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Synthesis and Transannular Diels-Alder Reactions of (E,E,E)-Cyclotetradeca-2,8,10-trienones

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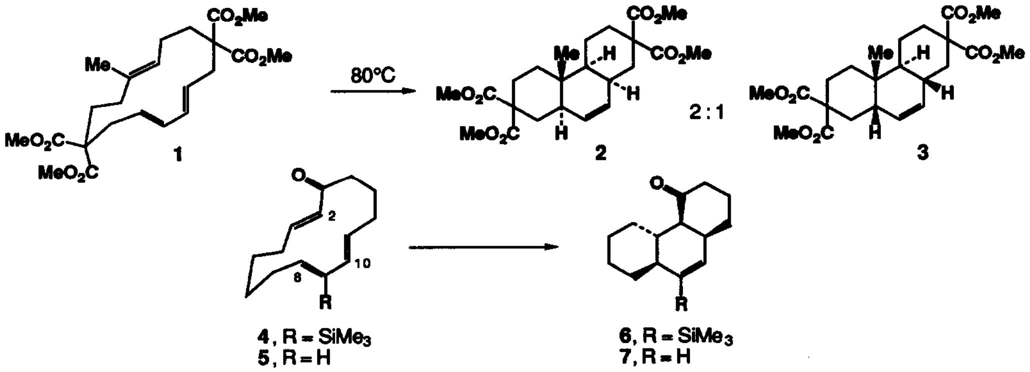
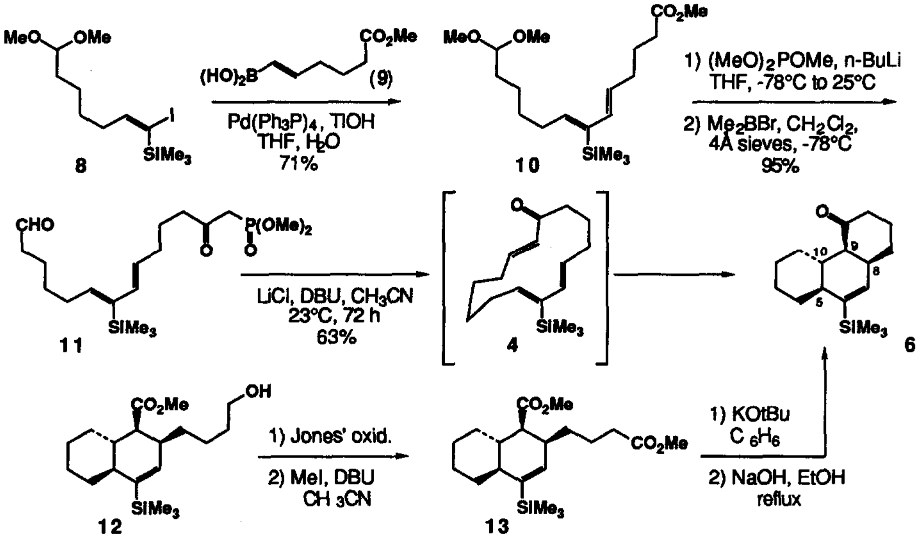
Abstract: (E,E,E)-Cyclotetradeca-2,8,10-trienones **4** and **5**, prepared by intramolecular Horner-Wadsworth-Emmons reactions, undergo highly stereoselective transannular Diels-Alder reactions to the trans-anti-cis tricyclic ketones **6** and **7**, respectively.

While the intramolecular version of the Diels-Alder reaction has found wide application in organic synthesis,[2] until recently the transannular variant has received relatively little attention.[3,4] Studies primarily by Deslongchamps and Takahashi have defined many of the key structural and stereochemical parameters of the transannular reaction, and several elegant synthetic applications have now appeared.[4] An important feature of the transannular process is that conformational constraints placed on the triene by the macrocycle cause the transannular reaction to be much more facile than conventional IMDA cyclizations. Several striking examples of transannular Diels-Alder reactions have been reported in cases where analogous IMDA cyclizations could not be achieved even under more forcing conditions.[4e,f,g] This, together with the potential for this process to generate stereochemically complicated tricyclic products, suggests that the transannular Diels-Alder reaction will have a bright future in organic synthesis.

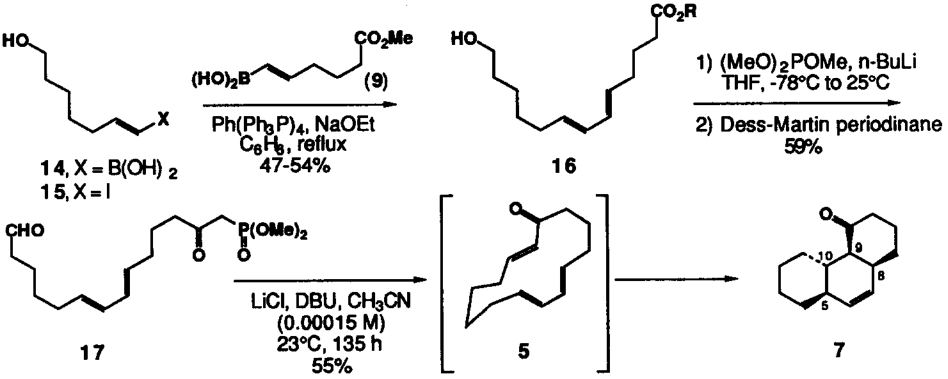
In connection with a planned application of transannular Diels-Alder technology in an ongoing problem in natural products synthesis, we became interested in the degree to which the stereochemical outcome could be influenced by substituent effects. Deslongchamps had shown that the cyclization of (E,E,E)-triene **1** provides a 2 : 1 mixture of the isomeric tricycles **2** and **3**.[4f] We reasoned that better levels of stereochemical control might be realized with (E,E,E)-cyclotetradeca-1,7,9-trienes if an activating substituent were placed on the dienophile, or if a steric directing substituent appeared on the diene.[5] Accordingly, we report herein the synthesis and transannular Diels-Alder reactions of (E,E,E)-cyclotetradeca-2,8,10-trienones **4** and **5**.[6]



We began by targeting macrocyclic trienone **4**, in anticipation that the TMS steric directing group would enable excellent stereocontrol to be achieved in the transannular Diels-Alder reaction leading to **6**.[5] Thus, (E)-α-iodo vinylsilane **8**[7a] (prepared by sequential treatment of the corresponding alkynyl silane with DIBAL (Et_2O, 25°C) followed by NIS and pyridine)[5] was coupled with vinylboronic acid **9**[8] under modified Suzuki conditions,[9] providing diene **10**[7a] in 71% yield. Treatment of **10** with dimethyl lithiomethylphosphonate followed by cleavage of the dimethyl acetal with Me_2BBr (CH_2Cl_2, 4Å molecular sieves, -78°C)[10] then provided aldehyde phosphonate **11**,[7a] the substrate for an intramolecular Horner-Wadsworth-Emmons reaction.[11] This was accomplished by adding a solution of **11** in CH_3CN to a 0.001 M solution (23 °C) of DBU (2 equiv) and LiCl (50 equiv) over a 60 h period.[12] The macrocyclic trienone **4** (not detected) cyclized rapidly to **6**[7a,b] which was isolated in 63% yield; no other cycloadducts were detected. The stereostructural assignment for **6**, assigned initially on the basis of ^1H NMR evidence ($J_{5,10}$ = 13.2 Hz, $J_{9,10}$ = 11.6 Hz, $J_{8,9}$ = 3.0 Hz), was confirmed by the independent preparation from the known trans fused octahydronaphthalene **12**[5] via the Dieckmann cyclization of **13**.[7a,b]



We turned next to the synthesis of the C(9)-unsubstituted trienone **5**, which would enable us to address whether a dienophilic activating group alone is sufficient to bias the transannular Diels-Alder transition state(s) to achieve high diastereoselectivity. Standard Suzuki cross coupling of vinyl iodide **15**[7a] (prepared by standard iodination of **14**)[13] and vinylboronic acid **9**[5] provided diene **16**[7a] in 47-54% yield [as a mixture of methyl (minor) and ethyl (major) esters)]. Treatment of this mixture with $LiCH_2PO(OMe)_2$ and then oxidation of the primary alcohol with the Dess-Martin periodinane then provided the HWE substrate **17**[7a] in 59% yield. Very slow addition (135 h)[12] of a CH_3CN solution of **16** to a mixture of LiCl (200 equiv) and DBU (8 equiv) in CH_3CN (0.00015 M final concentration) then provided tricycle **7**[7a] in 55% yield (no other cycloadducts were detected). That tricycle **7** has the indicated trans-anti-cis stereochemistry was verified by correlation with **6** via protodesilylation of the latter with $BF_3•Et_2O$ and EtSH. The very long addition time specified for the preparation of **7** was required to prevent HWE dimerization of **17**. For example, one experiment performed over a 72 h period at a final concentration of 0.001 M provided a ca. 1 : 1 mixture of **7** and the corresponding 28-membered symmetrical hexaenyl diketone[12b] in 38% combined yield. It is interesting to note that the dimerization problem was much less serious in the synthesis of **4**,[12a] suggesting that the TMS group influences the conformational preferences of **11** relative to **17**, thereby enhancing the rate of macrocyclization of **11**.



In summary, we have shown that a single dienophilic activating group is sufficient to permit (E,E,E)-2,8,10-cyclotetradecatrienones to undergo highly stereoselective transannular Diels-Alder reactions, in contrast to sterically and electronically unbiased systems (e.g., **1**) that cyclize with relatively poor stereoselectivity. Our conclusions are in complete agreement with data recently reported by Takahashi for the transannular Diels-Alder reaction of the 3-methyl analog of **5**.[4i] While the intramolecular Horner-Wadsworth-Emmons methodology provides a very convenient entry into the synthesis of **6** and **7** via **11** and **17**, we close by noting that attempts to extend this technology to the synthesis of various (E,E,E)-2,8,10-cyclotridecatrienones or (E,E,E)-2,7,9-cyclododecatrienones (potential precursors of [6,6,5]- and [5,6,5]-tricyclic ring systems) have proven largely unsuccessful.[14] Consequently, alternative means of synthesizing other classes of macrocyclic trienes are currently under investigation.

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6. After this work was completed, Takahashi and coworkers reported the synthesis and transannular Diels-Alder reaction of the 3-methyl analog of **5** (ref. 4i).
7. (a) The spectroscopic properties (400 or 500 MHz ^{1}H NMR, IR, HRMS) of all new compounds are in agreement with the assigned structures. (b) A correct C,H analysis was obtained.
8. Vinyl boronic acid **9** was prepared by treating methyl 5-hexynoate with catecholborane (1.0 equiv, 100°C) followed by aqueous hydrolysis and chromatographic purification (80% yield).
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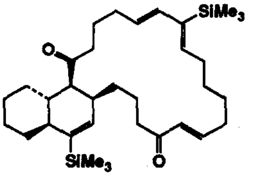
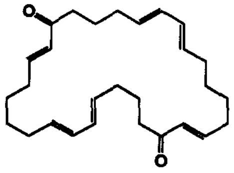
12. The yield of **6** was 20% and 49% from experiments in which DBU (inverse addition procedure) and the solution of **10** (normal procedure, as describe in text) were added over 1.5 h (0.0009 M final concentration) and 3 h (0.0003 M), respectively. A small amount of a "dimeric" product, *i*, was obtained from the inverse addition procedure. Other methods for accomplishing the Horner-Wadsworth-Emmons reaction were much less successful (KOtBu, 18-Cr-6, THF; K_2CO_3, 18-Cr-6, C_6H_6; LiHMDS, C_6H_6, HMPA, etc.). (b) As indicated in the text, significant quantities (up to 20%) of *ii* ^{7a} were obtained in the macrocyclization of **17** if the rate of addition was too rapid (≤90 h addition) or if the reaction mixture was too concentrated (≥0.001 M).

i





ii

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