In Table III[17] we list all torsions involving heavy atoms. We also summarize certain dihedral angles. The dihedral angles for a *tert*-butyl group never depart by more than 2 or 3° from 0-120-240. However, the two methyls of an isopropyl usually have a dihedral angle of 125-130°. The R_1R_2 dihedral angle ranges from about 125 to 142° as the size of the groups increases.

In selecting representative standard molecules for making a formal definition of FSE values it must be kept in mind that for any given series the first two or three members may not always be the best candidates since they may show departures of several tenths of a kilocalorie/mole from strict additivity.[25] This is not unexpected; for some series the first member (with $m = 0$) is a special case and cannot be expected to show additivity since the differences with higher homologues lie primarily in the formal bond enthalpy term.

For members having $m > 1$, the bonding perturbation for successive CH_2 units may be expected to be negligible from one series to another, and the effects may be treated as steric in origin. For $m = 1$ the CH_2 group is in a special α-position unless γ = alkyl or cycloalkyl. Similar considerations hold for other units as well. In the definition of the formal steric enthalpy the requirement for special sets of α units is an extnesion of these principles.

Acknowledgment. This work was supported by a grant from the National Science Foundation. We also acknowledge a grant of computing time at The Florida State University Computing Center.

Appendix

For the 15 esters $R_1R_2CHCOOMe$ there are 43 possible staggered conformations as shown in Figure 1. We have devised a nomenclature for these that relies on simplicity rather than generality. Of the R_i groups in the set, only two, Et and *i*-Pr, can adopt more than one staggered conformation. We denote the conformations of the ethyl group in terms of torsions for the sequence CCCC′, designating the three possibilities as $T \cong 180°$, $R \cong 60°$, or $L \cong 300°$. For the *i*-Pr group the unique sequence is HCCC′ with the designations *T*-BAR, *R*-BAR, and *L*-BAR to emphasize that a different sequence is used.

A torsion is defined by looking down a given bond and finding how many degrees in the clockwise direction we must rotate a reference group on the near atom to cause it to eclipse the reference group on the far atom. As an example, for compound **2** of Figure 1 (methyl propionate) the torsion defined by MeCC′=O is about 260°. Although a torsion is geometrically equivalent to a dihedral angle, it is convenient to restrict the term "dihedral angle" to relationships that are not torsions as defined above. An example would be to state that the dihedral angle between two methyl groups of compound **6** of Figure 1 (methyl isobutyrate) is about 130°. The dihedral angle in this example is defined by planes that intersect along the C-C′ bond, one plane passing through each methyl group.

We make use of a "standard" designation for each conformer based on the priority order *i*-Pr, Et, *t*-Bu, Me, H in clockwise sequence, looking from the α-carbon atom toward the carbonyl carbon. This provides a way to keep track of aliases and enantiomers. Since we are dealing with energies, we consider only one enantiomer. As an illustration, the "standard" designation *L*(Et,Me,H) (Figure 1 compound **7C**) is the mirror image of the nonstandard designation *R*(Et,H,Me) while *L*(Et,H,Me) denotes a different conformation, viz. *R*(Et,Me,H), compound **7B**. The sets of torsion values presented in Table III in the supplementary material are not necessarily in the "standard" form. The discrepancies arise from a decision to avoid transcription errors by reporting raw output data. The protocol we have chosen for preparing input data for the molecular mechanics computations was designed to minimize chances of errors; it does not necessarily yield the "standard" sequences.

Registry No. 1, 79-20-9; 2, 554-12-1; 3, 623-42-7; 4, 556-24-1; 5, 10250-48-3; 6, 547-63-7; 7, 868-57-5; 8, 30540-29-5; 9, 19910-30-6; 10, 816-11-5; 11, 32444-33-0; 12, 88246-54-2; 13, 94991-59-0; 14, 54461-01-7; 15, 10250-50-7.

Supplementary Material Available: Table III (formal steric enthalpies of conformations of methyl esters [methyl acetate ... methyl di-*tert*-butylacetate] and Appendix II (specification of conformation) (13 pages). Ordering information is given on any current masthead page.

(25) An excellent summary is given in Reference 23, p 238. The original work is that of Prosen, Johnson, and Rossini.[26]

(26) Prosen, E. J.; Johnson, W. H.; Rossini, F. D. *J. Res. Natl. Bur. Stand.* **1946**, *37*, 51.

Tandem Alkylation-Reduction. Highly Stereoselective Synthesis of (*E*)-1-Hydroxymethyl Methyl Propenyl Ethers from Aldehydes Using 1-Lithio-1-methoxyallene[1,2]

Franz J. Weiberth[3] and Stan S. Hall*

Department of Chemistry, Olson Laboratories, Rutgers University, Newark, New Jersey 07102

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Tandem alkylation-reduction of a series of aldehydes, by alkylating with 1-lithio-1-methoxyallene followed by reducing with lithium-ammonia, regiospecifically and highly stereoselectively affords the 1-hydroxymethyl methyl propenyl ether in which the alkene geometry is exclusively *E*. Aldehydes that have been subjected to this convenient procedure include aromatic, aliphatic, and heterocyclic aldehydes. Subsequent hydrolysis, in the aromatic and aliphatic cases, affords the corresponding α-hydroxy ethyl ketones. The stereochemistry of the propenyl ethers was established by ^{13}C NMR spectroscopy. A mechanism for the selective reduction of the methoxyallene system is proposed.

In ongoing studies extending the utility of tandem alkylation-reductions of carbonyl compounds,[2] we have demonstrated the usefulness of the method for rapid assembly of complex aromatic alkanes,[4a] aromatic alkenes,[4b]

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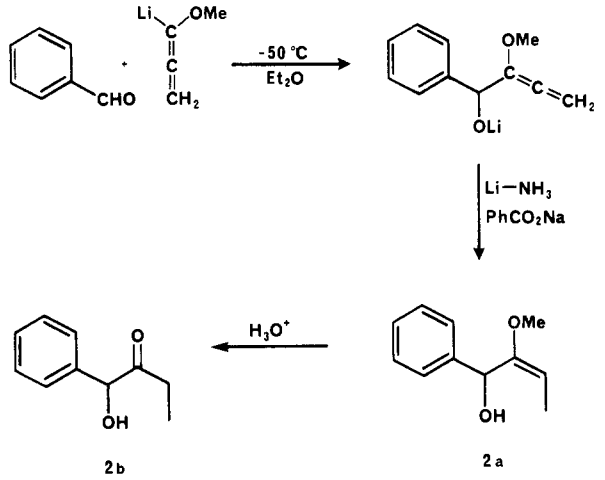
and dienes.[4c,d] Recently our attention turned to alkylating agents that might introduce other functionality using this methodology. Herein is described the use of 1-lithio-1-methoxyallene as a unique alkylating agent that generates the (*E*)-1-hydroxymethyl methyl propenyl ether functionality by alkylation–reduction of aldehydes and the α-hydroxy ethyl ketone functionality after hydrolysis.

An example of the tandem reaction sequence is as follows. Benzaldehyde is immediately added to an ethereal mixture of 1-lithio-1-methoxyallene, generated in situ by the addition of methoxyallene (**1**) to a solution of *n*-butyllithium in Et_2O at −50 °C,[5] in a metal–ammonia reaction assembly. Anhydrous liquid ammonia is condensed into the reaction vessel, and then an excess of lithium wire is added, which turns the mixture a dark blue after 5–10 min. The reluctance of the blue color to establish itself immediately indicates that a reduction is occurring. To avoid over-reductions,[6] the excess reducing agent is then destroyed by the introduction of the aprotic quenching agent sodium benzoate. Normal workup affords (*E*)-2-methoxy-1-phenyl-2-buten-1-ol (**2a**), exclusively, in 80% isolated yield after chromatography. If the crude reaction product containing **2a** is instead hydrolyzed in dilute aqueous hydrochloric acid, 1-hydroxy-1-phenyl-2-butanone (**2b**) is obtained in an overall isolated yield of 80%.



2b 2a

The stereochemistry of the single geometric isomer formed was established in the following manner. Taskinen has shown that the configurational assignments of the geometric isomers of 1,2-disubstituted methyl vinyl ethers can be made with confidence from ^{13}C NMR data[7] and are in agreement with the thermodynamic evidence.[8] With a series of *E* and *Z* 1-substituted methyl propenyl ethers, the signal for the 2-carbon of the *E* isomers was in a range of 87.8–93.9 ppm, while the signal for the 2-carbon of the *Z* isomers was in a range of 102.4–108.7 ppm. All of the 1-substituted methyl propenyl ethers prepared in this study had a C-2 resonance in the range of 91.7–93.6 ppm (Table I),[9] clearly indicating the *E* geometry.[10]

Table I. ^{13}C NMR Chemical Shifts (*E*)-1-Hydroxymethyl Methyl Propenyl Ethers[a]

vinyl ether	carbon (mult)[b]				
	C-1	C-2	C-1′	MeO	C-3
2a	155.01 (s)	93.08 (d)	69.33 (d)	54.47 (q)	11.16 (q)
3a	154.90	92.92	69.11	54.42	11.05
4a	154.96 (s)	92.75 (d)	68.94 (d)	54.42 (q)	10.99 (q)
5a[c]	157.00	91.71	68.06	53.81	10.94
6a	155.51	92.09	67.40	54.25	10.83
7a	154.40 (s)	92.75 (d)	69.28 (d)	54.25 (q)	10.55 (q)
8a	154.52 (s)	93.64 (d)	74.91 (d)	53.92 (q)	11.93 (q)
9a	155.35	92.81	73.53	54.19	11.16
10a[c]	156.67	91.65	71.04	53.48	10.88
11a[c]	156.17	91.82	63.31	53.97	11.00
12a[c]	155.84	92.04	63.92	53.86	10.94
13a	153.08	93.36	64.36	54.69	10.88

[a] Details are in the Experimental Section. Spectra were determined in $CDCl_3$, unless noted otherwise, and the chemical shifts are expressed in ppm relative to a Me_4Si internal standard. [b] In addition to noise (broad-band proton) decoupled spectra, off-resonance proton-decoupled spectra were collected on selected propenyl ethers. [c] Spectra were determined in Me_2SO-d_6 using the Me_2SO signal at 39.444 ppm as reference.

Table II is a listing of the aldehydes that were subjected to this tandem alkylation–reduction sequence, with the structures of the (*E*)-1-hydroxymethyl methyl propenyl ethers and the corresponding hydrolysis products, the α-hydroxy ethyl ketones. The yields represent the isolated yields after purification and are based on the starting aldehydes. Aldehydes **2–7** are a sampling of aromatic aldehydes whose aromatic rings, after alkylation of the carbonyl group, survived the mild reduction conditions. Apparently with **5**, the aprotic quench also ensured the resilience of the 3,4-methylenedioxy group to reductive cleavage. With *trans*-cinnamaldehyde (**6**), the trans double bond is expected to reduce, since after alkylation a styrene system is still present, which reduces rapidly in metal–ammonia.[11] The alkylation–reduction sequence apparently is not sensitive to steric effects since the alkyl aldehydes **8–10** all gave reasonable results. All of the heterocyclic rings of the heterocyclic aldehydes **11–13** after alkylation also survived these metal–ammonia conditions. The heterocyclic 1-hydroxymethyl methyl propenyl ethers **11a–13a** are all rather unstable, especially thiophene **12a**, and all polymerized during the hydrolysis sequence.

(1) Disclosed in part at: (a) 189th National Meeting of the American Chemical Society, Miami Beach, FL, April 28–May 3, 1985; Orgn 13. (b) 19th Middle Atlantic Regional Meeting of the American Chemical Society, West Long Branch, NJ, May 21–23, 1985; Orgn 206. And as a poster at: (c) 29th National Organic Chemistry Symposium of the American Chemical Society, Newark, DE, June 16–20, 1985; B4.

(2) (a) Alkylation-Reduction of Carbonyl Systems. 14. Part 13: Schumacher, D. P.; Hall, S. S. *J. Org. Chem.* **1981**, *46*, 5060–5064. See also: (b) Schumacher, D. P.; Hall, S. S. *J. Am. Chem. Soc.* **1982**, *104*, 6076–6080. (c) Hall, S. S.; Loebenberg, D.; Schumacher, D. P. *J. Med. Chem.* **1983**, *26*, 469–475.

(3) Address: Hoechst-Roussel Pharmaceuticals Inc., Somerville, NJ 08876; where this research was executed.

(4) (a) Hall, S. S.; Lipsky, S. D. *J. Org. Chem.* **1973**, *38*, 1735–1738. (b) McEnroe, F. J.; Sha, C.-K.; Hall, S. S. *J. Org. Chem.* **1976**, *41*, 3465–3468. (c) Ryan Zilenovski, J. S.; Hall, S. S. *J. Org. Chem.* **1979**, *44*, 1159–1161. (d) Ryan Zilenovski, J. S.; Hall, S. S. *J. Org. Chem.* **1981**, *46*, 4139–4142.

(5) (a) Hoff, S.; Brandsma, L.; Arens, J. F. *Recl. Trav. Chim. Pays-Bas* **1968**, *87*, 916–924; (b) 1179–1184; (c) **1969**, *88*, 609–619.

(6) Using the protic quenching agent ammonium chloride with 4-*tert*-butylbenzaldehyde afforded a mixture of **3a**, (*E*)-2-methoxy-1-(4-*tert*-butylphenyl)-2-butene, and 1-(4-*tert*-butylphenyl)butane.

(7) Taskinen, E. *Tetrahedron* **1978**, *34*, 425–427.

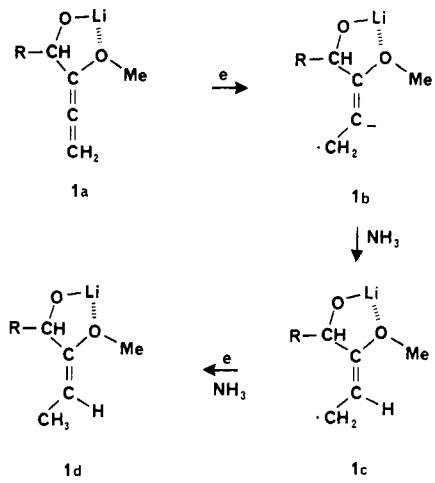
(8) (a) Taskinen, E. *J. Chem. Thermodyn.* **1974**, *6*, 271–280; (b) 345–353. (c) Taskinen, E.; Liukas, P. *Acta Chem. Scand.* **1974**, *B28*, 114–120.

(9) ^{13}C NMR spectra of the crude alkylation–reduction reactions contained no signal in the 102–109 ppm region, thus ruling out the possibility that had any *Z* 1-substituted methyl propenyl ether been formed it might have been selectively removed (or discarded) during the purification process.

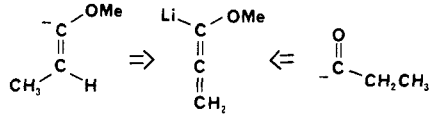
(10) Nuclear Overhauser enhancement experiments on **2a** reinforced the *E* configuration assignment. Irradiation at δ 3.53 (MeO) resulted in a 4% increase in the signal at δ 4.67 and a 14% decrease in the signal at δ 1.73. Irradiation at δ 1.73 (Me) enhanced the signal at δ 5.58 by 5% and reduced the signal at δ 3.53 by 2%.

(11) (a) Smith, M. In "Reduction"; Augustine, R. L., Ed.; Marcel Dekker: New York, 1968; pp 118–119. (b) Smith, H. In "Organic Reactions in Liquid Ammonia. Chemistry in Nonaqueous Ionizing Solvents", Part 2; Wiley: New York, 1963; Vol. I, p 228.

A suggested mechanism for the regiospecific and highly stereoselective reduction of the methoxyallene functional group is as follows. An electron adds to the less electron-rich double bond of the methoxyallene alkoxide intermediate **1a** to form the anion radical **1b**,[12] which is immediately trapped by protonation by ammonia to generate the allylic radical **1c**. This radical is then rapidly reduced to the allylic anion, which is protonated, and on workup the (*E*)-1-hydroxymethyl methyl propenyl ether is isolated. The stereoselectivity of the reduction is controlled by the geometry of vinylic anion radical **1b**. This anion radical intermediate **1b** prefers the s-cis conformation in which the lone-pair orbitals on oxygen of the methoxy group can overlap with the π orbital of the double bond as well as chelate with the lithium ion of the alkoxide.[8,13] This preferred s-cis conformation then dictates an *E* geometry to avoid serious steric interactions between the methyl of the methoxy group and the methylene radical group,[14] and when **1b** protonates, the stereochemistry (and the regiochemistry) of the reduction is established.



With this convenient tandem sequence, it has been demonstrated that (*E*)-1-hydroxymethyl methyl propenyl ethers and α-hydroxy ethyl ketones can be rapidly assembled from aldehydes.[15] Noteworthy as the alkylating agent in this tandem alkylation–reduction sequence is 1-lithio-1-methoxyallene, which serves as both a 1-lithio methyl (*E*)-propenyl ether equivalent and, coupled with hydrolysis, a propionyl anion equivalent.[16]



(12) (a) Dietz, R.; Peover, M. E.; Wilson, R. *J. Chem. Soc. B* **1968**, 75–80. (b) Dowd, P. *J. Chem. Soc., Chem. Commun.* **1965**, 568–569.

(13) Mersh, J. D.; Sanders, J. K. M. *Tetrahedron Lett.* **1981**, *22*, 4029–4032.

(14) An alternate explanation is that the anion of the vinylic anion radical **1b** prefers to be cis with the methyl ether to enable chelation through a lithiated four-membered ring. See: (a) Zweifel, G.; Rajagopalan, S. *J. Am. Chem. Soc.* **1985**, *107*, 700–701. (b) Lau, K. S. Y.; Schlosser, M. *J. Org. Chem.* **1978**, *43*, 1595–1598. (c) Vlattas, I.; Vecchia, L. D.; Lee, A. O. *J. Am. Chem. Soc.* **1976**, *98*, 2008–2010.

(15) To date, an analogous selective alkylation–reduction reaction with ketones has not been achieved.

(16) This procedure compliments the acyl anion equivalent method of Baldwin using (1-methoxyvinyl)lithium to prepare 1-hydroxymethyl methyl vinyl ethers and α-hydroxy methyl ketones. Baldwin, J. E.; Höfle, G. A.; Lever, O. W., Jr. *J. Am. Chem. Soc.* **1974**, *96*, 7125–7127.

Experimental Section[17]

All glassware was oven dried, quickly assembled, and then allowed to cool to ambient temperature under a nitrogen atmosphere. The alkylations were performed under a static nitrogen atmosphere with a Firestone oil bubbler valve. When ammonia was to be introduced, the N_2 source was disconnected and the reaction protected from moisture by attaching a soda–lime drying tube to the side arm of the Dewar condenser for the duration of the reduction. Anhydrous ethyl ether was further dried over 3-Å molecular sieves. *n*-Butyllithium (2.7 M in hexane) was from Aldrich Chemical Co. Methoxyallene (bp 51–52 °C) was prepared by a simplified method of Hoff et al.[5a] and is stable for at least 2 months when stored neat under nitrogen in all-glass containers at or below +5 °C. Potassium *tert*-butoxide was from Callery Chemical Co. 4-*tert*-Butylbenzaldehyde (bp 105–107 °C (4.6 torr)) from Givaudan Corp. and benzaldehyde (bp 106–108 °C (87 torr)), 4-methoxybenzaldehyde (bp 130–131 °C (27 torr)), and 3-methyl-2-thiophenecarboxaldehyde (bp 118–119 °C (45 torr)) from Aldrich Chemical Co. were redistilled just prior to use. 3,4-(Methylenedioxy)benzaldehyde, *trans*-cinnamaldehyde, phenylacetaldehyde, trimethylacetaldehyde, isobutyraldehyde, cyclohexanecarboxaldehyde, *N*-methyl-2-pyrrolecarboxaldehyde, 5-methyl-2-furfural, and methyl propargyl ether from Aldrich Chemical Co. were used without further purification. Anhydrous ammonia was distilled through a tower of potassium hydroxide pellets directly into the reaction vessel. Lithium wire (0.32-cm diameter, high purity,[18] Foote Mineral Co.) was wiped free of oil, rinsed in hexane, and cut into 0.5-cm pieces just prior to use. Gas–liquid chromatographic analyses were performed on a 180 cm × 4 mm (i.d.) glass column packed with 3% OV-17 (50% phenyl, methyl) supported on 60–80 mesh Gas-Chrom Q. Purification by column chromatography was accomplished on 100–200 mesh Floridin magnesium silicate (Florisil), 80–200 mesh alumina (Fisher), and 70–230 mesh silica gel 60 (E. Merck). The assigned structure of each product was consistent with the spectral data. Satisfactory composition analyses (±0.4% for C and H) were obtained for all products except for **11a** and **12a**, the latter of which was very unstable. As a precaution, all purified products were stored at −20 °C under N_2.

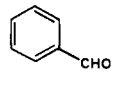
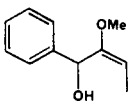
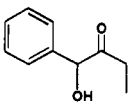
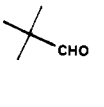
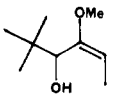
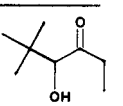
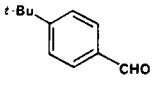
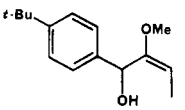
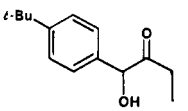
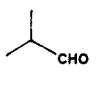
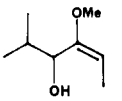
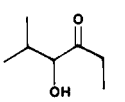
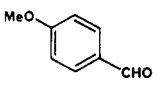
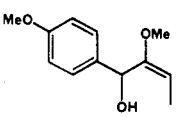
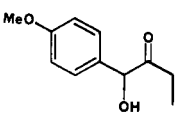
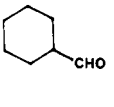
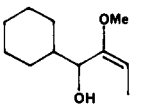
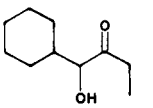
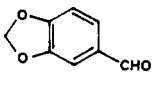
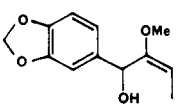
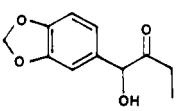
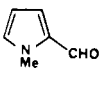
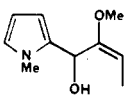
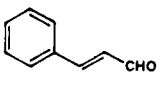
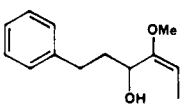
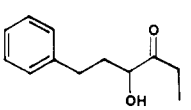
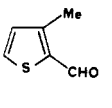
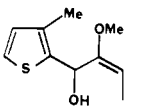
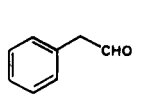
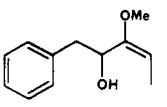
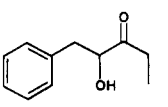
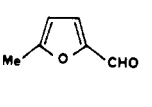
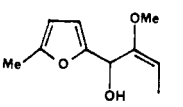
Methoxyallene (1). After the reflux temperature of a mixture of 84.0 g (1.20 mol) of methyl propargyl ether and 13.4 g (0.12 mol) of finely divided potassium *tert*-butoxide under N_2 had dropped from 55 to 52 °C (the refluxing liquor color changed from pale yellow to brown), the reflux condenser was replaced with a distillation head and condenser to afford 68.0 g (0.97 mol, 81%) of **1** as a colorless oil: bp 51–52 °C;[5a] ^{1}H NMR ($CDCl_3$) δ 6.77 (1 H, t, J = 5.9 Hz), 5.48 (2 H, d, J = 5.9 Hz), 3.42 (3 H, s).

(*E*)-2-Methoxy-1-phenyl-2-buten-1-ol (2a). To a cold (−50 °C), stirred solution of 10.66 mL (28.8 mmol, 2.7 M in hexane) of *n*-butyllithium in 30 mL of anhydrous Et_2O under a static N_2 atmosphere was added (ca. 1 min) a solution of 2.50 mL (2.29 g, 32.7 mmol) of methoxyallene in 7 mL of Et_2O. After 2 min, a solution of 1.59 g (15.0 mmol) of benzaldehyde in 7 mL of Et_2O_3 was added (1 min). After the mixture was stirred at −50 °C for 10 min, the N_2 source was replaced with a soda–lime drying trap and then ca. 175 mL of anhydrous ammonia was distilled into the mixture. Within ca. 5–10 min after the rapid addition of 600 mg (86.4 mmol, 32 pieces) of lithium wire, the vigorously stirred mixture turned dark blue. Fifteen minutes later ca. 2.0 g of sodium benzoate was added to discharge the dark blue mixture. After

(17) GLC analyses were performed on a Perkin-Elmer Model 2920B chromatograph (flame ionization detector) using a 30 mL/min helium gas flow rate. The IR spectra were determined with a Pye Unicam Model SP3-200 grating or a Perkin-Elmer Model 727 spectrophotometer. All NMR spectra were determined in $CDCl_3$ or Me_2SO-d_6, and the chemical shifts are expressed in δ values (ppm) relative to a Me_4Si internal standard. The ^{1}H NMR spectra were determined at 200 MHz with a Varian Model XL-200 Fourier transform spectrometer. The ^{13}C NMR spectra were determined at 15 MHz with a JEOL Model FX-60 spectrometer. Noise (broad-band proton) decoupled spectra was collected on all (*E*)-1-hydroxymethyl methyl propenyl ethers, and off-resonance proton-decoupled spectra were collected for a few selected propenyl ethers. Mass spectra were determined on a Finnigan Model 4023 spectrometer [EI or CI (methane)] with an INCOS data system attachment. Elemental analyses were performed by Micro-Tech Laboratories, Inc., Skokie, IL.

(18) This lot contained 0.012% Ca, 0.011% Na, and 0.008% K.

Table II. Tandem Alkylation-Reduction of Aldehydes with 1-Lithio-1-methoxyallene[a]

aldehyde	alkyln-redn product (% yield)[b]	hydrolysis product (% yield)[b]	aldehyde	alkyln-redn product (% yield)[b]	hydrolysis product (% yield)[b]
 2	 2a (80)	 2b (80)	 8	 8a (72)	 8b (67)
 3	 3a (79)	 3b (83)	 9	 9a (71)	 9b (61)
 4	 4a (83)	 4b (78)	 10	 10a (75)	 10b (73)
 5	 5a (61)	 5b (57)	 11	 11a (79)	
 6	 6a (63)	 6b (59)	 12	 12a (70)	
 7	 7a (52)	 7b (40)	 13	 13a (71)	

[a] Experimental details are in the Experimental Section. [b] Isolated yields, after column chromatography, are based on the starting aldehyde.

the ammonia was allowed to evaporate from the yellow-green slurry, the residue was partitioned between 60 mL of Et_2O and 125 mL of H_2O. The aqueous phase was subsequently extracted three times with 35-mL portions of Et_2O, and the combined organic phase was dried (Na_2SO_4), filtered, and concentrated at water aspirator pressure (40 °C water bath) to afford 2.87 g of a yellow oil. Following chromatography (Florisil, Et_2O–hexane gradient), 2.14 g (12.0 mmol, 80%) of **2a** was obtained as a pale yellow oil: IR ($CHCl_3$) 3570, 3475 (br), 3100, 3070, 3040, 3010, 2960, 2945, 2880, 2845, 1675, 1600, 1495, 1450, 1405, 1355, 1220, 1100, 1050, 1030, 985, 850, 700 cm^{-1}; ^1H NMR ($CHCl_3$) δ 7.44–7.24 (5 H, m), 5.58 (1 H, d, J = 9.0 Hz, collapses to a s with D_2O), 4.67 (1 H, q, J = 7.0 Hz), 3.53 (3 H, s), 2.85 (1 H, d, J = 9.1 Hz, exchanges with D_2O), 1.73 (3 H, d, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$, off-resonance proton and broad-band proton decoupling) 155.01 (s), 142.14 (s), 128.22 (2 C, d), 127.22 (d), 125.90 (2 C, d), 93.08 (d), 69.33 (d), 54.47 (q), 11.16 (q) ppm; mass spectrum, m/z (relative intensity) 179 (4), 178 (M^+, 28), 162 (35), 161 (100), 147 (11), 146 (12), 145 (11), 131 (32), 130 (18), 129 (58), 115 (18), 107 (33), 105 (47), 91 (20), 79 (43), 77 (54), 57 (28). Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 73.80; H, 7.80.

1-Hydroxy-1-phenyl-2-butanone (2b). After a mixture of 1.00 g of crude **2a** in 5.0 mL of 2 N HCl and 25 mL of H_2O was stirred for 16 h, the mixture was diluted with 25 mL of Et_2O and separated. The aqueous phase was saturated with NaCl and then extracted three times with 20-mL portions of Et_2O, and the combined organic phase was dried ($MgSO_4$), filtered, and concentrated at water aspirator pressure to afford 0.87 g of a pale yellow oil. Following chromatography (silica gel, Et_2O–hexane, 1:5), 0.69 g (4.2 mmol, 80% based on benzaldehyde) of **2b** was obtained as a pale yellow oil: IR ($CHCl_3$) 3470, 3060, 3010, 2980, 2940, 2880, 1710, 1600, 1490, 1455, 1380, 1350, 1190, 1135, 1095, 1025, 975, 700 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 7.38–7.30 (5 H, m), 5.97 (1 H, d, J = 4.6 Hz, exchanges with D_2O), 5.07 (1 H, d, J = 4.4 Hz, collapses to a s with D_2O), 2.48 (2 H, q, J = 7.4 Hz), 0.84 (3 H, t, J = 7.3 Hz); CI (CH_4) mass spectrum, m/z (relative intensity) 165 (M^+ + 1, 17), 148 (19), 147 (100), 119 (24), 107 (2), 105 (10). Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37. Found: C, 73.38; H, 7.53.

(*E*)-2-Methoxy-1-(4-*tert*-butylphenyl)-2-buten-1-ol (3a). Similar treatment of 2.43 g (15.0 mmol) of 4-*tert*-butylbenzaldehyde and 2.50 mL (2.29 g, 32.7 mmol) of methoxyallene, as described for **2a**, afforded 3.56 g of a yellow oil. Following chromatography (Florisil, Et_2O–hexane gradient), 2.76 g (11.9 mmol, 79%) of **3a** was obtained as a pale yellow oil: IR ($CHCl_3$) 3570, 3475 (br), 3090, 3050, 3010, 2970, 2910, 2870, 2840, 1670, 1605, 1510, 1460, 1410, 1390, 1360, 1270, 1220, 1100, 1040, 1020, 980, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40 (4 H, s), 5.58 (1 H, d, J = 9.0 Hz, collapses to a s with D_2O), 4.84 (1 H, q, J = 7.2 Hz), 3.56 (3 H, s), 2.85 (1 H, d, J = 9.0 Hz, exchanges with D_2O), 1.75 (3 H, d, J = 7.2 Hz), 1.33 (9 H, s); ^{13}C NMR ($CDCl_3$) 154.90, 150.04, 139.05, 125.57 (2 C), 125.13 (2 C), 92.92, 69.11, 54.42, 34.36, 31.27 (3 C), 11.05 ppm; mass spectrum, m/z (relative intensity) 235 (3), 234 (M^+, 21), 219 (9), 202 (2), 201 (2), 187 (25), 177 (7), 163 (25), 161 (28), 159 (12), 145 (24), 133 (14), 117 (12), 115 (16), 105 (17), 91 (30), 79 (11), 77 (19), 72 (55), 71 (31), 57 (100), 56 (27), 55 (19), 41 (100). Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.76; H, 9.64.

1-Hydroxy-1-(4-*tert*-butylphenyl)-2-butanone (3b). Similar treatment of 600 mg of crude **3a** in 2.3 mL of 2 N HCl and 15 mL of H_2O, as described for **2b**, afforded 550 mg of a pale yellow oil. Following chromatography (silica gel, Et_2O–hexane, 1:5), 462 mg (2.1 mmol, 83% based on 4-*tert*-butylbenzaldehyde) of **3b** was obtained as a colorless oil: IR ($CHCl_3$) 3470, 3080, 3020, 3000, 2970, 2900, 2865, 1710, 1605, 1500, 1455, 1405, 1385, 1360, 1350, 1265, 1130, 1120, 1105, 1080, 1020, 975, 870, 825 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.42 (2 H, dd, J = ca. 8 and 2 Hz), 7.26 (2 H, dd, J = ca. 8 and 2 Hz), 5.12 (1 H, br d, J = ca. 4 Hz, collapses to a s with D_2O), 4.33 (1 H, br d, J = 4 Hz, exchanges with D_2O), 2.42 (2 H, q, J = ca. 7 Hz), 1.32 (9 H, s), 1.04 (3 H, t, J = ca. 7 Hz); CI (CH_4) mass spectrum, m/z (relative intensity) 221 ($M^+ + 1$, 2), 219 (4), 205 (3), 175 (2), 163 (41), 161 (15), 149 (9), 148 (7), 147 (100), 133 (1), 119 (2), 107 (3), 105 (2). Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.04; H, 9.16.

(*E*)-2-Methoxy-1-(4-methoxyphenyl)-2-buten-1-ol (4a). Similar treatment of 2.04 g (15.0 mmol) of 4-methoxybenzaldehyde and 2.50 mL (2.29 g, 32.7 mmol) of methoxyallene, as described for **2a**, afforded 3.13 g of a yellow oil. Following chromatography (Florisil, Et_2O–hexane, 1:3), 2.59 g (12.5 mmol, 83%) of **4a** was obtained as a colorless oil: IR ($CHCl_3$) 3580, 3475 (br), 3075, 3040, 3010, 2970, 2950, 2850, 1670, 1615, 1585, 1510, 1465, 1395, 1305, 1250, 1210, 1175, 1105, 1035, 980, 870, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.33 (2 H, d, J = 8.9 Hz), 6.87 (2 H, d, J = 8.9 Hz), 5.53 (1 H, br d, J = ca. 5 Hz, collapses to a s with D_2O), 4.65 (1 H, q, J = 6.8 Hz), 3.79 (3 H, s), 3.54 (3 H, s), 2.81 (1 H, br d, J = ca. 5 Hz, exchanges with D_2O), 1.71 (3 H, d, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$, off-resonance proton and broad-band proton decoupling) 158.77 (s), 154.96 (s), 134.24 (s), 127.06 (2 C, d), 113.58 (2 C, d), 92.75 (d), 68.94 (d), 55.13 (q), 54.42 (q), 10.99 (q) ppm; mass spectrum, m/z (relative intensity) 209 (4), 208 (M^+, 31), 191 (19), 177 (10), 176 (21), 175 (8), 161 (13), 159 (11), 151 (7), 147 (11), 145 (10), 138 (16), 137 (92), 136 (16), 135 (74), 121 (46), 115 (15), 109 (81), 94 (65), 92 (20), 91 (27), 79 (20), 78 (24), 77 (90), 72 (98), 71 (41), 66 (45), 65 (42), 57 (57), 56 (42), 55 (44), 51 (41), 41 (100). Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.43; H, 7.85.

1-Hydroxy-1-(4-methoxyphenyl)-2-butanone (4b). Similar treatment of 800 mg of crude **4a** in 40 mL of 5% H_2SO_4, as described for **2b**, afforded 680 mg of a pale yellow oil. Following chromatography (silica gel, Et_2O–hexane, 1:5), 580 mg (3.0 mmol, 78% based on 4-methoxybenzaldehyde) of **4b** was obtained as a pale yellow oil: IR ($CHCl_3$) 3470, 3025, 3005, 2985, 2970, 2945, 2915, 2845, 1710, 1615, 1585, 1510, 1460, 1440, 1380, 1350, 1305, 1255, 1180, 1135, 1115, 1085, 1035, 980, 830 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.24 (2 H, dd, J = ca. 8 and 1 Hz), 6.91 (2 H, dd, J = ca. 8 and 1 Hz), 5.06 (1 H, br s), 4.31 (1 H, br s, exchanges with D_2O), 3.82 (3 H, s), 2.34 (2 H, q, J = 7 Hz), 1.00 (3 H, t, J = ca. 7.0 Hz); CI (CH_4) mass spectrum, m/z (relative intensity) 195 ($M^+ + 1$, 15), 178 (13), 177 (100), 149 (14), 137 (20), 135 (10), 109 (5). Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.26. Found: C, 67.86; H, 7.40.

(*E*)-2-Methoxy-1-[3,4-(methylenedioxy)phenyl]-2-buten-1-ol (5a). Similar treatment of 2.25 g (15.0 mmol) of 3,4-(methylenedioxy)benzaldehyde and 2.50 mL (2.29 g, 32.7 mmol) of methoxyallene, as described for **2a**, afforded 2.54 g of a pale yellow oil. Following chromatography (Florisil, Et_2O–hexane, 1:3), 2.03 g (9.2 mmol, 61%) of **5a** was obtained as a colorless oil: IR ($CHCl_3$) 3550, 3450 (br), 3040, 3000, 2940, 2900, 2840, 2795, 1670, 1610, 1500, 1485, 1440, 1400, 1350, 1240, 1100, 1035 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 6.86 (1 H, s), 6.80 (2 H, apparent s), 5.96 (2 H, s), 5.36 (2 H, apparent s, 1 H exchanges with D_2O), 4.49 (1 H, q, J = 7.0 Hz), 3.36 (3 H, s), 1.70 (3 H, d, J = 7.0 Hz); ^{13}C NMR (Me_2SO-d_6) 157.00, 146.83, 145.78, 137.23, 118.89, 107.45, 106.62, 100.60, 91.71, 68.06, 53.81, 10.94 ppm; mass spectrum, m/z (relative intensity) 223 (5), 222 (M^+, 36), 205 (11), 204 (6), 191 (5), 190 (7), 189 (5), 175 (15), 161 (7), 159 (6), 151 (53), 150 (24), 149 (54), 135 (18), 131 (11), 123 (18), 122 (13), 121 (19), 115 (7), 103 (20), 93 (100), 77 (22), 72 (31), 65 (96), 63 (32), 41 (44). Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.95; H, 6.32.

1-Hydroxy-1-[3,4-(methylenedioxy)phenyl]-2-butanone (5b). Similar treatment of 1.00 g of crude **5a** in 3.2 mL of 2 N HCl and 30 mL of H_2O, as described for **2b**, afforded 0.93 g of a yellow oil. Following chromatography (silica gel, Et_2O–hexane, 1:3), 0.70 g (3.4 mmol, 57% based on 3,4-(methylenedioxy)-benzaldehyde) of **5b** was obtained as a pale yellow oil: IR ($CHCl_3$) 3450, 3040, 2990, 2950, 2900, 2795, 1710, 1615, 1505, 1485, 1445, 1245, 1105, 1085, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.80 (2 H, s), 6.73 (1 H, s), 5.96 (2 H, s), 5.00 (1 H, s), 4.32 (1 H, br s, exchanges with D_2O), 2.37 (2 H, q, J = 7.3 Hz), 1.01 (3 H, t, J = 7.3 Hz); mass spectrum, m/z (relative intensity) 209 (1), 208 (M^+, 7), 179 (1), 151 (45), 150 (20), 149 (100), 123 (7), 121 (19), 93 (37), 65 (35), 63 (14). Anal. Calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.62; H, 5.82.

(*E*)-4-Methoxy-1-phenyl-4-hexen-3-ol (6a). Similar treatment of 1.99 g (15.0 mmol) of *trans*-cinnamaldehyde and 2.50 mL (2.29 g, 32.7 mmol) of methoxyallene, and using 750 mg (108 mmol) of lithium, as described for **2a**, afforded 3.17 g of a yellow oil. Following chromatography (Florisil, Et_2O–hexane, 1:4), 1.94 g (9.5 mmol, 63%) of **6a** was obtained as a pale yellow oil: IR ($CHCl_3$) 3555, 3475 (br), 3000, 2940, 2870, 2840, 2800, 1675, 1605, 1500, 1460, 1415, 1355, 990, 850 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 7.31–7.11 (5 H, m), 4.71 (1 H, d, J = 5.9 Hz, exchanges with D_2O), 4.44 (1 H, q, J = 6.9 Hz), 4.28 (1 H, td, J = 7.0 and 5.9 Hz, collapses to a t with D_2O), 3.42 (3 H, s), 2.59–2.46 (2 H, m), 1.80 (2 H, apparent septet, J = ca. 7.5 Hz), 1.54 (3 H, d, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) 155.51, 141.92, 128.33 (4 C), 125.68, 92.09, 67.40, 54.25, 36.96, 31.77, 10.83 ppm; mass spectrum, m/z (relative intensity) 206 (M^+, 0.6), 204 (0.7), 188 (0.5), 173 (1), 159 (3), 141 (2), 131 (2), 115 (4), 105 (7), 104 (4), 103 (9), 102 (100), 101 (22), 91 (29), 87 (10), 77 (8), 73 (6), 69 (11), 65 (7), 55 (6), 43 (6), 41 (18). Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.79. Found: C, 75.89; H, 8.58.

3-Hydroxy-1-phenyl-4-hexanone (6b). Similar treatment of 1.00 g of crude **6a** in 3.2 mL of 2 N HCl and 30 mL of H_2O, as described for **2b**, afforded 0.88 g of a yellow oil. Following chromatography (silica gel, Et_2O–hexane, 1:6), 0.53 g (2.8 mmol, 59% based on *trans*-cinnamaldehyde) of **6b** was obtained as a pale tan oil: IR ($CHCl_3$) 3460, 3070, 3040, 3005, 2990, 2950, 2875, 1710, 1605, 1500, 1455, 1390, 1350, 1265, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30–7.19 (5 H, m), 4.17 (1 H, dd, J = 8.3 and 3.4 Hz), 3.62 (1 H, br s, exchanges with D_2O), 2.75 (2 H, two overlapping m, at least a 10-line pattern), 2.45 (1 H, dq, J = 13.8 and 7.2 Hz) superimposed on 2.44 (1 H, dq, J = 13.8 and 7.2 Hz), 2.13 (1 H, complex m, at least an eight-line pattern), 1.81 (1 H, m, at least an eight-line pattern), 1.08 (3 H, t, J = 7.3 Hz); mass spectrum, m/z (relative intensity) 193 (0.1), 192 (M^+, 0.3), 175 (0.3), 134 (17), 117 (7), 105 (21), 92 (23), 91 (100), 88 (32), 78 (10), 77 (9), 65 (12), 59 (21), 57 (15), 51 (7), 41 (7). Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 75.35; H, 8.36.

(*E*)-3-Methoxy-1-phenyl-3-penten-2-ol (7a). Similar treatment of 1.80 g (15.0 mmol) of phenylacetaldehyde and 2.50 mL (2.29 g, 32.7 mmol) of methoxyallene, as described for **2a**, afforded 2.57 g of a yellow oil. Following chromatography (Florisil, Et_2O–hexane, 1:3), 1.50 g (7.8 mmol, 52%) of **7a** was obtained as a pale yellow oil: IR ($CHCl_3$) 3545, 3425 (br), 3070, 3050, 3025, 2980, 2930, 2860, 2835, 1665, 1595, 1490, 1445, 1400, 1345, 1300, 1240, 1090, 1025, 965 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.31–7.16 (5 H, m), 4.66 (1 H, td, J = 7.7 and 7.1 Hz, collapses to a t with D_2O), 4.45 (1 H, q, J = 6.9 Hz), 3.52 (3 H, s), 2.98 (1 H, dd, J = 13.2 and 7.0 Hz), 2.85 (1 H, dd, J = 13.1 and 7.1 Hz), 2.30 (1 H, d, J = 8.1 Hz, exchanges with D_2O), 1.35 (3 H, d, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$, off-resonance proton and broad-band proton decoupling) 154.40 (s), 138.05 (s), 129.44 (2 C, d), 128.17 (2 C, d), 126.23 (d), 92.75 (d), 69.28 (d), 54.25 (q), 41.99 (t), 10.55 (q) ppm; mass spectrum, m/z (relative intensity) 193 (1), 192 (M^+, 8), 175 (12), 161 (1), 143 (13), 115 (4), 103 (9), 102 (12), 101 (87), 100 (51), 92 (46), 91 (80), 77 (17), 73 (56), 71 (12), 70 (22), 69 (35), 65 (44), 57 (15), 55 (20), 51 (25), 45 (34), 43 (24), 42 (15), 41 (100). Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.95; H, 8.39. Found: C, 74.82; H, 8.34.

2-Hydroxy-1-phenyl-3-pentanone (7b). Similar treatment of 0.40 g of crude **7a** in 2.5 mL of 2 N HCl and 15 mL of H_2O, as described for **2b**, afforded 0.31 g of a yellow oil. Following chromatography (silica gel, Et_2O–hexane, 1:2), 0.17 g (1.0 mmol, 40%) of **7b** was obtained as a colorless oil: IR ($CHCl_3$) 3450, 3090, 3070, 3050, 3015, 2990, 2970, 2910, 2880, 2850, 1700, 1600, 1490, 1450, 1400, 1380, 1345, 1260, 1090, 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35–7.18 (5 H, m), 4.42 (1 H, br s, sharpens to a dd in D_2O), 3.40 (1 H, br s, exchanges with D_2O), 3.12 (1 H, dd, J = 14.1 and 4.7 Hz), 2.86 (1 H, dd, J = 14.1 and 7.4 Hz), 2.50 (1 H, dq, J = 10.2 and 7.2 Hz) superimposed on 2.49 (1 H, dq, J = 10.2 and 7.2 Hz), 1.08 (3 H, t, J = 7.2 Hz); mass spectrum, m/z (relative intensity) 179 (0.7), 178 (M^+, 0.7), 160 (7), 149 (3), 147 (3), 131 (4), 121 (38), 120 (62), 115 (5), 109 (8), 103 (27), 92 (20), 91 (100),

77 (10), 65 (14), 57 (6), 43 (11). Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 73.87; H, 8.04.

(*E*)-2,2-Dimethyl-4-methoxy-4-hexen-3-ol (8a). Similar treatment of 1.29 g (15.0 mmol) of trimethylacetaldehyde and 2.50 mL (2.29 g, 32.7 mmol) of methoxyallene, as described for **2a**, afforded 2.44 g of a pale yellow oil. Following chromatography (Florisil, Et_2O–hexane, 1:3), 1.71 g (10.8 mmol, 72%) of **8a** was obtained as a colorless oil: IR ($CHCl_3$) 3545, 3425 (br), 3030, 2990, 2940, 2900, 2855, 2820, 1660, 1475, 1460, 1445, 1400, 1390, 1360, 1345, 1250, 1095, 1045, 1010, 990 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.59 (1 H, q, J = 6.9 Hz), 4.13 (1 H, d, J = ca. 12 Hz, collapses to a s with D_2O), 3.51 (3 H, s), 2.48 (1 H, d, J = ca. 12 Hz, exchanges with D_2O), 1.61 (3 H, d, J = 7.0 Hz), 0.93 (9 H, s); ^{13}C NMR ($CDCl_3$, off-resonance proton and broad-band proton decoupling) 154.52 (s), 93.64 (d), 74.91 (d), 53.92 (q), 36.41 (s), 26.30 (3 C, q), 11.93 (q) ppm; mass spectrum, m/z (relative intensity) 159 (1), 158 (M^+, 7), 141 (3), 102 (37), 101 (100), 91 (12), 87 (11), 83 (10), 73 (15), 71 (24), 70 (52), 69 (48), 58 (16), 57 (83), 56 (10), 55 (22), 45 (12), 43 (67), 41 (83). Anal. Calcd for $C_9H_{18}O_2$: C, 68.31; H, 11.46. Found: C, 67.89; H, 11.60.

2,2-Dimethyl-3-hydroxy-4-hexanone (8b). Similar treatment of 800 mg of crude **8a** in 4.5 mL of 2 N HCl and 30 mL of H_2O, as described for **2b**, afforded 610 mg of a pale yellow oil. Following chromatography (silica gel, Et_2O–hexane, 1:2), 474 mg (3.3 mmol, 67% based on trimethylacetaldehyde) of **8b** was obtained as a colorless oil: IR ($CHCl_3$) 3475, 3035, 2960, 2950, 2910, 2870, 1705, 1485, 1465, 1400, 1370, 1350, 1090, 1025 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.88 (1 H, s), 3.28 (1 H, br s, exchanges with D_2O), 2.57 (1 H, dq, J = 10.9 and 7.3 Hz) superimposed on 2.52 (1 H, dq, J = 10.8 and 7.3), 1.10 (3 H, t, J = 7.2 Hz), 0.98 (9 H, s); mass spectrum, m/z (relative intensity) 145 (0.9), 144 (M^+, 0.3), 88 (65), 87 (100), 73 (13), 69 (47), 58 (11), 57 (78), 45 (20), 43 (24), 41 (49). Anal. Calcd for $C_8H_{16}O_2$: C, 66.63; H, 11.18. Found: C, 66.84; H, 11.06.

(*E*)-4-Methoxy-2-methyl-4-hexen-3-ol (9a). Similar treatment of 1.08 g (15.0 mmol) of isobutyraldehyde and 2.50 mL (2.29 g, 32.7 mmol) of methoxyallene, as described for **2a**, afforded 2.25 g of a pale yellow oil. Following chromatography (Florisil, Et_2O–hexane, 1:3), 1.53 g (10.6 mmol, 71%) of **9a** was obtained as a colorless oil: IR ($CHCl_3$) 3550, 3425 (br), 3075, 3040, 2995, 2950, 2920, 2860, 2825, 1665, 1460, 1445, 1400, 1380, 1365, 1235, 1095, 1020, 990 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.56 (1 H, q, J = 7.1 Hz), 4.05 (1 H, dd, J = ca. 12 and 7 Hz, collapses to a d with D_2O), 3.51 (3 H, s), 2.13 (1 H, br d, J = ca. 12 Hz, exchanges with D_2O), ca. 1.79 (1 H, m), 1.62 (3 H, d, J = 6.9 Hz), 1.02 (3 H, d, J = 6.7 Hz), 0.82 (3 H, d, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$) 155.35, 92.81, 73.53, 54.19, 32.87, 18.78 (2 C), 11.16 ppm; mass spectrum, m/z (relative intensity) 145 (2), 144 (M^+, 14), 127 (39), 102 (11), 101 (100), 97 (4), 95 (7), 73 (32), 71 (6), 69 (16), 57 (6), 55 (9), 45 (8), 43 (15), 41 (30). Anal. Calcd for $C_8H_{16}O_2$: C, 66.63; H, 11.18. Found: C, 66.71; H, 11.02.

4-Hydroxy-5-methyl-3-hexanone (9b). Similar treatment of 1.05 g of crude **9a** in 4.5 mL of 2 N HCl and 35 mL of H_2O, as described for **2b**, afforded 0.82 g of a yellow oil. Following chromatography (silica gel, Et_2O–hexane, 1:4), 0.55 g (4.2 mmol, 61% based on isobutyraldehyde) of **9b** was obtained as a pale yellow oil: IR ($CHCl_3$) 3600, 3480, 3020, 2970, 2935, 2900, 2875, 1710, 1460, 1405, 1385, 1365, 1345, 1260, 1210, 1175, 1110, 1050, 1015, 985, 940, 860 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.09 (1 H, br d, J = 2.0 Hz), 3.44 (1 H, br s, exchanges with D_2O), 2.50 (1 H, dq, J = 11.3 and 7.4 Hz) superimposed on 2.48 (1 H, dq, J = 11.3 and 7.2 Hz), 2.17 (1 H, septet of doublets, J = 7.2 and 6.8 Hz), 1.13 (3 H, t, J = 7.3 Hz) superimposed on 1.12 (3 H, d, J = 6.9 Hz), 0.72 (3 H, d, J = 6.8 Hz); CI (CH_4) mass spectrum, m/z (relative intensity) 132 (7), 131 ($M^+ + 1$, 90), 130 (2), 113 (18), 97 (5), 95 (10), 88 (20), 73 (100), 72 (15), 71 (24), 69 (8), 57 (94), 55 (38), 45 (9), 43 (16), 41 (7). Anal. Calcd for $C_7H_{14}O_2$: C, 64.58; H, 10.84. Found: C, 65.00; H, 10.98.

α-[(*E*)-1-Methoxypropenyl]cyclohexanemethanol (10a). Similar treatment of 1.68 g (15.0 mmol) of cyclohexanecarboxaldehyde and 2.50 mL (2.29 g, 32.7 mmol) of methoxyallene, as described for **2a**, afforded 2.97 g of a pale yellow oil. Following chromatography (Florisil, Et_2O–hexane, 1:3), 2.06 g (11.2 mmol, 75%) of **10a** was obtained as a colorless oil: IR ($CHCl_3$) 3550, 3425 (br), 3045, 3000, 2925, 2850, 1670, 1465, 1450, 1405, 1350, 1250, 1180, 1100, 1030, 995 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 4.45 (1 H, d, J = 6.0 Hz, exchanges with D_2O) superimposed on 4.45 (1 H, q, J = 6.8 Hz), 3.89 (1 H, dd, J = 8.8 and 6.4 Hz, collapses to a d with D_2O), 3.38 (3 H, s), 2.00 (1 H, apparent br d), 1.57 (3 H, d, J = 7.0 Hz) superimposed on 1.72–1.38 (5 H, m), 1.24–1.04 (3 H, m), 0.95–0.73 (2 H, m); ^{13}C NMR (Me_2SO-d_6) 156.67, 91.65, 71.04, 53.48, 29.33, 28.45 (2 C), 26.13 (2 C), 25.47, 10.88 ppm; mass spectrum, m/z (relative intensity) 185 (0.5), 184 (M^+, 4), 167 (1), 155 (1), 137 (1), 135 (1), 123 (2), 109 (1), 103 (5), 102 (81), 101 (100), 100 (8), 87 (9), 83 (8), 73 (25), 70 (21), 69 (22), 55 (46), 41 (72). Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.70; H, 10.94. Found: C, 71.27; H, 10.90.

1-Cyclohexyl-1-hydroxy-2-butanone (10b). Similar treatment of 1.00 g of crude **10a** in 3.0 mL of 2 N HCl and 30 mL of H_2O, as described for **2b**, afforded 0.89 g of a pale yellow oil. Following chromatography (silica gel, Et_2O–hexane, 1:4), 0.63 g (3.7 mmol, 73% based on cyclohexanecarboxaldehyde) of **10b** was obtained as a colorless oil: IR ($CHCl_3$) 3455, 3040, 2995, 2970, 2925, 2850, 2820, 1705, 1490, 1450, 1380, 1350, 1240, 1150, 1105 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 5.14 (1 H, d, J = 5.4 Hz, exchanges with D_2O), 3.68 (1 H, apparent t, J = 5.1 Hz, collapses to a d in D_2O), 2.51 (1 H, dq, J = 15.8 and 7.4 Hz) superimposed on 2.50 (1 H, dq, J = 15.8 and 7.4 Hz), 1.75–1.32 (6 H, m), 1.32–0.96 (5 H, m), 0.91 (3 H, t, J = 7.3 Hz); mass spectrum, m/z (relative intensity) 171 (0.3), 170 (M^+, 0.04), 113 (22), 112 (5), 96 (11), 95 (100), 93 (6), 88 (10), 83 (6), 69 (12), 67 (22), 57 (23), 55 (27), 43 (9), 41 (23), 40 (32). Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.57; H, 10.44.

α-[(*E*)-1-Methoxypropenyl]-1-methylpyrrole-2-methanol (11a). Similar treatment of 1.64 g (15.0 mmol) of *N*-methylpyrrole-2-carboxaldehyde and 2.50 mL (2.29 g, 32.7 mmol) of methoxyallene, as describe for **2a**, afforded 2.95 g of a yellow oil. Following chromatography (alumina, Et_2O–hexane, 1:2), 2.15 g (11.8 mmol, 79%) of **11a** was obtained as a yellow oil: IR ($CHCl_3$) 3540, 3450 (br), 3100, 3050, 2985, 2940, 2840, 1670, 1605, 1490, 1460, 1445, 1400, 1370, 1355, 1300, 1240, 1155, 1100, 1030, 965 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 6.60 (1 H, apparent d, J = 2.1 Hz), 5.83 (2 H, apparent t, J = ca. 2.2 Hz), 5.37 (1 H, d, J = 6.3 Hz, collapses to a s with D_2O), 5.14 (1 H, d, J = 6.4 Hz, exchanges with D_2O), 4.50 (1 H, q, J = 7.0 Hz), 3.57 (3 H, s), 3.44 (3 H, s), 1.62 (3 H, d, J = 7.0 Hz); ^{13}C NMR (Me_2SO-d_6) 156.17, 132.70, 122.47, 107.17, 105.74, 91.82, 63.31, 53.97, 33.86, 11.00 ppm; mass spectrum, m/z (relative intensity) 182 (7), 181 (M^+, 66), 166 (9), 164 (19), 163 (100), 162 (74), 149 (9), 148 (67), 147 (12), 138 (16), 134 (24), 132 (25), 122 (40), 120 (49), 110 (9), 106 (11), 96 (12), 94 (61), 93 (25), 81 (43), 77 (23), 65 (23), 55 (19), 45 (25), 42 (66). Anal. Calcd for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34. Found: C, 67.14; H, 8.63.

α-[(*E*)-1-Methoxypropenyl]-3-methylthiophene-2-methanol (12a). Similar treatment of 1.89 g (15.0 mmol) of 3-methyl-2-thiophenecarboxaldehyde and 2.50 mL (2.29 g, 32.7 mmol) of methoxyallene, as described for **2a**, afforded 3.09 g of a yellow oil. Following chromatography (Florisil, Et_2O–hexane, 1:5), 2.08 g (10.5 mmol, 70%) of **12a** was obtained as a pale yellow oil: IR ($CHCl_3$) 3580, 3475 (br), 3110, 3060, 3000, 2960, 2940, 2870, 2845, 1670, 1460, 1450, 1390, 1345, 1230, 1170, 1100, 1045, 970, 910, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.11 (1 H, d, J = 5.3 Hz), 6.78 (1 H, d, J = 5.2 Hz), 5.80 (1 H, br d, J = 6.2 Hz, collapses to a s with D_2O), 4.59 (1 H, q, J = 7.3 Hz), 3.60 (3 H, s), 2.78 (1 H, br d, J = ca. 6.0 Hz, exchanges with D_2O), 2.29 (3 H, s), 1.68 (3 H, d, J = 7.0 Hz); ^{13}C NMR (Me_2SO-d_6) 155.84, 140.15, 131.76, 129.27, 122.81, 92.04, 63.92, 53.86, 13.42, 10.94 ppm; mass spectrum, m/z (relative intensity) 199 (2), 198 (M^+, 18), 183 (10), 182 (19), 181 (100), 166 (14), 165 (10), 151 (26), 149 (13), 138 (11), 137 (15), 127 (76), 125 (28), 111 (23), 99 (30), 97 (18), 72 (18), 71 (14), 65 (14), 45 (19), 41 (15).

α-[(*E*)-1-Methoxypropenyl]-5-methylfuran-2-methanol (13a). Similar treatment of 1.65 g (15.0 mmol) of 5-methylfurfural and 2.50 mL (2.29 g, 32.7 mmol) of methoxyallene, as described for **2a**, afforded 2.87 g of a yellow oil. Following chromatography (Florisil, Et_2O–hexane, 1:4), 1.94 g (10.7 mmol, 71%) of **13a** was obtained as a pale yellow oil: IR ($CHCl_3$) 3555, 3450 (br), 3040, 3000, 2940, 2850, 1675, 1570, 1455, 1410, 1390, 1250, 1110, 1030, 960 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.10 (1 H, d, J = 3.0 Hz), 5.89 (1 H, dd, J = 3.0 and 0.9 Hz), 5.49 (1 H, d, J = 8.8 Hz, collapses to a s with D_2O), 4.63 (1 H, q, J = 7.0 Hz), 3.59 (3 H, s), 2.85 (1 H, d, J = 9.1 Hz, exchanges with D_2O), 2.28 (3 H, s), 1.65 (3 H, d, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) 153.08, 152.92, 151.92, 107.28,

106.12, 93.36, 64.36, 54.69, 13.59, 10.88 ppm; mass spectrum, m/z (relative intensity) 183 (4), 182 (M^+, 34), 167 (4), 165 (8), 164 (15), 151 (3), 150 (7), 149 (6), 140 (5), 139 (34), 135 (28), 125 (18), 121 (15), 111 (90), 109 (15), 107 (16), 100 (9), 97 (10), 95 (36), 91 (9), 82 (28), 79 (23), 77 (16), 72 (25), 69 (16), 65 (12), 57 (13), 55 (43), 53 (23), 51 (16), 45 (19), 43 (100), 41 (28). Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 66.19; H, 7.88.

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[^{18}O] Chiral Phosphate in d(CpA) and d(TpA): Synthesis via Phosphite Triesters and Assignment of Configuration

Wilhelm Herdering and Frank Seela*

Laboratorium für Bioorganische Chemie, Fachbereich Chemie, Universität Paderborn, D-4790 Paderborn, Federal Republic of Germany

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The dinucleoside monophosphates d(TpA) (**11a**) and d(CpA) (**19a**)—both chirally labeled with ^{18}O at phosphorus and representing cleavage sites in a number of restriction endonuclease recognition sequences—have been synthesized via the fully protected phosphate triesters **8a/b** and **16a/b**. The latter were obtained from condensation of the pyrimidine phosphoramidites **3a/b** and **5a/b** with an appropriately protected adenosine derivative (**1**). Oxidation of these intermediates with [^{18}O]H_2O and iodine furnished diastereomeric mixtures of the fully protected triesters (**8a/b** and **16a/b**). Chromatographic separation of the diastereomeric triesters was achieved by using flash chromatography on the detritylated compounds **9a/b** and **17a/b**. Complete deprotection of the materials of the "fast" migrating zones furnished stereochemically pure [^{18}O]d(TpA) as well as [^{18}O]d(CpA) (**11a** and **19a**). The absolute configuration at phosphorus was deduced from hydrolysis experiments in which dimers were digested with nuclease P1 in [^{17}O]H_2O to yield [^{16}O,^{17}O,^{18}O]dAMP by inversion. The configuration was determined after cyclization to cyclic 3′,5′-phosphate followed by methylation and NMR analysis and was found to be S_P. Consequently [^{18}O]d(TpA) and [^{18}O]d(CpA) obtained from the "fast" migrating zones on triesters both have the R_P configuration. From this analysis it is apparent that the detritylated pairs of phosphate triesters with identical configurations show the same trends in their shieldings of ^1H, ^{13}C, and ^{31}P NMR signals. Although it has been shown that the ^{31}P NMR chemical shifts of methylated stereochemically pure ^{18}O dinucleoside monophosphates **26a/b** and **28a/b** do not follow simple principles,[8,9] the stereochemical assignment of [^{18}O]d(TpA) or [^{18}O]d(CpA) can now be established by comparing the ^{31}P NMR shifts of their methylation products with those of the methyl esters **25** and **27** described in this manuscript.

Oxygen chirally labeled nucleoside phosphates are useful tools for the elucidation of the stereochemistry of reactions catalyzed by enzymes.[1] With the help of such substrates the stereochemical course of mechanisms of several nucleases has been elucidated.[1] Moreover, a study by Reed[2] has shown that chiral [α-^{16}O,^{17}O]ADP can be employed to investigate the first coordination sphere of the Mn^{2+} ion in the active site of kreatine kinase.

Until recently the elucidation of the stereochemical course of enzymatic phosphodiester hydrolysis was achieved by the use of stereochemically pure phosphorothioates.[3] However, due to the altered van der Waals radii of sulfur compared to oxygen, phosphorothioates are sometimes processed less efficiently, which can obscure the interpretation of stereochemical data.

Lowe[4] and Knowles[5] were the first to report the synthesis of phosphate monoesters chiral by virtue of oxgen isotopes. Chiral [^{16}O,^{17}O,^{18}O] phosphate monoesters were subsequently employed in many studies of phosphoryl transfer reactions.[1,6] The synthesis of a chirally ^{18}O-labeled dinucleoside monophosphate has been reported by Eckstein et al.[7] These authors converted diastereomerically pure phosphorothioates by a sulfur exchange into a chirally ^{18}O-labeled phosphate. By employing this chirally labeled product, (R_P)-[^{18}O]d(TpT), they were successful in elucidating the stereochemical course of phosphodiester hydrolysis by nuclease P1.

A direct approach using ^{18}O as well as ^{17}O labeling has been developed by our laboratory using phosphite inter-

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