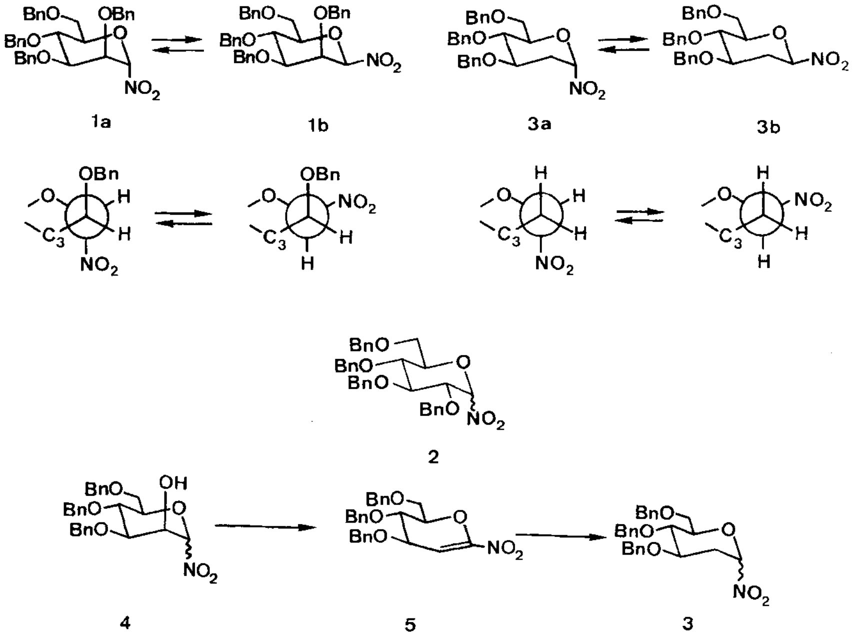
[1]) 4th Communication: [1].

[2]) The corresponding 1-deoxy-1-nitro-2,3,4,6-tetra-*O*-benzyl-D-glucopyranoses (**2**) decomposed partially in the course of the base-catalyzed anomerization [2].

effect of the nitro group in **3**. In the case of the tetrabenzyl-D-*manno*-pyranoses **1**, however, one must also consider the relative orientation of the 1-nitro and the 2-benzyloxy group, which are antiperiplanar in the α-D-anomer **1a** and synclinal in the β-D-anomer **1b** *(Scheme)*. A recent study of nitroalcohols has demonstrated that the synclinal conformation is qualitatively preferred [10], contradicting earlier suggestions [11]. In order to obtain quantitative results for the anticipated analogous preference for a synclinal orientation of the nitro- and the benzyloxy group we analyzed the conformations of 1-benzyloxy-2-nitroethane (**6**) obtained from benzyl alcoholate and nitroethylene.



Conformational Analysis of 1-Benzyloxy-2-nitroethane (*6*). – The vicinal H,H coupling constants in 1,2-disubstituted ethanes XCH_2CH_2Y can be used to determine the relative rotamer populations in these compounds. The conformers and coupling constants shown in *Fig. 1* are considered. The differentiation between

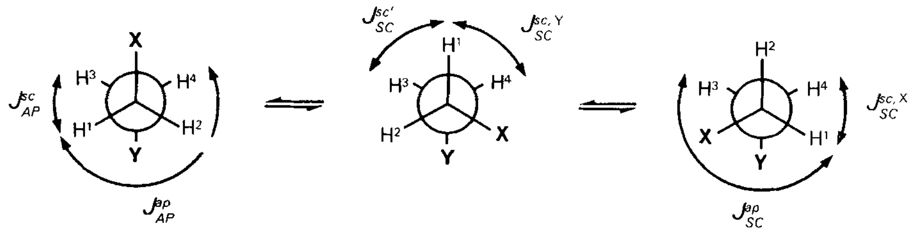


Fig. 1: *Coupling constants used in the conformational analysis of* **6** (*AP* (antiperiplanar) and *SC* (synclinal) refer to the groups X and Y, *ap* and *sc* to the H-atoms)

$J^{sc'}_{SC}$, $J^{sc,X}_{SC}$, and $J^{sc,Y}_{SC}$ takes into account the fact that the substituent effect on vicinal coupling constants, which depends on the electronegativity of substituents, is largest if they are in an antiperiplanar position [12] [13] to one of the coupled nuclei. For the observable coupling constants one obtains:

$$J(H^1,H^3) = n_{AP} \cdot J^{sc}_{AP} + n_{SC} \cdot \frac{1}{2}(J^{sc'}_{SC} + J^{ap}_{SC}) \qquad (1)$$

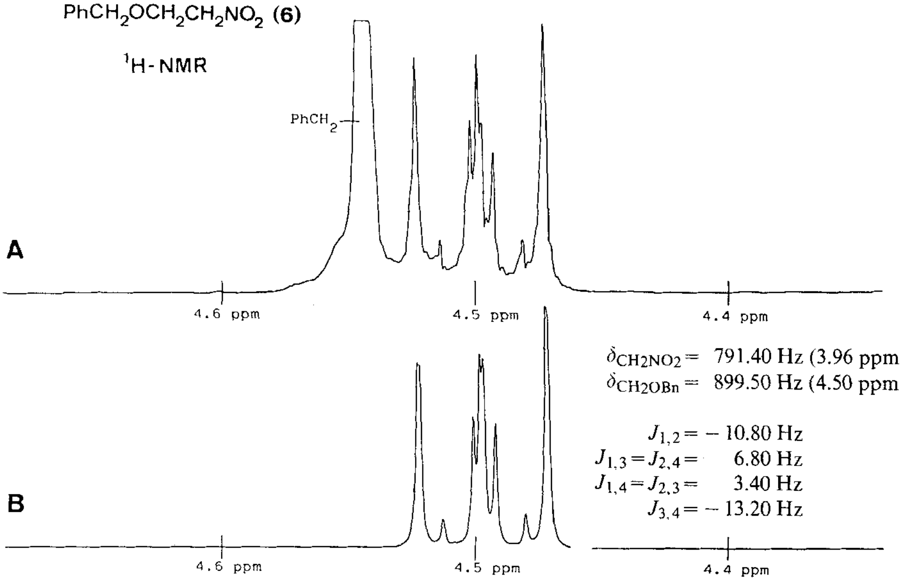
$$J(H^1,H^4) = n_{AP} \cdot J^{ap}_{AP} + n_{SC} \cdot \frac{1}{2}(J^{sc,Y}_{SC} + J^{sc,X}_{SC}), \qquad (2)$$

where n_{AP} and n_{SC} denote the *AP*- and *SC*-rotamer-populations, respectively ($n_{AP} + n_{SC} = 1$ and $n_{SC}/n_{AP} = 2 \cdot \exp\{(E_{AP} - E_{SC})/RT\}$). The application of *Equations 1* and *2* to the evaluation of n_{AP} requires knowledge of the coupling constants assigned to the fixed orientations of coupled nuclei and substituents. These coupling constants can be estimated through the set of equations derived by *Abraham & Gatti* [14] under the assumption that $J^{sc,X}_{SC} = J^{sc,Y}_{SC} = J^{sc}_{SC}$. Then we obtain:

$$J(H^1,H^3) = n_{AP}[1.35 + 0.63(E_X + E_Y)] + n_{SC}[13.46 - 1.02(E_X + E_Y)] \qquad (3)$$

$$J(H^1,H^4) = n_{AP}[18.07 - 0.88(E_X + E_Y)] + n_{SC}[8.94 - 0.94(E_X + E_Y)], \qquad (4)$$

with E_X, E_Y = electronegativity of X and Y according to *Huggins* [15]. Although *Eqn. 3* and *4* should provide the same value for n_{AP}, the value derived from $J(H^1,H^4)$ is generally preferred [16] since $J(H^1,H^4)$ is more strongly dependent on changes in rotamer populations than $J(H^1,H^3)$. The *Huggins* electronegativities for the substituents $PhCH_2O$ and NO_2, however, are not known, but the application of *Eqn. 3* and *4* allowed us to calculate $(E_X + E_Y)$ and n_{AP}.



δ_{CH2NO2} = 791.40 Hz (3.96 ppm)
δ_{CH2OBn} = 899.50 Hz (4.50 ppm)

$J_{1,2}$ = – 10.80 Hz
$J_{1,3} = J_{2,4}$ = 6.80 Hz
$J_{1,4} = J_{2,3}$ = 3.40 Hz
$J_{3,4}$ = – 13.20 Hz

Fig. 2. *200-MHz-^{1}H-NMR spectrum* ($CDCl_3$) *of the CH_2NO_2 group of* **6** *at 308 K.* A) experimental, B) calculated spectrum.

From ^{1}H-NMR spectrum of **6** at 200 MHz the values of chemical shifts and coupling constants were extracted by iterative analysis of the $AA'XX'$-type spectrum using a LAOCOON program *(Fig. 2)*. The assignment of $J_{AX} = 6.80$ Hz to $J(\mathrm{H}^1, \mathrm{H}^3)$ and $J_{AX'} = 3.40$ Hz to $J(\mathrm{H}^1, \mathrm{H}^4)$ is unambiguous in our case since the reverse assignment puts the 3.40 Hz coupling outside the calculated range *(Eqn. 3)* of $J(\mathrm{H}^1, \mathrm{H}^3)$. The correct assignment was confirmed by analyzing spectra taken at different temperatures. Solving *Eqn. 3* and *4* we obtained:

$$n_{AP} = 0.06\ (= 6\%),\ (E_\mathrm{X} + E_\mathrm{Y}) = 6.45$$[3]

The population analysis was also carried out by use of a *Karplus-Conroy*-type approximation[4] of the coupling constants contained in *Eqn. 1* and *2*. Varying the angle ∅ between the substituents X and Y from 60 to 65° we obtained a value of n_{AP} between 7 and 13%. A value for n_{AP} of $9 \pm 4\%$ was adopted for the calculation of the conformational free energy. This value covers the results of both approaches and does not overemphasize the attractive *gauche*-effect.

Equilibration of the Anomers. – Two samples each of **1** and **3**, characterized by different concentrations (C_0) of anomers were equilibrated in $CHCl_3$[5] at 37° in the presence of a weakly basic ion-exchange resin *(Amberlite IRA 193)*. The progress of equilibration was periodically checked by ^{1}H-NMR spectroscopy. The relative concentrations of the anomers at equilibrium (C_{eq}) were measured by integration of the H–C(1)-signals (200-MHz-^{1}H-NMR spectra; $\delta = 5.57$ ppm (**1a**); 5.17 ppm (**1b**); 5.58 ppm (**3a**) and 5.25 ppm (**3b**)), and the results are given in the *Table*.

Table. *Equilibration of* **1a, b** *and of* **3a, b**

Compound	C_0 (%) α-D : β-D	C_{eq} (%) α-D : β-D	$\Delta G°$ (kcal/mol)	Conditions (mg of compound/mg resin/time)
1	11.9 : 88.1	93.2 : 6.8	1.62	31/31/159 h
	> 95 : 5	94.0 : 6.0	1.70	48/48/159 h
3	48.2 : 51.8	91.7 : 8.3	1.48	65/65/370 h
	> 95 : 5	93.7 : 6.3	1.67	70/70/377 h

Calculation of the Anomeric Effect. – The anomeric effect of the nitro group in **3** is given by the sum of the 'A-value' of the nitro group and the $\Delta G°$-value characterizing the equilibrium between the α-D- and β-D-anomers [5] [7]. An 'A-value' of 0.78 kcal/mol for the nitro group has been determined by *Trager & Huitric* [17] by equilibration of 1-(*t*-butyl)-4-nitrocyclohexane under the same conditions as we have used for the equilibration of **1** and **3**. From the $\Delta G°$-values for the equilibrium

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[3] As a second mathematical solution one obtains $n_{AP} = 0.30$ and $(E_\mathrm{X} + E_\mathrm{Y}) = 13.31$ which is clearly outside the possible range of electronegativities.

[4] The following equation was used:
$J = J_0\ (1 + 0.83 \cos 2\theta - 0.17 \cdot \cos\theta)$; θ = dihedral angle between coupled protons.

[5] In $CDCl_3$ a partial H,D-exchange of H–C(1) occurred. The equilibration of **3** was discontinued after 377 h (slow decomposition). For details see *Exper. Part.*

3a$\rightleftharpoons$**3b** (1.48 and 1.67 kcal/mol, respectively; see the *Table*) one thus obtains an anomeric effect for the nitro group in **3** of 2.26 and 2.45 kcal/mol, respectively, *i.e.* of approximately 2.35 kcal/mol. The anomeric effect for the nitro group in **1** can be calculated only approximately since a small error in the conformer population of 1-benzyloxy-2-nitroethane is strongly reflected in the relative energy of the two conformers. The mean value $n_{AP} = 9 \pm 4\%$ for the antiperiplanar rotamer population corresponds to $\Delta G^{\circ 308\,K}_{(AP\text{-}SC)} = 1.42$ kcal/mol in favour of the synclinal conformers. Hence a free energy difference of 1 kcal/mol favouring the β-D anomer of **1** is deduced. From this value, the '*A*-value' of the nitro group and the $\Delta G°$-values for the equilibrium **1a**$\rightleftharpoons$**1b** ($\Delta G° = 1.62$ and 1.70 kcal/mol, respectively; see the *Table*) one obtains an anomeric effect of about 3.4 kcal/mol for the nitro group in **1**. The stronger anomeric effect of the nitro group in **1** is in keeping with the known influence on the anomeric effect of an (axial!) 2-alkoxy group [7] [18–20].

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Experimental Part

General Remarks. See [21].

3,4,6-Tri-O-benzyl-1,2-dideoxy-1-nitro-D-arabino-*hex-1-enopyranose* (**5**). To a solution of the crude 1-deoxy-1-nitromannose **4** [1] (obtained from 901 mg (2 mmol) of 3,4,6-tri-*O*-benzyl-D-mannose [22]) in 12 ml of anh. Et_2O were added at 0° 388 µl (5 mmol) of methanesulfonyl chloride and 1.11 ml (8 mmol) of Et_3N. The solution was warmed to r.t. and stirred for 45 min. TLC (AcOEt/toluene 1:9) showed the transformation of **4** (R_f 0.23) into a less polar product (R_f 0.58). The solution was poured into 20 ml of 1M $NaHCO_3$, and the org. layer was washed with brine, dried ($MgSO_4$) and concentrated. Chromatography of the yellow crude product on 100 g of silica gel (AcOEt/hexane 1:9) gave 538 mg (58%) of **5** as a pale yellow syrup, $[\alpha]_D = -1.9°$ ($c = 1.4$). IR: 3090*w*, 3060*w*, 3030*s*, 3010*m*, 2910*s*, 2870*m*, 1675*m*, 1548*s*, 1497*m*, 1454*m*, 1390*s*, 1365*m*, 1347*s*, 1340*s*, 1305*s*, 1290*m*, 1100*s* br, 1080*s*, 1029*s*, 910*w*, 871*w*. ^{1}H-NMR: 7.43-7.13 (*m*, 15 arom. H); 6.30 (*d*, $J = 3.3$, H−C(2)); 4.78, 4.63 (*AB*-syst., $J = 11.2$, $PhCH_2$); 4.68, 4.53 (*AB*-syst., $J = 11.2$, $PhCH_2$); 4.57 (*s*, $PhCH_2$); 4.4–4.25 (*m*, 2 H; irradiation at 6.3 ppm: 4.43, *ddt*, $J = 7.4$, 4.1, 0.7, H−C(3) and 4.32, *dd*, $J = 5.5$, 0.7, H−C(5)); 3.97 (*dd*, $J = 7.4$, 5.6, H−C(4)); 3.83 (*d*, $J = 4.1$, 2 H−C(6)). ^{13}C-NMR: 152.94 (*s*); 137.40 (*s*); 137.20 (*s*); 136.95 (*s*); 128.41 (*d*); 128.30 (*d*); 127.68 (*d*); 98.96 (*d*); 79.97 (*d*); 74.22 (*d*); 73.62 (*t*); 73.45 (*t*); 72.77 (*d*); 71.40 (*t*); 66.84 (*t*).

$C_{27}H_{27}NO_6$ (461.51) Calc. C 70.27 H 5.89 N 3.04% Found C 70.09 H 5.87 N 3.05%

3,4,6-Tri-O-benzyl-1,2-dideoxy-1-nitro-D-arabino-*hexopyranose* (**3**). A solution of 779 mg (1.69 mmol) of **5** in 3 ml of Et_2O and 12 ml abs. EtOH was treated at −15° with 95 mg (2.5 mmol) of $NaBH_4$. After 20 min, TLC (Et_2O/hexane 1:1) showed the transformation of **5** into two new products (R_f 0.37 and 0.32). The solution was neutralized with 600 µl (10 mmol) of AcOH diluted with Et_2O, extracted twice with aq. $NaHCO_3$, washed with brine, dried ($MgSO_4$) and concentrated. The resulting syrup was purified by flash-chromatography on 90 g of silica gel (Et_2O/hexane 1:4). Two fractions were isolated. The first one (R_f 0.37) contained 520 mg (66%) of the α-D anomer **3a**: $[\alpha]_D = +83.8°$ ($c = 1.2$). IR: 3090*w*, 3060*w*, 3030*s*, 3000*m*, 2930*s*, 2910*m*, 2870*m*, 1555*s*, 1495*w*, 1453*m*, 1442*s*, 1365*m*, 1355*s*, 1285*w*, 1170*m*, 1138*m*, 1100*s*, 1050*m*, 1028*m*, 950*w*, 910*w*. ^{1}H-NMR: 7.50–7.03 (*m*, 15 arom. H); 5.58 (*dd*, $J = 5.3$, 2.1, H−C(1)); 4.83, 4.50 (*AB*-syst., $J = 11.0$, $PhCH_2$); 4.63, 4.47 (*AB*-syst., $J = 11.9$, $PhCH_2$); 4.60 (*s*, $PhCH_2$); 4.27–3.95 (*m*, 1 H); 3.89–3.47 (*m*, 4 H); 2.88 (*ddd*, $J = 14.7$, 4.0, 2.1, H_{eq}−C(2)); 2.07 (*ddd*, $J = 14.7$, 10.7, 5.1, H_{ax}−C(2)). ^{13}C-NMR (CCl_4): 138.54 (*s*); 138.26 (*s*); 138.17 (*s*); 128.52 (*d*); 128.35 (*d*); 127.90 (*d*); 127.80 (*d*); 127.69 (*d*); 103.00 (*d*); 76.59 (*d*); 76.53 (*d*); 76.24 (*d*); 74.97 (*t*); 73.59 (*t*); 72.22 (*t*); 68.42 (*t*); 32.93 (*t*). MS (70 eV): 372 (8), 235 (9), 129 (14), 111 (8), 108 (15), 107 (31), 106 (11), 105 (16), 92 (30), 91 (100), 79 (20), 77 (24), 65 (24), 51 (11), 39 (9).

$C_{27}H_{29}NO_6$ (463.53) Calc. C 69.96 H 6.31 N 3.02% Found C 70.16 H 6.16 N 3.22%

The second fraction contained 69 mg (9%) of a 1:1 mixture of both anomers[6]). IR: 1568*s*, 1558*s*, 1310*w*; otherwise very similar to the IR spectrum of the α-D-anomer. ^{1}H-NMR: 7.50-7.05 (*m*, 15 arom. H); 5.58 (*dd*, J = 5.4, 2.1, 0.5 H–C(1) (**3a**)); 5.25 (*dd*, J = 9.6, 3.1, 0.5 H–C(1) (**3b**)); 4.83, 4.80 (2 *d*, both J = 11.0, 0.5 H); 4.72-4.35 (*m*, 5 H); 4.30-4.00 (*m*, 0.5 H); 3.92-3.42 (*m*, 4.5 H); 3.05-2.60 (*m*, 1 H); 2.37-1.82 (*m*, 1 H).

1-Benzyloxy-2-nitroethane (**6**). To a stirred solution of 390 mg (13 mmol) of NaH-dispersion (80%) in 15 ml benzyl alcohol was dropped 950 mg (13 mmol) nitroethylene [23] over 10 min (violent reaction). The solution was stirred for 90 min and neutralized with 780 mg (13 mmol) of AcOH (abundant precipitate). The mixture was taken up in a mixture of 50 ml Et_2O and 50 ml H_2O and filtered. The org. layer was washed with brine, dried ($MgSO_4$) and concentrated. The benzyl alcohol was carefully distilled over a 10-cm *Vigreux* column at 0.1 Torr, and the strongly colored residue was purified by flash-chromatography on 50 g of silica gel (AcOEt/hexane 1:4) giving 163 mg (7%) **6** (R_f 0.33) as a pale yellow liquid. Bulb-to-bulb distillation (100°/0.1 Torr) gave 152 mg of colorless **6**. IR (film): 3085*w*, 3060*w*, 3030*w*, 2920*m*, 2870*m*, 1561*s*, 1555*s*, 1495*m*, 1453*m*, 1420*m*, 1377*s*, 1360*s*, 1335*w*, 1267*w*, 1215*w*, 1117*s*, 1095*s*, 1030*m*, 915*w*, 875*m*, 848*w*, 740*s*, 698*s*. ^{1}H-NMR: 7.47-7.12 (*m*, 5 arom. H); 4.65-4.43 (*m*, with *s* at 4.55, 4 H, $H_2C(2)$, $PhCH_2$); 4.12-3.85 (*m*, $H_2C(1)$). MS (70 eV): 136 (1), 134 (2), 107 (64), 106 (30), 105 (55), 91 (100), 79 (17), 77 (18), 65 (18), 51 (11).

$C_9H_{11}NO_3$ (181.19) Calc. C 59.66 H 6.12 N 7.73% Found C 59.55 H 6.31 N 7.92%

Equilibration of **1** *and* **3**. A tube containing a magnetic stirring bar was charged with equal quantities (31-70 mg, see *Table*) of the 1-deoxy-1-nitroaldose and Amberlite IRA 93 (free base, *Fluka*). $CHCl_3$ (0.5 ml) was added, and the tube was sealed under vacuum. The solution was stirred at 37° in a thermostated bath. The progress of the equilibration was checked by ^{1}H-NMR of the residue obtained by filtration and evaporation of the $CHCl_3$ at r.t. The equilibration was continued under the same conditions, and the concentration of anomers at the equilibrium was determined by 200-MHz ^{1}H-NMR spectroscopy.

Equilibration of 30.7 mg of **1a/1b** (11.9:88.1) gave, after 159 h, 30 mg of **1a/1b** (93.2:6.8). Equilibration of 48 mg of **1a/1b** (96.8:3.2) gave after 159 h, 47 mg of **1a/1b** (94.0:6.0). The two samples were combined and chromatographed on prep. TLC-plates (silica gel, AcOEt/hexane 1:3) giving back 71 mg (90%) of **1**.

Equilibration of 65 mg of **3a/3b** (48.2:51.8) gave, after 370 h, 64 mg of **3a/3b** (91.7:8.3). Equilibration of 70 mg of pure **3a** gave after 377 h, 68 mg of **3a/3b** (93.7:6.3). The samples were then chromatographed on 6 g of silica gel (flash chromatography, Et_2O/hexane 1:4) giving 113 mg (84%) of **3**.

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