Registry No. 1, 51152-12-6; 2, 87727-48-8; 3, 87682-09-5; 4, 87682-10-8; (−)-β-pinene, 18172-67-3; Midland reagent, 76695-88-0; (S)-2-methyl-4-nonyn-3-ol, 87682-11-9; 3,3-dimethyl-2-butanone, 75-97-8; acetophenone, 98-86-2; ethyl phenyl ketone, 93-55-0; isopropyl phenyl ketone, 611-70-1; *tert*-butyl phenyl ketone, 938-16-9; α-tetralone, 529-34-0; isophorone, 78-59-1; 4-nonyn-3-one, 1817-61-4; 2-methyl-4-nonyn-3-one, 63098-60-2; 2,2-dimethyl-4-nonyn-3-one, 53723-95-8; phenyl (trimethylsilyl)ethynyl ketone, 13829-77-1; (R)-3,3-dimethyl-2-butanol, 1572-96-9; (R)-α-methylbenzenemethanol, 1517-69-7; (R)-α-ethylbenzenemethanol, 1565-74-8; (R)-α-(1-methylethyl)benzenemethanol, 14898-86-3; (R)-α-(1,1-dimethylethyl)benzenemethanol, 23439-91-0; (R)-α-tetralol, 23357-45-1; (S)-isophorol, 64543-48-2; (R)-4-nonyn-3-ol, 87682-12-0; (R)-2-methyl-4-nonyn-3-ol, 87682-13-1; (R)-2,2-dimethyl-4-nonyn-3-ol, 87682-14-2; (S)-α-((trimethylsilyl)-ethynyl)benzenemethanol, 70975-25-6.

2-Ethoxy-5-alkyl-3,4-dihydro-2*H*-pyrans in Organic Synthesis: A New Convenient Route to Branched δ-Ethoxy Alcohols

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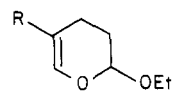
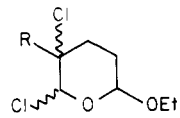
The reaction between 2-ethoxy-5-alkyl-5,6-dichlorotetrahydropyrans and Grignard reagents has been investigated, and the overall results clearly indicate that the reaction provides a useful route to the preparation of highly branched primary, secondary, and tertiary δ-ethoxy alcohols. Experimental evidence is presented to support the occurrence of suitable epoxides as reaction intermediates that may evolve to products either through a pinacol-type isomerization and/or via a cyclic intramolecular rearrangement of a halohydrin halomagnesium salt.

The synthetic utility of 2-ethoxy-5-alkyl-3,4-dihydro-2*H*-pyrans (**1a–c**) has been well-established.[1]



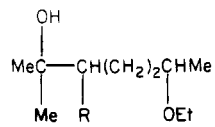
1a, R = H
b, R = Me
c, R = Pr^i

Recently, we reported that by starting from dichloro derivatives (**2b,c**) of **1b,c** 2-methyl-3-alkyl-6-ethoxy-



2

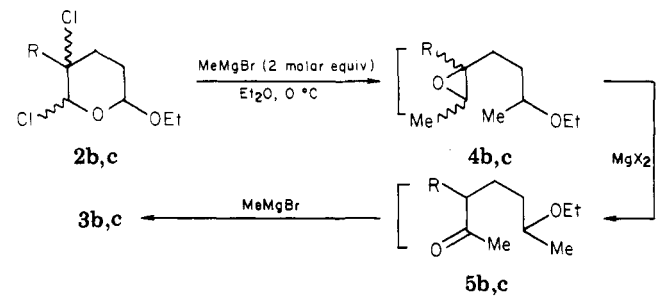
heptan-2-ols (**3b,c**) can be prepared readily and in very good overall yields, while an alternative route involving a more classical reaction sequence is lengthy and tedious.[2]



3

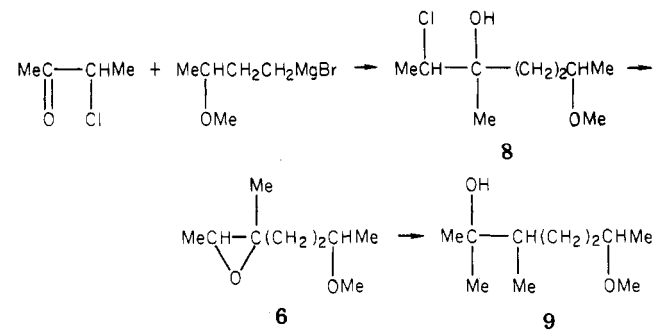
Since it is evident that these ethoxy alcohols represent valuable bifunctionalized intermediates in natural products, such as phythosterol synthesis,[3] we decided to undertake a more detailed examination of the reaction course of the dichloro derivatives **2a–c** with different Grignard reagents.

Scheme I



2b,c **4b,c** **5b,c** **3b,c**

Scheme II



8 **6** **9**

In this paper we provide insight into the mechanistic aspect of the reaction to clarify the origin of the regioselectivity observed as well as further demonstrate its usefulness in the preparation of polyfunctional molecules with relative ease.

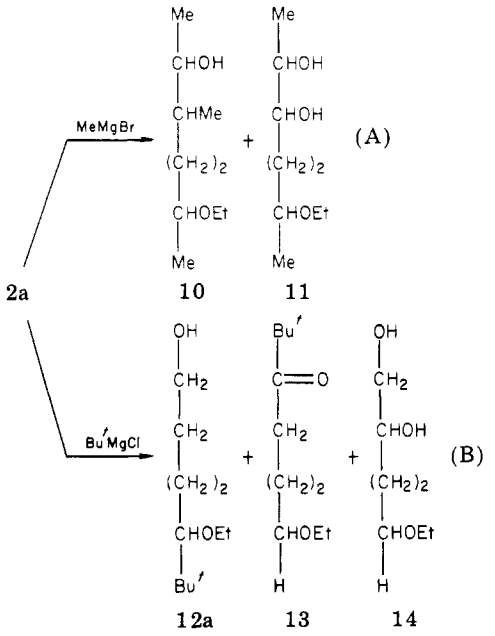
(1) (a) Tatone, D.; Dich, T. C.; Nacco, R.; Botteghi, C. *J. Org. Chem.* **1975**, *40*, 2987. (b) Fujii, T.; Hiraga, T.; Yoshguji, S.; Ohba, M.; Yoshida, K. *Chim. Pharm. Bull.* **1978**, *26*, 3233. (c) Weber, G. F.; Hall, S. S. *J. Org. Chem.* **1979**, *44*, 364 and references cited therein. (d) Menicagli, R.; Malanga, C.; Lardicci, L. *Ibid.* **1982**, *47*, 2288 and references cited therein.

(2) Menicagli, R.; Malanga, C.; Lardicci, L.; Tinucci, L.; Vecchiani, S. *Tetrahedron Lett.* **1982**, 1937.

(3) (a) Brooks, C. J. W. In "Chemistry of Carbon Compounds", 2nd ed.; Rodd, E. H., Ed.; Coffey: London, 1970; Vol. IId, p 154. (b) Goodwin, T. W. *Ibid.* 1970; Vol. IIe, p 103.

0022-3263/84/1949-0313$01.50/0

Scheme III



In our previous communication[2] we supposed that the reaction between the dichloro derivatives **2b,c** and MeMgBr afforded the intermediate 2,3-epoxy-3-alkyl-6-ethoxyheptane (**4b,c**) that, owing to a Lewis acid catalyzed isomerization,[4] gave 3-alkyl-6-ethoxyheptan-2-one (**5b,c**), precursor of **3b,c** via Grignard reagent alkylation (Scheme I).

Since any attempt to isolate either the epoxide **4** or the ketone **5** failed,[5] we at least wanted to verify if, in the reaction conditions adopted, 2,3-epoxy-3-methyl-6-methoxyheptane (**6**)[6] yields 2,3-dimethyl-6-methoxyheptan-2-ol (**9**).

The epoxide **6** was prepared, in very good yield, according to the general reaction sequence described in the Scheme II.[7]

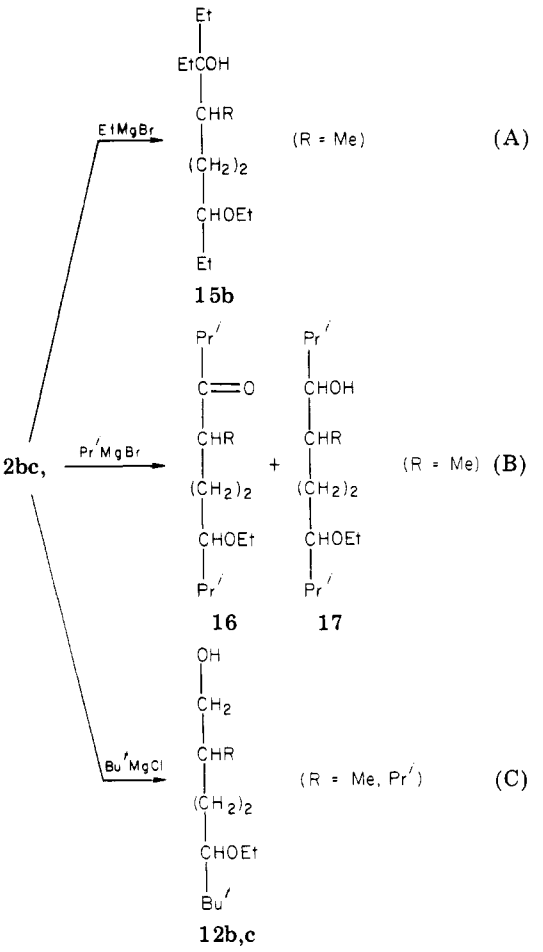
A sample of **6**, reacted at 0 °C with 2 molar equiv of MeMgBr, quantitatively yielded the alcohol **9**. Even if this finding agrees to the proposed hypothesis, it is not conclusive evidence since compound **9** may arise by coincidence.

Results and Discussion

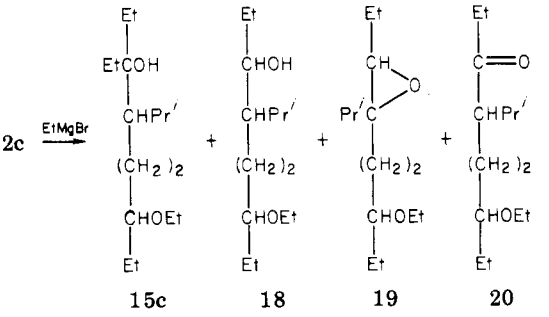
Compounds **1a–c** were reacted with chlorine in ether at −20 °C, and the reaction products were added to ethereal solutions of R′MgX (R′ = Me, Et, Pr^i, Bu^t).

The products were isolated from the reaction mixtures, and their structures were established by IR, ^{1}H and ^{13}C NMR,[8] and mass spectra (see Experimental Section and paragraph at the end of paper about supplementary material).

Scheme IV



Scheme V



By reaction of **2a** with MeMgBr, a 2:1 mixture of 3-methyl-6-ethoxyheptan-2-ol (**10**) and 6-ethoxyheptane-2,3-diol (**11**) was obtained (see Experimental Section and Scheme III, path A).

The products were separated by preparative GLC, and **10** was recovered in 64% overall yield.

On the other hand, the same dichloro derivative gave a more complex mixture when it was reacted with Bu^{t}MgCl: 5-ethoxy-6,6-dimethylheptan-1-ol (**12a**), 2,2-dimethyl-7-ethoxyheptan-3-one (**13**), and 5-ethoxypentane-1,2-diol (**14**), in the ratio 1:1:1, were obtained (Scheme III, path B). Also in this case the components of the mixture were isolated (see Experimental Section).

(4) Parker, R. E.; Isaacs, N. S. *Chem. Rev.* **1959**, *59*, 737 and references cited therein.
(5) Even if the reaction is stopped after a very short time, only the final product is detected (GLC).
(6) We prepared the epoxide **6** instead of **4** since we disposed of an appreciable amount of 1-bromo-3-methoxybutane (**7**).
(7) Cornforth, J. W.; Cornforth, R. H.; Mathew, K. K. *J. Chem. Soc.* **1959**, 112.
(8) Assignments were established by means of the additivity rule[9a–d] or by using correctional terms relating the carbon chemical shifts of aliphatic alcohols and the corresponding alkanes[9e] (e.g., C_2, C_{10}, C_{12}, C_{13} of **3c** and C_2, C_{10} of **15b**); further additive increments[10] were employed for C_2, C_{10} of **3c** and for C_9 of **10**. Steric interactions[11] help to account for deviations between the observed and calculated chemical shifts (e.g., the interactions between C_2 and C_6, C_1 and C_3, C_1 and C_2, and C_1 and C_9 of **3b**, **12b**, **16**, and **17**, respectively).
(9) (a) Paul, E. G.; Grant, D. M. *J. Am. Chem. Soc.* **1963**, *85*, 1701. (b) *Ibid.* **1964**, *86*, 2984. (c) Martin, M. L. *Org. Magn. Reson.* **1975**, *7*, 2. (d) Breitmayer, E.; Voelter, W. In "^{13}C NMR Spectroscopy", 2nd ed.; Verlag Chemie: New York, 1978. (e) Ejchart, A. *Org. Magn. Reson.* **1977**, *9*, 351.
(10) Mason, J. *J. Chem. Soc. A* **1971**, 1038.
(11) Werhli, F. W.; Wirthlin, T. In "Interpretation of ^{13}C NMR Spectra"; Heyden and Son Ltd: London, 1976; p 27.
(12) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

The reaction of **2b** with EtMgBr gave only 3-ethyl-4-methyl-7-ethoxynonan-3-ol (**15b**), which was recovered in satisfactory yield (80%) (Scheme IV, path A).

When Pr^{i}MgBr was used with the same dichloro derivative **2b**, an ca. 1:1 mixture of 2,4,8-trimethyl-7-ethoxynonan-3-one (**16**) and the corresponding alcohol **17** was recovered; both compounds were isolated by preparative GLC in 35% and 48% yield, respectively (Scheme IV, path B).

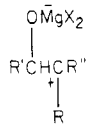
Either of the reactions of **2b** or **2c** with Bu^{t}MgCl gave 2-alkyl-6,6-dimethyl-5-ethoxyheptan-1-ols (**12b,c**) in very good yields (80–85%) (Scheme IV, path C).

By reaction of **2c** with EtMgBr, a very complex reaction mixture was obtained: the alcohol **15c**, 4-isopropyl-7-ethoxynonan-3-ol (**18**), 3,4-epoxy-4-isopropyl-7-ethoxynonane (**19**), and 4-isopropyl-7-ethoxynonan-3-one (**20**) were recovered in a ratio of 1.6:1:1.5:3 (Scheme V). Every component was obtained chemically pure by preparative GLC (see Experimental Section).

This last reaction was repeated by using the same reagent molar ratio, but the reaction was performed at room temperature (18 h) and then at the reflux of the solvent (30 h). In these reaction conditions a mixture of **15c**, **18**, **19**, and **20** was obtained once again, but compound **20** was the main reaction product (74%, GLC). Chemically pure **20** was recovered by Flash Chromatography[12] (60% yield).

If one considers the nature of the products recovered from the reaction of **2a–c** and Grignard reagents, and in particular the products obtained from **2c** and EtMgBr (Scheme V), it is evident that the previously proposed hypothesis[2] (Scheme I) is consistent. In this reaction both the epoxide **19** and the ketone **20** are recovered, and the alcohol **15c** obviously arises from alkylation of the ketone **20**, which is also partially reduced to **18**.

The formation of ketones, which can be isolated as they are or can be precursors of alcohols, is rationalized by considering a pinacol-type rearrangement of the precursor epoxides[4,13] through the intermediate zwitterion **21**. This



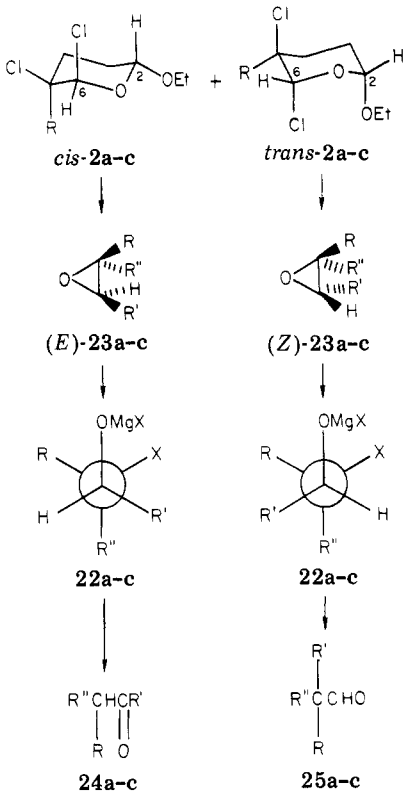
21, R″ = $(CH_2)_2C(OEt)HR'$

hypothesis fits the formation of compounds **3b,c**, **15b,c**, **16–20**, but to explain the recovery of compounds **10**, **12a–c**, and **13**, it is to be supposed an "erroneous migration" of the hydrogen instead of the alkyl group.

In an alternative explanation,[13] the halomagnesium salt of a halohydrin **22**[14] can give final products whose nature depends on the stereochemistry of **2a–c** (Scheme VI).

Since the chlorination of **1b,c** affords mainly (≥60%) *cis*-**2b,c** stereoisomers (see Experimental Section),[15,16] a similar mixture of *E* and *Z* epoxides **23a–c** has to be obtained (Scheme VI) if the substitution of the chlorine atoms in **2** occurs with a complete configurational inversion.

Scheme VI



Starting from this hypothesis and assuming that suggested by House,[13] while (*Z*)-**23a** through **22a** and **25a**[19] (Scheme VI) affords **10** (Scheme III), the isomeric ketone **24a** should arise from (*E*)-**23a**. Since no products arising from **24a** are detected, we conclude that (*E*)-**23a** affords the diol **11** (Scheme III). It is to be noted that compounds **10** and **11** are formed in a 2:1 ratio.

If our assumption regarding the stereochemistry of the formation of (*E*)- and (*Z*)-**23a** is correct, an extent of trans chlorination, larger than that observed for **1b,c**, has to be supposed when **1a** is reacted with chlorine.[20]

When **2b,c** are reacted with Bu^{t}MgCl, the alcohols **12b,c** are recovered in almost quantitative yields (Scheme IV, path C). By considering the structures of these alcohols, it is easy to understand that the dichloro derivatives **2b,c** are reduced at C_6 and alkylated at C_2. The resulting epoxides **23b,c** (R″ = $(CH_2)_2C(OEt)HBu^t$) (Scheme VI), either through **21** or **22**, afford the corresponding aldehydes **25b,c** from which the alcohols **12b,c** arise (Scheme IV, path C).[22]

When **2a** is reacted with the same Grignard reagent (Scheme III, path B), some further observations were made: (i) compound **12a** arises from a reaction sequence analogous to those affording **12b,c** and in contrast (ii) to

(13) (a) House, H. O. *J. Am. Chem. Soc.* **1955**, *77*, 3070. (b) *Ibid.* **1955**, *77*, 5083 and references cited therein.

(14) This intermediate may arise both from the oxirane magnesium halogenide complex and from the alkylation at C_2 and C_6 of **2** followed by fission of the endocyclic O–C bond.

(15) The ^{1}H NMR spectra of the samples of **2b,c** showed appreciable amounts (15–30%) of aldehyde impurities, the main component of which we suppose to be 2-alkyl-2,5-dichloro-5-ethoxypentanal arising from 1,4-addition of chlorine to **1b,c**.[1c] This hypothesis is supported by the absence of byproducts in the reactions performed.

(16) Our results regarding the percentages of cis and trans stereoisomers of **2b,c** well agree with the results reported for the chlorination of 3,4-dihydro-2*H*-pyran[17] and of 3,4,6-tri-*O*-acetyl-D-glucal.[18]

(17) Delaunay, J.; Lebouc, A.; Riobé, O. *Org. Magn. Reson.* **1979**, *12*, 278.

(18) Adamson, J.; Fostere, A. B. *Carbohydr. Res.* **1969**, *10*, 517.

(19) We assume that the isomerization of **22** always occurs by a cyclic transition state in which the oxymagnesium halide group and the largest group (R″) bonded to the adjacent carbon atom are oriented trans to one another.[13b]

(20) This supposition is not in contrast with that reported for the stereochemistry of electrophilic additions to 2-ethoxy-3,4-dihydro-2*H*-pyrans.[21] However, at present we cannot exclude that the chlorination of **1a** affords *cis*-**2a** as the main product. If this hypothesis is correct, a wide epimerization could occur during the reaction of *cis*-**2a** with MeMgBr (see note added in proof).

(21) Duggan, A. J.; Hall, S. S. *J. Org. Chem.* **1977**, *42*, 1057.

(22) Whitmore, F. C. *Recl. Trav. Chim. Pays-Bas* **1938**, *57*, 562.

gain compounds **13** or **14**, **2a** is, in the former case, reduced at C_2 and alkylated at C_6 and, in the latter, reduced both at C_2 and at C_6.

Starting from these evidences the alkylation at C_6 of **2a,c** must be affected by the sterical hindrance of the groups bonded at the C_5 (Scheme VI): only *cis*-**2a** can be alkylated and both *cis*-**2b,c** and *trans*-**2a–c** are reduced at the same carbon atom owing to the steric effect of the neighboring R or Cl, respectively. In this way (*E*)-**23a** (R″ = $(CH_2)_3OEt$) and **23a** (R″ = $(CH_2)_2C(OEt)HBu^t$) are formed. While **12a** arises from the latter compound (Scheme III, path B), independently from the mechanistic pathway assumed, different compounds could be formed from (*E*)-**23a** (R″ = $(CH_2)_3OEt$) if the corresponding intermediate **21** or **22** is postulated. Simple electronic and steric effects suggest that the reaction involves the halohydrin intermediate.

In conclusion, the overall results indicate that, when **2a** is reacted with Grignard reagents, most likely the intermediate epoxides evolve to the corresponding carbonyl compounds through the halohydrin salts; in contrast, epoxides arising from **2b,c** give the carbonyl derivatives following a pinacol-type rearrangement.

However, the two fashions of evolving may occur together, and it is impossible to establish the occurrence of one or the other if they afford the same final compounds.

An experimental result obtained by performing the reaction between **2c** and MeMgBr with inverse addition seems to confirm this last hypothesis. In this case a complex mixture of products was obtained, in which **3c**, together with 3-isopropyl-6-ethoxyheptan-3-one (**26**), 2,3-epoxy-3-isopropyl-6-ethoxyheptane (**27**), and 3-isopropyl-3-methyl-6-ethoxyheptan-2-ol (**28**), was present.[23] While the formation of **26** and **27** confirms once again the pinacol-type rearrangement, the presence of the alcohol **28** can be explained only if the intermediate aldehyde **25c**, arising from the corresponding halohydrin salt **22c**, is supposed. Probably the inverse addition causes in the reaction mixture a concentration of the Lewis acid suitable to partially promote the rearrangement via the halohydrin salt too.

Experimental Section

Materials and Instrumentation. Dry solvents were distilled under nitrogen from appropriate drying agents before use. 2-Ethoxy-5-alkyl-3,4-dihydro-2*H*-pyrans (**1a–c**)[1d,24] and 3-methoxybutan-1-ol[25] were synthesized according to reported procedures. Compounds **1** were purified by distillation under nitrogen from Na and then $LiAlH_4$ before use.

GLC analyses were performed on a Perkin-Elmer F 30 instrument equipped with 2 m × 0.29 cm columns packed with 2.5% SE 30 on 80–100-mesh Chromosorb G AW DMCS, 8% CW 20M + 2% KOH on 80–100-mesh Chromosorb W, and 10% BDS on 60–80-mesh Chromosorb W and a flame-ionization detector employing nitrogen as carrier gas.

Preparative GLC purifications were carried out on a Perkin-Elmer F 21 chromatograph equipped with 3 m × 0.95 cm columns packed with 2.5% SE 30 on 80–100-mesh Chromosorb W AMDS, 8% CW 20M + 2% KOH on 80–100-mesh Chromosorb W DMCS, and 15% BDS on 60–80-mesh Chromosorb W.

IR spectra were obtained on a Perkin-Elmer 225 spectrophotometer on liquid films.

^1H NMR and ^{13}C NMR Fourier-transform spectra were obtained with Varian T 60 (60 MHz), JEOL PS 100 (100 MHz), and Varian XL 100 (25.2 MHz) spectrometers in $CDCl_3$ solutions, unless otherwise stated; chemical shifts are reported as δ (ppm) values with Me_4Si as internal reference.

Mass spectra were taken at 70 eV on a Varian Mat CH 7 GC–MS spectrometer.

Chlorination of 1b,c. Dry chlorine (Matheson) was bubbled into an ethereal solution (5 mL) of 3.0 g (21.1 mmol) of **1b** at −20 °C until a pale-green color was obtained.

The solvent was accurately removed, and the crude **2b** (4.7 g) showed the following: ^1H NMR (100 MHz, CCl_4) δ 9.60–9.40 (m, 0.15 H), 6.10–6.00 (br s, 0.25 H, anomeric proton at C_2 of *trans*-**2b**), 5.82–5.72 (dd, 0.15 H), 5.72–5.60 (m, 0.60 H, anomeric proton at C_2 of *cis*-**2b**), 5.20–5.00 (m, 0.85 H, anomeric proton at C_6 of **2b**), 4.10–3.40 (m, 2 H), 2.60–1.75 (m, 4 H), 1.80–1.60 (m, 3 H), 1.22 (m, 3 H).

Analogously from 3.5 g (20.6 mmol) of **1c** was recovered 4.9 g of crude **2c** having the following: ^1H NMR (60 MHz, CCl_4) δ 9.80–9.60 (m, 0.30 H), 6.20–6.10 (br s, 0.28 H, anomeric proton at C_2 of *trans*-**2c**), 6.10–5.80 (m, 0.30 H), 5.80–5.60 (m, 0.42 H, anomeric proton at C_2 of *cis*-**2c**), 5.20–4.90 (m, 0.70 H, anomeric proton at C_6 of **2c**), 4.25–3.35 (m, 2 H), 2.80–1.60 (m, 5 H), 1.50–0.90 (m, 9 H).

Unfortunately any attempts to remove aldehyde impurities from the samples of **2b,c**, both by preparative HPLC and TLC, failed.

Reaction of 2a–c and Grignard Reagents (General Procedure). In a typical small-scale reaction, an ethereal solution (10 mL) of **1a–c** (30 mmol) was chlorinated, and the final reaction mixture was decolored with a few drops of **1a–c** and then siphoned, under nitrogen, into a dropping funnel cooled at −10 °C. This solution was then added to a cooled (0 °C) ethereal solution of Grignard reagent (0.1 mol) prepared and titrated as usual.[26]

Upon completion of the addition, the reaction mixture was stirred (12 h) at the same temperature and then hydrolyzed with brine. The aqueous phase was extracted with ether (4 × 50 mL), and the extracts were washed with water and dried (Na_2SO_4).

The relative percentages of the reaction products were established by GLC of the crude hydrolysis mixtures.

All unknown compounds were isolated: chemically pure **3b,c**, **15b**, **12b,c** were obtained by distillation of the hydrolysis mixtures; **10–14**, **15c**, **16–20** were purified by preparative GLC.

The structure of the obtained products were established by IR, ^1H and ^{13}C NMR, and mass spectra (see Tables I and II and Experimental Section).

Reaction of 2a with Methylmagnesium Bromide. Starting from **2a** and methylmagnesium bromide, a mixture of two products (A and B) in a ratio of 2:1 (SE 30, 110 °C) was obtained. By GLC purification (SE 30, 105 °C) chemically pure A and B in 64% and 25% yield, respectively, were recovered. These products were identified as A, 3-methyl-6-ethoxyheptan-2-ol (**10**) (for spectral data and physical properties, see Tables I, II) and B, 6-ethoxyheptane-2,3-diol (**11**) [bp 132 °C (20 mm); IR 3550, 3430, 2980, 2940, 2870, 1450, 1375, 1340, 1250, 1140, 1120, 1095, 960, 845 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 3.86–3.26 (m, 1 H), 3.50 (q, 2 H), 4.20–3.70 (m, 2 H), 2.95 (s, 1 H), 2.25–1.40 (m, 4 H), 1.40 (s, 1 H), 1.20 (t, 3 H), 1.15 (d, 6 H); ^{13}C NMR δ 74.73, 74.05, 70.60, 70.36, 70.14, 69.91, 69.14, 63.60, 33.94, 33.30, 33.07, 30.96, 30.33, 29.51, 28.93, 20.24, 19.72, 18.49, 18.39, 15.59; MS, *m/e* (I%) 45 (100), 73 (98), 43 (33), 55 (22), 57 (15), 41 (12), 81 (10), 99 (10), 42 (9), 59 (8), 113 (6), 85 (5), 131 (5), 145 (0.5)].

Reaction of 2a with *tert*-Butylmagnesium Chloride. Starting from **2a** and *tert*-butylmagnesium chloride, a mixture of three products (A–C) in a ratio of 1:1:1 (BDS, 140 °C) was obtained. By GLC purification [BDS, 120 °C (A and B), 140 °C (C)] chemically pure A–C in 23%, 27%, and 24% yield, respectively, were recovered. These products were identified as follows: A, 5-ethoxy-6,6-dimethylheptan-1-ol (**12a**) [bp 66 °C (0.3 mm); IR 3460, 2990, 2960, 2860, 1480, 1460, 1380, 1360, 1190, 1130, 1110, 1070, 1045, 1000, 930, 880 cm^{-1}; ^1H NMR (60 MHz) δ 3.80–3.10 (m, 3 H), 3.50 (q, 2 H), 2.10 (s, 1 H), 1.80–1.40 (m, 6 H), 1.20 (t, 3 H), 0.90 (s, 9 H); ^{13}C NMR δ 79.90, 70.69, 66.09, 34.97, 31.31, 29.79, 25.76, 23.89, 15.27; MS, *m/e* (I%) 85 (100), 57 (47), 43 (25), 131 (18), 59 (16), 55 (14), 71 (8), 127 (7), 109 (4), 170 (2), 171 (2),

(23) The structures of **26–28** were established by comparison of their mass fragmentations with those of homologous compounds **16**, **6** and **19**, **17** and **18**, respectively.

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188 (M^+, 0.3)]; B, 2,2-dimethyl-7-ethoxyheptan-3-one (**13**) [bp 57 °C (0.2 mm); IR 2980, 2940, 2860, 1705, 1475, 1460, 1390, 1375, 1365, 1200, 1150, 1110, 1055, 1010, 980, 880 cm^{-1}; ^1H NMR (60 MHz) δ 3.60–3.30 (m, 2 H), 3.52 (q, 2 H), 2.70–2.30 (m, 2 H), 2.05–1.50 (m, 4 H), 1.20 (t, 3 H), 1.12 (s, 9 H); ^{13}C NMR δ 215.23, 70.47, 66.10, 44.10, 36.25, 29.46, 26.49, 20.84, 15.30; MS, *m/e* (I%) 57 (100), 41 (76), 55 (70), 101 (67), 43 (36), 59 (36), 129 (18), 140 (3), 141 (2), 186 (M^+, 1), 157 (0.9), 187 ($M^+ + 1$, 0.5)]; C, 5-ethoxypentane-1,2-diol (**14**) [bp 78 °C (0.2 mm); IR 3550, 3420, 2990, 2960, 2870, 1460, 1380, 1355, 1275, 1190, 1160, 1110, 1070, 970, 875 cm^{-1}; ^1H NMR (60 MHz) δ 4.40–3.40 (m, 5 H), 3.75 (s, 1 H), 3.50 (q, 2 H), 3.42 (s, 1 H), 2.20–1.50 (m, 4 H), 1.20 (t, 3 H); ^{13}C NMR δ 74.32, 66.85, 66.16, 65.14, 31.18, 26.69, 26.52, 15.21; MS, *m/e* (I%) 85 (100), 57 (31), 43 (24), 131 (20), 31 (15), 59 (15), 55 (11), 69 (9), 101 (4), 109 (4), 132 (3)].

Reaction of 2c with Ethylmagnesium Bromide. Starting from **2c** and ethylmagnesium bromide, a mixture of four products (A–D) in a ratio of 1.6:1:1.5:3 (CW 20M, 155 °C) was obtained. By GLC purification [CW 20M, 130 °C (A and B), 140 °C (C and D)] chemically pure A–D in 18%, 12%, 18%, and 37% yield, respectively, were obtained. These products were identified as follows: A, 3-ethyl-4-isopropyl-7-ethoxynonan-3-ol (**15c**) [bp 88 °C (0.02 mm); IR 3490, 2990, 2940, 2880, 1460, 1390, 1370, 1175, 1150, 1110, 1080, 970, 870 cm^{-1}; ^1H NMR (60 MHz) δ 3.52 (q, 2 H), 3.40–3.00 (m, 1 H), 2.00–1.10 (m, 12 H), 1.52 (s, 1 H), 1.20 (t, 3 H), 0.95 (t, 3 H), 0.90 (d, 6 H), 0.86 (t, 6 H); ^{13}C NMR δ 81.13, 81.01, 77.81, 64.06, 49.49, 49.26, 36.19, 36.03, 29.20, 28.50, 27.05, 26.51, 24.48, 20.06, 18.06, 15.69, 9.79, 7.99, 7.82; MS, *m/e* (I%) 87 (100), 57 (63), 183 (35), 143 (29), 59 (26), 45 (23), 55 (22), 97 (9), 167 (7), 184 (6), 229 (3), 211 (2), 240 ($M^+ - H_2O$, 0.7)]; B, 4-isopropyl-7-ethoxynonan-3-ol (**18**) [bp 79 °C (0.01 mm); IR 3460, 2990, 2960, 2880, 1470, 1390, 1370, 1180, 1150, 1110, 1080, 970, 880 cm^{-1}; ^1H NMR (60 MHz) δ 3.90–3.50 (m, 1 H), 3.50 (q, 2 H), 3.40–2.98 (m, 1 H), 2.10–1.30 (m, 10 H), 1.86 (s, 1 H), 1.20 (t, 3 H), 0.95 (t, 3 H), 0.92 (d, 6 H), 0.86 (t, 3 H); ^{13}C NMR δ 80.85, 74.44, 74.27, 64.05, 49.02, 48.85, 33.45, 33.22, 28.90, 28.74, 27.46, 26.46, 21.91, 21.74, 20.53, 20.00, 15.69, 10.67, 9.68; MS, *m/e* (I%) 87 (100), 59 (58), 155 (31), 85 (28), 41 (25), 43 (17), 137 (13), 81 (12), 143 (11), 95 (8), 183 (5), 212 ($M^+ - H_2O$, 1)]; C, 3,4-epoxy-4-isopropyl-7-ethoxynonane (**19**) [bp 63 °C (0.01 mm); IR 2990, 2960, 2880, 1465, 1380, 1370, 1210, 1190, 1160, 1110, 990, 910, 895, 825 cm^{-1}; ^1H NMR (60 MHz) δ 3.50 (q, 2 H), 3.40–2.92 (m, 1 H), 2.72 (t, 1 H), 1.94–1.20 (m, 9 H), 1.15 (t, 3 H), 0.92 (d, 6 H), 0.90 (t, 6 H); ^{13}C NMR δ 80.44, 66.32, 66.16, 64.17, 64.01, 62.60, 62.43, 32.71, 32.47, 30.79, 29.37, 29.14, 26.99, 26.75, 26.40, 24.83, 24.66, 24.54, 24.10, 21.74, 18.60, 18.43, 17.67, 15.67, 10.72, 9.74; MS, *m/e* (I%) 87 (100), 59 (77), 41 (70), 85 (47), 57 (37), 71 (32), 141 (28), 99 (25), 95 (23), 153 (7), 199 (4), 228 (M^+, 0.6)]; D, 4-isopropyl-7-ethoxynonan-3-one (**20**) [bp 71 °C (0.007 mm); IR 2990, 2960, 2880, 1710, 1460, 1390, 1370, 1200, 1160, 1110, 1080, 1030, 950, 880 cm^{-1}; ^1H NMR (60 MHz) δ 3.50 (q, 2 H), 3.40–2.90 (m, 1 H), 2.42 (q, 2 H), 2.40–2.00 (m, 1 H), 1.95–1.20 (m, 7 H), 1.15 (t, 3 H), 1.04 (t, 3 H), 0.90 (d, 6 H), 0.86 (t, 3 H); ^{13}C NMR δ 221.42, 79.92, 79.46, 63.62, 63.43, 58.42, 36.44, 35.92, 31.21, 30.74, 29.69, 29.57, 25.96, 24.32, 23.68, 20.65, 19.38, 15.17, 9.17, 8.94, 7.03; MS, *m/e* (I%) 87 (100), 85 (88), 59 (62), 41 (36), 199 (30), 43 (19), 153 (15), 125 (9), 167 (8), 228 (M^+, 7), 200 (5), 229 ($M^+ + 1$, 2)].

The same reaction carried out at room temperature (18 h) and then at 35 °C (30 h) gave a mixture of **15c**, **18**, **19**, and **20** in a ratio of 7:1:1:37. Chemically pure **20** (CW 20M, 155 °C) was obtained (60% yield) by flash chromatography[12] [15 cm × 3 cm column packed with 400–230-mesh silica gel, eluant 10% ethyl acetate/petroleum ether (30–60 °C)].

3-Methoxy-1-bromobutane (7). To a solution of 39.9 g (0.38 mol) of 3-methoxybutan-1-ol[25] in dry pyridine (137 mL), cooled at −2 °C, was added 80.6 g (0.42 mol) of *p*-toluenesulfonyl chloride. The mixture was stirred at 2–3 °C (4 h) and then at room temperature (18 h).

The hydrolysis was carried out with a 6 M solution of HCl (2 L). The aqueous phase was extracted with ether, and the organic layer, washed with 5% $NaHCO_3$ and water and dried (Na_2SO_4), gave, after removal of the solvent under reduced pressure, 85.4 g of 1-(tosyloxy)-3-methoxybutane.

The dark yellow oil, without further purification, was dissolved in DMF (310 mL) and warmed at 90 °C and dropwise added to a 2 M solution of LiBr in the same solvent (193 mL). The mixture, cooled to room temperature, was hydrolyzed with water and extracted with ether. The ethereal phase, worked up as usual, gave by fractional distillation 46.2 g (72% yield) of chemically pure **7** (BDS, 80 °C) having the following: bp 89 °C (148 mm); IR 2960, 2940, 2880, 1465, 1440, 1375, 1135, 1085, 570 cm^{-1}; ^1H NMR (100 MHz, neat) δ 3.71–3.38 (m, 3 H), 3.33 (s, 3 H), 2.22–1.68 (m, 2 H), 1.13 (d, 3 H); MS, *m/e* (I%) 59 (100), 29 (19), 71 (18), 55 (17), 43 (14), 153 ($M^+ + 2 - CH_3$, 5), 151 ($M^+ - CH_3$, 5).

2-Chloro-3-methyl-6-methoxyheptan-3-ol (8). An ethereal solution (40 mL) of (3-methoxybutyl)magnesium bromide, prepared as usual from 12.2 g (64 mmol) of **7**, was cooled to −70 °C and then 6.2 g (58 mmol) of freshly distilled 3-chlorobutan-2-one in ether (5 mL) was slowly added.

After 0.4 h a slight excess of acetic acid in ether was added, and then the mixture was brought to room temperature and diluted with water. The aqueous layer was extracted with ether, and the combined ethereal solution, washed with 5% $NaHCO_3$ and water and dried (Na_2SO_4), gave 9.1 g (82% yield) of chemically pure **8** (SE 30, 70 °C) having the following: bp 119 °C (18 mm); ^1H NMR (60 MHz, CCl_4) δ 4.00 (dq, 1 H), 3.60–2.90 (m, 1 H), 3.30 (s, 3 H), 3.10 (s, 1 H), 1.90–1.30 (m, 4 H), 1.60 (s, 3 H), 1.15 (dd, 6 H).

2,3-Epoxy-3-methyl-6-methoxyheptane (6). In an Erlenmeyer flask 7.7 g (40 mmol) of **8** and a 1 N solution of NaOH (50 mL) were stirred at room temperature. After 1 h the solution was extracted with ether and the organic layer washed with water and dried (Na_2SO_4).

After removal of the solvent, the residue gave 4.7 g (76% yield) of chemically pure **6** (SE 30, 70 °C) having the following: bp 82 °C (18 mm); IR 2990, 2940, 2860, 1460, 1375, 1250, 1135, 1090, 870, 830 cm^{-1}; ^1H NMR (60 MHz) δ 3.60–3.10 (m, 1 H), 3.30 (s, 3 H), 2.92 (q, 1 H), 1.80–1.30 (m, 4 H), 1.30 (d, 3 H), 1.22 (s, 3 H), 1.12 (d, 3 H); ^{13}C NMR δ 76.36, 76.01, 60.26, 60.10, 59.79, 58.62, 58.34, 55.55, 36.14, 34.28, 33.91, 31.59, 31.41, 28.27, 28.04, 25.35, 21.92, 18.81, 16.25, 16.09, 13.92, 13.76; MS, *m/e* (I%) 59 (100), 45 (50), 72 (32), 41 (25), 99 (24), 30 (22), 67 (18), 43 (17), 86 (9), 126 (3), 143 (0.3), 158 (M^+, 0.3).

2,3-Dimethyl-6-methoxyheptan-2-ol (9). To a cooled (0 °C) solution of 50 mmol of methylmagnesium bromide in ether (40 mL) was added a solution of 3.7 g (23 mmol) of **6** in the same solvent (10 mL) (0.5 h). The mixture was stirred at the same temperature (12 h) and then worked up as usual to give 3.7 g (91% yield) of chemically pure **9** (SE 30, 120 °C) having the following: bp 62 °C (0.3 mm); IR 3460, 2980, 2940, 2860, 1460, 1370, 1160, 1135, 1090, 950, 910 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 3.57–3.00 (m, 4 H), 2.57 (s, 1 H), 1.93–0.60 (m, 17 H); MS, *m/e* (I%) 59 (100), 43 (59), 84 (29), 55 (26), 69 (18), 127 (13), 71 (11), 156 ($M^+ - H_2O$, 0.9), 159 ($M^+ - CH_3$, 0.9).

Note added in proof: After this manuscript had been accepted we were able to establish that the chlorination of **1a** affords mainly *trans*-**2a** along with aldehyde impurities (14%) [^1H NMR (80 MHz) δ 9.59–9.41 (m, 0.14 H), 6.18–6.00 (br s, 0.65 H, anomeric proton at C_2 of *trans*-**2a**), 5.93–5.83 (m, 0.14 H), 5.79–5.55 (m, 0.21 H, anomeric proton at C_2 of *cis*-**2a**), 5.18–4.83 (m, 0.86 H, anomeric proton at C_6 of **2a**), 4.39–3.36 (m, 3 H), 2.88–1.58 (m, 4 H), 1.39–1.09 (t, 3 H)].

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Registry No. **1b**, 2397-94-6; **1c**, 71237-04-2; **2a**, 88083-42-5; **2b**, 88083-40-3; **2c**, 88083-41-4; **6**, 88083-53-8; **7**, 54149-15-4; **8**, 88083-52-7; **9**, 88083-54-9; **10**, 88083-43-6; **11**, 88083-44-7; **12a**, 88083-45-8; **13**, 88083-46-9; **14**, 88083-47-0; **15c**, 88083-48-1; **18**, 88083-49-2; **19**, 88083-50-5; **20**, 88083-51-6; 3-methoxy-1-butanol, 2517-43-3; 1-(tosyloxy)-3-methoxybutane, 55524-92-0; 3-chloro-2-butanone, 4091-39-8; methylmagnesium bromide, 75-16-1; *tert*-butylmagnesium bromide, 677-22-5; ethylmagnesium bromide, 925-90-6.

Supplementary Material Available: Table I (boiling point and spectral data of compounds **3b,c**, **10**, **15b**, **16**, **17**, and **12b,c**) and Table II (observed and predicted ^{13}C NMR chemical shifts of the compounds reported in the Table I) (2 pages). Ordering information is given on any current masthead page.