Camphor-Based α-Bromo Ketones for the Asymmetric Darzens Reaction

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(1*R*)-2-*endo*-Bromoacetyl-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol (*endo*-2-bromoacetylisoborneol) **4** and its trimethylsilyl ether **3** are presented as efficient reagents for the asymmetric Darzens reaction. From the α,*β*-epoxy ketone adducts the chiral inductor camphor is removed, by treatment with ceric(IV) ammonium nitrate, to yield the corresponding epoxy acids which are isolated as their dicyclohexylammonium salts.

The reaction of α-halo esters with aldehydes or ketones promoted by base often results in the formation of α,*β*-epoxy (or glycidic) esters, the classical Darzens reaction,[1] or in the formation of halohydrins which then can be cyclized to the corresponding α,*β*-epoxy esters. The asymmetric version of this reaction has been realized by using chiral α-metalated methyl aryl sulfoxides,[2] chiral α-halogenated imide enolates,[3] chiral benzaldehyde−chromium complexes,[4] and chiral α-halo esters.[5] Some examples on the enantioselective Darzens reaction have also been documented; however, in all but a few cases,[6] the enantioselectivities are still rather poor.[7] On the other hand, competitive reactions[8] such as the Favorskii rearrangement, the nucleophilic addition at the carbonyl group, and the nucleophilic substitution of the halide have prevented α-halo ketones and α-halo aldehydes from being used in such a reaction.[9] Exceptionally, an α-bromo α′-hydroxy ketone, where no α′-hydrogen atoms are present, has been used. In this instance, the obtained α′-hydroxy α,*β*-epoxy ketone adduct generates, by oxidative cleavage of the α′-hydroxy ketone moiety, the corresponding α,*β*-epoxy ester.[10] However, to the best of our knowledge, there are no reports concerning the asymmetric version of the later approach, which would involve the use of chiral ketone reagents. In connection to this, we have recently reported on the use of the methyl ketone **2** (Scheme 1) for highly diastereoselective "acetate" aldol and Mannich reactions.[11] We now report on the preparation of α-halo ketones **3**−**5** and their use for the asymmetric Darzens reaction.

The bromo ketones **3** and **4** needed for the study were prepared according to a standard procedure, via the corresponding silyl enol ether and using *N*-bromosuccinimide (NBS) as the brominating agent, as shown in

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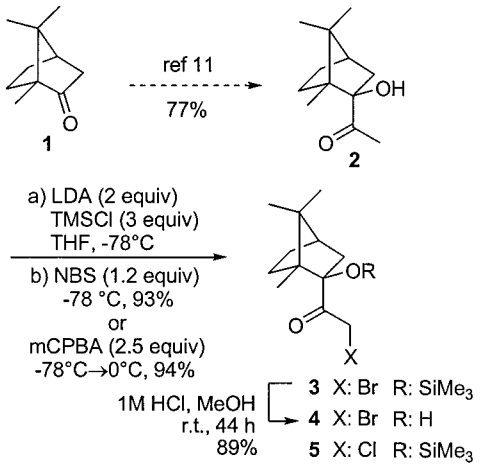
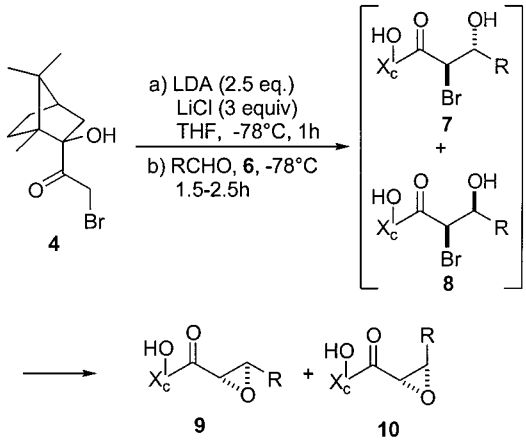
Scheme 1



Scheme 2



Scheme 1. Preparation of the chloro derivative **5**, however, was better accomplished by using a combination of TMS−Cl and mCPBA as the chlorination agent instead of NCS.[12] Darzens reactions of bromo ketone **4** with aldehydes (Scheme 2) were carried out by treatment of **4** with 2.5 equiv of LDA, in the presence of LiCl,[13] and subsequent addition of the aldehyde **6**. Other bases examined for that purpose, such as potassium bis(trimethylsilyl)amide and sodium bis(trimethylsilyl)amide, were less efficient in terms of both chemical yield and diastereoselectivity. From the results in Table 1, it is clear that the reaction of the dianion of **4** with aromatic aldehydes **6a**−**c** proceeded extremelly well to give the epoxide **9** essentially as the sole diastereomer (for configurational assignment of **9a**−**c**; see below). The reaction with aliphatic aldehydes **6d**−**g** gave rise to a mixture of both **9** and **10** in variable composition, with **10** as the major stereoisomer.[14] It appears that aliphatic aldehydes with large R groups (**6f**,**g**) lead to lower selectivities than the aldehydes with small R groups (**6d**) do. Although formation of epoxy ketones **9** and **10** should take place through cyclization of intermediate bromohydrins **7** (anti) and **8** (syn), respectively, no traces of either **7** or **8** was detected in the crude reaction products.

Table 1. Darzens Condensation of the Lithium Enolate of 4 with Representative Aldehydes[a]

aldehyde **6**	selectivity ratio **9**:**10**[b]	yield, %[c]
a, PhCHO	≥97:3	91[d]
b, 4-$MeOC_6H_4CHO$	≥97:3	*e*
c, 4-ClC_6H_4CHO	≥97:3	93[d]
d, CH_3CHO	5:95	93
e, CH_3CH_2CHO	20:80	86
f, $CH_3(CH_2)_2CHO$	37:63	86
g, $CH_3(CH_2)_3CHO$	35:65	96

[a] Reactions carried out on a 1 mmol scale; ketone:aldehyde 1:1.5. [b] For entries a−c only one isomer was detected by ^{13}C NMR; for other entries, the diastereomeric ratio was determined by integrating the easily distinguisable doublets corresponding to the α-H to the carbonyl group in the ^1H NMR spectra. Typical coupling constants for both isomers: $J_{cis} = 2$ Hz, $J_{trans} = 5$ Hz. [c] Yield of the mixture of diastereomers after purification by column chromatography unless otherwise stated. [d] Isolated yields of pure compound **9**. [e] Unstable adduct. Extensive decomposition was observed within a few hours.

On the other hand, previous studies have established that the size of the α-OR group is one of the main stereochemical control elements in lithium-mediated ketone aldol reactions.[15] In particular, it has been found that aldol reactions involving the metal enolates of α-hydroxy ethyl ketones provide substantially lower levels of diastereoselectivity than those involving the more sterically demanding α-trimethylsilyloxy derivatives.[16] On the basis of this evidence, we next examined the Darzens reaction of the silylated bromo ketone **3**. In this case, the reaction of the lithium enolate of ketone **3**, generated by treatment of **3** with 1 equiv of LDA, with benzaldehyde (Scheme 3) led to an almost equimolar mixture of epoxides **11** and **12**. The reaction conversion at −78 °C was uncomplete and warming to ambient temperature was necessary for complete disappearance of starting **3**. Compounds **11** and **12** were separated by HPLC and each isomer was submitted to a single-crystal X-ray structure analysis. On the other hand, desilylation of **11** provided in 90% yield a product which was identical to that directly obtained from Darzens condensation between the dianion of **4** and benzaldehyde. Therefore compounds **11** and **9a** are correlated and the configuration for the remaining compounds **9b**,**c** was established by analogy. When the reaction of the lithium enolate of **3** with aliphatic aldehydes was evaluated (Scheme 3), no epoxide formation took place at all. In these cases, the corresponding intermediate halohydrins **13** and **15** were produced instead,[17] in good yields and very high diastereoselectivity, as shown in Table 2. The reaction failed to go to completion in some cases, but after workup, the remaining unreacted α-bromo ketone could be easily separated from the mixture of aldols by column chromatography and reused. In general, *syn*-aldols **13** were formed as the major products, typically in a diastereomeric ratio of 95:5, over the minor *anti*-aldols **15**. The

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(13) For the influence of LiCl on the stereoselectivity of the aldol reactions of Li enolates, see ref 11a and references therein.

(14) Relative configurations for compounds **9c**−**g** (trans) and for **10c**−**g** (cis) were established by the value of the vicinal coupling constants measured for the *trans*-epoxides **9** (typically 2.5 Hz) and the *cis*-epoxides **10** (typically 5.0 Hz), respectively.

(15) For pertinent information on this aspect, see ref 11b and references therein.

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(17) The different reactivity observed for benzaldehyde (epoxides **11** and **12** are directly obtained) as compared with aliphatic aldehydes (halohydrins are isolated instead) can be rooted in the different reaction temperature employed. In fact, the "aliphatic" halohydrins **13** and **14** cyclized to the epoxides **10** when treated with a weak base at room temperature.

Scheme 3

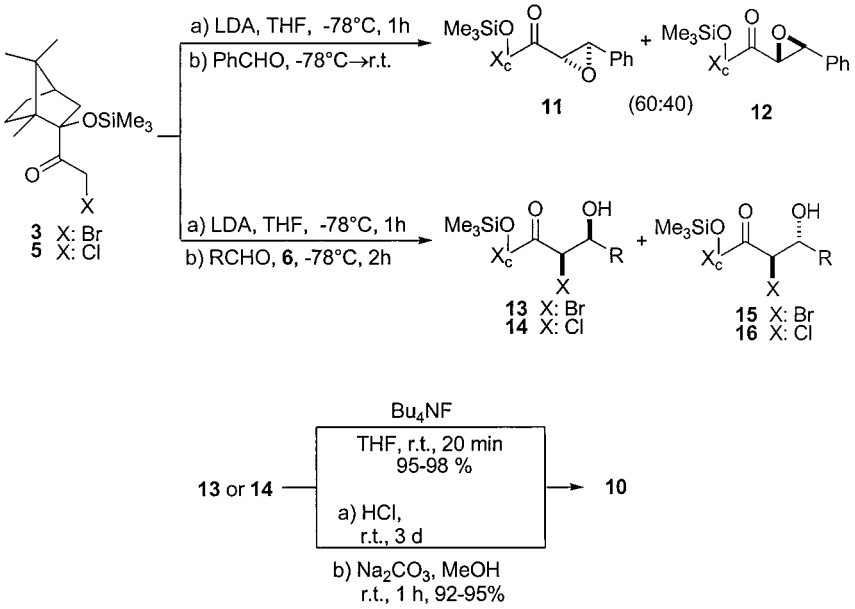

Table 2. Aldol Reactions of the Lithium Enolate of 3 and 5 with Aliphatic Aldehydes

entry	R	X	syn:anti[a]	yield, %[b]
1	CH_3CH_2	Br	92:8	72
2		Cl	89:11	65[d]
3	$CH_3(CH_2)_2$	Br	92:8[c]	89
4		Cl	89:11	68[d]
5	$CH_3(CH_2)_3$	Br	95:5[c]	68
6	$(CH_3)_2CHCH_2$	Br	94:6[c]	81
7		Cl	90:10	75
8	$PhCH_2CH_2$	Br	94:6[c]	53[e]

[a] Diastereomeric ratio determined by ^{1}H NMR, through integrating the signals corresponding to the proton COCHX in both stereoisomers. [b] Yield of pure isomer **13** or **14** after purification by flash column chromatography. [c] Corroborated by HPLC (±1%). [d] Unreacted **5** was recovered in 10% yield. [e] Unreacted **3** was recovered in 15% yield.

α-chloro ketone **5** led to similar results, although slighly lower diastereoselectivities were attained (entries 2, 4, and 7). The configurational assignment for adducts **13** and **14** was primarily made by conversion of compounds **13** and **14** into **10** and definitively by a single-crystal X-ray analysis of the aldol **13** (R = ^{n}Pr).[18] Assignment of the configuration for the minor isomers **15** and **16** was done by assuming a uniform reaction mechanism and also by ^{13}C chemical shift correlations. In this respect, it has been shown for related 1,2-halohydrins that the syn isomers exhibit a consistent downfield ^{13}C NMR shift of about 4−5 ppm with respect to the anti isomers.[3b] In our case, the same trend, albeit attenuated, was observed with a Δ ppm (δ syn − δ anti) value in the range 0.8−1.6.

The stereochemical outcome of these reactions involving aliphatic and aromatic aldehydes is consistent with transition structures A and B, respectively, depicted in Figure 1. The Zimmerman−Traxler type pericyclic transition state A, which nicely correlates metal enolate geometry and the relative configuration of aldol adducts,[19] fits well the metal chelating three-point coordination model previously postulated for this kind of aldol reaction.[20] If one assumes A as the lowest energy TS for these reactions, then the major products **8** and **13** (or **14**) would arise from the attack of the aldehyde from the less congested rear side of the chelated lithium (*Z*)-enolate.[21] Formation of major stereoisomers **9** and **11** from aromatic aldehydes can be better accounted for by invoking a boatlike TS B, which would lead to the intermediate anti halohydrins **7**, **15**, or **16**. The formation of *anti*-adducts from lithium enolates of carboxylic acid derivatives and aromatic aldehydes has been previously observed by

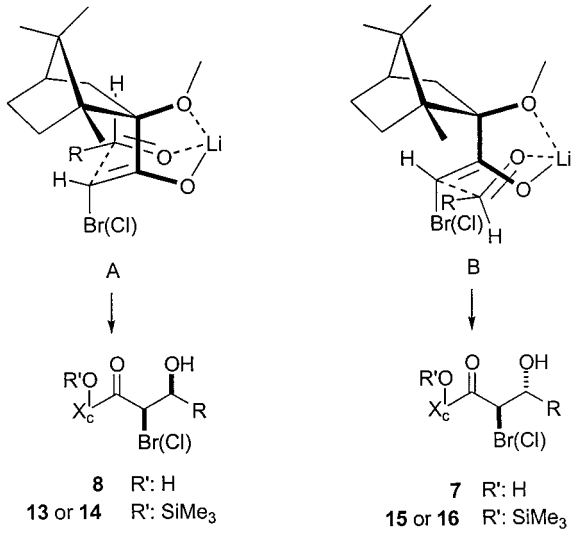

Figure 1. Proposed transition state structures that may account for the observed stereochemical outcome of the reactions involving aliphatic aldehydes (A) and aromatic aldehydes (B).

(18) The X-ray crystal structure analyses have been performed by one of us (A. L.) at the Organisch-Chemisches Institut der Universität Zürich. Atomic coordinates, bond lengths and angles, and thermal parameters for compounds **5**, **11**, **12** and **13** (R = ^{n}Pr) have been deposited at the Cambridge Crystallographic Data Center. The coordinates can be obtained, on request, from the Director, Cambridge Crystalographic Data Center, 12 Union Road, Cambridge, CB2 1EZ, UK. E-mail: deposit@ccdc.cam.ac.uk.

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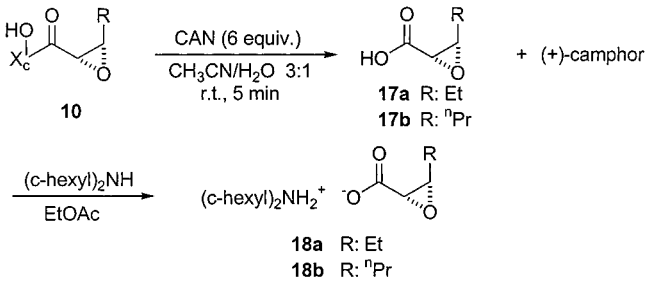
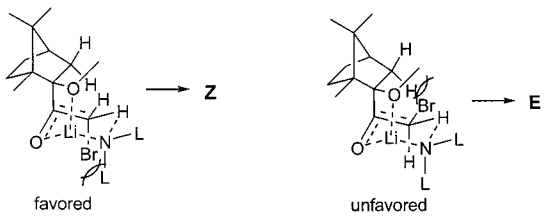
Scheme 4



several authors, who have proposed boatlike models to justify the results.[22]

Once the α,β-epoxy ketone adducts were available in a diastereoselective way, the question of the oxidative cleavage of the ketol moiety to form the corresponding carboxylic acids still remained. For instance, the treatment of either compounds **9**, **10,** or **13** with sodium periodate in a mixture of MeOH/water gave in all cases tested either a complex mixture of unidentified products (reaction conducted at reflux) or unmodified starting adducts (reaction at room temperature). No improvement was observed when mCPBA was employed as the oxidazing agent instead. Better results were obtained when adducts **13** (R = Et) and **11** were first reduced to the corresponding alcohol with $NaBH_4$ and then subjected to treatment with $Pb(OAc)_4$ in benzene. In both examples, a mixture of camphor and the corresponding α,β-epoxy aldehyde was obtained, albeit in yields lower than 40%. Furthermore, purification of the thus obtained epoxy aldehyde proved to be troublesome. Finally, conversion of the epoxy adducts into the corresponding epoxy acids was accomplished satisfactorily by treatment with ceric(IV) ammonium nitrate (CAN).[23] For instance, treatment of **10e** and **10f** in a mixture of CH_3CN/water with 6 equiv of CAN for 5 min at room temperature afforded the corresponding epoxy acids **17a** and **17b** along with camphor (Scheme 4). From the crude mixture, (+)-camphor was easily recovered in high yields either by column chromatography or extractions with *n*-hexane. However, the free epoxy acids **17a** and **17b** proved to be very difficult to purify. Neither the methyl esters, obtained by direct treatment with trimethylsilyl diazomethane, were purified satisfactorily. Instead, the corresponding salts **18a** and **18b** were isolated in yields of 60% and 66% from **10**, respectively, by precipitation of the epoxy acids as their dicyclohexylamine-derived salts in ethyl acetate. The analysis of the mother liquors, after evaporation of the solvent, showed no presence of the possible trans isomerization product.

(21) Formation of the *Z*-enolate, which was experimentally supported by trapping of it with TMSCl and isolation of the corresponding *Z*-silyl enol ester (see Supporting Information for details), can be rationalized according to Ireland's transition state model, assuming that the depicted intermolecular Br−L interaction is largely overwhelmed by the intramolecular Br−H interaction. For pertinent information on this topic, see: (a) R. E. Ireland, R. H. Mueller, A. K. Willard *J. Am. Chem. Soc.* **1976**, *98*, 2868. (b) L. Xie, K. M. Isenberg, G. Held, L. M. Dahl *J. Org. Chem.* **1997**, *62*, 7516.



(22) For a detailed information on this topic, see: (a) ref 3b. (b) Evans, D. A.; Takacs, J. M.; Mcgee, L. R.; Ennis, M. D.; Mathre, D. J.; Bartoli, J. J. *Pure Appl. Chem.* **1981**, *53*, 1109. (c) Nerz-Stormes, M.; Thornton, E. R. *J. Org. Chem.* **1991**, *56*, 2489.

(23) (a) Ho, T.-L. In *Organic Syntheses by Oxidation with Metal Compounds*; Mijs, W. J., De Jonge, C. R. H. I., Eds.; Plenum Press: New York, 1996; p.569. (b) Ho, T.-L. *Synthesis* **1973**, 347.

Experimental Section

Melting points were determined with a capillary apparatus and are uncorrected. Proton nuclear magnetic resonance (300 and 500 MHz) spectra and ^{13}C spectra (75 MHz) were recorded at room temperature for $CDCl_3$ solutions, unless otherwise stated. All chemical shifts are reported as δ values (ppm) relative to residual $CHCl_3$ (δ_H 7.26 ppm) or $CDCl_3$ (δ_C 77.0 ppm) as internal standards, respectively. Optical rotations were measured at 25 ± 0.2 °C in methylene chloride unless otherwise stated. HPLC analyses were performed on analytical columns (25 cm, phase Lichrosorb-Si60 and 25 cm, phase Chiralcel OD) with flow rates using 1 mL/min and 0.5 mL/min, respectively, using a DAD, and on preparative scale columns (25 cm, 2.5 Ø, phase Lichrosorb-Si60). Flash chromatography was executed with Merck Kiesegel 60 (230−400 Mesh) using mixtures of ethyl acetate and hexane as eluents. THF was distilled over sodium. MeOH was dried over magnesium metal and iodine.

(1*R*)-2-*endo*-Bromoacetyl-2-*exo*-trimethylsilyloxy-1,7,7-trimethylbicyclo[2.2.1]heptane (3). A mixture of diisopropylamine (1.6 mL, 12 mmol) in THF (20 mL) was cooled to −78 °C and *n*-BuLi (1.6 M in hexanes, 7.5 mL, 12 mmol) was added dropwise. After stirring for 30 min, a solution of trimethylsilyl chloride (2.2 mL, 16.7 mmol) in THF (12 mL) and methyl ketone **2**[11] (1.0 g, 5.0 mmol) in THF (12 mL) were successively added. The reaction mixture was allowed to stir for 1 h at −78 °C and warmed to room temperature, and the solvent was evaporated in vacuo at room temperature. The residue was extracted with pentane, filtered through a sintered glass funnel, and the solvent evaporated under reduced pressure at room temperature. The resulting viscous oil was dissolved in THF (25 mL), and to this solution, cooled to −78 °C, was added NBS (1 g, 5.6 mmol) in portions over a period of 10 min. The reaction mixture was stirred at −78 °C for a further period of 20 min, quenched with water (50 mL), and extracted with CH_2Cl_2. The combined organics were dried over $MgSO_4$, and the solvent was evaporated under reduced pressure to give **3** as a viscous oil which was purified to a clear oil by column chromatography (silica gel, eluent ethyl acetate: hexane 1:100): yield 1.62 g (93%); $[\alpha]^{25}_D = -20.7$ ($c = 1.0$, CH_2Cl_2); IR (neat) 1724 cm^{-1} (CO); ^1H NMR ($CDCl_3$, δ) 4.34 (d, J = 14.3 Hz, 1H), 4.07 (d, J = 14.3 Hz, 1H), 2.54 (d, J = 13.0 Hz, 1H), 1.30−1.90 (m, 4H), 1.04−1.18 (m, 1H), 1.02, 0.99 and 0.82 (s, 3H), 0.67−0.78 (m, 1H), 0.09 (s, 9H); ^{13}C NMR ($CDCl_3$, δ) 202.7, 91.8, 52.3, 51.4, 45.7, 41.2, 34.3, 31.0, 26.4, 21.5, 20.8, 11.8, 2.2.

(1*R*)-2-*endo*-Bromoacetyl-1,7,7-trimethylbicyclo[2.2.1]-heptan-2-ol (4). Silica gel 60 (230−400 mesh, 0.5 g) was added to a solution of **3** (0.347 g, 1 mmol) in a mixture of MeOH (4 mL) and 1 N HCl (2 mL), and the resulting slurry mixture was stirred at room temperature for 44 h. Then the mixture was diluted with CH_2Cl_2 and filtered, the organic layer was separated, washed with an aqueous saturated solution of $NaHCO_3$, and dried over $MgSO_4$, and the solvent was evaporated under reduced pressure. The solid thus obtained was purified by crystallization from a mixture of CH_2Cl_2/hexane (1:1): yield 0.245 g (89%); mp 77 °C; $[\alpha]^{25}_D = -11.3$ ($c = 1.0$, CH_2Cl_2); IR (film) 3423 (OH), 1705 cm^{-1} (CO); ^1H NMR ($CDCl_3$, δ) 4.44 (d, J = 14.2 Hz, 1H), 4.18 (d, J = 14.2 Hz, 1H), 2.36 (d, J = 12.8 Hz, 1H), 1.94−1.60 (m, 3H), 1.53−1.14 (m, 2H), 1.11, 1.01 and 0.86 (s, 3H), 0.89−0.99 (m, 1H); ^{13}C NMR ($CDCl_3$, δ) 204.7, 89.2, 53.1, 51.3, 45.6, 43.2, 35.1, 31.0, 26.9, 21.4, 21.2, 11.4. Anal. Calcd for $C_{12}H_{10}NO_2Br$ (275.18): C, 52.38; H, 6.96. Found: C, 52.63; H, 7.72.

(1*R*)-2-*endo*-Chloroacetyl-2-*exo*-trimethylsilyloxy-1,7,7-trimethylbicyclo[2.2.1]heptane (5). A mixture of diisopro-

pylamine (5.2 mL, 37.5 mmol) in THF (30 mL) was cooled to −78 °C and *n*-BuLi (2.5 M in hexanes, 15.0 mL, 37.5 mmol) was added dropwise. After stirring for 30 min, a solution of trimethylsilyl chloride (7.6 mL, 60 mmol) in THF (30 mL) and methyl ketone **2** (3.0 g, 15 mmol) in THF (30 mL) were successively added. The reaction mixture was allowed to stir for 1 h at −78 °C and then warmed to room temperature over a 30 min period. The reaction mixture was cooled to 0 °C and a solution of mCPBA (13 g, 37.5 mmol) in THF (30 mL) was then added. The resulting mixture was allowed to stir at room temperature for 15 min. The solid was filtered off and the filtrate was diluted with CH_2Cl_2 and washed sucesively with saturated Na_2SO_3 and saturated $NaHCO_3$. The organic phase was dried over $MgSO_4$ and the solvent evaporated under reduced pressure to give **5** as a viscous oil which solidified on standing. It was purified by crystallization from a mixture of ethyl acetate/hexane: yield 4.23 g (94%); mp 43−45 °C; $[\alpha]^{25}_D$ = −19.8 (*c* = 1.0, CH_2Cl_2); IR (film) 1724.5 cm^{-1} (CO); ^1H NMR ($CDCl_3$, δ) 4.56 (d, *J* = 15.8, Hz 1H), 4.18 (d, *J* = 15.8 Hz, 1H), 2.57 (d, *J* = 13.0 Hz, 1H), 1.95−0.70 (m, 6H), 1.05, 1.01 and 0.84 (s, 3H), 0.12 (s, 9H); ^{13}C NMR ($CDCl_3$, δ) 202.3, 91.0, 51.7, 50.9, 46.3, 45.1, 40.5, 30.2, 25.7, 20.8, 20.2. Anal. Calcd for $C_{15}H_{27}O_2SiCl$ (302.92): C, 59.48; H, 8.98. Found: C, 59.10; H, 8.92.

General Procedure for the Aldol Reactions of 4. A mixture of diisopropylamine (0.33 mL, 2.4 mmol) and anhydrous LiCl (0.25 g, 6 mmol) in dry THF (10 mL) was cooled to −78 °C under a nitrogen atmosphere and *n*-butyllithium (1.6 M in hexane, 1.50 mL, 2.4 mmol) was added dropwise. After stirring for 30 min at the same temperature, a solution of **4** (0.275 g, 1 mmol) in THF (5 mL) was added dropwise. The resulting mixture was allowed to stir for 1 h at −78 °C and then a precooled (−78 °C) solution of the corresponding aldehyde (1.5 mmol) in THF (10 mL) was added dropwise. The reaction was allowed to stir for 1.5−2.5 h at −78 °C and then was quenched with 5 mL of a saturated aqueous solution of $NaHCO_3$. The resulting mixture was allowed to warm to room temperature, after which the layers were separated, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organics were dried over $MgSO_4$, and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography, using a 1:50 EtOAc:hexane mixture as the eluent, except for compounds **9a** and **9c**, which were eluted with a EtOAc:hexane:Et_3N 2:100:0.2 mixture.

Compound 9a. yield 0.274 g (91%); mp 138−139 °C; $[\alpha]^{25}_D$ = +161.4 (*c* = 1.0, CH_2Cl_2); IR (KBr) 3436 (OH), 1716 cm^{-1} (CO); ^1H NMR ($CDCl_3$, δ) 7.20−7.41 (m, 5H), 4.03 (d, *J* = 1.7 Hz, 1H), 3.93 (d, *J* = 1.7 Hz, 1H), 2.37 (d, *J* = 13.0 Hz, 1H), 1.95−1.20 (m, 7H), 1.13, 1.09 and 0.88 (s, 3H); ^{13}C NMR ($CDCl_3$, δ) 206.3, 136.3, 129.5, 126.5, 88.9, 61.3, 60.4, 53.1, 51.6, 46.5, 45.7, 42.9, 30.9, 26.8, 21.4, 21.2, 11.7. Anal. Calcd for $C_{19}H_{24}O_3$ (300.40): C, 75.97; H, 8.05. Found: C, 76.16; H, 8.43.

Compound 9c. yield 0.311 g (93%); mp 144−145 °C; $[\alpha]^{25}_D$ = +164.2 (*c* = 1.0, CH_2Cl_2); IR (KBr) 3430 (OH), 1705 cm^{-1} (CO); ^1H NMR ($CDCl_3$, δ) 7.33 (d, *J* = 8.6 Hz, 2H), 7.23 (d, *J* = 8.6 Hz, 2H), 3.98 (d, *J* = 1.8 Hz, 1H), 3.91 (d, *J* = 1.8 Hz, 1H), 2.34 (d, *J* = 12.9 Hz, 1H), 1.95−1.05 (m, 7H), 1.13, 1.08 and 0.88 (s, 3H); ^{13}C NMR ($CDCl_3$, δ) 205.9, 135.4, 134.9, 129.4, 127.8, 89.0, 61.2, 59.7, 53.1, 51.7, 45.7, 43.0, 30.9, 26.9, 21.5, 21.2, 11.8. Anal. Calcd for $C_{19}H_{23}O_3Cl$ (334.84): C, 68.15; H, 6.92. Found: C, 67.81; H, 7.03.

General Procedure for the Aldol Reactions of 3/5. A mixture of diisopropylamine (0.196 mL, 1.4 mmol) in dry THF (10 mL) was cooled to −78 °C under a nitrogen atmosphere and *n*-butyllithium (1.6 M in hexane, 0.88 mL, 1.4 mmol) was added dropwise. After stirring for 30 min at the same temperature, a solution of either **3** or **5** (1 mmol) in THF (5 mL) was added dropwise. The resulting mixture was allowed to stir for 1 h at −78 °C, and then a precooled (−78 °C) solution of the corresponding aldehyde (1.5 mmol) in THF (10 mL) was added dropwise. The reaction was allowed to stir for 1.5−2.5 h at −78 °C and then was quenched with 5 mL of a saturated aqueous solution of $NaHCO_3$. The resulting mixture was allowed to warm to room temperature, after which the layers were separated, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organics were dried over $MgSO_4$, and the solvent was evaporated under reduced pressure. Purification of the product was effected by flash column chromatography, using a 1:50 EtOAc:hexane mixture as the eluent. In some cases, the major isomer was separated by preparative HPLC (eluent EtOAc:hexane 10:90).

Compound 13 (R = Et): yield 0.292 g (72%); colorless oil; $[\alpha]^{25}_D$ = −58.9 (*c* = 1.0, CH_2Cl_2); IR (film) 3500 (OH), 1697 cm^{-1} (CO); ^1H NMR ($CDCl_3$, δ) 4.96 (bs, 1H), 3.56−3.67 (m, 1H), 3.48 (d, *J* = 2.3 Hz, 1H), 2.50 (d, *J* = 13 Hz, 1H), 1.97−0.72 (m, 9H), 1.06 and 0.98 (s, 3H), 0.96 (t, *J* = 7.3 Hz, 3H), 0.85 (s, 3H), 0.22 (s, 9H); ^{13}C NMR ($CDCl_3$, δ) 209.1, 92.2, 70.5, 52.9, 51.9, 50.7, 45.6, 42.4, 31.1, 29.0, 26.4, 21.7, 20.9, 12.1, 10.3, 3.0.

Compound 13 (R = ^{n}Pr): yield 0.373 g (89%); mp 106−108 °C; $[\alpha]^{25}_D$ = −60.8 (*c* = 1.0, CH_2Cl_2); IR (KBr) 3509 (OH), 1699 cm^{-1} (CO); ^1H NMR ($CDCl_3$, δ) 4.91 (s, 1H), 3.62−3.76 (m, 1H), 3.44 (d, 1H, *J* = 2.3 Hz), 2.52 (d, 1H, *J* = 13.1 Hz), 1.95−1.10 (m, 6H), 1.04, 0.96 and 0.83 (s, 3H), 0.96−0.91 (m, 7H), 0.21 (s, 9H); ^{13}C NMR ($CDCl_3$, δ) 208.5, 91.5, 68.2, 52.3, 51.3, 50.8, 44.9, 41.7, 37.6, 30.5, 25.8, 21.0, 20.2, 18.4, 14.0, 11.5, 2.4. Anal. Calcd for $C_{19}H_{35}O_3BrSi$ (419.48): C, 54.40; H, 8.41. Found: C, 54.40; H, 7.90.

Compound 13 (R = ^{n}Bu): yield 0.295 g (68%); mp 63−65 °C; $[\alpha]^{25}_D$ = −56.6 (*c* = 1.0, CH_2Cl_2); IR (KBr) 3528, 3506 (OH), 1698 cm^{-1} (CO); ^1H NMR ($CDCl_3$, δ) 4.92 (s, 1H), 3.76−3.61 (m, 1H), 3.46 (d, 1H, *J* = 1.9 Hz), 2.50 (d, 1H, *J* = 13.2 Hz), 1.95−1.10 (m, 6H), 1.05, 0.97 and 0.84 (s, 3H), 0.92−0.89 (m, 9H), 0.22 (s, 9H); ^{13}C NMR ($CDCl_3$, δ) 209.1, 92.2, 69.1, 52.9, 51.9, 51.5, 45.6, 42.4, 35.8, 31.1, 27.9, 26.4, 23.2, 21.7, 20.9, 14.6, 12.2, 3.0. Anal. Calcd for $C_{20}H_{37}O_3BrSi$ (433.50): C, 55.41; H, 8.60. Found: C, 55.53; H, 8.10.

Compound 13 (R = ^{i}Bu): yield 0.351 g (81%); mp 72−73 °C; $[\alpha]^{25}_D$ = −54.7 (*c* = 1.0, CH_2Cl_2); IR (KBr) 3479 (OH), 1689 cm^{-1} (CO); ^1H NMR ($CDCl_3$, δ) 4.87 (s, 1H), 3.85−3.75 (m, 1H), 3.34 (s, 1H), 2.50 (d, 1H, *J* = 13.0 Hz), 1.95−0.78 (m, 9H), 1.06 and 0.97 (s, 3H), 0.96 (d, 3H, *J* = 4.4 Hz), 0.93 (d, 3H, *J* = 6.04 Hz), 0.85 (s, 3H), 0.22 (s, 9H); ^{13}C NMR ($CDCl_3$, δ) 208.2, 91.5, 66.4, 52.3, 52.0, 51.4, 45.9, 44.9, 41.7, 30.5, 25.8, 24.0, 23.5, 22.0, 21.1, 20.2, 11.4, 2.4. Anal. Calcd for $C_{20}H_{37}O_3BrSi$ (433.50): C, 55.41; H, 8.60. Found: C, 55.56; H, 8.22.

Compound 13 (R = $PhCH_2CH_2$): yield 0.240 g (53%); mp 60−62 °C; $[\alpha]^{25}_D$ = −67.6 (*c* = 1.0, CH_2Cl_2); IR (KBr) 3503 (OH), 1699 cm^{-1} (CO); ^1H NMR ($CDCl_3$, δ) 7.40−7.18 (m, 5H), 4.90 (d, 1H, *J* = 0.73 Hz), 3.76−3.64 (m, 1H), 3.42 (d, 1H, *J* = 1.65 Hz), 3.06−2.64 (m, 2H), 2.51 (d, 1H, *J* = 1.32 Hz), 2.32−2.10 (m, 1H), 1.98−1.84 (m, 1H), 1.82−1.54 (m, 3H), 1.39−1.10 (m, 2H), 1.06, 0.84, and 0.76 (s, 3H), 0.80−0.65 (m, 1H), 0.24 (s, 9H); ^{13}C NMR ($CDCl_3$, δ) 208.7, 141.3, 129.2, 129.1, 126.7, 92.1, 67.8, 52.9, 51.9, 45.5, 42.3, 38.1, 31.9, 31.0, 26.5, 21.7, 20.9, 11.8, 3.0. Anal. Calcd for $C_{24}H_{37}O_3BrSi$ (453.46): C, 59.86; H, 7.74. Found: C, 60.30; H, 7.76.

Compounds 11/12. The general procedure for aldol reactions with **3** was followed, except that the reaction mixture was allowed to rise to room temperature over a period of 1 h, before quenching. After usual workup and purification of the product by column chromatography, both diastereomers were separated by preparative HPLC (eluent EtOAc:hexane 1:50).

Compound **11**: yield 0.052 g (30%); mp 110 °C; $[\alpha]^{25}_D$ = −161.6 (*c* = 1.0, CH_2Cl_2); IR (KBr) 1715 cm^{-1} (CO); ^1H NMR ($CDCl_3$, δ) 7.25−7.34 (m, 5H), 4.07 (d, *J* = 1.7 Hz, 1H), 3.95 (d, *J* = 1.7 Hz, 1H), 2.55 (d, *J* = 13.0 Hz, 1H), 1.95−1.10 (m, 6H), 1.07 (s, 3H), 0.82 (s, 6H), 0.70−0.85 (m, 1H), 0.17 (s, 9H); ^{13}C NMR ($CDCl_3$, δ) 204.9, 136.4, 129.5, 129.4, 126.2, 91.5, 61.9, 61.8, 59.9, 59.8, 52.8, 51.5, 45.9, 40.6, 31.1, 26.5, 21.4, 21.0, 11.9, 2.4. Anal. Calcd for $C_{12}H_{32}O_3Si$ (372.58): C, 70.92; H, 8.66. Found: C, 71.31; H, 8.49.

Compound **12**: yield 0.064 g (37%); mp 70 °C; $[\alpha]^{25}_D$ = +154.2 (*c* = 1.0, CH_2Cl_2); IR (KBr), 1715 cm^{-1} (CO); ^1H NMR ($CDCl_3$, δ) 7.26−7.41 (m, 5H), 4.08 (d, *J* = 1.7 Hz, 1H), 4.00 (d, *J* = 1.7 Hz, 1H), 2.47 (d, *J* = 12.8 Hz, 1H), 1.95−1.15 (m, 6H), 1.14, 1.07 and 0.87 (s, 3H), 0.90−1.00 (m, 1H); ^{13}C NMR ($CDCl_3$, δ) 205.9, 136.3, 129.5, 129.3, 126.4, 91.4, 60.8, 60.6, 60.4, 60.3, 53.0, 51.0, 46.1, 41.2, 31.0, 26.3, 21.5, 20.9, 12.2,

2.1. Anal. Calcd for $C_{22}H_{32}O_3Si$ (372.58): C, 70.92; H, 8.66. Found: C, 70.82; H, 8.78.

Cyclization of Halohydrins 13/14 to Epoxides 10. Method A. The corresponding halohydrin (0.5 mmol) was dissolved in a mixture of MeOH (2 mL) and 1 N HCl (1 mL), silica gel 60 (230−400 mesh, 0.25 g) was added to the solution, and the mixture was stirred at room temperature for 4−5 days. After dilution with CH_2Cl_2 (10 mL), an aqueous solution of $NaHCO_3$ (saturated, 5 mL) was added, the organic layer was separated and dried over $MgSO_4$, and the solvent was evaporated under reduced pressure. The resulting crude product was dissolved in MeOH (5 mL), the solution cooled to 0 °C, and then Na_2CO_3 (0.265 g, 2.5 mmol) was added. The reaction was allowed to warm to room temperature and stirred at this temperature for 3 h. Then the solvent was evaporated under reduced pressure and CH_2Cl_2 (10 mL) was added. The resulting solution was washed with an aqueous saturated solution of NH_4Cl and $NaHCO_3$. The organic solution was dried over $MgSO_4$ and the solvent evaporated under reduced pressure. The corresponding epoxide was obtained as a white solid.

Method B. To a solution of the corresponding halohydrin (0.5 mmol) in THF (10 mL) was added TBAF (1 M solution in THF, 1 mL, 1 mmol), and the reaction mixture was stirred at room temperature for 20 min. The solvent was evaporated under reduced pressure, and the residue was dissolved in CH_2Cl_2 (20 mL) and washed with water (2 × 25 mL). The organic layer was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, eluent EtOAc:hexane 1:50).

Epoxide 10e. Method B was followed: yield from **13**, 0.122 g (97%); from **14**, 0.119 g (94%); mp 63−64 °C; $[\alpha]^{25}_D = -42.5$ ($c = 1$, CH_2Cl_2); IR (KBr) 3484 (OH), 1707 cm^{-1} (CO); ^1H NMR ($CDCl_3$, δ) 3.98 (d, $J = 5.0$ Hz, 1H), 3.25 (dt, $J = 5.0$ Hz, $J' = 6.0$ Hz, 1H), 2.27 (d, $J = 13.2$ Hz, 1H), 1.89−0.80 (m, 8H), 1.12 and 1.05 (s, 3H), 0.99 (t, $J = 7.4$ Hz, 3H), 0.87 (s, 3H); ^{13}C NMR ($CDCl_3$, δ) 206.4, 88.5, 60.7, 58.1, 52.4, 50.9, 45.0, 42.6, 29.9, 26.1, 20.8, 20.6, 19.9, 11.1, 10.3. Anal. Calcd for $C_{15}H_{24}O_3$ (252.35): C, 71.39; H, 9.59. Found: C, 71.66; H, 9.16.

Epoxide 10f. Method A was followed: yield from **13**. 0.124 g (93%); from **14**, 0.123 g (92%); mp 62−64 °C; $[\alpha]^{25}_D = -42.7$ ($c = 1$, CH_2Cl_2); IR (KBr) 3437 (OH), 1701 cm^{-1} (CO); ^1H NMR ($CDCl_3$, δ) 3.97 (d, 1H, $J = 4.96$ Hz), 3.35−3.20 (m, 1H), 2.34 (s, 1H), 2.28−2.20 (m, 1H), 1.83−1.14 (m, 6H), 1.11, 1.04 and 0.85 (s, 3H), 0.95−0.88 (m, 7H); ^{13}C NMR ($CDCl_3$, δ) 207.2, 89.4, 60.1, 58.6, 53.2, 51.7, 45.8, 43.4, 30.7, 29.3, 26.9, 21.6, 21.3, 20.4, 14.6, 11.8. Anal. Calcd for $C_{16}H_{26}O_3$ (266.38): C, 72.14; H, 9.84. Found: C, 71.94; H, 10.01.

Epoxide 10g. Method A was followed: yield from **13**, 0.129 g (92%); mp 76−78 °C; $[\alpha]^{25}_D = -40.9$ ($c = 1$, CH_2Cl_2); IR (KBr) 3438 (OH), 1699 cm^{-1} (CO); ^1H NMR ($CDCl_3$, δ) 3.98 (d, 1H, $J = 4.94$ Hz), 3.33−3.25 (m, 1H), 2.32−2.24 (m, 1H), 2.21 (s, 1H), 1.86−1.01 (m, 12H), 1.14, 1.06 and 0.88 (s, 3H), 1.09−0.85 (m, 3H); ^{13}C NMR ($CDCl_3$, δ) 207.1, 84.3, 60.3, 58.6, 53.2, 51.7, 45.8, 43.4, 30.6, 30.4, 29.1, 26.9, 23.0, 21.5, 21.3, 14.6, 11.8. Anal. Calcd for $C_{17}H_{28}O_3$ (280.40): C, 72.82; H, 10.06. Found: C, 71.24; H, 10.02.

Desilylation of 12. The general desilylation procedure, method B, was followed starting from compound **12** to yield 0.147 g (98%) of a product, which exhibited identical physical and spectroscopic data to that of compound **9a**, obtained as previously described.

General Procedure for Formation of Epoxy Acid Salts 18. To a solution of the corresponding epoxide **10** (1.5 mmol) in CH_3CN (18 mL) was added dropwise at room temperature a solution of CAN (4.11 g, 7.5 mmol) in H_2O (9 mL). The resulting yellowish solution was stirred for 5 min at room temperature and then diluted with H_2O and extracted twice with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and the solvent evaporated under reduced pressure to give an oil. The NMR analysis of the crude reaction product showed the presence of the corresponding epoxy acid **17** along with (+)-camphor in equimolar ratios. The thus obtained oily product was dissolved in EtOAc (10 mL), and dicyclohexylamine (0.363 g, 2 mmol) was added dropwise via syringe. From the resulting solution a precipitate slowly appeared which was filtered off after 14 h of standing. From the mother liquors, additional crops were obtained and combined.

Compound 18a: yield 0.268 g (60%); mp 149−150 °C; $[\alpha]^{25}_D = -8.8$ ($c = 1.0$, CH_2Cl_2); IR (film) 3416.0, 1602.4 cm^{-1} (CO); ^1H NMR ($CDCl_3$, δ) 3.42 (d, $J = 4.77$ Hz, 1H), 3.10−2.75 (m, 3H), 2.10−2.0 (m, 4H), 1.85−1.60 (m, 8H), 1.60−1.45 (m, 4H), 1.30−1.10 (m, 8H), 1.06 (t, $J = 7.7$ Hz, 3H); ^{13}C NMR ($CDCl_3$, δ) 173.0, 58.1, 55.6, 52.7, 29.3, 29.0, 25.2, 24.79, 24.76, 21.6, 10.5. Anal. Calcd for $C_{17}H_{31}O_3N$ (297.44): C, 68.65; H, 10.50; N, 4.71. Found: C, 68.12; H, 10.47; N, 4.70.

Compound 18b: yield 0.285 g (61%); mp 133−135 °C; $[\alpha]^{25}_D = -5.5$ ($c = 1.0$, CH_2Cl_2); IR (film) 3425.6, 1602.4 cm^{-1} (CO); ^1H NMR ($CDCl_3$, δ) 3.41 (d, $J = 4.77$ Hz, 1H), 3.10−3.05 (m, 1H), 3.05−2.90 (m, 2H), 2.10−1.95 (m, 4H), 1.85−1.75 (m, 4H), 1.70−1.60 (m, 4H), 1.60−1.40 (m, 6H), 1.35−1.10 (m, 8H), 0.94 (t, $J = 7.34$ Hz, 3H); ^{13}C NMR ($CDCl_3$, δ) 173.0, 56.7, 55.5, 52.7, 30.5, 29.6, 29.3, 25.2, 24.8, 24.7, 19.8, 14.0. Anal. Calcd for $C_{18}H_{33}O_3N$ (311.46): C, 69.41; H, 10.68; N, 4.50. Found: C, 69.28; H, 10.25; N, 4.38.

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Supporting Information Available: Experimental procedure for the trapping of the trimethylsilylenol ether derivative of the enolate of **3**, ORTEP representations of **5**, **11**, **12**, and **13** (R = ^{n}Pr), and NMR spectra of representative compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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