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MARINE CEMBRANOID SYNTHESIS

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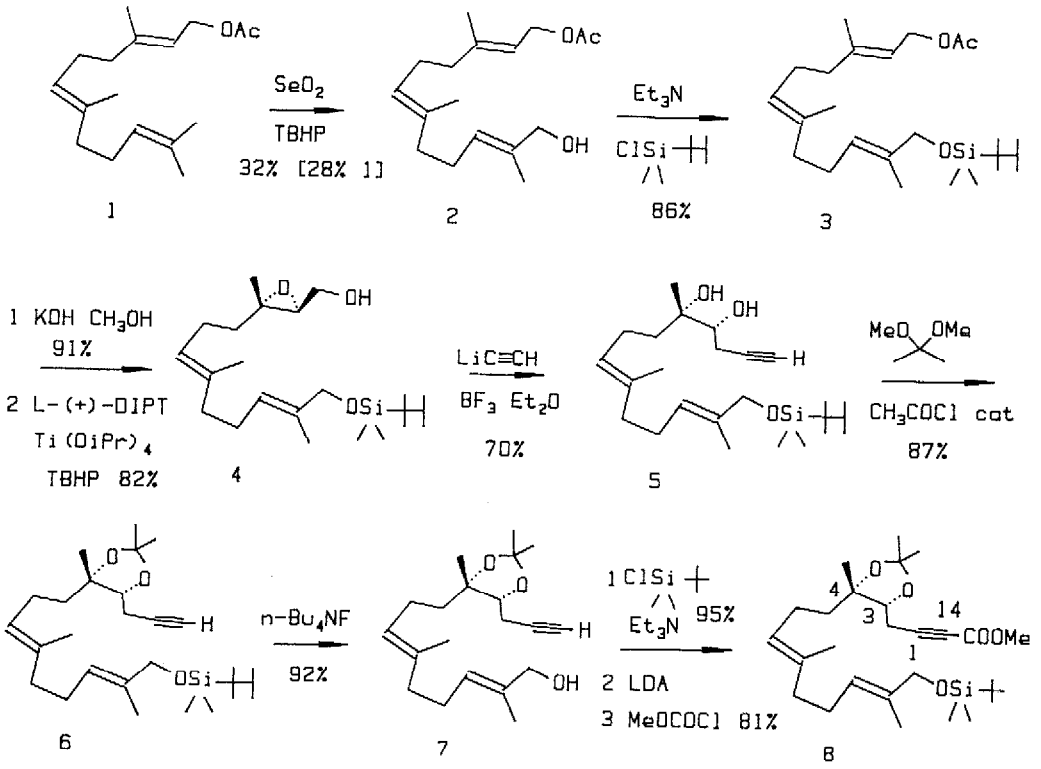
Summary: trans,trans-Farnesol can be converted to a versatile precursor for the synthesis of C-3,C-4 oxygenated marine cembranoids.

A large number of marine cembranoid natural products have been found to have pronounced biological activity in mammals.[2] This has spurred interest in the chemical synthesis of such compounds, since the isolation of these products from the natural source is often unsatisfactory: the organisms which produce the sought-after metabolites are often slow growing, scarce or they grow in geographically remote locations. Furthermore, concentrations of the cembranoids may vary seasonally depending upon the organism's life cycle.

There are two operations which must be performed for a successful cembranoid synthesis: the introduction, with appropriate stereochemistry, of the functional groups on the carbon chain, and the closure of the 14-membered ring. The macrocyclization reaction often presents the greatest challenge. An interest in developing a general synthesis of the family of C-3, C-4 oxygenated marine cembranoids,[3] and their analogs, suggested that a general strategy be developed. The conversion of trans, trans-farnesol to 3 has been described by Marshall.[4] By using farnesol, one can avoid having to perform the stereocontrolled synthesis of three trisubstituted alkenes. Farnesyl acetate 1 (**Scheme 1**) was exposed to 90% tert-butyl hydroperoxide in the presence of 0.02 equiv of SeO_2 and 0.1 equiv of salicylic acid in dichloromethane at 25° C. C-13 alcohol 2 was isolated by column chromatography in 32% yield along with 28% of unreacted 1, which was recycled. In order to differentiate between the two primary, allylic alcohols, 2 was converted in 86% yield to the thexyldimethylsilyl ether 3 by treatment with the silyl chloride in the presence of triethylamine and catalytic DMAP. Hydrolysis of the acetate (K_2CO_3, CH_3OH; 91% yield) was followed by Sharpless[5] epoxidation catalyzed by L-(+)-diisopropyl tartrate to produce epoxy alcohol 4 in 82% yield. The enantiomeric excess of 4 was determined to be 80% by Mosher's analysis.[6] The introduction of the remaining two carbon atoms which were needed to form the periphery of the 14-membered ring required that a carbon-carbon bond be made at C-2. This was accomplished in the following manner: a THF solution of 4 was added to 4 equiv of lithium acetylide at -78° C. After 5 min 5 equiv of freshly distilled $BF_3 \cdot Et_2O$ was added and the reaction mixture was stirred for 1 h.[7] Aqueous bicarbonate followed by column chromatography produced (3R,4S) diol 5 in 70% yield. The Payne rearrangement establishes the correct absolute stereochemistry for sinularin, sinulariolide and

Scheme 1



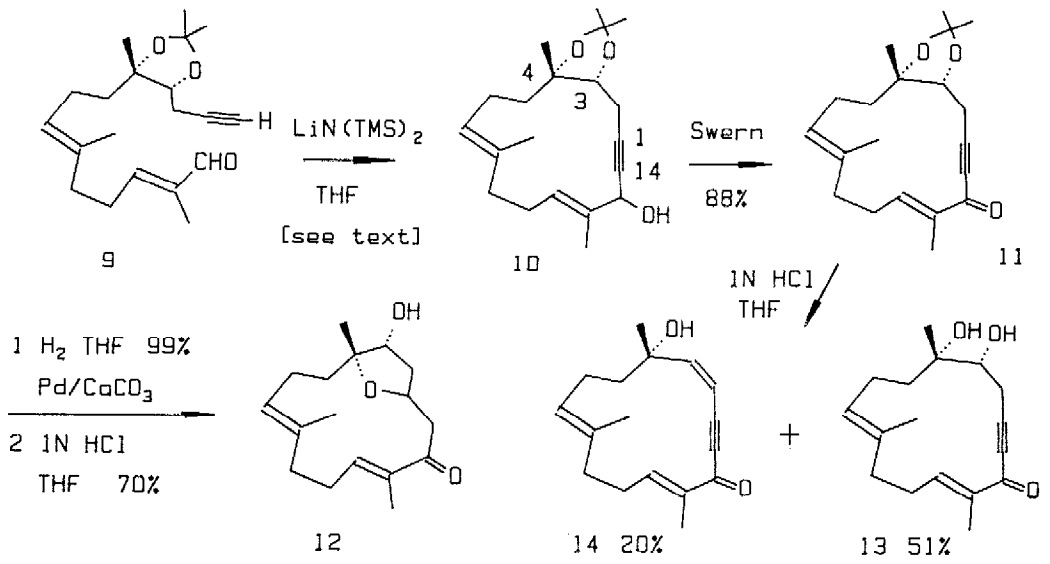
related cembranoids,[3] and introduces the remaining carbon atoms for the macrocycle in a very straightforward manner.

The diol functionality in **5** was converted in 87% yield to the corresponding acetonide **6**[8] by treatment in dichloromethane with an excess of 2,2-dimethoxypropane and catalytic HCl. Removal of the silicon protecting group from **6** was accomplished in 92% yield by treatment in THF solution with tetra-n-butylammonium fluoride at 0 °C. Before focusing attention on the crucial problem of macrocyclization, **7** was converted to acetylenic ester **8**[9] in two operations: O-silylation with tert-butyldimethylsilyl chloride and triethylamine (95% yield), followed by deprotonation of the acetylene with LDA and trapping of the lithioacetylide with methyl chloroformate (81% yield). The racemate of **8** (as the O-pivalate) has been used by Marshall in his inspired synthesis of isolobophytolide.[10] This work offers a more direct approach to **8**.

Attention was subsequently focused on the macrocyclization reaction. Swern oxidation[11] of **7** produced enal **9** in 91% yield (**Scheme 2**). The intramolecular reaction between the acetylide anion and the aldehyde carbonyl appeared to offer a direct entry into the cembrane ring system. Acetylene deprotonation by base was expected to take

place more rapidly than enolization of the unsaturated aldehyde. Indeed, slow dropwise addition of a 0.03 M (0.61 mmol in 20 mL THF) solution of **9** to a 0.009 M (0.58 mmol in 65.6 mL THF) solution of lithium hexamethyldisilyl amide at 25° C, followed by stirring for 1 h produced the desired cyclic alcohol **10**[12] in 32% yield (80% yield based on recovered **9**). The new asymmetric center of **10** was apparently formed with a high degree of selectivity, since the ^{1}H and ^{13}C nmr spectra do not show evidence for the presence of diastereomers. The intramolecular cyclization of acetylide anions onto aldehydes has precedents in the literature,[13] however, this appears to be the first example of an **enolizable** aldehyde, and the first application to cembrane synthesis.

Scheme 2



Swern oxidation[11] of **10** produced the cross conjugated ketone **11** in 88% yield. Partial hydrogenation of the alkyne with 1 atm of H_2 and 5% Pd on $CaCO_3$ in THF produced the C-1,C-14 **Z** isomer in quantitative yield; acid catalyzed acetonide hydrolysis with aqueous THF and HCl produced not the diol, but the internal Michael adduct **12** in 70% yield. Hydrolysis of **11** under identical conditions produced ketodiol **13** in 51 % yield along with 20% of elimination product **14**. This difference in reactivity is an indication that geometric or conformational constraints imposed by the acetylene prevent the tertiary alcohol group of **13** from approaching C-1.

Summary: trans,trans-Farnesol has been used for a short synthesis of the cembranoid ring. The key steps of this synthesis are the use of the Payne rearrangement[7] and acetylide displacement to set the stereochemistry of a vicinal diol, and the macrocyclization by the intramolecular acetylide addition to an enal. Products such as **11** and **13** will be useful for the synthesis of C-3, C-4 oxygenated marine cembranoids.

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References and Notes

1. Fellow of the Alfred P. Sloan Foundation, 1987-1989.
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8. **6**: HNMR (300 MHz, $CDCl_3$) 5.34 (t, J=6.0 Hz, 1 H), 5.12 (t, J=6.6 Hz, 1 H), 3.96 (s, 2 H), 3.90 (dd, J=7.5, 6.6 Hz, 1 H), 2.58 (ddd, J=16.8. 6.6, 2.7 Hz, 1 H), 2.36 (ddd, J=16.5, 7.8, 2.4 Hz, 1 H), 2.20-1.99 (m, 9 H), 1.59 (s, 3 H), 1.57 (s, 3 H), 1.40 (s, 3 H), 1.36 (s, 3 H), 1.34 (m, 1 H), 1.32 (s, 3 H), 0.88 (s, 3 H), 0.86 (s, 3 H), 0.84 (s, 6 H), 0.07 (s, 6 H) ppm; ir (neat) 3350, 2950, 2100, 1460, 1380, 1250, 1070, 830 cm^{-1}; mass spectrum m/e 462 (M^+), 447 (M^+-Me), 319, 279, 223, 185, 149 (100%), 107, 75; calcd for $C_{28}H_{50}O_3Si$ 462.3529, found 462.3500.
9. **8**: HNMR (300 MHz, $CDCl_3$) 5.35 (t, J=5.7 Hz, 1 H), 5.12 (t, J=7.2 Hz, 1 H), 3.98 (s, 2 H), 3.93 (dd, J=7.7, 6.7 Hz, 1 H), 3.74 (s, 3 H), 2.72 (dd, J=17.4, 6.6 Hz, 1 H), 2.50 (dd, J=17.1, 7.8 Hz, 1 H), 2.10-1.98 (m, 8 H), 1.60, 1.57, 1.39, 1.35, 1.32 (all s, 3 H), 0.89 (s, 9 H), 0.04 (s, 6 H) ppm; ir (neat) 2950, 2250, 1730, 1450, 1385, 1260, 1090, 840 cm^{-1}; mass spectrum m/e 492 (M^+), 477 (M^+-Me), 449, 435, 360, 253, 199, 135, 107, 89, 75 (100%); calcd for $C_{28}H_{48}O_5Si$ 492.3271, found 492.3264.
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12. **10**: HNMR (300 MHz, $CDCl_3$) 5.29 (dd, J=9.6, 4.5 Hz, 1 H), 5.18 (t, J=7.5 Hz, 1 H), 4.74 (s, 1 H), 3.77 (dd, J=7.8, 3.3 Hz, 1 H), 2.70 (ddd, J=17.4, 8.1, 1.5 Hz, 1 H), 2.54 (ddd, J=17.1, 2.7, 2.7 Hz, 1 H), 2.45-1.80 (m, 8 H), 1.72, (s, 3 H), 1.60 (s, 3 H), 1.44 (s, 3 H), 1.36 (s, 3 H), 1.23 (s, 3 H) ppm; CNMR (75 MHz, $CDCl_3$) 134.89, 132.45, 127.91, 127.80, 125.58, 106.95, 82.95, 81.13, 80.32, 68.91, 38.84, 36.75, 28.45, 27.05, 25.24, 23.56, 21.11, 19.14, 15.02, 11.34 ppm; ir (neat) 3430, 2950, 1460, 1390, 1215, 1085 cm^{-1}; mass spectrum m/e 318 (M^+), 303 (M^+-Me), 260, 227, 199, 157, 105, 91 (100%), 79; calcd for $C_{20}H_{30}O_3$ 318.2195, found 318.2188.
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