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SYNTHESIS OF BICYCLOGERMACRENE AND LEPIDOZENE

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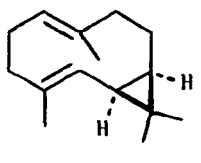
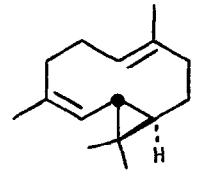
Abstract: Bicyclogermacrene (**1**) and lepidozene (**2**) have been synthesized by short routes starting from geranylacetone. Titanium-induced cyclizations of cis- and trans-2,2-dimethyl-3-(3-methyl-7-oxo-3E-octenyl)cyclopropanecarbaldehyde were used as the key steps.

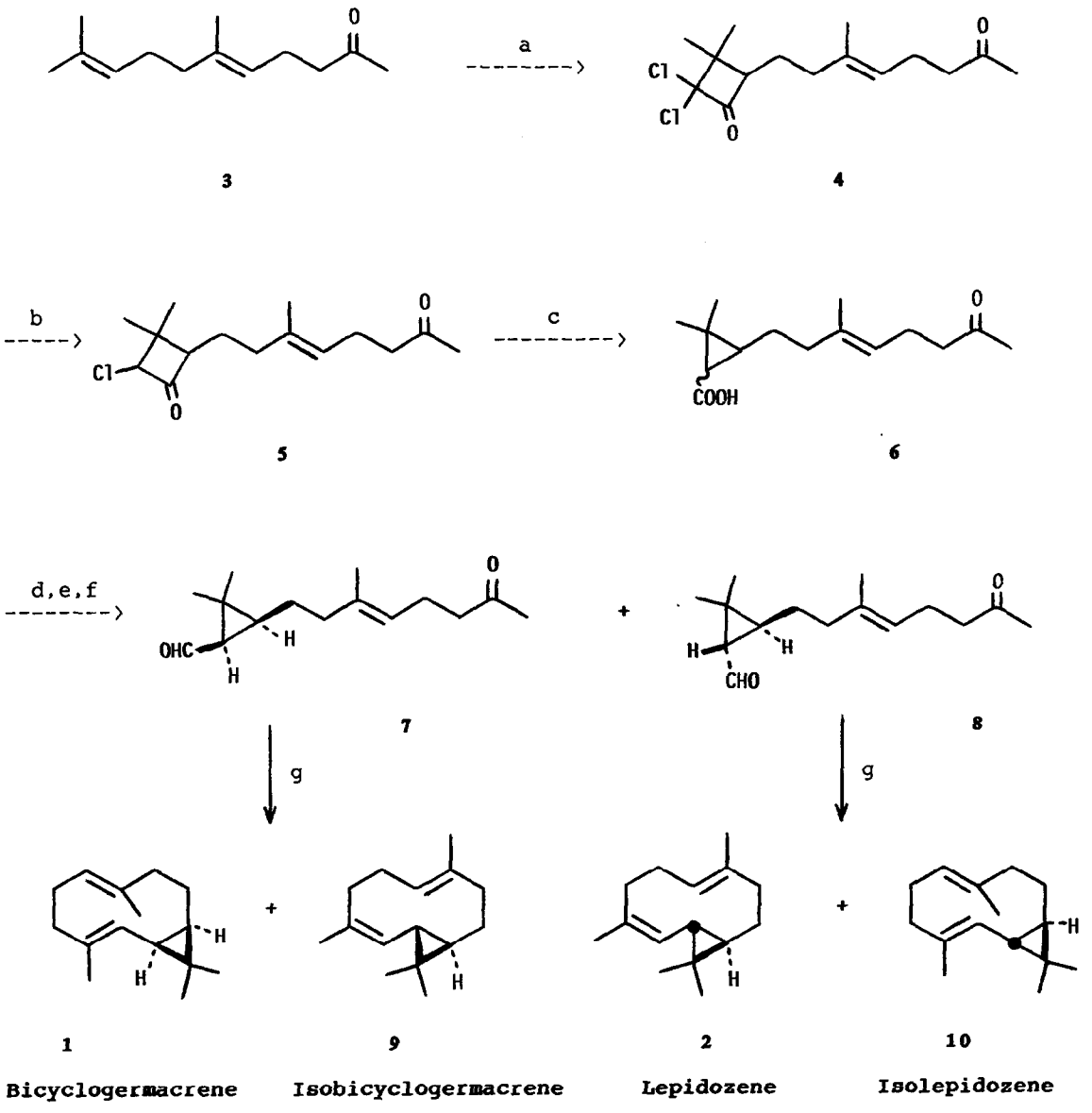
We have been involved for the last several years in exploring the value of titanium-induced carbonyl-coupling reactions[1] for natural-products synthesis. Among our successful efforts have been syntheses of flexibilene,[2] a 15-membered-ring diterpene, humulene,[3] an 11-membered-ring sesquiterpene, and isocaryophyllene,[4] a 9-membered-ring sesquiterpene. We now report the first total syntheses of bicyclogermacrene (**1**) and lepidozene (**2**), two members of the large 10-membered-ring germacrane family of sesquiterpenes. Bicyclogermacrene, a cis-fused bicyclo[8.1.0]undecadiene, is a natural product isolated[5] from the peel oil of Citrus junos. Lepidozene is not yet known to occur naturally, but has been prepared[6] by degradation of lepidozenal, a sesquiterpene found in the liverwort Lepidozia vitrea. Note that bicyclogermacrene and lepidozene have different stereochemistries at the double bond nearer the cyclopropane ring in each as well as at their ring-fusion positions. These structural assignments, which have been made[6,7] by ^{13}C NMR spectroscopy, appear firm.



Bicyclogermacrene (**1**)



Lepidozene (**2**)



Scheme: Syntheses of Bicyclogermacrene and Lepidozene.
(a) Cl_3COCl, $POCl_3$, Zn-Cu, ether, 45%; (b) Zn, CH_3COOH, 95%; (c) KOH, H_2O, room temp., 92%; (d) CH_3I, K_2CO_3, acetone, 85%; (e) $LiAlH_4$, ether, 99%; (f) pyridinium chlorochromate, NaOAc, CH_2Cl_2, 85%; (g) $TiCl_3$, Zn-Cu, dimethoxyethane, reflux, 30 hr addition.

Cis- and trans-2,2-dimethyl-3-(3-methyl-7-oxo-3E-octenyl)cyclopropanecarbaldehyde (**7** and **8**) were chosen as dicarbonyl precursors for the synthesis of **1** and **2** respectively. In both syntheses, the stereochemistries of the product ring fusion and one double bond are defined in the precursors; only the stereochemistry of the second double bond remains to be set in the titanium-induced cyclization. The successful synthetic routes are shown in the Scheme.

Because of its commercial availability and structural similarity to **7** and **8**, geranylacetone (**3**) was chosen as starting material. We felt that the most efficient route to both **7** and **8** would be a short reaction sequence that generated a mixture of the two isomers, which could be separated. Thus, our initial efforts were aimed at direct ethoxycarbonylcyclopropanation of **3** by reaction with ethyl diazoacetate. We were unable to effect this reaction in good yield, however, despite numerous attempts and experimental variations and were thus forced to use an alternative route.

We had previously shown in our synthesis of isocaryophyllene[4] that dichloroketene undergoes a selective cycloaddition[8] to the terminal double bond of ethyl geranylacetate. We therefore expected a similar selectivity for the terminal double bond of geranylacetone but found that, although dichlorocyclobutenone **4** was formed as the major product (45%) and could be isolated by preparative HPLC, a substantial amount (15%) of isomeric product produced by cycloaddition to the internal double bond was also formed. Monodechlorination of **4** with zinc in acetic acid, followed by Favorskii rearrangement,[9] gave an approximately 35:65 mixture of cis and trans keto acids **6** in 87% overall yield. Although it would presumably be possible to isomerize this mixture almost entirely to the more stable trans isomer if desired, we did not examine this point since both isomers were useful for our purposes.

Esterification followed by preparative HPLC separation yielded the individual keto esters, which were converted into keto aldehydes **7** and **8** by sequential $LiAlH_4$ reduction and pyridinium chlorochromate reoxidation. Structural assignments were made in each case by analysis of ^1H NMR coupling constants of the two cyclopropane protons in **7** and **8**. As expected,[10] the coupling in cis cyclopropane **7** (J = 8.0 Hz) is larger than that in trans cyclopropane **8** (J = 5.5 Hz).

Slow addition of **7** to a suspension prepared by reduction of $TiCl_3$ with Zn-Cu in refluxing dimethoxyethane produced an 80:20 mixture (61% yield) of double-bond isomers **1** and **9**, which could be separated by preparative HPLC. Both (±)-bicyclogermacrene (**1**) and (±)-isobicyclogermacrene (**9**) were identified by comparison of their IR and NMR spectra with those of authentic samples.[11] Trans-fused keto aldehyde **8** cyclized in a similar manner on treatment with $TiCl_3$/Zn-Cu to give a 40:60 mixture (75% yield) of double-bond isomers **2** and **10**, which could be separated by preparative HPLC. (±)-Lepidozene (**2**) was identified by comparison of its IR and NMR spectra with those of an authentic sample.[12] The previously unknown (±)-isolepidozene (**10**) was characterized[13]

by IR, ^{1}H NMR, ^{13}C NMR, and mass spectroscopy. To our knowledge, the above work represents the first total syntheses of any of these substances.

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11. We thank Dr. K. Nishimura, Suntory Limited, for providing copies of the IR spectra of (+)-bicyclogermacrene and (+)-isobicyclogermacrene.
12. We thank Dr. A. Matsuo, Hiroshima University, for providing copies of the IR and ^{1}H NMR spectra of (-)-lepidozene.
13. Spectroscopic details on isolepidozene (**10**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.81 (d, 1 H, J = 12 Hz), 4.58 (d, 1 H, J = 14.5 Hz), 1.61 (s, 3 H), 1.51 (s, 3 H), 1.12 (s, 3 H), 1.05 (s, 3 H), 0.78 (m, 1 H), -.096 (m, 1 H); ^{13}C NMR ($CDCl_3$) 134.9, 132.1, 131.9, 127.2, 42.3, 41.1, 40.4, 36.2, 29.3, 24.9, 24.3, 23.0, 21.9, 17.3, 16.4.

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