INVERSION OF ENANTIOSELECTIVITY IN THE DIELS-ALDER SYNTHESIS OF 2-AZABICYCLO[2.2.1]HEPT-5-EN-3-ONE FROM CYCLOPENTADIENE AND CHIRAL SULFONYL CYANIDES

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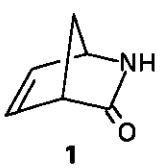
Abstract - Diels-Alder cycloaddition of (1*R*,3*S*,4*S*)-3-menthanesulfonyl cyanide to cyclopentadiene, followed by treatment with AcOH/H_2O, afforded an 11% ee of (+)-(1*S*)-2-azabicyclo[2.2.1]hept-5-en-3-one [(+)-*ent*-**1**]. The analogous process from (1*R*,3*R*,4*S*)-3-menthanesulfonyl cyanide afforded an estimated 12% ee of (−)-**1**.

(−)-(1*R*)-2-azabicyclo[2.2.1]hept-5-en-3-one (**1**) is a key intermediate in the synthesis of various biologically active compounds, among them **2**, a cyclic analogue of GABA,[1] and (-)-Carbovir (**3**), an antiviral agent comparable to Zidovudine (AZT) in anti-HIV activity.[2]



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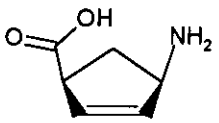

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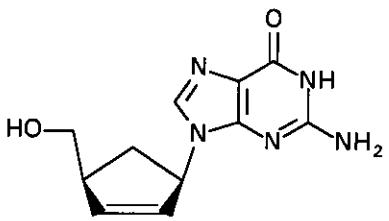

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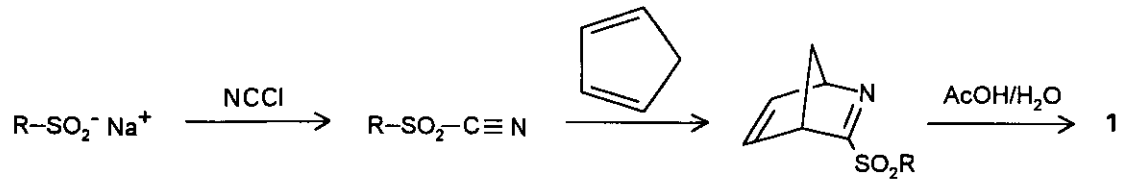
Multi-gram-scale synthesis of (±)-**1** is based on Diels-Alder reaction of tosyl cyanide (**5a**) with cyclopentadiene, which affords the rather unstable but nonetheless isolable adduct (**6a**), from which (±)-**1** is easily obtained by treatment with AcOH/H_2O (Scheme 1).[3] The starting sulfonyl cyanide is obtained from the corresponding sodium sulfinate (**4a**) by reaction with cyanogen chloride.[4] More recently, a one-pot procedure has been described that allows the synthesis of several hundreds of kilograms of (±)-**1** from methanesulfonyl cyanide (**5b**).[5]

Kinetic resolution of (±)-**1** using enzymes allows **1** to be obtained in 45% yield and ≥ 98% enantiomeric excess, together with the corresponding hydrolysis product of its enantiomer (**7**) (or (+)-*ent*-**1** and *ent*-**7**).[6a,b] Nonetheless, owing to the great interest in the development of a enantioselective synthesis of **1**, we selected Diels-Alder reaction of cyclopentadiene and chiral sulfonyl cyanides as the most direct route that would allow to synthesize **1** from achiral precursors, employing a potentially recoverable chiral auxiliary to control stereoselectivity. An alternative approach, using an



Scheme 1

achiral sulfonyl cyanide in the presence of chiral Lewis acids, has been recently reported.[6c] (1*R*,3*S*,4*S*)-3-Menthanesulfonyl cyanide (**5c**), and (1*R*,3*R*,4*S*)-3-menthanesulfonyl cyanide (**5d**) were prepared from the corresponding sodium sulfinates (**4c**)[7] and (**4d**) (see below) by reaction with cyanogen chloride. Compound (**5c**) was identical to that obtained by oxidation of (+)-neomenthyl thiocyanate.[8] We found no syntheses of menthyl thio compounds, in stereochemically pure form, described in the literature. Nonetheless, starting from a 59:41 mixture of thioneomenthol (**8c**) and thiomenthol (**8d**), prepared by reductive cleavage of menthone ethylenedithioacetal with butyl lithium,[9] a 41:59 a mixture of sulfonyl cyanides (**5c**) and (**5d**) was obtained as shown in Scheme 2.

Treatment of an isopropyl alcohol solution of the **8c/8d** mixture with sodium and then *N*-bromomethylphthalimide led, after purification, to a 54:46 mixture of the epimeric phthalimidomethyl sulfides (**9c**) and (**9d**) in 46% yield. Prolonged oxidation of these sulfides with permanganate, followed by column chromatography and recrystallization, afforded a 53:47 mixture of the phthalimidomethyl sulfones (**10c**) and (**10d**) in 80% yield. All attempts to separate the epimers of these sulfides and sulfones by fractional crystallization or column chromatography failed.

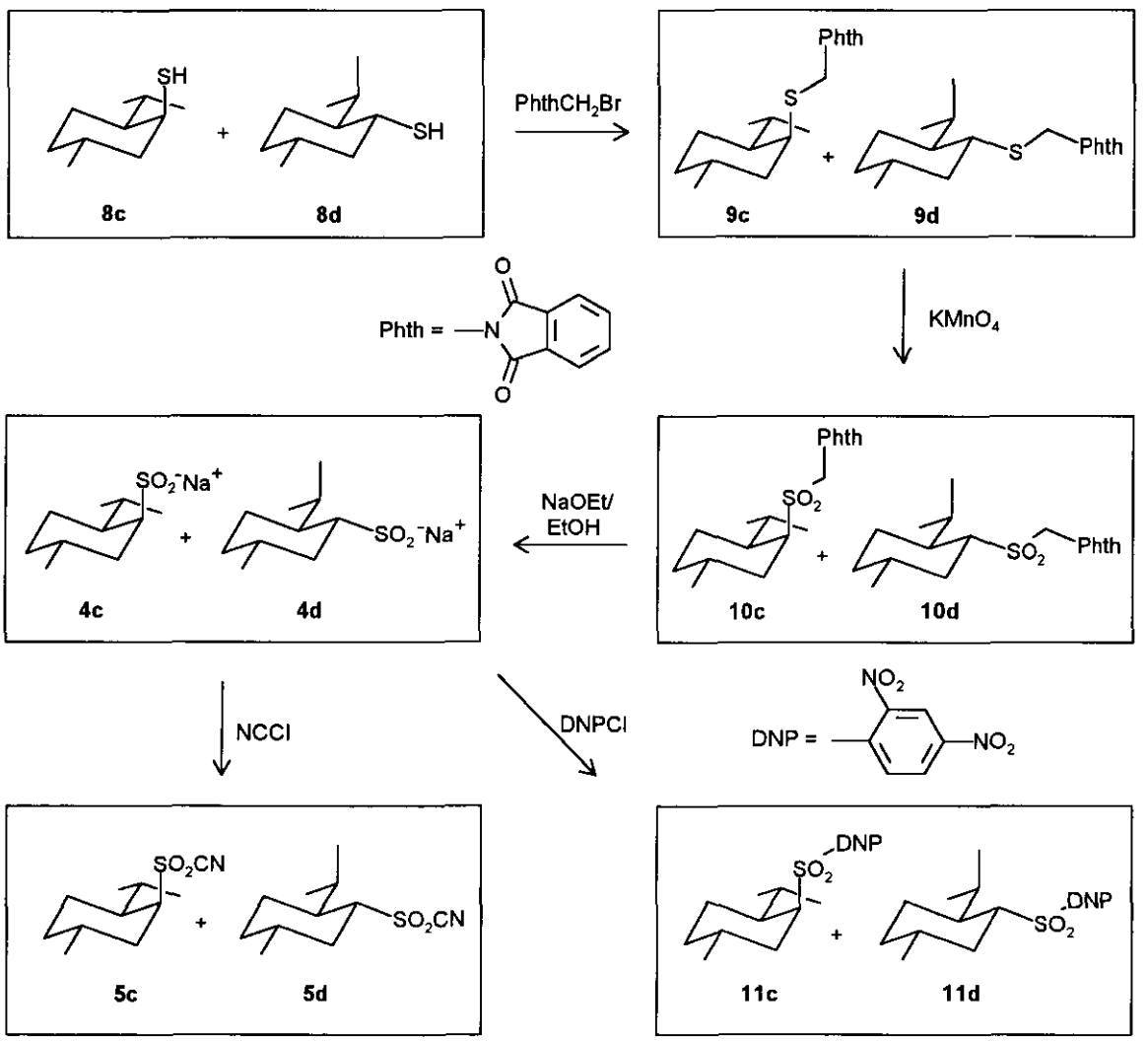
Refluxing sulfones (**10**) in ethanol with excess sodium ethoxide was selected for nucleophilic cleavage of the phthalimidomethyl group. The relative proportions of the crude sodium sulfinates (**4c** and **4d**) obtained could not be evaluated from the ^{1}H NMR spectrum, in which only the signals due to the methyl groups of each epimer, the 3*eq*-H of **4c** and the ethyl group of sodium ethoxide impurity could be positively identified. These sulfinates were nonetheless unequivocally characterized as the corresponding 2,4-dinitrophenyl sulfones (**11c**) and (**11d**) (obtained in the ratio 25:75), which have previously been prepared by an alternative route.[9] Finally, treatment of the crude sulfinates (**4**) with cyanogen chloride under standard conditions[4] afforded a crude mixture whose major component (> 93%, by GLC) was a 41:59 mixture of the sulfonyl cyanides (**5c**) and (**5d**).

The relative proportions of the epimers of compounds (**5**) and (**8** - **11**) were all calculated as the ratio of the integral of 3-H in the neomenthyl compounds (**c**) to that in the menthyl compounds (**d**). For the neomenthyl epimers, the *equatorial* 3-H appeared as an unresolved, narrow multiplet ($w_{½}$ = 9.2 ± 1.2 Hz, except for **8c**) and was consistently more deshielded than the *axial* 3-H for the menthyl epimers, observed as a doublet of triplets [J_d ($J_{3ax,2eq}$) = 3.4 ± 0.2 Hz; J_t ($J_{3ax,2ax} \simeq J_{3ax,4ax}$) = 11.4 ± 0.2 Hz], except for **8d**. In the case of thiols (**8**), additional coupling to the 3-SH broadened the signal of 3-H, for **8c**, and made it unresolved, for **8d**.

Diels-Alder cycloaddition of the sulfonyl cyanide (**5c**), or the 41:59 mixture of **5c** and **5d**, to cyclopentadiene led to the crude adducts (**6**), that were hydrolysed in aqueous acetic acid. Work up and chromatography of the products on silica gel afforded enantiomerically enrichened mixtures of lactames

(**1**) and (*ent*-**1**). Reactions were only partial (some of the unreacted starting materials being recovered), leading to 50-51% overall yields in the isolated products, pure by both GC and ^{1}H NMR spectroscopy. These products were then sublimated to obtain samples suitable for determination of optical rotations. The observed rotations were compared with the published value for **1** ($[\alpha]_D^{25}$ −557°, *c* 1, CH_2Cl_2) and *ent*-**1** ($[\alpha]_D^{25}$ +558°, *c* 1, CH_2Cl_2),[6b] to establish the absolute stereochemistry of the predominant enantiomer and the corresponding enantiomeric excess. Due to the large absolute value of these $[\alpha]_D^{25}$, ee obtained by this approach are more precise than those obtained by ^{1}H NMR spectroscopy of samples containing a chiral lanthanide shift reagent. Nevertheless, use of 1:5 mole ratio of (+)-Eu(hfc)$_3$/sample, to analyse the product of the reaction of **5c** led to an ee value within ± 0.5 % of the value furnished by the $[\alpha]_D^{25}$ method. Lactame from **5c** had an $[\alpha]_D^{25}$ +63.1°(*c* 1, CH_2Cl_2), what corresponds to a 11% ee of the 1*S* isomer (*ent*-**1**), while product from the (41:59) mixture of **5c** + **5d** had an $[\alpha]_D^{25}$ −16.3°(*c* 1, CH_2Cl_2), what corresponds to a 3% ee of the 1*R* isomer (**1**).

It is noteworthy that **5c** predominantly afforded the 1*S*-adduct, whereas **5d** favours formation of the 1*R*-



Scheme 2

adduct: the reaction of **5c** alone and that of the 41:59 mixture of **5c** and **5d** went with similar yields, therefore it was assumed that **5c** and **5d** reacted to the same extent; thus, from the composition of the mixture of **5c** and **5d**, and the enantiomeric excesses obtained for the reactions of **5c** and of **5c** + **5d**, it can be estimated that **5d** afforded around a 12% enantiomeric excess of (−)-1*R*-**1**.

Although the enantiomeric excesses were low, these are the first examples of heterodienophiles with local C_∞ symmetry showing opposite enantioselectivity in Diels-Alder additions, due to chiral auxiliaries that differ only in the configuration of the stereogenic centre nearest to the reactive moiety of the dienophile.

EXPERIMENTAL

For spectroscopic and analytical techniques and commercial materials see ref. 7. (1*R*,3*S*,4*S*)-3-Menthanesulfonyl cyanide (**5c**) was indistinctly prepared by treatment of sodium (1*R*,3*S*,4*S*)-3-menthanesulfinate (**4c**)[7] with cyanogen chloride, as described below for the mixtures of **5c** and **5d**, or by oxidation of neomenthyl thiocyanate.[8]

Mixture of phthalimidomethyl sulfides (9c) and (9d). Sodium metal (0.26 g, 11.6 mmol) was added to a 59:41 mixture of **8c** and **8d** (2.00 g, 11.6 mmol)[9] in dry isopropyl alcohol (45 mL), which was then stirred under argon for 2.5 h. *N*-Bromomethylphthalimide (2.80 g, 11.6 mmol) was added, and the mixture was heated under reflux for 26 h, whereupon it was cooled and the insoluble materials were filtered out. The filtrate was evaporated to dryness *in vacuo*, and the resulting residue (4.46 g) was chromatographed on silica gel (100 g), with 6:1 hexane/EtOAc (34 × 65 mL) as eluant. Crude **9c** and **9d** (1.93 g) were isolated from fractions 5-11 and then recrystallized from hexane to afford clean **9c** + **9d** (1.73 g, 46%); mp 60-63 °C (*cf.* lit.,[7] mp for **9c** alone, 94-95 °C); IR (KBr): 1774, 1718, 1612, 1466 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 0.61 and 0.80 (2 d, J = 6.9 Hz, 8,8-$(CH_3)_2$, **9d**), 0.75 and 0.82 (2 d, J = 6.5 Hz, 8,8-$(CH_3)_2$, **9c**), 0.85 (d, J = 6.3 Hz, 1-CH_3, **9c**), 0.91 (d, J = 6.5 Hz, 1-CH_3, **9d**), 0.93-1.74 (m), 1.83-1.96 (m), 2.03 (dm, J_d = 13.7 Hz), 2.03 (dq, J_d = 13.7 Hz, J_q = 3.1 Hz), 2.21-2.30 (m), 2.75 (dt, J_d = 3.6 Hz, J_t = 11.3 Hz, 3*ax*-H, **9d**), 3.42 (m, $w_{1/2}$ = 8.5 Hz, 3*eq*-H, **9c**), 4.68 and 4.81 (AB system, J = 14.1 Hz, SCH_2N, **9c**), 4.73 and 4.83 (AB system, J = 14.2 Hz, SCH_2N, **9d**), 7.71-7.75 (m), 7.86-7.89 (m). The integrals of 3-H signals in the ^1H NMR spectrum indicated a 54:46 ratio of **9c/9d**. Anal. Calcd for $C_{19}H_{25}NO_2S$: C, 68.85; H, 7.60; N, 4.23. Found: C, 69.05; H, 7.65; N, 4.13.

Mixture of phthalimidomethyl sulfones (10c) and (10d). Finely powdered $KMnO_4$ (1.62 g, 10.25 mmol) was added in a single portion to a solution of the 54:46 mixture of **9c** and **9d** (2.51 g, 7.57 mmol) in AcOH (85 mL), and the mixture was stirred at rt for 78 h. The solvent was removed by two-fold azeotropic distillation with toluene at reduced pressure, affording a blackish solid residue. This was stirred in 1 M aqueous $NaHSO_3$ (400 mL); the insoluble solids were filtered out; and the cake and the filtrate were each extracted with CH_2Cl_2 (3 × 200 mL). The extracts were combined, washed with water (2 × 100 mL), and dried (Na_2SO_4), and the solvent was evaporated *in vacuo*. The resulting white solid (2.62 g) was chromatographed on silica gel (150 g), with 4:1 toluene/EtOAc (10 × 75 mL) as eluant. The residue from fractions 5-7 was recrystallized from *i*-PrOH to give a clean mixture of sulfones (**10c** + **10d**) (2.21 g, 80%); mp 125-128 °C (*cf.* lit.,[7] mp for **10c** alone, 138-139 °C); IR (KBr): 1776, 1716, 1612, 1469, 1324, 1137 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 0.89 and 0.93 (2 d, J = 6.8 Hz, 8,8-$(CH_3)_2$, **10d**), 0.90 and 0.93 (2 d, J = 6.5 Hz, 8,8-$(CH_3)_2$, **10c**), 0.96 (d, J = 6.5 Hz, 1-CH_3, **10d**), 0.99 (d, J = 6.4 Hz, 1-CH_3, **10c**), 0.89-1.01 (m), 1.05-1.40 (m), 1.43-1.54 (m), 1.73-

1.91 (m), 2.09-2.20 (m), 2.34-2.54 (m), 3.17 (dt, J_d = 3.5 Hz, J_t = 11.3 Hz, 3*ax*-H, **10d**), 3.75 (m, $w_{1/2}$ = 10.3 Hz, 3*eq*-H, **10c**), 4.85 and 5.05 (AB system, J = 14.2 Hz, SCH_2N, **10c**), 4.88 and 5.05 (AB system, J = 14.2 Hz, SCH_2N, **10d**), 7.78-7.81 (m), 7.91-7.95 (m). The integrals of 3-H signals indicated a 53:47 ratio of **10c/10d**. Anal. Calcd for $C_{19}H_{25}NO_4S$: C, 62.79; H, 6.93; N, 3.85. Found: C, 62.91; H, 6.77; N, 3.78.

Mixture of sodium sulfinates (4c) and (4d). The 53:47 mixture of sulfones (**10c** + **10d**) (1.50 g, 4.13 mmol) was added to a stirred solution of sodium ethoxide prepared from freshly cut sodium metal (200 mg, 8.70 mmol) and anhydrous EtOH (30 mL). The mixture was refluxed under argon until TLC showed all of the sulfones (**10**) to have reacted (*ca.* 20 h), and then passed while hot through a sintered glass filter. The filtrate was evaporated to dryness; the resulting residue was extracted with hot benzene (2 × 30 mL); and the insoluble portion was dried under vacuum to afford a hygroscopic mixture (1.06 g) of NaOEt and sulfinates (**4c** + **4d**) (estimated yield, 80 %). This crude mixture was used in the following transformations. Partial ^{1}H NMR (DMSO-d_6) spectrum: δ = 0.72 and 0.83 (2 d, J = 6.6 Hz, 8,8-$(CH_3)_2$, **4c**), 0.77 and 0.82 (2 d, J = 7.0 Hz, 8,8-$(CH_3)_2$, **4d**), 0.87 (d, J = 6.5 Hz, 1-CH_3, **4d**), 0.95 (d, J = 6.4 Hz, 1-CH_3, **4c**), 4.68 (m, $w_{1/2}$ = 8.0 Hz, 3*eq*-H, **4c**).

Mixture of 2,4-dinitrophenyl sulfones (11c) and (11d). A mixture of the crude sodium sulfinates (**4c** + **4d**) (700 mg, including some NaOEt) in anhydrous EtOH (10 mL), and 2,4-dinitrochlorobenzene (1.10 g, 5.43 mmol) in anhydrous EtOH (15 mL), was refluxed under argon for 40 h and then left to stand at 5 °C overnight. The solids were removed by suction filtration, and the filtrate was then evaporated *in vacuo* to afford an oily residue (1.50 g). This was chromatographed on silica gel (150 g), with 19:1 toluene/EtOAc (30 × 25 mL) as eluant; the residue from fractions 10-19 (0.45 g), was a clean mixture of sulfones (**11c** + **11d**) that solidified below 5 °C but was liquid at room temperature (*cf.* lit.,[7] mp for **11c** alone, 198-199 °C); IR (KBr): 1605, 1540, 1512, 1495, 1348, 1140 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 0.81 (d, J = 6.2 Hz, 1-CH_3, **11c**), 0.85 (d, J = 6.3 Hz, 1-CH_3, **11d**), 0.93 and 1.00 (2 d, J = 6.8 Hz, 8,8-$(CH_3)_2$, **11d**), 0.99 and 0.99 (2 d, J = 6.5 Hz, 8,8-$(CH_3)_2$, **11c**), 1.08-1.57 (m), 1.74-2.06 (m), 2.54 (dsept, J_d = 2.7 Hz, J_{sept} = 6.8 Hz, 8-H, **11d**), 3.91 (dt, J_d = 3.4 Hz, J_t = 11.6 Hz, 3*ax*-H, **11d**), 4.41 (m, $w_{1/2}$ = 10.4 Hz, 3*eq*-H, **11c**), 8.32 (d, J = 8.6 Hz, 6'-H), 8.58 (dd, J = 8.6, 2.2 Hz, 5'-H), 8.72 (d, J = 2.2 Hz, 3'-H). The integrals of 3-H signals indicated a 25:75 ratio of **11c/11d**. Anal. Calcd for $C_{16}H_{22}N_2O_6S$: C, 51.88; H, 5.99; N, 7.56. Found: C, 52.14; H, 6.05; N, 7.52.

Further fractions from the column afforded a solid (0.51 g) that, after recrystallization from acetone, was identified as 2,4-dinitrophenetole; mp 87 °C (lit.,[10] mp 86-87 °C) and IR and ^{1}H NMR consistent with this structure.

Mixture of sulfonyl cyanides (5c) and (5d). Freshly prepared liquid cyanogen chloride (3 mL, 75 mmol)[11] was added to a cooled (0 °C) solution of the crude sodium sulfinates (**4c**) and (**4d**) (3.00 g, including some NaOEt), which was then stirred at 4 °C for 30 min. The mixture was extracted with CH_2Cl_2 (3 × 40 mL), and the extracts were combined, washed with brine (3 × 40 mL) and then dried (anhydrous Na_2SO_4). Evaporation of the solvent and the volatile impurities *in vacuo* afforded a mixture of **5c** and **5d** (1.06 g, estimated yield, 49%) as a colourless oil, that was used without further purification in the reaction with cyclopentadiene; IR (film): 2184, 1364, 1162 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 0.80-2.16 (m), 0.88 and 0.97 (2 d, J = 6.8 Hz, 8,8-$(CH_3)_2$, **5d**), 0.96 and 0.99 (2 d, J = 6.5 Hz, 8,8-$(CH_3)_2$, **5c**), 1.12 (d, J = 6.4 Hz, 1-CH_3, **5c**), 2.33-2.73 (m), 3.28 (dt, J_d = 3.2 Hz, J_t = 11.5 Hz, 3*ax*-H, **5d**), 3.85 (m, $w_{1/2}$ = 9.8 Hz, 3*eq*-H, **5c**). The integrals of 3-H signals in the ^{1}H

NMR spectrum indicated a 41:59 ratio of **5c/5d**.

2-Azabicyclo[2.2.1]hept-5-en-3-one (1 or *ent*-1). The sulfonyl cyanide (**5c** or the mixture **5c** + **5d**; 5 mmol) was added to freshly cracked, redistilled cyclopentadiene (7.3 mL, 88 mmol) at 0 °C, and the mixture was stirred under argon at 25 °C for 3 h. The excess cyclopentadiene was removed *in vacuo*; the residue was suspended in cold 1:4 AcOH/H_2O (40 mL); and 4N NaOH was slowly added until the suspension had pH 8. This mixture was then extracted with CH_2Cl_2 (4 × 25 mL), and the organic extracts were combined, dried (Na_2SO_4), and evaporated to dryness *in vacuo*. The resulting residue (0.80 g) was chromatographed on silica gel (24 g), with 25:75 hexane/EtOAc (15 × 20 mL) as eluant. Unreacted **5** eluted first and could be partially recovered; later fractions afforded pure (TLC, ^{1}H NMR), enantiomerically enriched lactam(**1**)(or *ent*-**1**). Analytical samples suitable for ee determinations were obtained by sublimation onto a cold finger at 70 °C/15 mm Hg; IR (KBr): 3394, 3017, 2954, 1686, 1562, 1386, 1301, 1224, 1119, 977, 944, 831, 754, 688 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 2.22 (1H, dt, J_d = 7.7 Hz, J_t = 1.7 Hz), 2.40 (1H, dt, J_d = 7.7 Hz, J_t = 1.7 Hz), 3.22 (1H, m), 4.34 (1H, quint, J = 1.8 Hz), 5.82 (1H, br s, D_2O exch.), 6.67 (1H, ddd, J = 5.3, 3.3, 1.6 Hz), 6.79 (1H, dd, J = 5.3, 2.1 Hz).

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