Reaction of 2-Hydroxy-1,2,2-triphenylethyl Propionate with Non-Activated Ketones and Enones: Stereoselective Aldol and Michael Addition

Manfred Braun,*[a] Brigitte Mai,[a] and Daniel Ridder[a]

Dedicated to Professor Leonhard Birkofer on the occasion of his 90th birthday

Keywords: Asymmetric synthesis / Aldol reaction / Michael addition / Titanium

The $TiCl_4$-mediated Mukaiyama-type reaction of the silyl ketene acetal **2**, derived from (*R*)-propionate **1**, with the ketones **3a**–**d** occurs in a stereoselective manner. The aldol product **4c** is obtained from the enone **3c**, whereas the homologous compound **3d** undergoes a 1,4 addition and leads to the keto ester **5**. The configurations of the deprotected aldol adduct **6** (obtained from **3c**) and the Michael product **5** are determined by crystal structure analyses. The diastereomerically and enantiomerically pure esters **4a**–**c**, **5**, and **6**, as well as the carboxylic acid **7** and the diol **8**, containing two or three contiguous stereogenic carbon centers, are prepared. The enantiomerically pure compounds **7** and **8** result from the cleavage of the chiral auxiliary reagent 1,1,2-triphenyl-1,2-ethanediol, which can be recovered.

Introduction

Numerous stereoselective variants of the aldol and Michael reactions have been developed in the past two decades.[1,2] Based on the chemistry of "preformed" enolates,[3] covalently bound chiral auxiliary groups were used in the beginning of this evolution and provided diastereofacial selectivity.[4] Enantioselective variants of those fundamental reactions were developed more recently, most of which take advantage of efficient chiral catalysts.[5] In almost all variants of stereoselective aldol reactions, aldehydes were used as electrophiles, whereas the corresponding additions to prochiral ketones are extremely rare. Only a few chiral acetate equivalents have been added to ketones, with moderate stereoselectivity in most cases.[6−8] One reason for the restriction of stereoselective aldol variants to aldehydes is the fact that ketones are in general more difficult substrates for enantiofacial and diastereofacial differentiation. Furthermore, the comparatively low reactivity of ketones prevents many of the chiral enolate reagents from reacting with the keto carbonyl group. As a consequence, the few examples of highly stereoselective aldol additions rely on activated ketones, in particular α-keto esters and α-diketones.[9−13] In this paper, we report on stereoselective Mukaiyama-type aldol additions[14] to non-activated ketones based on (*R*)- or (*S*)-2-hydroxy-1,2,2-triphenylethyl propionate (**1**).[15] When this chiral reagent is allowed to react with α,β-unsaturated ketones, a 1,4-addition competes with the 1,2-addition depending on the substitution pattern of the enone. Nevertheless, both simple diastereoselection and diastereofacial selectivity[16] are provided by the chiral propionate **1** in both the aldol[17] and the Michael reaction.

[a] Institut für Organische Chemie und Makromolekulare Chemie, Universität Düsseldorf,
40225 Düsseldorf, Germany
Fax: (internat.) + 49-211/811-5079
E-mail: braunm@uni-duesseldorf.de

Results and Discussion

Reaction of the Propionate (*R*)-1 with Ketones 3a−d

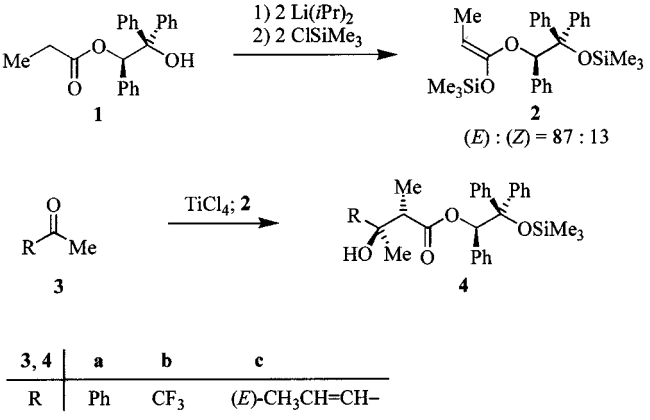
The propionate (*R*)-**1**, which is readily available[15] from (*R*)-1,1,2-triphenyl-1,2-ethanediol,[18] was doubly deprotonated with two equivalents of lithium diisopropylamide. The dianion formed thereby was quenched by the addition of chlorotrimethylsilane to give the silyl ketene acetal **2**, with concomitant protection of the tertiary hydroxy group. In all the Mukaiyama-type aldol and Michael reactions described below, the ketene acetal, which formed as a mixture of (*E*)- and (*Z*)-**2** in a ratio of 87:13, was used without further purification.[19] In order to find out whether the ketene acetal **2** is a suitable nucleophile for an addition to the carbonyl group of non-activated ketones, it was first treated with acetophenone (**3a**) in the presence of titanium tetrachloride. Indeed, a smooth conversion occurred with substantial diastereoselectivity. Although four diastereomeric aldol adducts could be expected to result, one stereoisomer

Table 1. Yields and diastereomeric ratios of carboxylic esters **4a**−**c** and **5** prepared from **2** and ketones **3**

Ketone **3**	Carboxylates **4a**−**c**, **5**		
	Yield[a]	Diastereomeric ratio[b]	
3a	**4a**	78%	85:15
3b	**4b**	80%	94:6
3c	**4c**	79%[c]	91:9
3d	**5**	71%	73:27

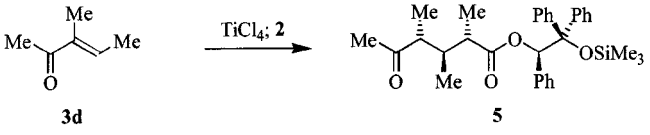
[a] Isolated yield of diastereomerically pure compound. − [b] Defined as the ratio of the major diastereomer to the sum of all others. − [c] After removal of the 1,4 adduct (4.5%).

  1434−193X/01/0816−3155 $ 17.50+.50/0



(**4a**) formed predominantly. The diastereomeric ratio amounted to 85:15, defined as the ratio of the major product to the sum of all others. The *anti*-configuration **4a** was assigned to the main product, which could be isolated as a pure stereoisomer after column chromatography. Even higher diastereoselectivity was obtained in the addition of **2** to trifluoroacetone (**3b**), which gave the carbinol **4b** predominantly (see Table 1).

Having shown that the silyl ketene acetal **2** is able to add to a keto-carbonyl group, the reaction with the enones **3c** and **3d** was tested next. In particular, it had to be found out whether site selectivity[20] (i.e. 1,2- versus 1,4-addition) can be provided along with stereoselectivity. Indeed, predominant 1,2-addition occurred when pentenone **3c** was submitted to a reaction with the ketene acetal **2** in the presence of titanium tetrachloride. NMR analysis of the crude product, which was obtained in 91% yield, revealed that the ratio of 1,2- to 1,4 adducts exceeded 95:5. Here again, one diastereomer had formed predominantly among the aldol adducts so that the ratio of the major stereoisomer **4c** to the sum of all others was 91:9. Careful column chromatography allowed us to isolate not only the main product **4c** but also the three minor diastereomers, which differ in their NMR spectra.



The enone **3d** contains an additional methyl substituent adjacent to the carbonyl group. Thus, steric hindrance around the keto group is enhanced, and, as a consequence, a Michael addition could be expected to be favored over the aldol addition. Indeed, the reaction of the ketene acetal **2** with methylpentenone (**3d**) according to the protocol outlined above led to a remarkable site selectivity of 95:5 in favor of the 1,4-adduct. Since the product of this Michael reaction contains three newly created stereogenic centers, eight diastereomers could result. Remarkably, the ketone **5** formed as the predominant stereoisomer, the diastereomeric ratio amounting to 73:27 (defined as the ratio of **5** to the sum of all other diastereomers). The main product **5**, which contains three contiguous stereogenic centers, could be isolated as a pure stereoisomer by careful column chromatography. Due to the fact that (*R*)-propionate (**1**) had been used, the products **4a**−**c** and **5** were obtained as pure enantiomers.

Structure Determinations and Conversions of Aldol and Michael Adducts 4a−c and 5

The relative configurations of the aldol and Michael products **4a**−**c** and **5** were not known and could not be assigned based on their spectroscopic data. Therefore, the conversion of the esters **4a**−**c** and **5** into suitable derivatives, combined with crystal structure analyses, seemed to be appropriate for solving the question of stereochemistry. For this purpose, the β-hydroxy ester **4c** was treated with tetrabutylammonium fluoride in order to bring about a desilylation and to liberate the tertiary hydroxy group. The diol **6** thus obtained in 74% yield formed suitable crystals for an X-ray structure analysis,[21] the result of which is shown in Figure 1. It clearly reveals the (2*S*,3*S*) configuration of the carboxylic acid moiety in the ester **6**. Surprisingly, the C1−C2 and the C3−C4 bonds are forced to occupy a *gauche* rather than an *antiperiplanar* conformation due to an intramolecular hydrogen bond between the tertiary hydroxy group at one of the stereogenic centers and the carbonyl oxygen atom.

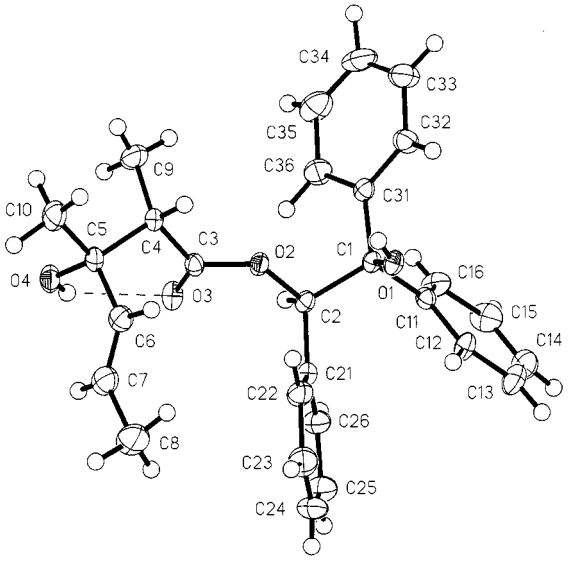
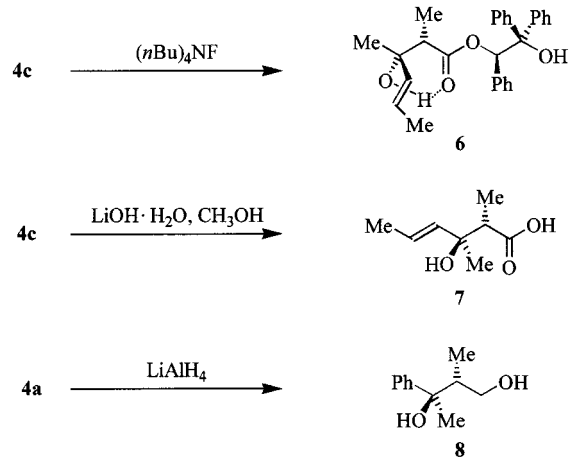


Figure 1. A view of the molecular structure of **6** in the crystal; selected bond lengths [Å] and angles [°]: O(1)−C(1) 1.415(4), O(2)−C(3) 1.341(4), O(2)−C(2) 1.470(3), O(3)−C(3) 1.204(4), O(4)−C(5) 1.426(4), C(1)−C(31) 1.528(4), C(1)−C(11) 1.535(4), C(1)−C(2) 1.560(4), C(2)−C(21) 1.500(4), C(3)−C(4) 1.510(5), C(4)−C(9) 1.537(6), C(4)−C(5) 1.546(5), C(5)−C(6) 1.501(5), C(5)−C(10) 1.525(5), C(6)−C(7) 1.297(6), C(7)−C(8) 1.527; C(1)−O(1)−H(01) 123(4), O(3)−C(3)−C(4) 125.0(3), C(3)−C(4)−C(9) 108.1(4), C(3)−C(4)−C(5) 109.9(3), C(9)−C(4)−C(5) 113.9(3), O(4)−C(5)−C(6) 111.6(3), O(4)−C(5)−C(10) 106.8(3), C(6)−C(5)−C(10) 109.1(3), O(4)−C(5)−C(4) 110.3(3), C(6)−C(5)−C(4) 108.3(3), C(7)−C(6)−C(5) 126.0(4), C(6)−C(7)−C(8) 124.1



The diastereomerically and enantiomerically pure ester **4c** served also to demonstrate that the chiral auxiliary can be removed and recovered when the synthetic target is liberated. For this purpose, the ester **4c** was submitted to a smooth alkaline hydrolysis by means of lithium hydroxide. Thus the carboxylic acid **7** was obtained as a pure stereoisomer in 65% yield, along with recovered (*R*)-1,1,2-triphenylethanediol. No epimerisation was observed during the saponification. A minor amount of propionic acid was formed by retroaldol addition, although this was easily removed by evaporation. Based on the crystal structure analysis of the ester **6**, generated from the same precursor **4c**, the absolute configuration of the carboxylic acid **7** could be assigned to be (2*S*,3*S*).

The *anti*-configuration at the adjacent stereocenters generated by the aldol addition was also confirmed in the case of the carboxylic ester **4a**. For this purpose, the pure stereoisomer **4a** was reduced with lithium aluminium hydride to afford the diol **8** with simultaneous formation of (*R*)-1,1,2-triphenyl-1,2-ethanediol, which could be removed by column chromatography. Both the *syn*- and the *anti*-diastereomers of the racemic diol **8** are known.[22] A comparison of the NMR spectroscopic data therefore allowed us to assign the *anti*-configuration to the diol **8** obtained from the ester **4a**. The absolute configuration of enantiomerically pure **8** as (2*R*,3*R*) was assigned by analogy, assuming the same topicity in the aldol addition to the carbonyl groups of the ketones **3a**−**c**. Based on this argumentation, both the relative and the absolute configuration were assigned to the ester **4b**. Finally, the configuration of the Michael adduct **5** was assigned by an X-ray structure analysis, after suitable crystals of diastereomerically and enantiomerically pure keto ester **5** had been obtained from petroleum ether. The crystal structure,[21] shown in Figure 2, clearly reveals the (2*S*,3*S*,4*R*)-configuration in the carbon chain of the keto ester. Thus, the 1,4-addition of the propionate **1** opens a route to δ-keto esters with three contiguous stereogenic centers in a stereocontrolled manner.

Conclusion

The protocol reported above offers, for the first time, a rather general route for aldol additions to non-activated ketones providing both simple diastereoselection and diastereofacial selectivity.[23] When enones are used as electrophiles, either aldol or Michael reactions occur, depending on the substitution pattern of the enone. The products originating from the aldol reaction such as, for example, **4a**−**c**, **6**, and **7**, contain two vicinal chiral centers, and the 1,4-type adducts **5** contain three contiguous stereogenic carbon centers.[24] One should be aware that the reactions and sequences described herein, which are based on (*R*)-propionate **1**, are equally feasible starting from (*S*)-propionate **1** thus opening a route to the enantiomers of **4a**−**c**, **5**, and **6**−**8**.

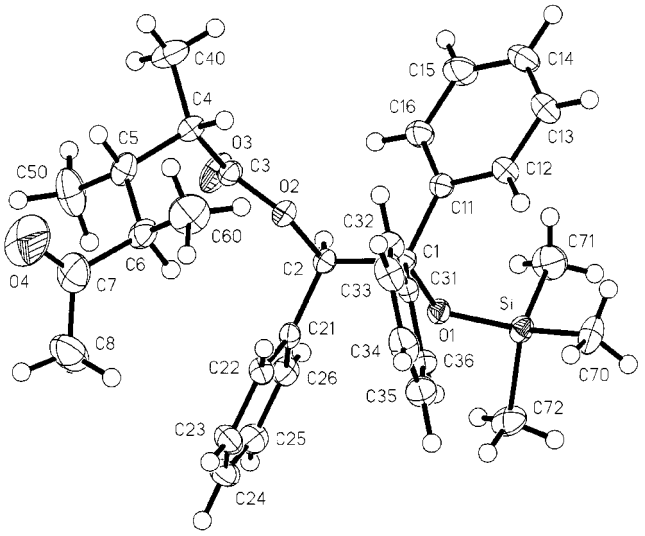


Figure 2. A view of the molecular structure of **5** in the crystal; selected bond lengths [Å] and angles [°]: Si−O(1) 1.645(2), O(1)−C(1) 1.427(3), O(2)−C(3) 1.337(3), O(2)−C(2) 1.451(3), O(3)−C(3) 1.194(4), O(4)−C(7) 1.180(6), C(1)−C(31) 1.522(4), C(1)−C(11) 1.536(4), C(1)−C(2) 1.556(4), C(2)−C(21) 1.499(4), C(3)−C(4) 1.514(4), C(4)−C(40) 1.518(5), C(4)−C(5) 1.540(5), C(5)−C(6) 1.514(4), C(5)−C(50) 1.517(7), C(6)−C(60) 1.510(7), C(6)−C(7) 1.529(6), C(7)−C(8) 1.483(8); C(1)−O(1)−Si 137.44(17), O(1)−C(1)−C(2) 102.3(2), O(2)−C(2)−C(1) 106.9(2), O(3)−C(2)−O(2) 123.2(3), O(3)−C(3)−C(4) 124.5(3), C(3)−C(4)−C(40) 110.0(3), C(3)−C(4)−C(5) 112.2(3), C(40)−C(4)−C(5) 111.5(3), C(6)−C(5)−C(50) 110.6(5), C(6)−C(5)−C(4) 113.8(3), C(5)−C(6)−C(60) 114.2(4), C(5)−C(6)−C(7) 111.1(3), C(60)−C(6)−C(7) 108.6(4), O(4)−C(7)−C(8) 121.3(6), O(4)−C(7)−C(6) 121.5(5), C(8)−C(7)−C(6) 117.1(5)

Experimental Section

Melting points (uncorrected): Büchi 540. − IR: Bruker NIR Vector 22. − NMR: Varian VXR 300, Bruker AM 200 SY and DRX 500. All spectra were recorded in $CDCl_3$, with TMS as internal standard. − MS: Varian MAT 311 A and Finnigan INCOS 50. − Specific rotations: Perkin−Elmer 314. − TLC: DC-Alufolien Sil-60G/UV254 (Merck). − CC: Kieselgel 60, mesh size 0.04−0.063 mm (Merck). − Elemental analyses: Institut für Pharmazeutische Chemie (Universität Düsseldorf). − Crystal structure analyses: Siemens P21/P3 diffractometer.

Solvents and Reagents: All reactions were carried out under an atmosphere of dry nitrogen. Tetrahydrofuran (THF) and diethyl ether were predried with KOH and distilled under N_2 from sodium/

benzophenone. They were taken from the reaction flask, which was closed by a septum, with a syringe or with a cannula. Diisopropylamine was distilled under nitrogen from calcium hydride. Dichloromethane was predried with calcium chloride, filtered, distilled from calcium hydride, and kept over molecular sieves (4 Å). Toluene and *n*-hexane were distilled from sodium/benzophenone. *n*-Butyllithium was purchased as a solution in *n*-hexane. Reactions at temperatures below −20 °C were monitored by a thermocouple connected to a resistance thermometer (Ebro). General remarks concerning the handling of lithium enolates and other organolithium compounds are given in ref.[25]

(*R*)-2-Hydroxy-1,2,2-triphenylethyl Propionate (1): Preparation according to ref.[15]

(*R*)-1-(Trimethylsiloxy)-1-[1,2,2-triphenyl-2-(trimethylsiloxy)-ethoxy]-1-propene (2): Preparation according to ref.[15] in 94−97% yield. The crude product was kept under nitrogen in a refrigerator and used without purification.

General Procedure for the $TiCl_4$-Mediated Addition of Silyl Ketene Acetal 2 to Ketones 3a−d: A 100-mL two-necked flask, connected to a combined nitrogen/vacuum line, was equipped with a magnetic stirrer and a septum. A thermocouple was introduced through the septum. The air in the flask was replaced by nitrogen, and dry dichloromethane (5 mL) and freshly distilled titanium tetrachloride (0.11 mL, 1.0 mmol) were injected through the septum with a syringe. The mixture was cooled to −78 °C, and a solution of the corresponding ketone **3** (1.0 mmol) in dichloromethane (1 mL) was added dropwise by syringe within three min. In a 25-mL flask, the silyl ketene acetal **2** (0.64 g, 1.3 mmol) was dissolved in 1 mL of dichloromethane under nitrogen. This solution was added slowly with a cannula to the 100-mL flask, which was then slightly evacuated. Stirring was continued for 3 h at −78 °C. Water (0.5 mL) and ethyl acetate (60 mL) were added, and the mixture was transferred into a separating funnel. The organic layer was separated, washed three times with 20 mL portions of water, and dried with Na_2SO_4. The solvent was removed on a rotary evaporator and the residue was submitted to an oil pump vacuum for several hours. After the diastereomeric ratio had been determined by ^{1}H NMR spectroscopy, the crude product was purified by column chromatography. According to this general procedure, the following compounds were obtained:

(1*R*)-1,2,2-Triphenyl-2-(trimethylsilyloxy)ethyl (2*S*,3*R*)-3-Hydroxy-2,3-dimethyl-3-phenylpropanoate (4a): Prepared from **2** (2.3 g, 4.7 mmol), freshly distilled titanium tetrachloride (0.37 mL, 3.6 mmol), and acetophenone **3a** (0.42 mL, 3.6 mmol). Crude yield 2.3 g (92%). Diastereomerically pure **4a** (1.95 g, 78%) was obtained by column chromatography (*n*-hexane/ethyl acetate, 6:1); R_f = 0.4. A mixture of the three other diastereomers was also isolated (0.34 g).

4a: $[\alpha]_D^{20}$ = −30.2 (*c* = 1 in chloroform). − ^{1}H NMR (300 MHz): δ = −0.14 [s, 9 H, Si(C*H*$_3$)$_3$], 1.22 [d, *J* = 7.1 Hz, 3 H, CH(C*H*$_3$)COO], 1.35 [s, 3 H, (C*H*$_3$)C(OH)], 2.99 (q, *J* = 7.1 Hz, 1 H, 2-H), 4.07 [s, 1 H, (CH$_3$)C(O*H*)], 6.34 [s, 1 H, C*H*(C$_6$H$_5$)], 6.75−7.51 (m, 20 H, aromatic H). The ^{1}H NMR spectra of the minor diastereomers differ in: δ = 0.82 (d, *J* = 7.1 Hz), 0.96 (d, *J* = 6.8 Hz), 1.20 (d, *J* = 7.1 Hz) (3 H each). − ^{13}C NMR (75 MHz): δ = 1.80 [Si(*C*H$_3$)$_3$], 12.3 [CH(*C*H$_3$)COOH], 26.9 [(*C*H$_3$)C(OH)], 48.8 (C-2), 74.5 (C-3), 78.3 [*C*H(C$_6$H$_5$)], 82.6 [(C$_6$H$_5$)$_2$*C*OSi(CH$_3$)$_3$], 175.9 (C-1). − MS (70 eV, EI): *m*/*z* (%) = 526 (1) [M$^+$ − CH$_3$], 509 (1) [M$^+$ − CH$_3$OH], 345 (45) [C$_{23}$H$_{25}$OSi$^+$], 255 (65) [C$_{22}$H$_{19}$OSi$^+$], 165 (6) [fluorenyl cation], 73 (100) [C$_3$H$_9$Si$^+$]. − C$_{34}$H$_{38}$O$_4$Si (538.7): calcd. C 75.78, H 7.09; found C 75.88, H 7.04.

(1*R*)-1,2,2-Triphenyl-2-(trimethylsilyloxy)ethyl (2*S*,3*R*)-3-Hydroxy-2,3-dimethyl-3-trifluoromethylpropanoate (4b): Prepared from **2** (2.3 g, 4.7 mmol), freshly distilled titanium tetrachloride (0.37 mL, 3.6 mmol), and trifluoroacetone (0.34 mL, 3.6 mmol). The latter volatile compound was precooled in an ice bath (0 °C) before being added by syringe. Crude yield 2.2 g (88%). Diastereomerically pure **4b** (2.0 g, 80%) was obtained by column chromatography (*n*-hexane/ethyl acetate, 7:1). A mixture of the three other diastereomers was also isolated (ca. 0.2 g).

4b: ^{1}H NMR (300 MHz): δ = −0.15 [s, 9 H, Si(C*H*$_3$)$_3$], 1.19 [d, *J* = 7.3 Hz, 3 H, CH(C*H*$_3$)COO], 1.20 [s, 3 H, (C*H*$_3$)C(OH)], 2.73 (q, *J* = 7.2 Hz, 1 H, 2-H), 3.78 [s, 1 H, (CH$_3$)C(O*H*)], 6.60 [s, 1 H, C*H*(C$_6$H$_5$)], 6.77−7.32 (m, 15 H, aromatic H). The ^{1}H NMR spectra of the minor diastereomers differ in: δ = 0.96 (d, *J* = 6.8 Hz), 1.09 (d, *J* = 7.1 Hz), 1.14 (d, *J* = 7.1) (3H each). − ^{13}C NMR (75 MHz): δ = 1.8 [Si(CH$_3$)$_3$], 12.0 [CH(*C*H$_3$)COOH], 20.9 [(*C*H$_3$)C(OH)], 44.4 (C-2), 74.2 (q, ^2J = 36 Hz, C-3], 79.4 [*C*H(C$_6$H$_5$)], 82.6 [(C$_6$H$_5$)COSi(CH$_3$)$_3$], 125.4 (q, ^1J = 246 Hz, CF$_3$), 173.6 (C-1). − MS (70 eV, EI): *m*/*z* (%) = 515 (1) [M$^+$ − CH$_3$], 345 (2) [C$_{23}$H$_{25}$OSi$^+$], 255 (90) [C$_{22}$H$_{19}$OSi$^+$], 165 (15) [fluorenyl cation], 105 (21) [C$_7$H$_5$O$^+$], 75 (18) [C$_2$H$_7$OSi$^+$], 73 (100) [C$_3$H$_9$Si$^+$]. − C$_{29}$H$_{33}$F$_3$O$_4$Si (530.6): Calcd. C 65.58, H 6.72; found C 65.46, H 6.32.

(1*R*)-1,2,2-Triphenyl-2-(trimethylsilyloxy)ethyl (2*S*,3*R*,4*E*)-3-Hydroxy-2,3-dimethyl-4-hexenoate (4c): Prepared by reaction of **2** (0.98 g, 2.0 mmol), freshly distilled titanium tetrachloride (0.17 mL, 1.5 mmol), and **3c** (0.15 mL, 1.5 mmol). Crude yield 0.68 g (91%). Column chromatography (*n*-hexane/ethyl acetate, 5:1) afforded diastereomerically pure **4c** (0.59 g, 79%; R_f = 0.5), 0.06 g of a mixture of the other diastereomers, and 0.034 g of the 1,4-adducts.

4c: ^{1}H NMR (300 MHz): δ = −0.14 [s, 9 H, Si(C*H*$_3$)$_3$], 1.10 [d, *J* = 7.2 Hz, 3 H, CH(C*H*$_3$)COO], 1.12 [s, 3 H, (*C*H$_3$)C(OH)], 1.33 [d, *J* = 6.2 Hz, 3 H, =CH(CH$_3$)], 2.47 (q, *J* = 7.2 Hz, 1 H, 2-H), 3.31 (s, 1 H, OH), 5.31 (dq, J_d = 14 Hz, J_q = 1.3 Hz, 1 H, 4-H), 5.40 (dq, J_d = 14 Hz, J_q = 6.2 Hz, 1 H, 5-H), 6.55 [s, 1 H, OC*H*(C$_6$H$_5$)], 6.78−7.29 (m, 15 H, aromatic H). The ^{1}H NMR spectra of the minor diastereomers of **4c** differ in: δ = 0.91 (d, *J* = 6.9 Hz), 0.93 (d, *J* = 6.8 Hz), 0.94 (d, *J* = 6.9 Hz) (3 H each).

(1*R*)-1,2,2-Triphenyl-2-(trimethylsilyloxy)ethyl (2*S*,3*S*,4*R*)-2,3,4-Trimethyl-5-oxohexanoate (5): Prepared from **2** (1.1 g, 2.3 mmol), freshly distilled titanium tetrachloride (0.19 mL, 1.8 mmol), and 3-methyl-3-penten-2-one (**3d**; 0.20 mL, 1.8 mmol). Crude yield 0.89 g (96%). Diastereomerically pure **5** (0.66 g, 71%) was obtained by column chromatography (*n*-hexane/ethyl acetate, 5:1); R_f = 0.5. A mixture of the other diastereomers (0.23 g) was also isolated.

5: ^{1}H NMR (300 MHz): δ = −0.16 [s, 9 H, Si(C*H*$_3$)$_3$], 0.67 (d, *J* = 6.9 Hz, 3 H, CH$_3$ at C-3), 0.99 (d, *J* = 7.0 Hz, 3 H, CH$_3$ at C-4), 1.05 (d, *J* = 7.1 Hz, 3 H, CH$_3$ at C-2), 1.88 (m, 1 H, 3-H), 2.03 (s, 3 H, 6-H), 2.45 (dq, J_d = 8.5 Hz, J_q = 7.0 Hz, 1 H, 4-H), 2.59 (dq, J_d = 7.0 Hz, J_q = 7.1 Hz, 1 H, 2-H), 6.64 [s, 1 H, C*H*(C$_6$H$_5$)], 6.79−7.36 (m, 15 H, aromatic H). The ^{1}H NMR spectra of the minor diastereomers differ in: δ = 6.56 (s), 6.59 (s), 6.61 (s), 6.63 (s), 6.66 (s) (3 H, each). − ^{13}C NMR (75 MHz): δ = 14.2 (*C*H$_3$ at C-3), 14.7 (*C*H$_3$ at C-4), 15.3 (*C*H$_3$ at C-2), 29.8 (C-6), 39.0 (C-2), 40.8 (C-4), 49.6 (C-3), 78.2 [*C*H(C$_6$H$_5$)], 82.6 [(C$_6$H$_5$)$_2$*C*], 173.9 (C-1), 212.4 (C-5). − MS (70 eV, EI): *m*/*z* (%) = 345 (2) [C$_{23}$H$_{25}$OSi$^+$], 255 (100) [C$_{22}$H$_{19}$OSi$^+$], 165 (4) [fluorenyl cation], 73 (35) [C$_3$H$_9$Si$^+$]. − C$_{32}$H$_{40}$O$_4$Si (516.7): calcd. C 74.38, H 7.77; found C 74.28, H 7.81. − Crystal data for **5**:[21] orthorhombic space group $P2_12_12_1$; *a* = 9.708(3), *b* = 10.710(3), *c* = 29.981(8) Å; *V* = 3013.2(15) Å^3; *Z* = 4; $d_{calcd.}$ = 1.139 Mg/m^3; μ(Mo-K_α) = 0.111 mm^{-1}; *F*(000) = 1112; intensity data 0 ≤ *h* ≤ 12, 0 ≤ *k* ≤ 13, 0 ≤ *l* ≤ 37; $2\theta_{max}$ = 27.56°; *R* = 0.0378, R_w = 0.0891.

(1*R*)-2-Hydroxy-1,2,2-triphenylethyl (2*S*,3*R*,4*E*)-3-Hydroxy-2,3-dimethyl-4-hexenoate (6): A 50-mL two-necked flask, equipped with a septum and a magnetic stirrer, was charged with **4c** (0.5 g, 1.0 mmol) and connected to the combined nitrogen/vacuum line. After the addition of THF (15 mL), the septum was opened and nBu$_4$NF·3H$_2$O (0.63 g, 2.0 mmol) was added rapidly while nitrogen passed through the flask. The flask was closed with the septum, and the mixture was stirred for 3 h at room temp. After cooling to 0 °C, another portion of nBu$_4$NF·3H$_2$O (0.55 g, 1.75 mmol) was added and stirring was continued at 0 °C for 12 h. The mixture was allowed to warm to room temp. and then concentrated on a rotary evaporator. Deionized water (6 mL) and NaCl (1.4 g) were added, and the mixture was extracted four times with a total amount of 120 mL of diethyl ether. The combined organic layers were washed twice with brine and dried with $MgSO_4$. Evaporation of the solvent on a rotary evaporator and subsequently under an oil-pump vacuum afforded a solid crude product which was recrystallized from petroleum ether to give white, crystalline **6**. Yield 0.317 g (74%). − $[\alpha]_D^{20}$ = 66.8 (c = 0.6 in chloroform). − ^{1}H NMR (300 MHz): δ = 0.97 [d, J = 7.1 Hz, 3 H, CH(CH_3)], 1.09 [s, 3 H, (CH_3)C(OH)], 1.35 (d, J = 6.1 Hz, 3 H, 6-H), 2.48 (q, J = 7.1 Hz, 1 H, 2-H), 2.85 [s, 1 H, (C$_6$H$_5$)$_2$COH], 3.19 [s, 1 H, (CH$_3$)C(OH)], 5.31 (dq, J_d = 14 Hz, J_q = 1.3 Hz, 1 H, 4-H), 5.40 (dq, J_d = 14 Hz, J_q = 6.1 Hz, 1 H, 5-H), 6.66 [s, 1 H, CH(C$_6$H$_5$)], 7.01−7.57 (m, 15 H, aromatic H). − ^{13}C NMR (75 MHz): δ = 11.7 [CH(*C*H$_3$)], 17.4 (C-6), 24.7 [(*C*H$_3$)C(OH)], 48.0 (C-2), 72.6 (C-3), 78.7 [*C*H(C$_6$H$_5$)], 80.3 [(C$_6$H$_5$)*C*OH], 123.8 (C-5), 136.5 (C-4), 175.7 (C-1). − MS (70 eV, EI): m/z (%) = 429 (7) [M$^+$]. − C$_{28}$H$_{30}$O$_4$ (430.5): calcd. C 78.11, H 7.02; found C 77.93, H 7.09. − Crystal data for **6**:[21] orthorhombic space group; $P2_12_12_1$; a = 10.658(3), b = 10.762(4), c = 21.472(6) Å; V = 2462.9(13) Å^3; Z = 4; $d_{calcd.}$ = 1.161 Mg/m^3; μ(Mo-K_α) = 0.076 mm^{-1}; F(000) = 920; intensity data $0 \le h \le 13$, $-14 \le k \le 0$, $0 \le l \le 27$; $2\theta_{max}$ = 27.56°; R = 0.0408, R_w = 0.0918.

(2*S*,3*S*)-3-Hydroxy-2,3-dimethyl-4-hexenoic Acid (7): A mixture of **4c** (0.31 g, 0.73 mmol), methanol (85 mL), and water (25 mL) was stirred in a 250-mL flask at 0 °C. A solution of LiOH·H$_2$O (0.33 g, 8.0 mmol) in 25 mL of water was then added. The mixture was stirred for 0.5 h at 0 °C and then for 3 days at room temp. Water (20 mL) was added, and the suspension was extracted three times with a total amount of 150 mL of diethyl ether in order to remove 1,1,2-triphenyl-1,2-ethanediol. The aqueous layer was cooled in an ice bath and acidified to pH = 3 by addition of 1 N hydrochloric acid. The solution was saturated with NaCl and extracted five times with ethyl acetate (150 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated on a rotary evaporator to give colorless, oily **7**. Yield 0.075 g (65%). − $[\alpha]_D^{20}$ = 25.5 (c = 1 in chloroform). − ^{1}H NMR (300 MHz): δ = 1.22 [d, J = 7.2 Hz, 3 H, CH(CH_3)], 1.27 [s, 3 H, (CH_3)C(OH)], 1.69 (d, J = 6.3 Hz, 3 H, 6-H), 2.57 (q, J = 7.2 Hz, 1 H, 2-H), 3.34 [s, 1 H, (CH$_3$)C(OH)], 5.55 (dq, J_d = 15 Hz, J_q = 1.3 Hz, 1 H, 4-H), 5.40 (dq, J_d = 15 Hz, J_q = 6.3 Hz, 1 H, 5-H), 7.2 (broad s, 1 H, COOH). − ^{13}C NMR (75 MHz): δ = 12.2 [CH(*C*H$_3$)], 17.7 (C-6), 24.0 [(*C*H$_3$)C(OH)], 48.2 (C-2), 73.3 (C-3), 124.4 (C-5), 136.2 (C-4), 180.6 (C-1).

(1*R*,2*R*)-1,2-Dimethyl-1-phenyl-1,3-propanediol (8): Under nitrogen, a solution of **4a** (0.70 g, 1.3 mmol) in 5 mL of THF was added slowly to a vigorously stirred suspension of $LiAlH_4$ (0.88 g, 22 mmol) in THF (50 mL) at room temp. Stirring was continued overnight. The mixture was cooled in an ice bath and water (5 mL) was added dropwise. Then, 1 N hydrochloric acid was added dropwise until the precipitate dissolved. The layers were separated, and the aqueous phase was extracted three times with chloroform and ethyl acetate. The combined organic layers were dried with $MgSO_4$ and the solvent was removed on a rotary evaporator. The crude product was submitted to column chromatography (*n*-hexane/ethyl acetate, 4:1). After elution of 1,1,2-triphenyl-1,2-ethanediol, compound **8** was isolated (R_f = 0.3) in 71% yield (0.17 g) as a colorless oil; $[\alpha]_D^{20}$ = −19.8 (c = 1 in chloroform). − ^{1}H NMR (300 MHz): δ = 0.92 [d, J = 7.1 Hz, 3 H, CH(CH_3)], 1.50 [s, 3 H, (CH_3)C(OH)], 1.98−2.03 (m, 1 H, CHCH$_3$), 3.37 [s, 1 H, CH$_2$(OH)], 3.45−3.53 (m, 2 H, CH_2), 3.89 [s, 1 H, (CH$_3$)C(OH)], 7.20−7.44 (m, 5 H, aromatic H). The ^{1}H NMR spectrum is in accordance with that of racemic (2*R**,3*R**)-2-methyl-3-phenyl-1,3-butanediol, described in ref.[22]

Acknowledgments

This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. We would like to thank Dr. A. Steigel, Mrs. M. Beuer, Mrs. I. Menzel, Dr. G. Broszeit, Mr. O. Koersgen, and Mr. R. Bürgel for recording the spectra. Special thanks go to Mrs. S. Houben for carrying out several experiments. Finally, we would like to thank Dr. W. Poll for assistance with the crystal structure analyses.

[1] M. Braun, in *Houben Weyl*, 4th ed., Vol 21b (Eds.: G. Helmchen, R. W. Hoffmann, J. Mulzer, E. Schaumann), Thieme, Stuttgart **1995**, pp. 1603−1666 and 1713−1735.
[2] B. L. Feringa, J. F. G. A. Jansen, in *Houben Weyl*, 4th ed., Vol 21b (Eds.: G. Helmchen, R. W. Hoffmann, J. Mulzer, E. Schaumann), Thieme, Stuttgart **1995**, pp. 2104−2155.
[3] C. H. Heathcock, in *Modern Synthetic Methods 1992* (Ed.: R. Scheffold), VHCA/VCH, Basel/Weinheim, **1992**, pp. 1−102 and references therein.
[4] [4a] D. A. Evans, J. V. Nelson, T. R. Taber, *Top. Stereochem.* **1982**, *13*, 1−115. − [4b] S. Masamune, W. Choy, J. S. Petersen, L. R. Sita, *Angew. Chem.* **1985**, *97*, 1−31; *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 1−30. − [4c] M. Braun, *Angew. Chem.* **1987**, *99*, 24−37; *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 24−37. − [4d] C. H. Heathcock, in *Comprehensive Organic Synthesis* (Eds.: B. M. Trost, I. Fleming, C. H. Heathcock), Pergamon Press, Oxford **1991**, vol. 2, chapter 1.6. − [4e] B. Moon Kim, S. F. Williams, S. Masamune, in *Comprehensive Organic Synthesis* (Ed.: B. M. Trost, I. Fleming, C. H. Heathcock), Pergamon Press, Oxford **1991**, vol. 2, chapter 1.7. − [4f] I. Paterson, in *Comprehensive Organic Synthesis* (Eds.: B. M. Trost, I. Fleming, C. H. Heathcock), Pergamon Press, Oxford **1991**, vol. 2, chapter 1.9. − [4g] M. Braun, H. Sacha, *J. Prakt. Chem.* **1993**, *335*, 653−668
[5] For reviews, see: [5a] M. Sawamura, Y. Ito, in *Catalytic Asymmetric Synthesis* (Ed.: I. Ojima), VCH, Weinheim **1993**, pp. 367−388. − [5b] H. Gröger, E. Vogl, M. Shibasaki, *Chem. Eur. J.* **1998**, *4*, 1137−1141. − [5c] S. G. Nelson, *Tetrahedron: Asymmetry* **1998**, *9*, 357−389. − [5d] R. Mahrwald, *Chem. Rev.* **1999**, *99*, 1095−1120. − [5e] J. S. Johnson, D. A. Evans, *Acc. Chem. Res.* **2000**, *33*, 325−335.
[6] M. Guetté, J. Capillon, J.-P. Guetté, *Tetrahedron* **1973**, *29*, 3659−3667.
[7] E. B. Dongala, D. L. Dull, C. Mioskowski, G. Solladié, *Tetrahedron Lett.* **1973**, 4983−4986.
[8] C. Mioskowski, G. Solladié, *Tetrahedron* **1980**, *36*, 227−236.
[9] S. Kobayashi, Y. Fujishita, T. Mukaiyama, *Chem. Lett.* **1989**, 2069−2072.
[10] J. C. Jacobson, G. P. Reddy, *Tetrahedron Lett.* **1996**, *51*, 8263−8266.
[11] D. A. Evans, M. C. Kozlowski, C. S. Burgey, D. W. C. MacMillan, *J. Am. Chem. Soc.* **1997**, *119*, 7893−7894.
[12] D. A. Evans, D. W. C. MacMillan, K. R. Campos, *J. Am. Chem. Soc.* **1997**, *119*, 10859−10860.

[13] N. Krause, A. Hoffmann-Röder, *Synthesis* **2001**, 171−196.
[14] T. Mukaiyama, *Org. React. N. Y.* **1982**, *28*, 203−331.
[15] H. Sacha, D. Waldmüller, M. Braun, *Chem. Ber.* **1994**, *127*, 1959−1968
[16] See refs.[4c,4g] for an explanation of these terms.
[17] Preliminary communication: M. Braun, B. Mai, D. Ridder, *Synlett* **1999**, 1600−1602.
[18] M. Braun, S. Gräf, S. Herzog, *Org. Synth.* **1993**, *72*, 32−37.
[19] A 1.3-molar ratio of ketene acetal to ketone or enone was used following a protocol for the Mukaiyama Michael reaction: J. Otera, Y. Fujita, S. Fukuzumi, *Tetrahedron* **1996**, *52*, 9409−9418.
[20] For a definition, see: G. Helmchen, in *Houben Weyl*, 4th ed., Vol 21a (Eds.: G. Helmchen, R. W. Hoffmann, J. Mulzer, E. Schaumann), Thieme, Stuttgart **1995**, p. 47−51.
[21] Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-152921. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) +44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].
[22] R. W. Hoffmann, T. Sander, *Chem. Ber.* **1990**, *123*, 145−152.
[23] Remarkably, activated ketones do not seem to be suitable substrates. Thus, the addition of silyl ketene acetal **2** to ethyl pyruvate provides a *syn-anti* ratio of 20:80 and the *anti* isomers are formed with only marginal diastereofacial selectivity.
[24] For approaches to racemic compounds with this type of structural unit, see: G. Courtemanche, A. Alexakis, J. Vaissermann, J.-F. Normant, *J. Organomet. Chem.* **1992**, *423*, 281−305. − For semisynthetic steroids containing this subunit, see: A. Y. L. Shu, C. Djerassi, *J. Chem. Soc., Perkin Trans. I* **1987**, 1291−1305. − For antidepressant indoles with side chains containing this substitution pattern, see: C. A. Demerson, L. G. Humber, G. Santroch, I. L. Jirkovsky, T. A. Dobson, K. Pelz, *Ger. Offen.* 2,306,809; *Chem. Abstr.* **1974**, *80*, 3534q.
[25] R. Devant, U. Mahler, M. Braun, *Chem. Ber.* **1988**, *121*, 397−406.

Received February 21, 2001
[O01086]