Convergent Synthesis of a *Trans*-fused 6-7-6 Tricyclic Ether System Based on a Ring-closing Metathesis Reaction

Tohru Oishi, Yoko Nagumo, and Masahiro Hirama*

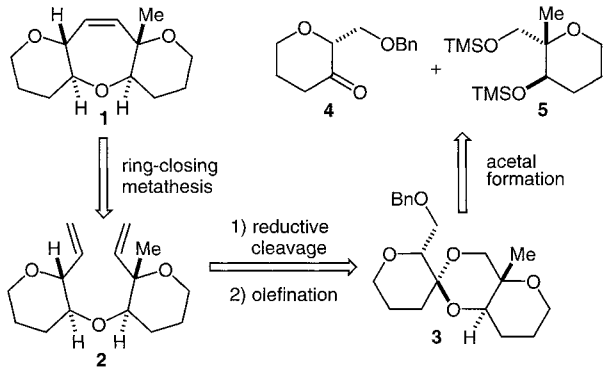
Department of Chemistry, Graduate School of Science, Tohoku University, Sendai 980-77, Japan

Fax +81(22)217-6566; E-mail hirama@ykbsc.chem.tohoku.ac.jp

Received 5 May 1997

Abstract: Synthesis of a *trans*-fused 6-7-6 tricyclic ether system was achieved *via* stereoselective acetal formation, reductive cleavage of the acetal, and a ring-closing metathesis reaction.

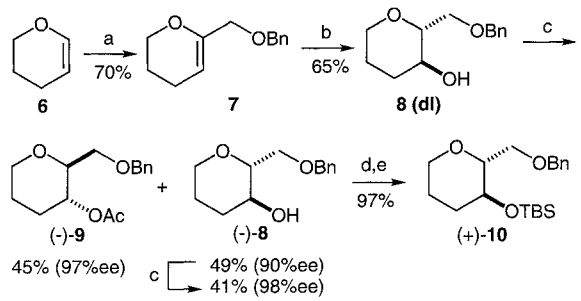
Considerable attention has been paid to the synthesis of polycyclic ethers of marine origin because of their striking structures and biological activities.[1] Although numerous techniques have been developed for the synthesis of cyclic ethers,[2] efficient methods for assembling fragments are still needed. In the course of our synthetic studies directed toward ciguatoxin,[3] we sought to develop a new strategy for combining two fragments, as outlined in Scheme 1. Acetal formation with **4** and **5** followed by reductive opening of the acetal **3**, and a ring-closing metathesis reaction[4] of the corresponding diene **2** should give the *trans*-fused 6-7-6 tricyclic ether system **1**. We report here a synthesis of **1** *via* a ring formation of the central ring based on a metathesis reaction. Very recently, related synthesis of a terminal ring of polycyclic ether system were reported by Nicolaou[5] and Clark,[6] which prompted us to disclose our own strategy.



Scheme 1. Synthetic strategy of **1**.

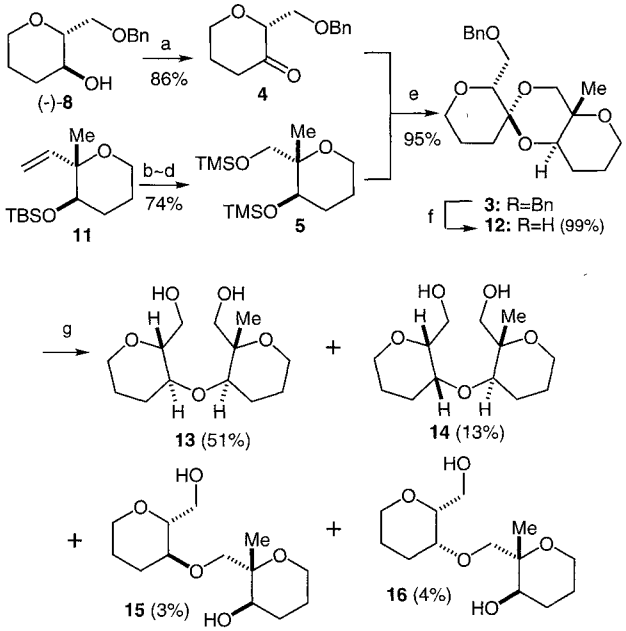
Although various methods have been reported for the synthesis of optically active *trans*-tetrahydropyran derivatives,[3a,7] we developed an expeditious method for preparing both enantiomers in four steps (Scheme 2). Lithiation of 3,4-dihydro-2*H*-pyran **6** with butyllithium followed by treatment with benzyloxymethyl chloride (BOMCl) resulted in the formation of **7** in 70% yield. Hydroboration of **7** gave *trans*-alcohol **8** in 63% yield, and chemoenzymatic resolution[3e] of the racemic **8** using lipase AK (Amano) furnished acetate (-)-**9** (45%) and intact alcohol (+)-**8** (49%). The enantiomeric excess of (-)-**9** and (+)-**8** was determined to be 97%ee $\{[\alpha]^{23}_D$ -55.3° (c 1.03, $CHCl_3)\}$ and 90%ee, respectively.[8] The enantiomeric purity of the recovered alcohol (+)-**8** was improved to 98% $\{[\alpha]^{24}_D$ +32.0° (c 1.15, MeOH)} by treating again with lipase. The absolute configuration of (+)-**10** $\{[\alpha]^{21}_D$ +50.3° (c 1.01, $CHCl_3)\}$ derived from (+)-**8** was determined by comparison with an authentic sample.[7]

Ketone **4** and bis-TMS ether **5**, derived from (+)-**8** and **11**,[7] respectively, were treated with TMSOTf [9] in dichloromethane at -78°C ~ 0°C to give **3** $\{[\alpha]^{24}_D$ +26.0° (c 1.33, $CHCl_3)\}$ as a single isomer (Scheme 3).[10] Hydrogenolysis of benzyl ether **3** followed by reduction of the acetal



Scheme 2. Reagents and Conditions. (a) (i) BuLi, TMEDA; (ii) BOMCl, THF; (b) (i) BH_3•SMe_2, THF; (ii) H_2O_2, NaOHaq; (c) Lipase AK (Amano), vinyl acetate, 35°C; (d) TBSCl, Im, DMF; (e) H_2, 5%Pd/C, AcOEt.

with chloroalane generated from $AlCl_3$ and $LiAlH_4$[11] resulted in regio- and stereoselective cleavage to yield **13** (51%) $\{[\alpha]^{24}_D$ +31.3° (c 1.41, $CHCl_3)\}$ as a major product together with other isomers, **14** (13%), **15** (3%), and **16** (4%).[12] The stereochemical outcome of this reaction can be explained by Cieplak's hypothesis (Figure 1). The axial C-O bond of **12** is prone to be cleaved more rapidly than the equatorial one, since the electron donating ability of σ_{CH} to σ_{CO}* appears to be higher than that of σ_{CC} or σ_{CO}.[13] Therefore, coordination of chloroalane to the axial oxygen atom of **12** resulted in the formation of oxocarbenium ion (A), followed by intramolecular (path a) rather than intermolecular hydride transfer (path b) to give the desired product **13**.



Scheme 3. Reagents and Conditions. (a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; (b) (i) O_3, CH_2Cl_2, MeOH; (ii) $NaBH_4$; (c) TBAF, THF; (d) TMSCl, Et_3N, THF; (e) TMSOTf, CH_2Cl_2; (f) H_2, Pd/C, MeOH; (g) $AlCl_3$ (10 eq), $LiAlH_4$ (10 eq), Et_2O, reflux, 1 week.

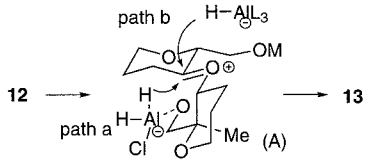
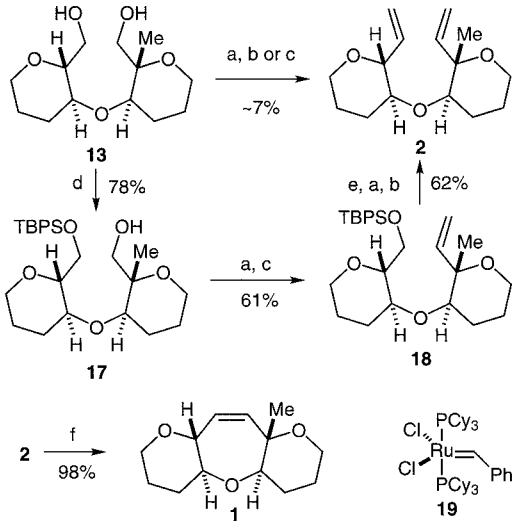


Figure 1

The synthesis of **1** from **13** was achieved as shown in Scheme 4. Bis-olefination of **13** to **2** *via* bis-aldehyde resulted in a low yield. Therefore, stepwise olefination was examined. Selective protection of the less-hindered alcohol as TBPS ether (78%) followed by oxidation of the remaining alcohol and olefination with Tebbe reagent gave **18** in 61% yield (2 steps).[14] Subsequent deprotection and oxidation followed by Wittig olefination gave **2** in 62% yield.[15] A ring-closing metathesis reaction of **2** with Grubbs' catalyst **19**[4a] proceeded smoothly to yield **1** as a single product.[16]

The present ring-forming strategy will be extended for synthesizing polycyclic marine toxins, which will be reported in due course.



Scheme 4. Reagents and Conditions: (a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; (b) $Ph_3P^+CH_3Br^-$, NaHMDS, THF; (c) Tebbe reagent, toluene, THF; (d) TBPSCl, Et_3N, DMAP, CH_2Cl_2; (e) TBAF, THF; (f) **19** (21 mol%), benzene, 60°C.

Acknowledgments. This work was supported in part by grants-in-aid from the Ministry of Education, Science and Culture of Japan, the Uehara Memorial Foundation, and the Naito Foundation. We thank Amano Pharmaceutical Co. Ltd. for the generous gift of lipases, and are grateful to Prof. Grubbs for the procedure for synthesizing the catalyst **19**.

References and Notes

(1) Yasumoto, T.; Murata, M. *Chem. Rev.* **1993**, *93*, 1897; Scheuer, P. J. *Tetrahedron* **1994**, *50*, 3.

(2) Elliot, M. C. *Contemp. Org. Synth.* **1994**, *1*, 457; Alvarez, E.; Candenas, M.-L.; Pérez, R.; Ravelo, J. L.; Martín, J. D. *Chem. Rev.* **1995**, *95*, 1953, and references cited therein.

(3) (a) Suzuki, T.; Sato, O.; Hirama, M. *Tetrahedron Lett.* **1990**, *31*, 4747; (b) Suzuki, T.; Sato, O.; Hirama, M.; Yamamoto, Y.; Murata, M.; Yasumoto, T.; Harada, N. *Tetrahedron Lett.* **1991**, *32*, 4505; (c) Sato, O.; Hirama, M. *Synlett* **1992**, 705; (d) Oguri, H.; Hishiyama, S.; Oishi, T.; Hirama, M. *Synlett* **1995**, 1252; (e) Oishi, T.; Shoji, M.; Maeda, K.; Kumahara, N.; Hirama, M. *Synlett*, **1996**, 1165; (f) Oguri, H.; Hishiyama, S.; Sato, O.; Oishi, T.; Hirama, M.; Murata, M.; Yasumoto, T.; Harada, N.; *Tetrahedron* , **1997**, *53*, 3057.

(4) (a) Zuercher, W. J.; Hashimoto, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 6634; (b) Fujimura, O.; Fu, G. C.; Grubbs, R. H. *J. Org. Chem.* **1994**, *59*, 4029; and references cited therein.

(5) Nicolaou, K. C.; Postema, M. H. D.; Claiborne, C. F. *J. Am. Chem. Soc.* **1996**, *118*, 1565; Nicolaou, K. C.; Postema, M. H. D.; Yue, E. W.; Nadin, A. *J. Am. Chem. Soc.* **1996**, *118*, 10335.

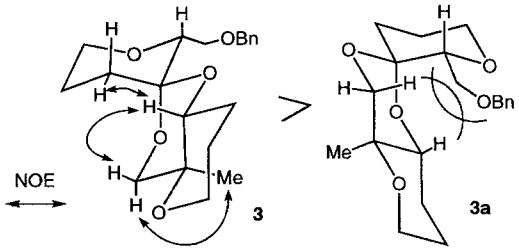
(6) Clark J. S.; Kettle J. G., *Tetrahedron Lett.* **1997**, *38*, 123 and 127.

(7) Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 5330.

(8) Optical purities of (-)-**9** and (+)-**9** derived from (+)-**8** were determined by HPLC analysis (DAICEL, CHIRALPAK AS, hexane/2-propanol=20/1, 1.0 mL/min, 254 nm).

(9) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357.

(10) The stereochemistry of **3** was determined by NOE experiments. **3** should be more stable than the stereoisomer **3a**.



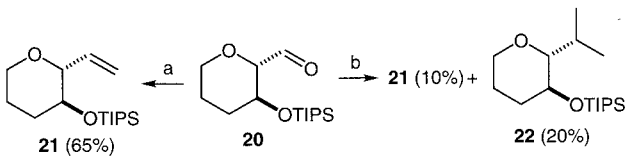
(11) Diner, U. E.; Davis, H. A.; Brown, R. K. *Can. J. Chem.* **1967**, *45*, 207; Bhattacharjee, S. S.; Gorin, P. A. J. *Can. J. Chem.* **1969**, *47*, 1195.

(12) Ishihara, K.; Mori, A.; Yamamoto, H. *Tetrahedron*, **1990**, *46*, 4595; Kotsuki, H. *Synlett*, **1992**, 97.

(13) Cieplak, A. S. *J. Am. Chem.Soc.* **1981**, *103*, 4540; Cieplak, A. S.; Tait, B. D.; Johnson, C. R. *J. Am. Chem.Soc.* **1989**, *111*, 8447.

(14) Wittig reaction resulted in a low yield (38%) and 12% of the aldehyde was recovered.

(15) Wittig reaction for a sterically less-hindered aldehyde with an α-hydrogen seemed to give a better result. For instance, Wittig reaction of **20** gave **21** in 65% yield, while olefination reaction with Tebbe reagent gave **21** (10%) and **22** (20%) as a by-product.[4b]



Scheme 5. Reagents and Conditions: (a) $Ph_3P^+CH_3Br^-$, NaHMDS, THF; (b) Tebbe reagent, toluene, THF.

(16) **(4a*S*,5a*R*,9a*S*,11a*R*)-9a-Methyl-3,4,4a,5a,6,7,9a,11a-octahydropyrano[3,2-b]pyrano[3',2'-f]oxepin (1):** colorless oil; $[\alpha]^{25}_D$ +6.1° (c 1.00, $CHCl_3$); ^1H NMR (600MHz, $CDCl_3$) δ 1.30 (3H, s, Me), 1.43-1.51 (1H, m, H4ax), 1.53-1.71 (5H, m, H6ax, H3, H7), 1.78-1.82 (1H, m, H6eq), 2.02-2.07 (1H, m, H4eq), 3.27 (1H, ddd, *J*=11.0, 9.1, 4.5 Hz, H4a), 3.27-3.32 (1H, m, H2ax), 3.46 (1H, dd, *J*=11.6, 4.5 Hz, H5a), 3.52 (1H, td,

J=11.9, 3.5 Hz, H8ax), 3.60 (1H, ddt, *J*=11.9, 4.8, 1.6 Hz, H8eq), 3.80 (1H, ddd, *J*=9.1, 2.7, 2.0 Hz, H11a), 3.87-3.90 (1H, m, H2eq), 5.43 (1H, dd, *J*=12.9, 1.8 Hz, H11), 5.69 (1H, dd, *J*=12.9, 2.7 Hz, H10); ^{13}C NMR (150MHz, $CDCl_3$) δ 14.62 (C12), 25.47, 25.76 (C3 or C7), 26.91 (C6), 31.25 (C4), 60.11 (C8), 67.50 (C2), 78.28 (C9a), 80.04 (C4a), 80.53 (C11a), 81.65 (C5a), 129.74 (C11), 139.53 (C10); HRMS(EI, 70eV) calcd for $C_{13}H_{20}O_3$ 224.1413, found 224.1415.