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A stereoselective route to multi-substituted tetrahydropyrans by vinyl radical cyclization

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Abstract—The tin-mediated 6-*exo-trig* radical cyclization of the acetylenic β-alkoxy acrylates proceeded smoothly to give fully substituted tetrahydropyrans in good yields with high equatorial selectivity irrespective of the stereochemistry of the propargylic position.

1. Introduction

The tetrahydropyran nucleus is an integral structural component of an increasing number of biologically significant marine polycyclic ether toxins.[1] The synthesis of such a fused ring system is receiving a great deal of attention, and a variety of approaches have been developed.[2] Among them, radical cyclization methods developed for the stereoselective synthesis of trans-fused tetrahydropyrans include the intramolecular addition of acyl,[3] ketyl,[4] and vinyl radicals[5] to β-alkoxy acrylates. However, these methods were limited to the construction of the general structure **I**, and the formation of fully substituted tetrahydropyrans such as structure **II** has not been studied (Fig. 1). The ring system **II** would serve as a potent precursor of 4-hydroxy-3-methyl-tetrahydropyrans **III** and **IV**,[6] which correspond to the I ring of yessotoxin[7] and adriatoxin[8] and the H ring of gambieric acids,[9] respectively. An efficient and straightforward construction of **II** is envisioned by the 6-*exo-trig* cyclization of vinyl radical **V** generated from a propargyl alcohol derivative.

Of particular concern is the influence of the alkoxy group adjacent to the vinyl radical on the cyclization. The stereochemistry and the protecting group of the hydroxy group might influence the reaction course of the radical reaction, such as cyclization, premature reduction (hydrostannation), and elimination.[10] We report here a tin-mediated radical reaction of propargyl alcohol derivatives to construct multi-substituted tetrahydropyrans.

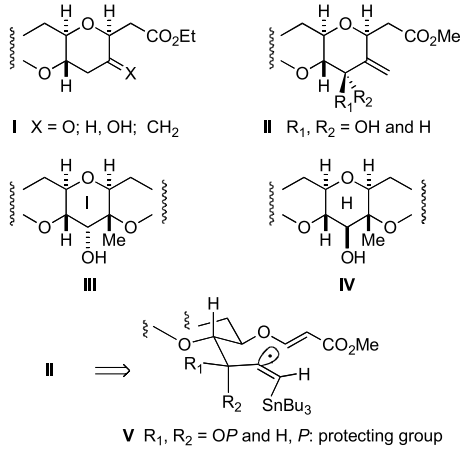

Figure 1.

2. Results and discussion

The synthesis of radical cyclization precursors is summarized in Scheme 1. Treatment of (2*S*,3*S*)-3-(*tert*-butyldimethylsilyloxy)tetrahydropyran-2-carboxaldehyde[11] with ethynylmagnesium bromide gave a separable mixture of propargyl alcohols **1** and **2** in 63 and 33% yield, respectively. The protection of each alcohol with methoxymethyl or *p*-methoxybenzyl groups, desilylation, and the hetero-Michael reaction with methyl propiolate in the presence of *N*-methylmorpholine afforded (*E*)-alkoxy acrylates **3** and **4**.

Keywords: Radical cyclization; Tetrahydropyrans; Polycyclic ethers; Alkoxy acrylates.
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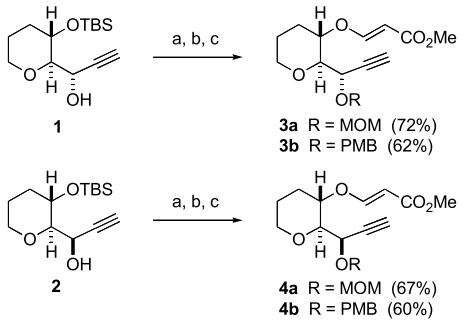
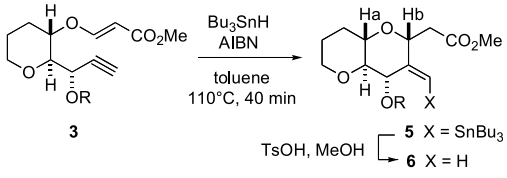


Scheme 1. Reagents and conditions: (a) MOM–Cl, NaH, DMF or PMB–Cl, NaH, DMF; (b) Bu_4NF, THF, rt; (c) methyl propiolate, NMM, CH_2Cl_2, rt.

Reaction of the acetylenic β-alkoxy acrylates **3** with Bu_3SnH and AIBN in toluene at a concentration of 0.05 M and at 110 °C for 40 min and the subsequent acidic destannylation of the products gave the 6,6-bicyclic ethers **6** having equatorial CH_2CO_2Me and OR groups in good yields (Table 1). The radical cyclization of the other isomers **4** also proceeded under the same reaction conditions to provide the bicyclic products **8**, which have equatorial CH_2CO_2Me and axial OR substituents (Table 2). The stereochemistry of the cyclization products was determined by an NOE interaction between the axial Ha and Hb protons of the newly formed tetrahydropyran ring (9% NOE for **6a**, 10% NOE for **8a**). Interestingly, the 6-*exo-trig* radical cyclization reaction of both isomers **3** and **4** proceeded with high diastereoselectivity and in good yields in such a way as to give products with an equatorial CH_2CO_2Me, irrespective of the stereochemistry of the alkoxy group at the propargylic position. It is worthwhile noting that the present reaction conditions (a 0.05 M solution in toluene at 110 °C) led the cyclization to be completed within 60 min. The reported radical cyclizations of β-alkoxy acrylates were carried out by the slow addition of a benzene solution of Bu_3SnH and AIBN over a period of hours by a syringe pump (80 °C, ~12 h).[3,5]

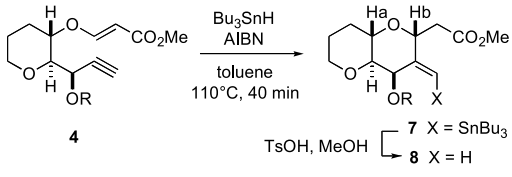
Table 1. Radical cyclization of **3**



Substrate	**5**/Yield (%)[a]	**6**/Yield (%)[a]	ds[b]
3a R=MOM	**5a**/90	**6a**/91	95:5
3b R=PMB	**5b**/75	**6b**/72	94:6

[a] Isolated yield after flash chromatography.
[b] Determined by ^{1}H NMR analysis.

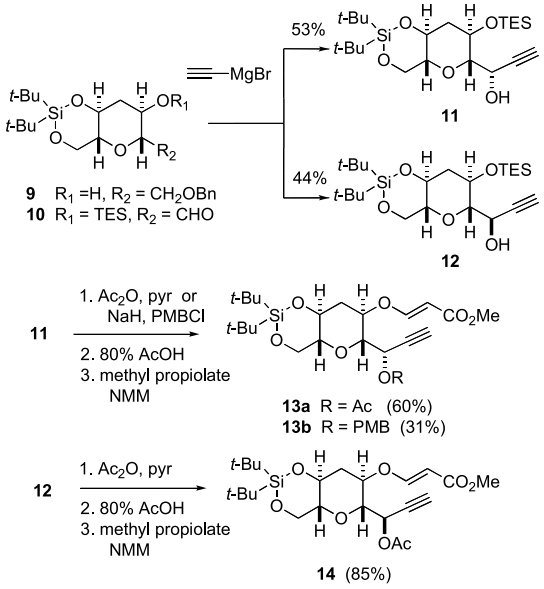
Table 2. Radical cyclization of **4**



Substrate	**7**/Yield (%)[a]	**8**/Yield (%)[a]	ds[b]
4a R=MOM	**7a**/87	**8a**/92[c]	95:5
4b R=PMB	**7b**/90	**8b**/69	94:6

[a] Isolated yield after flash chromatography.
[b] Determined by ^{1}H NMR analysis.
[c] Isolated as R=H.

The high stereoselectivity and good yields of the radical cyclization prompted us to extend this study to more functionalized precursors. The synthesis started with the known bicyclic alcohol **9**,[12] which was prepared in five steps according to our oxiranyl anion strategy.[13] Protection of the alcohol with the triethylsilyl group, hydrogenolysis of the benzyl ether, and oxidation with Dess–Martin periodinane afforded aldehyde **10** (Scheme 2).

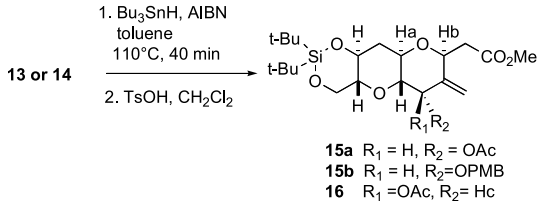


Scheme 2.

The reaction with ethynylmagnesium bromide gave a mixture of diastereoisomers **11** and **12**, which were easily separated by flash chromatography. The stereochemistry of both isomers was determined by the ^{1}H NMR analysis of the corresponding acetonide derivatives. After protection of the propargyl alcohol with an acetyl group, the triethylsilyl group was removed and then an acrylate moiety was introduced with methyl propiolate to give acetylenic β-alkoxy acrylates **13a** and **14** in 60 and 85% yield, respectively. A partial 1,3-migration of the acetyl group was observed during the hetero-Michael reaction with methyl propiolate: the extent of the migration was 1:3.5 for **13a** and 1:9 for **14**. The p-methoxybenzylation of **11** resulted in a low yield of the product due to the 1,3-migration of the triethylsilyl group and the partial decomposition of the silylene group under the reaction conditions.

Treatment of **13** and **14** with Bu_3SnH and AIBN in refluxing toluene furnished the tricyclic ethers **15** and **16** in good yields with high stereoselectivity (Table 3). The stereochemistry of **15a** and **16** was determined by the NOE experiments. An 11.6% NOE was observed between the Ha and Hb of **15a**, and in the case of **16**, 10.2 and 5.1% NOEs were detected between Ha and Hb and between Hb and Hc, respectively. The results showed again that the

Table 3. Radical cyclization of **13** and **14**

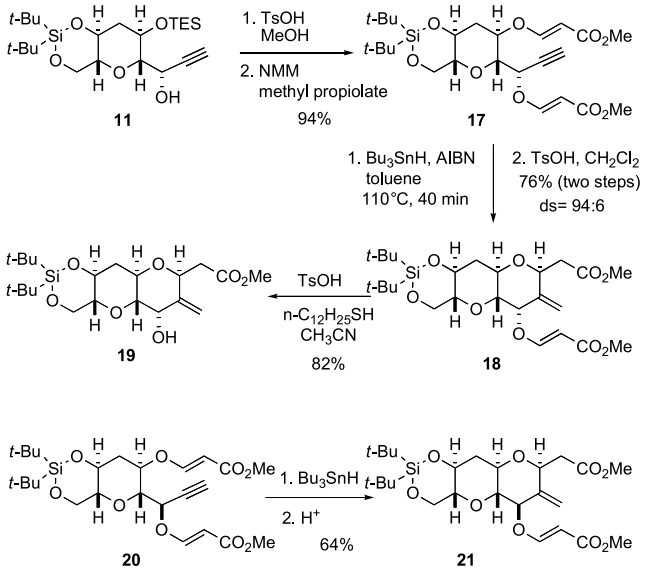


Substrate	Product	Yield (%)[a]	ds[b]
13a	**15a**	78[c]	92:8
13b	**15b**	82	96:4
14	**16**	81	93:7

[a] Isolated yield after flash chromatography.
[b] Determined by ^{1}H NMR analysis.
[c] Corrected yield based on pure **13a**.

stereochemistry of the substituent at the propargylic position did not affect the radical cyclization.

We next examined the protecting group of a propargyl alcohol to prevent the 1,3-migration of the acetyl and triethylsilyl groups in the synthesis of **13** and **14**. As the hetero-Michael reaction of an alcohol with methyl propiolate proceeded in an excellent yield, we decided to introduce two acrylate groups, one for a protecting group of a propargyl alcohol and the other for a radical acceptor. Removal of the triethylsilyl group of **11** followed by the reaction of the resulting diol with methyl propiolate in the presence of *N*-methylmorpholine gave bis(β-alkoxy acrylate) **17** in 94% yield (Scheme 3).



Scheme 3.

Although **17** could suffer radical cyclization in 4-*exo* and 6-*exo* fashions, leading to an oxetane and a tetrahydropyran, respectively, we anticipated that a group-selective cyclization via a 6-*exo* pathway would occur for an obvious steric reason. Indeed, the treatment of **17** with Bu_3SnH and AIBN in refluxing toluene followed by acidic destannylation furnished the desired tetrahydropyran **18** in good yields with high diastereoselectivity.

The following hydrolysis of the β-alkoxy acrylate group of **18** in the presence of the silylene group was carried out effectively with *p*-TsOH in the presence of *n*-dodecanthiol[14] in acetonitrile at 80 °C, giving the desired tetrahydropyran **19** in 82% yield. The principle of the group-selective radical cyclization also applied to the other isomer **20** and the functionalized tetrahyropyran **21** was constructed in good yield.

3. Conclusion

In summary, we developed a straightforward approach towards multi-substituted tetrahydropyrans via a vinyl radical generated from an acetylenic β-alkoxy acrylate moiety. We also demonstrated interesting group-selective radical cyclizations and the efficient thiol-mediated deprotection of β-alkoxy acrylate group. The tetrahydropyran ring constructed contains methoxycarbonylmethyl, hydroxy, and exocyclic methylene groups, which are useful for the partial and total synthesis of the related structurally and biologically interesting class of polycyclic ethers.

4. Experimental

4.1. General

IR spectra were recorded in $CHCl_3$ solution on a JASCO FTIR-420 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL A-400 or A-600 spectrometer in $CDCl_3$ solution using TMS and $CDCl_3$ (77.00 ppm) as internal standards, respectively. EI and FAB mass spectra were obtained on JEOL JMS-700 and HX-110 mass spectrometers, respectively. Optical rotations were determined on a JASCO DIP-370 digital polarimeter. All air- and moisture-sensitive reactions were carried out under an argon atmosphere in dry, freshly distilled solvents under anhydrous conditions. Flash chromatography was carried out with E. Merck silica gel 60 (230–400 mesh). The term 'dried' refers to the drying of an organic solution over $MgSO_4$ followed by filtration.

4.1.1. (*S*)-1-[(2*R*,3*S*)-3-(*tert*-Butyldimethylsilyloxy)tetrahydropyran-2-yl]prop-2-yn-1-ol (1) and (*R*)-1-[(2*R*,3*S*)-3-(*tert*-butyldimethylsilyloxy)tetrahydropyran-2-yl]-prop-2-yn-1-ol (2). To a stirred solution of 0.5 M ethynylmagnesium bromide in Et_2O (14.5 mL, 10.5 mmol) at 0 °C was added a solution of (2*S*,3*S*)-3-(*tert*-butyldimethylsilyloxy)tetrahydropyran-2-carboxaldehyde[11] (857 mg, 3.51 mmol) in THF (18 mL), and the reaction mixture was stirred for 1 h. The reaction was quenched with saturated aqueous NH_4Cl and the mixture was extracted with EtOAc. The extract was washed with water and brine, dried, and concentrated. Purification by flash chromatography (20% EtOAc in hexane) gave alcohols **1** (599 mg, 63%) and **2** (313 mg, 33%). Compound **1**: colorless oil; $[\alpha]_D^{25}$ +25.4 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3564, 3306, 1472, 1234, 1162, 837 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.10 (3H, s), 0.12 (3H, s), 0.89 (9H, s), 1.49 (1H, m), 1.62–1.71 (2H, m), 2.07 (1H, m), 2.45 (1H, d, J=2.0 Hz), 2.76 (1H, d, J=10.2 Hz, OH), 3.19 (1H, dd, J=8.8, 1.9 Hz), 3.45 (1H, m), 3.77 (1H, ddd, J=10.7, 8.8, 4.4 Hz), 4.00 (1H, m), 4.58

(1H, ddd, J=10.7, 1.9, 1.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.8, −4.0, 17.8, 25.2, 25.6, 25.7 (2×C), 33.0, 61.5, 67.3, 68.2, 72.6, 83.2, 83.6; HREIMS *m/z* calcd for $C_{14}H_{26}O_3Si$ 270.1650, found 270.1692. Compound **2**: colorless oil; $[\alpha]_D^{25}$ +65.2 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3563, 3306, 1472, 1254, 1104, 861 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.08 (3H, s), 0.10 (3H, s), 0.87 (9H, s), 1.47 (1H, dddd, J=13.2, 13.2, 10.7, 4.4 Hz), 1.62–1.79 (2H, m), 2.05 (1H, m), 2.49 (1H, d, J=2.4 Hz), 2.87 (1H, d, J=10.2 Hz, OH), 3.26 (1H, dd, J=9.3, 3.4 Hz), 3.37 (1H, ddd, J=11.7, 11.7, 2.9 Hz), 3.64 (1H, ddd, J=10.7, 9.3, 4.9 Hz), 4.02 (1H, m), 4.65 (1H, ddd, J=10.2, 3.4, 2.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.9, −4.0, 17.8, 25.0, 25.7 (3×C), 33.1, 62.8, 68.0, 68.4, 74.1, 81.7, 83.7; HREIMS *m/z* calcd for $C_{14}H_{26}O_3Si$ 270.1650, found 270.1269.

4.1.2. (*E*)-3-{(2*S*,3*S*)-2-[(*S*)-1-(Methoxymethoxy)prop-2-ynyl]tetrahydropyran-3-yloxy}acrylic acid methyl ester (3a). (*i*) *O-Methoxymethylation*. To a stirred solution of **1** (76 mg, 0.281 mmol) in THF were added NaH (60% in mineral oil, 79 mg, 1.976 mmol) and MOM–Cl (0.28 mL, 3.670 mmol), and the reaction mixture was refluxed for 1 h. After cooling to rt, the mixture was extracted with EtOAc. The extract was washed with water and brine, dried, and concentrated. Purification by flash chromatography (20% EtOAc in hexane) gave methoxymethyl ether (72 mg, 81%) as a colorless oil; $[\alpha]_D^{25}$ +101.6 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3306, 1464, 1253, 1104, 1029, 838 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.087 (3H, s), 0.094 (3H, s), 0.89 (9H, s), 1.45 (1H, dddd, J=13.2, 13.2, 10.7, 4.4 Hz), 1.62–1.79 (2H, m), 2.12 (1H, m), 2.45 (1H, d, J=2.0 Hz), 3.24 (1H, dd, J=8.8, 1.5 Hz), 3.42 (1H, ddd, J=11.7, 11.7, 2.4 Hz), 3.43 (3H, s), 3.80 (1H, ddd, J=10.7, 8.8, 4.4 Hz), 4.06 (1H, m), 4.71 and 4.97 (each 1H, d, J=6.8 Hz), 4.75 (1H, t, J=2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.7, −3.3, 17.9, 25.0, 25.8 (3×C), 33.5, 56.4, 64.5, 66.4, 68.5, 73.6, 81.3, 84.3, 95.3; EIMS *m/z* 314 (M^+).

(*ii*) *Desilylation*. The product obtained above (72 mg, 0.228 mmol) was dissolved in THF (2.3 mL), and 1.0 M TBAF in THF (0.3 mL, 0.300 mmol) was added at 0 °C. The reaction mixture was stirred at rt for 1.5 h and then concentrated. Purification by flash chromatography (50–60% EtOAc in hexane) gave alcohol (42.3 mg, 93%) as a colorless oil; $[\alpha]_D^{25}$ +157.1 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3536, 3306, 1465, 1348, 1153, 1099, 1026 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.47 (1H, dddd, J=12.7, 12.7, 10.7, 4.4 Hz), 1.63–1.81 (2H, m), 2.17 (1H, m), 2.52 (1H, d, J=2.0 Hz), 2.63 (1H, br, OH), 3.27 (1H, dd, J=9.3, 3.4 Hz), 3.40 (1H, ddd, J=11.7, 11.7, 3.0 Hz), 3.42 (3H, s), 3.89 (1H, ddd, J=10.7, 9.3, 4.9 Hz), 4.02 (1H, dddd, J=11.2, 4.4, 1.5, 1.5 Hz), 4.67 and 4.98 (each 1H, d, J=6.8 Hz,), 4.75 (1H, dd, J=3.4, 2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.9, 31.8, 56.0, 66.5, 66.7, 68.2, 75.3, 79.6, 81.7, 94.4; EIMS *m/z* 201 (MH^+).

(*iii*) *Reaction with methyl propiolate*. To a stirred solution of the alcohol obtained above (42.3 mg, 0.212 mmol) in CH_2Cl_2 (2.1 mL) were added methyl propiolate (76 μL, 0.846 mmol) and *N*-methylmorpholine (NMM) (47 μL, 0.423 mmol). After stirring at rt for 4 h, the reaction mixture was extracted with EtOAc and the extract was washed with water and brine, dried, and concentrated. Purification by flash chromatography (40% EtOAc in hexane) gave **3** (58 mg, 96%) as a colorless oil; $[\alpha]_D^{25}$ +114.5 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3306, 1705, 1645, 1623, 1438, 1335, 1147, 1070, 1022 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.56 (1H, dddd, J=17.6, 12.7, 11.2, 5.4 Hz), 1.73–1.85 (2H, m), 2.32 (1H, m), 2.49 (1H, d, J=2.0 Hz,), 3.34 (3H, s,), 3.47 (1H, ddd, J=11.2, 11.2, 3.4 Hz), 3.48 (1H, dd, J=5.4, 2.0 Hz), 3.69 (3H, s), 4.10 (1H, m), 4.16 (1H, ddd, J=10.7, 9.3, 4.9 Hz), 4.61 and 5.01 (each 1H, d, J=6.8 Hz), 4.67 (1H, t, J=2.2 Hz), 5.32 and 7.51 (each 1H, d, J=12.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.6, 29.1, 51.1, 56.2, 63.4, 68.4, 74.9, 75.6, 79.3, 80.8, 94.3, 98.1, 160.8, 167.9; HREIMS *m/z* calcd for $C_{14}H_{20}O_6$ 284.1259, found 284.1265.

4.1.3. (*E*)-3-{(2*S*,3*S*)-2-[(*S*)-1-(*p*-Methoxybenzyloxy)prop-2-ynyl]tetrahydropyran-3-yloxy}acrylic acid methyl ester (3b). To a solution of alcohol **1** (100 mg, 0.37 mmol) in DMF (1.8 mL) were added NaH (60% in mineral oil, 45 mg, 1.85 mmol) and PMB–Cl (0.15 mL, 1.11 mmol), and the reaction mixture was stirred at 0 °C for 17 h. The reaction was quenched with saturated aqueous NH_4Cl and the mixture was extracted with Et_2O. The extract was washed with water and brine, dried, and concentrated. Purification by flash chromatography (30% EtOAc in hexane) gave PMB ether (95 mg, 65%). The desilylation of the PMB ether and the reaction with methyl propiolate were carried out in the same manner as described for **3a** to give **3b** (82 mg, 95% for two steps) as a colorless oil; $[\alpha]_D^{25}$ +124.2 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3306, 1705, 1643, 1622, 1514, 1157, 1076 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.49 (1H, dddd, J=12.7, 12.7, 12.7, 5.4 Hz), 1.62–1.81 (2H, m), 2.02 (1H, m), 2.53 (1H, d, J=2.4 Hz), 3.37 (1H, dd, J=8.8, 2.4 Hz), 3.41 (1H, ddd, J=11.2, 11.2, 3.4 Hz), 3.72 (3H, s), 3.78 (3H, s), 4.05–4.18 (2H, m), 4.26 (1H, t, J=2.4 Hz), 4.44 and 5.77 (each 1H, d, J=11.7 Hz), 5.16 and 7.33 (each 1H, d, J=12.2 Hz), 6.83 and 7.24 (each 2H, d, J=8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.7, 29.2, 51.1, 55.1, 65.0, 68.4, 70.4, 74.9, 75.8, 79.8, 80.9, 97.7, 113.7 (2×C), 128.6, 130.5 (2×C), 159.5, 161.2, 168.0; HREIMS *m/z* calcd for $C_{20}H_{24}O_6$ 360.1571, found 360.1554.

4.1.4. (*E*)-3-{(2*S*,3*S*)-2-[(*R*)-1-(Methoxymethoxy)prop-2-ynyl]tetrahydropyran-3-yloxy}acrylic acid methyl ester (4a). The procedure used for the preparation of **3a** was employed. An experiment starting with alcohol **2** (102 mg, 0.378 mmol) provided **4a** (72 mg, 67%) as a colorless oil; $[\alpha]_D^{25}$ −56.0 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3305, 1701, 1645, 1623, 1438, 1150, 1028 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.59 (1H, dddd, J=17.5, 12.2, 10.7, 5.4 Hz), 1.73–1.85 (2H, m), 2.30 (1H, m), 2.53 (1H, d, J=2.4 Hz), 3.40 (3H, s), 3.45 (1H, m), 3.57 (1H, dd, J=9.3, 2.4 Hz), 3.70 (3H, s), 4.04 (1H, ddd, J=10.6, 9.3, 4.9 Hz), 4.08 (1H, m), 4.64 (1H, t, J=2.4 Hz), 4.68 and 5.98 (each 1H, d, J=6.8 Hz), 5.33 and 7.50 (each 1H, d, J=12.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.5, 29.2, 51.1, 55.8, 65.1, 67.8, 76.0, 77.1, 78.0, 80.4, 94.4, 98.3, 160.9, 168.0; HREIMS *m/z* calcd for $C_{14}H_{20}O_6$ 284.1259, found 284.1231.

4.1.5. (*E*)-3-{(2*S*,3*S*)-2-[(*R*)-1-(*p*-Methoxybenzyloxy)prop-2-ynyl]tetrahydropyran-3-yloxy}acrylic acid methyl ester (4b). The procedure used for the preparation

of **3b** was employed. An experiment starting with alcohol **2** (100 mg, 0.37 mmol) provided **4b** (80 mg, 60%) as a colorless oil; $[\alpha]_D^{25}$ −79.8 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3305, 1705, 1644, 1623, 1438, 1148, 1073 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.55 (1H, dddd, J=18.0, 12.3, 10.7, 5.8 Hz), 1.70–1.81 (2H, m), 2.23 (1H, m), 2.57 (1H, d, J=2.0 Hz), 3.41 (1H, m), 3.54 (1H, dd, J=9.3, 2.4 Hz), 3.70 (3H, s), 3.81 (3H, s), 3.98–4.07 (2H, m), 4.33 (1H, t, J=2.4 Hz), 4.51 and 4.81 (each 1H, d, J=11.2 Hz, OCH_2Ph), 5.25 and 7.45 (each 1H, d, J=12.2 Hz), 6.87 and 7.28 (each 2H, d, J=8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.7, 29.4, 51.4, 55.5, 67.9, 68.0, 71.0, 77.5, 77.6, 78.8, 80.9, 98.4, 114.1, 128.5, 130.3 (2×C), 159.7, 161.4 (2×C), 168.4; HREIMS *m*/*z* calcd for $C_{20}H_{24}O_6$ 360.1571, found 360.1538.

4.2. General procedure for radical cyclization and destannylation

(*i*) *Radical cyclization*. A solution of an alkynyl β-alkoxy acrylate (0.30 mmol, 1.0 equiv), Bu_3SnH (0.9 mmol, 1.3 equiv), and AIBN (5 mg, catalytic amount) in toluene (6 mL, 0.05 M solution) was heated at 110 °C for 30–60 min. After cooling to rt, the reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel flash chromatography (EtOAc/hexane) to give cyclization product.

(*ii*) *Destannylation*. The cyclization product (0.2 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (2 mL) or MeOH (2 mL) and *p*-TsOH·H_2O (0.3 mmol, 1.5 equiv) was added. The reaction mixture was stirred at rt for 1 h and the reaction was quenched with Et_3N (0.2 mL). The mixture was concentrated and purified by flash chromatography (EtOAc/hexane) to give a product.

4.2.1. (2*R*,4*S*,4a*S*,8a*S*)-(4-Methoxymethoxy-3-methyleneoctahydropyrano[3,2-*b*]pyran-2-yl)acetic acid methyl ester (6a). A colorless oil; $[\alpha]_D^{25}$ +83.2 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 1737, 1439, 1103, 1039 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.45 (1H, dddd, J=12.2, 12.2, 12.2, 5.4 Hz), 1.65–1.80 (2H, m), 2.06 (1H, m), 2.71 (1H, dd, J=15.1, 8.3 Hz), 2.78 (1H, dd, J=15.1, 5.4 Hz), 2.95 (1H, t, J=9.3 Hz), 3.30 (1H, ddd, J=11.2, 9.3, 4.4 Hz), 3.36 (1H, ddd, J=11.2, 11.2, 3.4 Hz), 3.43 (3H, s), 3.71 (3H, s), 3.95 (1H, m), 4.16 (1H, br d, J=9.3 Hz), 4.29 (1H, dd, J=8.3, 5.4 Hz), 4.74 and 4.88 (each 1H, d, J=6.8 Hz), 4.96 (1H, s,), 5.32 (1H, d, J=2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.2, 29.3, 36.9, 51.9, 55.8, 67.7, 74.2, 76.0, 77.3, 84.1, 96.4, 107.4, 144.4, 171.4; HREIMS *m*/*z* calcd for $C_{14}H_{22}O_6$ 286.1415, found 286.1453.

4.2.2. (2*R*,4*S*,4a*S*,8a*S*)-[4-(*p*-Methoxybenzyloxy)-3-methyleneoctahydropyrano[3,2-*b*]pyran-2-yl]acetic acid methyl ester (6b). A colorless oil; $[\alpha]_D^{25}$ +34.6 (*c* 0.82, CH_3Cl); IR ($CHCl_3$) 1735, 1613, 1514, 1439, 1248, 1102 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.45 (1H, dddd, J=12.2, 12.2, 12.2, 5.4 Hz), 1.66–1.79 (2H, m), 2.05 (1H, m), 2.71 (1H, dd, J=15.6, 8.3 Hz), 2.77 (1H, dd, J=15.6, 5.4 Hz), 3.03 (1H, t, J=9.3 Hz), 3.28 (1H, ddd, J=11.2, 9.3, 4.4 Hz), 3.38 (1H, ddd, J=11.7, 11.7, 3.4 Hz), 3.71 (3H, s), 3.80 (3H, s), 3.93–4.01 (2H, m), 4.22 (1H, dd, J=8.3, 5.4 Hz), 4.65 and 4.71 (each 1H, d, J=11.7 Hz), 4.95 (1H, s), 5.38 (1H, d, J=2.0 Hz), 6.87 and 7.32 (each 2H, d, J=8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.3, 29.3, 36.9, 51.8, 55.2, 67.7, 73.2, 74.2, 76.0, 80.3, 84.6, 107.7, 113.7 (2×C), 129.2 (2×C), 130.6, 144.3, 159.1, 171.5; HREIMS *m*/*z* calcd for $C_{20}H_{26}O_6$ 362.1727, found 362.1768.

4.2.3. (2*R*,4*R*,4a*R*,8a*S*)-(4-Hydroxy-3-methyleneoctahydropyrano[3,2-*b*]pyran-2-yl)acetic acid methyl ester (8a). A colorless oil; $[\alpha]_D^{25}$ +75.1 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3567, 1738, 1438, 1099, 960 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.43 (1H, dddd, J=12.2, 12.2, 12.2, 5.4 Hz), 1.65–1.78 (2H, m), 2.09 (1H, m), 2.42 (1H, s, OH), 2.63 (1H, dd, J=15.1, 8.8 Hz), 2.73 (1H, dd, J=15.1, 4.9 Hz), 3.06 (1H, dd, J=9.3, 2.9 Hz), 3.46 (1H, m), 3.71 (3H, s), 3.74 (1H, ddd, J=11.2, 9.3, 4.4 Hz), 3.92 (1H, m), 4.41 (1H, d, J=2.9 Hz), 4.71 (1H, dd, J=8.8, 4.9 Hz), 4.91 (1H, d, J=1.5 Hz), 5.16 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.3, 29.2, 36.8, 51.8, 68.1, 70.8, 72.5, 81.0, 113.1, 145.3, 171.4, 187.0; HREIMS *m*/*z* calcd for $C_{12}H_{18}O_5$ 242.1153, found 242.1178.

4.2.4. (2*R*,4*R*,4a*S*,8a*S*)-{4-(*p*-Methoxybenzyloxy)-3-methyleneoctahydropyrano[3,2-*b*]pyran-2-yl}acetic acid methyl ester (8b). A colorless oil; $[\alpha]_D^{25}$ +40.8 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 1736, 1612, 1514, 1439, 1247, 1099 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.37 (1H, dddd, J=12.7, 12.2, 12.2, 4.4 Hz), 1.64 (1H, m), 1.79 (1H, m), 2.08 (1H, m), 2.67 (1H, dd, J=15.6, 8.8 Hz), 2.72 (1H, dd, J=15.6, 3.4 Hz), 3.06 (1H, dd, J=9.3, 3.4 Hz), 3.37 (1H, ddd, J=11.7, 11.7, 2.4 Hz), 3.72 (3H, s), 3.80 (3H, s), 3.87 (1H, ddd, J=11.2, 9.3, 4.4 Hz), 4.01 (1H, m), 4.14 (1H, d, J=2.9), 4.37 and 4.59 (each 1H, d, J=12.2 Hz), 4.62 (1H, t, J=6.8 Hz), 5.03 (1H, d, J=2.0 Hz), 5.21 (1H, s), 6.86 and 7.27 (each 2H, d, J=8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.0, 29.7, 36.6, 51.8, 55.2, 68.4, 69.0, 70.5, 71.2, 78.2, 81.5, 113.1, 113.7 (2×C), 129.3 (2×C), 130.1, 143.8, 159.0, 171.4; HREIMS *m*/*z* calcd for $C_{20}H_{26}O_6$ 362.1727, found 362.1751.

4.2.5. (4a*R*,6*R*,7*R*,8a*S*)-2,2-Di(*tert*-butyl)-7-(triethylsilyloxy)hexahydro-1,3,5-trioxa-2-silanaphthalene-6-carbaldehyde (10). (*i*) *Triethylsilylation*. To a stirred solution of alcohol **9** (1.95 g, 4.79 mmol) and 2,6-lutidine (1.4 mL, 12.0 mmol) in CH_2Cl_2 (32 mL) was added TESOTf (1.30 mL, 5.75 mmol) at 0 °C, and the reaction mixture was stirred for 1 h. The reaction was quenched with saturated aqueous $NaHCO_3$ and the mixture was extracted with EtOAc. The extract was washed with water and brine, dried, and concentrated. Purification by flash chromatography (5% EtOAc in hexane) gave triethylsilyl ether (2.35 g, 94%) as a colorless oil; $[\alpha]_D^{25}$ −31.1 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 1473, 1365, 1091, 826 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.56 (6H, m), 0.91 (9H, t, J=6.7 Hz,), 0.98 (9H, s), 1.04 (9H, s), 1.53 (1H, q, J=11.2 Hz,), 2.38 (1H, ddd, J=11.2, 4.4, 4.4 Hz), 3.31 (1H, ddd, J=10.2, 10.2, 4.9 Hz), 3.35 (1H, ddd, J=9.3, 5.9, 2.0 Hz), 3.51 (1H, dd, J=10.3, 5.9 Hz), 3.61 (1H, ddd, J=11.2, 9.3, 4.9 Hz), 3.70 (1H, dd, J=10.3, 2.0 Hz), 3.75 (1H, ddd, J=11.2, 8.8, 4.4 Hz), 3.83 (1H, t, J=10.2 Hz), 4.19 (1H, dd, J=10.2, 4.9 Hz), 4.51 and 4.61 (each 1H, d, J=12.2 Hz), 7.23–7.34 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 4.9 (3×C), 6.8 (3×C), 19.9, 22.6, 27.0 (3×C), 27.4

(3×C), 42.5, 66.3, 66.9, 69.5, 72.0, 73.4, 77.1, 82.0, 127.5, 127.8 (2×C), 128.3 (2×C), 138.1; HREIMS *m/z* calcd for $C_{28}H_{50}O_5Si_2$ 522.3197, found 522.3210.

(*ii*) *Hydrogenolysis*. A mixture of the product (2.35 g, 4.51 mmol) and $Pd(OH)_2$/C (259 mg) in EtOAc (30 mL) was stirred under a hydrogen atmosphere for 1 h. The reaction mixture was filtered through a short column of Celite and the filtrate was concentrated. Purification by flash chromatography (10–30% EtOAc in hexane) gave the alcohol (1.77 g, 91%) as a colorless oil; $[\alpha]_D^{25}$ −45.9 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3596, 1473, 1098 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.63 (6H, q, J=7.8 Hz), 0.97 (9H, t, J=7.8 Hz), 0.99 (9H, s), 1.04 (9H, s), 1.56 (1H, q, J=11.7 Hz), 1.91 (1H, t, J=6.3 Hz, OH), 2.39 (1H, ddd, J=12.2, 4.4, 4.4 Hz), 3.25 (1H, ddd, J=8.8, 5.4, 2.9 Hz), 3.33 (1H, ddd, J=10.3, 9.3, 4.9 Hz,), 3.58–3.67 (2H, m), 3.73 (1H, ddd, J=11.2, 9.3, 4.4 Hz), 3.78 (1H, t, J=10.3 Hz), 3.83 (1H, m), 4.14 (1H, dd, J=10.2, 4.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 4.9 (3×C), 6.8 (3×C), 19.9, 22.6, 27.0 (3×C), 27.4 (3×C), 42.3, 62.4, 66.4, 66.8, 72.2, 76.9, 82.1; HREIMS *m/z* calcd for $C_{21}H_{44}O_5Si_2$ 432.2727, found 432.2656.

(*iii*) *Oxidation*. To a solution of the alcohol (1.94 g, 4.49 mmol) in CH_2Cl_2 (45 mL) was added Dess–Martin periodinane (2.10 g, 4.94 mmol) at 0 °C, and the reaction mixture was stirred at rt for 1.5 h. The reaction was quenched with saturated aqueous $Na_2S_2O_3$ and the mixture was extracted with CH_2Cl_2. The extract was washed with saturated aqueous $NaHCO_3$, water, and brine, dried, and concentrated. Purification by flash chromatography (30% EtOAc in hexane) gave aldehyde **10** (1.76 g, 91%) as a colorless oil; $[\alpha]_D^{25}$ −42.5° (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 1737, 1473, 1100 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.62 (6H, q, J=7.8 Hz), 0.96 (9H, t, J=7.8 Hz), 0.99 (9H, s), 1.04 (9H, s), 1.65 (1H, q, J=11.7 Hz), 2.47 (1H, ddd, J=12.2, 4.4, 4.4 Hz), 3.33 (1H, ddd, J=10.3, 10.3, 4.4 Hz), 3.77 (1H, dd, J=9.3, 1.0 Hz,), 3.78–3.87 (2H, m), 3.88 (1H, t, J=10.3 Hz), 4.19 (1H, dd, J=10.3, 4.4 Hz), 9.71 (1H, d, J=1.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 4.9 (3×C), 6.7 (3×C), 19.9, 22.6, 27.0 (3×C), 27.4 (3×C), 42.9, 66.5, 66.9, 71.4, 76.6, 84.8, 198.1; HREIMS *m/z* calcd for $C_{21}H_{42}O_5Si_2$ 430.2568, found 362.2561.

4.2.6. (1*S*)-1-[(4a*R*,6*S*,7*R*,8a*S*)-2,2-Di(*tert*-butyl)-7-(triethylsilyloxy)hexahydro-1,3,5-trioxa-2-silanaphthalen-6-yl]prop-2-yn-1-ol (11) and (1*R*)-1-[(4a*R*,6*S*,7*R*,8a*S*)-2,2-Di(*tert*-butyl)-7-(triethylsilyloxy)hexahydro-1,3,5-trioxa-2-silanaphthalen-6-yl]prop-2-yn-1-ol (12). The procedure used for the preparation of **1** was employed. An experiment starting with aldehyde **10** (988 mg, 2.29 mmol) provided the crude products, which were purified by flash chromatography (15–30% EtOAc in hexane). The first eluate gave alcohol **12** (454 mg, 44%) and the second eluate gave alcohol **11** (552 mg, 53%). Compound **11**: colorless oil; $[\alpha]_D^{25}$ −53.1 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3567, 3307, 1473, 1098, 1067, 1006 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.64 (6H, q, J=8.3 Hz), 0.97 (9H, t, J=8.3 Hz), 0.99 (9H, s), 1.05 (9H, s), 1.57 (1H, q, J=11.7 Hz,), 2.41 (1H, ddd, J=11.7, 4.4, 4.4 Hz), 2.45 (1H, d, J=2.4 Hz), 2.65 (1H, d, J=10.2 Hz, OH), 3.33 (1H, ddd, J=10.2, 10.2, 4.9 Hz), 3.36 (1H, dd, J=9.3, 3.4 Hz), 3.73–3.81 (2H, m), 3.85 (1H, t, J=10.2 Hz), 4.17 (1H, dd, J=10.2, 4.9 Hz), 4.63 (1H, ddd, J=10.2, 2.4, 2.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 5.0 (3×C), 6.8 (3×C), 20.0, 22.6, 27.0 (3×C), 27.4 (3×C), 42.2, 42.9, 62.6, 66.6, 67.3, 71.9, 74.5, 77.1, 83.3; HREIMS *m/z* calcd for $C_{23}H_{44}O_5Si_2$ 456.2727, found 456.2749. Compound **12**: colorless oil; $[\alpha]_D^{25}$ −42.3 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3570, 3307, 1473, 1095, 1063 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.66 (6H, q, J=8.3 Hz), 0.98 (9H, t, J=8.3 Hz), 0.99 (9H, s), 1.05 (9H, s), 1.57 (1H, q, J=11.2 Hz), 2.43 (1H, d, J=2.0 Hz), 2.44 (1H, m), 2.58 (1H, d, J=10.7 Hz, OH), 3.28 (1H, dd, J=9.3, 2.0 Hz), 3.39 (1H, ddd, J=9.3, 9.3, 4.9 Hz), 3.74 (1H, ddd, J=11.2, 9.3, 4.4 Hz), 3.81 (1H, t, J=10.2 Hz), 3.89 (1H, ddd, J=11.2, 6.3, 4.9 Hz), 4.18 (1H, dd, J=10.2, 4.9 Hz), 4.56 (1H, ddd, J=10.7, 2.0, 2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 5.0 (3×C), 6.7 (3×C), 19.9, 22.6, 27.0 (3×C), 27.4 (3×C), 42.0, 61.1, 66.0, 66.7, 71.9, 72.9, 77.3, 82.8, 83.1; HREIMS *m/z* calcd for $C_{23}H_{44}O_5Si_2$ 456.2727, found 456.2758.

4.2.7. (*E*)-(4a*R*,6*R*,7*R*,8a*S*)-3-{6-[(1*S*)-1-(Acetoxy)propynyl]-2,2-di(*tert*-butyl)hexahydro-1,3,5-trioxa-2-silanaphthalen-7-yloxy}acrylic acid methyl ester (13a). (*i*) *Acetylation*. To a stirred solution of alcohol **11** (294 mg, 0.645 mmol) in CH_2Cl_2 (3.0 mL) were added pyridine (0.2 mL) and acetic anhydride (0.2 mL), and the reaction mixture was stirred at rt for 3 h. The solvent was evaporated azeotropically with heptane three times. The residue was purified by flash chromatography (7% EtOAc in hexane) to give acetate (274 mg, 85%) as a colorless oil; $[\alpha]_D^{25}$ −21.4 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3307, 1743, 1473, 1366, 1237, 1099, 1070 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.66 (6H, q, J=7.8 Hz), 0.99 (9H, t, J=7.8 Hz), 0.99 (9H, s), 1.05 (9H, s), 1.57 (1H, q, J=11.7 Hz), 2.13 (3H, s), 2.43 (1H, ddd, J=11.7, 4.4, 4.4 Hz), 2.47 (1H, d, J=2.4 Hz), 3.33 (1H, ddd, J=10.2, 10.2, 4.9 Hz), 3.39 (1H, dd, J=9.3, 2.4 Hz), 3.73–3.81 (2H, m), 3.86 (1H, t, J=10.2 Hz), 4.22 (1H, dd, J=10.2, 4.9 Hz), 5.77 (1H, t, J=2.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 5.0 (3×C), 6.8 (3×C), 19.9, 21.0, 22.6, 27.1 (3×C), 27.4 (3×C), 42.2, 60.1, 63.6, 66.6, 66.7, 71.8, 75.4, 77.1, 82.2, 169.6; EIMS *m/z* 498 (M^+).

(*ii*) *Detriethylsilylation*. A solution of the acetate (281 mg, 0.565 mmol) in THF (3.0 mL) and 80% acetic acid (7.5 mL) was stirred for 5.5 h. The solution was neutralized with 15% NH_4OH to pH 8.0 and extracted with EtOAc. The extract was washed with water and brine, dried, and concentrated. Purification by flash chromatography (30% EtOAc in hexane) gave the alcohol (216 mg, 100%) as a colorless oil; $[\alpha]_D^{25}$ +2.4 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3601, 3306, 1741, 1473, 1366, 1235, 1104 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.99 (9H, s), 1.05 (9H, s), 1.56 (1H, q, J=11.4 Hz), 1.87 (1H, d, J=5.5 Hz, OH), 2.14 (3H, s), 2.51 (1H, d, J=2.2 Hz), 2.53 (1H, ddd, J=11.4, 4.8, 4.8 Hz), 3.34 (1H, ddd, J=10.3, 9.2, 4.8 Hz), 3.44 (1H, dd, J=9.5, 2.6 Hz), 3.80 (1H, ddd, J=11.4, 9.2, 4.4 Hz), 3.83 (1H, m), 3.85 (1H, t, J=10.3 Hz), 4.20 (1H, dd, J=10.3, 4.8 Hz), 5.79 (1H, t, J=2.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.9, 20.9, 22.6, 27.0 (3×C), 27.4 (3×C), 41.6, 63.7, 66.1, 66.6, 71.7, 75.8, 77.1, 77.2, 81.6, 169.8; EIMS *m/z* 384 (M^+).

(*iii*) *Reaction with methyl propiolate*. The procedure used for the preparation of **3a** was employed. An experiment

starting with the above alcohol (216 mg, 0.563 mmol) provided acetate (237 mg, 90%), which was assigned to be a 78:22 mixture of **13a** and its regioisomer by ^{1}H NMR analysis; IR ($CHCl_3$) 3306, 1741, 1706, 1645, 1235, 1104 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (signals of the major isomer **13a**) δ 0.98 (9H, s), 1.05 (9H, s), 1.63 (1H, q, J=11.4 Hz), 2.14 (3H, s), 2.50 (1H, d, J=1.8 Hz), 2.68 (1H, ddd, J=12.1, 4.8, 4.8 Hz), 3.38 (1H, ddd, J=9.9, 9.9, 4.1 Hz), 3.65 (1H, dd, J=9.5, 2.2 Hz), 3.71 (3H, s), 3.83 (1H, m), 3.86 (1H, t, J=10.2 Hz), 4.10 (1H, ddd, J=11.4, 9.5, 4.8 Hz), 4.23 (1H, dd, J=10.2, 5.1 Hz), 5.37 and 7.48 (each 1H, d, J=12.5 Hz, CH=CH), 5.63 (1H, t, J=2.2 Hz); HREIMS m/z calcd for $C_{23}H_{36}O_8Si$ 468.2179, found 456.2184.

4.2.8. (*E*)-(4a*R*,6*R*,7*R*,8a*S*)-3-{2,2-Di(*tert*-butyl)-6-[(1*S*)-1-(*p*-methoxybenzyloxy)-2-propynyl]hexahydro-1,3,5-trioxa-2-silanaphthalen-7-yloxy}acrylic acid methyl ester (13b). The procedures of **3b** (i) and **13a** (ii and iii) were employed. An experiment starting with alcohol **11** (18 mg, 0.039 mmol) provided **13b** (6.7 mg, 31%) as a colorless oil; $[\alpha]_D^{25}$ −60.6 (c 0.55, $CHCl_3$); IR ($CHCl_3$) 3307, 1705, 1644, 1622, 1516, 1235, 1100 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (9H, s), 1.04 (9H, s), 1.61 (1H, q, J=11.7 Hz), 2.53 (1H, d, J=2.0 Hz), 2.62 (1H, ddd, J=11.7, 4.4, 4.4 Hz), 3.36 (1H, ddd, J=10.3, 10.3, 4.9 Hz), 3.62 (1H, dd, J=9.8, 2.0 Hz), 3.70 and 3.81 (each 3H, s), 3.80 (1H, m), 3.86 (1H, t, J=10.3 Hz), 4.09 (1H, ddd, J=11.2, 9.8, 4.9 Hz), 4.23 (1H, dd, J=10.3, 4.9 Hz), 4.30 (1H, t, J=2.0 Hz), 4.47 and 4.80 (each 1H, d, J=11.7 Hz), 5.27 and 7.42 (each 1H, d, J=12.2 Hz), 6.87 and 7.27 (each 2H, d, J=9.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.9, 22.6, 27.0 (3×C), 27.4 (3×C), 38.2, 51.2, 55.2, 66.6, 67.3, 70.8, 71.4, 75.7, 76.6, 77.2, 78.1, 80.5, 98.5, 113.8 (2×C), 129.0, 129.9 (2×C), 159.6, 160.7, 178.1; HREIMS m/z calcd for $C_{29}H_{42}O_8Si$ 546.2646, found 546.2684.

4.2.9. (*E*)-(4a*R*,6*R*,7*R*,8a*S*)-3-{6-[(1*R*)-1-(Acetoxy)prop-2-ynyl]-2,2-di(*tert*-butyl)hexahydro-1,3,5-trioxa-2-silanaphthalen-7-yloxy}acrylic acid methyl ester (14). The procedure used for the preparation of **13a** was employed. An experiment starting with alcohol **12** (106 mg, 0.232 mmol) provided acetate **14** (92 mg, 85% as a 9:1 mixture of regioisomers) as a colorless oil; $[\alpha]_D^{25}$ −49.8 (c 1.0, $CHCl_3$); IR ($CHCl_3$) 3307, 1745, 1707, 1645, 1625, 1220, 1137, 1105 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (9H, s), 1.05 (9H, s), 1.63 (1H, q, J=11.7 Hz), 2.10 (3H, s), 2.50 (1H, d, J=2.4 Hz), 2.66 (1H, ddd, J=11.7, 4.9, 4.9 Hz), 3.39 (1H, ddd, J=10.2, 9.8, 4.9 Hz), 3.61 (1H, dd, J=9.3, 2.4 Hz), 3.70 (3H, s), 3.84 (1H, ddd, J=11.7, 9.3, 4.4 Hz), 3.90 (1H, t, J=10.2 Hz), 4.05 (1H, ddd, J=11.7, 9.8, 4.9 Hz), 4.21 (1H, dd, J=10.2, 4.9 Hz), 5.31 and 7.43 (each 1H, d, J=12.2 Hz), 5.58 (1H, t, J=2.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.9, 20.7, 22.6, 27.0 (3×C), 27.4 (3×C), 38.0, 51.2, 62.0, 66.4, 71.4, 74.5, 75.2, 77.7, 77.8, 79.0, 98.5, 160.3, 167.7, 169.3; HREIMS m/z calcd for $C_{23}H_{36}O_8Si$ 468.2179, found 468.2202.

4.2.10. (4a*R*,5*S*,7*S*,8a*R*,9a*S*,10a*R*)-[5-Acetoxy-2,2-di(*tert*-butyl)-6-methylenetetradecahydro-1,3,8,10-tetraoxa-2-silaanthracen-7-yl]acetic acid methyl ester (15a). According to the general procedure, a 78:22 mixture of **13a** and its regioisomer (257 mg, 0.550 mmol) was subjected to the radical cyclization and destannylation to give **15a** (155 mg, 61% as a 92:8 mixture of diastereoisomers, 78% corrected yield based on pure **13a**) as a colorless oil; $[\alpha]_D^{25}$ −27.5 (c 0.34, $CHCl_3$); IR ($CHCl_3$) 1741, 1473, 1439, 1371, 1236, 1107, 1047 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (9H, s), 1.04 (9H, s), 1.49 (1H, q, J=11.7 Hz), 2.08 (3H, s), 2.47 (1H, ddd, J=11.7, 4.4, 4.4 Hz), 2.61 (1H, dd, J=15.1, 9.3 Hz), 2.70 (1H, dd, J=15.1, 4.4 Hz), 3.22 (1H, dd, J=9.8, 3.4 Hz), 3.33 (1H, ddd, J=10.3, 10.3, 4.9 Hz), 3.72 (3H, s), 3.79 (1H, t, J=10.3 Hz), 3.80 (2H, m), 4.11 (1H, dd, J=10.3, 4.9 Hz), 4.54 (1H, dd, J=8.8, 4.9 Hz), 5.03 (1H, d, J=1.5 Hz), 5.29 (1H, s), 5.63 (1H, d, J=3.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.9, 21.3, 22.6, 27.0 (3×C), 27.4 (3×C), 36.7, 38.5, 51.9, 66.7, 67.0, 71.3, 72.2, 72.6, 77.8, 79.1, 115.3, 141.7, 169.9, 171.4; HREIMS m/z calcd for $C_{23}H_{38}O_8Si$ 470.2335, found 470.2312.

4.2.11. (4a*R*,5*S*,7*S*,8a*R*,9a*S*,10a*R*)-[2,2-Di(*tert*-butyl)-5-(*p*-methoxybenzyloxy)-6-methylenetetradecahydro-1,3,8,10-tetraoxa-2-silaanthracen-7-yl]acetic acid methyl ester (15b). According to the general procedure, **13b** (6.7 mg, 0.012 mmol) was subjected to the radical cyclization and destannylation to give **15b** (5.6 mg, 82% as a 96:4 mixture of diastereoisomers) as a colorless oil; $[\alpha]_D^{25}$ −30.6 (c 1.0, $CHCl_3$); IR ($CHCl_3$) 1738, 1513, 1102, 1054 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (9H, s), 1.03 (9H, s), 1.46 (1H, q, J=11.7 Hz), 2.45 (1H, ddd, J=11.7, 4.4, 4.4 Hz), 2.66 (1H, dd, J=15.1, 5.8 Hz), 2.72 (1H, dd, J=15.1, 5.8 Hz), 3.17 (1H, dd, J=9.8, 2.9 Hz), 3.31 (1H, ddd, J=9.8, 9.8, 4.4 Hz), 3.71 (3H, s), 3.84 (3H, s), 3.72–3.95 (2H, m), 3.92 (1H, t, J=10.3 Hz), 4.14 (1H, dd, J=10.3, 4.9 Hz), 4.15 (1H, d, J=2.9 Hz), 4.34 and 4.56 (each 1H, d, J=12.2 Hz), 4.60 (1H, br t, J=7.3 Hz), 5.00 (1H, s), 5.02 (1H, d, J=1.5 Hz), 6.86 and 7.24 (each 2H, d, J=8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.9, 22.5, 27.0 (3×C), 27.4 (3×C), 36.6, 38.7, 51.8, 55.2, 66.7, 69.2, 69.6, 70.6, 72.1, 77.9, 78.0, 81.2, 113.3, 113.7 (2×C), 129.2 (2×C), 130.1, 143.5, 159.1, 171.4; HREIMS m/z calcd for $C_{29}H_{44}O_8Si$ 548.2802, found 548.2857.

4.2.12. (4a*R*,5*R*,7*S*,8a*R*,9a*S*,10a*R*)-[5-Acetoxy-2,2-di(*tert*-butyl)-6-methylenetetradecahydro-1,3,8,10-tetraoxa-2-silaanthracen-7-yl]acetic acid methyl ester (16). According to the general procedure, **14** (90 mg, 0.192 mmol, a 9:1 mixture of regioisomers) was subjected to the radical cyclization and destannylation to give **16** (73 mg, 81% as a 93:7 mixture of diastereoisomers) as a colorless oil; $[\alpha]_D^{25}$ −27.5 (c 0.25, CH_3Cl); IR ($CHCl_3$) 1741, 1238, 1104, 1054 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (9H, s), 1.02 (9H, s), 1.55 (1H, q, J=11.7 Hz), 2.17 (3H, s), 2.47 (1H, ddd, J=11.7, 4.4, 4.4 Hz), 2.70 (1H, dd, J=15.1, 9.3 Hz), 2.77 (1H, dd, J=15.1, 4.9 Hz), 3.13 (1H, t, J=9.8 Hz), 3.29 (1H, ddd, J=10.2, 10.2, 4.9 Hz), 3.41 (1H, ddd, J=11.7, 9.3, 4.4 Hz), 3.71 (3H, s), 3.81 (1H, t, J=10.2 Hz), 3.84 (1H, ddd, J=11.7, 10.2, 4.4 Hz), 4.11 (1H, dd, J=10.2, 4.9 Hz), 4.35 (1H, dd, J=9.3, 4.9 Hz), 4.94 (1H, d, J=2.0 Hz), 5.00 (1H, d, J=2.0 Hz), 5.40 (1H, d, J=9.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.9, 20.8, 22.6, 27.0 (3×C), 27.4 (3×C), 36.9, 38.3, 51.9, 66.6, 72.2, 73.3, 74.30, 74.33, 77.4, 81.2, 107.7, 141.9, 169.9, 170.9; HREIMS m/z calcd for $C_{23}H_{38}O_8Si$ 470.2336, found 470.2345.

4.2.13. (*E*,*E*)-(4a*R*,6*R*,7*R*,8a*S*)-3-{2,2-Di(*tert*-butyl)-6-[(1*S*)-1-(2-methoxycarbonylvinyloxy)-2-propynyl]-hexahydro-1,3,5-trioxa-2-silanaphthalen-7-yloxy}acrylic acid methyl ester (17). (*i*) *Detriethylsilylation*. A solution of **11** (240 mg, 0.527 mmol) and *p*-TsOH·H_2O (5.0 mg, 0.026 mmol) in MeOH (5.3 mL) was stirred at rt for 1 h. The reaction was quenched with Et_3N (0.2 mL) and the reaction mixture was concentrated. Purification by flash chromatography (40% EtOAc in hexane) gave diol (169 mg, 94%) as a solid. Mp 190–191 °C; $[\alpha]_D^{25}$ −31.4 (*c* 1.0, CH_3Cl); ^1H NMR (400 MHz, acetone-d_6) δ 1.00 (9H, s), 1.42 (9H, s), 1.56 (1H, q, J=11.7 Hz), 2.44 (1H, ddd, J=11.7, 4.9, 4.9 Hz), 2.80 (1H, d, J=2.4 Hz), 3.33 (1H, dd, J=9.3, 3.4 Hz), 3.35 (1H, ddd, J=10.3, 10.3, 4.9 Hz), 3.70 (1H, m), 3.78 (1H, t, J=10.3 Hz), 3.80 (1H, ddd, J=11.2, 9.3, 4.9 Hz), 4.11 (1H, dd, J=10.3, 4.9 Hz), 4.25 (1H, d, J=5.4 Hz, OH), 4.54 (1H, d, J=8.3 Hz, OH), 4.62 (1H, ddd, J=8.3, 3.4, 2.4 Hz); ^{13}C NMR (100 MHz, acetone-d_6) δ 20.4, 23.1, 27.4 (3×C), 27.7 (3×C), 42.5, 63.3, 67.5, 73.2, 74.7, 77.7, 79.1, 83.1, 84.8; HREIMS *m*/*z* calcd for $C_{17}H_{30}O_5Si$ 342.1863, found 342.1852.

(*ii*) *Reaction with methyl propiolate*. The diol (507 mg, 1.48 mmol) dissolved in THF (10 mL), and treated with methyl propiolate (0.53 mL, 5.94 mmol) and NMM (0.65 mL, 5.94 mmol). The reaction mixture was stirred at rt for 17 h and extracted with EtOAc. The extract was washed with water and brine, dried, and concentrated. Purification by flash chromatography (20% EtOAc in hexane) gave **17** (756 mg, 100%) as a colorless oil; $[\alpha]_D^{25}$ −3.3 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3305, 1710, 1645, 1625, 1438, 1137 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.98 (9H, s), 1.05 (9H, s), 1.65 (1H, q, J=11.7 Hz), 2.66 (1H, d, J=2.4 Hz), 2.69 (1H, ddd, J=11.7, 4.4, 4.4 Hz), 3.39 (1H, ddd, J=10.2, 9.8, 4.9 Hz), 3.71 and 3.72 (each 3H, s), 3.74 (1H, dd, J=9.8, 2.0 Hz), 3.83 (1H, ddd, J=11.2, 9.8, 4.4 Hz), 3.86 (1H, t, J=10.2 Hz), 4.10 (1H, ddd, J=11.2, 9.8, 4.9 Hz), 4.20 (1H, dd, J=10.2, 4.9 Hz), 4.81 (1H, t, J=2.4 Hz), 5.37 and 7.46 (each 1H, d, J=12.7 Hz), 5.41 and 7.61 (each 1H, d, J=12.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.9, 22.6, 26.9 (3×C), 27.4 (3×C), 38.0, 51.2, 51.3, 66.3, 70.1, 71.2, 75.1, 75.3, 77.2, 78.9, 79.5, 99.1, 99.3, 159.8, 159.9, 167.5, 167.6; HREIMS *m*/*z* calcd for $C_{25}H_{38}O_9Si$ 510.2285, found 510.2297.

4.2.14. (*E*)-(4a*R*,5*S*,7*S*,8a*R*,9a*S*,10a*R*)-[2,2-Di(*tert*-butyl)-5-(2-methoxycarbonylvinyloxy)-6-methylenetetradecahydro-1,3,8,10-tetraoxa-2-silaanthracen-7-yl]acetic acid methyl ester (18). According to the general procedure, **17** (756 mg, 1.48 mmol) was subjected to the radical cyclization and destannylation to give **18** (577 mg, 76% as a 94:6 mixture of diastereoisomers) as a colorless oil; $[\alpha]_D^{25}$ −35.7 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 1739, 1707, 1473, 1438, 1139, 1107, 1047 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.97 (9H, s), 1.03 (9H, s), 1.48 (1H, q, J=11.7 Hz), 2.48 (1H, ddd, J=11.7, 4.4, 4.4 Hz), 2.63 (1H, dd, J=15.1, 8.8 Hz), 2.71 (1H, dd, J=15.1, 4.9 Hz), 3.26 (1H, dd, J=9.8, 2.9 Hz), 3.34 (1H, ddd, J=10.2, 10.2, 4.9 Hz), 3.68 and 3.71 (each 3H, s), 3.79–3.86 (2H, m), 3.85 (1H, t, J=10.2 Hz), 4.12 (1H, dd, J=10.2, 4.9 Hz), 4.50 (1H, dd, J=8.8, 4.9 Hz), 4.63 (1H, d, J=2.9 Hz), 5.11 (1H, d, J=1.5 Hz), 5.24 (1H, s), 5.35 and 7.45 (each 1H, d, J=12.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.9, 22.5, 27.0 (3×C), 27.4 (3×C), 36.6, 38.4, 51.1, 51.9, 66.5, 69.4, 70.8, 71.9, 72.9, 77.9, 79.9, 82.3, 98.9, 115.2, 141.9, 160.0, 170.1; HREIMS *m*/*z* calcd for $C_{25}H_{40}O_9Si$ 512.2442, found 512.2425.

4.2.15. (4a*R*,5*S*,7*S*,8a*R*,9a*S*,10a*S*)-[2,2-Di(*tert*-butyl)-5-hydroxy-6-methylenetetradecahydro-1,3,8,10-tetraoxa-2-silaanthracen-7-yl]acetic acid methyl ester (19). A solution of **18** (479 mg, 0.936 mmol, a 94:6 mixture of diastereoisomers), *n*-dodecanethiol (0.90 mL, 3.743 mmol), and TsOH·H_2O (53 mg, 0.281 mmol) in CH_3CN (9.4 mL) was heated at 80 °C for 1.5 h. After cooling to rt, Et_3N (0.2 mL) was added to the solution and the reaction mixture was concentrated. Purification by flash chromatography (30% EtOAc in hexane) gave pure **19** (322 mg, 82%) as a solid. Mp 155–156 °C; $[\alpha]_D^{25}$ −47.5 (*c* 0.28, $CHCl_3$); IR ($CHCl_3$) 3574, 1738, 1473, 1438, 1100, 1048 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.97 (9H, s), 1.04 (9H, s), 1.52 (1H, q, J=11.7 Hz), 2.16 (1H, s, OH), 2.47 (1H, ddd, J=11.7, 4.4, 4.4 Hz), 2.63 (1H, dd, J=15.1, 8.8 Hz), 2.73 (1H, dd, J=15.1, 4.9 Hz), 3.18 (1H, dd, J=9.3, 2.9 Hz), 3.41 (1H, ddd, J=10.3, 10.3, 4.9 Hz), 3.71 (3H, s), 3.82 (2H, ddd, J=9.3, 9.3, 4.4 Hz), 3.85 (1H, t, J=10.3 Hz), 4.14 (1H, dd, J=10.3, 4.9 Hz), 4.46 (1H, d, J=2.9 Hz), 4.68 (1H, dd, J=8.8, 4.9 Hz), 4.98 (1H, d, J=1.5 Hz), 5.17 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.9, 22.6, 27.0 (3×C), 27.4 (3×C), 36.8, 38.3, 51.9, 66.7, 69.0, 70.9, 72.2, 72.4, 77.8, 80.7, 113.7, 144.8, 171.4; HREIMS *m*/*z* calcd for $C_{21}H_{36}O_7$ 428.2230, found 428.2238.

4.2.16. (*E*,*E*)-(4a*R*,6*R*,7*R*,8a*S*)-3-{2,2-Di(*tert*-butyl)-6-[(1*R*)-1-(2-methoxycarbonylvinyloxy)-2-propynyl]-hexahydro-1,3,5-trioxa-2-silanaphthalen-7-yloxy}acrylic acid methyl ester (20). The procedure used for the preparation of **17** was employed. An experiment starting with alcohol **12** (111 mg, 0.243 mmol) provided acetate **20** (123 mg, 97%) as a colorless oil; $[\alpha]_D^{25}$ −97.4 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3305, 1711, 1646, 1626, 1483, 1137 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.98 (9H, s), 1.04 (9H, s), 1.63 (1H, q, J=11.7 Hz, H4ax), 2.65 (1H, d, J=2.4 Hz), 2.68 (1H, ddd, J=11.7, 4.4, 4.4 Hz), 3.39 (1H, ddd, J=10.3, 9.3, 4.9 Hz), 3.60 (1H, dd, J=9.3, 2.0 Hz), 3.69 and 3.70 (each 3H, s), 3.84 (1H, ddd, J=11.2, 9.3, 4.4 Hz), 3.89 (1H, t, J=10.3 Hz), 4.11 (1H, ddd, J=11.2, 9.3, 4.9 Hz), 4.21 (1H, dd, J=10.3, 4.9 Hz), 4.79 (1H, t, J=2.2 Hz), 5.33 and 7.41 (each 1H, d, J=12.2 Hz), 5.41 and 7.57 (each 1H, d, J=12.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.9, 22.6, 27.0 (3×C), 27.4 (3×C), 38.0, 51.2 (2×C), 66.3, 68.4, 71.3, 73.9, 76.5, 77.2, 77.9, 79.9, 99.1, 99.5, 159.5, 160.0, 167.4, 167.5; HREIMS *m*/*z* calcd for $C_{25}H_{38}O_9Si$ 510.2285, found 510.2296.

4.2.17. (*E*)-(4a*R*,5*R*,7*S*,8a*R*,9a*S*,10a*R*)-[2,2-Di(*tert*-butyl)-5-(2-methoxycarbonylvinyloxy)-6-methylenetetradecahydro-1,3,8,10-tetraoxa-2-silaanthracen-7-yl]acetic acid methyl ester (21). According to the general procedure, **20** (121 mg, 0.238 mmol) was subjected to the radical cyclization and destannylation to give **21** (90 mg, 74% as a 94:6 mixture of diastereoisomers) as a colorless oil; $[\alpha]_D^{25}$ −18.1 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 1734, 1706, 1473, 1438, 1139, 1104, 1054 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.96 (9H, s), 1.03 (9H, s), 1.55 (1H, q, J=11.7 Hz), 2.48 (1H, ddd, J=11.7, 4.4, 4.4 Hz), 2.72 (1H, dd, J=15.1, 4.4 Hz), 2.78 (1H, dd, J=15.1, 5.4 Hz), 3.18 (1H,

t, $J=9.3$ Hz), 3.29–3.38 (2H, m), 3.69 and 3.72 (each 3H, s), 3.80 (1H, t, $J=10.2$ Hz), 3.83 (1H, m), 4.15 (1H, dd, $J=10.2$, 5.4 Hz), 4.29–4.35 (2H, m), 5.03 (1H, t, $J=2.0$ Hz), 5.20 (1H, d, $J=2.0$ Hz), 5.37 and 7.53 (each 1H, d, $J=12.2$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.9, 22.6, 27.0 (3×C), 27.4 (3×C), 36.7, 38.1, 51.1, 52.0, 66.5, 72.2, 74.2, 74.3, 77.2, 81.7, 83.3, 98.2, 109.5, 141.3, 162.6, 168.0, 170.1; HREIMS *m/z* calcd for $C_{25}H_{40}O_9Si$ 512.2442, found 512.2473.

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