In the case of oxazolidines derived from 3-alkyl aldehydes, small chemical shifts differences can be observed only with high-field NMR; for instance, the 2-H peaks ($\delta \sim 3.90$) here again appear at lower field in configuration A where R^2 is the bulkiest alkyl group. However, partial overlap of signals prevents accurate determinations of the diastereomeric ratio. Therefore ^{13}C NMR spectroscopy is by far the most convenient method as regards 3-alkyl-substituted aldehydes.

The reliability of NMR techniques applied to the determination of enantiomeric compositions, compared to the polarimetric method, is widely attested.[1] The empirical rule we suggest is based on 14 compounds: **1–5** and **8–16** whose absolute configurations were already assigned (see Experimental Section). The absolute configuration of 3-*tert*-butylhexanal was deduced from the above general relationship via oxazolidine **6**: the levorotatory enantiomer of this aldehyde shows the *R* configuration and its ee value (66%) was measured from the NMR data. Therefore, the maximum optical rotation $[\alpha]^{20}_D$ may be calculated, −30.7 ± 1.2° (*c* 3, EtOH). Likewise, the calculated maximum optical rotation $[\alpha]^{20}_D$ of (*S*)-3-propylpent-4-enal (corresponding to oxazolidine **7**) is +8.6 ± 0.3° (*c* 1.5, EtOH).

In view of the active current interest[8] on chiral β-substituted aldehydes (and the parent primary alcohols and carboxylic acids), the above examples show that this NMR method may be a useful tool for structural determinations.

Experimental Section

The ^{13}C NMR spectra were recorded on a JEOL FX 90 Q spectrometer as solutions in $CDCl_3$. The ^1H NMR spectra were obtained on Varian T 60, on Brucker 270, and on Cameca 250 spectrometers ($CDCl_3$ solutions). Chemical shifts (δ) are given in ppm, downfield from tetramethylsilane as internal standard. The optical rotations were measured with a Perkin-Elmer 141 polarimeter.

3-Substituted Aldehydes. The optically active 3-substituted aldehydes were prepared by addition of organocuprates[6] to α,β-ethylenic oxazolidines derived from ephedrine and the following commercially available aldehydes: (*E*)-cinnamaldehyde, (*E*)-crotonaldehyde, (*E*)-hexenal, and (*E*)-3-naphthylpropenal.[9] Optical purities are in the range 10–50%. Both partially resolved enantiomers were obtained by using (+)- or (−)-ephedrine. The corresponding racemic aldehydes were prepared from a published procedure[10] and the preceding optically active aldehydes exhibited identical NMR, IR, and MS spectra.

3-Substituted Carboxylic Acids. Oxidations of the aldehydes to their parent carboxylic acids were performed by potassium permanganate under acidic conditions.[11] Optical rotations of the acids and/or the corresponding aldehydes were compared, under identical experimental conditions, to literature data (the following numbers refer to the oxazolidine derivatives): **1** (aldehyde),[12] **1** (acid),[13] **2** (acid),[14a] **3** (acid),[15] **4** (acid),[16] **5** (acid),[16] **8** (acid),[14b] **9** (aldehyde),[17] **10** (acid),[14b] **11** (aldehyde),[18] **12** (acid),[19] **14** (acid),[20] **15** (acid),[21] and **16** (acid).[22] Absolute configuration of **13** (acid) was deduced by chemical correlation (catalytic reduction over Raney nickel[23]) with the corresponding saturated compound **14** (acid).[20]

Oxazolidines were prepared by mixing the aldehyde (2 mmol), (−)-ephedrine (2 mmol)[24] in dichloromethane (4 mL) over molecular sieves (3 Å). The mixture was allowed to stand overnight at room temperature and was then filtered (Celite). The oxazolidines were obtained as colorless or pale yellow oils which were used without any further purification.

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(8) (a) Meyers, A. I.; Smith, R. K.; Whitten, C. E. *J. Org. Chem.* **1979**, *44*, 2250. (b) Mukaiyama, T.; Hayashi, H.; Miwa, T.; Narasaka, K. *Chem. Lett.* **1982**, 1637. (c) Mukaiyama, T.; Iawasawa, N. *Chem. Lett.* **1981**, 913. (d) Hashimoto, S. I.; Yamada, S. I.; Koga, K. *Chem. Pharm. Bull.* **1979**, *27*, 771. (e) Oppolzer, W.; Löher, H. J. *Helv. Chem. Acta* **1981**, *64*, 2808.
(9) Yasuhara, S.; Akiyama, S.; Nakagawa, M. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 3638.
(10) Bourgain-Commercon, M.; Foulon, J. P.; Normant, J. F. *J. Organomet. Chem.* **1982**, *228*, 321.
(11) Ruhoff, J. R.; Noller, C. R.; Patt, M. "Organic Syntheses"; Wiley: New York, 1963; Collect. Vol. II, p 315.
(12) Djerassi, C.; Geller, L. E. *J. Am. Chem. Soc.* **1959**, *81*, 2789.
(13) Overberger, C. G.; Cho, I. *J. Org. Chem.* **1968**, *33*, 3321.
(14) (a) Levene, P. A.; Marker, R. E. *J. Biol. Chem.* **1932**, *98*, 1. (b) Levene, P. A.; Marker, R. E. *J. Biol. Chem.* **1932**, *97*, 563.
(15) Levene, P. A.; Rothen, A. *J. Org. Chem.* **1936**, *1*, 76.
(16) Lardicci, L.; Menicagli, R.; Caporusso, A. M.; Giacomelli, G. *Chem. Ind. (London)* **1973**, 184.
(17) "Merck Index", 9th ed.; Merck & Co.: Rahway, 1976; p 2316.
(18) Hashimoto, S. I.; Kameshino, N.; Yamada, S. I.; Koga, K. *Chem. Pharm. Bull.* **1979**, *27*, 2437.
(19) Menicagli, R.; Lardicci, L.; Botteghi, C. *Chem. Ind. (London)* **1974**, 613.
(20) Brienne, M. J.; Ouannes, C.; Jacques, J. *Bull. Soc. Chim. Fr.* **1967**, 613.
(21) Meyers, A. I.; Whitten, C. E. *J. Am. Chem. Soc.* **1975**, *97*, 6266.
(22) Almy, J.; Cram, D. J. *J. Am. Chem. Soc.* **1969**, *91*, 4459.
(23) Sheenan, J. C.; Chandler, R. E. *J. Am. Chem. Soc.* **1961**, *83*, 4795.
(24) As pointed out by a referee, the accuracy of this method is highly dependent of the optical purity of the derivatizing agent. The optical purity of the (−)-ephedrine (Janssen Chemica) used here is higher than 98%.

Conversion of Shikimic Acid to 5-Enolpyruvylshikimate 3-Phosphate

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The synthesis of (−)-5-enolpyruvylshikimate 3-phosphate (**3**), a principle metabolite in the shikimic acid pathway, has been accomplished in 22% overall yield from the known acetonide **6**. A key intermediate in the synthesis is diester **9**. Direct cyclization of this material affords lactone **10** and distinguishes the three hydroxyl groups of the shikimate nucleus. The phosphate moiety is introduced efficiently with tetrabenzyl pyrophosphate, followed by deprotection with trimethylsilyl bromide. (−)-5-Enolpyruvylshikimic acid (**4**), a secondary metabolite in the shikimate/chorismate pathway, is formed on hydrolysis of **9**.

The shikimate/chorismate biosynthetic pathway is present in plants and a number of microorganisms, converting D-glucose to a variety of metabolites including the aromatic amino acids, folate coenzymes, and quinones of

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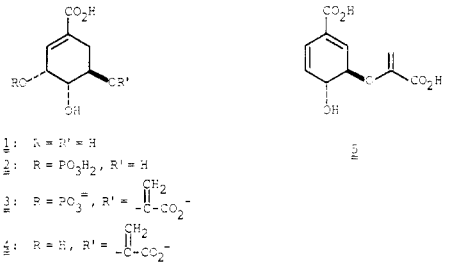
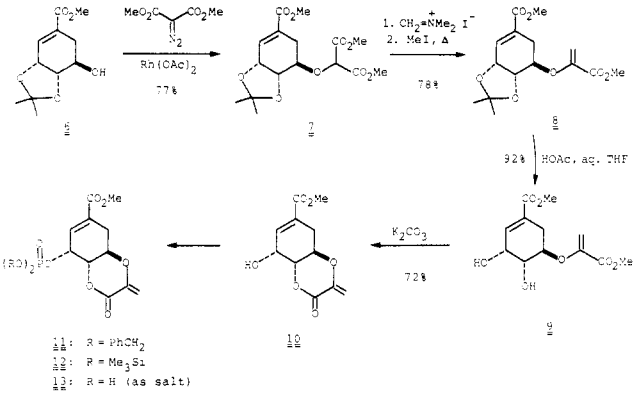
the electron transport system.[1] Chorismic acid (**5**), biosynthesized from shikimic acid (**1**) via shikimate 3-phosphate (**2**) and 5-enolpyruvylshikimate 3-phosphate (**3**) (EPSP), is the key branchpoint intermediate in this pathway. A number of secondary metabolites have also



been found, including 5-enolpyruvylshikimic acid ("compound Z_1") (**4**), arising from the hydrolytic cleavage of the phosphate group of **3**.[2] Interest in these intermediates as targets for synthesis has always been high,[1] but only recent efforts have resulted in the completion of routes to all of these compounds. A number of syntheses of shikimic acid (**1**) have been reported;[3,4] we have described the first synthesis of (±)-shikimate 3-phosphate (**2**);[4] the conversion of shikimic acid to EPSP has been reported by Teng, Yukimoto, and Ganem,[5] and Berchtold and Ganem and their co-workers have completed syntheses of (±)-chorismic acid (**5**)[6,7] and compound Z_1 (**4**).[6a,9] In this report we describe our independent work on the conversion of shikimic acid to EPSP, which leads to a route similar to that reported by Ganem.[5]

The acetonide methyl ester **6**[8] is converted to malonate **7** with dimethyl diazomalonate and rhodium acetate according to the procedure developed by Ganem.[7] In a two-step sequence, enolpyruvylation is accomplished by the condensation of **7** with dimethylmethyleneammonium iodide and triethylamine, followed by alkylation with iodomethane and fragmentation in refluxing acetonitrile. This sequence provides enolpyruvyl ether **8** in an overall yield of 60% from ketal ester **6**. Removal of the acetonide moiety with mild acid (65:35:10; acetic acid/water/tetrahydrofuran) produces diol **9**, which is cyclized directly with



potassium carbonate to give lactone **10** in 66% overall yield from **8**. This procedure represents an improvement of the reported one[5] in that it obviates the necessity of activating the side-chain carbonyl group for ring closure. Direct hydrolysis of diol **9** with 2 equiv of sodium hydroxide affords (−)-5-enolpyruvylshikimic acid (**4**) as reported.[8,9] The spectral characteristics we obtained for lactone **10** and diacid **4** and those reported by Ganem and Berchtold[5,8,9] were identical in all respects.

With the three hydroxy groups of the shikimic acid nucleus differentiated in lactone **10**, our attention focused on the introduction of the phosphate moiety. Any phosphorylation/deprotection scheme has to take into account several factors, including the sterically congested environment of the axial hydroxyl group in **10**, the acid lability of the enol ether side chain, and the propensity of phosphate esters to migrate between the 3- and 4-positions of the shikimate nucleus.[4,9] These factors require that the phosphate moiety be introduced and deprotected under alkaline conditions before the lactone ring of **10** is cleaved. In their solution to this problem, Ganem and co-workers introduced the phosphorus as the bis(*p*-nitrophenethyl) phosphite and converted it to the phosphate by oxidation and elimination.[5,10]

At the outset, we investigated the metaphosphate procedure of Ramirez for direct introduction of the free phosphate group.[11] We were able to generate the desired compound, **13**; however we were not able to drive the reaction to completion and the material proved to be difficult to purify from the polyphosphoric acid byproduct. The latter is presumably generated by competing polymerization of the transiently formed metaphosphate intermediate. In connection with our synthesis of shikimate 3-phosphate (**2**), we found that introduction of the dimethyl phosphate ester could be accomplished readily; however deprotection with trimethylsilyl bromide leads to unacceptable competition from cleavage of the allylic C–O bond.[4] This side reaction can be reduced if a catalytic amount of triphenylphosphine (10 mol %) is included in the reaction mixture. This procedure did not prove to be reproducible, however: hence we directed our effects toward phosphate esters that are more readily cleaved.

Tetrabenzyl pyrophosphate is a stable, crystalline solid formed by the dehydration of dibenzyl phosphate with dicyclohexylcarbodiimide.[12] Phosphorylation of the lithium salt of **10** (lithium diispropylamide) with tetrabenzyl pyrophosphate proceeds at low temperature and affords the labile phosphate triester **11** in 96% yield. On treatment of this material with trimethylsilyl bromide at 0 °C the benzyl esters are cleaved rapidly without competing

(1) Ganem, B. *Tetrahedron* **1978**, *34*, 3353.
(2) Davis, B. D.; Mingioli, E. S. *J. Bacteriol.* **1953**, *66*, 129.
(3) (a) Fischer, H. O. L.; Dangschat, G. *Naturwissenschaften* **1938**, *26*, 562. Dangschat, G.; Fischer, H. O. L. *Biochem. Biophys. Acta* **1950**, *4*, 199. (b) Grewe, R.; Jeschke, J. P. *Chem. Ber.* **1956**, *89*, 2080. Grewe, R.; Buttner, H.; Burmeister, G. *Angew. Chem.* **1957**, *69*, 61. Grewe, R.; Vangermain, E. *Chem. Ber.* **1965**, *98*, 104. (c) Smissman, E. E.; Suh, J. T.; Oxman, M.; Daniels, R. *J. Am. Chem. Soc.* **1959**, *81*, 2909; **1962**, *84*, 1040. (d) McCrindle, R.; Overton, K. H.; Raphael, R. A. *J. Chem. Soc.* **1960**, 1560. (e) Doshi, M. M. *Diss. Abstr.* **1964**, *24*, 3998. (f) Grewe, R.; Hinrichs, I. *Chem. Ber.* **1964**, *97*, 443. Grewe, R.; Kersten, S. *Ibid.* **1967**, *100*, 2546. (g) Bestmann, H. J.; Heid, H. A. *Angew. Chem., Int Ed. Engl.* **1971**, *10*, 336. (h) Cleophax, J.; Mercier, D.; Gero, S. D. *Angew. Chem., Int Ed. Engl.* **1971**, *10*, 652. (i) Snyder, C. D.; Rapoport, H. *J. Am. Chem. Soc.* **1973**, *95*, 7821. (j) Koreeda, M.; Ciufolini, M. A. *J. Am. Chem. Soc.* **1982**, *104*, 2308. (k) Coblens, K. E.; Muralidharan, U. B.; Ganem, B. *J. Org. Chem.* **1982**, *47*, 5040. (l) Yoshikawa, M.; Ikeda, Y.; Kayakiri, H.; Kitagawa, I. *Heterocycles* **1982**, *17*, 209. (m) Fleet, G. W. J.; Shing, T. K. M.; Warr, S. M. *J. Chem. Soc., Perkin Trans. 1* **1984**, 905. (n) Campbell, M. M.; Kaye, A. D.; Sainsbury, M.; Yavarzadeh, R. *Tetrahedron Lett.* **1984**, *25*, 1629. (o) Rajapaksa, D.; Keay, B. A.; Rodrigo, R. *Can. J. Chem.* **1984**, *62*, 826. (p) Mirza, S.; Vasella, A. *Helv. Chim. Acta* **1984**, *67*, 1562.
(4) Bartlett, P. A.; McQuaid, L. A. *J. Am. Chem. Soc.* **1984**, *106*, 7854–7860.
(5) Teng, C.-Y. P.; Yukimoto, Y.; Ganem, B. *Tetrahedron Lett.* **1985**, *26*, 21.
(6) (a) McGowan, D. A.; Berchtold, G. A. *J. Am. Chem. Soc.* **1982**, *104*, 1153; (b) **1982**, *104*, 7036. (c) Hoare, J. H.; Policastro, P. P.; Berchtold, G. A. *J. Am. Chem. Soc.* **1983**, *105*, 6264.
(7) Ganem, B.; Ikota, N.; Muralidharan, V. B.; Wade, W. S.; Young, S. D.; Yukimoto, Y. *J. Am. Chem. Soc.* **1982**, *104*, 6787.
(8) Diels, O.; Fritsche, P. *Chem. Ber.* **1911**, *44*, 3018.
(9) Weiss, U.; Mingioli, E. S. *J. Am. Chem. Soc.* **1956**, *78*, 2894.
(10) Himmelsbach, F.; Pfleiderer, W. *Tetrahedron Lett.* **1982**, *23*, 4793.
(11) Ramirez, F.; Marecek, J. F.; Yemul, S. S. *J. Org. Chem.* **1983**, *48*, 1417.
(12) Khorana, H. G.; Todd, A. R. *J. Chem. Soc.* **1953**, 2257.

formation of the allylic bromide.[13] Direct alkaline hydrolysis of the crude reaction mixture affords EPSP (3), which is purified by anion exchange chromatography on Sephadex A-25 and by cation exchange on Dowex 50W-X8 to give the tetrasodium salt in 63% yield. This procedure for the introduction of the phosphate ester is both higher yielding and considerably more convenient than alternatives involving bis(*p*-nitrophenethyl) phosphate or phosphite derivatives.[4,5]

Experimental Section[14]

Methyl [(1*R*),1α,5β,6α]-5-[Bis(methoxycarbonyl)methoxy]-8,8-dimethyl-7,9-dioxabicyclo[4.3.0]non-2-ene-3-carboxylate (7). To a solution of 6.00 g (26.3 mmol) of **6**[8] and 4.75 g (30.0 mmol) of dimethyl diazomalonate in anhydrous benzene (150 mL) was added 116 mg (0.263 mmol) of Rh_2OAc_4.[7] The greenish blue mixture was stirred at 85 °C for 1.5 h. The solvent was removed under reduced pressure and the residue was purified by chromatography on silica gel with 1.5:1 hexanes/ether to give 7.26 g (77% yield) of the malonate ether **7** as an oil: $[\alpha]^{21}_D$ −49.3° (*c* 4.05, $CHCl_3$); IR (film) 3000, 2960, 1770, 1750, 1720, 1435, 1285, 1245, 1210, 1160, 1130, 1055 cm^{-1}; ^1H NMR δ 6.91 (t, 1, *J* = 2.4), 4.94 (s, 1), 4.76 (m, 1), 4.28 (t, 1, *J* = 7.1), 3.82 (s, 3), 3.80 (s, 3), 3.77 (s, 3), 3.75 (m, 1), 2.88 (dd, 1, *J* = 4.7, 17.6), 2.38 (dddd, 1, *J* = 1.9, 1.9, 8.6, 17.5), 1.43 (s, 3), 1.38 (s, 3); ^{13}C NMR δ 166.9, 166.8, 166.1, 133.8, 130.1, 109.6, 78.33, 77.63, 76.69, 72.43, 52.82, 52.78, 52.05, 27.66, 27.34, 25.54. Anal. Calcd for $C_{16}H_{22}O_9$: C, 53.63; H, 6.19. Found: C, 53.26; H, 6.12.

Methyl [(1*R*),1α,5β,6α]-5-[[1-(Methoxycarbonyl)-ethenyl]oxy]-8,8-dimethyl-7,9-dioxabicyclo[4.3.0]non-2-ene-3-carboxylate (8). To a stirring solution of malonate **7** (14.1 g, 39.2 mmol) and triethylamine (7.10 mL, 39.2 mmol) in dry CH_2Cl_2 (250 mL) was added dimethylmethyleneammonium iodide[15] (8.70 g, 47.0 mmol). The yellow mixture was stirred at 21 °C for 21 h, diluted with CH_2Cl_2, washed with H_2O, and extracted with a 10% aqueous solution of Na_2CO_3. The organic phase was dried and evaporated to give 15.3 g (94% yield) of the Mannich base as a single spot on TLC: IR (film) 3000, 2960, 1770, 1745, 1725, 1250, 1105, 1055, 1045 cm^{-1}; ^1H NMR δ 6.82 (m, 1), 4.73 (m, 1), 4.50 (m, 2), 3.80 (s, 3), 3.79 (s, 3), 3.76 (s, 3), 2.98–2.80 (m, 2), 2.64–2.45 (m, 2), 2.24 (s, 6), 1.38 (s, 3), 1.33 (s, 3); high-resolution mass spectrum, calcd for $C_{19}H_{29}NO_8$ 415.1843, found 415.1850.

The tertiary amine and iodomethane (23.0 mL, 369 mmol) were dissolved in CH_3CN (125 mL) and heated at reflux for 24 h. The mixture was cooled, diluted with ether, and filtered. After evaporation of the solvent, the residue was purified by chromatography on silica gel (ether) to give 9.57 g (83% yield) of enol ether **8** as an oil: $[\alpha]^{21}_D$ −71.8° (*c* 3.09, $CHCl_3$); IR (film) 3000, 2970, 1730, 1625, 1440, 1250, 1205, 1170, 1060 cm^{-1}; ^1H NMR δ 6.92 (m, 1), 5.52 (d, 1, *J* = 2.7), 4.84–4.81 (m, 2), 4.41–4.38 (m, 2), 3.78 (s, 3), 3.77 (s, 3), 2.85–2.75 (m, 2), 2.55–2.42 (m, 2), 1.42 (s, 3), 1.40 (s, 3); ^{13}C NMR δ 166.4, 163.4, 149.6, 134.7, 128.7, 109.7, 97.55, 74.20, 71.94, 52.35, 52.10, 27.74, 25.77, 24.77. Anal. Calcd for $C_{15}H_{20}O_7$: C, 57.68; H, 6.45. Found: C, 57.43; H, 6.43.

(−)-5-Enolpyruvylshikimic Acid (5) and Methyl [(4a*R*),4aβ,8α,8aα]-2,3,4a,5,8,8a-Hexahydro-2-oxo-3-methylene-8-hydroxy-1,4-benzodioxin-6-carboxylate (10). A stirring solution of 3.45 g (11.0 mmol) of ketal **8** in 20 mL of a mixture of 65:35:10 acetic acid/water/tetrahydrofuran was heated at 70 °C for 6 h. The reaction mixture was diluted with CH_2Cl_2, washed with saturated Na_2CO_3, dried, and evaporated to give 2.76 g (92% yield) of diol **9** that proved to be homogenous by TLC: ^1H NMR δ 6.89 (m, 1), 5.52 (d, 1, *J* = 2.7), 4.89 (d, 1, *J* = 2.7), 4.55 (m, 1), 4.39 (m, 1), 3.97 (dd, 1, *J* = 4.0, 8.2), 3.80 (s, 3), 3.76 (s, 3), 2.94 (m, 1), 2.35 (m, 1).

A solution of 0.472 g (1.73 mmol) of **9** in THF (10 mL) was cooled to 0 °C and treated with 3.72 mL (3.63 mmol) of 0.98 N NaOH. The mixture was kept at 21 °C for 2 h and then acidified to pH 3.5 with Dowex 50W-X8 resin in the H^+ form. Filtration and lyophilization afforded a 3:1 mixture of **5** and shikimic acid, from which 0.225 g (53% yield) of pure (−))-5-enolpyruvylshikimic acid (**5**) was obtained by recrystallization from methanol/ether: mp 192–195 °C (lit.[6b] mp 191–193 °C); $[\alpha]^{21}_D$ −213° (*c* 3.00, MeOH); ^1H NMR (CD_3OD) δ 6.71 (m, 1), 5.22 (d, 1, *J* = 1.5), 4.53 (d, 1, *J* = 1.5), 4.41 (dd, 1, *J* = 4.3, 4.3), 4.30 (ddd, 1, *J* = 5.6, 8.5, 8.5), 3.85 (dd, 1, *J* = 4.3, 9.0), 3.10 (dd, 1, *J* = 5.3, 18.1), 2.15 (dd, 1, *J* = 7.4, 18.6).

The remainder of diol **9** (2.28 g, 8.39 mmol) was dissolved in CH_3CN (125 mL), treated with K_2CO_3 (60.0 mg, 0.419 mmol) and heated to 50 °C for 15 h with vigorous stirring. After the mixture was diluted with saturated aqueous NH_4Cl, CH_2Cl_2 was added, and the organic layer was separated, washed with H_2O and brine, dried, and evaporated to give 1.77 g of lactone **10** as a yellow solid. Chromatography on silica gel (4:1 CH_2Cl_2/Et_2O) afforded 1.45 g (72% yield) of pure material as a white solid: mp >220 °C; $[\alpha]^{21}_D$ −117° (*c* 2.23, $CHCl_3$); IR ($CHCl_3$) 3500, 1730, 1320, 1260 cm^{-1}; ^1H NMR δ 6.95 (m, 1), 5.70 (s, 1), 5.13 (s, 1), 4.41 (m, 2), 3.80 (s, 3), 3.18 (dd, 1, *J* = 5.8, 17.3), 2.96 (br s, 1), 2.39 (m, 1); ^{13}C NMR δ 165.8, 159.5, 146.3, 133.8, 130.8, 104.9, 79.26, 67.70, 63.91, 52.37, 30.08. Anal. Calcd for $C_{11}H_{12}O_6$: C, 55.00; H, 5.03. Found: C, 54.70; H, 5.01.

Methyl [(4a*R*),4aβ,8α,8aα]-2,3,4a,5,8,8a-Hexahydro-2-oxo-3-methylene-8-[[bis(phenylmethoxy)phosphinyl]oxy]-4-benzodioxin-6-carboxylate (11). To a solution of 100 mg (0.416 mmol) of lactone **10** in 15 mL of THF at −78 °C was added a solution of lithium diisopropylamide (0.437 mmol) in 10 mL of THF at 0 °C. After 15 min, 269 mg (0.500 mmol) of tetrabenzyl pyrophosphate[12] was added, and the mixture was kept at −78 °C for 1 h. The reaction was warmed to 0 °C over 1.5 h, quenched with 10 mL of saturated aqueous $NaHCO_3$ for 1 h, and partitioned between H_2O and CH_2Cl_2. The organic layer was separated, dried, and evaporated to give 200 mg (96% yield) of phosphate **11** which was of sufficient purity to be carried on to the next step: $[\alpha]^{21}_D$ −111° (*c* 2.05, $CHCl_3$); IR 3060, 3040, 2950, 1740, 1725, 1310, 1280, 1250, 1170, 1080, 1000 cm^{-1}; ^1H NMR δ 7.35 (m, 1), 6.86 (dd, 1, *J* = 2.2, 5.5), 5.71 (d, 1, *J* = 1.5), 5.12 (m, 6), 4.46 (ddd, 1, *J* = 2.0, 4.0, 10.6), 4.18 (ddd, 1, *J* = 6.5, 9.7, 10.0), 3.78 (s, 3), 3.12 (dd, 1, *J* = 6.4, 18.3), 2.34 (ddd, 1, *J* = 2.8, 9.5, 18.3); ^{31}P NMR δ −1.18. A small sample of this material was purified for combustion analysis by preparative plate chromatography (Et_2O). Anal. Calcd for $C_{25}H_{25}O_9P$: C, 60.00; H, 5.03; P, 6.19. Found: C, 59.98; H, 5.26; P, 5.89.

(−)-5-Enolpyruvylshikimate 3-Phosphate, Tetrasodium Salt (EPSP) (3). A solution of 104 mg (0.208 mmol) of phosphate **11** in 3 mL of CH_2Cl_2 at 0 °C was treated with a solution of 0.126 mL (0.957 mmol) of Me_3SiBr and 0.100 mL (2.40 mmol) of pyridine in 2 mL of CH_2Cl_2 at 0 °C for 1.5 h. After the addition of 4 mL of H_2O, the aqueous layer was separated, cooled to 0 °C, and made alkaline with 2.1 mL (2.08 mmol) of 1 N NaOH. After standing for 4.5 h, this solution was applied directly to an anion exchange column, pH 8.2, (DEAE Sephadex A-25, HCO_3^- form) and eluted with a linear gradient of triethylammonium bicarbonate

(13) McKenna, C. E.; Schmidhauser, J. *J. Chem. Soc., Chem. Commun.* **1979**, 739.

(14) All reactions involving moisture-sensitive reagents were performed under a dry nitrogen atmosphere. Tetrahydrofuran and diethyl ether were distilled from sodium/benzophenone. Acetonitrile and methylene chloride were distilled from calcium hydride. Commercial methyl iodide was purified by column chromatography on basic aluminum oxide 90 (Grade I, E. Merck, Darmstadt). Silica gel 60 (E. Merck, Darmstadt) was used in all chromatography. Materials obtained from commercial sources were used without further purification unless otherwise noted.

^1H NMR chemical shifts are reported in parts per million on the δ scale relative to internal tetramethylsilane; data are presented as: chemical shift (multiplicity, number of protons, coupling constants in hertz). The NMR solvent was $CDCl_3$ unless otherwise noted. The ^1H NMR reference in D_2O was residual DOH at 4.63 ppm, and in CD_3OD, the reference was residual CHD_2OD at 3.30 ppm. ^{13}C NMR spectra were acquired at 50.8 and 125 MHz using broad-band ^1H decoupling unless otherwise noted; chemical shifts are reported in ppm on the δ scale relative to $CDCl_3$ at 77.00 ppm and CH_3SOCH_3 at 42.50 ppm in D_2O. ^{31}P NMR spectra were acquired at 81.7 MHz using broad-band ^1H decoupling. Chemical shifts are reported in ppm on the δ scale (downfield positive) relative to dimethyl methylphosphonate at 33.94 ppm in $CDCl_3$ and 39.25 ppm in D_2O. High resolution mass spectral data were obtained with a CEC 21-110 spectrometer using peak matching. In general, reaction workups culminated in drying the organic phase over $MgSO_4$, filtering, and removing the solvent at reduced pressure on a rotary evaporator. Melting points (sealed Pyrex capillaries) are uncorrected. Microanalyses were performed by the Microanalytical Laboratory of the College of Chemistry, University of California, Berkeley.

(15) Schreiber, J.; Maag, H.; Hashimoto, N.; Eschenmoser, A. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 330.

(0.0–0.50 M, pH 8.2). The fractions absorbing at 240 nm were combined and lyophilized to give 106 mg of the tetrakis(triethylammonium) salt of EPSP: ^{1}H NMR (CD_3OD) δ 6.74 (d, 1, J = 3.9), 5.20 (d, 1, J = 1.3), 4.96 (ddd, 1, J = 4.0, 4.0, 8.8), 4.52 (d, 1, J = 1.0), 4.36 (ddd, 1, J = 6.2, 6.2, 7.3), 4.03 (dd, 1, J = 3.9, 8.1), 3.19 (q, 24), 3.99 (dd, 1, J = 5.2, 18.2), 2.25 (dd, 1, J = 5.9, 18.3), 1.29 (t, 36). Cation exchange (Dowex 50W-X8, Na^+ form) and lyophilization afforded 54 mg (63% yield) of **3** as the tetrasodium salt: $[\alpha]^{21}_D$ −124° (c 1.15, H_2O, pH 6.5); UV (H_2O, pH 6.5) $\lambda_{240\,nm}$ (ϵ 2550 M^{-1} cm^{-1}) based on 92% purity as determined by combustion analysis; ^{1}H NMR (D_2O) δ 6.41 (d, 1, J = 2.9), 5.05 (d, 1, J = 2.2), 4.74 (m, 1), 4.55 (d, 1, J = 2.2), 4.31 (ddd, 1, J = 5.5, 5.7, 7.3), 3.97 (dd, 1, J = 3.8, 7.7), 2.74 (dd, 1, J = 4.8, 18.5), 2.13 (dd, 1, J = 6.0, 19.1); ^{13}C NMR (D_2O) δ 174.4, 172.4, 157.0, 139.7, 133.3, 97.12, 76.23, 73.75 (d, J = 4.5), 71.43 (d, J = 3.6), 29.99; ^{31}P NMR (D_2O) δ 1.13. Anal. Calcd for $C_{10}H_9O_{10}PNa_4$: C, 29.14; H, 2.20; P, 7.52. Found: C, 26.88; H, 3.65; P, 7.31.

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Reactions of Oligoethylene Glycol Diglycidyl Ethers with Hydroxy Compounds

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The reactions between oligoethylene glycol diglycidyl ethers and hydroxy compounds were attempted in the presence of an appropriate base. New hydroxy lariat ethers were easily obtained in the reactions with alcohols or phenols in fair to good yields depending on the kind of template metal ions.

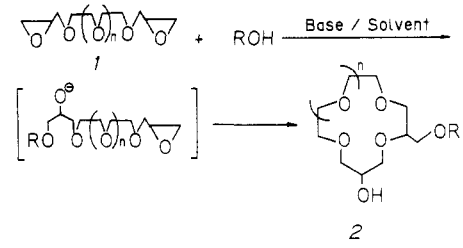
Oligoethylene glycol diglycidyl ethers, which are prepared from epichlorohydrin and oligoethylene glycols, are interesting chemicals used as cross-linking agents in polymer chemistry by utilizing the reactivity of their two epoxy rings.[1]

In a recent patent,[2] Ovchinnikov and Chernoivanov reported the preparation of benzo crown ether derivatives by the reaction of oligoethylene glycol diglycidyl ethers with catechol. we have also previously reported the reaction of these glycidyl ethers with primary amines and ammonia in water or methanol to give a new type of monoaza crown ethers with two hydroxyl groups in fair yields.[3]

In this paper, we describe the reactions of oligoethylene glycol diglycidyl ethers with alcohols, phenols, and glycols. It was found that alkoxymethyl crown ethers with a hydroxyl group (**2**) were obtained rather selectively from the reactions with alcohols, although these reactions were anticipated to give a variety of products including addition products of the objective crown ether and the diglycidyl ether and the linear compounds such as mono- and bis(alkoxymethyl)oligoethylene glycols, and oligomers.

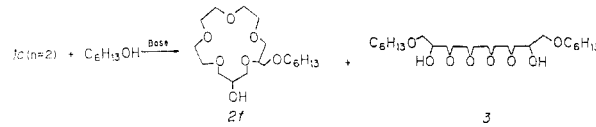
The crown compounds with functional group(s) can be easily converted to polymers,[4] bis(crown ethers),[5] lariat ethers,[6] cryptands,[7] and other derivatives.[8,9] Among the functional crown ethers, synthesis and application of hydroxy crown ethers[10] have been actively investigated re-

Scheme I



1 2

Scheme II



2f 3

Table I. Synthesis of Alkoxymethyl Hydroxy Crown Ethers

compd	R	n	base	solvent	yield (%)
2a	$C_{12}H_{25}$	1	Li	$C_{12}H_{25}OH$	72
2b	tetrahydrofurfuryl	1	Li	*t*-BuOH	59
2c	CH_3	2	Na	*t*-BuOH	34
2d	C_3H_7	2	Na	C_3H_7OH	61
2e	CH_2=$CHCH_2$	2	NaOH	dioxane	53
2f	C_6H_{13}	2	Na	$C_6H_{13}OH$	50
2g	$C_{12}H_{25}$	2	Na	$C_{12}H_{25}OH$	80
2h	$C_{18}H_{37}$	2	Na	*t*-BuOH	48
2i	C_6H_5	2	NaOH	dioxane	46
2j	$C_{12}H_{25}$	3	Na	$C_{12}H_{25}OH$	33

(1) (a) Ochi, M.; Shinbo, M. *Nippon Kagaku Kaishi* **1976**, 1004. (b) Ochi, M.; Takahama, T.; Shinbo, M. *Nippon Kagaku Kaishi* **1979**, 662. (c) Okano, T.; Ikemi, M.; Shinohara, I. *Nippon Kagaku Kaishi* **1977**, 1707.

(2) Ovchinnikov, N. F.; Chernoivanov, V. A. U.S.S.R. Pat. 937,456; *Chem. Abstr.* **1982**, *97*, 198230u.

(3) Kikui, T.; Maeda, H.; Nakatsuji, Y.; Okahara, M. *Synthesis* **1984**, 74.

(4) (a) Smid, J. *Ind. Eng. Chem. Prod. Res. Dev.* **1980**, *19*, 364. (b) Nakatsuji, Y.; Furuyoshi, S.; Okahara, M.; Takemoto, K. *Makromol. Chem.*, in press.

(5) Bourgoin, M.; Wong, K. H.; Hui, J. Y.; Smid, J. *J. Am. Chem. Soc.* **1975**, *97*, 3462.

(6) Dishong, D. M.; Diamond, C. J.; Cinoman, M. I.; Gokel, G. W. *J. Am. Chem. Soc.* **1983**, *105*, 586.

(7) Parsons, D. G. *J. Chem. Soc., Perkin Trans. 1* **1978**, 451.

(8) Nakatsuji, Y.; Kobayashi, H.; Okahara, M. *J. Chem. Soc., Chem. Commun.* **1983**, 800.

(9) Nakatsuji, Y.; Mori, T.; Okahara, M. *Tetrahedron Lett.* **1984**, *25*, 2171.

0022-3263/86/1951-0078$01.50/0