Macroexpansion Methodology. 3. Eight-Step Synthesis of (−)-(3Z)-Cembrene A[1]

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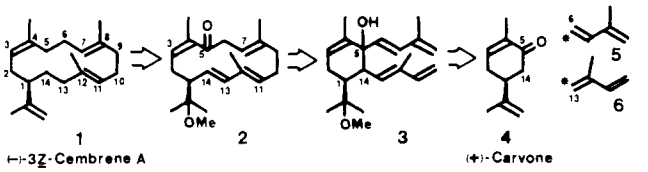
The demand for synthetic macrocycles has increased rapidly in recent years in concert with their growing theoretical, biological, and commercial importance. While these ring systems could be derived through acyclic closure, ring expansion, and polycyclic fragmentation strategies, in practice, only the first of these basic concepts has been explored and exploited extensively.[2] A general strategy for the highly convergent synthesis of enantiomerically pure macrocycles from the pool of chiral common ring precursors is described herein in the form of an eight-step synthesis of (−)-(3Z)-cembrene A (**1**),[3] which represents the first preparation of a member of the large cembrane class[4] based on ring expansion methodology.[1b,5]

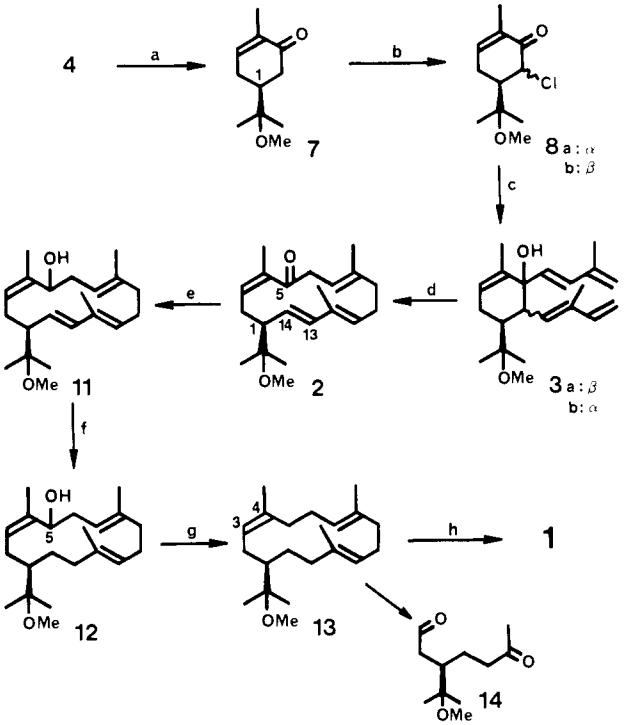
The synthetic advantages offered by this macroexpansion-based approach to the cembranes can be gleaned from the analysis depicted in Scheme I. It is seen that the target **1** and many related cembranoids could be derived through the elaboration of the strategically functionalized 14-membered ring **2**, which in turn could arise from the macroexpansion of the six-membered ring **3** by eight units. *A considerable simplification of the problem is thereby realized since 3 would be potentially produced from the conjunction of isoprene synthons 5 and 6 with the monoterpene carvone (4), abundantly available in either antipodal form.*[6]

The first task in the exploration of the above plan centered on the preparation of the expansion precursor **3**. Accordingly, commercially available *d*-carvone (**4**: $[\alpha]^{20}_D$ +55.3°; 95:5 = *d*:*l*)[7] was converted[8] with methanolic sulfuric acid to derivative **7**[9] whose methyl ether group served to protect securely the C-1 isopropenyl functionality from the alkene reduction required at a later synthetic stage. The configuration at C-1 was not affected by these acidic conditions as determined by conversion of **7** to its (*R*,*R*)-2,3-butanediol-derived[10] ketal which was shown to have the same C-1 composition (95:5) as starting material **4** by gas chromatographic analysis using a 50 meter SE-54 capillary column. Chlorination of **7** was accomplished[11] by its deprotonation with LDA at −78 °C followed by quenching of the resultant enolate with trifluoromethanesulfonyl chloride to afford chloro ketones **8a**,**b** (95% yield, 3.7:1, respectively), both of which were expected to figure

Scheme I



Scheme II[a]



[a] (a) 35% methanolic H_2SO_4, 2 days (38%); (b) LDA, THF, −78 °C, F_3CSO_2Cl (95%, α:β = 3.7:1); (c) (*E*)-1-lithio-2-methyl-1,3-butadiene, −78 °C; lithium isopropenyl acetylide; Δ; 0 °C, LAH (a, 57% at 68% conversion; b, 61% at 70% conversion); (d) KH, 18-crown-6, THF, room temperature, 2 h (48% from **3a**; 55% from **3b**); (e) $NaBH_4$, $CeCl_3$, MeOH (91%); (f) PtO_2, hexane–EtOAc (5:3), room temperature, 1 atm H_2 (59%); (g) Ac_2O, pyr; Li, $EtNH_2$, −78 °C (74%); (h) AcOMs, CH_3CN, room temperature, (34%).

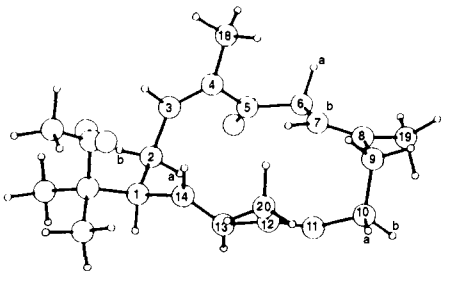


Figure 1. Conformation of **2** obtained from MMPI.

(1) (a) This work was presented, in part, at the 188th Meeting of the American Chemical Society, Philadelphia, August, 1984 and is taken, in part, from the Ph.D. Thesis of D. A. Holt, Harvard University, 1984. (b) For Parts 1 and 2 in this series, see: Wender, P. A.; Sieburth, S. M. *Tetrahedron Lett.* **1981**, *22*, 2471. Wender, P. A.; Sieburth, S. M.; Petraitis, J. J.; Singh, S. K. *Tetrahedron* **1981**, *37*, 3967.

(2) For a general review on macrocyclic synthesis, see: Story, P. R.; Busch, P. In "Advances in Organic Chemistry"; **1972**, *8*, 67. For discussion on acyclic closure, see: Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95. Galli, C.; Mandolini, L. *J. Chem. Soc., Chem. Commun.* **1982**, 251 and references cited therein.

(3) (a) Isolation: Wiemer, D. F.; Meinwald, J.; Prestwich, G. D.; Miura, I. *J. Org. Chem.* **1979**, *44*, 3950. (b) Synthesis: Shimada, K.; Kodama, M.; Itō, S. *Tetrahedron Lett.* **1981**, *22*, 4275.

(4) (a) For a review on naturally occurring cembranes, see: Weinheimer, A. J.; Chang, C. W.; Matson, J. A. *Fortschr. Chem. Org. Naturst.* **1979**, *36*, 285. For previous cembranoid syntheses, see: (b) Dauben, W. G.; Beasley G. H.; Broadhurst, M. D.; Muller, B.; Peppard, D. J.; Pesnelle, P.; Suter, C. *J. Am. Chem. Soc.* **1974**, *96*, 4724; *Ibid.* **1975**, *97*, 4973. (c) Kodama, M.; Takahashi, T.; Itō, S. *Tetrahedron Lett.* **1982**, *23*, 5175, ref 3b, and ref cited therein. (d) Kato, T.; Suzuki, M.; Kobayashi, T. *J. Org. Chem.* **1980**, *45*, 1126. Aoki, M.; Tooyama, Y.; Uyehara, T.; Kato, T. *Tetrahedron Lett.* **1983**, *24*, 2267 and references cited therein. (e) Still, W. C.; Mobilio, D. *J. Org. Chem.* **1983**, *48*, 4786. (f) For a recent report of approaches to cembranoids, see: Marshall, J. A.; Coghlan, M. J.; Watanabe, M. *J. Org. Chem.* **1984**, *49*, 747.

(5) Wender, P. A.; Holt, D. A.; Sieburth, S. M. *J. Am. Chem. Soc.* **1983**, *105*, 3348.

(6) For an excellent treatise on the subject of chiral carbon building blocks, see: Scott, J. W. In "Asymmetric Synthesis"; Morrison, J. D., Scott, J. W., Eds.; Academic Press: New York, 1984; Vol. 4.

(7) The sample of *d*-carvone used in this study is sold as 96% pure by Aldrich Chemical Co. The Merck Index lists a rotation for carvone of 61.2°.

(8) Compound **7** was obtained along with carvone hydrate (6%) and carvacrol (50%). For a related but optimized procedure for the hydration of carvone, see: Buchi, G.; Wuest, H. *J. Org. Chem.* **1979**, *44*, 546.

(9) Satisfactory NMR, IR, and MS data and either elemental or exact mass analyses were obtained on purified samples of all new compounds.

(10) The diol used ($[\alpha]^{25}_D$ −13.0°, neat) was derived from microbial fermentation and kindly provided by Professor W. S. Johnson.

(11) These chloro ketones were separated by HPLC (7.8 mm × 30 cm Porasil column, ether–hexane, 1:9 as eluant). Related research by this group on this chlorination procedure can be found in the Harvard University Ph.D. Dissertations of A. L. Feliu (1981), A. L. White (1981), and S. M. Sieburth (1982).

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in the synthesis of **2**. *Attachment of the isoprenyl equivalents* ***5*** *and* ***6*** *was then accomplished in one operation*[12] by treatment of the chloro ketone **8a** with 1 equiv of 1-lithio-2-methyl-1,3-butadiene (**9**)[13] at −78 °C which effected 1,2-addition after which an excess of lithium isopropenyl acetylide (**10**) was added and the mixture was heated in order to induce pinacol rearrangement and subsequent alkynylide addition to the transiently liberated carbonyl. Addition of $LiAlH_4$ to the resultant mixture (at 0 °C) proceeded with reduction of the alkyne and produced upon workup **3a** as a single isomer (57%). Similarly, chloro ketone **8b** was converted to a single bis-isoprenyl isomer (**3b**) in 61% yield (Scheme II).

At this point in the synthesis, all 20 carbons required for the cembrane skeleton were assembled in three operations and the stage was set for a test of the crucial macroexpansion step. Exposure of **3a** and **3b** separately to KH and 18-crown-6 ether in THF at room temperature for 2 h afforded upon workup crystalline ketone **2** (mp 62–62.5 °C; 48% and 55% yields, respectively) as the only 14-membered ring product. The stereochemistry of the olefinic units in **2** was established through two-dimensional homonuclear *J*-correlation spectroscopy (2D COSY NMR)[14] and difference NOE experiments. The observed enhancements were found to correlate well with internuclear distances in the conformer of **2** (Figure 1) obtained by energy minimization using the MMPI force field.[15]

Completion of the synthesis from the cembranoid **2** proved to be straightforward, requiring only removal of the oxygen at C-5, selective hydrogenation of the C-13,C-14 double bond, and deprotection of the C-1 isopropenyl group. Since ketone **2** was found to slowly isomerize in solution, it was first reduced[16] to the more stable alcohol **11** which was selectively hydrogenated over PtO_2 catalyst to give trienol **12**. Completion of the C-5 deoxygenation was then accomplished by conversion of **12** to its C-5 acetate and reduction of the latter to produce triene **13**. The stereo and positional integrity of the C-3,C-4 double bond was established by CMR and 2D COSY PMR spectroscopy and by ozonolysis of **13** which produced ketoaldehyde **14** identical with a sample obtained from ozonolysis of *O*-methyl terpineol. Finally, treatment of **13** with acetyl mesylate[17] resulted in liberation of the C-1 isopropenyl group to provide (−)-(3*Z*)-cembrene A (**1**; mp 33–33.5 °C; $[\alpha]^{20}_D$ −128.3° (MeOH, 0.63)).[18] The ^1H and ^{13}C NMR and IR spectra of this sample were identical with those previously reported.[3,19] Moreover, **1** obtained in this work and an authentic sample from the secretion of *Cubitermes umbratus*[20] exhibited the same retention times by capillary column (50 meter) gas chromatography using SE-54 and OV-1 stationary phases.

In summary, this study establishes a straightforward synthesis (eight steps) of (−)-(3*Z*)-cembrene A and, more generally, marks a fundamentally new approach to the preparation of chiral cembranoids and macrocycles from common ring precursors. The availability of **2**, possessing the complete cembrane skeleton, in only four steps from commercially available starting materials provides a point of divergence for other syntheses of chiral members of this class. Further studies are in progress.

Acknowledgment. We gratefully acknowledge the National Cancer Institute, DHHS, for support of this work through Grant CA31845. We thank Professors G. Prestwich (SUNY-Stony Brook) and D. Weimer (University of Iowa) for information on naturally occuring (3*Z*)-cembrene A.

Supplementary Material Available: Spectroscopic and analytical data for key compounds **2** and **11–13** along with tables on the correlation of NOE data and calculated (MMPI) internuclear distances and on the correlation of coupling constants and calculated (MMPI) dihedral angles for compound **2** (3 pages). Ordering information is given on any current masthead page.

(12) For related work, see: Holt, D. A. *Tetrahedron Lett.* **1981**, *22*, 2243 and ref 1b and 5.

(13) Prepared by reaction of *n*-BuLi with (*E*)-1-iodo-2-methyl-1,3-butadiene in THF or Et_2O at −78 °C. This stereo- and regiochemically pure iodide was prepared by zirconium-catalyzed methylalumination of vinylacetylene according to the procedure of: Negishi, E.; Van Horn, D. E.; King, A. O.; Okukado, N. *Synthesis* **1979**, 501. The reaction of **9** with **8a** or **8b** resulted in 1,2 addition to the carbonyl and deprotonation. Enolate intermediates resulting from the latter process survived the subsequent reaction conditions and gave upon workup chloro ketones **8a,b** as a 1:3 mixture.

(14) For a recent and related use of this technique and lead references, see: Lynn, D. G.; Graden, D. W. *J. Am. Chem. Soc.* **1984**, *106*, 1119.

(15) For a review, see: Allinger, N. L.; Burkert, U. *ACS Monogr.* 1982, 177.

(16) Gemal, A. L.; Luche, J. L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.

(17) Karger, M. H.; Mazur, Y. *J. Org. Chem.* **1971**, *36*, 532.

(18) An attempt to determine the sign of rotation of natural material produced a positive rotation, but due to the small sample size and its purity, the value was considered too uncertain for publication (Professor Weimer, personal communication, University of Iowa). When taken with our results, a positive rotation for the natural material would require that it have an *S* configuration.

(19) The originally reported data contained some ^{13}C NMR and ^1H NMR values which have since been corrected (reference 3b). We thank Professor Weimer (University of Iowa) for the proton and carbon NMR spectra of natural material.

(20) We thank Professor G. Prestwich (SUNY-Stony Brook) for this mixture.

Metalloketene Formation by Insertion of Carbon Suboxide into Tungsten and Rhenium Metal–Hydride Bonds

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Of the four stable oxides of carbon, only CO and CO_2 have received serious attention from chemists with regard to their reactivities with the transition metals. In light of the wealth of chemistry associated with these simple carbon oxides, we are investigating the organometallic chemistry of carbon suboxide, O=C=C=C=O.[1] Surprisingly, this aspect of C_3O_2 chemistry has been virtually neglected,[2] even though extensive studies of its organic and physical chemistries have shown it to be a remarkably reactive molecule.[3] One research area holding particular interest for us concerns the interaction of C_3O_2 with other ligands coordinated to metal centers, especially hydrides. Since allenes[4] and heterocumulenes (like carbon dioxide,[5] isocyanates,[6] and carbodiimides[7]) often participate in insertion reactions with metal hydrides, it seemed reasonable that similar insertions might occur with C_3O_2 to provide access to a new class of reactive ligands of the general type "HC_3O_2". Furthermore, the hydridic or protic nature of the particular metal hydride might determine whether the hydrogen is delivered to C-1 (favored for hydridic M–H species) or C-2 (favored for protic M–H complexes),[8] thus giving

(1) (a) Diels, O.; Wolf, B. *Ber. Dtsch. Chem. Ges.* **1906**, *39*, 689. (b) Diels, O.; Meyerheim, G. *Ibid.* **1907**, *40*, 355. (c) Glemser, O. In "Handbook of Preparative Inorganic Chemistry", 2nd ed.; Brauer, Ed.; Academic Press: New York, 1963; pp 648 ff.

(2) Literature concerning the interactions of C_3O_2 with transition-metal complexes: (a) Kolomnikov, I. S.; Koreshkov, Yu. D.; Lobeeva, T. S.; Vol'pin, M. E.; *Izv. Akad. Nauk SSSR, Ser. Khim.* **1972**, 1132. (b) Paiaro, G.; Pandolfo, L. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 288. (c) Paiaro, G.; Pandolfo, L. *Ibid.* **1981**, *20*, 289. (d) Paiaro, G.; Pandolfo, L.; Segala, P. *Congr. Naz. Chim. Inorg., [Atti], 12th* **1979**, 77. (e) Pandolfo, L.; Paiaro, G.; Valle, G.; Ganis, P. *Gazz. Chim. Ital.* **1985**, *115*, 59. (f) Pandolfo, L.; Paiaro, G.; Valle, G.; Ganis, P. *Ibid.* **1985**, *115*, 65. (g) Pandolfo, L.; Paiaro, G. *J. Mol. Catal.* **1984**, *27*, 343.

(3) For recent reviews describing the physical[3a] and organic[3b] chemistries of C_3O_2, see: (a) "Gmelins Handbuch der Anorganischen Chemie"; Verlag-Chemie: Weinheim, 1970; Kohlenstoff, C, Section 1, Syst. No. 14, pp 75 ff. (b) Kappe, T.; Ziegler, E. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 491.

(4) (a) Deeming, A. J.; Johnson, B. F. G.; Lewis, J. *J. Chem. Soc., Dalton Trans.* **1973**, 1848. (b) Thompson, M. E.; Bercaw, J. E. *Pure Appl. Chem.* **1984**, *56*, 1. (c) Roddick, D. M. Ph.D. Thesis, California Institute of Technology, Pasadena, CA, 1984.

(5) (a) Palmer, D. A.; van Eldik, R. *Chem. Rev.* **1983**, *83*, 651. (b) Darensbourg, D. J.; Kudaroski, R. A. *Adv. Organomet. Chem.* **1983**, *22*, 129.

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(7) Brown, L. D.; Robinson, S. D.; Sahajpal, A.; Ibers, J. A. *Inorg. Chem.* **1977**, *16*, 2728.

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