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Asymmetric reduction of *N*-methylglyoxyloyl- and *N*-phenylglyoxyloyl-(2*R*)-bornane-10,2-sultam

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Abstract

N-Methylglyoxyloyl- (**1a**) and *N*-phenylglyoxyloyl-(2*R*)-bornane-10,2-sultam (**1b**), when reduced under various conditions, afford mixtures of two diastereoisomeric alcohols. In both cases, the reaction conditions lead to excess of both (*S*) and (*R*) configuration at the newly created stereogenic center of diastereomeric products have been found. © 1999 Elsevier Science Ltd. All rights reserved.

1. Introduction

Optically active derivatives of α-hydroxy acids are frequently used as chiral building blocks in the synthesis of natural products.[1] Among methods of their preparation, the diastereoselective reduction of chiral α-keto acid derivatives presents a competitive approach in many cases. The use of a chiral auxiliary is a conventional way to proceed. The classic work by Prelog et al.,[2] wherein natural menthol was used as a chiral auxiliary, led to asymmetric induction of merely 10% d.e. in the reduction of the phenylglyoxyloyl derivative. Up to now many chiral auxiliaries have been synthesized and tested for this purpose.[3] (2*R*)-Bornane-10,2-sultam, introduced by Oppolzer et al.,[4] was reported to be an efficient chiral auxiliary for many different stereoselective transformations.[5] In this paper we selected *N*-methylglyoxyloyl-**1a** and *N*-phenylglyoxyloyl-**1b**[6] derivatives of (2*R*)-bornane-10,2-sultam[5] as model substrates for diastereoselective reduction (Scheme 1).

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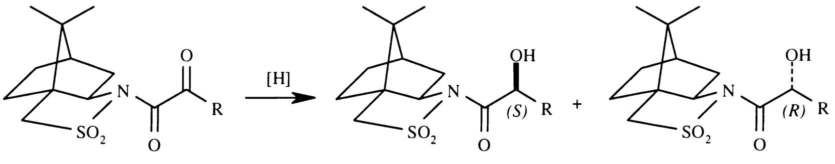


1a R=Me
1b R=Ph

2a R=Me
2b R=Ph

3a R=Me
3b R=Ph

Scheme 1.

2. Results and discussion

A perusal of the literature data prompted us to study the reduction of our model substrates in the broader range of reducing agents than to date. Studies on asymmetric induction were initiated by reduction of **1a** and **1b** with hydrogen in the presence of platinum catalysts. Hydrogenation of **1a** afforded an equimolar mixture of diastereomers **2a** and **3a** which were isolated chromatographically in a pure state; one of them was an oil, the other crystalline. Slow recrystallization from diethyl ether yielded monocrystals suitable for X-ray. The structural analysis proved unequivocally that the newly formed stereogenic center had the (*S*) configuration in this diastereomer (**2a**, Fig. 1).

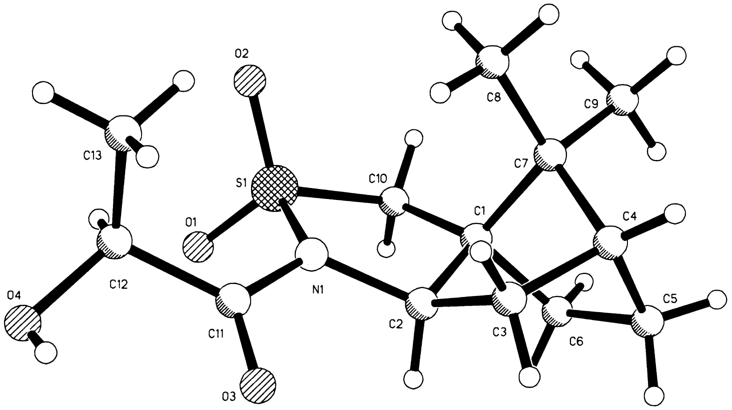


Figure 1. ORTEP diagram of compound **2a** showing labelling scheme and (*S*) configuration at C12

Similarly, hydrogenation of **1b** in the presence of Adam's catalyst gave the diastereomeric mixture of alcohols **2b** and **3b**, where the crystalline **2b** predominated. Its slow recrystallization from diethyl ether afforded monocrystals which were subjected to the X-ray analysis. It was found that the major diastereomer **2b** had the (*S*) configuration at the newly created stereogenic center as well (Fig. 2).

The presented configurational assignments were also confirmed by the chemical correlation, which consisted in hydrolysis of both crystalline compounds **2a** and **2b** (Scheme 2). It should be noted that this hydrolysis proceeded under mild conditions: 10% aqueous solution of sodium carbonate in methanol was sufficient to remove sultam auxiliary to give (*S*)-lactic (**4**) and (*S*)-mandelic (**5**) acids, respectively.

The relative ratios of diastereomeric products were determined from the ^{1}H NMR spectra. In the case of reduction of **1a**, the resulting diastereomer **2a** had two three-proton singlets in its ^{1}H NMR spectrum (corresponding to the methyl groups of the bornane moiety) at δ=0.98 and 1.13 ppm, whereas the diastereomer **3a** was characterized by the respective signals at 0.98 and 1.16 ppm. Integration of the signal at 1.16 ppm in relation to the signal at 1.13 ppm allowed determination of the ratio **2a**:**3a**. The problem of determination of diastereomeric excess was solved for the products of reduction of **1b**

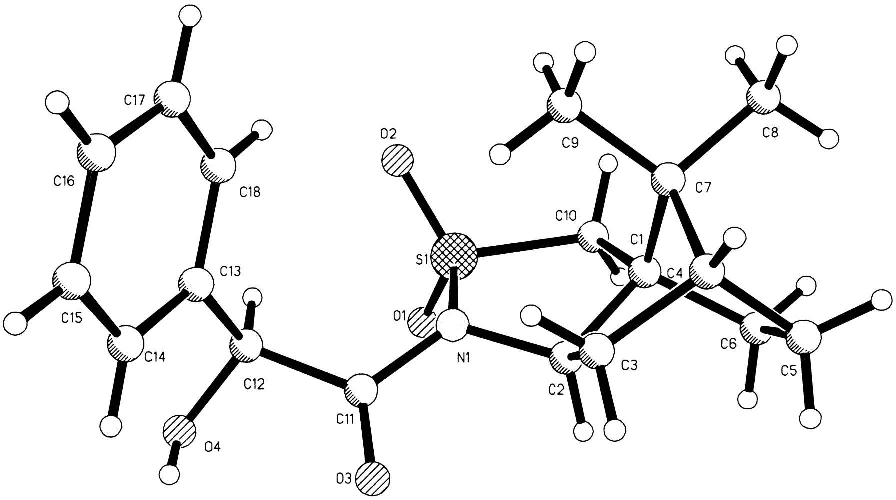
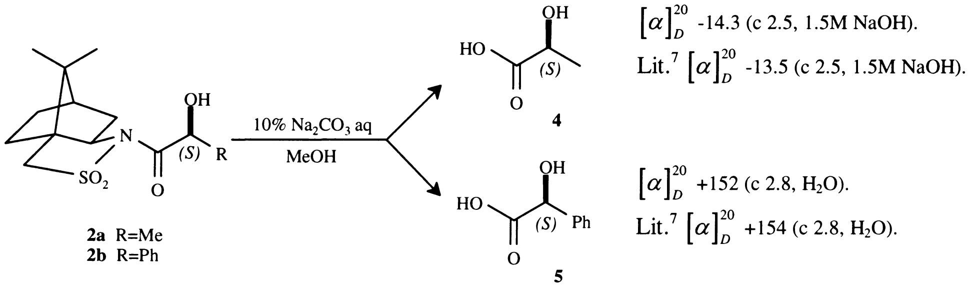


Figure 2. ORTEP diagram of compound **3a** showing labelling scheme and (*S*) configuration at C12



Scheme 2.

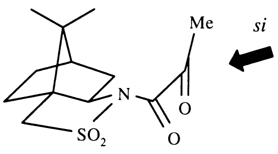
analogously. In this case, the signals appeared at δ=0.69 and 0.88 ppm for **2b**, and at 0.97 and 1.17 ppm for **3b**.

Results of studies on asymmetric induction in reduction of **1a** and **1b** are listed in Table 1. These data suggest that in each case investigated, reduction of the phenylglyoxyloyl derivative **1b** proceeds with the higher asymmetric induction than reduction of the methylglyoxyloyl derivative **1a**. For both substrates, the most effective hydride proved to be L-Selectride® (entry 8), whereas iridium on alumina was the most effective hydrogenation catalyst (entries 5 and 6). Although hydrogenation of **1b**, in the presence of Wilkinson's catalyst, gave excellent results the analogous reaction with **1a** did not proceed at all (entry 7). Zinc borohydride appeared to be a unique reducing reagent because it reduced both model substrates with the opposite asymmetric induction as compared to L-Selectride® to give predominating diastereomers with the (*R*) configuration at the newly created stereogenic center (Entry 11).

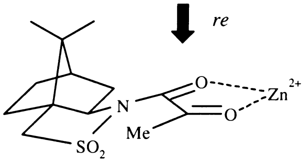
Results of reduction for **1a** may be rationalized analyzing the X-ray structure[4] of this compound. Thus, we assume that this molecule in solution adopts the most thermodynamically stable SO_2/NC=O synperiplanar, C=O/C=O orthogonal conformation **A**. The *si* approach of the reagent is sterically favoured in this case which is in agreement with our own results. Under chelation conditions the molecule appears to be in SO_2/NC=O antiperiplanar, C=O/C=O *s-cis* conformation **B**. The *re* attack is now sterically favoured. The hypothesis of C=O/C=O chelation is further supported by the significant bathochromic and hypsochromic shifts in the IR spectrum of *N*-glyoxyloyl-(2*R*)-bornane-10,2-sultam complex with $TiCl_4$.[8]

Table 1
Asymmetric reductions of **1a** and **1b**

Entry	Reducing agent	Solvent	Press. [bar]	Temp. [°C]	Time [h]	Reduction of **1a**		Reduction of **2a**	
						Yield [%]	**2a** : **3a**	Yield [%]	**2b** : **3b**
1	H_2/Pt	THF	1	25	24	-	-	77	69 :31
2	H_2/Pt	MeOH	1	25	48	93	50 :50	95	74 : 26
3	H_2/Pd-C (10%)	Toluene	55	25	48	-	-	98	85 : 15
4	H_2/Pd-C (10%)	MeOH	70	40	48	70	50 : 50	95	68 : 32
5	H_2/Ir-Al_2O_3 (5%)	Toluene	90	50	72	-	-	62	93 : 7
6	H_2/Ir-Al_2O_3 (5%)	MeOH	120	90	48	85	84 : 16	70	88 : 12
7	H_2/$RhCl(PPh_3)_3$	CH_2Cl_2	75	100	72	0		88	97 : 3
8	L-Selectride®	THF	1	-78	0.5	70	89 : 11	85	98 : 2
9	Super-H®	THF	1	-78	0.5	81	52 :48	80	82 : 18
10	$NaBH_4$	THF	1	0	0.5	0		0	
11	$Zn(BH_4)_2$	THF	1	-30	1	62	38 : 62	53	2 : 98

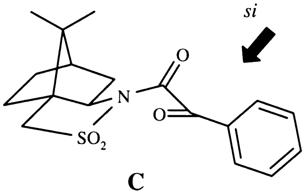


A

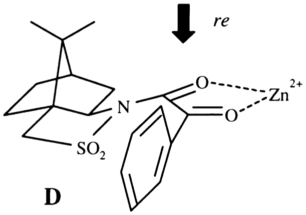


B

Similarly, the X-ray structure[4] analysis of **1b** suggests that the molecule adopts SO_2/NC=O antiperiplanar, C=O/C=O orthogonal conformation **C** which rationalizes the sterically-controlled *si* attack. The chelation conditions may favour SO_2/NC=O antiperiplanar, C=O/C=O *s-cis* conformation **D**. The *re* attack now prevails. The difference in steric demand of phenyl and methyl groups is probably responsible for generally higher diastereoselectivities in the case of reduction of the phenyl derivative **1b**.



C



D

3. Conclusions

We have found that (2*R*)-bornane-10,2-sultam is highly effective as a chiral auxiliary in the reduction of its α-ketoacyl derivatives. Also, we found that by merely changing the reduction conditions, we could reach high diastereoselectivities in each direction of asymmetric induction. Furthermore, the applied auxiliary was extremely easily removed and regenerated quantitatively.

4. Experimental

4.1. General

Tetrahydrofuran and toluene were distilled from a sodium–benzophenone ketyl, dichloromethane from calcium hydride, and methanol from magnesium. Zinc borohydride was prepared according to

Table 2
Crystal data and structure refinement for **2a** and **3a**

	2a	**3a**
Formula	$C_{13}H_{21}NO_4S$	$C_{18}H_{23}NO_4S$
Molecular weight	287.37	349.43
Crystal system	orthorhombic	
a[Å]	7.4710(10)	11.382(2)
b[Å]	11.502(2)	11.759(2)
c[Å]	16.351(3)	12.953(3)
V[Å^3]	1405.1(4)	1733.6(6)
Molecular multiplicity	Z = 4	
Calculated density [g x cm^{-3}]	1.358	1.339
Space group	$P2_12_12_1$	
Radiation (graphite monochromated)	CuK$_\alpha$	
Wavelenght [Å]	1.54178	
Linear absorption coefficient μ [mm^{-1}]	2.147	1.844
Number of electrons F (000)	616	744
Crystal size [mm]	0.14x0.14x0.21	0.14x0.07x0.28
Temperature [K]	293(2)	
Diffractometer	Enraf-Nonius MACH3	
Scan mode	$\omega/2\theta$	
Scan range 2θ [°]	4.70-70.95	5.08-71.93
Number of collected data	2145	1452
R_1	0.0345	0.0429
WR_2	0.0901	0.1117
GoF	1.054	1.106

the reported procedure.[9] All reactions with metal hydrides were carried out in an argon atmosphere. Column chromatography was performed using Merck silica gel 60 (230–400 mesh). Melting points were measured on Kofler-type (Boetius) hot-stage apparatus and not corrected. Optical rotations were determined on a Perkin–Elmer 241 polarimeter. Mass spectra were recorded using a AMD-604 spectrometer [EI=electron impact; m/z (rel.%)]. IR spectra were measured using a Nicolet FTIR Magna-500 spectrometer (in cm^{-1}). ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ using $SiMe_4$ as internal standard on Varian-Gemini-200 and Varian-Unity Plus-500 spectrometers (δ in ppm, J in Hz).

4.2. Crystal structure analysis of **2a** and **3a**

The crystals of **2a** and **3a** were measured on a MACH-3 (Enraf–Nonius) automated diffractometer using Cu-K$_\alpha$ radiation and an $\omega/2\theta$ scanning mode. The data were corrected for Lorentz, polarization and absorption effect. The structure was solved by direct method with SHELXS-86 (Sheldrick, 1986) and refined by a full-matrix least squares procedure using program SHELX-93 (Sheldrick, 1993). The positions of hydrogen atoms were generated from assumed geometries. Details of data collection and structure refinement are shown in Table 2.

4.3. Hydrogenation of ketoimides **1a** and **1b**: general procedure

A solution of ketoimide (0.5 mmol) with an appropriate solvent (3 ml) was placed in a glass liner and 10% (10 mol% in the case of Wilkinson catalyst) of catalyst added. The liner was then placed in an autoclave. The autoclave was washed twice with hydrogen and then pressure was adjusted to the required value. The desired temperature was ensured by using a heating mantle and electronic temperature control. After completion of the reaction, the vessel was cooled and discharged. The reaction mixture was filtered (if necessary) and evaporated.

*4.4. Reduction of ketoimides **1a** and **1b** with hydrides: general procedure*

A solution of ketoimide (0.5 mmol) in tetrahydrofuran (5 ml) was cooled to a desired temperature in an argon atmosphere. The hydride solution (1.2 equivalent) was added dropwise over 15 min and stirred for the stated period of time. In the case of reduction with $NaBH_4$ the reverse order of addition was applied, and excess of hydride was decomposed by addition of saturated aqueous solution of NH_4Cl (5 ml). The mixture was extracted with diethyl ether (2×10 ml), and the combined extracts dried with $MgSO_4$, filtered and evaporated.

4.5. Separation of reduction products

The crude mixture of products was chromatographed on silica gel. For the purpose of diastereomeric ratio determination, fractions containing both isomers were collected using hexane:EtOAc (4:1) as an eluent. For separation of **2a** and **3a**, a CH_2Cl_2:Et_2O (6:1) solvent system was applied. Pure **2b** and **3b** were isolated using a CH_2Cl_2:hexane (3:2) solvent system.

*4.6. (3a*S*,6*R*,7a*R*)-1,4,5,6,7,7a-Hexahydro-1-[(2′*S*)-2′-hydroxy-1′-oxopropyl]-8,8-dimethyl-3*H*-3a,6-methano[2.1]benzoisothiazole 2,2-dioxide **2a***

M.p. 172–174°C hexane. $[\alpha]_D^{27}$ −101.9 (c 3.0, $CHCl_3$). IR (KBr) 3520, 1690. ^1H NMR: 0.981 (s, 3H), 1.131 (s, 3H), 1.457 (d, 3H, J=6.8), 1.30–1.52 (m, 2H), 1.87–2.17 (m, 5H), 3.053 (d, 1H, J=7.8), 3.41–3.56 (m, 2H), 3.92–3.95 (m, 1H), 4.79–4.86 (m, 1H). ^{13}C NMR: 19.86, 20.63, 22.26, 26.45, 32.69, 38.03, 44.52, 47.87, 48.99, 52.88, 64.91, 67.53, 175.69. EIMS 288 ($[M+H]^+$, 0.3), 179 (25), 151 (42), 135 (100), 119 (18), 107 (38). Anal. calcd for $C_{13}H_{21}NO_4S$: C, 54.33; H, 7.37; N, 4.88. Found: C, 54.50; H, 7.59; N, 4.93.

*4.7. (3a*S*,6*R*,7a*R*)-1,4,5,6,7,7a-Hexahydro-1-[(2′*R*)-2′-hydroxy-1′-oxopropyl]-8,8-dimethyl-3*H*-3a,6-methano[2.1]benzoisothiazole 2,2-dioxide **3a***

Oil. $[\alpha]_D^{27}$ −86 (c 0.7, $CHCl_3$). IR (KBr) 3520, 1680. ^1H NMR: 0.976 (s, 3H), 1.155 (s, 3H), 1.421 (d, 3H, J=6.5), 1.26–1.49 (m, 2H), 1.85–2.22 (m, 5H), 3.204 (d, 1H, J=7), 3.46–3.55 (m, 2H), 3.88–3.92 (m, 1H), 4.70–4.76 (m, 1H). ^{13}C NMR: 19.92, 20.92, 22.31, 26.55, 32.65, 38.09, 44.53, 47.90, 48.95, 52.75, 64.51, 67.55, 175.60. EIMS: 288 ($[M+H]^+$, 0.6), 151 (40), 135 (95), 119 (100), 107 (90). Anal. calcd for $C_{13}H_{21}NO_4S$: C, 54.33; H, 7.37; N, 4.88. Found: C, 54.64; H, 7.49; N, 4.98.

*4.8. (3α*S*,6*R*,7a*R*)-1-[(2′*S*)-2′-Hydroxy-2′-phenylacetyl]-1,4,5,6,7,7a-hexahydro-8,8-dimethyl-3*H*-3a,6-methano[2.1]benzoisothiazole 2,2-dioxide **2b***

M.p. 151–152°C, $[\alpha]_D^{27}$ −42 (c 0.9, $CHCl_3$). ^1H NMR: 0.689 (bs, 3H), 0.879 (s, 3H), 1.28–1.44 (m, 2H), 1.73–1.92 (m, 4H), 1.96–2.02 (m, 1H), 3.424 (s, 2H), 3.708 (bs, 1H), 3.923 (bs, 1H), 5.723 (bs, 1H), 7.28–7.36 (m, 3H), 7.43–7.46 (m, 2H). ^{13}C NMR: 19.82, 19.96, 26.42, 32.58, 37.51, 44.42, 47.72, 48.93, 52.84, 64.70, 73.40, 127.23, 128.60, 128.64, 136.98, 171.72. IR (KBr): 3530, 1700. EIMS: 350 ($[M+H]^+$, 0.5), 178 (36), 151 (15), 107 (100). Anal. calcd for $C_{18}H_{23}NO_4S$: C, 61.97; H, 6.63; N, 4.01. Found: C, 61.95; H, 6.69; N, 4.07.

*4.9. (3a*S*,6*R*,7a*R*)-1-[(2′*R*)-2′-Hydroxy-2′-phenylacetyl]-1,4,5,6,7,7a-hexahydro-8,8-dimethyl-3*H*-3a,6-methano[2.1]benzoisothiazole 2,2-dioxide* ***3b***

Oil, $[\alpha]_D^{19}$ −98 (c 0.8, $CHCl_3$). ^1H NMR: 0.969 (s, 3H), 1.173 (s, 3H), 1.25–1.48 (m, 2H), 1.83–1.97 (m, 3H), 2.04–2.10 (m, 1H), 2.23–2.29 (m, 1H), 3.39–3.52 (AB, 2H), 3.621 (d, 1H, J=8), 3.88–3.91 (m, 1H), 5.672 (d, 1H, J=8), 7.31–7.44 (m, 5H). ^{13}C NMR: 19.85, 20.65, 26.39, 32.67, 38.05, 44.41, 47.91, 49.20, 52.74, 65.41, 73.04, 127.81, 128.42, 128.69, 137.15, 171.25. IR (KBr): 3530, 1700. EIMS 350 ($[M+H]^+$, 0.1), 178 (25), 151 (17), 107 (100). Anal. calcd for $C_{18}H_{23}NO_4S$: C, 61.97; H, 6.63; N, 4.01. Found: C, 62.05; H, 6.70; N, 4.11.

4.10. Hydrolysis of ***2a*** *and* ***2b***

To a solution of **2a** or **2b** (0.295 mmol) in methanol (2 ml), 10% aq. Na_2CO_3 (2 ml) was added and the mixture stirred at 40°C for 15 min. The methanol was evaporated, water (10 ml) was then added and the chiral auxiliary recovered by extraction with Et_2O (3×20 ml). The aqueous layer was then acidified with 10% aq. HCl to pH 2 and extracted with EtOAc (3×20 ml). Combined extracts were dried with $MgSO_4$, filtered and evaporated. Lactic acid: 77 mg (72%), $[\alpha]_D^{20}$ −14.3 (c 2.5, 1.5 M NaOH), lit.[7] $[\alpha]_D^{20}$ −13.5 (c 0.5, 1.5 M NaOH). Mandelic acid: 147 mg (82%), $[\alpha]_D^{20}$ +152 (c 2.8, H_2O), lit.[7] $[\alpha]_D^{20}$ +154 (c 2.8, H_2O).

Acknowledgements

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