Wacker oxidation of **3a** was then readily accomplished under Tsuji's conditions[9] to give dione **3b**[8,10] in 79% yield. In contrast to the aldol condensation of related cyclopentanones,[6] aldol cyclization of cyclohexanone **3b** with potassium *tert*-butoxide in *tert*-butyl alcohol afforded only the conjugated product **4**[8] (84% yield).

It was hoped that enone **4** might be made to suffer a palladium-hydrogen-induced migration of the double bond from the Δ^3 to the alternative tetrasubstituted, conjugated position. From previous studies it was known that the entering and leaving hydrogens are generally cofacial in this type of transformation,[11] and *thus a successful* $\Delta^3 \rightarrow \Delta^{3a(7a)}$ *migration was expected to deliver not only the required double bond isomer but also the necessary trans relationship at C-3 and C-7.* In the event, this key conversion proceeded readily to give *exclusively* the trans[12] product **5a**,[8] which under optimal conditions could be isolated in up to 63% yield. This means of transferring the relative stereochemistry generated through conjugate addition to the allylic (or other) substituents in cyclized products should be of general value.

The completion of the synthesis could be easily achieved. Hydrindenone **5a** was dimethylated with lithium diisopropylamide and methyl iodide in tetrahydrofuran to produce in 84% yield brasilenone,[8] which for steric reasons on reduction with lithium triethylborohydride afforded only racemic brasilenol,[8] mp 63-64 °C, in 92% yield. Spectral comparison of this material with the natural substance established unambiguously its identity.

Application of the same efficient sequence of reactions to (*R*)-(−)-cryptone,[13] secured from 4-isopropylcyclohexanone by using Koga's elegant enantioselective deprotonation-oxidation procedure,[14] readily produced optically pure (+)-brasilenol.[8] Thus, (+)-brasilenol has the absolute stereochemistry 3*R*,4*S*,7*R*.[4]

In summary, a concise, highly stereocontrolled route to brasilenol from cryptone has been developed based on a novel asymmetry transfer reaction. The synthesis establishes for the first time the absolute stereochemistry of the marine natural product as well as that of two congeneric metabolites.

Acknowledgment. Dr. J. L. Luche is thanked for his interest in this work and V. J. Paul for having supplied the spectra of brasilenone and brasilenol. Financial support from the CNRS (France) and the CNPq (Brazil) and fellowship awards from the CNPq to A.A.S. and P.R.R.C. are gratefully acknowledged.

Supplementary Material Available: Experimental procedures for compounds 1 and **3-5** (4 pages). Ordering information is given on any current masthead page.

(8) **2** → **3a**: To 8.27 g of CuI in 19 mL of THF at −20 °C was added 3-butenylmagnesium bromide in THF (from 8.9 mL of 4-bromo-1-butene and 2.11 g of Mg in 180 mL of THF). After 30 min, 3.00 g of **2** in 54 mL of THF was added and the mixture was stirred at 0 °C (2 h) and then processed as usual to give **3a** (4.10 g, 97%): IR (film) 3060, 1715, 1638, 995, 910 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.78 (m, 1 H), 5.00 (m, 2 H), 0.99 (d, J = 6.5 Hz, 3 H), 0.82 (d, J = 6.5 Hz, 3 H); mass spectrum, m/e 195 ($M^+ + 1$). Anal. ($C_{13}H_{22}O$) C, H. (+)-**3a** (ca. 65% ee): $[\alpha]^{26}_D$ +22° (c 4.6, $CHCl_3$). **3a** → **3b**: Under O_2, 401 mg of $PdCl_2$ and 6.76 g of CuCl in 68 mL of DMF-H_2O (7:1) were stirred 2 h and then treated with 2.20 g of **3a** in 23 mL of THF. After 3 h, normal isolation gave **3b** (1.87 g, 79%): IR (film) 1710, 1360, 1160 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.15 (s, 3 H), 0.99 (d, J = 6.8 Hz, 3 H), 0.84 (d, J = 6.8 Hz, 3 H); mass spectrum, m/e 211 ($M^+ + 1$). Anal. ($C_{13}H_{22}O_2$) C, H. (+)-**3b** (ca. 65% ee): $[\alpha]^{26}_D$ + 24° (c 4.6, $CHCl_3$). **3b** → **4**: Dione **3b** (105 mg) was stirred with 160 mg of *t*-BuOK in 10 mL of *t*-BuOH for 15 min to give after processing **4** (81 mg, 84%). **4**: IR (film) 1680, 1620, 1260, 1195, 930 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.75 (m, 1 H), 2.08 (m, 3 H), 0.97 (d, J = 6.9 Hz, 3 H), 0.84 (d, J = 6.9 Hz, 3 H); mass spectrum, m/e 193 ($M^+ + 1$). Anal. ($C_{13}H_{20}O$) C, H. (+)-**4** (ca. 65% ee): $[\alpha]^{26}_D$ +21° (c 5.1, $CHCl_3$). **4** → **5a**: Enone **4** (100 mg) was slowly stirred for 2.5 h with 50 mg of 10% Pd-C in 4 mL of benzene at 60 °C under H_2 to give after purification **5a**[3] (63 mg, 63%). **5a**: IR (film) 1660, 1615, 1380, 1200 cm^{-1}; ^1H NMR (C_6D_6, 300 MHz) δ 3.15 (m, 1 H), 1.26 (d, J = 6.9 Hz, 3 H), 0.72 (d, J = 6.8 Hz, 3 H), 0.54 (d, J = 6.8 Hz, 3 H); mass spectrum, m/e 192 (M^+). (+)-**5a** (two recrystallizations from pentane): mp 45-46 °C; $[\alpha]^{21}_D$ + 21.6° (c 1.7, $CHCl_3$). **5a** → **5b**:[3] 84% yield. (+)-**5b**: $[\alpha]^{21}_D$ +44.2° (c 0.6, $CHCl_3$) [lit.[1a] $[\alpha]^{21}_D$ +40.9° (c 0.95, $CHCl_3$)]. **5b** → **1**:[3] 92% yield. (+)-**1**: mp 55-56 °C (lit.[1a] mp 55-56 °C); $[\alpha]^{21}_D$ +44.0° (c 1.2, $CHCl_3$) [lit.[1a] $[\alpha]^{21}_D$ +33.4° (c 1.58, $CHCl_3$)].

(9) Tsuji, J.; Shimizu, I.; Yamamoto, K. *Tetrahedron Lett.* **1976**, 2975-2976. Tsuji, J.; Nagashima, H.; Nemoto, H. *Org. Synth.* **1984**, *62*, 9-13.

(10) This product was also obtained, but less satisfactorily, by conjugate addition of [3,3-(ethylenedioxy)butyl]magnesium iodide followed by acid hydrolysis.[6]

(11) Rylander, P. N. *Catalytic Hydrogenation in Organic Syntheses*; Academic: New York, 1979; pp 36-38, 290. Dana, G.; Weisbuch, F.; Drancourt, J. M. *Tetrahedron.* **1985**, *41*, 1233-1239.

(12) The complete absence of the corresponding cis isomer was confirmed through comparison (TLC, NMR) with an authentic cis sample. It should be noted that there is little difference in energy between the cis and trans isomers (ca. 1:1 after rhodium chloride catalyzed equilibration).[3]

(13) See: Klyne, W.; Buckingham, J. *Atlas of Stereochemistry*; Chapman and Hall: London, 1974; p 78.

(14) Shirai, R.; Tanaka, M.; Koga, K. *J. Am. Chem. Soc.* **1986**, *108*, 543-545. (*R*)-(+)-*N*-Isopropyl-*N*-(1-phenylethyl)amine was employed and gave (*R*)-(−)-cryptone with an enantiomeric excess of ca. 65%. [See: Galloway, A. S.; Dewar, J.; Reed, J. *J. Chem. Soc.* **1936**, 1595-1597. (−)-Cryptone can also be obtained by resolution (Soffer, M. D.; Gunay, G. E. *Tetrahedron Lett.* **1965**, 1355-1358) and from *Eucalyptus* oils (Cahn, R. S.; Penfold, A. R.; Simonsen, J. L. *J. Chem. Soc.* **1931**, 1366-1369).] Two recrystallizations of (+)-**5a** from pentane efficiently provided optically pure material [^1H NMR with Eu(hfc)$_3$] for the completion of the synthesis.

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Received November 12, 1986

A Versatile Protocol for the Stereocontrolled Elaboration of Vicinal Secondary and Tertiary Centers of Relevance to Natural Product Synthesis

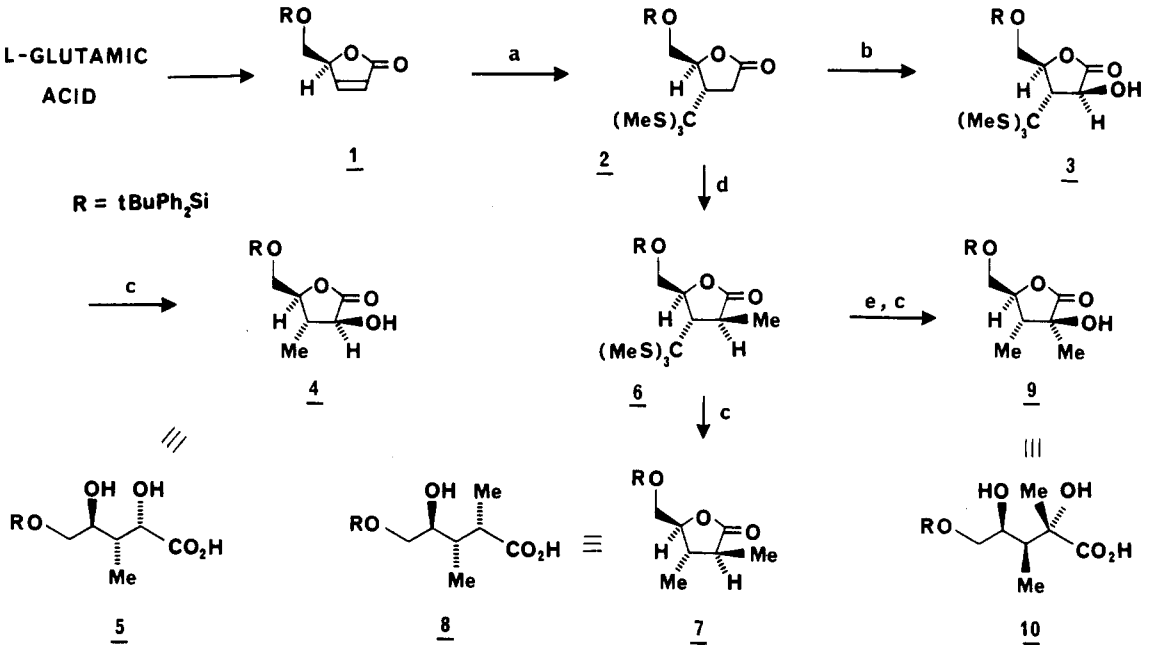
Summary: Chiral butenolides derived from L-glutamic acid, D-ribonolactone, or D-mannitol are versatile templates from the stereocontrolled introduction of functional groups. Vicinal and/or alternating patterns of secondary and tertiary substitution can be attained with a high degree of prediction.

Sir: Especially challenging to the synthetic chemist are those structures which possess sequences of consecutive, highly functionalized carbon atoms, a situation frequently encountered in many natural products.[1] Despite dramatic developments in acyclic stereoselection, most notably via

(1) See, for example: Paterson, I.; Mansuri, M. M. *Tetrahedron* **1985**, *41*, 3569. Wierenga, W. In *The Total Synthesis of Natural Products*; ApSimon, J. A., Ed.; Wiley-Interscience: New York, 1981; Vol. 4, p 263.

0022-3263/87/1952-1170$01.50/0

Scheme I[a]



[a] (a) $(MeS)_3CLi$, THF, −78 °C, 0.5 h, 86%; (b) LiHMDS, THF, −78 °C 0.5 h, then MoOPH, 50 °C, 1 h, 86%; (c) Raney Ni, THF/MeOH (4:1), reflux, 2 h, 60–65%; (d) LiHMDS, THF, −78 °C, 0.5 h, then MeI, −78 °C, 0.5 h, 91%; (e) KHMDS, THF, HMPA, −60 to −65 °C, 1.5 h, then MoOPH, −50 °C, 1 h, 77%.

the aldol condensation,[2] efficient and general methods are still sought for the construction of optically pure structural units that contain vicinal, stereochemically well-defined secondary and tertiary centers. Although methods are available for the elaboration of isolated tertiary and quaternary centers,[3] few address the problem of consecutive substitution, particularly those containing vicinal carbon substituents.[4] In some instances, recourse has been made to the degradation of naturally occurring terpenes[5] in order to obtain such subunits.

Recently we revealed how a "replicating lactone template" derived from L-glutamic acid permits the stereocontrolled synthesis of molecules containing remote 1,5-, 1,4-, or alternating 1,3-substitution patterns.[6] We now report that the butenolide **1** readily available in optically pure form[6,7] is an excellent chiral synthon (chiron)[8] for the extension of this methodology to vicinal 1,2-substituted systems (Scheme I).

Conjugate addition of [tris(methylthio)methyl]lithium[9] to the readily available butenolide **1**, mp 83–84 °C, $[\alpha]_D$ −85.2° (*c* 1.2, $CHCl_3$),[10] gave the butyrolactone derivative **2**, mp 140–142 °C, $[\alpha]_D$ +20.5° (*c* 1.1, $CHCl_3$) as the exclusive adduct. Having introduced a bulky substituent at C_3 in compound **2**, it was anticipated that the approach of electrophiles on the corresponding enolate would be directed from the β-face.[11] In fact, hydroxylation of the enolate of **2** with MoOPH[12,13] proceeded with complete stereocontrol to give the 2-hydroxy lactone **3**, $[\alpha]_D$ +8.1° (*c* 1.3, $CHCl_3$). Desulfurization of **3** with Raney nickel yielded **4**, $[\alpha]_D$ +12.5° (*c* 2.2, $CHCl_3$).[14] Likewise, alkylation of **2** with methyl iodide provided **6**, mp 74–75 °C, $[\alpha]_D$ +22.4° (*c* 2.8, $CHCl_3$), as a single isomer. Desulfurization with Raney nickel afforded **7**, mp 69–70 °C; $[\alpha]_D$ +15.6° (*c* 2.1, $CHCl_3$).

Using a sequential alkylation–hydroxylation protocol, it was possible to introduce stereochemically pure tertiary centers at C_2. Formation of the enolate of **6** using potassium hexamethyldisilazide in a mixture of THF–HMPA,

(2) See, for example: Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3 III. Evans, D. A.; Nelson, J. V.; Taber, T. R. In *Topics in Stereochemistry*; Eliel, E., Allinger, N. L. *Wilen*, S. H., Eds.; Wiley; New York, 1982; Vol. 13, p 1. Hoffmann, R. W. *Angew Chem. Int. Ed. Engl.* **1982**, *21*, 555. Masamune, S.; Choy, W. *Aldrichimica Acta* **1982**, *15*, 47. Mukaiyama, T. *Org. React.* (*N.Y.*) **1982**, *28*, 203.

(3) See, for example: Martin, S. F. *Tetrahedron Lett.* **1985**, *26*, 903. Tomioka, K.; Takano, S.; Yonaga, M.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1981**, 1153. Tomioka, K.; Cho, Y. S.; Sato, F.; Koga, K. *Chem. Lett.* **1981**, 1621.

(4) For recent examples, see: Tomioka, K.; Tamaka, M.; Koga, K. *Tetrahedron Lett.* **1982**, *23*, 3401. Takano, S.; Tamura, N.; Ogasawara, K.; Nakagawa, Y.; Sakai, T. *Chem. Lett.* **1982**, 933.

(5) Kokke, W. C. M. C.; Varkevisser, F. A. *J. Org. Chem.* **1974**, *39*, 1535. Hill, R. K.; Foley, P. J., Jr.; Gardella, L. A. *J. Org. Chem.* **1967**, *32*, 2330.

(6) Hanessian, S.; Murray, P. J.; Sahoo, S. P. *Tetrahedron Lett.* **1985**, *26*, 5623, 5627.

(7) For syntheses of the corresponding 5-trityl ether and 5-*tert*-butyldimethylsilyl ether, see: Ireland, R. E.; Anderson, R. C.; Badoud, R.; Fitzsimmons, B. J.; McGarvey, G. J.; Thaisrivong, S.; Wilcox, C. S. *J. Am. Chem. Soc.* **1983**, *105*, 1988. Atwood, S. V.; Barrett, A. G. M. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1315; *J. Am. Chem. Soc.* **1983**, *105*, 1988. Mann, J.; Thomas, A. *J. Chem. Soc., Chem. Commun.* **1985**, 737. Takano, S.; Kurotaki, A.; Takahashi, M.; Ogasawara, K. *Synthesis* **1986**, 403. Danilova, G. A.; Mel'nikoya, V. I.; Pivnitsky, K. K. *Tetrahedron Lett.* **1986**, *27*, 2489. Tomioka, K.; Ishiguro, T.; Koga, K. *Tetrahedron Lett.* **1980**, *21*, 2973 and references cited therein.

(8) Hanessian, S. *Total Synthesis of Natural Products–The Chiron Approach*; Baldwin, J. E., Ed.; Pergamon Press: Oxford, England, 1983.

(9) Damon, R. E.; Schlessinger, R. H. *Tetrahedron Lett.* **1976**, 1561.

(10) All new compounds were fully characterized by spectroscopic (400-MHz ^1H NMR, MS) techniques.

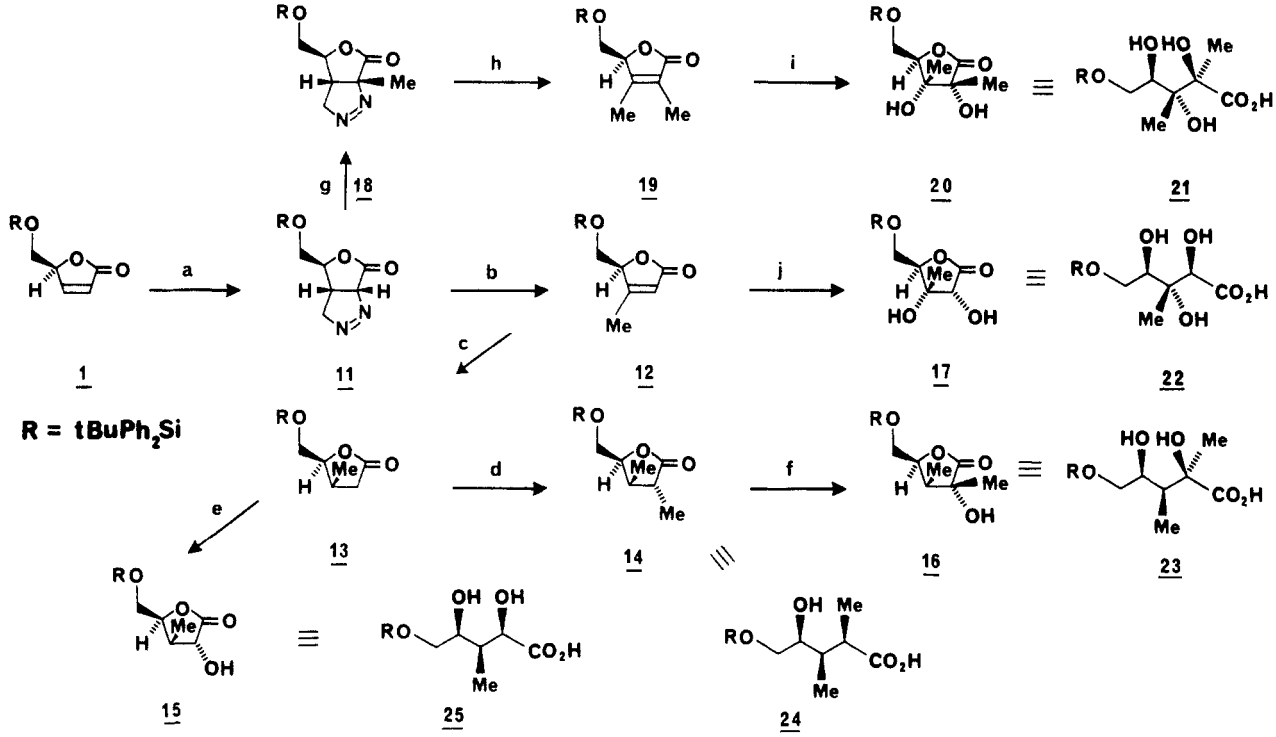
(11) For some other examples, see ref 6. See also: Vigneron, J. P.; Meric, R.; Larcheveque, M.; Debal, A.; Lallemand, J. Y.; Kunesch, G.; Zagatti, P.; Gallois, M. *Tetrahedron* **1984**, *40*, 3521. Charkraborty, T. K.; Chandrasekaran, S. *Tetrahedron Lett.* **1984**, *25*, 2891. See also the last citation in ref 7. See also: Stork, G. *15th IUPAC International Symposium on the Chemistry of Natural Products*, The Hague: The Netherlands, Aug 17–22, 1986; Pure and Appl. Chem., (in press).

(12) Vedejs, E.; Larsen, S. *Org. Synth.* **1986**, *64*, 127.

(13) Hanessian, S.; Sahoo, S. P.; Murray, P. J.; *Tetrahedron Lett.* **1985**, *26*, 2631. Takano, S.; Morimoto, M.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1984**, 82.

(14) When butenolide **1** was treated with lithium dimethylcuprate and the resulting 3-methyl derivative,[6] subjected to enolate formation then hydroxylation with MoOPH, compound **4** was formed together with its C_2 epimer (2:1 ratio, respectively).

Scheme II[a]



[a] (a) CH_2N_2, Et_2O, room temperature, 1 day, quant.; (b) toluene, $CaCO_3$, reflux, 3 h, 92%; (c) H_2, 50 psi, 10% Pd/Al_2O_3, EtOAc, room temperature, 1 h, quant.; (d) LiHMDS, THF, −78 °C, 0.5 h, then MeI, −78 °C, 0.5 h, 90%; (e) LiHMDS, THF, −78 °C, 0.5 h, then MoOPH, −50 °C, 1 h, 83%; (f) KHMDS, THF, −78 sC, 1 h, then MoOPH, −50 °C, 1 h, 86%; (g) LiHMDS, THF, −78 °C, 0.5 h, then MeI, −78 °C to −40 °C, 0.5 h, quant.; (h) toluene, $CaCO_3$ reflux, 2 h, 84%; (i) 4-methylmorpholine *N*-oxide, OsO_4, 0.1 equiv, THF, *t*-BuOH, H_2O, room temperature, 4 days, 72%; (j) as for i, room temperature, 1 day, 88%.

followed by treatment with MoOPH, led to the corresponding hydroxy lactone as the sole product, $[\alpha]_D$ +52.4° (*c* 1.9, $CHCl_3$). Desulfurization afforded the lactone **9**, $[\alpha]_D$ +23.5° (*c* 1.3, $CHCl_3$).

The template effect provided by the butenolide **1** could be further exploited to give products having other patterns of vicinal substitution with complete stereochemical control (Scheme II).

Treatment of **1** with diazomethane[15] afforded the crystalline pyrazoline **11**, mp 105–106 °C, $[\alpha]_D$ −215.4° (*c* 1.2, $CHCl_3$). Thermolysis of **11** cleanly afforded the enone **12**, $[\alpha]_D$ −20.0° (*c* 2.6, $CHCl_3$), which on catalytic hydrogenation gave exclusively the lactone **13**, mp 88–89 °C, $[\alpha]_D$ +50.8° (*c* 2.3, $CHCl_3$), which is epimeric at C_3 with a product previously reported by us.[6] With the two substituents in a cooperative, syn arrangement, it was predicted that subsequent reactions at C_2 would be highly stereoselective. In fact, methylation and hydroxylation of **13** gave **14**, mp 75–76 °C, $[\alpha]_D$ +77.3°, (*c* 3.1, $CHCl_3$), and **15**, mp 96–97 °C, $[\alpha]_D$ +90.6° (*c* 4.5, $CHCl_3$), respectively, as the only detectable products. Sequential alkylation and oxidation established a stereochemically homogeneous centre at C_2 providing **16**, $[\alpha]_D$ +45.5° (*c* 5.1, $CHCl_3$).

The pyrazoline **11** could also be readily alkylated to furnish **18**, $[\alpha]_D$ −264° (*c* 1, $CHCl_3$). Thermally induced extrusion of nitrogen yielded the butenolide **19**, $[\alpha]_D$ −20.1° (*c* 1.6, $CHCl_3$). When subjected to catalytic, cis hydroxylation,[17] butenolides **12** and **19** were transformed to the diols **17**, mp 43–45 °C, $[\alpha]_D$ +65.9° (*c* 7.4, $CHCl_3$), and **20**, $[\alpha]_D$ +45.0° (*c* 1.3, $CHCl_3$), respectively, the latter, notably possessing *two contiguous tertiary centres*.

We have demonstrated that the readily available butenolide **1**[6,7] is a versatile chiral template for the synthesis of highly functionalized, enantiomerically pure structural units containing vicinal substituents. It should be noted that the tris(methylthio)methyl group is also known to serve as a carboxyl equivalent.[18] By combining this with other features of functional duality, and with the inherent symmetry of some of the products shown in Schemes I and II, a multitude of substitution patterns are now readily available which are otherwise difficult to access. In order to emphasize this feature, the seco acids corresponding to the lactones are included in the schemes.[19] Enantiomeric compounds corresponding to the ones in Schemes I and II can be prepared from the readily available (*R*)-4-(hydroxymethyl)butenolide.[6,20] It is clear that such structural subunits can be congruent with related segments that are integral parts of many natural products, particularly those derived via the propionate biosynthetic pathway.[21]

Acknowledgment. We thank NSERCC and FCAR for financial assistance. We also thank Roger Lêger, a summer undergraduate research participant, for skillful technical assistance. We acknowledge the help of Dr. G. McCraw and Daniel Dubé in recording NMR spectra at 400 MHz and Michael Evans for mass spectra.

(15) Tomioka, K.; Sato, F.; Koga, K. *Heterocycles* **1982**, *17*, 311. See also: Pelletier, S. W.; Djarmati, Z.; Lajsic, S. D.; Micovic, I. V.; Yang, D. T. C. *Tetrahedron* **1975**, *31*, 1659.

(16) Hydrogenation of the corresponding 5-trityl ether is reported to give a 4:1 mixture of 3-methyl derivatives, see ref 15.

(17) Mukaiyama, T.; Tabusa, F.; Suzuki, K. *Chem. Lett.* **1983**, 173. See also: Schröber, M. *Chem. Rev.* **1980**, *80*, 187.

(18) Gröbel, B. T.; Seebach, D. *Synthesis* **1977**, 357 and references cited therein.

(19) Lactones of the types shown in Schemes I and II can be cleanly converted into the corresponding methyl esters by treatment with (a) aqueous LiOH, THF; (b) aqueous HCl, then CH_2N_2.

(20) Ho, P. T.; Davis, M. *Synthesis* **1983**, 462.

(21) Hanessian, S.; Murray, P. J. *Can. J. Chem.* **1986**, *64*, 2231. See also the last citation in ref 11.

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Received September 17, 1986