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ASYMMETRIC SYNTHESIS OF FUNCTIONALIZED α-AMINO-β-HYDROXY ACIDS VIA CHIRAL NOREPHEDRINE-DERIVED OXAZOLIDINES

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Abstract - Both anti and syn enantiomerically pure functionalized α-amino-β-hydroxy acids and derivatives were synthesized starting from norephedrine-derived oxazolidine (1). The key-steps of the synthesis were the nucleophilic epoxidation of (1) and the nucleophilic opening of epoxy acid (3) with ammonia, both reactions proved regio- and diastereospecific. High yield preparation of the target anti aldehyde (9) was accomplished using standard procedures. The complementary syn aldehyde (23) was obtained via alkaline isomerization of the cis oxazolidinone (13) to the trans one. The aldehyde function of (9) and (23) provides a useful handle for manipulation to more complex structures, allowing potential access to a range of optically pure α-amino-β-hydroxy acids. The formal total synthesis of the monocyclic β-lactam antibiotic "carumonam" was accomplished using the present methodology.

Over the past fifty years many unusual amino acids have been isolated from natural sources.[1] Whereas their biological role and biogenesis cannot always be clearly seen, the antibiotic activity demonstrated by many of these compounds either alone or as a part of larger systems (i.e. polypeptides) make them attractive synthetic targets. In particular α-amino-β-hydroxy acids of varying complexity are important as components of biologically active peptides[2a] (e.g. Echinocandins, S-520, Vancomycin, Ristocetin A, Teicoplanin, Bouvardin, Cyclosporine A), of toxic peptides,[2b] of peptidases,[2c] of the polyoxins,[2d] as enzyme inhibitors,[2e] as precursors to β-lactam antibiotics,[3] and offer considerable challenge in terms of stereochemical control and synthetic efficiency.

Our group has been interested in the asymmetric synthesis of α-amino acids using different methods: the asymmetric electrophilic amination[4] (Fig.1, disconnection a) and the glycine enolate synthon approach[5a-d] (Fig.1, disconnection c).

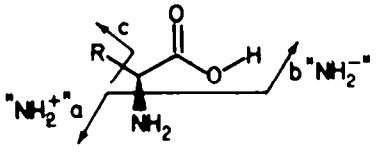
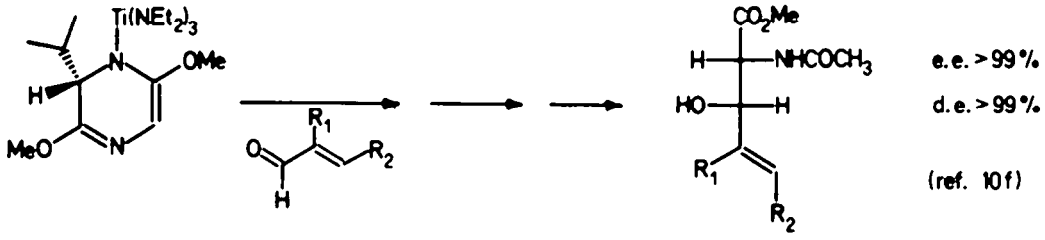


Fig.1

In this paper we disclose our results regarding the asymmetric synthesis of functionalized α-amino-β-hydroxy acids by the use of a nucleophilic amination approach[6] (Fig.1, disconnection b).

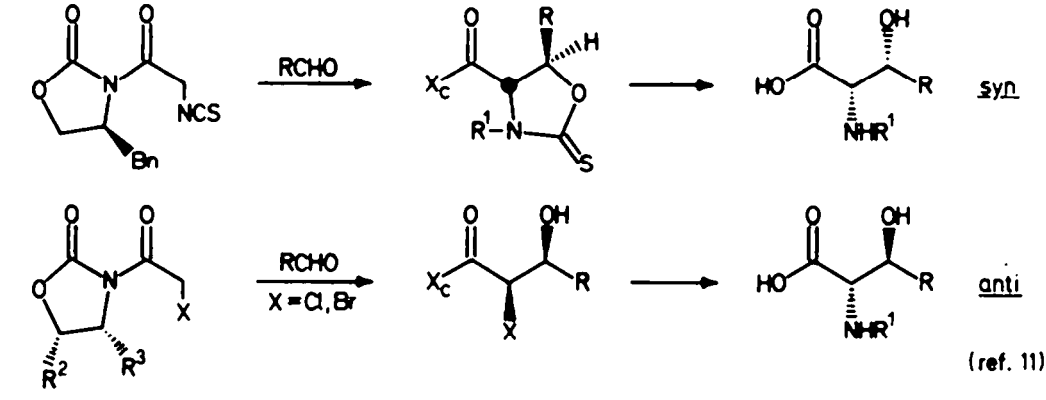
In recent years these compounds have been the target of a great deal of effort by many research groups,[7,8] particularly the groups of Mukaiyama,[9] Schollkopf,[10] Evans,[11] and Seebach.[12]

T. Mukaiyama and coworkers used both the nucleophilic amination approach[9a] and a chiral glycine enolate synthon[9b] in their enantioselective synthesis of polyhydroxy-α-amino acids. U. Schollkopf and coworkers used both an achiral glycine enolate synthon (ethyl isocyanoacetate)[10a,b] and the chiral one (bis-lactim ether)[10c-g] in their outstanding synthesis of functionalized α-amino-β-hydroxy acids (Scheme 1).



Scheme 1

D.A. Evans and coworkers synthesized both syn and anti enantiomerically pure α-amino-β-hydroxy acids via diastereoselective aldol addition of chiral 3-isothiocyanoacetyl- and 3-haloacetyl-2-oxazolidinones (Scheme 2).[11]

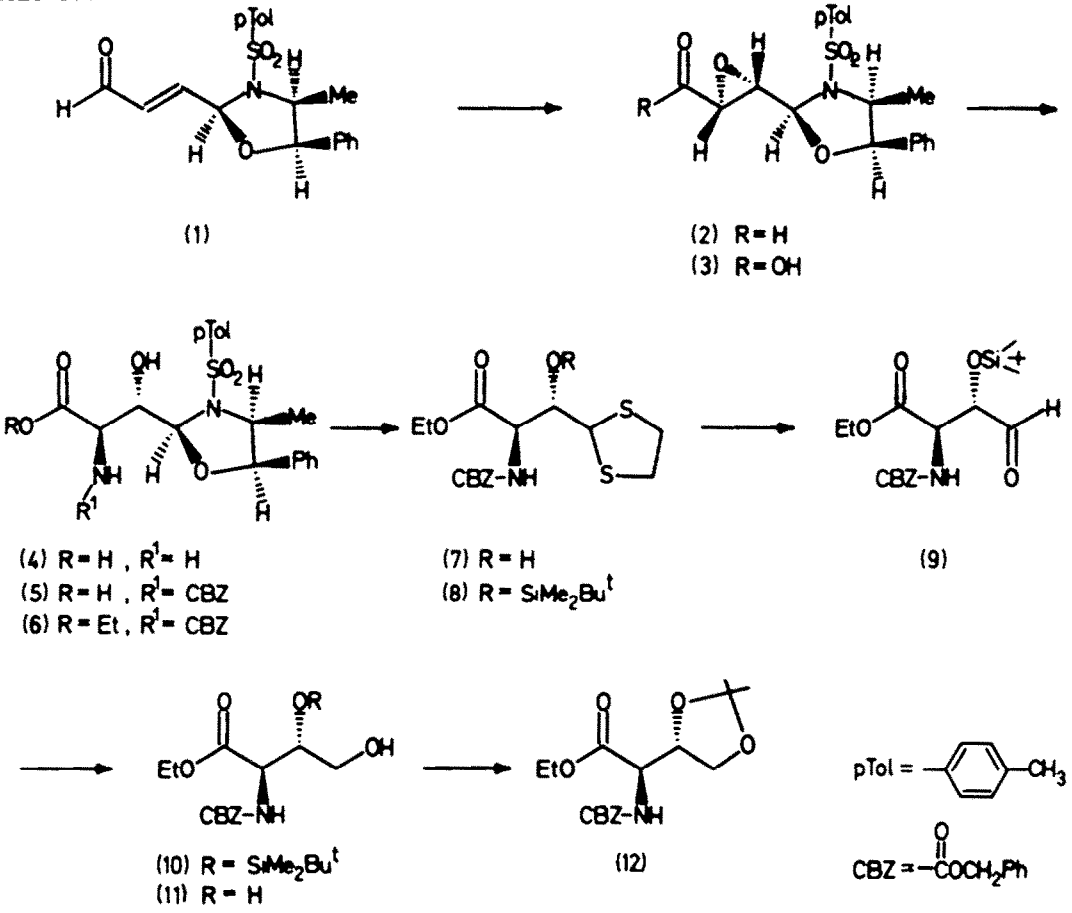


Scheme 2

Several syn α-amino-β-hydroxy acids of high enantiomeric purity were synthesized by Seebach and coworkers[12] via diastereoselective aldol reaction of chiral imidazolidinone-enolates with carbonyl compounds.

Our method starts with the α,β-unsaturated aldehyde (1), which can be easily prepared on a large scale from one of the two commercially available norephedrine enantiomers (1R,2S). It is known that these substrates show a high degree of π-face differentiation induced by the norephedrine-derived oxazolidine, and that nucleophilic additions to the conjugated system[13] give a better performance than electrophilic additions to the double bond.[14] Aldehyde (1) was subjected to various nucleophilic epoxidation conditions (sodium hypochlorite in aqueous pyridine,[15] alkaline hydrogen peroxide,[16] potassium tert-butyl peroxide[17]). The best results were obtained using potassium hypochlorite[18] in aqueous THF: the epoxidation was

complete after 1.5 hr at 0 deg.C, but the mixture was stirred two additional hours at room temperature to oxidize the epoxy aldehyde (2) to epoxy acid (3), which was obtained in 90% overall yield as a single isomer (>20:1 by ^{1}H NMR spectroscopy) (Scheme 3).



Scheme 3

The stereochemical outcome of this epoxidation can be rationalized using the transition structure models A and B (Fig. 2). The very electronegative allylic substituent (oxygen) is aligned "anti" to the forming bond in both A and B, so that the withdrawal of electrons from the π-system can be maximized (Felkin-Anh model).[19a] When the σ^*_{C-O} orbital is aligned "anti" to the forming bond, its overlap with the HOMO of the transition state, consisting of a mixture of the nucleophile HOMO and the electrophile LUMO, is increased, and stabilization is maximized.[19b] A is favored over B, apparently for steric reasons.[13]

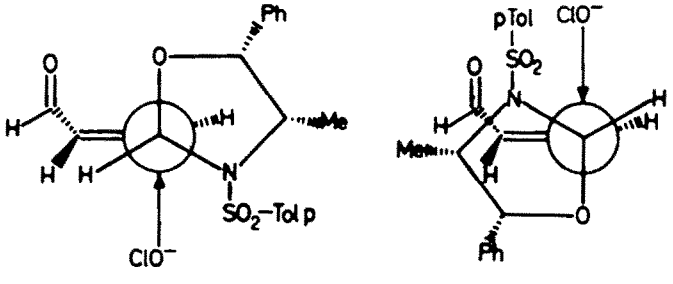
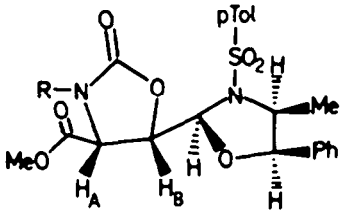
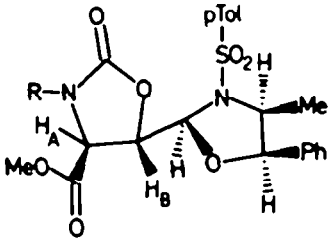


Fig. 2

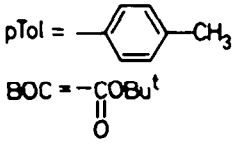
Trans epoxy acid (3) was then treated with 23% aqueous ammonia solution at 70 deg.C for 3 hr to give, regio- and stereospecifically,[20] the anti α-amino-β-hydroxy acid (4) in quantitative yield as a single isomer (>50:1 by ^{1}H NMR spectroscopy). The anti configuration was proved by conversion of (4) into the cis oxazolidinone (14) (a. $COCl_2$,KOH,H_2O; b. CH_2N_2; c.BOC_2O) characterized by a coupling constant J_{A-B}= 8.9 Hz.[21] Isomerization of cis (13) under alkaline conditions[5d] (KOH,MeOH,reflux) followed by standard derivatization (a. CH_2N_2; b. BOC_2O) gave complete conversion (>100:1) into the trans oxazolidinone (16) characterized by a coupling constant J_{A-B}= 2.9 Hz.[21] (Scheme 4)



(13) R = H
(14) R = BOC



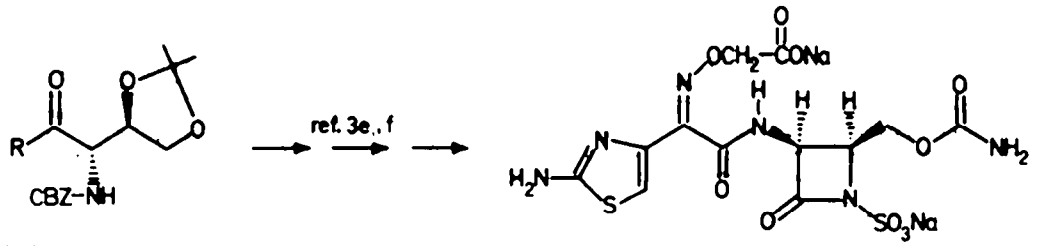
(15) R = H
(16) R = BOC



Scheme 4

α-Amino-β-hydroxy acid (4) was then transformed into the N-CBZ derivative (5) (CBZ_2O, Shotten-Baumann),[22] which was treated with diazoethane[23] to give, after flash-chromatography, ethyl ester (6) in 64% overall yield from compound (1) with no intermediate purification (91% average yield per step). The chiral oxazolidine was then removed by treatment of (6) with ethanedithiol and BF_3-OEt_2 in methylene chloride to give (7) (67%; 90% recovery of optically pure N-tosyl norephedrine), which was protected as TBDMS ether (TBDMS-OTf,lutidine,CH_2Cl_2,80%).[24] Dithiolane (8) was then hydrolysed (CH_3I,$CaCO_3$,acetone-water)[25] to give the target aldehyde (9) in 80% yield. The aldehyde function of (9) provides a useful handle for manipulation to more complex structures, allowing potential access into a range of optically pure polyfunctional α-amino-β-hydroxy acids, especially those of unusual, non-protein or unnatural types which are not easily accessible by fermentation. The absolute configuration and the optical purity of aldehyde (9) were confirmed by reduction to give (10) ($NaBH_4$,MeOH,H_2O,85%), hydrolysis of the silyl ether to give (11) (HF,CH_3CN,H_2O,85%),[26] and ketal formation (acetone,2,2-dimethoxypropane, p-TsOH, 90%) to give (12) with the same optical rotation as that reported for the compound previously synthesized by Moriwake and coworkers from D-tartaric acid.[8p]

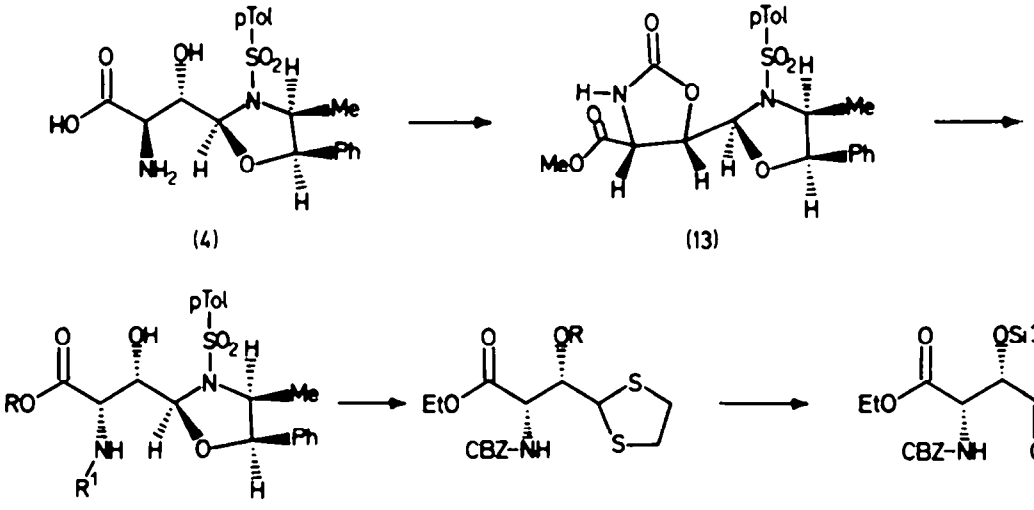
A simple and straightforward application of the method described above (preparation of enantiomerically pure functionalized anti α-amino-β-hydroxy acids) is the formal total synthesis of the monocyclic β-lactam antibiotic "carumonam", which is under joint development by Hoffmann-La Roche and Takeda Chemical Industries.[3e,f] Starting from 1S,2R norephedrine, and following our procedure, compound (17) was synthesized and subjected to solvolysis with methanolic ammonia to give amide (18) in 70% yield (Scheme 5).[27] Nine step conversion of (18) into "carumonam" was recently reported by Hoffmann-La Roche chemists, who utilized L-ascorbic acid as starting material.[3e,f]



(17) R = OEt
(18) R = NH_2

Scheme 5

The complementary syn α-amino-β-hydroxy acid series was easily accessible through the oxazolidinone chemistry described above (Scheme 4). Anti α-amino-β-hydroxy acid (4) was converted into the cis oxazolidinone (13) [a. $COCl_2$,KOH,H_2O b. CH_2N_2; 75% overall yield from (1)] which was completely isomerized to trans oxazolidinone (KOH,MeOH,reflux) and saponified (KOH,MeOH-H_2O) to give the syn α-amino-β-hydroxy acid (19). Treatment of (19) with CBZ_2O under Shotten-Baumann conditions[22] followed by diazoethane[23] gave, after flash-chromatography, ethyl ester (20) in 70% overall yield from oxazolidinone (13) without intermediate purification. The target syn-aldehyde (23) was easily prepared from (20) through the same sequence of reactions described above for the anti series (a. ethanedithiol, BF_3-OEt_2 b. TBDMS-OTf,lutidine c. CH_3I,$CaCO_3$,acetone-water)(Scheme 6).

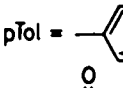


(4) (13)

(19) R = H , R^1 = H
(20) R = Et , R^1 = CBZ

(21) R = H
(22) R = $SiMe_2Bu^t$

(23)

pTol = 

CBZ = $-COCH_2Ph$

Scheme 6

In conclusion, norephedrine-derived oxazolidine (1) has proven to be a useful and versatile synthon for the synthesis of both anti and syn enantiomerically pure functionalized α-amino-β-hydroxy acids and derivatives.

EXPERIMENTAL

α,β-Unsaturated aldehyde (1). A solution of fumaraldehyde bisdimethyl acetal[28] (6.05 g, 34.38 mmol) in dry benzene (100 ml) was treated with (1R,2S) N-p-tosyl norephedrine[13] (4.20 g, 13.77 mmol) and pyridinium tosylate (1.38 g, 5.50 mmol), under nitrogen with stirring. The mixture was heated at reflux for 30 min, with a bypassed dropping funnel filled with 4 Å molecular sieves between the flask and the reflux condenser. Then the mixture was cooled to room temperature, ethyl ether (60 ml) and a saturated aqueous ammonium chloride solution (100 ml) were added, the organic phase was separated, dried over sodium sulfate, filtered and the solvent evaporated under reduced pressure. The crude product was purified by flash chromatography (n-hexane-ethyl acetate 8:2) to give the dimethyl acetal of aldehyde (1) in 89% yield. The dimethyl acetal was dissolved in acetone-water (5%:1; 55 ml) and treated with Amberlyst-15 (1.3 g). After stirring for 3 hr at room temperature, the resin was filtered off and the solvent evaporated under reduced pressure to give (1) in quantitative yield. $[\alpha]_D$=-47.6° (c=0.98, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 80 MHz) δ 0.75 (3H, d, J=6.70 Hz), 2.40 (3H, s), 3.75-4.25 (1H, m), 4.40 (1H, d, J=5.55 Hz), 5.70 (1H, dd, J=3.90, 0.80 Hz), 6.52 (1H, ddd, J=7.70, 16.10, 0.80 Hz), 6.93 (1H, dd, J=3.90, 16.10 Hz), 7.09-7.93 (9H, m), 9.60 (1H, d, J=7.70 Hz). IR ($CHCl_3$) ν 1695, 1600, 1355, 1165 cm^{-1} (selected values). Anal.Calcd for $C_{20}H_{21}NO_4S$: C, 64.67; H, 5.70; N, 3.77. Found: C, 64.00; H, 5.78; N, 3.88.

Trans epoxy acid (3). A solution of α,β-unsaturated aldehyde (1) (13.4 g, 36.1 mmol) in THF (99.5 ml) was treated with a ca. 1.5-2.0 N KClO aqueous solution[18] (142 ml) at 0°C. After 30 min more KClO aqueous solution (142 ml) was added and the mixture was stirred 1 hr at 0°C and 2 hr at room temperature to complete the epoxy aldehyde oxidation to epoxy acid. 5% aqueous KOH solution (268 ml) was then added and the reaction mixture was extracted with n-hexane-ethyl ether 4:1 (3 x 50 ml). The aqueous phase was acidified to pH=3 with 10% aqueous HCl at 0°C and extracted with ethyl acetate. The organic phase was washed with 5% aqueous HCl, 10% aqueous sodium sulfite solution, brine, dried over sodium sulfate, filtered and the solvent evaporated under reduced pressure to give, without further purification, the epoxy acid (3) . Yield: 90%. ^{1}H NMR ($CDCl_3$-D_2O, 80 MHz) δ 0.80 (3H, d, J=6.70 Hz), 2.47 (3H, s), 3.75 (1H, dd, J=1.92 Hz), 3.85 (1H, d, J=1.92 Hz), 3.90-4.21 (1H, m), 4.30 (1H, d, J=5.10 Hz), 5.35 (1H, d, J=1.92 Hz), 7.00-7.90 (9H, m). ^{13}C NMR ($CDCl_3$, 80 MHz) δ 16.6, 21.6, 50.3, 58.5, 58.6, 81.8, 87.3, 125.8, 127.9, 128.2, 128.4, 130.3, 134.3, 134.6, 144.9, 172.8. IR ($CHCl_3$) ν 3500, 1770, 1730, 1355, 1165 cm^{-1} (selected values).

α-Amino-β-hydroxy acid (4). Epoxy acid (3) (13.1 g, 32.5 mmol) was dissolved in 17% aqueous ammonia solution (174 ml), the reaction vessel was stoppered and the mixture stirred at 70°C for 2 hr. Then 34% aqueous ammonia solution (87 ml) was added, and the mixture stirred under the above conditions for 1 additional hr. Then the reaction mixture was concentrated in vacuo and azeotroped with absolute methanol (4 x 400 ml) to give compound (4) in quantitative yield with no further purification. ^{1}H NMR (DMSO-d_6/D_2O, 300 MHz) δ 0.80 (3H, d, J=7.50 Hz), 2.40 (3H, s), 3.57 (1H, d, J=3.75 Hz), 3.86 (1H, dd, J=3.75, 6.20 Hz), 3.96 (1H, d, J=5.20 Hz), 4.26-4.33 (1H, m), 5.60 (1H, d, J=6.20 Hz), 7.12-7.31 (5H, m), 7.50 (2H, d, J=8.50 Hz), 7.93 (2H, d, J=8.50 Hz).

N-CBZ-α-amino-β-hydroxy acid ethyl ester (6). A solution of α-amino-β-hydroxy acid (4) (3.21 g, 7.4 mmol) in 1,4-dioxane(74 ml) and 1N NaOH (8.1 ml) was treated with CBZ_2O[22] (2.7 g, 9.6 mmol). The reaction mixture was stirred at room temperature for 4.5 hr then concentrated in vacuo, acidified with 5% HCl at 0°C, extracted with ethyl acetate. The organic extracts were dried over sodium sulfate, and evaporated under reduced pressure. The crude product was dissolved in ethyl ether-MeOH (1:1) and treated with diazoethane[23] to give, after flash chromatography (n-hexane-ethyl acetate 7:3), ethyl ester (6) in 64% overall yield from compound (1) (without intermediate purification). $[\alpha]_D$=-13.7°(c=1.9, $CHCl_3$). mp 40-43°C. ^{1}H NMR ($CDCl_3$/D_2O, 80 MHz) δ 0.85 (3H, d, J=6.67 Hz), 1.25 (3H, t, J=7.47 Hz), 2.44 (3H, s), 4.09 (1H, dd, J=7.30, 2.20 Hz), 4.00-4.40 (4H, m), 4.91 (1H, dd, J=2.20, 9.02 Hz), 5.13 (2H, s), 5.21 (1H, d, J=7.30 Hz), 5.80 (1H, d, J=9.02 Hz), 7.00-7.90 (14H, m). ^{13}C NMR ($CDCl_3$, 80 MHz) δ 14.2, 17.2, 21.6, 56.3, 59.3, 61.8, 67.1, 76.7, 81.5, 90.4, 156.1, 169.3 (selected values). IR ($CHCl_3$) ν 3440, 1730, 1510, 1505, 1345, 1160 cm^{-1} (selected values). Anal.Calcd for $C_{30}H_{34}N_2O_8S$: C, 61.84; H, 5.88; N, 4.81. Found: C, 61.88; H, 5.89; N, 4.79.

Dithiolane (7). A solution of ethyl ester (6) (2.6 g, 4.47 mmol) in methylene chloride (44.7 ml) was treated with ethanedithiol (3.7 ml) and boron trifluoride etherate (1.6 ml, 13.41 mmol), under nitrogen with stirring. After stirring for 15 hr at room temperature, 5% sodium bicarbonate aqueous solution was added and the reaction mixture extracted with methylene chloride. The organic extracts were dried over sodium sulfate and evaporated in vacuo. The crude product was purified by flash chromatography (diisopropyl ether-benzene 6:4) to give dithiolane (7) in 67% yield. $[\alpha]_D$= -31.9°(c=0.97, $CHCl_3$). ^{1}H NMR ($CDCl_3$/D_2O, 80 Mhz) δ 1.30 (3H, t, J=7.20 Hz), 3.17 (4H, s), 3.69 (1H, dd, J=3.47, 8.67 Hz), 4.17 (2H, q, J=7.20 Hz), 4.60 (1H, d, J=8.67 Hz), 4.62 (1H, dd, J=3.47, 8.00 Hz), 5.09 (2H, s), 5.64 (1H, d, J=8.00 Hz), 7.20-7.32 (5H, m). ^{13}C NMR ($CDCl_3$, 80 MHz) δ 14.1, 37.7, 38.7, 55.6,

57.3, 61.9, 67.2, 77.4, 156.1, 169.4 (selected values). IR ($CHCl_3$) ν 3440, 1725, 1600, 1510, 1505 cm^{-1} (selected values). Anal. Calcd for $C_{16}H_{21}NO_5S_2$: C, 51.73; H, 5.70; N, 3.77. Found: C, 51.80; H, 5.65; N, 3.80.

O-TBDMS dithiolane (8). A solution of dithiolane (7) (1.1 g, 2.96 mmol) in dry methylene chloride (59.3 ml), at 0°C under nitrogen, was treated with 2,6-lutidine (2.8 ml, 23.68 mmol) and TBDMS-OTf (2.0 ml, 8.88 mmol).[24] After 30 min the reaction mixture was quenched with MeOH and the solvent evaporated under reduced pressure. The crude product was purified by flash chromatography (n-hexane-ethyl acetate 88:12) to give compound (8) in 80% yield. ^1H NMR ($CDCl_3$, 80 MHz) δ 0.28 (3H, s), 0.32 (3H, s), 1.05 (9H, s), 1.42 (3H, t, J=7.20 Hz), 3.27 (4H, s), 3.97 (1H, dd), 4.26 (2H, q, J=7.20 Hz), 4.72 (1H, d, J=9.30 Hz), 4.88 (1H, dd, J=6.60, 1.30 Hz), 5.15 (2H, s), 5.65 (1H, d, J=6.60 Hz), 7.26 (5H, s). Anal.Calcd for $C_{22}H_{35}NO_5S_2Si$: C, 54.40; H, 7.26; N, 2.88. Found: C, 54.48; H,7.23; N, 2.90.

Aldehyde (9). A solution of dithiolane (8) (1.9 g, 3.94 mmol) in acetone-water 4:1 (79 ml) was treated with calcium carbonate (1.2 g, 11.81 mmol) and methyl iodide (2.4 ml, 39.40 mmol). The mixture was stirred at 60° C for 24 hr, then filtered on a celite pad, washing the filter cake with methylene chloride. The organic phase was washed with a 5 M ammonium acetate solution, water, dried over sodium sulfate and the solvent evaporated under reduced pressure. The crude product was purified by flash chromatography (n-hexane-ethyl acetate 8:2). Yield: 80%. $[\alpha]_D$=-33.5° (c=1.5, $CHCl_3$). ^1H NMR ($CDCl_3$, 80 MHz) δ 0.00 (3H, s), 0.03 (3H, s), 0.88 (9H,s), 1.22 (3H, t, J=7.07 Hz), 4.00-4.34 (2H, m), 4.40 (1H, d, J=2.24 Hz), 4.80 (1H, dd, J=2.24, 7.37 Hz), 5.11 (2H, s), 5.62 (1H, d, J=7.37 Hz), 7.32 (5H, s), 9.62 (1H, s). IR ($CHCl_3$) ν 3430, 2950, 2930, 2860, 1740, 1570, 1500 cm^{-1} (selected values). Anal.Calcd for $C_{20}H_{31}NO_6Si$: C, 58.65; H, 7.63; N, 3.42. Found: C, 58.71; H, 7.60; N, 3.38.

Alcohol (10). A solution of aldehyde (9) (1.3 g, 3.18 mmol) in MeOH-water (10.5:1; 34.5 ml) at 0°C was treated with $NaBH_4$ (242 mg, 6.36 mmol). After 15 min the reaction mixture was acidified to pH=3 with 5% HCl, concentrated in vacuo and extracted with ethyl acetate. The organic extracts were dried over sodium sulfate, filtered and evaporated under reduced pressure. The crude product was purified by flash chromatography (n-hexane-ethyl acetate 7:3) to give alcohol (10) in 85% yield. ^1H NMR ($CDCl_3$,80 MHz) δ 0.05 (6H, s), 0.85 (9H, s), 1.27 (3H, t, J=7.18 Hz), 2.28 (1H, bs), 3.64 (2H, d, J=5.13 Hz), 3.92-4.10 (1H, m), 4.18 (2H, q, J=7.18 Hz), 4.52 (1H, dd, J=3.97, 8.33 Hz), 5.10 (2H, s), 5.67 (1H, d, J=8.33 Hz), 7.30 (5H, s). Anal.Calcd for $C_{20}H_{33}NO_6Si$: C, 58.37; H, 8.08; N, 3.40. Found: C, 58.43; H, 8.09; N, 3.42.

3,4-Dihydroxy ethyl ester (11). A solution of alcohol (10) (1.1 g, 2.7 mmol) was treated with a 1 M solution of HF (from 40% aqueous HF) in acetonitrile[26] (2.83 ml, 2.83 mmol) at 0°C. After stirring for 8 hr at 0°C, water was added and the reaction mixture was extracted with methylene chloride, the organic extracts dried over sodium sulfate and the solvent evaporated under reduced pressure. The product was purified by flash chromatography (ethyl acetate- n-hexane 75:25). Yield: 85%. $[\alpha]_D$=-11.0° (c=1.1, $CHCl_3$) ^1H NMR ($CDCl_3$, 80 MHz) δ 1.29 (3H, t, J=7.12 Hz), 2.65 (2H, bs), 3.67 (2H, d, J=4.24 Hz), 3.82-4.00 (1H, m), 4.21 (2H, q, J=7.12 Hz), 4.41 (1H,dd, J=5.39, 7.98 Hz), 5.10 (2H, s), 5.76 (1H, d, J=7.98 Hz), 7.32 (5H, s). Anal.Calcd for $C_{14}H_{19}NO_6$: C, 56.56; H, 6.44; N, 4.71. Found: C, 56.60; H, 6.40; N,4.78.

3,4-O-Isopropylidene ethyl ester (12). A solution of (11) (0.683 g, 2.3 mmol) in dry acetone (1.7 ml) and 2,2-dimethoxypropane (5.6 ml) was treated with monohydrate p-TsOH (8.7 mg, 0.046 mmol) at 0°C under nitrogen. After stirring for 8 hr, the reaction mixture was quenched with triethylamine and evaporated under reduced pressure. The crude product was purified by flash chromatography (ethyl acetate-n-hexane 25:75). Yield: 90%. $[\alpha]_D$=-29.9° (c=0.9, methylene chloride). ^1H NMR ($CDCl_3$, 200 MHz) δ 1.27 (3H, t, J=7.25 Hz), 1.30 (3H, s), 1.37 (3H, s), 3.98-4.12 (2H, m), 4.21 (2H, q, J=7.25 Hz), 4.30-4.38 (1H, m), 4.44 (1H, dd, J=4.25, 8.50 Hz), 5.11 (2H, s), 5.55 (1H, d, J=8.50 Hz), 7.33 (5H, s). Anal.Calcd for $C_{17}H_{23}NO_6$: C, 60.52; H, 6.87; N, 4.15. Found: C, 60.60; H, 6.89; N, 4.11.

Cis oxazolidinone (13). A solution of α-amino-β-hydroxy acid (4) (0.425 g, 1.01 mmol) in THF-toluene (5.89:1; 11.7 ml) at 0°C was treated with 0.25 N KOH (12.2 ml, 3.04 mmol) and a 20% phosgene solution in toluene (1.7 ml). After stirring for 30 min, the reaction mixture was acidified to pH=3 with 5% HCl, concentrated in vacuo and extracted with ethyl acetate. The organic extracts were dried over sodium sulfate, filtered and evaporated under reduced pressure. The crude product was dissolved in ethyl ether-MeOH 1:1 and treated with diazomethane to give, after flash chromatography (n-hexane-ethyl acetate 1:1), compound (13) in 75% yield. ^1H NMR ($CDCl_3$, 80 MHz) δ 0.71 (3H, d, J=7.20 Hz), 2.43 (3H,s), 3.72 (3H, s), 4.07-4.41 (1H, m), 4.62 (1H, d, J=5.61 Hz), 4.70 (1H, d, J=4.49 Hz), 4.72 (1H, d, J=2.24 Hz), 5.66 (1H, dd, J=4.49, 2.24 Hz), 6.01 (1H, bs), 7.02-7.91 (9H, m). IR ($CHCl_3$) ν 3460, 1790, 1755, 1600, 1160 cm^{-1} (selected values). Anal.Calcd for $C_{22}H_{24}N_2O_7S$: C, 57.38; H, 5.25; N, 6.08. Found: C, 57.40; H, 5.31; N,6.01.

Cis N-BOC oxazolidinone (14). A solution of cis oxazolidinone (13) (32.0 mg, 0.07 mmol) in THF (0.7 ml) was treated with BOC_2O (19.7 mg, 0.09 mmol), 4-dimethylamino

pyridine (1.7 mg, 0.01 mmol) and stirred for 4 hr at room temperature. The solvent was evaporated under reduced pressure and the product purified by flash chromatography (n-hexane-ethyl acetate 7:3). Yield: 80%. ^{1}H NMR ($CDCl_3$, 80 MHz) δ 0.72, (3H, d, J=7.20 Hz), 1.51 (9H, s), 2.45 (3H, s), 3.72 (3H, s), 4.18-4.52 (2H, m), 4.62 (1H, d, J=8.87 Hz), 4.86 (1H, t, J=8.87 Hz), 5.55 (1H, d, J=8.87 Hz), 7.05-7.85 (9H, m). Anal.Calcd for C, H, N, O, S: C, 57.85; H, 5.76; N, 5.00. Found:

[redacted]

in MeOH (0.9 ml) was treated with a 0.59 M solution of KOH (0.75 ml, 0.44 mmol) in MeOH and refluxed for 1 hr. The reaction mixture was cooled to 0°C and acidified with 5% HCl, diluted with water and extracted with ethyl acetate. The organic extracts were dried over sodium sulfate, filtered and evaporated in vacuo. The crude product was dissolved in ethyl ether-MeOH 1:1, treated with diazomethane and purified by flash chromatography (n-hexane-ethyl acetate 55:45) to give compound (15) in 70% yield. ^{1}H NMR ($CDCl_3$, 80 MHz) δ 0.81 (3H, d, J=6.67 Hz), 2.46 (3H, s), 3.87 (3H, s), 3.92-4.20 (1H, m), 4.45 (1H, d, J=5.98 Hz), 4.83 (1H, d, J=3.96 Hz), 5.18 (1H, dd, J=3.96, 1.87 Hz), 5.38 (1H, d, J=1.87 Hz), 5.65 (1H, bs), 7.03-7.92 (9H, m). Anal.Calcd for $C_{22}H_{24}N_2O_7S$: C, 57.38; H, 5.25; N, 6.08. Found: C, 57.30; H, 5.27; N, 6.12.

Trans N-BOC oxazolidinone (16). Trans N-BOC oxazolidinone (16) was obtained from trans oxazolidinone (15) as reported for the synthesis of (14). Yield: 82%. ^{1}H NMR ($CDCl_3$, 80 MHz) δ 0.80 (3H, d, J=6.67 Hz), 1.50 (9H, s), 2.46 (3H, s), 3.86 (3H, s), 3.87-4.20 (1H, m), 4.50 (1H, d, J=5.76 Hz), 4.96 (1H, dd, J=2.90, 1.80 Hz), 5.12 (1H, d, J=2.90 Hz), 5.30 (1H, d, J=1.80 Hz), 7.00-7.90 (9H, m). Anal.Calcd for $C_{27}H_{32}N_2O_9S$: C, 57.85; H, 5.75; N, 5.00. Found: C, 57.87; H, 5.70; N, 4.94.

3,4-O-Isopropylidene amide (18). A solution of 3,4-O-isopropylidene ethyl ester (17) (48 mg, 0.142 mmol) in MeOH (2 ml) was treated with anhydrous ammonia at -15°C for 1 hr and the mixture was stirred at room temperature for 8 hr. Then the solvent was evaporated under reduced pressure and the product purified by flash chromatography (ethyl acetate-n-hexane 7:3) to give amide (18) in 70% yield. $[\alpha]_D$=+5.6° (c=0.5, DMSO), lit.[30] $[\alpha]_D$=+6.11° (c=0.9665 ,DMSO). mp 181-182°C. ^{1}H NMR (DMSO-d_6, 200 MHz) δ 1.23 (3H, s), 1.31 (3H, s), 3.76 (1H, dd, J=8.61, 5.49 Hz), 3.90 (1H, dd, J=8.61, 6.22 Hz), 4.07-4.25 (2H, m), 5.02 (2H, s), 7.05 (1H, b.s), 7.30 (1H, b.s), 7.35 (1H, b.s), 7.32 (5H, s). Anal.Calcd for $C_{15}H_{20}N_2O_5$: C, 58.43; H, 6.54; N, 9.09. Found: C, 58.33; H, 6.62; N,9.04.

N-CBZ-α-amino-β-hydroxy acid ethyl ester (20). A solution of cis oxazolidinone (13) (287 mg, 0.624 mmol) in MeOH (2.5 ml) was treated with a 0.59 N solution of KOH in MeOH (2.1 ml) and heated at reflux for 1 hr. After adding a 2 N aqueous KOH solution (4.24 ml) and refluxing for 10 hr, the reaction mixture was cooled to 0°C, acidified to pH=3 with 5% HCl and concentrated in vacuo. The reaction mixture was extracted with methylene chloride, the extracts dried over sodium sulfate and evaporated under reduced pressure to give the syn α-amino-β-hydroxy acid hydrochloride (19) in 80% yield with no further purification. A solution of (19) (228 mg, 0.499 mmol) in 1,4-dioxane(5 ml) and 1 N aqueous NaOH (1.1 ml) was treated with CBZ_2O (186 mg, 0.649 mmol). The reaction mixture was stirred at room temperature for 2 hr then concentrated in vacuo, acidified with 5% HCl at 0°C, and extracted with ethyl acetate. The organic extracts were dried over sodium sulfate and evaporated under reduced pressure. The crude product was dissolved in ethyl ether-MeOH (1:1) and treated with diazoethane to give, after flash chromatography (n-hexane-ethyl acetate 7:3), ethyl ester (20) in 70% overall yield from compound (13). $[\alpha]_D$=-35.0° (c=1.02, $CHCl_3$). ^{1}H NMR ($CDCl_3/D_2O$, 80 MHz) δ 0.90 (3H, d, J=6.67 Hz), 1.30 (3H, t, J=7.20 Hz), 2.47 (3H, s), 4.00-4.60 (4H, m), 4.20 (1H, dd, J=1.53, 7.64 Hz), 4.82 (1H, d, J=7.64 Hz), 5.12 (2H, s), 7.00-7.90 (14H, m). IR ($CHCl_3$) ν 3500, 3430, 1730, 1600, 1505, 1500, 1345, 1160 cm^{-1} (selected values). Anal.Calcd for $C_{30}H_{34}N_2O_8S$: C, 61.84; H, 5.88; N, 4.81. Found: C, 61.87; H, 5.80; N, 4.83.

Dithiolane (21). A solution of ethyl ester (20)(0.122 g, 0.209 mmol) in dry methylene chloride (2.1 ml) was treated with ethanedithiol (0.173 ml) and boron trifluoride etherate (0.078 ml, 0.629 mmol) under nitrogen, and stirred for 40 hr at room temperature. During this period more boron trifluoride etherate was added (3x0.039 ml, 3x0.314 mmol). The reaction mixture was quenched and worked up as reported above for the preparation of (7). The crude product was purified by flash chromatography (n-hexane-ethyl acetate 7:3) to give (21) in 70% yield. ^{1}H NMR ($CDCl_3$, 80 MHz) δ 1.28 (3H, t, J=7.05 Hz), 2.70 (1H,b.s), 3.22 (4H, s), 3.88 (1H,dd, J=1.76, 9.36 Hz), 4.21 (2H, q, J=7.05 Hz), 4.50 (1H, d, J=9.36 Hz), 4.73 (1H, dd, J=1.76, 9.73 Hz), 5.12 (2H, s), 5.49 (1H, d, J=9.73 Hz), 7.36 (5H,s). IR ($CHCl_3$) ν 3550, 3440, 1725, 1510, 1330 cm^{-1} (selected values).

O-TBDMS dithiolane (22). (22) was obtained from dithiolane (21) as reported above for the preparation of (8) in 80% yield. ^{1}H NMR ($CDCl_3$, 80 MHz) δ 0.00 (3H, s), 0.20 (3H, s), 0.88 (9H, s), 1.28 (3H, t, J=7.37 Hz), 3.17 (4H, s), 4.02-4.30 (3H, m), 4.52 (1H, d, J=8.65 Hz), 4.83 (1H, dd, J=9.88, 0.96 Hz), 5.14 (2H, s), 5.37 (1H, d, J=9.88 Hz), 7.36 (5H, s).

Aldehyde (23). (23) was obtained from (22) as reported for the preparation of (9).

$[\alpha]_D^{20}$ +6.7° (c=0.75, $CHCl_3$). ^1H NMR ($CDCl_3$, 80 MHz) δ 0.00 (3H, s), 0.10 (3H, s), 0.88 (9H, s), 1.29 (3H, t, J=7.24 Hz), 4.00-4.40 (2H, m), 4.60 (1H, d, J=1.92 Hz), 4.83 (1H, dd, J=1.92, 9.61 Hz), 5.10 (2H, s), 5.41 (1H, d, J=9.61 Hz), 7.34 (5H, s), 9.58 (1H, s). IR ($CHCl_3$) ν 3440, 2960, 2930, 2860, 1760, 1510, 1505, 1260, 1250 cm^{-1} (selected values). Anal. Calcd for $C_{20}H_{31}NO_6Si$: C, 58.65; H, 7.63; N, 3.42. Found: C, 58.61; H, 7.70; N, 3.40.

NOTES AND REFERENCES

1 Wagner,I.; Musso,H. Angew.Chem.,Int.Ed.Engl. 1983,22,816.

2 a) "Amino Acids, Peptides and Proteins." Specialist Periodical Reports, Chem.Soc., London, 1968-1983; Vol.1-16. b) Wieland,T. Naturwissenschaften 1972,59,225. Wieland,T.; Hofer,A. Liebigs Ann.Chem. 1958,619,35. Pfaender,P.; Wieland,T. Liebigs Ann.Chem. 1966,700,126. Kahl,J.U.; Wieland,T. Liebigs Ann.Chem. 1981,1445. Buku,A.; Faulstich,H.; Wieland,T.; Dabrowski,J. Proc.Natl.Acad.Sci.USA 1980,77,2370. c) Kraut,J. Ann.Rev.Biochem. 1977,46,331. d) Isono,K.; Asahi,K.; Suzuki,S. J.Am.Chem.Soc. 1969,91,7490. e) Di Bello,I.C.; Dorling,P.; Fellows,L.; Winchester,B. FEBS Lett. 1984,176,61.

3 a) Floyd,D.M.; Fritz,A.W.; Pluscec,J.; Weaver,E.R.; Cimarusti,C.M. J.Org.Chem. 1982,47,5160. b) Labia,R.; Morin,C. J.Antibiotics 1984,37,1103. c) Miller,M.J. Acc.Chem.Res. 1986,19,49, and references therein. d) Holden,K.G. in "Cephalosporins and Penicillins: Chemistry and Biology", Flynn,E.H., ed.; Academic Press: New York, 1972, vol.2, pp.133-136. e) Wei,C.C.; De Bernardo,S.; Tengi,J.P.; Borgese,J.; Weigele,M. J.Org.Chem. 1985,50,3462. f) Christenson,J.; Squires,E. Drugs of the future 1985,10,967.

4 Gennari,C.; Colombo,L.; Bertolini,G. J.Am.Chem.Soc. 1986,108,6394. For related asymmetric elecrophilic amination reactions, see: Evans,D.A.; Britton,T.C.; Dorow,R.L.; Dellaria,J.F. J.Am.Chem.Soc. 1986,108,6395. Vederas,J.C.; Trimble,L.A. J.Am.Chem.Soc. 1986,108,6397. Oppolzer,W.; Moretti,R. Helv.Chim.Acta 1986,69,1923. Evans,D.A.; Britton,T.C. J.Am.Chem.Soc. 1987,109,6881.

5 a) Banfi,L.; Cardani,S.; Potenza,D.; Scolastico,C. Tetrahedron 1987,43,2317. b) Guanti,G.; Banfi,L.; Narisano,E.; Scolastico,C. Tetrahedron Lett. 1985,26,3517. c) Guanti,G.; Banfi,L.; Narisano,E.; Scolastico,C. Tetrahedron Lett. 1984,25,4693. d) Scolastico, C.; Conca,E.; Prati,L.; Guanti,G.; Banfi,L.; Berti,A.; Farina,P.; Valcavi,U. Synthesis 1985,850.

6 For early work on this subject using racemic substrates, see: Liwschitz,Y.; Rabinsohn,Y.; Perera,D. J.Chem.Soc. 1962,1116.

7 Racemic α-amino-β-hydroxy acids: a) Ichikawa,T.; Maeda,S.; Araki,Y.; Ishido,Y. J.Am.Chem.Soc. 1970,92,5514. b) Nakamura,I.; Harada,K. Chem.Lett. 1979,313. c) Ozaki,Y.; Maeda,S.; Miyoshi,M.; Matsumoto,K. Synthesis 1979,216, and references therein. d) Shiba,T.; Sawoda,K.; Mirotsu,Y. Heterocycles 1978,10,133. e) Shanzer,A.; Somekh,L.; Butina,D. J.Org.Chem. 1979,44,3967. f) references 5b,5c,6 of this paper. g) Obdan,S.; Ichikawa,T.; Araki,Y.; Ishido,Y. Bull.Chem.Soc.Jpn. 1974,47,1295. h) Oesterle,T.; Simchen,G. Synthesis 1985,403. i) Hvidt,T.; Martin,O.R.; Szarek,W.A. Tetrahedron Lett. 1986,27,3807. j) Pansare,S.V.; Vederas,J.C. J.Org.Chem. 1987,52,4804.

8 Optically active α-amino-β-hydroxy acids: a) Cardani,S.; Prati,L.; Tinti,O. Synthesis 1986,1032. b) Belokon',Y.N.; Zeltzer,I.E.; Loim,N.M.; Tsiryapkin,V.A.; Aleksandrov,G.C.; Kursanov,D.N.; Parnes,Z.N.; Struchkov,Y.T.; Belikov,V.M. Tetrahedron 1980,36,1089. c) Belokon',Y.N.; Bulychev,A.G.; Vitt,S.V.; Struchkov,Y.T.; Batsanov,A.S.; Timofeeva,T.V.; Tsyryapkin,V.A.; Ryzhov,M.G.; Lysova,L.A.; Bakhmutov,V.I.; Belikov,V.M. J.Am.Chem.Soc. 1985,107,4252. d) Garner,P. Tetrahedron Lett. 1984,25,5855. e) Wenger,R.M. Helv.Chim.Acta 1983,66,2308. f) references 5a,5d of this paper. g) Ito,Y.; Sawamura,M.; Hayashi,T. J.Am.Chem.Soc. 1986,108,6405. h) Aebi,J.D.; Dhaon,M.K.; Rich,D.H. J.Org.Chem. 1987,52,2881. i) Deyo,D.; Tung,R.D.; Rich,D.H. Abstracts of the 194th ACS National Meeting of the Division of Organic Chemistry, New Orleans, August 30-September 4, 1987, n.104. j) Bashyal,B.P.; Chow,H.F.; Fleet,G.W.J. Tetrahedron Lett. 1986,27,3205. k) Ohdan,S.; Okamoto,T.; Maeda,S.; Ichikawa,T.; Araki,Y.; Ishido,Y. Bull.Chem.Soc.Jpn. 1973,46,981, and references therein. l) Ohfune,Y.; Kurokawa,N. Tetrahedron Lett. 1985,26,5307. m) Depezay,J.C.; Durreault,A.; Prange,T. Carbohydrate Research 1983,112,51. n) Depezay,J.C.; Durreault,A. Tetrahedron Lett. 1984,25,1459. o) Hamel,E.E.; Painter,E.P. J.Am.Chem.Soc. 1953,75,1362. p) Saito,S.; Bunya,N.; Inaba,M.; Moriwake,T.; Torii,S. Tetrahedron Lett. 1985,26,5309. q) Hecht,S.M.; Rupprecht,K.M.; Jacobs,P.M. J.Am.Chem.Soc. 1979,101,3982. r) Hongo,C.; Yamada,S.; Chibata,I. Bull.Chem.Soc.Jpn. 1981,54,1905 (optical resolution). s) Soukup,M.; Wipf,B.; Hochuli,E.; Leuenberger,H.G.W. Helv.Chim.Acta 1987,70,232. t) Kurokawa,N.; Ohfune,Y. J.Am.Chem.Soc. 1986,108,6041.

9 a) Murakami,M.; Mukaiyama,T. Chem.Lett. 1982,1271. b) Nakatsuka,T.; Miwa,T.; Mukaiyama,T. Chem.Lett. 1981,279; Chem.Lett. 1982,145.

10 a) Schollkopf,U. Pure and Appl.Chem. 1979,51,1347. b) Hoppe,I.; Schollkopf,U. Liebigs Ann.Chem. 1982,1548. c) Schollkopf,U.; Nozulak,J.; Grauert,M. Synthesis 1985,55. d) Grauert,M.; Schollkopf,U. Liebigs Ann.Chem. 1985,1817. e) Schollkopf,U. Chemica Scripta 1985,25,105. f) Schollkopf,U.; Bardenhagen,J. Liebigs Ann.Chem. 1987,393. g) Schollkopf,U. Pure and Appl.Chem. 1983,55,1799.

11 a) Evans,D.A.; Weber,A.E. J.Am.Chem.Soc. 1986,108,6757. b) Evans,D.A.;

Sjogren,E.B.; Weber,A.E.; Conn,R.E. Tetrahedron Lett. 1987,28,39. c) Evans,D.A.; Weber,A.E. J.Am.Chem.Soc. 1987,109,7151.
12 a) Seebach,D.; Imwinkelried,R.; Weber,T. in Modern Synthetic Methods 1986; Scheffold,R.; ed.; Springer-Verlag: Berlin,1986; vol.4,p.125. b) Seebach,D.; Juaristi,E.; Miller,D.D.; Schickli,C.; Weber,T. Helv.Chim.Acta 1987,70,237.
13 Bernardi,A.; Cardani,S.; Poli,G.; Scolastico,C. J.Org.Chem. 1986,51,5042. Bernardi,A.; Cardani,S.; Pilati,T.; Poli,G.; Scolastico,C.; Villa,R. J.Org.Chem. in the press. For a related example of high diastereoface selectivity in allylic stereocenter directed conjugate addition, see: Roush,W.R.; Michaelides,M.R.; Tai,D.F.; Chong,W.K.M. J.Am.Chem.Soc. 1987,109,7575.
14 Colombo,L.; Gennari,C.; Poli,G.; Scolastico,C.; DeMunari,S. Tetrahedron Lett. 1985,26,5459.
15 Keane,D.D.; O'Sullivan,W.I.; Philbin,E.M.; Simons,R.M.; Teague,P.C. Tetrahedron 1971,27,3535, and references therein. Reamonn,L.S.S.; O'Sullivan,W.I. J.Chem.Soc.,Chem.Commun. 1976,1012. Jakubowski,A.A.; Guziec,F.S.; Sugiura,M.; Chan Tam,C.; Tishler,M.; Omura,S. J.Org.Chem. 1982,47,1221.
16 Keane,D.D.; O'Sullivan,W.I.; Philbin,E.M.; Simons,R.M.; Teague,P.C. Tetrahedron 1970,26,2533.
17 Still,W.C. J.Am.Chem.Soc. 1979,101,2493, and references therein.
18 For a discussion on the different reactivity of NaOCl and KOCl, see: Viret,J.; Gabard,J.; Collet,A. Tetrahedron 1987,43,891, and references therein.
19 a) Anh,N.T. Top.Curr.Chem. 1980,88,145. b) Houk,K.N., et al. Science 1986,231,1108.
20 Trans 2,3-epoxy acids are known to react regioselectively and stereospecifically with amines to give anti α-amino-β-hydroxy acids, see: ref. 5d,6,8t,9a of this paper; Chong,J.M.; Sharpless,K.B. J.Org.Chem. 1985,50,1560.
21 J(cis)= 8-10 Hz, J(trans)= 4-6 Hz, see: Futagawa,S.; Inui,T.; Shiba,T. Bull.Chem.Soc.Jpn. 1973,46,3308.
22 Wunsch,E.; Graf,W.; Keller,O.; Keller,W.; Wersin,G. Synthesis 1986,958.
23 McKay,A.F.; Ott,W.L.; Taylor,G.W.; Buchanan,M.N.; Crooker,J.F. Can.J.Res. 1951,28B,683.
24 Corey,E.J.; Cho,H.; Rucker,C.; Hua,D.H. Tetrahedron Lett. 1981,22,3455.
26 Newton,R.F.; Reynolds,D.P.; Finch,M.A.W.; Kelly,D.R.; Roberts,S.M. Tetrahedron Lett. 1979,3981.
27 6-8% epimerization was occasionally observed in the preparation of (18) with methanolic ammonia.
28 For the preparation of fumaraldehyde bisdimethyl acetal, see: Gree,R.; Tourbah,H.; Carrie,R. Tetrahedron Lett. 1986,27,4983.