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MACROEXPANSION METHODOLOGY: AN EFFICIENT EIGHT UNIT RING EXPANSION

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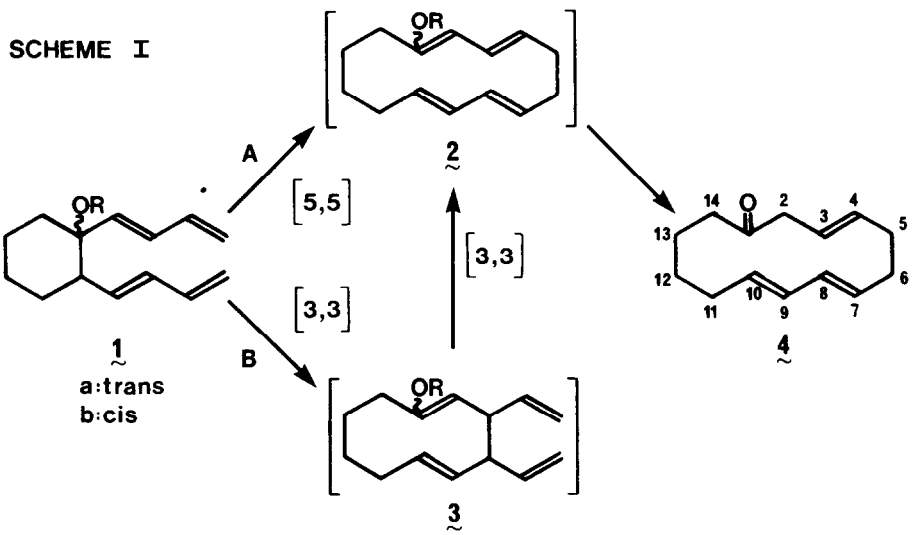
Abstract: An efficient eight unit ring expansion method which is postulated to proceed by either a [5,5] or consecutive [3,3] sigmatropic shifts is described.

Macrocyclic synthesis, once perceived as impossible,[2] has become the focus of intensive investigation stimulated not in small part by the increasing medicinal, theoretical, and commercial interest in large ring compounds.[3] Of the three fundamental concepts for large ring construction, ring expansion methodology[4] has found considerable synthetic service although, with few exceptions,[5] it has been limited to one operation expansions of, at most, 4 units.[6] Thus, while the set of common rings (five, six, and seven) can be connected by these 4 unit expansions to the set of nine-, ten-, and eleven-membered rings, macroexpansion methodology, which would allow for the conversion of the common rings to the rapidly increasing class of macrocycles of 12 or more members, has received little attention. We wish to describe a new method for macrocyclic synthesis involving an 8 unit, one operation expansion process which additionally offers the design benefits of stereochemical control typically associated with methodology based on pericyclic reactions.

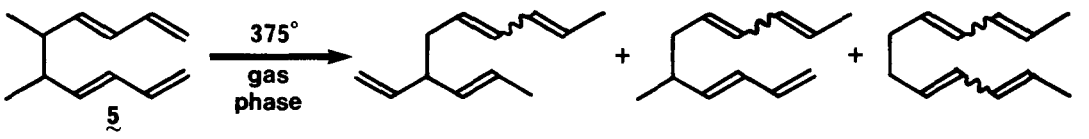
SCHEME I



We have found that when the cyclohexane derivative 1 (R=H, 1a/1b > 9)[7,8] is treated with KH in THF at room temperature for one hour and the reaction mixture quenched with saturated NH_4Cl solution and submitted to standard workup, the fourteen-membered ring trienone 4[9,10] is obtained in crystalline form (mp. 50.5-51.5°C) and in an isolated yield of 90%. The ^{13}C

NMR spectrum of 4 revealed only a single set of signals, suggesting that this novel rearrangement gives only one of several possible isomeric products. Furthermore, the infrared spectrum of 4 indicated the presence of a saturated ketone (1705 cm^{-1}), as would be expected from kinetic protonation of the dienolate intermediate, and E-substituted olefins (out-of-plane CH: 990 and 975 cm^{-1}). The ^1H NMR spectrum of 4 exhibited five multiplets in accord with the assigned structure. The quantitative conversion of 4, upon catalytic reduction (H_2, 5% Pd-C), to cyclotetradecanone (mp. 53-54.5°C; lit. 52°C, 53°C[11a]) and further derivatization of the latter ketone (cyclotetradecanone 2,4-DNP: mp. 117.5-118°C; lit. 117-118°C;[11b] cyclotetradecanol: mp. 78.5-79.5°C; lit. 78.6-79.4°C[11c]) unequivocally established the fourteen membered ring skeleton assigned to 4.

The cyclotetradecatrienone product of the above expansion is formally derived from either an unprecedented vinylogous oxy-Cope rearrangement[12] (path A) or an equally novel path involving consecutive [3,3] sigmatropic rearrangements (path B). We had expected, from the outset of this work, that either path would benefit from the charge effect described by Evans and coworkers[13] in their studies on the corresponding [3,3] sigmatropic rearrangement. If path A



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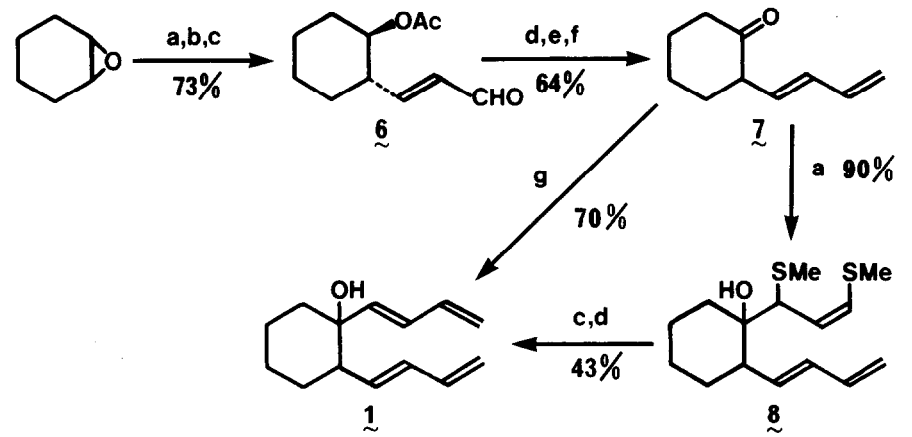
were indeed involved, the effect of charge acceleration would be dramatic since, in contrast to the above results, the rearrangement of tetraene 5, an all carbon acyclic analogue of 1, must be conducted in the gas phase at 375°C and provides seven products via a proposed homolytic cleavage, radical recombination mechanism.[12a] If instead path B were involved, the first [3,3] sigmatropic rearrangement would be driven by the charge on oxygen[14] while the second [3,3] rearrangement, that based on the divinylcyclodecadienolate intermediate (3), could be facilitated by the enolate charge[15,16] and the strain of the ten-membered ring.[17] In either event, a facile reorganization would be expected.

In our original plan, it was expected that the starting material (1) for the above rearrangement could be prepared in one operation by reaction of 2-chlorocyclohexanone with 1-metallo-1,3-butadiene.[18] However, difficulties in the preparation of the requisite organometallic, which have since been resolved (vide infra), prompted our development of the less direct route outlined in Scheme II. Thus acetoxy aldehyde 6 was prepared in 73% overall yield from cyclohexene oxide by the method of Corey, Erickson, and Noyori[19] and was converted to 7 in 64% overall yield by a sequence based, in part, on chemistry reported by Carlson and Mardis.[5b] The second butadiene unit was then introduced by reaction of reagent 9 with ketone 7 followed by a mercuric chloride hydrolysis step and, finally, aldehyde olefination with methylenetriphenylphosphorane. The olefinic units in 1 are assigned an E geometry on the basis of previous studies,[5b,19] the strong infrared absorption at 985 cm^{-1}, and their derivation from α,β-unsaturated aldehydes with an E double bond geometry. The ^{13}C NMR spectrum of 1 exhibits the expected fourteen carbon signals which are assigned to the trans-1,2-

SCHEME II



a) MeS–Li–SMe (9); b) Ac_2O; c) $HgCl_2$; d) ϕ_3PCH_2; e) $LiAlH_4$;

f) $CrO_3 \cdot Py_2$; g) Li (10)

dibutadienyl isomer and a much smaller set (at most 10% of major set) of similar signals which are assigned to the cis-1,2-dibutadienyl isomer. These assignments are based on the observations that additions of carbon nucleophiles to 2-methylcyclohexanone[20a] and 2-vinylcyclohexanone[20b] give predominantly the trans isomer. Notwithstanding its length, this sequence should prove useful in the preparation of more highly substituted butadienyl groups as would be required for natural product synthesis. Alternatively, we have recently succeeded in the preparation of 1-lithio-1,3-butadiene (10)[21] which upon reaction with 7 gave 1 directly in ca 70% yield. Moreover, through the reaction of this reagent with 2-chlorocyclohexanone,[20b] 7 can be prepared in two steps, thereby shortening the preparation of 1 to three steps. Further studies on the preparation of these reagents, the mechanism of the above rearrangement, and its application to natural product synthesis will be detailed in due course.

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References and Notes

1. (a) A.P. Sloan Foundation Fellow; Camille and Henry Dreyfus Teacher-Scholar Award Recipient (b) Merck Co. Foundation Fellow 1980-81.

2. Ruzicka, Leopold "Nobel Lectures: Chemistry"; Elsevier Publishing Co., New York, N.Y. (1966) 2, 459.

3. (a) Story, P.R.; Busch, P. "Advances in Organic Chemistry" (1972) 8, 67. (b) Masamune, S. Aldrichimica Acta (1978) 11 (2), 23. (c) Masamune, S.; Bates, G.S.; Corcoran, J.W. Angew. Chem. Int. Ed. Eng. (1977) 16, 585. (d) Nicolaou, K.C. Tetrahedron (1977) 33, 683. (e) Back, T.G. ibid. (1977) 33, 3041.

4. Gutsche, C.D.; Redmore, D. "Carbocyclic Ring Expansion Reactions", Academic Press, New York, N.Y., 1968; Boswell, G.A. "Organic Reactions in Steroid Chemistry" (1972) 2, 354, and reference 3.

5. These include: (a) Peroxide decomposition: see reference 3(a); (b) Photoinitiated fragmentation/recombination: Carlson, R.G.; Mardis, W.S. J. Org. Chem. (1975) 40, 817; (c) Trans lactonization/translactamization: for example see: Corey, E.J.; Brunelle, D.J.; Nicolaou, K.C. J. Am. Chem. Soc. (1977) 99, 7359. Stephanou, E.; Guggisberg, A.; Hesse, M. Helv. Chim. Acta (1979) 62, 1932; (d) Photo/thermal olefin metathesis: Bryce-Smith, D.; Gilbert, A. Tet. Lett. (1964) 3471.

6. For some recent examples see: Schmid, H.; Heimgartner, H.; Bruhn, J. Helv. Chim. Acta (1979) 62, 2630; Ziegler, F.E.; Piwinski, J.J. J. Am. Chem. Soc. (1980) 102, 880; Gopalan, A.; Magnus, P. ibid. (1980) 102, 1756; Thies, R.W.; Seitz, E.P. J. Org. Chem. (1978) 43, 1050; Vedejs, E.; Mullins, M.J. ibid. (1979) 44, 2947; Ceré, V.; Paolucci, C.; Pollicino, S.; Sandri, E.; Fava, A. ibid. (1979) 44, 4128. Wilson, S.R.; Misra, R.N. ibid. (1978) 43, 4903; Petrzilka, M. Helv. Chim. Acta (1978) 61, 3075. See also reference 14.

7. While this process was designed to exploit the stereochemical control associated with concerted reactions, the mechanistic details of this transformation are presently unknown.

8. Provided that the alkoxide group is axially oriented on the six membered ring, both 1a and 1b should lead to the same ketone product. Alcohol 1: ^{1}H NMR ($CDCl_3$) δ1.0-2.5 (m, 10H) 4.75-6.75 (m, 10H); IR (CCl_4) 3600, 1650, 1005, 985, 955, 905 cm^{-1}; UV (MeOH) 220 nm (4.65) exact mass: calc., 204.15141 found, 204.15117; calc. for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.29; H, 9.98; ^{13}C NMR (ppm rel. to TMS): 141.8, 137.3, 136.7, 135.0, 132.4, 128.4, 116.5, 115.7, 73.1, 47.9, 38.0, 26.6, 25.3, 21.2.

9. All new compounds reported were homogeneous by TLC and/or GC and gave satisfactory IR, NMR, and UV spectra, and exact mass and/or combustion analyses.

10. ^{1}H NMR ($CDCl_3$) δ1.25-1.75 (m, 4H), 1.8-2.3 (m, 6H), 2.3-2.7 (m, 2H), 2.75-3.1 (bd, 2H), 4.75-6.2 (m, 6H); IR (CCl_4) 1705, 1650, 1440, 1430, 1100, 990, 975 cm^{-1}; UV (MeOH) 233 nm (4.32); exact mass calc.: 204.15141, found: 204.15126; calc. for $C_{14}H_{20}O$: C, 82.30; H, 9.87, found: C, 82.37; H, 10.04; ^{13}C NMR (ppm rel. to TMS): 209.3, 134.2, 133.3 (2C), 131.2, 130.7, 125.4, 48.3, 42.6, 34.3, 32.7, 31.6, 26.4, 22.1.

11. (a) Ruzicka, L.; Stoll, M.; Schinz, H. Helv. Chim. Acta (1926) 9, 249. Schering-Kahlbaum D.R.P. 620904. (Chem. Abst. (1936) 30, 735). (b) Müller, E.; Bauer, M. Ann. (1962) 654, 92. (c) Kobelt, M.; Barman, P.; Prelog, V.; Ruzicka, L. Helv. Chim. Acta (1949) 32, 256; Zinkevich, E.P.; Sarycheva, I.K.; Preobrazhenskii, N.A. Zh. Organ. Khim. (1965) 1, 1591.

12. For studies related to [5,5] sigmatropic shifts, see: (a) Gibson, D.H.; Pettit, R. J. Am. Chem. Soc. (1965) 87, 2620. (b) Fráter, Gy.; Schmid, H. Helv. Chim. Acta (1970) 53, 269.

13. Evans, D.A.; Golob, A.M. J. Am. Chem. Soc. (1975) 97, 4765. For recent studies in this area see: Baillargeon, D.J.; Ph.D. Thesis, Cal. Inst. Tech., 1979; Evans, D.A.; Nelson, J.V. J. Am. Chem. Soc. (1980) 102, 774.

14. Still, W.C. J. Am. Chem. Soc. (1977) 99, 4186; idem. ibid. (1979) 101, 2493.

15. Results of investigations on this point will be communicated in due course.

16. Carpenter, B.K. Tetrahedron (1978) 34, 1877.

17. For work on related systems see Turner, R.B.; Mallon, B.J.; Tichy, M.; Doering, W. von E.; Roth, W.R.; Schröder, G. J. Am. Chem. Soc. (1973) 95, 8605.

18. Solomon, P.W.; U.S. Pat. 4087468; Chem. Abst. (1978) 89, 108113r.

19. Corey, E.J.; Erickson, B.W.; Noyori, R. J. Am. Chem. Soc. (1971) 93, 1724. Erickson, B.W.; Ph.D. Thesis, Harvard U.; 1970.

20. (a) Ashby, E.C.; Noding, S.A. J. Org. Chem. (1979) 44, 4371. Macdonald, T.L.; Still, W.C. J. Am. Chem. Soc. (1975) 97, 5280. (b) Kato, T.; Kondo, H.; Nishino, M.; Tanaka, M.; Hata, G.; Miyake, A. Bull. Chem. Soc. Jpn. (1980) 53, 2958. Holt, D.A.; manuscript submitted for publication.

21. Prepared by reaction of n-BuLi with 1-buta-1,3-dienyl tri-n-butylstannane in THF at -78°C for 15 minutes. Preparation of the requisite stannane will be reported shortly, cf. Piers, E.; Morton, H.E. J. Org. Chem. (1980) 45, 4263.

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