[5 + 2] Pyrone−Alkene Cycloaddition Approach to Tetrahydrofurans. Expeditious Synthesis of (±)-Nemorensic Acid

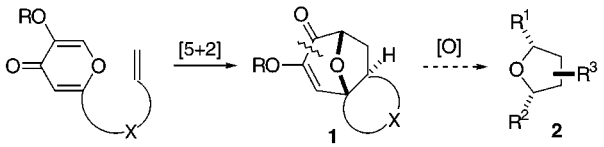
J. Ramón Rodríguez, Antonio Rumbo, Luis Castedo, and José L. Mascareñas*

Departamento de Química Orgánica y Unidad Asociada al CSIC, Universidad de Santiago de Compostela, 15706 Santiago de Compostela, Spain

Received February 8, 1999

Modern organic synthesis increasingly demands high efficiency in terms of minimizing the synthetic steps while maximizing target-relevant molecular complexity.[1] One of the best ways to address this challenge relies on the development of methods that allow the one-pot transformation of simple starting materials into complex building blocks that, by virtue of their skeletal and functional characteristics, may be susceptible to rapid transformation into the desired products without the need of laborious touch-ups. We have shown that thermolysis of β-silyloxy-γ-pyrones bearing temporary tethered alkenes promotes their internal [5 + 2] cycloaddition, giving relatively complex 8-oxabicyclo[3.2.1]octane architectures (**1**).[2] The rich functionalization and sterochemical bias of these frameworks has already allowed a rapid, divergent elaboration into a variety of valuable structures.[3] One of the more attractive options for manipulation of these systems arises from the rich oxygenation pattern of the cycloadducts, which suggested an immediate entry to *cis*-2,5-disubstituted tetrahydrofurans (**2**) by oxidative cleavage of the carbocycle (Scheme 1).[3a] This process is of interest owing to the large number of biologically important natural products that contain these skeletons as a main structural motif.[4] Herein, we describe details of this approach and demonstrate its synthetic potential by synthesizing (±)-nemorensic acid (**3**), the diacid portion of nemorensine (**4**) (Figure 1),[5] in roughly half the number of steps used in previously published syntheses.[6]

Scheme 1



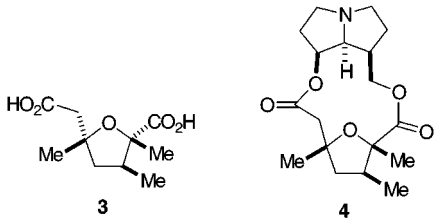


Figure 1.

Although connections through sulfur atoms have not been extensively used in temporary tethering strategies,[7] we have found that this type of linkage offers a practical solution to promote the otherwise unfeasible thermal [5 + 2] cycloaddition of β-silyloxy-γ-pyrones to nonactivated alkenes. Indeed, using this approach we readily assembled adducts such as **7** that are formally the result of a regio- and stereoselective [5C + 2C] cycloaddition between propene and α-deoxykojic acid (**5b**).[2] In implementing this strategy, it was somewhat surprising to find that desulfuration of cycloadduct **6** was accompanied by concurrent reactions at the enone.[8] Hence, heating an ethanolic solution of **6** under reflux with activated Raney nickel gave a roughly equimolecular mixture the desulfurized compounds **7a** and **7b**. Fortunately, carrying out the reaction in THF led to the exclusive formation of the ketone **7b** in 71% yield. The stereochemistry of the carbon atom bearing the *tert*-butyldimethylsilyl ether substituent was deduced from the characteristic 5 Hz coupling constant for the C-4 *exo*-H observed in the ^{1}H NMR spectrum (Figure 2).[9] The formation of **7b** can be explained assuming that, in addition to the desulfuration reaction, the Raney nickel promotes an electron-transfer reduction of the ketone that is followed by O-3 → O-4 migration of the silyl group. The generation of an α-silyloxyketone functionality during the desulfuration process pointed to this site as being particularly suitable for achieving the desired oxidative cleavage of the carbocycle. Indeed, **7b** was readily transformed into the tetrahydrofuran **8** by desilylation and treatment of the resulting hydroxyketone with $Pb(OAc)_4$ in MeOH. Remarkably, the oxidative cleavage can be carried out in a single pot by stirring **7b** with 3 equiv of TBAF and 1.5 equiv of $Pb(OAc)_4$ in MeOH.

(1) (a) Wender, P. A.; Miller, B. L. In *Organic Synthesis: Theory and Applications*; Hudlicky, T., Ed.; Jai Press: 1993; Vol. 2, p 27. (b) Bertz, S. H.; Sommer, T. J. In *Organic Syntheses: Theory and Applications*; Hudlicky, T., Ed.; Jai Press: 1993; Vol. 2, p 67. See also: (c) *Chem. Rev.* **1996**, *96*, 1.

(2) Rumbo, A.; Castedo, L.; Mouriño, A.; Mascareñas, J. L. *J. Org. Chem.* **1993**, *58*, 5585.

(3) (a) Mascareñas, J. L.; Rumbo, A.; Castedo, L. *J. Org. Chem.* **1997**, *62*, 8620. (b) Rodríguez, J. R.; Rumbo, A.; Castedo, L.; Mascareñas, J. L. *J. Org. Chem.* **1999**, *64*, 966.

(4) (a) Robinson, J. A. *Prog. Chem. Org. Nat. Prod.* **1991**, *58*, 1. (b) Dutton, C. J.; Banks, B. J.; Cooper, C. B. *Nat. Prod. Rep.* **1995**, 166. For reviews and leading references of approaches to *cis*-2,5-tetrahydrofurans, see: (c) Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309. (d) Harmange, J. C.; Figadere, B. *Tetrahedron: Asymmetry* **1993**, *4*, 1711. (e) Molander, G. A.; Swallow, S. *J. Org. Chem.* **1994**, *59*, 7148. (f) Arista, L.; Gruttadauria, M.; Thomas, E. J. *Synlett* **1997**, 627. (g) Molander, G. A.; Haas, J. *Tetrahedron* **1999**, *55*, 617.

(5) Warren, F. L. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1970; Vol. 12, Chapter 14.

(6) (a) Klein, L. L. *J. Am. Chem. Soc.* **1985**, *107*, 2573. (b) Klein, L. L.; Shanklin, M. S. *J. Org. Chem.* **1988**, *53*, 5202. Recently, an asymmetric synthesis from acyclic precursors of (+)-nemorensic acid has been described: (c) Dillon, M. P.; Lee, N. C.; Stappenback, F.; White, J. D. *J. Chem. Soc., Chem. Commun.* **1995**, 1645.

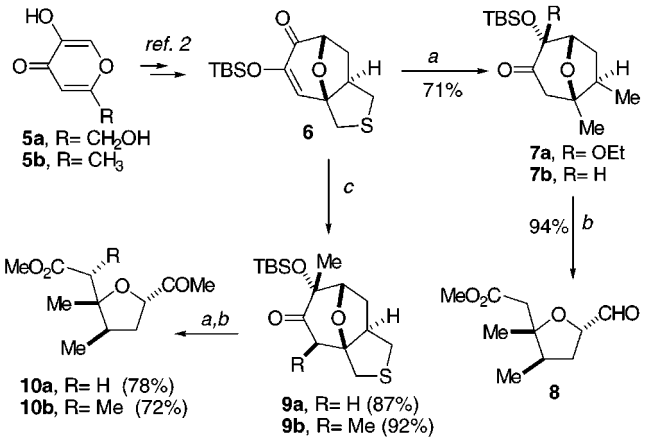
(7) Several strategies based on this type of connection have recently been reported: (a) Bachi, M. D.; Bilokin, Y. V.; Melman, A. *Tetrahedron Lett.* **1998**, *39*, 3035. (b) Castro, J.; Moyano, A.; Pericas, M. A.; Riera, A. *J. Org. Chem.* **1998**, *63*, 3346. See also ref 6a.

(8) It is known that activated Raney nickel can reduce ketones; see: (a) Takahashi, T.; Kitano, K.; Hagi, T.; Nihomantsu, H. *Chem. Lett.* **1989**, 597. (b) Caubére, P.; Coutrut, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds; Pergamon: New York, 1991; Vol. 8, Chapter 4.3 and references given therein.

(9) For a related system, see: Murray, D. M.; Albizati, K. M. *Tetrahedron Lett.* **1990**, *31*, 4109.

10.1021/jo990233c CCC: $18.00
Published on Web 05/26/1999

Scheme 2



(a) Raney Ni, THF, 65°C. (b) *i.* TBAF.3H_2O; *ii.* $Pb(OAc)_4$, MeOH, rt. (c) *i.* MeLi, THF, -78°C; *ii.* H^+ or MeI.

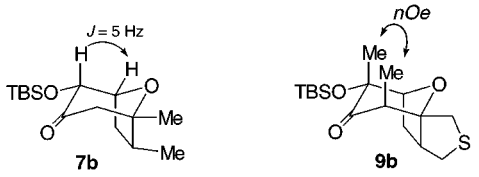
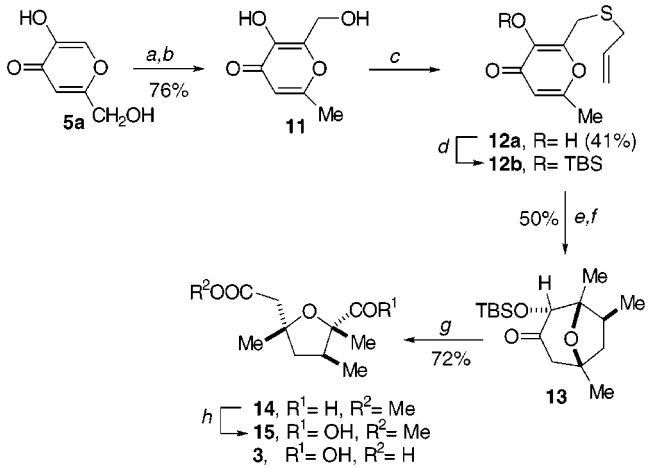


Figure 2.

Because the same type of α-silyloxyketone functionality can be generated by addition of organolithium reagents such as MeLi to cycloadducts such as **6**,[3a] the fragmentation strategy can be extended to obtain tetrahydrofurans with different substitution patterns (Scheme 2). Particularly remarkable is the possibility of introducing stereocenters in the side chain owing to the facial stereochemical bias offered by the oxabicyclic frame. This approach has allowed the stereoselective methylation of the enolate generated in the addition of the organolithium reagent to the enone. The stereochemistry of the dimethylated compound **9b** was ascertained by observation of NOE between the pseudoaxial methyl groups (Figure 2). Overall, the sequence established a succinct route to *cis*-2,5-disubstituted tetrahydrofurans with up to four stereocenters from the inexpensive commercial pyrone kojic acid (**5a**).

Synthesis of (±)-Nemorensic Acid. Nemorensic acid (**3**) is the diacid portion of nemorensine (**4**, Figure 1), a prominent member of the Senecio alkaloid family.[5] Despite the interesting structure and notable biological properties of this type of natural products, few efforts have been made to synthesize their necic acid portions.[6] We realized that the above approach to *cis*-2,5-tetrahydrofurans offered an excellent opportunity for the synthesis of nemorensic acid, provided that the required cycloaddition precursor could be rapidly assembled. Implementation of the strategy required preliminary conversion of kojic acid to the pyrone **11**, which was efficiently carried out in 76% overall yield using known α-deoxygenation[10] and hydroxymethylation procedures.[11] Assembly of the sulfide precursor **12a** was achieved in a single pot by treatment of **11** with $SOBr_2$ in $CHCl_3$,

Scheme 3



(a) *i.* $SOCl_2$, $CHCl_3$, 60°C; *ii.* H_2/Pd, NaOAc, MeOH, rt. (b) KOH, HCHO,H_2O, rt. (c) *i.* $SOBr_2$, $CHCl_3$, rt; *ii.* Et_3N, $HSCH_2CH{=}CH_2$, THF, rt. (d) imidazole, TBSCl, CH_2Cl_2. (e) Toluene, 175°C. (f) Raney Ni, THF, 65°C. (g) *i.* TBAF.3H_2O; *ii.* $Pb(OAc)_4$, MeOH, rt. (h) CrO_3, H_2SO_4, acetone, rt.

replacement of the solvent by THF and addition of allylmercaptan and Et_3N (41% yield).[12] After silylation, the thermal cycloaddition was carried out by heating **12b** in toluene in a sealed tube at 170 °C (60 h, 71% yield). It should be noted that this single reaction generates the three stereocenters of the target molecule. Raney nickel desulfuration of the resulting cycloadduct, with simultaneous carbonyl reduction and TBS migration at the α-silyloxyenone, required heating in THF for 14 h (70% yield). In contrast to the reduction of sulfide **6**, performing this Raney nickel reaction for only 30 min prevents the reduction of the ketone, thereby allowing the dimethylated compound to be obtained with an intact enone portion.

Oxidative cleavage of the carbocycle was best effected by treatment of **13** with TBAF in THF, replacement of the solvent by MeOH, and stirring of the resulting suspension for 60 min with 1.5 equiv of $Pb(OAc)_4$. By means of this process, the desired aldehyde **14** was obtained in 72% yield. The resulting tetrahydrofuran, by virtue of its unsymmetrical oxidation level, might be amenable to differential manipulation at one of the side chains, which is of potential interest for coupling to upper pyrrolizidine portions of the alkaloids. Smooth oxidation of aldehyde **14** with Jones′ reagent led to the acid **15**, and this compound was converted into nemorensic acid (**3**) upon basic aqueous workup (96%, overall yield approximately 10% from kojic acid). The synthesis involved just eight simple synthetic operations, roughly half the number of steps of the previously published approach to the racemic target.

In conclusion, the rich oxygenation and conformational rigidity of the oxabicyclic [5C + 2C] pyrone−alkene adducts offers unique opportunities for speeding up the synthesis of stereochemically rich tetrahydrofurans from simple precursors. We have demonstrated the potential of the route by developing a remarkably concise synthesis of nemorensic acid.

(10) (a) Brown, M. G. *J. Chem. Soc.* **1956**, 2558. (b) Hurd, C. D.; Trofimenko, S. *J. Org. Chem.* **1958**, *23*, 1276.

(11) Ellis, F. L.; Duhme, A. K.; Hider, R. C.; Hossain, M. B.; Rizvi, S.; Van der Helm, D. *J. Med. Chem.* **1996**, *39*, 3659.

(12) Attachment of allylmercaptan to the bromide can be carried out more efficiently (in approximately 85% yield) if the pyrone hydroxyl is protected prior to the reaction as the PMB ether, although this protocol introduces two additional steps into the synthesis.

Experimental Section

General Procedures. All dry solvents were freshly distilled under argon from the appropriate drying agent before use. Toluene and THF were distilled from sodium/benzophenone. CH_2Cl_2 was distilled from P_2O_5. MeOH was distilled from Mg/I_2. All reactions were conducted in dry solvents under argon atmosphere unless otherwise stated. Melting points (open capillary tubes) are uncorreted. Thin-layer chromatography (TLC) was performed on silica gel plates, and components were visualized by observation under UV light or by treating the plates with a phosphomolybdic reagent followed by heating. Flash chromatography was performed on silica gel unless otherwise stated. Dryings were performed with anhydrous Na_2SO_4. Concentrations were carried out in a rotary evaporator. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$, at 250 and 62.9 MHz, respectively, and in some cases at 300 or 500 MHz (75.4 or 125.7 for ^{13}C NMR). Carbon types were determined from DEPT ^{13}C NMR experiments. The following abbreviations are used to indicate signal multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad.

(1*S,4*R**,5*S**,7*R**)-4-[(*tert*-Butyldimethylsilyl)oxy]-1,7-dimethyl-8-oxabicyclo[3.2.1]octan-3-one (7b).** A suspension of activated Raney nickel (1.5 g) was added to a solution of thioether **6** (200 mg, 0.64 mmol) in THF (10 mL). The reaction mixture was refluxed for 2 h, allowed to come to room temperature, filtered, and poured into brine. Extraction with EtOAc, drying, and concentration gave a residue that was purified by flash chromatography (3−7% EtOAc/hexanes) to afford 130 mg of the bicyclic compound **7b** [71%, R_f 0.52 (10% EtOAc/hexanes), viscous oil]: ^{1}H NMR δ 4.36 (1 H, br t, J = 6.1 Hz), 4.18 (1H, br d, J = 5.6 Hz), 2.46 (1H, d, J = 14.6 Hz), 2.36 (1H, d, J = 14.5 Hz), 2.22 (1H, m), 1.94 (1H, m), 1.47 (1H, m), 1.30 (3H, s), 0.92 (3H, d, J = 7.1 Hz), 0.87 (9H, s), 0.11 (3H, s), 0.01 (3H, s); ^{13}C NMR δ 206.4 (C), 84.0 (C), 78.3 (CH), 77.0 (CH), 55.2 (CH_2), 38.6 (CH), 35.4 (CH_2), 25.6 (CH_3), 21.3 (CH_3), 19.0 (CH_3), 18.3 (C), −4.6 (CH_3), −5.5 (CH_3); HRMS calcd for $C_{15}H_{28}O_3Si$ 284.1807, found 284.1809.

Methyl 2-[(2*S,3*R**,5*S**)-5-Formyl-2,3-dimethyltetrahydro-2-furanyl]acetate (8).** ^{n}Bu$_4$NF·3H$_2$O (600 mg, 1.9 mmol) and Pb(OAc)$_4$ (430 mg, 0.97 mmol) were added to a solution of the silyloxyketone **7b** (183 mg, 0.64 mmol) in MeOH (12 mL). After stirring for 30 min, the solution was concentrated, and the residue was partitioned between Et_2O/H_2O (1:1), extracted with Et_2O, dried, filtered, and concentrated. The crude was purified by flash chromatography (7% EtOAc/hexanes) to give 121 mg of the tetrahydrofuran **8** [94%, R_f 0.58 (10% EtOAc/hexanes), viscous oil]: ^{1}H NMR δ 9.64 (1H, s), 4.27 (1H, d, J = 9.0 Hz), 3.67 (3H, s), 2.58 (2H, dd, J = 14.4 Hz), 2.25 (2H, m), 1.85 (1H, m), 1.18 (3H, s), 0.93 (3H, d, J = 6.7 Hz); ^{13}C NMR δ 203.5, 170.9, 84.7, 80.8, 51.5, 44.7, 39.8, 35.0, 21.0, 14.1; HRMS calcd for $C_{10}H_{16}O_4$ 200.23400, found 200.2335.

(1*S,5*R**,7*S**,8*R**)-8-[(*tert*-Butyldimethylsilyl)oxy]-8-methyl-11-oxa-3-thiatricyclo[5.3.1.0^{1,5}]undecan-9-one (9a).** MeLi (2 mL, 3.0 mmol, 1.5 M in THF) was added to a solution of **6** (700 mg, 2.24 mmol) in THF (25 mL) cooled at −78 °C. After stirring for 30 min, the mixture was poured into brine, extracted with Et_2O, dried, filtered, and concentrated. The crude was flash chromatographed (5−7% Et_2O/hexanes) to afford 640 mg of compound **9a** [87%, R_f 0.55 (10% Et_2O/hexanes), viscous oil]: ^{1}H NMR δ 4.07 (1H, d, J = 7.2 Hz), 3.12 (1H, d, J = 12.6 Hz), 2.94 (1H, d, J = 7.8 and 11.2 Hz), 2.8 (1H, d, J = 15 Hz), 2.73 (1H, d, J = 12.6 Hz), 2.51 (1H, dd, J = 7.3 and 11.3 Hz), 2.41 (1H, dd, J = 4.1 and 7.6 Hz), 2.33 (1H, d, J = 15 Hz), 2.20 (1H, dd, J = 13.7 and 8.8 Hz), 1.66 (1H, m), 1.3 (3H, s), 0.75 (9H, s), 0.06 (3H, s), 0.04 (3H, s); ^{13}C NMR δ 207.8 (C), 95.3 (C), 85.3 (CH), 80.7 (C), 50.8 (CH), 49.1 (CH_2), 40.1 (CH_2), 39.4 (CH_2), 33.0 (CH_2), 25.7 (CH_3), 24.2 (CH_3), 18.2 (C), −2.5 (CH_3), −2.7 (CH_3); HRMS calcd for $C_{16}H_{28}O_3SSi$ 328.1528, found 328.1529.

(1*S,5*R**,7*S**,8*R**,10*R**)-8-[(*tert*-Butyldimethylsilyl)oxy]-8,10-dimethyl-11-oxa-3-thiatricyclo[5.3.1.0^{1,5}]undecan-9-one (9b).** MeLi (2 mL, 3.0 mmol, 1.5 M in THF) was added to a solution of **6** (700 mg, 2.24 mmol) in THF (25 mL) cooled at −78 °C. After 10 min of stirring, MeI (180 μL, 2.91 mmol) was added, and the reaction was stirred for 10 h at room temperature. The mixture was poured into brine, extracted with Et_2O, dried, filtered, and concentrated. The crude was flash chromatographed (5−7% Et_2O/hexanes) to afford 705 mg of compound **9b** [92%, R_f 0.61 (10% Et_2O/hexanes), viscous oil]: ^{1}H NMR δ 4.10 (1H, d, J = 7 Hz), 3.0 (2H, m), 2.66 (1H, d, J = 12.7 Hz), 2.4 (4H, m), 1.62 (1H, m), 1.36 (3H, s), 1.2 (3H, d, J = 7.4 Hz), 0.78 (9H, s), 0.1 (3H, s), 0.05 (3H, s); ^{13}C NMR δ 212.7 (C), 97.1 (C), 85.1 (CH), 79.6 (C), 53.9 (CH), 51.1 (CH), 39.3 (CH_2), 38.9 (CH_2), 33.9 (CH_2), 26.2 (CH_3), 25.8 (CH_3), 18.3 (C), 14.9 (CH_3), −2.5 (CH_3), −2.9 (CH_3); HRMS calcd for $C_{17}H_{30}O_3SSi$ 342.568 20, found 342.567 96.

(1*S,4*R**,5*S**,7*R**)-4-[(*tert*-Butyldimethylsilyl)oxy]-1,4,7-trimethyl-8-oxabicyclo[3.2.1]octan-3-one.** A suspension of activated Raney nickel (4 g) was added to a solution of sulfide **9a** (500 mg, 1.53 mmol) in THF (25 mL). The reaction mixture was refluxed for 2 h, allowed to come to room temperature, filtered, and poured into water. Extraction with EtOAc, drying, and concentration gave a residue that was purified by flash chromatography (3−5% EtOAc/hexanes) to afford 371 mg of the expected desulfurized compound [82%, R_f 0.52 (10% Et_2O/hexanes), viscous oil]: ^{1}H NMR δ 3.93 (1H, d, J = 7.2 Hz), 2.54 (1H, d, J = 15 Hz), 2.26 (1H, m), 2.23 (1H, d, J = 14.8 Hz), 1.87 (1H, m), 1.43 (1H, m), 1.41 (3H, s), 1.28 (3H, s), 0.88 (3H, d, J = 8.0 Hz), 0.82 (9H, s), 0.13 (3H, s), 0.09 (3H, s); ^{13}C NMR δ 209.6 (C), 83.9 (C), 82.6 (CH), 80.7 (C), 53.6 (CH_2), 38.3 (CH), 35.8 (CH_2), 25.8 (CH_3), 24.1 (CH_3), 23.7 (CH), 21.3 (CH_3), 18.3 (C), −2.6 (CH_3), −2.8 (CH_3); HRMS calcd for $C_{16}H_{30}O_3Si$ 298.1964, found 298.1969.

Methyl 2-[(2*S,3*R**,5*S**)-5-Acetyl-2,3-dimethyltetrahydro-2-furanyl]acetate (10a).** ^{n}Bu$_4$NF·3H$_2$O (400 mg, 1.27 mmol) and Pb(OAc)$_4$ (280 mg, 0.63 mmol) were added to a solution of the previously obtained silyloxyketone (125 mg, 0.42 mmol) in MeOH (10 mL). After stirring for 30 min, the solution was concentrated, and the residue was partitioned between CH_2Cl_2/H_2O (1:1), extracted with CH_2Cl_2, dried, filtered, and concentrated. The residue was purified by flash chromatography (5% EtOAc/hexanes) to give 86 mg of the tetrahydrofuran **10a** [96%, R_f 0.58 (10% EtOAc/hexanes), viscous oil]: ^{1}H NMR δ 4.30 (1H, dd, J = 9.4 and 3.5 Hz), 3.66 (3H, s), 2.58 (2H, dd, J = 8.1 Hz), 2.19 (2H, m), 2.16 (3H, s), 1.90 (1H, m), 1.15 (3H, s), 0.94 (3H, d, J = 6.3 Hz); ^{13}C NMR δ 210.5 (C), 170.9 (C), 84.6 (C), 81.2 (CH_3), 51.5 (CH), 44.9 (CH_2), 39.7 (CH_3), 35.9 (CH_2), 26.1 (CH), 20.5 (CH_3), 19.1 (CH_3); HRMS calcd for $C_{11}H_{18}O_4$ 214.26082, found 214.26103.

(1*S,2*R**,4*R**,5*S**,7*R**)-4-[(*tert*-Butyldimethylsilyl)oxy]-1,2,4,7-tetramethyl-8-oxabicyclo[3.2.1]octan-3-one.** Same procedure as for sulfide **9a** [78%, R_f 0.71 (10% Et_2O/hexanes), viscous oil]: ^{1}H NMR δ 3.85 (1H, d, J = 7.6 Hz), 2.34 (1H, dd, J = 9.1 and 13.4 Hz), 2.24 (1H, q, J = 7.5 Hz), 1.83 (1H, m), 1.38 (3H, s), 1.35 (1H, m), 1.15 (3H, d, J = 7.5 Hz), 1.13 (3H, s), 0.92 (3H, d, J = 7.0 Hz), 0.81 (9H, s), 0.11 (6H, s); ^{13}C NMR δ 214.3 (C), 84.3 (C), 82,5 (CH), 79.6 (C), 56.7 (CH), 40.1 (CH), 35.1 (CH_2), 25.8 (CH_3), 25.5 (CH_3), 18.8 (CH_3), 18.3 (C), 17.2 (CH_3), 14.6 (CH_3), −2.0 (CH_3), −2.9 (CH_3).

(1*R,2*R**,3*R**,5*S**)-2-[1′-(Methoxycarbonyl)ethyl]-2,3-dimethyl-5-acetyltetrahydrofuran (10b).** Same procedure as used for **10a**, but starting from the desulfurized compound obtained in the preceding experiment. **10b** [92%, R_f 0.68 (10% EtOAc/hexanes), viscous oil]: ^{1}H NMR δ 4.27 (1H, d, J = 9.6 Hz), 3.65 (3H, s), 2.69 (1H, q, J = 7.1 Hz), 2.28 (2H, m), 2.14 (3H, s), 1.89 (1H, m), 1.24 (3H, d, J = 7.1 Hz), 1.09 (3H, s), 0.90 (3H, d, J = 6.4 Hz); ^{13}C NMR δ 210.1, 174.7, 86.5, 80.8, 51.4, 48.9, 39.8, 36.7, 25.9, 17.2, 15.1, 12.9; HRMS calcd for $C_{12}H_{20}O_4$ 228.1361, found 228.1362.

2-[(Allylsulfanyl)methyl]-3-hydroxy-6-methyl-4*H*-4-pyranone (12a). $SOBr_2$ (0.1 mL, 1.3 mmol) was added to a solution of **11** (100 mg, 0.641 mmol) in $CHCl_3$ (10 mL) cooled at 0 °C. The mixture was stirred at room temperature for 30 min, and the solvent was evaporated in the rotary evaporator without heating. The residue was dissolved in THF (15 mL), and allylmercaptan (0.4 mL, 5.6 mmol) and Et_3N (0.4 mL, 5.6 mmol) were slowly added. After stirring for 24 h at room temperature, the mixture was poured into water, extracted with CH_2Cl_2, dried, filtered and concentrated. The crude was flash chromatographed on silica gel (50% EtOAc/hexanes) to afford 56 mg of **12a** as a white solid [41%, R_f 0.23 (50% EtOAc/hexanes), mp 97−99 °C]: ^{1}H NMR δ 7.05 (1H, br s), 6.15 (1H, s), 5.72 (1H, m), 5.08 (2H, m), 3.62 (2H, s), 3.11 (2H, d, J = 6 Hz), 2.27 (3H, s); ^{13}C NMR 173.8 (C), 165.5 (C), 147.5 (C), 141.5 (C), 133.3 (CH), 117.9 (CH_2),

110.6 (CH), 34.9 (CH_2), 26.9 (CH_2), 20.1 (CH_3); HRMS calcd for $C_{10}H_{12}O_3S$ 212.0524, found 212.0528.

2-[(Allylsulfanyl)methyl]-3-[(*tert*-butyldimethylsilyl)-oxy]-6-methyl-4*H*-4-pyranone (12b). A mixture of compound **12a** (300 mg, 1.415 mmol), TBSCl (320 mg, 2.12 mmol), and imidazole (178 mg, 2.61 mmol) in CH_2Cl_2 (15 mL) was stirred at room temperature for 30 min. The resulting solution was poured into brine and extracted with CH_2Cl_2. Drying, filtering, and concentration gave a residue that was purified by flash chromatography on silica gel (6−8% EtOAc/ hexanes) to afford 438 mg of compound **12b** as a colorless oil [95%, R_f 0.5 (50% EtOAc/hexanes)]: ^{1}H NMR δ 6.07 (1H, s), 5.78 (1H, m), 5.03 (2H, m), 3.62 (2H, s), 3.19 (2H, d, J = 6 Hz), 2.21 (3H, s), 0.90 (9H, s), 0.20 (6H, s); ^{13}C NMR 174.7 (C), 163.5 (C), 153.1 (C), 141.3 (C), 133.5 (CH), 117.7 (CH_2), 113.1 (CH), 35.4 (CH_2), 27.3 (CH_2), 26.0 (CH_3), 19.6 (CH_3), 18.8 (C), −3.7 (CH_3); HRMS calcd for $C_{16}H_{26}O_3SSi - CH_3$ 311.1154, found 311.1160.

(1*S,5*S**,7*R**)-9-[(*tert*-Butyldimethylsilyl)oxy]-7-methyl-11-oxa-3-thia-tricyclo[5.3.1.0^{1,5}]undec-8-en-10-one.** A solution of thioether **12b** (970 mg, 2.98 mmol) in toluene (25 mL) was heated in a sealed tube at 170 °C for 60 h. The solvent was evaporated, and the residue was flash chromatographed (5% Et_2O/hexanes) to afford 690 mg of the desired cycloadduct [71%, R_f 0.7 (25% EtOAc/hexanes)]: ^{1}H NMR δ 6.11 (1H, s), 3.56 (1H, d, J = 12.5 Hz), 3.10 (1H, dd, J = 7.9 and 8.5 Hz), 2.81 (1H, d, J = 12.5 Hz), 2.75 (2H, m), 2.28 (1H, dd, J = 7.6 and 8.7 Hz), 1.68 (1H, m), 1.54 (3H, s), 0.92 (9H, s), 0.13 (6H, s); ^{13}C NMR 193.5 (C), 145 (C), 132 (CH), 99.3 (C), 82.7 (C), 51.5 (CH), 43.6 (CH_2), 37.7 (CH_2), 35.7 (CH_2), 25.5 (CH_3), 24.2 (CH_3), 18.3 (C), −4.7 (CH_3); HRMS calcd for $C_{16}H_{26}O_3SSi - CH_3$ 311.1154, found 311.1159.

(1*S,2*R**,5*R**,7*R**)-2-[(*tert*-Butyldimethylsilyl)oxy]-1,5,7-dimethyl-8-oxabicyclo[3.2.1]octan-3-one (13).** A suspension of activated Raney nickel (1.4 g) was added to a solution of the previously obtained thioether (100 mg, 0.306 mmol) in THF (7 mL). The reaction mixture was refluxed for 14 h, allowed to come to room temperature, filtered, and poured into water. Extraction with EtOAc, drying, and concentration gave a residue that was purified by flash chromatography (5% EtOAc/hexanes) to afford 64 mg of the bicyclic compound **13** [70%, R_f 0.52 (10% EtOAc/ hexanes), colorless oil]: ^{1}H NMR δ 3.91 (1H, s), 2.55 (1H, d, J = 14 Hz), 2.31 (1H, d, J = 13.8 Hz), 2.05−2.21 (3H, m), 1.38 (3H, s), 1.27 (3H, s), 0.9 (3H, d, J = 7.5 Hz), 0.89 (9H, s), 0.15 (3H, s), −0.01 (3H, s); ^{13}C NMR δ 206.6 (C), 86.9 (C), 83.1 (CH), 80.2 (C), 53.7 (CH_2), 46.8 (CH_2), 35.4 (CH_3), 26.3 (CH_3), 25.8 (CH_3), 19.6 (CH_3), 19 (CH_3), 18.4 (C), −4.1 (CH_3), −4.3 (CH_3); HRMS calcd for $C_{16}H_{30}O_3Si$ 298.1964, found 298.1968.

Methyl 2-[(2*R,4*S**,5*S**)-5-Formyl-2,4,5-trimethyltetrahydro-2-furanyl]acetate (14).** TBAF·$3H_2O$ (232 mg, 0.888 mmol) was added to a solution of **27** (120 mg, 0.402 mmol) in THF (10 mL). After 30 min of stirring at room temperature, the solvent was evaporated, and the residue was dissolved in MeOH (9 mL). $Pb(OAc)_4$ (197 mg, 0.444 mmol) was added, and the mixture was stirred for 60 min at room temperature. The mixture was concentrated, poured into brine, extracted with Et_2O, dried, filtered, and concentrated. The residue was purified by chromatography (10−12% EtOAc/hexanes) to give 59 mg of the desired aldehyde **14** as a colorless oil [72%, R_f 0.4 (25% EtOAc/ hexanes)]: ^{1}H NMR δ 9.45 (1H, s), 3.62 (3H, s), 2.50 (2H, s), 2.34 (2H, m), 1.71 (1H, m), 1.54 (3H, s), 1.1 (3H, s), 0.91 (3H, d, J = 6.9 Hz); ^{13}C NMR δ 202.6 (CH), 170.9 (C), 88.3 (C), 81.9 (C), 51.5 (CH_3), 46.1 (CH_2), 44.4 (CH_2), 36.8 (CH_3), 28.5 (CH_3), 16.6 (CH_3), 13.0 (CH_3); HRMS calcd for $C_{11}H_{18}O_4$ 214.1205, found 214.1210.

(2*S,3*S**,5*R**)-2,3,5-trimethyl-5-[(methyloxycarbonyl)-methyl]-tetrahydro-2-furancarboxylic Acid (15) and Nemorensic Acid (3).** Jones′ reagent (0.6 mL, 0.74 mmol), freshly prepared by dissolving CrO_3 (2 g) and concentrated H_2SO_4 (1.72 mL) in acetone (8 mL), was added to a solution of aldehyde **14** (40 mg, 0.187 mmol) in acetone (6 mL). After stirring for 15 min, the mixture was concentrated, and the residue was poured into water. Extraction with EtOAc, drying, filtering, and concentration gave a residue that was flash chromatographed on silica gel (EtOAc) to give 41 mg of acid **15** as a colorless oil [97%, R_f 0.4 (EtOAc)]: ^{1}H NMR δ 10−11 (1H, br s), 3.74 (3H, s), 2.48 (3H, m), 2.06 (1H, m), 1.7 (1H, t, J = 12 Hz), 1.34 (3H, s), 1.28 (3H, s), 1.08 (3H, d, J = 7 Hz); ^{13}C NMR δ 175.6 (C), 172.2 (C), 86.0 (C), 81.3 (C), 52.4 (CH_3), 46.7 (CH_2), 45.3 (CH_2), 40.7 (CH_3), 27.8 (CH_3), 19.6 (CH_3), 12.8 (CH_3).

Alternatively, if the residue of the oxidation reaction is stirred with an aqueous NaOH solution (5% NaOH), poured into aqueous HCl (10%), and extracted with EtOAc, 37 mg of nemorensic acid (**3**) were obtained as a white solid (99%) that was recrystallized from Et_2O (mp 143−145 °C): ^{1}H NMR (CD_3OD) δ 2.45−2.60 (2H, m), 2.37 (1H, d, J = 14 Hz), 2.13 (1H, dd, J = 13 and 7 Hz), 1.6 (1H, t, J = 12.5 Hz), 1.32 (3H, s), 1.22 (3H, s), 1.05 (3H, d, J = 7 Hz); ^{1}H NMR [$(CD_3)_2SO$] δ 2.48−2.60 (2H, m), 2.38 (1H, d, J = 14 Hz), 2.21 (1H, dd, J = 12.5 and 6.7 Hz), 1.53 (1H, t, J = 12.2 Hz), 1.27 (3H, s), 1.13 (3H, s), 0.99 (3H, d, J = 6.7 Hz); ^{13}C NMR (CD_3OD) δ 180 (C), 175.5 (C), 87.2 (C), 82.9 (C), 46.7 (CH_2), 46.4 (CH_2), 42.1 (CH_3), 28.1 (CH_3), 21.0 (CH_3), 14.6 (CH_3); LRMS m/z 111 (25), 109 (16), 107 (20), 83 (26), 72 (45), 69 (28), 67 (13), 57 (12), 55 (20). The ^{1}H NMR spectral data for the compound we obtained were fully consistent with those provided by one of the groups that previously synthesized nemorensic acid.[6c]

Acknowledgment. This work was supported by the Xunta de Galicia (XUGA 20901A94 and 20906B96) and by the Spanish Ministry of Education and Culture (PB97-0524). J.R.R. and A. R. thank the Xunta de Galicia for research grants. We also thank R. Gesto for running the NMR experiments and Prof. J. D. White for providing NMR data for nemorensic acid.

Supporting Information Available: Procedure for the preparation of **11**. Copies of ^{1}H and ^{13}C NMR spectra for selected products and lists of mass spectra and IR data. This material is available free of charge via the Internet at http://pubs.acs.org.

JO990233C