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Titanocene(III) mediated radical cyclizations of epoxides for the synthesis of medium-sized cyclic ethers

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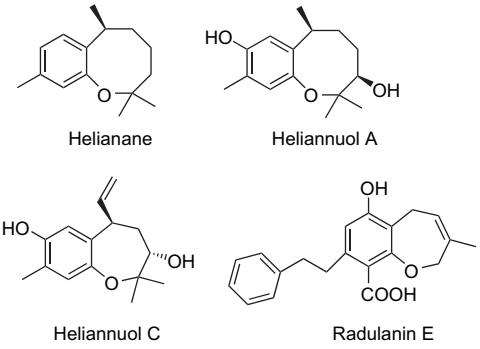
Abstract—Titanocene(III) chloride (Cp_2TiCl) mediated 7-*exo* and 8-*endo* radical cyclizations of epoxides towards the synthesis of 7- and 8-membered cyclic ethers have been described. Titanocene(III) chloride was prepared in situ from commercially available titanocene dichloride (Cp_2TiCl_2) and activated zinc dust in THF.

1. Introduction

The synthesis of medium and large-sized ring ethers especially those annulated with aromatic moieties such as benzo[*b*]oxocines and benzo[*b*]oxepines is of much current interest due to their presence in a number of bioactive natural products, e.g., helianane, heliannuols, radulanin-E, etc.[1] Although several methodologies including ring-closing metathesis have been developed for constructing medium-sized rings,[2] general methods for the synthesis of these systems selectively, atom economically and under mild reaction conditions are still scarce. The use of radical chemistry in organic synthesis witnessed a renaissance in recent years due to the approached mildness, high functional group tolerance and predictable behaviour in many organic transformations.[3] Although tin hydride mediated radical reactions have been used for the synthesis of medium-sized oxacyclic ring systems on several occasions,[2] its limitations in the substrate control on the course of the reaction and other reasons have led to an alternative method based on reagent control cyclization using titanocene(III) chloride (Cp_2TiCl) being established by Rajanbabu and Nugent.[4] Epoxides are an attractive class of radical precursors in organic synthesis due to their ready availability and predictable stereochemistry. Reductive opening of epoxides at room temperature with high regioselectivity mediated by titanocene(III) chloride as radical initiator have been employed in carbon–carbon bond formation reactions.[4,5] As a part of our activities[6] in titanocene(III) chloride mediated radical reactions, we report here in detail[7] towards the synthesis of medium-sized cyclic ethers by 7-*exo* and *8-endo* radical cyclization reactions.



2. Results and discussion

The synthesis of 8-membered cyclic ether **4a** has been accomplished through 8-*endo-dig* cyclization mediated by titanocene(III) chloride using 2-allyl phenol **1a** as the starting material (Scheme 1). 2-Allyl phenol **1a** on treatment with propargyl bromide and K_2CO_3 in acetone afforded the propargyl ether **2a**, which on epoxidation with *m*-CPBA in dichloromethane furnished **3a** in excellent yield. The epoxy ether **3a** treated with Cp_2TiCl in THF under argon afforded the 8-membered cyclic ether **4a** in moderate yield along with the reduced product **5a** (12%) and another unidentified product (18%, w/w). Similarly, the cyclic ethers **4b–d** were synthesized in moderate yield from the allyl phenols **1b—d**, respectively, following the same sequence along with the reduced product **5b–d** (9–10%) and another unidentified product (18–20%, w/w). It is noteworthy that

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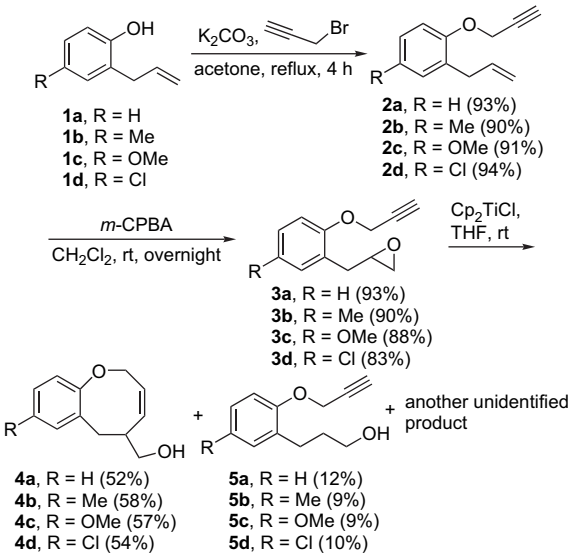
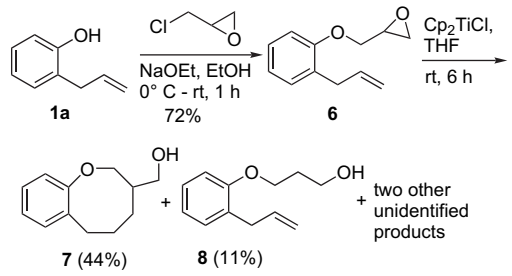


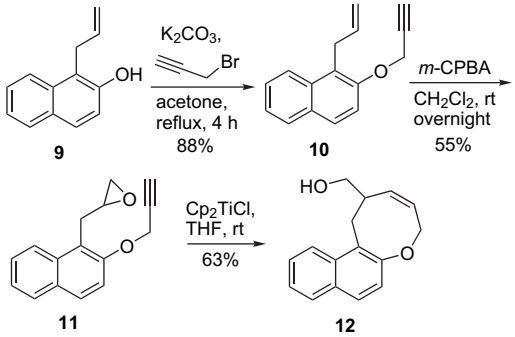
Scheme 1.

no 7-membered cyclic ethers were formed in any case by 7-*endo-dig* radical cyclizations. In another investigation, 2-allyl phenol **1a** was transformed into the epoxide **6** in a single-step using epichlorohydrin (Scheme 2). Reductive opening of the epoxide **6** using Cp_2TiCl in THF under argon afforded the 8-membered ether **7** (44%) along with the reduced product **8** (11%) and two other unidentified products (25%).

The 8-*endo* radical cyclization was further extended for the synthesis of naphthyl annulated cyclic ether **12** starting from the 1-allyl-2-naphthol **9** in a similar manner (Scheme 3). The



Scheme 2.



Scheme 3.

radical cyclization of the epoxide **11** yielded the cyclized product **12** along with a trace amount of reduced product, but pure cyclized compound **12** could easily be isolated in 63% yield by column chromatography over silica gel.

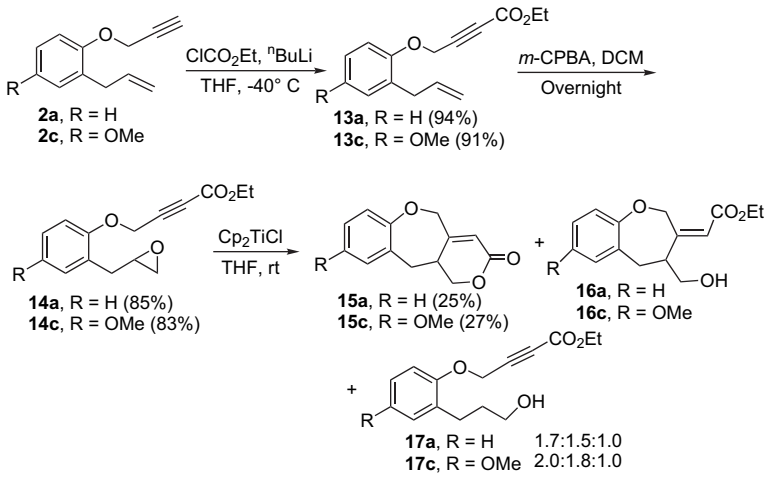
After successful synthesis of 8-membered cyclic ethers the radical methodology was applied to the preparation of 7-membered cyclic ethers. Since 8-*endo* cyclization was much favoured compared to 7-*exo* as we observed earlier, a radical stabilizing group,[8,9] namely, carbethoxy moiety was incorporated at the terminus of the acetylene moiety in **2a** forcing the cyclization to follow the 7-*exo* mode. Thus, compound **13a** was prepared from **2a** using ethyl chloroformate and *n*-BuLi. The epoxide **14a** was prepared from **13a** by epoxidation with *m*-CPBA (Scheme 4). Treatment of the epoxide **14a** in the presence of Cp_2TiCl in THF afforded a mixture of three compounds in a ratio of 1.7:1.5:1. The lactone **15a** was separated by preparative TLC in 25% yield but the other two compounds could not be separated by usual chromatographic methods. But from the ^1H NMR of the crude mixture left after preparative TLC, we could determine that it was a mixture of *trans*-ester **16a** and the reduced product **17a**. Similarly, **13c** was prepared from **2c**, which on epoxidation with *m*-CPBA afforded the epoxide **14c**. Radical cyclization of **14c** by Cp_2TiCl afforded a mixture of three compounds in a ratio of 2:1.8:1. The lactone **15c** was separated by preparative TLC in 27% yield. The other two compounds (a mixture of **16c** and **17c**) could not be separated by usual chromatographic methods.

On the other hand, the epoxide **19a**, prepared from the ester **18a**, on radical cyclization reaction with Cp_2TiCl in THF afforded a mixture of lactones **20a** and **21a** in a ratio of 2:3 (Scheme 5). The lactones were formed by 7-*exo-trig* radical cyclization[10] followed by in situ lactonization. The lactones **20a** and **21a** were separated by preparative TLC in 26% and 39% yields, respectively, as crystalline solids.

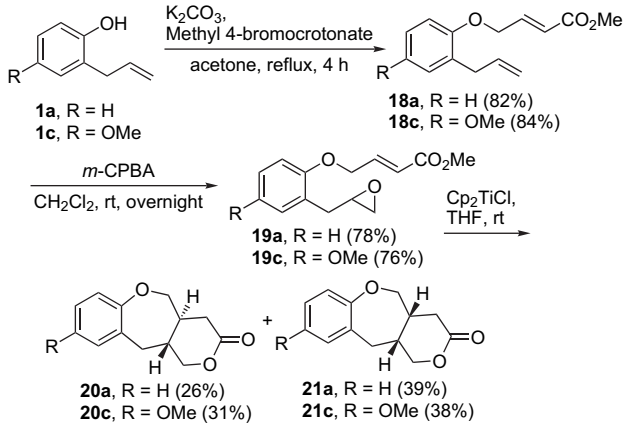
Similarly, lactones **20c** and **21c** were also synthesized by radical cyclization of the epoxide **19c** following the same reaction sequences in 31% and 38% yield, respectively, (Scheme 5). The absolute stereochemistry of the lactone **21a** was finally confirmed by single crystal X-ray analysis (Fig. 1, CCDC No. 646191).

The lactone **15a** under catalytic hydrogenation over Pd on C afforded the mixture of **20a** and **21a** in a ratio of 1:1. To prove the *E* stereochemistry of the ethyl ester around the double bond in **16c** or in **16a**, the inseparable probable mixture of **16c** and **17c** was subjected to catalytic hydrogenation over Pd on C and the crude product was column chromatographed over silica gel to afford the lactones **20c** and **21c** in 24% yield in a ratio of 1:9. All the new products were characterized thoroughly by IR, NMR and HRMS studies.

In summary, a detail study has been performed for the synthesis of 7- and 8-membered cyclic ethers by radical cyclizations of epoxides using titanocene(III) chloride as the radical source. The aromatic annulated medium-sized oxacyclic rings are important core structures of many naturally occurring bioactive compounds.



Scheme 4.



Scheme 5.

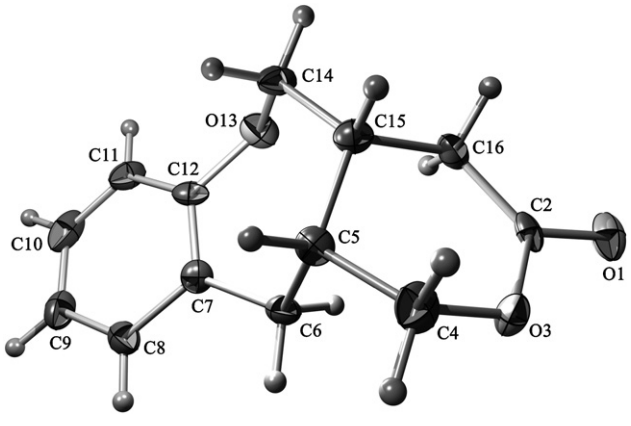


Figure 1. ORTEP diagram of **21a**.

3. Experimental section

3.1. General

The compounds described are all racemates. Melting points were determined in open capillary tubes and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ with Bruker DPX 300 spectrometer using tetramethyl silane as the internal standard. IR spectra were recorded on Shimadzu FTIR-8300. Column chromatography was performed on silica gel (60–120 mesh) and preparative TLC was performed using pre-coated silica 60 F 254 plates (0.2 mm). High-resolution mass spectra were obtained using a Qtof Micro YA263 instrument. Diethyl ether and tetrahydrofuran were freshly distilled from sodium. Methylene chloride was freshly distilled over calcium hydride. Light petroleum of boiling range 60–80 °C was used for chromatography.

3.1.1. 1-Allyl-2-prop-2-ynyloxy-benzene (2a). A mixture of 2-allyl phenol **1a** (670 mg, 5 mmol), K_2CO_3 (1.38 g, 10 mmol) and propargyl bromide (655 mg, 5.5 mmol) in dry acetone (30 mL) was heated to reflux under nitrogen for 4 h. After completion of the reaction (monitored by TLC), the mixture was cooled to room temperature. Most of the acetone was removed under reduced pressure and water (20 mL) was added to the residue. It was extracted with diethyl ether (3×100 mL). The combined organic extract was successively washed with water (1×10 mL), brine (1×10 mL) and finally dried (Na_2SO_4). After removal of the solvent under reduced pressure the residue obtained was purified by column chromatography over silica (5% ethyl acetate in light petroleum) to furnish **2a** (800 mg, 93%) as a viscous yellowish oil. R_f=0.60; IR (neat): 3294, 3076, 2912, 2117, 1490, 1220, 1028, 752 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.46 (t, J=2.3 Hz, 1H), 3.39 (d, J=6.5 Hz, 2H), 4.67 (d, J=2.3 Hz, 2H), 5.02–5.08 (m, 2H), 5.91–6.05 (m, 1H), 6.89–6.96 (m, 2H), 7.14–7.21 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 34.1, 55.9, 75.1, 78.8, 111.9, 115.4, 121.4, 127.1, 129.1, 129.9, 136.7, 155.2; HRMS calcd for $C_{12}H_{13}O$ 173.0966 $[M+H]^+$, found 173.0969.

3.1.2. 2-Allyl-4-methyl-1-prop-2-ynyloxy-benzene (2b). Compound **2b** was prepared from **1b** (740 mg, 5 mmol) as a colourless oil (837 mg, 90%) following the same procedure described for **2a**. R_f=0.58 (5% ethyl acetate in light petroleum); IR (neat) 3300, 3008, 2920, 2117, 1500, 1217, 1031, 758 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.26 (s, 3H), 2.45 (t, J=2.3 Hz, 1H), 3.36 (d, J=6.6 Hz, 2H), 4.64 (d, J=2.3 Hz, 2H), 5.01–5.08 (m, 2H), 5.91–6.04 (m, 1H), 6.84 (d, J=8.5 Hz, 1H), 6.93–6.96 (m, 2H); ^{13}C NMR

($CDCl_3$, 75 MHz): δ 20.4, 34.1, 56.1, 74.9, 79.0, 112.2, 115.3, 127.3, 129.0, 130.6, 130.7, 136.9, 153.1; HRMS calcd for $C_{13}H_{15}O$ 187.1123 $[M+H]^+$, found 187.1125.

3.1.3. 2-Allyl-4-methoxy-1-prop-2-ynyloxy-benzene (2c). Compound **2c** was prepared from **1c** (820 mg, 5 mmol) as a viscous oil (919 mg, 91%) following the same procedure described for **2a**. R_f=0.60 (5% ethyl acetate in light petroleum); IR (neat) 3290, 2937, 2833, 2117, 1496, 1213, 1045 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.50 (t, J=2.4 Hz, 1H), 3.41 (d, J=6.6 Hz, 2H), 3.77 (s, 3H), 4.66 (d, J=2.4 Hz, 2H), 5.06–5.13 (m, 2H), 5.93–6.06 (m, 1H), 6.71–6.77 (m, 2H), 6.93 (d, J=8.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 34.3, 55.5, 57.0, 75.0, 79.1, 111.3, 113.9, 115.7, 116.0, 130.8, 136.5, 149.5, 154.3; HRMS calcd for $C_{13}H_{15}O_2$ 203.1067 $[M+H]^+$, found 203.1059.

3.1.4. 2-Allyl-4-chloro-1-prop-2-ynyloxy-benzene (2d). Compound **2d** was prepared from **1d** (900 mg, 5.34 mmol) as a viscous oil (1.04 g, 94%) following the same procedure described for **2a**. R_f=0.62 (5% ethyl acetate in light petroleum); IR (neat) 3298, 3078, 2914, 2117, 1488, 1224, 1028 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.51 (t, J=2.4 Hz, 1H), 3.37 (d, J=6.6 Hz, 2H), 4.69 (d, J=2.4 Hz, 2H), 5.05–5.12 (m, 2H), 5.89–6.02 (m, 1H), 6.89 (d, J=7.4 Hz, 1H), 7.14–7.17 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 33.9, 56.3, 75.6, 78.4, 113.2, 116.3, 126.4, 126.8, 129.8, 131.2, 135.8, 153.8; HRMS calcd for $C_{12}H_{11}ClONa$ 229.0395 $[M+Na]^+$, found 229.0393.

3.1.5. 1-Allyl-2-prop-2-ynyloxy-naphthalene (10). Compound **10** was prepared from **9** (920 mg, 5 mmol) as a viscous oil (977 mg, 88%) following the same procedure described for **2a**. R_f=0.55 (5% ethyl acetate in light petroleum); IR (neat) 3292, 3066, 2117, 1595, 1218 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.48 (t, J=2.4 Hz, 1H), 3.88 (d, J=5.7 Hz, 2H), 4.81 (d, J=2.11 Hz, 2H), 4.96–5.03 (m, 2H), 6.00–6.11 (m, 1H), 7.31–7.38 (m, 2H), 7.48 (dt, J=6.9, 1.2 Hz, 1H), 7.73–7.81 (m, 2H), 7.95 (d, J=8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 29.3, 57.5, 75.4, 79.1, 115.2, 115.4, 122.6, 123.8 (2C), 126.4, 128.0, 128.5, 129.9, 133.2, 136.7, 152.6; HRMS calcd for $C_{16}H_{15}O$ 223.1123 $[M+H]^+$, found 223.1121.

3.1.6. 4-(2-Allyl-phenoxy)-but-2-enoic acid methyl ester (18a). Compound **18a** was prepared from **1a** (670 mg, 5 mmol) and methyl 4-bromo-crotonate (85%) (1.05 g, 5 mmol) as a viscous oil (951 mg, 82%) following the same procedure described for **2a**. R_f=0.58 (5% ethyl acetate in light petroleum); IR (neat) 3074, 1726, 1492, 1307, 1242 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 3.47 (d, J=6.6 Hz, 2H), 3.79 (s, 3H), 4.70 (dd, J=2.1, 3.8 Hz, 2H), 5.07–5.13 (m, 2H), 5.97–6.12 (m, 1H), 6.26 (dt, J=2.1, 15.7 Hz, 1H), 6.81 (d, J=7.9 Hz, 1H), 6.96 (td, J=0.8, 7.5 Hz, 1H), 7.10–7.22 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 34.3, 51.6, 66.4, 111.4, 115.5, 121.1, 121.2, 127.3, 128.9, 130.1, 136.7, 143.1, 155.6, 166.6; HRMS calcd for $C_{14}H_{16}O_3Na$ 255.0997 $[M+Na]^+$, found 255.0989.

3.1.7. 4-(2-Allyl-4-methoxy-phenoxy)-but-2-enoic acid methyl ester (18c). Compound **18c** was prepared from **1c** (820 mg, 5 mmol) and methyl 4-bromo-crotonate (85%) (1.05 g, 5 mmol) as a viscous oil (1.1 g, 84%) following the same procedure described for **2a**. Colourless oil (yield: 84%). R_f=0.57 (5% ethyl acetate in light petroleum); IR (neat) 2950, 1726, 1498, 1224, 1041 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 3.50 (d, J=6.5 Hz, 2H), 3.85 (s, 3H), 3.86 (s, 3H), 4.74 (dd, J=2.0, 3.7 Hz, 2H), 5.15–5.21 (m, 2H), 6.01–6.13 (m, 1H), 6.31 (td, J=2.0, 15.7 Hz, 1H), 6.76–6.85 (m, 3H), 7.19 (td, J=3.7, 15.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 34.6, 51.8, 55.7, 67.5, 111.5, 112.9, 116.0, 116.4, 121.2, 130.5, 136.6, 143.4, 150.0, 154.2, 166.8; HRMS calcd for $C_{15}H_{18}O_4Na$ 285.1103 $[M+Na]^+$, found 285.1101.

3.1.8. 4-(2-Allyl-phenoxy)-but-2-ynoic acid ethyl ester (13a). To a magnetically stirred solution of aryl propargyl ether **2a** (860 mg, 5 mmol) in THF (30 mL) a solution of n-BuLi (1.1 M in hexane) was added dropwise at -40 °C over a period of 30 min under argon. The reaction mixture was allowed to stir for another 30 min and then ethyl chloroformate (650 mg, 6 mmol) was added dropwise to it. After stirring for 1 h the reaction mixture was quenched with few drops of water. The solvent was removed under reduced pressure and the residue obtained was extracted with diethyl ether (3×100 mL). The combined organic layer was successively washed with water (1×10 mL), brine (1×10 mL) and finally dried (Na_2SO_4). After removal of the solvent under reduced pressure the crude mass was purified by column chromatography over silica (7% ethyl acetate in light petroleum) to furnish **13a** (1.15 g, 94%) as a colourless oil. R_f=0.68; IR (neat) 2981, 2908, 1716, 1490, 1253, 1024, 750 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.18 (t, J=7.1 Hz, 3H), 3.30 (d, J=6.6 Hz, 2H), 4.11 (q, J=7.1 Hz, 2H), 4.69 (s, 2H), 4.93–4.99 (m, 2H), 5.81–5.92 (m, 1H), 6.79–6.89 (m, 2H), 7.05–7.13 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.8, 34.0, 55.6, 62.1, 78.3, 81.9, 111.8, 115.5, 121.8, 127.2, 129.2, 130.0, 136.5, 152.8, 154.9; HRMS calcd for $C_{15}H_{17}O_3$ 245.1172 $[M+H]^+$, found 245.1171.

3.1.9. 4-(2-Allyl-4-methoxy-phenoxy)-but-2-ynoic acid ethyl ester (13c). Compound **13c** was prepared from **2c** (1.01 g, 5 mmol) as a colourless oil (1.25 g, 91%) following the same procedure described in **13a**. R_f=0.63 (7% ethyl acetate in light petroleum); IR (neat): 2981, 1716, 1498, 1253, 1024, 750 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.30 (t, J=7.1 Hz, 3H), 3.38 (d, J=6.6 Hz, 2H), 3.75 (s, 3H), 4.23 (q, J=7.1 Hz, 2H), 4.75 (s, 2H), 5.04–5.10 (m, 2H), 5.90–6.03 (m, 1H), 6.69–6.75 (m, 2H), 6.88 (d, J=8.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.9, 34.2, 55.5, 56.9, 62.1, 78.3, 82.3, 111.4, 114.0, 115.8, 116.1, 130.9, 136.4, 149.3, 152.9, 154.6; HRMS calcd for $C_{16}H_{19}O_4$ 275.1283 $[M+H]^+$, found 275.1281.

3.1.10. 2-(2-Prop-2-ynyloxy-benzyl)-oxirane (3a). A mixture of ether **2a** (688 mg, 4 mmol) and m-CPBA (1.5 g, 4.8 mmol, 55% dispersion) in dichloromethane (20 mL) was stirred overnight at room temperature. Aqueous saturated Na_2SO_3 solution (10 mL) was added to it and was further stirred for half an hour. The organic layer was separated and was washed successively with saturated $NaHCO_3$ solution (10 mL), water (10 mL), brine (10 mL) and finally dried (Na_2SO_4). After removal of the solvent under reduced pressure the residue obtained was purified by column chromatography over silica gel (10% ethyl acetate in light petroleum) to provide epoxy ether **3a** (700 mg, 93%) as

a yellowish oil. R_f=0.63; IR (neat): 3290, 3043, 2920, 2117, 1492, 1222, 1026, 754 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.49 (t, J=2.3 Hz, 1H), 2.57 (dd, J=2.7, 4.9 Hz, 1H), 2.77 (t_{app}, J=4.9 Hz, 1H), 2.82 (dd, J=5.8, 14.2 Hz, 1H), 2.97 (dd, J=5.2, 14.2 Hz, 1H), 3.17–3.22 (m, 1H), 4.72 (d, J=2.3 Hz, 2H) 6.94–6.99 (m, 2H), 7.21–7.26 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 33.2, 47.1, 51.5, 55.7, 75.3, 78.5, 111.7, 121.4, 126.1, 127.7, 130.7, 155.4; HRMS calcd for $C_{12}H_{13}O_2$ 189.0915 $[M+H]^+$, found 189.0920.

3.1.11. 2-(4-Methyl-2-prop-2-ynyloxy-benzyl)-oxirane (3b). Compound **3b** was prepared from **2b** (745 mg, 4 mmol) as a viscous oil (727 mg, 90%) following the same procedure described for **3a**. R_f=0.60 (10% ethyl acetate in light petroleum); IR (neat): 3286, 2920, 2117, 1500, 1217, 1029, 806 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.27 (s, 3H), 2.47 (t, J=2.3 Hz, 1H), 2.56 (dd, J=2.6, 5.0 Hz, 1H), 2.74–2.82 (m, 2H), 2.91 (dd, J=5.3, 14.2 Hz, 1H), 3.16–3.20 (m, 1H), 4.67 (d, J=2.3 Hz, 2H), 6.85 (d, J=8.8 Hz, 1H), 7.00–7.03 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.3, 33.2, 47.1, 51.6, 55.9, 75.1, 78.7, 111.8, 125.9, 127.9, 130.7, 131.4, 153.3; HRMS calcd for $C_{13}H_{15}O_2$ 203.1072 $[M+H]^+$, found 203.1075.

3.1.12. 2-(5-Methoxy-2-prop-2-ynyloxy-benzyl)-oxirane (3c). Compound **3c** was prepared from **2c** (810 mg, 4 mmol) as a viscous oil (767 mg, 88%) following the same procedure described for **3a**. R_f=0.58 (10% ethyl acetate in light petroleum); IR (neat): 3284, 2918, 2117, 1498, 1215, 1041 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.48 (t, J=2.4 Hz, 1H), 2.57 (dd, J=2.7, 5.1 Hz, 1H), 2.75–2.85 (m, 2H), 2.93 (dd, J=5.4, 14.4 Hz, 1H), 3.16–3.22 (m, 1H), 3.76 (s, 3H), 4.66 (d, J=2.4 Hz, 2H), 6.74 (dd, J=3.0, 9.0 Hz, 1H), 6.81 (d, J=3.0 Hz, 1H), 6.92 (d, J=9.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 33.4, 47.2, 51.6, 55.6, 56.8, 75.2, 78.9, 112.0, 113.5, 116.8, 127.7, 149.7, 154.2; HRMS calcd for $C_{13}H_{14}O_3Na$ 241.0841 $[M+Na]^+$, found 241.0842.

3.1.13. 2-(5-Chloro-2-prop-2-ynyloxy-benzyl)-oxirane (3d). Compound **3d** was prepared from **2d** (825 mg, 4 mmol) as a viscous oil (737 mg, 83%) following the same procedure described for **3a**. R_f=0.60 (10% ethyl acetate in light petroleum); IR (neat): 3292, 2995, 2117, 1488, 1226, 1026 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.50–2.55 (m, 2H), 2.76 (t_{app}, J=4.5 Hz, 1H), 2.84 (t_{app}, J=3.8 Hz, 2H), 3.14–3.19 (m, 1H), 4.69 (d, J=1.9 Hz, 2H), 6.89 (d, J=8.4 Hz, 1H), 7.16–7.20 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 33.1, 47.1, 51.2, 56.2, 75.8, 78.2, 113.1, 126.3, 127.5, 128.2, 130.6, 154.0; HRMS calcd for $C_{12}H_{11}ClO_2Na$ 245.0345 $[M+Na]^+$, found 245.0353.

3.1.14. 2-(2-Prop-2-ynyloxy-naphthalen-1-ylmethyl)-oxirane (11). Compound **11** was prepared from **10** (890 mg, 4 mmol) as a viscous oil (523 mg, 55%) following the same procedure described for **3a**. R_f=0.58 (10% ethyl acetate in light petroleum); IR (neat): 3288, 3053, 2117, 1595, 1220 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.49 (t, J=2.4 Hz, 1H), 2.65 (dd, J=2.6, 5.0 Hz, 1H), 2.71 (t_{app}, J=5.0 Hz, 1H), 3.22–3.26 (m, 1H), 3.33 (dd, J=5.9, 13.9 Hz, 1H), 3.50 (dd, J=4.5, 13.9 Hz, 1H), 4.83 (d, J=2.4 Hz, 2H), 7.33–7.40 (m, 2H), 7.51 (dt, J=1.2, 8.1 Hz, 1H), 7.78 (t_{app}, J=6.7 Hz, 2H), 8.02 (d, J=8.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 27.9, 47.4, 51.8, 57.2, 75.5, 78.9, 114.6, 119.8, 123.5, 123.9, 126.7, 128.5 (2C), 129.7, 133.5, 153.1; HRMS calcd for $C_{16}H_{14}O_2Na$ 261.0891 $[M+Na]^+$, found 261.0901.

3.1.15. 4-(2-Oxiranylmethyl-phenoxy)-but-2-ynoic acid ethyl ester (14a). Compound **14a** was prepared from **13a** (975 mg, 4 mmol) as a viscous oil (885 mg, 85%) following the same procedure described for **3a** after purification by column chromatography over silica gel using 10% ethyl acetate in light petroleum. R_f=0.53; IR (neat): 2985, 1714, 1492, 1253, 1022, 750 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.29 (t, J=7.1 Hz, 3H), 2.54 (dd, J=2.6, 4.8 Hz, 1H), 2.76 (dd, J=4.0, 4.8 Hz, 1H), 2.83 (dd, J=5.7, 14.3 Hz, 1H), 2.94 (dd, J=5.4, 14.3 Hz, 1H), 3.16–3.20 (m, 1H), 4.22 (q, J=7.1 Hz, 2H), 4.83 (s, 2H), 6.91–6.99 (m, 2H), 7.21–7.26 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.7, 33.0, 47.0, 51.4, 55.5, 62.1, 78.4, 81.5, 111.6, 121.8, 126.2, 127.8, 130.8, 152.7, 155.1; HRMS calcd for $C_{15}H_{17}O_4$ 261.1127 $[M+H]^+$, found 261.1131.

3.1.16. 4-(4-Methoxy-2-oxiranylmethyl-phenoxy)-but-2-ynoic acid ethyl ester (14c). Compound **14c** was prepared from **13c** (1.1 g, 4.01 mmol) as a viscous oil (966 mg, 83%) following the same procedure described for **3a**. R_f=0.50 (10% ethyl acetate in light petroleum); IR (neat): 2987, 1714, 1498, 1255, 1039 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.31 (t, J=7.1 Hz, 3H), 2.56 (dd, J=2.6, 4.8 Hz, 1H), 2.78 (t_{app}, J=4.8 Hz, 1H), 2.83 (dd, J=5.6, 14.4 Hz, 1H), 2.91 (dd, J=5.4, 14.4 Hz, 1H), 3.17–3.20 (m, 1H), 3.77 (s, 3H), 4.23 (q, J=7.1 Hz, 2H), 4.78 (s, 2H), 6.75 (dd, J=2.9, 8.8 Hz, 1H), 6.82 (d, J=2.9 Hz, 1H), 6.88 (d, J=8.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.9, 33.3, 47.1, 51.6, 55.6, 56.7, 62.2, 78.4, 82.0, 112.1, 113.6, 116.9, 127.9, 149.5, 152.9, 154.5; HRMS calcd for $C_{16}H_{18}O_5Na$ $[M+Na]^+$ 313.1052, found 313.1042.

3.1.17. 4-(2-Oxiranylmethyl-phenoxy)-but-2-enoic acid methyl ester (19a). Compound **19a** was prepared from **18a** (930 mg, 4 mmol) as a viscous oil (775 mg, 78%) following the same procedure described for **3a**. R_f=0.52 (10% ethyl acetate in light petroleum); IR (neat): 2950, 1724, 1494, 1242 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.54 (dd, J=2.7, 4.9 Hz, 1H), 2.76 (t, J=4.9 Hz, 1H), 2.88 (dd, J=5.4, 14.3 Hz, 1H), 2.96 (dd, J=5.4, 14.3 Hz, 1H), 3.17–3.22 (m, 1H), 3.75 (s, 3H), 4.70 (dd, J=1.8, 3.9 Hz, 1H), 6.19 (dd, J=1.8, 15.7 Hz, 1H), 6.80 (d, J=8.2 Hz, 1H), 6.93 (t, J=7.4 Hz, 1H), 7.10 (td, J=3.9, 15.7 Hz, 1H), 7.17–7.23 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 33.1, 47.0, 51.5 (2C), 66.3, 111.2, 121.1, 121.2, 125.8, 127.8, 130.7, 142.7, 155.7, 166.3; HRMS calcd for $C_{14}H_{16}O_4Na$ 271.0946 $[M+Na]^+$, found 271.0937.

3.1.18. 4-(4-Methoxy-2-oxiranylmethyl-phenoxy)-but-2-enoic acid methyl ester (19c). Compound **19c** was prepared from **18c** (1.05 g, 4 mmol) as a viscous oil (845 mg, 76%) following the same procedure described for **3a**. R_f=0.49 (10% ethyl acetate in light petroleum); IR (neat) 2950, 1724, 1500, 1305, 1224, 1039 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.46 (dd, J=2.6, 5.0 Hz, 1H), 269 (t_{app}, J=4.2 Hz, 1H), 2.75 (dd, J=5.5, 14.4 Hz, 1H), 2.84 (dd, J=5.4, 14.4 Hz, 1H), 3.08–3.12 (m, 1H), 3.67 (s, 6H), 4.57 (dd, J=2.0, 3.7 Hz, 2H), 6.10 (td, J=1.6, 15.8 Hz, 1H),

6.63–6.72 (m, 3H), 7.00 (td, J=4.0, 15.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 33.5, 47.2, 51.7, 51.8, 55.7, 67.4, 112.1, 112.7, 117.1, 121.3, 127.4, 143.2, 150.2, 154.1, 166.6; HRMS calcd for $C_{15}H_{18}O_5Na$ 301.1052 $[M+Na]^+$, found 301.1053.

3.1.19. 2-(2-Allyl-phenoxymethyl)-oxirane (6). Compound **1a** (670 mg, 5 mmol) in ethanol (10 mL) was added slowly to a solution of sodium ethoxide (340 mg, 5 mmol) in ethanol (10 mL) at 0 °C over 20 min. After complete generation of phenoxide ion (about 1 h), epichlorohydrin (573 mg, 6.2 mmol) was added slowly at 0 °C and was stirred for an additional 1 h at room temperature. The reaction mixture was then quenched by slow addition of water (5 mL). Most of the ethanol was removed under reduced pressure and the residue was extracted with diethyl ether (3×100 mL). Combined organic layer was washed successively with water (10 mL), brine (10 mL) and finally dried (Na_2SO_4). The residue obtained after removal of the solvent was purified by column chromatography over silica gel (5% ethyl acetate in light petroleum) to afford epoxy aryl ether **6** (685 mg, 72%) as colourless oil. R_f=0.40; IR (neat): 3062, 2923, 1492, 1242, 1031, 752 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.74 (dd, J=2.6, 4.5 Hz, 1H), 2.86 (t, J=4.5 Hz, 1H), 3.30–3.35 (m, 1H), 3.40 (d, J=6.6 Hz, 2H), 3.95 (dd, J=5.4, 11.0 Hz, 1H), 4.20 (dd, J=3.0, 11.0 Hz, 1H), 5.02–5.09 (m, 2H), 5.92–6.05 (m, 1H), 6.81 (d, J=8.0 Hz, 1H), 6.90 (t_{app}, J=7.3 Hz, 1H), 7.13–7.18 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 34.2, 44.4, 50.1, 68.6, 111.5, 115.3, 121.0, 127.2, 128.8, 129.8, 136.7, 156.0; HRMS calcd for $C_{12}H_{15}O_2$ 191.1072 $[M+H]^+$, found 191.1075.

3.1.20. (5,6-Dihydro-2*H*-benzo[*b*]oxocin-5-yl)-methanol (4a). A solution of titanocene dichloride (548 mg, 2.2 mmol) in dry THF (25 mL) was stirred with activated zinc dust (393 mg, 6 mmol) for 1 h under argon. The resulting green solution was then transferred through a cannula to a dropping funnel and was added dropwise to a magnetically stirred solution of epoxy propargylic ether **3a** (188 mg, 1 mmol) in dry THF (35 mL) at room temperature under argon over 8 h. The reaction mixture was stirred for an additional 6 h and then quenched with a saturated aqueous solution of NaH_2PO_4 (30 mL). The volatiles were removed under reduced pressure and the residue obtained was extracted with diethyl ether (3×50 mL). The combined ether layer was washed with brine (20 mL) and dried (Na_2SO_4). Removal of the solvent under reduced pressure afforded the product, which was chromatographed over silica gel (10% ethyl acetate in light petroleum) to yield **4a** (52%, R_f=0.23) as a colourless viscous oil along with the reduced product **5a** (12%) and another unidentified product. Spectral data for **4a**: IR (neat): 3398, 2920, 1490, 1207, 1006, 777; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.58 (dd, J=11.1, 15.9 Hz, 1H), 3.22 (dd, J=4.9, 15.9 Hz, 1H), 3.65–3.79 (m, 3H), 4.46 (dd, J=4.8, 15.5 Hz, 1H), 4.94 (td, J=2.4, 15.5 Hz, 1H), 5.44–5.50 (m, 1H), 5.56–5.63 (m, 1H), 7.00–7.08 (m, 3H), 7.15–7.21 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 35.6, 40.8, 67.3, 72.8, 122.7, 124.1, 126.7, 127.5, 130.7, 133.5, 133.4, 156.9; HRMS calcd for $C_{12}H_{14}O_2Na$ 213.0892 $[M+Na]^+$, found 213.0890.

3.1.21. (8-Methyl-5,6-dihydro-2*H*-benzo[*b*]oxocin-5-yl)-methanol (4b). Compound **4b** was prepared from **3b** (202 mg, 1 mmol) as a viscous oil (118 mg, 58%) following the same procedure described for **4a**. R_f=0.20 (10% ethyl acetate in light petroleum); IR (neat): 3398, 3012, 2920, 1498, 1203, 1014, 756 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.27 (s, 3H), 2.50 (dd, J=11.4, 15.9 Hz, 1H), 3.19 (dd, J=5.4, 15.9 Hz, 1H), 3.63–3.80 (m, 3H), 4.40 (dd, J=4.8, 15.6 Hz, 1H), 4.91 (td, J=2.1, 15.6 Hz, 1H), 5.43–5.49 (m, 1H), 5.54–5.61 (m, 1H), 6.87–6.99 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.6, 35.6, 40.5, 67.2, 72.8, 122.4, 126.7, 128.0, 131.2, 132.7, 133.3, 133.4, 154.6; HRMS calcd for $C_{13}H_{16}O_2Na$ 227.1048 $[M+Na]^+$, found 227.1053.

3.1.22. (8-Methoxy-5,6-dihydro-2*H*-benzo[*b*]oxocin-5-yl)-methanol (4c). Compound **4c** was prepared from **3c** (218 mg, 1 mmol) as a viscous oil (125 mg, 57%) following the same procedure described for **4a**. R_f=0.15 (10% ethyl acetate in light petroleum); IR (neat): 3396, 2918, 1496, 1202, 1012 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.51 (dd, J=11.7, 15.0 Hz, 1H), 3.22 (dd, J=6.0, 15.0 Hz, 1H), 3.68–3.79 (m, 6H), 4.37 (dd, J=4.5, 15.0 Hz, 1H), 4.91 (br d, J=15 Hz, 1H), 5.43–5.48 (m, 1H), 5.55–5.62 (m, 1H), 6.59 (d, J=3.0 Hz, 1H), 6.72 (dd, J=3.0, 9.0 Hz, 1H), 6.95 (d, J=9.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 36.5, 40.8, 55.8, 67.8, 73.7, 113.2, 115.8, 123.9, 127.5, 133.5, 134.6, 151.0, 156.3; HRMS calcd for $C_{13}H_{16}O_3Na$ 243.0997 $[M+Na]^+$, found 243.0987.

3.1.23. (8-Chloro-5,6-dihydro-2*H*-benzo[*b*]oxocin-5-yl)-methanol (4d). Compound **4d** was prepared from **3d** (222.5 mg, 1 mmol) as a viscous oil (121 mg, 54%) following the same procedure described for **4a**. R_f=0.15 (10% ethyl acetate in light petroleum); IR (neat): 3367, 2931, 1485, 1176, 1010 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.54 (dd, J=11.1, 16.2 Hz, 1H), 3.19 (dd, J=4.5, 16.2 Hz, 1H), 3.65–3.76 (m, 3H), 4.42 (dd, J=4.9, 15.3 Hz, 1H), 4.93 (td, J=2.4, 15.3 Hz, 1H), 5.43–5.49 (m, 1H), 5.55–5.62 (m, 1H), 6.94 (d, J=8.4 Hz, 1H), 7.05 (d, J=2.4 Hz, 1H), 7.13 (dd, J=2.4, 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 33.5, 40.5, 67.0, 73.0, 124.1, 126.6, 127.6, 128.9, 130.5, 133.5, 135.1, 155.6; HRMS calcd for $C_{12}H_{14}O_2Cl$ 225.0682 $[M]^+$, found 225.0674.

3.1.24. (3,4,5,6-Tetrahydro-2*H*-benzo[*b*]oxocin-3-yl)-methanol (7). Compound **7** was prepared from the epoxide **6** (190 mg, 1 mmol) as a viscous oil (85 mg, 44%) following the same procedure described for **4a**. R_f=0.18 (10% ethyl acetate in light petroleum); IR (neat): 3398, 2922, 2873, 1488, 1218, 1008, 744 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.43–1.57 (m, 2H), 1.62–1.78 (m, 2H), 1.96–2.04 (m, 1H), 2.65–2.73 (m, 1H), 2.78–2.88 (m, 1H), 3.41 (d, J=6.3 Hz, 2H), 3.85 (t_{app}, J=11.3 Hz, 1H), 4.24 (dd, J=4.3, 11.3 Hz, 1H), 7.01–7.21 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 30.2, 30.4, 30.9, 40.5, 65.0, 78.0, 121.2, 124.2, 127.5, 129.7, 136.7, 157.0; HRMS calcd for $C_{12}H_{16}O_2Na$ 215.1047 $[M+Na]^+$, found 215.1049.

3.1.25. (11,12-Dihydro-8*H*-7-oxa-cycloocta[*a*]naphthalen-11-yl)-methanol (12). Compound **12** was prepared from the epoxide **11** (238 mg, 1 mmol) as a viscous oil (151 mg, 63%) following the same procedure described for **4a**. R_f=0.15 (10% ethyl acetate in light petroleum); IR (neat): 3398, 2875, 1467, 1203, 1066 cm^{-1}; ^{1}H NMR

($CDCl_3$, 300 MHz): δ 3.18 (dd, J=11.7, 16.2 Hz, 1H), 3.32 (dd, J=4.5, 16.2 Hz, 1H), 3.77 (d, J=6.3 Hz, 2H), 3.91–3.99 (m, 1H), 4.58 (dd, J=4.2, 15.9 Hz, 1H), 4.94 (d, J=15.9 Hz, 1H), 5.36–5.42 (m, 1H), 5.49–5.64 (m, 1H), 7.19 (d, J=8.7 Hz, 1H), 7.38 (t_{app}, J=7.8 Hz, 1H), 7.46 (t_{app}, J=8.4 Hz, 1H), 7.68 (d, J=8.7 Hz, 1H), 7.77 (d, J=7.8 Hz, 1H), 7.98 (d, J=8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 31.4, 40.7, 67.8, 73.1, 122.8, 123.3, 124.6, 126.2, 126.4, 126.5, 128.5, 128.6, 131.1, 132.9, 133.3, 154.1; HRMS calcd for $C_{16}H_{16}O_2Na$ 263.1048 $[M+Na]^+$, found 263.1039.

3.1.26. 4a,5-Dihydro-4*H*,11*H*-3,10-dioxa-dibenzo [*a*,*d*]-cyclohepten-2-one (15a). The epoxide **14a** (260 mg, 1 mmol) was subjected to radical cyclization reaction using Cp_2TiCl following the same procedure described for **4a** to furnish a mixture of products in a ratio of 1.7:1.5:1. Compound **15a** was separated (54 mg) in pure form in 25% yield by preparative TLC (25% ethyl acetate in light petroleum) as a crystalline solid, mp 110–112 °C. R_f=0.26; IR (neat): 2918, 1732, 1488, 1228, 1051 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.72 (dd, J=3.8, 10.9 Hz, 1H), 2.87 (dd, J=10.9, 14.5 Hz, 1H), 2.99–3.07 (m, 1H), 4.11 (t_{app}, J=11.0 Hz, 1H), 4.45 (dd, J=5.4, 11.0 Hz, 1H), 4.53 (br d, J=14.5 Hz, 1H), 4.75 (d, J=14.5 Hz, 1H), 5.85 (s, 1H), 6.95–7.15 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 32.2, 34.9, 70.1, 73.6, 116.7, 120.8, 124.1, 128.4, 129.1, 130.5, 158.3, 158.8, 163.6; HRMS calcd for $C_{13}H_{13}O_3$ 217.0859 $[M+H]^+$, found 217.0853.

The remaining portion was probably a mixture of **16a** and **17a**, which could not be separated by usual chromatographic methods.

3.1.27. 7-Methoxy-4a,5-dihydro-4*H*,11*H*-3,10-dioxa-dibenzo[*a*,*d*]cyclohepten-2-one (15c). The epoxide **14c** (290 mg, 1 mmol) was subjected to radical cyclization reaction using Cp_2TiCl following the same procedure described for **4a** to furnish a mixture of products in a ratio of 2:1.8:1. Compound **15c** was separated (66 mg) in pure form in 27% yield by preparative TLC (25% ethyl acetate in light petroleum) as a crystalline solid, mp 122–124 °C. R_f=0.24; IR (neat): 2920, 1732, 1498, 1209, 1049 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.76 (dd, J=4.2, 14.3 Hz, 1H), 2.90 (dd, J=10.5, 14.3 Hz, 1H), 3.01–3.08 (m, 1H), 3.77 (s, 3H), 4.19 (t_{app}, J=10.4 Hz, 1H), 4.49–4.56 (m, 2H), 4.75 (d, J=14.8 Hz, 1H), 5.89 (s, 1H), 6.67 (d, J=3.0 Hz, 1H), 6.73 (dd, J=3.0, 8.6 Hz, 1H), 6.97 (d, J=8.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 32.6, 35.0, 55.6, 70.3, 74.4, 113.1, 115.7, 116.9, 121.8, 131.0, 152.2, 156.1, 159.1, 163.7; HRMS calcd for $C_{14}H_{14}O_4Na$ 269.0790 $[M+Na]^+$, found 269.0784.

The remaining portion was probably a mixture of **16c** and **17c**, which could not be separated by usual chromatographic methods.

3.1.28. 4a*R*,5,11,11a*S*-Tetrahydro-1*H*,4*H*-3,10-dioxa-dibenzo[*a*,*d*]cyclohepten-2-one (20a) and 4a*R*,5,11,11a*R*-tetrahydro-1*H*,4*H*-3,10-dioxa-dibenzo[*a*,*d*]cyclohepten-2-one (21a). The epoxide **19a** (248 mg, 1 mmol) was subjected to radical cyclization reaction using Cp_2TiCl following the same procedure described for **4a** to furnish a mixture of products **20a** and **21a** in a ratio of 2:3. Compounds **20a** (57 mg, 26%) and **21a** (85 mg, 39%) were separated by preparative TLC (25% ethyl acetate in light petroleum) as crystalline solids. **20a**: mp 142–144 °C; R_f=0.28; IR (KBr): 2945, 1732, 1490, 1226, 1035 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.75–1.88 (m, 1H), 1.98 (dd, J=12.7, 17.9 Hz, 1H), 2.27–2.42 (m, 1H), 2.47 (d, J=14.2 Hz, 1H), 2.63 (dd, J=5.3, 17.9 Hz, 1H), 2.82 (dd, J=11.4, 13.7 Hz, 1H), 3.32 (dd, J=10.4, 12.2 Hz, 1H), 4.08 (t_{app}, J=11.2 Hz, 1H), 4.24 (dd, J=3.6, 12.2 Hz, 1H), 4.47 (dd, J=4.7, 11.2 Hz, 1H), 7.01–7.06 (m, 2H), 7.13–7.21 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 31.6, 34.4, 37.6, 40.8, 73.7, 75.1, 121.3, 124.3, 128.3, 130.4, 131.8, 159.9, 168.9; HRMS calcd for $C_{13}H_{15}O_3$ 219.1016 $[M+H]^+$, found 219.1024. **21a**: mp 158–160 °C; R_f=0.26; IR (KBr): 2933, 1732, 1487, 1226, 1087 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.35–2.41 (m, 1H), 2.48–2.59 (m, 1H), 2.68 (dd, J=6.9, 17.8 Hz, 1H), 2.84–2.99 (m, 2H), 3.13 (dd, J=9.8, 15.1 Hz, 1H), 4.05–4.07 (m, 2H), 4.23 (dd, J=6.1, 11.5 Hz, 1H), 4.36 (dd, J=3.9, 11.5 Hz, 1H), 6.94–7.00 (m, 2H), 7.09 (d, J=6.1 Hz, 1H), 7.16 (dt, J=1.8, 7.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 30.0, 32.8, 34.4, 36.0, 72.5, 72.8, 120.7, 123.5, 128.2, 129.4, 131.1, 159.0, 170.8; HRMS calcd for $C_{13}H_{15}O_3$ 219.1016 $[M+H]^+$, found 219.1018.

3.1.29. 7-Methoxy-4a*R*,5,11,11a*S*-tetrahydro-1*H*,4*H*-3,10-dioxa-dibenzo[*a*,*d*]cyclohepten-2-one (20c) and 7-methoxy-4a*R*,5,11,11a*R*-tetrahydro-1*H*,4*H*-3,10-dioxa-dibenzo[*a*,*d*]cyclohepten-2-one (21c). The epoxide **19c** (278 mg, 1 mmol) was subjected to radical cyclization reaction using Cp_2TiCl following the same procedure described for **4a** to furnish a mixture of products **20c** and **21c** in a ratio of 5:6. Compounds **20c** (77 mg, 31%) and **21c** (94 mg, 38%) were separated by preparative TLC (25% ethyl acetate in light petroleum) as crystalline solids. **20c**: mp 166–168 °C; R_f=0.26; IR (KBr) 2920, 1732, 1487, 1224, 1087 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.75–1.88 (m, 1H), 1.97 (dd, J=12.7, 18.0 Hz, 1H), 2.26–2.43 (m, 2H), 2.62 (dd, J=5.3, 18.0 Hz, 1H), 2.83 (dd, J=11.5, 13.6 Hz, 1H), 3.27 (dd, J=10.7, 12.2 Hz, 1H), 3.78 (s, 3H), 4.08 (t, J=11.5 Hz, 1H), 4.22 (dd, J=3.8, 12.2 Hz, 1H), 4.47 (dd, J=4.7, 11.4 Hz, 1H), 6.69–6.72 (m, 2H), 6.96 (d, J=8.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 31.7, 34.7, 37.8, 41.0, 55.7, 73.8, 76.6, 112.6, 116.0, 122.1, 133.0, 153.9, 156.1, 169.2; HRMS calcd for $C_{14}H_{16}O_4Na$ 271.0946 $[M+Na]^+$, found 271.0952. **21c**: mp 132–134 °C; R_f=0.24; IR (KBr) 2929, 1728, 1496, 1207, 1072 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.29–2.37 (m, 1H), 2.45–2.55 (m, 1H), 2.65–2.80 (m, 2H), 2.98 (dd, J=9.8, 18.2 Hz, 1H), 3.14 (dd, J=10.2, 14.9 Hz, 1H), 3.77 (s, 3H), 3.97–3.99 (m, 2H), 4.27 (dd, J=5.5, 11.5 Hz, 1H), 4.38 (dd, J=3.8, 11.5 Hz, 1H), 6.64–6.70 (m, 2H), 6.91 (d, J=8.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 30.2, 33.2, 34.4, 36.5, 55.7, 73.1, 73.4, 112.7, 116.3, 121.7, 131.6, 153.4, 155.8, 170.7; HRMS calcd for $C_{14}H_{16}O_4Na$ 271.0946 $[M+Na]^+$, found 271.0956.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.08.072.

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