ditions have indeed been found under which lithium phenoxide can be made to undergo effective and regiospecific ortho lithiation, as evidenced by several different trapping experiments. This study complements our previous work on coordination-directed lithiation of unsymmetrical ketones.[19] The results reported here, along with theoretical calculations,[20] X-ray data,[21] and other dimetalation experiments,[22] point strongly to an unusual stability of two *proximate* dianionic centers associated with two lithium cations.[8] These results should encourage study of the structure, stability, and reactions of other ortho-Z,C-dilithiated aromatic species in which Z = O, NR,[23] or CO_2.

Acknowledgment. Financial support was provided by the NSF (CHE 83-12161) and in part by I.C.I. Americas, Inc., for which we are very grateful. We thank Professors Craig Townsend (Johns Hopkins) and Dieter Seebach (E.T.H.) and Dr. Heinz Gschwend (Ciba-Geigy) for some helpful comments during the course of this work.

(19) Posner, G. H.; Lentz, C. M. *J. Am. Chem. Soc.* **1979**, *101*, 934.
(20) (a) Schleyer, P. v. R. *Pure Appl. Chem.* **1983**, *55*, 355. (b) Brown, K. J.; Murdock, J. R. *J. Am. Chem. Soc.* **1984**, *106*, 7843.
(21) Boche, G.; Decher, G.; Etzrodt, H.; Dietrich, H.; Mahdi, W.; Kos, A. J.; Schleyer, P. v. R. *J. Chem. Soc., Chem. Commun.* **1984**, 1493 and references therein.
(22) (a) Shirley, D. A. *J. Org. Chem.* **1962**, *27*, 4421 and references therein. (b) Shatzmiller, S.; Lidor, R. *Synthesis* **1983**, 590. (c) Oster, T. A.; Harris, T. M. *J. Org. Chem.* **1983**, *48*, 4307. (d) Manceron, L.; Andrews, L. *J. Am. Chem. Soc.* **1985**, *107*, 563.
(23) For previous examples of Ar_2NLi ortho metalation, see: Dahlgren, T.; Hallberg, A.; Helitzer, R.; Martin, A. R. *J. Heterocycl. Chem.* **1983**, *20*, 341, Hallberg, A.; Martin, A. *Ibid.* **1982**, *19*, 433.

Total Synthesis of (±)-Nemorensic Acid

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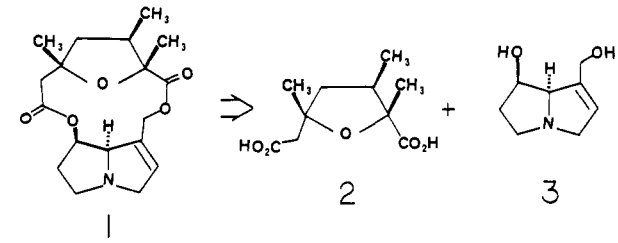
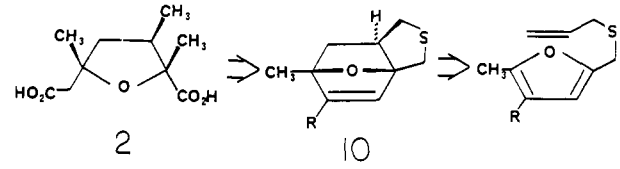
Received November 5, 1984

Nemorensic acid (**2**)[1] is the diacid portion of retroisosenine (**1**) a molecule belonging to the family of natural products known as the Senecio alkaloids (Scheme I). These compounds have been of great interest owing to their diverse biological activity ranging from potent hepatotoxicity to antitumor activity.[2,3] Only recently has progress been made in the total synthesis of some of the simple dilactone alkaloids in this class.[4] Although the necine base portion, retronecine (**3**), was prepared in 1962,[5] no synthesis of the cyclic necic acid moieties has been reported.[6] Recently, we have found an efficient and stereoselective method for the construction of these substituted tetrahydrofuran ring systems via an intramolecular Diels–Alder reaction of furfuryl allyl sulfides[7] and report here a successful application of this method resulting in the first synthesis of (±)-nemorensic acid.

Scheme I



Scheme II



The synthetic problems associated with the construction of an $\alpha,\alpha,\alpha',\alpha'$-tetrasubstituted tetrahydrofuran ring such as **2** are twofold: (1) the steric hindrance between the bonding centers during the typical O–C cyclitive bond formation and (2) the stereochemical requirements of the α, α', and β ring positions. Our approach circumvents both problems through the use of a cycloaddition reaction (Scheme II). It is known from previous work on similar systems that only the product derived from an exo approach of the dienophile side chain will be obtained.[8] Thus, the relative stereochemistry of the three ring fusion centers in the tricyclic cycloadduct **10** is established. Our scheme then involves an efficient oxidation–reduction sequence in which the olefin of cycloadduct **10** is cleaved and the sulfur link is eliminated. In this way the desired stereochemistry and the complete carbon skeleton can be quickly obtained.

The synthesis of the tricyclic sulfide **10** is shown in Scheme III. The known alcohol **4**,[9] which was produced from its corresponding methyl ester[10] by reduction with $LiAlH_4$ in THF, underwent subsequent benzylation (THF/DMF, 4:1) to give the desired furan **5** in a total 74% yield after purification.[11] Vilsmeier formylation to produce **6** was followed by treatment with NH_4SH[12] in ethanol at room temperature (5 h) to yield the crude furfuryl disulfide **7**. Without purification this disulfide was immediately reduced with $LiAlH_4$ to the mercaptan (ether reflux, 1 h) and directly allylated. Each step in this sequence produced a homogeneous product by TLC, and this allylthiomethylation could be performed in it entirety over 2 days. Only one purification at the final stage was necessary, thereby affording **9** from **5** in a 50–70% yield on a 40-g scale.

The cycloaddition took place in refluxing toluene over 24 h to produce the desired cycloadduct in 48% yield with 40–45% of recovered starting furan. This has been shown to be an equilibrium reaction[6] since this same ratio is obtained when either isolated product or starting material **9** were resubmitted to the reaction conditions. Since no side products were evident and recovery of materials was greater than 85%, **9** was recycled twice more in order to obtain the cycloadduct **10** in 66% yield and in a total yield of 50% from furan **5**.

Ozonolysis of **10** in ethanol at 0 °C was followed by reductive workup using $NaBH_4$ (Scheme IV). The dihydroxy sulfoxide

(1) (a) Klasek, A.; Sedmera, P.; Boeva, A.; Santavy, F. *Coll. Czech. Chem. Commun.* **1973**, *38*, 2504. (b) Kirfel, A.; Will, G.; Wiedenfeld, H.; Roeder, E.; *Cryst. Struct. Commun.* **1980**, *9*, 363. Roeder, E.; Wiedenfeld, H.; Frisse, M. *Phytochemistry* **1980**, *19*, 1725.
(2) Bull, L. B.; Culvenor, C. C. J.; Dick, A. T. "The Pyrrolizidine Alkaloids"; American Elsevier Publishing: New York, 1968. Culvenor, C. C. J. *J. Pharm. Sci.* **1968**, *57*, 1112. Dovach, J. S.; Ames, M. M.; Powis, G.; Moertel, C. G.; Hahn, R. G.; Creagan, E. T. *Cancer Res.* **1979**, *39*, 4540.
(3) General alkaloid references: Warren, F. L. *Prog. Chem. Org. Nat. Prod.* **1966**, *24*, 329. Leonard, N. J. "The Alkaloids"; Academic Press: New York, 1959; Vol. 6, p 35.
(4) Vedejs, E.; Larsen, S. D. *J. Am. Chem. Soc.* **1984**, *106*, 3030. Narasaka, K.; Sakamura, T.; Uchimura, T.; Guedin-Vuong, D. *J. Am. Chem. Soc.* **1984**, *106*, 2954.
(5) Geissman, T. A.; Waiss, A. C. *J. Org. Chem.* **1962**, *27*, 139. First isolated: Barger, G.; Seshadri, T. R.; Watt, H. E.; Yabuta, T. *J. Chem. Soc.* **1935**, 11.
(6) One synthesis of nemorensic acid in its "open chain form", i.e., 6-hydroxy-3,5,6-trimethyl-2-heptenedioic acid, was described. This material was obtained as a mixture of eight diastereomers in a total 1.1% yield. Roeder, E.; Wiedenfeld, H.; Frisse, M. *Arch. Pharm.* **1980**, *313*, 803.
(7) Klein, L. *J. Org. Chem.*, in press.
(8) Parker, K. A.; Adamchuk, M. R. *Tetrahedron Lett.* **1978**, 1689.
(9) Winberg, H. E.; Fawcett, F. S.; Mochel, W. E.; Theobald, C. W. *J. Am. Chem. Soc.* **1960**, *82*, 1428.
(10) Aldrich Chemical Co., Milwaukee, WI.
(11) All yields refer to isolated and purified compounds. Satisfactory NMR and/or HRMS data was obtained for selected intermediates.
(12) This reagent was prepared as described in ref 4 from: Kipnis, F.; Levy, I.; Ornfelt, J. *J. Am. Chem. Soc.* **1949**, *71*, 2270.

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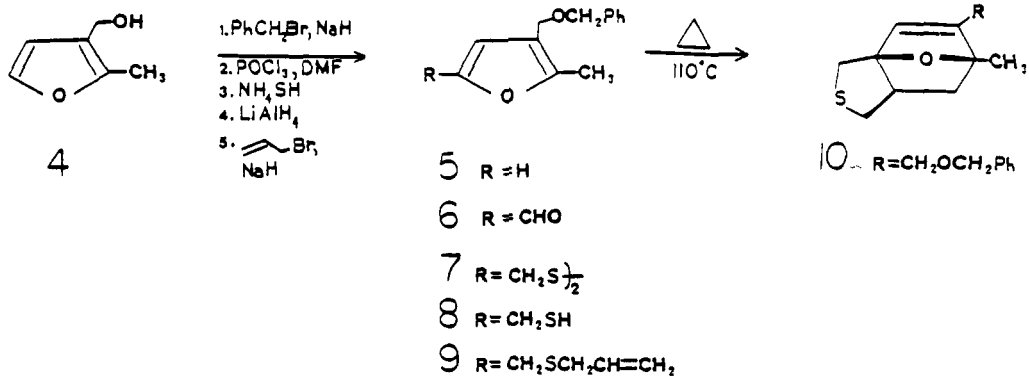
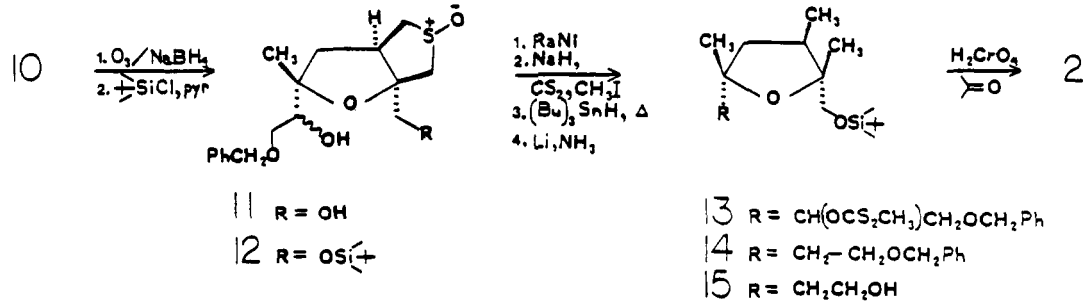
Scheme III

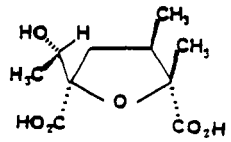


Scheme IV

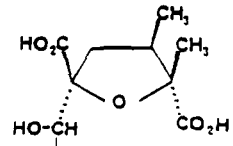


11 was produced as a mixture of diastereomers, which were used in subsequent reactions without separation. Direct silylation of **11** with *t*-BuMe$_2$SiCl was performed (pyridine, 70 °C, 2 h) and treatment of **12** with Raney nickel[13] in refluxing ethanol served to reduce the sulfoxide and desulfurize the resultant sulfide (in 68% from **10**). Deoxygenation of the epimeric hydroxy group proceeded cleanly using Barton's two-step method[14] (i.e., xanthate formation followed by reduction of the crude xanthates **13** with (*n*-Bu)$_3$SnH in refluxing toluene) to give diprotected **14** in 80% yield. The benzyl group in **14** could be removed by reaction with lithium in ammonia (3:2, NH_3/THF) to yield silyl alcohol **15**. Finally, treatment of **15** with Jones' reagent at room temperature directly afforded in 60% yield a diacid that was identical with natural nemorensic acid in terms of its ^{13}C and ^1H NMR spectra and its mass spectrum. Since compound **14** has the two pendant chains differentiated, through the use of deprotection and selective-oxidation strategies, one could have access to either monoacid.

In summary, this efficient and stereoselective approach to the highly substituted cyclic necic acids will allow selective preparation of monoester and dilactone natural products and their analogues. Application of these methods toward structures such as jaconecic acid (**16**)[15a] and petasitenecic acid (**17**),[15b] which would not require



16



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the deoxygenation steps, would be straightforward and is currently under way.

(13) Analogous to W-2, 50% slurry in H_2O, pH 10; Sigma Chemical Co., St. Louis, MO.

(14) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1*, **1975**, 1574.

(15) (a) Masamune, S. *J. Am. Chem. Soc.* **1960**, *82*, 5253. (b) Yamada, K.; Tatematsu, H.; Suzuki, M.; Hirata, Y.; Haga, M.; Hirono, I. *Chem. Lett.* **1976**, 461.

Supplementary Material Available: ^1H NMR and HRMS data for compounds **5–10** and **15**, ^{13}C NMR data for **5–10**, and ^1H NMR, ^{13}C NMR, and MS (70 eV) data for **2** (2 pages). Ordering information is given on any current masthead page.

Complementary Solutes Enter Nonpolar Preorganized Cavities in Lipophilic Noncomplementary Media[1]

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Received December 7, 1984

Ordinarily, when host and guest complex, each must desolvate. Most hosts containing enforced cavities of molecular dimensions (cavitands)[2] contain holes large enough to admit solvent.[3] Only the anisyl-based spherands[4] and the cyclotriveratrylene-based cavitands[5] contain unsolvated interior surfaces. We report here complexation studies in $CDCl_3$ and C_6D_6 between nonpolar partners containing complementary surfaces. New cavitands **1–3** contain cylindrical wells of varying depths whose limited diameters

(1) We warmly thank the National Science Foundation for NSF Grant CHE 81-09532, which supported all of the work except the crystal structure determination, which was supported on NSF Grant CHE 82-05803.

(2) (a) Cram, D. J. *Science (Washington, D.C.)* **1983**, *219*, 1177–1183. (b) Moran, J. R.; Karbach, S.; Cram, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 5826–5828.

(3) (a) Gutsche, C. D.; Levine, J. A. *J. Am. Chem. Soc.* **1982**, *104*, 2652–2653. (b) Miller, S. P.; Whitlock, H. W., Jr. *J. Am. Chem. Soc.* **1984**, *106*, 1492–1494. (c) Mock, W. L.; Shih, N. Y. *J. Org. Chem.* **1983**, *48*, 3618–3619. (d) Mock, W. L.; Irra, T. A.; Wepsiec, J. P.; Manimaran, T. L. *Ibid.* **1983**, *48*, 3619–3620.

(4) (a) Cram, D. J.; Kaneda, T.; Helgeson, R. C.; Lein, G. M. *J. Am. Chem. Soc.* **1979**, *101*, 6752–6754. (b) Cram, D. J.; Kaneda, T.; Helgeson, R. C.; Brown, S. B.; Knobler, C. B.; Maverick, E.; Trueblood, K. N. *Ibid.*, in press.

(5) (a) Canceill, J.; Lacombe, L.; Collet, A. *C. R. Acad. Sci., Ser. 2* **1984**, *298*, 39–42. (b) Canceill, J.; Collet, A.; Gabard, J.; Kotzyba-Hibert, F.; Lehn, J.-M. *Helv. Chim. Acta* **1982**, *65*, 1894–1897.

0002-7863/85/1507-2574$01.50/0