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On the Origins of the Diastereoselectivity in the Bromine/Lithium Exchange of 3-Alkoxy-1,1-dibromoalkanes

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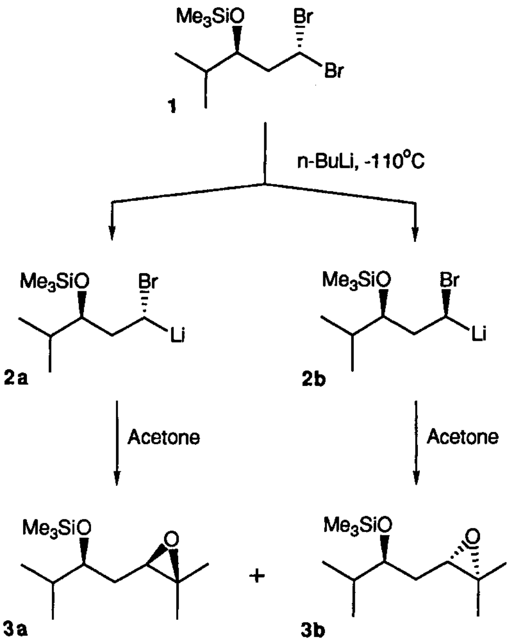
The 3-alkoxy-1,1-dibromopentanes **5** are compounds, which according to MM2 calculations populate one conformation to >80% at −110°C. On reaction with *n*-butyllithium the bromine atom which resides in the extended position is exchanged with selectivities around 80:20, irrespective of the nature of the oxy residue at C-3. The role of this substituent is solely to bias the conformational equilibria in favor of the conformer **17**. Coordination of the butyllithium to the oxygen functionality plays an important role only in the carbamoyl derivative **5f**, for which the sense of the asymmetric induction is reversed.

We reported recently on the stereoselective exchange of one of the two diastereotopic bromine atoms in **1** for a lithium atom[2]. The resulting diastereomeric α-bromoalkyllithium compounds **2** have been trapped by various electrophiles, e.g. trapping by acetone led to the diastereomeric epoxides **3**. It has been shown[3] that the diastereomer ratio (85:15) of **3a**/**3b**, which resulted from in situ trapping experiments, reflects the kinetic diastereoselection in the exchange of the diastereotopic bromine atoms of **1**.

The relative configurations of the products **3** have also been determined[3]. Based on the assumption that the bromine/lithium exchange as well as the addition of **2** to acetone proceed with retention of configuration at C-1, it becomes apparent that it is the "*unlike*" bromine atom[4] in **1** that is exchanged preferentially. Can this result be rationalized?

Scheme 1

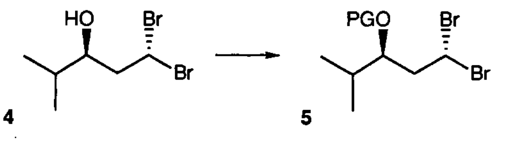


When we started these investigations[5] we envisioned that the silyloxy substituent might coordinate the incoming butyllithium and could influence the diastereoselectivity by a proximity effect[6]. On the other hand, a silyloxy group is known to be a poor chelator[7]. In order to find out, whether coordination of the butyllithium to this oxygen functionality is decisive for the observed diastereoselection, we investigated the reaction of a series of dibromo compounds **5** having different oxygen "protecting" groups.

Reaction of 3-Alkoxy-1,1-dibromo-4-methylpentanes with Butyllithium

The alcohol **4**[2] was converted by standard techniques into a set of variously protected derivatives **5**. The groups were chosen to span the range from noncoordinating bulky silyloxy groups over simple alkoxy groups to the highly lithium-coordinating MEM and carbamoyloxy groups.

Scheme 2



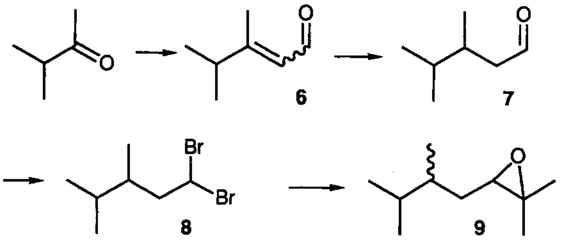
	PG[a]	Yield (%)	Ref.
a	iPr$_3$Si	90	–
b	tBuMe$_2$Si	75	[3]
c	CH_3	50	–
d	$PhCH_2$	78	–
e	$CH_3OCH_2CH_2OCH_2$	66	–
f	iPr$_2$NC(O)	80	–

[a] PG: "protecting" group.

0009–2940/92/1212–2741 $ 3.50+.25/0

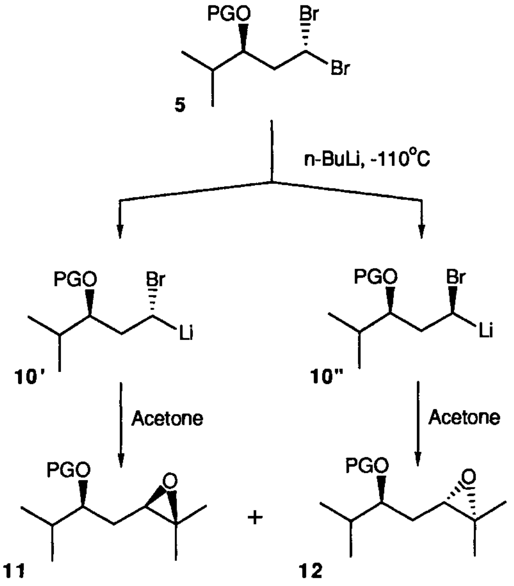
In order to evaluate simple steric effects in this system, the dibromo alkane **8** was synthesized from 3-methylbutanone by conversion into the enal **6** using the Meyers procedure[8], followed by hydrogenation and introduction of the bromine atoms[9].

Scheme 3



The α-bromoalkyllithium derivatives **10** were generated from the dibromoalkanes **5** under standard conditions (*n*-butyllithium, Trapp solvent mixture[10], −115 °C) and trapped by 2 equiv. of acetone in situ. The diastereomer ratios of the resulting epoxides **11** and **12** were determined either by gas chromatography or by ^{13}C-NMR spectroscopy. The results are compiled in Scheme 4.

Scheme 4



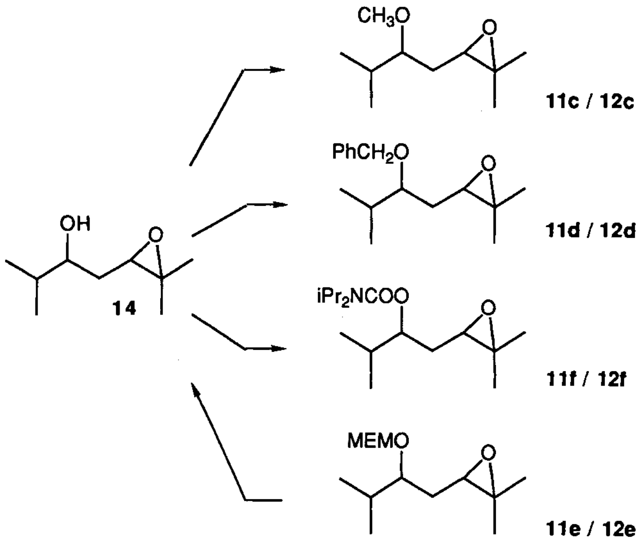
	PG[a]	Yield (%)	11:12
a	*i*Pr$_3$Si	82	(70:30)[b]
b	*t*BuMe$_2$Si	88	80:20[b]
c	CH$_3$	73	82:18[c]
d	PhCH$_2$	93	82:18[c]
e	CH$_3$OCH$_2$CH$_2$OCH$_2$	94	78:22[b]
f	*i*Pr$_2$NC(O)	63	41:59[b]

[a] PG: "protecting" group. — [b] Determined by GC. — [c] Determined by ^{13}C NMR.

Likewise, the dibromo compound **8** was converted into a mixture of the two epoxides **9** in 59% yield. The diastereomer ratio of **9** was determined by gas chromatography to be 69:31.

Of course, any discussion on the influence of the various protective groups on the extent of asymmetric induction in the exchange of the diastereotopic bromine atoms in **5** requires knowledge on the relative configuration of the products **11** and **12** formed. The structures of **11b** and **12b** had previously been correlated[3] with those of **3a** and **3b**. In view of the similar diastereoselectivities obtained in the reactions of **1**, **5a**, and **5b**, we are confident that also in this case **11a** is the predominant product diastereomer. The relative configuration of each of the diastereomeric alcohols **14** is known[3]. Therefore, we used an 80:20 mixture of (2'*R**,3*S**)- and (2'*R**,3*R**)-**14** as a basis to assign the structures of **11/12c**, **d** and **f**. Upon reaction of **14** with the various alkylating agents, the compounds **11/12c**, **d**, **f** were obtained with diastereomeric compositions similar to those of the alcohols **14** used. In the case of the MEM derivative **11/12e**, the diastereomeric epoxides obtained from **5e** were treated with ZnBr$_2$ to furnish the hydroxy epoxides **14**. In this manner, the relative configuration of most of the products was established, whereas attempts to reach a structural correlation for the epoxides **9** remained unsuccessful.

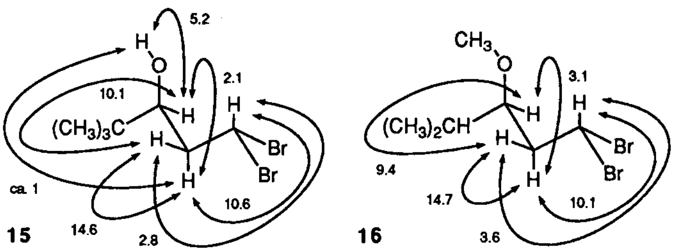
Scheme 5



Discussion

The aim of this study was to establish to what extent and in which manner the alkoxy groups in **5** differentiate the diastereotopic bromine atoms in the bromine/lithium exchange reaction. Whenever the origin of an asymmetric induction is discussed, ideally one would require knowledge of the conformation of the two diastereomeric transition states. This information is not available for the case at hand. Faute de mieux, one resorts to a discussion of the ground-state conformations of the substrates. All of the compounds **5** showed well-resolved coupling patterns in the ^{1}H-NMR spectra, cf. **16**. Even more diagnostic is the ^{1}H-NMR spectrum of **15**[2], the *tert*-butyl analogue of **4**. Here, a long-range coupling to the hydroxy proton differentiates the hydrogen atoms at C-2. Thus, it appears from all these spectra that the compounds **5** populate mainly the conformation **17**.

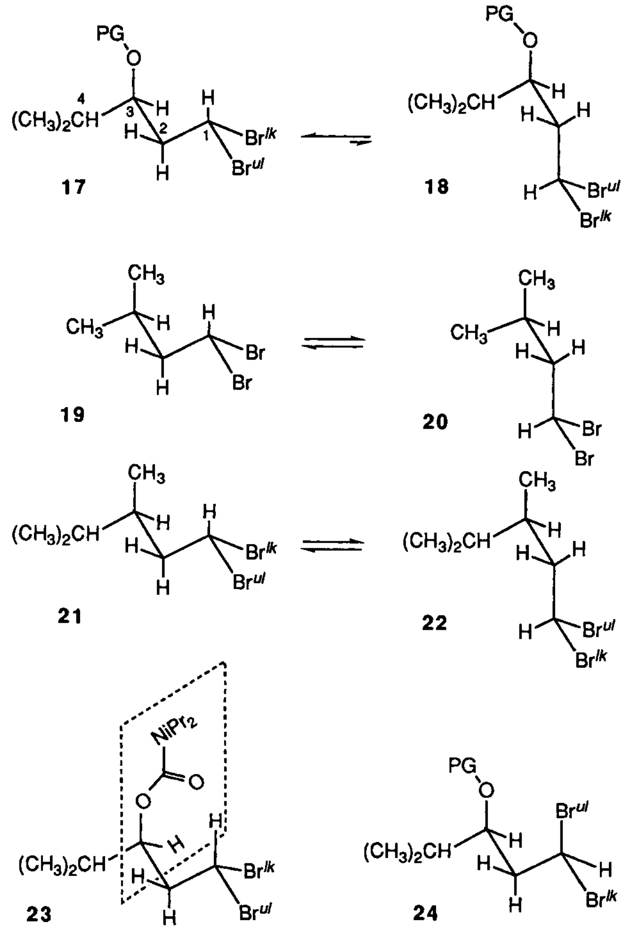
Scheme 6



These findings are in line with MM2 calculations carried out with the MACROMODEL program[11] for the methoxy compound **5c**. According to these calculations[12], the conformation **16** should be populated to 73% at room temperature and to 94% at −110°C.

It is in fact surprising that one conformation **17** should be populated to such a high extent, because **17** is just one of two conformations **17** and **18**, in which the g^+g^- interactions[13] between the substituents at C-1 and those at C-3 are avoided. In 1,1-dibromo-3-methylbutane the two conformations **19** and **20** are degenerate and, according to MM2 calculations, populated each to 49% at −110°C. A similar situation should prevail for **8**, in which steric effects alone should operate. MM2 calculations for **8** show a 56% population for **21** and 43% for **22** at −110°C. One notes, that in **21** it is the *ul*-bromine atom that is in the extended position, whereas in **22** it is the *lk*-bromine atom. Therefore, the low diastereoselectivity observed in the reaction of **8** is not surprising.

Scheme 7



The reason for the preference of the conformation **17** over **18** stems probably from the fact that an ether oxygen atom is "slimmer" than an alkyl (methyl) group, cf. the difference in the *A* values between methoxy (0.6 kcal/mol) and methyl (1.7 kcal/mol), which give the energy difference between the axial and equatorial arrangement of a substituent at a cyclohexane ring. Therefore, conformation **17** which has an oxygen atom/hydrogen atom 1,3-parallel arrangement[14] is favored over **18** with an alkyl group/hydrogen atom 1,3-parallel arrangement. It therefore appears that the only and decisive effect of the C-3 oxygen functionality in **5** is to stabilize the conformation **17**, in which the "*unlike*" bromine atom is in the extended position. On this basis the results of the diastereoselective bromine/lithium exchange reactions with **1**, **5a−e**, and **8** are most readily accounted for, if one assumes that (i) conformation **17** is not only the preferred ground-state conformation, but also the reactive conformation and (ii) that the sterically most accessible bromine atom in the extended position is preferentially attacked.

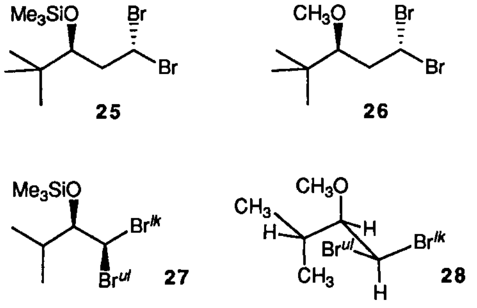
The only divergent result was obtained with the carbamoyloxy derivative **5f**. The carbamate function is one of the best coordinators for alkyllithium reagents[15]. Compound **5f** should likewise prefer conformation **17** which is redrawn as **23** giving the carbamoyloxy residue the typical conformation[16] of an ester of a secondary alcohol (cf. the plane indicated). Now the carbonyl group as the ligating position for the lithium ion points close to the *lk*-bromine atom. In this case the proximity effect may direct the butyllithium to this particular bromine atom without causing any additional strain.

One may ask why this does not hold for the MEM derivative **5e** as well. The C-3−OMEM bond is not confined to a single conformation. In fact the OMEM group should turn away from the bulky dibromoethyl group. Thus, there is no marked chance for the proximity effect to operate in the reaction of **5e**.

Of course, butyllithium should coordinate to the oxygen function of the ethers **5c** and **5d**. But if this occurs in conformation **17**, it is likely to be unproductive, as in the case of the MEM derivative **5e**, because the *lk*-bromine atom is not close enough. To bring one bromine atom, e.g. the *ul*-bromine atom, in proximity to the oxygen function, cf. **24**, would require ca. 2.4 kcal/mol of energy according to the MM2 calculations.

The considerations here should also be valid for the selective bromine/lithium exchange of other chiral 1,1-dibromoalkanes. The high asymmetric induction (94:6)[2] observed with **25** is in line with a high conformational bias as observed in the ^1H-NMR coupling constants of **25** and calculated for **26** (98% at −110°C). MM2 calculations for the dibromo compound **28** indicate that the conformer shown is populated to 87% at −110°C. This matches the selectivity of ca. 87:13[17] observed for the exchange of the *lk*-bromine atom in **27**. We do not want to imply that the conformer populations calculated by MM2 agree numerically with the observed diastereoselectivities. We believe, however, that these calculations reproduce the trends correctly.

Scheme 8



In an attempt to understand the asymmetric induction occuring in the reaction of the 3-alkoxy-1,1-dibromopentanes **5** with butyllithium we have found a qualitative correlation with the ground-state conformer populations of these compounds. The sense of the asymmetric induction is accounted for by postulating that the bromine atom in the extended position (i.e. not being impeded by *gauche* interactions) is exchanged with high preference.

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Experimental

All temperatures quoted are not corrected. — ^1H, ^{13}C NMR: Bruker AC-300 and WH-400. — Boiling range of petroleum ether: 40−60°C. — Column chromatography: Kieselgel 60 (0.063−0.200 mm, Merck, Darmstadt). — Flash chromatography: Kieselgel 60 (0.040−0.063 mm, Merck, Darmstadt). — Analytical gas chromatography: Siemens Sichromat 3 with a 30 m × 0.35 mm quartz capillary column with SE 52 (A) or a 30 m × 0.25 mm quartz capillary column with 0.25 μ Durabond 5 (J & W. Scientific Co., Folsom, California) (B).

1. *1,1-Dibromo-4-methyl-3-(triisopropylsilyloxy)pentane* (**5a**): To a solution of 1.95 g (7.5 mmol) of **4**[2] and 1.50 g (15 mmol) of triethylamine in 20 ml of anhydrous CH_2Cl_2 was added at 0°C 3.37 g (11 mmol) of triisopropylsilyl triflate[18]. After stirring for 12 h at room temperature, 50 ml of ether was added. The mixture was washed with 15 ml of 1 N hydrochloric acid. The aqueous phase was extracted twice with 20 ml each of ether, and the combined organic phases were washed with brine and dried with $MgSO_4$. Concentration in vacuo gave 3.30 g of an oily residue which was chromatographed on 50 g of silica gel with CH_2Cl_2; yield 2.80 g (90%) of **5a** as a yellowish oil. — ^1H NMR (300 MHz, $CDCl_3$): δ = 0.87 (d, J = 7.0 Hz, 3H), 0.93 (d, J = 6.9 Hz, 3H), 1.08 (s, 21H), 1.85−1.91 (m, 1H), 2.39−2.55 (m, 2H), 3.88 (dt, J = 8.4 and 3.3 Hz, 1H), 5.77 (dd, J = 9.3 and 4.4 Hz, 1H). — ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.0, 16.2, 18.0, 18.2, 18.3, 33.4, 44.3, 48.6, 75.4.

$C_{15}H_{32}Br_2OSi$ (416.3)	Calcd.	C 43.28	H 7.75
	Found	C 43.33	H 7.76

2. *1,1-Dibromo-3-methoxy-4-methylpentane* (**5c**): 1.73 g (15.3 mmol) of a 35% suspension of KH in white oil was digested twice with 20 ml each of anhydrous THF. The potassium hydride was taken up in 20 ml of anhydrous THF, 8.00 g (56.0 mmol) of iodomethane was added, and the mixture was cooled to 0°C. Upon addition of a solution of 3.60 g (13.9 mmol) of **4** in 3 ml of anhydrous THF a vigorous hydrogen evolution started. After stirring for 30 min at 0°C, 40 ml of saturated aqueous NH_4Cl solution was added very carefully. The mixture was extracted three times with 20 ml each of ether. The combined organic phases were washed with 40 ml of brine, dried with $MgSO_4$, and concentrated. The residue was purified by flash chromatography with petroleum ether/ether (100:1) to give 1.89 g (50%) of **5c** as a colorless liquid. — ^1H NMR (300 MHz, $CDCl_3$): δ = 0.82 (d, J = 6.9 Hz, 3H), 0.85 (d, J = 7.0 Hz, 3H), 1.93 (septd, J = 6.9 and 4.6 Hz, 1H), 2.32 (ddd, J = 14.7, 10.1, and 3.1 Hz, 1H), 2.41 (ddd, J = 14.7, 9.3, and 3.5 Hz, 1H), 3.16 (ddd, J = 9.4, 4.6, and 3.1 Hz, 1H), 3.32 (s, 3H), 5.76 (dd, J = 10.1 and 3.6 Hz, 1H). — ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.8, 18.1, 29.3, 44.1, 46.9, 58.0, 83.7.

$C_7H_{14}Br_2O$ (274.0)	Calcd.	C 30.69	H 5.15
	Found	C 30.65	H 5.21

3. *3-Benzyloxy-1,1-dibromo-4-methylpentane* (**5d**): 762 mg (6.60 mmol) of a 35% suspension of KH in white oil was treated as described under 2. and taken up in 20 ml of anhydrous dimethylformamide. Ca. 50 mg of tetrabutylammonium iodide and 4.10 g (24.0 mmol) of benzyl bromide were added. To the resulting suspension was added at 0°C a solution of 1.58 g (6.00 mmol) of **4** in 2 ml of anhydrous dimethylformamide. After stirring for 30 min at room temperature, 40 ml of saturated aqueous NH_4Cl solution was added very carefully, and the aqueous phase was extracted three times with 30 ml each of petroleum ether. The combined organic phases were washed with 30 ml of brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography using petroleum ether/ether (20:1) to give 1.64 g (78%) of **5d** as a colorless liquid. — ^1H NMR (300 MHz, $CDCl_3$): δ = 0.92 (d, J = 6.9 Hz, 3H), 0.92 (d, J = 7.0 Hz, 3H), 2.06 (septd, J = 6.9 and 4.4 Hz, 1H), 2.39 (ddd, J = 14.7, 10.6, and 2.7 Hz, 1H), 2.53 (ddd, J = 14.7, 9.8, and 3.2 Hz, 1H), 3.49 (ddd, J = 9.8, 4.4, and 2.7 Hz, 1H), 4.41 and 4.61 (AB system, J = 11.1 Hz, 2H), 5.78 (dd, J = 10.5 and 3.2 Hz, 1H), 7.20−7.40 (m, 5H). — ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.8, 18.3, 29.7, 44.3, 46.7, 72.3, 82.0, 127.77, 127.83, 128.5, 138.3.

$C_{13}H_{18}Br_2O$ (350.1)	Calcd.	C 44.60	H 5.18
	Found	C 44.81	H 5.20

4. *1,1-Dibromo-3-[(2-methoxyethoxy)methoxy]-4-methylpentane* (**5e**): To a solution of 5.20 g (20.0 mmol) of **4** in 30 ml of anhydrous CH_2Cl_2 were added at 0°C 2.74 g (22.0 mmol) of (2-methoxyethoxy)methyl chloride and 2.85 g (22.0 mmol) of ethyldiisopropylamine. The mixture was stirred for 12 h at room temperature and eventually refluxed for 5 d until TLC indicated the completion of the reaction. Aqueous 1 N hydrochloric acid was added until the mixture became slightly acidic. The phases were separated, and the aqueous phase was extracted three times with 30 ml each of CH_2Cl_2. The combined organic phases were washed with 20 ml of brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on 100 g of silica gel with CH_2Cl_2 to give 4.60 g (66%) of **5e** as a colorless liquid. — ^1H NMR (400 MHz, $CDCl_3$): δ = 0.88 (d, J = 6.8 Hz, 3H), 0.90 (d, J = 6.9 Hz, 3H), 1.94 (septd, J = 6.9 and 4.3 Hz, 1H), 2.33 (ddd, J = 15.0, 10.5, and 2.5 Hz, 1H), 2.50 (ddd, J = 15.0, 9.5, and 3.3 Hz, 1H), 3.39 (s, 3H), 3.52−3.58 (m, 3H), 3.64−3.76 (m, 2H), 4.73 (s, 2H), 5.89 (dd, J =

10.5 and 3.3 Hz, 1H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.9, 18.0, 30.8, 44.2, 47.2, 59.1, 67.6, 71.8, 81.5, 95.5.

$C_{10}H_{20}Br_2O_3$ (348.1) Calcd. C 34.51 H 5.79
Found C 34.57 H 5.81

5. *1,1-Dibromo-3-(N,N-diisopropylcarbamoyloxy)-4-methylpentane* (**5f**): A mixture containing 2.6 g (10 mmol) of **4**, 1.8 g (11 mmol) of *N,N*-diisopropylcarbamoyl chloride, and 1.5 ml (11 mmol) of triethylamine was stirred for 6 d at 40°C. 10 ml of saturated aqueous NH_4Cl solution was added and the mixture extracted 5 times with 10 ml each of ether. The combined organic phases were dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography using petroleum ether/ether (10:1) to give 1.8 g (46%) of **5f** as a colorless liquid. 0.9 g (35%) of **4** was recovered next to 0.4 g (20%) of 1-bromo-3-hydroxy-4-methyl-1-pentene.

5f: ^1H NMR (300 MHz, $CDCl_3$): δ = 0.89 (d, *J* = 6.9 Hz, 6H), 1.15 (d, *J* = 6.8 Hz, 6H), 1.16 (d, *J* = 6.8 Hz, 6H), 1.88 (septd, *J* = 6.8 and 4.7 Hz, 1H), 2.55 (ddd, *J* = 15.1, 9.6, and 3.0 Hz, 1H), 2.65 (ddd, *J* = 15.1, 8.8, and 4.0 Hz, 1H), 3.75 (br. s, 1H), 3.94 (br. s, 1H), 4.82 (ddd, *J* = 8.7, 4.7, and 3.0 Hz, 1H), 5.64 (ddd, *J* = 9.6 and 4.0 Hz, 1H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.7, 18.1, 20.7, 21.4, 31.8, 42.3, 45.6, 48.1, 76.6, 155.0.

$C_{13}H_{25}Br_2NO_2$ (387.2) Calcd. C 40.33 H 6.51 N 3.62
Found C 40.35 H 6.46 N 3.54

6. *3,4-Dimethyl-2-pentenal* (**6**): Into a solution of 20.2 g (0.20 mol) of anhydrous diisopropylamine in 250 ml of anhydrous THF was added over 30 min at −10°C 140 ml (204 mmol) of a 1.46 M solution of *n*-butyllithium in hexane. The mixture was cooled to −78°C, and 9.92 g (0.10 mol) of *N-tert*-butylethylideneamine[19] was added dropwise. After stirring for 30 min at −78°C, 17.3 g (0.10 mol) of freshly distilled diethyl chlorophosphate were added. After stirring for 2 h at −78°C, the mixture was brought to −10°C and recooled to −78°C. 6.03 g (70.0 mmol) of 3-methylbutanone was added, and the mixture was stirred for 1 h at −78°C. After reaching room temperature, 200 ml of a 1 N aqueous solution of oxalic acid was added. After stirring for 12 h, the phases were separated, and the aqueous phase was extracted 6 times with 200 ml each of ether. The combinded organic phases were washed with 200 ml of 5% aqueous oxalic acid, 200 ml of 15% aqueous K_2CO_3 solution, and 200 ml of brine. The organic phases were dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by chromatography on silica gel with petroleum ether/ether (6:1) to give 2.94 g (37%) of **6** as a slightly yellowish liquid. The product was obtained as a (*E*)/(*Z*) mixture (85:15).

(*E*)-**6**: ^1H NMR (300 MHz, $CDCl_3$): δ = 1.06 (d, *J* = 6.8 Hz, 6H), 2.11 (d, *J* = 1.1 Hz, 3H), 2.37 (sept, *J* = 6.8 Hz, 1H), 5.85 (dd, *J* = 8.0 and 0.9 Hz, 1H), 9.98 (d, *J* = 8.0 Hz, 1H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.6, 37.8, 125.3, 169.3, 191.7.

(*Z*)-**6**: ^1H NMR (300 MHz, $CDCl_3$): δ = 1.09 (d, *J* = 6.9 Hz, 6H), 1.85 (d, *J* = 1.5 Hz, 3H), 3.59 (sept, *J* = 6.9 Hz, 1H), 5.75 (br. d, *J* = 8.3 Hz, 1H), 10.01 (d, *J* = 8.5 Hz, 1H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.0, 37.8, 127.5 169.3, 189.9. These data correspond to those given in ref.[20].

7. *3,4-Dimethylpentanal* (**7**): A solution of 1.19 g (10.6 mmol) of **6** in 10 ml of anhydrous methanol was hydrogenated over ca. 50 mg of 10% Pd on C. When the hydrogen uptake had ceased, the mixture was filtered and concentrated by distillation. The residue was purified by flash chromatography using petroleum ether/ether (4:1) to give 0.66 g of a colorless liquid, which turned out to be 1,1-dimethoxy-3,4-dimethylpentane. – ^1H NMR (300 MHz, $CDCl_3$): δ = 0.79 (d, *J* = 6.6 Hz, 3H), 0.81 (d, *J* = 6.0 Hz, 3H), 0.83 (d, *J* = 6.0 Hz, 3H), 1.22–1.70 (m, 4H), 3.27 (s, 3H), 3.29 (s, 3H), 4.42 (dd, *J* = 7.2 and 4.5 Hz, 1H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.5, 18.0, 19.8, 32.4, 34.4, 36.6, 52.0, 52.8, 103.6.

$C_9H_{20}O_2$ (160.3) Calcd. C 67.45 H 12.58
Found C 67.67 H 12.50

The obtained acetal was dissolved in 4 ml of THF and stirred with 2 ml of 2 N aqueous hydrochloric acid. The aqueous phase was separated and extracted twice with 10 ml of ether. The combined organic phases were dried with $MgSO_4$ and concentrated in vacuo. The crude product was used without further purification.

8. *1,1-Dibromo-3,4-dimethylpentane* (**8**): To a solution of 3.72 g (12.0 mmol) of triphenyl phosphite in 6 ml of anhydrous CH_2Cl_2 was added over 30 min 1.92 g (12 mmol) of bromine. The mixture was cooled to −15°C, and a solution of 0.98 g (8.40 mmol) of the crude **7** in 1.5 ml of CH_2Cl_2 was added over 1 h. After warming to 0°C, 1.5 g of basic alumina was added. The mixture was filtered through a pad of 5 g of basic alumina which was eluted with 60 ml of petroleum ether. The combined filtrates were concentrated to give a reddish oil from which phenol crystallized. The mixture was separated by flash chromatography using petroleum ether to give 0.36 g (17%) of **8** as a colorless oil. – ^1H NMR (300 MHz, $CDCl_3$): δ = 0.80 (d, *J* = 6.7 Hz, 3H), 0.81 (d, *J* = 6.7 Hz, 3H), 0.85 (d, *J* = 6.7 Hz, 3H), 1.58 (septd, *J* = 6.7 and 4.3 Hz, 1H), 1.54–1.68 (m, 1H), 2.14 (ddd, *J* = 14.5, 8.7, and 5.0 Hz, 1H), 2.41 (ddd, *J* = 14.5, 9.3, and 4.5 Hz, 1H), 5.66 (dd, *J* = 9.3 and 5.0 Hz, 1H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.4, 18.0, 19.8, 31.5, 37.9, 45.5, 50.2.

$C_7H_{14}Br_2$ (258.0) Calcd. C 32.59 H 5.47
Found C 32.70 H 5.44

9. *3-[3-Methyl-2-(triisopropylsilyloxy)butyl]-2,2-dimethyloxirane* (**11a**/**12a**): 830 mg (2.00 mmol) of **5a** was dissolved in a mixture of 12 ml of anhydrous THF, 6 ml of petroleum ether, 5 ml of anhydrous ether, and 230 mg (4.00 mmol) of acetone. After cooling to −110°C, 1.40 ml (2.20 mmol) of a 1.55 M solution of *n*-butyllithium in *n*-hexane was slowly added along the wall of the vessel. After stirring for 1 h at −110°C, the mixture was allowed to reach room temperature. 50 ml of saturated aqueous NH_4Cl solution was added. The phases were separated, and the aqueous phase was extracted three times with 30 ml each of ether. The combined organic phases were washed with 10 ml of brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography with 4% ether in petroleum ether to give 520 mg (82%) of a colorless oil. GC (column A; 180°C) showed this to be a 7:3 diastereomer mixture.

Major diastereomer: ^1H NMR (300 MHz, $CDCl_3$): δ = 0.89 (d, *J* = 6.8 Hz, 3H), 0.95 (d, *J* = 7.0 Hz, 3H), 1.08 (s, 21H), 1.26 (s, 3H), 1.31 (s, 3H), 1.62–1.88 (m, 3H), 2.90 (m, 1H), 3.86 (br. dt, 1H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.9, 17.6, 17.7, 18.3, 18.8, 24.8, 32.7, 33.4, 55.1, 61.8, 75.3.

$C_{18}H_{38}O_2Si$ (314.6) Calcd. C 68.72 H 12.18
Found C 68.50 H 12.12

10. *3-[2-Methoxy-3-methylbutyl]-2,2-dimethyloxirane* (**11c**/**12c**): 411 mg (1.50 mmol) of **5c** was allowed to react as described under 9. to give 197 mg (73%) of **11c**/**12c** as a colorless liquid. The diastereomer ratio was determined to be 82:18 (^{13}C NMR).

Major diastereomer (2′*S**,3*R**): ^1H NMR (300 MHz, $CDCl_3$): δ = 0.85 (d, *J* = 6.8 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 3H), 1.21 (s, 3H), 1.26 (s, 3H), 1.60–1.76 (m, 2H), 1.84 (septd, *J* = 6.8 and 5.7 Hz, 1H), 2.80 (t, *J* = 6.1 Hz, 1H), 2.98 (dt, *J* = 6.6 and 5.3 Hz, 1H), 3.31 (s, 3H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.0, 18.1, 18.8, 24.8, 29.8, 30.8, 57.6, 58.1, 61.8, 84.8.

Minor diastereomer (2′*S**,3*S**): ^1H NMR (300 MHz, $CDCl_3$): δ = 0.83 (d, *J* = 6.8 Hz, 3H), 0.84 (d, *J* = 6.8 Hz, 3H), 1.21 (s, 3H), 1.26 (s, 3H), 1.40–1.52 (m, 2H), 1.84 (septd, J = 6.8 and 5.7 Hz, 1H), 2.84 (dd, J = 7.1 and 4.7 Hz, 1H), 3.09 (ddd, J = 9.0, 4.7, and 3.6 Hz, 1H), 3.34 (s, 3H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.5, 18.0, 19.0, 24.8, 30.2, 30.8, 57.8, 58.6, 82.2, 83.9.

$C_{10}H_{20}O_2$ (172.3) Calcd. C 69.72 H 11.70
Found C 69.90 H 11.80

0.26 g (1.60 mmol) of a 77:23 mixture of (2'S*,3R*)/(2'S*,3S*)-**14** was methylated with 1.13 g (8.00 mmol) of iodomethane as described under 3. This resulted in 0.19 g (69%) of a **11c**/**12c** mixture, which showed identical NMR data as the material obtained above.

11. *3-(2-Benzyloxy-3-methylbutyl)-2,2-dimethyloxirane* (**11d**/**12d**): 501 mg (1.40 mmol) of **5d** was allowed to react as described under 9. to give 325 mg (93%) of **11d**/**12d**. The diastereomer ratio was determined to be 82:18 (^{13}C NMR).

Major diastereomer (2'S*,3R*): ^1H NMR (300 MHz, $CDCl_3$): δ = 0.92 (d, J = 6.8 Hz, 6H), 1.22 (s, 3H), 1.24 (s, 3H), 1.62–1.86 (ABXY system, J = 14.6, 6.5, 6.0 and 4.6 Hz, 2H), 1.96 (septd, J = 6.7 and 5.7 Hz, 1H), 2.86 (t, J = 6.0 Hz, 1H), 3.28 (td, J = 7.0 and 5.0 Hz, 1H), 4.52 (m, 2H), 7.20–7.40 (m, 5H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.0, 18.3, 18.8, 24.8, 30.0, 31.0, 57.8, 61.7, 71.5, 82.4, 127.4, 127.6, 128.3, 138.8.

Minor diastereomer (2'S*,3S*): ^1H NMR (300 MHz, $CDCl_3$): δ = 0.91 (d, J = 6.7 Hz, 6H), 1.23 (s, 3H), 1.27 (s, 3H), 1.50–1.62 (m, 2H), 1.96 (m, 1H), 2.88 (t, J = 6.4 Hz, 1H), 3.41 (ddd, J = 8.6, 4.3 and 3.7 Hz, 1H), 4.52 (m, 2H), 7.20–7.40 (m, 5H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.6, 18.1, 19.0, 24.8, 30.2, 31.0, 59.2, 62.3, 72.2, 82.0, 127.4, 127.6, 127.7, 138.9.

$C_{16}H_{24}O_2$ (248.4) Calcd. C 77.37 H 9.74
Found C 77.18 H 9.54

0.48 g (3.00 mmol) of a 77:23 mixture of (2'S*,3R*)/(2'S*,3S*)-**14** was benzylated with 2.05 g (12.0 mmol) of benzyl bromide as described under 3. This resulted in 0.59 g (80%) of a **11d**/**12d** mixture, which showed identical NMR data as the material obtained above.

12. *3-[2-(2-Methoxyethoxy)methoxy-3-methylbutyl]-2,2-dimethyloxirane* (**11e**/**12e**): 1.05 g (3.00 mmol) of **5e** was allowed to react as described under 9. to give 0.70 g (94%) of **11e**/**12e**. The diastereomer ratio was determined by gas chromatography (column B; 150°C) to be 78:22.

Major diastereomer (2'S*,3R*): ^1H NMR (300 MHz, $CDCl_3$): δ = 0.92 (d, J = 6.8 Hz, 3H), 0.93 (d, J = 6.7 Hz, 3H), 1.27 (s, 3H), 1.32 (s, 3H), 1.61–1.81 (m, 2H), 1.89–2.0 (m, 1H), 2.88 (t, J = 5.9 Hz, 1H), 3.39 (s, 3H), 3.53–3.64 (m, 2H), 3.69–3.82 (m, 3H), 4.78 (s, 2H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.8, 18.3, 18.9, 24.8, 30.2, 31.2, 57.7, 59.1, 61.8, 67.2, 71.8, 80.9, 94.7.

Minor diastereomer (2'S*,3S*): ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.3, 17.8, 20.4, 24.9, 30.2, 31.3, 58.4, 59.0, 61.9, 67.2, 71.8, 80.4, 95.1.

$C_{13}H_{26}O_4$ (246.4) Calcd. C 63.38 H 10.64
Found C 63.44 H 10.67

13. *3-[2-(N,N-Diisopropylcarbamoyloxy)-3-methylbutyl]-2,2-dimethyloxirane* (**11f**/**12f**): 387 mg (1.00 mmol) of **5f** was allowed to react as described under 9. to give 180 mg (63%) of **11f**/**12f**. The diastereomer ratio was determined by GC (column A; 100°C + 2°C/min) to be 41:59.

Major diastereomer (2'S*,3S*): ^1H NMR (300 MHz, $CDCl_3$): δ = 0.88 (d, J = 6.8 Hz, 6H), 1.16 (d, J = 6.8 Hz, 12H), 1.22 (s, 3H), 1.23 (s, 3H), 1.68–1.92 (m, 3H), 2.73 (t, J = 4.0 Hz, 1H), 3.85 (br. s, 2H), 4.84 (ddd, J = 8.1, 5.0, and 4.7 Hz, 1H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.3, 18.5, 18.7, 20.6, 24.5, 31.1, 31.6, 45.5, 58.2, 61.9, 76.2, 154.9.

Minor diastereomer (2'S*,3R*): ^1H NMR (300 MHz, $CDCl_3$): δ = 0.88 (d, J = 6.8 Hz, 6H), 1.16 (d, J = 6.8 Hz, 12H), 1.22 (s, 3H), 1.23 (s, 3H), 1.63 (ddd, J = 14.6, 6.8, and 3.8 Hz, 1H), 1.81–1.92 (m, 2H), 2.73 (dd, J = 6.7 and 5.5 Hz, 1H), 3.79 (br. s, 1H), 3.94 (br. s, 1H), 4.77 (ddd, J = 8.7, 5.9, and 3.7 Hz, 1H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 18.1, 18.3, 23.1, 26.4, 29.0, 30.9, 43.5, 57.8, 61.2, 77.3, 154.9.

$C_{16}H_{31}NO_3$ (285.4) Calcd. C 67.33 H 10.95 N 4.91
Found C 67.55 H 10.84 N 4.92

0.50 g (3.20 mmol) of a 85:15 mixture of (2'S*,3R*)/(2'S*,3S*)-**14** was treated with 0.65 g (4.00 mmol) of *N,N*-diisopropylcarbamoyl chloride as described under 5. This resulted in a 85:15 mixture of **11f**/**12f**, which showed identical NMR data as the material obtained above.

14. *3-(2,3-Dimethylbutyl)-2,2-dimethyloxirane* (**9**): 305 mg (1.20 mmol) of **8** was allowed to react as described under 9. to give 109 mg (59%) of **9** as a colorless oil. The diastereomer ratio was determined by GC (column A; 60°C) to be 69:31.

Major diastereomer: ^1H NMR (300 MHz, $CDCl_3$): δ = 0.78 (d, J = 6.8 Hz, 3H), 0.83 (d, J = 6.7 Hz, 3H), 0.85 (d, J = 6.7 Hz, 3H), 1.21 (s, 3H), 1.24 (s, 3H), 1.40–1.64 (m, 4H), 2.69 (t, J = 6.0 Hz, 1H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.9, 18.3, 18.8, 20.0, 24.9, 32.1, 33.1, 37.6, 57.6, 63.9.

Minor diastereomer: ^1H NMR (300 MHz, $CDCl_3$): δ = 0.79 (d, J = 6.6 Hz, 3H), 0.83 (d, J = 6.7 Hz, 3H), 0.85 (d, J = 6.7 Hz, 3H), 1.21 (s, 3H), 1.25 (s, 3H), 1.40–1.64 (m, 4H), 2.68 (t, J = 5.9 Hz, 1H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.4, 18.2, 19.0, 19.9, 24.8, 32.4, 32.8, 36.6, 58.4, 63.9.

$C_{10}H_{20}O$ (156.3) Calcd. C 76.86 H 12.90
Found C 76.64 H 12.91

15. *3-(2-Hydroxy-3-methylbutyl)-2,2-dimethyloxirane* (**14**): 0.40 g (1.62 mmol) of a 78:22 mixture of **11e**/**12e** was dissolved in 5 ml of CH_2Cl_2 and treated with 14.8 ml (4.87 mmol) of a 0.33 M solution of $ZnBr_2$ in ether. After stirring for 1 h, the mixture was washed with 10 ml of saturated aqueous $NaHCO_3$ solution. The aqueous phase was extracted three times with 50 ml of ether, and the combined organic phases were dried with $MgSO_4$ and concentrated. Flash chromatography with petroleum ether/ether (1:1) furnished 0.17 g (66%) of **14** as a 75:25 mixture of the (2'S*,3R*) and (2'S*,3S*) isomers identified by GC (column B; 120°C) and the NMR-spectroscopic data.

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4: 142321-70-8 / **5a**: 142321-52-6 / **5b**: 142362-45-6 / **5c**: 142321-53-7 / **5d**: 142362-46-7 / **5e**: 142321-54-8 / **5f**: 142321-55-9 / (*E*)-**6**: 118495-23-1 / (*Z*)-**6**: 129872-09-9 / **7**: 19353-21-0 / **8**: 142321-67-3 / **9** (isomer 1): 142321-68-4 / **9** (isomer 2): 142321-69-5 / **11a**: 142321-56-0 / **11b**: 132047-63-3 / **11c**: 142321-58-2 / **11d**: 142321-60-6 / **11e**: 142321-62-8 / **11f**: 142321-64-0 / **12a**: 142321-57-1 / **12b**: 132047-62-2 / **12c**: 142321-59-3 / **12d**: 142321-61-7 / **12e**: 142321-63-9 / **12f**: 142321-65-1 / **14** (isomer 1): 132047-65-5 / **14** (isomer 2): 132047-64-4 / 1,1-dimethoxy-3,4-dimethylpentane: 142321-66-2 / 3-methylbutanone: 563-80-4