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SYNTHESIS OF FLEXIBILENE, A NATURALLY OCCURRING 15-MEMBERED-RING DITERPENE

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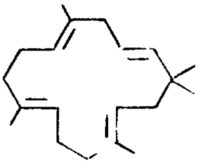
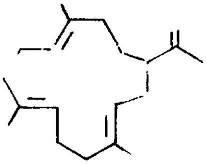
Abstract: A total synthesis of the naturally occurring 15-membered ring diterpene, flexibilene, was accomplished using a titanium-induced cyclization of the keto-aldehyde 3,3,7,11-tetramethyl-15-oxohexadeca-4*E*,7*E*,11*E*-trienal as the key step.

Flexibilene (1) is the only 15-membered-ring diterpene yet found in nature. It was isolated in 1976 from the soft coral *Sinularia flexibilis*, and its structure was independently determined by two groups,[1,2] both of whom relied heavily on NMR studies for their structural assignments. Although the gross skeletal features of the molecule were readily identifiable, the stereochemistry of the four olefinic linkages was assigned largely by analogy with that of cembrene A,[3] (2), a 14-membered-ring diterpene with which flexibilene co-occurs.



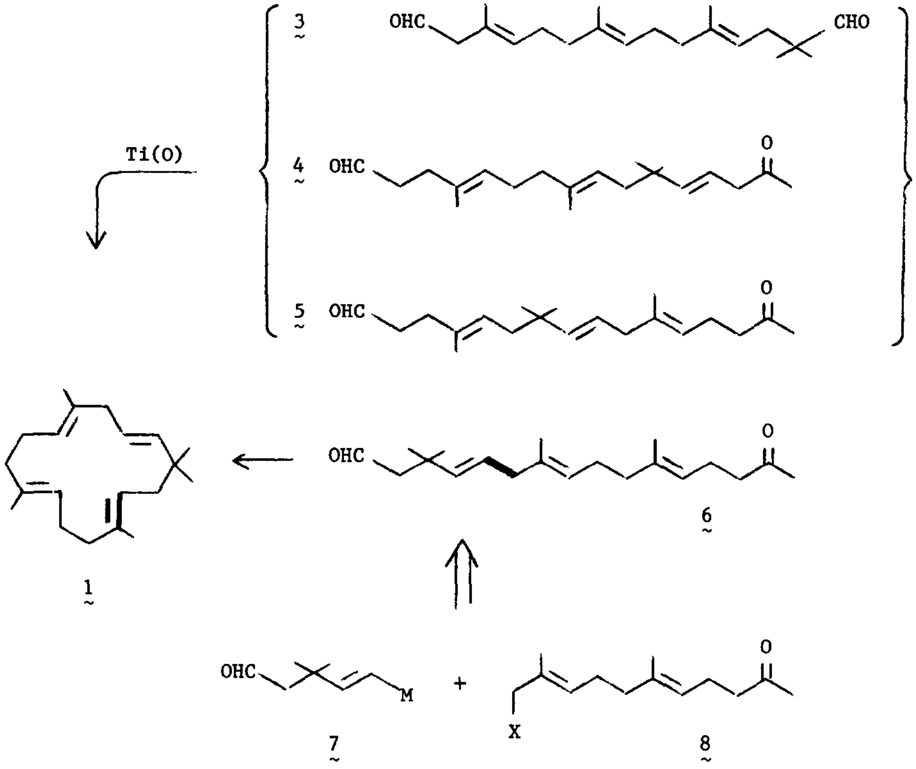
1 flexibilene



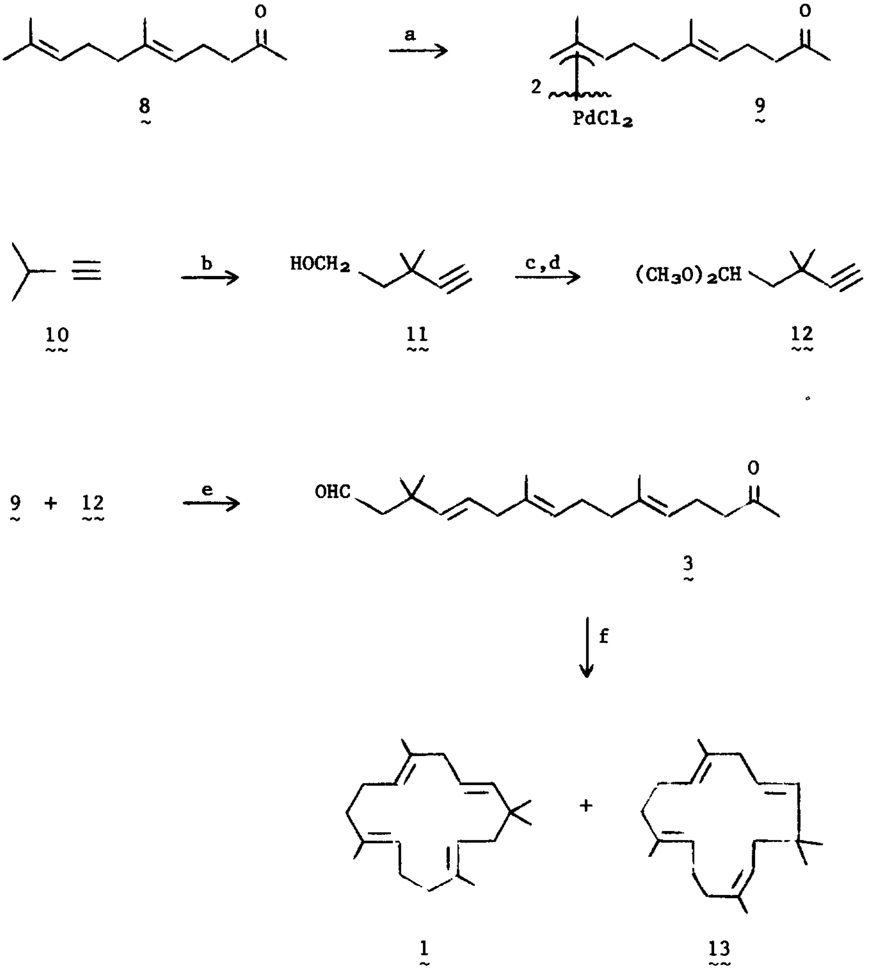
2 cembrene A

Our own interest in large ring chemistry stems from our recently reported finding[4] that cycloalkenes can be prepared in high yield by treatment of a dicarbonyl precursor with active titanium metal. We therefore undertook a stereoselective total synthesis of flexibilene, both to confirm its structural assignment and to provide a test of the value of our synthetic method.

Flexibilene could, in principle, be prepared by titanium-induced cyclization of any one of the four dicarbonyl precursors 3-6, since four double bonds are present in the molecule. We settled, however, on keto aldehyde 6 (3,3,7,11-tetramethyl-15-oxohexadeca-4*E*,7*E*,11*E*-trienal) as the most likely choice. A large part of 6 (carbons 6-16) might be derivable from geranylacetone (8, X=H) by selective functionalization (SeO_2 oxidation[5] or palladation[6]) of the terminal *E* methyl group. Alkylation of such a functionalized derivative of 8 with a seven-carbon vinyl organometallic fragment 7 would then lead to the desired keto aldehyde. Of the four double bonds in flexibilene, this plan would allow us to start from a precursor (geranylacetone) in which two trisubstituted double bonds were of guaranteed stereochemistry and the third double bond (trans-disubstituted) could be prepared by *syn* hydrometallation of an alkyne. Thus, this plan would allow full stereocontrol of three of the four double bonds, and the fourth double bond would be prepared in the cyclization step.



Our plan was reduced to practice by the sequence of reactions shown in Scheme 1. Dianion alkylation[7] of 3-methyl-1-butyne with one equivalent ethylene oxide gave alcohol 11 which was oxidized to the aldehyde by treatment with pyridinium chlorochromate[8] and protected as the dimethoxy acetal 12. Hydrozirconation[9] of 12 with bis(cyclopentadienyl)zirconium hydridochloride then gave the vinyl zirconium reagent. Concurrently, terminal π-allyl palladium complex 9 was prepared[6] by treatment of geranylacetone[10] with Pd(OCOCF$_3$)$_2$ followed by anion exchange with tetrabutylammonium chloride. Addition of this π-allyl palladium complex to a freshly prepared solution of vinyl zirconium reagent at -78° in methylene chloride in the presence of maleic anhydride,[11] followed by quenching with dilute aqueous HCl, gave the desired keto aldehyde 3 in 76% yield. Note that the dimethyl acetal was evidently cleaved in the acidic workup. Both ^{13}C and 300 MHz ^{1}H NMR indicated the stereochemical purity of 3, and the stage was thus set for the final ring closure.



Scheme 1. (a) $Pd(OCOCCF_3)_2$, acetone, then Bu_4NCl, 40%; (b) 2.0 equiv. *n*-BuLi, TMEDA, 50°, 15 hr, ether; then 0.95 equiv. ethylene oxide, -78°, 78%; (c) pyridinium chlorochromate, CH_2Cl_2, 69%; (d) $(CH_3O)_3CH$, CH_3OH, *p*-TsOH, CH_2Cl_2, 0°, 83%; (e) 12, Cp_2ZrClH, CH_2Cl_2, then 9, maleic anhydride, CH_2Cl_2, -78°, 76%; (f) 6.0 equiv. $TiCl_3$, Zn-Cu, DME, reflux, 36 hr, 78%.

Slow addition by syringe pump of a dimethoxyethane (DME) solution of 3 to a refluxing slurry of titanium prepared by reducing $TiCl_3$ with Zn-Cu in DME gave a 2:1 ratio (NMR) of cyclized products in 78% yield. Preparative HPLC, followed by preparative GC, gave an analytical sample of the major component which was spectroscopically identical with natural flexibilene by m.s., i.r., 300 MHz ^1H NMR, and ^{13}C NMR.[12] The minor product differs only slightly in its spectroscopic properties,[13] and is assigned the isoflexibilene structure 13.[14]

It is a measure of the progress made in the field of organic synthesis that this total synthesis of flexibilene appears "simple." We would point out, however, that of the six or so reactions used in this work, *none were even known a decade ago.* The titanium-induced dicarbonyl cyclization reaction, in particular, has proven to be a powerful method in the synthesis of macrocarbocyclic molecules; without this reaction, the synthesis of a molecule as complex as flexibilene would be a far more difficult task.

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12. We thank Dr. R. Kazlauskas for providing us with an authentic sample of natural flexibilene.
13. ^{13}C NMR: δ 140.9, 134.0, 133.8, 133.6, 124.8, 124.5(2), 122.7, 42.0, 41.2, 39.1, 35.5, 30.9, 29.4, 28.0, 25.2, 22.7, 17.0, 15.9.
14. The corresponding double bond isomer of cembrene A, (3*Z*)-cembrene A, is a known compound, recently isolated from the termite soldier *(Isoptera termitidae termitinae)*, D. F. Wiemer, J. Meinwald, G. D. Prestwich, and I. Miura, J. Org. Chem., *44*, 3950 (1979). It is interesting to speculate that our synthetic flexibilene isomer may also be a yet undiscovered natural product.

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