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Total synthesis of 8-methoxygoniodiol related compounds via chiron approach

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ABSTRACT

The stereoselective synthesis of 8-methoxygoniodiol related compounds was accomplished by using readily available δ-gluconolactone as a chiral source. The stereoselective addition of an aryl Grignard reagent on an aldehyde, stereoselective reduction of a keto group and regioselective opening of a chiral epoxide by ethyl propiolate are the key steps involved in this synthesis.

1. Introduction

The genus *Goniothalamus* (Annonaceae) consists of 115 species, spread over the entire tropic and subtropic regions,[1] some of them are used extensively as traditional medicines.[2] Several bioactive styryllactones have been isolated from *Goniothalamus* species.[3,4] The seeds of *G. amuyon* are reported to be useful for the treatment of edema and rheumatism.[5] In particular, 8-methoxygoniodiol was isolated from the stems and leaves of *Goniothalamus amuyon* along with seven styrylpyrones.[6] These styryllactones are found to possess significant cytotoxicity against several human tumors.[7] The structures of some styryllactones including their related compounds are depicted in Figure 1.

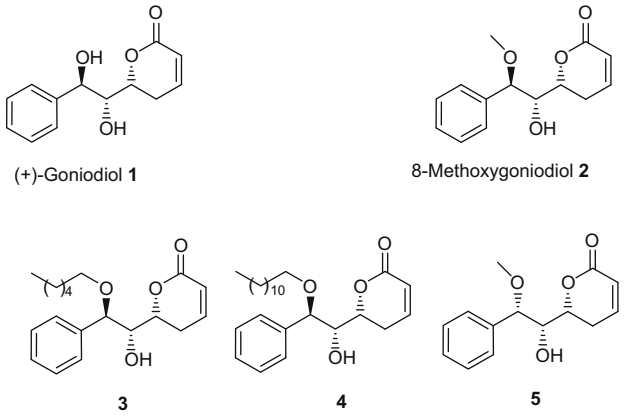

Figure 1.

Owing to their potent biological activity, and structural architecture, several methods have been reported for the synthesis of (+)-goniodiol and related molecules.[8] However, reports on the synthesis of 8-methoxygoniodiol are scarce.[9] 8-Methoxygoniodiol exhibits very different cytotoxicity compared to (+)-goniodiol, depending on the type of human cancer cell lines. Hence we have synthesised the analogues containing different alkyl groups. As part of our ongoing program in the synthesis of heavily oxygenated lactones from sugars, we have recently disclosed, from δ-gluconolactone one of these novel styryllactone ((+)-8-methoxygoniodiol).[10] As an extension of our previous synthetic endeavor, we now describe stereoselective synthesis of **3**–**5** from δ-gluconolactone as replenishable starting material with full experimental details. Retrosynthetic analysis of **3**–**5** is depicted in Scheme 1.

The retrosynthetic analysis of **3**–**5** illustrates that optically active epoxides **15a**, **15b**, **23** could be prepared from δ-gluconolactone **6** by a sequence of reactions. Subsequently, epoxides **15a**, **15b**, **23** could be easily converted into target molecules **3**–**5** by means of ring opening by ethyl propiolate followed by partial hydrogenation using Lindlar's catalyst.

2. Results and discussion

The synthesis of styryllactones **3**, **4**, **5** began with δ-gluconolactone **6**, which could be easily obtained from a commercial source. Accordingly, δ-gluconolactone **6** was treated with methanol in the presence of *p*-TSA followed by 2,2-dimethoxypropane to give compound **7** in 86% yield.[11] Reduction of ester **7** with $LiAlH_4$ gave diol **8** in 96% yield, which upon treatment with $NaIO_4$ furnished aldehyde **9** in 90% yield. The addition of phenylmagnesium bromide to an aldehyde **9** predominantly gave compound **10** along with a minor amount of compound **10a**. The diastereomeric ratio of **10** to **10a** was 95:5, which could be easily separated by column chromatography. The configuration of the newly formed hydroxyl group was assigned by converting the compound **10** into a known product.[12]

The hydroxyl group of major isomer **10** was protected as its alkyl ethers **11a** and **11b** using *n*-hexyl bromide, *n*-dodecylbromide, and NaH in THF in the presence of a catalytic amount of TBAI. Hydrolysis

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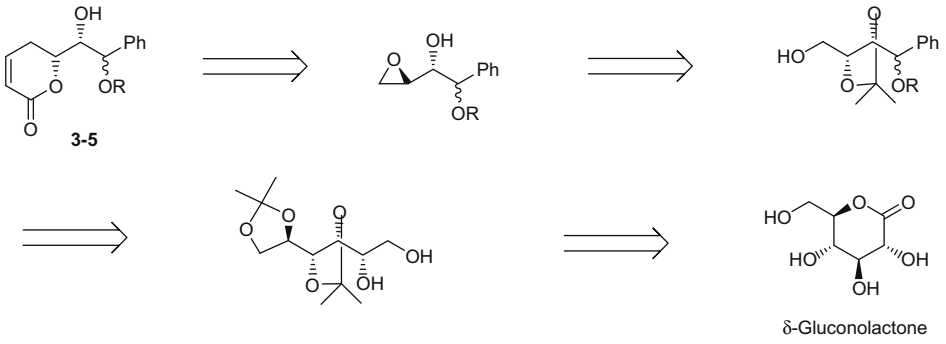
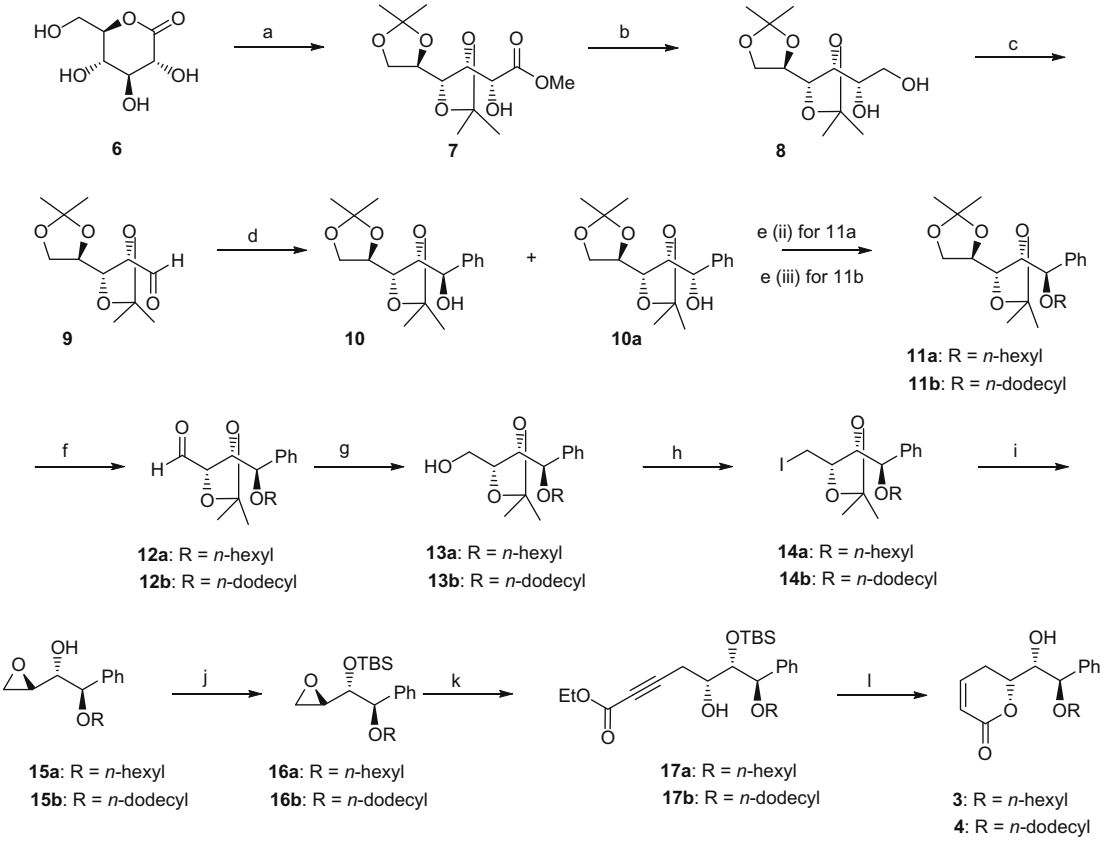


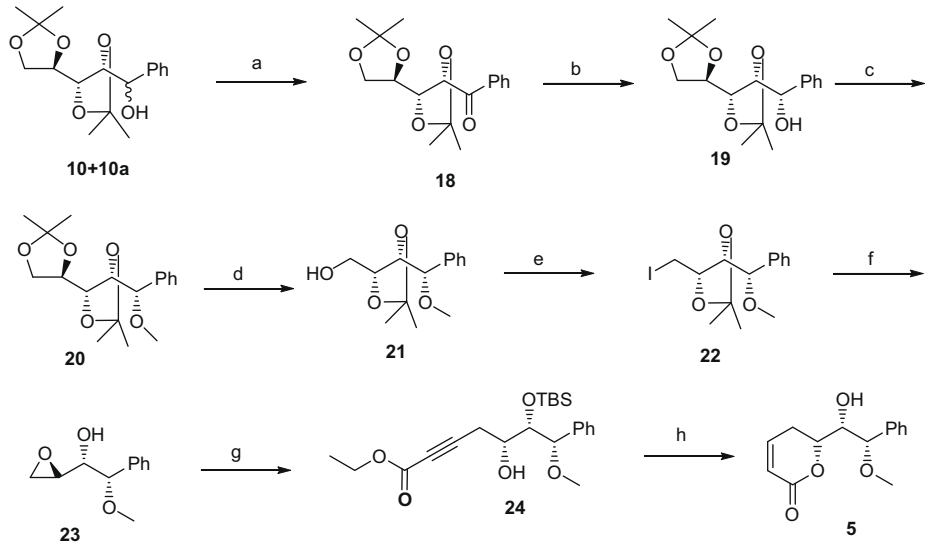
Scheme 1. Retrosynthetic analysis of **3**–**5**.

of the primary acetonide and cleavage of the resulting diol occurred simultaneously with H_5IO_6 at room temperature resulting in the corresponding aldehydes **12a** and **12b** in 95% yield.[13] Reduction of aldehydes **12a** and **12b** with $NaBH_4$ in methanol gave the corresponding alcohols **13a** and **13b** in 90% yield, which were then converted into the corresponding iodides **14a** and **14b** by using I_2, TPP and imidazole. Upon treatment of iodides **14a** and **14b** with 1 M HCl in ethanol for 3 days, followed by the addition of excess K_2CO_3 we obtained the corresponding hydroxy epoxides **15a** and **15b** in 70% yield.[14] The hydroxyl group of the epoxides were then protected as the corresponding TBS ethers **16a** and **16b** using TBSCl and imidazole. Treatment of the obtained ethers **16a** and **16b** with ethyl propiolate in the presence of *n*-BuLi and $BF_3.OEt_2$ afforded the ring opened products **17a** and **17b** in 80% yield. Partial hydrogenation of these compounds **17a** and **17b** under Lindlar's conditions followed by treatment with 1 M HCl gave the corresponding target molecules **3** and **4** in 60% yield (Scheme 2).

Having successfully studied the formation of **3** and **4** using δ-gluconolactone **6**, we then proceeded to apply a similar strategy to construct the 8-methoxy goniodiol epimer **5** from the same starting material (δ-gluconolactone). The diastereomeric mixture of alcohols **10** and **10a** were then oxidized to corresponding keto compound **18** using IBX in THF at room temperature. The keto group of compound **18** was reduced stereoselectively to compound **19** as a major isomer (95:5) using $NaBH_4/CeCl_3$ system at −78 °C. Compound **19** was smoothly converted to 8-methoxygoniodiol epimer **5** using the same reaction sequence as mentioned in Scheme 2. The structures of the newly synthesized styryllactones



Scheme 2. Reagents and conditions: (a) 2,2-DMP, *p*-TSA, acetone, MeOH, 12 h, rt, 86%; (b) $LiAlH_4$, THF, 0 °C–rt, 4 h, 96%; (c) $NaIO_4$, DCM, aq satd $NaHCO_3$, 5 h, 90%; (d) PhMgBr, THF, −5 °C–0 °C–rt (a:b: 95:5) 1/2 h, 95%; (e) (i) NaH, *n*-hexyl bromide, TBAI, THF, 0 °C–rt, 2 h, 97%; (ii) NaH, *n*-dodecyl bromide, TBAITHF, 0 °C–rt, 2 h, 97%; (f) H_5IO_6, EtOAc, 0 °C–rt, 1 h, 95%; (g) $NaBH_4$, MeOH, 0 °C–rt, 2 h, 90%; (h) TPP, I_2, imidazole, CH_3CN:ether (1:3) 0 °C–rt, 2 h, 90%; (i) 1 M HCl, EtOH, 0 °C–rt, 3 days then K_2CO_3, 70%; (j) imidazole, TBSCl, CH_2Cl_2, 0 °C–rt, 2 h, 90%; (k) $\equiv\!\!-CO_2Et$,, BuLi, BF_3OEt_2, THF, −78 °C, 2 h, 80%; (l) (i) Lindlar, EtOAc; (ii) 1 M, HCl, 60%.



Scheme 3. Reagents and conditions: (a) IBX, DMSO, THF, rt, 2 h, 91%; (b) $NaBH_4$, $CeCl_3$, MeOH, −78 °C, 2 h, 86%; (c) NaH, MeI, THF, 0 °C–rt, 2 h, 96%; (d) (i) H_5IO_6, EtOAc, 0 °C–rt, 1 h, 95%; (ii) $NaBH_4$, MeOH, 0 °C–rt, 2 h, 90%; (e) TPP, I_2, imidazole, CH_3CN:ether (1:3) 0 °C–rt, 2 h, 90%; (f) 1 M HCl, EtOH, 0 °C–rt, 3 days then K_2CO_3, 70%; (g) (i) imidazole, TBSCl, CH_2Cl_2, 0 °C–rt, 2 h, 90%; (ii) $\equiv CO_2Et$,, BuLi, BF_3OEt_2, THF, −78 °C, 2 h, 80%; (h) (i) Lindlar, EtOAc; (ii) 1 M HCl, 60%.

3, **4**, **5** were fully characterized using ^{1}H NMR, ^{13}C NMR, IR, HRMS including rotation values (Scheme 3).

3. Conclusions

In conclusion, we have described a concise and highly stereoselective synthetic route for the synthesis of 8-methoxygoniodiol related compounds using the readily available δ-gluconolactone as a chiral precursor. The synthesis involves direct and straightforward reactions such as the aryl Grignard addition, the stereoselective reduction of the keto group, the epoxide formation from an iodohydrin and the stereoselective ring opening of epoxide by an alkyne, which makes it quite simple and more convenient for scale-up products.

4. Experimental

4.1. General

Melting points were recorded on Buchi R-535 apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer FT-IR 240-c spectrophotometer using KBr optics. ^{1}H NMR and ^{13}C spectra were recorded on Gemini-200 and Varian Bruker-300 spectrometer in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV. The optical rotations were measured on a Jasco Dip 360 Digital polarimeter.

4.1.1. (*R*)-Methyl 2-hydroxy-2-((4*R*,4′*R*,5*R*)-2,2,2′,2′-tetramethyl-4,4-bis(1,3-dioxolan)-5-yl) acetate 7

D-Glucono-1,5-lactone **6** (89 g, 400 mmol) in 2,2-dimethoxy propane (150 mL), dry acetone (50 mL) and absolute methanol (15 mL) were added to *p*-TSA (1.0 g, 4.2 mmol). After stirring for 12 h, the homogenous solution was neutralized with $NaHCO_3$ and filtered, evaporated and the resulting residue in DCM (400 mL) was washed with brine solution, and dried over Na_2SO_4. Concentration of the solvent followed by silica gel column chromatography gave the α-hydroxy-ester **7** (123 g, 86%) as a yellowish oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.25 (d, J = 7.17 Hz, 1H), 4.15–3.94 (m, 5H), 3.84 (s, 3H), 2.89 (d, J = 8.30 Hz, 1H), 1.41, 1.37, 1.34 and 1.32 (4s, 12H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 172.9, 110.0, 109.8, 80.8, 77.2, 76.4, 69.4, 67.8, 52.6, 27.1, 26.6, 26.5, 25.2. IR (KBr): ν_{max} 3475, 2986, 2925, 1741, 1456, 1375, 1244, 1152, 1070, 845 cm^{-1}, $[\alpha]_D^{25} = +10.2$ (c 1.0, $CHCl_3$).

4.1.2. (*S*)-1-((4*R*,4′*R*,5*R*)-2,2,2′,2′-Tetramethyl-4,4′-bi(1,3-dioxolan)-5-yl)ethane-1,2-diol 8

To a suspension of $LiAlH_4$ (4.70 g, 231 mmol) in anhydrous THF (200 mL) at 0 °C, was added hydroxy-ester **7** (25 g, 154 mmol) in THF (65 mL). The mixture was stirred for 4 h at room temperature and quenched with aqueous Na_2SO_4 solution at 0 °C. The clear solution was filtered and the residue was washed with ethyl acetate (100 mL). The combined organic layers were washed with brine solution, dried over Na_2SO_4 and concentrated in vacuo. The resulting residue was purified by column chromatography to give pure diol **8** (21.1 g, 96%) as a white crystalline solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.17–3.90 (m, 5H), 3.74–3.70 (m, 3H), 2.62 and 2.44 (2s, 2H), 1.41, 1.39, 1.36 and 1.32 (4s, 12H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.6, 117.4, 96.2, 56.9, 51.3, 48.7, 38.9, 32.5, 23.9, 23.1. IR (KBr): ν_{max} 3446, 2987, 2925, 1638, 1457, 1376, 1248, 1214, 1156, 1068, 846 cm^{-1}, LC–MS: m/z 285 (M+Na)$^+$, $[\alpha]_D^{25} = +7.24$ (c 1.75, $CHCl_3$).

4.1.3. (*R*)-Phenyl((4*R*,4′*R*,5*R*)-2,2,2′,2′-tetramethyl-4,4′-bi(1,3-dioxolan)-5-yl)methanol 10

A solution of diol **8** (25 g, 430 mmol) in DCM (500 mL) containing aqueous saturated $NaHCO_3$ (35 mL) was treated with $NaIO_4$ (41 g, 860 mmol) portionwise at 0 °C and stirred at below 20 °C for 5 h. Solid Na_2SO_4 (50 g) was added, and the mixture was stirred for an additional 15 min, filtered, washed with DCM (250 mL) and the solvent evaporated to afford aldehyde **9** (19.5 g, 90%) as a yellowish oil, which was immediately used for the next reaction without additional purification.

To a solution of Grignard reagent [prepared in situ from Mg (2.82 g, 300 mmol) and phenylbromide (18.4 g, 300 mmol) in THF (450 mL)] at −5 °C was added a solution of the crude aldehyde **9** (18.0 g, 200 mmol) in THF (150 mL). The mixture was allowed to reach from 0 °C to room temperature slowly and after 30 min, quenched with aqueous saturated NH_4Cl. Workup with Et_2O (3 × 200 mL), brine wash, dried (Na_2SO_4) and removal of the solvent followed by purification gave enantiomerically pure alcohol

10 (21.75 g, 95%) as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.41, 1.37, 1.34, 1.32 (4s, 12H), 3.90–4.20 (m, 5H), 4.25 (d, J = 4.6 Hz, 1H), 7.3 (m, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 25.1, 26.3, 26.6, 27.1, 72.6, 75.4, 76.7, 82.6, 83.6, 109.0, 110.0, 126.8, 127.7, 128.5, 140.0. IR (KBr): ν_{max} 3438, 2990, 2874, 1376, 1153, 1070, 843, 702 cm^{-1}. HRMS calcd for $C_{17}H_{24}O_5$ [M+Na]$^+$ 331.1521. Found: 331.1512.

4.1.4. (4*R*,4′*R*,5*R*)-5-((*R*)-Hexyloxy(phenyl)methyl)-2,2,2′,2′-tetramethyl-4,4′-bi(1,3-dioxolane) 11a

To a stirred suspension of NaH (1.29 g, 150 mmol, 60% w/v dispersion in mineral oil) in anhydrous THF (60 mL), a solution of alcohol **10** (6 g, 100 mmol) in dry THF (25 mL) was added dropwise at 0 °C. After 30 min, *n*-hexyl bromide (9.58 g, 300 mmol) and tetrabutylammonium iodide (0.35 g, 5 mmol) was added. Stirring was continued for 2 h at room temperature, the reaction mixture was quenched with ice pieces. The aqueous layer was extracted with EtOAc (3 × 5 mL). The organic phase was washed with brine, dried (Na_2SO_4) and concentrated followed by column chromatography to afford the compound **11a** (7.40 g, 97%) as a white solid. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.87 (t, J = 6.25 Hz, 3H), 1.17–1.61(m, 20H), 3.21–3.39 (m, 2H), 3.79–4.09 (m, 5H), 4.25 (d, J = 3.12 Hz, 1H), 7.18–7.39 (m, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.9, 22.5, 25.2, 25.8, 26.4, 26.9, 27.6, 29.7, 31.5, 66.5, 69.2, 78.8, 81.6, 82.5, 83.0, 109.2, 109.9, 127.8, 128.1, 139.0 IR (KBr): ν_{max} 3451, 2929, 2861, 1455, 1374, 1069, 761, 703 cm^{-1}. HRMS calcd for $C_{23}H_{36}O_5$ [M+Na]$^+$ 415.2460. Found: 415.2442. $[\alpha]_D^{25} = +29.3$ (*c* 7.85, $CHCl_3$).

4.1.5. (4*R*,4′*R*,5*R*)-5-((*R*)-Dodecyloxy(phenyl)methyl)-2,2,2′,2′-tetramethyl-4,4′-bi(1,3-dioxolane) 11b

Compound **11b** was prepared (97%, white solid) in the same way as compound **11a**. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.88 (t, J = 6.58 Hz, 3H), 1.19–1.54 (m, 32H), 3.19–3.39 (m, 2H), 3.82–4.11 (m, 5H), 4.32 (d, J = 3.65, 1H), 7.27–7.34 (m, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.8, 22.4, 25.0, 29.9, 26.1, 26.8, 26.9, 27.3, 27.4, 29.0, 29.1, 29.3, 29.4, 31.6, 69.3, 76.7, 78.7, 81.7, 82.2, 82.9, 109.3, 110.0, 127.8, 128.2, 128.3, 138.9. IR (KBr): ν_{max} 3457, 2926, 2854, 1452, 1374, 1068, 761, 700 cm^{-1} HRMS calcd for $C_{29}H_{48}O_5$ [M+Na]$^+$ 499.3399 Found: 499.3416. $[\alpha]_D^{25} = +26.5$ (*c* 4.1, $CHCl_3$).

4.1.6. ((4*R*,5*R*)-5-((*R*)-Hexyloxy(phenyl)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol 13a

A solution of compound **11a** (6 g, 100 mmol) in EtOAc (100 mL) containing H_5IO_6 (6.97 g, 200 mmol) was stirred for 2 h at rt and then quenched with solid $NaHCO_3$. The resulting mixture was filtered and concentrated to give aldehyde **12a** (4.65 g, 95%) which was used as such for the next reaction immediately without purification.

To a stirred solution of above aldehyde **12a** (4.65 g, 50 mmol) in dry MeOH (50 mL), $NaBH_4$ (1.04 g, 100 mmol) was added at 0 °C and stirred at room temperature for 2 h. Methanol was evaporated and the residue was dissolved in aqueous NH_4Cl (50 mL) and then extracted with EtOAc (3 × 15 mL). The organic phase was washed with brine solution, dried over Na_2SO_4, concentrated in vacuo and the resulting residue was purified by column chromatography to afford alcohol **13a** (4.21 g, 90% or 86% overall yield for two steps) as a colorless oil. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.90 (t, J = 6.79 Hz, 3H), 1.39 (s, 3H), 1.29–1.40 (m, 9H), 1.54–1.66 (m, 2H), 3.13–3.42 (m, 5H), 3.75 (m, 1H), 4.02 (dd, J = 6.04 and 8.30 Hz, 1H), 4.42 (d, J = 6.04 Hz, 1H), 7.25–7.36 (m, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.9, 22.5, 25.6, 26.6, 27.2, 29.5, 31.5, 62.6, 69.4, 77.5, 80.1, 82.4, 109.2, 127.8, 128.1, 128.2, 137.3, IR (KBr): ν_{max}: 3449, 2925, 2856, 1636, 1215, 760, 704, 669 cm^{-1}. HRMS calcd for $C_{19}H_{30}O_4$ [M+Na]$^+$ 345.2041. Found: 345.2054. $[\alpha]_D^{25} = +43.9$ (*c* 1.65, $CHCl_3$).

4.1.7. ((4*R*,5*R*)-5-((*R*)-Dodecyloxy(phenyl)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol 13b

Compound **13b** was prepared starting from **11b** (86% overall yield for two steps, colorless oil) in the same way as **13a**. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.88 (t, J = 6.61 Hz, 3H), 1.12 (s, 3H), 1.19–1.33 (m, 18H), 1.35 (s, 3H), 1.52–1.61 (m, 2H), 3.09–3.47 (m, 4H), 3.69–3.78 (m, 1H), 4.01 (dd, J = 5.87, 8.08 Hz, 1H), 4.42 (d, J = 5.87 Hz, 1H), 7.25–7.32 (m, 5H), ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.9, 24.3, 25.5, 25.9, 26.6, 27.1, 29.3, 29.3, 29.6, 31.8, 62,5, 69.5, 77.50, 80.1, 82.4, 109.1, 127.2, 127.8, 128.2, 137.3, IR (KBr): ν_{max}: 3404, 2924, 2853, 1458, 756, 698 cm^{-1}. HRMS calcd for $C_{25}H_{42}O_4$ [M+Na]$^+$ 429.2980. Found: 429.2977, $[\alpha]_D^{25} = +31.5$ (c 1.40, $CHCl_3$).

4.1.8. (4*R*,5*S*)-4-((*R*)-Hexyloxy(phenyl)methyl)-5-(iodomethyl)-2,2-dimethyl-1,3-dioxolane 14a

A mixture of **13a** (3.0 g, 50 mmol), triphenyl phosphine (4.8 g, 100 mmol), imidazole (1.57 g, 125 mmol) and iodine (4.71 g, 100 mmol) in DCM (180 mL) was stirred at room temperature for 5 h then cooled to 0 °C, after which excess of iodine was removed by the addition and washing with aqueous $Na_2S_2O_3$ (45 mL). The reaction mixture was extracted with DCM (3 × 15 mL), washed with brine, dried over Na_2SO_4 and concentrated. Purification by column chromatography yielded compound **14a** (3.61 g, 90%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.94 (t, J = 5.90 Hz, 3H), 1.29–1.43 (m, 9H), 1.50 (s, 3H), 1.60–1.68 (m, 2H), 2.67 (dd, J = 5.16, 10.33 Hz, 1H), 2.96 (dd, J = 3.68, 10.33 Hz, 1H), 3.42 (t, J = 5.09 Hz, 3H), 3.55–3.64 (m, 1H), 3.94–4.03 (m, 1H), 4.41 (d, J = 5.90 Hz, 1H), 7.33–7.41 (m, 5H), ^{13}C NMR ($CDCl_3$, 75 MHz): δ 7.3, 14.0, 22.5, 25.7, 27.1, 27.5, 29.6, 31.5, 69.2, 76.1, 82.7, 83.5, 109.6, 127.6, 128.4, 128.5, 137.7, IR (KBr): ν_{max} 3858, 3755, 3448, 2926, 2858, 1740, 760 cm^{-1}. LC–MS: [M+Na]$^+$ 455, $[\alpha]_D^{25} = +53.2$ (*c* 1.75, $CHCl_3$).

4.1.9. (4*R*,5*S*)-4-((*R*)-Dodecyloxy(phenyl)methyl)-5-(iodomethyl)-2,2-dimethyl-1,3-dioxolane 14b

Compound **14b** was prepared starting from **13b** (90%, colorless oil) in the same way as **14a**. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.91 (t, J = 6.79 Hz, 3H), 1.25–1.46 (m, 24H), 1.53–1.66 (m, 2H), 2.62 (dd, J = 5.28, 10.57 Hz, 1H), 2.92 (dd, J = 3.77, 10.57 Hz, 1H), 3.33–3.43 (m, 2H), 3.52–3.58(m, 1H), 3.94 (t, J = 6.79 Hz, 1H), 4.38 (d, J = 6.04 Hz, 1H), 7.28–7.40 (m, 5H), ^{13}C NMR ($CDCl_3$, 75 MHz): δ 7.3, 14.0, 22.6, 26.1, 27.5, 29.5, 31.9, 69.2, 76.1, 82.6, 83.5, 109.6, 127.1, 127.6, 128.4, 137.7, IR (KBr): ν_{max} 3449, 2924, 2856, 2365, 1457, 760, 703 cm^{-1}. HRMS calcd for $C_{25}H_{41}O_3I$ [M+Na]$^+$ 539.1998. Found: 539.2018, $[\alpha]_D^{25} = +33.3$ (*c* 0.90, $CHCl_3$).

4.1.10. (1*R*,2*R*)-2-(Hexyloxy)-1-((*R*)-oxiran-2-yl)-2-phenylethanol 15a

Iodo derivative **14a** (2.5 g, 40 mmol) in ethanol (25 mL) was treated with 1 M HCl (10 mL) at 0 °C and stirred at room temperature for 3 days. After completion of the reaction by TLC, the reaction mixture was basified (pH 10) with solid K_2CO_3 then stirred for 12 h. The reaction mixture was filtered and washed with chloroform (3 × 30 mL). The combined organic layers dried over anhydrous Na_2SO_4 and concentrated. The crude residue was purified by column chromatography on silica gel to furnish pure diol **15a** (1.06 g, 70%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.88 (t, J = 6.61 Hz, 3H), 1.24–1.56 (m, 8H), 2.50–2.54 (m, 2H), 2.70–2.72 (m, 1H), 3.28–3.40 (m, 3H), 3.63–3.67 (m, 1H), 4.25 (d, J = 8.08 Hz, 1H), 7.25–7.36 (m, 5H), ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.9, 22.5, 25.7, 29.6, 31.5, 44.1, 51.5, 69.2, 74.2, 83.5, 127.4, 128.3, 128.5, 138.2, IR (KBr): ν_{max} 3457, 2927, 2862, 1713, 1457, 1097, 759, 703 cm^{-1}, HRMS calcd for $C_{16}H_{24}O_3$ [M+Na]$^+$ 287.1623. Found: 287.1635, $[\alpha]_D^{25} = +28.0$ (*c* 0.25, $CHCl_3$).

4.1.11. (1*R*,2*R*)-2-(Dodecyloxy)-1-((*R*)-oxiran-2-yl)-2-phenylethanol 15b

Compound **15b** was prepared starting from **14b** (70%, colorless oil) in the same way as **15a**. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.89 (t, J = 6.60 Hz, 3H), 1.09–1.43 (m, 18H), 1.49–1.62 (m, 2H), 2.49–2.57 (m, 2H), 2.69–2.72 (m, 2H), 3.28–3.41 (m, 2H), 3.61–3.68 (m, 1H), 4.25 (d, J = 8.80 Hz, 1H), 7.28–7.37 (m, 5H), ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.0, 22.6, 26.1, 29.3, 29.4, 29.5, 29.7, 31.8, 44.5, 51.8, 69.6, 73.8, 77.2, 83.6, 127.2, 128.06, 128.4, 138.7, IR (KBr): ν_{max} 3401, 2927, 2858, 2370, 1716, 1393, 757, 699 cm^{-1}, LC–MS: [M+Na]$^+$ 371, $[\alpha]_D^{25} = -34$ (c 1.0, $CHCl_3$).

4.1.12. (5*R*,6*S*,7*R*)-Ethyl 6-(*tert*-butyldimethylsilyloxy)-7-(hexyloxy)-5-hydroxy-7-phenylhept-2-ynoate 17a

To a solution of epoxy alcohol **15a** (1.0 g, 25 mmol), and imidazole (0.77 g, 75 mmol) in dry DCM (30 mL) at room temperature was added TBDMSCl (0.82 g, 37.5 mmol) in small portions and then DMAP (23 mg, 1.25 mmol). The mixture was stirred for 5 h, poured into a dilute solution of $NaHCO_3$ and extracted with DCM (3 × 10 mL). The organic phase was washed with brine, dried (Na_2SO_4) and concentrated followed by column chromatography to give protected epoxide **16a** (1.28 g, 90%) as a colorless oil.

To a stirred solution of the ethyl propiolate **16a** (0.26 gm, 24 mmol) in dry THF (20 mL), *n*-BuLi (0.20 g, 24 mmol) and $BF_3.OEt_2$ (0.44 g, 24 mmol) was added at −78 °C and stirred for 30 min at the same temperature. Next the protected epoxide (1.0 g, 20 mmol) in dry THF was added to the reaction mixture and stirred for 2 h at −78 °C. The reaction mixture was quenched with aqueous NH_4Cl solution (30 mL) and extracted with EtOAc (3 × 25 mL). The organic layer was washed with brine, dried (Na_2SO_4), evaporated and the residue obtained was purified by column chromatography to afford alcohol **17a** (1.0 g, 80% or 71% overall yield for two steps) as a colorless oil. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.18 (s, 3H), 0.20 (s, 3H), 0.90 (t, J = 6.61 Hz, 3H), 0.94 (s, 9H), 1.20–1.38 (m, 11H), 2.37–2.41 (m, 2H), 3.17–3.28 (m, 2H), 3.89 (d, J = 8.08 Hz, 1H), 4.04–4.25 (m, 5H), 7.28–7.34 (m, 5H), ^{13}C NMR ($CDCl_3$, 75 MHz): δ −3.8, −4.8, 13.9, 18.5, 25.1, 25.7, 26.1, 29.6, 31.5, 68.8, 68.8, 74.7, 76.7, 84.0, 85.4, 127.8, 128.1, 128.5, 138.9, 153.4, IR (KBr): ν_{max} 3529, 2929, 2857, 2235, 1714, 1252, 1069, 758, 702 cm^{-1}, HRMS calcd for $C_{27}H_{44}O_5Si$ [M+Na]$^+$ 499.2855. Found: 499.2850, $[\alpha]_D^{25} = +71.0$ (c 1.0, $CHCl_3$).

4.1.13. (5*R*,6*S*,7*R*)-Ethyl 6-(*tert*-butyldimethylsilyloxy)-7-(dodecyloxy)-5-hydroxy-7-phenylhept-2-ynoate 17b

Compound **17b** was prepared starting from **15b** same as **16a** followed by **17a** (71% overall yield for two steps, colorless oil). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.16 (s, 3H), 0.20 (s, 3H), 0.88 (t, J = 6.79 Hz, 3H), 0.93 (s, 9H), 1.24–1.30 (m, 20H), 1.32 (t, J = 6.79 Hz, 3H), 2.35–2.41 (m, 2H), 3.10–3.30 (m, 3H), 3.87 (d, J = 7.54 Hz, 1H), 4.08–4.26 (m, 3H), 7.25–7.35 (m, 5H), ^{13}C NMR ($CDCl_3$, 75 MHz): δ −3.8, −4.8, 13.9, 14.0, 18.5, 22.6, 25.1, 26.0, 26.3, 29.5, 29.6, 31.9, 61.7, 68.7, 68.8, 74.6, 77.4, 84.0, 85.4, 127.8, 128.1 (2C), 128.5, 138.9, 153.4, IR (KBr): ν_{max} 3401, 2927, 2858, 2235, 1713, 1636, 1391, 1252, 1072, 758, 701 cm^{-1}. HRMS calcd for $C_{33}H_{56}O_5Si$ [M+Na]$^+$ 583.3794. Found: 583.3792, $[\alpha]_D^{25} = +54.10$ (c 1.0, $CHCl_3$).

4.1.14. (*R*)-6-((1*S*,2*R*)-2-(Hexyloxy)-1-hydroxy-2-phenylethyl)-5,6-dihydro-2*H*-pyran-2-one 3

A mixture of **17a** (0.50 g, 6.4 mmol) in EtOAc (10 mL) containing 10% Lindlar catalyst (30 mg) was stirred under a hydrogen atmosphere for 1 h at room temperature. Aqueous 1 M HCl (0.5 ml) solution was added to the reaction mixture and stirring continued for 2 h at room temperature. The reaction mixture was quenched with $NaHCO_3$, filtered through Celite pad, washed with EtOAc (15 mL) and concentrated. The residue was purified by silica gel column chromatography to afford pure saturated compound **3** (0.190 g, 60%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.87 (t, J = 6.25 Hz, 3H), 1.16–1.41 (m, 6H), 1.48–1.68 (m, 2H), 2.09 (ddd, J = 3.90, 6.25, 18.75 Hz, 1H), 2.82–3.04 (m, 1H), 3.26 (br m, –OH, 1H), 3.36 (t, J = 7.03 Hz, 2H), 3.64 (d, J = 8.59 Hz, 1H), 3.99 (dd, J = 2.34, 12.50 Hz, 1H), 4.64 (d, J = 8.59 Hz, 1H), 5.95 (dd, J = 1.56, 9.37 Hz, 1H), 6.82 (ddd, J = 3.90, 7.03, 14.84 Hz, 1H), 7.30–7.55 (m, 5H), ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.9, 22.5, 25.7, 25.8, 29.6, 31.5, 69.2, 75.5, 75.9, 81.6, 120.7, 127.6, 128.4 (2C), 128.6, 137.9, 145.6, 163.8, IR (KBr): ν_{max} 3455, 2926, 2856, 1731, 1250, 1095, 703, 633 cm^{-1}, HRMS calcd for $C_{12}H_{26}O_4$ [M+Na]$^+$ 341.1728. Found: 341.1739, $[\alpha]_D^{25} = -0.8$ (c 0.50, $CHCl_3$).

4.1.15. (*R*)-6-((1*S*,2*R*)-2-(Dodecyloxy)-1-hydroxy-2-phenylethyl)-5,6-dihydro-2*H*-pyran-2-one 4

Compound **4** was prepared starting from **17b** (60%, colorless oil) in the same way as **4**. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.88 (t, J = 6.79 Hz, 3H), 1.21–1.33 (m, 18H), 1.51–1.60 (m, 2H), 2.09 (ddd, J = 3.37, 5.28, 18.12 Hz, 1H), 2.87–3.30 (m, 1H), 3.34 (t, J = 6.79 Hz, 2H), 3.62 (d, J = 9.06 Hz, 1H), 3.99 (dd, J = 2.26, 12.08 Hz, 1H), 4.65 (d, J = 8.30 Hz, 1H), 5.96 (dd, J = 1.51, 9.82 Hz, 1H), 6.86 (ddd, J = 1.15, 6.79, 14.35 Hz, 1H), 7.30–7.43 (m, 5H), ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.0, 22.6, 25.8, 26.1, 29.3, 29.6, 31.9, 69.2, 75.5, 75.9, 81.6, 120.8, 127.7, 128.4, 128.6, 138.0, 145.6, 163.8, IR (KBr): ν_{max} 3450, 2925, 2854, 1734, 816, 760, 701 cm^{-1}, HRMS calcd for $C_{25}H_{38}O_4$ [M+Na]$^+$ 425.2667. Found: 425.2655, $[\alpha]_D^{25} = -3.50$ (c 1.0, $CHCl_3$).

4.1.16. Phenyl((4*R*,4′*R*,5*S*)-2,2,2′,2′-tetramethyl-4,4′-bi(1,3-dioxolan)-5-yl)-methanone 18

To a stirred solution of IBX (5.11 g, 200 mmol) in DMSO (15 ml) at 25 °C was added dropwise a solution of **10** and **10a** (6.0 g, 180 mmol) in THF (60 ml). The resulting mixture was stirred at 25 °C for 2 h. Solid was filtered and washed with ether. The filtrate was extracted with ether, washed with water, brine and dried over Na_2SO_4. Concentrated under reduced pressure and purification by silica gel chromatography afforded compound **18** (5.42 g, 91%) as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.29, 1.32, 1.37, 1.48 (4s, 12H), 3.97 (dd, J = 4.53 and 8.30, 1H), 4.10–4.21 (m, 2H), 4.63–4.68 (m, 1H), 5.12 (d, J = 4.53 Hz, 1H), 7.48 (t, J = 7.55 Hz, 2H), 7.55–7.60 (m, 1H), 8.10(d, J = 6.79 Hz, 1H) ^{13}C NMR ($CDCl_3$, 75 MHz): δ 24.7, 25.9, 26.0, 27.0, 66.6, 76.1, 77.4, 79.4, 79.4, 127.9, 128.9, 132.9, 196.0 IR (KBr): ν_{max} 2990, 2874, 1720, 1376, 1153, 1070, 843, 702 cm^{-1}. HRMS calcd for $C_{17}H_{22}O_5$ [M+Na]$^+$ 329.1521. Found: 329.1512, $[\alpha]_D^{25} = +11.6$ (c 0.8, $CHCl_3$).

4.1.17. (*S*)-Phenyl((4*R*,4′*R*,5*R*)-2,2,2′,2′-tetramethyl-4,4′-bi(1,3-dioxolan)-5-yl)methanol 19

To a stirred solution of compound **18** (4.5 g, 100 mmol) in dry MeOH (45 L) was added $CeCl_3{\cdot}7H_2O$ (6.3 g, 120 mmol) and the solution was stirred for 15 min. Next $NaBH_4$ was then added portion wise over a period of 1 h and stirred at the same temperature for 1.5 h. The reaction mixture was cautiously quenched with water (60 mL) and extracted with EtOAc (3 × 50 mL). The organic phase was washed with brine solution, dried over Na_2SO_4, evaporated and the residue obtained was purified by column chromatography afforded the required alcohol **19** (3.67 g, 86%) predominantly (dr 95:5) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.34, 1.37, 1.40, 1.47 (4s, 12H), 3.84–4.23 (m, 5H), 4.70 (d, J = 6.79 Hz, 1H), 7.27–7.43 (m, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 25.1, 26.2, 27.1, 27.3, 67.2, 72.7, 76.6, 77.6, 83.2, 109.6, 109.9, 126.6, 127.7, 128.1, 140.6. IR (KBr): ν_{max} 3438, 2990, 2874, 1376, 1153, 1070, 843, 702 cm^{-1}. HRMS calcd for $C_{17}H_{24}O_5$ [M+Na]$^+$ 331.1521. Found: 331.1512, $[\alpha]_D^{25} = +15.7$ (c 1.0, $CHCl_3$).

4.1.18. (4*R*,4′*R*,5*R*)-5-((*S*)-Methoxy(phenyl)methyl)-2,2,2′,2′-tetramethyl-4,4′-bi(1,3-dioxolane) 20

To a well stirred suspension of NaH (1.40 g, 300 mmol, 60% w/v dispersion in mineral oil) in anhydrous THF (100 mL), a solution of alcohol **19** (5.0 g, 150 mmol) in dry THF (20 mL) was added dropwise at 0 °C. After 30 min, methyliodide (4.6 g, 300 mmol) was added dropwise at same temperature. The resulting mixture was further stirred for 2 h at room temperature. After completion of the reaction, a few ice pieces and water were added. The aqueous layer was extracted with EtOAc (3 × 50 mL) and the organic phase was washed with brine, dried (Na_2SO_4), concentrated and the residue was purified on column chromatography to afford the compound **20** (5.0 g, 96%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.41, 1.37, 1.34, 1.32 (4s, 12H), 3.26 (s, 3H), 3.71–4.03 (m, 5H), 4.22 (d, J = 3.67 Hz, 1H), 7.38–7.30 (m, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 25.1, 26.3, 26.5, 27.2, 56.4, 72.3, 75.4, 76.6, 82.5, 83.4, 109.0, 110.0, 126.0, 127.7, 128.5, 138.5. IR (KBr): ν_{max} 2987, 1456, 1372, 1214, 1076, 848, 706 cm^{-1}. HRMS calcd for $C_{18}H_{26}O_5$ [M+Na]$^+$ 345.1676. Found: 345.1669. $[\alpha]_D^{25} = +59.6$ (c 0.5, $CHCl_3$).

4.1.19. ((4*R*,5*R*)-5-((*S*)-Methoxy(phenyl)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol 21

Compound **21** was prepared starting from **20** (86% overall yield for two steps, colorless oil) in the same way as **13a**. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.22 (s,3H), 1.32 (s, 3H), 2.82 (m, 1H), 3.08 (dd, J = 3.02, 370 Hz, 1H), 3.30 (s, 3H), 3.70 (m, 1H), 4.05 (dd, J = 6.7, 8.3 Hz, 1H), 4.25 (d, J = 6.7 Hz, 1H), 7.25–7.36 (m, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 26.0, 29.0, 56.0, 62.0, 78.0, 79.0, 85.0, 109.0, 127.0, 128.0, 136.0. IR (KBr): ν_{max} 3462, 2987, 1455, 1375, 1097, 860, 705 cm^{-1}. HRMS calcd for $C_{14}H_{20}O_4$ [M+Na]$^+$ 275.1259. Found: 175.1250. $[\alpha]_D^{25} = +55.9$ (c 2.1, $CHCl_3$).

4.1.20. (4*S*,5*R*)-4-(Iodomethyl)-5-((*S*)-methoxy(phenyl)methyl)-2,2-dimethyl-1,3-dioxolane 22

Compound **22** was prepared starting from **21** (90%, colorless oil) in the same way as **14a**. ^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.33 (s, 3H), 1.46 (s, 3H), 2.37 (dd, J = 5.46, 10.93 Hz, 1H), 2.71(dd, J = 3.12, 10.15 Hz, 1H), 3.27 (s, 3H), 3.42–3.54 (m, 1H), 3.93(t, J = 7.03 Hz, 1H), 4.23 (d, J = 6.25 Hz, 1H), 4.23 (d, J = 6.25 Hz, 1H), 7.25–7.46 (m, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 6.9, 27.1, 27.3, 56.5, 76.1, 83.4, 85.0, 109.4, 127.5, 128.6, 128.9, 136.4. IR (KBr): ν_{max} 2987, 1455, 1375, 1097, 860, 705, 520 cm^{-1}. (LC–MS): m/z 401 [M+Na]$^+$. $[\alpha]_D^{25} = +63.1$ (c 1.0, $CHCl_3$).

4.1.21. (1*R*,2*S*)-2-Methoxy-1-((*R*)-oxiran-2-yl)-2-phenylethanol 23

Compound **23** was prepared starting from **22** (70%, colorless oil) same as **15a**. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.45–2.52 (m, 2H), 2.70 (dd, J = 3.0, 3.7 Hz, 1H), 3.25 (s, 3H), 3.62 (dd, J = 2.2, 7.5 Hz, 1H), 4.13 (d, J = 7.5 Hz, 1H), 7.30 (m, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 45.0, 52.0, 57.0, 75.0, 86.0, 127.0, 128.0, 129.0, 138.0. IR (KBr): ν_{max} 3424, 2927, 1724, 1453, 1102, 760, 701 cm^{-1}. HRMS calcd for $C_{11}H_{14}O_3$ [M+Na]$^+$ 217.0840. Found: 217.0843, $[\alpha]_D^{25} = +36.9$ (c 2.9, $CHCl_3$).

4.1.22. (5*R*,6*S*,7*S*)-Ethyl-6-(*tert*-butyldimethylsilyloxy)-5-hydroxy-7-methoxy-7-phenylhept-2-ynoate 24

Compound **24** was prepared starting from **23** (71% overall yield for two steps, colorless oil) in the same way as **17a**. ^{1}H NMR ($CDCl_3$, 300 MHz) : δ 0.16 (s, 3H), 0.18 (s, 3H), 0.94 (s, 9 H), 1.29 (t, J = 7.0 Hz, 3H), 2.40 (dd, J = 3.2, 6.4 Hz, 2H), 3.13 (s, 3H), 3.23 (m, 1H), 3.86 (d, J = 7.6 Hz, 1H), 4.11 (d, J = 7.8 Hz, 1H), 4.18 (q, J = 7.0 Hz, 2H), 7.26–7.45 (m, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ -4.9, -3.7, 14.0, 25.1, 26.2, 29.7, 56.3, 61.8, 68.7, 76.6, 85.3, 85.8, 127.8, 128.3, 128.6, 138.1, 150.4. IR (KBr): ν_{max} 3423, 3300, 2927, 1742, 1458, 1105, 760 cm^{-1}. MASS (LC–MS): m/z 429 [M+Na]$^+$, $[\alpha]_D^{25} = +60.5$ (c 1.4, $CHCl_3$).

4.1.23. (*R*)-6-((1*S*,2*S*)-1-Hydroxy-2-methoxy-2-phenylethyl)-5,6-dihydro-2*H*-pyran-2-one 5

Compound **5** was prepared starting from **24** (60%, colorless oil) in the same way as **4**. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.07 (ddd, J = 4.1, 6.35, 18.5 Hz, 1H), 2.94 (ddd, J = 2.4, 13.0, 18.5 Hz, 1H), 3.26 (s, 3H), 3.54 (d, J = 8.2 Hz, 1H), 3.94 (ddd, J = 3.7, 12.5, 17.5 Hz, 1H), 4.52 (d, J = 8.4 Hz, 1H), 5.93 (dd, J = 3.2, 10.4 Hz, 1H), 6.84 (ddd, J = 2.4, 6.2, 9.4 Hz, 1H), 7.30–7.39 (m, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 25.4, 56.5, 61.7, 75.5, 75.7, 83.4, 120.7, 127.7, 128.6, 128.7, 137.3, 145.7, 163.8. IR (KBr): ν_{max} 3441, 2909, 1719, 1380, 1109, 1057, 757 cm^{-1}. HRMS calcd for $C_{14}H_{16}O_4$ [M+Na]$^+$ 271.0946. Found: 271.0945, $[\alpha]_D^{25} = +23.4$ (c 0.35, $CHCl_3$).

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