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Transannular Diels-Alder Reaction of A Macrocyclic Triene, (*E,E,E*)-13-Trideca-2,8,10-trienolactone[1]

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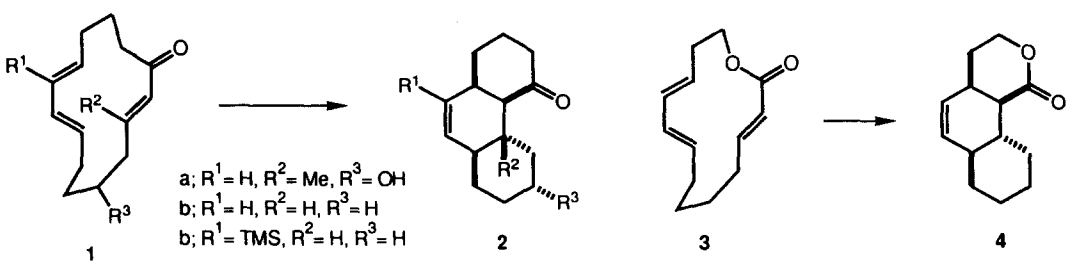
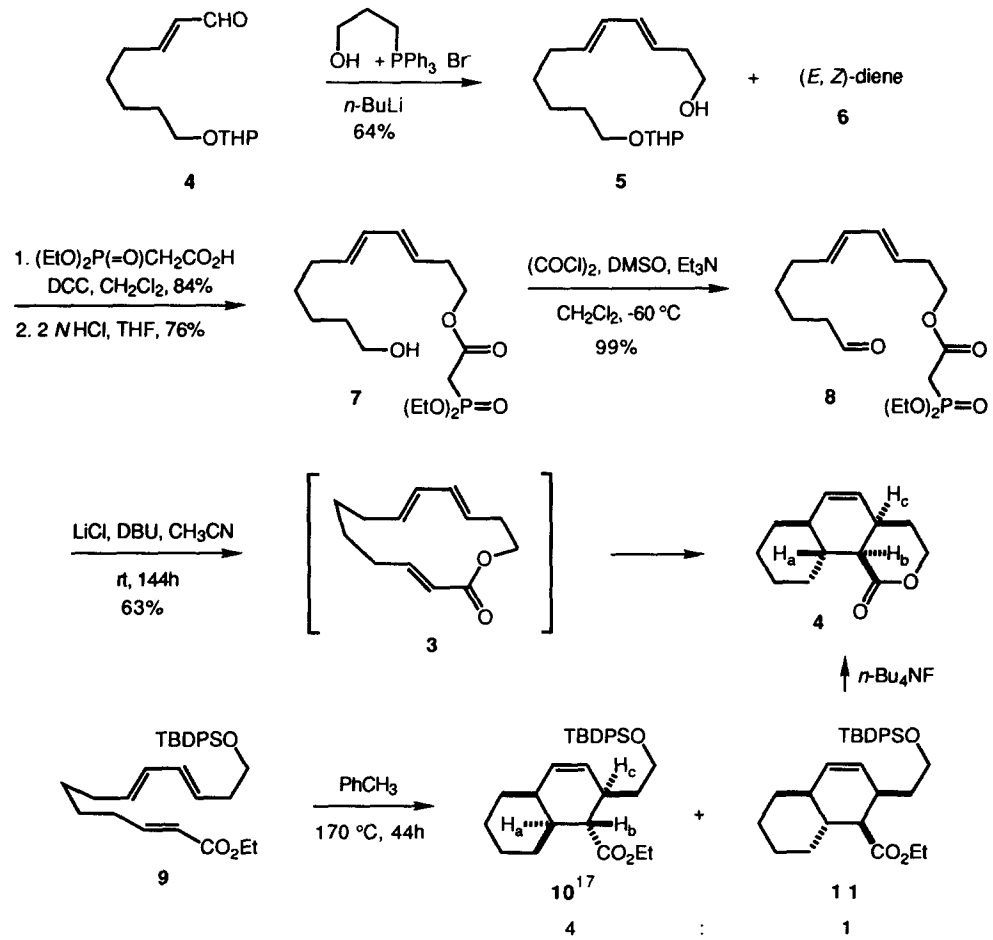
Abstract: (*E,E,E*)-13-trideca-2,8,10-trienolactone **3** undergoes rapid transannular Diels-Alder reaction to produce the *trans-anti-cis* tricyclic lactone **4** as a single cycloadduct.

The intramolecular Diels-Alder reaction has been widely used in synthetic organic chemistry. Many reviews[3] and innumerable natural product synthesis attest to the elegance and efficacy of this cycloaddition reaction to complex targets. However, the transannular version of this reaction has not been used frequently in synthesis until recently,[4] although it is envisioned to be facile due to conformational restrictions placed on the triene by macrocycles. Since Deslongchamps' and Takahashi's recent reports[5] on structural and stereochemical aspects of the transannular cyclization, considerable attention has been given to synthetic applications of this reaction.[6] Our interests in this area center on the substituent effects on the stereochemical outcome of the reaction. We envisioned that in contrast to Turecek's and Deslongchamps' results,[4a,5a] the higher level of stereoselection could be achieved with macrocyclic trienes containing activating groups on the dienophilic unit. Very recently, Takahashi[6g] and Roush[7] have reported this line of observations,[8] namely, highly stereoselective transannular Diels-Alder reactions of (*E,E,E*)-cyclotetradeca-2,8,10-trienones **1a-1c**, in which the keto group is placed on the dienophiles. Herein we report the synthesis and transannular Diels-Alder reaction of (*E,E,E*)-13-trideca-2,8,10-trienolactone **3**.



Synthesis of the target macrocyclic triene **3** started with the coupling of a known aldehyde **4**[9] with the ylide prepared from (3-hydroxypropyl)triphenylphosphonium bromide.[10] Thus, the Wittig reaction yielded an inseparable mixture of (*E,E*)-diene **5** and (*E,Z*)-diene **6** in a 3:1 ratio. The diene mixture was coupled with diethyl phosphonoacetic acid[11] using DCC to afford ester **7**. Removal of the tetrahydropyranyl group followed by the Swern oxidation[12] provided aldehydophosphonoacetate **8**. The intramolecular Horner-Emmons reaction was accomplished by the high dilution technique (1.5×10^{-4} M). When the solution of **8** in acetonitrile was added via a syringe pump to a mixture of LiCl (237 eqiv) and DBU (9 eqiv) in CH_3CN[13] at the room temperature over a period of 144 h, the macrocyclization was followed rapidly (with no detection of the macrocyclic triene **3**) by transannular Diels-Alder reaction of macrocyclic triene **3** to produce the tricyclic compound **4**[14] as a single adduct in 63% yield and no other cycloadducts were detected. The stereochemical assignment of **4** was made initially on the basis of an analysis of the ^{1}H NMR spectroscopic data (J_{ab}= 11.0 Hz, J_{bc}= 6.3 Hz), and was confirmed by the transformation of the Diels-Alder adduct **11** (prepared from the cyclization of the triene **9**[15]) into **4**.[16] Thus, the Diels-Alder reaction of the macrocyclic triene **3** took place with a high endo selectivity,



which is in sharp contrast to the results obtained from the cycloadditon of the acyclic triene **9** (*vide supra*). It should be noted that the high dilution and slow addition method was crucial for the success of the macrocyclization of **9**. Serious dimerization was accompanied when the Horner-Emmons reaction was conducted by the rapid addition or under concentrated conditions. While attempts were also made to synthesize (*E,E,E*)-12-dodeca-2,8,10-trienolactone and (*E,E,E*)-11-undeca-2,7,9-trienolactone by employing the present method, these met with failure.

In conclusion, the transannular Diels-Alder reaction of (*E,E,E*)-13-trideca-2,8,10-trienolactone **3**, containing the ester on the dienophilic unit as an activating group, takes place with high stereoselectivity. These results are in complete agreement with Takahashi's and Roush' results[6g,7] for the Diels-Alder reaction of (*E,E,E*)-cyclotetradeca-2,8,10-trienone and its analogs. Since the (4+2) cycloaddition of **3** proceed in opposite stereochemical sense to that of an acyclic triene **9**, the present methodology provides a valuable and complementary (to the conventional IMDA methodology) means for the construction of [6,6,6] tricyclic lactone systems. Studies are in progress to explore effective methods for the preparation of various macrocyclic trienolactones.

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14. mp 59-60.5 °C; 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, 12H); 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.
15. Acyclic triene **9** was prepared from the diene **5** by the following sequence of reactions: (a) TBDPSCl, imidazole, CH_2Cl_2, quantitative (b) 2*N* HCl, THF, 73% (c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -60 °C (d) $(EtO)_2P(=O)CH_2CO_2Et$, NaH, THF, 61% (two steps)
16. While removal of the TBDPS group of **11** with *n*-Bu_4NF in THF led quickly to the tricyclic lactone **4**, treatment of **10** furnished the corresponding desilylated alcohol.
17. ^1H NMR data (H_b, δ 2.55, triplet, $J_{ab}=J_{bc}$= 10.5 Hz) observed for **10** are related closely to Roush's results.[18]
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