Convergent synthesis of the *trans*-fused 6-*n*-6-6 (*n* = 7–10) tetracyclic ether system based on a ring-closing metathesis reaction

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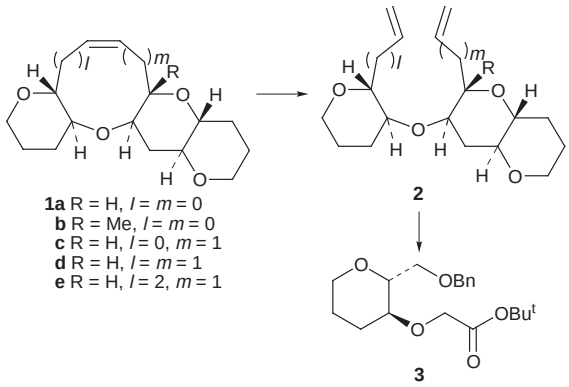
A convergent synthesis of the *trans*-fused 6-*n*-6-6 (*n* = 7–10) tetracyclic ether system was achieved *via* stereoselective alkylation and ring-closing metathesis reaction.

The synthesis of ciguatoxin[1] has received considerable attention because of its striking structure and biological activity. Although numerous techniques have been developed for the synthesis of medium ring ethers,[2] efficient methods for assembling fragments are still needed. In the course of our synthetic study of ciguatoxin,[3] we developed a convergent route to the *trans*-fused 6-7-6 tricyclic ether system *via* formation of the central oxepene ring by alkene metathesis.[4–6] Here we describe a new technique for synthesizing *trans*-fused 6-*n*-6-6 (*n* = 7–10) tetracyclic polyether systems (**1a**–**e**) from glycolate **3** (Scheme 1). The central *n*-6 bicyclic rings of these systems are efficiently constructed by stereoselective alkylation and the subsequent ring-closing metathesis reaction of dienes (**2**).

Syntheses of the dienes **2a** and **2b**, precursors for 6-7-6-6 systems (**1a** and **1b**), are shown in Scheme 2. Coupling of *tert*-butyl ester **3** with iodide **4**‡ using LDA in the presence of HMPA gave **5** and the diastereomer **6** in a 3 : 1 ratio. These compounds were separated using silica gel column chromatography. Removal of the TIPS group of **5** using TBAF followed by treatment with $TsOH{\cdot}H_2O$ in toluene at 90 °C gave lactone **7**. The addition of vinylmagnesium bromide to **7** gave hemiacetal **8**, and reduction of **8** with Et_3SiH in the presence of $BF_3{\cdot}OEt_2$[7] proceeded stereoselectively, giving **10** as a single isomer. Methylation of the hemiacetal **8** using Me_3Al and $BF_3{\cdot}OEt_2$[8] gave **11** only in low yield (~4%); however, the alkylation of the corresponding methyl acetal **9** under the same reaction conditions gave **11** in good yield (72%) as a single isomer. Reductive removal of the benzyl groups of **10** and **11** using lithium naphthalenide[9] followed by Swern oxidation and subsequent Wittig olefination gave dienes **2a** and **2b**, respectively.

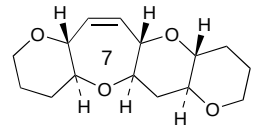
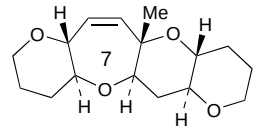
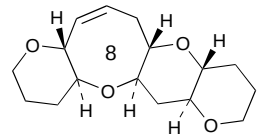
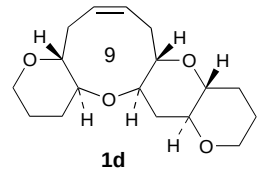
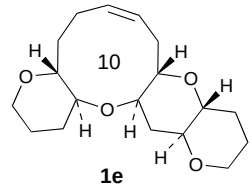
Syntheses of dienes **2c**–**e**, precursors for **1c**–**e**, respectively, are also shown in Scheme 2. Treatment of **7** with allylmagnesium bromide followed by reduction of the resulting hemiacetal (Et_3SiH, $BF_3{\cdot}OEt_2$) gave **12** as a single isomer. The olefin **12** was converted to **2c** in the same manner as **2a** and **2b**. Syntheses of **2d** and **2e** were performed using triflate chemistry.[10] Treatment of the triflate derived from alcohol **13** using lithium acetylide in the presence of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidone (DMPU) followed by partial hydrogenation gave **2d**, whereas treatment of the same triflate using allylmagnesium bromide in the presence of CuBr gave **2e**.

Ring-closing metathesis reactions of dienes **2a**–**e** using Grubbs' catalyst ($(PCy_3)_2Cl_2Ru{=}CHPh$ (**14**) were examined (Table 1). The reactions of **2a** and **2b** in benzene gave 6-**7**-6-6 tetracyclic ethers **1a**, and **1b** having an angular methyl group in

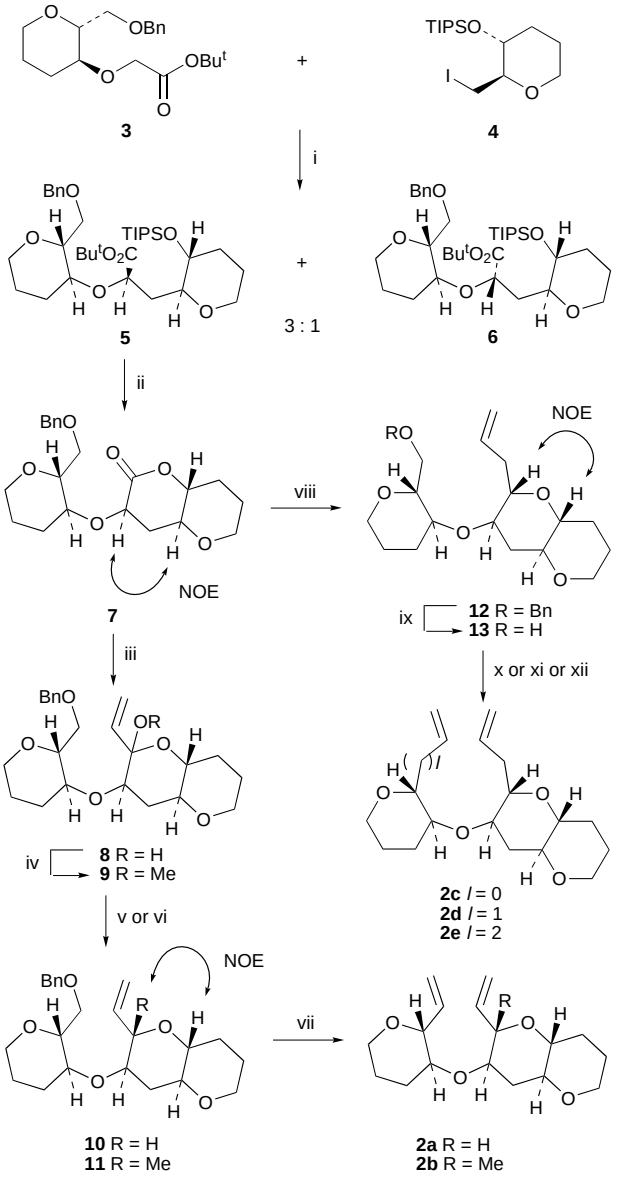


Scheme 1

Table 1 Ring-closing metathesis reaction of **2a**–**e**[a]

Diene	Product	*J*/Hz[b]	Yield (%)
2a	 **1a**	12.9	81[d]
2b	 **1b**	12.8	94[d] 82[e]
2c	 **1c**	11.0	94[e]
2d	 **1d**	10.5[c]	87[e]
2e	 **1e**	10.9	68[e]

[a] Reactions were carried out in the presence of 12–21 mol% of catalyst **14**. [b] Coupling constants between the olefin protons. [c] The value at −40 °C. [d] In benzene at 50–60 °C for 5–7 days (0.04 M). [e] In CH_2Cl_2 at 35 °C for 1–2 days (0.004–0.04 M).



Scheme 2 *Reagents and conditions*: i, LDA, HMPA, THF, −78 to 0 °C, 61%; ii, Bu_4NF, THF, $TsOH·H_2O$ (cat.), toluene, 90 °C, 84%; iii, H_2C=CHMgBr, THF, −78 °C, 80%; iv, $CH(OMe)_3$, CSA, CH_2Cl_2, 80; v, Et_3SiH, $BF_3·OEt_2$, MeCN, −20 °C, 71%; vi, Me_3Al, $BF_3·OEt_2$, CH_2Cl_2, 0 °C to room temp., 72%; vii, Li, $C_{10}H_8$, THF; $(COCl)_2$, Et_3N, DMSO, CH_2Cl_2, −78 to −40 °C; $Ph_3P^+MeBr^-$ $NaN(SiMe_3)_2$, THF, 0 °C to room temp., 72% (for **2a**), 64% (for **2b**); viii, H_2C=$CHCH_2MgBr$, THF, Et_2O, −78 °C; Et_3SiH, $BF_3·OEt_2$, MeCN, −20 °C to room temp., 90%; ix, Li, $C_{10}H_8$, THF, 91%; x, $(COCl)_2$, Et_3N, DMSO, CH_2Cl_2, −78 to 0 °C; $Ph_3P^+MeBr^-$, $NaN(SiMe_3)_2$, THF, 0 °C to room temp., 83%; xi, Tf_2O, Py, CH_2Cl_2, −15 °C; LiC≡CH, DMPU, THF, −78 to 0 °C; H_2, Lindlar cat. AcOEt, 47%; xii, Tf_2O, Py, CH_2Cl_2, −15 °C; H_2C=$CHCH_2MgBr$, CuBr, Et_2O, 0 to 10 °C, 84%

81 and 94% yield, respectively. These reactions required five to seven days. However, we found a remarkable solvent effect because the reaction of **2b** in CH_2Cl_2 proceeded smoothly and was completed within two days. This method was also quite effective in the construction of the larger rings. Cyclic polyethers **1c** (6-**8**-6-6), **1d** (6-**9**-6-6) and **1e** (6-**10**-6-6 system) were synthesized from **2c**–**e**, respectively, in good yields. The structures of these products were unambiguously determined by NMR and mass spectroscopy.

The present technique will serve as a versatile synthetic tool for the synthesis of polyether marine toxins. Further synthetic studies of ciguatoxin are presently being conducted in our laboratory.

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Notes and References

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‡ Compounds **3** and **4** were prepared from (*2R*,*3S*)- and (*2S*,*3R*)-2-(benzyloxymethyl)tetrahydropyran-3-ol, respectively, by standard procedures.[4]

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