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SYNTHESIS OF TRICYCLO[6.2.2.0^{1,6}]DODECA-6,9-DIENES. AN APPROACH TO CLERODANE DITERPENES.

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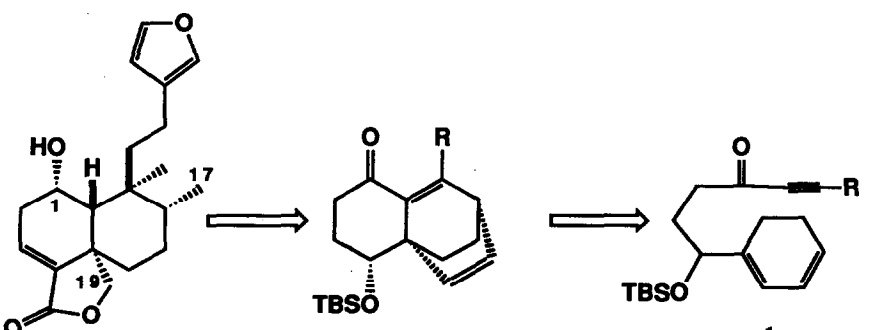
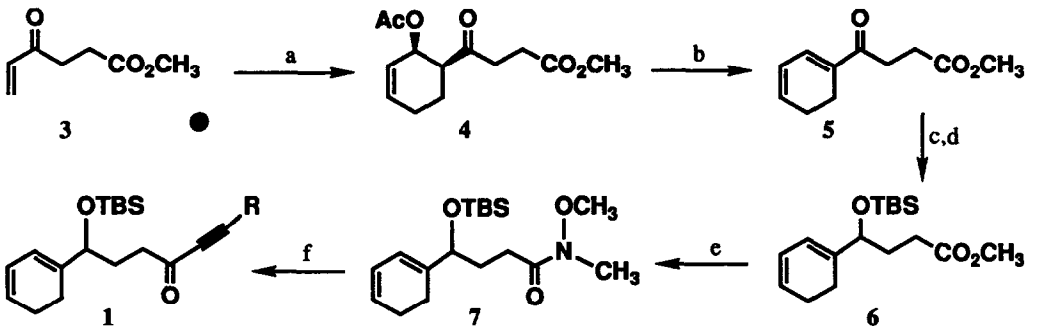
Abstract: The preparation of tricyclo[6.2.2.0^{1,6}]dodeca-6,9-dienes via Lewis acid catalyzed intramolecular cycloadditions is reported. The cycloadditions proceed through boat transition states.

The clerodanes and the *ent*-clerodanes are a large group of diterpenoid natural products[1] which have been found to possess a broad spectrum of biological activity. Some have been shown to be potent insect antifeedants.[2] Others have been found to have antitumor,[3] antimicrobial,[4] antiviral,[5] or antiulcer activity.[6] A number of them have been isolated from plants which have been utilized as medicinal herbs and folk medicines.[7] The main difference between the members of this group is the level of oxidation at the various positions of the decalin skeleton. These structurally and functionally interesting natural products have attracted a reasonable amount of attention from synthetic chemists,[8] largely due to their insect antifeedant properties.[9] We sought to formulate a versatile and flexible approach to intermediates which would allow for the selective introduction and/or removal of oxygen functionality *en route* to members of this class of natural products.

Outlined below for Bacchofertin,[10] a representative member of the clerodane diterpenes, is the basic strategy to be employed in this synthetic undertaking. It was envisioned that the relative stereochemistry between the C17 and C19 would be controlled by linking these two carbon atoms in the form of an ethylene bridge. This would serve not only to control the stereochemical relationship between these two substituents but also allow for the introduction of necessary oxygen functionality present at these positions in some of the natural products via an oxidative cleavage at a subsequent stage in the synthesis. The tricycle **2** produced by this connection appeared ideally suited to construction via an intramolecular cycloaddition of a 1-substituted-1,3-cyclohexadiene and an appropriately substituted acetylene connected by a four-carbon tether.



Bacchofertin **2** **1**



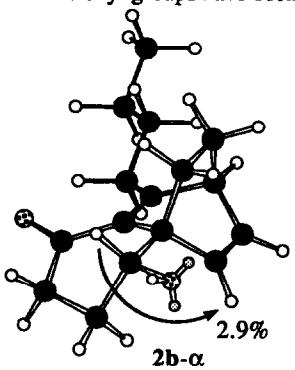
(a) 1-acetoxy-1,3-butadiene, $PhCH_3$, 110°C; (b) DBU, CH_2Cl_2, R.T.; (c) $NaBH_4$, $CeCl_3$, CH_3OH, 0°C; (d) *t*-Bu(Me)$_2$SiCl, imidazole, DMF, 45°C; (e) Me_3Al, $Me(MeO)H_2N^+Cl^-$, PhH, R.T.; (f) RC≡CLi, THF, 0°C→R.T.

The requisite cyclohexadiene with a functionalized side-chain suitable for elaboration into the desired cycloaddition substrates was assembled in a short sequence of reactions initiating with the condensation of vinyl ketone **3**[11] with 1-acetoxy-1,3-butadiene[12] which afforded the β-acetoxy ketone **4** in 90% yield as a 9:1 mixture of endo:exo cycloadducts(only the endo isomer is shown for convenience). Treatment of **4** with DBU produced the dienone **5** in 89% yield. This intermediate undergoes aromatization on attempted storage and was immediately reduced to the corresponding allylic alcohol with $NaBH_4$ in the presence of $CeCl_3$.[13] To avoid the undesired formation of a γ-lactone, the resultant alcohol, without purification, was protected as its *t*-butyldimethylsilyl ether[14] to provide cyclohexadiene-ester **6** in 86% overall yield. The ester **6** was transformed into the *N*-methoxy-*N*-methyl amide **7** using the conditions developed by Weinreb.[15] The amide **7** was combined with a number of 1-lithioalkynes to provide the required acetylenic ketones **1a-f** in 73-85% yields.[16] Reaction of these substrates under thermal conditions or in the presence of catalytic amounts of a variety of different Lewis acids proved to be ineffectual. However, treatment of the acetylenic ketones **1a-f** with 1.2 equivalents of Et_2AlCl in CH_2Cl_2 at room temperature induced smooth cyclizations to afford the tricyclic enones **2a-f** in 74-85% yields. The tricycles proved to be mixtures of α:β isomers at the silyloxy center with the α-isomer predominating. Shown in Table 1 are the results of the cycloaddition reactions.

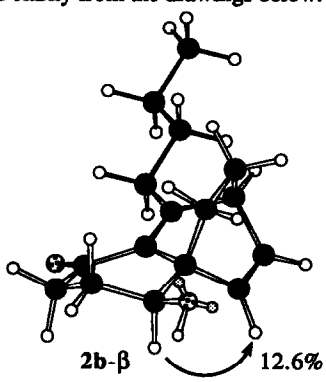
Table 1. Et_2AlCl catalyzed cycloadditions of **1a-f**.

R	Time (min)	Ratio (α:β)	% Yield
a, CH_3	10	4.1:1	80
b, *n*-C_4H_9	50	5.2:1	82
c, Ph	65	6.2:1	85
d, CH_2CH_2OMOM	120	5.2:1	81
e, CH_2CH_2OBn	40	4.0:1	79
f, CH_2OMOM	15	4.8:1	74

The stereochemistry of the cycloadducts was not intuitively obvious from examination of the coupling constants of the proton adjacent to the silyloxy center in the ^{1}H-NMR spectra, although we had a reasonably good idea which was the major diastereomer by analysis of the potential transition states for the cycloaddition (*vide infra*). In an effort to unambiguously assign the stereochemistry, the diastereomeric cycloadducts **2b**α,β were separated by HPLC and independently subjected to an NOE study. In the case of the major cycloadduct **2b**-α, there was only a 2.9% enhancement on irradiation of the methine proton next to the silyloxy center and the proximal proton on the ethylene bridge. However, the minor product **2b**-β exhibited a 12.6% enhancement between the silyloxy methine and the olefin proton. The silyl groups have been removed for clarity from the drawings below.

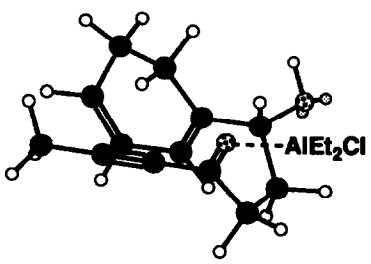


2b-α

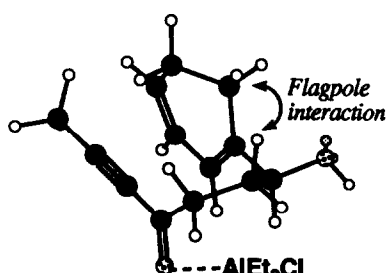


2b-β

Of the eight possible conformations which the cycloaddition substrates could adopt during the transition state, the four which involve chair-like conformations of the bridging atoms between the diene and dienophile were eliminated because of the strain incurred in the tether during proper alignment of the diene and dienophile for cycloaddition. This left consideration only of the four diastereomeric transition states in which the tethering atoms adopt boat-like conformations. These boat-like conformations allow cyclization through relatively strain-free transition states. Roush has observed a similar phenomena in intramolecular diene-acetylene cycloadditions in which there is a four atom bridge between the diene and dienophile. The two boat transition states, endo-boat and exo-boat, which have the silyloxy group axial were excluded because of the eclipsing between the silyloxy group and the cyclohexadiene. The exo-boat and endo-boat transition states which had the silyloxy groups equatorially disposed best accounted for the cycloadducts obtained. The preference for the exo-boat-equatorial silyloxy group conformation, which leads to the major product, over the endo-boat-equatorial silyloxy group conformation was presumably due to an unfavorable flagpole interaction between the β–hydrogen on the carbon adjacent to the silyloxy center and the nearest hydrogen on proximal methylene of the cyclohexadiene. Again, the silyl groups have been removed from the depictions below for clarity.



Exo-boat-equatorial -OR



Endo-boat-equatorial -OR

The introduction of the C9 methyl substituent as well as further elaborations of these tricyclic intermediates towards the clerodane diterpenes will be the subjects of future communications from these laboratories.[18]

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