Synthesis of Highly Substituted Bicyclo[3.2.0]heptanones from 3-Homoallylcyclobutenones. A Total Synthesis of (±)-Precapnelladiene

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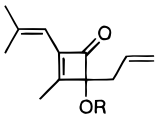
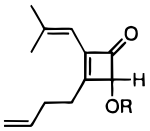
Previous reports from this laboratory describe the synthesis and thermolysis of 4-allylcyclobutenones **1**, precursors to the corresponding vinylketenes that undergo subsequent intramolecular [2 + 2] cycloaddition to afford bicyclo[3.2.0]heptenones.[2,3] Selected examples of these bicyclic compounds were observed to be useful synthetic intermediates to linearly and angularly fused polyquinanes through an anion accelerated [3,3] sigmatropic rearrangement and subsequent transannular ring closure.[4,5] In continuation of these studies, we now report a new general synthesis of bicyclo[3.2.0]heptanones through intermediary cyclobutenones **2** substituted with homoallyl groups at position 3. An application of this new rearrangement as a key step in the total synthesis of the marine natural product (±)-precapnelladiene is also presented herein.[6]



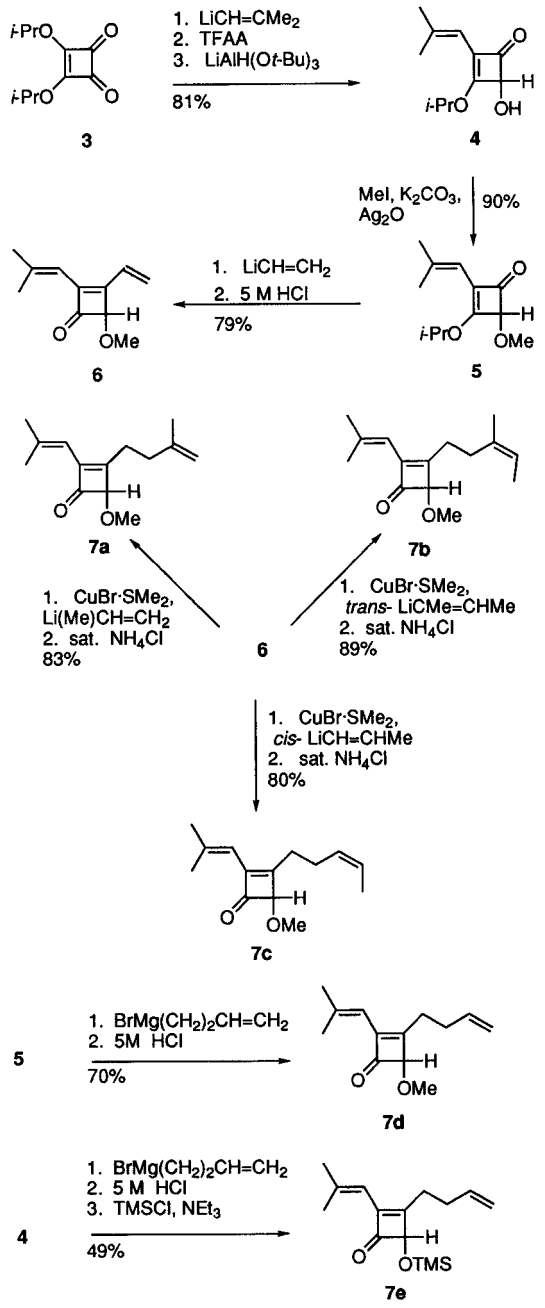
1



2

Syntheses of the requisite 3-homoallylcyclobutenone precursors are depicted in Scheme 1. Addition of 1-lithio-2-methylpropene to **3** was followed by trifluoroacetylation and aqueous workup (91%). Chemoselective reduction of the intermediate dione afforded alcohol **4** (89%),[7] which was protected as its methyl ether **5** (90%). Treatment with vinyllithium followed by acid hydrolysis gave **6** (79%), which is a key intermediate in the synthesis of the 3-homoallylcyclobutenones. For example, subsequent 1,6-addition of organocuprates to the dienone moiety of **6** gave **7a**−**c** in good yields (80−89%).[8] Alternatively, treatment of **5** with the Grignard reagent from 4-bromo-1-butene followed by acid hydrolysis afforded **7d** in 70% yield. In a similar fashion, **7e**, needed for the synthesis of (±)-precapnelladiene (**15**), was synthesized by treatment of **4** with an excess of the above Grignard reagent

Scheme 1



followed by hydrolysis (76%) and trimethylsilylation of the resulting 4-hydroxyl group (65%).[9]

Heating (xylene, 138−140 °C) **7a**−**e** gave the bicyclo[3.2.0]heptanones **9a**−**e** through a mechanistic sequence involving electrocyclic ring opening to the vinylketene **8** followed by intramolecular [2 + 2] cycloaddition (Scheme 2). When the terminal positions (R_3, R_4) of the 3-homoallyl side chain were unsubstituted, the bicyclo[3.2.0]-heptanones **9a,d,e** were isolated as the only product. In contrast, incorporation of a methyl group at the terminal position of the homoallyl side chain resulted in the formation of **9b,c** along with a minor amount of the bicyclo[3.1.1]heptanones **10b,c**.[10] The diastereoselective formation of the exocyclic *E*-enol ethers **9a**−**e** is consis-

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(2) Moore, H. W.; Xia, H.; Xu, S. L. *J. Org. Chem.* **1991**, *56*, 6094.
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(6) For previous syntheses of precapnelladiene see: (a) Birch, A. M.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1913. (b) Mehta, G.; Murthy, A. N. *J. Org. Chem.* **1987**, *52*, 2875. (c) Kinney, W. A.; Coghlan, M. J.; Paquette, L. A. *J. Am. Chem. Soc.* **1985**, *107*, 7352. (d) Petasis, N. A.; Patane, M. A. *Tetrahedron Lett.* **1990**, *31*, 6799.
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(9) The structures of **7a**−**e** as well as the other new compounds (**9a**−**e**, **10d,e**, **11**−**14**) reported here are based upon their spectral data including NOE studies, which are in agreement with their assigned stereochemistry.

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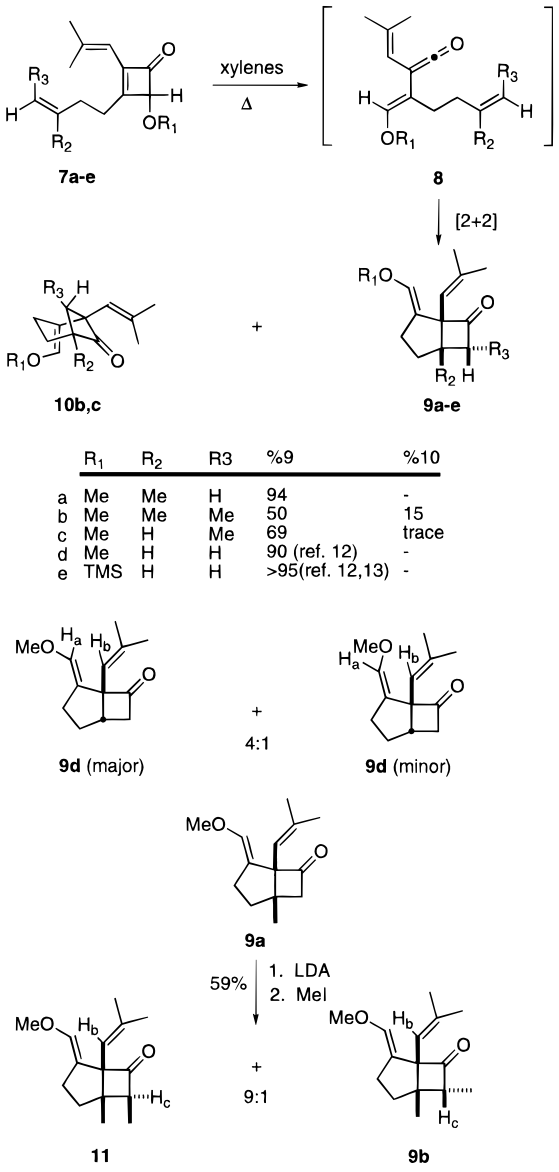
Scheme 2



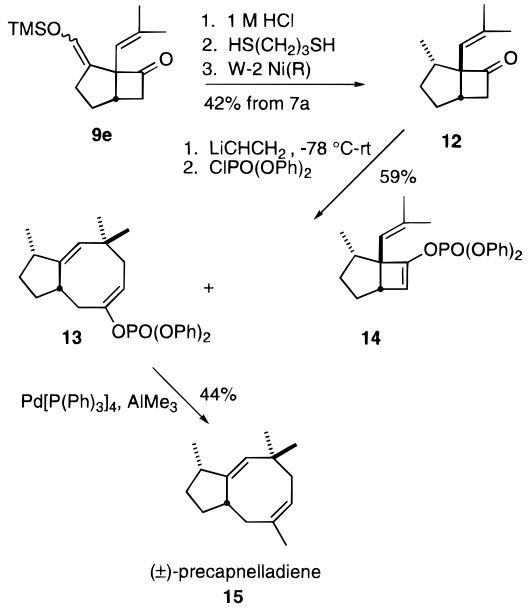
	R_1	R_2	R3	%9	%10
a	Me	Me	H	94	-
b	Me	Me	Me	50	15
c	Me	H	Me	69	trace
d	Me	H	H	90 (ref. 12)	-
e	TMS	H	H	>95(ref. 12,13)	-

tent with a torquoselective, conrotatory, outward rotation of the OR_1 substituents in the parent cyclobutenone.[11]

The stereochemistry of the major isomer of **9d** was established from NOE data to have the *E*-configuration of the exocyclic enol ether group; i.e., irradiation of the H_a-absorption of the major isomer showed an enhancement (10%) in the absorption of H_b while an analogous study using the minor isomer showed a weaker effect. On the basis of these data, *E*-stereochemistry is assumed for the 2-methoxyethenyl group in the other bicyclo[3.2.0]-heptanones, all of which were formed as single diastereomers.

A *trans* relationship between the methyl groups in **9b** would be expected assuming a concerted intramolecular ketene/alkene cycloaddition. This was confirmed by NOE studies. That is, **9a** was methylated (LDA, CH_3I, 59%)

Scheme 3



to give a 9:1 mixture of **11** and **9b**. Irradiation of the H_b-absorption in these diastereomers showed an enhancement (2%) of the H_c-absorption in **9b** and no effect in **11**. On the basis of these data, the indicated stereochemistry of **9c** is also reasonable.

An application of the 3-homoallylcyclobutenone rearrangement to bicyclo[3.2.0]heptanones is shown in Scheme 3, which depicts the total synthesis of the sesquiterpene natural product (±)-precapnelladiene (**15**). Hydrolysis of **9e** gave a 10:1 mixture of diastereomeric aldehydes, which favored the desired α-epimer.[14] Chemoselective thioacetalization of the aldehyde carbonyl followed by reduction with W-2 Raney nickel afforded ketone **12** (42% from **9e**).[15] The addition of vinyllithium, followed by oxy-Cope rearrangement[4,5,16,17] and trapping of the resulting enolate as its diphenyl phosphate derivative,[18] afforded a 5:1 mixture of **13** and **14** (59%). Exposure of **13** to $AlMe_3$ in the presence of catalytic $Pd[PPh_3]_4$[18] provided **15** (44%).[19] Highlights of the above synthesis include establishment of the stereochemistry of the cyclopentyl methyl group at the bicyclo[3.2.0]heptanone stage and control of the 1,5-cyclooctadiene regiochemistry through the oxy-Cope ring expansion.

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Supporting Information Available: A complete description of the synthesis and characterization of all compounds in the paper (12 pages).

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(10) For examples of intramolecular ketene/alkene cycloadditions leading to bicyclo[3.1.1] systems see: Allentoff, A. J.; Kulkarni, Y. S.; Snyder, B. B. *J. Org. Chem.* **1988**, *53*, 5320.

(11) (a) Houk, K. N.; Rondan, N. G. *J. Am. Chem. Soc.* **1985**, *107*, 2099. (b) Niwayama, S.; Kallel, E. A.; Sheu, C.; Houk, K. N. *J. Org. Chem.* **1996**, *61*, 2517.

(12) The silyl enol ether was not purified but appears to be greater than 95% pure by ^1H NMR analysis.

(13) Isolated as a 4:1 mixture of diastereomers.

(14) The structure of the major aldehyde is based upon its spectral properties as well as a complete X-ray analysis.

(15) W-2 Raney nickel was prepared by the method of Monzigo. *Organic Syntheses*; Wiley: New York, 1955; Collect. Vol. III, pp 181−183.

(16) For a general review of the oxy-Cope reaction see: Paquette, L. A. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 609.

(17) For oxy-Cope rearrangements on similar bicyclo[3.2.0] ring systems, see: Gadwood, R. C.; Lett, R. M.; Wissinger, J. E. *J. Am. Chem. Soc.* **1986**, *108*, 6343 and references cited therein.

(18) Takai, K.; Sato, M.; Oshima, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 108.

(19) The authors are grateful to Professor Leo Paquette for providing an ^1H NMR spectrum of an authentic sample of (±)-precapnelladiene.