acterization of **2a** and **2b**, see Table II.

Preparation of 3a and 3b. The 6-*O*-[(*R*)-2-hydroxypropyl] derivative **3a** was prepared by reacting a solution of 1 (40 g) in 10.7 M aqueous NaOH (160 mL) with (*R*)-propylene oxide (6 mL) at ice-bath temperature for 3 days. The mixture was neutralized (10 M HCl) and dialyzed for 9 H. The retained solution was concentrated (150 mL) and stirred with toluene (25 mL) whereby a mixture of 1 and **3a** precipitated as inclusion complexes with toluene (33.5 g). The complexes were decomposed by removing the toluene by azeotroping with water to give 27 g of residue. The residue, a mixture of 1 and **3a**, was dissolved in water (1215 mL) and stirred with toluene (5.4 mL) for 10 h. Filtration and evaporation of the filtrate gave a mixture (5.9 g) enriched with **3a**. Pure **3a** was then obtained by paper chromatography (Whatman, 3 mm) of the mixture using 1-propanol/1-butanol/water, 5:3:4, as eluent, followed by precipitation of **3a** as a toluene complex giving eventually pure **3a**, in 5% overall yield. Anal. Calcd for $C_{45}H_{76}O_{36}\cdot 7H_2O$: C, 40.96; H, 6.83. Found: C, 40.87; H, 6.75. The 6-*O*-[(*S*)-2-hydroxypropyl] derivative was prepared in a similar manner. Anal. Calcd for $C_{45}H_{76}O_{36}\cdot 7H_2O$: C, 40.96; H, 6.83. Found: C, 40.92; H, 6.79. For further characterization of **3a** and **3b**, see Table II.

Acknowledgment. We thank Dr. H. Fales for the mass spectra and Dr. K. Harata for the structure confirmation of **2a** by single-crystal X-ray analysis.

Registry No. 1, 7585-39-9; **2a**, 130904-74-4; **2b**, 130981-23-6; **3a**, 130904-75-5; **3b**, 130981-24-7; (*R*)-propylene oxide, 15448-47-2; (*S*)-propylene oxide, 16088-62-3; toluene, 108-88-3; phenolphthalein, 77-09-8.

Supplementary Material Available: ^{1}H NMR spectra of compounds **2a**, **2b**, **3a**, and **3b** (4 pages). Ordering information is given on any current masthead page.

Stereoselective Synthesis of an Important Prostaglandin Synthetic Intermediate[1]

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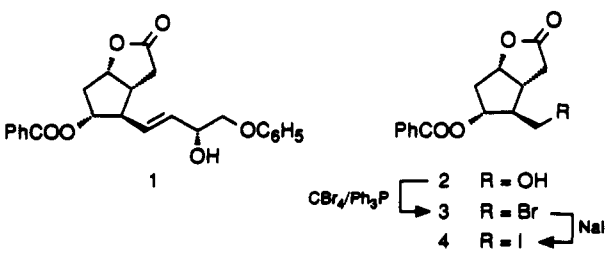
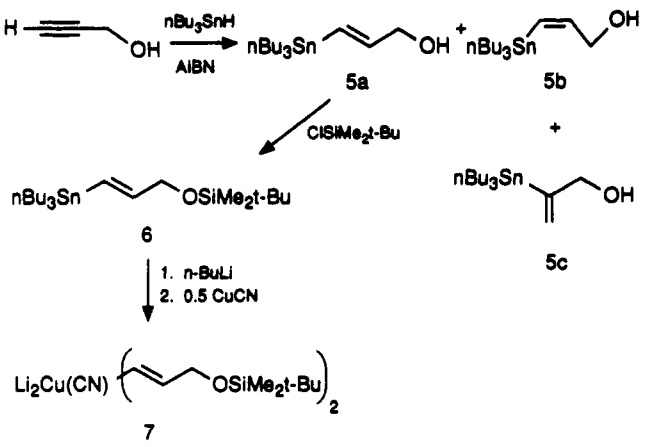
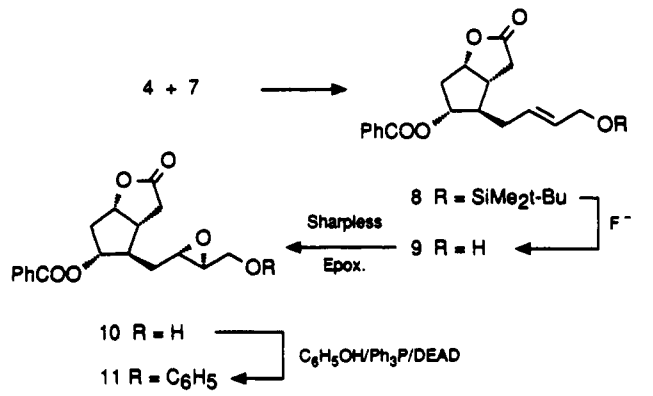
Phenoxy lactone 1[2] and its substituted aromatic congeners are useful in the synthesis of medicinally important prostaglandin analogues.[3] The required *R* configuration of the allylic alcohol in such molecules is usually obtained by hydride reduction of the corresponding α,β-unsaturated ketone.[3,4] In order to obtain high diastereoselectivity in this reduction expensive reagents and very low temperatures (−100 to −120 °C) are required.[5] We required a method which could be conducted on a large scale, would not use expensive reagents, and would avoid the difficult chromatographic separation of even the smallest amount of the allylic alcohol epimer. We report here an approach to such a stereoselective synthesis of 1.



Scheme I



Scheme II



The 1,2-dioxa functionality in the side chain of **1**, which includes the asymmetric alcohol group, suggested the Sharpless asymmetric epoxidation method[6] as a means of introducing the desired stereochemistry. The strategy then was to prepare the α,β-epoxy alcohol **10**, convert it to the phenyl ether **11** and then effect β-elimination of the epoxide to the desired allylic alcohol.

Treatment of lactone benzoate **2**[7] with CBr_4 and Ph_3P in acetonitrile gave the bromide **3**[8] in 90% yield. The bromide was easily converted to the iodide **4** with sodium iodide in acetone in 80% yield. Coupling of iodide **4** with the higher order organocuprate[9] C_3 reagent **7** provided the allylic alcohol needed for the asymmetric epoxidation.

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(1) Contribution number 789 from the Institute of Organic Chemistry, Syntex Research, Palo Alto, CA 94304.
(2) CAS name: [3a*R*-[3aα,4α(1*E*,3*R**),5β,6aα]]-5-(benzoyloxy)hexahydro-4-(3-hydroxy-4-phenoxy-1-butenyl)-2*H*-cyclopenta[*b*]furan-2-one.
(3) US patent 3,985,791 to Syntex; *Chem. Abstr.* **1977**, *86*, 43281k. Schaaf, T. K.; Bindra, J. S.; Eggler, J. F.; Plattner, J. J.; Nelson, A. J.; Johnson, M. R.; Constantine, J. W.; Hess, H. J.; Elger, W. *J. Med. Chem.* **1981**, *24*, 1353.
(4) Corey, E. J.; Becker, K. B.; Varma, R. K. *J. Am. Chem. Soc.* **1972**, *94*, 8616. Iguchi, S.; Nakai, H.; Hayashi, M.; Yamamoto, H. *J. Org. Chem.* **1979**, *44*, 1363. European Patent Appl. EP 219,580 from Upjohn; *Chem. Abstr.* **1988**, *108*, 94282s. Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C. P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925.
(5) Noyori, R.; Tomimo, I.; Nishizawa, M. *J. Am. Chem. Soc.* **1979**, *101*, 5843.
(6) (a) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765. (b) Katsuki, T.; Sharpless, K. B. *Ibid.* **1980**, *102*, 5974.
(7) Corey, E. J.; Schaaf, T. K.; Huber, W.; Koelliker, U.; Weinshenker, N. M. *J. Am. Chem. Soc.* **1970**, *92*, 397.
(8) Satisfactory elemental analyses and spectral data were obtained for 1 (poorly characterized in patent literature) and all new compounds (**3**, **4**, **8**, **9**, **10**, **11**, **12a**, **13**).
(9) (a) Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A.; Parker, D. *J. Org. Chem.* **1984**, *49*, 3928. (b) Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A., *Tetrahedron* **1984**, *40*, 5005.

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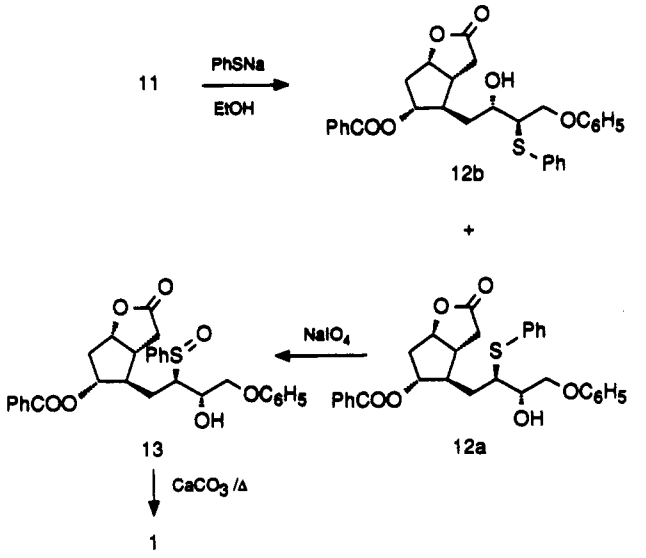
The known *trans*-vinylstannane **6**[10] was required to prepare **7** (Scheme I). Vinylstannanes are commonly prepared by hydrostannylation of acetylenes,[11] and the process is reported to be highly stereoselective in certain cases.[12] However, numerous attempts to prepare **5a** by stereoselective hydrostannylation of propargyl alcohol were unsuccessful.[13] In all cases the cis and vinylidene isomers (**5b** and **5c**) were present in varying amounts (25–30%) even when long reaction times, excess Bu_3SnH/azobisisobutyronitrile (AIBN) and different reaction temperatures were used. The trans isomer **5a** could, however, be isolated from the mixture in 35% yield by simple column chromatography on silica gel. Silylation of **5a** with *tert*-butyldimethylchlorosilane[14] gave **6** in 90% yield. Conversion of **6** to the higher order organocuprate reagent **7** was accomplished in the usual manner with 1 equiv of *n*-BuLi/hexane at −78 °C in tetrahydrofuran (THF) followed by 0.5 equiv of CuCN and warming briefly to 5 °C.[9a] Although bromide **3** failed to react with **7**, iodide **4** reacted with 2 equiv of **7** to give the coupled product **8** in 73% yield (Scheme II). Desilylation of **8** with *n*-Bu_4NF in THF[14] gave allylic alcohol **9** in 93% yield.

Stereoselective epoxidation of **9** by the Sharpless method using L-(+)-diethyl tartrate[6b] gave the desired α-epoxide **10** in 92% yield. Preparation of an authentic mixture of α- and β-epoxides by nonstereoselective epoxidation of **9** with *m*-chloroperbenzoic acid showed that the β-epoxide could easily be detected by NMR. NMR analysis of **10** showed no β-epoxide (±5%). The observed diastereoselectivity is probably the result of cooperative stereoinduction of the reagent and the stereocenters present in **9**.[15] Phenylation of **10** by Mitsunobu coupling with phenol[16] gave **11** in 85% yield.

The final isomerization of **11** to **1** proved to be a problem. What had originally been envisioned as a one-step transformation[17] could not be realized. Most of the reagents reported to effect this isomerization failed with **11**. Thus diethylaluminum 2,2,6,6-tetramethylpiperidide,[18] lithium diisopropylamide,[19] magnesium cyclohexylisopropylamide,[20] methylmagnesium *N*-cyclohexylisopropylamide[21] and iodotrimethylsilane/1,8-diazabicyclo[5.4.0]undec-7-ene[22] all either reacted with the lactone ring (deprotonation) or opened the epoxide without giving any **1**.

Epoxide **11** was converted to **1** by a three-step procedure as shown in Scheme III. Regioselective opening of the epoxide could be accomplished in the desired sense with sodium phenylselenolate.[23] However, since the goal was

Scheme III



a procedure which could be conducted safely and economically on a large scale, the corresponding sulfur reagent was investigated.[24] Reaction of **11** with sodium phenylthiolate in EtOH/THF (1:1) at 40–45 °C gave a mixture of regioisomers **12a** and **12b**. The desired **12a** was isolated in 85% yield by an easy chromatographic separation. Attempts to improve the regioselectivity by carrying out the reaction in the presence of $Ti(O\text{-}iPr)_4$[25] showed no significant difference. Oxidation of **12a** with $NaIO_4$ in aqueous methanol[24] gave sulfoxide **13** in 70% yield as a mixture of diastereomers. Thermolysis of **13** in refluxing toluene in the presence of $CaCO_3$[26] gave **1** in 80% yield.

This procedure is a convenient method for preparing diastereomerically pure lactones such as **1** without the use of expensive reagents, extremely low temperatures, or tedious chromatography of **1** and its epimer, and thus we believe it has the potential for significant scale-up. Use of the appropriately substituted phenol in the Mitsunobu coupling would allow the synthesis of substituted aromatic congeners of **1**.

Experimental Section

General Procedures. Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. Tetrahydrofuran (THF) was dried over 3A molecular sieves prior to use. All reactions involving air- or moisture-sensitive compounds were performed under a nitrogen atmosphere. During workup, all extracts were dried over $MgSO_4$ prior to evaporation of the solvents in vacuo. Gravity column chromatography was performed with Merck silica gel 60 (70–230-mesh ASTM). Thin-layer chromatography (TLC) was performed with Analtech silica gel FG TLC plates (250 μm). ^1H NMR spectra were measured in $CDCl_3$ solutions at 300 or 500 MHz. Coupling constants are given in hertz. Optical rotations were measured in $CHCl_3$ unless otherwise stated.

(3a*R*,4*R*,5*R*,6a*S*)-5-(Benzoyloxy)hexahydro-4-(bromomethyl)-2*H*-cyclopenta[*b*]furan-2-one (3). To a stirred solution of alcohol **2**[7] (9.92 g, 35.9 mmol) and Ph_3P (14.24 g, 54.29 mmol) in acetonitrile (200 mL) was added CBr_4 (18.0 g, 54.29 mmol) at room temperature. After 1 h the reaction mixture was concentrated in vacuo. Crystallization of the solid from ethyl acetate/hexanes gave 10.95 g (90%) of bromide **3** as a white

(10) Wender, P. A.; Sieburth, S. M.; Petraitis, J. J.; Singh, S. K. *Tetrahedron* **1981**, *37*, 3967. Labadie, J. W.; Tueting, D.; Stille, J. K. *J. Org. Chem.* **1983**, *48*, 4634.
(11) Pereyse, M.; Quintard, J. P.; Rohm, A. In *Tin in Organic Synthesis*; Butterworths: London, 1987; p 23.
(12) Tolstikov, G. A.; Miftakhov, M. S.; Danilova, N. A.; Vel'der, Y. L. *Synthesis* **1986**, 496.
(13) Jung, M. E.; Light, L. A. *Tetrahedron Lett.* **1982**, *23*, 3851.
(14) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.
(15) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1.
(16) Mitsunobu, O. *Synthesis* **1981**, 1. Walba, D. M.; Vohra, R. T.; Clark, N. A.; Handschy, M. A.; Xue, J.; Parmar, D. S.; Lagerwall, S. T.; Skarp, K. *J. Am. Chem. Soc.* **1986**, *108*, 7424.
(17) For a review of this transformation, see: Smith, J. G. *Synthesis* **1984**, 629.
(18) Yasuda, A.; Tanaka, S.; Oshima, K.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1974**, *96*, 6513.
(19) Apparu, M.; Barrelle, M. *Tetrahedron* **1978**, *34*, 1541.
(20) Corey, E. J.; Marfat, A.; Falck, J. R.; Albright, J. O. *J. Am. Chem. Soc.* **1980**, *102*, 1433.
(21) Mosset, P.; Sukumar, M.; Viala, J.; Falck, J. R. *Tetrahedron Lett.* **1986**, *27*, 299.
(22) Sakurai, H.; Sasaki, K.; Hosomi, A. *Tetrahedron Lett.* **1980**, *21*, 2329. Kraus, G. A.; Frazier, K. *J. Org. Chem.* **1980**, *45*, 2579.
(23) Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 2697.
(24) Mitra, R. B.; Muljiani, Z.; Deshmukh, A. R. A. S.; Joshi, V. S.; Gadre, S. R. *Synth. Commun.* **1984**, *14*, 101.
(25) Caron, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1557.
(26) Sato, T.; Okura, S.; Otera, J.; Nozaki, H. *Tetrahedron Lett.* **1987**, *28*, 6299.

crystalline solid: mp 167–168 °C; $[\alpha]^{25}_D$ = −83.6° (c = 1); IR (KBr) 1760, 1710, 1270, 1165, 1105 cm^{-1}; ^{1}H NMR δ 2.35 (br dd, 1 H, J = 2.2, 15.7), 2.60 (m, 2 H), 2.95 (m, 3 H), 3.50 (dd, 1 H, J = 6.9, 10.6), 3.57 (dd, 1 H, J = 5.0, 10.6), 5.09 (br dd, 1 H, J = 4.7, 6.1), 5.34 (ddd, 1 H, J = 2.2, 4.1, 6.5), 7.45 (br dd, 2 H, J = 7.7, 8.5), 7.58 (br dd, 1 H, J = 7.7, 7.7), 8.0 (dd, 2 H, J = 8.5, 1.5); ^{13}C NMR δ 33.50, 35.81, 38.29, 42.63, 54.09, 78.41, 83.89, 128.5, 129.46, 129.75, 133.46, 165.98, 175.92. Anal. Calcd for $C_{15}H_{15}BrO_4$: C, 53.12; H, 4.46; Br, 23.56. Found: C, 52.98; H, 4.42; Br, 23.79.

(3a*R*,4*R*,5*R*,6a*S*)-5-(Benzoyloxy)hexahydro-4-(iodomethyl)-2*H*-cyclopenta[*b*]furan-2-one (4). To a solution of NaI (11.76 g, 78.5 mmol) in acetone (120 mL) was added toluene (80 mL), and the mixture was concentrated to dryness. The solid was redissolved in acetone (150 mL), and bromide **3** (8.0 g, 23.6 mmol) was added. The reaction mixture was refluxed for 1 h, after which it was concentrated to dryness. Water was added to dissolve the salt, and the product was extracted with CH_2Cl_2. Trituration of the concentrated product with ethyl acetate gave 7.30 g (80%) of iodide **4** as a white crystalline solid: mp 170–172 °C; $[\alpha]^{25}_D$ = −68.3° (c = 0.308); IR (KBr) 1765, 1715, 1265, 1165, 1100 cm^{-1}; ^{1}H NMR δ 2.35 (m, 1 H), 2.40 (m, 1 H), 2.58 (dd, 1 H, J = 1.3, 17.8), 2.60 (m, 1 H), 2.86 (m, 1 H), 2.97 (dd, 1 H, J = 10.0, 17.8), 3.24 (dd, 1 H, J = 3.6, 10.4), 3.38 (dd, 1 H, J = 5.1, 10.4), 5.09 (ddd, 1 H, J = 1.8, 6.3, 6.3), 5.29 (m, 1 H), 7.44 (dd, 2 H, J = 7.6, 8.4), 7.58 (dd, 1 H, J = 7.6, 7.6), 8.02 (dd, 2 H, J = 1.6, 8.4); ^{13}C NMR δ 6.81, 35.72, 37.98, 44.41, 54.02, 79.45, 83.63, 128.56, 129.40, 129.73, 133.44, 165.90, 175.93. Anal. Calcd for $C_{15}H_{15}IO_4$: C, 46.65; H, 3.92; I, 32.86. Found: C, 46.39; H, 3.89; I, 33.00.

(3a*R*,4*R*,5*R*,6a*S*)-5-(Benzoyloxy)hexahydro-4-(4-(*tert*-butyldimethylsiloxy)-2(*E*)-butenyl)-2*H*-cyclopenta[*b*]furan-2-one (8). To a solution of stannane **6**[13,14] (5.00 g, 10.84 mmol) in THF (15 mL) was added dropwise *n*-BuLi (6.78 mL, 1.6 M solution in hexane, 10.84 mmol) at −78 °C. After stirring for an hour, CuCN (0.49 g, 5.42 mmol) was added. The heterogeneous mixture was allowed to warm slowly to −5 °C, giving a homogeneous yellow solution. After cooling to −70 °C, iodide **4** (0.95 g, 2.46 mmol) dissolved in THF (20 mL) was added dropwise. The reaction mixture was kept at −65 °C for 3 h, allowed to warm to −20 °C and quenched with saturated aqueous NH_4Cl. The product was extracted with ether, and the extracts washed with water and brine. Chromatography (hexanes/ethyl acetate, 10:1) gave 0.78 g (73%) of **8** as a white solid: mp 78–80.5 °C; $[\alpha]^{25}_D$ = −54.7° (c = 0.57); IR (KBr) 1765, 1711, 1275, 1057 cm^{-1}; ^{1}H NMR δ 0.07 (s, 6 H), 0.91 (s, 9 H), 2.08 (m, 1 H), 2.27 (m, 1 H), 2.30 (m, 1 H), 2.35 (br d, 1 H, J = 15.9), 2.44 (ddd, 1 H, J = 6.1, 6.1, 15.9), 2.54 (dd, 1 H, J = 2.4, 18.6), 2.77 (m, 1 H), 2.91 (dd, 1 H, J = 11.1, 18.6), 4.13 (br s, 2 H), 5.11 (ddd, 1 H, J = 1.8, 7.2, 7.2), 5.26 (m, 1 H), 5.3–5.7 (m, 2 H), 7.44 (dd, 2 H, J = 7.8, 7.8), 7.55 (dd, 1 H, J = 7.8, 8.0), 7.99 (br d, 2 H, J = 8.0); MS (*m/e*, relative intensity) 373 ((M − C_4H_9)$^+$, 20), 251 (60), 179 (100), 131 (48), 105 (39), 75 (16). Anal. Calcd for $C_{24}H_{34}O_5Si$: C, 66.94; H, 7.96. Found: C, 67.20; H, 7.99.

(3a*R*,4*R*,5*R*,6a*S*)-5-(Benzoyloxy)hexahydro-4-(4-hydroxy-2(*E*)-butenyl)-2*H*-cyclopenta[*b*]furan-2-one (9). A mixture of compound **8** (1.33 g, 2.09 mmol) and tetrabutylammonium fluoride (4.5 mL, 1.1 M solution in THF, 4.95 mmol) in THF (10 mL) was stirred at ambient temperature for 2 h. The mixture was diluted with water, and the product was extracted with ethyl acetate. The extracts were washed with water and brine and concentrated to give an orange oil. Chromatography (hexanes/ethyl acetate, 2:1) gave 0.91 g of the allylic alcohol **9** (93%) as a white solid: mp 90–92 °C; $[\alpha]^{25}_D$ = −92.6° (c = 0.706); IR (KBr) 3480, 1750, 1710, 1600, 1270, 1190, 1045 cm^{-1}; ^{1}H NMR δ 1.97 (t, 1 H, J = 5.5), 2.12 (ddd, 1 H, J = 5.2, 10.5, 10.5), 2.21 (ddd, 1 H, J = 5.3, 5.3, 10.5), 2.22 (m, 1 H), 2.33 (br d, 1 H, J = 15.6), 2.41 (ddd, 1 H, J = 1.4, 6.8, 6.8), 2.51 (dd, 1 H, J = 18.4, 2.7), 2.72 (m, 1 H), 2.90 (dd, 1 H, J = 10.6, 18.4), 4.07 (dd, 2 H, J = 4.9, 5.5), 5.09 (ddd, 1 H, J = 1.4, 6.8, 6.8), 5.27 (m, 1 H), 5.70 (m, 2 H), 7.44 (dddd, 2 H, J = 0.4, 1.3, 7.5, 8.0), 7.56 (dddd, 1 H, J = 1.3, 1.3, 7.5, 7.5), 7.98 (ddd, 2 H, J = 0.4, 1.3, 8.0); MS (*m/e*, relative intensity) 316 (M + H)$^+$ 194 (50), 176 (84), 105 (100). Anal. Calcd for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37. Found: C, 68.43; H, 6.36.

(3a*R*,4*R*,5*R*,6a*S*)-5-(Benzyloxy)hexahydro-4-((2*R*,3*R*)-2,3-epoxy-4-hydroxybutyl)-2*H*-cyclopenta[*b*]furan-2-one (10). Titanium tetraisopropoxide (0.84 mL, 2.80 mmol) and L-(+)-diethyl tartrate (0.48 mL, 2.80 mmol) were added sequentially via syringe to CH_2Cl_2 (7 mL) at −30 °C. The mixture was stirred for 5 min before adding allylic alcohol **9** (0.80 g, 2.55 mmol) dissolved in CH_2Cl_2 (6 mL) and a toluene solution of *tert*-butyl hydroperoxide (0.93 mL, 5.5 M, 5.1 mmol). The resulting homogeneous solution was stored overnight in a refrigerator at ca. −20 °C in the sealed reaction vessel. After 11 h, the flask was placed in a −23 °C bath, and 10% aqueous tartaric acid solution (7 mL) was added with stirring. After 30 min, the cooling bath was removed and stirring was continued at room temperature until the aqueous layer became clear. The organic layer was separated and washed 3–4 times with water and concentrated to give a colorless oil. Chromatography (CH_2Cl_2/acetone, 49:1) gave 0.78 g (92%) of **10** as a white solid: mp 84–86 °C; $[\alpha]^{25}_D$ = −100.8° (c = 0.747); IR (KBr) 3500, 1765, 1705, 1270, 1180, 720 cm^{-1}; ^{1}H NMR δ 1.63 (ddd, 1 H, J = 7.7, 7.7, 15.3), 1.77 (ddd, 1 H, J = 4.6, 6.8, 15.3), 2.35 (m, 1 H), 2.36 (br d, 1 H, J = 15.8), 2.51 (ddd, 1 H, J = 6.1, 6.1, 15.8), 2.54 (dd, 1 H, J = 2.4, 18.1), 2.77 (m, 1 H), 2.93 (dd, 1 H, J = 10.4, 18.1), 2.95 (1 H, obscured by overlapping resonances), 3.13 (ddd, 1 H, J = 2.2, 4.6, 6.9), 3.72 (dd, 1 H, J = 3.9, 12.6), 3.85 (dd, 1 H, J = 3.3, 12.6), 5.12 (ddd, 1 H, J = 1.6, 7.9, 7.9), 5.38 (ddd, 1 H, J = 3.7, 3.7, 5.8), 7.45 (dd, 2 H, J = 7.7, 8.2), 7.57 (dddd, 1 H, J = 1.5, 1.5, 7.7, 7.7), 7.99 (dd, 2 H, J = 1.5, 8.2); MS (NH_3) (*m/e*, relative intensity) 350 ((M + NH_4)$^+$, 80), 332 ((M + NH_4)$^+$ − H_2O, 10), 306 ((M + NH_4)$^+$ − CO_2, 20), 226 (70), 224 (100), 200 (50), 210 (16), 139 (18). Anal. Calcd for $C_{18}H_{20}O_6$: C, 65.05; H, 6.07. Found: C, 65.06; H, 6.11.

(3a*R*,4*R*,5*R*,6a*S*)-5-(Benzoyloxy)hexahydro-4-((2*R*,3*R*)-2,3-epoxy-4-phenoxybutyl)-2*H*-cyclopenta[*b*]furan-2-one (11). To a stirred solution of α-epoxide **10** (0.60 g, 1.8 mmol) in THF (15 mL) was added sequentially phenol (0.24 g, 2.7 mmol), Ph_3P (0.66 g, 2.7 mmol), and diethyl azodicarboxylate (DEAD, 0.43 mL, 2.7 mmol).[16] After the mixture was stirred for 2.5 h water was added and the product was extracted with ethyl acetate. Chromatography (CH_2Cl_2/acetone, 99:1) gave 0.63 g (85%) of phenyl ether **11** as a white solid: mp 84–88 °C; $[\alpha]^{25}_D$ = −67.8° (c = 0.528); IR (KBr) 1755, 1715, 1595, 1240 cm^{-1}; ^{1}H NMR δ 1.68 (ddd, 1 H, J = 7.1, 7.1, 14.3), 1.81 (ddd, 1 H, J = 4.5, 7.3, 14.3), 2.33 (dd, 1 H, J = 1.9, 15.6), 2.36 (m, 1 H), 2.51 (ddd, 1 H, J = 6.2, 6.2, 15.6), 2.56 (dd, 1 H, J = 2.3, 18.3), 2.80 (m, 1 H), 2.92 (dd, 1 H, J = 11.4, 18.3), 3.11 (m, 1 H), 3.15 (m, 1 H), 4.04 (dd, 1 H, J = 5.1, 11.0), 4.12 (dd, 1 H, J = 5.1, 11.0), 5.09 (ddd, 1 H, J = 1.5, 6.7, 6.7), 5.36 (ddd, 1 H, J = 4.0, 4.0, 6.0), 6.89 (br d, 2 H, J = 7.8), 6.96 (br dd, 1 H, J = 7.5, 7.5), 7.27 (dd, 2 H, J = 7.5, 7.8), 7.42 (br dd, 2 H, J = 7.6, 8.0), 7.55 (dddd, 1 H, J = 1.3, 1.3, 7.6, 7.6), 8.0 (dd, 2 H, J = 1.3, 8.0); MS (NH_3) (*m/e*, relative intensity) 427 (26), 426 ([M + NH_4]$^+$, 100), 108 (12), 286 (11), 194 (10), 105 (8). Anal. Calcd for $C_{24}H_{24}O_6$: C, 70.57; H, 5.92. Found: C, 70.61; H, 6.05.

(3a*R*,4*R*,5*R*,6a*S*)-5-(Benzoyloxy)hexahydro-4-((2*R*)-2-(phenylthio)-(3*S*)-3-hydroxy-4-phenoxybutyl)-2*H*-cyclopenta[*b*]furan-2-one (12a). A solution of thiophenol (0.15 mL, 1.44 mmol) and sodium methoxide (0.08 g, 1.44 mmol) in ethanol was heated to 45 °C. After 0.5 h, epoxide **11** (0.20 g, 0.48 mmol) in THF (2 mL) was added. After 6.0 h, the reaction mixture was concentrated, water was added, and the product was extracted with ethyl acetate. Isomer **12a**, 0.21 g (85%), was isolated by prep TLC (CH_2Cl_2/acetone, 32:1) as a viscous oil: $[\alpha]^{25}_D$ = −106.8° (c = 0.067); IR (KBr) 3244, 1753, 1697, 1246, 1089 cm^{-1}; ^{1}H NMR δ 1.98 (m, 1 H), 2.05 (m, 1 H), 2.32 (br d, 1 H, J = 15.3), 2.44 (ddd, 1 H, J = 6.1, 6.1, 15.3), 2.56 (dd, 1 H, J = 2.2, 18.2), 2.68 (m, 2 H), 2.90 (dd, 1 H, J = 10.7, 18.2), 3.54 (m, 1 H), 3.99 (dd, 1 H, J = 4.6, 4.6), 4.08 (m, 2 H), 5.06 (ddd, 1 H, J = 1.4, 6.5, 6.5), 5.35 (ddd, 1 H, J = 2.6, 2.6, 5.7), 6.75 (dd, 2 H, J = 1.4, 7.8), 6.93 (dd, 1 H, J = 8.1, 8.1), 7.18 (m, 5 H), 7.43 (m, 4 H), 7.56 (dd, 1 H, J = 7.8, 7.8), 7.98 (dd, 2 H, J = 1.5, 8.2); MS (*m/e*, relative intensity) 518 (M$^+$, 4), 407 (24), 286 (28), 285 (100), 259 (24), 136 (63), 105 (64), 79 (8). Anal. Calcd for $C_{30}H_{30}O_6S$: C, 69.47; H, 5.83; S, 6.18. Found: C, 69.88; H, 5.60; S, 6.22.

(3a*R*,4*R*,5*R*,6a*S*)-5-(Benzoyloxy)hexahydro-4-((2*S*)-2-hydroxy-(3*S*)-3-(phenylthio)-4-phenoxybutyl)-2*H*-cyclopenta[*b*]furan-2-one (12b): ^{1}H NMR δ 1.74 (m, 2 H), 2.36 (br d, 1 H J = 15.4), 2.46 (m, 1 H), 2.54 (dd, 1 H, J = 2.4, 18.4), 2.70 (m, 2 H), 2.91 (dd, 1 H, J = 10.8, 18.4), 3.60 (m, 1 H) 4.15 (m, 1 H) 4.26 (m, 1 H), 5.07 (ddd, 1 H, J = 1.4, 6.7, 6.7), 5.30 (ddd, 1 H, J = 2.7, 2.7, 5.9), 6.85 (br d, 2 H, J = 7.8), 6.98 (br dd, 1 H,

J = 7.5, 7.5), 7.27 (m, 5 H), 7.49 (m, 4 H), 7.57 (dddd, 2 H, J = 1.3, 1.3, 7.5, 7.5), 8.0 (dd, 2 H, J = 1.3, 8.0); MS (m/e, relative intensity) 518 (M^+, 2), 303 (32), 289 (2), 193 (28), 136 (30), 123 (70), 105 (100), 77 (21).

(3a*R*,4*R*,5*R*,6a*S*)-5-(Benzoyloxy)hexahydro-4-((2*R*)-2-(phenylsulfinyl)-(3*S*)-3-hydroxy-4-phenoxybutyl)-2*H*-cyclopenta[*b*]furan-2-one (13). To a stirred solution of $NaIO_4$ (0.115 g, 0.53 mmol) in water (2 mL) was added sulfide **12a** (0.27 g, 0.52 mmol) in methanol (8 mL), and the mixture was heated to 40–42 °C. After 24 h methanol was removed to give a viscous crude, which was dissolved in water. The product was extracted with CH_2Cl_2. Prep TLC (hexanes/ethyl acetate, 1:5.7) gave 0.20 g (70%) of sulfoxide **13** as a foam: mp 78–79.5 °C; NMR showed that **13** was a mixture of diastereomers (1:1); $[\alpha]^{25}_D$ = −64.9° (c = 0.69); IR (KBr) 3435, 1768, 1713, 1277 cm^{-1}; ^1H NMR δ 1.5–3.6 (9 H), 3.7–4.7 (3 H), 4.8–5.4 (2 H), 6.6–7.3 (5 H), 7.3–8.1 (10 H); MS (NH_3) (m/e, relative intensity) 552 ($(M + NH_4)^+$, 20), 535 ($(M + H)^+$, 3), 428 (17), 427 (49), 426 (100), 334 (7), 269 (18), 268 (52), 159 (16). Anal. Calcd for $C_{30}H_{30}O_7S$: C, 67.39; H, 5.65; S, 6.00. Found: C, 67.12; H, 5.78; S, 5.69.

(3a*R*,4*R*,5*R*,6a*S*)-5-(Benzoyloxy)hexahydro-4-((3*R*)-3-hydroxy-4-phenoxy-1(*E*)-butenyl)-2*H*-cyclopenta[*b*]furan-2-one (1). A solution of sulfoxide **13** (0.14 g, 0.26 mmol) in toluene (3 mL) with a few crystals of $CaCO_3$ was refluxed for 24 h. The mixture was allowed to cool to room temperature and diluted with water. The product was extracted with ethyl acetate and purified by preparative TLC (hexanes/ethyl acetate, 2:3) to give 80 mg (80%) of **1** as a white solid: mp 122–122.5 °C; $[\alpha]^{25}_D$ = −76.9° (c = 0.1); IR (KBr) 3519, 1767, 1710, 1598, 1279, 1230, 1176 cm^{-1}; ^1H NMR δ 2.27 (dd, 1 H, J = 4.3, 15.7), 2.54 (d, 1 H, J = 15.9), 2.60 (ddd, 1 H, J = 6.3, 6.3, 15.7), 2.80 (m, 1 H), 2.85 (1 H, obscured by overlapping resonances), 2.88 (dd, 1 H, J = 11.2, 18.4), 3.82 (dd, 1 H, J = 8.8, 16.8), 3.95 (dd, 1 H, J = 3.5, 9.3), 4.53 (m, 1 H), 5.09 (m, 1 H), 5.30 (m, 1 H), 5.73 (dd, 1 H, J = 4.8, 15.7), 5.83 (dd, 1 H, J = 7.3, 15.5), 6.87 (br d, 2 H, J = 8.5), 6.97 (br dd, 1 H, J = 7.2, 7.2), 7.26 (dd, 2 H, J = 7.5, 7.8), 7.43 (br dd, 2 H, J = 7.4, 7.4), 7.57 (dddd, 1 H, J = 1.3, 1.3, 7.5, 7.5), 8.0 (dd, 2 H, J = 1.3, 8.0); MS (m/e, relative intensity): 408 (M^+, 8), 301 (10), 286 (26), 179 (48), 108 (40), 105 (100), 94 (28), 77 (45). Anal. Calcd for $C_{24}H_{24}O_6$: C, 70.57; H, 5.92. Found: C, 70.20; H, 5.87.

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Reactions of Thianthrene Cation Radical with Oximes of Cinnamaldehydes and Unsaturated Aromatic Ketones in Acetonitrile

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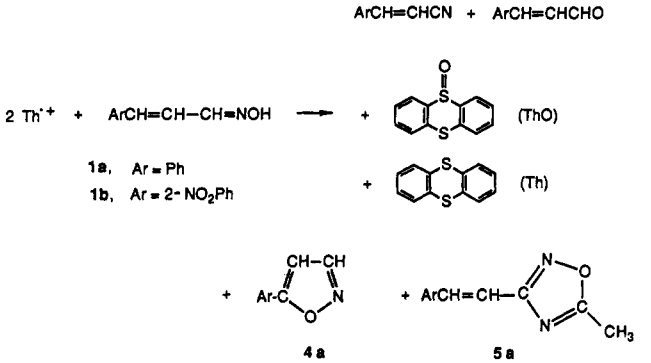
Recently we reported the reactions of aldehyde oximes (RCH=NOH) with thianthrene cation radical perchlorate ($Th^{\bullet+}ClO_4^-$) in nitrile solvents (R'CN). Among these reactions, and dependent on the nature of R, were conversions of an oxime in acetonitrile solvent into two isomeric oxadiazoles, 3-R-5-methyl- and 3-methyl-5-R-1,2,4-oxadiazole, overall dehydration to form RCN, and hydrolysis to form RCHO. The last two reactions involved prior complexation of RCH=NOH with $Th^{\bullet+}$.[1] In earlier work we found that oxidative intramolecular cyclization occurred in reactions of $Th^{\bullet+}ClO_4^-$ with arylhydrazones of chalcones and benzalacetones, with the formation of pyrazoles in excellent yields.[2] We have now completed our analogous study of the reactions of some representative unsaturated aromatic aldoximes and ketoximes.

Scheme I



Cinnamaldoxime (**1a**) underwent small and comparable amounts of intramolecular cyclization, forming 5-phenylisoxazole (**4a**), and cycloaddition to solvent, forming 5-methyl-3-styryl-1,2,4-oxadiazole (**5a**). The major fate of **1a** was conversion to cinnamonitrile. A small amount of cinnamaldehyde was formed, too (Scheme I). In contrast, 2-nitrocinnamaldoxime (**1b**) failed to undergo cyclization or cycloaddition, the only products being the corresponding aldehyde (27.7%) and nitrile (62%). In the presence of 2,4-di-*tert*-butyl-6-methylpyridine (DTBMP) **1a** failed to give **4a** and **5a** but gave only cinnamaldehyde (5.7%) and cinnamonitrile (84.5%). Correspondingly, **1b** in the presence of DTBMP gave mainly 2-nitrocinnamonitrile (83.5%) and some of the aldehyde (7.9%) (Table I). None of the cyclic products (i.e., **4b** and **5b**) was obtained. These reactions can be understood in the light of our earlier work with aldoximes.[1] That is, **1a** was oxidized, in part, to its cation radical which, in the absence of DTBMP, led to the cyclization (**4a**) and cycloaddition (**5a**) products. Complexation of **1a** with $Th^{\bullet+}$ led to aldehyde and nitrile formation, the latter pathway being enhanced by the presence of DTBMP. The failure of **1b**, with its presumed higher oxidation potential, to undergo the oxidative reactions, and instead to yield nitrile and aldehyde is also in line with our earlier experiences. These reactions can be understood with the help of our earlier mechanistic schemes.[1] In harmony with our earlier work is the balance of products, particularly for reactions in the presence of DTBMP. That is, the millimolar sum of the yields of aldehyde and nitrile (e.g., runs 1, 2, and 4) is balanced by that of thianthrene 5-oxide (ThO).

Reactions with the three ketoximes (**2a,b** and **3**) were incomplete in the absence of DTBMP. That is, about 30–40% of oxime was recovered (runs 5, 7, and 9). At the same time substantial amounts (14–24%) of ThO were obtained, attributable in good part to the reaction of workup water with unreacted $Th^{\bullet+}$. The amount of Th formed in these runs, however, was larger than can be accounted for on the basis of the amounts of products obtained. It seems that much of the $Th^{\bullet+}$ was reduced to Th without revealing the fate of the reductant. The major products of runs 5, 7, and 9 were the isoxazoles, 3-methyl-5-phenyl- (**6a**), 5-(*p*-chlorophenyl)-3-methyl- (**6b**), and 5-(*p*-methoxyphenyl)-3-methylisoxazole (**8**), formed by oxidative cyclization of the oximes. The yields, based on the amount of oxime that reacted, were substantial, namely 62% of **6a**, 63% of **6b**, and 71% of **8**. Traces of

(1) Chiou, S.; Hoque, A. K. M. M.; Shine, H. J. *J. Org. Chem.* **1990**, *55*, 3227.

(2) Kovelesky, A. C., Shine, H. J. *J. Org. Chem.* **1988**, *53*, 1973.

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