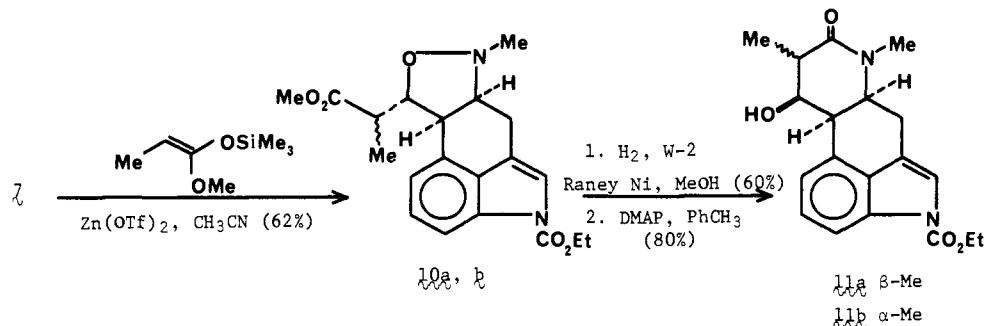
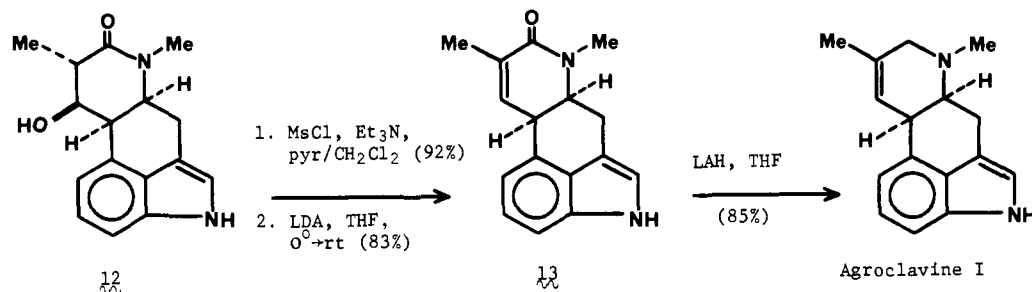


Scheme III



Scheme IV



and **10b** resulted. Proof that these compounds differed only in the stereochemistry of their C-8 centers was gleaned by hydrogenating the mixture and cyclizing the resulting  $\delta$ -amino esters to the corresponding lactams (**11a**,  $J_{8,9} = 4$ ,  $J_{9,10} < 1$ ,  $J_{5,10} = 5.7$  Hz; **11b**,  $J_{8,9} < 1$ ,  $J_{9,10} = 2.1$ ,  $J_{5,10} = 5.5$  Hz). Accordingly, the cyclic oxonium ion formed from **7** suffers addition only from its *Si* face (convex face addition). Again, no discrimination is observed for the faces of the ketene silyl acetal.

To demonstrate the utility of this novel isoxazolidine  $\rightarrow$   $\gamma$ -amino alcohol transformation in synthesis, **11b** was further converted to the newly isolated ergot alkaloid agroclavine I. The *N*-carboethoxy group of **11b** was first removed (KOH, MeOH, 85%), as its removal later on proved deleterious to the subsequent LAH reduction. Upon mesylation and LDA promoted elimination, **12** was transformed to the enamide **13**. Attempts to effect this elimination reaction with DBU in refluxing benzene led instead to generation of the deconjugated ( $\Delta^9$ ) isomer. Such an isomerization event is noteworthy, for it could prove valuable to the procurement of the ergot alkaloid lysergine.<sup>8</sup>

From **13**, a simple LAH reduction in refluxing tetrahydrofuran led to the desired, C,D-cis-fused ergot, agroclavine I (Scheme IV). The UV, IR, NMR and mass spectra of the synthetic material matched precisely that available from the literature.<sup>9</sup>

In conclusion, we have demonstrated that one can utilize the Lewis acid assisted condensation of silicon-based nucleophiles with an alkoxy-substituted isoxazolidine substrate so as to access functionalized  $\gamma$ -amino alcohols.<sup>10</sup> One can thus extend the Lewis acid promoted C-C bond-forming methodology to heterocyclic systems containing adjacent ring heteroatoms.<sup>11</sup> The divergent behavior of the zinc and titanium salts in the course of the reactions reported is presumably a function of the charge/radius ratio of the metal as well as of ability of the solvent to participate through complexation to the metal and through interaction with the onium

ion intermediate.

**Acknowledgment.** We are indebted to the National Institutes of Health for their generous support of these investigations.

**Registry No.** 1, 95484-69-8; 2, 95484-70-1; 3, 95484-71-2; 4, 73805-09-1; 5, 95484-72-3; 6, 95484-73-4; ( $\pm$ )-7, 95484-74-5; ( $\pm$ )-8 (isomer 1), 95484-75-6; ( $\pm$ )-8 (isomer 2), 95586-11-1; ( $\pm$ )-9a, 95484-76-7; ( $\pm$ )-9b, 95484-77-8; ( $\pm$ )-10a, 95484-78-9; ( $\pm$ )-10b, 95586-09-7; ( $\pm$ )-11a, 95484-79-0; ( $\pm$ )-11b, 95484-80-3; ( $\pm$ )-12, 95484-81-4; ( $\pm$ )-13, 95484-82-5;  $\text{CH}_3\text{CH}=\text{C}(\text{OCH}_3)\text{OTMS}$ , 34880-70-1; ( $\pm$ )-agroclavine I, 95586-10-0; phenyl isocyanate, 103-71-9.

**Supplementary Material Available:** Melting points, IR, <sup>1</sup>H NMR, and high-resolution mass spectral data for compounds **4/5**, **7**, **10a, b**, **11b**, **12**, **13**, and agroclavine I (3 pages). Ordering information is given on any current masthead page.

## Phenoxide-Directed Ortho Lithiation

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Received January 14, 1985

Heteroatom-facilitated ortho lithiation is a very popular and powerful technique which can lead to regioselective attachment of an electrophile ortho to a heteroatom-containing substituent on an aromatic ring.<sup>1</sup> Recently some significant and creative applications of this methodology to the synthesis of several different classes of aromatic intermediates<sup>2</sup> and natural products<sup>3</sup> have been

(8) For other recent efforts in the ergot area, see: Kruse, L. I.; Meyer, M. D. *J. Org. Chem.* **1984**, *49*, 4761 and references therein.

(9) Sakharovsky, V. G.; Kozlovsky, A. G. *Tetrahedron Lett.* **1984**, 25, 109. Kozlovsky, A. G.; Solovieva, T. F.; Sakharovsky, V. G.; Adanin, V. M. *Prikl. Biokhim. Mikrobiol.* **1982**, *18*, 535.

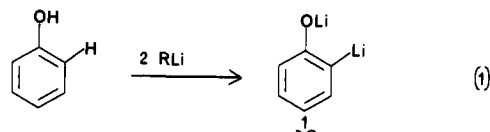
(10) Tufariello, J. J. *Acc. Chem. Res.* **1979**, *12*, 396. Jäger, V.; Schohe, R. *Tetrahedron* **1984**, *40*, 2199.

(11) The use of silicon reagents in the functionalization of heterocycles containing a single heteroatom in the ring has proven quite popular, especially in the carbohydrate area: Hosomi, A.; Sakata, Y.; Sakurai, H. *Tetrahedron Lett.* **1984**, *25*, 2383 and references therein.

(1) (a) Gilman, H.; Morton, J. W., Jr. *Org. React. (N.Y.)* **1954**, *8*, 258. (b) Gschwend, H. W.; Rodriguez, H. R. *Ibid.* **1979**, *26*, 1 and references therein. (c) Narasimhan, N. S.; Mali, R. S. *Synthesis* **1983**, 965. (d) Fraser, R. R.; Bresse, M.; Mansour, T. S. *J. Am. Chem. Soc.* **1983**, *105*, 7790.

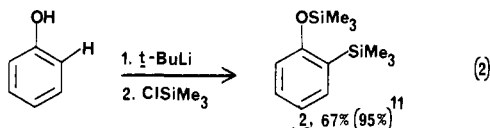
(2) (a) Billedeau, R. J.; Sibi, M. P.; Snieckus, V. *Tetrahedron Lett.* **1983**, *24*, 4515. (b) Uemura, M.; Isobe, K.; Take, K.; Hayashi, Y. *J. Org. Chem.* **1983**, *48*, 3855. (c) Shankaran, K.; Snieckus, V. *Ibid.* **1984**, *49*, 5022. (d) Narasimhan, N. S.; Ranade, A. C.; Deshpande, H. R.; Gokhale, U. B.; Jayalakshmi, G. *Synth. Commun.* **1984**, *14*, 373.

reported. Conventional wisdom indicates that a phenolic *hydroxyl* group, in contrast to other substituents such as a phenolic *methoxyl* group, is almost totally ineffective in directing ortho lithiation.<sup>1,4</sup> For example, Gilman reported in 1945 that treating phenol with 4 equiv of *n*-butyllithium and then with excess carbon dioxide gave salicylic acid in only 0.7% yield,<sup>5</sup> and a 1983 review of this subject concluded that "lithiation reactions directed by groups such as hydroxy, amino, and carboxy do not proceed in good yield".<sup>1c</sup> We reasoned, however, that under suitable conditions the oxygen atom of lithium phenoxide might still coordinate with an organolithium reagent (kinetic effect)<sup>1b,6</sup> and/or might stabilize an ortho lithium atom (thermodynamic effect)<sup>7</sup> thus facilitating dianion formation (eq 1); such a dianion associated with two lithium cations can be



considered as an ion triplet<sup>8</sup> belonging to a class of ionic clusters having surprisingly high relative stability apparently due to Coulombic attraction of *each* lithium cation to *both* proximate anionic centers.<sup>8</sup> This paper reports (1) suitable experimental conditions for generating *o*-lithiophenolate **1**, (2) attachment of five different electrophiles to form various ortho-substituted phenols, and (3) a competition experiment between phenolic OLi and OMe toward ortho lithiation.

After considerable experimentation with various temperatures, ethereal solvents, and bases (e.g., *n*-butyllithium-potassium *t*-butoxide,<sup>9</sup> *n*-butyllithium-TMEDA,<sup>10</sup> *sec*-butyllithium), we found that adding 2.8 equiv of *tert*-butyllithium in pentane to 1.0 equiv of phenol in 4.2 equiv of tetrahydropyran (THP) at 25 °C (exothermic reaction) was most effective in converting phenol instantaneously into insoluble lithium phenoxide and then surprisingly slowly (~ 0.5 h) into its *soluble ortho*-lithiated dianion **1**, as assayed by capillary GC analysis of O,C-bissilylated adduct **2**<sup>7b</sup> formed by reaction of the dianion with excess trimethylsilyl chloride (eq 2).<sup>11</sup> Preforming lithium (*t*-BuOLi), sodium (NaH),



(3) (a) Adrenaline models: Slocum, D. W.; Acherman, W. *J. Chem. Soc., Chem. Commun.* **1974**, 968. (b) Mellein and kigelin: Sibi, M. P.; Jalil Miah, M. A.; Snieckus, V. *J. Org. Chem.* **1984**, *49*, 737. (c) Hydrangenol and phylloquin: Watanabe, M.; Sahara, M.; Kubo, M.; Furukawa, S.; Billedeau, R. J.; Snieckus, V. *Ibid.* **1984**, *49*, 742. (d) Anthramycin: Reed, J. N.; Snieckus, V. *Tetrahedron Lett.* **1984**, *25*, 5505.

(4) For effective Lewis acid methods to achieve selective ortho substitution of phenols, see: (a) Casnati, G.; Casiraghi, G.; Pochini, A.; Sartori, G.; Ungaro, R. *Pure Appl. Chem.* **1983**, *55*, 1677. (b) Citterio, A.; Gandolphi, M.; Piccolo, O.; Filippini, L.; Tinucci, L.; Valoti, E. *Synthesis* **1984**, 760. Cf.: (c) Fahmy, A. M.; Mahgoub, S. A.; Aly, M. M.; Badr, M. Z. *Indian J. Chem., Sect. B* **1984**, *23*, 474. (d) Ranken, P. F.; McKinnie, B. G. *Synthesis* **1984**, 117.

(5) Gilman, H.; Arntzen, C. E.; Webb, F. J. *J. Org. Chem.* **1945**, *10*, 374.

(6) For a pioneering example of arenoxide directed ortho lithiation, see: (a) Gilman, H.; Cook, T. H. *J. Am. Chem. Soc.* **1940**, *62*, 2813. Cf.: (b) Shirley, D. A.; Hendrix, J. D. *J. Organomet. Chem.* **1968**, *11*, 217. (c) Seebach, D. *Chem. Ind.* **1978**, *17*, 121. (d) Al-Aseer, M.; Beak, P.; Hay, D.; Kempf, J.; Mills, S.; Smith, S. G. *J. Am. Chem. Soc.* **1983**, *105*, 2080. (e) Meyers, A. I.; Rieker, W. F.; Fuentes, L. M. *Ibid.* **1983**, *105*, 2082. (f) Posner, G. H.; Tang, P. W.; Mallamo, J. P. *Tetrahedron Lett.* **1978**, 3995.

(7) (a) Lau, K. S. Y.; Schlosser, M. *J. Org. Chem.* **1978**, *43*, 1595 and references therein. (b) For some reactions of ortho-lithiated lithium phenoxide prepared via bromine → lithium exchange, see: Heinecke, J.; Tzschach, A. *J. Prakt. Chem.* **1983**, *325*, 232. Talley, J. J.; Evans, I. A. *J. Org. Chem.* **1984**, *49*, 5267. Cf.: (c) Huddle, P. A.; Perold, G. W. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2617. (d) Meyers, A. I.; Pansegrau, P. D. *Tetrahedron Lett.* **1983**, *24*, 4935.

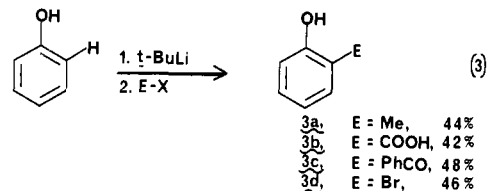
(8) (a) For simplicity, coordinating solvent molecules are omitted in representation **1**. (b) For an excellent up-to-date review of ion triplets, see: Streitwieser, A. *Acc. Chem. Res.* **1984**, *17*, 353.

(9) (a) Lochmann, L.; Pospisil, J.; Lim, D. *Tetrahedron Lett.* **1966**, 257. (b) Schlosser, M. *J. Organomet. Chem.* **1967**, *8*, 9.

(10) (a) Langer, A. W., Jr. *N. Y. Acad. Sci.* **1965**, *27*, 741. (b) Crowther, G. P.; Sundberg, R. J.; Sarpeshkar, A. M. *J. Org. Chem.* **1984**, *49*, 4657.

and potassium (KH)<sup>12</sup> phenoxides before adding *tert*-butyllithium resulted in lower yields of silyl adduct **2**. Using 2-methyltetrahydropyran in an attempt to diminish *tert*-butyllithium reaction with the solvent<sup>13</sup> offered no advantage over using THP itself.

Quenching ortho-lithiated phenolate **1** with such electrophiles as methyl iodide<sup>7b</sup> (or dimethyl sulfate), carbon dioxide, benzoic anhydride, and carbon tetrabromide<sup>14a</sup> (or 1,2-dibromoethane)<sup>14b,c</sup> led in 42–48% yields to isolated, purified ortho-substituted phenols **3a–d** (eq 3).<sup>15</sup> The methyl iodide quench gave no *m*- or *p*-



methylphenol, indicative of exclusive ortho lithiation of phenoxide, and no O-methyl product, consistent with the expectation that the carbanionic center in dianion **1** is more reactive than the oxyanionic center. Under the very basic conditions of this reaction, very little, if any, benzylic deprotonation of the product *o*-methylphenol (**3a**) occurred as indicated by the absence of any *o*-ethylphenol product. The quench with carbon tetrabromide or 1,2-dibromoethane gave *o*-bromophenol rather than any alkylated phenol adducts;<sup>14</sup> since aryl bromides are versatile precursors to synthetically useful arynes<sup>16</sup> and are effective partners in coupling reactions with organometallic reagents,<sup>17</sup> this direct and regio-specific conversion of phenol into *o*-bromophenol has good synthetic potential. Trapping O,C dianion **1** with *bifunctional* electrophiles should lead directly to various oxygen heterocycles.

To assay *quantitatively* the ability of a phenolic OLi functionality to direct ortho lithiation, an intramolecular competition experiment was carried out using *p*-methoxyphenol. As expected,<sup>1</sup> exposing *p*-methoxyphenol to *tert*-butyllithium as in eq 2 and then quenching with excess carbon dioxide led to carboxylation predominantly adjacent to the methoxyl group; by <sup>1</sup>H NMR integration of the characteristic OMe singlets,<sup>18</sup> the ratio of carboxylation ortho to OMe ( $\delta$  4.0) vs. ortho to OH ( $\delta$  3.8) was found to be approximately 35:1.

Despite the relative weakness of the phenolic OLi group as an ortho-lithiation director, we have shown here that suitable con-

(11) A typical experimental procedure is represented by preparation of *o*-(trimethylsilyl)phenol trimethylsilyl ether (**2**). To a 25-mL round-bottomed flask equipped with a condenser and a rubber septum under nitrogen was added 94.2 mg (1.01 mmol) of recrystallized phenol (mp 38.5–41.5 °C) and 407  $\mu$ L (4.16 mmol) of dry tetrahydropyran. *tert*-Butyllithium (1.58 mL of a 1.74 M pentane solution, 2.75 mmol) was added dropwise via syringe during 3–5 min with evolution of heat. Stirring was continued at room temperature for 2 h; after 0.5 h, the initial suspension turned into a slightly cloudy solution. Trimethylsilyl chloride (1.3 mL, 10.0 mmol, supernatant from Me<sub>3</sub>SiCl + Et<sub>3</sub>N) was added via syringe rapidly producing a white precipitate. After stirring for 14 h at room temperature, rotary evaporation, addition of 50 mL of diethyl ether, filtration through a sintered glass funnel, and evaporation there was isolated 422 mg of a liquid. Kugelrohr distillation (100 °C, 2 mmHg) gave 295 mg of a liquid which was analyzed by calibrated capillary GC to contain bis(silyl) ether **2** in 95% yield. Preparative TLC on silica gel using benzene/hexane/triethylamine (49.5:49.5:1.0) gave bis(silyl) ether **2** in 67% yield with <sup>1</sup>H NMR data (CDCl<sub>3</sub>,  $\delta$  0.21 and 0.27, each 9 H) identical with those of an authentic sample prepared from *o*-bromophenol by a literature procedure.<sup>7b</sup>

(12) Cf.: Meyers, A. I.; Loewe, M. F. *Tetrahedron Lett.* **1984**, *25*, 2641.

(13) A slow but significant side reaction was always observed: *t*-BuLi + THP → *t*-Bu(CH<sub>2</sub>)<sub>5</sub>OLi.

(14) (a) Hori, Y.; Nagano, Y.; Uchiyama, H.; Yamada, Y.; Taniguchi, H. *Chem. Lett.* **1978**, 73. (b) Klumpp, G. W.; Kool, M.; Veeffkind, A. H.; Schakel, M.; Schmitz, R. F. *Recl. Trav. Chim. Pays-Bas* **1983**, *102*, 542. (c) Bahl, J. J.; Bates, R. B.; Beavers, W. A.; Mills, N. S. *J. Org. Chem.* **1976**, *41*, 1620.

(15) Characterization was done by <sup>1</sup>H NMR and IR spectroscopy and by matching physical constants (e.g., melting point, boiling point) with those of authentic samples.

(16) Heaney, H. *Chem. Rev.* **1962**, *62*, 81.

(17) Cf.: Posner, G. H. *Org. React. (N.Y.)* **1975**, *22*, 253.

(18) For example, the <sup>1</sup>H NMR singlets for the OMe groups of 2-methoxyphenol and 4-methoxyphenol occur at  $\delta$  4.0 and 3.8, respectively ("The Aldrich Library of NMR Spectra"; Pouchart, C. J., Campbell, J. R., Eds.; Aldrich Chemical Co.: Milwaukee, WI 1974 Vol. VI).

ditions have indeed been found under which lithium phenoxide can be made to undergo effective and regioselective ortho lithiation, as evidenced by several different trapping experiments. This study complements our previous work on coordination-directed lithiation of unsymmetrical ketones.<sup>19</sup> The results reported here, along with theoretical calculations,<sup>20</sup> X-ray data,<sup>21</sup> and other dimetalation experiments,<sup>22</sup> point strongly to an unusual stability of two proximate dianionic centers associated with two lithium cations.<sup>8</sup> These results should encourage study of the structure, stability, and reactions of other ortho-Z,C-dilithiated aromatic species in which Z = O, NR,<sup>23</sup> or CO<sub>2</sub>.

**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.

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 (23) For previous examples of Ar<sub>2</sub>NLi 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

Larry L. Klein

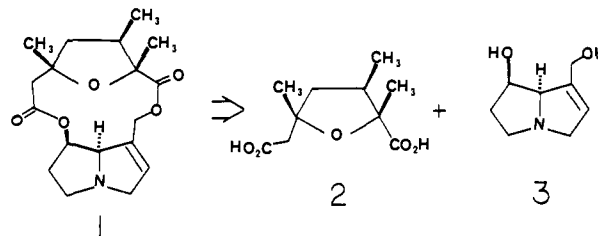
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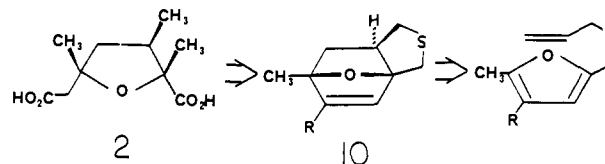
Nemorensic acid (**2**)<sup>1</sup> is the diacid portion of retroisosenine (**1**) a molecule belonging to the family of natural products known as the Senecio alkaloids (Scheme I). These compounds have been of great interest owing to their diverse biological activity ranging from potent hepatotoxicity to antitumor activity.<sup>2,3</sup> Only recently has progress been made in the total synthesis of some of the simple dilactone alkaloids in this class.<sup>4</sup> Although the necine base portion, retronecine (**3**), was prepared in 1962,<sup>5</sup> no synthesis of the cyclic necic acid moieties has been reported.<sup>6</sup> Recently, we have found an efficient and stereoselective method for the construction of these substituted tetrahydrofuran ring systems via an intramolecular

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 (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.

### Scheme I



### Scheme II



Diels-Alder reaction of furfuryl allyl sulfides<sup>7</sup> and report here a successful application of this method resulting in the first synthesis of (±)-nemorensic acid.

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  $\alpha$ ,  $\alpha'$ , and  $\beta$  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.<sup>8</sup> 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**,<sup>9</sup> which was produced from its corresponding methyl ester<sup>10</sup> by reduction with LiAlH<sub>4</sub> in THF, underwent subsequent benzylation (THF/DMF, 4:1) to give the desired furan **5** in a total 74% yield after purification.<sup>11</sup> Vilsmeier formylation to produce **6** was followed by treatment with NH<sub>4</sub>SH<sup>12</sup> in ethanol at room temperature (5 h) to yield the crude furfuryl disulfide **7**. Without purification this disulfide was immediately reduced with LiAlH<sub>4</sub> to the mercaptan (ether reflux, 1 h) and directly allylated. Each step in this sequence produced a homogeneous product by TLC, and this allythiomethylation could be performed in its 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<sup>6</sup> 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<sub>4</sub> (Scheme IV). The dihydroxy sulfoxide

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 (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.