48. 1,2-Stereoinduction in Radicals and Anions: A Comparison between Hydrogen Abstraction and Protonation

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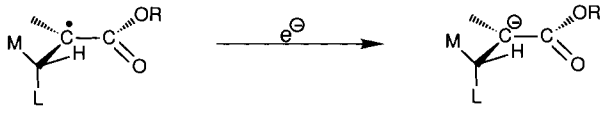
Chiral enolates **5** and **10**, generated by radical addition and subsequent reduction, show diastereofacial selectivity during protonation. In the presence of substituted amines, diastereoselectivity is enhanced and becomes comparable to radical stereoselection. Diastereoselectivities up to 99:1 and yields up to 90% are reached.

Introduction. – Recently, it was demonstrated that ester-substituted radicals with a tertiary stereogenic C-atom adjacent to the prochiral radical center often react with high 1,2-stereoinduction [1][2]. Because of allylic strain effects, these radicals adopt the preferred conformation **1** (*Scheme 1*), where L and M are large- and medium-sized substituents, respectively [3]. Attack occurs predominantly '*anti*' to the large substituent L.

Scheme 1



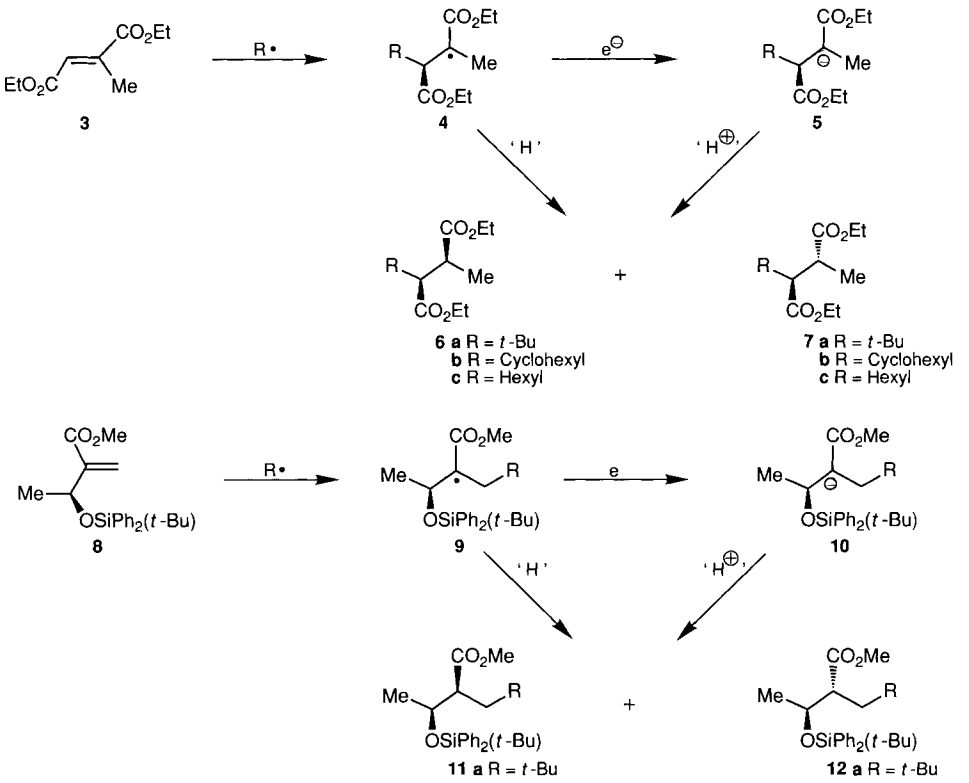
1 **2**

It was already shown that protonation of acyclic enolate anions can also occur with 1,2-stereoinduction [4]. We were now interested to compare the stereoselectivity of the H-abstraction by radicals **1** with the protonation of the corresponding anions **2** which are substituted by the same groups.

Results and Discussion. – The enolate anions **5** and **10** were generated by radical addition to alkenes **3** and **8** and subsequent reduction of the adduct radicals **4** and **9**, respectively (*Scheme 2*). Metallic Zn or the cathode was used as electron source. Protonation of the enolate anions **5** and **10** led to products **6/7** and **11/12**, respectively[1]).

[1]) All experiments were carried out with racemic mixtures. For simplicity, only one enantiomer is given in the *Schemes*.

Scheme 2



Suitable methods for these radical and ionic transformations are reactions of alkyl halides with catalytic amounts of vitamin B_{12a} or the analogous Co complexes **13** and **14** under reductive conditions. Alkylcobalt complexes are formed as intermediates that add to alkenes in a sequence of radical-reaction steps [5]. Deuteration experiments in the presence of small amounts of D_2O proved that products are formed *via* the anions.

An alternative method for the formation of enolate anions is the direct reduction of alkyl halide with Zn using sonication (')))))'; *Scheme 3*). Under these conditions, radicals are formed in the first step [6]. Trapping of these radicals by alkenes **3** and **8** led to adduct radicals **4** and **9** that were reduced to the anions **5** and **10**, respectively. Deuteration experiments with C_2H_5OD again proved that the products are formed in an ionic reaction step.

Using the reductive addition of *t*-BuBr to diethyl mesaconate (**3**), we compared the different methods. The data in *Table 1* show the 1,2-stereoinduction to be independent upon the method. Similarly to the radical reaction, the ionic protonation yielded isomer **6a** as the main product. However, the product ratio **6a/7a** of 85:15[2]) in the ionic reaction was much smaller than the 96.5:3.5 ratio of the H-abstraction step by radical **4**.

[2]) The observed product ratio is the result of kinetic control, because isomerization under the conditions of the experiments could not be observed.

Scheme 3

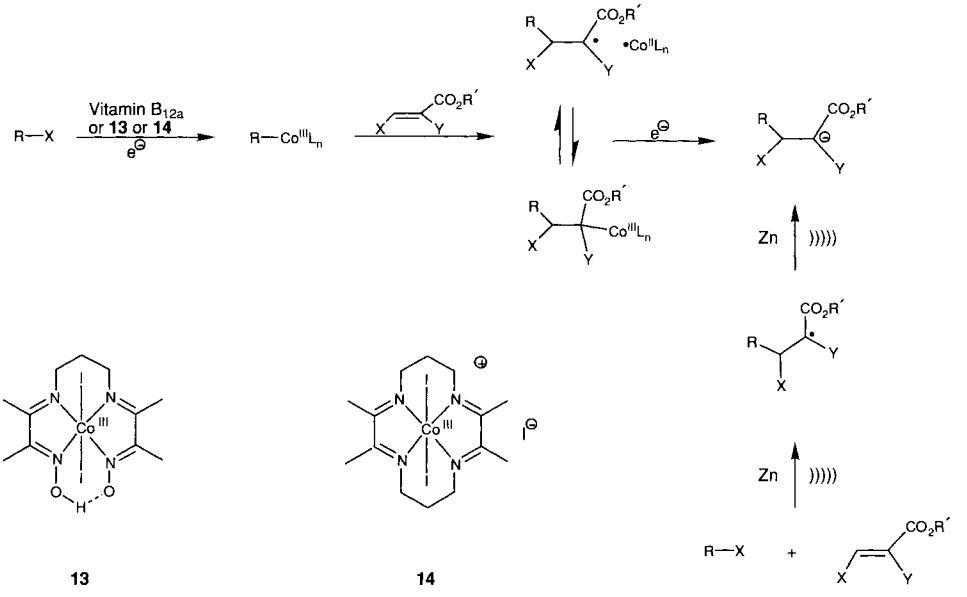


Table 1. *Reaction of* t-*BuBr with Diethyl Mesaconate* (**3**) *in DMF at 20° Using Different Methods*

Reduction method		Product ratio **6a/7a**	Yield [%]
Vitamin B_{12a}[a])	Zn	87:13	74[f])
Vitamin B_{12a}[b])	cathode	84:16	40[f])
13[a])	Zn	85:15	52[f])
14[a])	Zn	85:15	69[f])
Zn,)))))[c])		85:15	31[f])
Zn,)))))[d])		85:15	87[f])
RHgCl, $NaBH_4$, CH_2Cl_2[e])		96.5:3.5	80

[a]) 0.05 Equiv. [b]) 0.25 Equiv. [c]) Sonication in DMF. [d]) Sonication in H_2O. [e]) H-Atom abstraction, *cf.* [3]. [f]) GC yields.

Further experiments demonstrated that the stereoselectivity of the protonation step can be easily affected by the addition of amines (*Table 2*). Whereas NH_4Cl slightly reduced the selectivity, with primary, secondary, and tertiary amines, the 1,2-stereoinduction was increased. The most effective amine was Et_3N, where selectivities reached 99:1 **6a/7a** with Co complexes as catalysts. Under the conditions of sonication, (–)-*N*-methylephedrine turned out to be most effective.

Table 2. *Reaction of* t-*BuBr with Diethyl Mesaconate* (**3**) *Using Vitamin* B_{12a}, *Co Complex* **14**, *or Sonication in the Presence of Different Amines at 20°*

Amine[a])	Product ratio **6a/7a**		
	Vitamin B_{12a}[b])	Co Complex **14**[b])	Zn /)))))[c])
NH_4Cl	82:18	81:19	83:17
Cyclohexylamine	–	85:15	–
$(i\text{-}Pr)_2NH$	97:3	91:9	82:18
(+)-*N*-Methylephedrine	97.5:2.5	–	93.5:6.5
(–)-*N*-Methylephedrine	98:2	–	95.5:4.5
Me_3N	98.5:1.5	98:2	–
Et_3N	99:1	98:2	91:9

[a]) 14.4 Equiv. for the Co-complex methods, 7 equiv. for the sonication method. [b]) 0.05 Equiv. of Co complex, DMF as solvent. [c]) H_2O as solvent.

The concentration of the added amine also plays a role. The *Figure* shows that the selectivity increased with increasing amine concentration. With 1.1M solutions, a maximum was reached. Higher concentration of Et_3N gave no improvement in 1,2-stereoinduction.

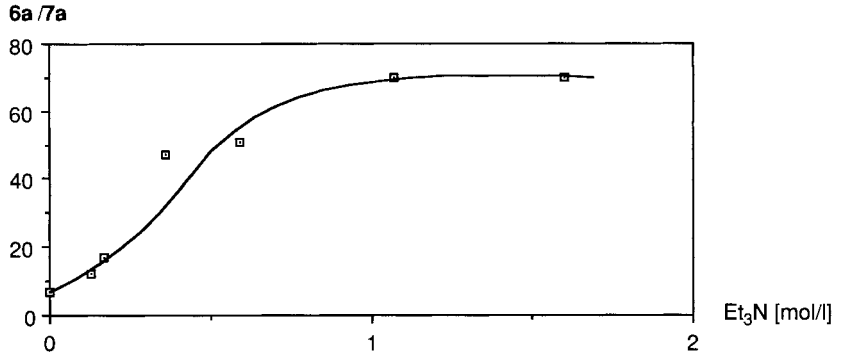


Figure. *Influence of the concentration of* Et_3N *on the product ratio* **6a/7a** *using vitamin* B_{12a} *as catalyst*

Using these optimized conditions, the reaction of primary, secondary, and tertiary alkyl bromides with alkene **3** were carried out. The data in *Table 3* show that the selectivities of ionic protonation steps in the presence of tertiary amines were similar to those of radical H-atom abstractions. Product ratios up to 99:1 and yields up to 90% could be reached. The stereoselectivity decreased on decrease of the bulk of the alkyl substituent from *t*-Bu, to cyclohexyl to hexyl.

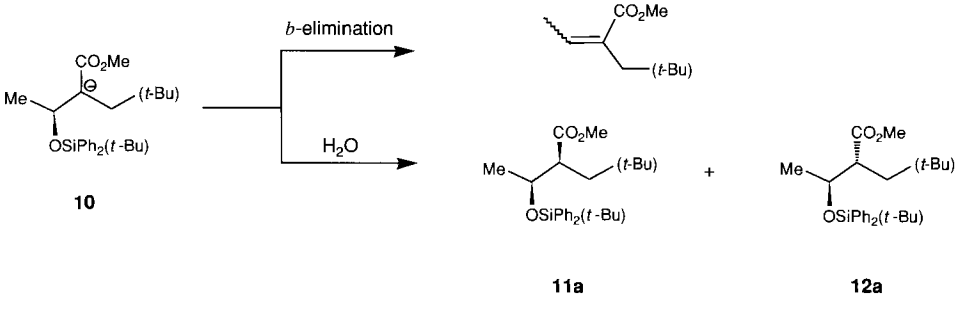
Similar stereoselectivities were also observed with alkene **8**, where the ionic route led to relatively low yields, because β-elimination competed with the protonation of anion **10** (*Table 3*, *Scheme 4*).

Table 3. *Stereoselectivity in the Synthesis of* **6/7** *and* **11/12** *from Alkyl Bromides and Alkene* **3** *and* **8**, *Respectively, at 20°*

Alkyl bromide	Alkene	Vitamin B_{12a}, Zn, DMF [a])		Zn,))))), H_2O [b])		Radical method [c])	
		6/7	Yield [%]	**6/7**	Yield [%]	**6/7**	Yield [%]
t-BuBr	**3**	99:1	90	95.5:4.5	75	96.5:3.5	80
Cyclohexyl bromide	**3**	96:4	81	93.5:6.5	56	93:7	60
Hexyl bromide	**3**	60:40	63	75:25	65	60:40	35
t-BuBr	**8**	1.5:98.5[d])	24	6.5:92.5[d])	43	5:95[d])	97

[a]) 1.4 Equiv. of Et_3N added. [b]) 7.0 Equiv. of (–)-*N*-methylephedrine added. [c]) With alkene **3**, the mercury method, and with alkene **8**, the tin method was used [3]. [d]) Products **11/12** are formed.

Scheme 4



Conclusions. – H-Abstraction reactions of radicals **4** and **9** exhibit similar 1,2-stereoinduction as the protonation of anions **5** and **10**, respectively. This is another example demonstrating the similarity between radical and ionic stereoselection [7].

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Experimental Part

1. *General.* All reactions were carried out under Ar at r.t. (20°). Electrochemical experiments: *HEKA* potentiostate *PG 284*, cathode, *Sigratherm GFA 5* carbon felt. Ultrasonic cleaning bath: *Telsonic TEC-25*, 60 W, 33 kHz. Chromatography: silica gel *C 560/KV* 35–70 mm, *Chemische Fabrik Uetikon*. GC: *Carlo Erba 6000*, flame-ionization detector coupled to a *Shimadzu-C-R4A* integrator; conditions: 25m *SE-52*, 50–280° at 15°/min. GC/MS: *Hewlett-Packard 5790A* gas chromatograph coupled to a *Hewlett-Packard 5790A* mass-selective detector; conditions: 25 m *OV-1*, 50–270° at 10°/min. IR (cm^{-1}): *Perkin Elmer-781* spectrophotometer. ^1H- and ^{13}C-NMR: *Varian Gemini 300*; TMS as internal standard. δ in ppm, J in Hz. MS (*m/z* (rel%)): *VG 70-250* or *Varian MAT 212*.

2. *General Procedures.* 2.1. *Ultrasound Method.* CuI (406 mg, 2.14 mmol) and Zn (556 mg, 8.58 mmol) were placed in a flask (25 ml) together with Ar-sat. H_2O (15 ml). The flask was flushed with Ar for 5 min, stoppered with a septum, and than sonicated in a cleaning bath (cooled with tap-water) for 2 min (→ black Cu-Zn alloy). After the

successive addition of alkene (0.43 mmol) and alkyl halide (4.28 mmol), the flask was stoppered with a septum and connected *via* a syringe to an Ar-filled balloon. After 2-h sonication, the grey dispersion was filtered and the residue extracted with Et_2O(20 ml) by sonication for 5 min. Brine (15 ml) was added to the filtrate which was then extracted 3 times with Et_2O (20 ml each). The combined org. phases were dried ($MgSO_4$) and evaporated. Product ratios were determined by GC (comparison with authentic material) or ^{1}H-NMR.

2.2. *Vitamin-B_{12}-Catalysis Method.* A suspension of vitamin B_{12a} (aquacob(III)alamin hydrochloride; 210 mg, 0.15 mmol) and activated Zn dust (1.80 g, 34.0 mmol; activation by treating with 2N HCl (2 × 10 ml) followed by washing with H_2O (2 × 10 ml), EtOH (2 × 10 ml), and Et_2O (2 × 10 ml) and drying *in vacuo*) in DMF (20 ml) was stirred vigorously under Ar. After 15 min, the mixture became dark-green. Then, a degassed soln. of alkyl halide (30.0 mmol), alkene (3.00 mmol), and, in the optimized cases, Et_3N (6.0 ml, 43 mmol) in DMF (10 ml) was added. Stirring was continued for several h until the reaction was completed (determination of product ratios and yields by GC using dodecane as internal standard). The reaction was quenched by adding H_2O (30 ml). Filtration of Zn and addition of 2N HCl (10 ml) was followed by extraction with Et_2O (3 × 100 ml). The Et_2O extracts were washed with H_2O (20 ml), dried ($MgSO_4$), and evaporated. The crude product was distilled or purified by FC.

Co Complexes **13** *and* **14** *as Catalysts.* Complexes **13** and **14** were synthesized according to [8] and [9] and used as catalyst instead of vitamin B_{12a} in *2.2.* by reducing **13** (84.0 mg, 0.15 mmol) or **14** (103 mg, 0.15 mmol).

3. *Electrochemical Experiments* . In a H-type cell with glass-frit (*G4*), a three-electrode arrangement with a C-felt as cathode material, Pt as anode, and an Ag/AgCl reference electrode ($E = -36$ mV *vs.* SCE) seperated by a diaphragma was used. A degassed soln. of *t*-BuBr (685 mg, 5.00 mmol), alkene **3** (186 mg, 1.00 mmol), and vitamin B_{12a} (346 mg, 0.25 mmol) in a soln. of $LiClO_4$ (0.25M) in DMF (40 ml) was electrolysed at a constant potential (–800 mV) under irradiation with a lamp (visible light). The products were analyzed by GC, and yields were determined using dodecane as internal standard.

4. *Variation of Amines.* 4.1. *Ultrasound Method.* According to *2.1,* **3** (80.0 mg, 0.43 mmol) was reacted with *t*-BuI (788 mg, 4.28 mmol) in aq. soln. (15 ml) containing 3.00 mmol of amine. The crude product was analyzed by GC.

4.2. *Vitamin-B_{12}-Catalysis Method.* According *2.2,* **3** (186 mg, 1.00 mmol) was reacted with *t*-BuBr (1.37 g, 10.0 mmol) in a soln. containing vitamin B_{12a} (70 mg, 0.05 mmol), activated Zn dust (600 mg, 11.5 mmol), and amine (14.4 mmol) in DMF (10 ml).

Variation of the amine concentration was carried out by adding different amounts of Et_3N (0.14 mmol, 0.19 mmol, 4.2 mmol, 7.0 mmol, 14.4 mmol, 21.6 mmol) to the mixture.

5. *Diethyl* 3-(tert-*Butyl*)-2-*methylbutanedioate* (**6a,7a**). According to *2.1* and *4.1,* **3** (80.0 mg, 0.43 mmol) was reacted with *t*-BuI (788 mg, 4.28 mmol) in H_2O (15 ml) containing (–)-*N*-methylephedrine (537 mg, 3.00 mmol). The crude **6a/7a** (95.5:4.5 by GC) was purified by bulb-to-bulb distillation at 140° (bath)/0.5 mbar: **6a/7a** (78.8 mg, 75%)[3]. When the reaction was run in C_2H_5OD, more than 95% of the product was diethyl *3-*(tert-*butyl*)-*2-methyl(2-$^2H_1$)butanedioate* (by ^{1}H-NMR and GC/MS).

Following *2.2* and *4.2,* **3** (558 mg, 3.00 mmol) was reacted with *t*-BuBr (4.10 g, 30.0 mmol) in a soln. containing Et_3N(6.0 ml, 43 mmol) in DMF (30 ml). After 2 h, usual workup and bulb-to-bulb distillation gave **6a/7a** 99:1 (GC; 659 mg, 90%). Addition of 10 vol-% of ^2H_2O afforded ^{2}H-incorporation identical to the ultrasound method.

Data of **6a**: Oil. IR (film): 1740. ^{1}H-NMR: 4.04 (*q, J* = 7.1, 4 H); 2.83 (*quint, J* = 7.2, 1H); 2.35 (*d, J* = 7.5, 1H); 1.27 (*d, J* = 7.1, 3 H); 1.16 (*m*, 6 H); 0.99 (*s*, 9 H). ^{13}C-NMR: 176.1; 174.2; 60.3; 59.8; 58.3; 39.7; 33.0; 28.44; 19.0; 13.9; 13.7. EI-MS: 199 (44), 188 (38), 183 (16), 171 (12), 143 (18), 142 (100), 127 (10), 115 (59), 114 (19), 99 (17), 97 (19), 87 (36), 83 (28), 69 (35), 57 (38), 55 (29), 43 (15), 41 (47). Anal. calc. for $C_{13}H_{24}O_4$ (244.33): C 63.91, H 9.90; found: C 63.82, H 9.74.

6. *Diethyl 3-Cyclohexyl-2-methylbutanedioate* (**6b/7b**). According to *2.1.* and *4.1.,* **3** (80.0 mg, 0.43 mmol) was reacted with cyclohexyl iodide (899 mg, 4.28 mmol) in H_2O (15 ml) containing (–)-*N*-methylephedrine (537 mg, 3.00 mmol). The crude **6b/7b** (93.5:6.5 by GC) was purified by bulb-to-bulb distillation at 150° (bath)/0.5 mbar: **6b/7b** (65.1 mg, 56%)[3].

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[3]) The structure of **6** and **7** were assigned by ^{1}H-NMR spectroscopy analogously to [1a] [3a].

Following *2.2* and *4.2*, **3** (558 mg, 3.00 mmol) was reacted with cyclohexyl bromide (4.90 g, 30.0 mmol) in a soln. containing Et_3N (6.0 ml, 43 mmol) in DMF (30 ml). After 12 h, usual workup and bulb-to-bulb distillation gave **6b/7b** 96:4 (GC; 654 mg, 81%).

Data of **6b**: Oil. IR (film): 1740. ^{1}H-NMR: 4.12 (*q*, *J* = 7.1, 4 H); 2.86 (*dq*, *J* = 9.3, 7.3, 1 H); 2.49 (*dd*, *J* = 9.3, 4.8, 1 H); 1.25, 1,24 (2*t*, *J* = 7.1, 6 H); 1.19 (*d*, *J* = 7.3, 3 H); 2.0–0.8 (*m*, 11 H). ^{13}C-NMR: 175.4; 173.6; 60.3; 59.9; 53.4; 38.6; 36.8; 32.0; 28.5; 26.7; 26.3; 26.2; 15.0; 14.1; 14.0. EI-MS: 225 (29), 188 (66), 169 (23), 151 (19), 142 (100), 141 (14), 127 (4), 123 (19), 115 (40), 114 (15), 99 (12), 95 (10), 87 (22), 81 (23), 69 (23), 67 (18), 55 (26), 41 (27). Anal. calc. for $C_{15}H_{26}O_4$ (270.37): C 66.63, H 9.69; found: C 66.33, H 9.68.

7. *Diethyl 3-Hexyl-2-methylbutanedioate* (**6c**/**7c**). According to *2.1* and *4.1*, **3** (80.0 mg, 0.43 mmol) was reacted with hexyl bromide (706 mg, 4.28 mmol) in H_2O (15 ml) containing (–)-*N*-methylephedrine (537 mg, 3.00 mmol). The crude **6c/7c** (75:25 by GC) was purified by bulb-to-bulb distillation at 150° (bath)/0.5 mbar: **6c/7c** (76.1 mg, 65%).

Following *2.2* and *4.2*, **3** (558 mg, 3.00 mmol) was reacted with hexyl bromide (5.00 g, 30.0 mmol) in a soln. containing Et_3N (6.0 ml, 43 mmol) in DMF (30 ml). After 20 h, usual workup and bulb-to bulb distillation led to **6c/7c** 60:40 (GC; 512 mg, 63%). Anal. calc. for $C_{15}H_{28}O_4$ (272.38): C 66.14, H 10.36; found: C 66.13, H 10.21.

The two isomers were separated by flash chromatography (FC; silica gel; pentane/Et_2O 9:1): **6c** (165 mg, 20%) and **7c** (195 mg, 24%).

Data of **6c**: Oil. IR (film): 1740. ^{1}H-NMR: 4.11 (*m*, 4 H); 2.75 (*dq*, *J* = 8.3, 7.1, 1 H); 2.63 (*ddd*, *J* = 8.3, 8.3, 4.4, 1 H);1.7–1.1 (*m*, 16 H); 1.14 (*d*, *J* = 7.1, 3 H); 0.85 (*t*, *J* = 7.0, 3 H). ^{13}C-NMR: 175.2; 174.7; 60.4; 60.3; 47.4; 40.8; 31.6; 29.2; 28.6; 26.7; 22.5; 14.2; 14.2; 14.1; 14.0. EI-MS: 227 (78), 188 (44), 172 (15), 171 (98), 153 (23), 143 (38), 142 (100), 125 (17), 115 (76), 102 (66), 101 (18), 87 (38), 83 (43), 74 (25), 73 (20), 69 (85), 55 (94), 45 (18), 43 (50), 41 (78).

Data of **7c**: Oil. IR (film): 1740. ^{1}H-NMR: 4.13 (*q*, *J* = 7.1, 4 H); 2.6 (*m*, 2 H); 1.7–1.1 (*m*, 10 H); 1.24 (*t*, *J* = 7.1, 6 H); 1.10 (*d*, *J* = 6.4, 3 H); 0.85 (*t*, *J* = 7.0, 3 H). ^{13}C-NMR: 174.9; 174.2; 60.5; 60.3; 48.6; 42.2; 31.6; 30.6; 29.0; 27.3; 22.5; 15.1; 14.3; 14.2; 14.0. EI-MS: 227 (53), 188 (24), 172 (17), 171 (100), 153 (14), 143 (33), 142 (46), 125 (13), 115 (31), 102 (50), 101 (17), 87 (17), 83 (24), 74 (20), 73 (17), 69 (54), 55 (61), 45 (12), 43 (29), 41 (53).

8. *Methyl 2-{1-[(*tert*-Butyl)diphenylsilyloxy]ethyl}-4,4-dimethylpentanoate* (**11**,**12**). According to *2.1* and *4.1*, **8** (158 mg, 0.43 mmol) was reacted with *t*-BuI (788 mg, 4.28 mmol) in H_2O (15 ml) containing (–)-*N*-methylephedrine (537 mg, 3.00 mmol). The crude **11/12** (6.5:92.5 by ^{1}H-NMR) was submitted to FC (pentane/AcOEt 32:1): **11/12** [3c] (78.9 mg, 43%). When the reaction was run in C_2H_5OD, more than 95% of the product was *methyl 2-{1-[(*tert*-butyl)diphenylsilyloxy]ethyl}-4,4-dimethyl(2-*$^2H_1$*)pentanoate* (by ^{1}H-NMR).

Following *2.2* and *4.2*, **8** (1.10 g, 3.00 mmol) was reacted with *t*-BuBr (4.10 g, 30.0 mmol) in a soln. containing Et_3N(6.0 ml, 43 mmol) in DMF (30 ml). After 2 h, usual workup and FC (pentane/AcOEt 32:1) led to **11/12** (307 mg, 24%), ratio 1.5:98.5 (GC comparison by an authentic sample).

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