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STEREOSELECTIVE SYNTHESIS OF CEMBRANOLIDES VIA CONJUGATE ADDITION TO CYCLOALKYNONES

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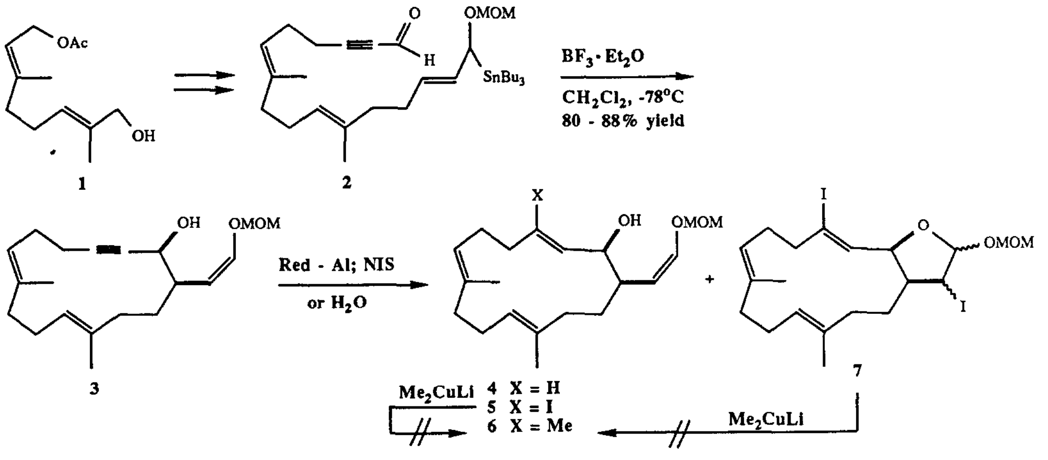
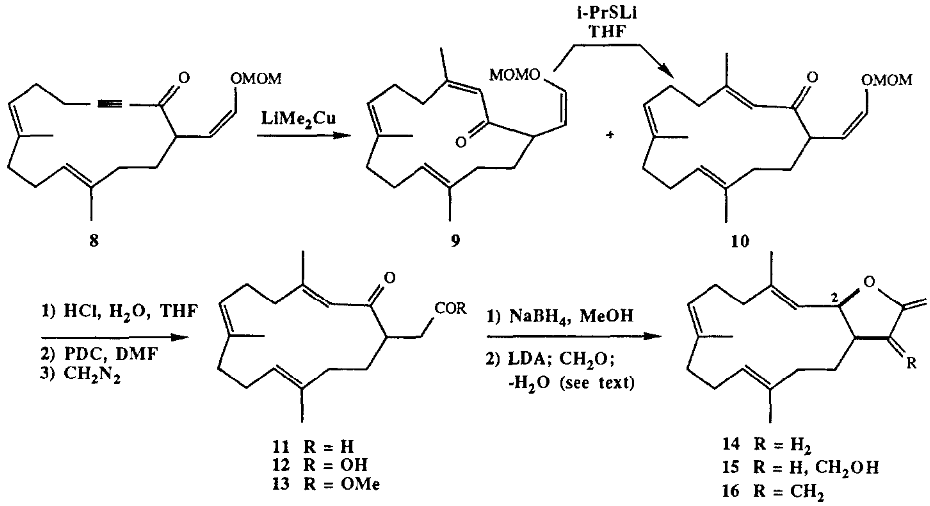
Abstract: Addition of lithium dimethylcuprate to the conjugated cycloalkynone **8** yielded, after equilibration, a single (*E*)-enone **10** which was converted via acidic hydrolysis, oxidation, and reduction to the *cis* lactone **14**. α-Methylenation afforded the natural cembranolide **16**.

We recently described a new synthetic route to the 14-membered cycloalkynol **3**, a potential cembranolide precursor, starting from oxidized geranyl acetate **1**[1] and proceeding via a novel α-alkoxy allylstannane macrocyclization (80% yield, >7:1 syn:anti) of the derived aldehyde **2**.[2] Our subsequent efforts to further elaborate cycloalkynol **3** along conventional lines to the cembranoid **6** met with unforeseen problems. Although directed hydroalanation of propargylic alcohol **3** with Red-Al[3] followed by protonolysis proceeded smoothly to the trans allylic alcohol **4**, attempts to trap the intermediate alanate with iodine[4] or N-iodosuccinimide[5] afforded complex mixtures from which the desired vinyl iodide **5** was isolated in low yield (~30%). It appeared that competitive iodoetherification of the enol ether double bond of **3** leading to iodo tetrahydrofuran products **7** constituted a major side reaction. In addition, the purified vinyl iodide **5** failed to undergo coupling with methylcuprate reagents, the unchanged iodide being recovered under a variety of forcing conditions.[6] Attempts to methylate the iodo ether byproducts **7** along similar lines led to decomposition.



Consequently, we were obliged to seek other options for the requisite methylation of acetylene **3**. In that regard, we examined the conjugate addition of lithium dimethylcuprate to ynone **8** derived from alcohol **3** via buffered PCC oxidation.[7] The desired (*E*) isomer **10** was judged to be of lower energy than the (*Z*) isomer so we employed conditions for the conjugate addition favorable to thermodynamic control.[8,9] However, a nearly 1:1 mixture of both isomeric enones **9** and **10** resulted. Fortunately, equilibration of this mixture was readily effected with lithio isopropylthiolate[10] to give **10** as the sole product.



Hydrolysis of the enol ether **10** with aqueous HCl-THF followed by oxidation of the resulting keto aldehyde **11** and esterification of the crude keto acid **12** with CH_2N_2 yielded the keto ester **13**. Molecular modeling showed a distinct bias for attack on the enone carbonyl anti to the acetic side chain.[9] Accordingly, reduction of **13** with methanolic $NaBH_4$ afforded the cis lactone **14** as the major (10:1) isomer. The chemical shift of the carbinyl proton at 5.3 ppm was in the range expected for such cis lactones.[2] Final confirmation of stereochemistry was secured through α-methylenation of lactone **14** via hydroxymethylation and dehydration of the α-hydroxymethyl lactone **15** with 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho *p*-toluenesulfonate and $CuCl_2$ in $THF\text{-}CH_3CN$.[11] The resulting α-methylene lactone **16** was identified through comparison of spectral properties as an unnamed cembranolide isolated by Coll and coworkers from the soft coral *Lobophytum michaelae*.[12]

The foregoing synthesis of cembranolide **16** is noteworthy in its utilization of macrocyclic conformational preferences to control stereochemistry via both thermodynamic (**9** → **10**) and kinetic (**13** → **14**) processes.

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