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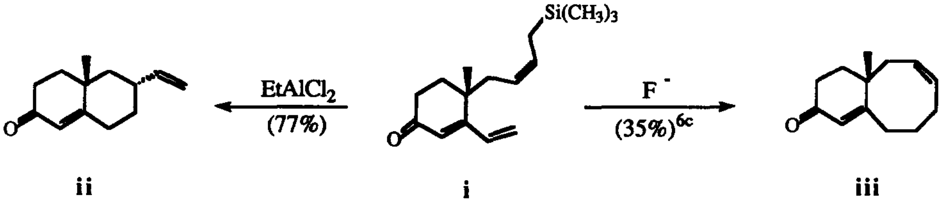
A Direct Synthesis of (±)-Neolemnanyl Acetate§1

George Majetich,* Derric Lowery and Vikram Khetani
Department of Chemistry, *The University of Georgia*
Athens, Georgia 30602

Summary: A direct synthesis of (±)-neolemnanyl acetate is reported.

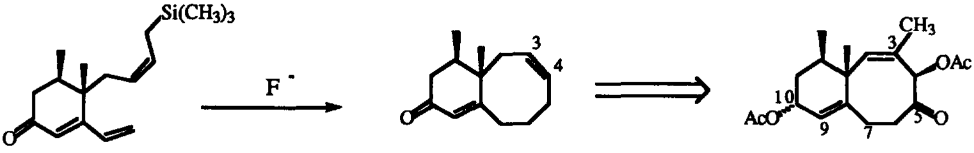
We have shown that the intramolecular addition of allylsilanes to conjugated dienones is a powerful means of constructing a wide range of functionalized bi- and tricyclic systems.[2,3] For example, cyclization of conjugated dienone **i**, a 4-butenyl-dienone,[4] using ethylaluminum dichloride produced solely the 6,6-fused bicyclic enone **ii** while treatment of **i** with fluoride ion gave fused cyclooctane **iii**.[5,6]

Equation 1



This study suggested a direct approach to neolemnanyl acetate (**1**), an unusual 6,8-fused sesquiterpene isolated from the widely distributed Pacific soft coral *Lemnalia africana* May (Eq. 2).[7] We were confident that the C(3)-C(4) double bond of **3** would permit functionalization of the eight-membered ring using traditional procedures. Accordingly, we undertook a stereocontrolled synthesis of trienone **2**.

Equation 2

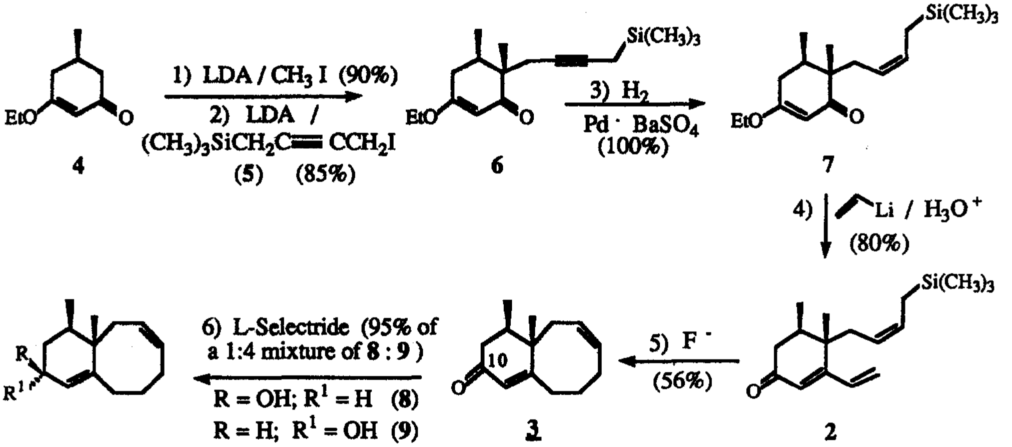


2 **3** **Neolemnanyl Acetate (1)**

§ Dedicated to Professor N. L. Allinger on the occasion of his receipt of an Arthur C. Cope Scholar Award

The stereochemistry of the vicinal methyl groups in trienone **2** was controlled by successive alkylations of the enol ether of dihydroorcinol **4**;[8] the relative configuration at the adjacent asymmetric centers was determined by the order of alkylation.[9] Indeed, initial alkylation of **4** with methyl iodide and then with iodide **5**[10] provided an 8:1 mixture of diastereomers of which compound **6** is the major isomer (Eq. 3).[11] Lindlar reduction of the internal alkyne moiety generated the cis-disubstituted allylsilane **7** with complete geometric integrity. This material was converted into trienone **2** using standard procedures. The formation of fused cyclooctane **3** routinely occurred in greater than 56% yield; scaling up the reaction to 7 grams of substrate had little impact (± 5%) upon the overall yield.[12]

Equation 3

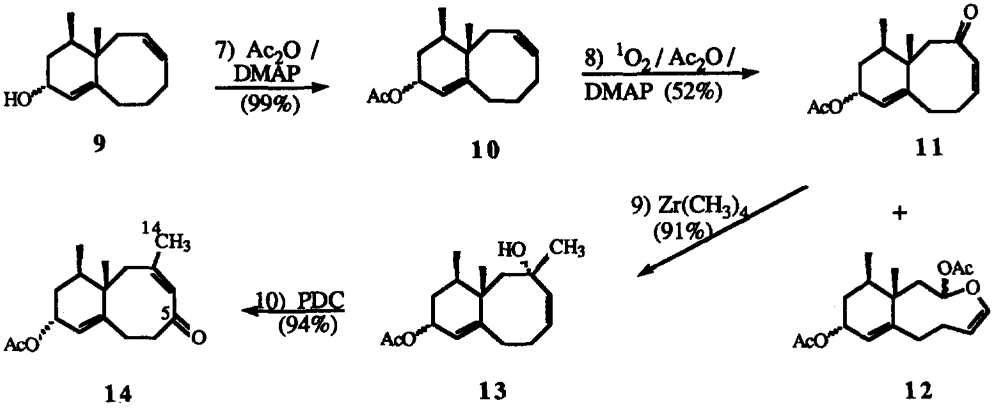


Treatment of enone **3** with LAH provided exclusively the equatorial allylic alcohol **8** in 95% yield,[13] whereas reduction using L-selectride gave both C(10) alcohols with the desired axial alcohol (**9**) as the major isomer [76% yield]. The equatorial alcohol could not be cleanly inverted using either Mitsunobu methodology[14] or classical displacement protocols.[15]

In previous research, photooxygenation has proven useful for the preparation of cycloalkenones.[16] We were pleased to discover that photooxygenation of acetate **10** using *meso*-tetraphenylporphine, in the presence of DMAP and acetic anhydride, led to a mixture of enone **11**, unreacted starting material, and enol ether **12**, in 52%, 25%, and 13% yield, respectively; recycling recovered **10** afforded enone **11** in 70% yield (Eq. 4). Addition of tetramethyl zirconium[17,18] to enone **11** produced tertiary allylic alcohol **13** which was cleanly oxidized to enone **14**. Note that these three transformations introduce both the C(14) methyl group and the C(5) carbonyl.

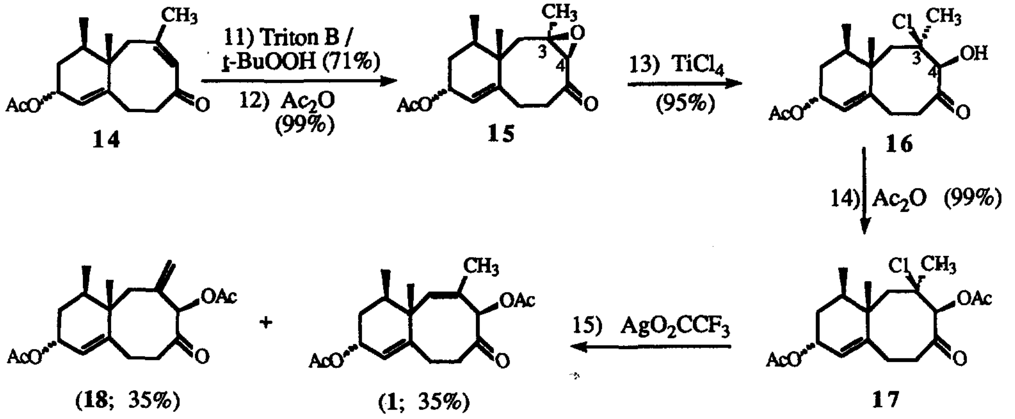
Three manipulations remained to complete our synthesis: 1) the migration of the C(3)-C(4) olefin to C(2)-C(3); 2) the stereospecific hydroxylation of C(4); and 3) acetylation of the C(4) hydroxyl group. Our strategy for achieving these functionalizations relied upon the stereospecific construction of a C(3)-

Equation 4



C(4) epoxide (Eq. 5). Molecular models indicate that epoxidation would occur exclusively from the less-hindered peripheral face of **14**, thus introducing an oxygen atom with the correct stereochemistry at C(4). Epoxidation of enone **14** was achieved using triton-B and t-butyl hydroperoxide (71% yield).[19] Under the basic conditions used, deacetylation occurred thus necessitating reprotection of the C(10) hydroxyl.

Equation 5



We anticipated that Lewis acid-catalyzed opening of epoxide **15** would generate the requisite C(2)-C(3) double bond.[20] Instead, reaction of epoxide **15** with either $TiCl_4$ or $EtAlCl_2$ gave chlorohydrin **16** in good yield. The C(4) hydroxyl group was then acetylated. Dehydrohalogenation of tertiary chloride **17** with silver trifluoroacetate[21] yielded a separable mixture of neolemnanyl acetate (**1**) in 35% yield and an equal amount of isomer **18** having an exocyclic double bond.[22] The NMR (300 MHz), infrared, and mass spectra as well as the chromatographic properties of synthetic (±)-neolemnanyl acetate were identical with those of a sample kindly furnished by Professor William Fenical, thus confirming the first total synthesis of this sesquiterpene.

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References and Notes:

1. This work was presented at the 198th National Meeting of the ACS in Miami Beach, Fla., September, 1989.
2. For a review of intramolecular additions of allylsilanes to dienones, see: Majetich,G.; Hull, K.; Lowery, D.; Ringold, C.; Defauw, J. *Intramolecular Additions of Allysilanes to Dienones.* A chapter in "Selectivities in Lewis Acid-Promoted Reactions," D. Schinzer, Ed., Kluwer Academic Publishers Group, Dordrecht, Holland.
3. For recent surveys of allylsilane chemistry, see: a) Majetich, G. *Allylsilanes in Organic Synthesis* in "Organic Synthesis, Theory and Applications: Hudlicky, T. Ed., Jai Press, Inc., Greenwich, CT., **1989**. b) Schinzer, D. Synthesis, **1988**, 263. c) Hosomi, A. Acc. Chem. Res., **1988**, *21*, 200. d) Fleming,I.; Dunogues, J. Organic Reactions, *38*, Chapter 2 (in press).
4. We have developed several methods to produce both seven- and eight-membered rings based on the intramolecular addition of an allylsilane to a 3-vinylcycloalkenone. For convenience's sake, we use the following conventions to describe these various cyclizations: 1) the suffix "dienone" describes the 3-vinylcycloalkenone unit; 2) a locant for the allylsilane appendage is stated; 3) the nature of the allylsilane side chain is defined either as an isoalkenyl or n-alkenyl substituent; and 4) geometric isomers or substitutions are ignored.
5. Majetich, G.; Hull, K.; Desmond, R. Tetrahedron Lett. **1985**, *26*, 2751.
6. a) All structures drawn here represent racemates, with only one enantiomer shown. b) The spectroscopic data obtained for all new compounds [^{1}H NMR, ^{13}C NMR, IR, and MS] were fully consistent with the assigned structures. c) Reaction conditions have not been optimized. d) All yields are isolated yields.
7. *Isolation:* a) Izac, R.R.; Fenical, W.; Tagle, B.; Clardy, J. Tetrahedron **1981**, *37*, 2569. b) Izac, R. R.; Schneider, P.; Swain, M.; Fenical, W. Tetrahedron Lett. **1982**, *23*, 817. c) Bowden, B.F.; Coll, J.C.; Mitchell, S.J. Aust. J. Chem., **1980**, *33*, 885.
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9. Stork, G.; Danheiser, R.L. J. Org. Chem. **1973**, *38*, 1775.
10. 4-(trimethylsilyl)-2-butyn-1-ol [Mastalerz, H. J. Org. Chem. **1984**, *49*, 4094]was converted into iodide **5** via standard Finkelstein conditions in 80% overall yield.
11. This strategy has been utilized in two syntheses of the eremophilane nootkatone and the marine algae metabolite perforenone. See; a) Heathcock, C.H.; Graham, S.L.; Pirrung, M.C.; Plavac, F.; White, C.T. In "The Total Synthesis of Natural Products"; Apsimon, J., Ed.; Wiley-Interscience; New York, 1983; Vol V, pp 184. b) Majetich, G.; Behnke, M.; Hull, K. J. Org. Chem. **1985**, *50*, 3615. c) Majetich, G.; Ringold, C. Hetereocycles, **1987**, *25*, 271.
12. We believe this cyclooctane annulation proceeds via a tandem Michael addition / enolate-accelerated Cope rearrangement mechanism. See: Majetich, G.; Hull, K. Tetrahedron Lett. **1988**, *29*, 2773.
13. a) Henbest, H.B.; McEntee, J. J. Chem. Soc. **1961**, 4478. b) Dauben, W.G.; Ashcraft, A. C. J. Am. Chem. Soc. **1963**, *85*, 3673.
14. For a comprehensive review of this method, see: Mitsunobu, O. Synthesis **1981**, 22.
15. In our hands, mesylation of **8** and subsequent reaction with lithium acetate or cesium acetate gave mixtures of an equatorial acetate and **12**.
16. a) Herz, W.; Juo, R.-R. J. Org. Chem. **1985**, *50*, 618. b) Mihelich, E.D.; Eickhoff, D.J. J. Org. Chem. **1983**, *48*, 4135. c) Paquette, L. A.; Crouse, G.D.; Sharma, A.K. J. Am. Chem. Soc. **1982**, *104*, 4411.
17. Reetz, M. T. von; Steinbach, R.; Westermann, J.; Urz, R.; Wenderoth, B.; Peter, R. Angew. Chem. **1982**, *94*, 133.
18. Enone **14** failed to react with methyllithium under either harsh conditions [excess methyllithium at reflux for 14 hours] or in the presence of cerium catalysts or Lewis acids.
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22. To date all attempts to isomerize **18** to **1** have been unsuccessful, due to the sensitivity of the allylic acetate moiety.

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