Dimerization in the Intramolecular Horner-Emmons Reaction : Synthesis of Macrocyclic Diels-Alder Substrates, Hexaenodilactones

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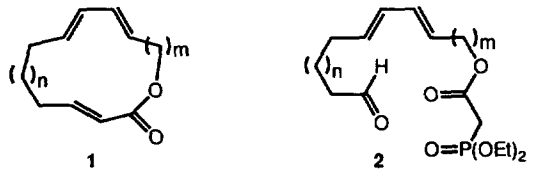
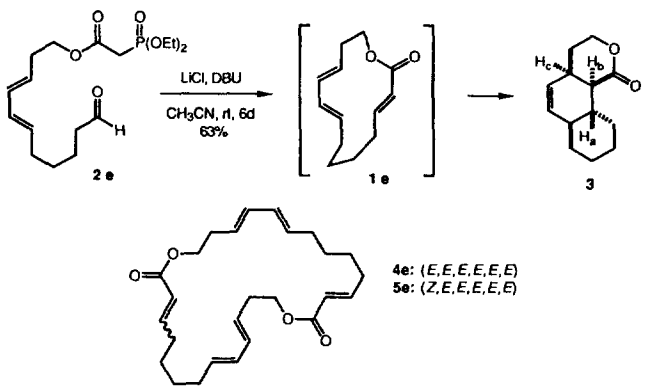
The intramolecular Diels-Alder reaction has been widely used in organic synthesis. The transannular version of this reaction has not been used frequently until recently.[2] Since Deslongchamps' and Takahashi's reports[3] on structural and stereochemical aspects of the transannular cyclization, however, considerable attention has been given to synthetic applications[4] of this reaction. Because of conformational restrictions placed on the triene by macrocycles, the transannular cyclization is thought to be much more facile than conventional intramolecular Diels-Alder reactions.[5] Therefore, this macrocyclic Diels-Alder process has great potential to construct complex tricyclic molecules. In connection with our studies on substituent effects on the stereochemical outcome of the reaction, we needed to prepare various macrocyclic trienes such as trienolactones **1**, as key Diels-Alder substrates. This need led us to investigate intramolecular Horner-Emmons reaction of a series of aldehyde phosphonates **2** under various reaction conditions.

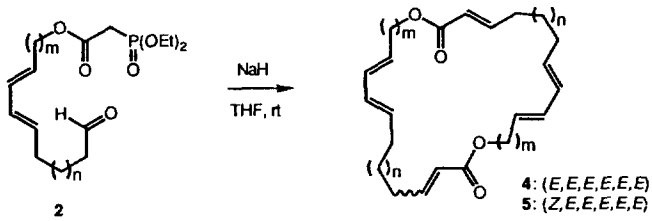


a: m=n=1; **b**: m=1, n=2, **c**: m=1, n=3
d: m=2, n= 1; **e**: m=n=2

We initially examined the intramolecular Horner-Emmons reaction of **2e**[6] at various reaction conditions. To our interest, we have found that the product distribution of this reaction is highly dependent upon reaction conditions. Under the Masamune-Roush conditions[7] (DBU, LiCl, CH_3CN) using high dilution technique (1.5×10^{-4} M), the aldehydophosphonate **2e** underwent the Horner-Emmons cyclization. The macrocyclic triene **1e** was so reactive that the transannular Diels-Alder reaction took place without detection of **1e**, under the reaction conditions, to produce the tricyclic compound **3**[8] as a single adduct in 63% yield and no other cycloadducts were detected. However, when the Masamune-Roush procedure was conducted by the rapid addition or under concentrated conditions, some of dimers **4d** and **5d** were formed. These dimers did not undergo cyclization under the reaction conditions. When attempts to prepare macrocyclic trienes **1a-e** by



employing the Masamune-Roush method met with failure, we turned our attention to the formation of dimers. We envisioned that Diels-Alder adducts of these dimers, upon cleavage, might give access to the same tricyclic structures as cycloadducts of trienolactones **1**. Therefore, many reaction conditions, varying bases, solvents, and additives, were examined. Among the various reaction conditions examined, NaH/THF combination gave the best results. For example, when **2a**[6] was treated with NaH in THF at rt for 5 h, a 4 : 1 mixture of hexaenodilactones **4a** and **5a** was obtained in acceptable 52% yield. Employment of higher concentration (generally $>1.0\times10^{-3}$ M) and/or shorter addition time resulted in the better yield of dimers. The existence of the molecular ion peak at m/z=356 in the mass spectrum, along with the presence of **5a**, supported the structure of the dimer **4a**. Additional experiments with aldehyde phosphonates **2b-d**[6] were carried out to afford a mixture of dimers **4b-d** and **5b-d** with a selectivity of >99 : 1, 10 : 1 and 12 : 1, in 61%, 45% and 47% yield, respectively. Under the NaH/THF combination (2×10^{-3} M), dimerization of **2e** gave a >20 : 1 mixture of **4e** and **5e**, in 38% yield.



a: m=n=1; **b**: m=1, n=2, **c**: m=1, n=3
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In summary, this note describes synthesis of macrocyclic hexaenodilactones **4a-e** by utilization of unusual dimerization phenomena in the intramolecular Horner-Emmons reaction. The present technique may be of value in other synthesis of dimeric macrocycles. To test the feasibility and to look at the stereochemical features, Diels-Alder cyclizations of these dimers are under investigation.

Experimental

^{1}H NMR spectra were recorded on a Varian Gemini-300 (300 MHz) and a Bruker AM-200 (200 MHz) spectrometer. The chemical shifts are reported in ppm from TMS with the solvent resonance as an internal standard ($CDCl_3$, 7.27 ppm). IR spectra were measured on MIDAC 101025 spectrometer. GC/Mass spectra were taken on HP 5988A. NaH was

purchased from Aldrich Chemical Co. Tetrahydrofuran was distilled from sodium benzophenone ketyl.

Preparation of hexaenodilactones 4a and 5a: General Procedure. To a stirred suspension of NaH (60%, 32 mg, 0.81 mmol) in 180 mL of THF at rt was added a solution of aldehyde phosphonate **2a** (190 mg, 0.54 mmol) in THF (80 mL) *via* syringe pump over a 4 h period. After additional stirring for 1 h, the reaction mixture was quenched with water (5 mL) and extracted with ether (50 mL×2). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude residue was purified by column chromatography (5% ethyl acetate in hexane) to give **4a** (40 mg, 42%) and **5a** (10 mg, 10%). **4a**: mp. 89-92 ℃; IR (KBr) 2930, 2853, 2361, 2334, 1717, 1653, 1447 cm^{-1}, ^1H NMR ($CDCl_3$) δ 6.91 (dt, 2H, J=15.6, 7.7 Hz), 6.26 (dd, 2H, J=15.3, 10.4 Hz), 6.01 (dd, 2H, J=15.1, 10.4 Hz), 5.82 (d, 2H, J=15.6 Hz), 5.62 (m, 4H), 4.65 (d, 4H, J=6.1 Hz), 2.27 (m, 4H), 2.18 (m, 4H), 1.68 (m, 4H); GC/MS m/z 356 (M^+), 310, 207, 178, 133, 91. **5a**: ^1H NMR ($CDCl_3$) δ 6.91 (dt, 1H, J=15.7, 7.6 Hz), 6.10-6.35 (m, 3H), 5.93-6.09 (m, 2H), 5.83 (d, 1H, J=15.7 Hz), 5.80 (d, 1H, J=11.6 Hz), 5.58-7.73 (m, 4H), 4.68 (d, 2H, J=6.3 Hz), 4.66 (d, 2H, J=6.6 Hz), 2.63 (m, 2H), 2.27 (m, 2H), 2.20 (m, 4H), 1.55-1.80 (m, 4H). By the same procedure for the preparation of **4a** and **5a**, the following compounds were obtained. **4b**: mp. 119-121 ℃; IR (KBr) 2926, 2857, 1717, 1642, 1247 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.94 (dt, 2H, J=15.9, 7.0 Hz), 6.28 (dd, 2H, J=15.2, 10.5 Hz), 6.03 (dd, 2H, J=15.0, 10.5 Hz), 5.80 (d, 2H, J=15.9 Hz), 5.70 (m, 4H), 4.63 (d, 4H, J=6.8 Hz), 2.11-2.19 (m, 8H), 1.42 (m, 8H). **4c**: mp. 114-116 ℃; IR (KBr) 2928, 2855, 1721, 1655, 1260 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.94 (dt, 2H, J=15.7, 7.5 Hz), 6.30 (dd, 2H=15.1, 10.4 Hz), 6.04 (dd, 2H, J=15.0, 10.4 Hz), 5.85 (d, 2H, J=15.7 Hz), 5.70 (m, 4H), 4.65 (d, 4H, J=6.3 Hz), 2.23 (m, 4H), 2.12 (m, 4H), 1.24-1.54 (m, 12H). **4d**: mp. 128-130 ℃; IR (KBr) 2928, 2851, 2359, 2322, 1721, 1645, 1267 cm^{-1}. ^1H NMR ($CDCl_3$ δ 6.93 (dt, 2H, J=15.8, 7.0 Hz), 5.98-6.07 (m, 4H), 5.83 (d, 2H, 15.8 Hz), 5.51-5.61 (m, 4H), 4.21 (t, 4H, 5.9 Hz), 2.42 (m, 4H), 2.20 (m, 4H), 2.08 (m, 4H), 1.56 (m, 4H). **4e**: mp. 129-130 ℃; IR (KBr) 2926, 2855, 2334, 1717, 1653, 1454 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.96 (dt, 2H, J=15.7, 7.1 Hz), 5.99-6.14 (m, 4H), 5.83 (d, 2H, 15.7 Hz), 5.55-5.68 (m, 4H), 4.21 (t, 4H, J=5.3 Hz), 2.43 (m, 4H), 2.23 (m, 4H), 2.09 (m, 4H), 1.45 (m, 8H).

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1. Present address: Organic Chemistry Laboratory (I), Korea Institute of Science & Technology, Seoul 136-791.
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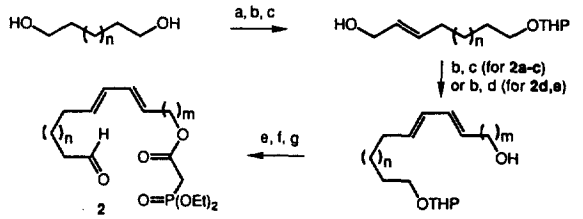
6. Aldehyde phosphonates **2** required for this study were prepared as follows.



Reagents: (a) DHP, PPTS, CH_2Cl_2, rt, 59-60% (b) i. $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -50°C ii. $(EtO)_2POCH_2CO_2Et$, NaH, THF, 60-80% for two steps (c) DIBAH, CH_2Cl_2,-78°C, 83-90% (d) $Ph_3P^+CH_2CH_2CH_2OH$, *n*-BuLi,THF, -78°C-0°C (e) $(EtO)_2POCH_2CO_2H$, DCC, CH_2Cl_2, 91-99% (f) 2*N* HCl, THF, 75-89% (g) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -50°C, 96-99%

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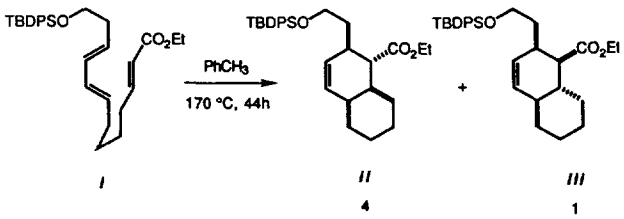
8. The stereochemical assignment of **3** was made initially on the basis of an analysis of the ^1H NMR spectroscopic data (J_{ab}=11.0 Hz, J_{bc}=6.3 Hz), and was confirmed by the transformation of the Diels-Alder adduct *iii* (prepared from the cyclization of the triene *i* as shown below) into **3**.



Physical data for **3**: mp. 59-60.5 ℃; IR (KBr) 2920, 2849, 1725, 1481, 1451, 1408, 1302, 1254 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.56 (s, 2H), 4.41 (m, 1H), 4.24 (m, 1H), 2.67 (m, 1H), 2.59 (dd, J=11.0, 6.3 Hz, 1H), 1.52-1.91 (m, 10H); GC/MS m/z 206 (M^+) 178, 161, 133, 120, 91, 79, 41; exact mass 206.1297, calcd for $C_{13}H_{18}O_2$ 206.1307.