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 ciguatoxin¹ 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 tertbutyl 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·H₂O in toluene at 90 °C gave lactone 7. The addition of vinylmagnesium bromide to 7 gave hemiacetal 8, and reduction of 8 with Et₃SiH in the presence of BF₃·OEt₂⁷ proceeded stereoselectively, giving 10 as a single isomer. Methylation of the hemiacetal 8 using Me₃Al 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 naphthalenide9 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 (Et₃SiH, BF₃·OEt₂) gave 12 as a single isomer. The olefin 12



Scheme 1

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 (PCy₃)₂Cl₂Ru=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

Table 1 Ring-closing metathesis reaction of 2a-ea



^{*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 CH₂Cl₂ 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, Bu₄NF, THF, TsOH·H₂O (cat.), toluene, 90 °C, 84%; iii, H₂C=CHMgBr, THF, -78 °C, 80%; iv, CH(OMe)₃, CSA, CH₂Cl₂, 80; v, Et₃SiH, BF₃·OEt₂, MeCN, -20 °C, 71%; vi, Me₃Al, BF₃·OEt₂, CH₂Cl₂, 0 °C to room temp., 72%; vii, Li, C₁₀H₈, THF; (COCl)₂, Et₃N, DMSO, CH₂Cl₂, -78 to -40 °C; Ph₃P·MeBr⁻ NaN(SiMe₃)₂, THF, 0 °C to room temp., 72% (for 2a), 64% (for 2b); viii, H₂C=CHCH₂MgBr, THF, Et₂O, -78 °C; Et₃SiH, BF₃·OEt₂, MeCN, -20 °C to room temp., 90%; ix, Li, C₁₀H₈, THF, 91%; x, (COCl)₂, Et₃N, DMSO, CH₂Cl₂, -78 to 0 °C; Ph₃P·MeBr⁻, NaN(SiMe₃)₂, THF, 0 °C to room temp., 83%; xi, Tf₂O, Py, CH₂Cl₂, -15 °C; LiC=CH, DMPU, THF, -78 to 0 °C; H₂ Lindlar cat. AcOEt, 47%; xii, Tf₂O, Py, CH₂Cl₂, -15 °C; H₂C=CHCH₂MgBr, CuBr, Et₂O, 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 CH₂Cl₂ 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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