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Stereoselective Exchange of Diastereotopic Iodine Atoms by Magnesium in 3-Alkoxy-1,1-diiodoalkanes

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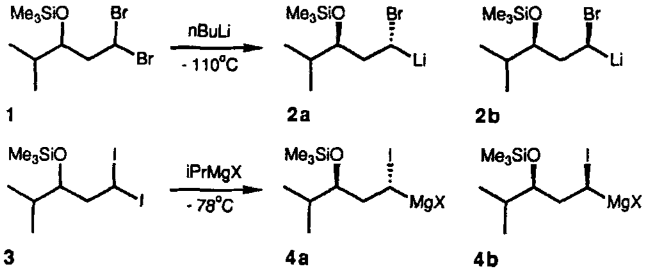
α-Iodoalkylmagnesium species were generated by reaction of 3-oxygenated 1,1-diiodoalkanes with isopropylmagnesium halides at −78°C. The resulting magnesium carbenoids were found to be configurationally stable at temperatures up to −20°C and were trapped by benzaldehyde or allyl iodide at low temperatures. Stereoselectivity on exchange of the diastereotopic iodine atoms in **3** was found to be low.

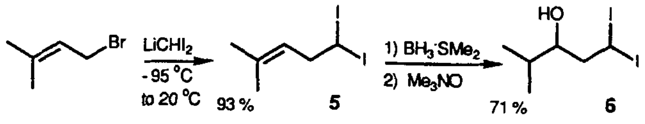
We have studied the bromine/lithium exchange reaction with the dibromo compounds **1**, a reaction in which one of the diastereotopic bromine atoms is exchanged with selectivities up to 85:15[2,3]. Due to the thermal instability of the carbenoids **2** generation and reactions had to be performed at temperatures below −100°C. Carbenoids involving metals other than lithium, e.g. magnesium[4] or zinc[5], have a substantial higher thermal stability[6] and would allow reactions to be carried out at more convenient temperatures.

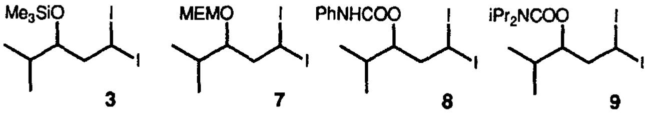


The facile generation of magnesium carbenoids by treatment of geminal diiodoalkanes or related iodoalkanes with isopropylmagnesium halides[4,7,8] suggested an investigation of the generation of the magnesium carbenoids **4** from the diiodo compound **3**. The results reported below give information on the diastereoselectivity in the iodine/magnesium exchange on **3** as well as on the thermal and configurational stability of the magnesium carbenoids **4**.

Starting Materials

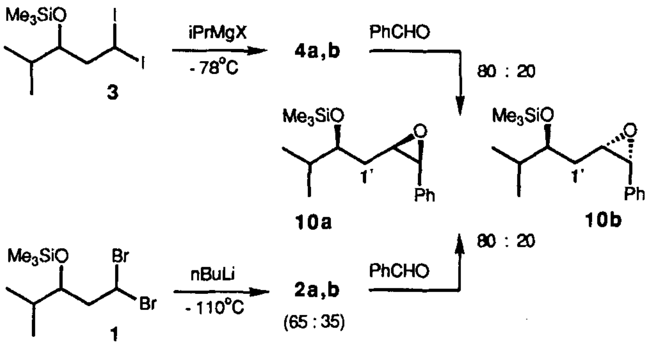
The preparation of the diiodo compound **3** followed the pathway used in the synthesis of the analogous dibromo compound **1**[2]. Thus, diiodomethyllithium was alkylated[9] with prenyl bromide. Hydroboration and oxidation of the resulting 1,1-diiodoalkene **5** furnished the alcohol **6**. The latter was converted by standard transformations into the silylated starting material **3** as well as into compounds **7**−**9** carrying other protective groups on oxygen.





Diastereoselective Iodine/Magnesium Exchange Reaction

In initial experiments the magnesium carbenoids **4** were generated from the diiodo compound **3** by reaction with 1.5 equivalents of isopropylmagnesium bromide in THF at −78°C (45 min). Subsequent addition of benzaldehyde and warming to −18°C resulted in 70% of a 4:1 mixture of the epoxides **10**.



The compounds **10** were both assigned to contain a *cis*-disubstituted oxirane moiety, because both showed the ^{13}C-

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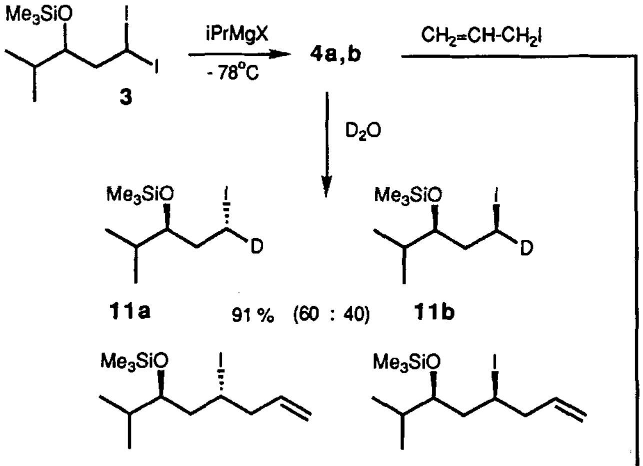
NMR signal of C-1′ at high field (δ = 33). This preference for the formation of a *cis* epoxide demonstrates a high simple diastereoselectivity on addition of the magnesium carbenoid **4** to benzaldehyde. This is an advantageous feature found in several instances using α-hetero-substituted alkylmagnesium reagents[10].

In order to assign the relative configuration of the racemic adducts **10a** and **10b** we took a roundabout way: A 65:35 mixture of the lithium carbenoids **2a** and **2b** of known relative configuration[2] was generated from the dibromo compound **1**. Subsequent addition of benzaldehyde resulted in the two oxiranes **10a** and **10b** in a 4:1 ratio in 76% yield. The major isomer should have the structure **10a** and is identical with the major isomer resulting from the diiodo compound **3**. Thus, the iodine/magnesium exchange reaction on **3** follows the same stereochemical preference as the bromine/lithium exchange on **1**.

In the latter experiment the diastereomer ratio of the epoxides **10** was higher than the diasteromer ratio of the carbenoids **2**. Probably, the two diastereomeric carbenoids **2** react at unequal rate. The faster reacting one, **2a**, reacted (close to) completely, whereas reaction of the slower reacting one, **2b**, remained incomplete. We were also surprised to find only two *cis* epoxides **10a** and **10b** instead of four epoxides which were obtained by reaction of the carbenoids **2** with several aliphatic aldehydes[2]. The reasons for this unexpected high simple diastereoselectivity on addition of the lithium carbenoids **2** to benzaldehyde are not known.

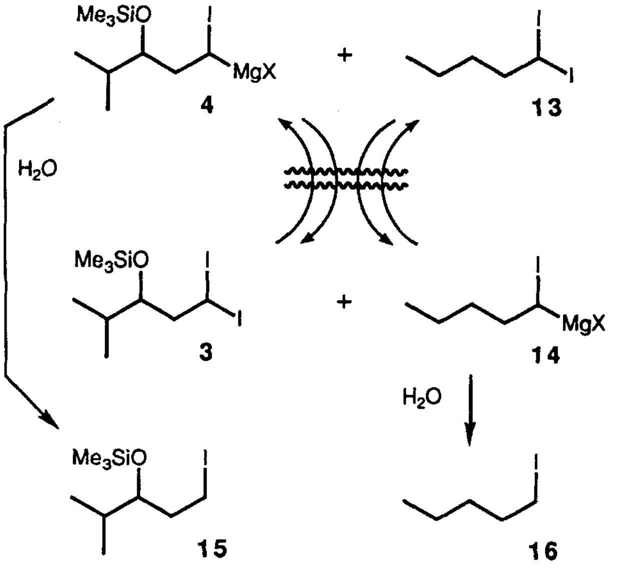
Coming back to the magnesium carbenoids **4**, we tested other electrophilic trapping reagents which would react at low (<−20°C) temperatures. For instances, deuteriolysis and the well-known[8,9,11] allylation with allyl iodide could be realized. However, we were dismayed by the low reactivity of **4** which resisted addition to carbon dioxide, (trimethylsilyl)imidazole, methyl chloroformate, or trimethyltin chloride under these conditions.



The diastereomer ratio of the products **11** or **12** could be determined by ^{1}H-, ^{2}H-, or ^{13}C-NMR spectroscopy in the case of **12**. The relative configuration of the diastereomeric products **11** and **12** was not assigned. Retention of configuration may be assumed for the deuteriolysis of the carbon-magnesium bond. However, there is no precedent for the stereochemical course of the allylation reaction (retention?). The diastereomer ratios of **11** and **12** agreed well with each other, but were lower than the value obtained on trapping of **4** with benzaldehyde (80:20). A dependence of the product ratio on the trapping agent would result when the two magnesium carbenoids interconvert rapidly, i.e. more rapidly than they are being trapped by the electrophiles[12,13]. However, experiments described below render this explanation unlikely. Rather, we feel that as in the reaction of **2** diastereomer resolution occurred on incomplete reaction of **4** with benzaldehyde.

Mechanistic Aspects

The manner in which the diastereomeric magnesium carbenoids **4** may be applied in stereoselective synthesis depends on whether their ratio is kinetically controlled[14] or thermodynamically controlled[13]. In other words, information is required as to whether the carbenoids **4** have equilibrated under the conditions of their generation prior to being trapped by electrophiles or not. In the case of the lithium carbenoids **2** partial equilibration can occur by lithium exchange between the carbenoids **2** and the starting material **1**[14]. We therefore wanted to see, whether a similar iodine/magnesium exchange is possible between the magnesium carbenoids **4** and a diiodoalkane. For this reason we carried out the following cross-over experiments, cf. ref.[1].



One equivalent of the diiodo compound **3** was treated with 1.3 equivalents of isopropylmagnesium chloride to generate the magnesium carbenoids **4**. In an attempt to destroy the small excess of isopropylmagnesium chloride, carbon dioxide was bubbled through the reaction mixture at −78°C. Then, 1,1-diiodopentane (**13**) was added, and after stirring for 15 min at −78°C the mixture was hydrolyzed. Gas chromatography of the products revealed the presence of equivalent amounts of **15** and **13**. Significantly, the diiodo compound **3** was absent. A small amount of 1-iodopentane (**16**) could be detected. This arises probably from the reaction of the diiodopentane **13** with the residual isopropylmagnesium chloride to give **14** followed by hydrolysis. A second cross-over experiment was carried out in the same manner by starting with 1,1-diiodopentane (**13**) which was transformed to the carbenoid **14**. After addition of the diiodo compound **3** and stirring for 15 min quenching resulted in a mixture of **3** and **16**. Significantly, **13** was absent, and again a small amount of the second monoiodo compound **15** could be detected.

From these experiments it may be concluded that interconversion of the magnesium carbenoids such as **4** or **14** with diiodo compounds such as **3** or **13** is slow at −78°C and does not have to be considered further as a potential source of a diastereomer equilibration of **4a** with **4b**.

Diastereomer equilibration of **4** could also occur by direct epimerization of the metal-bearing stereogenic center. While the configurational stability of secondary alkylmagnesium reagents at 0°C[12,15] suggests that the magnesium carbenoids **4** might possess similar configurational stability, this is by no means established. For this reason we investigated the thermal lability of the magnesium carbenoids **4**: The intermediates **4** were generated as before at −78°C in THF. The temperature of the solution was then allowed to reach −20 or 0°C whereupon the reaction was quenched by addition of D_2O in THF. The diastereomer ratio of the isotopomers **11** was analyzed by ^{1}H- or ^{2}D-NMR spectrometry. The results are collected in Table 1.

Table 1. Temperature effects on the diastereomer ratio of the magnesium carbenoids **4** as taken from the ratio of the trapping products **11**

Maximal temp. [°C]	Yield of **11** (%)	Diastereomer ratio of **11**
−78	91	60:40
−20	83	60:40
0	75	50:50
0[a]	74	50:50

[a] Quenching at −78°C.

The data show that a change in the diastereomer ratio resulted when the temperature exceeded −20°C. This change could not be reverted by cooling the mixture to −78°C before quenching. This change therefore reflects an equilibration of the α-iodoalkyl-magnesium halides above −20°C to a 1:1 diastereomer ratio. In turn, the diastereomer ratio obtained in reactions carried out a low temperatures should be kinetically controlled and reflect the diastereoselectivity in the exchange of the diastereotopic iodine atoms of **3**. Unfortunately, this diastereoselectivity is small and is, moreover, smaller than the one recorded for the bromine/lithium exchange in the corresponding 1,1-dibromo compound **1**[2].

Influence of Magnesium Reagent, Solvent, Temperature, and Protecting Groups on the Diastereoselectivity

While the diastereoselectivity in the exchange of the diastereotopic iodine atoms of **3** was found to be low, there was a chance to improve this by a change of the magnesium reagent, the solvent, or the reaction temperature. A series of experiments are summarized in Table 2.

Table 2. Diastereoselective iodine/magnesium exchange on 1,1-diiodo-4-methyl-3-(trimethylsilyloxy)pentane (**3**), effects of solvent, magnesium species and temperature

Entry	Magnesium reagent	Temp. [°C]	Solvent	Addition mode [b]	Diastereomer ratio on quenching with D_2O **11a** : **11b** (Yield in %)	allyliodide **12a** :**12b** (Yield in %)
1	EtMgBr	-78	THF	N	60 : 40 (78)	---
2	*i*PrMgCl	-78	THF	N	60 : 40 (91)	---
3	*i*PrMgBr	-78	THF	N	60 : 40 (91)	---
4	*i*PrOPiv[a]	-78	THF	I	65 : 35 (84)	---
5	$(i\text{Pr})_2$Mg	-78	THF	N	67 : 33 (83)	---
6	$(i\text{Pr})_2$Mg	-78	THF	I	67 : 33 (85)	---
7	$(i\text{Pr})_2$Mg	-78	Et_2O	I	75 : 25 (86)	---
8	$(i\text{Pr})_2$Mg	-78	Toluene	I	75 : 25 (84)	---
9	*i*PrMgCl	-78	Toluene	N	63 : 37 (78)	---
10	*i*PrMgCl	-110	Toluene/Ethylbenzene/THF, (64:32:4)	N	67 : 33 (76)	---
11	*i*PrMgCl	-110	MeO*t*Bu/THF (95:5)	N	70 : 30 (86)	---
12	*i*PrMgOPiv[a]	-110	MeTHF	I	75 : 25 (40)	---
13	$(i\text{Pr})_2$Mg	-110	MeTHF	I	78 : 22 (59)	---
14	*i*PrMgBr	-78	Toluene	N	---	74 : 26 (77)
15	*i*PrMgBr	-78	THF	N	---	62 : 38 (81)
16	*i*PrMgBr	-110	Toluene/petroleum ether/MeTHF (2:2:1)	N	---	69 : 31 (78)

[a] Piv = $(CH_3)_3C{-}CO$. – [b] N = RMgX added to **3**; I = **3** added to RMgX.

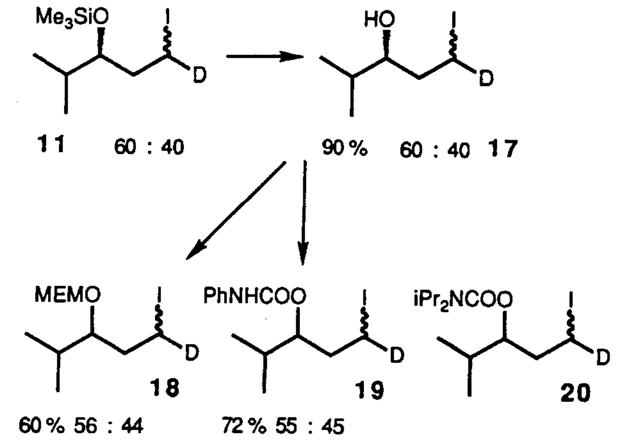
The results allow the following statements to be made: No significant change in diastereoselectivity is observed on variation of the magnesium reagents (entries 1−5), on going from the normal addition mode to the inverse addition mode (entries 5, 6). Changing to less basic solvents such as diethyl ether, methyl-THF or *tert*-butyl methyl ether as well as lowering the temperature leads to a small increase in the diastereoselectivity. Several reactions performed in toluene as a solvent gave no consistent picture. The changes are, however, too small to warrant any further discussion.

While these simple variations did not lead to higher diastereoselectivities, perhaps a change of the oxygen-protecting group could be beneficial. The compounds **7**−**9** were chosen, because the MEM and the carbamoyl protecting groups offer good chances to coordinate the incoming magnesium reagents. The results obtained with **7**−**9** are compiled in Table 3.

Table 3. Diastereoselective iodine/magnesium exchange on 1,1-diiodo-4-methyl-3-pentanol derivatives, influence of the protective group (reaction performed with *i*PrMgBr in THF at −78°C, quenching by D_2O)

Starting material	Protective group	Product	Yield (%)	Diastereomer ratio
3	$SiMe_3$	**5**	91	60:40
7	MEM	**18**	97	29:71
8	CONHPh	**19**	86	39:61
9	$CON(i\text{Pr})_2$	**20**	86	47:53

In order to correlate the diastereomer ratios of pairs of the isotopomeric products within the different experiments



each of **11**, **18**, and **19**, the silyl ethers **11** were cleaved to give the alcohols **17**. The latter were converted to the MEM ethers **18** or to the *N*-phenylcarbamates **19**. All compounds should have the same isotopomer ratio. The differences recorded reflect inaccuracies in the integration of the broadend NMR signals.

These correlations revealed (cf. Table 3) that the coordinating protecting groups reverse the direction of the asymmetric induction on exchange of the diastereotopic iodine atoms by magnesium. A similar reversal was found in the corresponding bromine/lithium exchange reaction[3]. The effects found on changing **1** to either **7**, **8**, or **9** remained small, however, and thus render practical applications of this reaction unattractive.

While the chemistry of the halo*methyl*magnesium compounds had been thoroughly explored[4], very little is known[16] on the chemistry of other α-halo*alkyl*magnesium compounds. We were able to show that such species are configurationally stable in THF up to ca. −20°C. Generation of such species by stereoselective exchange of diastereotopic iodine atoms in substrates such as **3** by treatment with isopropylmagnesium halides could be realized in high yield, yet the stereoselectivity remained low.

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Experimental

All temperatures quoted are not corrected. – ^{1}H, ^{13}C NMR: Bruker AC-300. – Boiling range of petroleum ether: 40–60°C. – Flash chromatography: Kieselgel 60 (0.040–0.063 mm, Merck, Darmstadt). – Analytical gas chromatography: Siemens Sichromat 3 with a 30 m × 0.35 mm column with Durabond 5, 1.0 bar He, 10 min at 120°C followed by a temperature increase of 2°C/min.

1. *5,5-Diiodo-2-methyl-2-pentene* (**5**): To a solution of 16.38 g (100 mmol) of hexamethyldisilazane in 70 ml of anhydrous THF was added at −20°C during 10 min 65.0 ml (100 mmol) of a 1.61 M solution of *n*-butyllithium in hexane. After stirring for 20 min the mixture was cooled to −95°C. Then a solution of 26.9 g (100 mmol) of diiodomethane in 50 ml of THF was slowly added. The mixture was stirred for 2 h at temperatures below −90°C. A solution of 15.0 g (100 mmol) of 1-bromo-3-methyl-2-butene in 35 ml of THF was added dropwise, and the mixture was allowed to reach room temp. overnight. Then 30 ml of a saturated aqueous NH_4Cl solution was added, the phases were separated, and the aqueous phase was extracted three times with 150 ml each of ether. The combined organic phases were washed with 50 ml of a saturated aqueous $Na_2S_2O_3$ solution and 50 ml of brine. The organic phase was dried with $MgSO_4$ and concentrated in vacuo to give 31.5 g (93%) of **5** as a yellowish oil. For analysis a sample was purified by flash chromatography (eluent petroleum ether). – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.57 (s, 3H), 1.65 (s, 3H), 3.10 (t, *J* = 6.8 Hz, 2H), 4.91 (t, *J* = 6.4 Hz, 1H), 5.04 (tq, *J* = 6.1 and 1.2 Hz, 1H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = −24.4, 18.6, 25.9, 46.6, 123.1, 136.4. – $C_6H_{10}I_2$ (336.0): calcd. C 21.45, H 3.00; found C 21.38, H 3.31.

2. *1,1-Diiodo-4-methyl-3-pentanol* (**6**): To a solution of 19.5 g (58 mmol) of **5** in 40 ml of THF was added during 10 min 10.0 ml (100 mmol) of the borane–dimethyl sulfide complex. After stirring for 40 h the mixture was cooled to 0°C, and 9.14 g (122 mmol) of trimethylamine oxide was added slowly. During stirring for 40 h at white solid precipitated. The mixture was hydrolyzed by careful addition of 40 ml of 1,2-dihydroxyethane and 120 ml of water. The mixture was extracted four times with 150 ml each of ether, and the combined extracts were dried with $MgSO_4$ and purified by flash chromatography (ether/petroleum ether, 1:5) to give 14.4 g (71%) of **6** as a yellowish oil. The product was stored at −78°C. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (d, *J* = 6.9 Hz, 6H), 1.50 (broad s, 1H), 1.65 (d sept, *J* = 6.8 and 1.4 Hz, 1H), 2.39 (m, 2H), 3.28–3.38 (m, 1H), 5.17 (dd, *J* = 10.1 and 4.5 Hz, 1H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = −28.2, 17.6, 18.5, 33.1, 52.5, 77.4. – $C_6H_{12}I_2O$: calcd. 353.8897, found 353.8987 (MS).

3. *1,1-Diiodo-4-methyl-3-(trimethylsilyloxy)pentane* (**3**): To a solution of 2.00 g (5.66 mmol) of **6** in 10 ml of ether was added 0.95 g (6.8 mmol) of 1-(trimethylsilyl)imidazole. After stirring for 50 h the solvent was removed in vacuo, and the residue was purified by flash chromatography (ether/petroleum ether, 1:10) to give 2.34 g (97%) of **3** as a slightly yellowish oil. The product was stored at −78°C. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.11 (s, 9H), 0.81 (d, *J* = 6.9 Hz, 3H), 0.84 (d, *J* = 6.8 Hz, 3H), 1.67 (d sept, *J* = 6.9 and 4.3 Hz, 1H), 2.37 (m, 2H), 3.41 (ddd, *J* = 8.8, 4.5, and 4.1 Hz, 1H), 4.95 (dd, *J* = 10.7 and 4.0 Hz, 1H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = −27.9, 0.75, 17.5, 17.9, 33.0, 51.6, 77.9. – $C_9H_{20}I_2OS$ (426.2): calcd. C 25.37, H 4.73; found C 25.67, H 4.57.

4. *1,1-Diiodo-3-[(2-methoxyethoxy)methoxy]-4-methylpentane* (**7**): To a solution of 5.00 g (14.1 mmol) of **6** in 20 ml of CH_2Cl_2 were added 2.64 g (21.2 mmol) of (2-methoxyethoxy)methyl chloride and 4.10 ml (24.0 mmol) of ethyldiisopropylamine. The solution was kept for 11 d under reflux. The solvents as well as excess methoxyethoxymethyl chloride were removed in vacuo. Flash chromatography of the residue (ether/petroleum ether, 1:5) furnished 4.08 g (66%) of **7** as a yellowish oil. The product was stored at −78°C. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.84 (d, *J* = 6.9 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 3H), 1.91 (d sept, *J* = 6.8 and 4.2 Hz, 1H), 2.41 (ddd, *J* = 15.0, 11.1, and 2.4 Hz, 1H), 2.52 (ddd, *J* = 15.0, 9.1, and 3.4 Hz, 1H), 3.30 (ddd, *J* = 9.1, 4.0, and 2.5 Hz, 1H), 3.37 (s, 3H), 3.51–3.56 (m, 2H), 3.62–3.75 (m, 2H), 4.72 (s, 2H), 5.17 (dd, *J* = 11.1 and 3.4 Hz, 1H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = −28.5, 17.1, 17.9, 30.4, 50.2, 59.1, 67.6, 71.8, 83.9, 95.7. – $C_{10}H_{20}I_2O_3$ (442.1): calcd. C 27.17, H 4.56; found C 27.28, H 4.67.

5. *1,1-Diiodo-4-methyl-3-(phenylcarbamoyloxy)pentane* (**8**): A mixture of 5.00 g (14.1 mmol) of **6** and 2.30 ml (21.2 mmol) of phenyl isocyanate was heated for 20 h to 80°C. Excess phenyl isocy-

anate was removed in vacuo at 70°C, and the residue was purified by flash chromatography (ether/petroleum ether/ethyl acetate, 47.5:47.5:5) to give 5.75 g (86%) of **8** as yellow crystals, m.p. 86–90°C. – ^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.99 (broad d, J = 6.9 Hz, 6H), 2.00 (m, 1H), 2.68 (ddd, J = 15.3, 10.5, and 2.4 Hz, 1H), 2.81 (ddd, J = 15.3, 9.3, and 3.8 Hz, 1H), 4.77 (ddd, J = 9.0, 4.7, and 2.5 Hz, 1H), 5.07 (dd, J = 10.6 and 3.8 Hz, 1H), 6.75 (broad s, NH), 7.10 (t, J = 7.3 Hz, 1H), 7.30–7.49 (m, 4H). – ^{13}C NMR (75 MHz, CDCl$_3$): δ = −32.9, 17.6, 18.0, 31.4, 50.3, 79.7, 118.7, 123.6, 129.2, 137.7, 153.1. – $C_{13}H_{17}I_2NO_2$ (473.1): calcd. C 33.01, H 3.62, N 2.96; found C 33.11, H 3.74, N 2.96.

6. *3-(Diisopropylcarbamoyloxy)-1,1-diiodo-4-methylpentane* (**9**): To a solution of 9.33 g (26.4 mmol) of **6** in 40 ml of CH_2Cl_2 were added 11.4 ml (67.2 mmol) of ethyldiisopropylamine and 9.70 g (59.3 mmol) of diisopropylcarbamoyl chloride. The mixture was kept under reflux for 7 d. The solvent and excess components were removed in vacuo, and the residue was purified by flash chromatography (ether/petroleum ether, 1:10) to give 9.90 g (79%) of **9** as a yellowish oil. The product was stored at −78°C. – ^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.88 (d, J = 6.9 Hz, 6H), 1.14 (d, J = 6.4 Hz, 6H), 1.15 (d, J = 6.8 Hz, 6H), 1.86 (d sept, J = 6.9 and 4.6 Hz, 1H), 2.60 (ddd, J = 15.1, 10.4, and 2.7 Hz, 1H), 2.72 (ddd, J = 15.1, 8.8, and 4.0 Hz, 1H), 3.74 (broad s, 1H), 3.98 (broad s, 1H), 4.61 (ddd, J = 8.8, 4.5, and 2.7 Hz, 1H), 4.96 (dd, J = 10.4 and 4.0 Hz, 1H). – ^{13}C NMR (75 MHz, CDCl$_3$): δ = −32.3, 17.6, 18.1, 21.5, 31.2, 45.4, 51.0, 78.7, 155.0. – $C_{13}H_{25}I_2NO_2$ (481.2): calcd. C 32.45, H 5.24, N 2.91; found C 32.76, H 5.43, N 3.09.

7. *(2R*,3S*)-2-[3-Methyl-2-(trimethylsilyloxy)butyl]-3-phenyloxirane* (**10**): To a solution of 0.800 g (1.8 mmol) of **3** in 12 ml of THF was added at −78°C 1.72 ml (2.76 mmol) of a 2.08 M solution of isopropylmagnesium bromide in ether. After stirring for 45 min 1.20 g (11.3 mmol) of benzaldehyde was added, and the mixture was stirred for 2 h at −78°C. After storing for 20 h at −18°C 10 ml of a saturated aqueous NH_4Cl solution was added, subsequently 1.00 g of $NaHSO_3$. After stirring for 30 min the mixture was extracted four times with 40 ml each of ether. The combined extracts were dried with $MgSO_4$ and concentrated. Flash chromatography (ether/petroleum ether, 1:5) resulted in 0.366 g (70%) of the epoxide **10**. Gas chromatography revealed the presence of two products in a 4:1 ratio.

From **1**: To a solution of 0.50 g (1.5 mmol) of 1,1-dibromo-4-methyl-3-(trimethylsilyloxy)pentane (**1**)[2] in 6 ml of a Trapp solvent mixture[17] was added at −110°C 1.31 ml (1.96 mmol) of a 1.50 M solution of *n*-butyllithium in hexane. After stirring for 1 h a solution of 0.32 g (3.0 mmol) of benzaldehyde in 2 ml of 2-methyltetrahydrofuran was added. The mixture was stirred for further 2 h at −110°C and was then allowed to reach room temp. Then 10 ml of a saturated aqueous NH_4Cl solution and 1.00 g of $NaHSO_3$ were added. Workup as above furnished 0.32 g (76%) of the epoxides **10** as a 4:1 diastereomer mixture. – Major diastereomer, ^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.07 (s, 9H), 0.56 (d, J = 6.8 Hz, 3H), 0.75 (d, J = 6.8 Hz, 3H), 1.16–1.36 (m, 1H), 1.55–1.67 (m, 2H), 3.30–3.39 (m, 2H), 4.05 (d, J = 4.3 Hz, 1H), 7.22–7.38 (m, 5H). – ^{13}C NMR (75 MHz, CDCl$_3$): δ = 0.4, 17.6, 18.1, 31.0, 33.2, 56.9, 57.1, 75.1, 126.4, 127.5, 128.0, 135.6. – Minor diastereomer: ^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.09 (s, 9H), 0.70 (d, J = 6.8 Hz, 3H), 0.78 (d, J = 6.9 Hz, 3H), 1.16–1.36 (m, 1H), 1.55–1.67 (m, 2H), 3.30–3.39 (m, 2H), 4.09 (d, J = 4.2 Hz, 1H), 7.22–7.38 (m, 5H). – ^{13}C NMR (75 MHz, CDCl$_3$): δ = 0.8, 17.5, 18.4, 30.9, 33.6, 57.8 (2 C), 75.0, 126.4, 127.5, 128.0, 135.6. – Mixture, $C_{16}H_{26}O_2Si$ (278.5): calcd. C 69.01, H 9.41; found C 69.14, H 9.43.

8. *1-Deuterio-1-iodo-4-methyl-3-(trimethylsilyloxy)pentane* (**11**): To a solution of 0.20 g (0.47 mmol) of **3** in 2 ml of THF was added at −78°C 0.34 ml (0.71 mmol) of a 2.08 M solution of isopropylmagnesium bromide in ether. After stirring for 45 min a solution of 0.5 ml D_2O in 1 ml of THF was added, and the mixture was stirred for 5 min at −78°C and for 10 min at room temp. After addition of 4 ml of a saturated aqueous NH_4Cl solution the mixture was extracted three times with 50 ml each of ether. The combined extracts were dried with $MgSO_4$ and concentrated. Flash chromatography of the residue furnished 0.129 g (91%) of **11** as a yellowish oil. The ratio of the isotopomers was determined by ^{1}H- and ^{2}H-NMR spectroscopy to be 60:40. – ^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.08 (s, 9H), 0.79 (d, J = 6.8 Hz, 3H), 0.82 (d, J = 7.0 Hz, 3H), 1.63 (d sept, J = 6.8 and 4.8 Hz, 1H), 1.82 (t, J = 6.7 Hz, 2H), 3.08 (t, J = 8.0 Hz) and 3.21 (d, J = 6.0 Hz), together = 1H, 3.47 (q, J = 5.4 Hz, 1H). – ^{13}C NMR (75 MHz, CDCl$_3$): δ = 0.53, 4.1 (t), 17.8, 18.9, 33.3, 35.9, 77.0. – $C_9H_{20}DIOSi$ (301.3): calcd. C 35.88, H 7.02; found C 35.69, H 6.85.

9. *4-Iodo-7-methyl-6-(trimethylsilyloxy)-1-octene* (**12**): To a solution of 0.20 g (0.47 mmol) of **3** in 2 ml of THF was added at −78°C 0.34 ml (0.71 mmol) of a 2.08 M solution of isopropylmagnesium bromide in ether. After stirring for 45 min 0.316 g (1.88 mmol) of 3-iodo-1-propene was added. The mixture was stirred for 1 h at −78°C and stored for 20 h at −18°C. Then 4 ml of a saturated aqueous NH_4Cl solution was added, and the mixture was extracted three times with 50 ml each of ether. The combined extracts were dried with $MgSO_4$ and concentrated. Flash chromatography of the residue (ether/petroleum ether, 0:10 followed by 1:70) furnished 0.129 g (81%) of **12** as a yellowish oil. The diastereomer ratio was determined by ^{13}C-NMR spectral analysis to be 62:38. – Major diastereomer, ^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.12 (s, 9H), 0.81 (d, J = 6.9 Hz, 3H), 0.83 (d, J = 6.9 Hz, 3H), 1.47–1.57 (m, 1H), 1.65 (d sept, J = 6.9 and 4.2 Hz, 1H), 1.73–1.92 (m, 1H), 2.44–2.66 (m, 2H), 3.68 (ddd, J = 9.8, 4.4, and 1.9 Hz, 1H), 4.00–4.16 (m, 1H), 5.03–5.14 (m, 2H), 5.70–5.85 (m, 1H). – ^{13}C NMR (75 MHz, CDCl$_3$): δ = 0.9, 17.7, 18.2, 32.0, 34.0, 43.0, 45.7, 77.1, 117.6, 136.5. – Minor diastereomer, ^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.06 (s, 9H), 0.76 (d, J = 6.9 Hz, 3H), 0.84 (d, J = 6.9 Hz, 3H), 1.47–1.57 (m, 1H), 1.65 (d sept, J = 6.9 and 4.2 Hz, 1H), 1.73–1.92 (m, 1H), 2.44–2.66 (m, 2H), 3.51–3.68 (m, 1H), 4.00–4.16 (m, 1H), 5.03–5.14 (m, 2H), 5.70–5.85 (m, 1H). – ^{13}C NMR (75 MHz, CDCl$_3$): δ = 0.6, 16.4, 18.6, 32.0, 36.2, 44.0, 44.1, 76.1, 117.9, 136.3. – Mixture, $C_{12}H_{25}IOSi$ (340.3): calcd. C 42.35, H 7.40; found C 42.57, H 7.55.

10. *Cross-Over Experiments:* To a solution of 0.100 g (0.23 mmol) of **3** in 2 ml of THF was added at −78°C 0.11 ml (0.33 mmol) of a 2.7 M solution of isopropylmagnesium chloride in ether. After stirring for 30 min carbon dioxide was bubbled through the solution for 5 min. Then a solution of 75 mg (0.23 mmol) of 1,1-diiodopentane (**13**) in 1 ml of THF was added, and the mixture was stirred for 15 min. Subsequently, 4 ml of a saturated aqueous NH_4Cl solution was added, and the mixture was extracted three times with 50 ml each of ether. The combined extracts were dried with $MgSO_4$ and concentrated. Gas chromatography of the crude product revealed the presence of 1-iodo-4-methyl-3-(trimethylsilyloxy)pentane (**15**), **13**, and 1-iodopentane (**16**) in the ratio of 46:46:8.

A similar experiment was carried out by starting from **13** with addition of **3** in the second step. Analogous workup and GC analysis showed the presence of **16**, **3**, and **15** in a ratio of 45:45:10.

11. *Temperature Dependence of the Diastereomer Ratio:* Reactions were carried out as described under 8. After the magnesium carbenoid **4** had been generated the mixture was stirred for 45 min

at −78°C. It was kept for 1 h at −20 or 0°C, before a solution of 0.5 ml of D_2O in 1 ml of THF was added. Workup and analysis of the isotopomers were carried out as described under 8.

12. *1-Deuterio-1-iodo-4-methyl-3-pentanol* (**17**): To a solution of 976 mg (3.24 mmol) of **11** was added a solution of 1.30 g (6.5 mmol) of a 10-% solution of HF in acetonitrile/water. After stirring for 2 h 3 ml of a saturated aqueous $NaHCO_3$ solution was added, and the mixture was stirred for further 30 min. The mixture was extracted four times with 50 ml each of ether. The combined extracts were dried with $MgSO_4$ and concentrated. The residue was purified by flash chromatography (ether/petroleum ether, 1:5) to give 0.67 g (90%) of **17** as a colorless liquid. − ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.85$ (d, $J = 6.8$ Hz, 6H), 1.60 (d sept, $J = 6.6$ and 6.6 Hz, 1H), 1.66−1.94 (m, 2H), 3.20 (t, $J = 8.0$ Hz) and 3.27 (t, $J = 5.9$ Hz) together 1H, 3.33−3.45 (m, 1H). − ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 4.0$ (t), 17.5, 18.7, 33.7, 37.7, 76.5. − $C_6H_{12}DIO$ (229.1): calcd. C 31.46, H 5.68; found C 31.72, H 5.42.

13. *1-Deuterio-1-iodo-3-[(2-methoxyethoxy)methoxy]-4-methylpentane* (**18**): 200 mg (0.45 mmol) of **7** and 0.33 ml (0.68 mmol) of a 2.08 M solution of isopropylmagnesium bromide in ether were allowed to react as described under 8. Flash chromatography (ether/petroleum ether, 1:5) furnished 0.138 g (97%) of **18** as a yellowish oil. − ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.82$ (d, $J = 6.9$ Hz, 3H), 0.89 (d, $J = 6.9$ Hz, 3H), 1.85 (d sept, $J = 6.9$ and 4.6 Hz, 1H), 1.91 (t, $J = 6.6$ Hz, 2H), 3.13 (t, $J = 8.0$ Hz) and 3.23 (t, $J = 6.6$ Hz) together = 1H, 3.33 (s, 3H), 3.33−3.41 (m, 1H), 3.48−3.52 (m, 2H), 3.64−3.70 (m, 2H), 4.70 (s, 2H). − ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 3.1$ (t), 17.4, 18.2, 30.7, 35.0, 59.1, 67.5, 71.9, 82.9, 95.4. − $C_{10}H_{20}DIO_3$ (317.2): calcd. C 37.87, H 6.67; found C 38.02, H 6.46.

From the Alcohol **17**: 0.150 g (0.65 mmol) of **17** in 2 ml of dichloromethane, 0.121 g (0.98 mmol) of (methoxyethoxy)methyl chloride, and 0.143 g (1.11 mmol) of ethyldiisopropylamine were allowed to react as described under 4. Workup as above furnished 0.124 g (60%) of **18**. The isotopomer ratio in the materials obtained were determined by ^1H-NMR spectroscopy.

14. *1-Deuterio-1-iodo-4-methyl-3-(phenylcarbamoyloxy)pentane* (**19**): 0.200 g (0.42 mmol) of **8** and 0.74 ml (1.23 mmol) of a 1.65 M solution of isopropylmagnesium bromide in ether were allowed to react as described under 8. Flash chromatography (ether/petroleum ether, 1:3) furnished 0.123 g (86%) of **19** as a yellowish oil. − ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.98$ (d, $J = 6.9$ Hz, 6H), 1.95 (d sept, $J = 6.6$ and 6.6 Hz, 1H), 2.18 (t, $J = 6.9$ Hz, 2H), 3.17 (t, $J = 8.1$ Hz) and 3.23 (t, $J = 7.3$ Hz) together = 1H, 4.79 (q, $J = 5.9$ Hz, 1H), 6.71 (broad s, NH), 7.10 (t, $J = 7.3$ Hz, 1H), 7.29−7.47 (m, 4H). − ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 0.55$ (t), 17.6, 18.2, 31.5, 36.0, 79.6, 118.7, 123.5, 129.0, 137.8, 153.4. − $C_{13}H_{17}DINO_2$ (348.2): calcd. C 44.82, H 5.21, N 4.02; found C 44.56, H 5.07, N 4.05.

From the Alcohol **17**: 0.150 g (0.65 mmol) of **17** in 2 ml of dichloromethane and 0.117 g (0.98 mmol) of phenyl isocyanate were allowed to react as described under 5. Workup as above furnished 0.162 g (72%) of **19**. The isotopomer ratio in both materials was determined by ^1H-NMR spectroscopy.

15. *1-Deuterio-3-(diisopropylcarbamoyloxy)-1-iodo-4-methylpentane* (**20**): 0.200 g (0.41 mmol) of **9** and 0.30 ml (0.62 mmol) of a 2.08 M solution of isopropylmagnesium bromide in ether were allowed to react as described under 8. Flash chromatography (ether/petroleum ether, 1:10) furnished 0.127 g (86%) of **20** as a yellow oil. − ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.86$ (d, $J = 6.8$ Hz, 6H), 1.14 (d, $J = 6.8$ Hz, 6H), 1.15 (d, $J = 6.8$ Hz, 6H), 1.82 (m, 1H), 2.10−2.11 (m, 2H), 3.05 (t, $J = 8.0$ Hz) and 3.08 (t, $J = 9.3$ Hz) together = 1H, 3.72 (broad s, 1H), 3.98 (broad s, 1H), 4.66 (dt, $J = 7.5$ and 5.0 Hz, 1H). − ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 1.1$ (t), 17.9, 18.5, 21.5 (4 C), 31.7, 36.8, 45.6 (2 C), 79.9, 155.5. − MS: $M^+ - CH_2 = C_{12}H_{22}DINO$: calcd. 341.0836, found 341.0827.

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