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NUCLEOPHILIC CLEAVAGE OF ACETALS USING ORGANOMETALLIC REAGENTS

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Summary

A highly chemo- and stereo-selective cleavage of acetals derived from (−)-(2*R*,4*R*)-2,4-pentanediol with organoaluminum and organotitanium reagents has been demonstrated. The reactions proceed under mild conditions with excellent yields and high chemoselectivities to give, after removal of the auxiliary, chiral alcohols of high enantiomeric purities.

The problem of devising general methods for the asymmetric synthesis of chiral, optically active alcohols via nucleophilic additions to carbonyl compounds which are efficient both with regard to the optical and material yield remains a major challenge despite extensive studies in this area for many years [1]. The direct formation of such alcohols with high enantiomeric purities is not possible using classical synthetic reactions, and consequently indirect approaches have been required, e.g. a sequence employing the nucleophilic addition of Main Group organometallics to chiral acetals [2]. Indeed, a number of methods for the cleavage of simple acetals have been investigated previously. These include: (a) the reaction that proceeds via the free ketone produced by proton abstraction from a ketal methylene [3]; (b) the nucleophilic opening of a cyclic acetal which takes place in the presence of reagents that can function as Lewis acids [4,5].

The derivation of the present approach to asymmetric synthesis was based on the following conditions: (1) that the starting chiral alcohol be readily available; (2) that the carbonyl compound be combined with a chiral diol to form a ring of a single diastereoisomer; (3) that the cleavage product be readily convertible by a simple operation to a chiral alcohol. We thus chose to investigate the acetals of type **1** formed by the reaction of ketones and aldehydes with readily available (−)-(2*R*,4*R*)-2,4-pentanediol as potential chiral synthetic equivalents of carbonyl compounds.

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Reductive cleavage of acetals using aluminum reagents

One of the most widely studied processes for the asymmetric induction of a chiral center into a molecule is the asymmetric reduction of a prochiral ketone. Considerable success has been achieved in obtaining high asymmetric inductions in this process, particularly with modified lithium aluminum hydride reagents [6]. However, one of the major drawbacks of existing methods is that they are effective only for aromatic or α,β-unsaturated ketones. This lack of generality is rather disappointing in view of the importance of the process in organic synthesis. For some time, we have been intrigued with the supposition that the optically active acetal may be cleaved regio- and stereo-selectively by organoaluminum reagents under proper conditions [7]. Were this found to be the case, we felt that this might provide a practical solution to this problem. Scheme 1 illustrates how such a process would proceed.

TABLE 1

REDUCTION OF CHIRAL ACETALS WITH HYDRIDE REAGENTS [a]

Acetal **1**		Hydride reagent (equiv.)	Conditions solvent (°C, h)	**2**		% e.e. of **3** [c,d] (configuration)
R^1	R^2			Yield (%)	Ratio [b]	
c-Hexyl	Me	DIBAH (5)	CH_2Cl_2 (0, 0.5)	88	13/1	88
		DIBAH (2)	CH_2Cl_2 (0, 1.5)	65	7/1	
		DIBAH (5)	Ether (0, 6)	76	8/1	76
		DIBAH (5)	Toluene (0, 0.5)	74	9/1	
		DIBAH (5)	Hexane (0, 1)	87	12/1	
		Et_2AlH (5)	Toluene (0, 0.5)	88	3/1	
		Et_2AlH (5)	Ether (0, 1.5)	81	8/1	
		Cl_2AlH (6)	Ether (0, 0.5)	98	19/1	92 (*S*) [f]
		Br_2AlH (6)	Ether (−20, 0.5)	99	23/1	95
n-Hexyl	Me	DIBAH (5)	CH_2Cl_2 (0, 2)	58	3.5/1	55 [e]
		Cl_2AlH (6)	Ether (0, 1.5)	73	2/1	
		Br_2AlH (6)	Ether (0, 0.75)	69	4/1	
		Br_2AlH (20)	Ether (−40, 2)	87	4/1	58 [e] (*S*) [f]
		Br_2AlH (20)	Ether (−78, 1)	64	8/1	78 [e]
Ph	Me	DIBAH (5)	CH_2Cl_2 (0. 1.5)	88	28/1	93
		Br_2AlH (6)	Ether (−78,1; 0, 0.5)	94	57/1	96 (*S*) [f]
Ph	n-Pr	DIBAH (5)	CH_2Cl_2 (0, 0.5)	72	20/1	
		Br_2AlH (6)	Ether (−20, 0.5)	92	42/1	94 (*S*) [f,g]

[a] Reduction of the chiral acetal was carried out as described in the Experimental section. [b] The diastereomeric ratio was determined by GLC on a 20-m PEG-HT capillary column. The reduction product **2** (R^1 = cyclohexyl, R^2 = Me) was also converted into the trimethylsilyl ether, which showed clean separation on GLC. [c] Unless otherwise specified, the optical yield was determined by GLC analysis of (−)-(*S*) MTPA esters. See, J.A. Dale, D.L. Dull and H.S. Mosher, J. Org. Chem., 34 (1969) 2543. [d] The alcohols **3** were obtained by the two-step sequence from **2** in yields of 70–83% (see Experimental section). [e] Determined by ^1H NMR analysis of the MTPA derivative in the presence of tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium(III). [f] Optical rotation values of **3** were $[\alpha]^{25}_D$ +4.58° (neat, d = 0.92) for R^1 = cyclohexyl, R^2 = Me; $[\alpha]^{25}_D$ −55.36° (c 0.98, cyclopentane) for R^1 = Ph, R^2 = Me; $[\alpha]^{25}_D$ +5.34° (neat, d = 0.82) for R^1 = n-hexyl, R^2 = Me; $[\alpha]^{25}_D$ −38.41° (c 2.90, benzene) for R^1 = Ph, R^2 = n-Pr. [g] Optical yield after correction for (−)-(2*R*,4*R*)-2,4-pentanediol of 93% optical purity.

SCHEME 1

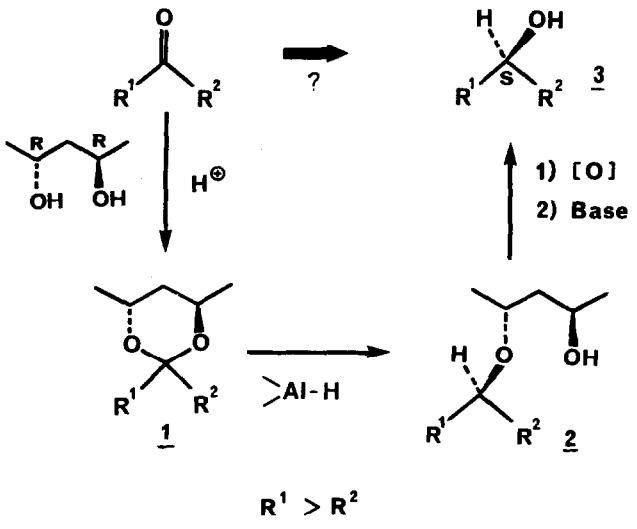
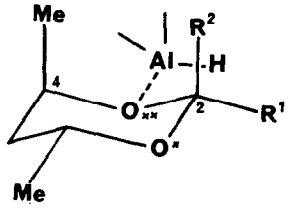


Table 1 illustrates the results obtained with four different ketone systems under various conditions. Thus, reagent, temperature, and solvent, the three variables in the reduction, were explored in detail. Although almost every readily available aluminum hydride was tried, only diisobutylaluminum hydride (DIBAH), Cl_2AlH, and Br_2AlH gave satisfactory results [8]. Tetrahydrofuran and other basic solvents were generally found to be unsatisfactory for the reaction. A low reaction temperature gave us slightly better selectivities.

Swern oxidation [9] of the resulting alcohol **2** followed by base-catalyzed β-elimination gave the optically pure alcohol **3** in good yield.

Structure **A** shows a view of the aluminum reagent-acetal complex in what appears to be the energetically favorable structure.



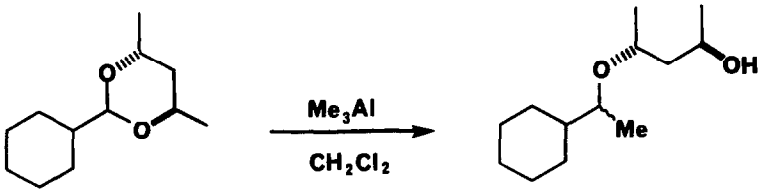
A

Thus, the steric efffect should influence the reactivity of the oxygen atoms of the acetal function, hence their relative ease of coordination to aluminum metal, and consequently the least sterically congested of several possible structures would appear to be **A**. Furthermore, the C–O* bond in conformer **A** should be shorter than a normal C–O ether bond because it has a partial double-bond character due to the anomeric effect [10], whereas the C–O** bond should be longer than usual because of electron donation from the other oxygen. Such lengthening of the C–O** bond should relieve at least part of the severe 2,4-diaxial interaction of **A** [11]. This

transient species can undergo smooth cleavage of the C–O** bond by the attack of hydride ion of aluminum metal from the direction *syn* to this departing oxygen, which would lead to the *S* configuration at the resulting ether carbon, as observed [12].

Alkylic cleavage of acetals

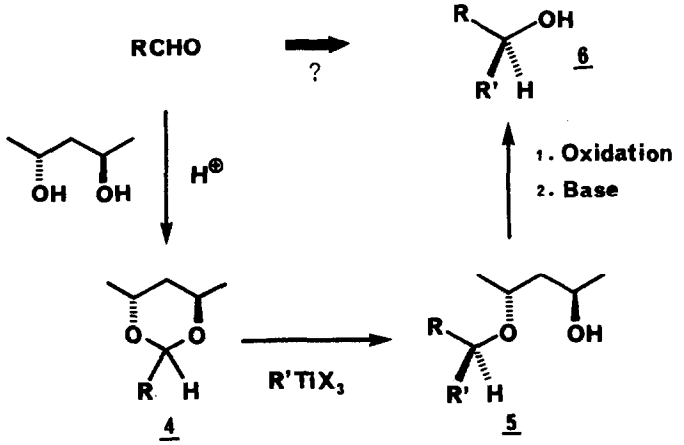
In view of the efficiency of the mild and stereospecific cleavage of chiral acetals by aluminum reagents, the behavior of trialkylaluminum has been studied systematically. It was soon realized that treatment of acetals in dichloromethane with trialkylaluminum leads to a mixture of diastereoisomers. These rather disappointing



64 % (2 : 3)

results are consistent with a common S_N2-type alkylation of organoaluminum reagents in non-polar or less polar solvents such as hexane or dichloromethane [13]. The results may be attributed to the aggregated form of the aluminum reagent. In view of the inefficiency of the aluminum reagent, the behavior of certain anionic organometallic reagents having Lewis acidic character was studied. Of these reagents, the titanium reagent prepared by the reaction of dialkylzinc with titanium tetrachloride was clearly the most effective [14]. The new process is illustrated in Scheme 2.

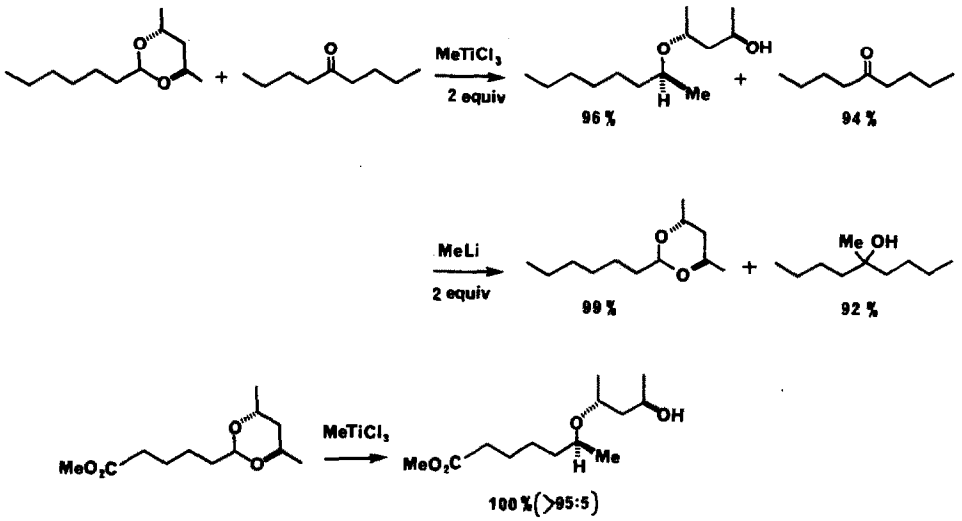
SCHEME 2



When the chiral acetal **4** was exposed to equimolar amounts of CH_3TiCl_3 [15] at −78°C, the corresponding methylated product **5** (R′ = Me) was obtained quantita-

tively. The chiral auxiliary was removed in the manner described previously. Several examples of this transformation are given in Table 2.

It has also been possible to show that the reaction between acetal and titanium reagent is highly chemoselective [14] and that this is a factor of considerable importance in organic synthesis. Indeed, essentially complete chemoselectivity is observed in the following reactions.



It should also be noted that treatment of **4** (R = c-hexyl) with titanium tetrachloride at low temperature followed by the addition of n-butyllithium at −78°C results

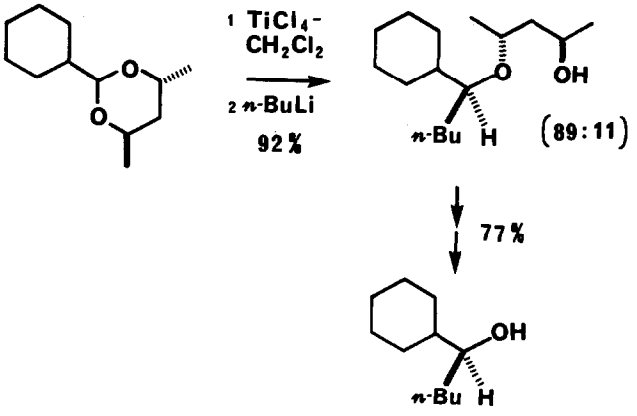
TABLE 2

NUCLEOPHILIC CLEAVAGE OF ACETALS USING ORGANOTITANIUM REAGENTS [a]

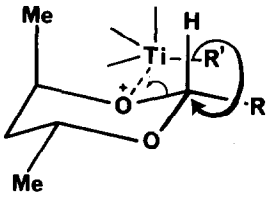
Acetal **4** R	Method	**5** R′	Yield	Ratio [b]	**6** Configuration
c-Hexyl	A	Me	100	24/1	*S* [c]
	B	Me	100	24/1	*S* [c]
	C	Me	91	32/1	*S* [c]
	D	Me	92	8/1	*S* [d]
n-Hexyl	A	Me	93	16/1	*S* [c]
	C	Me	77	32/1	*S* [c]
	E	Et	100	4/1	*S* [e]
	F	Et	100	4/1	*S* [e]
	D	n-Bu	47	10/1	–
n-Bu	A	Me	81	32/1	–
	E	Et	86	3.5/1	–
Et	D	n-Bu	45	7/1	–
Me	D	n-Bu	34	24/1	–

[a] For methods A–F, see Experimental section. [b] The diastereomeric ratio was determined by GLC on a 25-m PEG-HT capillary column. [c] Determined by comparison with authentic samples which were prepared by reductive cleavage of chiral acetals. [d] $[\alpha]_D$ −8.85° (*c* 1.10, benzene), see ref. 17. [e] $[\alpha]_D$ +6.17° (*c* 2.35, $CHCl_3$), see ref. 18.

in stereoselectivity of 89% with a high chemical yield. The method involves in situ butyltitanium formation in the presence of dichloromethane and acetal, thus avoiding the troublesome procedure with the preformed butyltitanium trichloride [16].



A feasible mechanistic explanation for these titanium reagents must be very similar to that of reductive cleavage of acetal as shown in Structure **A**. Unfortunately, however, it is not clear that the same model suggested for the transition state of the aluminum reagent is applicable to titanium cases. Thus, the nucleophile approaches the alkyl group from the *si*-face of the carbonyl (inversion), while hydride was shown to approach from the *re*-face of the carbonyl, i.e *anti*-addition [12]:



It should also be pointed out that only one equivalent of titanium reagent was used in the reaction, thus an intermolecular reaction mechanism may be unlikely. Further study is required before the mechanistic details of these reactions can be fully understood.

In summary, the process described above opens up a practical and highly chemo- and stereo-selective methodology to nucleophilic addition to carbonyl compounds.

Experimental

General

Infrared (IR) spectra were recorded on a Hitachi 260-10 spectrometer. ^{1}H NMR spectra were measured on a JNM-PMX 60 spectrometer. The chemical shifts are expressed in parts per million downfield from internal tetramethylsilane ($\delta = 0$). Splitting patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad peak. Gas liquid phase chromatographic (GLC) analyses were performed on Hitachi Model 163, 164 or Gasukuro Kogyo Model 370 instruments equipped with a flame ionization detector, using nitrogen as the carrier gas. Mass

spectra (MS) were recorded on a Hitachi MU-6L spectrometer, and exact mass on a Hitachi M-80 spectrometer. All experiments were carried out under an atmosphere of dry argon. For thin layer chromatographic (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF_{254}, 0.25 mm) were used. The products were purified by preparative column chromatography on silica gel E, Merck Art 9385. Microanalyses were done at the Institute of Applied Organic Chemistry, Faculty of Engineering, Nagoya University. In experiments requiring dry solvents, ether and tetrahydrofuran (THF) were distilled from sodium-benzophenone. Benzene, hexane, and toluene were dried over sodium metal. Dichloromethane was distilled from phosphorus pentoxide and stored over 4A molecular sieves. The optical purity of (−)-(2*R*,4*R*)-2,4-pentanediol from Wako Pure Chemical Industries Ltd. should be checked before use [19]. Other chemicals were purchased and used as such.

1-Cyclohexylethanone

To a solution of cyclohexanecarboxylic acid (25.6 g, 0.200 mol) in dry ether (100 ml) was added methyllithium (312 ml of a 1.28 *M* ethereal solution, 0.400 mol) dropwise at 0°C. After stirring for 1 h at room temperature, the mixture was poured into 2 *N* HCl (200 ml). The aqueous layer was extracted twice with ether (100 ml). The combined organic layers were dried over sodium sulfate and the solvent was removed in vacuo to give the crude product, which was distilled to yield the ketone as a colorless oil (20.4 g): b.p. 73°C (20 Torr); ^{1}H NMR (CCl_4) δ 2.10 (3H, s, Me); IR (film) 1705s cm^{-1}.

Preparation of chiral acetals

Method I. A mixture of ketone (20 mmol), (−)-(2*R*,4*R*)-2,4-pentanediol (2.08 g, 20 mmol), and pyridinium *p*-toluenesulfonate (20 mg) in benzene (20 ml) was heated at reflux for 10 h with continuous azeotropic removal of water. After cooling to room temperature, the mixture was poured into aq. $NaHCO_3$ (20 ml), and the product was extracted twice with ether (20 ml). The combined organic layers were dried over sodium sulfate and concentrated in vacuo. Chromatography on silica gel afforded chiral acetal as a colorless oil. **1** (R^1 = c-hexyl, R^2 = Me): 77% yield; TLC, R_f = 0.61 (hexane/EtOAc, 5/1); IR (film) 2960s, 2915s cm^{-1}; ^{1}H NMR (CCl_4) δ 3.50–4.27 (2H, m, OCH), 1.04–1.17 (9H, m, CH_3). Anal. Found: C, 73.21; H, 11.72. $C_{13}H_{24}O_2$ calcd.: C, 73.54; H, 11.39%. **1** (R^1 = n-hexyl, R^2 = Me): 87% yield; TLC, R_f = 0.76 (hexane/EtOAc, 5/1); IR (film) 2980s, 2950s, 2870s cm^{-1}; ^{1}H NMR (CCl_4) δ 3.57–4.12 (2H, m, OCH); Anal. Found: C, 72.57; H, 12.50. $C_{13}H_{26}O_2$ calcd.: C, 72.84; H, 12.23%.

Method II. A mixture of ketone (10 mmol), trimethyl orthoformate (2.12 g, 20 mmol) and *p*-toluenesulfonic acid (10 mg) in methanol (10 ml) was stirred at 0°C for 2 h. The mixture was poured into aq. $NaHCO_3$ and the product was extracted twice with ether. The combined organic layers were dried over sodium sulfate and concentrated in vacuo. Chromatography on silica gel afforded dimethyl acetal as a colorless oil. A mixture of dimethyl acetal (2.0 mmol), (−)-(2*R*,4*R*)-2,4-pentanediol (0.23 g, 2.2 mmol) and pyridinium *p*-toluenesulfonate (2 mg) in benzene was heated with continuous removal of methanol for 30 min. After cooling to room temperature, the mixture was poured into aq. $NaHCO_3$ and the product was extracted twice with ether. The organic layers were dried over sodium sulfate and concentrated in vacuo.

Chromatography on silica gel afforded chiral acetal as a colorless oil. **1** (R^1 = Ph, R^2 = Me): 77% yield from acetophenone; TLC, R_f = 0.62 (hexane/EtOAc, 5/1); IR (film) 750s, 690s cm^{-1}; ^1H NMR (CCl_4) δ 7.16 (5H, m, ArH), 3.16–4.33 (2H, m, OCH), 1.40 (3H, s, CH_3), 1.13 (6H, m, CH_3), Anal. Found: C, 75.45; H, 9.03. $C_{13}H_{18}O_2$ calcd.: C, 75.69; H, 8.79%. **1** (R^1 = Ph, R^2 = n-Pr): 80% yield from butyrophenone; TLC, R_f = 0.63 (hexane/EtOAc, 3/1); IR (film) 770m, 750m, 695s cm^{-1}; ^1H NMR (CCl_4) δ 7.23 (5H, m, ArH), 3.30–4.36 (2H, m, OCH); Anal. Found: C, 76.65; H, 7.69. $C_{15}H_{22}O_2$ calcd.: C, 76.88; H, 9.46%.

Reduction of chiral acetal 1 (R^1 = c-hexyl, R^2 = Me) using DIBAH

To a solution of diisobutylaluminum hydride (DIBAH, 2.5 ml of a 1 *M* hexane solution) in dry dichloromethane (5 ml) was added dropwise at 0°C the acetal **1** (R^1 = c-hexyl, R^2 = Me) (106 mg, 0.50 mmol) and the mixture was stirred for 30 min. After excess aluminum reagent had been destroyed with cold dilute HCl, the product was extracted with ether. Removal of the dried solvent left a crude oil which was purified by column chromatography on silica gel (hexane/EtOAc, 5/1) to afford the alcohol **2** (R^1 = c-hexyl, R^2 = Me) as an oil (94 mg). The diastereomeric ratio was determined by GLC (13/1). TLC, R_f = 0.37 (hexane/EtOAc, 3/1); IR (film) 3100–3600br cm^{-1}; ^1H NMR (CCl_4) δ3.03–4.30 (3H, m, OCH), 2.95 (1H, br, OH), 0.97–1.20 (9H, m, Me); Anal. Found: C, 72.72; H, 12.36. $C_{13}H_{26}O_2$ calcd.: C, 72.85; H, 12.23%.

Reduction of 1 (R^1 = c-hexyl, R^2 = Me) using Br_2AlH

Lithium aluminum hydride (57 mg, 1.50 mmol) was added to a solution of aluminum bromide (1.20 g, 4.5 mmol) in dry ether (10 ml) at 0°C for 10 min. To the resulting suspension was added dropwise at −20°C the acetal **1** (212 mg, 1.00 mmol) in dry ether (1 ml), and the mixture was stirred for 30 min. After excess aluminum reagent had been decomposed with cold dilute HCl, the product was extracted with ether. Removal of dried solvent left a crude oil which was purified by column chromatography on silica gel (hexane/EtOAc, 5/1) to afford the alcohol **2** (R^1 = c-hexyl, R^2 = Me) (212 mg). The diastereomeric ratio of the product was determined by GLC.

Reductive cleavage of the other chiral acetals was carried out in the manner described above. The physical properties and analytical data of the alcohols thus obtained are listed below.

2 (R^1 = n-hexyl, R^2 = Me). TLC, R_f = 0.39 (hexane/EtOAc, 3/1); IR (film) 3070–3700br cm^{-1}; ^1H NMR (CCl_4) δ 3.16–4.23 (3H, m, OCH), 2.47 (1H, br, OH); Anal. Found: C, 72.01; H, 13.20. $C_{13}H_{28}O_2$ calcd.: C, 72.17; H, 13.04%.

2 (R^1 = Ph, R^2 = Me). TLC, R_f = 0.33 (hexane/EtOAc, 3/1); IR (film) 3100–3700br, 750s, 690s cm^{-1}; ^1H NMR (CCl_4) δ 7.13 (5H, s, ArH), 3.10–4.56 (3H, m, OCH), 2.43 (1H, br, OH); Anal. Found: C, 75.11; H, 9.53. $C_{13}H_{20}O_2$ calcd.: C, 74.96; H, 9.68%.

2 (R^1 = Ph, R^2 = n-Pr). TLC, R_f = 0.36 (hexane/EtOAc, 3/1); IR (film) 3100–3580br, 690s cm^{-1}; ^1H NMR (CCl_4) δ 7.20 (5H, s, ArH), 3.17–4.50 (3H, m, OCH), 2.00 (1H, br, OH); Anal. Found: C, 76.07; H, 10.40. $C_{15}H_{24}O_2$ calcd.: C, 76.23; H, 10.24%.

Removal of chiral auxiliary. Preparation of 1-cyclohexylethanol

To a solution of oxalyl chloride (0.20 ml, 2.2 mmol) in dichloromethane (2 ml)

was added DMSO (0.34 ml, 4.8 mmol) in dichloromethane (0.35 ml) at −78°C. The mixture was stirred for 2 min and the alcohol **2** (R^1 = c-hexyl, R^2 = Me) (174 mg, 0.81 mmol) was added. Stirring was continued for an additional 15 min. Triethylamine (0.48 ml, 5.0 mmol) was added and the mixture was stirred at −78°C for 5 min and at room temperature for 30 min. Water (10 ml) was added and the aqueous layer was extracted with dichloromethane. The dried organic layers were concentrated in vacuo. The crude ketone thus obtained was dissolved in methanol (10 ml) and treated with K_2CO_3 (1.38 g, 10 mmol) and the suspension was stirred at room temperature for 12 h. The mixture was diluted with water and the product was purified by column chromatography on silica gel (hexane/EtOAc, 5/1) to give 1-cyclohexylethanol as a colorless oil (84 mg, 81%), identical with an authentic sample.

*Preparation of chiral acetals from aldehydes. The acetal **4** (R = c-hexyl)*

A mixture of cyclohexanecarbaldehyde (2.24 g, 20 mmol), (−)-(2*R*,4*R*)-2,4-pentanediol (2.29 g, 22 mmol) and *p*-toluenesulfonic acid (20 mg) in benzene (20 ml) was heated at reflux for 3 h with continuous azeotropic removal of water. After cooling to room temperature, the mixture was poured into aqueous $NaHCO_3$ (20 ml) and extracted with ether. The organic layer was dried over sodium sulfate and concentrated in vacuo. Chromatography on silica gel (hexane/EtOAc, 30/1) afforded the chiral acetal **4** (R = c-hexyl) as a colorless liquid (3.72 g, 94%): b.p. 50–53°C (0.9 Torr); IR (film) 2990s, 2950s, 2870s cm^{-1}; ^1H NMR δ 3.53–4.57 (3H, m, OCH), 1.07–1.33 (6H, m, Me); Anal. Found: C, 72.52; H, 11.34. $C_{12}H_{22}O_2$ calcd.: C, 72.68; H, 11.18%.

Syntheses of other chiral acetals from the corresponding aldehydes and (−)-(2*R*,4*R*)-2,4-pentanediol were carried out in the manner described above. The physical properties and analytical data of the acetals obtained are listed below.

***4** (R = n-hexyl).* 79% yield; TLC, R_f = 0.58 (hexane/EtOAc, 3/1); IR (film) 2920s, 2840s cm^{-1}; ^1H NMR δ 4.73 (1H, m, OCHO), 3.50–4.45 (2H, m, OCH); Anal. Found: C, 71.62; H, 12.41. $C_{12}H_{24}O_2$ calcd.: C, 71.95; H, 12.08%.

***4** (R = n-Bu).* 68% yield; b.p. 98–99°C (30 Torr); IR (film) 2920s, 2840s cm^{-1}; ^1H NMR δ 4.47 (1H, m, OCHO), 3.50–4.46 (2H, m, OCH); MS Found: *m/z* 172.1433. $C_{10}H_{26}O_2$ calcd.: *M* 172.1463.

***4** (R = Et).* 73% yield; b.p. 59–62°C (28 Torr); IR (film) 2970s, 2925s, 2850s cm^{-1}; ^1H NMR (CCl_4) δ 4.62 (1H, t, *J* 5 Hz, OCHO), 3.50–4.45 (2H, m, OCH); MS *m/z* 144.1152. $C_8H_{16}O_2$ calcd.: *M* 144.1150.

***4** (R = $(CH_2)_4COOMe$).* 61% yield; TLC, R_f = 0.54 (hexane/EtOAc, 1/1); IR 1730s cm^{-1}; ^1H NMR (CCl_4) δ 4.70 (1H, br, OCHO), 3.45–4.40 (2H, m, OCH), 3.57 (3H, s, Me); Anal. Found: C, 62.70; H, 9.51. $C_{12}H_{22}O_4$ calcd.: C, 62.58; H, 9.63%.

*Preparation of chiral acetal **4** (R = Me)*

A mixture of ethyl vinyl ether (0.96 ml, 10 mmol), (−)-(2*R*,4*R*)-2,4-pentanediol (1.04 g, 10 mmol) and *p*-toluenesulfonic acid (10 mg) in dry ether (10 ml) was stirred at room temperature for 1 h. The mixture was poured into aq. $NaHCO_3$ and the product was extracted with pentane. The combined organic layers were dried over sodium sulfate and concentrated in vacuo. Chromatography on silica gel afforded the chiral acetal **4** (R = Me) as a colorless oil (0.87 g, 67%): b.p. 138°C (760 Torr);

IR 2960s, 2950s, 2850s cm^{-1}; ^1H NMR (CCl_4)δ 4.83 (1H, q, J 5 Hz, OCHO), 3.40–4.40 (2H, m, OCH); MS Found: m/z 130.0963. $C_7H_{14}O_2$ calcd.: M 130.0994.

Reaction of chiral acetal 4 (R = c-hexyl) with trimethylaluminum

To a solution of trimethylaluminum (1.25 ml of a 2 M hexane solution) in dichloromethane (2.5 ml) was added a solution of **4** (R = c-hexyl) (99 mg, 0.50 mmol) in dichloromethane (0.5 ml) at 0°C. The resulting mixture was stirred at 0°C for 30 min, at room temperature for 3.5 h, and at 40°C for 1.5 h. The mixture was then poured into cold dilute HCl and extracted with dichloromethane. Concentration by evaporation followed by column chromatography on silica gel (hexane/EtOAc, 5/1) furnished the alcohol **5** (R = c-hexyl, R′ = Me) (69 mg). The diastereomeric ratio was confirmed to be 2/3 by GLC.

General methods for nucleophilic cleavages of chiral acetals using organotitanium reagents

Method A. To a solution of dimethylzinc (0.18 ml of a 1.4 M hexane solution, 0.25 mmol) in dry dichloromethane (5 ml) was added $TiCl_4$ (0.50 ml of a 1 M dichloromethane solution, 0.50 mmol) at −78°C. The chiral acetal (0.50 mmol) was added at −78°C and the mixture was stirred for 30 min. The solution was poured into water and the product was extracted with ether. The organic layers were dried over sodium sulfate and concentrated in vacuo. Chromatography on silica gel afforded the product as an oil. The diastereomeric ratio was determined by GLC.

Method B. To a solution of dimethylzinc (0.50 mmol) in dichloromethane was added $TiCl_4$ at −78°C. The chiral acetal (0.50 mmol) was added at −78°C and the mixture was stirred for 30 min.

Method C. To a solution of dimethylzinc (0.25 mmol) in dichloromethane was added $TiBr_4$ (0.183 g, 0.50 mmol) at −78°C. The acetal was added at −78°C and the mixture was stirred for 30 min.

Method D. To a solution of acetal (0.50 mmol) in dichloromethane was added $TiCl_4$ (0.50 mmol) at −78°C. n-Butyllithium (0.62 ml of a 1.61 M hexane soltuion, 1.00 mmol) was added at the same temperature and the mixture was stirred for 30 min.

Method E. To a solution of acetal (0.50 mmol) in dichloromethane was added a solution of $TiCl_4$ (0.50 mmol) at −78°C. Diethylzinc (0.45 ml of a 1.1 M hexane solution, 0.50 mmol) was added at −78°C and the mixture was stirred for 30 min.

Method F. To a solution of acetal (0.50 mmol) in dry dichloromethane was added a solution of $TiBr_4$ (0.50 mmol) at −78°C. Diethylzinc (0.50 mmol) was added and the mixture was stirred for 30 min.

***5** (R = c-hexyl, R′ = n-Bu).* TLC, R_f = 0.37 (hexane/EtOAc, 5/1); IR (film) 3030–3630br cm^{-1}; ^1H NMR (CCl_4) δ 3.40–4.30 (2H, m, OCHO), 3.03 (1H, m, OCHO), 2.58 (1H, br OH); Anal. Found: C, 77.42; H, 13.18. $C_{16}H_{32}O_2$ calcd.: C, 77.58; H, 13.02%.

***5** (R = n-hexyl, R′ = Et).* TLC, R_f = 0.45 (hexane/EtOAc, 3/1); IR (film) 3050–3730br cm^{-1}; ^1H NMR (CCl_4) δ 3.00–4.23 (3H, m, OCH), 2.27 (1H, br. OH); Anal. Found: C, 72.72; H, 13.40. $C_{14}H_{30}O_2$ calcd.: C, 72.99; H, 13.13%.

***5** (R = n-hexyl, R′ = n-Bu).* TLC, R_f = 0.52 (hexane/EtOAc, 3/1); IR (film) 3050–3610br cm^{-1}; ^1H NMR (CCl_4) δ 3.03–4.27 (3H, m, OCH), 2.60 (1H, br, OH); Anal. Found: C, 74.25; H, 13.37. $C_{16}H_{34}O_2$ calcd.: C, 74.36; H, 13.26%.

5 (R = n-Bu, R' = Me). TLC, $R_f = 0.31$ (hexane/EtOAc, 3/1); IR (film) 3030–3600br cm^{-1}; ^1H NMR (CCl_4) δ 3.20–4.27 (3H, m, OCH), 2.47 (1H, br, OH); Anal. Found: C, 69.93; H, 13.08. $C_{11}H_{24}O_2$ calcd.: C, 70.16; H, 12.85%.

5 (R = n-Bu, R' = Et). TLC, $R_f = 0.44$ (hexane/EtOAc, 3/1); IR (film) 3040–3610br cm^{-1}; ^1H NMR (CCl_4) δ 2.97–4.13 (3H, m, OCH), 2.37 (1H, br, OH); Anal. Found: C, 70.96; H, 13.22. $C_{12}H_{26}O_2$ calcd.: C, 71.23; H, 12.95%.

Chemoselective reaction of acetal 4 (R = n-hexyl) in the presence of 5-nonanone

To a solution of $MeTiCl_3$ (2.0 mmol) in dichloromethane was added a mixture of the acetal **4** (R = n-hexyl) (0.20 g, 1.0 mmol) and 5-nonanone (0.142 g, 1.00 mmol) at −78°C. The mixture was stirred for 30 min. Isolation by extraction, removal of dried solvent, and chromatography on silica gel (hexane/EtOAc, 5/1) afforded 0.207 g of **5** (R = n-hexyl, R' = Me) (96%) and 0.133 g of 5-nonanone (94%).

To a mixture of **4** (R = n-hexyl) (0.50 mmol) and 5-nonanone (0.50 mmol) in ether (5 ml) was added methyllithium (0.78 ml of a 1.28 *M* ether solution, 1.00 mmol) at 0°C. The mixture was stirred at 0°C for 15 min. Extractive workup and chromatography on silica gel gave **4** (R = n-hexyl) (99 mg, 99%) and 5-methyl-5-nonanol (73 mg, 92%).

Chemoselective reaction of acetal in the presence of an ester function

To a solution of $MeTiCl_3$ (1.00 mmol) in dichloromethane (5 ml) was added the acetal **4** (R = $(CH_2)_4COOMe$) at −78°C. The mixture was stirred for 30 min. Isolation by extraction, removal of solvent and chromatography on silica gel (hexane/EtOAc, 1/1) afforded **5** (R = $(CH_2)_4COOMe$, R' = Me) (0.127 g, 100%) as the sole product. TLC, $R_f = 0.37$ (hexane/EtOAc, 1/1); IR (film) 3070–3700br, 1730s cm^{-1}; ^1H NMR (CCl_4) δ 3.57 (3H, s, Me), 3.13–4.27 (3H, m, OCH), 2.43 (1H, br, OH); Anal. Found: C, 63.26; H, 10.77. $C_{13}H_{26}O_4$ calcd.: C, 63.37; H, 10.66%. The diastereomeric ratio was confirmed to be 20/1 by GLC.

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