Triisobutylaluminum-Assisted Reductive Rearrangement of Alkyl 1-Alkenyl Acetals: An Easy Synthesis of β-Alkoxy Alcohols

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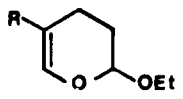
Alkyl 1-alkenyl acetals react with Al-*i*-Bu_3 to give very good yields of β-alkoxy alcohols through a reductive rearrangement. The reaction is totally regioselective, but no stereocontrol occurs.

The reaction of 2-ethoxy-5-alkyl-3,4-dihydro-2*H*-pyrans **1** and of 2-ethoxy-4-alkyl-2,3-dihydrofurans **2** with Al-*i*-Bu_3 gives *t*-2-ethoxy-*r*-1-(hydroxymethyl)-1-alkylcyclobutanes **3**[1] and *c*- and *t*-2-ethoxy-*r*-1-(hydroxymethyl)-1-alkylcyclopropanes **4**.[2]



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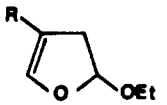

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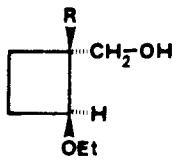

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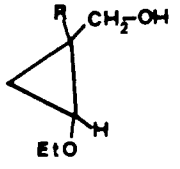

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Apart from the stereochemical implications, the reaction is synthetically useful, and some new alkyl 1-alkenyl acetals structurally different from **1** and **2** were reacted with Al-*i*-Bu_3 in order to obtain further evidence of its applicability to organic synthesis.

Results and Discussion

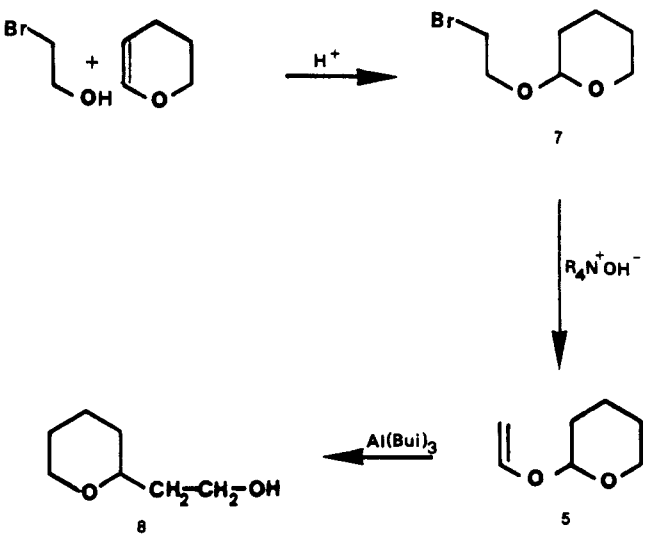
This paper describes the syntheses and reactions of 2-(vinyloxy)tetrahydropyran (**5**) and of unsaturated acetals **6a–g** with Al-*i*-Bu_3 (Schemes I and II, respectively).

The synthesis of **5** was carried out, in 74% overall yield, starting from 1-bromo-2-[(tetrahydropyran-2-yl)oxy]ethane (**7**) which in its turn is prepared by reacting of dihydropyran with 2-bromoethanol (Scheme I).

Alkyl 2-alkenyl acetals **9a–g**, precursors of **6a–g**, were prepared according to the experimental procedure described by Suzuki.[3] Complex mixtures were obtained of **9a,b** and their diethyl and di-2-alkenyl acetals. Chemically pure compounds **9a,b** were isolated (55% yield) only by careful distillation through a Fischer–Spaltrohr column. In further experiments, it was found that the slow addition of the required unsaturated alcohol to a solution of a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS) in the suitable alkyl enol ether, supplied higher yield of asymmetric unsaturated acetals (**9d–f**) and smaller amounts (5–12%) of symmetric derivatives. In this way compounds **9d–f** were obtained in 80–90% yields. Compound **9c** was obtained (39% yield) by transacetalization[4] of benzaldehyde diethyl acetal in the presence of allylic alcohol and a catalytic amount of 7 N HCl, according to a procedure described for other compounds.[5] Analogously, starting from acetaldehyde diethyl acetal and cinnamyl alcohol compound **9g** was prepared in 90% yield. The isomerization[3,6] of **9a–g**, performed at 160 °C in the presence of $H_2Ru(PPh_3)_4$,[7] gave *E*/*Z* (≃ 1:1) mixtures of chemically pure samples of **6a–f**[8] that were recovered, in >95% yields, by bulb-to-bulb distillation of the reaction mixtures (Scheme II).

Compounds **5** and **6a–f** were reacted with Al-*i*-Bu_3 (1:2 molar ratio) (Scheme II, paths a and b) in *n*-hexane at 60 °C and, in all cases, good yields (75–91%) of chemically pure samples of the expected products **8** and **10**, respectively, were obtained.

Scheme I



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[‡] Centro di Studio del CNR per le Macromolecole Stereordinate ed Otticamente Attive.

(1) Menicagli, R.; Malanga, C.; Lardicci, L. *J. Org. Chem.* **1982**, *47*, 2288.

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(6) (a) Suzuki, H.; Yashina, H.; Hirise, T.; Takahashi, M.; Moro-Oka, Y.; Ikawa, T. *Tetrahedron Lett.* **1980**, 4927. (b) Takahashi, M.; Suzuki, H.; Moro-Oka, Y.; Ikawa, T. *Chem. Lett.* **1981**, 1435.

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(8) Isomerization of **9g** afforded a complex mixture of products in which only traces of **6g** were present [MS, *m*/*z* 118 (80.3), 117 (100), 115 (48.1), 91 (35.4), 78 (6.9), 77 (6.5), (23.6)].

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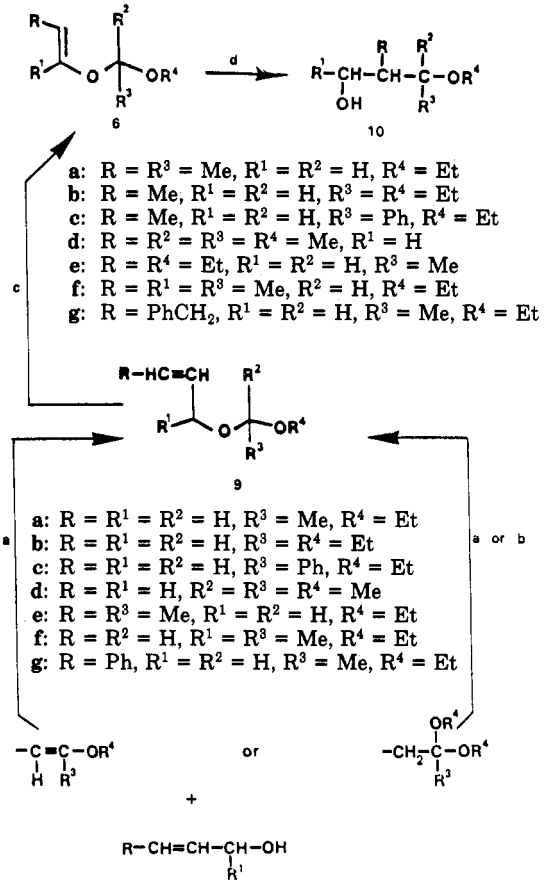
Scheme II[a]



[a] (a) TsOH, Py; (b) $CaCl_2$, HCl (concentrated); (c) $H_2Ru(PPh_3)_4$, 150 °C; (d) Al-*i*-Bu_3.

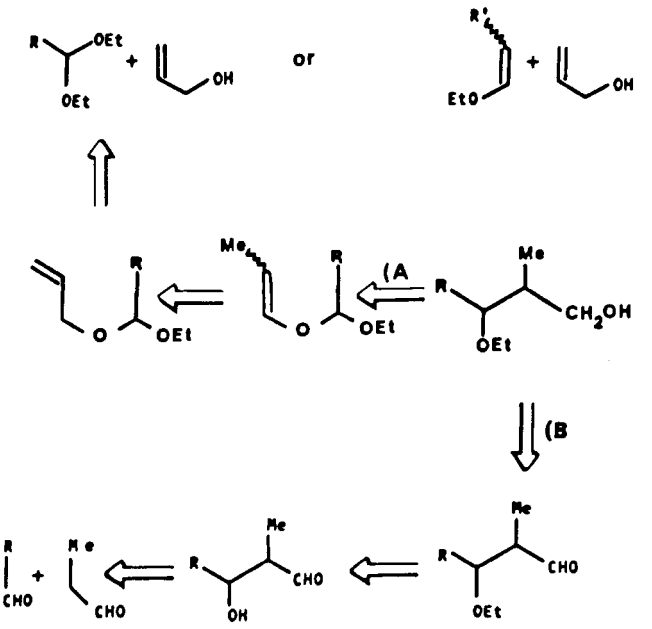
It should be noted that the reductive rearrangement of **6a–f** into **10a–f** mainly (84%) provides, whenever possible, an almost equimolar amount of both erythro and threo isomers in contrast with what was obtained by starting from **1** and in the same way as **2**.[2]

It was verified that this feature is independent of the stereochemistry of the double bond of the precursors: indeed, when samples of either (*E*)- or (*Z*)-**6a,b**[9] and either (*E*)- or (*Z*)-1-(benzyloxy)-1-(prop-1-enyloxy)propane (**11**)[9] (see infra) were reacted with Al-*i*-Bu_3, once again, equimolar erythro and threo mixtures of the corresponding β-alkoxy alcohols were obtained.[10]

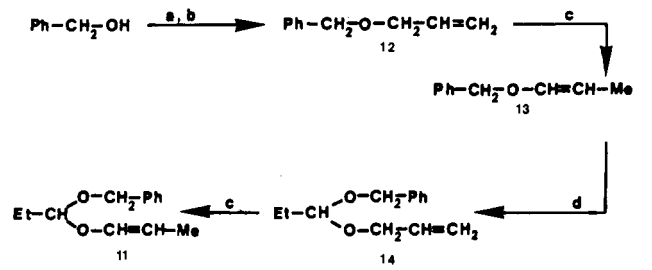
From a synthetical point of view, it must stressed that the reductive rearrangement of alkyl 1-alkenyl acetals makes it possible to prepare, in one step, monoprotected 1,3-diols that could otherwise must be synthesized in a multistep reaction sequence (Scheme III).

The preparation of 1,3-diols may be another useful application of the reaction if it is possible to easily remove the protective alkoxy group.[11] In this context, a sample of 1-(benzyloxy)-1-(prop-1-enyloxy)propane (**11**) was prepared in 63% overall yield according to the reaction sequence described in Scheme IV.

Scheme III



Scheme IV[a]



[a] (a) NaH, THF; (b) CH_2=$CHCH_2Cl$; (c) $H_2Ru(PPh_3)_4$, 160 °C, 2 h; (d) CH_2=$CHCH_2OH$, PPTs, 6 h.

Compound **11** was then reacted with Al-*i*-Bu_3, and the resulting 2-methyl-3-(benzyloxy)butan-1-ol (**10h**) was quantitatively converted into the corresponding 1,3-diol **15** by hydrogenolysis.[12]

In conclusion, the results reported clearly show the general character of the reductive rearrangement, and the wide range of products obtainable by the reaction described can be useful for organic chemists.

Experimental Section

All the chemicals used were reagent grade. All solvents used were freshly distilled, under nitrogen, as follows: ether, THF, and hexane from $LiAlH_4$; DMSO from CaH_2; ethyl vinyl ether, ethyl prop-1-enyl ether, and benzene from Na. ^1H NMR spectra were recorded with a Varian T 60; the solvent was CCl_4 unless otherwise stated. All ^{13}C NMR were recorded by using a complete decoupling program; either a Varian XL 100, Varian FT 80, or a Varian CFT 20 spectrometer was used; the solvent was $CDCl_3$; signals of diastereoisomeric carbon atoms are collected together in brackets. Chemical shifts are reported in parts per million downfield from Me_4Si as the internal reference; the multiplicity and the number of hydrogens are also given in brackets. IR spectra were taken with either a Perkin-Elmer 180 or a Perkin-Elmer 225 instrument, and data are given in cm^{-1}. Mass spectra,

(9) Pure (*E*)-**6a,b** (*E*)-**11**, (*Z*)-**6a**, and (*Z*)-**11** were obtained by preparative GC separations of isomerization mixtures; a sample of *E*/*Z* = 3:97 **6b** was prepared by isomerization, in DMSO, of **9b** in the presence of potassium *tert*-butoxide.[3]

(10) Alcohols having smaller retention times have been assigned as the threo stereoisomers. Such a configuration was established by oxidation (PCC) of a sample of **10b** (preparative GLC separation) to the corresponding known threo aldehyde[6b] [^1H NMR ($CDCl_3$) 9.6 (d, 1 H, J = 2 Hz), 3.7–3.1 (m, 3 H), 2.7–2.2 (m, 1 H), 1.6–0.6 (m, 11 H)].

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reported as m/z (relative intensity), were taken at 70 eV with a Hewlett-Packard HP-5995 instrument equipped with a Hewlett-Packard HP-9825A data station. GC analyses were performed with either a Perkin-Elmer F 30 (2 m × 0.29 cm column) or a Dani 3900 (25 m × 0.23 mm column) flame ionization GC instrument. The columns used were 8% Carbowax 20M + 2% KOH on Chromosorb W 80–100 mesh (CW 20M), 2.5% silicone gum rubber on Chromosorb G AW DMCS 80–100 mesh (SE 30), and a Permaphase PEG capillary column. Preparative GC purifications were performed on a Perkin-Elmer F 21 chromatograph equipped with a 3 m × 0.95 cm column filled with CW 20M. MPLC refers to medium-pressure liquid chromatography and utilizes a Lobar column (E. Merk) with LiChroprep Si 60 (40–63 μm) and a preparative Knawer detector and a Duramat CfG pump operating between 0 and 88 psi.

1-Bromo-2-[(tetrahydropyran-2-yl)oxy]ethane (7). In a three-necked flask equipped with a dropping funnel, a mechanic stirrer, and a condenser, 2-bromoethanol (3.2 g 0.25 mol) was reacted at 0 °C with 2,3-dihydropyran (35.3 g, 0.42 mol). The mixture was stirred (16 h) at room temperature, and then 5.0 g of Na_2CO_3 was added portionwise. The solid was filtered off and the residue distilled to give chemically pure (SE 30) **7** (41.0 g, 78%) having bp 122 °C (18 Torr): IR 2940, 2865, 2850, 1460, 1440, 1350, 1320, 1270, 1260, 1120, 1070, 1030, 980, 905, 870, 810; ^{1}H NMR 4.9–4.4 (m, 1 H), 4.2–3.2 (m, 6 H), 2.4–1.4 (m, 6 H); MS, m/z 201 (M^+, 7.6), 109 (30.5), 107 (31.8), 85 (100.0), 56 (55.4), 55 (26.8), 43 (30.8), 41 (68.4), 31 (29.1), 29 (62.9), 28 (39.1), 27 (91.0). Anal. Calcd for $C_7H_{13}O_2Br$: C, 40.20; H, 6.27; Br, 38.23. Found: C, 40.17; H, 6.29; Br, 38.27.

2-(Vinyloxy)tetrahydropyran (5). In an Erlenmeyer flask, 59 mL of benzene, 17 mL of a 50% NaOH solution, **7** (2.90 g 0.014 mol), and tetra-*n*-butylammonium acid sulfate (TBAS) (4.80 g, 0.014 mol) were magnetically stirred for 6 h at 50 °C. The organic phase, recovered and washed with water, was dried (K_2CO_3). Distillation gave chemically pure (SE 30) **5** (1.70 g, 95%) having bp 105 °C (18 Torr): IR 2940, 2880, 2830, 1640, 1440, 1380, 1370, 1355, 1320, 1280, 1260, 1200, 1170, 1140, 1120, 1110, 1080, 1040, 1020, 1000, 970, 945, 890, 870, 570; ^{1}H NMR 6.6–6.0 (dd, 1 H), 5.0–4.7 (m, 1 H), 4.6–4.2 (dd, 1 H), 4.1–3.8 (dd, 1 H), 3.8–3.2 (m, 2 H), 2.0–1.2 (m, 6 H); MS, m/z 128 (M^+, 5.3), 85 (88.1), 67 (38.9), 57 (36.5), 55 (34.5), 44 (14.6), 43 (56.9), 42 (16.1), 41 (79.8), 39 (24.0), 31 (11.3), 29 (100.0), 28.0 (21.8), 27.0 (51.5); ^{13}C NMR 148.98, 97.71, 90.88, 61.87, 29.63, 25.05, 18.61. Anal. Calcd for $C_7H_{12}O_2$: C, 65.59; H, 9.44. Found C, 66.03; H, 9.47.

Preparation of Alkyl 2-Alkenyl Acetals 9a,b. General Procedure. In a three-necked flask equipped with a condenser and a magnetic stirrer, allylic alcohol (1.76 mol) was reacted under N_2 and for 1 h, in the presence of a catalytic amount of PPTS, with the suitable enol ether (2.11 mol). After an additional 6 h at room temperature, the mixture was neutralized with K_2CO_3 and stirred for further 30 min. The solid was filtered off and the excess of ether removed at reduced pressure to give a mixture of the corresponding diethyl, ethyl 2-alkenyl, and di-2-alkenyl acetals. Careful fractional distillation gave the following.

1-Ethoxy-1-(prop-2-enyloxy)ethane (9a): 55% yield; bp 130 °C; IR 3080, 2980, 2940, 2900, 2880, 1650, 1450, 1380, 1340, 1130, 1110, 1060, 990, 930, 870; ^{1}H NMR 6.2–5.6 (m, 1 H), 5.4–4.9 (m, 2 H), 4.5 (q, 1 H), 4.0 (d, 2 H), 3.8–3.2 (m, 2 H), 1.2 (t, 3 H), 1.2 (d, 3 H); MS, m/z 129 ($M^+ - 1$, 1.1), 115 (40.6), 85 (34.2), 73 (100.0), 57 (19.0); ^{13}C NMR 135.06, 116.38, 99.17, 66.08, 60.64, 19.90, 15.36. Anal. Calcd for $C_7H_{14}O_2$: C, 64.58; H, 10.84. Found: C, 64.55; H, 10.89.

1-Ethoxy-1-(prop-2-enyloxy)propane (9b): 56% yield; bp 148 °C; IR 3080, 2970, 2940, 2880, 1650, 1460, 1420, 1390, 1340, 1260, 1130, 1090, 1040, 995, 920; ^{1}H NMR 6.2–5.5 (m, 2 H), 5.4–4.9 (m, 2 H), 4.4 (t, 1 H), 4.2–3.8 (m, 2 H), 3.8–3.1 (m, 2 H), 1.9–1.3 (m, 2 H), 1.1 (t, 3 H), 1.0 (t, 3 H); Ms, m/z 143 ($M^+ - 1$, 0.8), 115 (100), 99 (17.7), 87 (58.8), 59 (47.1), 57 (36.9), 41 (70.3), 29 (31.0), 27 (20.9). Anal. Calcd for $C_8H_{16}O_2$: C, 66.63; H, 11.18. Found: C, 66.67; H, 11.15.

Diethoxyphenylmethane. Benzaldehyde (14.8 g, 0.14 mol), triethyl orthoformate (178.2 g, 1.20 mol), and Amberlyst H-15 (0.35 g) were reacted at 0 °C, under N_2 (3 h). The catalyst was filtered off, the excess of triethyl orthoformate was removed at reduced pressure, and distillation of the residue gave chemically pure (CW 20M) diethoxyphenylmethane (23.4 g, 93%) having bp 90 °C (0.04 Torr): ^{1}H NMR 7.5–7.1 (m, 5 H), 5.4 (s, 1 H), 3.7–3.1 (dq, 4 H), 1.2 (t, 6 H); MS, m/z 181 ($M^+ + 1$, 0.1), 136 (12.1), 135 (100), 107 (59.6), 105 (12.4), 79 (34.8), 77 (19.2), 29 (18.9). Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.33; H, 8.91.

Ethoxy(prop-2-enyloxy)phenylmethane (9c). Diethoxyphenylmethane (9.0 g, 0.05 mol), allylic alcohol (9.0 g, 0.16 mol), and a few drops of 7 N ethanolic HCl were warmed (120 °C) under N_2, in a flask equipped with a short fractionating column. The theoretical amount of ethanol was removed, and further diethoxyphenylmethane (19.0 g, 0.11 mol) was added. After heating (3 h) the mixture was dissolved into 70 mL of ether, washed with a 5% solution of K_2CO_3, and dried (K_2CO_3). The mixture of diethoxyphenylmethane, **9c**, and bis(prop-2-enyloxy)phenylmethane (CW 20M) was accurately distilled to give chemically pure (CW 20M) **9c** (11.2 g, 39%) having bp 114 °C (18 Torr): IR 3080, 3060, 3030, 2980, 2930, 2880, 1645, 1490, 1450, 1430, 1405, 1370, 1355, 1345, 1305, 1205, 1105, 1070, 1055, 1045, 920, 750, 700; ^{1}H NMR 7.6–7.0 (m, 5 H), 6.3–5.6 (m, 1 H), 5.5 (s, 1 H), 5.4–4.9 (m, 2 H), 4.1–3.8 (dt, 2 H), 3.5 (q, 2 H), 1.2 (t, 3 H); MS, m/z 191 ($M^+ - 1$, 0.1), 147 (40.4), 135 (100), 107 (58.3), 105 (62.2), 91 (21.8), 79 (47.0), 77 (35.6), 41 (53.6), 29 (22.2). Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.95; H, 8.42.

1-Ethoxy-1-[(3-phenylprop-2-enyl)oxy]ethane (9g). According to the procedure above described, starting from acetaldehyde diethyl acetal (19.3 g, 0.14 mol) and cinnamyl alcohol (20.0 g, 0.14 mol), 85% chemically pure (CW 20M) **9g** was recovered. Chemically pure **9g** (22.7 g, 79%) was obtained by MPLC (eluent, hexane/ether, 60/40). Compound showed the following: bp, product decomposes by distillation; IR: 3080, 3060, 3040, 2990, 2940, 2900, 2870, 1600, 1495, 1450, 1370, 1340, 1130, 1090, 1060, 1030, 970, 740, 735, 690; ^{1}H NMR 7.4–7.0 (m, 5 H), 6.8–5.9 (m, 2 H), 4.8 (q, 1 H), 4.2–4.0 (m, 2 H), 3.8–3.2 (m, 2 H), 1.4 (d, 3 H), 1.2 (t, 3 H); MS, m/z 206 (M^+, 0.1), 117 (45.4), 115 (27.3), 77 (5.6), 73 (43.3), 45 (100). Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.71; H, 8.76.

Benzyl Prop-2-enyl Ether (12). To a THF solution of the sodium salt of benzylic alcohol, prepared from benzylic alcohol (27.8 g, 0.26 mol) and NaH (6.3 g, 0.26 mol), was slowly added allyl chloride (19.7 g, 0.26 mol) in 150 mL of the same solvent. The mixture was heated (6 h) at the reflux and then hydrolyzed with water. After the usual workup, chemically pure (CW 20M) **12** (35.0 g, 92%) was recovered. The product showed bp 95 °C (18 Torr); IR 3090, 3070, 3040, 2980, 2860, 1650, 1500, 1460, 1425, 1390, 1360, 1350, 1265, 1205, 1100, 1030, 990, 925, 735, 695; ^{1}H NMR 7.2 (s, 5 H), 6.2–5.5 (m, 1 H), 5.4–4.9 (m, 2 H), 4.4 (s, 2 H), 4.1–3.8 (dt, 2 H); MS, m/z 96 ($M^+ - 52$, 0.1), 92 (100), 79 (64.8), 78 (13.6), 77 (59.7), 65 (67.3), 63 (17.4), 51 (28.6), 50 (11.0), 41 (43.6), 39 (44.6). Anal. Calcd for $C_{10}H_{12}O$: C, 81.04; H, 8.18. Found: C, 81.08; H, 8.20.

Benzyl Prop-1-enyl Ether (13). With the procedure adopted for isomerization of **9** into **6**, **12** (10.0 g, 0.067 mol) was heated at 160 °C for 2 h in the presence of $H_2Ru(PPh_3)_4$ (0.26 g, 0.225 mmol). Bulb-to-bulb distillation yielded pure (CW 20M) **13** (9.2 g, 92%) having the following: IR 3090, 3060, 3040, 2920, 2860, 1705, 1670, 1500, 1450, 1400, 1380, 1355, 1270, 1200, 1125, 1075, 1030, 980, 930, 735, 695; ^{1}H NMR 7.2 (s, 5 H), 6.4–5.7 (m, 1 H), 4.7, 4.5 (2 s, 2 H), 4.6–4.0 (dq, 1 H), 1.8–1.4 (2dd, 3 H); MS, m/z 92 (8.1), 91 (100) 65 (14.0), 39 (7.0). Anal. Calcd for $C_{10}H_{12}O$: C, 81.04; H, 8.16. Found: C, 81.00; H, 8.13.

Preparation of Alkyl 2-Alkenyl Acetals 9d–f and 14. General Procedure. In a typical run, to the solution of a catalytic amount of PPTS in the suitable ethyl enol ether (0.4 mol) was added dropwise the required allylic alcohol (0.12 mol) under N_2. After being stirred (6 h) the reaction mixture was neutralized with Na_2CO_3 and then filtered. Distillation gave the following.

2-Methoxy-2-(prop-2-enyloxy)propane (9d): 85% yield: bp 53 °C (18 Torr); IR 3080, 3000, 2940, 2830, 1650, 1465, 1425, 1410, 1380, 1260, 1215, 1185, 1165, 1120, 1075, 1045, 990, 920, 855, 830, 760; ^{1}H NMR 6.2–5.5 (m, 1 H), 5.4–4.8 (m, 2 H), 4.0–3.7 (m, 2 H), 3.1 (s, 3 H), 1.3 (s, 6 H); ^{13}C NMR 135.48, 115.81, 100.19, 61.95, 48.48, 24.52; MS, m/z 100 ($M^+ - 30$, 1.3), 99 (17.2), 73 (100), 43 (31.3), 42 (11.0), 41 (56.9), 39 (15.9). Anal. Calcd for $C_7H_{14}O_2$: C, 64.58; H, 10.84. Found: C, 64.62; H, 10.80.

1-Ethoxy-1-(but-2-enyloxy)ethane (9e): 80% yield; bp 70 °C (18 Torr); IR 2980, 2940, 2920, 2880, 1680, 1450, 1370, 1340, 1180, 1050, 1040, 1060, 1030, 970, 930, 870; ^{1}H NMR 5.8–5.1 (m,

2 H) 4.6 (q, 1 H), 4.0–3.7 (m, 2 H), 3.7–3.1 (m, 2 H), 1.8–1.6 (m, 3 H), 1.3 (d, 3 H) 1.2 (t, 3 H); MS, m/z 144 (M^+, 3.3), 99 (63.0), 71 (10.5), 57 (11.0), 55 (10.8), 45 (100), 43 (12.6). Anal. Calcd for $C_8H_{16}O_2$: C, 66.63; H, 11.18. Found: C, 66.63; H, 18.21.

1-Ethoxy-1-(but-3-en-2-yloxy)ethane (9f): 89% yield; bp 80 °C (18 Torr); IR 3080, 2990, 2930, 2900, 2870, 1645, 1420, 1380, 1370, 1330, 1315, 1170, 1130, 1095, 1045, 1030, 1000, 980, 960, 920, 870; ^{1}H NMR 6.1–5.4 (m, 1 H), 5.4–4.8 (m, 2 H), 4.8–4.4 (dq, 1 H), 4.4–3.8 (m, 1 H), 4.8–3.2 (m, 2 H), 1.4–1.0 (m, 9 H); MS, m/z 131 (M^+ – 13, 0.2), 129 (10.9), 99 (10.3), 75 (13.9), 73 (49.5), 55 (87.5), 45 (100), 43 (38.0), 39 (17.1). Anal. Calcd for $C_8H_{16}O_2$: C, 66.63; H, 11.18. Found: C, 66.66; H, 11.14.

1-(Benzyloxy)-1-(prop-2-enyloxy)propane (14): 89% yield; bp 140 °C (18 Torr); IR: 3090, 3070, 3040, 2965, 2940, 1880, 1700, 1605, 1500, 1460, 1380, 1350, 1310, 1260, 1210, 1130, 1080, 1050, 1030, 950, 740, 700; ^{1}H NMR 7.2 (s, 5 H), 6.2–5.5 (m, 1 H), 5.4–4.9 (m, 2 H), 4.7–4.4 (m, 3 H), 4.1–3.9 (m, 2 H), 1.9–1.4 (m, 2 H), 1.0 (t, 3 H); MS, m/z 92 (13.6), 91 (100), 77 (5.2), 65 (11.4), 57 (13.6), 42 (21.6), 39 (11.3). Anal. Calcd for $C_{13}H_{18}O_2$: C, 70.54; H, 10.66. Found: C, 70.55; H, 10.68.

Isomerization of 9a–f into 6a–f. In a typical run, the required starting compound was placed under argon in a round-bottomed vial equipped with a cap, a Teflon septum-type ring, and a magnetic stirrer. $H_2Ru(PPh_3)_4$ was added, and the mixture was heated at 160 °C with an oil bath. When the mixture became pale yellow, the reaction product was recovered by bulb-to-bulb distillation. In the following the molar ratio catalyst/substrate as well as the required time and yields are reported in brackets.

(*E*/*Z*)-6a [1/320; 4 h; 93%]: IR 3040, 2980, 2880, 1670, 1450, 1385, 1340, 1255, 1245, 1180, 1150, 1080, 1060, 1000, 950, 930, 870, 730; ^{1}H NMR 6.4–6.1 (m, 1 H), 5.3–4.2 (m, 4 H), 1.8–1.0 (m, 9 H); ^{13}C NMR (140.63, 139.18), (101.18, 100.79), (98.39, 97.45), (60.79, 60.45), (19.71, 19.41), 14.46, (11.94, 8.68); MS, m/z 115 (M^+ – 15, 2.4), 84 (70.5), 73 (47.9), 57 (14.9), 56 (61.6), 55 (79.9), 53 (20.8), 51 (13.9), 50 (15.5), 45 (100), 43 (29.3), 41 (58.2), 39 (52.1). Anal. Calcd for $C_7H_{14}O_2$: C, 64.58; H, 10.84. Found: C, 64.55; H, 10.81.

(*E*)-6a:[9] ^{1}H NMR (100 MHz C_6D_6) 6.4–6.0 (dq, J = 12.4 Hz, 1 H), 5.2 (q, 1 H), 5.0–4.5 (m, 1 H), 3.9–3.0 (m, 2 H), 1.6–1.4 (dd, 3 H), 1.3 (d, 3 H), 1.0 (t, 3 H).

(*Z*)-6a:[9] ^{1}H NMR (100 MHz C_6D_6) 6.4–6.0 (dq, J = 6.2 Hz, 1 H), 4.7 (q, 1 H), 4.7–4.2 (m, 1 H), 3.9–3.0 (m, 2 H), 1.8–1.6 (dd, 3 H), 1.3 (d, 3 H), 1.0 (t, 3 H).

(*E*/*Z*)-6b [1/188; 3.5 h; 92%]: IR 3480, 3080, 2980, 2940, 2880, 1740, 1690, 1460, 1370, 1340, 1130, 1080, 1060, 970, 880; ^{1}H NMR 6.3–6.0 (m, 1 H), 5.2–4.1 (m, 2 H), 4.0–3.1 (m, 2 H), 1.9–0.6 (m, 11 H); ^{13}C NMR (140.99, 139.54), (103.57, 102.99), (101.00, 100.59), (61.19, 60.84), (26.52, 26.23), 14.45, (11.89, 8.63), 8.38; MS, m/z 99 (40.8), 59 (23.3), 57 (57.11), 41 (100), 39 (31.8), 31 (5.2). Anal. Calcd for $C_8H_{16}O_2$: C, 66.63; H, 11.18. Found: C, 66.59; H, 11.21.

(*E*)-6b:[9] ^{1}H NMR (100 MHz C_6D_6) 6.3–6.0 (dq, J = 12.5 Hz, 1 H), 5.2–4.7 (dq, 1 H), 4.3 (t, 1 H), 3.8–3.2 (m, 2 H), 1.9–1.4 (m, 2 H), 1.6–1.4 (dd, 3 H), 1.2 (t, 3 H), 0.85 (t, 3 H); ^{13}C NMR (C_6D_6) 141.00, 102.99, 101.01, 60.82, 26.23, 14.43, 11.90, 8.38.

(*Z*)-6b:[9] ^{1}H NMR (C_6D_6) 6.2–6.0 (dq, J = 6.5 Hz, 1 H), 4.7–4.4 (m, 2 H), 3.9–3.3 (m, 2 H), 1.9–1.4 (m, 2 H), 1.7–1.4 (dd, 3 H), 1.2 (t, 3 H), 0.8 (t, 3 H); ^{13}C NMR (C_6D_6) 139.53, 103.57, 100.60, 61.20, 26.52, 14.45, 8.63, 8.38.

(*E*/*Z*)-6c [1/100; 2.5 h; 91%]: IR 3095, 3060, 3040, 2980, 2930, 2880, 1670, 1460, 1410, 1340, 1310, 1240, 1210, 1120, 1095, 1045, 930, 750, 700; ^{1}H NMR 7.7–7.0 (m, 5 H), 6.4–6.0 (2 dq, 1 H), 5.8, 5.6 (2 s, 1 H), 5.4–4.8 (dq, 0.33 H), 4.8–4.2 (dq, 0.67 H), 4.0–3.4 (m, 2 H), 1.8–1.6 (dd, 2.01 H), 1.6–1.4 (dd, 0.99 H), 1.2 (t, 3 H); MS, m/z 147 (8.1), 135 (100), 107 (69.0), 105 (14.0), 79 (56.9), 77 (26.5), 51 (12.0). Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.94; H, 8.41.

(*E*/*Z*)-6d [1/300; 7 h; 89%]: IR 3050, 3000, 2940, 2860, 2830, 2730, 1670, 1460, 1400, 1380, 1375, 1250, 1220, 1185, 1155, 1120, 1065, 1045, 1000, 930, 860, 780, 730, 620; ^{1}H NMR 6.3–6.0 (m, 1 H), 5.1–4.1 (m, 1 H), 3.1 (s, 3 H), 1.6–1.4 (dd, 3 H), 1.3 (s, 6 H); ^{13}C NMR (139.06, 137.95), (104.17, 102.98), 101.25, 48.91, 24.79, (12.65, 9.28); MS, m/z 87 (10.8), 85 (64.5), 83 (100), 48 (16.1), 47 (34.2), 3(23.9). Anal. Calcd for $C_7H_{14}O_2$: C, 64.58; H, 10.84. Found: C, 64.60; H, 10.80.

(*E*/*Z*)-6e [1/305; 4 h; 92%]: ^{1}H NMR 6.3–5.3 (m, 1 H), 5.2–4.2 (m, 2 H), 3.7–3.1 (m, 2 H), 1.4–1.6 (m, 2 H), 1.4–0.7 (m, 9 H); MS, m/z 143 (M^+ – 1, 0.1), 99 (13.6), 83 (11.1), 73 (83.3), 55 (80.4), 45 (100), 43 (22.9), 39 (14.2).

(*E*/*Z*)-6f [1/100; 24 h; 85%]: IR 3080, 3040, 2980, 2930, 2880, 1670, 1445, 1380, 1340, 1315, 1210, 1180, 1140, 1080, 1050, 970, 950, 930, 880, 850, 820, 800, 780; ^{1}H NMR 5.5–4.8 (m, 1 H), 4.8–4.6 (m, 1 H), 3.8–3.2 (m, 2 H), 1.9–1.4 (m, 3 H), 1.3, 1.2 (2 d, 3 H), 1.25 (d, 3 H), 1.2 (t, 3 H); MS, m/z 103 (17.4), 73 (38.8), 47 (17.1), 45 (100), 43 (24.6).

(*E*/*Z*)-11 [1/294; 1 h; 84%]: IR 3095, 3060, 3030, 2970, 2940, 2880, 1670, 1600, 1455, 1380, 1350, 1310, 1250, 1205, 1155, 1130, 1090, 1050, 1030, 940, 745, 700; ^{1}H NMR 7.2 (s, 5 H), 6.4–6.0 (m, 1 H), 5.2–4.2 (m, 4 H), 2.9–1.4 (m, 5 H), 1.2–0.6 (m, 3 H); MS, m/z 206 (M^+, 0.1), 149 (5.8), 91 (100), 77 (4.4), 65 (11.1), 29 (10.2).

(*E*)-11:[9] ^{1}H NMR 7.4–7.0 (m, 5 H), 6.4–6.0 (dq, J = 13.0 Hz, 1 H), 5.4–4.9 (dq, 1 H), 4.9–4.4 (m, 3 H), 1.9–1.4 (m, 2 H), 1.6–1.3 (dd, 3 H), 0.9 (t, 3 H).

(*Z*)-11:[9] ^{1}H NMR 7.3 (s, 5 H), 6.3–6.0 (dq, J = 6.5 Hz, 1 H), 4.9–4.3 (m, 4 H), 2.0–1.5 (m, 2 H), 1.7–1.4 (dd, 3 H), 0.9 (t, 3 H).

Reaction of Unsaturated Acetals 5, 6a–f, and 11 with Al-*i*-Bu$_3$. General Procedure. All reactions were carried out at least in duplicate under dry argon. In a typical reaction a weighed amount of Al-*i*-Bu$_3$ (0.42 mol) was transferred to a two-necked, 100-mL, round-bottomed flask containing n-hexane (20 mL), equipped with a magnetic stirrer a dropping funnel, and a reflux condenser. The vessel was cooled at 0 °C, and the required amount (0.21 mol) of the suitable acetal, dissolved in 10 mL of the same solvent, was added dropwise. The reaction mixture was stirred for 30 min at room temperature and then heated by means of a previously thermostated (60 °C) oil bath for 5 h. The hydrolysis was carried out at 0 °C with water, the organic product was extracted with ether (4 × 50 mL), and the ether extracts were washed with water and dried (K_2CO_3). The solvent was removed, and the reaction product was recovered by distillation.

2-(Tetrahydropyran-2-yl)ethanol (8): 77% yield; bp 110 °C (18 Torr); ^{1}H NMR 4.2–3.2 (m, 5 H), 2.9 (s, 1 H), 2.8–1.1 (m, 8 H); MS, m/z 130 (M^+, 2.8), 101 (12.8), 88 (13.8), 85 (100), 67 (23.4), 57 (29.8), 56 (25.4), 55 (26.8), 45 (13.1), 43 (36.6), 41 (67.9), 39 (23.8), 31 (40.0), 29 (55.9), 28 (43.2), 27 (38.5). Anal. Calcd for $C_7H_{14}O_2$: C, 64.58; H, 10.84. Found: C, 64.57; H, 10.83.

***erythro*/*threo*-2-Methyl-3-ethoxybutan-1-ol (10a)**: 88% yield; bp 67 °C (18 Torr); IR 3040, 2980, 2930, 2880, 1450, 1375, 1340, 1230, 1160, 1150, 1040, 940, 895, 845; ^{1}H NMR 3.7–3.3 (m, 6 H), 2.0–1.3 (m, 1 H), 1.4–1.0 (m, 6 H), 0.7 (d, 3 H); ^{13}C NMR (78.38, 76.24), (65.03, 64.09), (63.10, 63.00), (40.10, 39.32), 16.14, (15.20, 14.91), (12.70, 11.12); MS, m/z 132 (M^+, 2), 117 (2), 104 (4), 100 (4), 75 (19), 73 (23), 60 (26), 58 (44), 42 (47), 33 (28), 32 (40), 30 (72), 29 (100), 28 (36). Anal. Calcd for $C_7H_{16}O_2$: C, 63.59; H, 12.20. Found: C, 63.60; H, 12.19.

***erythro*/*threo*-2-Methyl-3-ethoxypentan-1-ol (10b)**: 87% yield; bp 89 °C (18 Torr); IR 3400, 2970, 2930, 2880, 1460, 1405, 1375, 1350, 1220, 1100, 1080, 1050, 1025, 975, 950, 890, 870; ^{1}H NMR 3.8–3.0 (m, 5 H), 2.7 (s, 1 H), 2.2–0.7 (m, 12 H); ^{13}C NMR: (83.92, 82.53), (65.11, 64.58), (64.35, 64.12), (36.72, 36.74), (22.63, 22.50), (14.98, 13.24), (10.90, 10.33), (9.92, 8.11); MS m/z 146 (M^+, 2), 117 (62.0), 89 (22.4), 88 (22.8), 86 (43.2), 73 (32.4), 71 (93.7), 59 (17.1), 58 (28.3), 56 (38.1), 43 (28.1), 42 (17.4), 41 (24.8), 40 (93.7), 31 (85.1), 29 (100), 28 (95.0). Anal. Calcd for $C_8H_{18}O_2$: C, 65.71; H, 12.41. Found: C, 65.60; H, 12.45.

***erythro*-10b**:[9] ^{1}H NMR (C_6D_6) 3.8–3.1 (m, 5 H), 2.9 (s, 1 H), 2.4–1.6 (m, 1 H), 1.6–1.3 (m, 2 H), 1.2 (t, 3 H), 1.0 (t, 3 H), 0.9 (d, 3 H).

***threo*-10b**:[9] ^{1}H NMR (C_6D_6) 4.0–3.0 (m, 6 H), 2.4–1.5 (m, 3 H), 1.5–0.8 (m, 9 H).

***erythro*/*threo*-2-Methyl-3-ethoxy-3-phenylpropan-1-ol (10c)**: 75% yield; bp 84 °C (0.4 Torr); IR: 3440, 3080, 3060, 3020, 2970, 2920, 2880, 1600, 1490, 1450, 1400, 1370, 1340, 1300, 1200, 1090, 1070, 1030, 970, 910, 880, 750, 695; ^{1}H NMR 7.2 (s, 5 H), 4.4, 4.1 (2 d, 1 H), 3.7–3.0 (m, 5 H), 2.3–1.4 (m, 1 H), 1.15, 1.13 (2 t, 3 H), 0.8, 0.7 (2 d, 3 H); MS, m/z 135 (100), 117 (8.7), 107 (53.8), 91 (16.3), 79 (34.9), 77 (15.3), 31 (12.3). Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.00; H, 9.42.

2,3-Dimethyl-3-methoxybutan-1-ol (10d): 88% yield; bp 91 °C (18 Torr); IR 3400, 2980, 2900, 2830, 1645, 1370, 1240, 1185, 1155, 1110, 1080, 1030, 980, 935, 890, 830; ^{1}H NMR 3.9–3.3 (m, 3 H), 3.2 (s, 3 H), 2.2–1.4 (m, 1 H), 1.15, 1.13 (2 s, 6 H), 0.9 (d, 3 H); ^{13}C NMR 65.41, 48.69, 43.01, 24.43, 20.20, 12.88; MS, m/z

73 (100), 70 (6.2), 59 (7.5), 55 (20.8), 43 (28.2), 41 (26.3), 39 (11.4), 31 (15.7), 29 (19.9), 27 (13.3). Anal. Calcd for $C_7H_{16}O_2$: C, 63.59; H, 12.20. Found: C, 63.70; H, 12.15.

***erythro*/*threo*-2-Ethyl-3-ethoxybutan-1-ol (10e)**: 87% yield; bp 100 °C (18 Torr); ^{1}H NMR 4.2-3.0 (m, 5 H), 1.8 (s, 1 H), 1.6-0.6 (m, 12 H); ^{13}C NMR (79.81, 78.86), (64.50, 64.24), (63.75, 63.72), (47.77, 45.26), (21.37, 19.80), 17.60, (15.40, 14.56), (12.26, 11.63); MS, *m/z* 146 (M^+, 0.1), 73 (100), 55 (14.4), 45 (87.8), 43 (16.0), 41 (14.5), 31 (16.0). Anal. Calcd for $C_8H_{18}O_2$: C, 65.71; H, 12.41. Found: C, 65.80; H, 12.40.

3-Methyl-4-ethoxypentan-2-ol (10f): 86% yield; bp 71 °C (18 Torr); IR 3440, 2980, 2940, 2880, 1450, 1370, 1165, 1110, 1090, 990, 940, 930, 870; ^{1}H NMR 4.2-3.5 (m, 2 H), 3.5-3.0 (m, 2 H), 2.7 (s, 1 H), 1.8-1.4 (m, 1 H), 1.4-0.8 (m, 12 H); MS, *m/z* 147 (M^+ + 1, 0.5), 91 (14.9), 73 (46.9), 56 (48.7), 45 (100), 43 (25.2), 41 (21.7). Anal. Calcd for $C_8H_{18}O_2$: C, 65.71; H, 12.41. Found C, 65.65; H, 12.35.

***erythro*/*threo*-2-Methyl-3-(benzyloxy)pentan-1-ol (10h)**: 87% yield; bp 120 °C (9 Torr); IR 3400, 3090, 3060, 3030, 2970, 2940, 2880, 1670, 1500, 1455, 1380, 1350, 1255, 1210, 1090, 1070, 1050, 1030, 950, 735, 700; ^{1}H NMR 7.2 (s, 5 H), 4.7-4.2 (m, 3 H), 3.6-3.1 (m, 2 H), 3.0-2.6 (m, 1 H), 2.1-1.2 (m, 3 H), 1.1-0.7 (m, 6 H); ^{13}C NMR (138.85, 138.52), (128.34, 127.77), (127.67, 127.60), 127.48, (83.99, 82.76), (71.95, 71.58), (65.99, 65.50), 37.49, (23.33, 22.94), (13.62, 11.56), (10.49, 8.78); MS, *m/z* 131 (30.5), 99 (26.7), 77 (2.9), 71 (100), 59 (12.0), 55 (11.6), 46 (13.6), 45 (11.0), 41 (33.0), 39 (13.4), 29 (27.1), 28 (12.0). Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.84; H, 9.76.

2-Methylpentane-1,3-diol (15). A mixture of **10h** (1.43 g, 6.9 mmol), cyclohexene (30 mL), and Pd/C (10%) (0.25 g) in methanol (15 mL) was stirred (10 h), at room temperature. The catalyst was filtered off, and distillation gave chemically pure (SE 30) **15** (0.63 g, 88%) having bp 97 °C (0.3 Torr): IR 3350, 2960, 2940, 2880, 1460, 1380, 1135, 1105, 1030, 970, 870, 820; ^{1}H NMR 4.4 (s, 2 H), 3.8-3.2 (m, 3 H), 2.0-1.1 (m, 3 H), 1.5 (t, 3 H), 0.9 (d, 3 H); ^{13}C NMR (78.17, 75.54), (67.39, 66.68), (39.40, 38.85), (27.83, 26.89), (13.84, 10.67), (10.04, 9.49); MS, *m/z* 118 (M^+, 6.8), 100 (M^+ - 18, 5.1). Anal. Calcd for $C_6H_{14}O_2$: C, 60.98; H, 11.94. Found C, 61.05; H, 11.73.

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Registry No. **5**, 22408-41-9; (*E*)-**6a**, 80060-26-0; (*Z*)-**6a**, 80060-25-9; (*E*)-**6b**, 80060-32-8; (*Z*)-**6b**, 80060-31-7; (*E*)-**6c**, 111160-15-7; (*Z*)-**6c**, 111160-16-8; (*E*)-**6d**, 62322-65-0; (*Z*)-**6d**, 62322-41-2; (*E*)-**6e**, 80060-30-6; (*Z*)-**6e**, 80060-29-3; (*E*)-**6f**, 82477-76-7; (*Z*)-**6f**, 82477-75-6; (*E*)-**6g**, 111160-17-9; (*Z*)-**6g**, 111160-18-0; **7**, 17739-45-6; **8**, 38786-79-7; **9a**, 22092-24-6; **9b**, 80060-21-5; **9c**, 111160-13-5; **9d**, 62322-46-7; **9d** (enol ether), 6380-95-6; **9e**, 80060-20-4; **9f**, 87384-21-2; **9g**, 20615-52-5; *erythro*-**10a**, 86335-64-0; *threo*-**10a**, 86335-63-9; *erythro*-**10b**, 111160-19-1; *threo*-**10b**, 86335-65-1; *erythro*-**10c**, 111160-20-4; *threo*-**10c**, 111160-21-5; **10d**, 58330-06-6; *erythro*-**10e**, 111160-22-6; *threo*-**10e**, 111160-23-7; **10f**, 111160-24-8; *erythro*-**10h**, 111160-25-9; *threo*-**10h**, 111160-26-0; (*E*)-**11**, 84736-38-9; (*Z*)-**11**, 84736-39-0; **12**, 14593-43-2; **13**, 15895-87-1; **14**, 111160-14-6; **15**, 149-31-5; $Et(OEt)C{=}CH_2$, 4181-12-8; $HOCH_2CH{=}CH_2$, 107-18-6; $Br(CH_2)_2OH$, 540-51-2; $CH_2{=}C(Me)OEt$, 926-66-9; PhCHO, 100-52-7; $CH(OEt)_3$, 122-51-0; $PhCH(OEt)_2$, 774-48-1; $MeCH(OEt)_2$, 105-57-7; $PhCH{=}CHCH_2OH$, 104-54-1; $PhCH_2OH{\cdot}Na$, 20194-18-7; $CH_2{=}CHCH_2Cl$, 107-05-1; $MeCH{=}CHCH_2OH$, 6117-91-5; $CH_2{=}CHCH(Me)OH$, 598-32-3; $Al(Bu\text{-}i)_3$, 100-99-2; 2,3-dihydropyran, 110-87-2.

A Synthetic Approach to (-)-Quassimarin Based on Intramolecular Diels-Alder Strategy

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A novel approach to the tetracyclic precursor **32** for the total synthesis of (-)-quassimarin based on an intramolecular Diels-Alder strategy is described. The key tricyclic species **22** was constructed from the triene **6** via a highly endo-selective intramolecular Diels-Alder reaction followed by hydrolysis. The dihydrofuranone moiety in **6** was assembled via a magnesium ion controlled diastereoselective addition of α-lithio-α-methoxyallene to an appropriate α-alkoxy ketone. Oxidation of **22** followed by chemo- and stereoselective reduction with lithium triethylborohydride provided the inverted alcohol. The resulting acetate **25** gave **31** by an intramolecular Claisen condensation.

The quassinoids[1] comprise one of the most widely distributed groups of naturally occurring terpenoids. Of the many quassinoids, quassimarin **1** and bruceantin **2** (Figure 1), isolated from *Quassia amara*[2] and *Brucea antidysenterica*,[3] respectively, by Kupchan, display promising biological profiles[4] as well as complex molecular architecture and as such are intriguing candidates for synthetic investigation. Thus, in the past decade many stimulating synthetic efforts[5] have been focused on both of the quassinoids. To date, however, no total syntheses have yet been achieved.

In connection with our project aimed at the total synthesis of the quassinoids,[6] we have undertaken the de-

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