Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 10307–10312

TETRAHEDRON

A novel and stereospecific synthesis of (+)-preussin☆

Sadagopan Raghavan* and M. Abdul Rasheed

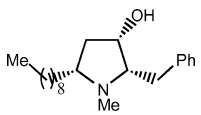
Organic Division I, Indian Institute of Chemical Technology, Habsiguda, Hyderabad 500 007, India

Received 14 July 2003; revised 16 September 2003; accepted 9 October 2003

Abstract—A novel and stereospecific approach to (+)-preussin that would permit the synthesis of analogs for structure activity relationship studies, is disclosed. The key step includes the regio- and stereoselective elaboration of a bromohydrin via intramolecular sulfinyl group participation.

1. Introduction

(+)-Preussin (L-657,398, **1**), a pyrrolidine alkaloid isolated from the fermentation broths of *Aspergillus ostraceus*[1a] and subsequently from those of *Preussia* sp.,[1b] has been shown to possess potent antifungal activity against both filamentous fungi and yeasts. Recently, preussin has been shown to be a potent inhibitor of cell growth in yeast mutants with defective *cdc 2* regulatory genes[2] and a potent inhibitor of cyclin E kinase in human tumor cell lines.[3]



1

Due to its unique structure and potent bioactivity, preussin has attracted the attention of synthetic chemists and several approaches have been reported.[4] Almost all of them utilize chiral pool starting materials except those reported by Ghosh[4d] and Greene.[4h]

2. Results and discussion

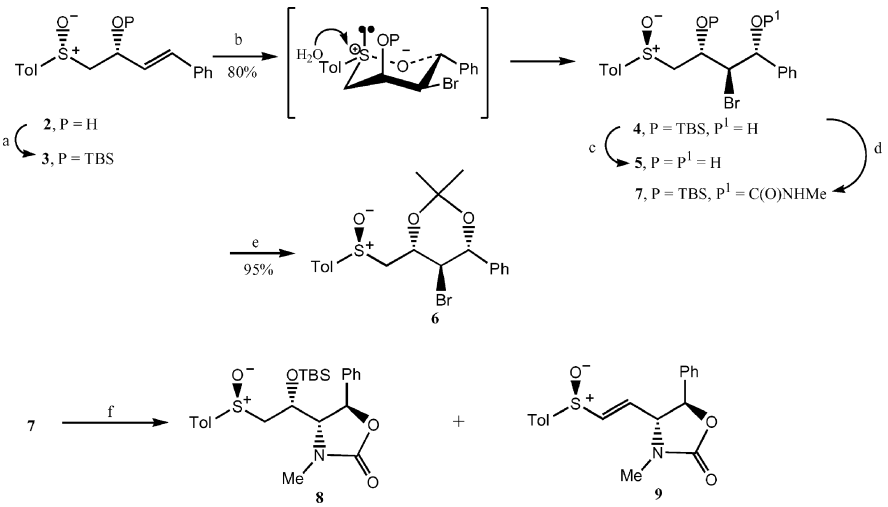
Investigations in our laboratory over the past few years have demonstrated the merit of the sulfinyl moiety as an internal nucleophile to functionalize olefins regio- and stereoselectively.[5] Herein we illustrate the potential of this methodology to access pyrrolidines through a synthesis of (+)-preussin. The synthesis commenced with the alcohol **2**,[5a,6] which upon treatment with *t*-butyldimethylchlorosilane afforded the silyl ether **3**. Upon subjecting **3** to treatment with *N*-bromosuccinimide in toluene in the presence of water, the bromohydrin **4** was isolated, regio- and stereospecifically, as the sole product. The structure of **4** was confirmed by transforming it to the acetonide **6**.[5a] Thus deprotection of the silyl ether and subsequent reaction of the resulting diol **5** with 2,2-dimethoxypropane in the presence of catalytic amounts of CSA afforded acetonide **6** (Scheme 1). In the ^{1}H NMR spectrum of **6** the C*H*Br resonated at δ 3.62 as a triplet (J=10.3 Hz) proving beyond doubt the *anti* disposition of bromine relative to the hydroxy and silyloxy group in **4**.

Treatment of the bromohydrin **4** with methyl isocyanate in the presence of Et_3N afforded the carbamate **7**. The carbamate **7** on treatment with NaHMDS afforded the oxazolidinone **8**, by internal S_N2 displacement of the bromide, along with minor quantities of the alkene **9**. It is instructive to note that treatment of bromohydrin **4** with a variety of alkyl/aryl isocyanates would permit the preparation of *N*-alkyl/aryl analogs of preussin following the route detailed herein. The internal substitution strategy served not only to introduce the *N*-Me group of preussin, but also served as protecting group for the hydroxy and the amino groups. The *t*-butyldimethysilyl group in **8** was removed by treatment with *n*-Bu_4NF to afford the alcohol **10**. Attempted acylation of the dianion derived from **10** with methyl decanoate **11** to afford β-keto sulfoxide **12** failed, under a variety of reaction conditions (Scheme 2). The bases used to generate the dianion include LDA, LiHMDS, NaHMDS and KHMDS in THF alone as the solvent or in the presence of HMPA as co-solvent. Subjecting **8** to Pummerer reaction[7] conditions followed by treatment of the resulting intermediate **13** with a solution of sodium borohydride in 5% aq. $NaHCO_3$ afforded alcohol **14**. Attempted condensation[8] of the anion generated from dithiane **15**,[9] with the iodide **16** or the triflate **17**, derived from alcohol **14**, returned only unreacted starting material (Scheme 2).

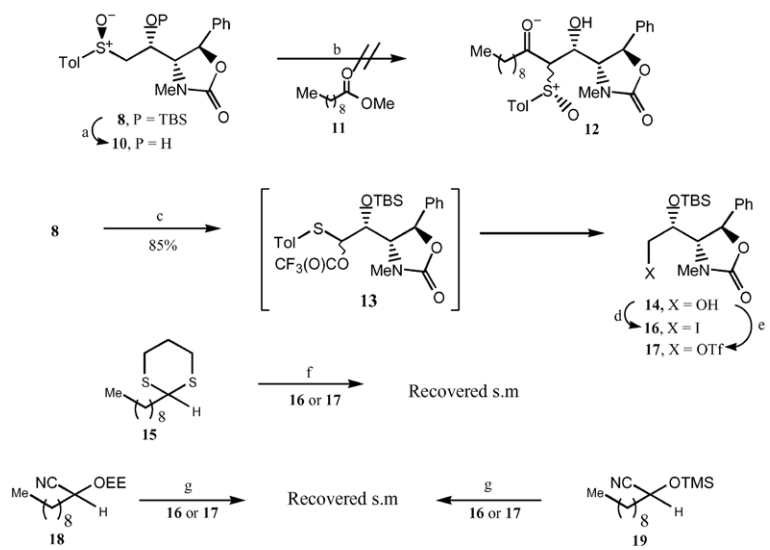
☆ IICT Communication No. 030618.

Keywords: (+)-preussin; sulfoxide; bromohydrin; stereospecific.
* Corresponding author. Tel.: +91-40-27160123; fax: +91-40-27160512; e-mail: sraghavan@iict.ap.nic.in

0040–4020/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2003.10.032



Scheme 1. *Reaction conditions*: (a) TBS–Cl, imidazole, DCM, rt, 1 h, 90%. (b) NBS, H_2O, toluene, rt, 1 h. (c) *n*-Bu_4NF, AcOH, THF, rt, 2 h, 90%. (d) MeNCO, Et_3N, DCM, rt, 8 h, 85%. (e) 2,2-Dimethoxypropane, cat. CSA, acetone, rt, 1 h. (f) NaHMDS, THF, 0°C, 1 h, **8**, 70%, **9**, 10% and **7**, 10%.

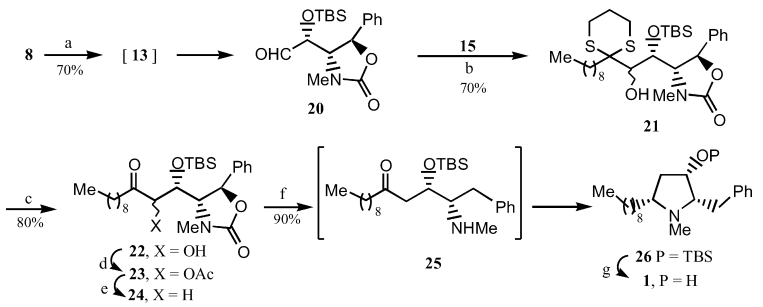


Scheme 2. *Reaction conditions*: (a) *n*-Bu_4NF, THF, 0°C, 1 h, 95%. (b) See the text. (c) TFAA, Et_3N, acetonitrile, 10 min, aq. $NaHCO_3/NaBH_4$. (d) Ph_3P, I_2, imidazole, THF, 0°C, 1 h, 95%. (e) Tf_2O, 2,6-lutidine, CH_2Cl_2, 0°C, 10 min, 95%. (f) *n*-BuLi, THF, −23°C, 2 h, then **16/17**, −78°C-rt, 16 h. (g) *n*-BuLi, THF, −23°C, 1 h, then **16/17**, −78°C-rt, 16 h.

Likewise, alkylation of the anions derived from cyanohydrins **18**[10a] and **19**,[10b] with the iodide **16** or triflate **17**, did not bear fruit.

The successful route to preussin is detailed below. Hydrolysis of the intermediate **13**, with aq. saturated $NaHCO_3$ afforded the aldehyde **20**. The alkyl chain was introduced by condensation[8] of the aldehyde **20** with the anion generated from the dithiane **15** to afford an epimeric mixture of alcohols **21** in almost equimolar quantities. Condensation of the aldehyde with dithianes derived from other aliphatic/aromatic aldehydes would yield analogs of preussin. The poor stereoselectivity in this reaction was of no consequence since the hydroxy group eventually needed to be removed. The dithiane moiety was deprotected by treatment with $PhI(OCOCF_3)_2$[11] to afford the keto alcohol **22**. Acetylation afforded the ketoacetate **23**, which on treatment with Na–Hg under buffered conditions[12] in trifluoroethanol as the solvent yielded cleanly the ketone **24**. It is worthy to note that attempted removal of the acetyl group with Na–Hg in methanol as the solvent afforded in addition to the desired ketone **24**, considerable quantities of hydroxy ketone **22** arising from the hydrolysis of the acetate. The use of non-nucleophilic trifluoroethanol avoided the undesired hydrolysis of **23**. Compound **24** on treatment with $Pd(OH)_2$ under an atmosphere of hydrogen in ethanol as the solvent afforded the pyrrolidine **26** as the only product, via hydrogenolysis to yield the methylamine **25**, which then underwent reductive amination. Deprotection of the silyl ether in **26** by treatment with TBAF afforded (+)-preussin (**1**) (Scheme 3) with physical characteristics in excellent agreement with that reported in the literature.[4a]

In summary, we have disclosed a novel and stereospecific route to (+)-preussin. The key steps of the route include: (a) regio- and stereospecific bromohydration of the olefin (**3**) using the sulfinyl group as the internal nucleophile; (b) use



Scheme 3. *Reaction conditions*: (a) TFAA, Et_3N, CH_3CN, 0°C, 15 min, aq. $NaHCO_3$, 30 min. (b) **15**, *n*-BuLi, THF, −23°C, 2 h, then **20** in THF −78°C, 10 min. (c) $PhI(OCOCF_3)_2$, 1:9 H_2O, CH_3CN, 0°C, 1 h. (d) Ac_2O, Et_3N, cat. DMAP, DCM, rt, 30 min, 90%. (e) Na−Hg, Na_2HPO_4, CF_3CH_2OH, 0°C rt, 2 h, 70%. (f) $Pd(OH)_2/C$, EtOH, H_2, rt, 1 h. (g) *n*-Bu_4NF, THF, 0°C, 1 h, 85%.

of MeNCO to introduce the *N*-Me substituent thus avoiding an additional step to introduce the same later in the synthesis. Also the use of other isocyanates would permit the elaboration of analogs with a variety of *N*-alkyl/aryl substituent; (c) the dithiane methodology to introduce the alkyl chain, which again would permit the introduction of other alkyl/aryl chains of variable lengths and thus access analogs of preussin; (d) one pot 3 step transformation of **24** to **26** and use of minimal protecting groups.

3. Experimental

3.1. General

All air or moisture sensitive reactions were carried out under nitrogen atmosphere. Solvents were distilled freshly over Na/benzophenone ketyl for THF, over P_2O_5 followed by CaH_2 for DCM and over P_2O_5 for toluene. Commercially available reagents were used without further purification except NBS, which was freshly recrystallized from hot water before use. Thin layer chromatography was performed with precoated silica gel plates. Column chromatography was carried out using silica gel (60–120 mesh). NMR spectra were recorded on a 200, 300 or 400 MHz spectrometer. ^{1}H NMR and ^{13}C NMR samples were internally referenced to TMS (0.00 ppm). Melting points are uncorrected.

3.1.1. (*R*s)-2-*tert*-Butyldimethylsilyloxy-4-phenyl-(2*R*,3*E*)-3-butenyl-4-methylphenyl sulfoxide 3. To the solution of β-hydroxy sulfoxide (**2**)[5a,6] (2.86 g, 10 mmol) and imidazole (1.5 g, 22 mmol) in DCM (20 mL was added *t*-butyldimethylsilyl chloride (1.66 g, 11 mmol)) at rt and stirred for 1 h. The reaction mixture was taken into ether (200 mL) and washed successively with water and brine. The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude reaction mixture was purified by column chromatography using 20% ethyl acetate/petroleum ether (v/v) as the eluent to afford **3** (3.6 g, 9 mmol) in 90% yield. Gummy liquid. IR (neat) 2953, 1651, 1598, 1047, 968 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (d, J=8.3 Hz, 2H), 7.40–7.10 (m, 7H), 6.60 (d, J=15.9 Hz, 1H), 6.20 (dd, J=15.9, 7.2 Hz, 1H), 4.60 (m, 1H), 3.05 (dd, J=12.8, 4.9 Hz, 1H), 2.75 (dd, J=12.8, 7.9 Hz, 1H), 2.35 (s, 3H), 0.80 (s, 9H), 0.0 (s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 141.5, 136.3, 131.7, 129.9, 128.5, 127.9, 126.6, 124.1, 69.6, 66.6, 25.7, 21.3, 18.1, −4.1, −4.8. MS (FAB) 401 $[M+H]^+$. $[\alpha]_D^{25}$=+81.7 (*c* 1.28, $CHCl_3$). Anal. calcd for $C_{23}H_{32}O_2SSi$: C, 68.95; H, 8.05; S, 8.0. Found: C, 68.65; H, 8.26; S, 7.72.

3.1.2. 2-Bromo-3-*tert*-butyldimethylsilyloxy-(4-*S*s)-(4-methylphenylsulfinyl)-1-phenyl-(1*R*,2*R*,3*S*)-butan-1-ol 4. To the solution of silyl ether (**3**) (3.4 g, 8.5 mmol) in toluene (34 mL) was added water (0.26 mL, 14.5 mmol) followed by *N*-bromosuccinimide (1.82 g, 10.2 mmol) and the mixture was stirred at rt under nitrogen atmosphere for 1 h. The reaction was quenched by adding 10% aq. $NaHCO_3$. The reaction mixture was extracted with ethyl acetate and washed successively with water, brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure afforded the crude product which was purified by column chromatography using 20% EtOAc/petroleum ether (v/v) as the eluent to afford **4** (3.38 g, 6.8 mmol) in 80% yield. Gummy liquid. IR (neat) 3326, 2954, 1256, 1090, 1033, 700, 625, 515 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.47 (d, J=8.2 Hz, 2H), 7.35 (m, 7H), 4.70 (m, 2H), 4.30 (dd, J=8.2, 2.2 Hz, 1H), 3.25 (d, J=13.4 Hz, 1H), 2.91 (dd, J=13.4, 8.9 Hz, 1H), 2.44 (s, 3H), 0.95 (s, 9H), 0.20 (s, 3H), 0.13 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.4, 141.2, 140.4, 130.0, 128.4, 128.2, 127.0, 123.9, 75.5, 65.9, 65.0, 64.1, 25.7, 21.4, 18.0, −4.7, −4.8. MS (FAB) 497 $[M+H]^+$. $[\alpha]_D^{25}$=−141.4 (*c* 1.44, $CHCl_3$). Anal. calcd for $C_{23}H_{33}O_3BrSSi$: C, 55.52; H, 6.68; S, 6.44. Found: C, 55.38; H, 6.85; S, 6.23.

3.1.3. 2-Bromo-(4-*S*s)-(4-methylphenylsulfinyl)-1-phenyl-(1*R*,2*R*,3*S*)-butan-1-ol 5. To the solution of compound (**4**) (149 mg, 0.3 mmol) in dry THF (0.6 mL) and glacial acetic acid (54 mg, 0.9 mmol) at 0°C was added dropwise tetrabutylammonium fluoride (1 M in THF, 0.45 mL) and stirred at rt for 1 h. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography using 20% EtOAc/petroleum ether (v/v) as eluent to afford **5** (108 mg, 0.28 mmol) in 95% yield. White solid. Mp 123–125°C. IR (neat) 3357, 2973, 1254, 1089, 1023, 701, 605, 525 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (d, J=8.2 Hz, 2H), 7.32 (d, J=8.2 Hz, 2H), 7.28 (bs, 5H), 5.0 (bs, 1H), 4.94 (d, J=8.0 Hz, 1H), 4.40 (m, 1H), 4.25 (t, J=8.0 Hz, 1H), 3.90 (bs, 1H), 3.27 (dd, J=13.4, 10.7 Hz, 1H), 3.18 (dd, J=13.4, 2.7 Hz, 1H), 2.45 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 141.9, 140.4, 138.6, 130.2, 128.3, 126.9, 124.1, 74.2, 68.6, 61.8, 59.3, 21.4. MS (FAB) 383 $[M+H]^+$. $[\alpha]_D$=−124.9 (*c* 1.47, $CHCl_3$). Anal. calcd for $C_{17}H_{19}BrO_3S$: C, 53.27; H, 5.00; S, 8.36. Found: C, 53.38; H, 5.05; S, 8.23.

3.1.4. 5-Bromo-2,2-dimethyl-(*S*s)-(4-methylphenylsulfinylmethyl)-6-phenyl-(4*S*,5*R*,6*R*)-1,3-dioxane 6. To the solution of the bromodiol (**5**) (76 mg, 0.2 mmol) in acetone (0.5 mL) was added 2,2-dimethoxypropane (0.5 mL) and catalytic amounts of CSA and the mixture stirred at rt for 1 h. Et_3N, enough to neutralise CSA, was added and the volatiles were removed under reduced pressure. The residue was purified by column chromatography using 30% EtOAc/petroleum ether as the eluent to afford **6** (76 mg, 0.18 mmol) in 90% yield. Gummy liquid. IR (neat) 2954, 1256, 1070, 1033, 700, 625, 523 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 7.56 (d, J=8.0 Hz, 2H), 7.36 (m, 7H), 4.90 (d, J=10.3 Hz, 1H), 4.67 (td, J=10.3, 2.2 Hz, 1H), 3.62 (t, J=10.3 Hz, 1H), 3.36 (dd, J=13.2, 2.2 Hz, 1H), 2.76 (dd, J=13.2, 10.3 Hz, 1H), 2.45 (s, 3H), 1.76 (s, 3H), 1.57 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 141.6, 141.3, 138.1, 130.0, 128.3, 127.8, 124.0, 123.7, 100.7, 77.4, 69.3, 62.4, 52.4, 29.5, 21.4, 19.4. MS (FAB) 423 $[M+H]^+$. $[\alpha]_D^{25}=-127.5$ (c 1.04, $CHCl_3$). Anal. calcd for $C_{20}H_{23}BrO_3S$: C, 56.74; H, 5.48; S, 7.57. Found: C, 56.58; H, 5.55; S, 7.53.

3.1.5. 2-Bromo-1-*tert*-butyldimethylsilyloxy-3-*N*-methylaminocarbonyloxy-(4*S*s)-[4-methylphenylsulfinyl]-1-phenyl-(1*R*,2*R*,3*S*)-butane 7. To the solution of bromohydrin (**4**) (3.18 g, 6.4 mmol) in dry DCM (26 mL) was added triethylamine (2.7 mL, 19.2 mmol), methyl isocyanate (1.14 mL, 19.2 mmol) and the reaction mixture was stirred at rt for 8 h under an atmosphere of nitrogen. 10% aq. $NaHCO_3$ solution was added and the mixture stirred for another 30 min. The reaction mixture was then diluted with ether, the two layers were separated and the organic layer washed successively with water, brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to afford a residue which was purified by column chromatography using 25% EtOAc/petroleum ether (v/v) as the eluent to afford **7** (3.0 g, 6.4 mmol) in 85% yield. White solid. Mp 89–90°C. IR (neat) 3343, 2952, 2360, 1723, 1532, 1254, 1104, 833, 770, 635, 513 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 7.50 (d, J=8.2 Hz, 2H), 7.34 (m, 7H), 5.80 (d, J=8.2 Hz, 1H), 5.20 (bs, 1H), 4.62 (m, 1H), 4.35 (dd, J=8.2, 2.2 Hz, 1H), 3.09 (dd, J=12.6, 1.5 Hz, 1H), 2.95–2.70 (m, 4H), 2.44 (s, 3H), 0.93 (s, 9H), 0.04 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.1, 141.5, 141.3, 138.0, 130.0, 128.7, 128.6, 127.1, 123.9, 77.0, 65.4, 64.3, 62.0, 27.6, 25.7, 21.4, 18.0, −4.8. MS (FAB) 554 $[M+H]^+$. $[\alpha]_D^{25}=-128.5$ (c 1.76, $CHCl_3$). Anal. calcd for $C_{25}H_{36}NBrO_4SSi$: C, 54.14; H, 6.54; N, 2.53; S, 5.78. Found: C, 54.38; H, 6.36; N, 2.23; S, 5.75.

3.1.6. 4-[1-*tert*-Butyldimethylsilyloxy-2-(4-methylphenylsulfinyl)-(1*R*,2*S*s)-ethyl]-3-methyl-5-phenyl-(4*S*,5*R*)-1,3-oxazolan-2-one 8. To the solution of methylcarbamate (**7**) (2.77 g, 5.0 mmol) in dry THF (100 mL) cooled at 0°C was added dropwise NaHMDS (2 M in THF, 2.5 mL, 5 mmol) and stirred for 1 h at the same temperature. The reaction was quenched by adding aq. saturated NH_4Cl solution. The reaction mixture was then extracted into ethyl acetate and washed successively with water, brine and dried over Na_2SO_4. The solvent was removed under reduced pressure to afford a residue which was purified by column chromatography using 30% EtOAc/petroleum ether (v/v) as the eluent to afford initially **9** (171 mg, 0.5 mmol) in 10% yield. Gummy liquid. IR (neat) 2953, 1754, 1635, 1572, 1037, 968 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 7.46 (d, J=8.2 Hz, 2H), 7.40–7.20 (m, 7H), 6.50 (dd, J=15.3, 8.2 Hz, 1H), 6.26 (d, J=15.3 Hz, 1H), 5.20 (d, J=7.10 Hz, 1H), 3.90 (dd, J=8.2, 7.1 Hz, 1H), 2.80 (s, 3H), 2.45 (s, 3H). Further elution afforded **8** (1.66 g, 3.5 mmol) in 70% yield. White solid. Mp 95–96°C. IR (neat) 2930, 2858, 1760, 1434, 1257, 1087, 1041, 837 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 7.40 (d, J=8.3 Hz, 2H), 7.23 (m, 7H), 5.24 (d, J=3.4 Hz, 1H), 4.40 (m, 1H), 3.67 (t, J=3.4 Hz, 1H), 3.0 (dd, J=13.6, 8.7 Hz, 1H), 2.91 (s, 3H), 2.86 (dd, J=13.6, 3.8 Hz, 1H), 2.35 (s, 3H), 0.80 (s, 9H), 0.09 (s, 3H), 0.00, (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 157.5, 142.0, 140.5, 139.4, 130.2, 128.8, 128.6, 125.2, 123.9, 75.5, 68.5, 66.3, 61.4, 30.6, 25.6, 21.3, 17.9, −4.6, −4.7. MS (FAB) 474 $[M+H]^+$. $[\alpha]_D^{25}=+79.9$ (c 0.54, $CHCl_3$). Anal. calcd for $C_{25}H_{35}NO_4SSi$: C, 63.39; H, 7.45; N, 2.96; S, 6.77. Found: C, 63.03; H, 7.27; N, 2.67; S, 6.90.

3.1.7. 4-[1-Hydroxy-2-(4-methylphenylsulfinyl)-(1*R*,2*S*s)-ethyl]-3-methyl-5-phenyl-(4*S*,5*R*)-1,3-oxazolan-2-one 10. To the solution of compound (**8**) (0.95 g, 2.0 mmol) in dry THF (4.0 mL) at 0°C was added dropwise tetrabutylammonium fluoride (1 M in THF, 2.2 mL) and stirred at rt for 1 h. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography using 40% EtOAc/petroleum ether (v/v) as eluent to afford **10** (0.68 g, 1.9 mmol) in 95% yield. Gummy liquid. IR (neat) 3420, 2933, 2859, 1754, 1077, 1034, 971 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 7.40 (d, J=8.3 Hz, 2H), 7.23 (m, 7H), 5.32 (d, J=3.4 Hz, 1H), 4.63 (m, 1H), 3.80–3.70 (t, J=3.4 Hz, 1H), 3.32–3.10 (m, 2H), 2.80 (s, 3H), 2.46 (s, 3H). MS (FAB) 360 $[M+H]^+$. Anal. calcd for $C_{19}H_{21}NO_4S$: C, 63.49; H, 5.89; N, 3.90; S, 8.92. Found: C, 63.23; H, 5.67; N, 3.97; S, 8.90.

3.1.8. 4-[2-Hydroxy-1-*tert*-butyldimethylsilyloxy-(1*R*)-ethyl]-3-methyl-5-phenyl-(4*S*,5*R*)-1,3-oxazolan-2-one 14. To the solution of the oxazolidinone (**8**) (0.85 g, 1.8 mmol) in dry acetonitrile (9 mL) at 0°C was added dry triethylamine (0.76 mL, 5.4 mmol), trifluoroacetic anhydride (0.76 mL, 5.4 mmol) and stirred for 15 min. The solution of $NaHCO_3$ (1.5 g, 18 mmol) and $NaBH_4$ (0.14 g, 3.6 mmol) in water (9 mL) was added dropwise and stirred for 30 min. The reaction mixture was then extracted into ethyl acetate and washed with water, brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to afford a residue, which was purified by column chromatography using 20% EtOAc/petroleum ether (v/v) as the eluent to afford **14** (0.54 g, 1.53 mmol) in 85% yield. Gummy liquid. IR (neat) 3426, 2930, 1740, 1440, 1122, 1055, 836, 776, 698 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 7.40–7.24 (m, 5H), 5.20 (d, J=3.7 Hz, 1H), 4.10–3.95 (m, 1H), 3.75 (d, J=7.2 Hz, 2H) 3.62 (t, J=3.7 Hz, 1H), 2.97 (s, 3H), 0.90 (s, 9H), 0.15 (s, 3H), 0.05 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.1, 139.7, 128.8, 128.6, 125.3, 76.1, 72.0, 67.1, 62.8, 30.8, 25.7, 18.0, −4.6, −4.8. MS (FAB) 352 $[M+H]^+$. Anal. calcd for $C_{18}H_{29}NO_4Si$: C, 61.50; H, 8.32; N, 3.98. Found: C, 61.63; H, 8.27; N, 3.67.

3.1.9. 4-[2-Iodo-1-*tert*-butyldimethylsilyloxy-(1*R*)-ethyl]-3-methyl-5-phenyl-(4*S*,5*R*)-1,3-oxazolan-2-one 16. To the solution of compound (**14**) (88 mg, 0.25 mmol) in dry THF (1.0 mL) at 0°C was added imidazole (26 mg, 0.38 mmol),

triphenyl phosphine (72 mg, 0.28 mmol), iodine (70 mg, 0.28 mmol) at 0°C and stirred for 1 h. The reaction mixture was diluted with ether, washed with 10% aq. sodium thiosulphate, water, brine, dried over sodium sulphate and evaporated. The residue was purified by column chromatography using 10% EtOAc/petroleum ether (v/v) as eluent to afford **16** (114 mg, 0.24 mmol) in 95% yield. Gummy liquid. IR (neat) 2922, 1759, 1463, 1257, 773, 700 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 7.43–7.25 (m, 5H), 5.25 (d, J=3.4 Hz, 1H), 4.15–4.05 (m, 1H), 3.75 (t, J=3.4 Hz, 1H), 3.40–3.16 (m, 2H), 2.98 (s, 3H), 0.95 (s, 9H), 0.25 (s, 3H), 0.05 (s, 3H). MS (FAB) 462 $[M+H]^+$. Anal. calcd for $C_{18}H_{28}INO_3Si$: C, 46.86; H, 6.12; N, 3.04. Found: C, 46.93; H, 6.24; N, 2.97.

3.1.10. Hydroxy-1-*tert*-butyldimethylsilyloxy-2-[3-methyl-2-oxo-5-phenyl-(4*S*,5*R*)-1,3-oxazolan-4-yl]ethyl-trifluoromethylsulfonate 17. To the solution of compound (**14**) (88 mg, 0.25 mmol) in dry dichloromethane (1.0 mL) at 0°C was added 2,6-lutidine (32 μL, 0.28 mmol) followed by the dropwise addition of triflic anhydride (46 μL, 0.28 mmol) in dry DCM (1 mL) and stirred for 10 min. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography using 15% EtOAc/petroleum ether (v/v) as eluent to afford **17** (115 mg, 0.24 mmol) in 95% yield. Gummy liquid. ^1H NMR (200 MHz, $CDCl_3$) δ 7.40–7.20 (m, 5H), 5.30 (d, J=3.4 Hz, 1H), 4.56 (d, J=6.8 Hz, 2H), 4.30 (m, 1H), 3.65 (t, J=3.4 Hz, 1H), 2.98 (s, 3H), 2.55 (s, 3H), 0.95 (s, 9H), 0.25 (s, 3H), 0.05 (s, 3H). The triflate was used in the next reaction without further characterization.

3.1.11. 2-Hydroxy-1-*tert*-butyldimethylsilyloxy-2-[3-methyl-2-oxo-5-phenyl-(4*S*,5*R*)-1,4-oxazolan-4-yl]-acetaldehyde 20. To the solution of oxazolidinone (**8**) (1.6 g, 3.38 mmol) in dry acetonitrile (17 mL) at 0°C was added dry triethylamine (1.4 mL, 10.1 mmol), trifluoroacetic anhydride (1.4 mL, 10.1 mmol) and stirred for 15 min. The solution of $NaHCO_3$ (2.84 g, 33.8 mmol) in water (17 mL) was added dropwise and stirred for 30 min. The reaction mixture was then extracted into ethyl acetate and washed with water, brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to afford a residue which was quickly purified by column chromatography using 20% EtOAc/petroleum ether (v/v) as the eluent to afford **20** (0.94 g, 2.7 mmol) in 70% yield. Gummy liquid. ^1H NMR (200 MHz, $CDCl_3$) δ 9.56 (s, 1H), 7.20–7.06 (m, 5H), 5.0 (d, J=3.7 Hz, 1H), 3.96 (d, J=3.7 Hz, 1H), 3.68 (t, J=3.7 Hz, 1H), 2.57 (s, 3H), 0.78 (s, 9H), 0.02 (s, 6H). $[\alpha]_D^{25}$=+8.9 (c 0.5, $CHCl_3$).

3.1.12. 4-[2-Hydroxy-1-*tert*-dimethylsilyloxy-2-(2-nonyl-1,3-dithian-2-yl)-(1*R*)-ethyl]-3-methyl-5-phenyl-(4*S*,5*R*)-1,3-oxazolan-2-one 21. To the solution of thioacetal (**15**) (0.89 g, 3.6 mmol) in dry THF (8 mL) cooled at −23°C was added *n*-butyl lithium (1.6 M in hexanes, 2.25 mL, 3.6 mmol) and stirred for 2 h. The reaction mixture was cooled to −78°C and the solution of the aldehyde (**20**) (850 mg, 2.4 mmol) in THF (4.8 mL) was added dropwise. The reaction was quenched after 10 min by adding aq. saturated NH_4Cl solution. The layers were separated and the aq. layer was extracted with ethyl acetate. The organic layer was washed with water, brine, dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography using 10% EtOAc/petroleum ether (v/v) as the eluent to yield **21** (1.0 g, 1.68 mmol) in 70% yield. Gummy liquid. IR (neat) 3320, 2926, 2859, 2679, 2858, 2658, 1760, 1434, 1257, 1077, 1049, 836, 655, 613 cm^{-1}. ^1H NMR of the epimeric mixture of alcohols (200 MHz, $CDCl_3$) δ 7.20 (m, 10H), 5.70 (d, J=5.2 Hz, 1H), 4.95 (d, J=6.7 Hz, 1H), 4.45 (m, 1H), 4.25 (m, 1H) 3.94 (m, 2H), 3.45 (m, 1H), 3.25 (d, J=7.4 Hz, 1H), 2.90 (s, 3H), 2.85 (s, 3H), 2.82–2.40 (m, 8H), 2.0–1.60 (m, 4H), 1.30–1.0 (m, 32H), 0.80 (m, 15H), 0.66 (s, 9H), 0.07 (s, 3H), 0.02 (s, 3H), −0.01 (s, 3H), −0.04 (s, 3H). MS (FAB) 596 $[M+H]^+$. $[\alpha]_D^{25}$=+23.5 (c 0.6, $CHCl_3$). HRMS (FAB) m/z calcd for $C_{31}H_{53}NO_4S_2Si$ 596.3264; found, 596.3229.

3.1.13. 2-Hydroxy-1-*tert*-butyldimethylsilyloxy-1-[3-methyl-2-oxo-5-phenyl-(4*S*,5*R*)-1,3-oxazolan-4-yl]-(1*R*)-dodecan-3-one 22. To the solution of the hydroxy thioketal (**21**) (446 mg, 0.75 mmol) in a mixture of 9:1 acetonitrile/water (7.5 mL) at 0°C was added iodobenzene bistrifluoroacetate (484 mg, 1.13 mmol) and stirred for 1 h. The reaction mixture was diluted with ether and washed successively with 10% aq. $NaHCO_3$, water, brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography using 10% EtOAc/petroleum ether (v/v) as the eluent to yield **22** (303 mg, 0.6 mmol) in 80% yield. Gummy liquid. IR (neat) 3320, 2953, 2930, 2675, 1755, 1720, 1430, 1370, 1172 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 7.32 (m, 10H), 5.80 (d, J=5.2 Hz, 1H), 5.50 (d, J=3.7 Hz, 1H), 4.45–4.08 (m, 4H), 3.58 (m, 2H), 2.95 (s, 3H), 2.88 (s, 3H), 2.77–2.40 (m, 4H), 1.57 (m, 4H), 1.27 (m, 24H), 0.86 (m, 15H), 0.78 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H), −0.05 (s, 3H), −0.13 (s, 3H). MS (FAB) 506 $[M+H]^+$. $[\alpha]_D^{25}$=−4.8 (c 0.32, $CHCl_3$). HRMS (FAB) m/z calcd for $C_{28}H_{47}NO_5Si$ 506.3302; found, 506.3315.

3.1.14. 1-*tert*-Butyldimethylsilyloxy-[3-methyl-2-oxo-5-phenyl-(4*S*,5*R*)-1,3-oxazolan-4-yl]-methyl-2-oxoundecyl acetate 23. To the solution of hydroxyketone (**22**) (250 mg, 0.5 mmol) in dry DCM (2 mL) was added triethylamine (0.2 mL, 1.5 mmol), cat. DMAP, acetic anhydride (0.1 mL, 1 mmol) and stirred for 30 min at rt. The reaction mixture was diluted with ether and washed successively with water, 10% aq. citric acid, 10% aq. $NaHCO_3$, water, brine, dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography using 10% EtOAc/petroleum ether (v/v) as the eluent to yield **23** (246 mg, 0.45 mmol) in 90% yield. Gummy liquid. IR (neat) 2939, 2928, 2675, 1759, 1753, 1716, 1429, 1182 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 7.39 (m, 10H), 5.69 (d, J=2.3 Hz, 1H), 5.64 (d, J=2.2 Hz, 1H), 5.35 (d, J=4.6 Hz, 1H), 5.19 (d, J=3.7 Hz, 1H), 4.61 (m, 2H), 3.68 (m, 2H), 3.0 (s, 3H), 2.87 (s, 3H), 2.80–2.15 (m, 4H), 2.30 (s, 3H), 2.28 (s, 3H), 1.56 (m, 4H), 1.34 (m, 24H), 0.94 (m, 15H), 0.18 (s, 3H), 0.13 (s, 3H), 0.10 (s, 3H), 0.00 (s, 3H). MS (FAB) 548 $[M+H]^+$. $[\alpha]_D^{25}$=−9.6 (c 0.5, $CHCl_3$). HRMS (FAB) m/z calcd for $C_{30}H_{49}NO_6Si$ 548.3770; found, 548.3741.

3.1.15. 1-*tert*-Butyldimethylsilyloxy-1-[3-methyl-2-oxo-5-phenyl-(4*S*,5*R*)-1,3-oxazolan-4yl]-(1*S*)-dodecan-3-one

24. To the solution of the acetoxyketone (**23**) (218 mg, 0.4 mmol) in 2,2,2-trifluoroethanol (4 mL) at 0°C was anhydrous disodiumhydrogenphosphate (227 mg, 1.6 mmol), Na–Hg (6% Na atom, 600 mg) and stirred at rt for 2 h. The reaction mixture was diluted with ether and washed with water, brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography using 10% EtOAc/petroleum ether (v/v) as the eluent to yield **24** (137 mg, 0.28 mmol) in 70% yield. Gummy liquid. IR (neat) 2943, 2923, 2665, 1757, 1720, 1428, 1364, 1146 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.34 (m, 5H), 5.33 (d, J=3.6 Hz, 1H), 4.68 (m, 1H), 3.57 (m, 1H), 2.84 (s, 3H), 2.67 (dd, J=17.0, 6.0 Hz, 1H), 2.58 (dd, J=17.0, 4.8 Hz, 1H), 2.44 (m, 2H), 1.60 (m, 2H), 1.43 (m, 2H), 1.28 (m, 12H), 0.90 (t, 3H), 0.84 (s, 9H), 0.06 (s, 3H), 0.00 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.8, 157.7, 139.9, 128.8, 128.7, 126.0, 75.5, 68.4, 66.9, 44.5, 44.3, 31.8, 30.0, 29.4, 29.2, 29.1, 25.7, 25.4, 23.4, 22.7, 17.9, 14.1, −3.6, −4.0. MS (FAB) 490 $[M+H]^+$. $[\alpha]_D^{25}$=−15.8 (c 1.0, $CHCl_3$). Anal. calcd for $C_{28}H_{47}NO_4Si$: C, 68.67; H, 9.67; N, 2.86. Found: C, 68.48; H, 9.72; N, 2.97.

3.1.16. (2*S*,3*S*,5*R*)-2-Benzyl-3-*tert*-butyldimethylsilyloxy-1-methyl-5-nonylazolidine 26. To the solution of the keto oxazolidinone (**24**) (100 mg, 0.2 mmol) in ethanol (0.8 mL) was added $Pd(OH)_2$ (20% by weight, 20 mg) and stirred under an atmosphere of hydrogen for 1 h. The catalyst was filtered through a small pad of celite and the filtrate evaporated under reduced pressure to afford (**26**) (78 mg, 0.18 mmol) in 90% yield. Gummy liquid. IR (neat) 2926, 2855, 2675, 1731, 1460, 1378, 1354, 1054, 750, 701 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 7.20 (m, 5H), 4.10 (m, 1H), 3.10–2.68 (m, 2H), 2.50 (m, 1H), 2.30–1.90 (m, 5H), 1.80–1.0 (m, 16H), 0.9 (m, 12H), −0.05 (s, 3H), −0.13 (s, 3H). MS (FAB) 432 $[M+H]^+$. $[\alpha]_D^{25}$=+8.8 (c 1.37, $CHCl_3$).

3.1.17. (2*S*,3*S*,5*R*)-2-Benzyl-3-hydroxy-1-methyl-5-nonylazolidine [(+)-preussin (1)]. To the solution of compound (**26**) (50 mg, 0.12 mmol) in dry THF (0.3 mL) at 0°C was added dropwise tetrabutylammonium fluoride (1 M in THF, 0.14 mL) and stirred at rt for 1 h. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography using 20% EtOAc/petroleum ether (v/v) as eluent to afford (+)-preussin (**1**) (31 mg, 0.1 mmol) in 85% yield. Waxy solid. IR (neat) 3426, 2953, 2890, 2775, 1468, 1455, 1348, 1132, 1030, 966, 743 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.20 (m, 5H), 3.73 (m, 1H), 2.83 (dd, J=13.2, 10.2 Hz, 1H), 2.73 (dd, J=13.2, 4.5 Hz, 1H), 2.27 (s, 3H), 2.20–2.08 (m, 4H), 1.59 (m, 1H), 1.40 (m, 1H), 1.20 (m, 16H), 0.85 (t, J=13.6, 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.4, 129.4, 128.4, 126.2, 74.0, 70.2, 66.3, 39.2, 38.4, 34.2, 33.2, 31.9, 29.8, 29.6, 29.5, 29.3, 26.4, 22.7, 14.1. MS (ESI) 318 $[M+H]^+$. $[\alpha]_D^{25}$=+31.5 (c 0.6, $CHCl_3$), (lit.[4a] $[\alpha]_D^{25}$=+29.3 (c 1.17, $CHCl_3$). HRMS (FAB) m/z calcd for $C_{21}H_{35}NO$ 318.2797; found 318.2802.

Acknowledgements

S. R. is thankful to Dr J. S. Yadav, Head, Organic Div. I, Dr K. V. Raghavan, Director, I.I.C.T., for constant support and encouragement, to Dr A. C. Kunwar for NMR spectra and M. Vairamani for the mass spectra. M. A. R. is thankful to CSIR (New Delhi) for the senior research fellowship. Financial assistance from DST is gratefully acknowledged.

References

1. (a) Schwartz, R. E.; Leisch, J.; Hensens, O.; Zitano, L.; Honeycutt, S.; Garitty, G.; Fromtling, R. A.; Onishi, J.; Monaghan, R. *J. Antibiot.* **1988**, *41*, 1774. (b) Johnson, J. H.; Phillipson, D. W.; Kahle, A. D. *J. Antibiot.* **1989**, *42*, 1184.
2. Kasahara, K.; Yoshida, M.; Eishima, J.; Takasako, K.; Beppu, T.; Horinouchi, S. *J. Antibiot.* **1997**, *50*, 267.
3. Achenbach, T. V.; Slater, E. P.; Brummerhop, H.; Bach, T.; Muller, R. *Antimicrob. Agents Chemother.* **2000**, *44*, 2794.
4. For earlier approaches refer: (a) Okue, M.; Watanabe, H.; Kitahara, T. *Tetrahedron* **2001**, *57*, 4107. (b) Lee, K.-Y.; Kim, Y.-H.; Oh, C.-Y.; Ham, W.-H. *Org. Lett.* **2000**, *2*, 4041. (c) Bach, T.; Brummerhop, H.; Harms, K. *Chem. Eur. J.* **2000**, *6*, 3838. (d) Verma, R.; Ghosh, S. K. *J. Chem. Soc., Perkin Trans. 1* **1999**, 265. (e) Bach, T.; Brummerhop, H. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 3400. (f) Veeresa, G.; Dutta, A. *Tetrahedron* **1998**, *54*, 15673. (g) Dong, H. Q.; Lin, G. Q. *Chin. J. Chem.* **1998**, *16*, 458. (h) Kanazawa, A.; Gillet, S.; Delair, P.; Greene, A. E. *J. Org. Chem.* **1998**, *63*, 4660. (i) deArmas, P.; Garcia-Tellado, F.; Marrero-Tellado, J. J.; Robles, J. *Tetrahedron Lett.* **1998**, *39*, 131. (j) Kadota, I.; Saya, S.; Yamamoto, Y. *Heterocycles* **1997**, *46*, 335. (k) Dong, H. Q.; Lin, G. Q. *Chin. Chem. Lett.* **1997**, *8*, 693. (l) Beier, C.; Schaumann, E. *Synthesis* **1997**, 1296. (m) Verma, R.; Ghosh, S. K. *J. Chem. Soc., Chem. Commun.* **1997**, 1601. (n) Kadota, I.; Yamamoto, Y. *J. Synth. Org. Chem.* **1997**, *55*, 619. (o) Yoda, H.; Yamazaki, H.; Takabe, K. *Tetrahedron: Asymmetry* **1996**, *7*, 373. (p) Overhand, M.; Hecht, S. *J. Org. Chem.* **1994**, *59*, 4721. (q) Deng, W.; Overman, L. E. *J. Am. Chem. Soc.* **1994**, *116*, 11241. (r) Shimazaki, M.; Okazaki, F.; Nakajima, F.; Ishikawa, T.; Ohta, A. *Heterocycles* **1993**, *36*, 1823. (s) McGrane, P. L.; Livinghouse, T. *J. Am. Chem. Soc.* **1993**, *115*, 11485. (t) Pak, C. S.; Lee, G. H. *J. Org. Chem.* **1991**, *56*, 1128.
5. (a) Raghavan, S.; Rasheed, M. A. *Tetrahedron: Asymmetry* **2003**, *14*, 1371. (b) Raghavan, S.; Joseph, S. C. *Tetrahedron: Asymmetry* **2003**, *14*, 101. (c) Raghavan, S.; Ramakrishna Reddy, S.; Tony, K. A.; Naveen Kumar, Ch.; Varma, A. K.; Nangia, A. *J. Org. Chem.* **2002**, *67*, 5838. (d) Raghavan, S.; Rasheed, M. A.; Joseph, S. C.; Rajender, A. *J. Chem. Soc., Chem. Commun.* **1999**, 1845.
6. Solladie, G.; Demailly, G.; Greck, C. *J. Org. Chem.* **1985**, *50*, 1552.
7. (a) Pummerer, R. *Chem. Ber.* **1909**, *42*, 2282. (b) Sugihara, H.; Tanikaga, R.; Kaji, A. *Synthesis* **1978**, 881. (c) Padwa, A.; Gunn, D. E., Jr.; Osterhout, M. H. *Synthesis* **1997**, 1353.
8. (a) Corey, E. J.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 1075. see also p 1077. (b) For a review refer: Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 639.
9. Marshall, J. A.; Belletire, J. L. *Tetrahedron Lett.* **1971**, 871.
10. (a) Stork, G.; Maldonado, L. *J. Am. Chem. Soc.* **1971**, *93*, 5286. (b) Hunig, S.; Wehner, G. *Synthesis* **1975**, 180.
11. Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 287.
12. Trost, B. M.; Arndt, H. C.; Strege, P. E.; Verhoeven, T. R. *Tetrahedron Lett.* **1976**, 3477.