De Novo Asymmetric Synthesis of Protected 5-*O*-Carbamoylpolyoxamic Acid

Cécile Dehoux, Céline Monthieu, Michel Baltas,* Liliane Gorrichon

Laboratoire de Synthèse et Physicochimique de Molécules d'Intérêt Biologique, UMR 5068 Associée au CNRS, Université Paul Sabatier, 118 route de Narbonne, 31062 Toulouse Cedex 04, France

Tel. 330(5)61556293; Fax 330(5)61556011; E-mail: baltas@iris.ups-tlse.fr

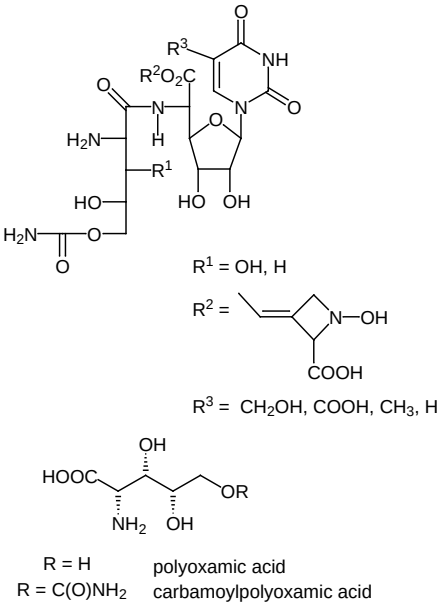
Received 23 March 2000; revised 23 May 2000

Abstract: The synthesis of 5-*O*-carbamoylpolyoxamic acid from a non carbohydrate precursor was achieved in 12 steps and 7% yield starting from chiral α,β-epoxyaldehyde readily available from *cis*-2-butene-1,4-diol. The main steps concern the Sharpless asymmetric epoxidation of a suitable chosen allylic alcohol, the use of thiazolyl group for carbon homologation, the stereo- and regioselective opening of the epoxide and the transformation of the primary alcohol to the acid functionality of the final product.

Key words: amino acids, antifungal agents, asymmetric synthesis, epoxide, azide

Polyoxins form an important class of antifungal antibiotics isolated from the culture broths of *Streptomyces cacoi var. asoensis* by Isono and coworkers.[1,2] They act as competitive inhibitors of the enzyme chitin synthase (E.C.2.4.1.16). This enzyme catalyses the production of chitin, a linear β-1,4-*N*-acetyl glucosamine polymer that constitutes one of the major structural components of the fungal cell walls.[3] Among these compounds, polyoxin D is used as an agricultural antifungal agent to treat rice sheath blight and pear black spot.[4] Polyoxins are peptidonucleosides comprising a nucleosidic aminoacid moiety connected by a peptide linkage to an unusual hydroxylated aminoacid, the 5-*O*-carbamoylpolyoxamic acid (except for polyoxins E and G) (Figure). As a consequence of the potent antifungal activity associated with this type of peptidyl nucleosides, a variety of chemical syntheses of the nucleosidic[5] and polyoxamic parts[6] have been reported over the years, most of them based on carbohydrate templates as starting materials. A number of polyoxamic acid syntheses have been reported utilising L-tartric acid. A very useful strategy towards the synthesis of the nucleosidic part (thymine polyoxin C) and 5-*O*-carbamoylpolyoxamic acid have been developed from D-serinal by Garner and Park.[5c,6c] Only Trost and co-workers have described a de novo asymmetric synthesis of polyoxamic acid using a Pd-based opening of a vinyl epoxide by phtalamide, in the presence of a chiral ligand.[6l]

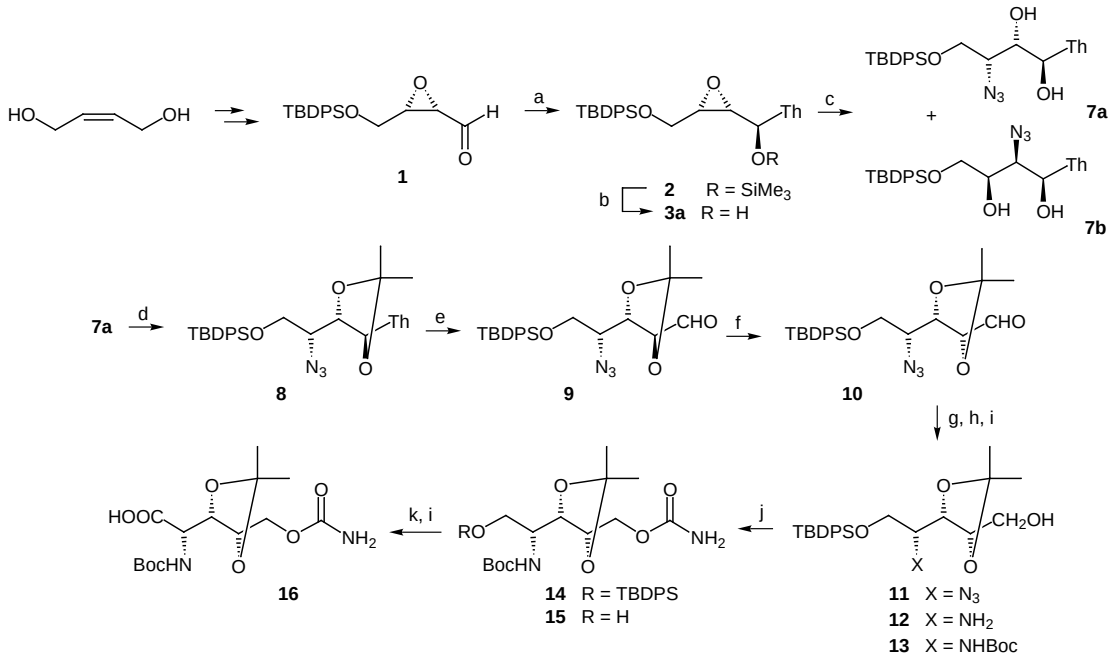
We have recently described the synthesis of a thymine 2′-deoxypolyoxin C analogue[7] from a non carbohydrate precursor. It was achieved in ten steps and 9% yield, starting from a chiral γ,δ-epoxy-β-hydroxyester readily available from *cis*-2-butene-1,4-diol. Herein, we would like to report a de novo stereocontrolled access to the protected 5-*O*-carbamoylpolyoxamic acid starting from the same achiral precursor. Our methodology is based on four key steps (Scheme 1): a) Sharpless asymmetric epoxidation,



Figure

b) homologation of the epoxyaldehyde, c) stereo- and regioselective opening of the oxirane and, d) epimerisation of the C2 carbon on the aldehyde.

The (2*R*,3*R*)-4-(tertbutyldiphenylsilyloxy)-2,3-epoxybutan-1-al (**1**) is obtained in three steps and 56% yield after monoprotection, Sharpless asymmetric epoxidation[8] using (−)DET as chiral agent (ee = 84%) and Doering oxidation[9] of the corresponding epoxyalcohol. Condensation of compound **1** with 2-trimethylsilylthiazole[10] and deprotection of the silylated intermediate **2** leads exclusively to the *anti*-2,3-epoxythiazolyl compound **3a** in 86% yield after silica gel purification**.** The stereochemical assignment of the aldol product **3a** was established by conversion to the six membered acetonide (Scheme 2). Reduction of compound **3a** in the presence of RedAl in THF and treatment of the 1,3-diol **4** formed with 2,2-dimethoxypropane with *p*-toluenesulfonic acid (catalytic) leads to the six membered acetonide **5**. ^{1}H NMR analysis of the coupling constants and ^{13}C NMR shifts of the acetal carbons[11] correspond to a *syn* configuration of compound **5** and thus an *anti* configuration for compound **3a**. The diastereoselectivity observed is in agreement with the results concerning addition of 2-trimethylsilylthiazole on α,β-alkoxy aldehydes.[10a]

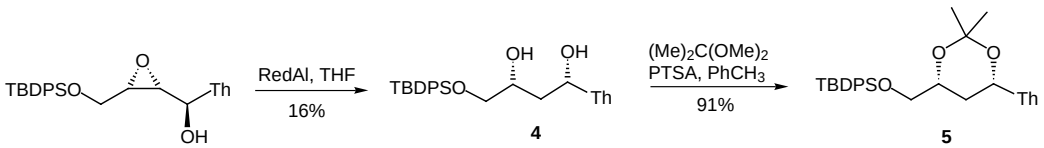


Reagents and conditions: (a) 1.5 equiv 2-trimethylsilylthiazole, CH_2Cl_2, −30 °C to r.t.; (b) Amberlite IR 120, MeOH (86% from **1**); (c) 5 equiv NaN_3, 2.5 equiv NH_4Cl, reflux (93%); (d) $(CH_3)_2C(OCH_3)_2$, *p*-toluenesulfonic acid, $PhCH_3$, 30 min, reflux (93%); (e) i) 1.2 equiv TMSTf, CH_3CN, molecular sieves 4 Å, ii) 2 equiv $NaBH_4$, MeOH, iii) $HgCl_2$, $MeCN/H_2O$ (10:1); (f) K_2CO_3, MeOH, 0 °C, 12 h; (g) $NaBH_4$, MeOH (36% from **5**); (h) H_2, Pd/C (10%), $EtOH/H_2O$ (9:1); (i) Boc_2O, CH_2Cl_2 (87%); (j) *p*-nitrophenylchloroformate, pyridine, 30 min then NH_3, MeOH, 1 h, 0 °C (70%); (k) HF/pyridine, THF/pyridine (100%); (l) BAIB, TEMPO, CH_3CN/H_2O (48%)

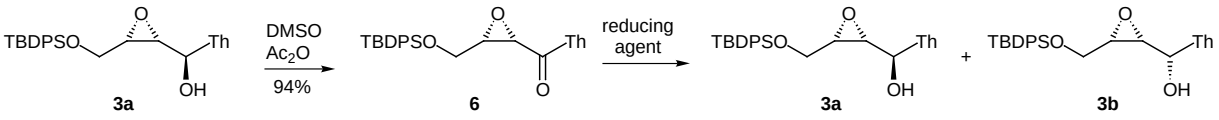
Scheme 1

Considering the absolute configuration of the final polyoxamic acid, we have to reverse the configuration of the carbon atom C1 of compound **3a**. Oxidation of compound **3a** in the presence of dimethylsulfoxide and acetic anhydride gives the corresponding ketone **6** in 94% yield (Scheme 3). Reduction of the ketone **6** in presence of sodium borohydride or K-selectride (Table), gives as the major or sole compound the adduct **3a**. *syn*-Adduct **3b** was only obtained in 20% yield when operating with two equivalents of $NaBH_4$ at −78 °C. It is noteworthy that this result is in contrast with that obtained from reduction of α,β-alkoxythiazolyl ketones which are reported to give the *syn*-adducts under the same experimental conditions.[10a]

In order to circumvent this problem, a different approach was investigated. Stereo- and regioselective opening of the oxirane under non-chelating conditions with sodium azide and ammonium chloride[12] gives a mixture of regioisomers **7a** and **7b** (**7a**/**7b** = 90/10) easily separated by silica gel chromatography (93% global yield). Protection of the diol **7a** in the presence of 2,2-dimethoxypropane gives acetonide **8** in 93% yield that was followed by demasking of the thiazolyl group to the corresponding aldehyde **9**. The thiazol to formyl protocol consists of a three reaction sequence (N-methylation, reduction, and metal assisted hydrolysis), each step taking place under almost neutral or non oxidative conditions.[10a,d] This one pot transformation affords the aldehyde **9** in 89% yield which is further transformed without any purification. Treatment of the aldehyde under basic conditions (K_2CO_3, MeOH) allows the epimerisation of the C2 carbon of the aldehyde and leads exclusively to the more stable epimer **10**. Reduction of aldehyde with sodium borohydride affords alcohol **11**, which is obtained in 36% yield starting from compound **8** after silica gel purification. Reduction of the azido functionality (H_2, Pd/C) followed by *tert*-butyloxycarbonyl protection of the amino derivative **12** yields compound **13** (87% for the two steps). The primary alcohol is then carbamoylated via a two steps procedure using *p*-nitrophenylchloroformate in pyridine and treatment of the



Scheme 2



Scheme 3

carbamate intermediate at 0 °C with methanolic ammonia[10c] to give compound **14** in 70% yield. The *tert*-butyldiphenylsilyl group is then removed quantitatively with HF/pyridine and the primary alcohol **15** was oxidised to the corresponding acid **16** in 48% yield through one step oxidation using BAIB (bis-acetoxyiodobenzene) with a catalytic amount of TEMPO[13] (2,2,6,6-tetramethyl-1-piperidinyloxy) free radical. Acid **16** shows spectral properties (^{1}H, ^{13}C) identical to those of literature.[10c,6m]

In conclusion this methodology, based on the use of suitably chosen epoxyalcohol, can lead to the protected 5-*O*-carbamoylpolyoxamic acid **16** obtained in 12 steps and 7.0% overall yield from epoxyaldehyde **1**. It compares with that of the only group[6l] which realised the de novo synthesis of polyoxamic acid. An advantage of the methodology resides also in the possibility of creating any epimer of this optically active aminoacid compound. Further work dealing with construction of the nucleoside moiety and applications of these results to the total synthesis of polyoxin J is currently underway.

All chemicals were obtained from commercial suppliers. Solvents were distilled prior to use. THF, Et_2O were distilled over Na; CH_2Cl_2 was distilled over CaH_2; and pyridine over KOH. TLC was performed on silica gel 60-coated aluminium sheets (Merck) with detection UV at 254 nm. Products were purified by medium pressure liquid chromatography. The following spectrometers were used to record physical data. NMR: Bruker 250 MHz (250 MHz for ^{1}H and 62.9 MHz for ^{13}C using $CDCl_3$ with internal TMS as reference). IR: Perkin–Elmer 1725X. MS: Nermag R10-10. Optical rotations were recorded on a Perkin–Elmer 241 polarimeter.

(1*S*,2*R*,3*S*)-4-*tert*-Butyldiphenylsilyloxy-2,3-epoxy-1-(thiazol-2-yl)butanol (3a)

At −30 °C, to a solution of epoxyaldehyde **1** (4.2 g, 12.5 mmol) in CH_2Cl_2 (58 mL) was added slowly a solution of 2-trimethylsilylthiazole (3 mL, 18.7 mmol) in CH_2Cl_2 (40 mL).The mixture was stirred for 20 minutes at −30 °C and 12 h at r.t. CH_2Cl_2 was evaporated to give the compound **2**. To a solution of the crude product in MeOH (58 mL) was added Amberlite IR120 (2 g), and the mixture was stirred for 6 h at r.t. After filtration and concentration, the residue was chromatographed on silica gel with petroleum ether/Et_2O, 5:5 (R_f = 0.22) to give compound **3a**; yield: 4.5 g (86%).

$[\alpha]_D^{24}$ = +24.6° (*c* 0.92, $CHCl_3$).

IR ($CHCl_3$): ν = 3466, 3133, 1050 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.78 (d, 1H, *J* = 3.0 Hz, CH thiazole), 7.73–7.68 (m, 4H, phenyl), 7.47–7.35 (m, 7H, phenyl and CH thiazole), 4.90 (d, 1H, *J* = 7.3 Hz, H1), 4.04 (dd, 1H, *J* = 5.5, 11.0 Hz, H4), 3.95 (dd, 1H, *J* = 5.3, 11.0 Hz, H4), 3.37 (dd, 1H, *J* = 4.1, 7.3 Hz, H2), 3.35 (ddd, 1H, *J* = 4.1, 5.3, 5.5 Hz, H3), 1.08 (s, 9H, TBDPS).

^{13}C NMR ($CDCl_3$): δ = 170.4 (Cq thiazole), 142.4 (CHN thiazole), 135.9, 135.8, 135.8, 132.6, 130.1, 127.9 (phenyl), 119.8 (CHS thiazole), 89.9 (C1), 62.5 (C4), 58.3, 56.8 (C3 and C2), 28.8 (Me TBDPS), 19.2 (Cq TBDPS).

MS (DCI, NH_3): *m/z* = 426 (MH^+, 100%).

Anal. Calcd for $C_{23}H_{27}NO_3SSi$: C, 64.90; H, 6.39; N, 3.29. Found: C, 64.90; H, 6.35; N, 3.23.

(1*S*,3*R*)-4-*tert*-Butyldiphenylsilyloxy-1,3-dihydroxy-1-(thiazol-2-yl)-butane (4)

At 0 °C, a solution of RedAl (3.5 M, 121 μL, 0.70 mmol) in toluene was added to a solution of **3a** (60 mg, 0,14 mmol) in THF (1.7 mL). The mixture was stirred for 3 h at r.t. After dilution with Et_2O, the mixture was slowly hydrolysed with H_2O (2.3 mL). After stirring for 1 h, the aqueous phase was extracted with Et_2O. The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel with CH_2Cl_2/EtOAc, 8:2 (R_f = 0.28) to give 10 mg of compound **4** (16%).

^{1}H NMR ($CDCl_3$): δ = 7.70–7.63 (m, 5H, phenyl and CHN), 7.42–7.26 (m, 7H, phenyl and CHS), 5.28 (dd, 1H, *J* = 2.8, 9.5 Hz, H1), 4.17 (m, 1H, H3), 3.66 (dd, 1H, *J* = 3.6, 10.2 Hz, H4), 3.53 (dd, 1H, *J* = 7.0, 10.2 Hz, H4), 2,10 (m, 2H, H2), 1,07 (s, 9H, Me TBDPS).

(1*S*,3*R*)-1,3-Dioxyisopropylidene-4-*tert*-butyldiphenylsilyloxy-1-(thiazol-2-yl)-butane (5)

A mixture of compound **4** (10 mg, 0.023 mmol), dimethoxypropane (500 μL) and *p*-tolunesulfonic acid (0.5 mg) in anhyd toluene (2 mL) was refluxed for 15 min. At r.t., the mixture was hydrolysed with sat. $NaHCO_3$, and the aqueous phase was extracted with toluene. The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was chromatographed with petroleum ether/CH_2Cl_2/EtOAc, 7:24:6 (R_f = 0.22) to give 10 mg of compound **5** (91%).

^{1}H NMR ($CDCl_3$): δ = 7.78–7.64 (m, 5H, phenyl and CHN), 7.39–7.26 (m, 7H, phenyl and CHS), 5.28 (dd, 1H, *J* = 2.9, 11.8 Hz, H1), 4.13 (m, 1H, H3), 3.74 (dd, 1H, *J* = 5.2, 10.4 Hz, H4), 3.58 (dd, 1H, *J* = 6.0, 10.4 Hz, H4), 2.16 (m, 2H, H2), 1.53 (s, 3H, acetonide), 1.48 (s, 3H, acetonide), 1.05 (s, 9H, TBDPS).

^{13}C NMR ($CDCl_3$): δ = 172.4 (Cq thiazole), 142.2 (CHN), 135.7, 133.8, 132.4, 129.6, 127.6 (phenyl), 119.0 (CHS), 97.7 (Cq acetonide), 70.0, 69.5 (C1 and C3), 67.2 (C4), 34.9 (C2), 29.8 (Me acetonide), 26.8 (Me TBDPS), 19.8 (Me acetonide), 19.1 (Cq TBDPS).

Table

Reducing agent	Conditions	**3a**/**3b**	Yield %
$NaBH_4$	2 equiv MeOH, –78 °C	80/20	99
$NaBH_4$	2 equiv MeOH, 0 °C to r.t.	80/20	70
K-selectride	2 equiv THF, –78 °C	100/0	62

(2*S*,3*S*)-4-*tert*-Butyldiphenylsilyloxy-2,3-epoxy-1-(thiazol-2-yl)-butan-1-one (6)

To a solution of compound **3a** (124 mg, 0.28 mmol) in dimethylsulfoxide (1.4 mL) was slowly added freshly distilled acetic anhydride (630 µL). After stirring for 12 h at r.t., sat. $NaHCO_3$ (10 mL) was added, and stirring was maintained for 5 min. The aqueous layer was extracted with Et_2O and the combined organic layers were washed with H_2O, dried (Na_2SO_4) and concentrated. The residue was chromatographed with petroleum ether/Et_2O, 6:4 (R_f = 0.30) to give 111 mg of compound **6** (94%).

$[\alpha]_D^{24}$ = +9.1° (*c* 0.55, $CHCl_3$).

IR ($CHCl_3$): ν = 1696 (C=O), 1111 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 8.08 (d, 1H, *J* = 3.0 Hz, CHN), 7.75 (d, 1H, *J* = 3.0 Hz, CHS), 7.60−7.52 (m, 4H, phenyl), 7.42−7.26 (m, 6H, phenyl), 4.82 (d, 1H, *J* = 4.3 Hz, H2), 3.96 (dd, 1H, *J* = 7.0, 13.5 Hz, H4), 3.70 (dd, 1H, *J* = 5.7, 13.5 Hz, H4), 3.70 (ddd, 1H, *J* = 4.3, 5.7, 7.0 Hz, H3), 0.92 (s, 9H, TBDPS).

^{13}C NMR ($CDCl_3$): δ = 186.1 (C1), 165.2 (Cq thiazole), 145.3 (CHN thiazole), 135.5, 135.4, 132.9, 129.8, 127.8, 127.7 (phenyl), 126.8 (CHS thiazole), 60.8 (C4), 59.1, 55.5 (C2 and C3), 26.6 (Me TBDPS), 19.1 (Cq TBDPS).

MS (DCI, NH_3): *m/z* (%) = 299 (100), 424 (MH^+, 25,), 441 (MNH_4^+, 2.6)

Anal. Calcd for $C_{23}H_{25}NO_3SSi$: C, 65.25; H, 5.95; N, 3.31. Found: C, 64.55; H, 6.07; N, 3.36.

Reduction with K-selectride

At −78 °C, to a solution of compound **6** (160 mg, 0.380 mmol) in THF (25 mL) was slowly added a solution 1 M of K-selectride (760 µL) in THF. The mixture was stirred for 1 h at -78 °C and then hydrolysed at 0 °C with H_2O (1 mL). THF was evaporated, and the residue was dissolved in CH_2Cl_2 and H_2O. The organic layer was dried ($MgSO_4$), concentrated and the resulting crude product was chromatographed with petroleum ether/Et_2O, 5:5 (R_f = 0.22) to yield 100 mg of **3a** (62%).

Reduction with $NaBH_4$

At 0 °C (or at −78 °C), $NaBH_4$ (20 mg, 0.522 mmol) was added to compound **6** (110 mg, 0.261 mmol) in MeOH (10 mL). After stirring for 1 h at r.t.(or −78 °C), acetone (1 mL) was added. The mixture was concentrated and the residue was dissolved in EtOAc and washed with H_2O. The organic phase was dried (Na_2SO_4) and the solvent evaporated. The residue was chromatographed with petroleum ether/CH_2Cl_2/EtOAc, 30:56:17 (R_{f3a} = 0.27, R_{f3b} = 0.20) to yield 60 mg of compound **3a**, 12 mg of **3b** and 7 mg of ketone **6** (70%).

(1*R*,2*R*,3*S*)-4-*tert*-Butyldiphenylsilyloxy)-2,3-epoxy-1-(thiazol-2-yl)-butan-1-ol (3b)

IR (film): ν = 3349, 1110 (C-O) cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.78 (d, 1H, *J* = 3.2 Hz, CHN), 7.70−7.62 (m, 4H, phenyl), 7.47−7.35 (m, 7H, phenyl and CHS), 4.35 (dd, 1H, *J* = 2.0, 9.2 Hz, H1), 3.88 (m, 1H, H2), 3.85−3.81 (m, 2H, H4), 3.37 (m, 1H, H3), 2.52 (d, 1H, *J* = 9.2 Hz, OH), 1,08 (s, 9H, TBDPS).

Reaction of 3a with NaN_3/NH_4Cl

A mixture of compound **3a** (4.5 g, 10.6 mmol), NaN_3 (3.44 g, 5 equiv) and NH_4Cl (2.5 equiv) in MeOH/H_2O, 8:1 (100 mL) was refluxed for 44 h. The MeOH was evaporated and the aqueous layer was extracted with Et_2O. The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel with petroleum ether/CH_2Cl_2/EtOAc (3:56:14) to give 4.2 g of compound **7a** (R_f = 0.30) and 400 mg of compound **7b** (R_f = 0.18) (global yield = 93%).

(1*S*,2*S*,3*R*)-3-Azido-4-*tert*-butyldiphenylsilyloxy-2-hydroxy-1-(thiazol-2-yl)-butanol (7a)

$[\alpha]_D^{24}$ = −16.0° (*c* 0.58, $CHCl_3$).

IR ($CHCl_3$): ν = 3607, 3453, 3074, 2114, 1058 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.75−7.61 (m, 5H, phenyl and CHN), 7.46−7.31 (m, 7H, phenyl and CHS), 4.99 (d, 1H, *J* = 7.3 Hz, H1), 4.07−3.77 (m, 4H, H2, H3 and H4), 1.08 (s, 9H, Me TBDPS).

^{13}C NMR ($CDCl_3$): δ = 172.4 (Cq thiazole), 142.1 (CHN), 135.6, 132.7, 129.9, 127.9 (phenyl), 119.7 (CHS thiazole), 73.7 (C1), 71.7 (C2), 64.8 (C4), 62.9 (C3), 26.8 (Me TBDPS), 19.1 (Cq TBDPS).

MS (DCI, NH_3): *m/z* = 469 (MH^+, 100%).

Anal. Calcd for $C_{23}H_{28}N_4O_3SSi$: C, 58.95; H, 6.02; N, 11.95. Found: C, 59.01; H, 5.91; N, 11.66.

(1*S*,2*R*,3*S*)-2-Azido-4-*tert*-butyldiphenylsilyloxy-3-hydroxy-1-(thiazol-2-yl)-butanol (7b)

IR (film): ν = 3665, 3072, 2110 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.75−7.61 (m, 5H, phenyl and CHN), 7.46−7.31 (m, 7H, phenyl and CHS), 5.35 (d, 1H, *J* = 3.6 Hz, H1), 4.06 (m, 1H, H3), 3.96 (t, 1H, *J* = 3.6 Hz, H2), 3.82−3.77 (m, 2H, H4), 1.08 (s, 9H, TBDPS).

^{13}C NMR ($CDCl_3$): δ = 172.0 (Cq thiazole), 142.4 (CHN thiazole), 135.9, 132.9, 129.9, 127.9 (phenyl), 119.9 (CHS thiazole), 73.7 (C1), 72.9 (C2), 66.6 (C3), 64.8 (C4), 26.9 (Me TBDPS), 19.2 (Cq TBDPS).

MS (DCI, NH_3): *m/z* = 469 (MH^+, 100%).

Anal. Calcd for $C_{23}H_{28}N_4O_3SSi$: C, 58.95; H, 6.02; N, 11.95. Found: C, 59.10; H, 6.05; N, 11.80.

(1*S*,2*S*,3*R*)-3-Azido-1,2-dioxyisopropylidene-4-*tert*-butyldiphenylsilyloxy-(1-thiazol-2-yl)-butane (8)

To a solution of compound **7a** (936 mg, 2.0 mmol) in anhyd toluene (30 mL) were added dimethoxypropane (7.5 mL) and *p*-toluenesulfonic acid (38 mg, 0.2 mmol), and the mixture was refluxed for 20 min. It was then diluted with toluene and hydrolysed with sat. $NaHCO_3$. The organic phase was washed with H_2O, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel with petroleum ether/CH_2Cl_2/EtOAc, 8:16:2 (R_f = 0.30) to afford 945 mg of compound **8 (**93%).

$[\alpha]_D^{24}$ = −7.9° (*c* 0.66, $CHCl_3$).

IR ($CHCl_3$): ν = 3100, 2125, 1054 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.76 (d, 1H, *J* = 3.2 Hz, CHN), 7.70−7.45 (m, 4H, phenyl), 7.45−7.35 (m, 6H, phenyl), 5.45 (d, 1H, *J* = 7.2 Hz, H1), 4.62 (dd, 1H, *J* = 4.0, 7.2 Hz, H2), 3.88 (dd, 1H, *J* = 5.6, 10.0 Hz, H4), 3.77 (dd, 1H, *J* = 6.5, 10.0 Hz, H4), 3.46 (ddd; 1H, *J* = 4.0, 5.6, 6.5 Hz, H3), 1.70 and 1.44 (2s, 6H, acetonide), 1.05 (s, 9H, TBDPS).

^{13}C NMR ($CDCl_3$): δ = 170.1 (Cq thiazole), 143.0 (CHN thiazole), 135.7, 132.9, 129.9, 127.8 (phenyl), 119.8 (CHS thiazole), 110.4 (Cq acetonide), 77.1 (C1), 76.7 (C2), 64.3 (C4), 61.1 (C3), 26.7 (Me TBDPS), 26.6, 24.8 (Me acetonide), 19.0 (Cq TBDPS).

MS (DCI, NH_3): *m/z* = 509 (MH^+, 100%).

Anal. Calcd for $C_{26}H_{32}N_4O_3SSi$: C, 61.39; H, 6.34; N, 11.01. Found: C, 61.28; H, 6.22; N, 10.80.

(2*S*,3*S*,4*R*)-4-Azido-2,3-dioxyisopropylidene-5-*tert*-butyldiphenylsilyloxy-pentanol (11)

A mixture of compound **8** (960 mg, 1.89 mmol) and activated molecular sieves 4 Å (4 g) in anhyd MeCN (20 mL) was stirred for 10 min. at r.t., and then methyltriflate (267 µL, 2.27 mmol) was added. The suspension was stirred for 35 min. at r.t. and concentrated

to dryness. The residue was diluted in MeOH (20 mL), cooled to 0 °C, treated with $NaBH_4$ (142 mg, 3.80 mmol), and stirred for 40 min. Acetone (2 mL) was added and the mixture was stirred for 1 h. The suspension was filtered through Celite and concentrated. The crude product was then dissolved in MeCN/H_2O, 10:1 (20 mL) and the solution treated with $HgCl_2$ (500 mg) in 2 mL of the same solvent mixture. The mixture was stirred for 30 min., filtered through Celite and concentrated. The crude product was dissolved in CH_2Cl_2 and washed with 10% aqueous KI. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were dried (Na_2SO_4) and concentrated. The residue was dissolved in Et_2O and quickly filtered through a pad of Fluorisil. After concentration, aldehyde **9** (760 mg) was obtained as a clear yellow syrup (89%).

Compound 9

IR ($CHCl_3$): ν = 3074, 2959, 2111, 1729 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 9.80 (d, 1H, *J* = 2.0 Hz, H1), 7.70−7.65 (m, 4H, phenyl), 7.46−7.26 (m, 6H, phenyl), 4.52 (dd, 1H, *J* = 2.0, 8.3 Hz, H2), 4.35 (dd, 1H, *J* = 2.0, 8.3 Hz, H3), 3.95 (dd, 1H, *J* = 7.7, 10.4 Hz, H5), 3.87 (dd, 1H, *J* = 5.6, 10.4 Hz, H5), 3.46 (ddd, 1H, *J* = 2.0, 5.6, 7.7 Hz, H4), 1.70 and 1.44 (2s, 6H, acetonide), 1.05 (s, 9H, TBDPS).

^{13}C NMR ($CDCl_3$): δ = 202.4 (C1), 135.6, 132.8, 130.0, 129.7, 128.2, 127.9 (phenyl), 111.2 (Cq acetonide), 80.4, 78.4 (C2 and C3), 63.6 (C5), 59.9 (C4), 26.7 (Me TBDPS), 26.9, 24.5 (Me acetonide), 19.2 (Cq TBDPS).

A mixture of aldehyde **9** (760 mg, 1.68 mmol) and K_2CO_3 (232 mg, 1.68 mmol) in MeOH (20 mL) was stirred for 12 h at 0 °C. After dilution with H_2O, MeOH was evaporated. The aqueous phase was extracted with Et_2O and the combined organic layers were washed with sat. NaCl and dried (Na_2SO_4). Concentration afforded 760 mg of the epimer **10** (100%).

Compound 10

IR ($CHCl_3$): ν = 3073, 2934, 2111, 1733 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 9.76 (d, 1H, *J* = 1.6 Hz, H1), 7.70−7.65 (m, 4H, phenyl), 7.46−7.26 (m, 6H, phenyl), 4.34 (dd, 1H, *J* = 1.6, 7.0 Hz, H2), 4.18 (dd, 1H, *J* = 3.4, 7.0 Hz, H3), 3.91−3.85 (m, 2H, H5), 3.47 (m, 1H, H4), 1.49 and 1.39 (2s, 6H, acetonide), 1.06 (s, 9H, TBDPS).

^{13}C NMR ($CDCl_3$): δ = 201.3 (C1), 135.6, 132.8, 130.0, 129.7, 127.9, 127.8 (phenyl), 111.9 (Cq acetonide), 81.5, 76.2 (C2 and C3), 63.8 (C5), 62.6 (C4), 26.7 (Me TBDPS), 26.4, 26.1 (Me acetonide), 19.1 (Cq TBDPS).

To a solution of aldehyde **10** (750 mg, 1.65 mmol) in MeOH (40 mL) was added $NaBH_4$ (63 mg, 1.65 mmol) at 0 °C. The mixture was stirred for 10 min. at 0 °C, and 3 h at r.t. Acetone was then added (6 mL) and the mixture was stirred for 15 min. The solvents were evaporated and the residue was dissolved with CH_2Cl_2 and sat. NaCl. The aqueous phase was extracted with CH_2Cl_2, dried (Na_2SO_4) and concentrated. The crude product was chromatographed on silica gel with petroleum ether/CH_2Cl_2/EtOAc, 70:24:6 (R_f = 0.17) to afford 310 mg of compound **11** (41%).

Compound 11

IR ($CHCl_3$): ν = 3679 (OH), 3055 (CH arom.), 2112 (N_3), 1111 (C-O) cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.69−7.40 (m, 10H, phenyl), 4.09 (ddd, 1H, *J* = 3.6, 4.4, 8.3 Hz, H2), 3.98 (dd, 1H, *J* = 3.3, 8.3 Hz, H3), 3.90 (dd, 1H, *J* = 7.5, 10.0 Hz, H5), 3.82 (dd, 1H, *J* = 4.9, 10.0 Hz, H5), 3.76 (dd, 1H, *J* = 3.6, 12.1 Hz, H1), 3.59 (dd, 1H, *J* = 4.4, 12.1 Hz, H1), 3.37 (ddd, 1H, *J* = 3.3, 4.9, 7.5 Hz, H4), 1.85 (br s, 1H, OH), 1.42 and 1.38 (2s, 6H, acetonide), 1.07 (s, 9H, TBDPS).

^{13}C NMR ($CDCl_3$): δ = 135.7, 132.8, 130.0, 129.7, 127.9 (phenyl), 109.9 (Cq acetonide), 77.8, 76.2 (C2 and C3), 64.3 (C5), 62.6 (C4), 61.7 (C1), 27.2 (Me acetonide), 26.8 (Me TBDPS), 26.7 (Me acetonide), 19.2 (Cq TBDPS).

MS (DCI, NH_3): *m/z* = 473 (MNH_4^+, 100%).

Anal. Calcd for $C_{26}H_{33}N_4O_3SSi$: C, 63.27; H, 7.30; N, 9.22. Found: C, 63.30; H, 7.00; N, 9.10.

(2*S*,3*S*,4*R*)-4-(*tert*-Butyloxycarbonylamino)-2,3-dioxyisopropylidene-5-*tert*-butyldiphenylsilyloxy-pentanol (13)

A suspension of alcohol **11** (300 mg, 0.66 mmol) and 10% Pd/C (74 mg) in EtOH/H_2O. 9:1l (8.3 mL) was degassed and then pressurised with H_2. After stirring for 4 h, the suspension was filtered on Celite and then concentrated in vacuo to give 256 mg of compound **12** (90%).

Compound 12

^1H NMR ($CDCl_3$): δ = 7.87−7.25 (m, 10H, phenyl), 4.01 (dt, 1H, *J* = 4.6, 8.4 Hz, H2), 3.87 (dd, 1H, *J* = 3.7, 8.4 Hz, H3), 3.77 (dd, 1H, *J* = 4.9, 10.1 Hz, H5), 3.60 (dd, 1H, *J* = 7.5, 10.1 Hz, H5), 3.63 (d, 2H, *J* = 4.6 Hz, H1), 3.07 (ddd, 1H, *J* = 3.7, 4.9, 7.5 Hz, H4), 2.24 (m, 3H, OH and NH_2), 1.36 and 1.33 (2s, 6H, acetonide), 1.06 (s, 9H, TBDPS).

^{13}C NMR ($CDCl_3$): δ = 135.6, 133.3, 133.2, 129.9, 127.8 (phenyl), 108.7 (Cq acetonide), 79.0, 77.4 (C2 and C3), 65.8 (C5), 62.3 (C1), 53.1 (C4), 27.1, 26.9 (Me acetonide), 26.7 (Me TBDPS), 19.3 (Cq TBDPS).

A mixture of compound **12** (256 mg, 0.60 mmol) and Boc_2O (130 mg, 0.60 mmol) in CH_2Cl_2 (12 mL) was stirred for 12 h at r.t. After concentration, the residue was chromatographed on silica gel with petroleum ether/CH_2Cl_2/EtOAc (5:4:1) to afford 300 mg of compound **13** (95%).

Compound 13

IR ($CHCl_3$): ν = 3607, 3445, 1708, 1109 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.69−7.63 (m, 4H, phenyl), 7.43−7.33 (m, 6H, phenyl), 4.76 (d, 1H, *J* = 9.5 Hz, NH), 4.18 (dd, 1H, *J* = 1.0, 8.5 Hz, H3), 3.90 (dd, 1H, *J* = 5.0, 10.0 Hz, H5), 3.87 (dd, 1H, *J* = 5.5, 10.0 Hz, H5), 3.82 (dddd, 1H, *J* = 1.0, 5.0, 5.5, 9.5 Hz, H4), 3.71 (m, 3H, H1+H2), 2.14 (br s, 1H, OH), 1.53 (s, 9H, Boc), 1.45 and 1.42 (2s, 6H, acetonide), 1.04 (s, 9H, TBDPS).

^{13}C NMR ($CDCl_3$): δ = 156.0 (C=O Boc), 135.6, 133.3, 129.8, 127.8, 127.7 (phenyl), 109.0 (Cq acetonide), 79.7 (Cq Boc), 77.1, 76.2 (C2 and C3), 64.1 (C5), 61.6 (C1), 51.0 (C4), 28.4 (Me Boc), 27.4, 27.0 (Me acetonide), 26.8 (Me TBDPS), 19.2 (Cq TBDPS).

MS (DCI, NH_3): *m/z* (%) = 530 (MH^+, 100), 547 (MNH_4^+, 7).

Anal. Calcd for $C_{29}H_{43}NO_6Si$: C, 65.75; H, 8.18; N, 2.64. Found: C, 65.70; H, 8.24; N, 2.60.

(2*S*,3*S*,4*R*)-4-(*tert*-Butyloxycarbonylamino)-1-*O*-carbamoyl-2,3-dioxyisopropylidene-5-*tert*-butyldiphenylsilyloxy-pentanol (14)

To compound **13** (60 mg, 0.113 mmol) in pyridine (500 μL) was added *p*-nitrophenylchloroformate (34 mg, 0.169 mmol). After being stirred for 30 min., the mixture was diluted with EtOAc, washed with sat. $NaHCO_3$ and then with sat. NaCl. The organic phase was dried (Na_2SO_4) and concentrated. The carbonate intermediate was dissolved in MeOH (1.5 mL) and a 7 N solution of NH_3 in MeOH (600 μL) was added at 0 °C. The mixture was stirred at 0 °C for 1 h and MeOH was evaporated. The residue was chromatographed on silica gel with petroleum ether/CH_2Cl_2/EtOAc, 3:56:14 (R_f = 0.19) to afford 45 mg of compound **14** (70%).

IR ($CHCl_3$): ν = 3546, 3436, 3074, 2961, 1731, 1711, 1112 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.69−7.65 (m, 4H, phenyl), 7.43−7.34 (m, 6H, phenyl), 4.87−4.76 (d and large s, 3H, *J* = 9.8 Hz, NHBoc and NH_2), 4.22 (d, 2H, *J* = 5.1 Hz, H1), 4.19 (dd, 1H, *J* = 8.0, 1.5 Hz, H3), 4.00 (td, 1H, *J* = 5.1, 8.0 Hz, H2), 3.98 (dddd, 1H, *J* = 1.5, 5.8, 8.3, 9.8 Hz, H4), 3.72 (dd, 1H, *J* = 5.8, 9.9 Hz, H5), 3.65 (dd, 1H, *J* = 8.3, 9.9 Hz, H5), 1.42 (s, 9H, Boc), 1.41 and 1.39 (2s, 6H, acetonide), 1.05 (s, 9H, TBDPS).

^{13}C NMR ($CDCl_3$): δ = 156.3, 155.7 (C=O), 135.6, 133.2, 129.7, 127.7, 127.6 (phenyl), 109.4 (Cq acetonide), 79.7 (Cq acetonide), 76.6, 75.0 (C2 and C3), 64.5, 63.8 (C1 and C5), 50.8 (C4), 28.3 (Me Boc), 26.9, 26.8 (Me acetonide), 19.2 (Cq TBDPS).

MS (DCI, NH_3): *m/z* (%) = 573 (MH^+, 100), 590 (MNH_4^+, 26.5).

Anal. Calcd for $C_{30}H_{44}O_7N_2Si$: C, 62.91; H, 7.74; N, 4.89. Found: C, 62.83; H, 7.68; N, 4.89.

(2*R*,3*S*,4*S*)-2-(*tert*-Butyloxycarbonylamino)-5-O-carbamoyle-3,4-dioxyisopropylidene-pentanol (15)

To a solution of **14** (34 mg, 0.059 mmol) in a mixture of THF/pyridine (300 μL/150 μL) was added HF/pyridine (120 μL), and the reaction mixture was stirred for 8 h at r.t. It was then diluted with EtOAc and hydrolysed with sat. $NaHCO_3$. The aqueous phase was extracted with EtOAc and the combined organic layers were dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel with CH_2Cl_2/EtOAc (8:2) to give 20 mg of alcohol **15** (100%).

IR ($CHCl_3$): ν = 3621, 3507, 3438, 3054, 2978, 1729, 1708 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 5.12 (d and large s, 3H, *J* = 10 Hz, NHBoc and NH_2), 4.25 (dd, 1H, *J* = 5.0, 11.5 Hz, H1), 4.20 (dd, 1H, *J* = 4.5, 11.5 Hz, H1), 4.06 (dd, 1H, *J* = 1.0, 8.5 Hz, H3), 3.98 (td, 1H, *J* = 5.0, 8.5 Hz, H2), 3.84 (dddd, 1H, *J* = 1.0, 4.7, 6.3, 10.0 Hz, H4), 3.74 (dd, 1H, *J* = 4.7, 11.0 Hz, H5), 3.64 (dd, 1H, *J* = 6.3, 11.0 Hz, H5), 3.30 (large s, 1H, OH), 1.43 (s, 9H, Boc), 1.42 and 1.38 (2s, 6H, acetonide).

^{13}C NMR ($CDCl_3$): δ = 156.6, 156.3 (C=O), 109.8 (Cq acetonide), 80.1 (Cq Boc), 78.3, 75.5 (C2 and C3), 68.0 (C5), 64.3 (C1), 50.7 (C4), 28.3 (Me Boc), 26.9 (Me acetonide).

MS (DCI, NH_3): *m/z* (%) = 335 (MH^+, 100), 352 (MNH_4^+, 54.8).

Anal. Calcd for $C_{14}H_{26}N_2O_7$: C, 50.29; H, 7.84; N, 8.38; Found C, 50.30; H, 7.78; N, 8.30.

(2*S*,3*S*,4*S*) 2-(*tert*-Butyloxycarbonylamino)-5-*O*-carbamoyle-3,4-dioxyisopropylidene pentanoic Acid (16)

To a solution of compound **15** (32 mg, 0.096 mmol) in CH_3CN/H_2O (300 μL/300 μL) were added TEMPO (3 mg, 0.019 mmol) and BAIB (67 mg, 0.21 mmol). The mixture was stirred for 5 h at r.t. and then concentrated. The residue was chromatographed with a gradient from CH_2Cl_2/EtOAc (7:3) to EtOAc to give 16 mg of compound **16** (48%); mp: 60 °C.

IR ($CHCl_3$): ν = 3674−3000, 3510, 3436, 3054, 2978, 1729, 1708 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 9.64 (s, 1H, COOH), 5.37−5.30 (d and large s, 3H, *J* = 8.4 Hz, NHBoc and NH_2), 4.52 (d, 1H, *J* = 8.4 Hz, H2), 4.38 (m, 1H, H3), 4.30 (m, 2H, H5), 4.00 (m, 1H, H4), 1.46 (s, 9H, Boc), 1.43 and 1.40 (2s, 6H, acetonide).

^{13}C NMR ($CDCl_3$): δ = 173.1, 157.1, 156.2 (C=O), 110.2 (Cq acetonide), 80.7 (Cq Boc), 78.5, 75.0 (C2 and C3), 64.0 (C5), 52.9 (C2), 28.3 (Me Boc), 26.9 (Me acetonide).

MS (DCI, NH_3): *m/z* (%) = 158 (100), 349 (MH^+, 12.5), 366 (MNH_4^+, 13.9).

References

(1) Isono, K.; Asahi, K.; Suzuki, S. *J. Am. Chem. Soc.* **1969**, *91*, 7490.
(2) Isono, K.; Suzuki, S. *Heterocycles* **1979**, *13*, 333.
(3) Hori, M.; Kakiki, K.; Misato, T. *Agric. Biol. Chem.* **1974**, *38*, 691.
(4) Ko, K. In *Pesticide Chemistry: Human Welfare and the Environment;* Miyamato, J., Ed.; Pergamon Press: Elmsford, NY, 1983; p 247.
(5) a) Damadaran, N. P.; Jones, G. H.; Mofatt, J. G. *J. Am. Chem. Soc.* **1971**, *93*, 3812.
b) Tabusa, F.; Yamada, T.; Suzuki, K.; Mukaiyama, T. *Chem. Lett.* **1984**, 405.
c) Garner, P.; Park, J. M. *J. Org. Chem.* **1990**, *55*, 3853.
d) Auberson, Y.; Vogel, P. *Tetrahedron* **1990**, *46*, 7019.
e) Dondoni, A.; Junquera, F.; Merchan, F. L.; Merino, P.; Tejero, T. *Tetrahedron Lett.* **1994**, *35*, 9439.
f) Ghosh, A. K.; Wang, Y. *J. Org. Chem.* **1998**, *63*, 6735.
(6) a) Kuzuhara, H.; Emoto, S. *Tetrahedron Lett.* **1973**, *50*, 5051.
b) Saksena, A. K.; Lovey, R. G.; Girijavallabham, V. M.; Guanguly, A. K. *J. Org. Chem.* **1986**, *51*, 5024.
c) Garner, P.; Park, J. M. *J. Org. Chem.* **1988**, *53*, 2979.
d) Savage, I., Thomas, E. J. *J. Chem. Soc., Chem. Commun.* **1989**, 717.
e) Mukaiyama, T.; Suzuki, K.; Yamada, T.; Tabusa, F. *Tetrahedron* **1990**, *46*, 265.
f) Dureault, A.; Carreaux, F.; Depezay, J. C. *Synthesis* **1991**, 150.
g) Dondoni, A.; Franco, S.; Merchan, F. L.; Merino, P.; Tejero, T. *Tetrahedron Lett.* **1993**, *34*, 5479.
h) Chida, N.; Koisumi, K.; Kitada, Y.; Yokoyama, C.; Ogawa, S. *J. Chem. Soc., Chem. Commun.* **1994**, 111.
i) Marshall, J. A.; Seletsky, B. M.; Coan, P. S. *J. Org. Chem.* **1994**, *59*, 5139.
j) Matsuura, F.; Hamada, Y.; Shiori, T. *Tetrahedron Lett.* **1994**, *35*, 733.
k) Jackson, R. F. W.; Palmer, N. J.; Wythes, M. J.; Clegg, W.; Elsegood, M. R. J. *J. Org. Chem.* **1995**, *60*, 6431.
l) Trost, B. M.; Krueger, A. C.; Bunt, R. C.; Zambrano, J. *J. Am. Chem. Soc.* **1996**, *118*, 6520.
m) Ghosh, A. K.; Wang, Y. *J. Org. Chem.* **1999**, *64*, 2789.
n) Uchida, K.; Kato, K.; Akita, H. *Synthesis* **1999**, *9*, 1541.
(7) Dehoux, C.; Fontaine, E.; Escudier, J. -M.; Baltas, M.; Gorrichon, L. *J. Org. Chem.* **1998**, *63*, 2601.
(8) Hanson, R. M.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 1922. Chong, J. M.; Wong, S. *J. Org. Chem.* **1987**, *52*, 2596.
(9) Parikh, J. R.; Von, E.; Doering, W. *J. Am. Chem. Soc.* **1967**, *89*, 5505.
(10) a) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P. *J. Org. Chem.* **1989**, *54*, 693. Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P. *J. Org. Chem.* **1989**, *54*, 702.
b) Dondoni, A.; Perrone, D.; Merino, P. *J. Org. Chem.* **1995**, *60*, 8074.
c) Dondoni, A.; Franco, S.; Junquera, F.; Merchan, F. L.; Merino, P.; Tejero, T. *J. Org. Chem.* **1997**, *62*, 5497.
d) Dondoni, A. *Synthesis* **1998**, 1681.
(11) Rychnovsky, S. D.; Rogers, B.; Yang, G. *J. Org. Chem.* **1993**, *58*, 3511.
(12) Caron, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1557.
(13) De Nooy, A. E. J.; Besemer, A. C.; van Bekkum, H. *Synthesis* **1996**, 1153.
Epp, J. B.; Widlanski, T. S. *J. Org. Chem.* **1999**, *64*, 293.

Article Identifier:
1437-210X,E;2000,0,10,1409,1414,ftx,en;P02800SS.pdf