A Simple Convergent Method for the Construction of Fused Tri- and Tetracyclic Ethers

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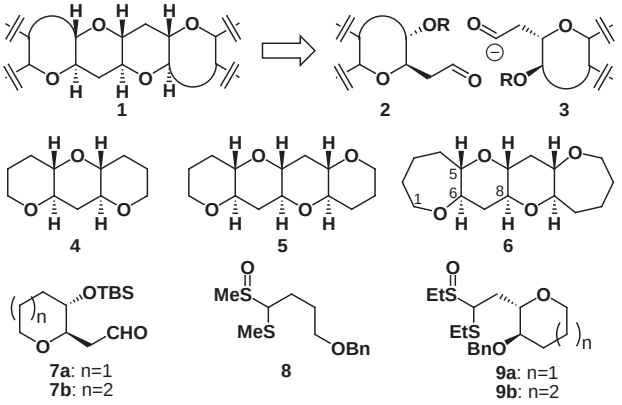
Abstract: Starting from monocyclic ethereal aldehyde and dithioacetal *S*-oxide segments, *trans*-fused tri- and tetracyclic ethers were synthesized in high yields in short steps involving acetal cyclization and reductive etherification reactions. This sequence could offer a simple convergent approach to the synthesis of natural *trans*-fused polycyclic ethers.

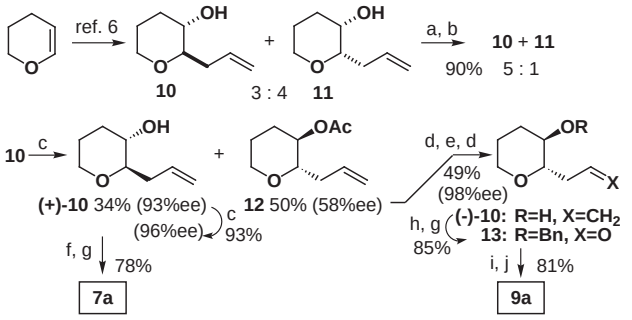
Key words: polycyclic ethers, acyl anion equivalent, dithioacetal *S*-oxide, acetal cyclization, reductive etherification

Polycyclic ethers originated from marine bioorganisms, represented by brevetoxins[1] and ciguatoxin,[2] are of significant interest to synthetic chemists due to their novel structures and strong biological activities. For the synthesis of these large polycycles, efficient convergent strategies have been desired and explored actively.[3] In this paper, a simple convergent method for the synthesis of *trans*-fused tri- and tetracyclic ethers having a perhydropyranopyran structure is described.



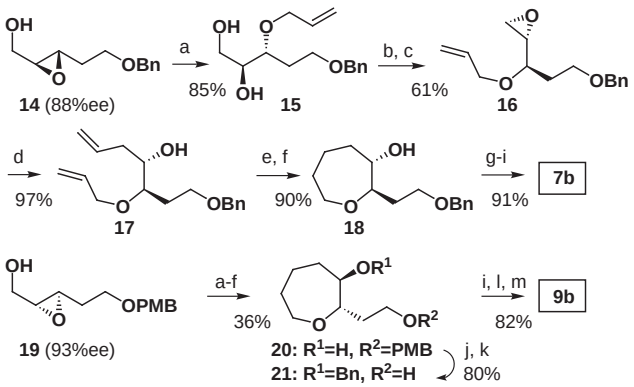
Figure

We designed the synthesis of polycyclic ether **1** starting from aldehyde segment **2** and acyl anion segment **3**, because the addition of **3** to **2** could execute the requisite oxygen functions for the subsequent construction of the perhydropyranopyran structure. Here, the dithioacetal *S*-oxide group was adopted as an acyl anion equivalent due to the low basicity and high nucleophilicity of its anion as well as its easy transformation to a carbonyl group on acidic treatment.[4] On the basis of the above strategy, tricyclic **4**[3i] and tetracyclic **5**[3c] and **6** were planned to be synthesized from aldehydes **7** and dithioacetal *S*-oxides **8**[5] and **9**.



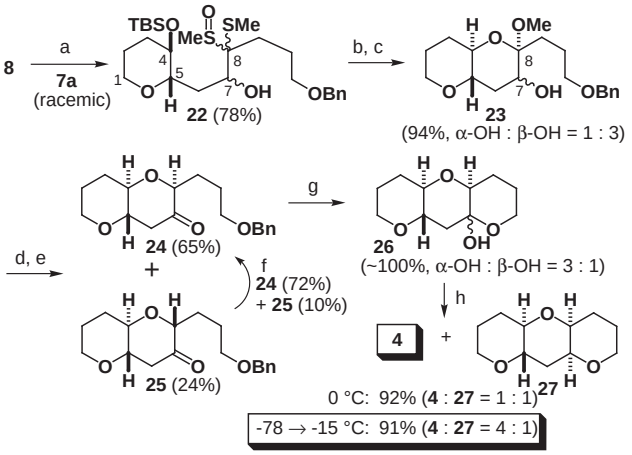
Scheme 1 Reagents and conditions: (a) $(COCl)_2$, DMSO, CH_2Cl_2, -78 °C, then Et_3N, -78 → 0 °C; (b) $LiAlH_4$, Et_2O-THF (1:1), -78 °C; (c) lipase Amano P, vinyl acetate, 21-24 °C, 20-58 h; (d) K_2CO_3, MeOH, 21-22 °C, 3 h; (e) lipase Amano P, vinyl acetate, 21 °C, 5.5 h; (f) TBSCl, imidazole, DMF, 22 °C, 80 min; (g) OsO_4 (cat.), NMO, 1,4-dioxane-H_2O (3:1), 19-22 °C, 3-4 h, then $NaIO_4$, 19-22 °C, 1.5 h; (h) NaH, *t*-BuOK, BnBr, TBAI, THF, 0 → 22 °C, 5 h; (i) TMSSEt, ZnI_2, CH_2Cl_2, 20 °C, 2 h; (j) *m*-CPBA, CH_2Cl_2, -78 °C, 1 h.

Tetrahydropyran segments **7a** and **9a** were prepared as shown in Scheme 1. Dihydropyran was converted to a 3:4 mixture of **10** and **11** according to Rousseau's method.[6] To attain increased yield of the desired **10**, the mixture was subjected to Swern oxidation[7] followed by reduction with $LiAlH_4$ to give **10** in 75% yield. Optical resolution of **10** was achieved by repeated treatment with lipase Amano P in vinyl acetate {**(+)-10**: 96%ee,[8] $[\alpha]_D^{23}$+22.6 (*c* 1.14, $CHCl_3$); **(-)-10**: 98%ee,[8] $[\alpha]_D^{22}$ -25.7 (*c* 1.04, $CHCl_3$)}.[9] Protection of **(+)-10** with TBSCl followed by one-pot dihydroxylation-oxidative cleavage led to **7a** (78%). Another alcohol **(-)-10** was protected and the resultant benzyl ether was converted to aldehyde **13** (85%), by the same one-pot process as the above, which was transformed to **9a** (81%) by Evans' method[10] followed by oxidation with *m*-CPBA. On the other hand, oxepane segments **7b** and **9b** were provided from the respective hydroxy epoxides **14** {88%ee,[11] $[\alpha]_D^{25}$ -29.4 (*c* 0.999, $CHCl_3$)} and **19** {93%ee,[11] $[\alpha]_D^{25}$+25.8 (*c* 1.01, $CHCl_3$)}, easily derived from the corresponding allyl alcohols by Sharpless asymmetric epoxidation,[12] via a ring-closing metathesis reaction[13] (Scheme 2). An allyloxy group was introduced to **14** according to Sharpless' method[14] affording **15**

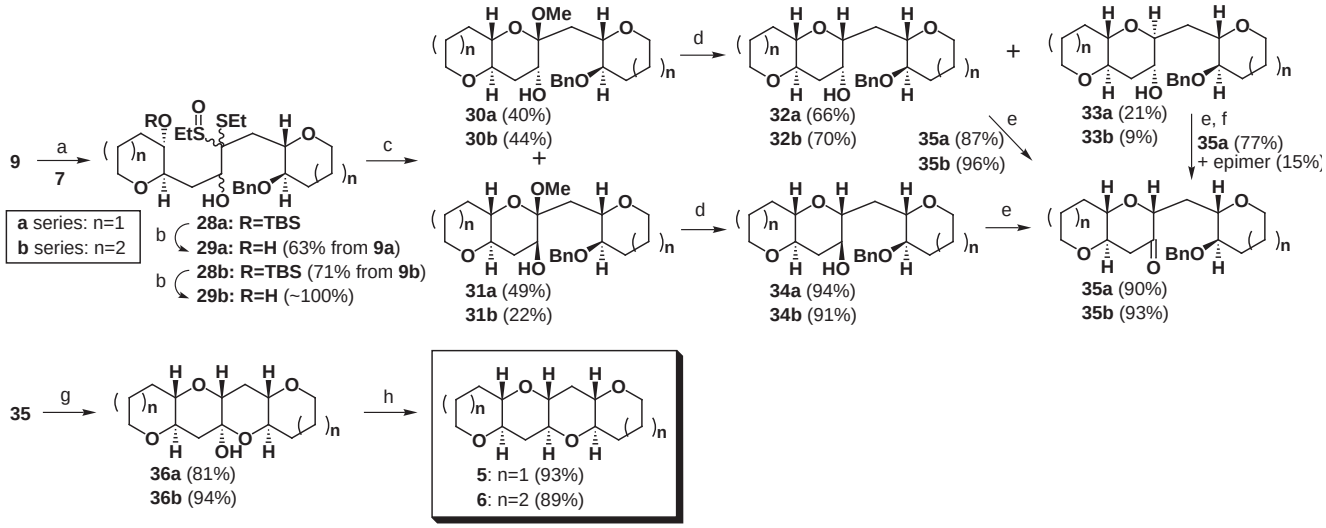


Scheme 2 Reagents and conditions: (a) allyl alcohol, Ti(*i*-PrO)$_4$, toluene, reflux, 5 h; (b) 2,4,6-triisopropylbenzenesulfonyl chloride, DMAP, pyridine, CH_2Cl_2, 22-25 °C, 11-14 h; (c) K_2CO_3, MeOH, 20-23 °C, 4-6 h; (d) CuCN, CH_2=CHMgBr, THF, -78 → -40 °C, 1 h, then **16**, -40 °C, 1.3 h; (e) $(PCy_3)_2Cl_2Ru$=CHPh (cat.), CH_2Cl_2, reflux, 2 h; (f) H_2, $RhCl(PPh_3)_3$, benzene, 21 °C, 7-9 h; (g) TBSCl, imidazole, DMF, 24 °C, 3 h; (h) H_2, 10% Pd/C, MeOH, 21 °C, 2 h; (i) $(COCl)_2$, DMSO, CH_2Cl_2, -78 °C, then Et_3N, -78 → 0 °C; (j) *t*-BuOK, BnBr, TBAI, THF, 0 → 24 °C, 25 min; (k) DDQ, CH_2Cl_2-H_2O (10:1), 23 °C, 45 min; (l) TMSSEt, ZnI_2, CH_2Cl_2, 23 °C, 17 h; (m) *m*-CPBA, CH_2Cl_2, -78 °C, 1.5 h.

(85%). Selective sulfonylation of the primary hydroxyl group of **15** followed by basic treatment gave epoxide **16** (61%), which was converted to **17** (97%) on treatment with a vinyl copper reagent. The diene **17** was cleanly cyclized by Grubbs' catalyst,[13] and the resultant oxepene produced oxepane **18** {90% yield, $[\alpha]_D^{23}$+4.7 (*c* 1.00, $CHCl_3$)} on hydrogenation. After a three-step sequence (protection of the hydroxy group with TBSCl, removal of the benzyl group, and Swern oxidation[7]), **18** gave aldehyde **7b** (91%). Another oxepane **20** {$[\alpha]_D^{14}$ -3.0 (*c* 0.625, $CHCl_3$)} antipodal to **18** was prepared from **19** through a process similar to **18**. Benzylation of **20** followed by removal of the *p*-methoxybenzyl group afforded **21** (80%), which was transformed to **9b** (82%) by successive reactions (oxidation of alcohol, dithioacetal formation, and mono-oxidation of the dithioacetal).



Scheme 3 Reagents and conditions: (a) LDA (1 eq), THF, -78 °C, 5 min, then racemic **7a** (0.67 eq), -78 °C, 20 min; (b) TBAF, THF, 26 °C, 40 min; (c) TsOH·H_2O (cat.), MeOH-$(MeO)_3CH$ (10:1), 25 °C, 40 min; (d) Et_3SiH (6 eq), $SnCl_4$ (2 eq), -78 → 0 °C, 20 min; (e) $(COCl)_2$, DMSO, CH_2Cl_2, -78 °C, then Et_3N, -78 → 0 °C; (f) DBU (5 eq), benzene-d_6, 20 °C, 35 h; (g) H_2, 10% Pd/C, MeOH, 25 °C, 12.5 h; (h) Et_3SiH (10 eq), TMSOTf (2 eq), CH_2Cl_2, 0 °C, 10 min, or -78 → -15 °C, 1 h.



Scheme 4 Reagents and conditions: (a) LDA (1 eq), THF, -78 °C, 20 min, then **7** (0.67 eq), -78 °C, 15-20 min; (b) TBAF, THF, 25 °C, 2-3 h; (c) TsOH·H_2O (cat.), MeOH-$(MeO)_3CH$ (**a** series, 10:1; **b** series, 1:1), 20-25 °C, 2-3 h; (d) Et_3SiH (6 eq), $SnCl_4$ (2 eq), -78 → 0 °C; (e) $(COCl)_2$, DMSO, CH_2Cl_2, -78 °C, then Et_3N, -78 → 0 °C; (f) DBU (5 eq), benzene-d_6, 20 °C, 5 days; (g) H_2, 10% Pd/C, MeOH, 20-25 °C, 3-22 h; (h) Et_3SiH (10 eq), TMSOTf (2 eq), CH_2Cl_2, 0 °C, 40-150 min.

Firstly, construction of tricyclic **4** from aldehyde **7a** (racemic) and acyclic **8** was examined as the simplest model system for convergent synthesis of polycyclic ethers (Scheme 3). Deprotonation of **8** with LDA (1 equiv) in THF at -78 °C followed by addition of aldehyde **7a** (racemic, 0.67 equiv) provided **22** in good yield (78% based on **7a**) as a mixture of diastereomers together with the recovered **7a** (22%) and **8** (45%). After desilylation and treatment with *p*-toluenesulfonic acid in MeOH-$(MeO)_3CH$ (9:1) system,[15] **22** produced the desired bicyclic compounds **23** (94%) as an inseparable mixture of epimers at C7 (a-OH:b-OH = 1:3). The acetal **23** was reduced with Et_3SiH in the presence of $SnCl_4$[16] to give an isomeric mixture of bicyclic ethers which afforded the desired ketone **24** (65%) and its C8-epimer **25** (24%) after oxidation. When **25** was treated with DBU in benzene-d_6 at ambient temperature, the reaction attained equilibrium (**24**:**25** = 7:1) to give **24** (72%) mainly. The benzyl group of **24** was removed by hydrogenolysis to provide cyclic hemiacetal **26** (~100%) as an anomeric mixture. While TMSOTf-catalyzed reduction of **26** with Et_3SiH[16] at 0 °C gave a 1:1 mixture of the desired **4**[3i,17] and its epimer **27**,[3i,17] the ratio of **4** to **27** was improved by lowering the reaction temperature (-78 → -15 °C, **4**:**27** = 4:1). Thus, **4** was synthesized from **7a** in 8 steps, including an isomerization step. The overall yield of **4** amounted to 44% from **7a**.

Next, tetracyclic **5** and **6**, as the advanced model systems, were synthesized (Scheme 4). Both 6-membered (**7a**+**9a**) and 7-membered cyclic series (**7b**+**9b**) gave the respective diols **29a** and **29b** in good yields through the segment connection and the desilylating steps. Acidic treatment of each diol in MeOH-$(MeO)_3CH$[15] produced separable a-hydroxy acetals **30** and its b-isomers **31**. Under reductive etherification conditions, both **31a** and **31b** showed exclusive production of **34a** and **34b**, respectively. On the other hand, both **30** afforded mixtures of **32** and **33**, and the distribution of the isomers altered with the size of the respective outside rings (**32a**:**33a** = 3:1, **32b**:**33b** = 8:1). Swern oxidation[7] of both **32** and **34** led to the common ketones **35**, respectively. The alcohol **33a** was also converted to **35a** in good yield via an oxidation-isomerization sequence. After debenzylation followed by reductive etherification, ketones **35a** and **35b** produced tetracyclic ether **5**[3c, 17] and **6**[17] in good yields (overall yields, **5**:34% from **7a** in 8 steps, **6**:29% from **7b** in 7 steps), respectively, via cyclic hemiacetals **36a** and **36b**.

trans-Fused tri- and tetracyclic ethers **4**, **5**, and **6** were thus synthesized in high yields in short steps involving acetal cyclization and reductive etherification reactions starting from monocyclic ethereal aldehyde **7** and dithioacetal *S*-oxide segments **8** and **9**. This sequence could provide a simple convergent approach to the synthesis of various condensed polycyclic ethers. Application of the present work to the synthesis of natural polycyclic ethers is currently underway in our laboratory.

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(17) Spectral data of the cyclic ethers **4**, **27**, and **5** agreed well with those of the literatures. Representative data for **6**: colorless needles, mp. 203-206 °C (ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38-1.48 (4H, m, H4a and H7ax), 1.50-1.78 (6H, m, H2a, H3a, and H3b) 1.82-1.90 (2H, H2b), 2.07-2.13 (2H, H4b), 2.29 (2H, brtd, *J* = 4.4, 11.7 Hz, H7eq), 2.93-3.00 (2H, m, H8) 3.12 (2H, dt, *J* = 4.4, 9.2 Hz, H5), 3.20 (2H, ddd, *J* = 4.4, 9.2, 10.8 Hz, H6) 3.71 (2H, td, *J* = 6.0, 11.9 Hz, H1a), 3.83 (2H, ddd, *J* = 6.7, 7.7, 11.9 Hz, H1b); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.9 (C3), 28.9 (C2), 34.3 (C4), 37.2 (C7), 69.0 (C1), 76.0 (C8), 77.1 (C6), 82.1 (C5); IR (KBr) ν 2924, 2889, 2856, 1445, 1307, 1349, 1298, 1285, 1253, 1156, 1146, 1129, 1102, 1073, 1038, 988, 939, 896, 655, 552, 506, 478, 430 cm^{-1}; HR-EIMS calcd. for $C_{16}H_{26}O_4$ [M]:282.1831, found:282.1833.

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