(McLafferty rearrangement), and $M^+ - 18$ ions.

Synthesis of the diastereomeric diols **15** and **18** was accomplished as outlined in Scheme I. Condensation of anisaldehyde with acetonitrile in the presence of base yielded a 5.6:1 mixture of the *E* and *Z* olefins **11** and **12**. After separation by chromatography, the isomeric nitriles were reduced with lithium aluminum hydride to the corresponding amines, which were then formylated by refluxing with ethyl formate. Osmylation of the isomeric formamides yielded the diastereomeric diols **15** and **18**. ^1H NMR signals (Table I) for the side-chain protons of these diols did not match those of bursatellin measured in the same solvent.

Experimental Section[4]

Isolation of Bursatellin. Specimens of *B. leachii leachii* (two specimens, average length 14 cm) collected at Naples and *B. leachii savignyana* (100 animals; average length 5 cm) collected at Taranto were dissected, and the digestive glands and mantles were extracted separately with acetone. The concentrated acetone extracts were diluted with water and extracted sequentially with diethyl ether and 1-butanol. Bursatellin (**1**) was isolated by SiO_2 chromatography of the 1-butanol solubles (eluant, $CHCl_3$ and increasing amounts of CH_3OH). Yields of bursatellin were as follows: (a) *B. leachii leachii* mantles, 21 mg; digestive glands, none; (b) *B. leachii savignyana* mantles, 24 mg; digestive glands, 52 mg; $[\alpha]_D$ for the pooled isolates, −8.8° (*c* 2.4, CH_3OH).

(*E*)- and (*Z*)-*p*-Methoxycinnamonitrile (11, 12). A mixture of (*E*)- and (*Z*)-*p*-methoxycinnamonitrile was prepared by following the analogous preparation of (*E*)- and (*Z*)-cinnamonitrile.[5] From 6.81 g of anisaldehyde (**10**), 7.0 g of a mixture of **11** and **12** was obtained (*E*:*Z* ratio ca. 5.6 by ^1H NMR). The mixture was chromatographed on silica gel with CH_2Cl_2/petroleum ether (4:6) as the eluant to obtain 0.46 g of the less polar *Z* isomer **12** and 4.10 g of the *E* isomer **11**. ^1H NMR (80 MHz, $CDCl_3$): (**12**) δ 7.78 (2 H, d, J = 8.8 Hz), 7.02 (1 H, d, J = 12.1 Hz), 6.91 (2 H, d, J = 8.8 Hz), 5.28 (1 H, d, J = 12.1 Hz), 3.81 (3 H, s); (**11**) δ 7.40 (2 H, d, J = 8.6 Hz), 7.35 (1 H, d, J = 15.7 Hz), 6.90 (2 H, d, J = 8.6 Hz), 5.71 (1 H, d, J = 15.7 Hz), 3.85 (3 H, s).

(*E*)- and (*Z*)-*p*-Methoxycinnamylamine (13, 16). A solution of **11** (1.6 g) in anhydrous diethyl ether (30 mL) was added during 10 min to a stirred 1 M solution of $LiAlH_4$ in anhydrous diethyl ether (10 mL). After 15 min at room temperature, 15% aqueous NaOH (50 mL) was added. The usual workup afforded 1.15 g of crude **13**. An analytical sample of **13** was obtained by flash chromatography on a silica gel column ($CHCl_3$/MeOH, 7:3): MS, m/z 163 (M^+, base peak), 132, 121; ^1H NMR (270 MHz, $CDCl_3$) δ 7.30 (2 H, d, J = 8.7 Hz), 6.85 (2 H, d, J = 8.7 Hz), 6.44 (1 H, d, J = 15.8 Hz), 6.18 (1 H, dd, J = 15.8, and 5.9 Hz), 3.80 (3 H, s), 3.45 (2 H, dd, J = 5.9, and 1.3 Hz).

Following the same procedure, 0.35 g of crude **16** was obtained from 0.46 g of **12**. An analytical sample of **16** showed the following: MS, m/z 163 (M^+), 132, 121; ^1H NMR (500 MHz, $CDCl_3$) δ 7.15 (2 H, d, J = 8.6 Hz), 6.86 (2 H, d, J = 8.6 Hz), 6.38 (1 H, d, J = 11.6 Hz), 5.63 (1 H, dd, J = 11.6, 6.5 Hz), 3.80 (3 H, s), 3.58 (2 H, dd, J = 6.5, 1.6 Hz).

(*E*)- and (*Z*)-*N*-Formyl-*p*-methoxycinnamylamine (14, 17). A solution of **13** (0.5 g) in ethyl formate (10 mL) was refluxed for 2 h. Removal of the solvent and silica gel column chromatography ($CHCl_3$/MeOH, 98:2) afforded 0.46 g of pure **14**, which was crystallized from CH_2Cl_2/diethyl ether: mp 87–89 °C; IR ν_{max} ($CHCl_3$) 1641 cm^{-1}; MS, m/z 191 6.4, (M^+) 162, 146 (base peak), 121; ^1H NMR (270 MHz, $CDCl_3$) δ 8.23 (1 H, s), 7.28 (2 H, d, J = 8.7 Hz), 6.85 (2 H, d, J = 8.7 Hz), 6.49 (1 H, d, J = 15.8 Hz), 6.04 (1 H, dt, J = 15.8, 6.4 Hz), 5.79 (1 H, br m), 4.06 (2 H, dd, J = 6.4, ~1.5 Hz), 3.80 (3 H, s).

Similar treatment of 0.19 g of **16** resulted in the isolation of 0.15 g of pure **17**: mp 75–78 °C (from diethyl ether); MS, m/z 191 (M^+), 162, 146 (base peak), 121; ^1H NMR (500 MHz, $CDCl_3$) δ 8.18 (1 H, s), 7.16 (2 H, d, J = 8.6 Hz), 6.87 (2 H, d, J = 8.6 Hz), 6.53 (1 H, d, J = 11.4 Hz), 5.75 (1 H, br m), 5.55 (1 H, dt, J = 11.4, 6.8 Hz), 4.20 (2 H, dd, J = 6.8, ~1.5 Hz), 3.80 (3 H, s).

***threo*- and *erythro*-2-Hydroxy-3-(formylamino)-1-(4-methoxyphenyl)propanol (15, 18).** To a stirred solution of **14** (76 mg) in pyridine (0.5 mL) was added a solution of OsO_4 (100 mg) in pyridine (1 mL). Stirring was continued overnight, and then a solution of $Na_2S_2O_5$ (172 mg) in water (3 mL) and pyridine (2 mL) was added. The solution was extracted with butanol (3 × 10 mL), and the butanol solubles were chromatographed on a silica gel column ($CHCl_3$/MeOH 9:1) to obtain 41 mg of pure **15**: MS, m/z 225 (M^+), 207, 182, 180, 162, 137 (base peak); ^1H NMR, Table I. **17** (56 mg) on similar treatment afforded 18 mg of pure **18**: MS, m/z 225 (M^+), 207, 182, 180, 162, 137 (base peak); ^1H NMR, Table I.

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(4) General experimental conditions are as described earlier; see: Reference 2. Cimino, G.; De Rosa, S.; De Stefano, S.; Morrone, R.; Sodano, G. *Tetrahedron* **1985**, *41*, 1093.

(5) Di Biase, S. A.; Beadle, J. R.; Gokel, G. W. *Org. Synth.* **1984**, *62*, 179.

Facile Synthesis of Chiral *O*-Alkyl Enol Ethers

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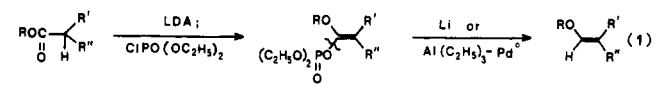
O-Alkyl enol ethers are routinely used in a variety of well-known reactions such as the Diels–Alder reaction, ketene cycloaddition, cyclopropanation, and the Claisen rearrangement, yet general, stereoselective methods for their preparation are rare.[1] More surprisingly, however, useful approaches to chiral (nonracemic) alkyl enol ethers appear to be virtually nonexistent[2] in spite of the obvious potential of these compounds in asymmetric synthesis.[3] In this paper a simple, selective method is reported for the obtention of acyclic enol ethers, including those with chiral *O*-alkyl groups.[4]

The procedure (eq 1) that has been developed is in essence an extrapolation of an effective method for ketone–olefin conversion.[5] The appropriate ester in tetra-



(1) For excellent reviews on the preparation and reactions of enol ethers, see: Hesse, G. In *Methoden Org. Chem. (Houben–Weyl), 4th Ed.* **1978**, *6*(1d), 1–216. Fischer, P. In *Chemistry of Ethers, Crown Ethers, Hydroxyl Groups and Their Sulphur Analogues*; Patai, S., Ed.; Wiley: New York, 1980; Vol 2, Chapter 17. For more recent references, see: Carless, H. A. J.; Haywood, D. J. *J. Chem. Soc., Chem. Commun.* **1980**, 980–981. Miller, R. D.; McKean, D. R. *Tetrahedron Lett.* **1982**, *23*, 323–326. Marsi, M.; Gladysz, J. A. *Ibid.* **1982**, *23*, 631–634. Gilbert, J. C.; Weerasooriya, U. *J. Org. Chem.* **1983**, *48*, 448–453. Luengo, J. I.; Koreeda, M. *Tetrahedron Lett.* **1984**, *25*, 4881–4884. Aguero, A.; Kress, J.; Osborn, J. A. *J. Chem. Soc., Chem. Commun.* **1986**, 531–533.

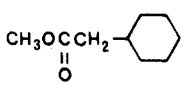
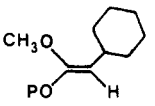
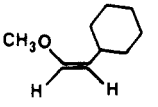
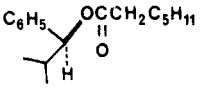
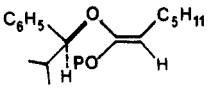
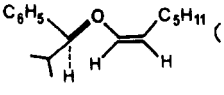
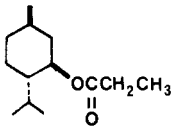
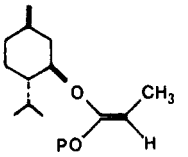
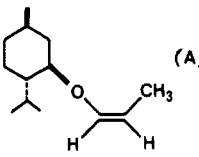
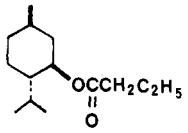
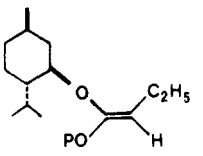
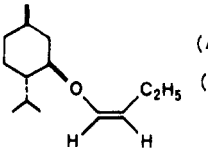
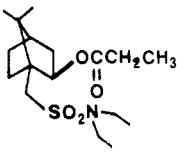
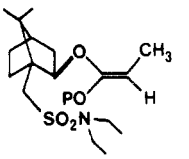
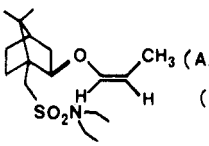
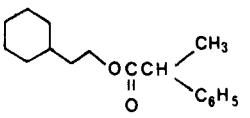
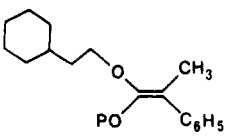
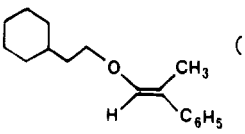
(2) With the exception, of course, of simple vinyl ethers. See, for example: Posner, G. H.; Wettlaufer, D. G. *Tetrahedron Lett.* **1986**, *27*, 667–670. *J. Am. Chem. Soc.* **1986**, *108*, 7373–7377.

(3) For the use of chiral alkyl enol ethers with dichloroketene, see: Greene, A. E.; Charbonnier, F. *Tetrahedron Lett.* **1985**, *26*, 5525–5528.

(4) For an alternative approach, see: Moyano, A.; Charbonnier, F.; Greene, A. G. *J. Org. Chem.*, in press.

0022-3263/87/1952-2303$01.50/0

Table I. *O*-Alkyl Enol Ethers from Esters[a]

entry	ester	phosphate[b] (yield[c])	enol ether (method,[d] *Z*:*E*,[e] yield[c])
1	 **1**	 (94%) **2**	 (B, 10:1, 52%) **3**
2	 **4**	 (74%) **5**	 (B, 15:1, 89%) **6**
3	 **7**	 (76%) **8**	 (A, >20:1, 88%) **9**
4 5	 **10**	 (85%) **11**	 (A, 10:1, 78%) (B, 1:1, 85%) **12**
6 7	 **13**	 (88%) **14**	 (A, >20:1, 64%) (B, 4:1, 68%) **15**
8	 **16**	 (84%)[f] **17**	 (B, 1:4, 73%)[g] **18**

[a] Esters 4, 7, 10, and 13 are optically pure with the indicated absolute stereochemistry. For the reaction conditions and physical properties of the products, see Experimental Section. [b] Phosphate stereochemical purity is assumed[8] to be ≥90% except for 17. P = $-PO(OC_2H_5)_2$. [c] Yield of purified material. [d] Method A: Li, NH_3 or CH_3NH_2, THF, *t*-BuOH. Method B: $Al(C_2H_5)_3$, $Pd[P(C_6H_5)_3]_4$, $ClCH_2CH_2Cl$. [e] By ^1H NMR analysis. [f] Enolization was carried out in THF–HMPA. [g] Use of $Al(CH_3)_3$ gave the corresponding methylated derivative in 65% yield.[6]

hydrofuran is converted through reaction with lithium diisopropylamide and diethyl chlorophosphate to the corresponding α-alkoxy enol phosphate, which in turn is reduced under Birch conditions. Alternatively, the intermediate phosphate can be treated with $Al(C_2H_5)_3$ in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium to effect cleanly (albeit less selectively) the hydrogenolysis.[6] In Table I examples of this enol ether synthesis are presented.

It can be seen that the Birch procedure produces the *Z* enol ethers[7] in excellent stereochemical purity (entries 3, 4, and 6). This reflects a high degree of stereoselectivity in the enolization—trapping[8] that is not significantly altered in the subsequent Birch reduction.[5]

Entry 2 illustrates an application of the $Al(C_2H_5)_3$–Pd^0 hydrogenolysis procedure[6] where the Birch reduction is inapplicable. The possibility of easily obtaining derivatives such as **6** is of interest in that Posner and Wettlaufer have

(5) Fetizon, M.; Jurion, M.; Anh, N. T. *J. Chem. Soc., Chem. Commun.* **1969**, 112. Ireland, R. E.; Pfister, G. *Tetrahedron Lett.* **1969**, 2145–2148. Welch, S. C.; Walters, M. E. *J. Org. Chem.* **1978**, *43*, 2715–2717 and references cited therein.

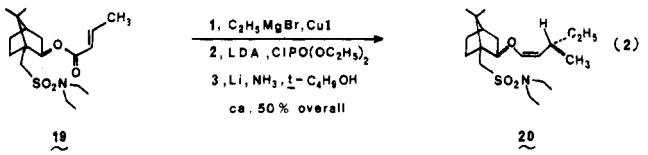
(6) Cf.: Takai, K.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1980**, *21*, 2531–2534. Sato, M.; Takai, K.; Oshima, K.; Nozaki, H. Ibid. **1981**, *22*, 1609–1612.

(7) Although the *E* enol ethers could be obtained from the *Z* α-alkoxy enol phosphates (prepared by effecting the enolization in 23% HMPA–THF), predictably[8] the stereochemical purity was less satisfactory (e.g., menthyl propionate (**7**) gave menthoxy-1-propene (**9**), *E*:*Z* ~2.5:1).[4]

(8) See: Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868–2877. Wilcox, C. S.; Babston, R. E. *J. Org. Chem.* **1984**, *49*, 1451–1453.

shown[2] chiral 2-methyl-1-phenylpropyl vinyl ether to be highly effective in an asymmetric inverse electron demand Diels–Alder reaction. Although the conversion of **2** to **3** (entry 1) with $Al(C_2H_5)_3$–Pd^0 also proceeds quite stereoselectively, comparison of the results of entries 4 and 5 and those of entries 6 and 7 suggests that the Birch reduction is generally a more reliable method for effecting the hydrogenolysis.[9]

Finally, the possibility of effecting conjugate addition to create a chiral center[10] prior to enol ether formation should be noted (eq 2).



19 **20** (2)

It is expected that this simple approach to enol ethers will find considerable use, particularly in asymmetric synthesis.

Experimental Section

Solvents were normally distilled prior to use. Tetrahydrofuran and ether were distilled from sodium hydride–lithium aluminum hydride, hexamethylphosphoric triamide and *tert*-butyl alcohol were distilled from calcium hydride, and dichloromethane and dichloroethane were distilled from calcium chloride. Reaction mixtures were generally stirred under a nitrogen or argon atmosphere. Analytical thin-layer chromatography was performed on Merck $60F_{254}$ (0.25 mm) sheets, which were visualized with molybdophosphoric acid in ethanol. Merck 70-230 silica gel 60 and Aldrich 60–100 mesh florisil were employed for column chromatography.

Typical α-Alkoxy Enol Phosphate Preparation. Phosphate 2. To a stirred solution of lithium diisopropylamide (1.45 mmol, prepared from 188 mg (1.86 mmol) of diisopropylamine in 0.2 mL of tetrahydrofuran and 0.570 mL (1.45 mmol) of a 2.55 M solution of *n*-butyllithium in hexane) at −78 °C was added over 5 min 150 mg (0.96 mmol) of methyl cyclohexylacetate (**1**) in 1 mL of tetrahydrofuran. After being stirred at −78 °C for an additional 15 min, the solution was treated with 334 mg (1.94 mmol) of diethyl chlorophosphate in 2 mL of hexamethylphosphoric triamide and was then allowed to warm to room temperature over 1.5 h. After the addition of water, the mixture was extracted with ether, which was then washed successively with 0.25 N aqueous sodium hydroxide, water, and brine. The ethereal phase was dried over potassium carbonate, filtered, and concentrated, and the resulting residue was purified by dry column chromatography (silica gel pretreated with 2.5% v/v of triethylamine) with ether–pentane to yield 263 mg (94%) of phosphate **2** as a pale yellow oil: IR (film) 2980, 2925, 2850, 1690, 1445, 1390, 1365, 1340, 1280, 1235, 1200, 1160, 1120, 1030, 980, 960, 925, 890, 850, 810 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 0.74–2.96 (m, 11 H), 1.36 (dt, J = 1 Hz, 7 Hz, 6 H), 3.59 (s, 3 H), 3.78 (d, J = 9 Hz, 1 H), 3.89–4.44 (m, 4 H).

Phosphate 5. Treatment of ester **4**, prepared in essentially quantitative yield by the method of Hassner and Alexanian,[11] under the above conditions gave in 74% yield phosphate **5**: IR (film) 3075, 3050, 3025, 2950, 2925, 2875, 2850, 1685, 1450, 1370, 1280, 1160, 1130, 960, 820, 750, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 0.50–1.50 (m, 21 H), 1.50–2.42 (m, 3 H), 3.50–4.69 (m, 5 H), 4.72 (d, J = 8 Hz, 1 H), 7.28 (s, 5 H).

Phosphate 8. Treatment of ester **7**, obtained in essentially quantitative yield by using propionic anhydride in pyridine, under the above conditions afforded in 76% yield phosphate **8**: IR (film) 2950, 2900, 2850, 1690, 1445, 1380, 1360, 1320, 1270, 1160, 1140, 1090, 1020, 950, 910, 870, 845, 820, 790, 740 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 0.65–2.50 (m, 21 H), 1.35 (dt, J = 1 Hz, 7 Hz, 6 H), 3.50–4.70 (m, 6 H).

Phosphate 11. Treatment of ester **10**, secured in 90% yield by using butyric anhydride in pyridine, under the above conditions gave in 85% yield phosphate **11**: IR (film) 2950, 2925, 2860, 1690, 1450, 1370, 1300, 1280, 1165, 1100, 1030, 960, 820 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 0.57–2.46 (m, 23 H), 1.37 (dt, J = 1 Hz, 7 Hz, 6 H), 3.50–4.69 (m, 6 H).

Phosphate 14. Treatment of ester **13**, obtained in essentially quantitative yield by the method of Hassner and Alexanian,[11] under the conditions employed above provided in 88% yield phosphate **14**: IR (film) 2960, 2930, 2860, 1690, 1450, 1380, 1330, 1280, 1200, 1140, 1030, 960, 940, 870, 780, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 0.90 (s, 3 H), 1.05 (s, 3 H), 1.20 (t, J = 7 Hz, 6 H), 1.35 (dt, J = 1 Hz, 7 Hz, 6 H), 1.56 (dd, J = 2 Hz, 7 Hz, 3 H), 0.59–2.30 (m, 7 H), 2.74 (A of ABq, J = 14 Hz, 1 H), 3.28 (q, J = 7 Hz, 4 H), 3.44 (B of ABq, J = 14 Hz, 1 H), 3.93–4.76 (m, 6 H).

Phosphate 17. A solution of lithium diisopropylamide (6.88 mmol, prepared from 830 mg (8.22 mmol) of diisopropylamine in 0.9 mL of tetrahydrofuran and 2.75 mL (6.88 mmol) of a 2.50 M solution of *n*-butyllithium in hexane) was added over 5 min to a stirred solution at −78 °C of 1.19 g (4.58 mmol) of ester **16** (prepared in essentially quantitative yield[11]) and 2.36 g (13.7 mmol) of diethyl chlorophosphate in 1.59 mL of hexamethylphosphoric triamide and 5 mL of tetrahydrofuran. The reaction mixture was allowed to warm to room temperature over 1.5 h and then treated as above to yield 1.52 g (84%) of phosphate **17** as an *E*–*Z* mixture (ca. 1:1 by TLC and ^1H NMR): IR (film) 3050, 2975, 2925, 2850, 1680, 1600, 1440, 1390, 1365, 1280, 1190, 1170, 1120, 1100, 1040, 980, 885, 820, 800, 760, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 0.41–2.11 (m, 13 H), 1.17 (dt, J = 1 Hz, 8 Hz, 3 H), 1.39 (dt, J = 1 Hz, 8 Hz, 3 H), 2.00 (pseudo t, J = 3 Hz, 3 H), 3.50–4.50 (m, 6 H), 7.00–7.50 (m, 5 H).

Typical Enol Ether Preparation under Birch Conditions (Method A): Enol Ether 9. To 10 mL of dry, distilled methylamine was added a solution of 238 mg (0.68 mmol) of phosphate **8** in 1.4 mL of *tert*-butyl alcohol and 0.7 mL of tetrahydrofuran. Then 50 mg (7.2 mmol) of lithium wire in small pieces was added. After being stirred at reflux for 1 h (no remaining lithium), the reaction mixture was treated with 2 mL of ethyl alcohol and then processed with pentane in the usual manner to afford, following filtration with pentane through florisil, 118 mg (88%) of enol ether **9**: $[\alpha]^{21}_D$ −15.7° (*c* 2.1, cyclohexane); IR (film) 3025, 2950, 2925, 2850, 1660, 1450, 1400, 1360, 1340, 1250, 1180, 1120, 1100, 1080, 1065, 1050, 915 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 0.53–2.39 (m, 18 H), 1.59 (dd, J = 2 Hz, 7 Hz, 3 H), 3.34 (dt, J = 4 Hz, 10 Hz, 1 H), 4.33 (pseudo quint, J = 7 Hz, 1 H), 6.00 (dq, J = 2 Hz, 6 Hz, 1 H); mass spectrum, m/e 196 (M^+, 13%), 139 (30%), 138 (51%), 97 (35%), 83 (100%). This material was indistinguishable from an independently prepared sample.[3]

Anal. Calcd for $C_{13}H_{24}O$: C, 79.53; H, 12.32. Found: C, 79.72; H, 12.15.

Enol Ether 12. Treatment of phosphate **11** as described above for phosphate **8** gave in 78% yield enol ether **12**: $[\alpha]^{21}_D$ −12.3° (*c* 2.3, cyclohexane); IR (film) 3025, 2950, 2925, 2875, 1660, 1450, 1370, 1340, 1250, 1140, 1100, 1085, 1070, 1055 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 0.50–2.44 (m, 23 H), 3.55 (dt, J = 5 Hz, 10 Hz, 1 H), 4.30 (pseudo q, J = 7 Hz, 1 H), 5.95 (dt, J = 1 Hz, 6 Hz, 1 H). This material was identical with an independently prepared sample.[4]

Anal. Calcd for $C_{14}H_{26}O$: C, 79.93; H, 12.46. Found: C, 79.80; H, 12.55.

Enol Ether 15. An 85-mg (0.18 mmol) sample of phosphate **14** in 0.7 mL of tetrahydrofuran, 0.4 mL of *tert*-butyl alcohol, and 10 mL of dry, distilled ammonia was treated with 50 mg (7.2 mmol) of lithium as described above for phosphate **8** to afford 37 mg (64%) of enol ether **15**: $[\alpha]^{20}_D$ −47.1° (*c* 5.1, cyclohexane); IR (film) 3025, 2960, 2925, 2860, 1660, 1450, 1380, 1350, 1330, 1250, 1200, 1175, 1145, 1125, 1085, 1020, 930, 770, 705 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 0.88 (s, 3 H), 1.05 (s, 3 H), 1.20 (t, J = 7 Hz, 6 H), 1.54 (dd, J = 2 Hz, 7 Hz, 3 H), 0.61–2.15 (m, 7 H), 2.70 (A of ABq, J = 14 Hz, 1 H), 3.25 (q, J = 7 Hz, 4 H), 3.38 (B of ABq, J = 14 Hz, 1 H), 4.00–4.21 (m, 1 H), 4.33 (pseudo quint, J = 7 Hz, 1 H), 6.07 (dq, J = 2 Hz, 6 Hz, 1 H); mass spectrum, m/e 329

(9) It is worth noting that an even purer *Z* enol ether can often be obtained by florisil chromatography to remove the minor *E* isomer.

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(M+, 3%), 272 (100%), 218 (9%), 175 (3%), 135 (100%), 120 (24%), 107 (33%), 93 (33%). This product was indistinguishable from an independently prepared sample.[3]

Anal. Calcd for $C_{17}H_{31}O_3NS$: C, 61.98; H, 9.49. Found: C, 61.75; H, 9.61.

Enol Ether 20. Copper-catalyzed conjugate addition of ethylmagnesium bromide to crotonate **19**,[10] prepared with crotonyl chloride and silver cyanide,[12] provided the adduct as a ca. 80:20 mixture of diastereomers (by ^{13}C NMR) in 89-97% yield. This adduct had the following properties: mp 53-54 °C; $[\alpha]^{20}_D$ -47.2° (c 1.7, chloroform); IR (film) 2950, 2925, 2875, 1725, 1455, 1385, 1375, 1350, 1330, 1280, 1260, 1200, 1180, 1145, 1100, 1050, 1020, 935, 775, 705, 670 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 1.20 (t, J = 7 Hz, 6 H), 0.63-2.50 (m, 24 H), 2.72 (A of ABq, J = 14 Hz, 1 H), 3.25 (B of ABq, J = 14 Hz, 1 H), 3.26 (q, J = 7 Hz, 4 H), 4.81-5.07 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75.4 MHz, resonances of major diastereomer) 11.18, 14.41, 19.15, 19.84, 20.28, 26.92, 29.28, 29.93, 31.91, 39.60, 41.43, 41.71, 44.40, 48.64, 49.13, 49.46, 78.00. Mass spectrum, m/e 387 (M+, 1%), 372 (1%), 323 (2%), 315 (3%), 272 (25%), 252 (11%), 183 (36%), 135 (83%), 115 (100%). Anal. Calcd for $C_{20}H_{37}O_4NS$: C, 61.99; H, 9.62. Found: C, 62.15; H, 9.64. The crude enol phosphate, derived as usual from this adduct, was reduced as described above for phosphate **14** to provide in 55% yield (based on 64% conversion) enol ether **20** (>95% Z): $[\alpha]^{20}_D$ -27.3° (c 0.8, $CHCl_3$); IR (film) 3025, 2975, 2950, 2875, 1660, 1460, 1380, 1350, 1335, 1250, 1240, 1200, 1150, 1120, 1090, 1020, 940, 770, 710, 670 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 1.19 (t, J = 7 Hz, 6 H), 0.50-2.50 (m, 22 H), 2.68 (A of ABq, J = 14 Hz, 1 H), 3.27-3.66 (q, J = 7 Hz, 4 H; B of ABq, J = 14 Hz, 1 H), 3.94-4.23 (m, 2 H), 5.98 (dd, J = 3 Hz, 6 Hz, 1 H); mass spectrum, m/e 371 (M+, 3%), 272 (47%), 208 (6%), 135 (100%), 120 (23%), 107 (44%), 93 (59%).

Anal. Calcd for $C_{20}H_{37}O_3NS$: M_r, 371.24945. Found: M_r (mass spectrum), 371.24818.

Typical Enol Ether Preparation with Triethylaluminum (Method B): Enol Ether 3. To a stirred solution of 350 mg (1.20 mmol) of phosphate **2** and 42 mg (0.04 mmol) of tetrakis(triphenylphosphine)palladium(0) in 1.5 mL of 1,2-dichloroethane at 0 °C was added over 5 min 3.0 mL (3.0 mmol) of a 1 M solution of triethylaluminum in hexane. Following the addition, the reaction mixture was allowed to warm to room temperature and was then stirred for 30 min, after which it was diluted with ether. After being washed successively with cold 2% aqueous hydrochloric acid, water, and brine, the ethereal solution was dried over potassium carbonate and then concentrated. Filtration of the residue through florisil with ether in pentane provided 88 mg (52%) of enol ether **3**: IR (film) 3025, 3000, 2925, 2850, 2825, 1660, 1445, 1390, 1290, 1260, 1230, 1110, 1085, 975, 935, 885, 740 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) 0.65-2.11 (m, 10 H), 2.11-2.71 (m, 1 H), 3.56 (s, 3 H), 4.22 (dd, J = 6 Hz, 9 Hz, 1 H), 5.77 (dd, J = 1 Hz, 6 Hz, 1 H); mass spectrum, m/e 140 (M+, 38%), 108 (34%), 97 (100%).

Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 77.06; H, 11.56.

Enol Ether 6. Treatment of 114 mg (0.29 mmol) of phosphate **5** in 0.7 mL of dichloroethane with 16 mg (0.01 mmol) of the palladium catalyst and 1.2 mL (1.2 mmol) of the triethylaluminum solution gave 63 mg (89%) of enol ether **6**: $[\alpha]^{23}_D$ 64.7° (c 1.2, cyclohexane); IR (film) 3050, 3025, 2950, 2925, 2860, 2840, 1660, 1465, 1445, 1380, 1250, 1120, 1090, 1070, 745, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 0.50-1.59 (m, 9 H), 0.82 (d, J = 7 Hz, 3 H), 0.99 (d, J = 7 Hz, 3 H), 1.59-2.35 (m, 3 H), 4.23 (d, J = 6 Hz, 1 H), 4.28 (pseudo q, J = 7 Hz, 1 H), 5.84 (dt, J = 1 Hz, 6 Hz, 1 H), 7.26 (s, 5 H); mass spectrum, m/e 246 (M+, 3%), 205 (18%), 133 (100%), 132 (34%), 105 (9%).

Anal. Calcd for $C_{17}H_{26}O$: C, 82.87; H, 10.64. Found: C, 82.93; H, 11.06.

Enol Ether 18. Treatment of 136 mg (0.34 mmol) of phosphate **17** in 1 mL of dichloroethane with 20 mg (0.02 mmol) of the palladium catalyst and 0.69 mL (0.69 mmol) of the triethylaluminum solution for 15 h afforded 61 mg (73%) of enol ethers **18**: IR (film) 3075, 3050, 3025, 2925, 2850, 1650, 1600, 1490, 1440, 1390, 1370, 1280, 1190, 1170, 1140, 1070, 1025, 755, 595 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 0.50-2.00 (m, 13 H), 1.93 (d, J = 1 Hz, Z-CH_3), 2.00 (d, J = 1 Hz, E-CH_3), 3.90 (t, J = 7 Hz, Z-CH_2O), 3.95 (t, J = 7 Hz, E-CH_2O), 6.26 (q, J = 1 Hz, Z-HC=), 6.57 (q, J = 1 Hz, E-HC=), 7.00-7.50 (m, 5 H). ^1H NMR at 300 MHz indicated a 4:1 mixture of E and Z isomers (assigned by NOE studies). Mass spectrum, m/e 244 (M+, 100%), 134 (100%), 111 (26%), 105 (38%), 69 (100%).

Anal. Calcd for $C_{17}H_{24}O$: C, 83.55; H, 9.90. Found: C, 83.41; H, 9.74.

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A Computational Investigation of the "Ortho"-Directing Effect in Cubanecarboxamide

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I. Introduction

A very useful route for the regiospecific synthesis of a variety of polysubstituted aromatic systems makes use of the fact that certain functional groups X promote lithiation of an ortho position on the ring, which is subsequently susceptible to electrophilic attack (Scheme I).[1]

A number of different groups have this directing ability, with tertiary amides being the most effective.[1,2] Other very useful ones include oxazines[3] and oxazolines;[4] these have the advantage of being readily hydrolyzable (to carboxylic acids) once their ortho directing function has been performed. The directing group X is believed to exert its effect via several different mechanisms, including enhancement of the acidity of the neighboring hydrogen (to permit its replacement by Li^+) and also interactions between X and first the lithiating agent and then the lithium after it is in the ortho position.[1b,5]

In recent years, the ortho-lithiation technique has been extended to the synthesis of other types of compounds, including nonaromatic systems.[5,6] In particular, it has been shown that this approach can be used to achieve the functionalization of cubane.[7] *N,N*-Diisopropylcubanecarboxamide was treated with lithium tetramethylpiperidide and, after formation of a mercurated intermediate, eventually yielded both the 2-iodo and the 2,6-diiodo derivatives of the starting amide. It was suggested that the initial lithiated system is stabilized by an interaction

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