5. Synthesis and Reactions of Optically Active 1,3-Diols

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The *'syn'*-1,3-diols **3**, **4**, and **5** with a C_7, C_6, and C_5 chain, respectively, were synthesized from methyl hydrogen 3-hydroxyglutarate (**2**; *Schemes 1* and *2*). The latter is available in (*R*)- and (*S*)-configuration. Octyl (3*R*)-4-chloro-3-hydroxybutanoate (**17**) is an alternative starting material for the preparation of **5** *(Scheme 3)*. The epoxide **20**, derived from **5** in a one-pot reaction, is a versatile synthon, which selectively reacts with a great number of nucleophiles *(Scheme 4)*.

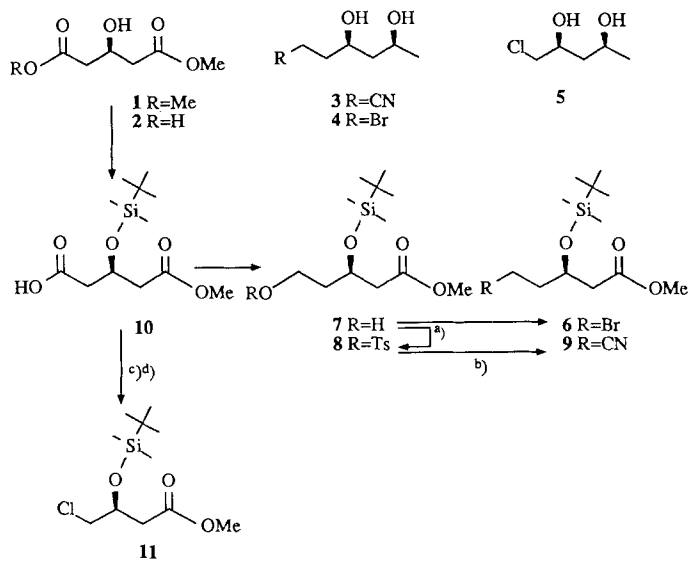
The total synthesis of many biologically active natural products, such as compactin [1a], amphotericin B [1b], or phomenoic acid [1c], require enantiomerically pure 1,3-diols containing variable functional groups. In connection with our current studies on the preparation of chiral synthons from *meso*- or prochiral compounds by enzymatic enantioselective reactions [2], a series of new, optically active 1,3-diols has become available in both enantiomeric forms.

We have recently [2] re-investigated the α-chymotrypsin-catalyzed hydrolysis of dimethyl 3-hydroxyglutarate (**1**) to optically active 1-methyl hydrogen 3-hydroxyglutarate (**2**). The enantiomeric excess (e.e.) of **2** was only 70%, but *Gopalan* and *Sih* [3] have found that esterases from *Corynebacterium equi* and *Acinetobuctex lowfii* yield the (*R*)- and (*S*)-half-esters **2** with much higher enantioselectivity. Therefore, **2** is a versatile starting material for the preparation of optically active synthons.

The *'syn'*-1,3-diols **3**, **4**, and **5** which have a chain consisting of 7, 6, and 5 C-atoms, respectively, are desirable for the synthetic work *(Scheme 1)*. The structural similarity of these compounds suggested **2** as a common starting material for their preparation. Since there is neither a reagent nor a double-diastereocontrolled step in the synthetic pathway, the optical purity of the starting material is not relevant. Hence, the half-ester **2** with only 70% e.e. (α-chymotrypsin) was converted to methyl 5-bromo-3[(*tert*-butyl)dimethylsilyloxy]pentanoate (**6**) *via* 1-methyl hydrogen 3-[(*tert*-butyl)dimethylsilyloxy]glutarate (**10**) and methyl 3-[(*tert*-butyl)dimethylsilyloxy]-5-hydroxypentanoate (**7**) as described earlier [2a]. Conventional tosylation of the free OH group of **7** led to methyl 3-[(*tert*-butyl)dimethylsilyloxy]-5-(tosyloxy)pentanoate (**8**). Methyl 3-[(*tert*-butyl)dimethylsilyloxy]-5-cyanopentanoate (**9**) was obtained in excellent yield, after a S_N2-displacement reaction of the Ts group by the CN group [4] by treatment of **8** with Bu_4NCN in CH_2Cl_2.

The half-ester **10** is sensitive to both acid and base. For this reason, the transformation of the carboxyl group of **10** into a chloride to form compound **11** was only possible by mild radical fragmentation according to the procedure of *Barton et al.* [5]. The

Scheme 1



[a])TsCl, pyridine, CH_2Cl_2. [b])$(Bu)_4NCN$, CH_2Cl_2. [c])$SOCl_2$, MgO. [d])Na salt of *N*-hydroxypyridine-2-thione, cat. 4-(dimethylamino)pyridine, CCl_4.

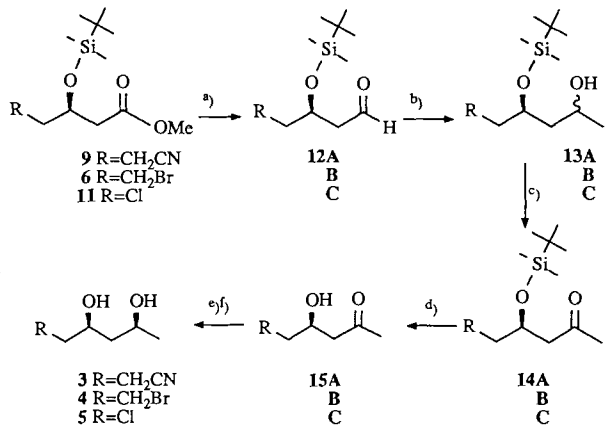
carboxylic acid **10** was first converted to the acyl chloride with $SOCl_2$/MgO. The powdery base neutralised HCl formed in this reaction. The acyl chloride was converted to the thiohydroxamic ester using the Na salt of *N*-hydroxypyridine-2-thione with a catalytic amount of 4-(dimethylamino)pyridine. The resulting diester was heated in CCl_4, without further purification, in order to perform the radical fragmentation leading to **11**. The overall yield of these three steps was *ca.* 40%. Since the centre of chirality is not involved in the course of these reactions, the e.e. of **6**, **9**, and **11** is 70%, *i.e.* the optical purity is the same as for **2**.

Following the desired functionalization of the 1,3-diols **3**, **4**, and **5**, the remaining ester group in **6**, **9**, and **11** had to be transformed into a hydroxyethyl group under stereocontrolled conditions. According to *Reetz* and *Jung* [6], benzyl-protected 3-hydroxyaldehydes are readily converted to *'anti'*-1,3-diols with CH_3TiCl_3 in CH_2Cl_2 at −78° with high selectivity. We, therefore, intended to protect the 3-hydroxy group of **6** by a benzyl group instead of the silyl group, because the former is required due to its *Lewis* basicity. However, we were not able to isolate the desired product in reasonable yields; even under very mild conditions fast elimination took place. An alternative method using optically active isopropoxy(methyl)[(2*R*,3*R*)-1,1,4,4-tetraphenyl-2,3-(isopropylidenedioxy)butan-1,4-dioxy]titanium or the (2*S*,3*S*)-enantiomer, according to *Seebach et al.* [7], for a double-diastereoselective conversion of the aldehyde **12B** to the *'syn'*-diol **4** showed no selectivity.

Therefore, the conversions of **6**, **9**, and **11** into **3**, **4**, and **5**, respectively, were carried as outlined in *Scheme 2*.

Reduction of the esters with diisobutylaluminium hydride (DIBAH) in hexane at −78° led to the aldehydes **12**. The yields were good, except in the case of **12A**, where small

Scheme 2



A R=CH_2CN, **B** R=CH_2Br, **C** R=Cl

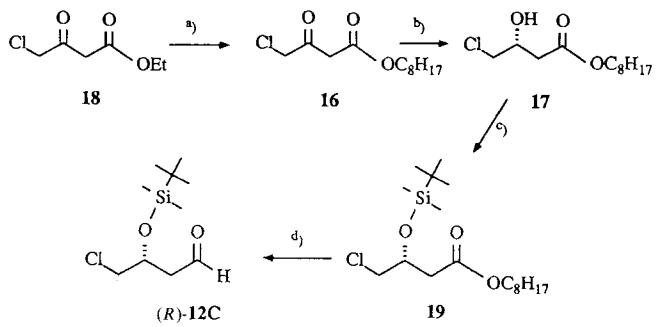
a)DIBAH, hexane, −78°. b)$(i\text{-}PrO)_3TiMe$ or MeMgBr. c)PCC, NaOAc, CH_2Cl_2. d)H^+/THF or H^+/MeOH. e)$(Bu)_3B$. f)$NaBH_4$, −78°.

amounts of dialdehyde were formed. The subsequent reaction with triisopropoxy-(methyl)titanium [7] resulted in diastereoisomeric mixtures of the alcohols **13** in good yields. In the case of the reaction with **12A**, it is highly recommended to use this organometallic reagent because of its high selectivity for the aldehyde group in the presence of other electrophilic centers. In other cases, the *Grignard* reagent can also be used. However, the yields are lower. The subsequent oxidation of the alcohols **13** to the methyl ketones **14** was carried out in a very mild way with pyridinium chlorochromate (PCC) [8] in CH_2Cl_2, with a small amount of NaOAc as buffer. The overall yields were good, *e.g.* 80–85% for the conversion of **11** into **14C**. The subsequent removal of the silyl protecting group in **14** was achieved by treatment with HCl/THF overnight, leading to the 3-hydroxy-ketones **15**. There was no loss of optical activity during this sequence of reactions, as expected (see below).

The fastidious diastereoselective reduction of the 3-hydroxy-ketones to the *'syn'*-diols **3**, **4**, and **5** was achieved with Bu_3B and $NaBH_4$ [9a] ($\geq$ 10:1) according to *Narasaka* and *Pai*. The use of $(i\text{-}Bu)_3B$ instead of Bu_3B did not increase the diastereoselectivity [9b]. The small amount of the undesired *'anti'*-by-product was easily removed by column chromatography. Two other reduction methods, DIBAH in THF [10] (*'syn'*-selective) or $Cl(i\text{-}Pr)_2SiH$ [11] (*'anti'*-selective), also did not lead to higher selectivity. Preliminary experiments with tetramethylammonium triacetoxyborohydride to obtain *'anti'*-1,3-diols, a method published very recently by *Evans* and *Chapman* [12] gave *'anti'*/*'syn'*-selectivity of *ca.* 5:1 in the case of **15C**. The selectivity of the reductions were determined by GC of the acetonide-protected diols.

So far, we have achieved the synthesis of the *'syn'*-1,3-diols **3**, **4**, and **5** using **1** as a common starting material. Since **2** is available in the (*R*)- (> 80% e.e. [3]) and the (*S*)- (> 97% e.e. [3]) form, it is now possible to prepare both enantiomers of each *'syn'*-product. By improvement of the conditions of the reduction according to *Evans*, the *'anti'*-

Scheme 3



[a])(i-PrO)$_4$Ti, 1-octanol/toluene 1:1. [b])Baker's yeast. [c])(*tert*-Butyl)chlorodimethylsilane, imidazol, DMF. [d])DIBAH, hexane, −78°.

products will also become available. The described sequence does not represent the shortest way to prepare the desired compounds, but selectivity and yields are good. In addition, no problems should be encountered in upscaling of the amounts.

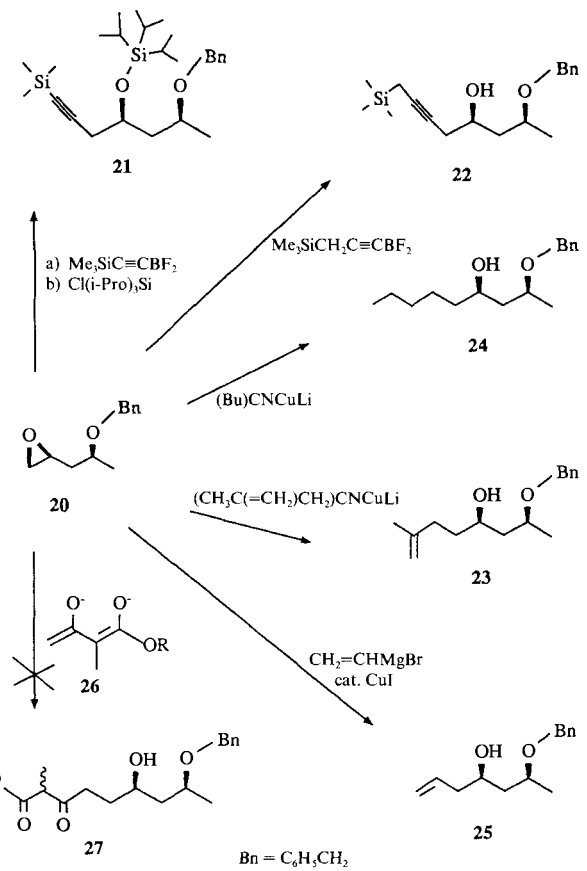
Sih and coworkers [13] reported on the baker's-yeast reduction of octyl 4-chloro-3-oxo-butanoate (**16**) to the (3*R*)-ester **17** with 95% e.e. The similarity of **17** and **11**, the easy availability, and the low price of yeast led us to investigate an additional approach to the 'chloride series'. Therefore, we synthesized **16** from the commercially available ethyl ester **18** by transesterification with (i-PrO)$_4$Ti and 1-octanol.

An improvement of the reaction and the isolation of the products was achieved, as compared to known literature procedures for transesterification, by decreasing the amount of 1-octanol, addition of toluene, and subsequent azeotropic removal of EtOH/toluene and i-PrOH/toluene. The enzymatic reduction of **16** with baker's yeast was carried out according to [13] and led to **17** in a yield of 40% with only about 75% e.e. Probably, the selectivity strongly depends on the type of yeast. The subsequent protection of the OH group as (*tert*-butyl)dimethylsilyl ether and the reduction of the octyl ester **19** to the aldehyde (*R*)-**12C** was realized without any difficulty. This reaction sequence represents a new approach for the preparation of (*R*)-**15C**. The e.e. value of (*R*)-**15C** obtained from **16** by baker's-yeast reduction was 73%, *i.e.* nearly the same found for the intermediate **17**. It was determined by NMR spectroscopy using Eu(hfc)$_3$ as a chiral shift reagent. It, therefore, can be concluded that all reactions took place without racemization.

To increase the versatility of **5**, the diol was converted into the epoxide **20**. This conversion was conducted in a one-pot reaction by treatment with NaH in DMF to generate the dianion for the direct cyclization to the epoxide, and after 30 min, with benzyl chloride in order to protect the free OH group. Compound **20** is not stable when chromatographed on silica gel.

It is well known that monosubstituted epoxides such as **20** are attacked with high selectivity at the less substituted C-atom, *e.g.* by alkinylboranes [14], organo(cyano)-copper(I)lithium reagents (R(CN)CuLi) [15], mixed organocuprates of higher order ($R_2Cu(CN)Li_2$) [16], and Cu(I) catalyzed *Grignard* reagents [17]. To demonstrate the

Scheme 4



utility of **20**, we tested several nucleophiles of this kind which carry either no or additional functional groups.

After treatment of **20** with (trimethylsilyl)acetylene [18] and subsequent protection of the free OH group as triisopropylsilyl ether, compound **21** was obtained in high yield. The reaction with trimethyl(propargyl)silane [18] gave **22** in equally high yield. In both cases, the attack of the corresponding reactive alkinyldifluoroborane intermediate [14] at C(1) of the epoxide **20** took place with a regioselectivity of $> 95\%$, according to a NMR analysis. The same excellent selectivity of the reaction was observed using lithium cyanocuprates [15]. The reagents were either derived from an *in-situ* Sn/Li exchange (2-methyl-2-propenyillithium) or directly used as in the case of BuLi. Thus, **23** and **24** were obtained in good yield. Also, the conversion of **20** into **25** with CuI-catalyzed vinylmagnesium bromide [17] took place with the same high selectivity. The new functional groups in **21**, **22**, **23**, and **25** are very versatile for further transformations.

Finally, it is worthwhile to mention that we were not able to detect a significant amount of product **27**, which is a direct precursor of nonactic acid [19], when the dianions of several 2-methyl-acetoacetates **26** [20] were reacted with the epoxide **20**, even after

variation of solvents and cosolvents with various bases, ratios of reactants, and temperatures. Very recently, *Lygo* and *O'Connor* [21] were able to isolate the desired **27** in 52% yield, but they used a racemic and diastereoisomeric mixture of **20**.

A variety of interesting new chiral compounds are now available for further transformations.

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Experimental Part

General. Water- and air-sensitive reactions were carried out under inert gas. CC = column chromatography. Cap. GC: cross-linked phenylmethylsilicone (25 m), He as carrier gas. $[\alpha]_D$: *Perkin-Elmer-141* polarimeter. IR spectra (cm^{-1}): *Perkin-Elmer-781* IR spectrophotometer. ^{1}H-NMR spectra: *Varian EM 360* and *Varian EM 390* spectrometer. ^{13}C-NMR spectra: *Bruker WH-90* spectrometer. Chemical shifts in ppm relative to internal TMS, or relative to the *s* of $(CH_3)_2Si$ or $(CH_3)_3Si$ of silylated compounds as indicated in parentheses. MS: *VG-70-250* spectrometer.

*Methyl (3R)-3-[(*tert*-Butyl)dimethylsilyloxy]-5-hydroxypentanoate* (**7**). See [2a].

*Methyl (3R)-5-Bromo-3-[(*tert*-butyl)dimethylsilyloxy]pentanoate* (**6**). See [2a].

*Methyl (3R)-3-[(*tert*-Butyl)dimethylsilyloxy]-5-(tosyloxy)pentanoate* (**8**). At 0°, 30 ml of abs. CH_2Cl_2, 2.3 g (8.8 mmol) of **7** (70% e.e.) 2.86 g (15 mmol) of TsCl, and 2 ml (25 mmol) of abs. pyridine were added, in this sequence, into a 50-ml flask. After 2 d, the mixture was quenched with 5 g of ice, extracted twice with ice-cold 1M Na_2CO_3 and once with brine, dried, and evaporated at r.t. to yield the crude product which was quickly purified by CC (CH_2Cl_2): 2.65 g (72%, 70% e.e.) of **7**, colorless oil (purity > 95% by GC). IR (film): 2940, 2920, 2840, 1760, 1590, 1350, 1250, 1180, 1170, 1090, 830, 770, 660. ^{1}H-NMR (90 MHz, CCl_4, $(CH_3)_2Si$): 0.0 (*s*, $(CH_3)_2Si$); 0.85 (*s*, $(CH_3)_3CSi$); 1.85 (*q*, $CH_2(4)$); 2.4 (*d*, $CH_2(2)$); 2.48 (*s*, $CH_3C_6H_4$); 3.6 (*s*, $COOCH_3$); 4.1 (*t*, $CH_2(5)$); 4.2 (*quint.*, CH(3)); 7.5 (*AA'BB'*, arom. H).

*Methyl (3R)-3-[(*tert*-Butyl)dimethylsilyloxy]-5-cyanopentanoate* (**9**). To a soln. of 665 mg (1.6 mmol) of **8** (70% e.e.) in 5 ml of abs. CH_2Cl_2, 430 mg (1.6 mmol) of Bu_4NCN in 5 ml of abs. CH_2Cl_2 were added. After 1 h, the mixture was evaporated at r.t. and directly purified by CC (CH_2Cl_2): 400 mg (92%, 70% e.e.) of **9**, colorless oil (purity > 95% by GC). IR (film): 2980, 2965, 2880, 2250, 1740, 1440, 1250, 1100, 1000, 840, 780. ^{1}H-NMR (90 MHz, $CDCl_3$, $(CH_3)_2Si$): 0.0 (*s*, $(CH_3)_2Si$); 0.9 (*s*, $(CH_3)_3CSi$); 1.9 (*m*, $CH_2(4)$); 2.45 (*m*, $CH_2(2)$, $CH_2(5)$); 3.65 (*s*, $COOCH_3$); 4.25 (*quint.*, CH(3)).

*Methyl (3S)-3-[(*tert*-Butyl)dimethylsilyloxy]-4-chlorobutanoate* (**11**). A mixture of 1.325 g (4.8 mmol) of *methyl hydrogen 3-[(*tert*-butyl)dimethylsilyloxy]glutarate* (**10**; 70% e.e.) and 0.5 g of MgO in a 10-ml flask with reflux condensor was treated with 1.5 ml (20 mmol) of $SOCl_2$ and heated (80°) for 1 h. After cooling to r.t., the solid was removed by filtration with suction and the filtrate evaporated at r.t. The resulting orange oil was dissolved in 20 ml of CCl_4, and 1.49 g (10 mmol) of the Na salt of *N*-hydroxypyridine-2-thione and a catalytic amount of 4-(dimethylamino)pyridine were added. The mixture was heated under reflux for 36 h at 80°, cooled to r.t., treated with 100 ml of Et_2O, extracted twice with brine, dried, and evaporated. Purification by CC (3.5% Et_2O in petroleum ether) yielded 528 mg (41%, 70% e.e.) of pure **11** (purity > 95% by GC). ^{1}H-NMR (90 MHz, $CDCl_3$, $(CH_3)_2Si$): 0.0 (*s*, $(CH_3)_2Si$); 0.85 (*s*, $(CH_3)_3CSi$); 2.6 (*AB* of *ABX*, $CH_2(2)$); 3.5 (*d*, $CH_2(4)$); 3.65 (*s*, $COOCH_3$); 4.3 (*m*, CH(3)).

General Procedure for the Reduction of the Esters **9**, **6**, *and* **11** *to the Aldehydes* **12**. A soln. of 0.47 mmol of the ester (70% e.e.) in 10 ml of abs. hexane was cooled to −78°. Then, 0.55 mmol of DIBAH (1M in hexane) were added dropwise. After 1 h, the reaction was quenched with 0.5 ml of MeOH and warmed up to r.t. After addition of 20 ml of sat. NH_4Cl soln. and 10 ml of Et_2O, the org. phase was extracted once with ice-cold 1M HCl and once with brine, dried, and evaporated at r.t.

*(4R)-4-[(*tert*-Butyl)dimethylsilyloxy]-6-oxohexanenitrile* (**12A**). Purification by CC (CH_2Cl_2) yielded 45.5% (70% e.e.). IR (film): 2980, 2960, 2900, 2860, 2250, 1725, 1250, 1100, 850, 775, 730. ^{1}H-NMR (90 MHz, $CDCl_3$, TMS): 0.1 (*s*, $(CH_3)_2Si$); 0.9 (*s*, $(CH_3)_3CSi$); 1.9 (*m*, $CH_2(3)$); 2.55 (*m*, $CH_2(2)$, $CH_2(5)$); 4.3 (*sext.*, CH(4)); 9.8 (*t*, CH(6)).

*(3S)-5-Bromo-3-[(*tert*-butyl)dimethylsilyloxy]pentanal* (**12B**). Purification by CC (CH_2Cl_2) yielded 80–90% (70% e.e.). ^{1}H-NMR (60 MHz, CCl_4, TMS): 0.1 (*s*, $(CH_3)_2Si$); 0.9 (*s*, $(CH_3)_3CSi$); 2.0 (*m*, $CH_2(4)$); 2.4 (*dd*, $CH_2(2)$); 3.3 (*t*, $CH_2(5)$); 4.25 (*quint.*, CH(3)); 9.65 (*m*, CH(1)).

*(3S)-3-[(*tert*-Butyl)dimethylsilyloxy]-4-chlorobutanal* (**12C**). Purification by CC (CH_2Cl_2) yielded 95% (70% e.e.) of a colorless oil. IR (film): 2960, 2940, 2900, 2860, 2730, 1730, 1250, 1100, 840, 780. ^{1}H-NMR (90 MHz, $CDCl_3$, $(CH_3)_2Si$): 0.0 (*s*, $(CH_3)_2Si$); 0.9 (*s*, $(CH_3)_3CSi$); 2.7 (*dd*, $CH_2(2)$); 3.5 (*AB* of *ABX*, $CH_2(2)$); 4.45 (*quint.*, CH(3)). CI-MS (NH_3): 254, 256 ($[M + NH_4]^+$), 237, 239 ($[M + H]^+$).

General Procedure for the Conversion of **12** *to the Secondary Alcohols* **13**. To a soln. of 1.3 g (5 mmol) of Cl(i-Pro)$_3$Ti in 5 ml of abs. hexane at 0°, 3 ml (4.8 mmol) of MeLi in Et_2O were added, and the white suspension was stirred for 1 h. Then, 0.5 mmol of **12** (70% e.e.) in a small amount of Et_2O were added. After 4 h, the reaction was slowly quenched with 5 ml of ice-cold 1M HCl. The mixture was extracted 3 times with 20 ml of Et_2O, and the org. phases were washed with 20 ml of 1M HCl and 20 ml of brine, dried, and evaporated at r.t.

*(4R,6RS)-4-[(*tert*-Butyl)dimethylsilyloxy]-6-hydroxyheptanenitrile* (**13A**). Yield 50% (70% e.e.) after purification by CC (Et_2O). ^{1}H-NMR (90 MHz, $CDCl_3$, TMS): 0.1 (*s*, $(CH_3)_2Si$); 0.9 (*s*, $(CH_3)_3CSi$); 1.2 (*d*, $CH_3(7)$); 1.6 (*m*, $CH_2(5)$); 1.9 (*m*, $CH_2(3)$); 2.4 (*t*, $CH_2(2)$); 2.75 (br. *s*, OH); 4.0 (*m*, CH(4), CH(6)).

*(2RS,4S)-6-Bromo-4-[(*tert*-butyl)dimethylsilyloxy]hexan-2-ol* (**13B**). MeMgBr was used instead of the Ti reagent. Yield 70–80% (70% e.e.) after purification by CC (CH_2Cl_2). ^{1}H-NMR (60 MHz, $CDCl_3$, $(CH_3)_2Si$): 0.0 (*s*, $(CH_3)_2Si$); 0.8 (*s*, $(CH_3)_3CSi$); 1.1 (*d*, $CH_3(1)$); 1.6 (*t*, $CH_2(3)$); 2.0 (*m*, $CH_2(5)$); 2.5 (br. *s*, OH); 3.4 (*dd*, $CH_2(6)$); 4.0 (*m*, CH(2), CH(4)).

*(2RS,4S)-4-[(*tert*-Butyl)dimethylsilyloxy]-5-chloropentan-2-ol* (**13C**) (70% e.e.) was not further purified. IR (film): 3600–3100, 2960, 2930, 2900, 2860, 1460, 1250, 1100, 950, 840, 780. ^{1}H-NMR (60 MHz, $CDCl_3$, TMS): 0.1 (*s*, $(CH_3)_2Si$); 0.9 (*s*, $(CH_3)_3CSi$); 1.2 (*d*, $CH_3(1)$); 1.8 (*m*, $CH_2(3)$); 2.5 (br. *s*, OH); 3.5 (*dd*, $CH_2(5)$); 4.1 (*m*, CH(2), CH(4)).

General Procedure for the Oxidation of **13** *to the Ketones* **14**. To a soln. of 0.42 mmol of **13** (70% e.e.) in 2 ml of abs. CH_2Cl_2, a small amount of NaOAc and 215 mg (1 mmol) of PCC were added. The suspension quickly turned to black and after 4 h, TLC showed absence of educt. Then, 5 ml of abs. Et_2O were added and the soln. (with the rubberlike solid) was filtered through 2 cm of *Florisil* with 15 ml more Et_2O and the solvents were evaporated at r.t.

*(4R)-4-[(*tert*-Butyl)dimethylsilyloxy]-6-oxoheptanenitrile* (**14A**). Purification by CC (CH_2Cl_2) yielded 80% (70% e.e.). IR (film): 2960, 2940, 2900, 2860, 2250, 1730, 1360, 1255, 1090, 910, 840, 770, 730. ^{1}H-NMR (90 MHz, $CDCl_3$, TMS): 0.1 (*d*, $(CH_3)_2Si$); 0.85 (*s*, $(CH_3)_3CSi$); 1.8 (*m*, $CH_2(3)$); 2.1 (*quint.*, CH(4)).

*(4S)-6-Bromo-4-[(*tert*-butyl)dimethylsilyloxy]hexan-2-one* (**14B**). Purification by CC (CH_2Cl_2) yielded 80–90% (70% e.e.). ^{1}H-NMR (90 MHz, $CDCl_3$, TMS): 0.1 (*d*, $(CH_3)_2Si$); 0.85 (*d*, $(CH_3)_3CSi$); 2.0 (*q*, $CH_2(5)$); 2.15 (*s*, $CH_3(1)$); 2.6 (*AB* of *ABX*, $CH_2(3)$); 3.4 (*t*, $CH_2(6)$); 4.3 (*m*, CH(4)).

*(4S)-4-[(*tert*-Butyl)dimethylsilyloxy]-5-chloropentan-2-one* (**14C**). Purification by CC yielded 85–95% (70% e.e.). IR (film): 2960, 2940, 2900, 2860, 1720, 1350, 1250, 1100, 900, 840, 770, 730. ^{1}H-NMR (90 MHz, $CDCl_3$, TMS): 0.1 (*d*, $(CH_3)_2Si$); 0.9 (*s*, $(CH_3)_3CSi$); 2.2 (*s*, $CH_3(1)$); 2.7 (*d*, $CH_2(3)$); 3.45 (*d*, $CH_2(5)$); 4.3 (*quint.*, CH(4)). ^{13}C-NMR (22.63 MHz, $CDCl_3$, TMS): −4.8, −4.9 ($(CH_3)_2Si$); 18.4 ($(CH_3)_3CSi$); 25.7 ($(CH_3)_3CSi$); 31.0 (C(1)); 48.4 (C(3), C(5)); 68.7 (C(4)); 205.4 (C(2)). CI-MS (NH_3): 251, 253 ($[M + H]^+$).

General Procedure for Cleaving of **14**. After treatment of 32 mmol of **14** (70% e.e.) with 1 ml of conc. HCl in 100 ml THF for 1 d, Na_2SO_4 and Na_2CO_3 were added as long as CO_2 was evolved to neutralize and dry the soln. Then, the solids were removed by filtration and the solvents evaporated at r.t.

(4R)-4-Hydroxy-6-oxoheptanenitrile (**15A**). Purification by CC (Et_2O) yielded 53% (70% e.e.). IR (film): 3700–3200, 2940, 2250, 1720, 1430, 1360, 1160, 1100. ^{1}H-NMR (90 MHz, $CDCl_3$, TMS): 1.8 (*m*, $CH_2(3)$); 2.2 (*s*, $CH_3(7)$); 2.5 (*m*, $CH_2(2)$, $CH_2(5)$); 3.4 (*d*, OH); 4.1 (*quint.*, CH(4)).

(4S)-6-Bromo-4-hydroxyhexan-2-one (**15B**). The hydrolysis was achieved in MeOH/HCl, and after workup and purification by CC (Et_2O), 55% (70% e.e.) of pure **15B** was isolated. ^{1}H-NMR (90 MHz, $CDCl_3$, TMS): 1.9 (*m*, $CH_2(5)$); 2.15 (*s*, $CH_3(1)$); 2.6 (*d*, $CH_2(3)$); 2.8 (br. *s*, OH); 3.5 (*m*, $CH_2(6)$); 4.25 (*m*, CH(4)).

(4S)-5-Chloro-4-hydroxypentan-2-one (**15C**). Purification by FC (2.5% AcOEt/CH_2Cl_2) yielded 70% (70% e.e.) of pure **15C**, a colorless oil. IR (film): 3600–3200, 2960, 2920, 1720, 1440, 1360, 1160, 1100, 1070. ^{1}H-NMR (90 MHz, $CDCl_3$, TMS): 2.25 (*s*, $CH_3(1)$); 2.8 (*d*, $CH_2(3)$); 2.9 (br. *s*, OH); 3.6 (*d*, $CH_2(5)$); 4.3 (*quint.*, CH(4)).

General Procedure for the 'syn'-*Selective Reduction of* **15**. To a soln. of 0.28 mmol of **15** (70% e.e.) in 1 ml of abs. THF, 0.3 ml (0.3 mmol) of Bu_3B were added. Then, 0.5 ml of air was bubbled through and the mixture was stirred for 2 h. After cooling to −78°, 0.01 g (0.3 mmol) of $NaBH_4$ was added. After 4 h, the reaction was quenched with 4 ml of H_2O_2/MeOH/buffer (pH 7) 1:1:2 and the inorg. phase extracted 5 times with CH_2Cl_2. Then, the org. layers were dried and evaporated at r.t., and the remaining colorless oil was treated 4 times with 1 ml of 1% HCl in MeOH and evaporated again. Purification by CC (Et_2O) yielded a colorless oil free of undesired *'anti'*-by-product.

A small amount of crude diol was treated with 2,2-dimethoxypropane and 1 drop of conc. HCl and stirred for 24 h. Then, the reaction was quenched with Na_2CO_3, diluted with Et_2O, and used directly for cap.-GC analyses.

(4R,6S)-4,6-Dihydroxyheptanenitrile (**3**). Yield 70% (70% e.e.), *'syn'/'anti'* 10.5:1. ^{1}H-NMR (90 MHz, $CDCl_3$, TMS): 1.2 (*d*, CH_3(7)); 1.65 (*t*, CH_2(5)); 1.8 (*m*, CH_2(3)); 2.5 (*t*, CH_2(2)); 3.65 (br. *s*, 2 OH); 4.15 (*m*, CH(4), CH(6)).

(2S,4S)-6-Bromo-2,4-hexanediol (**4**). Yield 81% (70% e.e.), *'syn'/'anti'* = 10:1. ^{1}H-NMR (90 MHz, $CDCl_3$, TMS): 1.2 (*d*, CH_3(1)); 1.6 (*t*, CH_2(3)); 2.0 (*q*, CH_2(5)); 3.0 (br. *s*, 2 OH); 3.5 (*t*, CH_2(6)); 4.1 (*m*, CH(2), CH(4)).

(2S,4S)-1-Chloro-2,4-pentanediol (**5**). Yield 91% (70% e.e.), *'syn'/'anti'* 15:1. IR (film): 3600–3100, 2980, 2940, 2920, 2900, 1430, 1380, 1320, 1140, 1080, 950, 740. ^{1}H-NMR (90 MHz, $CDCl_3$, TMS): 1.25 (*d*, CH_3(5)); 1.65 (*m*, CH_2(3)); 3.5 (*d*, CH_2(1)); 3.65 (*s*, 2 OH); 4.1 (*m*, CH(2), CH(4)).

Octyl 4-Chloro-3-oxobutanoate (**16**). Under inert gas, 29.4 g (179 mmol) of *ethyl 4-chloro-3-oxobutanoate* (**18**), 300 ml of 1-octanol/toluene 1:1 and 15 ml (50 mmol) of (i-PrO)$_4$Ti were mixed in a 500-ml round-bottomed flask equipped with a condenser for downward destillation. During 8 h, azeotropic mixtures toluene/i-PrOH and toluene/EtOH were slowly distilled off. At the end, the temp. reached the b.p. of toluene. After addition of 200 ml of Et_2O, the mixture was extracted twice with 200 ml of 1N HCl, dried, and evaporated at r.t., until an orange mixture of **16** and 1-octanol remained. A vacuum distillation (95°/15) removed most of the 1-octanol, and a FC (CH_2Cl_2) yielded 34.5 g (77%) of **16**, slightly orange oil (purity > 95% by NMR). IR (film): 2960, 2930, 2860, 1750, 1730, 1650, 1560, 1400, 1320, 1220. ^{1}H-NMR (90 MHz, $CDCl_3$, TMS): 1.3 (br. *s*, CH_2(3') to CH_2(7'), CH_3(8')); 1.65 (*s*, CH_2(2')); 3.65 (*s*, CH_2(2)); 4.1 (*t*, CH_2(1')); 4.2 (*s*, CH_2(4)).

Octyl (3R)-4-Chloro-3-hydroxybutanoate (**17**). For 3 h, 5 1000-ml *Erlenmeyer* flasks containing each 3 g (12 mmol) of **16**, 60 g of baker's yeast, and 300 ml of H_2O were agitated on a shaking machine (200 r.p.m.). After this time, TLC showed absence of educt. The combined suspensions were extracted 3 times with each 1.5 l of AcOEt. After drying and evaporation of the solvent, the crude product was purified by CC (CH_2Cl_2) yielding 6.1 g (40%) of **17** as colorless oil (75% e.e., by MTPA ester). $[\alpha]_D = +12.6°$ (*c* = 10.2, $CHCl_3$). IR (film): 3600–3200, 2960, 2930, 2860, 1730, 1470, 1400, 1300, 1250, 1190, 1150, 1050, 750. ^{1}H-NMR (90 MHz, $CDCl_3$, TMS): 1.3 (br. *s*, CH_2(3') to CH_2(7'), CH_3(8')); 1.65 (*d*, CH_2(2')); 2.6 (*d*, CH_2(2)); 3.0 (br. *s*, OH); 3.55 (*d*, CH_2(4)); 4.1 (*t*, CH_2(1')); 4.2 (*m*, CH(3)).

*Octyl (3R)-3-[(*tert*-Butyl)dimethylsilyloxy]-4-chlorobutanoate* (**19**). To 10 ml of abs. DMF in a 50-ml flask were added 1.35 g (5.4 mmol) of **17** (75% e.e.) 0.97 g (6.5 mmol) of (*t*-Bu)Me$_2$SiCl, and 1.02 g (15 mmol) of imidazole. After 14 h, the mixture was quenched with ice, taken up in 100 ml of Et_2O, extracted twice with 100 ml of sat. NH_4Cl soln., and once with brine. The org. layer was dried and evaporated at r.t. Purification by CC (CH_2Cl_2) yielded 1.95 g (98%, 75% e.e.) of pure **19**, as colorless oil. IR (film): 2960, 2930, 2860, 1740, 1470, 1310, 1250, 1100, 850, 780. ^{1}H-NMR (90 MHz, $CDCl_3$, TMS): 0.1 (*d*, $(CH_3)_2$Si); 0.9 (*s*, $(CH_3)_3$CSi); 1.4 (br. *s*, CH_2(3') to CH_2(2'), CH_3(8')); 1.7 (*m*, CH_2(2')); 2.65 (*AB* of *ABX*, CH_2(2)); 3.5 (*d*, CH_2(4)); 4.1 (*t*, CH_2(1')); 4.35 (*quint.*, CH(3)). CI-MS (NH_3): 365, 367 ($[M + H]^+$).

(2SR,4SR)-4-(Benzyloxy)-1,2-epoxypentane (**20**). A soln. of 450 mg of *rac*-**5** in 15 ml of abs. DMF was slowly treated (attention: H_2 evolution) with 0.45 g (15 mmol) of NaH (80% in white oil) at 0°. After 0.5 h, 0.63 g (5 mmol) of $C_6H_5CH_2Cl$ were added dropwise and the mixture was stirred for another 2 h. Then, the grey-to-brown suspension was carefully hydrolyzed with 1M HCl (cooling!), taken up in 100 ml H_2O/Et_2O 1:1, and the aq. layer extracted twice with 50 ml of Et_2O. The org. phases were washed twice with brine, dried, and evaporated at r.t. A quick purification by CC (1% MeOH/CH_2Cl_2) yielded 335 mg (54%) of pure **20**, a colorless oil which must be stored at −30° under Ar. IR (film): 3030, 2980, 2930, 2865, 1500, 1455, 1375, 1340, 1130, 1100, 1070, 1030, 910, 830, 730, 700. ^{1}H-NMR (90 MHz, $CDCl_3$, TMS): 1.25 (*d*, CH_3(5)); 1.75 (*m*, CH_2(3)); 2.4 (*dd*, CH(1)); 2.7 (*dd*, CH(1)); 3.0 (*m*, CH(2)); 3.7 (*sext.*, CH(4)); 4.5 (*AB*, PhCH_2); 7.3 (*s*, arom. H). ^{13}C-NMR (22.63 MHz, $CDCl_3$, TMS): 19.7 (C(1)); 39.5 (C(3)); 46.6 (C(1)); 49.3 (C(2)); 70.3 (PhCH_2); 72.7 (C(4)); 127.4 (arom. C); 127.5, 128.3 (2 × 2 arom. C); 139.0 (arom. C). EI-MS (70 eV): 192 (M^+), 191 ($[M - 1]^+$), 91 (100).

(4RS,6SR)-6-(Benzyloxy)-4-(triisopropylsilyloxy)-1-(trimethylsilyl)hept-1-ine (**21**). A soln. of 0.211 ml (1.5 mmol) of (trimethylsilyl)ethine in 2 ml of abs. THF was cooled to −78°. After addition of 1.34 ml (1.5 mmol) of BuLi (in hexane), the mixture was stirred at −78° for 10 min. Then, 0.2 ml (1.55 mmol) of $BF_3 \cdot Et_2O$ were added. The mixture was stirred again for 10 min, 192 mg (1 mmol) of **20** in 0.5 ml of abs. THF were added, and after 0.5 h, the reaction was quenched with 2 ml of sat. NH_4Cl soln. The suspension was taken up in 5 ml of sat. NH_4Cl soln. and 10 ml of AcOEt and the inorg. phase was extracted twice with 10 ml of AcOEt. After drying and evaporation of the solvent, the crude product was directly used for the next step. It was dissolved in 2 ml of abs. DMF and treated with 0.29 g (1.5 mmol) of (i-PrO)$_3$SiCl and 0.24 g (3.5 mmol) of imidazole. After 14 h, the mixture was worked up in the same manner as **19**. Purification by CC (CH_2Cl_2) yielded 340 mg (76%) of **21**, as colorless oil.

^{1}H-NMR (90 MHz, $CDCl_3$, $(CH_3)_3Si$–C(1)): 0.0 (*s*, $(CH_3)_3Si$); 1.0 (br. *s*, $(CH_3)_2CH$–Si); 1.1 (*m*, $(CH_3)_2CH$–Si); 1.2 (*d*, CH_3(7)); 1.7 (*t*, CH_2(5)); 2.4 (*d*, CH_2(3)); 3.9 (*m*, CH(4), CH(6)); 4.5 (*AB*, PhCH_2); 7.2 (*s*, arom. H). ^{13}C-NMR (22.63 MHz, $CDCl_3$, $CDCl_3$): 0.0 ($(CH_3)_3Si$); 12.5 ($(CH_3)_2CH$–Si); 17.7 ($(CH_3)_2CH$–Si); 19.3 (C(7)); 28.7, 42.1 (C(3), C(5)); 67.3, 72.7 (C(4), C(6)); 70.7 (PhCH_2); 87.1, 103.6 (C(1), C(2)); 127.7, 128.4 (5 arom. C); 138.6 (arom. C).

*(2*RS,*4*SR*)-2-(Benzyloxy)-8-(trimethylsilyl)oct-6-in-4-ol* (**22**). The reaction was carried out as for **21**, except using 3-(trimethylsilyl)prop-1-ine instead of (trimethylsilyl)ethine. The crude product was purified by CC (CH_2Cl_2) yielding 85% of pure **22**. IR (film): 3600–3200, 3100, 3070, 3040, 2960, 2900, 1600, 1550, 1250, 1100, 850, 730, 700. ^{1}H-NMR (90 MHz, $CDCl_3$, $(CH_3)_3Si$): 0.0 (*s*, $(CH_3)_3Si$); 1.15 (*m*, CH_2(3)); 2.2 (*m*, CH_2(5)); 2.8 (br. *s*, OH); 3.9 (*m*, CH(2), CH(4)); 4.4 (*AB*, PhCH_2); 7.2 (*s*, arom. H). ^{13}C-NMR (22.63 MHz, $CDCl_3$, $CDCl_3$): –2.1 ($(CH_3)_3Si$); 7.0 (C(8)); 19.6 C(1)); 28.0, 42.4 (C(3), C(5)); 67.5, 72.6 (C(2), C(4)); 70.5 (PhCH_2); 75.0, 79.9 (C(6), C(7)); 127.5, 128.2 (5 arom. C); 138.6 (arom. C). CI-MS (NH_3): 305 (100, $[M + H]^+$).

*(2*RS,*4*SR*)-2-Benzyloxy-7-methyl-7-octene-4-ol* (**23**). To a soln. of 2 g (4.94 mmol) of (2-methyl-2-propenyl)-triphenyltin in 15 ml of abs. Et_2O at 0°, 2.5 ml (5 mmol) of PhLi (2M in benzene/Et_2O) were added. Upon stirring the mixture for 0.5 h, white tetraphenyltin precipitated. After cooling to –50°, 450 mg (5 mmol) of Cu(I)CN were added, and the mixture was warmed up to –20° during 1 h. Then the orange suspension was cooled again to –50°, and 430 mg (2.2 mmol) of **20** in 2 ml of abs. Et_2O were added. After slowly warming up to r.t. and a reaction time of 16 h, 2 ml of sat. NH_4Cl soln. were added and the solids were removed by filtration. The filtrate was extracted twice with 20 ml of Et_2O, and the org. phases were washed with brine. Drying, evaporation of the solvent at r.t., and purification by CC (0.5% CH_3OH in CH_2Cl_2) yielded 346 mg (62%) of pure **23**, as colorless oil. IR (film): 3600–3200, 3080, 3040, 2980, 2940, 2880, 1650, 1600, 1450, 1380, 1140, 1100, 1070, 1030, 910, 730, 700. ^{1}H-NMR (90 MHz, $CDCl_3$, TMS): 1.2 (*d*, CH_3(1)); 1.6 (*m*, CH_2(3), CH_2(5)); 1.7 (*s*, CH_3–C(7)); 2.1 (*m*, CH_2(6)); 3.3 (br. *s*, OH); 3.8 (*m*, CH(2), CH(4)); 4.5 (*AB*, PhCH_2); 4.7 (br. *s*, CH_2(8)); 7.3 (*s*, arom. H). ^{13}C-NMR (22.63 MHz, $CDCl_3$, TMS): 19.5 (C(1)); 22.4 (CH_3–C(7)); 34.0 (C(5)); 35.8 (C(6)); 43.4 (C(3)); 68.3, 72.7 (C(2), C(4)); 70.6 (PhCH_2); 109.9 (C(8)); 127.6, 127.7, 128.4 (5 arom. C); 138.7 (arom. C); 145.6 (C(7)).

*(2*SR,*4*RS*)-2-(Benzyloxy)nonan-4-ol* (**24**). A mixture of 6.25 ml (10 mmol) of BuLi (1.6M in hexane) and 30 ml of abs. Et_2O was cooled to –50°. After addition of 895 mg (10 mmol) of Cu(I)CN, the mixture was warmed up to r.t. during 1 h. It turned to dark green. Then, it was again cooled to –50°, 580 mg (3 mmol) of **20** in 1 ml of abs. Et_2O were added, and after coming up to r.t. over night, the mixture was taken up in 50 ml of Et_2O. The inorg. layer was extracted twice with Et_2O, and the org. phases were washed with brine. After drying and evaporation at r.t., the crude product was purified by FC (CH_2Cl_2) yielding 500 mg (66.5%) of pure **24**. IR (film): 3600–3200, 3100, 3080, 3040, 2970, 2940, 2870, 1500, 1460, 1360, 1150, 1120, 1100, 1070, 1030, 740, 700. ^{1}H-NMR (90 MHz, $CDCl_3$, TMS): 0.9 (br. *t*, CH_3(9)); 1.3 (br. *m*, CH_3(1), CH_2(5) to CH_2(8)); 1.6 (*m*, CH_2(3)); 3.1 (br. *s*, OH); 3.85 (*m*, CH(2), CH(4)); 4.5 (*AB*, PhCH_2); 7.3 (*s*, arom. H). ^{13}C-NMR (22.63 MHz, $CDCl_3$, TMS): 14.0 (C(9)); 19.5 (C(1)); 22.7, 25.2, 32.0, 37.8, 43.4 (C(3), C(5) to C(8)); 68.5, 72.9 (C(2), C(4)); 70.6 (PhCH_2); 127.5, 127.7, 128.4 (5 arom. C); 138.8 (arom. C).

*(4*RS,*6*SR*)-6-(Benzyloxy)-1-hepten-4-ol* (**25**). A mixture of 10 mg of Cu(I)I and 10 ml of abs. Et_2O was cooled to –78° and treated with 3.5 ml (3.5 mmol) of vinylmagnesiumbromide (1M in THF). After 15 min, 576 mg (3 mmol) of **20** in 1 ml of Et_2O were added, and the mixture was brought to r.t. during the night. The mixture was hydrolyzed with 2 ml of 1M HCl and taken up in 50 ml of Et_2O. The inorg. phase was extracted twice with 50 ml of Et_2O and the org. layer was washed with brine. Drying, evaporation of the solvents at r.t., and purification by CC (Et_2O/petroleum ether 1:1) yielded 450 mg (68%) of pure **25**. IR (film): 3600 3200, 3080, 3040, 2980, 2940, 2880, 1650, 1500, 1380, 1350, 1100, 1070, 1030, 920, 740, 700. ^{1}H-NMR (90 MHz, $CDCl_3$, TMS): 1.2 (*d*, CH_3(7)); 1.55 (*m*, CH_2(5)); 2.2 (br. *t*, CH_2(3)); 3.5 (br. *s*, OH); 3.9 (*m*, CH(4), CH(6)); 4.5 (*AB*, PhCH_2); 5.1 (br. *d*, CH_2(1)); 5.9 (*m*, CH(2)); 7.3 (br. *s*, arom. H). ^{13}C-NMR (22.63 MHz, $CDCl_3$, TMS): 19.7 (C(7)); 42.3, 43.1 (C(3), C(5)); 67.6, 72.6 (C(4), C(6)); 70.6 (PhCH_2); 117.1 (C(1)); 127.5, 127.6, 128.3 (5 arom. C); 135.1 (C(2)); 138.8 (arom. C). CI-MS (NH_3): 221 ($[M + H]^+$).

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