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Efficient strategy for the iterative synthesis of *trans*-fused polycyclic ether via SmI_2-induced reductive intramolecular cyclization

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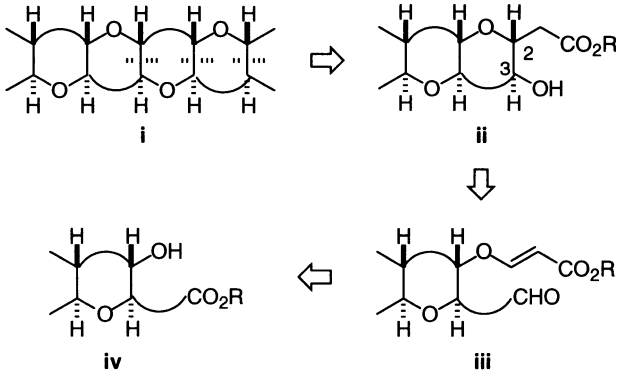
Abstract—A highly efficient strategy for the iterative synthesis of a *trans*-fused polycyclic ether ring system has been developed. The new iterative method involves SmI_2-induced reductive intramolecular cyclization of an aldehyde and a β-alkoxy acrylate as the key step, producing a 2,3-*trans*-tetrahydropyran or oxepane ring. The syntheses of *trans*-fused 6,6,6-tricyclic, 6,7,6-tricyclic, and 6,7,7,6-tetracyclic ethers were effectively achieved based on the newly developed method.

1. Introduction

Since the first isolation of brevetoxin-B, a potent neurotoxin produced by the red tide organism *Gymnodinium breve*,[1] a number of marine polycyclic ethers, exemplified by ciguatoxins, yessotoxin, and maitotoxin, have been reported.[2] The most characteristic structural feature of these natural products is a *trans*-fused polycyclic ether ring system, in which medium- and large-membered ethers are involved. The synthetically challenging unique structures and their potent biological activities have attracted the attention of numerous synthetic organic chemists. Thus, a large number of methods for the synthesis of cyclic ethers towards the total synthesis of marine polycyclic ethers have been reported.[3] Herein, we describe in detail an extremely facile and highly efficient strategy for the iterative synthesis of the *trans*-fused polycyclic ether ring system based on SmI_2-induced reductive intramolecular cyclization.[4]

2. Results and discussion

Our strategy for the iterative synthesis of *trans*-fused polycyclic ether **i** is shown in Scheme 1. The key step involves a stereoselective C–C bond formation for the construction of every cyclic ether ring. Retrosynthetic cleavage of the indicated C–C bond in **i** reveals a key precursor **ii**, which has a C2-alkoxycarbonylmethyl and a C3-hydroxyl group. From Lee's pioneering work using β-alkoxyacrylate as an radical acceptor,[3g] the C–C bond formation at C-2 and C-3



Scheme 1.

was expected by radical-mediated cyclization of **iii**. We anticipated that highly stereoselective construction of 2,3-*trans*-cyclic ether **ii** would be realized by SmI_2-induced reductive cyclization[5] of **iii**. Since **iii** will be prepared from **iv** having the same functional groups as those of **ii**, repetition of the same reaction sequences would stereoselectively provide the desired *trans*-fused polycyclic ether **i**.

First, the required substrates **4** and **7** for the construction of 2,3-*trans*-tetrahydropyran and oxepane were synthesized from the known triflate **1**,[3n] prepared from tri-*O*-acetyl-D-glucal, via thioacetals **3** and **6**, respectively (Scheme 2). Treatment of **1** with NaI in refluxing acetone afforded iodide **2** in 98% yield. Addition of lithiated 1,3-dithiane to **2** followed by deprotection of the TBS group with TBAF afforded thioacetal **3** in 75% yield. On the other hand, thioacetal **6** was synthesized from **1** by three steps: (1) allylation with allylMgCl in the presence of CuI,[6] (2) ozonolysis of the

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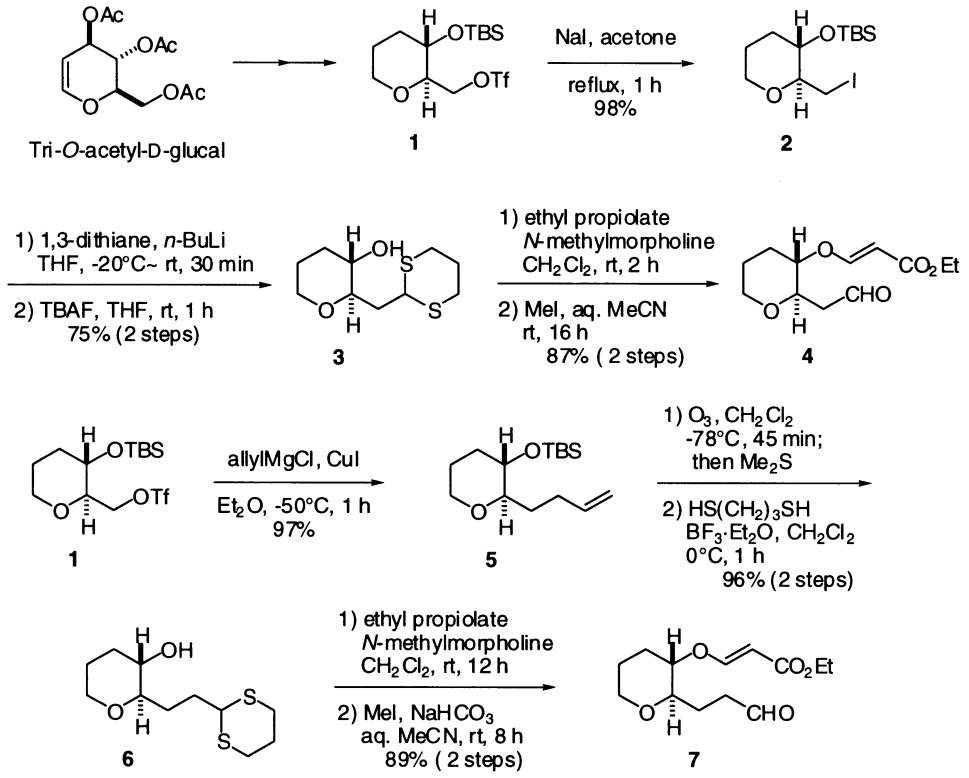
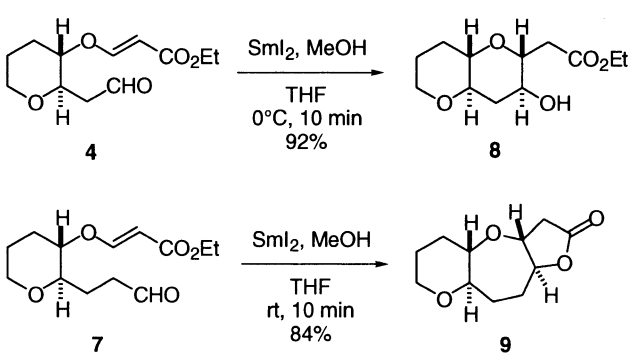


Scheme 2.

olefin, and (3) thioacetalization with 1,3-propanedithiol and $BF_3{\cdot}Et_2O$. The hetero-Michael reaction of **3** with ethyl propiolate in the presence of *N*-methylmorpholine in CH_2Cl_2 gave β-alkoxyacrylate,[7] the thioacetal of which was removed by treatment with MeI[8] to give the required aldehyde **4**[9] in 87% yield. Under the same reaction conditions, the thioacetal **6** was also converted into aldehyde **7** in 89% yield.

Then, radical-mediated reductive cyclization of **4** and **7** with SmI_2,[10] the key reaction for our iterative strategy, was investigated (Scheme 3). Upon treatment of **4** with 2.2 equiv. of SmI_2 in the presence of 2.2 equiv. of MeOH in THF, the reductive cyclization smoothly proceeded at 0°C and was completed within 10 min to give a product **8** in 92% yield with complete stereoselection.[11] The ^1H and ^{13}C NMR, NOE and HMBC analyses suggested that the structure of the newly formed ring in **8** is our desired 2,6-*syn*-2,3-*trans*-tetrahydropyran (Fig. 1). To our knowledge, this is the first report for the construction of cyclic ethers by SmI_2-induced intramolecular reductive cyclization.[12] On the other hand, cyclization of **7** with SmI_2 and MeOH in THF also completed at room temperature in 10 min to give oxepane **9** as the sole product in 84% yield, accompanied with γ-lactone formation.[13] The structure of **9** was unequivocally confirmed to be the desired 2,7-*syn*-2,3-*trans*-oxepane by extensive NMR analysis (Fig. 1). Thus, SmI_2-induced cyclization performed the construction of the 2,3-*trans*-tetrahydropyran and oxepane with complete stereoselection. It is noteworthy that the products **8** and **9** possess a C2-carbonylmethyl and a C3-hydroxyl groups, which will be easily converted into the required functional groups for further cyclization.

A plausible mechanism for the stereoselective cyclization of **4** leading to **8** would be explained as shown in Fig. 2. Initial



Scheme 3.

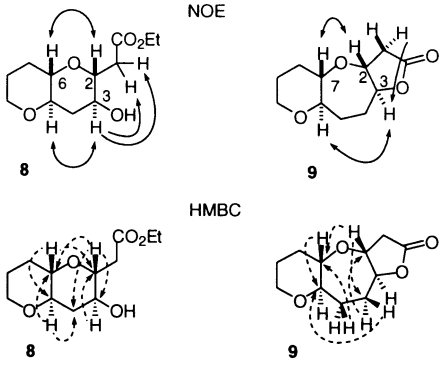


Figure 1. NOE and HMBC of products **8** and **9**.

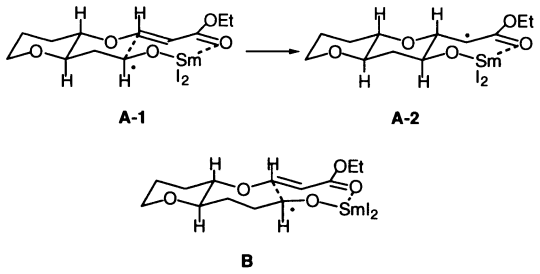
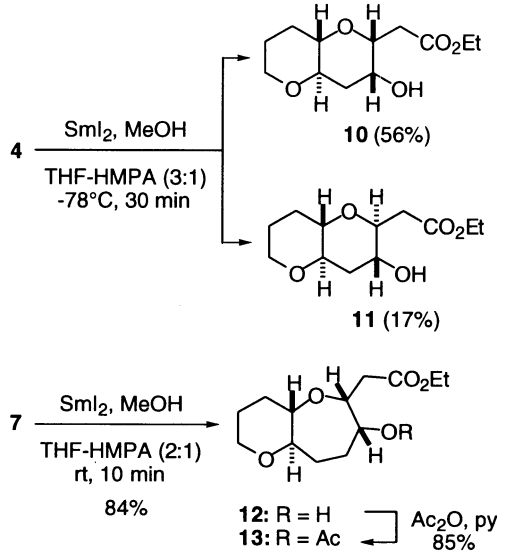


Figure 2.

single-electron reduction of the aldehyde **4** with SmI_2 produces the ketyl radical, and subsequent C–C bond formation stereoselectively would take place through the chelation transition state A-1. The second equivalent of SmI_2 would reduce the radical in A-2 to an anion, which should be protonated by MeOH to give 2,3-*trans*-cyclic ethers **8**.[14] The use of MeOD instead of MeOH resulted in deuteration at the α-position of the ester. Reaction of **7** would also proceed via chelation transition state B to produce **9**. Thus, the chelation of Sm(III) to the ester would make an important contribution towards achieving complete stereoselectivity in the present cyclization reaction.

In various SmI_2-induced reactions, hexamethylphosphoramide (HMPA) is generally and frequently used to activate the reactions.[15] Here, we examined the reaction conditions using HMPA as an additive. After several attempts, very interesting results were obtained, i.e. addition of HMPA completely changed the stereoselectivity in the present reaction (Scheme 4). When THF/MPA (3:1) was used as the solvent system, reaction of **4** with SmI_2 in the presence of MeOH proceeded smoothly at −78°C for 30 min to give two cyclized products, 2,6-*syn*-2,3-*cis*-tetrahydropyran **10** (56%) and 2,6-*anti*-2,3-*trans*-isomer **11** (17%). In addition, reaction of **7** under the same reaction conditions predominantly gave 2,7-*syn*-2,3-*cis*-oxepane **12** in 84% yield. Extensive NMR analysis of **10**, **11**, and the corresponding acetate **13** prepared from **12** (Fig. 3) also confirmed the



Scheme 4.

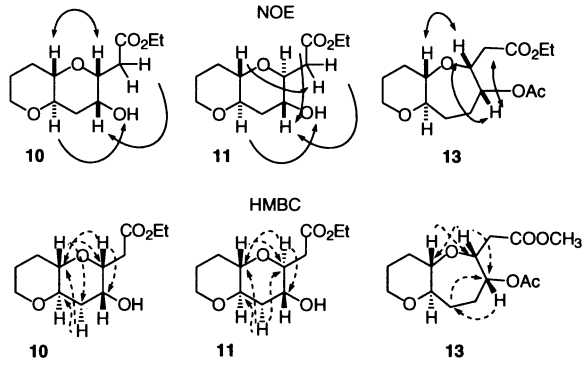


Figure 3. NOE of products **10**, **11**, and **13**.

stereostructures of the products. The tetrahydropyrans **10** and **11** and oxepane **12** would be produced via transition states C, D, and E, in which the chelation between Sm(III) and the ester should be very difficult because of steric hindrance due to the tight coordination[16] of HMPA to Sm(III) (Fig. 4).

Based on the SmI_2-induced reductive cyclization, a highly effective iterative synthesis of the *trans*-fused 6,6,6,6-membered tetracyclic ether ring system was accomplished as shown in Scheme 5. The tetrahydropyran **8** was first converted into aldehyde **15** having the requisite functional groups for the second reductive cyclization. Reduction of **8** with DIBAH followed by treatment with 1,3-propanedithiol in the presence of $BF_3{\cdot}Et_2O$ gave thioacetal **14** in 99% yield. The alcohol **14** was subjected to the hetero-Michael reaction with ethyl propiolate and deprotection of the thioacetal with MeI to afford aldehyde **15** in 90% yield. The second cyclization of **15** with SmI_2 was achieved under the same reaction conditions as those of **4** to give *trans*-fused 6,6,6-membered ether **16** exclusively in 86% yield. Following the same four-step sequence, **16** was converted into aldehyde **18** via thioacetal **17** in 78% overall yield. The third SmI_2-induced cyclization of **18** stereoselectively furnished *trans*-fused 6,6,6,6-membered ether **19** in 83% yield. The stereostructures of products **16** and **19** were also confirmed by extensive NMR analysis.

Further ring construction of a polycyclic ether ring system containing tetrahydropyran and oxepane rings was then investigated. First, construction of the *trans*-fused 6,7,6-membered ether ring system was examined as shown in Scheme 6. Successive treatments of lactone **9** with DIBAH and 1,3-propanedithiol/$BF_3{\cdot}Et_2O$ afforded

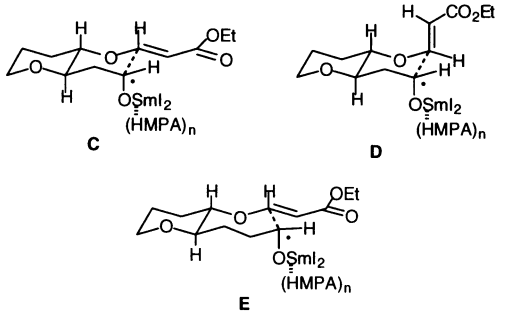
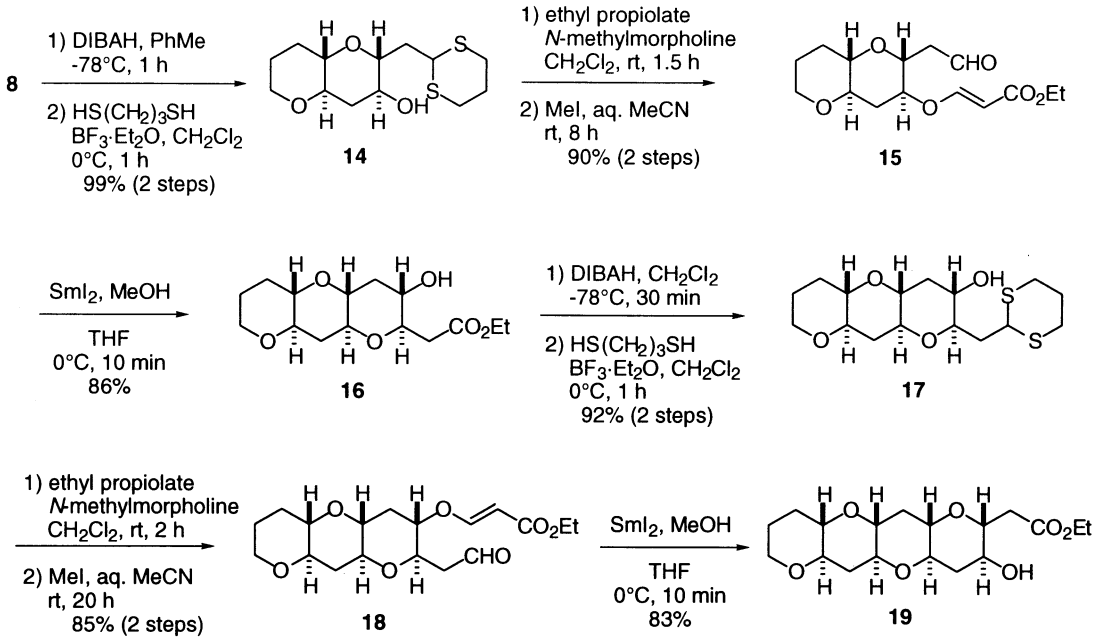


Figure 4.



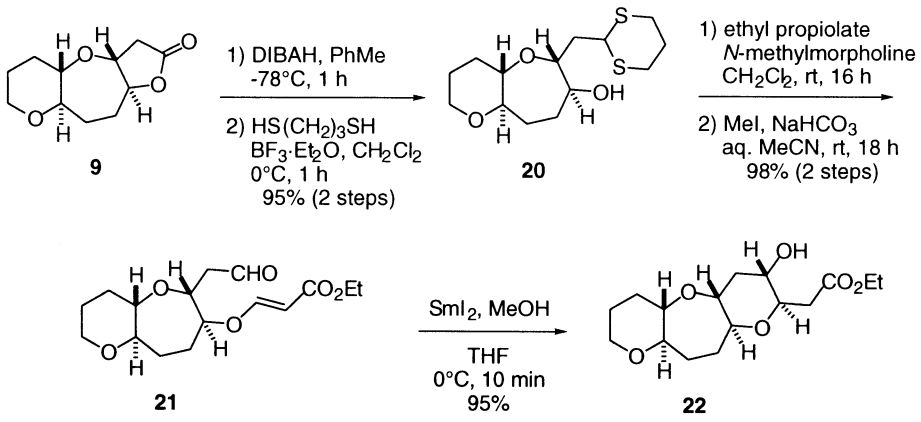
Scheme 5.

thioacetal **20** in 95% yield. The hetero-Michael reaction of **20** with ethyl propiolate followed by dethioacetalization gave aldehyde **21** in 98% yield. Treatment of **21** with SmI_2 in THF in the presence of MeOH at 0°C also effected the construction of the 2,3-*trans*-tetrahydropyran ring with complete stereoselection to give *trans*-fused 6,7,6-membered ether **22** in 95% yield.

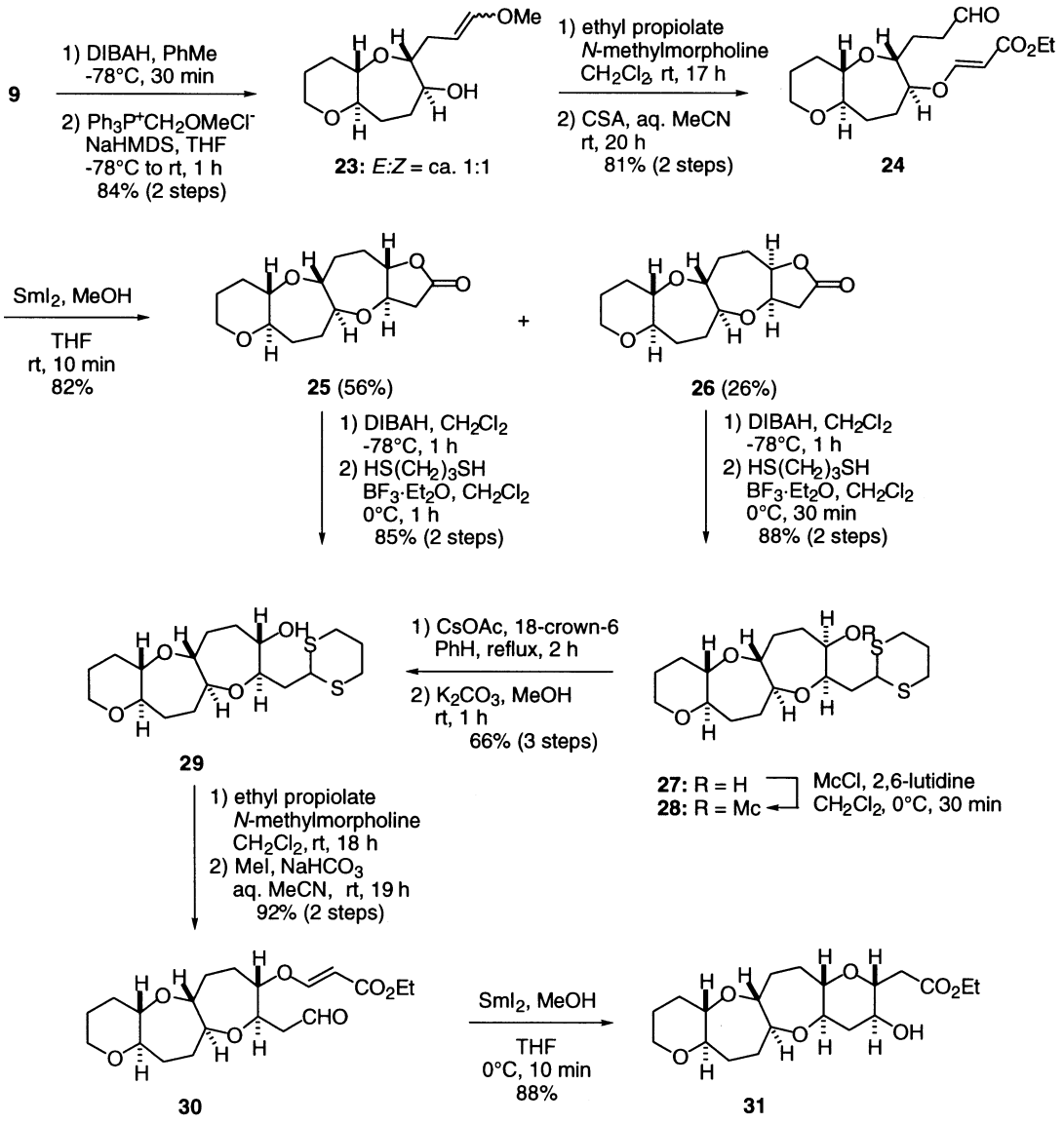
Next, construction of a *trans*-fused 6,7,7,6-membered ether ring system was investigated as shown in Scheme 7. Reduction of **9** with DIBAH followed by the Wittig reaction using $Ph_3P{=}CHOMe$[17] afforded methyl enol ether **23** (*E*/*Z*=ca. 1:1) in 84% yield. The hetero-Michael reaction of **23** with ethyl propiolate, and subsequent CSA treatment in aqueous MeCN gave aldehyde **24** in 81% yield. Reaction of **24** with SmI_2 produced *trans*- and *cis*-oxepanes, **25** and **26**, in 56 and 26% yields, respectively. Both isomers **25** and **26** were converted into the same *trans*-fused tricyclic ether **29**. DIBAH reduction of the *trans*-**25** followed by thioacetalization afforded thioacetal **29** in 85% yield. Following the same reactions, the *cis*-isomer **26** was also converted into thioacetal **27** in 88% yield. The β-alcohol in **27** was then inverted to an α-alcohol by our method using a monochloromethanesulfonate (monochlate) as an efficient leaving group.[18] Treatment of **27** with $ClCH_2SO_2Cl$ (=McCl) afforded monochlate **28**, which was subjected to the inversion reaction with CsOAc in the presence of 18-crown-6, and methanolysis with K_2CO_3 to afford **29** in 66% overall yield from **27**. The hetero-Michael reaction of **29** followed by dethioacetalization provided aldehyde **30** in 92% yield. Reaction of **30** with SmI_2 also effected the construction of the 2,3-*trans*-tetrahydropyran ring with complete stereoselection to afford the desired *trans*-fused 6,7,7,6-membered ether **31** in 88% yield.

3. Conclusion

We have developed a very reliable and powerful method for the iterative synthesis of a *trans*-fused polycyclic ether ring system based on SmI_2-induced reductive cyclization. The usefulness of the present method was demonstrated by the



Scheme 6.



Scheme 7.

stereoselective synthesis of *trans*-fused 6,6,6,6-, 6,7,6-, and 6,7,7,6-membered polycyclic ethers, which are often found in marine polycyclic ethers. The advantages of the present method are: (1) high yield and simple procedure for each reaction step, (2) high stereoselectivity in the construction of cyclic ether, and (3) no need of any asymmetric reactions and chiral reagents; the chirality of the new rings arises from the stereochemistry of the starting material.

The present method has been successfully applied to the construction of ether rings in marine polycyclic ethers.[19] Further studies on the SmI_2-induced reductive cyclization and synthetic studies towards marine polycyclic ethers are now in progress in this laboratory.

4. Experimental

4.1. General

All reactions were carried out under an argon atmosphere. Flash column chromatography was performed using Kanto silica gel 60 N (spherical, neutral; 40–100 μm). Melting points were determined using a Yanaco MP-500 apparatus and are uncorrected. Optical rotations were measured using a JASCO DIP-370 digital polarimeter. Infrared spectra were recorded using a JASCO VALOR-III FT-IR spectrometer. Mass spectra were measured using a JEOL AX-505. ^1H and ^{13}C NMR spectra were recorded on a JEOL JNM-EX270, a JEOL JNM-AL, a JEOL JNM-GSX, a JEOL JNM-ECP, and a JEOL JNM-α spectrometer.

4.1.1. (2*S*,3*S*)-*tert*-Butyl-(2-iodomethyl-tetrahydro-pyran-3-yloxy)-dimethyl-silane (2). A solution of **1** (0.77 g, 2.03 mmol) and NaI (1.52 g, 10.14 mmol) in acetone (40 mL) was heated at 60°C for 1 h. The mixture was diluted with Et_2O, washed with saturated aqueous $Na_2S_2O_3$ and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (*n*-hexane/EtOAc, 20:1) to give **2** (0.71 g, 98%) as a colorless oil. $[\alpha]^{24}_D=+57.8$ (*c* 1.87, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 3.97 (m, 1H), 3.51 (dd, *J*=10.4,

2.8 Hz, 1H), 3.46–3.34 (m, 2H), 3.32 (dd, J=10.4, 5.3 Hz, 1H), 2.82 (ddd, J=8.4, 5.8, 2.8 Hz, 1H), 2.03 (m, 1H), 1.78–1.62 (m, 2H), 1.48 (m, 1H), 0.88 (s, 9H), 0.12 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 80.7, 71.2, 67.9, 33.1, 25.8, 25.5, 17.9, 9.4, −3.8, −4.4; HRMS (FAB) calcd for $C_{12}H_{26}O_2SiI$ ($M+H^+$) 357.0747, found 357.0746.

4.1.2. (2*R*,3*S*)-2-[1,3]Dithian-2-ylmethyl-tetrahydro-pyran-3-ol (3). To a solution of 1,3-dithiane (279.5 mg, 2.32 mmol) in THF (7.8 mL) was added *n*-BuLi (1.5 mL, 1.53 M solution in *n*-hexane, 2.28 mmol) at −30°C. The mixture was stirred at −20°C for 1.5 h, and a solution of **2** (162.4 mg, 0.46 mmol) in THF (4.6 mL) was added. After stirring at rt for 30 min, the mixture was diluted with Et_2O, washed with saturated aqueous NH_4Cl. The aqueous layer was extracted with Et_2O and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (*n*-hexane/EtOAc, 20:1) to give a thioacetal (158.9 mg). To a solution of the thioacetal in THF (9 mL) was added TBAF (595.9 mg, 2.28 mmol). After stirring at rt for 1 h, the mixture was quenched with H_2O and extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (*n*-hexane/EtOAc, 10:1→5:1→3:1→1:1) to give **3** (80.2 mg, 75%) as colorless crystals. Mp 91–92°C (recrystallized from Et_2O); $[\alpha]^{23}_D$=+32.2 (*c* 1.00, $CHCl_3$); IR (nujol) 3468 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.28 (dd, J=10.3, 4.1 Hz, 1H), 3.90 (m, 1H), 3.32 (m, 3H), 2.88 (m, 4H), 2.32 (ddd, J=14.5, 10.0, 2.1 Hz, 1H), 2.13 (m, 2H), 1.88 (m, 2H), 1.69 (m, 2H), 1.43 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 78.8, 70.3, 67.5, 43.1, 38.4, 33.1, 30.2, 29.7, 26.0, 25.5; HRMS (FAB) calcd for $C_{10}H_{19}O_2S_2$ ($M+H^+$) 235.0826, found 235.0822. Anal. Calcd for $C_{10}H_{18}O_2S_2$: C, 51.25; H, 7.74; S, 27.36. Found: C, 51.18; H, 7.70; S, 27.41.

4.1.3. (2*R*,3*S*)-(*E*)-3-[2-(2-Oxo-ethyl)-tetrahydro-pyran-3-yloxy]-acrylic acid ethyl ester (4). To a solution of **3** (117.1 mg, 0.50 mmol) in CH_2Cl_2 (3 mL) were added *N*-methylmorpholine (0.22 mL, 2.00 mmol) and ethyl propiolate (0.10 mL, 1.00 mmol) at rt. After stirring for 2 h, the mixture was diluted with EtOAc, washed with H_2O. The aqueous layer was extracted with EtOAc and the combined organic layers were dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (*n*-hexane/EtOAc, 4:1) to give an ester (224.2 mg). To a solution of the ester in MeCN (5 mL) and H_2O (1.25 mL) was added MeI (1.56 mL, 25.0 mmol) at rt. After stirring for 16 h, the mixture was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc and the combined organic layers were dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (*n*-hexane/EtOAc, 2:1) to give **4** (104.9 mg, 87%) as a colorless oil. $[\alpha]^{25}_D$=+28.3 (*c* 1.00, $CHCl_3$); IR (neat) 1727, 1708, 1645, 1625 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.77 (dd, J=2.8, 1.6 Hz, 1H), 7.46 (d, J=12.5 Hz, 1H,), 5.29 (d, J=12.5 Hz, 1H), 4.16 (q, J=7.0 Hz, 2H), 3.92 (m, 1H), 3.81 (ddd, J=9.1, 8.9, 3.5 Hz, 1H), 3.68 (ddd, J=10.8, 9.1, 4.7 Hz, 1H), 3.42 (ddd, J=11.7, 11.7, 3.7 Hz, 1H), 2.75 (ddd, J=16.4, 3.5, 1.6 Hz, 1H), 2.54 (ddd, J=16.4, 8.9, 2.8 Hz, 1H), 2.29 (m, 1H), 1.74 (m, 2H), 1.55 (m, 1H), 1.27 (t, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.0, 167.5, 160.4, 98.7, 79.8, 75.0, 67.7, 59.9, 46.1, 29.3, 24.9, 14.3; HRMS (FAB) calcd for $C_{12}H_{19}O_5$ ($M+H^+$) 243.1232, found 243.1234.

4.1.4. (2*R*,3*S*)-(2-But-3-enyl-tetrahydro-pyran-3-yloxy)-*tert*-butyl-dimethyl-silane (5). To a stirred suspension of CuI (545 mg, 2.86 mmol) in Et_2O (5 mL) was added a solution of **2** (1.06 g, 2.86 mmol) in Et_2O (15 mL) at −50°C. After stirring for 10 min, allylMgCl (2.86 mL, 2.0 M solution in THF, 5.71 mmol) was added and the mixture was stirred at the same temperature for 1 h. The mixture was quenched with saturated aqueous NH_4Cl, extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (*n*-hexane/EtOAc, 20:1) to give **5** (745.3 mg, 97%) as a colorless oil. $[\alpha]^{20}_D$=+55.0 (*c* 2.28, $CHCl_3$); IR (neat) 1642 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.77 (dddd, J=16.9, 13.0, 6.6, 6.6 Hz, 1H), 4.92 (m, 2H), 3.81 (br d, J=10.6 Hz, 1H), 3.23 (m, 2H), 2.94 (t like, J=8.8 Hz, 1H), 2.17 (m, 1H), 2.09–1.79 (m, 3H), 1.62–1.54 (m, 2H), 1.42–1.27 (m, 2H), 0.82 (s, 9H), 0.00 (s, 3H), −0.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.9, 114.2, 82.0, 71.3, 67.7, 33.7, 31.4, 29.5, 25.8, 17.9, −4.0, −4.7; MS (FAB) *m/z* 379 ($M+Na^+$).

4.1.5. (2*R*,3*S*)-2-(2-[1,3]Dithian-2-yl-ethyl)-tetrahydro-pyran-3-ol (6). To a solution of **5** (4.82 g, 17.9 mmol) in CH_2Cl_2 (150 mL) was bubbled O_3 at −78°C for 45 min. After N_2 was bubbled to the mixture, Me_2S (5 mL) was added. After stirring at −78°C for 30 min and at rt for 30 min, the mixture was concentrated in vacuo to give the crude aldehyde. To a solution of the aldehyde in CH_2Cl_2 (150 mL) were added 1,3-propanedithiol (5.4 mL, 53.7 mmol) and $BF_3{\cdot}Et_2O$ (6.6 mL, 53.7 mmol) at 0°C. After stirring at 0°C for 1 h, the mixture was quenched with H_2O and extracted with EtOAc. The combined organic layers were washed with 10% aqueous NaOH, saturated aqueous NH_4Cl, and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (*n*-hexane/EtOAc, 2:1→1:1) to give **6** (4.25 g, 96%) as colorless crystals. Mp 100–101°C (recrystallized from Et_2O); $[\alpha]^{24}_D$=+35.4 (*c* 0.78, $CHCl_3$); IR (nujol) 3510, 3355, 3256 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.06 (dd, J=7.3, 6.4 Hz, 1H), 3.89 (m, 1H), 3.34 (m, 2H), 3.01 (ddd, J=11.0, 8.7, 2.3 Hz, 1H), 2.91–2.81 (m, 4H), 2.14–2.00 (m, 4H), 1.91–1.80 (m, 2H), 1.73–1.57 (m, 5H), 1.40 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 81.8, 70.4, 67.5, 47.6, 32.8, 31.3, 30.31, 30.28, 29.0, 26.0, 25.6; HRMS (FAB) calcd for $C_{11}H_{21}O_2S_2$ ($M+H^+$) 249.0983, found 249.0995. Anal. Calcd for $C_{11}H_{20}O_2S_2$: C, 53.19; H, 8.12. Found: C, 53.08; H, 8.18.

4.1.6. (2*R*,3*S*)-(*E*)-3-[2-(3-Oxo-propyl)-tetrahydro-pyran-3-yloxy]-acrylic acid ethyl ester (7). To a solution of **6** (4.70 g, 19.0 mmol) in CH_2Cl_2 (200 mL) were added *N*-methylmorpholine (4.14 mL, 37.9 mmol) and ethyl propiolate (3.80 mL, 37.9 mmol) at rt. After stirring for 12 h, the mixture was diluted with EtOAc, washed with H_2O and brine, dried over $MgSO_4$, and concentrated in

vacuo. The residue was purified by flash column chromatography (*n*-hexane/EtOAc, 3:1) to give an ester (7.16 g). To a solution of the ester in MeCN (160 mL) and H_2O (40 mL) were added $NaHCO_3$ (4.80 g, 56.9 mmol) and MeI (1.5 mL, 23.5 mmol) at rt. After stirring for 8 h, the mixture was diluted with EtOAc, washed with H_2O. The aqueous layer was extracted with EtOAc and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (*n*-hexane/EtOAc, 2:1) to give **7** (4.32 g, 89%) as a colorless oil. $[\alpha]^{22}_D$=+41.6 (*c* 1.10, $CHCl_3$); IR (neat) 1713, 1644 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.76 (dd, *J*=1.8, 1.4 Hz, 1H), 7.49 (d, *J*=12.4 Hz, 1H), 5.29 (d, *J*=12.4 Hz, 1H), 4.16 (q, *J*=6.9 Hz, 2H), 3.89 (m, 1H), 3.61 (ddd, *J*=9.2, 9.2, 4.6 Hz, 1H), 3.32 (ddd, *J*=11.5, 11.5, 3.2 Hz, 1H), 3.22 (ddd, *J*=11.5, 9.2, 2.7 Hz, 1H), 2.62–2.49 (m, 2H), 2.25 (m, 1H), 2.12 (m, 1H), 1.75–1.64 (m, 3H), 1.50 (m, 1H), 1.27 (t, *J*=6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.0, 167.6, 161.0, 98.1, 80.7, 78.6, 67.4, 59.8, 39.7, 29.3, 25.0, 24.7, 14.3; HRMS (FAB) calcd for $C_{13}H_{21}O_5$ ($M+H^+$) 257.1389, found 257.1385.

4.1.7. (2*R*,3*S*,4a*R*,8a*S*)-(3-Hydroxy-octahydro-pyrano-[3,2-*b*]pyran-2-yl)-acetic acid ethyl ester (8). To a solution of **4** (213.6 mg, 0.88 mmol) and MeOH (80 μL, 1.94 mmol) in THF (8 mL) was added SmI_2 (19.4 mL, 0.1 M solution in THF, 1.94 mmol) at 0°C. After stirring at 0°C for 10 min, the mixture was diluted with EtOAc, washed with H_2O. The aqueous layer was extracted with EtOAc, and the combined organic layers were dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (*n*-hexane/EtOAc, 3:2) to give **8** (198.2 mg, 92%) as colorless crystals. Mp 73–74°C (recrystallized from Et_2O); $[\alpha]^{25}_D$=+26.1 (*c* 1.00, $CHCl_3$); IR (nujol) 3426, 1737 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.17 (q, *J*=7.0 Hz, 2H, C*H*$_2$CH$_3$), 3.90 (m, 1H, 6β-H), 3.59 (ddd, *J*=9.5, 7.3, 4.3 Hz, 1H, 2β-H), 3.49 (br ddd, *J*=11.0, 9.5, 4.3 Hz, 1H, 3α-H), 3.37 (m, 1H, 6α-H), 3.04 (ddd, *J*=11.0, 8.9, 4.2 Hz, 1H, 8aβαH), 2.98 (ddd, *J*=11.0, 8.9, 4.0 Hz, 1H, 4aα-H), 2.81 (dd, *J*=15.3, 4.3 Hz, 1H, C*H*CO$_2$), 2.51 (dd, *J*=15.3, 7.3 Hz, 1H, C*H*CO$_2$), 2.37 (ddd, *J*=11.9, 4.3, 4.0 Hz, 1H, 4α-H), 2.05 (m, 1H, 8β-H), 1.70 (m, 2H, 7-H$_2$), 1.50 (ddd, *J*=11.9, 11.0, 11.0 Hz, 1H, 4β-H), 1.40 (m, 1H, 8α-H), 1.26 (t, *J*=7.0 Hz, 3H, CH$_2$C*H*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.0 (CO), 78.8 (C-2), 77.9 (C-8a), 76.7 (C-4a), 69.8 (C-3), 67.8 (C-6), 60.7 (*C*H$_2$CH$_3$), 39.2 (C-4), 38.2 (*C*H$_2$CO$_2$), 29.1 (C-8), 25.4 (C-7), 14.2 (CH$_2$*C*H$_3$); HRMS (FAB) calcd for $C_{12}H_{21}O_5$ ($M+H^+$) 245.1389, found 245.1396. Anal. Calcd for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25. Found: C, 58.72; H, 8.17.

4.1.8. (3a*R*,4a*S*,8a*R*,10a*S*)-Decahydro-1,4,8-trioxa-benzo-[*f*]azulen-2-one (9). To a solution of **7** (338.0 mg, 1.32 mmol) in MeOH (0.16 mL, 3.96 mmol) and THF (13 mL) was added SmI_2 (39.6 mL, 0.1 M solution in THF, 3.96 mmol) at rt. After stirring for 10 min, the reaction mixture was diluted with EtOAc, washed with H_2O. The aqueous layer was extracted with EtOAc and the combined organic layers were dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (*n*-hexane/EtOAc, 3:1) to give **9** (236.0 mg, 84%) as colorless crystals. Mp 83–84°C (recrystallized from Et_2O); $[\alpha]^{27}_D$=+17.1 (*c* 0.78, $CHCl_3$); IR (nujol) 1780 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 4.22 (ddd, *J*=10.8, 8.3, 8.3 Hz, 1H, 10aα-H), 4.14 (ddd, *J*=10.3, 8.3, 7.8 Hz, 1H, 3aβ-H), 3.88 (m, 1H, 7β-H), 3.26 (m, 1H, 7α-H), 3.18 (ddd, *J*=11.2, 8.3, 4.4 Hz, 1H, 4aβ-H), 3.08 (ddd, *J*=10.8, 8.3, 2.0 Hz, 1H, 8aα-H), 2.83 (dd, *J*=17.6, 7.8 Hz, 1H, 3β-H), 2.64 (dd, *J*=17.6, 10.3 Hz, 1H, 3α-H), 2.39 (dddd, *J*=14.2, 10.8, 8.3, 8.3 Hz, 1H, 10α-H), 2.11 (m, 1H, 5β-H), 2.01 (dddd, *J*=14.7, 8.3, 2.0, 2.0 Hz, 1H, 9α-H), 1.96 (dddd, *J*=14.7, 10.8, 10.8, 8.3 Hz, 1H, 9β-H), 1.79 (dddd, *J*=14.2, 10.8, 8.3, 2.0 Hz, 1H, 10β-H), 1.68 (m, 2H, 6-H$_2$), 1.44 (m, 1H, 5α-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.0 (CO), 83.4 (C-10a), 81.6 (C-4a), 79.6 (C-8a), 76.5 (C-3a), 67.6 (C-7), 36.3 (C-3), 30.4 (C-5), 30.2 (C-9), 25.4 (C-6), 25.2 (C-10). Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.33; H, 7.66.

4.1.9. (2*R*,3*R*,4a*R*,8a*S*)-(3-Hydroxy-octahydro-pyrano-[3,2-*b*]pyran-2-yl)-acetic acid ethyl ester (10) and (2*S*,3*R*,4a*R*,8a*S*)-(3-hydroxy-octahydro-pyrano[3,2-*b*]-pyran-2-yl)-acetic acid ethyl ester (11). To a solution of **4** (119.7 mg, 0.42 mmol) and MeOH (52 μL, 1.27 mmol) in THF (3 mL) and HMPA (1 mL) was added SmI_2 (12.7 mL, 0.1 M in THF, 1.27 mmol) at −78°C. After stirring at −78°C for 30 min, the mixture was diluted with EtOAc, washed with H_2O. The aqueous layer was extracted with EtOAc and the combined organic layers were dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (*n*-hexane/EtOAc, 2:3) to give **10** (67.0 mg, 56%) and **11** (20.3 mg, 17%). **10**: colorless oil; $[\alpha]^{25}_D$=−1.2 (*c* 2.00, $CHCl_3$); IR (neat) 3458, 1733, 1644 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.16 (q, *J*=7.1 Hz, 2H, C*H*$_2$CH$_3$), 3.94 (m, 1H, 3β-H), 3.92 (m, 1H), 3.91 (m, 1H, 6β-H), 3.41 (ddd, *J*=11.7, 11.7, 3.9 Hz, 1H, 6α-H), 3.30 (ddd, *J*=11.7, 9.3, 4.4 Hz, 1H, 5aα-H), 3.12 (ddd, *J*=10.7, 9.3, 4.4 Hz, 1H, 8aβ-H), 2.67 (dd, *J*=15.6, 7.3 Hz, 1H, C*H*CO$_2$), 2.61 (dd, *J*=15.6, 6.4 Hz, 1H, C*H*CO$_2$), 2.22 (ddd, *J*=13.2, 4.4, 3.4 Hz, 1H, 4α-H), 2.09 (br d, *J*=7.8 Hz, 1H, OH), 2.02 (m, 1H, 8β-H), 1.72 (m, 2H, 7-H$_2$), 1.68 (ddd, *J*=13.2, 11.7, 2.9 Hz, 1H, 4β-H), 1.50 (m, 1H, 8α-H), 1.26 (t, *J*=7.1 Hz, 3H, CH$_2$C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3 (*C*O$_2$Et), 78.8 (C-8a), 76.4 (C-2), 74.0 (C-4a), 68.4 (C-3), 68.1 (C-6), 60.7 (*C*H$_2$CH$_3$), 37.0 (C-4), 36.6 (*C*H$_2$CO$_2$), 29.3 (C-8), 25.5 (C-7), 14.1 (CH$_2$*C*H$_3$); HRMS (FAB) calcd for $C_{12}H_{21}O_5$ ($M+H^+$) 245.1389, found 245.1392. **11**: $[\alpha]^{24}_D$=−29.8 (*c* 2.28, $CHCl_3$); IR (neat) 3446, 1738, 1733, 1717, 1645 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 4.28 (br dd, *J*=8.3, 6.8 Hz, 1H. 2α-H), 4.16 (m, 2H, C*H*$_2$CH$_3$), 3.93 (m, 1H, 3β-H), 3.91 (m, 1H, 6β-H), 3.42 (m, 1H, 6α-H), 3.40 (ddd, *J*=11.7, 9.3, 4.4 Hz, 1H, 4aα-H), 3.31 (ddd, *J*=9.8, 9.3, 4.4 Hz, 1H, 8aβ-H), 2.81 (dd, *J*=14.9, 8.3 Hz, 1H, C*H*CO$_2$), 2.55 (dd, *J*=14.9, 6.8 Hz, 1H, C*H*CO$_2$), 2.10 (dddd, *J*=13.2, 4.4, 3.4, 1.0 Hz, 1H, 4α-H), 1.92 (m, 1H, 8β-H), 1.72 (m, 3H, 4β-H), 1.48 (m, 1H, 8α-H), 1.27 (t, *J*=7.1 Hz, 3H, CH$_2$C*H*$_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.6 (CO), 75.6 (C-2), 74.1 (C-4a), 71.1 (C-8a), 69.2 (C-3), 68.2 (C-6), 60.8 (*C*H$_2$CH$_3$), 35.4 (*C*H$_2$CO$_2$), 32.4 (C-4), 29.4 (C-8), 25.8 (C-7), 14.1 (CH$_2$*C*H$_3$); HRMS (FAB) calcd for $C_{12}H_{21}O_5$ ($M+H^+$) 245.1389, found 245.1389.

4.1.10. (4a*S*,6*R*,7*S*,9a*R*)-(7-Acetoxy-octahydro-1,5-dioxa-benzocyclohepten-6-yl)-acetic acid ethyl ester (13). To a solution of **7** (54.9 mg, 0.21 mmol) and MeOH (26 μL,

0.64 mmol) in THF (1.4 mL) and HMPA (0.7 mL) was added SmI_2 (6.4 mL, 0.1 M solution in THF, 0.64 mmol) at −78°C. After stirring at −78°C for 30 min, the mixture was diluted with EtOAc, washed with saturated aqueous $Na_2S_2O_3$. The aqueous layer was extracted with EtOAc and the combined organic layers were dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (*n*-hexane/EtOAc, 3:2) to give ester **12** (46.3 mg, 84%) as a colorless oil. A solution of **12** (33.0 mg, 0.13 mmol) in pyridine (1 mL) and Ac_2O (1 mL) was stirred at rt for 2.5 h. The mixture was co-evaporated with toluene and the residue was purified by flash column chromatography (*n*-hexane/EtOAc, 2:1) to give **13** (33.2 mg, 85%) as a colorless oil. $[\alpha]^{26}_D$=+26.9 (*c* 3.73, $CHCl_3$); IR (neat) 1738, 1644 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 4.87 (ddd, *J*=6.4, 3.4, 3.4 Hz, 1H, 7β-H), 4.16 (q, *J*=7.3 Hz, 2H, CH_2CH$_3$), 3.98 (ddd, *J*=9.3, 6.4, 3.9 Hz, 1H, 6β-H), 3.87 (ddd, *J*=13.2, 3.9, 2.4 Hz, 1H, 2β-H), 3.31 (ddd, *J*=13.2, 7.8, 5.4 Hz, 1H, 2α-H), 3.18 (ddd, *J*=11.2, 9.3, 4.4 Hz, 1H, 4β-H), 2.97 (ddd, *J*=9.8, 9.3, 4.9 Hz, 1H, 9α-H), 2.53 (dd, *J*=15.6, 3.9 Hz, 1H, C*H*CO$_2$), 2.48 (dd, *J*=15.6, 9.3 Hz, 1H, C*H*CO$_2$), 2.07 (s, 3H, OCOCH_3), 2.00 (m, 1H, 4β-H), 1.95–1.83 (m, 2H, 8-H$_2$), 1.88–1.78 (m, 2H, 9-H$_2$), 1.66 (m, 2H, 3-H$_2$), 1.40 (m, 1H, 4α-H), 1.27 (t, *J*=7.3 Hz, 3H, CH$_2$CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.0 (*C*O$_2$Et), 170.3 (O*C*OMe), 82.7 (C-4a), 82.5 (C-9a), 79.9 (C-6), 75.6 (C-7), 67.7 (C-2), 60.5 (*C*H$_2$CH$_3$), 40.1 (*C*H$_2$CO$_2$), 31.1 (C-4), 27.6 (C-9), 26.3 (C-8), 25.7 (C-3), 21.3 (OCO*C*H$_3$), 14.2; HRMS (FAB) calcd for $C_{15}H_{25}O_6$ (M+H$^+$) 301.1651, found 301.1664.

4.1.11. (2*R*,3*S*,4a*R*,8a*S*)-2-[1,3]Dithian-2-ylmethyl-octahydro-pyrano[3,2-*b*]pyran-3-ol (14). To a solution of **8** (118.0 mg, 0.48 mmol) in toluene (5 mL) was added DIBAH (1.13 mL, 0.94 M solution in *n*-hexane, 1.06 mmol) at −78°C. After stirring for 1 h, *i*-PrOH (1 mL) was added at the same temperature and silica gel was added at rt. The mixture was diluted with EtOAc, stirred for 1 h, and filtrated through a Celite pad to give the crude aldehyde. To a solution of the aldehyde in CH_2Cl_2 (5 mL) were added 1,3-propanedithiol (0.14 mL, 1.44 mmol) and $BF_3{\cdot}Et_2O$ (0.18 mL, 1.44 mmol) at 0°C. After stirring at 0°C for 1 h, the mixture was diluted with ether, washed with 3% aqueous NaOH. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with saturated aqueous NH_4Cl, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (*n*-hexane/EtOAc, 1:1) to give **14** (137.2 mg, 99%) as a colorless oil. $[\alpha]^{24}_D$=+47.3 (*c* 1.30, $CHCl_3$); IR (neat) 3441 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.27 (dd, *J*=10.3, 4.0 Hz, 1H), 3.90 (m, 1H), 3.38 (m, 3H), 3.01 (ddd, *J*=12.9, 8.7, 4.2 Hz, 1H), 2.97 (ddd, *J*=11.1, 8.7, 4.2 Hz, 1H), 2.87 (m, 4H), 2.35 (m, 2H), 2.10 (m, 2H), 1.88 (m, 2H), 1.70 (m, 2H), 1.48 (ddd, *J*=11.0, 11.0, 11.0 Hz, 1H), 1.41 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 78.5, 77.6, 76.7, 69.8, 67.8, 43.1, 39.3, 38.1, 30.0, 29.5, 29.2, 25.9, 25.4; HRMS (FAB) calcd for $C_{13}H_{22}O_3S_2$ (M$^+$) 290.1010, found 290.1010.

4.1.12. (2*R*,3*S*,4a*R*,8a*S*)-(*E*)-3-[2-(2-Oxo-ethyl)-octahydro-pyrano[3,2-*b*]pyran-3-yloxy]-acrylic acid ethyl ester (15). Following the same procedure as described for **4**, **14** (136.2 mg) gave **15** (126.4 mg, 90%) as a colorless oil. $[\alpha]^{23}_D$=+42.5 (*c* 1.30, $CHCl_3$); IR (neat) 1732, 1716, 1699, 1652, 1645, 1627 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.76 (dd, *J*=2.4, 1.5 Hz, 1H), 7.44 (d, *J*=12.2 Hz, 1H), 5.31 (d, *J*=12.2 Hz, 1H), 4.16 (q, *J*=7.3 Hz, 2H), 3.90 (m, 2H), 3.77 (ddd, *J*=10.7, 9.3, 4.4 Hz, 1H), 3.37 (m, 1H), 3.10 (ddd, *J*=11.2, 9.3, 4.4 Hz, 1H), 2.99 (ddd, *J*=11.7, 9.3, 4.4 Hz, 1H), 2.73 (ddd, *J*=16.6, 3.4, 1.5 Hz, 1H), 2.53 (m, 2H), 2.05 (m, 1H), 1.72 (m, 2H), 1.59 (ddd, *J*=11.7, 11.7, 11.7 Hz, 1H), 1.39 (m, 1H), 1.27 (t, *J*=7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.6, 167.3, 160.1, 99.1, 78.8, 78.1, 76.0, 74.7, 67.9, 60.0, 45.6, 35.4, 28.9, 25.2, 14.3; HRMS (FAB) calcd for $C_{15}H_{23}O_6$ (M+H$^+$) 299.1495, found 299.1494.

4.1.13. (2*R*,3*S*,4a*R*,8a*R*,9a*S*,10a*S*)-(3-Hydroxy-decahydro-1,8,10-trioxa-anthracen-2-yl)-acetic acid ethyl ester (16). Following the same procedure as described for **7**, **15** (119.3 mg) gave **16** (103.5 mg, 86%) as colorless crystals. Mp 166–167°C (recrystallized from Et_2O); $[\alpha]^{21}_D$=+15.6 (*c* 0.55, $CHCl_3$); IR (nujol) 3469, 1713, 1704 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 4.17 (q, *J*=7.1 Hz, 2H, CH_2CH$_3$), 3.91 (m, 1H, 8β-H), 3.58 (ddd, *J*=9.3, 7.3, 4.4 Hz, 1H, 2α-H), 3.50 (dddd, *J*=11.2, 9.3, 6.4, 4.4 Hz, 1H, 3β-H), 3.38 (ddd, *J*=10.8, 9.8, 4.4 Hz, 1H, 8α-H), 3.12 (ddd, *J*=11.2, 8.9, 3.9 Hz, 1H, 10aα-H), 3.09 (ddd, *J*=11.2, 8.9, 4.0 Hz, 1H, 4aβ-H), 3.05 (ddd, *J*=11.2, 8.9, 4.4 Hz, 1H, 5aβ-H), 3.02 (ddd, *J*=11.2, 8.8, 3.9 Hz, 1H, 9aα-H), 2.81 (dd, *J*=15.6, 4.4 Hz, 1H, C*H*CO$_2$), 2.53 (dd, *J*=15.6, 7.3 Hz, 1H, C*H*CO$_2$), 2.41 (ddd, *J*=11.7, 4.4, 4.0 Hz, 1H, 4β-H), 2.29 (ddd, *J*=11.2, 3.9, 3.9 Hz, 1H, 10α-H), 2.18 (d, *J*=6.4 Hz, 1H, OH), 2.06 (m, 1H, 6β-H), 1.72 (m, 2H, 7-H$_2$), 1.49 (ddd, *J*=11.7, 11.2, 11.2 Hz, 1H, 4α-H), 1.47 (ddd, *J*=11.2, 11.2, 11.2 Hz, 1H, 10β-H), 1.44 (m, 1H, 6α-H), 1.26 (t, *J*=7.1 Hz, 3H, CH$_2$CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.9 (CO), 78.7 (C-2), 78.2 (C-5a), 77.2 (C-9a), 76.8 (C-10a), 76.3 (C-4a), 69.8 (C-3), 68.0 (C-8), 60.8 (*C*H$_2$CH$_3$, 38.8 (C-4), 38.1 (*C*H$_2$CO$_2$), 35.4 (C-10), 29.2 (C-6), 25.5 (C-7), 14.2 (CH$_2$*C*H$_3$); HRMS (FAB) calcd for $C_{15}H_{25}O_6$ (M+H$^+$) 301.1651, found 301.1634. Anal. Calcd for $C_{15}H_{24}O_6$: C, 59.98; H, 8.05. Found: C, 59.72; H, 7.89.

4.1.14. (2*R*,3*S*,4a*R*,8a*R*,9a*S*,10a*S*)-2-[1,3]Dithian-2-ylmethyl-decahydro-1,8,10-trioxa-anthracen-3-ol (17). Following the same procedure as described for **14**, **16** (115.2 mg) gave **17** (122.8 mg, 92%) as a colorless oil. $[\alpha]^{23}_D$=+31.7 (*c* 1.30, $CHCl_3$); IR (neat) 3446 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.28 (dd, *J*=10.7, 4.1 Hz, 1H), 3.91 (m, 1H), 3.40 (m, 3H), 3.06 (m, 4H), 2.88 (m, 4H), 2.40 (ddd, *J*=11.4, 3.8, 3.8 Hz, 1H), 2.33 (m, 2H), 2.10 (m, 2H), 1.88 (m, 2H), 1.72 (m, 2H), 1.45 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 78.5, 78.1, 76.6, 76.4, 69.7, 68.0, 43.0, 38.9, 38.0, 35.5, 30.0, 29.5, 29.2, 25.9, 25.5; HRMS (FAB) calcd for $C_{16}H_{26}O_4S_2$ (M$^+$) 346.1273, found 346.1273.

4.1.15. (2*R*,3*S*,4a*R*,8a*R*,9a*S*,10a*S*)-(*E*)-3-[2-(2-Oxo-ethyl)-decahydro-1,8,10-trioxa-anthracen-3-yloxy]-acrylic acid ethyl ester (18). Following the same procedure as described for **4**, **17** (44.9 mg) gave **18** (37.8 mg, 82%) as a colorless solid. $[\alpha]^{23}_D$=+48.8 (*c* 1.30, $CHCl_3$); IR (neat) 1727, 1708, 1645, 1625 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.77 (dd, *J*=2.0, 1.4 Hz, 1H), 7.43 (d, *J*=12.5 Hz, 1H), 5.31 (d,

J=12.5 Hz, 1H), 4.16 (q, J=7.0 Hz, 2H), 3.90 (m, 2H), 3.78 (ddd, J=11.1, 9.7, 4.5 Hz, 1H), 3.38 (m, 1H), 3.18 (ddd, J=11.1, 9.0, 4.2 Hz, 1H), 3.10 (ddd, J=11.1, 9.0, 4.2 Hz, 1H), 3.04 (m, 2H), 2.73 (ddd, J=16.4, 3.1, 1.4 Hz, 1H), 2.57 (m, 2H), 2.30 (ddd, J=11.1, 4.2, 4.2 Hz, 1H), 2.06 (m, 1H), 1.73 (m, 2H), 1.59 (ddd, J=11.5, 11.5, 11.5 Hz, 1H), 1.47 (ddd, J=11.1, 11.1, 11.1 Hz, 1H), 1.44 (m, 1H), 1.25 (t, J=7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.4, 167.3, 160.0, 99.2, 78.6, 78.4, 75.6, 74.8, 68.0, 60.0, 45.5, 35.3, 35.1, 29.1, 25.4, 14.3; HRMS (FAB) calcd for $C_{18}H_{27}O_7$ ($M+H^+$) 355.1757, found 355.1749.

4.1.16. (2*R*,3*S*,4a*R*,5a*S*,6a*R*,10a*S*,11a*R*,12a*S*)-(3-Hydroxy-tetradecahydro-1,5,7,11-tetraoxa-naphthacen-2-yl)-acetic acid ethyl ester (19). Following the same procedure as described for **7**, **18** (57.4 mg) gave **19** (47.8 mg, 83%) as colorless crystals. Mp 265–268°C (recrystallized from Et_2O); $[\alpha]^{24}_D$=+34.5 (c 0.40, pyridine); IR (nujol) 3462, 1709 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$/CD_3OD, 4:1) δ 4.17 (q, J=7.1 Hz, 2H, CH_2CH$_3$), 3.92 (m, 1H, 8β-H), 3.57 (ddd, J=9.3, 8.8, 2.9 Hz, 1H, 2β-H), 3.40 (m, 1H, 8α-H), 3.38 (m, 1H, 3α-H), 3.15 (m, 2H, 11aβ-H), 3.13 (m, 1H, 12aβ-H), 3.09 (m, 1H, 4aα-H), 3.08 (m, 1H, 10aβ-H), 3.07 (m, 1H, 6aα-H), 2.88 (dd, J=15.6, 2.9 Hz, 1H, CHCO$_2$), 2.40 (dd, J=15.6, 8.8 Hz, 1H, CHCO$_2$), 2.38 (m, 1H, 4α-H), 2.32 (m, 1H, 12β-H), 2.31 (m, 1H, 6α-H), 2.08 (m, 1H, 10β-H), 1.75 (m, 2H, 9-H$_2$), 1.50 (m, 2H, 4β-H and 6β-H), 1.45 (m, 2H, 10α-H and 12α-H), 1.27 (t, J=7.1 Hz, 3H, CH$_2$CH_3); ^{13}C NMR (150 MHz, $CDCl_3$/CD_3OD, 4:1) δ 172.0 (CO), 78.7 (C-2), 78.0 (C-10a), 76.8 (C-6a), 76.6 (C-5a), 76.5 (C-11a), 76.3 (C-4a), 76.1 (C-12a), 68.2 (C-3), 67.6 (C-8), 60.4 (CH_2CH$_3$), 37.7 (C-4), 37.2 (CH_2CO$_2$), 34.9 (C-9), 34.5 (C-12), 28.6 (C-10), 25.0 (C-9), 13.5 (CH$_2$CH_3); HRMS (FAB) calcd for $C_{18}H_{28}O_7Na$ ($M+Na^+$) 379.1733, found 379.1740.

4.1.17. (4a*S*,6*R*,7*S*,9a*R*)-6-[1,3]Dithian-2-ylmethyl-octahydro-1,5-dioxa-benzocyclohepten-7-ol (20). To a solution of **9** (732.5 mg, 3.46 mmol) in toluene (30 mL) was added DIBAH (4.40 mL, 0.95 M solution in n-hexane, 4.15 mmol) at rt. After stirring at rt for 1 h, the mixture was quenched with i-PrOH (1 mL) and H_2O (0.5 mL) at −78°C and returned to rt. After addition of silica gel and $MgSO_4$, the mixture was diluted with EtOAc and stirred for 1 h. The mixture was filtrated through a Celite-pad and then concentrated in vacuo to give a lactol. To a solution of the lactol in CH_2Cl_2 (30 mL) were added 1,3-propanedithiol (0.65 mL, 6.45 mmol) and $BF_3{\cdot}Et_2O$ (0.79 mL, 6.45 mmol) at 0°C. After stirring at 0°C for 1 h, the mixture was diluted with EtOAc, washed with 10% aqueous NaOH. The aqueous layer was extracted with EtOAc and the combined organic layers were washed with saturated aqueous NH_4Cl and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (n-hexane/EtOAc, 3:2) to give **20** (995.3 mg, 95%) as colorless crystals. Mp 102–103°C (recrystallized from Et_2O); $[\alpha]^{25}_D$=+39.6 (c 0.83, $CHCl_3$); IR (nujol) 3462 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.20 (dd, J=10.1, 4.1 Hz, 1H), 3.88 (m, 1H), 3.70 (br, 1H), 3.59 (ddd, J=10.1, 7.3, 2.8 Hz, 1H), 3.31 (ddd, J=11.0, 11.0, 4.1 Hz, 1H), 3.16 (ddd, J=11.0, 9.6, 4.6 Hz, 1H), 2.96 (ddd, J=9.2, 8.7, 4.6 Hz, 1H), 2.89–2.78 (m, 4H), 2.18–2.08 (m, 3H), 1.93–1.83 (m, 6H), 1.68–1.66 (m, 3H), 1.44 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 83.3, 83.2, 82.5, 74.5, 67.8, 43.9, 40.5, 31.2, 30.8, 30.0, 29.5, 27.2, 26.0, 25.8. Anal. Calcd for $C_{14}H_{24}O_3S_2$: C, 55.23; H, 7.95. Found: C, 55.19; H, 8.01.

4.1.18. (4a*S*,6*R*,7*S*,9a*R*)-(*E*)-3-[6-(2-Oxo-ethyl)-octahydro-1,5-dioxa-benzocyclohepten-7-yloxy]-acrylic acid ethyl ester (21). To a solution of **20** (595.9 mg, 1.96 mmol) in CH_2Cl_2 (20 mL) were added N-methylmorpholine (0.43 mL, 3.92 mmol) and ethyl propiolate (0.40 mL, 0.76 mmol) at rt. After stirring for 16 h, the mixture was diluted with EtOAc, washed with H_2O. The aqueous layer was extracted with EtOAc and the combined organic layers were dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (n-hexane/EtOAc, 3:1) to give an ester (830.5 mg). To a solution of the ester in MeCN (16 mL) and H_2O (4 mL) were added $NaHCO_3$ (494.0 mg, 5.88 mmol) and MeI (0.33 mL, 5.22 mmol) at rt. After stirring for 18 h, the mixture was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc and the combined organic layers were dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (n-hexane/EtOAc, 3:1→1:1) to give **21** (595.2 mg, 98%) as a colorless oil. $[\alpha]^{25}_D$=+50.7 (c 0.83, $CHCl_3$); IR (neat) 1709, 1644, 1622 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.75 (dd, J=1.9, 1.4 Hz, 1H), 7.44 (d, J=12.4 Hz, 1H), 5.25 (d, J=12.4 Hz, 1H), 4.16 (q, J=6.9 Hz, 2H), 4.13 (m, 1H), 4.00 (ddd, J=10.1, 6.9, 3.2 Hz, 1H), 3.87 (m, 1H), 3.30 (m, 1H), 3.24 (ddd, J=11.0, 9.2, 4.1 Hz, 1H), 2.96 (ddd, J=9.2, 9.2, 5.0 Hz, 1H), 2.65 (ddd, J=17.0, 9.2, 2.3 Hz, 1H), 2.58 (ddd, J=17.0, 3.7, 1.4 Hz, 1H), 2.10–2.00 (m, 2H), 1.92–1.80 (m, 3H), 1.77–1.65 (m, 2H), 1.38 (m, 1H), 1.27 (t, J=6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.6, 167.5, 160.5, 98.8, 84.0, 82.8, 82.5, 77.7, 67.7, 59.9, 48.1, 31.0, 27.0, 26.1, 25.6, 14.3; HRMS (FAB) calcd for $C_{16}H_{25}O_6$ ($M+H^+$) 313.1651, found 313.1634.

4.1.19. (2*R*,3*S*,4a*R*,5a*S*,9a*R*,11a*S*)-(3-Hydroxy-dodecahydro-1,5,9-trioxa-dibenzo[*a*,*d*]cyclohepten-2-yl)-acetic acid ethyl ester (22). To a solution of **21** (111.6 mg, 0.36 mmol) and MeOH (44 μL, 1.08 mmol) in THF (3 mL) was added SmI_2 (10.8 mL, 0.1 M solution in THF, 1.08 mmol) at 0°C. After stirring at 0°C for 10 min, the mixture was diluted with EtOAc, washed saturated aqueous $Na_2S_2O_3$. The aqueous layer was extracted with EtOAc and the combined organic layers were dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (n-hexane/EtOAc, 1:2) to give **22** (107.1 mg, 95%) as a colorless solid. $[\alpha]^{25}_D$=+18.2 (c 0.67, $CHCl_3$); IR (nujol) 3419, 1702 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.16 (q, J=7.3 Hz, 2H, CH_2CH$_3$), 3.86 (m, 1H, 8β-H), 3.48 (ddd, J=9.3, 7.3, 4.4 Hz, 1H, 2α-H), 3.42 (m, 1H, 3β-H), 3.28 (m, 2H, 4aβ-H and 8α-H), 3.20 (ddd, J=10.7, 8.8, 3.9 Hz, 1H, 5aβ-H), 3.17 (ddd, J=9.3, 9.3, 5.9 Hz, 1H, 11aα-H), 3.07 (ddd, J=9.3, 8.8, 5.9 Hz, 1H, 9aα-H), 2.78 (dd, J=15.1, 4.4 Hz, 1H, CHCO$_2$), 2.47 (dd, J=15.1, 7.3 Hz, 1H, CHCO$_2$), 2.40 (ddd, J=11.7, 4.4, 4.4 Hz, 1H, 4β-H), 2.11 (br d, J=4.4 Hz, 1H, OH), 2.07 (m, 1H, 6β-H), 1.97 (m, 1H, 11-H), 1.95 (m, 1H, 10-H), 1.86 (m, 1H, 11-H), 1.84 (m, 1H, 10-H), 1.66 (m, 2H, 7-H$_2$),

1.50 (ddd, J=11.7, 11.2, 11.2 Hz, 1H, 4α-H), 1.43 (m, 1H, 6α-H), 1.26 (t, J=7.3 Hz, 3H, CH_2CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.0 (CO), 82.5 (C-9a), 81.9 (C-11a), 80.8 (C-5a), 78.7 (C-4a), 78.6 (C-2), 70.0 (C-3), 67.9 (C-8), 60.7 (CH_2CH_3), 40.8 (C-4), 38.3 (CH_2CO_2), 31.4 (C-6), 29.9 (C-10), 29.0 (C-11), 25.9 (C-7), 14.2 (CH_2CH_3); HRMS (FAB) calcd for $C_{16}H_{27}O_6$ ($M+H^+$) 315.1808, found 315.1814.

4.1.20. (4a*S*,6*R*,7*S*,9a*R*)-6-[(*E*,*Z*)-3-Methoxy-allyl]-octahydro-1,5-dioxa-benzocyclohepten-7-ol (23). To a solution of **9** (669.6 mg, 3.16 mmol) in toluene (20 mL) was added DIBAH (4.0 mL, 0.94 M solution in *n*-hexane, 3.79 mmol) at −78°C. After stirring at −78°C for 30 min, *i*-PrOH (3 mL) was added and brought to rt. Silica gel and EtOAc were added and the mixture was stirred at rt for 1 h. The mixture was filtrated through a Celite-pad and concentrated in vacuo to give the crude lactol. To a suspension of $Ph_3P^+CH_2OMeCl^-$ (6.64 g, 18.79 mmol) in THF (10 mL) was added NaHMDS (18.2 mL, 1.0 M in THF, 18.2 mmol) at −78°C and the mixture was stirred at −78°C for 30 min and then at rt for 30 min to give an ylide as an orange solution. To a solution of the lactol in THF (20 mL) was slowly added the ylide solution at −78°C until the color of the solvent turned to orange. After stirring at rt for 1 h, the mixture was quenched with saturated aqueous NH_4Cl, and extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (*n*-hexane/EtOAc, 3:2→1:1) to give **23** (639.0 mg, 84%; *E*/*Z*=1:1) as a colorless oil. IR (neat) 3439, 1659 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6,36 (d, J=12.8 Hz, 0.5H, (*E*)-CH=C*H*OMe), 5.98 (d, J=5.0 Hz, 0.5H, (*Z*)-CH=C*H*OMe), 4.81 (ddd, J=12.8, 7.3, 7.3 Hz, 0.5H, (*E*)-C*H*=CHOMe), 4.49 (q like, J=6.8 Hz, 0.5H, (*Z*)-C*H*=CHOMe), 3.87 (br d, J=11.0 Hz, 1H), 3.75 (br, 1H), 3.60 (s, 1.5H), 3.53 (s, 1.5H), 3.35–3.23 (m, 2H), 3.11 (m, 1H), 2.97 (m, 1H), 2.42 (m, 0.5H), 2.22 (m, 1H), 2.13–2.05 (m, 2H), 1.89–1.83 (m, 4.5H), 1.66 (m, 2H), 1.43 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.7, 147.6, 102.3, 99.1, 86.7, 86.0, 83.11, 83.05, 82.8, 82.6, 73.8, 67.7, 59.5, 56.0, 33.2, 31.3, 31.2, 30.2, 29.9, 29.3, 27.4, 27.1, 25.83, 25.79; HRMS (FAB) calcd for $C_{13}H_{23}O_4$ ($M+H^+$) 243.1596, found 243.1580.

4.1.21. (4a*S*,6*R*,7*S*,9a*R*)-(*E*)-3-[6-(3-Oxo-propyl)-octahydro-1,5-dioxa-benzocyclohepten-7-yloxy]-acrylic acid ethyl ester (24). To a solution of **23** (0.98 g, 4.05 mmol) in CH_2Cl_2 (40 mL) was added *N*-methylmorpholine (0.89 mL, 8.10 mmol) and ethyl propiolate (0.82 mL, 8.10 mmol) at rt. After stirring for 17 h, the mixture was diluted with EtOAc, washed with H_2O and brine. The organic layer was dried over $MgSO_4$ and evaporated. The residue was purified by flash column chromatography (*n*-hexane/EtOAc, 2:1) to give an ester (1.41 g). To a solution of the ester in MeCN (20 mL) and H_2O (5 mL) was added CSA (94.1 mg, 0.41 mmol) at rt. After stirring for 20 h, the mixture was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (*n*-hexane/EtOAc, 2:1→1:1) to give **24** (1.09 g, 81%) as a colorless oil. $[\alpha]^{24}_D$=+45.5 (*c* 1.28, $CHCl_3$); IR (nujol) 1713, 1644, 1621 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.47 (m, 1H), 7.45 (d, J=12.8 Hz, 1H), 5.25 (d, J=12.8 Hz, 1H), 4.16 (q, J=7.3 Hz, 2H), 3.98 (m, 1H), 3.86 (m, 1H), 3.51 (m, 1H), 3.29 (m, 1H), 3.07 (m, 1H), 2.94 (ddd, J=9.2, 9.2, 4.6 Hz, 1H), 2.57–2.50 (m, 2H), 2.05–1.60 (m, 9H), 1.40 (m, 1H), 1.27 (t, J=7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.9, 167.7, 160.8, 98.5, 85.3, 82.6, 82.5, 82.3, 67.7, 59.9, 40.7, 30.9, 27.5, 27.0, 26.1, 25.6, 14.3; HRMS (FAB) calcd for $C_{17}H_{27}O_6$ ($M+H^+$) 327.1808, found 327.1824.

4.1.22. (3a*R*,4a*S*,6a*R*,10a*S*,11a*R*,13a*S*)-Dodecahydro-1,4,7,11-tetraoxa-tetracyclononadenane-2-one (25) and (3a*R*,4a*S*,6a*R*,10a*S*,11a*R*,13a*R*)-dodecahydro-1,4,7,11-tetraoxa-tetracyclononadenane-2-one (26). Following the same procedure as described for **9**, **24** (604.6 mg) gave **25** (293.1 mg, 56%) and **26** (133.9 mg, 26%). **25**: colorless crystals, mp 175–179°C (recrystallized from Et_2O); $[\alpha]^{26}_D$=−9.5 (*c* 0.78, $CHCl_3$); IR (nujol) 1790, 1780, 1740, 1640, 1622 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 4.17 (ddd, J=13.2, 8.3, 4.9 Hz, 1H, 13aβ-H), 3.87 (m, 1H, 8β-H), 3.85 (ddd, J=11.2, 8.3, 7.8 Hz, 2H, 4aα-H), 3.54 (ddd, J=7.8, 5.4, 2.9 Hz, 1H, 5aα-H), 3.47 (ddd, J=11.2, 7.8, 3.9 Hz, 1H, 11aβ-H), 3.31 (m, 1H, 8α-H), 3.11 (ddd, J=11.2, 9.3, 3.9 Hz, 1H, 10aβ-H), 2.92 (ddd, J=9.8, 9.3, 4.4 Hz, 1H, 6aα-H), 2.81 (dd, J=17.1, 7.8 Hz, 1H 3α-H), 2.68 (dd, J=17.1, 11.2 Hz, 1H, 3β-H), 2.37 (dddd, J=13.7, 10.7, 5.4, 4.9 Hz, 1H, 13β-H), 2.19 (dddd, J=13.7, 10.7, 5.4, 3.9 Hz, 1H, 12β-H), 2.04 (m, 1H, 10β-H), 2.02 (m, 1H, 5β-H), 1.94 (m, 1H, 5α-H), 1.93 (dddd, J=13.7, 11.2, 10.3, 5.4 Hz, 1H, 12α-H), 1.84 (m, 1H, 6α-H), 1.81 (m, 1H, 6β-H), 1.73 (dddd, J=13.7, 13.2, 10.3, 5.4 Hz, 1H, 13α-H), 1.68 (m, 2H, 9-H_2), 1.45 (m, 1H, 10α-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.6 (CO), 85.3 (C-4a), 85.1 (C-10a), 83.6 (C-6a), 83.5 (C-11a), 82.4 (C-13a), 80.8 (C-3a), 67.9 (C-8), 36.3 (C-3), 31.6 (C-10), 30.0 (C-12), 29.7 (C-5), 27.9 (C-6), 26.0 (C-9), 25.2 (C-13); HRMS (FAB) calcd for $C_{15}H_{23}O_5$ ($M+H^+$) 283.1545, found 283.1537. Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 63.76; H, 7.95. **26**: colorless crystals, mp 211–216°C (recrystallized from Et_2O/EtOAc); $[\alpha]^{24}_D$=+41.5 (*c* 1.46, $CHCl_3$); IR (nujol) 1771, 1736, 1708, 1641, 1621 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 4.55 (ddd, J=9.8, 5.4, 3.9 Hz, 1H, 13aα-H), 4.41 (ddd, J=7.8, 5.4, 3.9 Hz, 1H, 3aα-H), 3.87 (m, 1H, 8β-H), 3.43 (ddd, J=9.3, 9.3, 3.4 Hz, 1H, 11aβ-H), 3.29 (m, 1H, 8α-H), 3.22 (ddd, J=9.3, 5.9, 5.9 Hz, 1H, 4aα-H), 3.17 (ddd, J=11.2, 8.8, 3.9 Hz, 1H, 10aβ-H), 2.98 (ddd, J=8.8, 7.8, 4.4 Hz, 1H, 6aα-H), 2.84 (dd, J=18.5, 7.8 Hz, 1H, 3α-H), 2.57 (dd, J=18.5, 3.9 Hz, 1H, 3β-H), 2.14 (m, 2H, 12β-H and 13α-H), 2.06 (m, 1H, 10β-H), 2.03 (m, 1H, 5-H), 1.93 (m, 1H, 5-H), 1.90 (m, 1H, 6-H), 1.85 (m, 1H, 6-H), 1.83 (m, 1H, 13β-H), 1.68 (m, 2H, 9-H_2), 1.45 (m, 1H, 12α-H), 1.40 (m, 1H, 10α-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.5 (CO), 85.4 (C-4a), 83.5 (C-13a), 83.1 (C-11a), 82.5 (C-6a), 81.8 (C-10a), 77.6 (C-3a), 67.9 (C-8), 36.3 (C-3), 31.4 (C-10), 30.7 (C-5), 29.6 (C-12), 29.2 (C-6), 25.9 (C-9), 25.2 (C-13); HRMS (FAB) calcd for $C_{15}H_{23}O_5$ ($M+H^+$) 283.1545, found 283.1547. Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 63.11; H, 7.80.

4.1.23. (4a*S*,5a*R*,8*S*,9*R*,10a*S*,12a*R*)-9-[1,3]Dithian-2-ylmethyl-dodecahydro-1,5,10-trioxa-benzo[*b*]heptalen-8-ol (29). Following the same procedure as described for **20**, **25** (206.5 mg) gave **29** (233.0 mg, 85%) as colorless crystals. Mp 158–160°C (recrystallized from Et_2O); $[\alpha]^{24}_D$=+44.1 (*c* 0.71, $CHCl_3$); IR (nujol) 3399 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.19 (dd, *J*=11.0, 4.1 Hz, 1H), 3.86 (m, 1H), 3.53 (m, 2H), 3.46 (m, 2H), 3.28 (ddd, *J*=11.0, 7.8, 4.6 Hz, 1H), 3.12 (m, 1H), 3.01 (ddd, *J*=8.7, 8.2, 3.7 Hz, 1H), 2.93–2.78 (m, 4H), 2.18–2.05 (m, 4H), 1.94–1.79 (m, 4H), 1.68–1.59 (m, 3H), 1.41 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 85.2, 83.1, 82.5, 81.9, 81.3, 74.8, 67.7, 43.9, 39.9, 31.3, 30.1, 30.03, 30.00, 29.6, 29.5, 28.5, 26.1, 25.9. Anal. Calcd for $C_{18}H_{30}O_4S_2$: C, 57.72; H, 8.07. Found: C, 57.48; H, 8.07.

4.1.24. (4a*S*,5a*R*,8*R*,9*R*,10a*S*,12a*R*)-9-[1,3]Dithian-2-ylmethyl-dodecahydro-1,5,10-trioxa-benzo[*b*]heptalen-8-ol (27). Following the same procedure as described for **20**, **26** (66.6 mg) gave **27** (77.5 mg, 85%) as a colorless foam. $[\alpha]^{25}_D$=+35.2 (*c* 0.63, $CHCl_3$); IR (neat) 3455 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.17 (dd, *J*=10.5, 4.1 Hz, 1H), 3.85 (m, 1H), 3.73 (m, 2H), 3.56 (m, 1H), 3.39 (m, 1H), 3.27 (m, 1H), 3.11 (m, 1H), 3.00 (ddd, *J*=8.7, 8.7, 3.7 Hz, 1H), 2.94–2.80 (m, 4H), 2.21–2.01 (m, 6H), 1.93–1.68 (m, 6H), 1.66–1.61 (m, 2H), 1.39 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 85.5, 82.7, 81.7, 81.6, 81.5, 71.8, 67.7, 44.2, 37.7, 31.2, 30.2, 30.0, 29.8, 29.7, 29.64, 29.59, 28.0, 26.0, 25.8; HRMS (FAB) calcd for $C_{18}H_{31}O_4S_2$ ($M+H^+$) 375.1664, found 375.1661.

4.1.25. (4a*S*,5a*R*,8*S*,9*R*,10a*S*,12a*R*)-9-[1,3]Dithian-2-ylmethyl-dodecahydro-1,5,10-trioxa-benzo[*b*]heptalen-8-ol (29). To a solution of **27** (22.8 mg, 70.0 μmol) in CH_2Cl_2 (1 mL) were added 2,6-lutidine (28 μL, 0.24 mmol) and McCl (11 μL, 0.12 mmol) at 0°C. After stirring at 0°C for 30 min, the mixture was diluted with Et_2O, washed with H_2O. The aqueous layer was extracted with Et_2O and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give monochlate **28**. To a solution of **28** in benzene (1 mL) were added CsOAc (35 mg, 0.18 mmol) and 18-crown-6 (8.1 mg, 30.5 μmol), and the mixture was refluxed for 2 h. The mixture was diluted with Et_2O, washed with H_2O. The aqueous layer was extracted with Et_2O and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (*n*-hexane/EtOAc, 4:1) to give an acetate (19.3 mg). To a solution of the acetate in MeOH (1 mL) was added K_2CO_3 (1 mg, 6.9 μmol) and the mixture was stirred at rt for 1 h. The mixture was filtrated through Dowex (50W-X2; 50–100 mesh; H^+ form) and concentrated in vacuo. The residue was purified by flash column chromatography (*n*-hexane/EtOAc, 1:1) to give **29** (15.0 mg, 66% overall yield).

4.1.26. (4a*S*,5a*R*,8*S*,9*R*,10a*S*,12a*R*)-(*E*)-3-[9-(2-Oxo-ethyl)-dodecahydro-1,5,10-trioxa-benzo[*b*]heptalen-8-yloxy]-acrylic acid ethyl ester (30). Following the same procedure as described for **21**, **29** (233.0 mg) gave **30** (219.5 mg, 92%) as a colorless oil. $[\alpha]^{27}_D$=+37.1 (*c* 0.78, $CHCl_3$); IR (neat) 1707, 1642, 1623 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.73 (dd, *J*=3.2, 1.8 Hz, 1H), 7.43 (d, *J*=12.8 Hz, 1H), 5.24 (d, *J*=12.8 Hz, 1H), 4.16 (q, *J*=6.9 Hz, 2H), 4.10 (m, 1H), 3.91–3.84 (m, 2H), 3.53 (m, 1H), 3.40 (m, 1H), 3.28 (ddd, *J*=11.5, 9.2, 6.9 Hz, 1H), 3.12 (ddd, *J*=11.0, 11.0, 4.1 Hz, 1H), 2.99 (ddd, *J*=8.7, 8.7, 4.1 Hz, 1H), 2.58 (m, 2H), 2.04–1.99 (m, 3H), 1.89–1.78 (m, 6H), 1.65 (m, 2H), 1.41 (m, 1H), 1.27 (t, *J*=6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.7, 167.5, 160.5, 98.8, 84.8, 84.2, 82.6, 82.3, 81.8, 78.1, 67.8, 59.9, 47.7, 31.3, 30.1, 29.1, 28.0, 25.9, 25.4, 14.3; HRMS (FAB) calcd for $C_{20}H_{31}O_7$ ($M+H^+$) 383.2070, found 383.2074.

4.1.27. (2*R*,3*S*,4a*R*,5a*S*,7a*R*,11a*S*,12a*R*,14a*S*)-(3-Hydroxy-hexadecahydro-1,5,8,12-tetraoxa-dibenzo[*b*,*h*]heptalen-2-yl)-acetic acid ethyl ester (31). Following the same procedure as described for **7**, **30** (48.9 mg) gave **31** (43.4 mg, 88%) as colorless crystals. Mp 111–114°C (recrystallized from Et_2O); $[\alpha]^{24}_D$=+9.3 (*c* 1.53, $CHCl_3$); IR (nujol) 3522, 1716 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 4.16 (q, *J*=7.3 Hz, 2H, C*H*$_2$CH$_3$), 3.86 (m, 1H, 9β-H), 3.52 (m, 1H, 5aα-H), 3.51 (m, 1H, 12aβ-H), 3.47 (ddd, *J*=9.3, 7.3, 4.4 Hz, 1H, 2β-H), 3.42 (m, 1H, 3α-H), 3.28 (m, 1H, 9α-H), 3.13 (ddd, *J*=11.2, 8.8, 4.4 Hz, 1H, 4aα-H), 3.06 (m, 2H, 11aβ-H and 14aβ-H), 2.94 (ddd, *J*=9.3, 9.3, 3.4 Hz, 1H, 7aα-H), 2.77 (dd, *J*=15.6, 4.4 Hz, 1H, C*H*CO$_2$), 2.46 (dd, *J*=15.6, 7.3 Hz, 1H, C*H*CO$_2$), 2.38 (ddd, *J*=11.7, 4.4, 4.4 Hz, 1H, 4α-H), 2.04 (m, 1H, 11β-H), 2.02 (m, 1H, 13-H), 1.97 (d, *J*=5.4 Hz, 1H, OH), 1.97 (m, 1H, 6-H), 1.88 (m, 1H, 14-H), 1.85 (m, 1H, 6-H), 1.84 (m, 2H, 7-H$_2$), 1.79 (m, 1H, 13-H), 1.75 (m, 1H, 14-H), 1.66 (m, 2H, 10-H$_2$), 1.48 (ddd, *J*=11.7, 11.2, 11.2 Hz, 1H, 4β-H), 1.41 (m, 1H, 11α-H), 1.26 (t, *J*=7.3 Hz, 3H, CH$_2$C*H*$_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.9 (CO), 83.1 (C-12a), 83.0 (C-11a), 82.6 (C-7a), 82.5 (C-5a), 81.4 (C-14a), 80.7 (C-4a), 78.4 (C-2), 70.0 (C-3), 67.8 (C-9), 60.7 (*C*H$_2$CH$_3$), 40.7 (C-4), 38.2 (*C*H$_2$CO$_2$), 31.4 (C-11), 29.9 (C-7a), 29.8 (C-13), 28.8 (C-6), 28.3 (C-14), 25.9 (C-10), 14.2 (CH$_2$*C*H$_3$). Anal. Calcd for $C_{20}H_{32}O_7$: C, 62.48; H, 8.39. Found: C, 62.34; H, 8.44.

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