12b (2.82 g, 17.8 mmol), dropwise. After 1 h, the mixture was quenched by the controlled, dropwise addition of aqueous NaOH (10 mL, 3.0 N.) (*Caution! H_2 evolution!*). Pentane (30 mL) and water (30 mL) were added, and after separation, the aqueous layer was extracted with ether (3 × 30 mL). The combined organic layers were dried (K_2CO_3), concentrated, and distilled to give 2.67 g (93%) of pure **13b** (bp 130–2 °C, 95 Torr) [lit.[23] bp 122 °C (11 Torr)]: ^{1}H NMR ($CDCl_3$) δ 0.62 (q, 6 H, J = 7.8 Hz); 1.00 (t, 9 H, J = 7.8 Hz), 1.32 (d, 3 H, J = 7.5 Hz), 1.1–1.5 (b, 1 H), 3.64 (q, 1 H, J = 7.5 Hz); IR (TF) 3360 (OH), 1460, 1420, 1240, 980 ($SiEt_3$) cm^{-1}; MS m/z 131 (24, M – Et), 115 (18), 103 (33), 87 (100), 75 (50), 59 (57), 58 (18), 47 (29). Anal. Calcd for $C_8H_{20}OSi$: C, 59.90; H, 12.59. Found: C, 60.03; H, 12.55.

1-(Triisopropylsilyl)ethanol (13c). As for **13b**, from **12c** (1.94 g, 9.7 mmol) and BMS (1.50 mL, 10.0 M, 15.0 mmol) in THF (10 mL) was obtained 1.60 g (82%) of pure **13c** (bp 82 °C, 0.2 Torr): ^{1}H NMR ($CDCl_3$) δ 1.0–1.4 (m, 22 H), 1.47 (d, 3 H, J = 7.5 Hz), 3.91 (q, 1 H, J = 7.5 Hz); ^{29}Si NMR δ 2.09; IR (TF) 3390 (OH), 1380, 1368, 883 ($Si(i\text{-}Pr)_3$) cm^{-1}, MS m/z 202 (0.6), 159 (24), 157 (16), 131 (40), 129 (16), 115 (48), 103 (40), 101 (21), 89 (17), 87 (43), 75 (83), 73 (61), 61 (90), 59 (100), 47 (17). Anal. Calcd for $C_{11}H_{26}OSi$: C, 65.24; H, 12.96. Found: C, 65.41; H, 12.90.

Acknowledgment. We are indebted to the NIH-RCMI Program (RR03641) for the funds to purchase the Ge 300-MHz NMR spectrometers (QE-300 and GN-300) which made this study possible. The support of the NSF-EPSCoR and NIH-MBRS Programs (RR08102) is gratefully acknowledged. We also wish to thank Professors J. A. Prieto and D. Seyferth for helpful discussions regarding this work.

Registry No. **1a**, 754-05-2; **1b**, 1112-54-5; **1c**, 121675-48-7; **2a**, 72610-05-0; **2b**, 121675-52-3; **2c**, 121675-53-4; **3b**, 2916-67-8; **3c**, 121675-55-6; **5**, 17947-98-7; **6**, 58458-84-7; **7**, 917-57-7; **8**, 1112-56-7; **9**, 81177-91-5; **10**, 42722-80-5; **11a**, 79678-01-6; **11b**, 121675-49-8; **11c**, 121675-50-1; **12a**, 13411-48-8; **12b**, 30608-91-4; **12c**, 121675-51-2; **13b**, 18825-02-0; **13c**, 121675-54-5; CH_2=CHBr, 593-60-2; Et_3SiCl, 994-30-9; $(i\text{-}Pr)_3SiCl$, 13154-24-0; $(i\text{-}Pr)_3SiOH$, 17877-23-5; $((i\text{-}Pr)_3Si)_2O$, 121675-56-7; $Vi_2Sn(n\text{-}Bu)_2$, 7330-43-0; $ViSn(n\text{-}Bu)_3$, 7486-35-3; $(n\text{-}Bu)Si(i\text{-}Pr)_3$, 121675-57-8; $(n\text{-}Hx)Si(i\text{-}Pr)_3$, 121675-58-9.

Organocyanocopper–Trifluoroborane Mediated 1,3-Chirality Transfer Reaction of γ-(Mesyloxy)-α-alkyl α,β-Enoates for the Construction of Chiral Quaternary Carbon Centers with High Optical Purity

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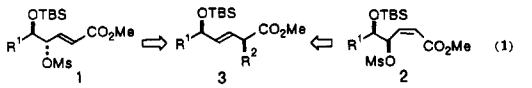
Received February 7, 1989

The mesylates of chiral γ-hydroxy-α-methyl (*E*)-α,β-enoates undergo 1,3-chirality transfer to form chiral α-alkyl-α-methyl (*E*)-β,γ-enoates with high optical purity using organocyanocopper–trifluoroborane reagents. The degree of asymmetric induction, regiochemistry, and chemoselectivity has been found to be uniformly high. THF or mixed solvents involving THF, a γ-(methylsulfonyl)oxy leaving group, and organocopper–Lewis acid reagents prepared from CuCN, RLi, and BF_3-Et_2O were found to be necessary to ensure the success of the preparation of chiral quaternary carbon centers with high optical purity via the 1,3-chirality transfer. The present efficient procedure is compatible with a variety of oxygenated groups such as mesyl, benzyl, *tert*-butyldimethylsilyl, and isopropylidene functions.

As synthetic targets with high biological activities increase in complexity, the requirements for mild and efficient methods for constructing chiral quaternary carbon centers with high optical purity increase.[1] Considerable efforts have been made on the synthesis of chiral quaternary centers and several interesting synthetic procedures have been developed. Except for a few synthetic routes,[2] recently described synthetic methods for construction of chiral quaternary carbon centers have involved the use of the enantio- or diastereoselective α-alkylation of chiral bicyclic lactams,[3] acyclic α-alkyl-α-cyanoacetamides with pyrrolidines as chiral auxiliaries,[4] chiral β-hydroxy esters,[5] and other carbonyl compounds.[6] However, an organocopper–trifluoroborane assisted 1,3-chirality-transfer strategy of γ-oxygenated-α-alkyl α,β-enoates for constructing chiral quaternary carbon centers has no precedent as far as we are aware.

We reported recently that both *E* and *Z* chiral γ-mesyloxy α,β-enoates **1** and **2** can be effectively converted to α-alkyl (*E*)-β,γ-enoates **3** with very high optical purity by treatment with organocyanocopper–trifluoroborane reagents[7] (eq 1).



(1)

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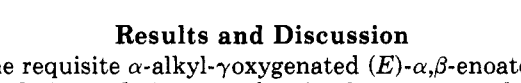
Table I. Chemical Yields and Enantio- or Diastereoselectivity in the Reaction of α-Alkyl-γ-oxygenated α,β-Enoates with Organocopper Reagents

entry	leaving group at C-4	substrate	reagent	product (chem yield, %)	enantio- or diastereoselectv[a] (abs confgn at C-2)
1	OTBS	**9a** or **9b**	$EtCu(CN)Li\cdot BF_3$	*d*	
2	OAc	**11**	$MeCu(CN)Li\cdot BF_3$ (LiBr)[b]	*d*	
3	OAc	**11**	$Me_2Cu(CN)Li_2\cdot BF_3$ (LiBr)[b]	*d*	
4	OAc	**11**	$n\text{-}Bu_2Cu(CN)Li_3\cdot BF_3$	*e*	
5	OMs	**12a**	$Me_2Cu(CN)Li_2\cdot BF_3$ (LiBr)[b]	**13** (22)	
6	OMs	**12a**	$MeCu(CN)Li\cdot BF_3$ (LiBr)[b]	**13** (82)	
7	OMs	**22b**	$Me_2Cu(CN)Li_2\cdot BF_3$ (LiI)[c]	**23** (96)	
8	OMs	**22b**	$MeCu(CN)Li\cdot BF_3$ (LiI)[c]	**23** (56)[f]	
9	OMs	**29**	$Me_2Cu(CN)Li_2\cdot BF_3$ (LiI)[c]	**30** (99)	
10	OMs	**29**	$MeCu(CN)Li\cdot BF_3$ (LiI)[c]	**30** (52)[g]	
11	OMs	**40**	$MeCu(CN)Li\cdot BF_3$ (LiBr)[b]	**41** (95)	
12	OMs	**12a**	$n\text{-}BuCu(CN)Li\cdot BF_3$	**14** (92)	99:1 (*S*)
13	OMs	**12b**	$EtCu(CN)Li\cdot BF_3$	**15** (92)[h]	99:1 (*R*)
14	OMs	**12b**	$n\text{-}BuCu(CN)Li\cdot BF_3$	**16** (97)	98:2 (*R*)
15	OMs	**22a**	$EtCu(CN)Li\cdot BF_3$	**24** (89)	99:1 (*S*)
16	OMs	**22a**	$n\text{-}PrCu(CN)Li\cdot BF_3$	**25** (95)	99:1 (*S*)
17	OMs	**22a**	$n\text{-}BuCu(CN)Li\cdot BF_3$	**26a** (96)	99:1 (*S*)
18	OMs	**22b**	$n\text{-}BuCu(CN)Li\cdot BF_3$	**26b** (98)	98:2 (*R*)
19	OMs	**22b**	$n\text{-}Bu_2Cu(CN)Li_2\cdot BF_3$	**26b** (74)	98:2 (*R*)
20	OMs	**29**	$n\text{-}PrCu(CN)Li\cdot BF_3$	**31** (98)	99:1 (*R*)
21	OMs	**29**	$n\text{-}BuCu(CN)Li\cdot BF_3$	**32** (94)	99:1 (*R*)
22	OMs	**29**	$n\text{-}Bu_2Cu(CN)Li_2\cdot BF_3$	**32** (70)	99:1 (*R*)
23	OMs	**35**	$n\text{-}PrCu(CN)Li\cdot BF_3$	**36** (91)	99:1 (*S*)
24	OMs	**35**	$n\text{-}BuCu(CN)Li\cdot BF_3$	**37** (99)	99:1 (*S*)
25	OMs	**40**	$n\text{-}BuCu(CN)Li\cdot BF_3$	**42** (95)	99:1 (*S*)

[a] Determined by 200-MHz ^1H NMR spectroscopy with $Eu(hfc)_3$. [b] Prepared from ethereal MeLi (as complexed with LiBr). [c] Prepared from ethereal MeLi (as complexed with LiI). [d] Recovered unchanged starting material. [e] An inseparable mixture of products was obtained. [f] Unchanged starting material (42%) with recovered. [g] Unchanged starting material (46%) was recovered. [h] Obtained along with ca. 3.5% of S_N2 substitution product.

The success of these reactions encouraged us to investigate extensions to the synthesis of chiral quaternary carbon centers. Our preliminary communication described studies with some α-amino acid and sugar-derived α-alkyl-γ-oxygenated (*E*)-α,β-enoates.[8] We have explored in more detail the reaction conditions of organocopper–trifluoroborane-promoted 1,3-chirality transfer reactions of α-alkyl-γ-oxygenated (*E*)-α,β-enoates to shed more light on this chemistry. We detail here an attractive and broadly applicable synthesis of chiral quaternary carbon centers suitable for large-scale preparation via a 1,3-chirality transfer reaction of α-alkyl-γ-mesyloxy α,β-enoates **4** with organocyanocopper–trifluoroborane reagents (eq 2). Since both protected chiral (*E*)-allylic alcohol and ester functions are available for further chemical manipulations, chiral α,α-dialkyl-δ-oxygenated (*E*)-β,γ-enoates **5** are promising intermediates for the synthesis of natural products with quaternary carbon centers.



(2)

Results and Discussion

The requisite α-alkyl-γoxygenated (*E*)-α,β-enoates **11**, **12a**, **12b**, **22a**, **22b**, **29**, **35**, and **40** for the present study were readily prepared in acceptable yields from the known (*R*)- and (*S*)-2,2-dimethyl-1,3-dioxolane-4-carboxaldehydes (**6a**[9] and **6b**[10] (for **6a** and **6b**, see Scheme I), methyl (2*S*,3*R*)-, (2*S*,3*S*)-, and (2*R*,3*S*)-2-(mesyloxy)-3-(*tert*-butyldimethylsiloxy)butanoates (**20a**,[7b,11] **20b**,[7b,11] and **27**[7b,11] (for **20a**, **20b**, and **27**, see Scheme III), D-xylose dibenzyl ether (**33**),[12] and L-arabinoase monoacetonide (**38**)[13] (for **33** and **38**, see Scheme III), respectively, according to the usual method as shown in Schemes I and III (for details, see Experimental Section). The *E* stereochemistry of the substrates **7a**, **7b**, **22a**, **22b**, **29**, **34**, and **39** was inferred from the well-known fact that reaction of aldehydes with (α-carbalkoxyethylidene)triphenylphosphorane leads to the more stable *E* isomers either predominantly or exclusively.[14] Furthermore, the *E* stereochemistry could easily be determined by the NOE measurement. For example, the *E* stereochemistry of **22b** could be established unequivocably from the NOE difference spectroscopy (ca. 3% enhancement) of the C-4-hydrogen at δ 5.15 on irradiation of the C-2-methyl hydrogens at δ 1.99. The same *E* configuration is assumed for all other substrates.

It has been reported that treatment of acetates or benzoates of simple allylic alcohols with organocopper reagents led to predominant or exclusive formation of γ-substitution products.[15] Similarly, we had noted previously that re-

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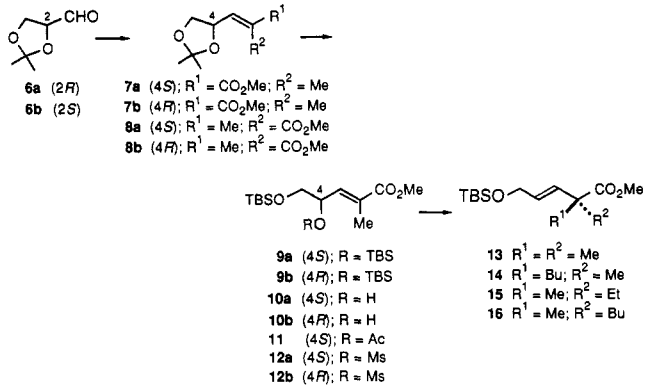
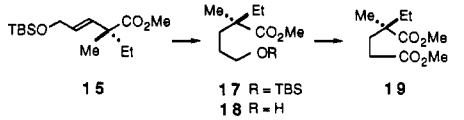
Scheme I



actions of cyclic γ-acetoxy α,β-enoates with organocopper–Lewis acid reagents resulted in the formation of α- and γ-substitution products.[16] Consequently, it was assumed that the acyclic γ-acetoxy α,β-enoates **11** would provide substitution compounds. However, this was not to be the case and we did not detect any substitution reaction product by treatment of the acetate **11** with 3 molar equiv of either $MeCu(CN)Li{\cdot}BF_3$ or $Me_2Cu(CN)Li_2{\cdot}BF_3$[17] (prepared from an ethereal MeLi–LiBr solution) at −78 °C for 30 min. The only compound isolated was the starting material (Table I, entries 2 and 3). Likewise, treatment of the γ-(*tert*-butyldimethylsiloxy) α,β-enoate **9a** or **9b** with a poorer leaving group with an excess of $EtCu(CN)Li{\cdot}BF_3$ in THF at −78 °C for 1 h and then at −40 °C for 30 min recovered unchanged starting material (Table I, entry 1). On the other hand, treatment of the acetate **11** with $Bu_2Cu(CN)Li_2{\cdot}BF_3$ gave an inseparable mixture of products [at least six spots on TLC (Table I, entry 4)]. As stated above, while seemingly straightforward, several structure–reactivity features rendered an expected 1,3-chirality transfer inoperative. We expected that the reaction of α-alkyl-γ-mesyloxy α,β-enoates with organocopper–trifluoroborane reagents would give α,α-dialkylation products with anti relationship of the entering nucleophile and the departing γ-mesyloxy group. The essential factors for the clean 1,3-chirality transfer were quite similar to that recently described in the preparation of tertiary carbon centers,[7b] and the following points were found to be necessary to ensure the success of the preparation of chiral quaternary centers with high optical purity via the 1,3-chirality transfer.

Scheme II



(1) Excellent results were obtained by reaction with organocopper–Lewis acid reagents prepared from CuCN, RLi, and $BF_3{\cdot}Et_2O$. Proper preparation of organocopper reagent is essential for optimal reaction rates and chemical yield. We had previously noted the importance of using the higher order reagent $Me_2Cu(CN)Li_2{\cdot}BF_3$ prepared from an ethereal MeLi–LiI solution[7,8] and this recommendation holds in all methylation reactions: the lower order reagent $MeCu(CN)Li{\cdot}BF_3$ formed from an ethereal MeLi–LiI solution will result in a lowering of chemical yield (Table I, entries 7–10). Thereafter, it was found that considerably different chemical yields were obtained not only with different molar ratios of MeLi and CuCN but also with a reagent prepared from MeLi–LiI or MeLi–LiBr complexes. Thus, $MeCu(CN)Li{\cdot}BF_3$ was more useful than $Me_2Cu(CN)Li_2{\cdot}BF_3$ when prepared from an ethereal MeLi–LiBr solution (Table I, entries 5, 8, and 11). Therefore, the expressions such as $MeCu(CN)Li{\cdot}BF_3$ (LiI) and $Me_2Cu(CN)Li_2{\cdot}BF_3$ (LiBr) are intended to indicate that the reagents have been prepared from MeLi as the LiI or LiBr complex, respectively.[18] Other lower order organocyanocopper–trifluoroborane complexes such as $EtCu(CN)Li{\cdot}BF_3$, $PrCu(CN)Li{\cdot}BF_3$, and $BuCu(CN)Li{\cdot}BF_3$ gave satisfactory results.

(2) A γ-mesyloxy leaving group is essential for clean 1,3-chirality transfer. It is expected that, although not performed, α-methyl α,β-enoates with a γ-tosyloxy group[7b] would lead to the same results.

(3) It was found that the use of THF or mixed solvents involving THF rather than Et_2O alone was essential.[19] It should be clearly noted that the chemical yield of the present chirality transfer varies dramatically depending upon the solvent used. Although Et_2O has been widely used with great success for both conjugate and substitution reactions, THF or mixed solvents involving THF [e.g., THF/Et_2O (ca. 10:2) or THF/*n*-hexane (ca. 10:2)] is the solvent of choice since reaction in Et_2O, a poorer Lewis base than THF,[20] is quite reluctant to undergo the 1,3-chirality transfer with organocyanocopper–trifluoroborane reagents.

Reaction of the mesylates **12a** and **12b** with $BuCu(CN)Li{\cdot}BF_3$ at −78 °C for 30 min gave the regioselective, *E* stereoselective, and enantioselective alkylation products **14** and **16** as the major products (Table I, entries 12 and

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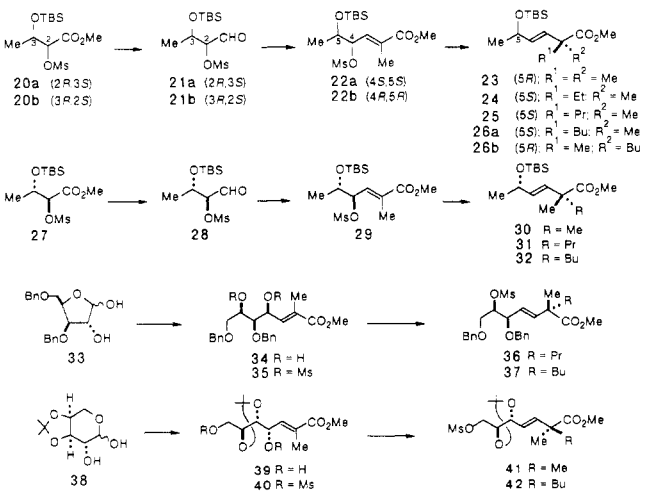
Scheme III



14). Similarly, treatment of the mesylate **12b** with $EtCu(CN)Li\cdot BF_3$ gave the ethylation product **15** in 92% yield as the major product after flash chromatography over silica gel (Table I, entry 13). Progress of the reaction could easily be monitored by TLC and/or GLC. Compared with the usual 1,4-addition reaction of organocopper reagents to α,β-unsaturated carbonyl compounds,[21] the present 1,3-chirality transfer reaction of γ-(mesyloxy)-α-alkyl α,β-enoates with organocyanocopper–trifluoroborane reagents in THF or mixed solvents involving THF was much faster and usually attained completion in short periods of reaction time, even at −78 °C.

The *E* stereochemistry of the products **14**, **15**, and **16** was inferred from the ca. 15.6 Hz coupling constant of the two olefinic protons. The enantioselection of the products **14**, **15**, and **16** has been found to be uniformly high (>98:2) by ^1H NMR analysis with $Eu(hfc)_3$. Thus, the γ-mesyloxy group is essential for clean chirality transfer as noted above. The absolute configuration of the quaternary carbon center, although clear from the reaction course of the anti S_N2' attack of organocyanocopper–trifluoroborane reagents and from the *E* geometry of the β,γ-double bond of the products, could be firmly established by chemical transformation. For example, Swern oxidation[22] followed by Masamune oxidation[23a] and methylation with diazomethane of alcohol **18**, derived from **15** by catalytic hydrogenation over 5% $Rh-Al_2O_3$ followed by removal of the *tert*-butyldimethylsilyl group, gave the known dimethyl (*R*)-(+)-α-methyl-α-ethylglutarate (**19**),[24] a key degradation product for structure elucidation of the potent tumor-promoting indole alkaloid teleocidin A_2[25] (Scheme II).

Comparable very high diastereoselectivities and chemical yields were obtained by reaction of the mesylates **22a**, **22b**, and **29** with $RCu(CN)Li\cdot BF_3$ (R = Et, Pr, Bu; Table I, entries 15–18, 20, and 21). In all cases stated above, it should be clearly noted that the chemical yields of products were critically dependent upon the organocyanocopper–trifluoroborane reagents used. For example, compared with the lower order BF_3 reagents [$RCu(CN)Li\cdot BF_3$, R = Et, Pr, Bu], the yields with the higher order BF_3 reagents [$R_2Cu(CN)Li_2\cdot BF_3$, R = Et, Pr, Bu] were considerably lower (Table I, entries 19 and 22).

Chirality transfer involving polyoxygenated α,β-enoates was next attempted to see if the presence of other oxygenated functional groups in any way interfered with the selectivity (Scheme III). Thus, treatment of ϵ,γ-dimesylate **35** with $PrCu(CN)Li\cdot BF_3$ and $BuCu(CN)Li\cdot BF_3$ gave products **36** and **37**, respectively, in high chemical and optical yields (Table I, entries 23 and 24). Likewise, reaction of the dimesylate **40** with $MeCu(CN)Li\cdot BF_3$ (LiBr) and $BuCu(CN)Li\cdot BF_3$ yielded desired products **41** and **42**, respectively, in high yields (Table I, entries 11 and 25). Clearly, only the γ-mesyloxy group in **35** or **40** is involved in the reaction.

In summary, the described methodology involving organocyanocopper–trifluoroborane reagents has several advantages in terms of mildness, selectivity, efficiency, and convenience. The reactions used in the 1,3-chirality transfer are mild enough as to permit selective reaction of only the γ-mesyloxy group in the presence of a number of other functional groups such as mesyl, *tert*-butyldimethylsilyl, benzyl, and *O*-isopropylidene groups. The present strategy detailed provides easy access to synthetically useful chiral quaternary carbon centers with high optical purity from readily available α-amino acids and sugars.

Experimental Section

General Methods. All reactions were carried out under a position pressure of argon. All glassware and syringes were dried in an electric oven at 110 °C prior to use. Solvents were freshly distilled from $LiAlH_4$. Ethereal MeLi (as complexed with LiI or LiBr) was purchased from Aldrich. EtLi and *n*-PrLi were prepared by reaction of EtBr and *n*-PrBr with metallic Li in the usual way. *n*-BuLi was purchased from Nacalai Chemicals. CuI was purchased from Mitsuwa chemicals and purified by a published method. CuCN was obtained from Mitsuwa Chemicals and dried in an Abderhalden under vacuum at 50 °C. All melting points are uncorrected. The ^1H and ^{13}C NMR spectra were recorded at 200 or 400 MHz for ^1H and at 50 or 100 MHz for ^{13}C in $CDCl_3$. For flash chromatographies, silica gel 60 H (silica gel for thin-layer chromatography, Merck) or silica gel 60 (finer than 230 mesh, Merck) was employed. The purity of all title compounds was judged to be >95% by GC and/or ^1H NMR spectral determinations.

Methyl (4*S*,2*E*)-4,5-(Isopropylidenedioxy)-2-methyl-2-pentenoate (7a) and Its 2*Z* Isomer (8a). To a solution of 2,3-*O*-isopropylidene-D-glyceraldehyde (**6a**)[9] (2.0 g, 15.4 mmol) in 15 mL of CH_2Cl_2 at 0 °C was added portionwise 4.8 g (15.4 mmol) of (α-carbomethoxyethylidene)triphenylphosphorane and stirring was continued for 1 h. The usual workup[26] of the reaction mixture led to an oily residue, which was flash chromatographed on a silica gel column. Elution with *n*-hexane–EtOAc (10:1) gave 170 mg (5.5% yield) of **8a**, and further elution gave 2.7 g (89% yield) of **7a**. **7a**: a colorless oil (Kugelrohr distillation, 140 °C/9 mmHg); $[\alpha]^{25}_D$ +20.37° (*c* 1.28, $CHCl_3$); IR ($CHCl_3$) 3030, 2980, 2930, 1715, 1663, 1440, 1386, 1376, 1319, 1259, 1152, 1060, 1028, 974, 948, 900, 853, 833 cm^{-1}; ^1H NMR (200 MHz) δ 1.41 (s, 3 H), 1.45 (s, 3 H), 1.90 (d, J = 1.46 Hz, 3 H), 3.63 (dd, J = 8.30, 7.81 Hz, 1 H), 3.76 (s, 3 H), 4.16 (dd, J = 8.3, 6.35 Hz, 1 H), 4.86 (m, 1 H), 6.70 (dq, J = 8.06, 1.47 Hz, 1 H). Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 59.96; H, 8.27. **8a**: a colorless oil (Kugelrohr distillation, 120 °C/9 mmHg); $[\alpha]^{25}_D$ +90.4° (*c* 1.23, $CHCl_3$); IR ($CHCl_3$) 3010, 2970, 2920, 1715, 1655, 1454, 1437, 1384, 1374, 1323, 1233, 1148, 1130, 1057, 1014, 994, 954, 858 cm^{-1}; ^1H

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NMR (200 MHz) δ 1.38 (d, J = 0.49 Hz, 3 H), 1.45 (d, J = 0.74 Hz, 3 H), 1.93 (dd, J = 1.46, 0.97 Hz, 3 H), 3.60 (dd, J = 8.3, 7.08 Hz, 1 H), 3.75 (s, 3 H), 4.31 (dd, J = 8.3, 6.84 Hz, 1 H), 5.26 (m, 1 H), 6.09 (dq, J = 6.84, 1.46 Hz, 1 H). Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 59.68; H, 8.22.

Methyl (4*S*,2*E*)-4,5-Bis(*tert*-butyldimethylsiloxy)-2-methyl-2-pentenoate (9a) and Methyl (4*S*,2*E*)-4-Hydroxy-2-methyl-5-(*tert*-butyldimethylsiloxy)-2-pentenoate (10a). To a solution of enoate **7a** (2.7 g, 13.5 mmol) in 51 mL of a mixture of MeOH–H_2O (50:1) was added 5 mL of Dowex 50 × 8 in. resin (H^+ form), and the mixture was stirred for 1 h at 50 °C. The resin was removed by filtration and the filtrate was concentrated under reduced pressure to leave an oily residue, which was used without purification for the next step. *tert*-Butyldimethylsilyl chloride (2.03 g, 13.5 mmol) was added portionwise to a stirred solution of the above oil in a mixture of CH_2Cl_2 (20 mL), DMF (2 mL), triethylamine (5 mL), and 4-(dimethylamino)pyridine (10 mg) at 0 °C, and the mixture was stirred for 1 h. The usual workup[27] led to a colorless oil, which was flash chromatographed over a silica gel column. Elution with *n*-hexane–EtOAc (10:1) gave 260 mg (5% yield) of bis(*tert*-butyldimethylsilyl ether) **9a** and further elution gave 3.22 g (87% yield) of mono(silyl ether) **10a**. **9a**: a colorless oil (Kugelrohr distillation, 130 °C/1 mmHg); $[\alpha]^{25}_D$ −4.88° (*c* 0.78, $CHCl_3$); IR ($CHCl_3$) 2950, 2880, 1713, 1661, 1474, 1467, 1443, 1393, 1365, 1324, 1257, 1124, 1087, 1060, 1010, 967, 943, 838 cm^{-1}; ^1H NMR (200 MHz) δ 0.03 (s, 3 H), 0.04 (s, 6 H), 0.06 (s, 3 H), 0.87 (s, 9 H), 0.88 (s, 9 H), 1.88 (d, J = 1.47 Hz, 3 H), 3.46 (dd, J = 10.01, 6.10 Hz, 1 H), 3.63 (dd, J = 10.01, 6.35 Hz, 1 H), 3.75 (s, 3 H), 4.50 (m, 1 H), 6.57 (dq, J = 9.77, 1.46 Hz, 1 H). Anal. Calcd for $C_{19}H_{40}O_4Si_2$: C, 58.72; H, 10.37. Found: C, 58.65; H, 10.56. **10a**: a colorless oil (Kugelrohr distillation, 140 °C/1 mmHg); $[\alpha]^{25}_D$ +6.24° (*c* 0.90, $CHCl_3$); IR ($CHCl_3$) 3550, 2980, 2960, 2880, 1714, 1663, 1465, 1442, 1393, 1365, 1316, 1257, 1137, 1103, 1062, 1007, 941, 884, 839 cm^{-1}; ^1H NMR (200 MHz) δ 0.09 (s, 6 H), 0.91 (s, 9 H), 1.91 (d, J = 1.22 Hz, 3 H), 3.50 (dd, J = 10.01, 7.81 Hz, 1 H), 3.64 (dd, J = 10.01, 3.66 Hz, 1 H), 3.75 (s, 3 H), 4.50 (m, 1 H), 6.63 (dq, J = 8.05, 1.47 Hz, 1 H). Anal. Calcd for $C_{13}H_{26}O_4Si$: C, 56.89; H, 9.55. Found: C, 57.13; H, 9.57.

Methyl (4*S*,2*E*)-4-Acetoxy-2-methyl-5-(*tert*-butyldimethylsiloxy)-2-pentenoate (11). To a solution of alcohol **10a** (274 mg, 1 mmol) in CH_2Cl_2 (5 mL) were added pyridine (2 mL) and Ac_2O (1 mL) at 0 °C. After 24 h at 0 °C, 2 mL of 5% $NaHCO_3$ was added with stirring at 0 °C. The mixture was extracted with Et_2O and the extract was washed successively with 5% HCl, 5% $NaHCO_3$, and water and dried over $MgSO_4$. Concentration under reduced pressure gave a colorless oil, which was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (5:1) to give **11** (305 mg, 97% yield); colorless oil; $[\alpha]^{26}_D$ +8.7° (*c* 1.35, $CHCl_3$); IR ($CHCl_3$) 2970, 2940, 2870, 1723, 1664, 1467, 1442, 1378, 1124, 1076, 1042, 1008, 942, 840 cm^{-1}; ^1H NMR (200 MHz) δ 0.06 (s, 6 H), 0.88 (s, 9 H), 1.96 (d, J = 1.46 Hz, 3 H), 2.07 (s, 3 H), 3.66 (dd, J = 10.74, 4.88 Hz, 1 H), 3.75 (s, 3 H), 3.75 (dd, J = 10.74, 6.59 Hz, 1 H), 5.58 (ddd, J = 8.79, 6.59, 4.88 Hz, 1 H), 6.55 (ddd, J = 8.79, 2.69, 1.22 Hz, 1 H); nominal mass spectrum, *m/z* 316 (M^+), 286, 259, 227, 199, 185, 157, 117 (base peak), 89, 75, 74; exact mass spectrum, *m/z* calcd for $C_{15}H_{28}O_5Si$ 316.1701, found 316.1710.

Methyl (4*S*,2*E*)-4-[(Methylsulfonyl)oxy]-2-methyl-5-(*tert*-butyldimethylsiloxy)-2-pentenoate (12a) and Its 4*R* Isomer (12b). Methanesulfonyl chloride (0.2 mL) was added dropwise at −78 °C to a stirred solution of enoate **10a** (54.8 mg, 0.2 mmol) in a mixture of pyridine (1 mL), 4-(dimethylamino)-pyridine (10 mg), and CH_2Cl_2 (2 mL). The solution was allowed to warm to room temperature, and stirring was continued for 1 h. The usual workup[28] and flash chromatography over silica gel with *n*-hexane–EtOAc (5:1) gave mesylate **12a** (69 mg, 98% yield). By a procedure identical with that described for the preparation of **12a**, alcohol **10b** (54.8 mg, 0.2 mmol) was converted to the mesylate **12b** (68 mg, 96% yield). **12a**: a colorless oil; $[\alpha]^{20}_D$ +14.0° (*c* 1.20, $CHCl_3$). **12b**: a colorless oil; $[\alpha]^{24}_D$ −13.9° (*c* 1.20, $CHCl_3$). **12a** and **12b**: IR ($CHCl_3$) 2970, 2950, 2880, 1720, 1662, 1466, 1440, 1360, 1335, 1260, 1177, 1120, 1070, 1009, 971, 921, 838 cm^{-1}; ^1H NMR (200 MHz) δ 0.08 (s, 6 H), 0.90 (s, 9 H), 1.98 (d, J = 1.71 Hz, 3 H), 3.03 (s, 3 H), 3.70 (dd, J = 11.48, 4.40 Hz, 1 H), 3.77 (s, 3 H), 3.85 (dd, J = 11.23, 7.08 Hz, 1 H), 5.39 (m, 1 H), 6.63 (dq, J = 9.04, 1.46 Hz, 1 H); nominal mass spectrum, *m/z* 353 $(M + H)^+$, 322, 295, 263, 257, 199, 153 (base peak), 129, 111, 97, 89, 75, 73.

General Procedure Using RCu(CN)Li·BF_3 (R = Et, *n*-Pr, *n*-Bu). The following procedure is representative for all reactions of γ-(mesyloxy)-α-alkyl α,β-enoates with EtCu(CN)Li·BF_3, *n*-PrCu(CN)Li·BF_3, and *n*-BuCu(CN)Li·BF_3. **Methyl (2*S*,3*E*)-2-Butyl-2-methyl-5-(*tert*-butyldimethylsiloxy)-3-pentenoate (14) from 12a.** To a stirred slurry of CuCN (135 mg, 1.5 mmol) in 6 mL of dry THF at −78 °C was added by syringe 0.94 mL (1.5 mmol) of a 1.6 M solution of *n*-BuLi in *n*-hexane and stirring was continued for 10 min. BF_3·Et_2O (0.185 mL, 1.5 mmol) was added to the above mixture at −78 °C and stirring was continued for 5 min. A solution of **12a** (176 mg, 0.5 mmol) in THF (2 mL) was added dropwise to the above reagent at −78 °C and stirring was continued for 30 min. A mixture of saturated NH_4Cl (2 mL) and 28% NH_4OH (2 mL) was added to the above mixture, and the mixture was allowed to warm to ambient temperature and stirring was continued for 30 min. The mixture was extracted with Et_2O and the extract was washed successively with 5% HCl, 5% $NaHCO_3$, and water and dried over $MgSO_4$. Concentration under reduced pressure gave an oily residue, which was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (20:1–10:1) to give **14** (144 mg, 97% yield) as a colorless oil (Kugelrohr distillation, 140 °C/1 mmHg). **14**: diastereoselection, >99:1, Eu(hfc)$_3$; $[\alpha]^{20}_D$ +5.50° (*c* 0.91, $CHCl_3$); IR ($CHCl_3$) 2950, 2880, 1726, 1466, 1436, 1383, 1365, 1255, 1131, 1109, 978, 841 cm^{-1}; ^1H NMR (200 MHz) δ 0.06 (s, 6 H), 0.90 (s, 9 H), 1.27 (s, 3 H), 3.66 (s, 3 H), 4.18 (dd, J = 5.13, 1.71 Hz, 2 H), 5.57 (dt, J = 15.62, 4.88 Hz, 1 H), 5.84 (dt, J = 15.62, 1.46 Hz, 1 H). Anal. Calcd for $C_{17}H_{34}O_3Si$: C, 64.92; H, 10.90. Found: C, 64.96; H, 11.12.

Methyl (2*R*,3*E*)-2-Ethyl-2-methyl-5-(*tert*-butyldimethylsiloxy)-3-pentenoate (15) and Methyl (2*E*)-4-Ethyl-2-methyl-5-(*tert*-butyldimethylsiloxy)-2-pentenoate. By use of a procedure similar to that described for the preparation of **14**, mesylate **12b** (704 mg, 2 mmol) was reacted with EtCu(CN)Li·BF_3 (6 mmol) in THF (13 mL) at −78 °C for 30 min. The usual workup led to a colorless oil, which was flash chromatographed over silica gel with *n*-hexane–EtOAc (98:2) to yield 528 mg (92.3% yield) of **15** and 20 mg (3.5% yield) of methyl (2*E*)-4-ethyl-2-methyl-5-(*tert*-butyldimethylsiloxy)-2-pentenoate. **15**: a colorless oil (Kugelrohr distillation, 130 °C/1 mmHg); $[\alpha]^{17}_D$ −4.67° (*c* 0.856, $CHCl_3$); IR ($CHCl_3$) 2970, 2950, 2870, 1722, 1460, 1434, 1382, 1252, 1142, 1121, 1102, 1060, 976, 839 cm^{-1}; ^1H NMR (200 MHz) δ 0.06 (s, 6 H), 0.83 (t, J = 7.57 Hz, 3 H), 0.90 (s, 9 H), 1.26 (s, 3 H), 1.50–1.83 (m, 2 H), 3.66 (s, 3 H), 4.18 (dd, J = 4.88, 1.47 Hz, 2 H), 5.57 (dt, J = 15.87, 4.88 Hz, 1 H), 5.83 (dt, J = 15.87, 1.47 Hz, 1 H); diastereoselection, >99:1, Eu(hfc)$_3$. Anal. Calcd for $C_{15}H_{30}O_3Si$: C, 62.89; H, 10.56. Found: C, 62.67; H, 10.86. Methyl (2*E*)-4-ethyl-2-methyl-5-(*tert*-butyldimethylsiloxy)-2-pentenoate: a colorless oil (Kugelrohr distillation, 135 °C/1 mmHg); $[\alpha]^{17}_D$ +19.7° (*c* 0.81, $CHCl_3$); IR ($CHCl_3$) 2970, 2940, 2870, 1703, 1651, 1462, 1438, 1389, 1362, 1288, 1279, 1133, 1096, 1007, 838 cm^{-1}; ^1H NMR (200 MHz) δ 0.02 (s, 3 H), 0.03 (s, 3 H), 0.86 (t, J = 6.84 Hz, 3 H), 0.87 (s, 9 H), 1.87 (d, J = 1.47 Hz, 3 H), 2.50 (m, 1 H), 3.53 (m, 2 H), 3.74 (s, 3 H), 6.54 (dq, J = 11.72, 1.47 Hz, 1 H); diastereoselection, >98:2, Eu(hfc)$_3$. Anal. Calcd for $C_{15}H_{30}O_3Si$: C, 62.89; H, 10.56. Found: C, 62.95; H, 10.85.

Methyl (2*R*)-2-Ethyl-2-methyl-5-(*tert*-butyldimethylsiloxy)pentanoate (17). A mixture of **15** (180 mg, 0.63 mmol) and 5% Rh–Al_2O_3 (15 mg) in MeOH (5 mL) was subjected to catalytic hydrogenation at atmospheric pressure for 1 h. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure to leave an oily residue, which was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (10:1) to yield 181 mg (99% yield) of **17**: colorless oil (Kugelrohr distillation, 130 °C/1 mmHg); $[\alpha]^{22}_D$ +5.26° (*c* 0.654, $CHCl_3$); IR ($CHCl_3$) 2980, 2950, 2880, 1723, 1464, 1437, 1388, 1367, 1349, 1254, 1146, 1098, 1008, 941, 838 cm^{-1}; ^1H NMR (200 MHz) δ 0.04 (s, 6 H), 0.82 (t, J = 7.57 Hz, 3 H), 0.89 (s, 9 H), 1.12 (s, 3 H), 1.35–1.73 (m, 6 H), 3.58 (m, 2 H), 3.65 (s, 3 H). Anal. Calcd for $C_{15}H_{32}O_3Si$: C, 62.45; H, 11.18. Found: C, 62.23; H, 11.47.

Methyl (2*R*)-2-Ethyl-2-methyl-5-hydroxypentanoate (18). To a solution of silyl ether **17** (144 mg, 0.5 mmol) in 2 mL of MeCN

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at 0 °C was added 0.04 mL of 46% HF, and stirring was continud for 15 min. The mixture was made basic with 5% $NaHCO_3$ and extracted with CH_2Cl_2. The extract was washed with water, dried over $MgSO_4$, and concentrated under reduced pressure to leave an oily residue, which was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (3:1) to give **18** (85 mg, 97% yield) as a colorless oil: $[\alpha]^{23}_D$ +6.76° (*c* 0.68, $CHCl_3$); IR ($CHCl_3$) 3600, 3450, 2950, 2880, 1722, 1461, 1444, 1387, 1344, 1240, 1169, 1142, 1054, 1008, 916 cm^{-1} ^1H NMR (200 MHz) δ 0.83 (t, *J* = 7.32 Hz, 3 H), 1.13 (s, 3 H), 1.33–1.80 (m, 6 H), 3.61 (m, 2 H), 3.67 (s, 3 H); nominal mass spectrum, *m/z* 174 (M^+), 154, 146, 143, 141, 115, 97, 69, 55 (base peak); exact mass spectrum, *m/z* calcd for $C_9H_{18}O_3$ 174.1255, found 174.1243.

Dimethyl (2*R*)-2-Ethyl-2-methylglutarate (19). To a solution of oxalyl chloride (0.42 mL, 4.8 mmol) in 1 mL of dry CH_2Cl_2 was added dropwise a solution of DMSO (0.72 mL, 10 mmol) in 2 mL of CH_2Cl_2 at −78 °C. After 10 min, a solution of alcohol **18** (60 mg, 0.345 mmol) in 2 mL of CH_2Cl_2 was added to the above reagent and the mixture was stirred at −78 °C for 30 min. Triethylamine (2.76 mL, 20 mmol) was added dropwise to the above solution, and the mixture was allowed to warm up slowly to room temperature and then cooled down to −78 °C. A saturated NH_4Cl solution (5 mL) was added to the mixture and the mixture was allowed to warm to ambient temperature. The usual workup and flash chromatography over silica gel with *n*-hexane–EtOAc (5:1) gave 50 mg (84.3% yield) of an aldehyde as a colorless oil. By use of a published procedure,[23a] the above aldehyde (45 mg, 0.26 mmol) was oxidized with the use of *t*-BuOH (3 mL), 1.25 M NaH_2PO_4 (2 mL), and 1 M $KMnO_4$ (3 mL) to give 52 mg of a carboxylic acid as a colorless oil, which was methylated with ethereal diazomethane. The usual workup and flash chromatography over silica gel with *n*-hexane–EtOAc (20:1) followed by Kugelrohr distillation (130 °C/20 mmHg) gave 46 mg (86% yield) of diester **19** as a colorless oil: $[\alpha]^{20}_D$ +8.05° (*c* 0.58, $CHCl_3$); IR ($CHCl_3$) 3050, 2950, 2880, 1723, 1463, 1435, 1384, 1375, 1307, 1168, 1138, 989 cm^{-1}; ^1H NMR (200 MHz) δ 0.83 (t, *J* = 7.57 Hz, 3 H), 1.12 (s, 3 H), 1.40–2.37 (m, 6 H), 3.67 (s, 6 H); optical purity, 99% [Eu(hfc)$_3$]; nominal mass spectrum, *m/z* 202 (M^+), 171, 143, 142, 129, 116, 111 (base peak), 101, 83, 69, 59, 55; exact mass spectrum, *m/z* calcd for $C_{10}H_{18}O_4$ 202.1204, found 202.1200.

Methyl (4*S*,5*S*)-3-[(Methylsulfonyl)oxy]-2-methyl-5-(*tert*-butyldimethylsiloxy)-2-hexenoate (22a). To a solution of mesylate **20a** (800 mg, 2.45 mmol) in CH_2Cl_2 (20 mL) at −78 °C was added dropwise 2.45 mL (2.45 mmol) of a 1 M solution of DIBAH in *n*-hexane, and the mixture was stirred for 2 h at −78 °C. Saturated NH_4Cl (2 mL) was added with vigorous stirring at −78 °C. The mixture was allowed to warm to 0 °C and stirring was continued for 30 min. The inorganic salts were removed by filtration through Celite. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure below 10 °C to an oil, which was used without purification for the next step. (α-Carbomethoxyethylidene)triphenylphosphorane (840 mg, 2.42 mmol) was added to the above oil in 20 mL of CH_2Cl_2 at −78 °C, and the mixture was stirred at −20 °C for 5 h. The mixture was concentrated under reduced pressure to an oil, which was flash chromatographed over silica gel with *n*-hexane–EtOAc (3:1) to yield **22a** (580 mg, 65% yield) as a rather labile colorless oil: $[\alpha]^{19}_D$ −5.75° (*c* 0.80, $CHCl_3$); IR ($CHCl_3$) 2980, 2950, 2880, 1720, 1663, 1475, 1468, 1441, 1365, 1258, 1180, 1120, 1100, 1090, 995, 977, 948, 840, 830, 813 cm^{-1}; ^1H NMR (200 MHz) δ 0.09 (s, 3 H), 0.09 (s, 3 H), 0.90 (s, 9 H), 1.17 (d, *J* = 6.35 Hz, 3 H), 1.99 (d, *J* = 1.47 Hz, 3 H), 2.97 (s, 3 H), 3.78 (s, 3 H), 4.01 (m, 1 H), 5.15 (dd, *J* = 9.77, 5.86 Hz, 1 H), 6.67 (dq, *J* = 9.77, 1.47 Hz, 1 H); exact mass spectrum, *m/z* calcd for $C_{15}H_{30}O_6SSi$ 366.1531, found 366.1532.

Methyl (4*S*,5*R*,6*R*,2*E*)-5,7-Bis(benzyloxy)-4,6-dihydroxy-2-methyl-2-heptenoate (34). To a solution of D-(+)-xylose 3,5-bis(benzyl ether) (**33**)[12] (800 mg, 2.4 mmol) in 5 mL of CH_2Cl_2 was added 835 mg (2.4 mmol) of (α-carbomethoxyethylidene)triphenylphosphorane, and the resulting solution was stirred for 5 h at room temperature. The usual workup led to an oily residue, which was flash chromatographed over silica gel. Elution with *n*-hexane–EtOAc (2:1) gave 800 mg (82% yield) of **34**: colorless syrup; $[\alpha]^{21}_D$ −2.36° (*c* 1.27, $CHCl_3$); IR ($CHCl_3$) 3560, 3040, 2890, 1714, 1457, 1443, 1096, 1032, 915 cm^{-1}; ^1H NMR (200 MHz) δ 1.88 (d, *J* = 1.46 Hz, 3 H), 3.75 (s, 3 H), 6.71 (dq, *J* = 8.55, 1.46 Hz, 1 H), 7.24–7.40 (m, 10 H).

Methyl (4*S*,5*R*,6*R*,2*E*)-5,7-Bis(benzyloxy)-4,6-bis[(methylsulfonyl)oxy]-2-methyl-2-heptenoate (35). By use of a procedure similar to that described for **12a**, **34** (80 mg, 0.2 mmol) in a mixture of pyridine (1 mL) and CH_2Cl_2 (2 mL) was mesylated with methanesulfonyl chloride (0.3 mL) at 0 °C for 10 h to give 105 mg (94% yield) of **35**: colorless syrup; $[\alpha]^{25}_D$ +16.98° (*c* 0.55, $CHCl_3$); IR ($CHCl_3$) 3050, 2950, 2880, 1720, 1659, 1605, 1498, 1456, 1439, 1414, 1364, 1179, 1108, 972, 912 cm^{-1}; ^1H NMR (200 MHz) δ 1.86 (d, *J* = 1.46 Hz, 3 H), 2.94 (s, 3 H), 2.96 (s, 3 H), 3.76 (s, 3 H), 3.78–3.97 (m, 3 H), 4.55 (s, 2 H), 4.65 (m, 2 H), 4.87 (m, 1 H), 5.53 (dd, *J* = 9.28, 3.66 Hz, 1 H), 6.74 (dq, *J* = 9.28, 1.46 Hz, 1 H), 7.72–7.42 (m, 10 H). This material is a rather labile syrup and was used immediately for the 1,3-chirality-transfer reaction.

Methyl (5*R*,6*R*,2*S*,3*E*)-5,7-Bis(benzyloxy)-6-[(methylsulfonyl)oxy]-2-methyl-2-propyl-3-heptenoate (36). By use of a procedure similar to that for **14**, 56 mg (0.1 mmol) of enoate **35** in dry THF (5 mL) was converted to 46 mg (91% yield) of **36** by treatment with PrCu(CN)Li·BF_3 (0.3 mmol) at −78 °C for 30 min. **36**: a colorless oil; $[\alpha]^{24}_D$ −9.31° (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3050, 3020, 2960, 2880, 1725, 1498, 1454, 1436, 1354, 1174, 973, 922, 700 cm^{-1}; ^1H NMR (200 MHz) δ 0.88 (t, *J* = 6.84 Hz, 3 H), 1.27 (s, 3 H), 2.964 (s, 3 H), 3.67 (s, 3 H), 4.11 (m, 1 H), 4.32–4.62 (m, 4 H), 4.76 (m, 1 H), 5.43 (dd, *J* = 15.87, 7.81 Hz, 1 H), 7.98 (dd, *J* = 15.87, 0.73 Hz, 1 H), 7.15–7.39 (m, 10 H); nominal mass spectrum, *m/z* 504 (M^+), 489, 462, 445, 413, 408, 396, 375, 349, 300, 276, 275, 258, 242, 232, 211, 183, 151, 130, 107, 92, 91 (base peak); exact mass spectrum, *m/z* calcd for $C_{27}H_{36}O_7S$ 504.2181, found 504.2179.

Methyl (5*R*,6*R*,2*S*,3*E*)-5,7-Bis(benzyloxy)-2-butyl-6-[(methylsulfonyl)oxy]-2-methyl-3-heptenoate (37). By use of a procedure similar to that described for **14**, **35** (80 mg, 0.144 mmol) was reacted with BuCu(CN)Li·BF_3 (0.432 mmol) at −78 °C for 30 min to give 74 mg (99% yield) of **37**: colorless oil; $[\alpha]^{25}_D$ −9.83° (*c* 0.997, $CHCl_3$); IR ($CHCl_3$) 2960, 2880, 1727, 1457, 1354, 1176, 973, 927 cm^{-1}; ^1H NMR (200 MHz) δ 0.88 (t, *J* = 6.59 Hz, 3 H), 1.28 (s, 3 H), 2.97 (s, 3 H), 3.67 (s, 3 H), 4.12 (m, 1 H), 4.33–4.63 (m, 4 H), 4.74 (m, 1 H), 5.43 (dd, *J* = 16.11, 7.81 Hz, 1 H), 6.02 (dd, *J* = 16.11, 0.73 Hz, 1 H), 7.24–7.37 (m, 10 H); diastereoselection, >99:1, Eu(hc)$_3$; nominal mass spectrum, *m/z* 518 (M^+), 459, 427, 422, 410, 375, 321, 314, 290, 289, 272, 225, 197, 181, 165, 144, 121, 107, 92, 91 (base peak), 65; exact mass spectrum, *m/z* calcd for $C_{28}H_{38}O_7S$ 518.2337, found 518.2347.

Methyl (5*R*,4*S*,6*S*,2*E*)-4,7-Dihydroxy-5,6-(isopropylidenedioxy)-2-methyl-2-heptenoate (39). To a solution of 3,4-*O*-isopropylidene-L-arabinopyranose (**38**) (1.9 g, 0.01 M) in toluene (20 mL) was added 3.48 g of (α-carbomethoxyethylidene)triphenylphosphorane, and the mixture was heated under reflux for 20 h. The solvent was evaporated under reduced pressure to leave a colorless residue, which was purified by flash chromatography over silica gel with *n*-hexane–EtOAc–MeOH (5:10:0.3) to yield 1.4 g (54% yield) of **39** as a colorless syrup. **39**: $[\alpha]^{20}_D$ +9.87° (*c* 1.54, $CHCl_3$); IR ($CHCl_3$) 3400, 3010, 2970, 1712, 1660, 1441, 1389, 1164, 1139, 1074, 1035, 985, 939, 872, 850 cm^{-1}; ^1H NMR (200 MHz) δ 1.39 (s, 3 H), 1.54 (s, 3 H), 1.95 (d, *J* = 1.47 Hz, 3 H), 2.68 (s, 2 H), 3.76 (s, 3 H), 3.80 (m, 2 H), 4.15 (dd, *J* = 7.08, 3.91 Hz, 1 H), 4.28 (dt, *J* = 6.83, 4.64 Hz, 1 H), 4.60 (dd, *J* = 8.79, 3.91 Hz, 1 H), 6.73 (ddd, *J* = 8.79, 2.69, 1.22 Hz, 1 H); nominal mass spectrum, *m/z* 260 (M^+), 245, 229, 183, 171, 153, 131, 130, 101, 59 (base peak); exact mass spectrum, *m/z* calcd for $C_{12}H_{20}O_6$ 260.1259, found 260.1255.

Methyl (5*R*,4*S*,6*S*,2*E*)-4,7-Bis[(methylsulfonyl)oxy]-5,6-(isopropylidenedioxy)-2-methyl-2-heptenoate (40). By use of a procedure identical with that described for the preparation of **12a**, 52 mg (0.2 mmol) of **39** was converted to dimesylate **40** (81.5 mg, 98% yield): colorless oil; $[\alpha]^{20}_D$ +9.9° (*c* 1.07, $CHCl_3$); IR ($CHCl_3$) 3040, 3010, 2970, 1722, 1661, 1440, 1363, 1176, 1088, 994, 964, 929, 889, 860, 821 cm^{-1}; ^1H NMR (200 MHz) δ 1.39 (s, 3 H), 1.53 (s, 3 H), 2.05 (d, *J* = 1.46 Hz, 3 H), 3.05 (s, 3 H), 3.09 (s, 3 H), 3.79 (s, 3 H), 4.34–4.53 (m, 4 H), 5.48 (dd, *J* = 9.77, 5.38 Hz, 1 H); nominal mass spectrum, *m/z* 401 (M − 15), 385, 354, 320, 263, 245, 231, 209, 167, 151 (base peak), 112, 95, 79; exact mass spectrum, *m/z* calcd for $C_{13}H_{21}O_{10}S_2$ (M − 15) 401.0576, found 401.0579.

Methyl (5*R*,6*S*,3*E*)-2,2-Dimethyl-5,6-(isopropylidenedioxy)-7-[(methylsulfonyl)oxy]-3-heptenoate (41). To a stirred slurry of CuCN (89 mg, 1 mmol) in 6 mL of dry THF at −78 °C

in an argon atmosphere was added dropwise by syringe 0.66 mL (1 mmol) of a 1.5 M ethereal MeLi–LiBr solution, and stirring was continued at −78 °C for 20 min. BF_3·Et_2O (0.122 mL, 1 mmol) was added to the above mixture at −78 °C, and the mixture was stirred for 5 min. A solution of **40** (139 mg, 0.33 mmol) in dry THF (3 mL) was added to the above reagent at −78 °C with stirring and stirring was continued for 30 min. The usual workup of the reaction mixture led to an oily residue, which was flash chromatographed on a silica gel column. Elution with *n*-hexane–EtOAc (3:1) gave 106 mg (95% yield) of **41** as a colorless oil: $[\alpha]^{20}_D$ −48.1° (*c* 1.09, $CHCl_3$); IR ($CHCl_3$) 3050,3010, 2970, 1729, 1672, 1472, 1463, 1439, 1365, 1179, 1150, 1085, 996, 966, 892, 869, 826 cm^{-1}; ^1H NMR (200 MHz) δ 1.33 (s, 6 H), 1.39 (s, 3 H), 1.52 (s, 3 H), 3.06 (s, 3 H), 3.68 (s, 3 H), 4.10 (dd, *J* = 10.75, 6.84 Hz, 1 H), 4.17 (dd, *J* = 10.75, 4.64 Hz, 1 H), 4.40 (td, *J* = 6.84, 4.39 Hz, 1 H), 4.72 (m, 1 H), 5.50 (dd, *J* = 15.63, 7.33 Hz, 1 H), 6.06 (dd, *J* = 15.63, 0.97 Hz, 1 H); nominal mass spectrum, *m/z* 336 (M^+), 321, 277, 261, 235, 219, 198, 183, 165, 137, 123, 97 (base peak); exact mass spectrum, *m/z* calcd for $C_{14}H_{24}O_7S$ 336.1242, found 336.1246.

Methyl (5*R*,2*S*,6*S*,2*E*)-2-Butyl-5,6-(isopropylidenedioxy)-7-[(methylsulfonyl)oxy]-2-methyl-3-heptenoate (42). By a procedure identical with that described for the preparation of **14**, **40** (139 mg, 0.33 mmol) was converted to **42** (120 mg, 95% yield) by treatment with BuCu(CN)Li·BF at −78 °C for 30 min. **42**: a colorless oil; $[\alpha]^{20}_D$ −31.1° (*c* 1.08, $CHCl_3$); IR ($CHCl_3$) 3050, 3010, 2960, 2880, 1727, 1670, 1463, 1458, 1439, 1362, 1345, 1180, 1086, 988, 966, 894, 870, 827 cm^{-1}; ^1H NM (200 MHz) δ 0.89 (t, *J* = 6.84 Hz, 3 H), 1.29 (s, 3 H), 1.39 (s, 3 H), 1.52 (s, 3 H), 3.06 (s, 3 H), 3.68 (s, 3 H), 4.05–4.20 (m, 2 H), 4.40 (td, *J* = 6.83, 4.63 Hz, 1 H), 4.72 (m, 1 H), 5.47 (dd, *J* = 15.62, 7.32 Hz, 1 H), 6.04 (dd, *J* = 15.62, 0.98 Hz, 1 H); nominal mass spectrum, *m/z* 378 (M^+), 363, 319, 303, 277, 261,240, 235, 207, 137, 97 (base peak); exact mass spectrum, *m/z* calcd for $C_{17}H_{30}O_7S$ 378.1711, found 378.1705.

Acknowledgment. A part of this work was supported by the Grant-in-Aid from the Ministry of Education, Science and Culture (Japan).

Supplementary Material Available: Synthetic methods and spectral data [$[\alpha]_D$, IR, ^1H NMR, and MS] for **7b**, **8b**, **9b**, **10b**, **13**, **16**, **24**, **25**, **26a**, **22b**, **23**, **26b**, **29**, **30**, **31**, and **32** (6 pages). Ordering information is given on any current masthead page.

A New Building Block Method To Synthesize Symmetrical and Asymmetrical Per-*N*-alkyl-Substituted Polyaza-Crown Compounds

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Received February 7, 1989

A new approach for the synthesis of a variety of per-N-alkylated polyaza-crown compounds is described. *N*-[2-(2-Chloroethoxy)ethyl]acetamide (**25**) and its benzamide analogue **26** are the key building blocks for the synthesis of the new polyaza-crowns. These chloroamides were reacted with primary amines or secondary diamines, followed by reduction of the resulting diamides, to produce polyamine intermediates containing two terminal *N*-ethyl or *N*-benzyl secondary amine functional groups. These secondary diamines were further reacted with dihalides in the presence of metal carbonates to form the polyaza-crowns. The overall yields for crown formation were generally very good. All of the new polyaza-crowns were prepared without the need for special nitrogen protecting reagents. Thus, the crowns were formed in a minimum number of steps. Twenty-three new polyaza-crowns containing from three to six nitrogen atoms in the macroring and from 16 to 36 ring members are reported.

Introduction

There is continuing interest in the synthesis of aza-crown compounds. The aza-crowns have complexation properties that are intermediate between the all-oxygen crowns, which strongly complex alkali and alkaline earth metal ions, and the all-nitrogen cyclams, which strongly complex heavy metal cations.[1] The aza-crowns also complex organic cations and anions and have important uses as synthetic receptors in molecular recognition processes.[2] In some cases, anion complexation by aza-crowns is similar to complexation processes in certain biological systems.[3-5] The aza-crowns have an enhanced affinity for ammonium salts compared to the all-oxygen crown compounds.[1,6] The aza-crowns are also important intermediates for the synthesis of the cryptands[7,8] and the nitrogen-pivot lariat crown ethers,[9] as catalysts in nucleophilic substitution and oxidation reactions,[10,11] and in the design of chromogenic reagents, which are sensitive to the alkali and alkaline earth metal ions.[12-14]

Silica gel bound aza-crown compounds have the same affinity for metal ions in aqueous solution as do the unbound crowns for the same metal ion.[15] These silica gel materials have been used to separate specific metal ions from mixtures of metal ions.[16-18] Thus, using a silica gel

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