Tetrahedron Letters, Vol.31, No.29, pp 4117-4120, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

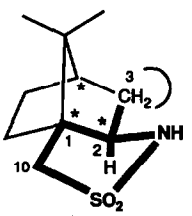
CHIRAL TOLUENE-2,α-SULTAM AUXILIARIES: PREPARATION AND STRUCTURE OF ENANTIOMERICALLY PURE (*R*)- AND (*S*)-ETHYL-2,1'-SULTAM [1]

Wolfgang Oppolzer*, Martin Wills, Christian Starkemann and Gérald Bernardinelli
Département de Chimie Organique, Université de Genève, CH-1211 Genève 4, Switzerland

Abstract: Crystalline sultams (*R*)-2 or (*S*)-2 were selectively prepared from prochiral saccharine (3) in two steps (53% overall yield) *via* Ru-(*R*)-BINAP- or Ru-(*S*)-BINAP catalyzed asymmetric hydrogenation of imine 4. Alternatively, pure (*R*)-2 was synthesized (37% overall yield) from (*R*)-α-phenethylamine in 4-5 steps involving the *ortho*-sulfination 6 → 7 and the highly diastereoselective cyclization of sulfinic acid 7 to the sulfinamide 8. X-ray diffraction analyses of sulfinamide 8 and sultam (*R*)-2 are presented.

Bornane-10,2-sultam 1 and its antipode, accessible from inexpensive (+)- and (-)-camphorsulfonic acid in two simple operations, were introduced in 1984 and rank today among the most practical chiral auxiliaries (Scheme 1). Various addition reactions to their *N*-enoyl derivatives I, as well as reactions of their *N,O*-ketene acetal derivatives II with electrophiles proceed in high yield and with good to excellent π-face discrimination providing, after crystallization, ~100% diastereomerically pure products. [2]

Scheme 1



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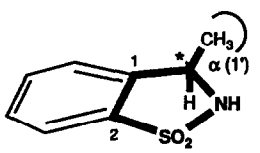

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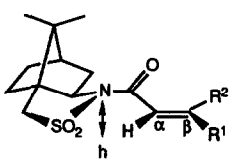

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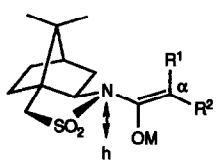


II

To gain a deeper understanding and an even broader scope of this stereoface-directing bias we designed related chiral sultam auxiliaries along the following guidelines:

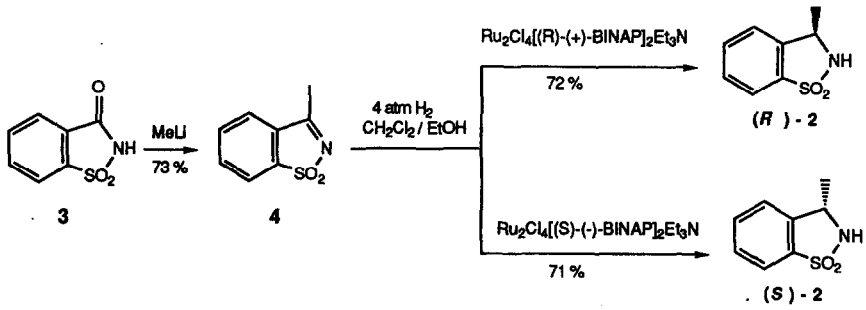
1) Simpler, but crystalline sultams containing a single stereogenic center instead of the bornane skeleton . The substituent attached to this center may be varied.
2) No (acidic) proton at the carbon atom vicinal to the SO_2 group.
3) Easier NMR- and HPLC-analyses (aryl chromophore) of substrates and products.

Methyl-substituted sultam 2 (Scheme 1) meets these criteria and we report here two different syntheses of its pure enantiomers.

Preparation of (R)-2 and (S)-2 from Saccharine (3).

The first approach provides enantiomerically pure sultams (*R*)-2 and (*S*)-2 from non-chiral 3 (Scheme 2).

Scheme 2

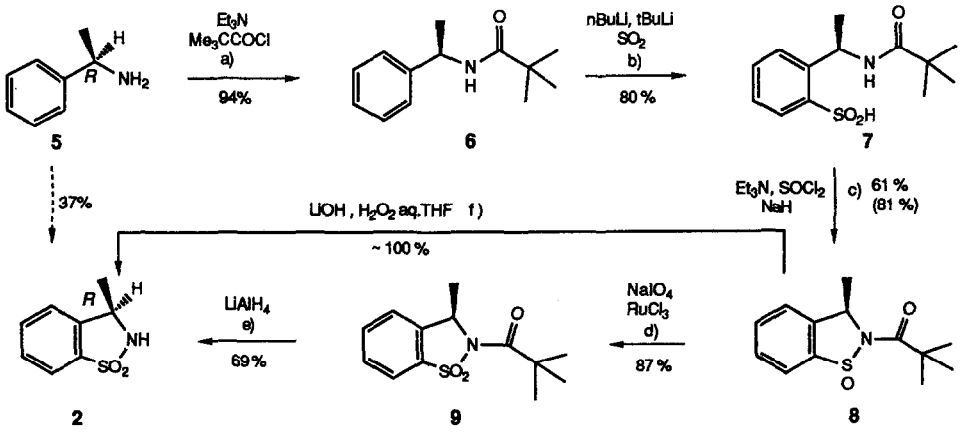


Addition of methyllithium (2.25 molequiv.) in Et_2O to saccharine (3, THF, -78°C, 16h), aq. workup (sat. aq. NH_4Cl) and crystallization (MeOH) furnished prochiral imine 4 [3] (m.p. 218-219°C) in 73% yield. Remarkably, [4] asymmetric hydrogenation of imine 4, catalyzed by $Ru_2Cl_4[(R)-(+)-BINAP]_2(NEt_3)$ [7] furnished, after crystallization, enantiomerically pure sultam (*R*)-2 [8] in 72% yield. [9] Analogous (*S*)-(-)-BINAP-directed hydrogenation of imine 4 afforded crystallized pure (*S*)-2 [8] in 71% yield.

Thus, starting from relatively inexpensive saccharine each antipodal sultam 2 was prepared on a multi-gram scale, *via* two simple steps, in ~53% overall yield. The absolute configurations of products 2 were assigned *via* comparison of (*R*)-2 ([α_D], mixed m.p.) with a sample obtained by the following, alternative route.

Preparation of (R)-2 from (R)-α-phenethylamine 5.

Scheme 3



(a) NEt_3, Me_3CCOCl (1.1 equiv each), CH_2Cl_2, 0°C, 16 h. (b) *n*BuLi (1 equiv), Et_2O, -78°C, 0.5 h; then *t*BuLi (1.4 equiv), -78°C, 4 h; → 0°C over 20 min; 0°C, 45 min; SO_2 gas, -78°C, 0.5 h; then → 0°C, extraction with i) aq NaOH, ii) HCl, CH_2Cl_2. (c) $SOCl_2$ (1.26 equiv), NEt_3 (1 equiv), CH_2Cl_2, -78°C; 0°C, 6 h; then NaH (2.6 equiv), RT, 16 h. (d) $RuCl_3$ (0.0007 equiv), $NaIO_4$ (1.2 equiv), CCl_4/aq. MeCN, 0°C, 2 h. (e) $LiAlH_4$ (1.1 molequiv), THF, 0°C, 1 h. (f) LiOH (2 equiv), 30% aq. H_2O_2 (4 equiv), aq. THF, RT, 1 h.

Acylation of (*R*)-(+)-5 (>97% e.e., *Fluka*) with pivaloylchloride and crystallization (hexane/CH_2Cl_2) afforded amide 6 [8] (94% yield) in > 99% e.e.. *Ortho*-deprotonation [10] of 6 using *n*-BuLi followed by *t*-BuLi and trapping of the di-lithiated intermediate with SO_2, [11] afforded sulfinic acid 7 [8] (80% yield). Cyclization of 7 with $SOCl_2$/NEt_3 and NaH provided sulfinamide 8 [8] in 61 % yield (81% based on recovered 7) and in 98.4% purity (GC). It thus appears that the cyclization 7 → 8 proceeded with ≥ 98.5% diastereoselectivity. [12] A sample of 8, purified by FC and crystallization was analyzed by X-ray diffraction [13] which showed *syn*-disposed S-O and C(α)-CH_3 bonds. Further structural features of 8 will be discussed below in comparison with those of sultam 2 (Scheme 4).

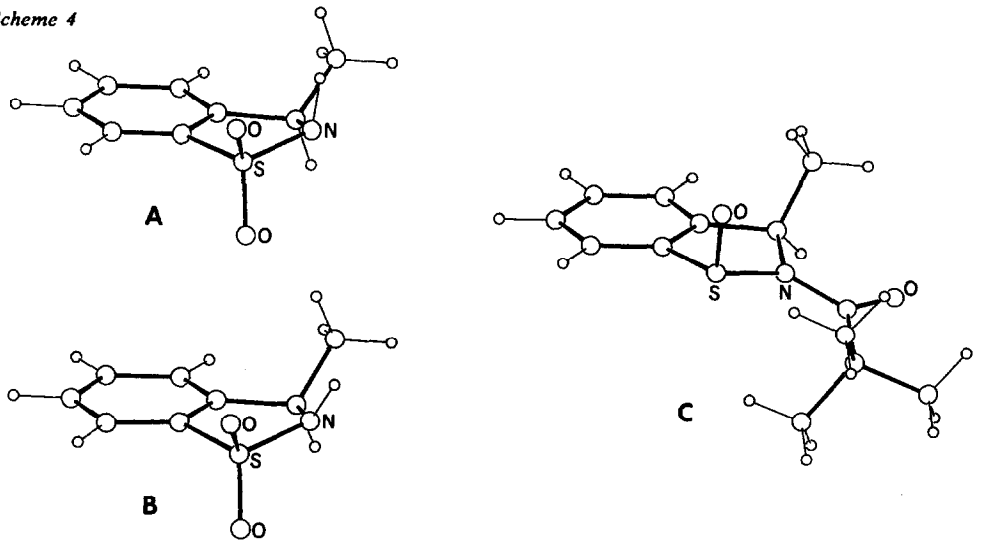
Oxidation [14] 8 → 9 followed by reductive deprotection of non-purified amide 9 [8] and crystallization provided (*R*)-sultam 2 [8] (69% yield) in > 99 e.e. as determined by GC analysis of its (*R*)-α-methoxy-α-trifluoromethyl-phenylacetamide. [15] More directly, sultam (*R*)-2 was obtained in one operation from sulfinamide 8 (~100% yield with $LiOH/H_2O_2$ [16]).

In summary, amine 5 was converted into sultam 2 in 37% overall yield on a multigram scale without chromatography until the final step. Thus, the absolute configuration of sultam 2 follows unambiguously from that of educt 5. A further bonus is provided by the easy access to cyclic chiral sulfinamide 8 which opens additional perspectives in asymmetric synthesis.

Structural Studies

X-ray diffraction analysis of (*R*)-sultam 2 [13] shows two crystallographically distinct conformers A and B in a 1:1 ratio (Scheme 4).

Scheme 4



The observed position of the proton on the nitrogen atom showed the latter to be pyramidal in each case. [17] This pyramid is higher in conformer A (h = 0.51 Å) than in conformer B (h = 0.33 A) indicating a certain flexibility. Presumably for reasons of orbital overlap the "lone electron pair" in conformers A and B intersects the O-S-O angle [18] enforcing a *s-cis* disposition of N-H and C-CH_3 bonds. Consequently, the pyramid is tilted in the opposite sense as compared to *N*-acyl- and *N,O*-ketene acetal derivatives of sultam 2 [19a] and its analogues I and II [19b]. In this context it is worth noting that the X-ray structure C of cyclic sulfinamide 8 reveals a flat (h = 0.000 Å) endocyclic nitrogen [7] attached to the (less electronegative?) S-O group.

Conclusion

The two enantiomers 2 being readily accessible, the question is how they perform as chiral auxiliaries. This will be addressed in two following communications and further studies are currently underway.

Acknowledgements: Financial support of this work by the *Swiss National Science Foundation*, *Sandoz Ltd.*, Basel and *Givaudan SA*, Vernier, is gratefully acknowledged. We are grateful to Mr. *J.P. Saulnier*, Mr *A. Pinto* and Mrs. *C. Clément* for NMR and MS measurements. We thank the Royal Society, London for the award of a European Fellowship to M. W..

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4) Initial attempts to extend the known reduction 4 → (±)-2 ($NaBH_4$) [5] to chiral hydride reagents failed to give (*R*)-2 in more than 50% e.e.. Hydrogenations of prochiral aryl-substituted imines are catalyzed either by complexes of Rh(I) with chiral diphosphines [22-91% induction] [6a] or by a chiral cobalt(I) complex [20% induction].[6b] The here described asymmetric imine hydrogenation is, to our knowledge, the first catalyzed by a ruthenium complex and the first proceeding with >98% induction.

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8) All new compounds were characterized by IR, ^{1}H-NMR, ^{13}C-NMR and MS. Melting points (°C)= 4: 122-124; 5: 62-64; 6: 115-117; 7: 64-66; 2: 92. $[\alpha]_D$ values (°C, c = g/100ml in EtOH)= (*R*)-2: +31.0 (20, 0.6); (*S*)-2: -30° (20, 1.21, $CHCl_3$); 6: +107.6 (20, 0.8); 7: -23.5 (20, 1.8); 8: +8.84 (20, 0.215); 9: +3.06 (25.2, 0.49); .

9) The following procedure is representative: *Catalyst*: Using a Schlenk tube and argon atmosphere, the brown suspension of [$RuCl_2$(COD)] (38 mg, 0.13 mmole), (*R*)-(+)-BINAP (90.2 mg, 0.14 mmole) and NEt_3 (75 µl, 0.54 mmole) in toluene (3.5 ml) was stirred under reflux for 6h. Evaporation (*in vacuo*) of the resulting clear solution, extraction of the solid residue with CH_2Cl_2, filtration and evaporation of the extracts furnished an orange crystalline residue which was used directly for the following hydrogenation step. (*R*)-*Sultam* 2: The above catalyst (850 mg, 0.49 mmole) in CH_2Cl_2 (10ml) was cannulated into a solution of imine 4 (8.14 g, 44 mmole) in EtOH/CH_2Cl_2 (2:1, 1.5 l) and the solution was stirred under hydrogen (4 atm) at 22°C for 12 h. Partial evaporation, filtration of the concentrated mixture through SiO_2 (to remove the catalyst) and evaporation of the filtrate gave crude (*R*)-2 (84% yield) in >99% e.e. (GC of Mosher derivative) which was crystallized twice from hexane/CH_2Cl_2 giving pure (*R*)-2 (5.8 g, 72% yield).

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13) Crystallographic data have been deposited at the *Cambridge Crystallographic Data Centre*. Structure factors may be obtained from one of us (G.B.). *Philips PW 1100 diffractometer (MoKα)*. The structures were solved by a direct method (*Multan-84*) and refined by least squares analyses. The crystals of sulfinamide 8 (hexane/CH_2Cl_2) are orthorhombic, a = 8.404 (1), b = 11.213 (2), c = 14.221 (2) Å; $P2_12_12_1$, Z = 4; d_c = 1.25 g.cm^{-3}; *F(000)* = 536. R = 0,066 for 1328 observed reflections [$|F_0| \geq 4\sigma(F_0)$]. The crystals of sultam (*R*)-2 (hexane/CH_2Cl_2) are orthorhombic, a = 8.294 (2), b = 13.543 (3), c = 15.443 (3) Å; $P2_12_12_1$, Z = 8 (2 molecules/A.U.); d_c = 1.40 g.cm^{-3}; *F(000)* = 768. R = 0,047 for 1175 observed reflections [$|F_0| \geq 4\sigma(F_0)$].

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(Received in Germany 31 May 1990)