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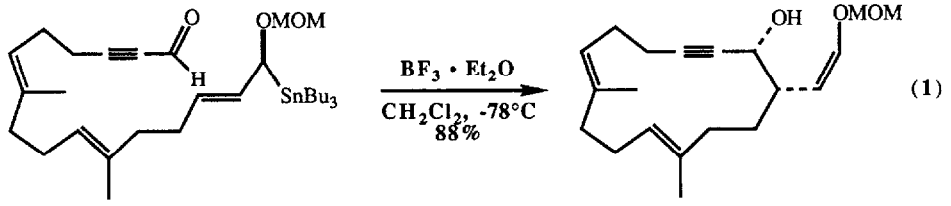
STEREOSELECTIVE CYCLIZATION OF α-ALKOXYALLYLSTANNANE ALKYNALS AND THEIR Co-COMPLEXES. A NEW ROUTE TO CYCLODODECYNE-1,2-DIOL DERIVATIVES

James A. Marshall* and Wei Yi Gung
Department of Chemistry, University of South Carolina
Columbia, South Carolina 29208 U.S.A.

Summary: The α-alkoxyallylstannane dicobalt hexacarbonyl alkynal complex **18** afforded the cyclododecadienyne alcohol complex **19** as a single diastereoisomer in 70% yield upon treatment with $BF_3 \cdot Et_2O$ at -78°C. The reaction is thought to proceed by prior isomerization to the γ-alkoxyallylstannane.

We recently developed an efficient route to 14-membered cembranoid precursors through S_E' cyclization of α-alkoxyallylstannane aldehydes (eq. 1).[1] The efficiency of this cyclization and its high



(1)

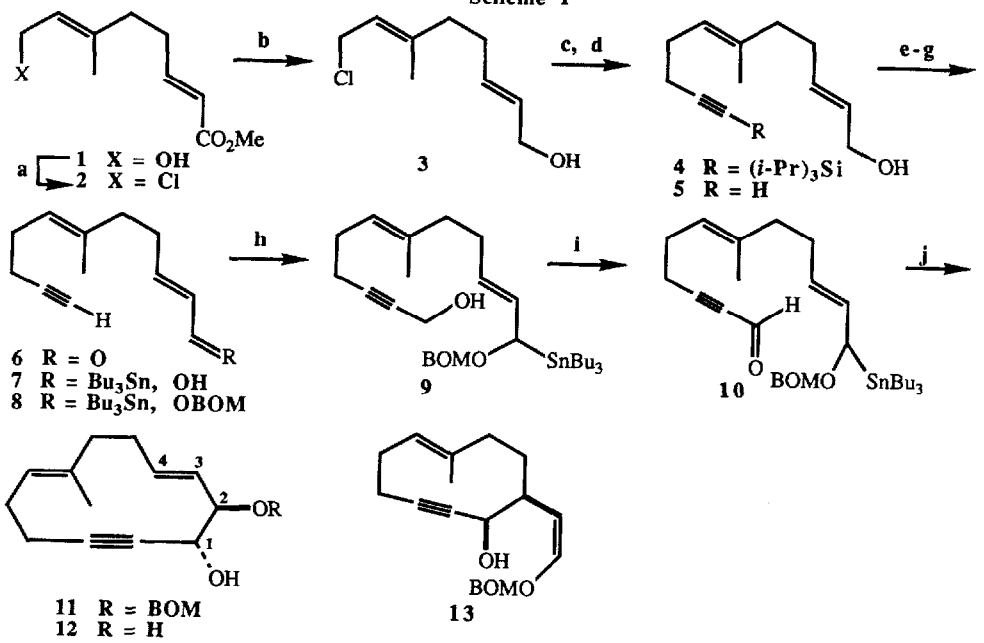
I II (80%)

potential for control of relative and absolute stereochemistry suggested that other ring sizes might likewise be accessible. As an initial test of this premise, we selected the widespread and synthetically challenging 10-membered ring system characteristic of the germacrane sesquiterpenes.[2] Our starting point for this study, aldehyde **10**, was synthesized starting from alcohol 1[3] by the sequence outlined in Scheme I.[1] Alcohol 1 is available from geranyl acetate through selective ozonolysis,[4] Wittig condensation and methanolysis as previously described.[3]

Slow addition of allylstannane aldehyde **10** to a cold dilute rapidly stirring solution of $BF_3 \cdot Et_2O$ in CH_2Cl_2 at -78°C gave a single isolable cyclization product in 25% yield, along with appreciable non-identifiable decomposition by-products. The reaction was significantly slower than the previously examined cyclization of I (eq. 1). The ^1H NMR spectrum of the crude material pointed to the cyclododecynol **11** as the only pure product formed. None of the ten-membered alcohol **13** could be detected.

The stereochemistry of **11** was surmised from the ^1H NMR coupling constants of the vinylic and carbinyl protons ($J_{H3/H4}$ = 14.8 Hz; $J_{H1/H2}$ = 9.0 Hz). The former falls into the range expected for an *E* double bond and the latter is in close agreement with the calculated coupling constant, $J_{H1/H2}$ = 8.6 Hz, of the lowest energy conformer of the diol **13** whose structure was derived through molecular modeling (Figure 1).[5] As an added check we prepared the cis diol derivative **15** by treatment of alcohol **11** with DEAD, $PhCO_2H$[6] followed by reductive cleavage of the inverted benzoate **14** (eq. 2). The ^1H NMR coupling constant for the carbinyl protons, $J_{H1/H2}$ = 2.8 Hz, was likewise in close agreement with that of the calculated structure for diol **16** ($J_{H1/H2}$ = 2.9) shown in Figure 1.

Scheme I[a, b]



[a] (a) MsCl, LiCl, Et_3N, Me_2NCHO (60%); (b) *i*-Bu_2AlH, Et_2O (100%); (c) EtMgBr; TIPS–C≡CCH_2MgBr, CuI (75%); (d) Bu_4NF, THF (95%); (e) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2 (85%); (f) Bu_3SnLi, THF; (g) BOMCl, (*i*-Pr)$_2$NEt (80%); (h) LiN(*i*-Pr)$_2$, THF; CH_2O (90%); (i) *t*-BuOMgBr, THF; ADD (85%); (j) $BF_3 \cdot Et_2O$, CH_2Cl_2, -78°C (25%)

[b] Abbreviations: ADD = $(CH_2)_5NCON{=}NCON(CH_2)_5$; BOM = $PhCH_2OCH_2$; TIPS = (*i*-Pr)$_3$Si

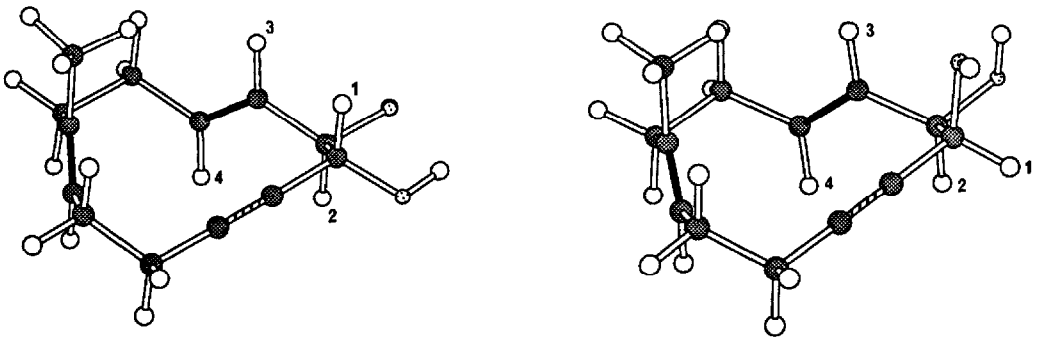
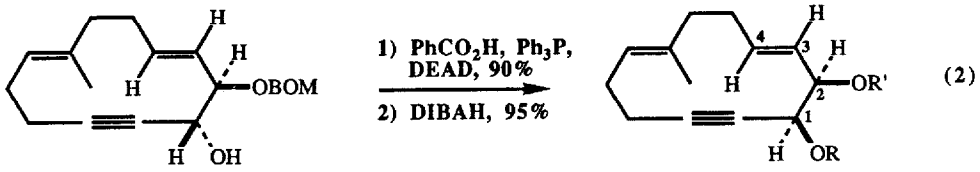


Figure 1. Calculated structures for diols **12** and **16** showing the relationship between H1/H2 and H3/H4.

Alcohol **11** most likely arises from the α-alkoxyallylstannane **10** by initial isomerization to the γ-alkoxyallylstannane followed by S_E' cyclization. A similar pathway has been proposed for an intermolecular aldehyde addition.[7] Attempts to isolate the isomerized alkoxystannane were not



11

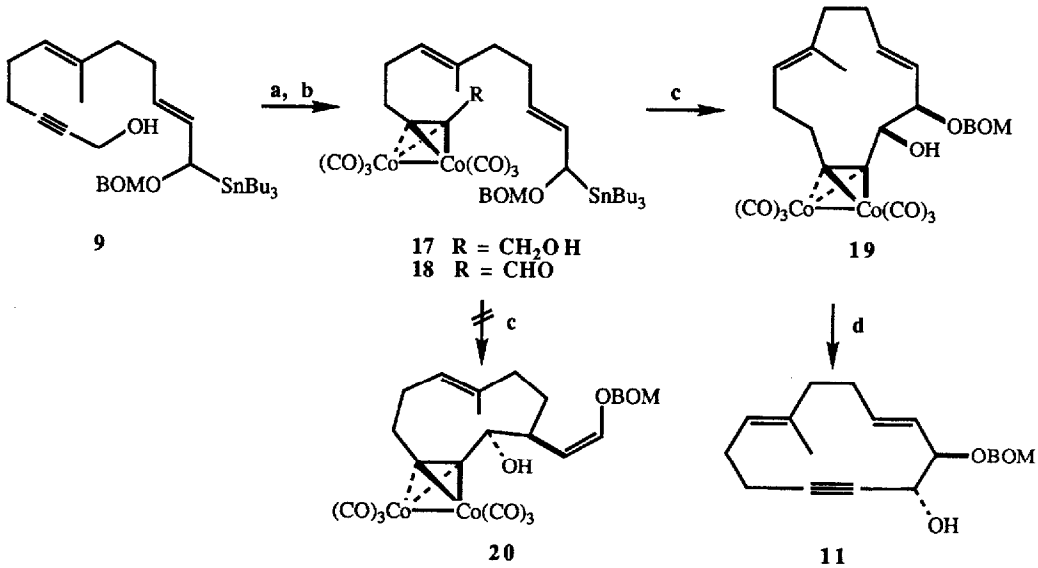
14 R = COPh, R' = BOM
15 R = H, R' = BOM
16 R = R' = H

(2)

successful. Only dimeric and cyclization products could be detected along with starting material upon short exposure of **10** to $BF_3 \bullet Et_2O$ at low temperature.

On the assumption that the linear arrangement of the ynal prevents close approach of the aldehyde carbonyl of **10** to the γ-position of the α-alkoxyallylstannane moiety, we explored the use of the dicobalt hexacarbonyl complex **18** prepared as shown in Scheme II.[8] Addition of **18** to a cold solution of $BF_3 \bullet Et_2O$ in CH_2Cl_2 as before led to a single product in 70% yield. The ^1H NMR spectrum of this product was suggestive of the 12-membered alcohol **19**. Removal of the Co groupings afforded the previously obtained alcohol **11** in 95% yield. No other cyclic products could be detected by ^1H NMR analysis of the crude material.

Scheme II[a]



9

17 R = CH_2OH
18 R = CHO

19

20

11

[a] (a) $Co_2(CO)_8$, Et_2O, 0°C (95%); (b) *t*-BuOMgBr, THF; ADD (84%); (c) $BF_3 \bullet Et_2O$, -78°C, CH_2Cl_2 (70%); (d) $Ce(NH_4)_2(NO_3)_6$, MeOH (91%)

These findings show that cobalt carbonyl complexed ynals can serve as useful substrates in allylstannane additions. They also indicate that rings of various sizes can be accessed through the alkoxyallylstannane methodology[1] although medium-rings may prove problematical. The high degree of diastereoselectivity in the cyclization of both the uncomplexed and complexed ynal **10** and **18** suggests that the presumed 1,3 rearrangement of the α-alkoxystannane moiety proceeds with high stereoselectivity. If so, the methodology outlined here could be used to produce homochiral cyclic 1,2-

diol derivatives and transformation products thereof. Additional studies along these lines will be described in due course.

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5. The Multiconformer submode of Clark Still's program MacroModel was used. The five lowest energy conformers of the *trans*-diol **12** with energies of 16.8, 23.0, 24.8, 25.0 and 25.4 Kj have essentially the identical local conformation at C1-C4. The same is true for the *cis*-diol **16** with energies of 16.2, 23.5, 23.6, 23.8 and 24.2 Kj. Only the lowest energy conformers are shown in Figure 1. Coupling constants were obtained on the calculated structures through the Analysis submode of MacroModel.

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