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FORMATION OF MACROCYCLIC STRUCTURES BY USE OF THE DIELS-ALDER REACTION

E. J. Corey and Martin Petrzilka
Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138, USA

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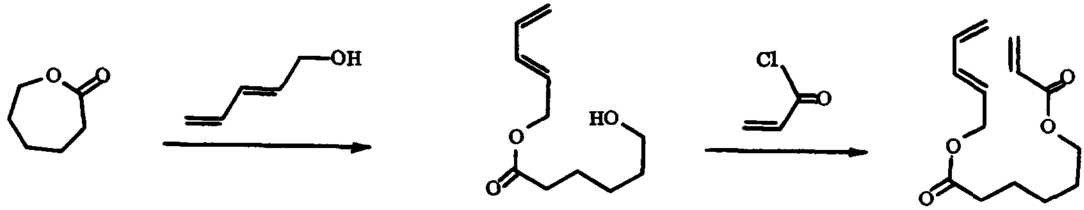
The intramolecular version of the Diels-Alder reaction[1] generates in addition to the characteristic six-membered ring another ring, usually of five or six members, either fused to or bridged across the cyclohexene unit. It appeared to us possible that the intramolecular Diels-Alder reaction could be utilized to form medium/large ring structures as well. The realization of such a process is described herein.

The test substrate chosen was structure III which contains diene and dienophile units at a separation of 10 atoms. The preparation of III[2,3] was readily accomplished in two steps (34% overall yield): (1) base-catalyzed (NaH) transesterification of ε-caprolactone (I) with 2 equiv. of trans-2,4-pentadien-1-ol[4] (no solvent) at 25° to form the oily diene-alcohol II,[3] and (2) acylation with 2 equiv. of acryloyl chloride in the presence of 2.2 equiv. of pyridine in ether (3 hr. at 0°).

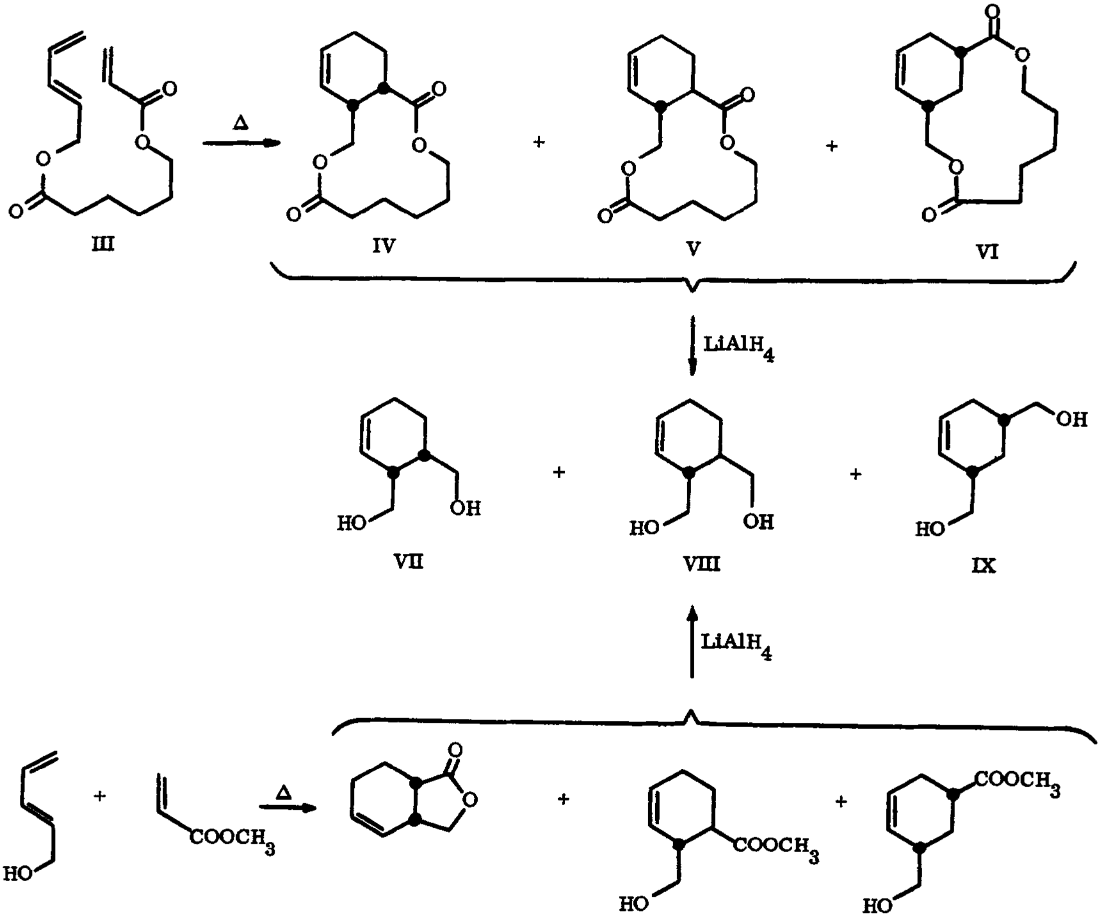


I

II

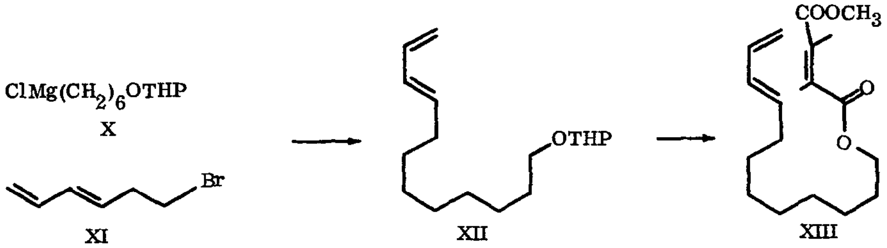
III

Slow addition of III to benzonitrile at reflux resulted in the desired intramolecular reaction[5] with formation (77% yield) of a mixture of the three Diels-Alder products IV, V, and VI in a ratio of ca. 6.2 : 6.8 : 1. Although these substances could not be separated chromatographically, the mixture could be analyzed and characterized in a straightforward way. Reduction of the mixture using lithium aluminum hydride in ether at 0° afforded quantitatively the same three[6] isomeric unsaturated diols (VII : VIII : IX = 6.2 : 6.8 : 1) as were obtained in a similar ratio (VII : VIII : IX = 3.3 : 1.9 : 1) by Diels-Alder reaction of trans-2,4-pentadien-1-ol with methyl acrylate in refluxing toluene (70 hr.) and subsequent reduction with lithium aluminum hydride in ether at 0° (74% overall yield). Assignment of structure and stereochemistry to the two isomers VII and VIII was achieved by spectroscopic identification of the corresponding saturated diols (prepared by hydrogenation over Pd-C catalyst) with authentic samples obtained by diborane reduction of the commercially available cis- and trans-1,2-cyclohexanedicarboxylic acids in tetrahydrofuran at 0°. The third isomeric product must therefore be a 1,3-bridged cyclohexene. Structure VI is assigned on the basis that this is both an "endo" addition product and the thermodynamically more stable 1,3-bridged isomer.

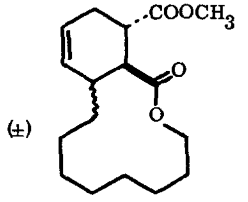


A noteworthy aspect of these results is the similarity in product distribution for the intramolecular and intermolecular Diels-Alder reactions summarized above, which suggests that during cyclization the two mutually reactive units in III behave almost as though they were not in the same molecule.

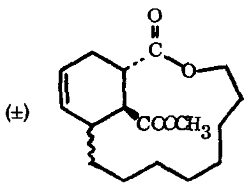
Efficient internal cyclization was also observed for the diene-fumarate ester XIII which was synthesized simply from X and XI via XII by the sequence shown.[7] Cyclization of XIII in benzonitrile at



reflux, as described for III, produced a mixture of four isomeric adducts, F_1, F_2, B_1, and B_2, in a ratio of 7 : 3 : 4 : 1[8] and a total yield of 80% (after chromatography). Compounds B_1 and B_2 were shown to be stereoisomers by base-catalyzed isomerization (KOtBu in THF at 0°) which converted B_2 completely into B_1. Compounds F_1 and F_2 were similarly equilibrated to a mixture containing approximately equal amounts of the two. Comparison of pmr spectra of these substances with the adducts from the reaction of trans-piperylene and dimethyl fumarate indicated that F_1 and F_2 are stereoisomeric fused ring

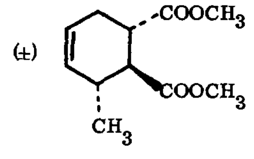


XIV

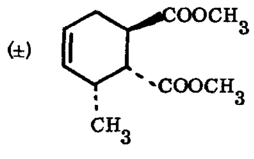


XV

macrolactones (XIV) and that B_1 and B_2 are the bridged structures XV. From the stability of B_1 relative to B_2 it is clear that B_1 and B_2 are cis- and trans-bridged structures, respectively. It is of interest that equilibration (KOtBu) of the Diels-Alder adducts XVI and XVII affords a 1 : 1 mixture[9] as does the



XVI



XVII

equilibration of the fused-ring products F_1 and F_2. This fact indicates that the relative stabilities of F_1 and F_2 depend mainly on the interactions involving axial and equatorial substituents on the six-membered ring and not on conformational effects involving the macrolactone part.

The studies described above clearly demonstrate that the internal Diels-Alder reaction can be used to effect the formation of medium/large ring structures.[10]

References

1. For a review see R. G. Carlson in *Ann. Rep. Med. Chem.*, **9**, 270 (1974).
2. Satisfactory infrared, proton magnetic resonance (pmr), and mass spectral data were obtained for all new substances reported herein.
3. Undergoes slow polymerization at room temperature and was thus routinely kept in solution at -20°.
4. Prepared by lithium aluminum hydride reduction of methyl *trans*-2,4-pentadienoate (S. Oida and E. Ohki, *Chem. Pharm. Bull.* (Japan), 1990 (1969)).
5. To 25 ml of dry, distilled (from CaH) benzonitrile at reflux (190°) containing 22 mg (0.1 mmol) of 2,6-di-*tert*-butyl-4-methylphenol as radical trap was added slowly a solution of 479 mg (1.90 mmol) of pure triene diester III in 20 ml of benzonitrile by means of a mechanically driven syringe over 30 hr. under argon. Refluxing was continued for an additional 2 hr. The solvent was removed under reduced pressure and the residue was subjected to column chromatography on 80 g of silica gel (10% ethyl acetate in benzene for elution) to afford 368 mg (77%) of a mixture of internal cyclization products as a colorless viscous oil which was chromatographically homogeneous (tlc analysis on silica gel plates using 9:1 benzene--ethyl acetate; R_f 0.48).
6. Separation was cleanly effected by column chromatography on silica gel (125 fold amount) using 9:1 chloroform-methanol as eluent. Each isomer showed characteristic staining on tlc with vanillin spray: VII (R_f 0.44) (light violet), VIII (R_f 0.36) (dark violet), IX (R_f 0.29) (intense blue).
7. The bromide XI was prepared by addition of acrolein to a solution of the Grignard reagent of cyclopropyl bromide in THF at 20° to afford cyclopropylvinyl carbinol and subsequent reaction with 48% HBr at 0° according to the method of Julia (M. Julia, S. Julia, and R. Guegan, *Bull. Soc. Chim. France*, 1072 (1960)). The Grignard reagent X was obtained starting with commercially available 6-chlorohexanol which was converted to the tetrahydropyranyl ether in the usual way. The coupling of X and XI (65% yield) was catalyzed by Li_2CuCl_4 (see M. Tamura and J. Kochi, *Synthesis*, 303 (1971), and C. Descoins and C. A. Henrick, *Tetrahedron Lett.*, 731 (1965)).
8. This ratio was obtained by a combination of tlc separation into two isomeric pairs and pmr analysis of each pair.
9. *Cf.* B. H. Mahmoud and K. W. Greenlee, *J. Org. Chem.*, **27**, 2369 (1962).
10. This research was assisted financially by the Swiss National Science Foundation (Fellowship to M. P.) and the U. S. National Institutes of Health.