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Synthesis of chiral 4-hydroxy-2,3-unsaturated carbonyl compounds from 3,4-epoxy alcohols by oxidation: application in the formal synthesis of macrosphelide A

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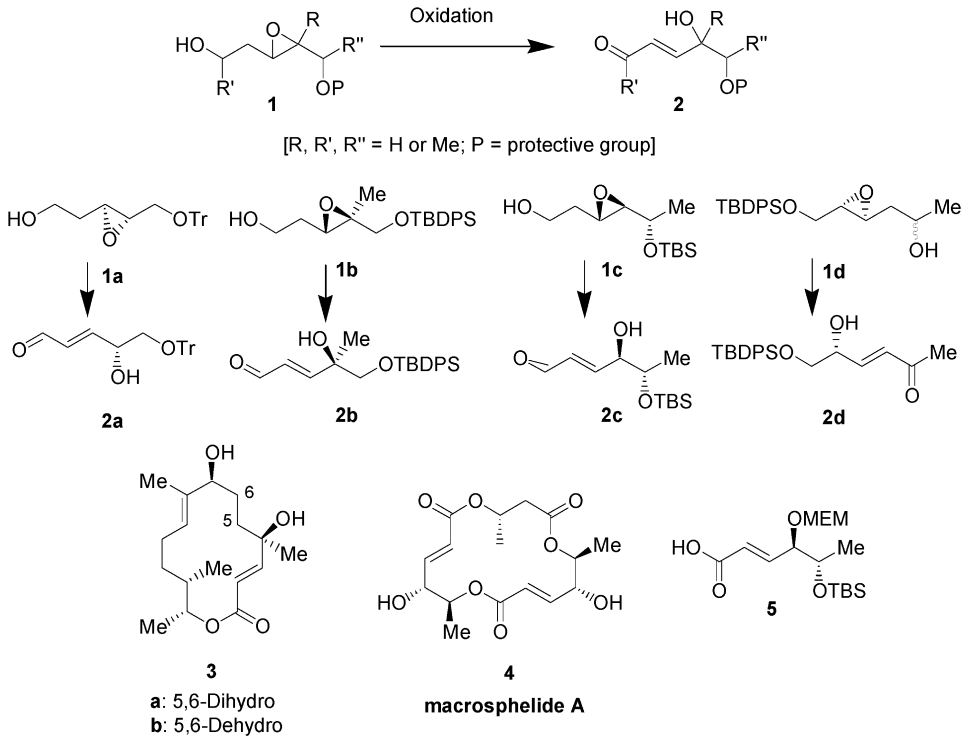
Abstract—An interesting transformation during the oxidation of 3,4-epoxy alcohols **1a**–**d**, derived from the corresponding homoallylic alcohols, led to the formation of 4-hydroxy-2,3-unsaturated carbonyls **2a**–**d** in very good yields. One of these products **2c** was transformed into the functionalised carboxylic acid **5**, an advanced stage intermediate from which the total synthesis of macrosphelide A has been reported.

1. Introduction

Ring-opening reactions of epoxides[1,2] constitute an important class of methodologies developed and employed extensively in organic synthesis, especially in the area of asymmetric synthesis due to the easy availability of chiral epoxides by the Sharpless asymmetric epoxidation method.[3] Many of these reactions are used routinely by synthetic organic chemists to construct a wide variety of structural moieties en route to various natural products. During the



Keywords: epoxy alcohols; Sharpless epoxidation; epoxide opening; macrosphelides.
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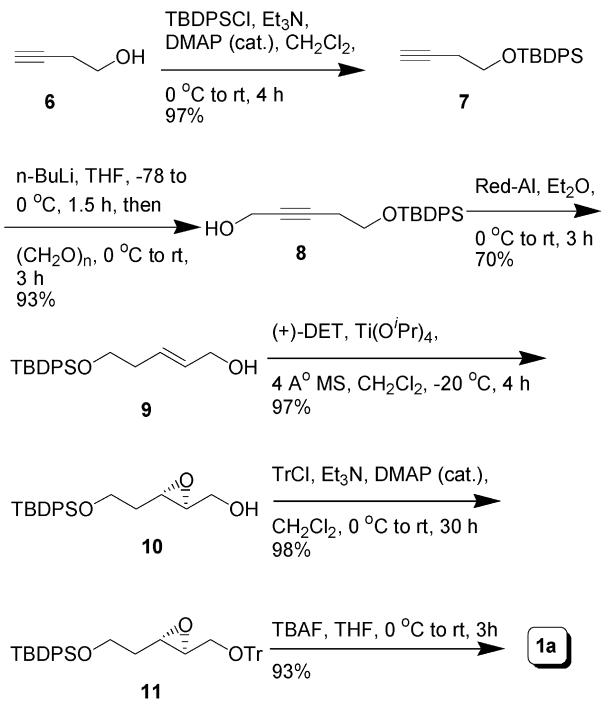
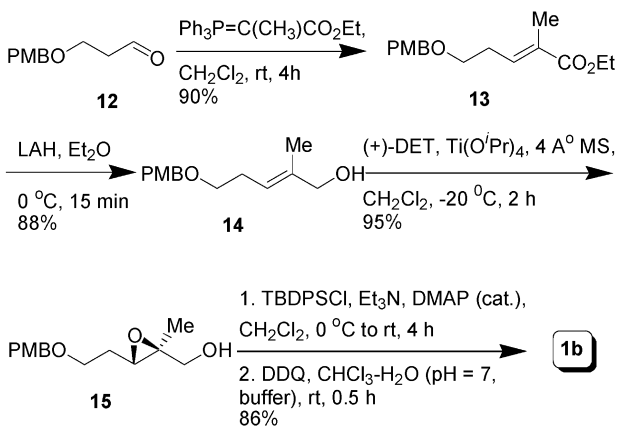
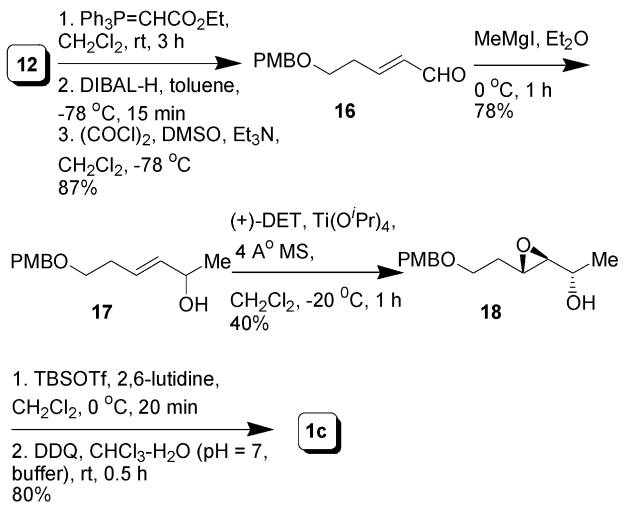


Scheme 1.

synthesis of such compounds, we encountered an unusual transformation while oxidizing various 3,4-epoxy alcohols, like **1a**–**d**, derived from the corresponding homoallylic alcohols. Under standard oxidation reaction conditions, this led to the formation of unexpected products, 4-hydroxy-2,3-unsaturated carbonyl compounds **2a**–**d**, exclusively and in good yields. These structural moieties are present in many polyketide natural products, like cineromycins B[4] (**3**) and the related compounds, macrosphelides A-L[5] (**4**). Our present work provides a simple methodology for the efficient synthesis of *trans* 4-hydroxy-2,3-unsaturated carbonyl compounds in optically pure form. Finally, one of these products **2c** is transformed into an appropriately protected form of (*E*)-(4*R*,5*S*)-4,5-dihydroxyhex-2-enoic acid **5**, the major structural component of highly potent antitumor compounds, macrosphelides.[5,6] Total synthesis of macrosphelide A has already been achieved from **5**.[6i]



Scheme 2.

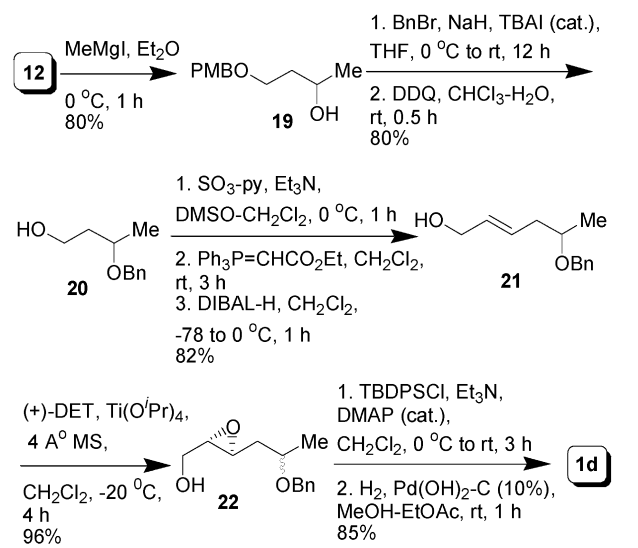


Scheme 3.

2. Results and discussion

The starting 3,4-epoxy alcohols **1a**–**d** were prepared following the routes shown in Schemes 1–4. The salient feature of the common strategy adopted in these syntheses is the construction of an appropriate intermediate in each case that carries an allylic alcohol moiety at one end of the molecule and a protected hydroxyl group in the homoallylic position at the other terminal. While the former served as a prerequisite template to introduce chirality in the molecule by Sharpless asymmetric epoxidation, the deprotected hydroxyl of the other end finally provided the required 3,4-epoxy alcohol moieties of the oxidation substrates **1a**–**d**.

Synthesis of **1a** started with but-3-yn-1-ol **6** that was silylated to give compound **7** in 97% yield (Scheme 1). The Li-acetylide prepared from **7** using *n*-BuLi was reacted with paraformaldehyde to furnish the addition product **8** in 93% yield. Reduction of **8** with Red-Al provided the *E*-allylic alcohol **9** that was subjected to Sharpless epoxidation using (+)-DET to give the chiral epoxy alcohol **10** (96% ee)[7] in



Scheme 4.

97% yield. The primary hydroxyl group of **10** was protected as a trityl ether to provide compound **11** in 98% yield. Subsequent desilylation at the other end furnished the requisite oxidation substrate **1a** in 93% yield.

The starting material for the synthesis of **1b** was the aldehyde **12**[8] (Scheme 2), prepared from mono-PMB-protected propane-1,3-diol by oxidation. Olefination of **12** with the stabilized ylide provided the α,β-unsaturated ester **13** in 90% yield with complete *E*-selectivity. No *Z*-isomer was detected. Reduction of **13** with LAH gave the allylic alcohol **14** in 88% yield. Sharpless epoxidation of **14** using (+)-DET furnished the chiral epoxy alcohol **15** (96% ee)[7] in 95% yield. Routine functional group manipulations finally led to the required epoxy alcohol **1b** in two steps in 86% yield from **15**.

Compound **1c** was prepared starting from the same aldehyde **12** (Scheme 3) that was used in Scheme 2. Olefination of **12** provided an α,β-unsaturated ester that was reduced to an allylic alcohol using DIBAL-H. Finally, Swern oxidation of the allylic alcohol furnished the requisite aldehyde **16** in 87% overall yield in three steps from **12**. Grignard addition to **16** led to the allylic alcohol **17** (78% yield) that was subjected to Sharpless catalytic kinetic resolution using (+)-DET to furnish the chiral epoxy alcohol **18** (94% ee by Mosher ester method) in 40% yield. A two-step protection–deprotection protocol converted **18** to the required product **1c** in 80% yield.

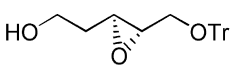
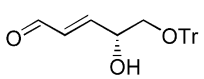
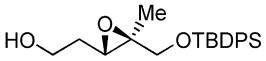
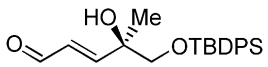
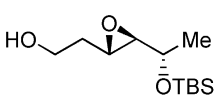
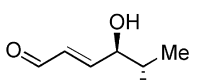
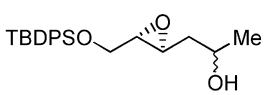
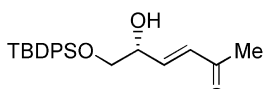
A Grignard addition to the aldehyde **12** constituted the first step in the synthesis of **1d** as depicted in Scheme 4. The resulting addition product **19** was next transformed into **20** in 80% yield following a two-step protection–deprotection sequence.

Oxidation of **20** was followed by olefination using stabilized ylide to give the α,β-unsaturated ester in 82% yield. Reduction using DIBAL-H gave the allylic alcohol **21** in 92% yield. Epoxidation of **21** by Sharpless method using (+)-DET led to the formation of chiral epoxy alcohol **22** as a mixture of diastereomers in 96% yield. Routine reaction sequences were followed next to convert **22** to the required compound **1d** in 85% yield.

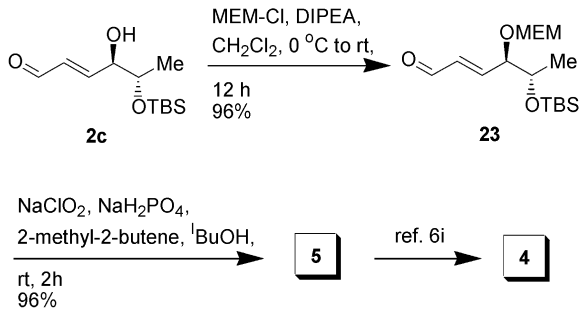
Having thus prepared the starting materials **1a–d**, the stage was now set to carry out their oxidation reactions. Compound **1a** was oxidized under four different reaction conditions: (a) Swern oxidation using $(COCl)_2$, DMSO, Et_3N in CH_2Cl_2; (b) PDC in CH_2Cl_2; (c) IBX in DMSO and (d) TPAP, NMO in CH_2Cl_2. In all these reactions, the only product that could be isolated after the work-up was the 4-hydroxy-2,3-unsaturated aldehyde **2a**. Presumably, the aldehyde intermediate that was first formed during the oxidation process underwent an in situ β-elimination reaction leading to the formation of **2a** in very good yields. The results of these oxidation reactions are summarized in Table 1. Oxidation of the other 3,4-epoxy alcohols **1b** and **1c** under Swern oxidation conditions led to the formation of similar products (**2b** and **2c**, respectively), exclusively and in excellent yields. The keto intermediate that was formed during the oxidation of **1d**, under Swern oxidation method and also with SO_3-py/Et_3N/DMSO, underwent the same kind of β-elimination process, but only partially during the reaction. However, the transformation was complete when the crude oxidation product was subjected to purification by column chromatography using a long silica gel column that was eluted slowly with 5–20% EtOAc in petroleum ether or simply by stirring in the presence of silica gel in the same solvent system to furnish the corresponding γ-hydroxy-α,β-unsaturated keto product **2d** in excellent yield.

Finally, the free hydroxyl group of compound **2c** was protected as MEM-ether to give the intermediate **23** (Scheme 5). The aldehyde function of **23** was next oxidized to the acid to furnish the protected (*E*)-(4*R*,5*S*)-4,5-dihydroxyhex-2-enoic acid **5**. As the conversion of **5** to macrosphelide A **4** is already reported,[6i] the present work

Table 1. Oxidation of 3,4-epoxy alcohols **1** under various conditions

Entry	3,4-Epoxy alcohols (**1**)	Products (**2**)	Oxidation conditions[a]	Yield (%)
1	 **1a**	 **2a**	A B C D	82 85 80 80
2	 **1b**	 **2b**	A	92
3	 **1c**	 **2c**	A	90
4	 **1d**	 **2d**	A E	90 88

[a] A: $(COCl)_2$ (1.5 equiv.), DMSO (3.2 equiv.), Et_3N (5 equiv.), CH_2Cl_2, −78 to 0°C; B: PDC (2 equiv.), 4 Å MS, CH_2Cl_2, rt. C: IBX (2 equiv.), DMSO, 0°C to rt. D: TPAP (0.05 equiv.), NMO (1.5 equiv.), 4 Å MS, CH_2Cl_2, rt. E: SO_3–py (5 equiv.), Et_3N (5 equiv.), CH_2Cl_2–DMSO (0.8:1), 0°C.



Scheme 5.

pertains to a formal total synthesis of the latter. Compound **5** synthesized here is identical in all respects with that prepared earlier, having all spectroscopic data matching with those reported.[6i]

The method described here for the synthesis of 4-hydroxy-2,3-unsaturated carbonyl compounds should find useful applications in the synthesis of many other natural products that carry such structural moieties.

3. Experimental

3.1. General procedures

All reactions were carried out in oven or flame-dried glassware with magnetic stirring under nitrogen atmosphere using dry, freshly distilled solvents, unless otherwise noted. Reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm silica gel plates with UV light, I_2, 7% ethanolic phosphomolybdic acid-heat and 2.5% ethanolic anisaldehyde (with 1% AcOH and 3.3% conc. H_2SO_4)-heat as developing agents. Silica gel finer than 200 mesh was used for flash column chromatography. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated. IR spectra were recorded as neat liquids or KBr pellets. NMR spectra were recorded on 200, 300 and 400 MHz spectrometers at room temperature of ~21°C in $CDCl_3$ using tetramethylsilane as internal standard or the solvent signal as secondary standard and the chemical shifts are shown in δ scales. Multiplicities of NMR signals are designated as s (singlet), d (doublet), t (triplet), q (quartet), br (broad), m (multiplet, for unresolved lines), etc. ^{13}C NMR spectra were recorded with complete proton decoupling. Mass spectra were obtained under electron impact (EI) and liquid secondary ion mass spectrometric (LSIMS) techniques.

3.1.1. Synthesis of 7.[9,10] To a solution of compound **6** (0.42 mL, 5.53 mmol) in dry CH_2Cl_2 (20 mL), Et_3N (1.15 mL, 8.29 mmol) and TBDPSCl (1.57 mL, 6.08 mmol) were added sequentially at 0°C, followed by the addition of DMAP (67 mg, 0.55 mmol). After being stirred for 4 h at room temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2. The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, 2.5% EtOAc in petroleum ether eluant) to give **7** (1.65 g, 97%) as colorless oil. R_f 0.75 (silica gel, 20% EtOAc in petroleum ether); IR (neat): ν_{max} 3294, 3069, 2912, 2856, 1463, 1419, 1094, 694 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.7–7.38 (m, 10H, aromatic), 3.75 (t, J=6.1 Hz, 2H, C4–H_2), 2.41 (dt, J=6.1, 1.5 Hz, 2H, C3–H_2), 1.84 (t, J=1.5 Hz, 1H, C1–H), 1.02 (s, 9H, ^{t}Bu); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.6, 133.5, 129.7, 127.7, 81.4, 69.3, 62.3, 26.8, 22.6, 19.2; Mass (EI): m/z: 252 $[M-isobutene]^+$.

3.1.2. Synthesis of 8.[9,10] To a stirred solution of **7** (1.53 g, 4.98 mmol) in dry THF (15 mL), n-BuLi (1.6 M in hexane, 3.42 mL, 5.4 mmol) was added at −78°C and the reaction mixture was slowly warmed up to 0°C in 1 h. Paraformaldehyde (448.6 mg, 14.94 mmol) was then added and the reaction mixture was stirred at room temperature for 3 h. It was quenched with saturated aqueous NH_4Cl solution, extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated in vacuo. Purification of the residue by column chromatography (SiO_2, 10–15% EtOAc in petroleum ether eluant) provided compound **8** (1.57 g, 93%) as a colorless oil. R_f 0.4 (silica gel, 20% EtOAc in petroleum ether); IR (neat): ν_{max} 3369 (b), 3062, 2937, 1094, 694 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.74–7.33 (m, 10H, aromatic), 4.27–4.16 (m, 2H, C1–H_2), 3.70 (t, J=6.8 Hz, 2H, C5–H_2), 2.57–2.44 (m, 2H, C4–H_2), 1.43 (t, J=4.6 Hz, 1H, OH), 1.08 (s, 9H, ^{t}Bu); ^{13}C NMR (50 MHz, $CDCl_3$): δ 135.6, 133.7, 129.7, 127.6, 83.8, 79.7, 62.5, 51.3, 26.8, 22.9, 19.2; Mass (LSIMS): m/z: 320 $[M-H_2O]^+$, 307 $[M-CH_2OH]^+$.

3.1.3. Synthesis of 9. To a stirred solution of compound **8** (1.44 g, 4.27 mmol) in dry ether (15 mL), Red-Al (3.5 M in toluene, 2.44 mL, 8.54 mmol) was added slowly over a period of 15 min at 0°C. After being stirred for 3 h, the solution was quenched by careful addition of saturated aqueous NH_4Cl solution and extracted with EtOAc. The combined organic extracts were washed successively with water (8 mL) and brine (6 mL), dried over Na_2SO_4 and concentrated. The resulting oil was purified by column chromatography (SiO_2, 12–16% EtOAc in petroleum ether eluant) to give compound **9** (1.02 g, 70%) as colorless oil. R_f 0.4 (silica gel, 25% EtOAc in petroleum ether); IR (neat): ν_{max} 3306, 3912, 2850, 1094, 694 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.68–7.38 (m, 10H, aromatic), 5.70–5.66 (m, 2H, olefinic), 4.10–4.01 (m, 2H, C1–H_2), 3.72 (t, J=6.0 Hz, 2H, C5–H_2), 2.32 (dt, J=11.4, 6.0 Hz, 2H, C4–H_2), 1.05 (s, 9H, ^{t}Bu); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.6, 133.9, 130.96, 129.6, 129.5, 127.6, 63.7, 63.4, 35.5, 26.8, 19.2; Mass (EI): m/z: 283 $[M+H-isobutene]^+$.

3.1.4. Synthesis of 10. To a suspension of activated powdered 4 Å molecular sieves (177 mg, 20 wt%) in CH_2Cl_2 (10 mL), $Ti(O^iPr)_4$ (0.77 mL, 2.6 mmol) and (+)-DET (0.53 mL, 3.12 mmol) were added sequentially at −20°C. After being stirred for 0.5 h, a solution of **9** (884 mg, 2.6 mmol) in CH_2Cl_2 (8 mL) was added and stirring continued for another 0.5 h at the same temperature. TBHP (3.5 M in toluene, 2.22 mL, 7.8 mmol) was then added to it and stirred for 3 h at −20°C. The reaction was quenched by adding water (15 mL) and allowed to come to room temperature where it was stirred for 1 h. After re-cooling it to 0°C, an aqueous solution of NaOH (30%

w/v, 5 mL), saturated with NaCl was added to it and stirred at 0°C for 10 min. CH_2Cl_2 was removed under reduced pressure and the compound was extracted with ether, washed with brine, dried (Na_2SO_4), filtered and concentrated in vacuo. Purification by column chromatography (SiO_2, 25–30% EtOAc in petroleum ether eluant) afforded pure **10** (898 mg, 97%) as a syrupy liquid. R_f 0.4 (silica gel, 40% EtOAc in petroleum ether); $[\alpha]_D^{22}=-19.4$ (*c* 1.37, $CHCl_3$); IR (neat): ν_{max} 3437, 3075, 2931, 2856,1469,1431, 1094, 694 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.68–7.29 (m, 10H, aromatic), 4.93–3.51 (m, 4H, C1–H_2, C5–H_2), 3.08 (dt, *J*=5.8, 1.8 Hz, 1H, C3–*H*), 2.92 (m, 1H, C2–*H*),1.77 (q, *J*=5.8 Hz, 2H, C4–H_2); 1.53 (m, 1H, O*H*), 1.04 (s, 9H, ^{t}Bu); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.5, 133.5, 129.6, 127.6, 61.7, 60.7, 58.6, 53.7, 34.7, 26.7, 19.1; Mass (LSIMS): *m/z*: 357 $[M+H]^+$.

3.1.5. Synthesis of 11. A solution of alcohol **10** (812 mg, 2.28 mmol), Et_3N (0.48 mL, 3.42 mmol) and DMAP (28 mg, 0.23 mmol) in CH_2Cl_2 (10 mL) at 0°C was treated with TrCl (763 mg, 2.74 mmol). The reaction was stirred at ambient temperature for 12 h and then quenched with saturated aqueous NH_4Cl solution, extracted with ether. The combined organic extracts were washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, 2–4% EtOAc in petroleum ether eluant) to give **11** (1.34 g, 98%) as a white solid. R_f 0.4 (silica gel, 10% EtOAc in petroleum ether); $[\alpha]_D^{22}=7.28$ (*c* 1.2, $CHCl_3$); IR ($CHCl_3$): ν_{max} 3069, 2944, 2875, 1435, 1094, 694 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.68–7.12 (m, 25H, aromatic), 3.86–3.72 (m, 2H, –CH_2–O–), 3.32 (dd, *J*=10.1, 2.2 Hz, 1H, –C*H*–O–), 3.15 (t, *J*=10.1 Hz, 1H, –C*H*–O–), 3.05 (m, 1H, C3–*H*), 2.88 (m, 1H, C1–*H*), 1.87–1.68 (m, 2H, C4–H_2), 1.04 (s, 9H, ^{t}Bu); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.8, 135.5, 133.6, 133.5, 129.6, 128.6, 127.8, 127.6, 127.0, 86.6, 77.2, 64.2, 60.7, 57.4, 53.7, 35.0, 26.8, 19.1; Mass (LSIMS): *m/z*: 597 $[M-H]^+$, 355 $[M-CPh_3]^+$, 243 $[CPh_3]^+$.

3.1.6. Synthesis of 1a. To a solution of compound **11** (1.27 g, 2.12 mmol) in dry THF (9 mL), TBAF (1 M solution in THF, 2.54 mL, 2.54 mmol) was added under nitrogen atmosphere, at 0°C. After stirring for 3 h at room temperature, the reaction was quenched with saturated aqueous NH_4Cl solution, extracted with EtOAc, washed with brine, dried over Na_2SO_4 and concentrated in vacuo. Purification by column chromatography (SiO_2, 40–50% EtOAc in petroleum ether eluant) afforded **1a** (708 mg, 93%) as a syrupy liquid. R_f 0.4 (Silica gel, 40% EtOAc in petroleum ether). $[\alpha]_D^{22}=-9.76$ (*c* 0.815, $CHCl_3$); IR ($CHCl_3$): ν_{max} 3419, 3021, 2912, 1488, 1444, 1056, 700 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.49–7.13 (m, 15H, aromatic), 3.73 (t, *J*=7.6 Hz, 2H, CH_2OH), 3.28 (dd, *J*=10.5, 3.8 Hz, 1H, –C*H*OTr), 3.14 (dd, *J*=10.5, 4.7 Hz, 1H, –C*H*?OTr), 3.05–2.92 (m, 2H, epoxy*H*), 1.81–1.6 (m, 3H, CH_2, O*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.7, 128.6, 127.8, 127.0, 86.7, 64.2, 59.8, 56.6, 54.3, 33.9; Mass (LSIMS): *m/z*: 360 $[M]^+$, 243 $[CPh_3]^+$.

3.1.7. Synthesis of 13. To a solution of the aldehyde **12** (820 mg, 4.23 mmol) in CH_2Cl_2 (15 mL), stabilized ylide $Ph_3P{=}C(CH_3)CO_2Et$ (1.83 g, 5.07 mmol) was added at room temperature and the reaction mixture stirred for 3 h. Solvent was evaporated under reduced pressure and the residue was purified by column chromatography (SiO_2, 6% EtOAc in petroleum ether eluant) to yield **13** (1.06 g, 90%) as a syrup. R_f 0.6 (silica gel, 30% EtOAc in petroleum ether); IR (neat): ν_{max} 2938, 2856, 1700, 1506, 1240, 1090, 825 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.20 (d, *J*=8.5 Hz, 2H, aromatic), 6.83 (d, *J*=8.5 Hz, 2H, aromatic), 6.72 (t, *J*=7.2 Hz, 1H, olefinic), 4.43 (s, 2H, OCH_2Ar), 4.176 (q, *J*=6.7 Hz, 2H, $CO_2CH_2CH_3$), 3.79 (s, 3H, PMB–OCH_3), 3.49 (t, *J*=7.2 Hz, 2H, PMBOCH_2), 2.53 (q, *J*=7.2 Hz, 2H, allylic), 1.84 (s, 3H,=CCH_3), 1.30 (t, *J*=6.7 Hz, 3H, $CO_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$, 200 MHz): δ 159.2, 138.2, 130.3, 129.4, 129.2, 113.8, 72.6, 68.3, 60.4, 55.2, 29.4, 14.2, 12.5; Mass (EI): *m/z*: 278 $[M]^+$, 234 $[M-CH_3CHO]^+$, 205 $[M-CO_2Et]^+$.

3.1.8. Synthesis of 14. Ester **13** (945 mg, 3.4 mmol) was taken in dry ether (12 mL), cooled at 0°C and to it LAH (258 mg, 6.8 mmol) was added portion wise and stirred at that temperature for 15 minutes. The reaction was then quenched with saturated aqueous Na_2SO_4 solution (5 mL) at 0°C and stirred for 15 minutes. Precipitated solid was filtered through a short pad of Celite and the filter cake was washed with ether. The filtrate and washings were combined and washed with brine, dried (Na_2SO_4) and concentrated in vacuo. After column chromatography (SiO_2, 24–30% EtOAc in petroleum ether eluant), the product **14** (706 mg, 88%) was obtained as syrupy liquid. R_f 0.4 (silica gel, 50% EtOAc in petroleum ether); IR (neat): ν_{max} 3426, 2850, 1600, 1506, 1238, 1088, 1027, 825 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.20 (d, *J*=8.8 Hz, 2H, aromatic), 6.83 (d, *J*=8.8 Hz, 2H, aromatic), 5.30 (br t, *J*=7.2 Hz, 1H, olefinic), 4.41 (s, 2H, OCH_2Ar), 3.96 (br s, 2H, C1–H_2), 3.79 (s, 3H, PMB–OCH_3), 3.42 (t, *J*=7.2 Hz, 2H, PMBOCH_2), 2.32 (q, *J*=7.2 Hz, 2H, allylic), 1.66 (s, 3H=CCH_3), 1.43 (br s, 1H, O*H*); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.0, 136.6, 130.3, 129.1, 121.7, 113.6, 72.4, 69.3, 68.4, 55.1, 28.1, 13.6; Mass (LSIMS): *m/z*: 236 $[M]^+$, 235 $[M-H]^+$.

3.1.9. Synthesis of 15. The allylic alcohol **14** (597 mg, 2.53 mmol) was subjected to Sharpless asymmetric epoxidation following the same procedure as described for the preparation of **10**. Purification by column chromatography (SiO_2, 25–40% EtOAc in petroleum ether eluant) afforded the epoxide **15** (606 mg, 95%). R_f 0.3 (silica gel, 50% EtOAc in petroleum ether); $[\alpha]_D^{22}$ −15.5 (*c* 2.0, $CHCl_3$); IR(neat): ν_{max} 3450, 2928, 2856, 1612, 1508, 1452, 1237, 1093, 1038, 820 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.20 (d, *J*=8.6 Hz, 2H, aromatic), 6.83 (d, *J*=8.6 Hz, 2H, aromatic), 4.41 (s, 2H, OCH_2Ar), 3.80 (s, 3H, PMB–OCH_3), 3.66–3.50 (m, 4H), 3.13 (t, *J*=6. 1 Hz, 1H, epoxy-*H*), 1.94–1.74 (m, 2H), 1.68 (br m, 1H, O*H*), 1.27 (s, 3H, C2CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.1, 130.2, 129.1, 113.7, 72.6, 67.0, 65.4, 60,8, 57.9, 55.1, 28.8, 14.2; Mass (LSIMS): *m/z*: 252 $[M]^+$, 251 $[M-H]^+$.

3.1.10. Synthesis of 1b. The epoxy alcohol **15** (479 mg, 1.90 mmol) was subjected to TBDPS-protection following the same procedure as described above for the preparation of **7**. Chromatographic purification (SiO_2, 5–7% EtOAc in petroleum ether eluant) provided the silylated intermediate

(890 mg, 98%) as colorless syrupy liquid that was used directly in the next step.

To a solution of the silyl ether prepared above (763 mg, 1.60 mmol) and DDQ (555 mg, 2.4 mmol) in $CHCl_3-H_2O$ (32 mL:1.6 mL) buffered by using 0.2 M aqueous solutions of Na_2HPO_4 and NaH_2PO_4 (5.8:4.2, 8 mL) was stirred at room temperature for 0.5 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (40 mL) and the layers were separated. The aqueous phase was extracted with ethyl acetate. The combined organic phases were washed with water, brine, dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, 30–40% EtOAc in petroleum ether eluant) to give **1b** (521 mg, 88%) as colorless syrupy liquid. R_f=0.4 (silica gel, 40% EtOAc in petroleum ether); $[\alpha]_D^{22}=-4.27$ (*c* 2.9, $CHCl_3$); IR (neat): ν_{max} 3447, 2930, 2853, 1410, 1112, 808, 698 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.70–7.30 (m, 10H, aromatic), 3.81 (m, 2H, C5–H_2), 3.66 and 3.59 (Abq, 2H, C1–H_2), 2.92 (dd, *J*=7.5, 5.2 Hz, 1H, epoxy-*H*), 1.90–1.60 (m, 2H, C4–H_2), 1.35 (s, 3H, C2–CH_3), 1.08 (s, 9H, ^{t}Bu); ^{13}C NMR ($CDCl_3$; 75 MHz): δ 135.6, 135.5, 133.3, 133.2, 129.7, 127.7, 76.6, 68.3, 60.6, 60.5, 58.9, 31.0, 26.7, 19.2, 14.5; Mass (ESI): *m/z*: 393 $[M+Na]^+$.

3.1.11. Synthesis of 16. To a solution of the aldehyde **12** (3.34 g 17.2 mmol) in CH_2Cl_2 (55 mL), the stabilized ylide $Ph_3P{=}CHCO_2Et$ (8.99 g, 25.8 mmol) was added at room temperature and the reaction mixture was stirred for 3 h. Solvent was evaporated under reduced pressure and the residue was chromatographed (SiO_2, 10–12% EtOAc in petroleum ether eluant) the desired α,β-unsaturated ester (4.45 g, 98%) as a syrupy liquid that was used directly in the next step.

To a solution of the above ester (4.35 g, 16.5 mmol) in dry toluene at −78°C, DIBAL-H (1.2 M solution in toluene, 28.8 mL, 34.6 mmol) was added. After 15 minutes the reaction mixture was quenched by adding methanol and saturated aqueous K–Na-tartrate solution and allowed to warm to room temperature. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with water, brine, dried (Na_2SO_4) concentrated in vacuo. The crude product was purified by column chromatography (SiO_2, 30–40% EtOAc in petroleum ether eluant) to give compound an allylic alcohol intermediate (3.55 g, 97%) as a colorless oily liquid that was used directly in the next step for oxidation.

To a solution of oxalyl chloride (2.02 ml, 23.32 mmol) in dry CH_2Cl_2 (50 ml) at −78°C, DMSO (3.53 ml, 49.76 mmol) was added slowly and drop-wise with stirring under nitrogen atmosphere. After 15 min, the allylic alcohol (3.45 g, 15.55 mmol), prepared as above and dissolved in dry CH_2Cl_2 (20 mL), was added to the reaction mixture. After stirring for 0.5 h at −78°C, Et_3N (10.84 mL, 77.75 mmol) was added and stirred for another 0.5 h at the same temperature and then for 1 h at 0°C. The reaction mixture was then quenched with saturated aqueous NH_4Cl solution and extracted with ether. The combined organic layers were washed with water, brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, 16–20% EtOAc in petroleum ether eluant) to give **16** (3.15 g, 92%) as a syrupy liquid. R_f 0.4 (silica gel, 40% EtOAc in petroleum ether); IR (neat): ν_{max} 2850, 1687, 1602, 1513, 1251, 1099, 813 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 9.48 (d, *J*=8.2 Hz, 1H, C*H*O), 7.19 (d, *J*=8.8 Hz, 2H, aromatic), 6.83 (d, *J*=8.8 Hz, 2H, aromatic), 6.82 (dt, *J*=16.3, 6.2 Hz, 1H, C*H*=CHCHO), 6.13 (ddt, *J*=16.3, 8.2, 1.5 Hz, 1H, CH=C*H*CHO), 4.43 (s, 2H, OCH_2Ar), 3.79 (s, 3H, PMB–OCH_3), 3.56 (t, *J*=6.2 Hz, 2H, PMBOCH_2–), 2.59 (dq, *J*=6.2, 1.5 Hz, 2H, allylic); ^{13}C NMR (50 MHz, $CDCl_3$): δ 193.7, 159.3, 155.0, 134.0, 129.9, 129.2, 113.8, 72.7, 67.5, 55.2, 33.0; Mass (EI): *m/z*: 220 $[M]^+$.

3.1.12. Synthesis of 17. To a solution of **16** (3.047 mg, 13.85 mmol) in dry Et_2O (40 mL) at 0°C, MeMgI (1 M in Et_2O, 20.8 ml, 20.8 mmol) was added drop-wise with stirring under nitrogen atmosphere. After stirring at the same temperature for 1 h, the reaction mixture was quenched with saturated aqueous NH_4Cl solution and the mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated in vacuo. Column chromatography (SiO_2, 25–30% EtOAc in petrolium ether eluant) afforded pure **17** (2.55 g 78%) as a colorless syrupy liquid. R_f 0.3 (silica gel, 40% EtOAc in petroleum ether); IR (neat): ν_{max} 3446, 2920, 1615, 1218, 1069 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.20 (d, *J*=8.9 Hz, 2H, aromatic), 6.83 (d, *J*=8.9 Hz, 2H, aromatic), 5.73–5.48 (m, 2H, olefinic), 4.42 (s, 2H, OCH_2Ar), 4.23 (dq, *J*=6.0 Hz, 1H, C*H*(OH)CH_3), 3.81 (s, 3H, OCH_3), 3.45 (t, *J*=6.7 Hz, 2H, PMBOCH_2–) 2.31 (q, *J*=6.7 Hz, 2H, allylic), 1.55 (m, 1H, OH), 1.25 (d, *J*=6.0 Hz, 3H, CH(OH)CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.1, 136.0, 130.3, 129.2, 126.9, 113.7, 72.4, 69.3, 68.6, 55.2, 32.4, 23.2; Mass (LSIMS): *m/z*: 236 $[M]^+$.

3.1.13. Synthesis of 18. Compound **17** (2.46 g, 10.4 mmol) was subjected to Sharpless asymmetric epoxidation following the same procedure as described above for the preparation of **10**. Purification by column chromatography (SiO_2, 35–40% EtOAc in petroleum ether eluant) afforded epoxide **18** (1.05 g, 40%) as a colorless syrupy liquid. R_f 0.4 (silica gel, 50% EtOAc in petrolium ether); $[\alpha]_D^{22}=-2.58$ (*c* 1.4, $CHCl_3$); IR (neat): ν_{max} 3437, 2921, 2845, 1598, 1506, 1236, 1088, 1020, 800 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.20 (d, *J*=8.9 Hz, 2H, aromatic), 6.83 (d, *J*=8.9 Hz, 2H, aromatic), 4.43 (ABq, 2H, OCH_2Ar), 3.89 (m, 1H, C*H*(OH)CH_3), 3.79 (s, 3H, OCH_3), 3.54 (t, *J*=6.0 Hz, 2H, PMBOCH_2–), 3.07 (dt, *J*=6.0, 2.2 Hz, 1H, epoxy-*H*), 2.75 (dd, *J*=3.8, 2.2 Hz, 1H, epoxy-*H*), 1.83 (q, *J*=6.0 Hz, 2H, PMBOCH_2CH_2–), 1.80 (m, 1H, O*H*), 1.22 (d, *J*=6.7 Hz, 3H, CH(OH)CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 159.2, 130.3, 129.2, 113.8, 72.7, 66.6, 64.99, 61.6, 55.2, 52.9, 32.1, 18.7; Mass (EI): *m/z*: 252 $[M]^+$.

3.1.14. Synthesis of 1c. To a solution of **18** (950 mg, 3.77 mmol) in dry CH_2Cl_2 (12 mL), 2,6-lutidine (0.88 mL, 7.54 mmol) and TBSOTf (1.03 mL, 4.52 mmol) were added sequentially at 0°C. After 0.5 h, the reaction was quenched by saturated aqueous NH_4Cl solution, extracted with EtOAc, washed thoroughly with saturated aqueous $CuSO_4$ solution, water, brine, dried (Na_2SO_4) and concentrated in vacuo. Column chromatography (SiO_2, 5–6% EtOAc in

petrolium ether eluant) gave pure silyl ether intermediate (1.35 g, 98%) as a colorless syrupy liquid that was used directly in the next step.

The silyl ether (1.296 g, 3.54 mmol), thus prepared, was subjected to PMB-deprotection following the same procedure described above in the second step during the synthesis of **1b** from **15**. Chromatographic purification (SiO_2, 18–24% EtOAc in petroleum ether eluant) provided **1c** (714 mg, 82%) as an oily liquid. R_f 0.3 (silica gel, 10% EtOAc in petroleum ether); $[\alpha]_D^{22}=-9.76$ (*c* 2.1, $CHCl_3$); IR (neat): ν_{max} 3449, 2925, 2830, 1460, 1225, 1073, 824, 764 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 3.76 (t, *J*=6.0 Hz, 2H, C*H*$_2$OH), 3.66 (m, 1H, C*H*(OTBS)CH$_3$), 2.99 (ddd, *J*=6.0, 4.5, 2.2 Hz, 1H, epoxy-*H*), 2.69 (dd, *J*=4.5, 2.2 Hz, 1H, epoxy-*H*), 2.05–1.62 (m, 2H, –C*H*$_2$CH$_2$OH), 1.23 (d, *J*=6.0 Hz, 3H, CH(OTBS)C*H*$_3$), 0.88 (s, 9H, ^{t}Bu), 0.048 and 0.041 (two s, 6H, $SiMe_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 67.8, 61.4, 59.88, 54.8, 34.0, 25.7, 20.8, 18.0, −4.75, −4.8; Mass (LSIMS): *m*/*z*: 247 $[M+H]^+$.

3.1.15. Synthesis of 19. Compound **19** was prepared from **12** (2.165 g, 11.16 mmol) following the same procedure as described above for the preparation of **17**. Purification by column chromatography (SiO_2, 25–30% EtOAc in petroleum ether eluant) afforded compound **19** (1.87 g, 80%) as colorless oily liquid. R_f 0.2 (silica gel, 30% EtOAc in petroleum ether); IR (neat): ν_{max} 3451, 2925, 2828, 1620, 1510, 1242, 1076, 1005, 820 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.20 (d, *J*=8.8 Hz, 2H, aromatic), 6.83 (d, *J*=8.8 Hz, 2H, aromatic), 4.43 (s, 2H, OC*H*$_2$Ar), 3.95 (m, 1H, C*H*(OH)CH$_3$), 3.79 (s, 3H, OC*H*$_3$), 3.69–3.52 (m, 2H, PMBOC*H*$_2$–), 2.74 (br s, 1H, O*H*), 1.79–1.60 (m, 2H, C*H*$_2$), 1.18 (d, *J*=6.0 Hz, 3H, CH(OH)C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.1, 130.0, 129.2, 113.7, 72.80, 68.6, 67.4, 55.1, 38.0, 23.2; Mass (LSIMS): *m*/*z*: 210 $[M]^+$, 209 $[M^+-H]$.

3.1.16. Synthesis of 20. Sodium hydride (60% dispersion in oil, 501.6 mg, 12.54 mmol) was added portion wise to a solution of **19** (1.756 g, 8.36 mmol) in THF (24 mL) at 0°C under nitrogen atmosphere. After the addition was complete, the reaction mixture was stirred at 0°C for 15 minutes. Then BnBr (1.49 mL, 12.54 mmol) was added slowly to the stirred reaction mixture followed by the addition of TBAI (308.8 mg, 0.836 mmol). After stirring for 12 h at room temperature, the reaction mixture was quenched slowly by the addition of saturated aqueous NH_4Cl solution. THF was removed on a rotary evaporator and the product was extracted from the aqueous layer with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated in vacuo. Purification by column chromatography (SiO_2, 4–5% EtOAc in petroleum ether eluant) afforded the benzyl ether intermediate as a colorless liquid that was used directly in the next step.

Compound **20** was prepared from the above benzyl ether (1.665 g, 5.55 mmol) following the same procedure as described above during the preparation of **1b** from **15**. Chromatographic purification (SiO_2, 35–45% EtOAc in petroleum ether eluant) provided compound **20** (800 mg, 80% from **19**) as a liquid. R_f 0.2 (silica gel, 20% EtOAc in petroleum ether); IR (neat): ν_{max} 3420, 2952, 2926, 2808, 1445, 1349, 1051, 718, 682 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.29 (m, 5H, aromatic), 4.63–4.42 (ABq, 2H, PhC*H*$_2$), 3.74 (m, 3H, C*H*$_2$OH, C*H*(OBn)CH$_3$), 2.32 (m, 1H, O*H*), 1.75 (q, *J*=5.7 Hz, 2H, –C*H*$_2$CH$_2$OH), 1.25 (d, *J*=6.0 Hz, 3H, CH(OBn)C*H*$_3$); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 138.4, 128.4, 127.6, 127.6, 74.4, 70.4, 60.6, 38.8, 19.3; Mass (LSIMS): *m*/*z*: 181 $[M+H]^+$.

3.1.17. Synthesis of 21. To a solution of compound **20** (674 mg, 3.74 mmol) in dry CH_2Cl_2 (6 mL) was added with stirring, DMSO (7.48 mL), Et_3N (2.60 mL, 18.7 mmol) and portion wise SO_3–py complex (2.97 g, 18.7 mmol) at 0°C and under nitrogen atmosphere. After 1 h, the reaction mixture was quenched with saturated aqueous NH_4Cl solution. The layers were separated and the aqueous phase extracted with EtOAc. The combined organic extracts were washed with water and brine (15 mL), dried (Na_2SO_4) and concentrated in vacuo. The aldehyde thus obtained was directly subjected to the next step without purification.

To the crude aldehyde in dry CH_2Cl_2 (15 mL), $Ph_3P{=}CHCO_2Et$ (1.95 g, 5.61 mmol) was added at room temperature and the reaction mixture was stirred for 3 h. Solvent was evaporated under reduced pressure and the residue was purified by column chromatography (SiO_2, 6–7% EtOAc in petroleum ether) to give the α,β-unsaturated ester intermediate as an oily liquid. The ester was subjected directly to DIBAL-H reduction following the same procedure used earlier for the preparation of **16**. Chromatographic purification (SiO_2, 25–30% EtOAc in petroleum ether eluant) gave compound **21** (632 mg, 82%) as an oily colourless liquid. R_f 0.3 (silica gel, 30% EtOAc in petroleum ether); IR (neat): ν_{max} 3422, 2926, 2862, 1448, 1373, 1080, 968, 738, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.4–7.2 (m, 5H, aromatic), 5.7 (m, 2H, olefin), 4.55 (ABq, 2H, OC*H*$_2$Ph), 4.1 (m, 2H, C*H*$_2$OH), 3.6 (m, 1H, C*H*CH$_3$), 2.4–2.2 (m, 2H, allylicH), 1.2 (d, *J*=6.7 Hz, 3H, C*H*$_3$); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.7, 131.5, 128.7, 128.2, 127.7, 127.6, 127.4, 74.4, 70.3, 63.5, 39.0, 19.4; Mass (LSIMS): *m*/*z*: 206 $[M]^+$.

3.1.18. Synthesis of 22. The allylic alcohol **21** (426 mg, 2.07 mmol) was subjected to Sharpless asymmetric epoxidation following the same procedure described for the preparation of **10**. Purification by column chromatography (SiO_2, 30–45% EtOAc inpetroleum ether eluant) afforded compound **22** (441 mg, 96%), an oily liquid, as a mixture of diastereomers (1:1). R_f 0.5 (silica gel, 50% EtOAc in petroleum ether); IR (neat): ν_{max} 3418, 2977, 2914, 2873, 1496, 1453, 1378, 1342, 1218, 1130, 1069, 1026, 902, 859, 770, 698 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$, mixture of diastereomers): δ 7.29 (m, 5H, aromatic), 4.65–4.38 (two ABq, 2H, PhC*H*$_2$O–), 3.91–3.49 (m, 3H, C*H*(OBn), C*H*$_2$OH), 3.12–2.99 (m, 1H, epoxy-*H*), 2.92–2.81 (m, 1H, epoxy-*H*), 1.92–1.45 (m, 2H, C*H*$_2$), 1.57 (1H), 1.28 and 1.25 (two d, *J*=6.0 Hz, 3H, C*H*$_3$). ^{13}C NMR (50 MHz, $CDCl_3$, mixture of isomers 1:1): δ 138.6, 128.3, 127.6, 127.5, 72.7, 72.3, 70.6, 70.2, 61.7, 58.8, 58.1, 53.4, 53.2, 39.2, 38.4, 19.9, 19.6; Mass (LSIMS): *m*/*z*: 223 $[M+H]^+$.

3.1.19. Synthesis of 1d. Compound **22** (353 mg, 1.59 mmol) was subjected to TBDPS protection following

the same procedure described for the preparation of **7**. Chromatographic purification (SiO_2, 4–5% EtOAc in petroleum ether eluant) gave the silylated intermediate as colorless oily liquid that was used directly in the next step.

The silyl ether, thus obtained, was dissolved in MeOH–EtOAc (2:1, 3 mL). $Pd(OH)_2$ on C (10%, 200 mg) was added and subjected to hydrogenation under atmospheric pressure using a H_2-filled balloon. After 1 h, the reaction mixture was filtered through a short pad of Celite and the filter cake was washed with MeOH. The filtrate and washings were combined and concentrated in vacuo. Chromatographic purification (SiO_2, 20–24% EtOAc in petroleum ether eluant) gave compound **1d** (500 mg, 85% from **22**), a colorless liquid, as a mixture of diastereomers. R_f 0.2 (silica gel, 25% EtOAc in petroleum ether); IR (neat): ν_{max} 3435, 3069, 2933, 2861, 1467, 1428, 1387, 1111, 947, 824, 743, 703, 614, 505 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.72–7.30 (m, 10H, aromatic), 3.98 (m, 1H, C*H*(OH)CH_3), 3.75 (d, J=4.0 Hz, 2H, –CH_2OTBDPS), 3.04–2.84 (m, 2H, epoxy-*H*s), 1.85–1.42 (m, 2H, CH_2), 1.25 and 1.22 (two d, J=6.0 Hz, 3H, CH(OH)CH_3), 1.05 (s, 9H, ^{t}Bu); ^{13}C NMR (75 MHz, $CDCl_3$, mixture of isomers): δ 135.6, 135.5, 133.2, 129.7, 127.7, 77.2, 66.5, 65.4, 64.0, 63.9, 58.0, 57.9, 54.3, 54.0, 40.6, 39.8, 26.7, 23.5, 23.4, 19.2; Mass (LSIMS): m/z: 393 $[M+Na]^+$.

3.1.20. Synthesis of 2a. Compound **1a** (497 mg, 1.38 mmol) was subjected to Swern oxidation following the same procedure described for the preparation of **16**. Purification by column Chromatography (SiO_2, 25–30% EtOAc in petroleum ether eluant) afforded **2a** (405 mg, 82%) as an oily liquid. R_f 0.5 (silica gel, 40% EtOAc in petroleum ether); $[\alpha]_D^{22}$=12.75 (c 2.3, $CHCl_3$); IR (neat): ν_{max} 3445, 3063, 3025, 2905, 2855, 1680, 1480, 1433, 1208, 1075, 964, 750, 705 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 9.49 (d, J=6.9 Hz, 1H, C*H*O), 7.44–7.12 (m, 15H, aromatic), 6.64 (dd, J=17.1, 3.9 Hz, 1H, C3–*H*), 6.3 (ddd, J=17.1, 6.9, 2.1 Hz, 1H, C2–*H*), 4.46 (m, 1H, C4–*H*), 3.34 (dd, J=10.57, 4.2 Hz, 1H, C5–*H*), 3.21 (dd, J=10.57, 6.8 Hz, 1H, C5–*H*′), 2.49 (d, J=4.3 Hz, 1H, O*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.3, 155.0, 143.3, 131.9, 128.5, 127.9, 127.2, 87.2, 70.4, 66.4; Mass (LSIMS): m/z: 281 $[M-Ph]^+$, 243 $[CPh_3]^+$.

3.1.21. Synthesis of 2b. Compound **1b** (400 mg, 1.08 mmol) was subjected to Swern oxidation following the same procedure described for the preparation of **16**. Purification by column Chromatography (SiO_2, 15% EtOAc in petroleum ether eluant) afforded **2b** (366 mg, 92%) as an oily liquid. R_f 0.48 (silica gel, 40% EtOAc in petroleum ether); $[\alpha]_D^{22}$=45.3 (c 1.4, $CHCl_3$); IR (neat): ν_{max} 3370, 3060, 2926, 2824, 1686, 1474, 1436, 1005, 696, 494 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.52 (d, J=7.1 Hz, 1H, C*H*O), 7.68–7.37 (m, 10H, aromatic), 6.7 (dd, J=17.3 Hz, 1H, C3–*H*), 6.37 (dd, J=17.3, 7.1 Hz, 1H, C2–*H*), 3.64 (s, 2H, C5–H_2), 2.84 (s, 1H, O*H*), 1.3 (s, 3H, C4–CH_3), 1.08 (s, 9H, *t*-butyl); ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.3, 160.6, 135.6, 135.5, 132.6, 132.5, 130.9, 130.1, 130.0, 127.8, 77.4, 73.5, 70.3, 29.6, 26.8, 23.4, 19.2; Mass (LSIMS): m/z: 369 $[M+H]^+$, 351 $[M-OH]^+$.

3.1.22. Synthesis of 2c. Compound **1c** (638 mg, 2.59 mmol) was subjected to Swern oxidation following the same procedure described for the preparation of **16**, Purification by column chromatography (SiO_2, 14–16% EtOAc in petroleum ether eluant) afforded **2c** (569 mg, 90%) as an oily liquid. R_f 0.2 (silica gel, 20% EtOAc in petroleum ether); $[\alpha]_D^{22}$=40.9 (c 2.2, $CHCl_3$); IR (neat): ν_{max} 3450, 2927, 2845, 1681, 1230, 1085, 975, 825, 773 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 9.56 (d, J=6.35 Hz, 1H, C*H*O), 6.72 (dd, J=16.9, 4.2 Hz, 1H, C3–*H*), 6.32 (ddd, J=16.9, 6.35, 1.27 Hz, 1H, C2–*H*), 4.28 and 3.92 (two sets of m, 2H, C4–H and C5–*H*), 2.37 (d, J=5.1 Hz, 1H, O*H*), 1.12 (d, J=6.3 Hz, 3H, C5–CH_3), 0.91 (s, 9H, *t*-butyl), 0.08 (s, 6H, Si(CH_3)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.3, 154.6, 132.3, 75.0, 70.8, 25.7, 18.2, 18.0, −4.5, −4.9; Mass (LSIMS): m/z: 227 $[M-OH]^+$,

3.1.23. Synthesis of 2d. Compound **1d** (352 mg, 0.95 mmol) was subjected to Swern oxidation following the same procedure described for the preparation of **16**. Purification by column Chromatography (SiO_2, 18–24% EtOAc in petroleum ether eluant) afforded **2d** (315 mg, 90%) as an oily liquid. R_f 0.3 (silica gel, 25% EtOAc in petroleum ether); $[\alpha]_D^{22}$=30.6 (c 0.72, $CHCl_3$); IR (neat): ν_{max} 3437, 3071, 3050, 2931, 2859, 1677, 1632, 1470, 1427, 1362, 1257, 1111, 980, 824, 742, 704, 612, 506 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.6–7.32 (m, 10H, aromatic), 6.64 (dd, J=16.8, 3.44 Hz, 1H, C3–*H*), 6.32 (dd, J=16.8, 1.9 Hz, 1H, C4–*H*), 4.4 (m, 1H, C2–*H*), 3.78 (dd, J=9.9, 3.82 Hz, 1H, C1–*H*), 3.59 (dd, J=9.9, 6.2 Hz, 1H, C1–*H*′), 2.7 (d, J=3.9 Hz, 1H, O*H*), 2.24 (s, 3H, C5–CH_3), 1.1 (s, 9H, *t*-butyl); ^{13}C NMR (75 MHz, $CDCl_3$): δ 198.0, 144.5, 135.5, 132.7, 130.6, 130.0, 127.8, 71.5, 67.0, 27.3, 26.8, 19.2; Mass (LSIMS): m/z: 391 $[M+Na]^+$, 351 $[M-OH]^+$.

3.1.24. Synthesis of 23. To a stirred solution of **2c** (464 mg, 1.9 mmol) in dry CH_2Cl_2 (8 mL) at 0°C, DIPEA (3.30 mL, 19 mmol) followed by MEMCl (1.73 mL, 15.2 mmol) were added under nitrogen atmosphere. Then the reaction mixture was allowed to come to room temperature and stirred for 12 h. The reaction was quenched with saturated aqueous NH_4Cl solution and extracted with EtOAc. The organic extracts were combined and washed with brine, dried (Na_2SO_4) and concentrated in vacuo. Purification by column chromatography (SiO_2, 13–16% EtOAc in petroleum ether eluant) gave compound **23** (606 mg, 96%) as an oily liquid. R_f 0.33 (silica gel, 20% EtOAc in petroleum ether); $[\alpha]_D^{22}$=−26.3 (c 4.2, $CHCl_3$); IR (neat): ν_{max} 2925, 1687, 1443, 1325, 1230, 1100, 1025, 818 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 9.58 (d, J=8.2 Hz, 1H, C*H*O), 6.80 (dd, J=15.6, 6.0 Hz, 1H, olefinic), 6.27 (dd, J=15.6, 8.2 Hz, 1H, olefinic), 4.74 (ABq, 2H, –OCH_2O–), 4.18 (t, J=6.0 Hz, 1H, –C*H*(OMEM)–), 3.89 (dq, J=6.0 Hz, 1H, –C*H*(OTBS)CH_3), 3.82–3.48 (m, 4H, –OCH_2–CH_2O–), 3.37 (s, 3H, OCH_3), 1.18 (d, J=6.0 Hz, 3H, CH(OTBS)CH_3), 0.87 (s, 9H, ^{t}Bu), 0.056 and 0.033 (two s, 6H, $SiMe_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.2, 154.5, 133.5, 94.2, 79.9, 71.5, 70.5, 67.3, 58.9, 25.6, 20.1, 17.9, −4.6, −4.8; Mass (LSIMS): m/z: 333 $[M+H]^+$.

3.1.25. Synthesis of 5. The aldehyde **23** (495 mg, 1.49 mmol) was taken in *t*BuOH/2-methyl-2-butene (3:1, 40 mL) and to it a solution of $NaClO_2$ (539 mg, 5.96 mmol) and $NaH_2PO_4.H_2O$ (1.39 g, 8.9 mmol) in water (2 mL) was

added at room temperature. After being stirred for 1 h, the solvent was removed in rotary evaporator, under reduced pressure. Residue was taken in ethyl acetate, washed with brine, dried (Na_2SO_4), filtered and concentrated in vacuo. Purification by column chromatography (SiO_2, 30–50% EtOAc in petroleum ether eluant) afforded compound **5** (498 mg, 96%) as a colorless oily liquid. R_f 0.3 (silica gel, 60% EtOAc in petroleum ether); $[\alpha]_D^{22}=-26.8$ (*c* 2.4, $CHCl_3$); IR (neat): ν_{max} 2933, 1702, 1257, 1107, 1040, 835, 774 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 6.98 (dd, J=15.6, 6.0 Hz, 1H, olefinic), 6.02 (d, J=15.6 Hz, 1H, olefinic), 4.74 (ABq, 2H, $-OCH_2O-$), 4.10 (t, J=6.0 Hz, 1H, $-CH(OMEM)-$), 3.84 (dq, J=6.0 Hz, 1H, $-CH(OTBS)CH_3$), 3.82–3.48 (m, 4H, $-OCH_2-CH_2O-$), 3.38 (s, 3H, OCH_3), 1.17 (d, J=6.0 Hz, 3H, $CH(OTBS)CH_3$), 0.87 (s, 9H, ^{t}Bu), 0.05 and 0.03 (two s, 6H, $SiMe_2$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.9, 148.3, 122.5, 94.2, 80.0, 71.7, 70.6, 67.3, 58.9, 25.7, 19.9, 18.0, −4.6, −4.8; Mass (LSIMS): *m/z*: 349 $[M+H]^+$.

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References

1. (a) Li, J. J. *Tetrahedron* **2001**, *57*, 1–24. (b) Taylor, S. K. *Tetrahedron* **2000**, *56*, 1149–1163.
2. It is not possible to list all the references here. However, a quick search in http://organic.chemweb.com under ring opening of epoxides will provide a complete list of relevant references. For a few example references see: (a) Dowsland, J.; McKerlie, F.; Procter, D. J. *Tetrahedron Lett.* **2000**, *41*, 4923–4928. (b) Schaus, S. E.; Jacobsen, E. N. *Org. Lett.* **2000**, *2*, 1001–1004. (c) Brandes, B. D.; Jacobsen, E. N. *Synlett* **2001**, 1013–1015. (d) Sasaki, M.; Tanino, K.; Miyashita, M. *Org. Lett.* **2001**, *3*, 1765–1767. (e) Asao, N.; Kasahara, T.; Yamamoto, Y. *Tetrahedron Lett.* **2001**, *42*, 7903–7906. (f) Sharghi, H.; Nasseri, M. A.; Niknam, K. *J. Org. Chem.* **2001**, *66*, 7287–7293. (g) Sabitha, G.; Babu, R. S.; Rajkumar, M.; Yadav, J. S. *Org. Lett.* **2002**, *4*, 343–345. (h) Hodgson, D. M.; Miles, T. J.; Witherington, J. *Synlett* **2002**, 310–312. (i) Barluenga, J.; Vázquez-Villa, H.; Ballesteros, A.; González, J. M. *Org. Lett.* **2002**, *4*, 2817–2819. (j) Sasaki, M.; Tanino, K.; Hirai, A.; Miyashita, M. *Org. Lett.* **2003**, *5*, 1789–1791.
3. (a) Katsuki, T.; Martin, V. S. *Org. React.* **1996**, *48*, 1–299. (b) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765–5780.
4. (a) Schiewe, H. J.; Zeeck, A. *J. Antibiot.* **1999**, *52*, 635–642. (b) Taddei, A.; Zeeck, A. *J. Antibiot.* **1997**, *50*, 526–528. (c) Furumai, T.; Nagahama, N.; Okuda, T. *J. Antibiot.* **1968**, *21*, 85–91. (d) Miyairi, N.; Takashima, M.; Shimizu, K.; Sakai, H. *J. Antibiot.* **1966**, *19*, 56–62.
5. (a) Yamada, T.; Iritani, M.; Minoura, K.; Numata, A.; Kobayashi, Y.; Wang, Y.-G. *J. Antibiot.* **2002**, *55*, 147–154. (b) Yamada, T.; Iritani, M.; Doi, M.; Minoura, K.; Ito, T.; Numata, A. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3046–3053. (c) Fukami, A.; Taniguchi, Y.; Nakamura, T.; Rho, M.-C.; Kawaguchi, K.; Hayashi, M.; Komiyama, K.; Omura, S. *J. Antibiot.* **1999**, *52*, 501–504. (d) Numata, A.; Iritani, M.; Yamada, T.; Minoura, K.; Matsumura, E.; Yamori, T.; Tsuruo, T. *Tetrahedron Lett.* **1997**, *38*, 8215–8218. (e) Takamatsu, S.; Hiraoka, H.; Kim, Y.-P.; Hayashi, M.; Natori, M.; Komiyama, K.; Omura, S. *J. Antibiot.* **1997**, *50*, 878–880. (f) Takamatsu, S.; Kim, Y.-P.; Hayashi, M.; Hiraoka, H.; Natori, M.; Komiyama, K.; Omura, S. *J. Antibiot.* **1996**, *49*, 95–98. (g) Hayashi, M.; Kim, Y.-P.; Hiraoka, H.; Natori, M.; Takamatsu, S.; Kawakubo, T.; Masuma, R.; Komiyama, K.; Omura, S. *J. Antibiot.* **1995**, *48*, 1435–1439.
6. For earlier works on the syntheses of macrosphelides see: (a) Sharma, G. V. M.; Mouli, C. C. *Tetrahedron Lett.* **2002**, *43*, 9159–9161. (b) Nakamura, H.; Ono, M.; Shida, Y.; Akita, H. *Tetrahedron: Asymmetry* **2002**, *13*, 705–713. (c) Nakamura, H.; Ono, M.; Makino, M.; Akita, H. *Heterocycles* **2002**, *57*, 327–336. (d) Kobayashi, Y.; Acharya, H. P. *Tetrahedron Lett.* **2001**, *42*, 2817–2820. (e) Kobayashi, Y.; Kumar, B. G.; Kurachi, T.; Acharya, H. P.; Yamazaki, T.; Kitazume, T. *J. Org. Chem.* **2001**, *66*, 2011–2018. (f) Ono, M.; Nakamura, H.; Konno, F.; Akita, H. *Tetrahedron: Asymmetry* **2000**, *11*, 2753–2764. (g) Kobayashi, Y.; Kumar, B. G.; Kurachi, T. *Tetrahedron Lett.* **2000**, *41*, 1559–1563. (h) Kobayashi, Y.; Nakano, M.; Kumar, G. B.; Kishihara, K. *J. Org. Chem.* **1998**, *63*, 7505–7515. (i) Sunazuka, T.; Hirose, T.; Harigaya, Y.; Takamatsu, S.; Hayashi, M.; Komiyama, K.; Omura, S. *J. Am. Chem. Soc.* **1997**, *119*, 10247.
7. The other enantiomer could not be detected by ^1H NMR analysis of the Mosher ester.
8. Chakraborty, T. K.; Das, S. *Tetrahedron Lett.* **2001**, *42*, 3387–3390.
9. Zacharie, B.; Gagnon, L.; Attardo, G.; Connolly, T. P.; St-Denis, Y.; Penney, C. L. *J. Med. Chem.* **1997**, *40*, 2883–2894.
10. Awakura, D. A.; Fujiwara, K.; Murai, A. *Synlett* **2000**, 1733–1736.