to the position ortho to C-2″ in the C ring.

The CH_2 protons (H_β) correlate to C-1 through a two-bond coupling and to the two equivalent carbons (C-2 and C-6) through three-bond couplings. The carbons C-2 and C-6 show a correlation to the proton H-4 and reciprocally C-4 shows a correlation to the protons H-2 and H-6. Thus, the B ring is connected to the three-carbon chain at C-1 with C-2, C-6 ortho, C-3,5 meta, and C-4 para.

A carbon–carbon connectivity experiment (2D-INADEQUATE) was also performed and while not all of the correlations were observed, much of the structural information deduced from the long-range heterocorrelation was also independently confirmed. The following bonds were unequivocally confirmed: C=O,1′; C=O,α; α,β; β,1; 1,2-6; 3-5,4; 4′,5′; 6′,5′; 3′,4′; 2″,3″; 3″,4″; 2‴,1‴; 6‴,1‴; 6‴,5‴; 5‴,4‴; 4‴,3‴; and 2‴,3‴.

On the basis of the above arguments the structure for angoluvarin (1) has been established. All of the proton and carbon assignments are listed in Table I.

Experimental Section

The one-dimensional 60-MHz ^1H NMR and the 15-MHz ^{13}C NMR data were obtained in acetone-d_6 on JEOL C-60 and JEOL FX-60 spectrometers, respectively. The multiplicities were confirmed by SFORD. The 300-MHz ^1H and 75-MHz ^{13}C NMR data (Table I) were run on a Varian XL-300 spectrometer.

The 2D heteronuclear one-bond and long-range chemical shift correlation data were obtained with the pulse sequence of Bax.[4] Both experiments were run with a spectral width of 5000 Hz in F2 (the carbon chemical shift axis) and 1400 Hz in F1 (the proton chemical shift axis), with the spectral windows centered around the protonated carbons and the corresponding protons, respectively. Some correlation peaks were lost, and others folded into the spectrum, but these disadvantages were more than offset by the improved digital resolution that could be maintained with the restricted spectral windows. A data acquisition time of 205 ms gave 2048 data points in F2. The number of increments was 128, and after Fourier transformation and zero-filling in F1 to 512 data points, a second Fourier transformation gave a data matrix of 2048 × 512. Contour plotting was used to identify the proton–carbon correlation peaks. Pulse sequence timing was determined by setting the value of J_{CH}, the direct coupling constant, to 140 Hz, and J_{nCH}, the long-range coupling constant, to 7 Hz.

Carbon–carbon connectivities were verified with the CCC2DQ 2D-INADEQUATE pulse sequence with quadrature detection in both dimensions as reported by Bax et al.[5] A spectral width of 14084.5 Hz in both F2 (the carbon chemical shift axis) and F1 (the double quantum frequency axis) was employed, with an acquisition time of 145 ms and 128 increments. Zero-filling to 512 data points in F1 gave a data matrix of 4096 × 512 data points to present the transformed 2D data. The high concentration of the sample (130 mg in 0.2 mL) in DMSO-d_6 resulted in sufficiently short $T1$'s for all carbons to optimize magnetization recovery with a sequence repetition time of 0.645 s. Acquisition of 2560 pulses per increment resulted in a total data acquisition of 59 h. Contour plotting revealed carbon–carbon connectivities as pairs of doublets with the same double quantum frequency appearing opposite the chemical shift positions of carbons joined by a chemical bond. A compromise value of J_{CC} = 50 Hz was used to determine the pulse-sequencing timing in order to detect both single bonds and aromatic C–C bonds.

Extraction and Chromatographic Separation. The plant material used, the extraction procedures, and chromatographic separations have been reported previously.[2a,b] Angoluvarin was eluted in a fraction along with (+)-6,8-C-dimethylpinocembrin 6-methyl ether from the silicic acid column. Further chromatography ove alumina as described previously[2b] gave 50 mg of angoluvarin (elution with 5% MeOH–$CHCl_3$).

Angoluvarin: mp 154–156 °C; UV (MeOH) λ_{max} 326 mm (ϵ 1.27 × 10^4), 286 (9.97 × 10^4), 250 (6.34 × 10^3), and 218 (2.84 × 10^4); IR (KBr) ν_{max} 3540, 3260, 1630, and 1600 cm^{-1}; MS, m/z (relative intensity) 484 (M^+, 39), 379 (M^+ – 105, 15), 352 (22), 273 (17), 179 (100); R_f 0.45 ($CHCl_3$–EtOH, 19:1). Anal. Calcd for $C_{30}H_{28}O_6$: C, 74.36; H, 5.82. Found: C, 74.04; H, 6.01.

Antimicrobial Activity. The antimicrobial assay was performed as previously described.[6] Angoluvarin had MIC values of 0.78, 1.56, and 3.12 μg/mL against *Bacillus subtilis*, *Staphylococcus aureus*, and *Mycobacterium smegmatis*, respectively.

(4) Bax, A. *J. Mag. Reson.* **1983**, *53*, 517.

(5) Bax, A.; Freeman, R.; Frankiel, T.; Levitt, M. *J. Mag. Reson.* **1982**, *44*, 409.

(6) Hufford, C. D.; Lasswell, W. L. *Lloydia* **1978**, *41*, 156.

Communications

Asymmetric Oxidation of Chiral Enolates in the Preparation of Acyclic Tertiary α-Hydroxy Amides in High Optical Purity

Summary: Asymmetric oxidation of chiral acyclic, tetrasubstituted enolate **4c** with oxaziridines (+)-**1**/(−)-**2** in the presence and absence of HMPA affords optically active tertiary α-hydroxy amide **5c** in high optical purity (88–91% de). The application of (+)-**1**/(−)-**2** as "chiral probes" of enolate–electrophile reaction mechanisms is proposed.

Sir: Optically active acyclic tertiary α-hydroxy carbonyl compounds are valuable intermediates in the enantioselective synthesis of complex natural products such as insect pheromones[1] and antibiotics.[2] Generally these compounds are prepared by addition of organometallic reagents to optically active α-keto amides,[3] esters,[1b] oxazolines,[4] 1,3-oxathianes[1c,2,5] or the alkylation of α-keto amide dianions.[6] Recently we described methodology for the direct introduction of the hydroxy group adjacent to the carbonyl group via asymmetric enolate oxidation using the readily available camphorylsulfonyl oxaziridines (+)-**1** and (−)-**2** (50–95% ee).[7,8] High diastereofacial selectivity has also been reported for the oxidation of chiral enolates using 2-(phenylsulfonyl)-3-phenyloxaziridine (**3**),[9,10] MoOPH[11]

(1) (a) Sakito, Y.; Mukaiyama, T. *Tetrahedron Lett.* **1979**, 1027. (b) Whitesell, J. K.; Buchanan, C. M. *J. Org. Chem.* **1986**, *51*, 5443. (c) Eliel, E. L.; Ko, K.-Y. *J. Org. Chem.* **1986**, *51*, 5353.

(2) Kogure, T.; Eliel, E. L. *J. Org. Chem.* **1984**, *49*, 576.

(3) Soai, K.; Ishizaki, M. *J. Org. Chem.* **1986**, *51*, 3290.

(4) Meyers, A. I.; Slade J. *J. Org. Chem.* **1980**, *45*, 2785.

(5) Eliel, E. L. *Phosphorus and Sulfur* **1985**, *24*, 73 and references cited therein.

(6) Koft, E. R.; Williams, M. D. *Tetrahedron Lett.* **1986**, *27*, 2227.

(7) Davis, F. A.; Haque, M. S.; Ulatowski, T. G.; Towson, J. C. *J. Org. Chem.* **1986**, *51*, 2402.

(8) Davis, F. A.; Haque, M. S. *J. Org. Chem.* **1986**, *51*, 4083.

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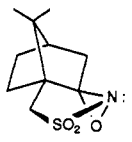
Table I. Asymmetric Oxidation of the Lithium Enolates of 2-Phenylpropanoic Amides 4 at −78 °C in THF

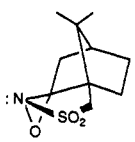
				tertiary α-hydroxy amides 5		
entry	oxaziridine	4 (Z =)	conditions	% de (ee)	(config)	% yield[a]
1	(+)-1	OMe		24.0[b]	(*R*)	61
2	(−)-2			28.0	(*S*)	57
3	(+)-1	NC_4H_8		35.0[c]	(*S*)	40
4			HMPA	20.0	(*R*)	35
5	3			67.0[d]	(*R*)	35
6	(+)-1			46.0	(*S*)	25 (40)[f]
7			HMPA	50.0	(*S*)	24 (37)[f]
8	(−)-2			30.0	(*S*)	30 (42)[f]
9	3			55.0[e]	(*S*)	54
10	(+)-1			48.4	(*S*)	60
11			HMPA[g]	88.7	(*S*)	53
12			HMPA[h]	89.5	(*S*)	65
13	(−)-2			88.3	(*S*)	55
14			HMPA[g]	90.7	(*S*)	55
15			HMPA[h]	86.2	(*S*)	50

[a] Isolated yield of pure material (>98%). [b] Based on a value of $[\alpha]_D$ +5° (*c* 4.9, EtOH) reported for pure (*S*)-methyl atrolactate.[28a] [c] See ref 17a. [d] See ref 17b. [e] % de determined by reverse-phase HPLC: Rainin Dynamax C-18 scout column 250 × 4.6 mm; solvent, MeOH/H_2O (60/40); flow rate 0.2 mL/min. First to be eluted was (*R*)-5c (R = Me). [f] Yield based on recovered starting material. [g] Ratio of THF/HMPA, 20:1. [h] Ratio of THF/HMPA added after enolate formation, 20:1.

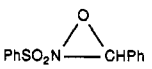
and dibenzyl peroxydicarbonate (80–98% de).[12] However, in the only example where the chiral enolate was tetrasubstituted, MoOPH oxidation resulted in low diastereoselectivity (40% de) and poor conversion (10%).[11]



(+)(2R,8aS)-1



(-)(2S,8aR)-2



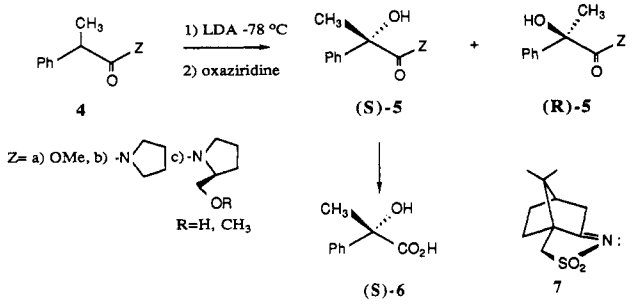
3

The oxidation or, for that matter, the reaction of any electrophile with an acyclic tetrasubstituted enolate with high enantio- or diastereoselectivity is expected to be problematic for several reasons. First, as discussed by Chamberlin and Reich, is the difficulty in forming a specific enolate regioisomer, particularly when the enolate is nearly symmetrically substituted.[13] For the same reason the enantio- or diastereofacial discrimination between the *si* and *re* faces of the enolate is also expected to be poor. Double asymmetric induction, the asymmetric oxidation of a chiral enolate, is a potentially useful strategy for preparing tertiary α-hydroxy carbonyl compounds in high optical purity.[14] In this context we describe preliminary results of our studies of the asymmetric oxidation of chiral tetrasubstituted enolates using (+)-1 and (−)-2 which afford tertiary α-hydroxy amides in high optical purity (90% de). In addition, the application of 1 or 2 as "chiral probes" for studying enolate–electrophile transition states is demonstrated.

The enolates chosen for study were those derived from 2-phenylpropionic acid and the chiral auxiliaries (*S*)-2-pyrrolidinemethanol and (*S*)-2-(methoxymethyl)-pyrrolidine.[15] For comparison we also explored the asymmetric oxidation of the achiral enolates of the methyl ester and pyrrolidine amide of this acid, **4a–b**. The lithium enolates were preformed by addition of a THF solution (4 mL) of **4a–c** (0.8 mmol) to 2.5 equiv of lithium diisopropylamide (LDA) in 10 mL of THF at −78 °C. After being warmed to 0 °C for 30 min, the solution was cooled to −78 °C and 2.5 equiv of oxaziridines **1**, **2**, or **3**, dissolved in 8 mL of THF, was added. After 30 min the reaction was quenched by addition of saturated NH_4Cl solution. The reaction mixture was then diluted with 30 mL of ether, washed with brine, and dried and the solvent was removed. The residue was extracted with cold ether (3 × 3 mL) to separate **5** from the insoluble sulfonimine **7**. Sulfonimine **7** was recovered in 70–80% yield. The α-hydroxy amides were further purified first by preparative TLC (silica gel) eluting with ether followed by preparative TLC (silica gel) eluting with ethyl acetate/chloroform/hexane (4:4:1).[16] The diastereoisomer composition of the products **5a–c** was determined by NMR and by HPLC. Absolute configurations were established by basic hydrolysis to give atrolactic acid (**6**) in 70–89% yield without racemization,[17] and reduction to 2-phenyl-1,2-propanediol in 60–70% yield using Red-Al/$NaBH_4$.[6,19] These results are summarized in Table I.

(9) Davis, F. A.; Vishwakarma, L. C. *Tetrahedron Lett.* **1985**, *26*, 3539.
(10) Evans, D. A.; Morrissey, M. M.; Dorow, R. L. *J. Am. Chem. Soc.* **1985**, *107*, 4346.
(11) Gamboni, R.; Tamm, C. *Tetrahedron Lett.* **1986**, *27*, 3999.
(12) Gore, M. P.; Vederas, J. C. *J. Org. Chem.* **1986**, *51*, 3700.
(13) Chamberlin, A. R.; Reich, S. H. *J. Am. Chem. Soc.* **1985**, *107*, 1440.
(14) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1 and references cited therein.

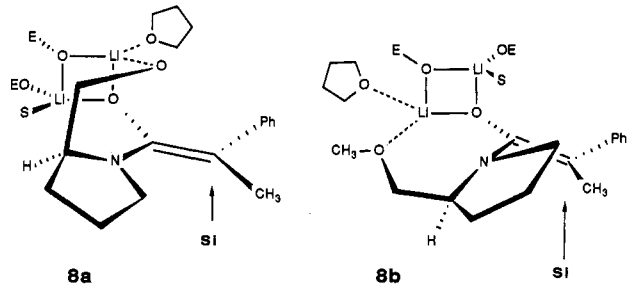
(15) Amide **4c** (R = H) was prepared by treatment of (*S*)-pyrrolidinemethanol with 2-phenylpropionyl chloride in the presence of triethylamine (57%) and had the following properties: bp 140 °C; 0.1 mm; $[\alpha]_D$ −49.3° (*c* 10, $CHCl_3$). Amide **4c** (R = Me) was prepared by treating the lithium salt of (*S*)-2-(methoxymethyl)pyrrolidine with 2-phenylpropionyl chloride (90%) and had the following properties: bp 130–135 °C; 0.05 mm; $[\alpha]_D$ −43.4° (*c* 2.0 $CHCl_3$). All new compounds where characterized by ^1H NMR and IR and gave satisfactory elemental analyses.
(16) α-Hydroxy amides (*S*)-**5c** (H) and (*S*)-**5c** (Me) had the following properties: oil, 50% de, $[\alpha]_D$ −76.9° (*c* 3.5, EtOH); oil, 88.7 % de $[\alpha]_D$ −120° (*c* 4.5, EtOH)
(17) (a) α-Hydroxy amides (−)-**5b,c** were hydrolyzed by refluxing with 1 N NaOH for 16 h to give (+)-(*S*)-atrolatic acid.[18] (b) The diastereoisomers of **5c** (R = H) were separated by preparative TLC (silica gel) double elution with 60:40 $CHCl_3/Et_2O$. At 250 MHz the CH_3 protons in (*R*)-**5c** (R = H) appear at δ 1.81 and in (*S*)-**5c** (R = H) appear at δ 1.76.
(18) Meyers, A. I.; Slade, *J. Synth. Commun.* **1976**, 601.
(19) Based on a value of $[\alpha]_D$ +4.2 (*c* 4.5, EtOH) reported for optically pure (*S*)-2-phenyl-1,2-propanediol by Lynch and Eliel.[20]
(20) Lynch, J. E.; Eliel, E. L. *J. Am. Chem. Soc.* **1984**, *106*, 2943.



As expected, the enantioselectivity for the asymmetric oxidation of the methyl ester and pyrrolidine amide enolates **4a,b** were low to moderate (24–35% ee) (entries 1–4). Since the *Z*/*E* enolate geometry of **4a** (Z = OMe) is 74:26,[21] and undoubtedly higher for the amide,[23] the enolate geometry can only be partially responsible for the low stereoselectivity. The other major influence must be the poor enantiofacial discrimination between the *re* and *si* faces of these enolates.

Asymmetric enolate oxidation of the (*S*)-2-pyrrolidinemethanol amide **4c** (R = H) with oxaziridine **3** gave (*S*)-**5** in 67% de and moderate chemical yield (entry 5). By contrast, oxidation with (+)-**1** or (−)-**2** gave (*R*)-**5** in poor chemical yield and only moderate de's (30–50%) (entries 6–8). Best results were observed for the (*S*)-2-(methoxymethyl)pyrrolidine amide enolates **4c** (R = Me) affording (*S*)-**5** in 88–91% de (entries 9–15). In all cases oxaziridines **1** and **2** gave (*S*)-**5c**, indicating that the resident chirality in the enolate controls the sense of the stereoselection. With **4c** (R = Me) lower diastereoselectivity was observed with (+)-**1**, mismatched pair, compared to (−)-**2**, matched pair (compare entries 10 and 13). However, the diastereoselectivity for the mismatched pair was improved from 48% to 89% by addition of HMPA. No effect was observed on addition of HMPA to the matched pair (entries 13–15). It is worthwhile noting that the improvement in de's occurs on addition of HMPA *after* enolate formation. This strongly suggests that HMPA changes the solution structure of the enolate, not its geometry (compare entries 10, 11, and 12). To the best of our knowledge this is the highest asymmetric induction reported for the reaction of any electrophile with a chiral, acyclic tetrasubstituted enolate.

Analogous to our original studies,[8] the results summarized in Table I are best interpreted in terms of an "open" transition state controlled by nonbonded steric interactions and the tetrameric cubic model suggested by Seebach et al. for reactions of lithium enolates.[24a] Little is known of the solution structure of lithium amide enolates except that they are dimers in the solid state.[24c] Lithium enolates of ketones exist as solvated, cubic tetrameric aggregates in the solid state,[24b,25] and Jackman[26] and Seebach[24] have shown that these structures also exist in solution. While still the subject of debate, there is increasing evidence that some aggregated form of the enolate is the actual reacting species in solution. We speculate that **8a**, the lithium enolate derived from **4c** (R = H), would be highly ordered and relatively inaccessible to attack by the bulky oxaziridine reagent. This could account for the low yields and moderate stereoselectivities observed for this enolate. On the other hand, enolate **8b** (**4c**, R = Me) is somewhat less ordered and reacts more easily with the oxaziridine. The enolates oxidized in the presence of HMPA should be the ones most accessible to the oxaziridine because HMPA is generally thought to disrupt metal chelation.[7,26] While these hypotheses can explain the stereoselectivities for the oxidation of **4** with (+)-**1** and (−)-**2**, it does not explain the change in configuration observed with oxaziridine **3** (entry 5). However, the active-site structures of oxaziridines **1** and **2** are different than in **3** and one is mindful that the energy differences are relatively small.



In summary the asymmetric oxidation of chiral enolates (double asymmetric induction) is a potentially useful strategy for the synthesis of chiral tertiary α-hydroxy carbonyl compounds in high optical purity. Camphorylsulfonyl oxaziridines (+)-**1** and (−)-**2** are "chiral probes" for exploring enolate–electrophile reaction mechanisms. Arguments based on structure–reactivity trends should be more reliable with these reagents because they have a well-defined active site and are conformationally rigid.

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Registry No. (+)-(2*R*,8a*S*)-**1**, 104322-63-6; (−)-(2*S*,8a*R*)-**2**, 104372-31-8; **3**, 19871-46-6; **4a**, 31508-44-8; **4b**, 74931-56-9; **4c** (R = H), 110457-27-7; **4c** (R = Me), 110457-28-8; (*R*)-**5a**, 13448-81-2; (*S*)-**5a**, 13448-80-1; (*S*)-**5b**, 107644-82-6; (*R*)-**5b**, 107644-83-7; (*R*)-**5c** (R = H), 110457-29-9; (*S*)-**5c** (R = H), 110457-30-2; (*S*)-**5c** (R = Me), 78805-22-8; **7**, 104319-35-9; (*S*)-2-pyrrolidinemethanol, 23356-96-9; 2-phenylpropionyl chloride, 22414-26-2; (*S*)-2-(methoxymethyl)pyrrolidine, 63126-47-6.

(21) The enolate geometry was determined by trapping with *tert*-butyldimethylsilyl chloride according to the procedure of Ireland et. al.[22]

(22) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868.

(23) Attempts to trap the pyrrolidine amide enolate **4** (Z = NC_4H_8) using *tert*-butyldimethylsilyl chloride were unsuccessful. This enolate is expected to have predomently (>74%) the *Z* geometry on the basis of previous observations.[9]

(24) (a) Seebach, D.; Amstutz, R.; Dunitz, J. D. *Helv. Chim. Acta* **1981**, *64*, 2622. (b) Amstutz, R.; Schweizer, W. B.; Seebach, D.; Dunitz, J. D. *Helv. Chim. Acta* **1981**, *64*, 2617. (c) Bauer, W.; Laube, T.; Seebach, D. *Chem. Ber.* **1985**, *118*, 764. Laube, T.; Dunitz, J. D.; Seebach, D. *Helv. Chim. Acta* **1985**, *68*, 1373. (d) Seebach, D.; Amstuts, R.; Laube, T.; Schweizer, W. B.; Dunitz, J. D. *J. Am. Chem. Soc.* **1985**, *107*, 5403. (e) Seebach, D. *Proceedings of the R. A. Welch Foundation Conference*, Houston, Nov 7–9, 1983; pp 83–145.

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(26) (a) Jackman, L. M.; Lange, B. C. *Tetrahedron* **1977**, *33*, 2737 and references cited therein. (b) Jackman, L. M.; Szeverenyi, N. M. *J. Am. Chem. Soc.* **1977**, *99*, 4954.

(27) Seebach et al. have proposed that HMPA reorganizes the lithium enolate tetramers, displacing the enolate from a coordination site within the cube.[24a]

(28) (a) Bonner, W. A.; Zderic, J. A.; Gasaletto, G. A. *J. Am. Chem. Soc.* **1952**, *74*, 5086. (b) Bonner, W. A.; Grimm, R. A. *J. Org. Chem.* **1967**, *32*, 3022.

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