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Modular and stereoselective formal synthesis of MeBmt, an unusual amino acid constituent of cyclosporin A☆

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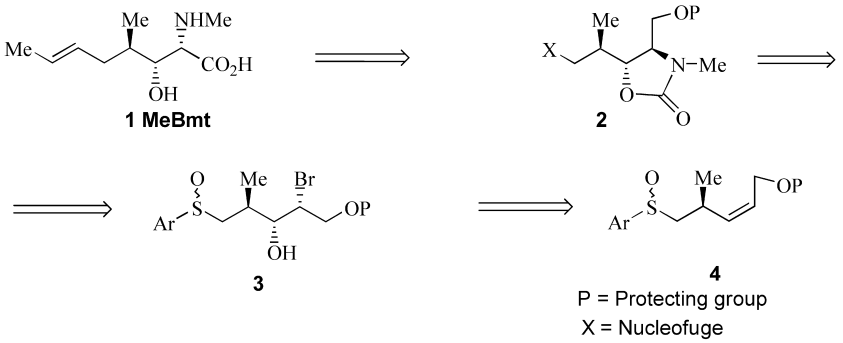
Abstract—A convergent, flexible and stereoselective formal synthesis of MeBmt, the nonproteinogenic amino acid constituent of cyclosporin A is disclosed. The sulfinyl moiety has been exploited as the internal nucleophile to stereo- and regioselectively functionalize an allylic carbamate.

1. Introduction

Cyclosporin A is a cyclic undecapeptide isolated from the fungus *Tolypocladium inflatium* Gams.,[1] possessing immunosuppressive activity, thus preventing organ rejection after transplantation. The structure of cyclosporin A is characterized by the presence of many *N*-methylated α-amino acids and a unique γ-alkyl-β-hydroxy-α-amino acid, MeBmt (**1**). MeBmt itself does not show any bioactivity, however modification of the MeBmt moiety in cyclosporin greatly affects its immunosuppressive activity. Many routes have been reported for the synthesis of MeBmt, employing starting materials from the chiral pool,[2] chiral epoxides[3] and the aldol reaction[4] in the key step of the reaction sequence. The syntheses employing the aldol reaction as the key step require chiral α-alkyl branched aldehyde and a chiral glycine synthon for good diastereoselection. The other syntheses require expensive catalysts or additional steps for the *N*-methylation of the final amino acid, thereby limiting their potential for the large scale preparation of MeBmt. As part of our interest in employing the sulfinyl moiety as an internal nucleophile[5] to stereo- and regioselectively functionalize allylic olefins and use of the resulting bromohydrins as intermediates for the synthesis of bioactive target molecules,[6] we detail herein a stereoselective and modular synthesis of MeBmt.

2. Results and discussion

MeBmt has three contiguous chiral centers, an *N*-Me group and a *trans* double bond. By retrosynthetic analysis (Scheme 1), MeBmt can be derived from the retron **2**, the forward sequence would require chain extension by a propenyl cuprate followed by oxidation of the primary hydroxy group and hydrolysis of the oxazolidinone. The oxazolidinone **2**



Scheme 1.

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Keywords: MeBmt; Sulfoxide; Neighbouring group participation; Bromohydrin.
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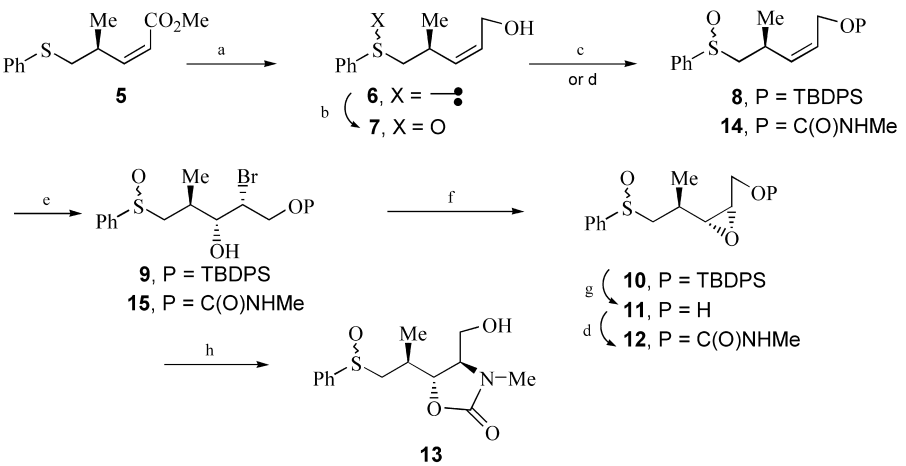
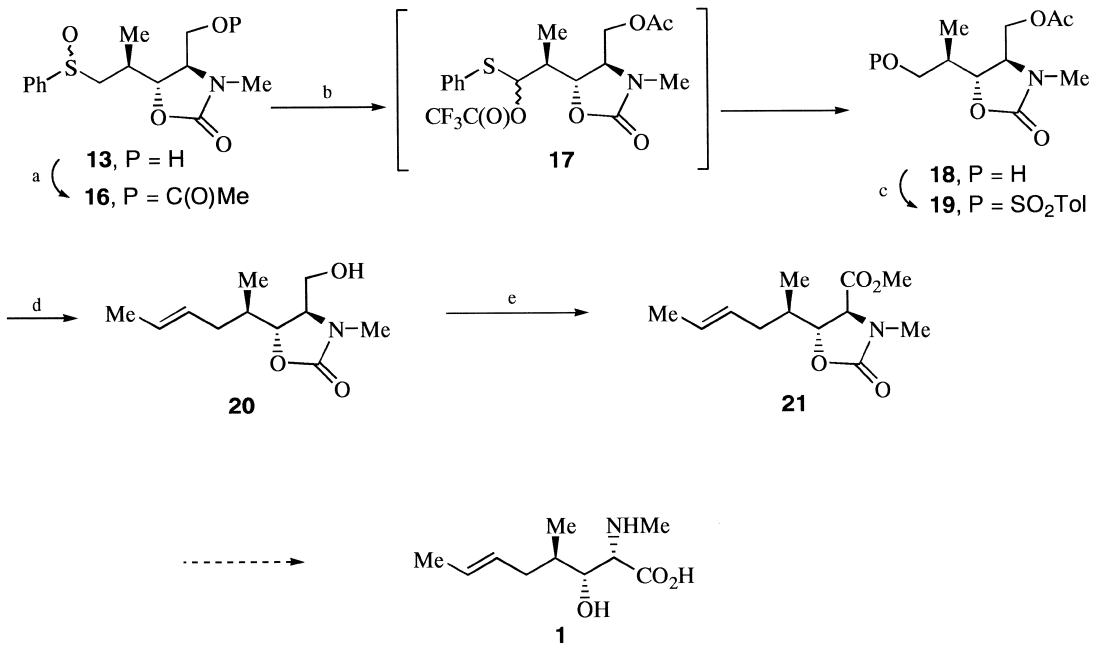


Scheme 2. (a) $LiAlH_4/AlCl_3$, THF/ether 0 °C, 1 h, 93%; (b) $NaIO_4$, CH_3OH/H_2O, rt, 16 h, 95%; (c) TBDPSCl, imidazole, CH_2Cl_2, rt, 2 h, 95%; (d) CH_3NCO, Et_3N, CH_2Cl_2, rt, 6 h, **14**, 90%, **12**, 95%; (e) NBS, H_2O, toluene, rt, 30 min, **9**, 80% **15**, 80%; (f) K_2CO_3, CH_3OH, rt, 1 h, **10**, 95%, **12**, 95%; (g) TBAF/AcOH, THF, rt, 2 h, 85%; (h) NaHMDS, THF, 0 °C, 30 min, 95%.

can itself be derived from bromohydrin **3** which in turn can be readily obtained from the olefinic substrate **4**. In the proposed strategy, the methyl group would serve to introduce the other two chiral centers stereoselectively by asymmetric induction.

The synthesis began with the unsaturated ester **5**,[6b] which was reduced with alane, generated in situ, to afford the primary alcohol **6**. Oxidation of the sulfide with $NaIO_4$ afforded an inseparable equimolar mixture of sulfoxides **7**, which was transformed into the silyl ether **8** by treatment with *t*-butyldiphenylchloro silane. No efforts were made to separate the epimeric sulfoxides **8**, since the sulfur chirality was of no consequence in the subsequent steps of the synthesis.[5b] Treatment of the sulfoxide **8** with NBS in toluene in the presence of water afforded bromohydrin **9**, the structure of which has been rigorously established.[5b] The product **9** has three stereocenters other than the sulfoxide, that are disposed both in a relative and an absolute sense as in MeBmt; the *N*-Me group therefore needed to be introduced by a double inversion procedure. Toward that direction, subjecting a methanolic solution of **9** to treatment with K_2CO_3 in methanol afforded the epoxide **10**. Deprotection of the silyl group by treatment with buffered TBAF[7] in anhydrous THF afforded epoxy alcohol **11**. Reaction of the epoxy alcohol **11** with methyl isocyanate afforded the carbamate **12**, which when subjected to treatment with NaHMDS in anhydrous THF afforded the rearranged oxazolidinone[8] **13** exclusively (Scheme 2).

It occurred to us that if the bromohydration could be done on the allylic carbamate **14**, two steps could be reduced in the overall synthetic sequence. Homoallylic carbamates have been reported to function as internal nucleophiles and afford



Scheme 3. (a) Ac_2O, Et_3N, cat. DMAP, CH_2Cl_2, rt, 30 min, 95%; (b) TFAA, Et_3N, CH_3CN, rt, 30 min, then aq. $NaHCO_3$, $NaBH_4$, at 0 °C, 30 min, 65%; (c) TsCl, Et_3N, cat. DMAP, CH_2Cl_2, rt, 1 h, 85%; (d) 1-(*E*)-propenylmagnesium bromide, CuI, THF, −78 °C to rt, 2 h, 70%; (e) $PhI(OAc)_2$, TEMPO, CH_3CN/H_2O, rt, 2 h, then ethereal CH_2N_2, rt, 10 min, 80% for 2 steps.

iodocarbonates upon treatment with iodine in a biphasic system after a prolonged reaction period. A single example of a carbamate derived from an allyl alcohol was reported to yield the iodocarbonate in moderate yield under similar reaction conditions.[9] We were therefore not certain if the carbamate or the sulfinyl moiety would function as the intramolecular nucleophile in the reaction of **14** with NBS. Gratifyingly, reaction of **14**, prepared from alcohol **7** by treatment with methyl isocyanate, with NBS in toluene afforded exclusively, the bromohydrin **15**, as an epimeric mixture, within a period of 30 min. Subjecting bromohydrin **15** to treatment with K_2CO_3 in methanol afforded epoxy carbamate **12** identical to that prepared from the allyl silylether **8**. The cyclization of epoxycarbamate **12** to yield **13** not only served to introduce the *N*-methyl substituent but also served to simultaneously protect the hydroxy and amino groups. Having access to the oxazolidinone **13**, the next step of the synthesis called for the introduction of the olefinic side chain and oxidation of the primary hydroxy group. Acetylation of the hydroxy group in **13** afforded compound **16** which was more conveniently obtained in a one pot operation from **12** by quenching the reaction with Ac_2O. Subjecting **16** to Pummerer rearrangement[10] conditions followed by treatment of the resulting intermediate **17** with sat. aq. $NaHCO_3$ and $NaBH_4$ afforded alcohol **18** in an one pot operation. Tosylation of the hydroxy group yielded product **19** which upon treatment with excess (*E*)-propenyl magnesium bromide in the presence of cat. amount of CuI afforded olefinic alcohol[2a] **20** by concomitant deprotection of the acetyl group. The primary hydroxy group was oxidized by treatment with $PhI(OAc)_2$/TEMPO[11] to yield the acid which was esterified by treatment with excess of diazomethane to afford the ester **21**. Compound **21** had physical and spectroscopic properties similar to that reported in the literature.[2a] Oxazolidinone **21** has been transformed to MeBmt[2a,4a,g] and thus we have completed a formal synthesis of the unusual amino acid, MeBmt (Scheme 3).

In summary, we have disclosed a novel, modular and stereoselective synthesis of MeBmt. The key steps in the reaction sequence include regio- and stereoselective bromohydration of a double bond utilizing the sulfinyl group as an internal nucleophile, the use of a carbamate as an internal nucleophile to open the epoxide to yield the required *trans* oxazolidinone and the use of the sulfoxide as a masked hydroxyl group.

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. ^1H NMR and ^{13}C NMR samples were internally referenced to TMS (0.00 ppm). Insufficient resonances in the ^{13}C NMR data of the diastereomeric mixture of compounds is due to resonance overlap. Melting points are uncorrected.

3.1.1. 4-Methyl-5-phenylsulfanyl-(*Z*,4*S*)-2-pentene-1-ol 6. To the suspension of $LiAlH_4$ (0.91 g, 24 mmol) in dry ether (20 mL) maintained at 0 °C was added the solution of $AlCl_3$ (1.07 g, 8 mmol) in anhydrous ether (37 mL) and the reaction mixture stirred at the same temperature for 30 min. The solution of the ester **5**[6b] (3.78 g, 16 mmol) in anhydrous ether (37 mL) was then added to reaction mixture and the stirring continued at 0 °C for a further 30 min. The reaction mixture was diluted with ether and quenched by adding ice pieces. The reaction mixture was passed through a small pad of celite and the filtrate evaporated under reduced pressure to afford the crude product which was purified by column chromatography using 30% EtOAc/petroleum ether (v/v) as the eluent to yield allyl alcohol **6** (3.1 g, 14.9 mmol) in 93% yield. Viscous oil. R_f 0.3 (10% EtOAc/petroleum ether). $[\alpha]_D^{25}=-21.0$ (*c* 1.0, $CHCl_3$). *ms* LSIMS 209 $[M+H]^+$. IR (neat) 3554, 2889, 1087, 954, 690. ^1H NMR (200 MHz, $CDCl_3$) δ 7.38–7.10 (m, 5H), 5.68 (m, 1H), 5.35 (t, J=8.3 Hz, 1H), 4.20–3.95 (m, 2H), 3.0–2.70 (m, 3H), 1.13 (d, J=6.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.8, 32.1, 40.8, 58.3, 126.0, 128.9, 129.2, 136.1, 136.6. Anal. calcd for $C_{12}H_{16}OS$: C, 69.19; H, 7.74; S, 15.39. Found: C, 69.35; H, 7.56; S, 15.25.

3.1.2. 4-Methyl-5(S_S)-phenylsulfinyl-(*Z*,4*S*)-2-pentene-1-ol and 4-methyl-5(R_S)-phenylsulfinyl-(*Z*,4*S*)-2-pentene-1-ol 7. To the solution of the sulfide **6** (3.0 g, 14.5 mmol), in 1:1 MeOH/THF (146 mL) was added the solution of $NaIO_4$ (3.4 g, 15.9 mmol) in water (73 mL) and the reaction mixture stirred at rt for 16 h. The precipitated solid was removed by filtration and the filtrate evaporated under reduced pressure. The aq. layer was extracted with ethyl acetate and the combined organic layers washed with water, brine and dried over Na_2SO_4. The organic layer was evaporated under reduced pressure to afford the crude product which was purified by column chromatography using 50% EtOAc/petroleum ether (v/v) as the eluent to yield sulfoxide **7** (3.08 g, 13.77 mmol) as a 1:1 diastereomeric mixture in 95% yield. Viscous oil. R_f 0.2 (50% EtOAc/petroleum ether). *ms* LSIMS 225 $[M+H]^+$. IR (neat) 3327, 2953, 1651, 1598, 1047, 968 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 7.60–7.48 (m, 10H), 5.90 (m, 1H), 5.75 (m, 1H), 5.39 (t, J=10.4 Hz, 1H), 5.25 (t, J=10.4 Hz, 1H), 4.40–3.90 (m, 4H), 3.42–3.0 (m, 2H), 2.95–2.75 (m, 2H), 2.61–2.40 (m, 2H), 1.20 (d, J=7.8 Hz, 3H), 1.10 (d, J=7.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.5, 20.8, 27.4, 27.7, 57.8, 57.9, 64.3, 64.6, 123.8, 123.9, 129.1, 129.2, 129.3, 131.0, 131.1, 133.7, 134.6, 143.5, 143.7. Anal. calcd for $C_{12}H_{16}O_2S$: C, 64.25; H, 7.19; S, 14.29. Found: C, 64.16; H, 7.04; S, 14.12.

3.1.3. 1(S_S)-[5-*tert*-Butyldiphenylsiloxy-2-methyl-(2*S*,3*Z*)-3-pentenylsulfinyl]-benzene and 1(R_S)-[5-*tert*-butyldiphenylsiloxy-2-methyl-(2*S*,3*Z*)-3-pentenylsulfinyl]-benzene 8. To the solution of the alcohol **7** (0.45 g, 2 mmol) in dry DCM (3.8 mL) was added imidazole (204 mg, 3 mmol) followed by the addition of TBDPS-Cl (0.56 mL,

2.2 mmol). The reaction mixture was stirred at rt for 3 h under an atmosphere of nitrogen. The reaction mixture was diluted with DCM (30 mL) and washed successively with water, brine and dried over Na_2SO_4. The organic layer was evaporated under reduced pressure to afford the crude product which was purified by column chromatography on silica gel using 10% EtOAc/pet. ether (v/v) as the eluent to yield **8** (0.71 g, 1.54 mmol) in 78% yield. A small amount of the epimeric sulfoxide was separated for characterization purposes into **8a** and **8b**.

Compound **8a**. Liquid. R_f 0.3 (20% EtOAc/petroleum ether). $[\alpha]_D^{25}=-38.6$ (*c* 1.0, $CHCl_3$). *ms* (EI) 405 ($M^+-C_4H_9$). IR (neat) 2953, 1655, 1595, 1032, 968, 854, 690 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 7.68–7.30 (m, 15H), 5.56 (m, 1H), 5.23 (m, 1H), 4.19 (d, *J*=6.38 Hz, 2H), 2.77 (m, 1H), 2.73 (dd, *J*=12.7, 5.1 Hz, 1H), 2.50 (dd, *J*=12.7, 8.9 Hz, 1H), 1.13 (d, *J*=6.3 Hz, 3H), 1.03 (s, 9H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.6, 20.3, 26.9, 27.9, 60.2, 65.1, 124.1, 127.7, 129.2, 129.6, 130.9, 133.7, 135.6, 144.0. Anal. calcd for $C_{28}H_{34}O_2SSi$: C, 72.68; H, 7.41; S, 6.93. Found: C, 72.52; H, 7.73; S, 7.28.

Compound **8b**. Liquid. R_f 0.25 (20% EtOAc/petroleum ether). $[\alpha]_D^{25}=+135.8$ (*c* 1.0, $CHCl_3$). *ms* (EI) 405 [$M^+-C_4H_9$]. IR (neat) 2953, 1655, 1595, 1032, 968, 854, 690 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 7.70–7.30 (m, 15H), 5.70 (m, 1H), 5.25 (m, 1H), 4.30 (d, *J*=6.3 Hz, 2H), 2.92 (m, 1H), 2.73 (dd, *J*=13.2, 5.1 Hz, 1H), 2.40 (dd, *J*=13.2, 9.1 Hz, 1H), 1.04 (bs, 12H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.1, 20.9, 26.8, 28.3, 60.3, 65.7, 123.8, 127.5, 127.6, 129.1, 129.5, 130.9, 133.8, 135.5, 144.8. Anal. calcd for $C_{28}H_{34}O_2SSi$: C, 72.68; H, 7.41; S, 6.93. Found: C, 72.84; H, 7.65; S, 7.30.

3.1.4. 2-Bromo-1-*tert*-butyldiphenylsilyloxy-4-methyl-5(S_S)-phenylsulfinyl-(2*R*,3*R*,4*S*)-pentan-3-ol and 2-bromo-1-*tert*-butyldiphenylsilyloxy-4-methyl-5(R_S)-phenylsulfinyl-(2*R*,3*R*,4*S*)-pentan-3-ol 9. To the solution of the sulfoxide **8** (0.56 g, 1.2 mmol) in dry toluene (4.8 mL) was added water (32 μL, 1.8 mmol), followed by NBS (256 mg, 1.44 mmol) and the reaction mixture stirred at rt for 1 h. The reaction was quenched by the addition of an aq. saturated $NaHCO_3$ solution. The layers were separated and the aq. layer extracted with EtOAc (2×25 mL). The combined organic layers were washed with water, brine and dried over Na_2SO_4. The organic layer was evaporated under reduced pressure to afford the crude product which was purified by column chromatography using 20% EtOAc/pet. ether (v/v) as the eluent to yield bromohydrin **9** (0.5 g, 0.9 mmol) in 75% yield. Viscous oil. A small sample of the epimeric mixture of bromohydrins was separated into the individual isomers for the purpose of characterization.

Compound **9a**. Viscous oil. R_f 0.25 (20% EtOAc/petroleum ether). $[\alpha]_D^{25}=+49.1$ (*c* 1.0, $CHCl_3$). *ms* (FAB) 559, 501. IR (neat) 3326, 2943, 1554, 1043, 972, 698, 625 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 7.70–7.58 (m, 6H), 7.52–7.33 (m, 9H), 4.15–3.94 (m, 3H), 3.66 (d, *J*=8.6 Hz, 1H), 3.10 (dd, *J*=13.1, 3.8 Hz, 1H), 2.92 (dd, *J*=13.1, 3.8 Hz, 1H), 2.39 (m, 1H) 1.06 (s, 9H), 1.02 (d, *J*=6.7 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.3, 19.8, 26.9, 34.7, 57.9, 61.2, 65.5, 72.4, 124.2, 127.9, 129.3, 129.9, 131.1, 133.7, 135.6, 144.0. Anal. calcd for $C_{28}H_{35}BrO_3SSi$: C, 60.09; H, 6.30; S, 5.73. Found: C, 60.18; H, 6.46; S, 5.98.

Compound **9b**. Viscous oil. R_f 0.2 (20% EtOAc/petroleum ether). $[\alpha]_D^{25}=-63.6$ (*c* 0.5, $CHCl_3$). *ms* (FAB) 559, 501. IR (neat) 3326, 2943, 1554, 1043, 972, 698, 625 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 7.72–7.63 (m, 6H), 7.58–7.40 (m, 9H), 4.12–3.86 (m, 3H), 3.57 (d, *J*=8.8 Hz, 1H), 3.22 (dd, *J*=12.6, 4.0 Hz, 1H), 2.61 (dd, *J*=12.6, 7.0 Hz, 1H), 2.41 (m, 1H), 1.55 (d, *J*=6.3 Hz, 3H) 1.06 (s, 9H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.6, 19.2, 26.8, 34.7, 57.9, 62.4, 65.6, 73.2, 124.1, 127.9, 129.3, 130.0, 131.0, 133.2, 135.5, 135.6, 144.3. Anal. calcd for $C_{28}H_{35}BrO_3SSi$: C, 60.09; H, 6.30; S, 5.73. Found: C, 60.26; H, 6.43; S, 5.87.

3.1.5. 2-*tert*-Butyldiphenylsilyloxymethyl-3-[1-methyl-2(S_S)-phenylsulfinyl-(1*S*)-ethyl]-(2*R*,3*S*)-oxerane and 2-*tert*-butyldiphenylsilyloxymethyl-3-[1-methyl-2(R_S)-phenylsulfinyl-(1*S*)-ethyl]-(2*R*,3*S*)-oxerane 10. To the solution of bromohydrin **9** (0.44 g, 0.8 mmol) in methanol (4 mL) was added K_2CO_3 (0.22 g, 1.6 mmol) at 0 °C and stirred for 2 h at rt The reaction mixture was diluted with ether and filtered through a small pad of celite and the solvent evaporated under reduced pressure. The crude product was purified by column chromatography using 20% EtOAc/petroleum ether (v/v) as the eluent to afford **10** (0.38 g, 0.8 mmol) as a 1:1 epimeric mixture in quantitative yield. Gummy liquid. R_f 0.3 (30% EtOAc/petroleum ether). *ms* LSIMS 479 $[M+H]^+$. IR (neat) 2961, 2932, 1588, 1471, 1428, 1062, 823, 698, 625 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.65–7.35 (m, 30H), 3.90–3.60 (m, 4H), 3.20–3.0 (m, 4H), 2.85–2.55 (m, 4H), 2.0 (m, 1H), 1.75 (m, 1H), 1.25 (d, *J*=7.0 Hz, 3H), 1.20 (d, *J*=7.0 Hz, 3H), 1.05 (s, 18H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.1, 19.2, 26.8, 28.6, 57.4, 59.9, 60.3, 61.8, 63.1, 124.2, 127.8, 129.2, 129.9, 131.0, 133.0, 135.5, 144.0. Anal. calcd for $C_{28}H_{34}O_3SSi$: C, 70.25; H, 7.16; S, 6.7. Found: C, 70.12; H, 7.24; S, 6.43.

3.1.6. 3-[1-Methyl-2(S_S)-phenylsulfinyl-(1*S*)-ethyl]-(2*R*,3*S*)-oxiran-2-ylmethanol and 3-[1-methyl-2(R_S)-phenylsulfinyl-(1*S*)-ethyl]-(2*R*,3*S*)-oxiran-2-ylmethanol 11. To the solution of compound **10** (0.34 g, 0.71 mmol) in dry tetrahydrofuran (1.4 mL) was added acetic acid (0.13 mL, 2.13 mmol) and tetrabutylammonium fluoride (1.0 mL, 1 M in THF 1.0 mmol) at 0 °C and stirred for 2 h. The reaction mixture was then diluted with ether, washed successively with water, brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by column chromatography using 40% EtOAc/petroleum ether (v/v) as the eluent to afford **11** (0.154 g, 0.64 mmol) as a 1:1 epimeric mixture in 90% yield. Gummy liquid. R_f 0.2 (50% EtOAc/petroleum ether). *ms* (EI) 208 $[M^+]$. IR (Neat) 3354, 2964, 2932, 1586, 1462, 1425, 1047, 862, 625 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 7.70–7.40 (m, 10H), 3.95–3.6 (m, 4H), 3.25–3.05 (m, 4H), 2.95–2.75 (m, 4H), 2.65–2.50 (m, 2H), 2.35–2.15 (m, 1H) 2.10–1.90 (m, 1H), 1.30 (d, *J*=7.0 Hz, 3H), 1.15 (d, *J*=7.0 Hz, 3H).

3.1.7. 2-*N*-Methylcarbonyloxymethyl-3-[1-methyl-2(S_S)-phenylsulfinyl-(1*S*)-ethyl]-(2*R*,3*S*)-oxirane and 2-*N*-methylcarbonyloxymethyl-3-[1-methyl-2(R_S)-phenylsulfinyl-(1*S*)-ethyl]-(2*R*,3*S*)-oxirane 12. To the solution of

compound **11** (0.12 g, 0.5 mmol) in dry CH_2Cl_2 (2 mL) was added Et_3N (0.2 mL, 1.5 mmol) and CH_3NCO (0.1 mL, 1.6 mmol) at rt and stirred for 2 h. The reaction mixture was then cooled to 0 °C, quenched by adding 10% aq. $NaHCO_3$ solution and diluted with ether. The organic layer was separated and washed successively with water, brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by column chromatography using 30% EtOAc/petroleum ether (v/v) as the eluent to afford **12** (0.13 g, 0.45 mmol) as a 1:1 epimeric mixture in 90% yield. Gummy liquid. R_f 0.2 (50% EtOAc/petroleum ether). *ms* LSIMS 298 $[M+H]^+$. IR (Neat) 3330, 2964, 1798, 1714, 1538, 1142, 1086, 1016, 750, 690 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 7.70–7.50 (m, 10H), 5.50 (bs, 2H), 4.43–4.30 (m, 2H), 4.16–3.98 (m, 2H), 3.31–3.20 (m, 2H), 2.96–2.86 (m, 4H), 2.80 (d, J=5.2 Hz, 6H), 2.70–2.55 (m, 2H), 2.20–1.90 (m, 2H), 1.30 (d, J=6.7 Hz, 3H), 1.17 (d, J=6.7 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 15.8, 16.6, 28.4, 29.0, 54.2, 54.9, 59.4, 59.9, 61.9, 62.9, 63.5, 123.6, 123.9, 129.1, 131.0, 143.7, 144.4, 156.4. Anal. calcd for $C_{14}H_{19}NO_4S$: C, 56.55; H, 6.44; N, 4.71; S, 10.78. Found: C, 56.47; H, 6.21; N, 4.62; S, 10.63.

3.1.8. 1(S_S)-[5-*N*-Methylcarbonyloxy-2-methyl-(2*S*,3*Z*)-3-pentenylsulfinyl]-benzene and 1(R_S)-[5-*N*-methylcarbonyloxy-2-methyl-(2*S*, 3*Z*)-3-pentenylsulfinyl]-benzene 14. To the solution of compound **7** (1.9 g, 8.48 mmol) in dry CH_2Cl_2 (34 mL) was added Et_3N (3.5 mL, 25.4 mmol) and CH_3NCO (1.5 mL, 25.4 mmol) at rt and stirred for 2 h. The reaction mixture was then cooled to 0 °C, quenched by adding 10% aq. $NaHCO_3$ solution and diluted with ether. The organic layer was separated and washed successively with water, brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by column chromatography using 30% EtOAc/petroleum ether (v/v) as the eluent to afford **14** (2.14 g, 7.63 mmol) as a 1:1 epimeric mixture in 90% yield. Gummy liquid. R_f 0.3 (50% EtOAc/petroleum ether). *ms* LSIMS 282 $[M+H]^+$. IR (Neat) 3321, 2963, 1712, 1537, 1446, 1263, 1037, 821 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 7.60–7.40 (m, 10H), 5.80–5.60 (m, 2H), 5.50–5.30 (m, 2H), 4.70–4.50 (m, 4H), 3.30 (m, 2H), 3.0–2.40 (m, 10H), 1.30 (d, J=6.7 Hz, 3H), 1.10 (d, J=6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.0, 21.3, 27.4, 28.5, 28.9, 60.3, 61.3, 65.7, 66.2, 123.8, 124.7, 125.9, 129.2, 129.9, 130.9, 135.8, 136.5, 144.3, 144.8, 156.7. Anal. calcd for $C_{14}H_{19}NO_3S$: C, 59.76; H, 6.81; N, 4.98; S, 11.39. Found: C, 59.87; H, 6.68; N, 4.73; S, 11.19.

3.1.9. 2-Bromo-1-*N*-methylcarbonyloxy-4-methyl-5(S_S)-phenylsulfinyl-(2*R*,3*R*,4*S*)-pentan-3-ol and 2-bromo-1-*N*-methylcarbonyloxy-4-methyl-5(R_S)-phenylsulfinyl-(2*R*,3*R*,4*S*)-pentan-3-ol 15. To the solution of compound **14** (2.1 g, 7.47 mmol) in toluene (30 mL) at rt was added water (0.23 mL, 12.7 mmol), *N*-bromosuccinimide (1.6 g, 8.96 mmol) and stirred for 30 min. When TLC examination revealed completion of the reaction. The reaction mixture was taken into ethyl acetate (70 mL) and washed successively with 10% aq. $NaHCO_3$, 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 30% EtOAc/petroleum ether (v/v) as the eluent to afford **15** (2.26 g, 5.98 mmol) as a 1:1 epimeric mixture in 80% yield. Gummy liquid. R_f 0.2 (50% EtOAc/petroleum ether). *ms* LSIMS 378 $[M+H]^+$. IR (Neat) 3319, 2969, 1798, 1714, 1538, 1086, 1016, 750, 690 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 7.70–7.50 (m, 10H), 5.50 (bs, 1H), 4.90 (bs, 1H), 4.60–4.10 (m, 8H), 3.50 (bs, 2H), 3.20–2.90 (m, 4H), 2.80 (d, J=4.5 Hz, 6H), 2.63 (m, 1H), 2.45 (m, 1H), 1.30 (d, J=7.4 Hz, 3H), 1.10 (d, J=7.4 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.8, 17.2, 27.5, 29.2, 34.2, 34.8, 54.9, 61.1, 62.0, 65.1, 65.5, 72.1, 74.2, 123.9, 124.0, 129.3, 131.2, 143.9, 156.8. Anal. calcd for $C_{14}H_{20}BrNO_4S$: C, 44.45; H, 5.33; N, 3.70; S, 8.48. Found: C, 44.26; H, 5.30; N, 3.56; S, 8.29.

3.1.10. *N*-Methylcarbonyloxymethyl-3-[1-methyl-2(S_S)-phenylsulfinyl-(1*S*)-ethyl]-(2*R*,3*S*)-oxerane and 2-*N*-methylcarbonyloxymethyl-3-[1-methyl-2(R_S)-phenylsulfinyl-(1*S*)-ethyl]-(2*R*,3*S*)-oxerane 12. To the solution of compound **15** (2.2 g, 5.82 mmol) in methanol (58 mL) was added K_2CO_3 (0.88 g, 6.4 mmol) and the mixture stirred at rt for 1 h. The reaction mixture was diluted with ether, filtered through a small pad of celite and the solvent evaporated under reduced pressure. The residue was purified by column chromatography using 30% EtOAc/petroleum ether (v/v) as the eluent to afford **12** (1.64 g, 5.53 mmol) as a 1:1 epimeric mixture in 95% yield which was identical to the sample obtained from **11**.

3.1.11. 4-Hydroxymethyl-3-methyl-5-[1-methyl-2(S_S)-phenylsulfinyl-(1*S*)-ethyl]-(4*R*,5*R*)1,3-oxazolan-2-one and 4-hydroxymethyl-3-methyl-5-[1-methyl-2(R_S)-phenylsulfinyl-(1*S*)-ethyl]-(4*R*,5*R*)1,3-oxazolan-2-one 13. To the solution of compound **12** (1.6 g, 5.39 mmol) in dry THF (108 mL) at 0 °C was added NaHMDS (3 mL, 2 M/THF, 6 mmol) and stirred for 30 min. The reaction mixture was quenched by adding saturated aq. NH_4Cl solution and diluted with ether (60 mL). The organic layer was separated and washed successively with water, brine, dried over anhydrous Na_2SO_4 and the solvent evaporated under reduced pressure to afford a residue which was purified by column chromatography using 70% EtOAc/petroleum ether (v/v) as the eluent to afford **13** (1.52 g, 5.12 mmol) as a 1:1 epimeric mixture in 95% yield. Viscous oil. R_f 0.1 (80% EtOAc/petroleum ether). *ms* LSIMS 298 $[M+H]^+$. IR (Neat) 3331, 2922, 1744, 1520, 1443, 1255, 1087, 1033, 754 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.60–7.50 (m, 10H), 4.40–4.30 (m, 2H), 3.80–3.60 (m, 4H), 3.50–3.40 (m, 2H), 3.05–2.90 (m, 2H), 2.85 (s, 3H), 2.80 (s, 3H), 2.70–2.50 (m, 2H), 2.32 (m, 2H), 1.30 (d, J=6.8 Hz, 3H), 1.0 (d, J=6.8 Hz, 3H). Anal. calcd for $C_{14}H_{19}NO_4S$: C, 56.55; H, 6.44; N, 4.71; S, 10.78. Found: C, 56.37; H, 6.53; N, 4.79; S, 10.89.

3.1.12. 3-Methyl-5-[1-methyl-2(S_S)-phenylsulfinyl-(1*S*)-ethyl]-2-oxo-(4*R*,5*R*)-1,3-oxazolan-4-yl-methylacetate and 3-methyl-5-[1-methyl-2(R_S)-phenylsulfinyl-(1*S*)-ethyl]-2-oxo-(4*R*,5*R*)-1,3-oxazolan-4-yl-methylacetate 16. To the solution of compound **13** (1.48 g, 4.98 mmol) in dry CH_2Cl_2 (20 mL) was added triethylamine (1.04 mL, 7.47 mmol) followed by acetic anhydride (0.52 mL, 5.48 mmol) and stirred at rt for 30 min. The reaction mixture was diluted with EtOAc (20 mL) 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 50% EtOAc/petroleum ether (v/v) as the eluent to afford **16** (1.6 g, 4.73 mmol) as a 1:1 epimeric mixture in 95% yield. Viscous oil. R_f 0.4 (80% EtOAc/petroleum ether). *ms* LSIMS 340 $[M+H]^+$. IR (Neat) 2918, 1747, 1444, 1230, 1088, 1037, 755, 692 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 7.60–7.50 (m, 10H), 4.40–4.02 (m, 6H), 3.73–3.54 (m, 2H), 3.05–2.45 (m, 4H), 2.90 (s, 3H), 2.80 (s, 3H), 2.50–2.30 (m, 2H), 2.10 (s, 6H), 1.40 (d, J=6.7 Hz, 3H), 1.0 (d, J=6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.0, 15.9, 20.4, 20.5, 29.0, 29.1, 33.1, 33.2, 58.7, 58.9, 59.0, 59.6, 62.1, 62.3, 77.2, 78.4, 123.6, 123.8, 129.2, 129.3, 131.2, 143.2, 143.3, 156.8, 156.9, 170.2. Anal. calcd for $C_{16}H_{21}NO_5S$: C, 56.62; H, 6.24; N, 4.13; S, 9.45. Found: C, 56.47; H, 6.14; N, 4.05; S, 9.36.

3.1.13. 5-[2-Hydroxy-1-methyl-(1*R*)-ethyl]-3-methyl-2-oxo-(4*R*,5*R*)-1,3-oxazolan-4-yl-methylacetate 18. To the solution of compound **16** (1.50 g, 4.42 mmol) in acetonitrile (24 mL) at rt was added triethylamine (6.15 mL, 44.2 mmol) followed by trifluoroacetic anhydride (6.2 mL, 44.2 mmol) and stirred for 30 min. A solution of $NaHCO_3$ (7.40 g, 88.4 mmol) in water (24 mL) was added at 0 °C followed by solid $NaBH_4$ (1.68 g, 44.2 mmol) and the reaction mixture stirred for another 30 min. 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 **18** (0.66 g, 2.87 mmol) in 65% yield. Viscous oil. R_f 0.3 (80% EtOAc/petroleum ether). $[\alpha]_D^{25}$=+24.6 (*c* 0.66, $CHCl_3$). *ms* LSIMS 232 $[M+H]^+$. IR (Neat) 3327, 2925, 1741, 1442, 1233, 1141, 1038 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 4.35 (dd, J=11.8, 4.1 Hz, 1H), 4.23 (t, J=5.9 Hz, 1H), 4.06 (dd, J=11.8, 4.1 Hz, 1H), 3.70–3.60 (m, 3H), 2.90 (s, 3H), 2.10 (s, 3H), 2.05–1.95 (m, 1H), 1.0 (d, J=7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.6, 20.7, 29.4, 39.2, 59.0, 62.8, 63.8, 77.5, 157.5, 170.2. Anal. calcd for $C_{10}H_{17}NO_5$: C, 51.94; H, 7.41; N, 6.06. Found: C, 51.74; H, 7.32; N, 6.12.

3.1.14. 3-Methyl-5-[1-methyl-2-(4-methylphenylsulfonyl-oxy)-(1*R*)-ethyl]-2-oxo-(4*R*,5*R*)-1,3-oxazolan-4-yl-methylacetate 19. To the solution of compound **18** (0.6 g, 2.6 mmol) in dry DCM (11 mL), was added catalytic amounts of DMAP, Et_3N (0.54 mL, 3.9 mmol), *p*-toluenesulfonyl chloride (0.55 g, 2.86 mmol) and the mixture stirred at rt for 2 h. The reaction mixture was diluted with EtOAc (20 mL) and washed successively with water, brine, dried over anhydrous Na_2SO_4 and the solvent evaporated under reduced pressure. The residue was purified by column chromatography using 40% EtOAc/petroleum ether (v/v) as the eluent to yield **19** (0.85 g, 2.21 mmol) in 85% yield and used immediately in the next step. Viscous oil. R_f 0.2 (50% EtOAc/petroleum ether). $[\alpha]_D^{25}$=+17.7 (*c* 0.23, $CHCl_3$). *ms* LSIMS 386 $[M+H]^+$. IR (Neat) 2987, 1747, 1651, 1633, 1435, 1036, 969 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J=7.0 Hz, 2H), 7.38 (d, J=7.0 Hz, 2H), 4.32 (dd, J=12.7, 3.2 Hz, 1H), 4.12 (dd, J=12.7, 2.0 Hz, 1H), 4.05–3.95 (m, 3H), 3.70–3.60 (m, 1H), 2.85 (s, 3H), 2.46 (s, 3H), 2.20–2.05 (m, 4H), 1.0 (d, J=6.8 Hz, 3H).

3.1.15. (4*R*,5*R*)-4-Hydroxymethyl-3-methyl-5-[(*E*,1*R*)-1-methyl-3-pentenyl)-oxazolidin-2-one 20. To the suspension of CuI (0.2 g, 1.04 mmol) in dry THF (2 mL) at −78 °C was added compound **19** (0.4 g, 1.04 mmol) in dry THF (2 mL) and stirred for 30 min. 1-(*E*)-propenylmagnesium bromide (prepared from 0.49 g of Mg and 2.42 g of 1-(*E*)-propenyl bromide in 40 mL of THF) was added dropwise and the reaction mixture gradually allowed to attain rt and stirred further for 2 h. The reaction mixture was cooled to 0 °C and decomposed with sat. aq NH_4Cl solution. The reaction mixture was diluted with EtOAc and washed successively with water, brine, dried over anhydrous Na_2SO_4 and the solvent evaporated under reduced pressure. The residue was purified by column chromatography using 30% EtOAc/petroleum ether (v/v) as the eluent to yield **20** (155 mg, 0.73 mmol) in 70% yield. White solid. Mp 82–83 °C. R_f 0.25 (50% EtOAc/petroleum ether). $[\alpha]_D^{25}$=+76.0 (*c* 0.85, CH_2Cl_2). (Lit.[2a] $[\alpha]_D^{25}$=+76.9 (*c* 0.92, CH_2Cl_2). *ms* LSIMS 214 $[M+H]^+$. IR (Neat) 3445, 1767, 1717, 1472, 980, 690 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 5.60–5.30 (m, 2H), 4.20 (t, J=6.2 Hz, 1H), 3.83–3.78 (dd, J=12.2, 3.1 Hz, 1H), 3.56–3.50 (dd, J=12.2, 3.4 Hz, 1H), 3.39 (m, 1H), 2.87 (s, 3H), 2.20 (m, 1H), 1.91–1.76 (m, 2H), 1.70 (d, J=5.0 Hz, 3H), 0.90 (d, J=6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 17.9, 29.3, 34.5, 37.4, 61.2, 61.6, 78.8, 127.7, 158.3. Anal. calcd for $C_{11}H_{19}NO_3$: C, 61.95; H, 8.98; N, 6.57. Found: C, 61.78; H, 8.85; N, 6.53.

3.1.16. Methyl-(4*S*,5*R*)-3-methyl-5-[(*E*,1*R*)-1-methyl-3-pentenyl)-oxazolidin-2-one-4-carboxylate 21. To the solution of the compound **20** (100 mg, 0.47 mmol) in 1:1 acetonitrile/H_2O (3.0 mL) was added TEMPO (16 mg, 0.08 mmol) followed by $PhI(OAc)_2$ (314 mg, 0.98 mmol). The reaction mixture was stirred at rt for 2 h and the solvent was evaporated under reduced pressure. The reaction mixture was then extracted into ethyl acetate and washed with water. The organic layer was washed with 10% aq. $NaHCO_3$. The bicarbonate layer was acidified to pH 2 with 5 N HCl and extracted with ethyl acetate. To the ethyl acetate layer was added cold (0 °C) ethereal CH_2N_2, generated in situ from *N*-methyl *N*-nitroso urea (0.28 g, 2.59 mmol) in ether (10 mL) and 50% aq. KOH (4 mL) at 0 °C, and stirred at rt for 10 min. 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 **21** (90 mg, 0.38 mmol) in 80% overall yield for two steps. Clean oil. R_f. 0.5 (50% EtOAc/petroleum ether). $[\alpha]_D^{25}$=+37.0 (*c* 0.80, CH_2Cl_2). (Lit.[2a] $[\alpha]_D^{25}$=+39.2 (*c* 1.67, CH_2Cl_2). *ms* LSIMS 242 $[M+H]^+$. IR (neat) 1753, 1442, 1402, 1235, 1046, 986, 700 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 5.55–5.31 (m, 2H), 4.28 (dd, J=6.2, 4.8 Hz, 1H), 3.97 (d, J=4.8 Hz, 1H), 3.82 (s, 3H), 2.91 (s, 3H), 2.25–2.17 (m, 1H), 2.0–1.83 (m, 2H), 1.66 (d, J=6.0 Hz, 3H), 0.95 (d, J=6.6 Hz, 3H). Anal. calcd for $C_{12}H_{19}NO_4$: C, 59.74; H, 7.94; N, 5.81. Found: C, 59.70; H, 7.80; N, 5.70.

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