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STEREOSELECTIVE SYNTHESIS OF CEMBRANOLIDE PRECURSORS VIA MACROCYCLIZATION OF α-ALKOXYALLYLSTANNANE ALDEHYDES

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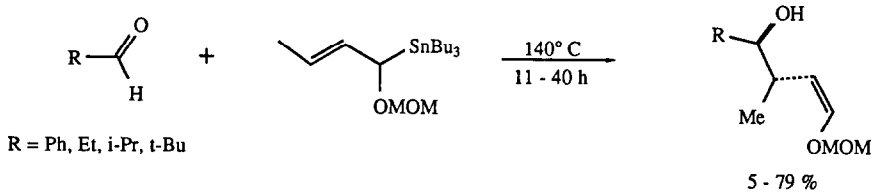
Abstract: An efficient route to the MOM-protected α-hydroxylallylstannane propargylic aldehyde **15** starting from geraniol is described. Cyclization of **15** to the 14-membered cembranolide intermediate **16**, a 7:1 mixture of cis and trans isomers, is effected in 80% yield with $BF_3 \cdot OEt_2$ at -78°C.

In recent years the cembranes have emerged as a major class of natural products.[1] With origins in plants, insects and marine organisms, these 14-membered isoprenoids are now recognized as the most populated subgroup of the diterpene family.[2] Synthetic efforts in this area have been hampered by the lack of reliable methods for constructing the fourteen-membered carbocyclic ring bearing requisite functionality and stereochemistry.[3] In connection with a program to develop efficient macrocyclization strategies for carbocyclic synthesis we have found that α-alkoxyallylstannanes undergo a remarkably facile macrocyclization with acetylenic aldehydes to give homoallylic alcohols suitable for elaboration to fused gamma-lactones.

Our investigation was inspired by the report that α-alkoxy derivatives of crotyl tri-*n*-butylstannane undergo a highly stereoeselective addition to aldehydes upon prolonged heating at 130-140°C (equation 1).[4] The observed stereochemistry was suggestive of an associated six-membered transition state.

(1)

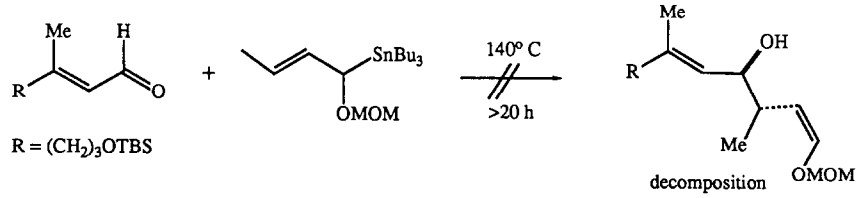


R = Ph, Et, i-Pr, t-Bu

5 - 79 %

Our attempts to effect an analogous addition to β,β-disubstituted acroleins uniformly failed. Prolonged heating resulted in gradual decomposition of the reactants with no sign of addition product (equation 2).

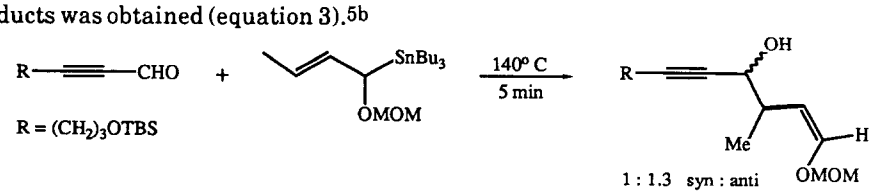
(2)



R = $(CH_2)_3$OTBS

Taking a clue from a previous study involving Lewis acid catalyzed additions of allylstannanes to related aldehydes, we employed an acetylenic aldehyde as the electrophilic partner.[5] The contrast was dramatic. Complete reaction occurred within 5 min of mixing at 140°C. Unfortunately, a 1:1.3 mixture of syn and anti products was obtained (equation 3).[5b]

(3)

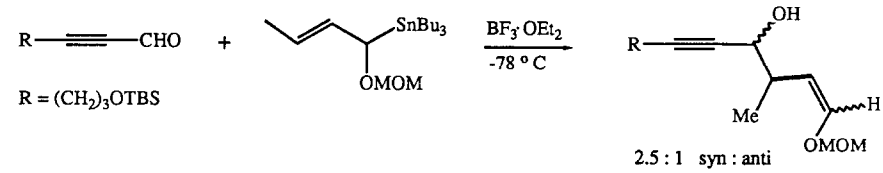


R = $(CH_2)_3$OTBS

1 : 1.3 syn : anti

Hoping to improve the stereoselectivity of the process we examined the low temperature Lewis acid catalyzed addition depicted in equation (4). In this case a 2.5:1 mixture of stereoisomers was produced.

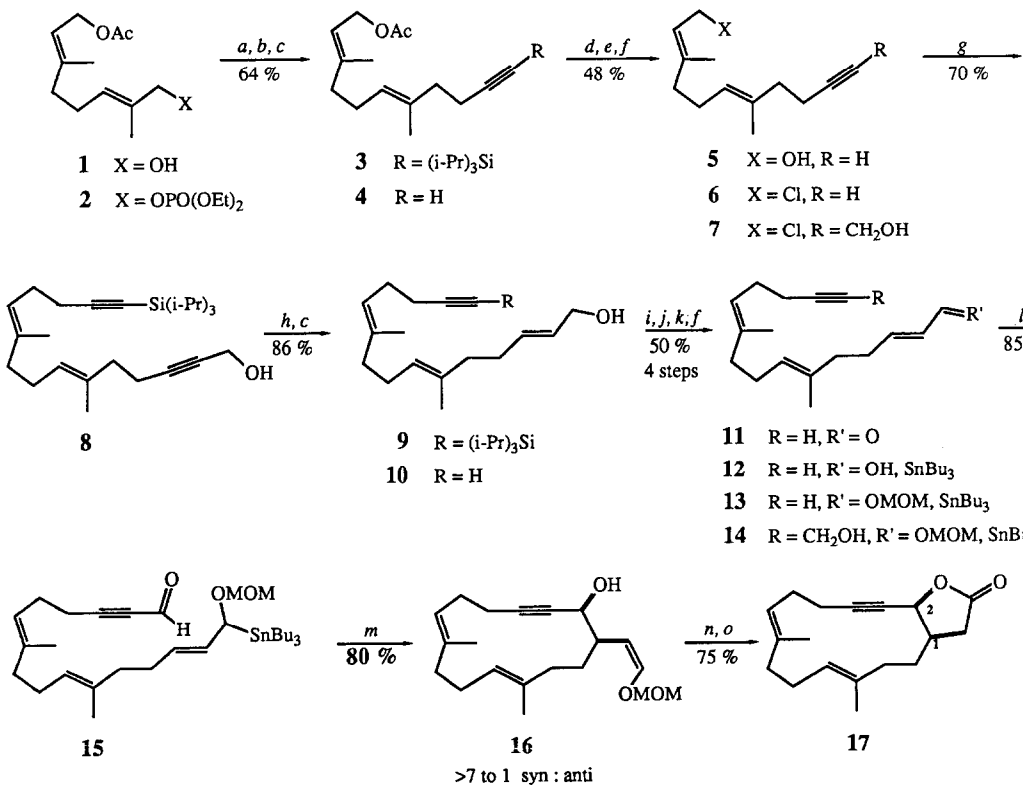
(4)



2.5 : 1 syn : anti
1 : 1 (Z) : (E)

Although these initial results suggest that intramolecular applications of alkoxyallylstannane couplings might be unrewarding, experience from several other macrocyclization studies taught us that conformational factors can play a dominant role in controlling cyclization stereochemistry.[3,6] Thus the presence of three (E) double bonds and one triple bond in a cyclization precursor such as **15** would impose severe conformational restrictions possibly conducive to a highly ordered transition state. Accordingly we elected to pursue the matter. Toward that end an efficient sequence was devised for the synthesis of the prototype aldehyde **15** (Scheme I).

Scheme I



>7 to 1 syn : anti

a) $ClP(O)(OEt)_2$, pyridine, -40°C, 1 h; *b*) TIPSC≡CCH_2MgCl, CuI, THF, Me_2S, -78°C to -20°C; *c*) n-Bu_4NF, THF; *d*) K_2CO_3, MeOH, 0°C; *e*) LiCl, MsCl, 2,6-lutidine, DMF, 0°C; *f*) LDA, THF, -78°C then $(CH_2O)_n$; *g*) TIPSC≡CCH_2MgCl, 0.5 eq CuI, THF, -78°C to -20°C, 7 h; *h*) Red-Al, THF, 25°C; *i*) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; *j*) 2 eq $LiSnBu_3$, THF, -78°C; *k*) MOMCl, (*i*-Pr)$_2$NEt, CH_2Cl_2, 0°C; *l*) 1,1'-azodicarbonyl)dipiperidine, *t*-BuOMgBr, THF, 0°C; *m*) $BF_3 \bullet OEt_2$, CH_2Cl_2, -78°C; *n*) 1:1 10% HCl-THF; *o*) PCC, NaOAc, CH_2Cl_2.

The cornerstone of this sequence was the efficient coupling of TIPS propargylmagnesium bromide[7] with the allylic derivatives **2** and **7**.[8] In each case negligible amounts of allenes and S_N2' products were formed. Cleavage of the TIPS groupings and addition of formaldehyde in turn to the respective terminal acetylenes allowed efficient introduction of the remaining carbon centers. Reduction of propargylic alcohol **8** with Red-Al[9] followed by desilylation and Swern oxidation[10] gave the aldehyde **11**. Addition of Bu_3SnLi yielded an unstable alcohol which was immediately treated with MOMCl to afford the stable α-alkoxy allylstannane **13**.[11] Oxidation of the derived propargylic alcohol **14** could be effected via the Swern protocol[10] but the method employed by Denmark for a similar transformation proved superior for the production of aldehyde **15**.[12]

Attempted thermal cyclization of aldehyde **15** led to no useful product.[4] Treatment with $BF_3 \cdot OEt_2$, on the other hand, afforded the macrocyclic alcohol **16** as a 7:1 mixture[13] of stereoisomers in 80% yield.[14] The stereochemistry of the major product could be tentatively assigned as cis through hydrolysis of the enol ether and oxidation of the resulting lactol to the lactone **17**. The chemical shift (5.19 ppm) and coupling constant ($J = 7.0$ Hz) of the carbinyl proton (H-2) were in close agreement with those reported for 1,2-*cis*-fused cembranolide γ-lactones.[15a] A small peak at 4.70 ppm ($J = 2$ Hz) could be ascribed to the minor trans fused isomer of **17**. This assignment is consistent with data reported for other 1,2-*trans*-fused cembranolides.[15b]

Thus alkoxyallylstannanes are capable of efficient intramolecular coupling with aldehydes under Lewis acid catalysis to yield macrocyclic products. The high stereoselectivity of the addition is suggestive of a highly ordered transition state possibly amenable to asymmetric induction via chiral alkoxy substituents.[16] Further investigation of these matters is in progress.

Acknowledgement. Support from the National Institute of General Medical Sciences through research grant 5-RO1 GM29475 is gratefully acknowledged. We thank the NSF for funding of an AM-300 NMR spectrometer through instrument grant CHE-8411172.

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13. Analysis of stereoisomers was effected via capillary g.c. and high field ^1H NMR measurements.

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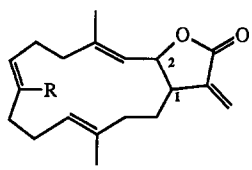
15. a) Reported for *i*: H-2 = 5.39 ppm, $J_{2,1} = 7.5$ Hz (Coll, J. C.; Mitchell, S. J.; Stokie, G. J. *Aust. J. Chem.* **1977**, *30*, 1859; *ii*: H-2 = 5.44 ppm, $J_{2,1} = 7.5$ Hz (Uchio, Y.; Toyota, J.; Nozaki, H.; Nakayama, M.; Nishizono, Y.; Hase, T. *Tetrahedron Lett.* **1981**, *22*, 4089. b) Reported for *iii*: H-2 = 4.86 ppm, $J_{2,1} = 3.5$ Hz (Uchio, Y.; Eguchi, S.; Nakayama, M.; Hase, T. *Chemistry Lett.* **1982**, 277); *iv*: H-2 = 4.86 ppm, $J_{2,1} = 4.1$ Hz (ref. 6).



i R = Me, cis fused lactone
ii R = CO_2H, cis fused lactone
iii R = Me, trans fused lactone
iv R = CO_2H, trans fused lactone

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