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Application of (2*R*,3*R*)-dihydroxy-1,2,3,4-tetrahydronaphthalene to asymmetric synthesis

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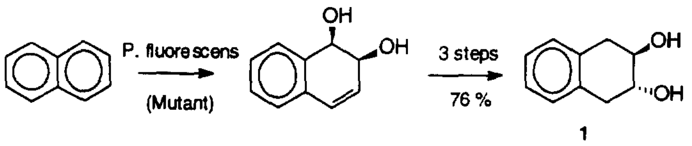
Abstract: (2*R*,3*R*)-Dihydroxy-tetrahydronaphthalene, prepared via an efficient chemoenzymatic procedure from naphthalene, has been successfully tested, as a chiral auxiliary in diastereoselective conjugate additions of lithium dialkylcuprates to α,β-unsaturated esters and in stereoselective alkylations of β-ketoesters. © 1997 Published by Elsevier Science Ltd

In a previous paper we reported a high yield, three steps synthesis of (2*R*,3*R*)-dihydroxy-1,2,3,4-tetrahydronaphthalene **1** from (1*R*,2*S*)-dihydroxy-1,2-dihydronaphthalene[1], the latter obtained by bioconversion of naphthalene with a modified strain of *Pseudomonas fluorescens* (Scheme 1). In this paper we report some applications of the diol **1** as a chiral auxiliary to asymmetric synthesis: in particular in diastereoselective conjugate additions to α,β-unsaturated esters **2** and **3**, and in diastereoselective alkylations of derivatives **8** and **9**, obtained by reaction of **1** with β-keto esters.



Scheme 1.

Diastereoselective conjugate addition to esters

The esters **2** and **3**, prepared by usual acylation methods with crotonic anhydride and cinnamoyl chloride respectively, were chosen as substrates for conjugate additions. The best results in terms of yield and diastereoisomeric ratio were obtained in the addition of lithium dibutylcuprate and lithium diphenylcuprate to the monocrotonate **2** (Scheme 2, Table 1) in diethyl ether. The diastereoisomeric ratio and the absolute configuration of the new stereocentre formed by addition of lithium dibutylcuprate to the monocrotonate **2** was determined by $LiAlH_4$ reduction of **4** to (*S*)-3-methylheptanol[2] and measurement of its specific rotation. The enantiomeric excess of (*S*)-3-methylheptanol was further confirmed by analysis of the ^1H NMR spectrum taken in the presence of a chiral europium(III) shift reagent.

The diastereoisomeric ratio and the absolute configuration of the new stereocentre formed by addition of lithium diphenylcuprate to **2** were determined by ^1H NMR analysis of the corresponding Mosher's ester [(+)-α-methoxy-α-trifluoromethyl-phenylacetic ester][3a,4] and comparison with the ^1H NMR data obtained using (1*R*,2*R*)-dihydroxycyclohexandiol as the chiral auxiliary[3b]. The absolute configuration was also confirmed by hydrolysis of **5** to (*R*)-3-phenylbutyric acid[5].

Less satisfactory results were obtained when the monocinnamate **3** was used, due to its low solubility in diethyl ether. Little of the 1,4-addition product **6** was obtained, albeit with a high diastereoisomeric ratio, by addition of lithium dimethylcuprate (Scheme 3). Analogously, traces of

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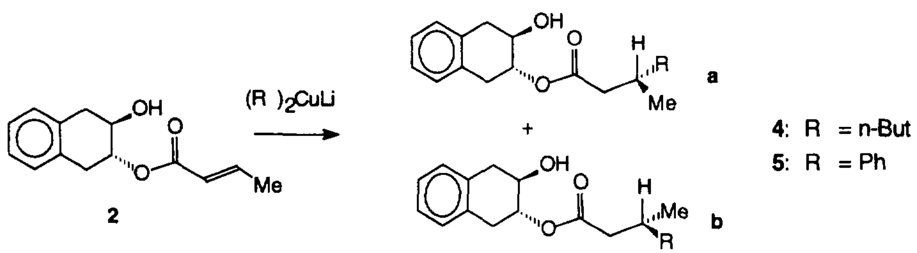


4 R = n-But
5 R = Ph

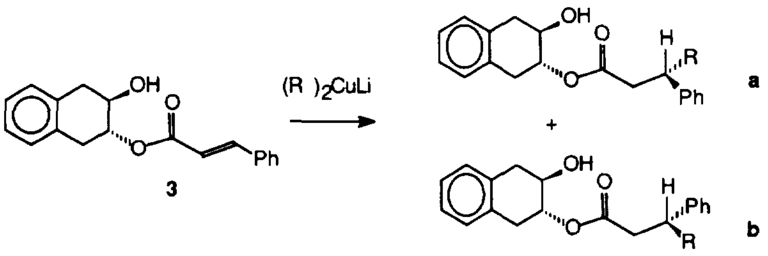
Scheme 2.

Table 1. Conjugate additions to the monocrotonate 2

Compound	R	Solvent	Temperature (°C)	Yield (%)	Diastereisomeric ratio **a** : **b**	Configuration of the new stereo-centre
4	n-Butyl	Et_2O	- 30	92	93/7	S^a
5	Phenyl	Et_2O	- 30	64	94/6	R^b

a) Determined by reduction to (S)-3-methylheptanol. b) Determined by hydrolysis to (R)-3-phenylbutyric acid and by ^1H NMR analysis of the corresponding Mosher's ester.

the 1,4-addition product **7** were detected in the ^1H NMR spectrum of the recovered starting product **3** when lithium dibutylcuprate was used. To overcome the problem, either addition of a co-solvent or change of the solvent were considered. Addition of solvents such as dimethylformamide (DMF) or hexamethylphosphoric triamide (HMPT) (the minimum amount required to solubilize the substrate) produced higher yields of the addition product, but lowered, to different degrees, the diastereoisomeric ratio (Table 2). DMF appeared to be the best co-solvent, giving a reasonable yield and diastereoisomeric ratio. Changing the solvent from diethyl ether to dichloromethane did not improve the results either. Dichloromethane was selected because the monocinnamate **3** is soluble in this solvent at low temperature and because lithium dimethylcuprate was reported to have, in this solvent, the same dimeric structure as in diethyl ether[6].



6 R = Me
7 R = n-But

Scheme 3.

The diastereoisomeric ratio and the absolute configuration of compound **6** and **7** were determined by ^1H NMR analysis of the corresponding Mosher's esters[3] and comparison with the ^1H NMR data of compound **5**. Compound **6a**, obtained as the major diastereoisomer from the addition of lithium dimethylcuprate to **3** was identical to the minor diastereoisomer **5b** obtained by addition of lithium

Table 2. Conjugate additions to the monocinnamate **3**

Compound	R	Solvent	Temp. (°C)	Yield (%)	Diastereisomeric ratio **a** : **b**	Configuration of the new stereo-centre
6	Methyl	Et_2O	0	5	90/10	S[a]
"	"	CH_2Cl_2	0	53	70/30	S[b]
"	"	"	-30	20	70/30	S
7	n-Butyl	CH_2Cl_2	0	50	70/30	S[c]
"	n-Butyl	Et_2O DMF	0	30	82/18	S
"	n-Butyl	Et_2O HMPT	0	30	60/40	S

a) Determined by hydrolysis to (S)-3-phenylbutyric acid. b) Determined by ^1H NMR analysis of the corresponding Mosher's ester. c) Determined by hydrolysis to (S)-3-phenylheptanoic acid.

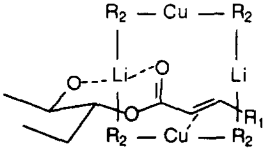


Figure 1.

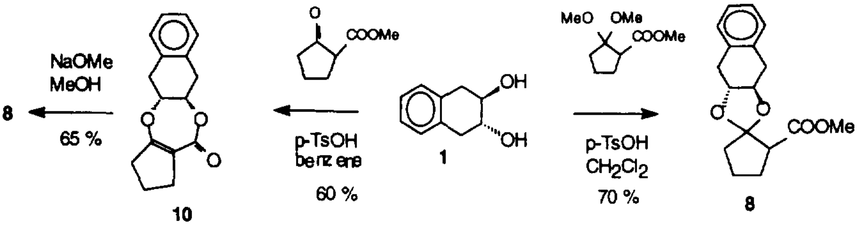
diphenylcuprate to the monocrotonate **2**. The absolute configuration of the stereocentre created during the addition of lithium dibutylcuprate to **3** was further confirmed by hydrolysis to (*S*)-3-phenylheptanoic acid[7].

The stereochemical outcome of the reaction can be rationalized assuming the formation of a chelate complex between the free hydroxyl group and the carbonyl oxygen of the substrate with the lithium of the cuprate in a dimeric form, followed by complexation of copper with the double bond[6] (Figure 1). Attack of the alkyl residue of the cuprate is therefore oriented such as to produce the observed configuration of the new stereocentre created during the addition. The dimeric structure of the cuprate therefore plays a key role for the stereoselectivity of the addition. The mechanism depicted in Figure 1 is an agreement with the different diastereoisomeric ratios obtained by changing the reaction medium from ether to ether–DMF or HMPT. The structure of organometallic reagents can be, in fact, strongly influenced by the reaction medium: in particular lithium dialkylcuprates have a dimeric structure in ether, whereas more polar and coordinating solvent such as THF, DMF or HMPT can break the dimeric structure, therefore lowering the diastereoselection.

The low diastereoisomeric ratio obtained in dichloromethane was somewhat unexpected and, if the mechanism depicted in Figure 1 holds true, disagrees with a dimeric structure of $Li(R_1)_2Cu$ in this solvent, as, on the contrary, suggested by ^1H NMR studies[6]. Apparently, the presence of non dimeric, highly reactive species in very low concentrations (non observable by NMR) can not be ruled out and can offer a reasonable explanation for the low diastereoselection obtained in this solvent.

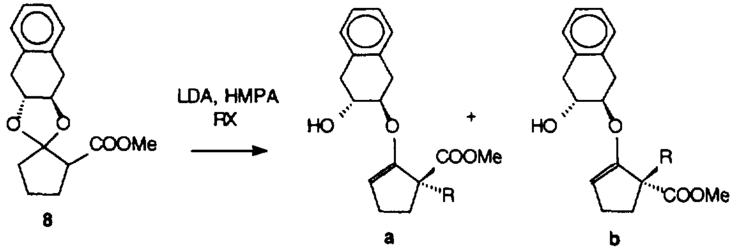
Alkylation of β-carbonyl compounds

The alkylation of β-dicarbonyl compounds was tested on methyl 2-oxocyclopentanecarboxylate and on ethyl 2-methylacetoacetate (chosen as model compounds for cyclic and acyclic β-keto esters respectively), previously converted to the acetals **8** and **9**. To this purpose methyl 2-oxocyclopentanecarboxylate and ethyl 2-methyl acetoacetate were converted to the corresponding dimethyl acetals which were further reacted with (2*R*,3*R*)-dihydroxy-1,2,3,4-tetrahydronaphthalene. Direct acetalyzation of methyl 2-oxocyclopentanecarboxylate with (2*R*,3*R*)-dihydroxy-1,2,3,4-tetrahydronaphthalene in refluxing benzene (azeotropic conditions), in the presence of p-toluene sulphonic acid, yielded the lactone **10** which was converted to **8** by base treatment (Scheme 4)[8].



Scheme 4.

Alkylation was performed in tetrahydrofuran at −78°C in the presence of HMPA and an eccess of LDA. As observed when (1*R*,2*R*)-cyclohexandiol was used as the chiral auxiliary[8], the alkylated products lost their original acetal structure and the enol ethers **11–13** were formed (see Scheme 5 and Table 3).



11 R = Me
12 R = n-nonyl

Scheme 5.

Alkylation of **8** with iodomethane or 1-bromononane yielded the alkylation product in good yield and with a good diastereoisomeric ratio. The diastereoisomeric ratio and the absolute configuration of the quaternary centre formed in the alkylation were determined by hydrolysis of the enol ethers **11** and **12** to (*S*)-2-carbomethoxy-2-methyl- and (*S*)-2-carbomethoxy-2-nonyl-cyclopentanone[9] of 96% and 94% enantiomeric purity respectively. The enantiomeric excess was determined by measure of the specific optical rotation and by analysis of the ^{1}H NMR spectrum taken in the presence of a chiral europium(III) shift reagent.

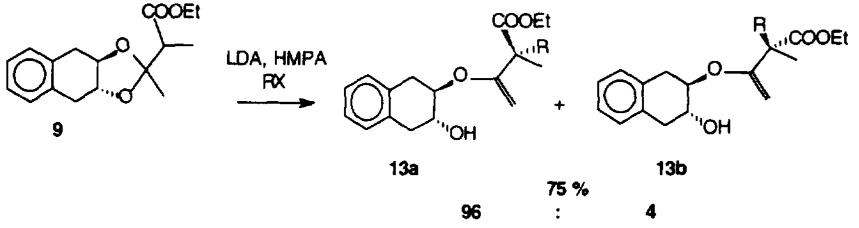
Table 3. Alkylation of methyl 2-oxocyclopentanecarboxylate acetal

Compound	RX	Yield (%)	Diastereoisomeric ratio	Absolute Configuration
11	Iodomethane	65	98/2	S[a]
12	n-Bromo nonane	70	97/3	S[b]

a) Determined by hydrolysis to (S)-2-carbomethoxy-2-methyl cyclopentanone. b) Determined by hydrolysis to (S)-2-carbomethoxy-2-nonyl cyclopentanone

It must be noted that the acetals obtained from methyl 2-oxocyclopentanecarboxylate and acyclic chiral diols such as (2*R*,3*R*)-butandiol and (2*R*,4*R*)-pentandiol were less effective, and yielded lower diastereoisomeric excesses (from 37% to 73%)[10].

A high yield and diastereoisomeric ratio were also obtained by alkylation of **9** with benzylbromide. The diastereoisomeric ratio and the absolute configuration of the quaternary centre formed in the alkylation were determined by hydrolysis of **13** to (*R*)-ethyl-2-benzyl-2-methyl acetoacetate[11] of 92% enantiomeric excess (Scheme 6) (determined by measure of the specific optical rotation and by ^{1}H NMR analysis in the presence of a chiral shift reagent).



Scheme 6.

The results reported above demonstrate the effectiveness of the diol **1** as chiral auxiliary in asymmetric synthesis. The yields and the observed diastereoisomeric excesses were in general better or comparable to those obtained with other chiral diols with C_2 symmetry (acyclic or cyclic). The very low solubility in water and the crystallinity of **1** are added advantages which allow an easy and quantitative recovery at the end of the reactions.

Experimental

Starting materials and procedures

Reagents grade tetrahydrofuran and pyridine were refluxed over $LiAlH_4$ and distilled. Reagent grade dichloromethane was refluxed over P_2O_5 and distilled. Reagent grade dimethylformamide was distilled at low pressure under nitrogen and kept over 4A molecular sieves. Reagent grade HMPA was distilled over CaH_2 at low pressure under nitrogen and kept over 13X molecular sieves. The monocrotonate **2** was prepared as previously described[1]. Proton nuclear magnetic resonance (^{1}H NMR) spectra were obtained with Varian L-200 and Bruker AC-300 instruments. IR spectra were recorded with a Perkin–Elmer 681 spectrophotometer and mass spectra with a VG 7070 E 9 spectrometer. Melting points were obtained by using a Buchi 535 apparatus, the $[\alpha]_D$ were obtained with a Perkin–Elmer 241 Polarimeter and the microanalyses for the new compounds were determined on a Perkin–Elmer 240 Elemental Analyzer. Flash-column chromatography was performed on silica gel Merck Kieselgel 60 (230–400 mesh ASTM). Thin-layer chromatography was carried out on silica gel plates (60 F254, Merk): zones were detected visually by ultraviolet irradiation (254 nm) or by spraying with methanol/H_2SO_4 9:1, followed by heating at 100°C.

All reactions were carried out at 25°C in a dry nitrogen atmosphere, using glassware dried by flaming in a stream of dry nitrogen (if not otherwise stated).

Enantiomers were detected and determined quantitatively from the ^{1}H NMR spectra taken in the presence of a chiral europium(III) shift reagent (tris[3-(heptafluoropropylhydroxymethylene)-d-camphorato]-europium(III), Fluka).

Synthesis of the monocinnamate 3

To a solution of the diol **1** (0.30 g, 1.83 mmol) in dry methylene chloride (4.0 ml) and dry pyridine (1.5 ml) was slowly added dropwise a solution of cinnamoyl chloride (0.40 ml, 2.43 mmol) and 4-dimethylaminopyridine (0.022 g) in dry methylene chloride (3 ml). The reaction was monitored by thin-layer chromatography (silica gel, n-hexane/ethyl acetate 1/1). The reaction was stirred at room temperature for 5 hr, diluted with ethyl acetate (10 ml) and washed with brine. The aqueous phase was extracted three times with ethyl acetate (3×10 ml). The combined organic phases were washed with water, dried (Na_2SO_4), and the solvent removed under reduced pressure. The crude material was flash-chromatographed (silica gel, n-hexane/ethyl acetate 1/1) to afford monocinnamate **3** (0.340 g, 1.16 mmol, 64.0%) and dicinnamate (0.42 g, 0.28 mmol, 15.4%). **3**: colorless crystals, mp: 104–105°C; $[\alpha]_D$: −26.99 (c=1.5, MeOH); IR ($CHCl_3$): 3500, 1710, cm^{-1}; ^1H NMR ($CDCl_3$): δ, 2.60 (s, 1H, OH), 2.85 (dd, 1H, J=16.5, J=9.0 Hz), 2.88 (dd, 1H, J=16.5, J=9.0 Hz), 3.25 (dd, 1 H, J=16.5, J=6.0, Hz), 3.38 (dd, 1H, J=16.5, J=6.0 Hz), 4.15 (ddd, 1H, J=18.0, J=3.6 Hz), 5.15 (ddd, 1H, J=18.0, J=3.6 Hz), 6.5 (d, 1H, J=15.8 Hz), 7.01–7.5 (m, 9H), 7.7 (d, 1H, J=15.8 Hz); ^{13}C NMR: δ 33.21 (t), 33.38 (t), 69.49 (d), 74.92 (d), 117.77 (d), 145.59 (d), 126.46 (d), 2×126.67 (d), 128.17 (d), 128.64 (d), 128.80 (d), 128.93 (d), 2×130.49 (d), 132.91 (s), 133.43 (s), 134.24 (s), 167.11 (s); MS, m/z: 294 (M^+), 276 (M^+-H_2O). Anal. Calcd for $C_{19}H_{18}O_3$: C, 77.55%; H, 6.12%. Found: C, 77.33%, H, 6.04%.

Typical procedure for conjugated additions in ethereal solution

To a suspension of freshly crystallized[12] $CuBr\times(CH_3)_2S$ (0.42 g, 2.0 mmol) in dry ethyl ether (10 ml) was added, at 0°C, dimethyl sulfide (1 ml). To the obtained solution, phenyllithium in cyclohexane–ether solution (1.8 M, 2.2 ml, 4 mmol) was added dropwise, and the reaction mixture was stirred for 10 min. The monocrotonate **2** (0.100 g, 0.43 mmol) in ethyl ether (1 ml) was added at −30°C and the reaction was monitored by thin-layer chromatography (silica gel, n-hexane/ethyl acetate 1/1). After being stirred for 5 hr, the reaction mixture was diluted with ethyl acetate (5 ml), and washed with a saturated NH_4Cl solution. When all the solid dissolved and the aqueous layer turned deep blue, the two phases were separated and the aqueous phase was extracted three times with ethyl acetate (3×20 ml). The combined organic extracts were washed with brine, dried (Na_2SO_4), and the solvent removed under reduced pressure. The crude material was flash-chromatographed (silica gel, n-hexane/ethyl acetate 8/2) to give the 1,4-adduct **5** as a 94/6 mixture of diastereoisomers (0.086 g, 0.28 mmol, 64%).

5a (major diastereoisomer): IR ($CHCl_3$): 1732 cm^{-1}; ^1H NMR: δ 1.35 (d, 3H, J=7.3 Hz), 2.05 (s, 1H, disappears with D_2O), 2.62 (dd, 1H, J=15.4, J=8.1 Hz), 2.65 (m, 2H), 2.78 (dd, 1H, J=15.4, J=8.1 Hz), 3.12 (dd, 1H, J=15.4, J=5.8 Hz), 3.20 (dd, 1H, J=15.4, J=5.8 Hz), 3.3 (m, 1H), 3.90 (ddd, 1H, J=8.1, J=8.1, J=5.8 Hz), 4.92 (ddd, 1H, J=8.1, J=8.1, J=5.8 Hz), 6.9–7.5 ppm (m, 9H); ^{13}C NMR: 22.10 (q), 33.9 (d), 36.21 (t), 37.2 (t), 43.4 (t), 69.2 (d), 77.0 (d), 127.0 (d), 2×127.3 (d), 2×127.8 (d), 2×128.8 (d), 2×129.5 (d), 2×133.0 (s), 145.8 (s), 172.5 (s); MS, m/z: 310 (M^+), 293 (M^+-OH), 146 (diol **1**$-H_2O$). Anal. Calcd for $C_{20}H_{22}O_3$: C, 77.42%; H, 7.10%. Found: C:, 77.50%; H, 7.14%.

5b (minor diastereoisomer): see **6a**.

4a (major diastereoisomer)[1]; colorless oil; IR ($CHCl_3$): 3600, 1730 cm^{-1}; ^1H NMR: δ, 0.9 (t, 3H, J=6.8, J=6.8, J=6.8 Hz), 0.95 (d, 3H, J=7.9 Hz), 1.35 (m, 6H), 1.97 (ddq, 1H, J=7.9, J=7.9, J=7.9, J=7.5, J=6.0 Hz), 2.18 and 2.38 (ABX system, 2H, J_{AB}=15.0, J_{AX}=7.5, J_{BX}=6.0 Hz), 2.15 (s, 1H, disappears with D_2O), 2.82 (dd, 1H, J=16.5, J=7.5 Hz), 2.85 (dd, 1H, J=16.5, J=9.0 Hz), 3.20 (dd, 1H, J=16.5, J=6.0 Hz), 3.28 (dd, 1H, J=16.5, J=6.0 Hz), 4.05 (ddd, 1H, J=9.0, J=6.0, J=6.0 Hz), 5.20 (ddd, 1H, J=7.5, J=6.0, J=6.0 Hz), 7.1 (m, 4H); ^{13}C NMR: 14.61 (q), 20.34 (q), 23.41 (t), 29.74 (t), 31.11 (d), 33.99 (t), 36.79 (t), 37.05 (t), 42.69 (t), 70.21 (d), 75.19 (d), 129.28 (d), 129.32 (d), 129.35, (d), 129.48 (d), 133.76 (s), 134.10 (s), 174.13 (s); MS, m/z: 290 (M^+), 273 (M^+-H_2O). Anal. calcd. for $C_{18}H_{26}O_3$: C, 74.48%; H, 8.96%. Found: C, 74.24%; H, 8.58%.

Typical procedure for conjugate additions in the presence of a co-solvent

To a suspension of $CuBr\times(CH_3)_2S$ (0.560 g, 2.72 mmol) in dry ethyl ether (8 ml) was added, at 0°C, dimethyl sulfide (1 ml). To the obtained yellow solution, butyllithium in n-hexane (1.6 M in n-hexane, 2.4 ml, 3.6 mmol) was added dropwise, and the reaction mixture was stirred for 10 min. The monocinnamate **3** (0.200 g, 0.68 mmol) in dry ethyl ether (4 ml) and dry dimethylformamide (0.7 ml) was added at 0°C and the reaction was monitored by thin-layer chromatography (silica gel, n-hexane/ethyl acetate 1/9). After being stirred for 6 hr, the reaction mixture was diluted with ethyl acetate (5 ml), and washed with a saturated NH_4Cl solution. When all the solid dissolved and the aqueous layer turned deep blue, the two phases were separated and the aqueous phase was extracted three times with ethyl acetate (3×20 ml). The combined organic extracts were washed with brine, dried (Na_2SO_4), and the solvent removed under reduced pressure. The crude material was flash-chromatographed (silica gel, n-hexane/ethyl acetate 9/1) to give starting monocinnamate **3** (0.05 g, 25%), (2*R*,3*R*)-dihydroxy-1,2,3,4-tetrahydronaphthalene (0.028 g, 0.17 mmol, 25%) and the 1,4-adduct **7** as a 82/18 mixture of diastereoisomers (0.073 g, 0.21 mmol, 30%).

7a (major diastereoisomer): ^{1}H NMR: δ, 0.85 (t, 3H, J=6.5, J=6.5 Hz), 1.05–1.28 (m, 4H), 1.55–1.75 (m, 2 H), 2.54 (dd, 1H, J=17.0, J=8.5 Hz), 2.7 (m, 2H), 2.70 (dd, 1H, J=17.0, J=8.5 Hz), 3.1 (m, 1H), 3.25 (dd, 1H, J=17.0, J=6.0 Hz), 3.11 (dd, 1H, J=17.0, J=6.0 Hz), 3.79 (ddd, 1H, J=6.0, J=7.5, J=8.5 Hz), 3.8 (ddd, 1H, J=6.0, J=7.5, J=8.5 Hz), 6.94–7.4 (m, 9H); ^{13}C-NMR: 12.01 (q), 23.23 (t), 30.16 (t), 33.86 (t), 36.61 (t), 37.07 (t), 42.41 (t), 43.03 (d), 69.73 (d), 75.44 (d), 2×127.06 (d), 127.30 (d), 2×129.0 (d), 2×129.23 (d), 129.24 (d), 129.28 (d), 2×133.5 (s), 146.8 (s,), 172.29 (s). Anal. Calcd for $C_{23}H_{28}O_3$: C, 78.41%; H, 7.95%. Found: C, 78.61%; H, 8.05%.

7b (minor diastereoisomer): IR ($CHCl_3$): 3610, 1734 cm^{-1}; ^{1}H NMR: δ, 0.85 (t, 3H, J=6.5, J=6.5 Hz), 1.05–1.28 (m, 4H), 1.55–1.75 (m, 2H), 2.68 (dd, 1H, J=17.0, 8.5 Hz), 2.7 (m, 2H), 2.75 (dd, 1H, J=17.0, J=8.5 Hz), 3.03 (dd, 1H, J=17.0, J=6.0 Hz), 3.1 (m, 1H), 3.3 (dd, 1H, J=17.0, J=6.0 Hz), 3.8 (ddd, 1H, J=8.5, 7.5, J=6.0 Hz), 3.86 (ddd, 1H, J=6.0, J=8.5, J=7.5 Hz) 6.94–7.4 (m, 9H); ^{13}C NMR: 12.01 (q), 23.23 (t), 30.16 (t), 33.86 (t), 36.88 (t), 37.07 (t), 42.85 (t), 43.66 (d), 70.01 (d), 75.44 (d), 2×127.06 (d), 127.30 (d), 2×129.0 (d), 2×129.23 (d), 129.25 (d), 129.28 (d), 2×133.5 (s), 146.8 (s), 172.29 (s); MS m/z: 352 (M^+).

Typical procedure for conjugate additions in methylene chloride

Lithium dimethylcuprate was prepared by addition of the methyllithium in toluene to a suspension of Cu(I)Br×$CH_3)_2S$ (0.14 g, 0.68 mmol) in toluene (1.2 ml) at 0°C After the addition of one equivalent of methyllithium a yellow precipitate was observed, which turned white after the addition of the second equivalent of methyllithium. After stirring for 15 min, dry methylene chloride was added (5 ml). The monocinnamate **3** (0.1 g, 0.43 mmol), dissolved in dry methylene chloride (1 ml) was added to lithium dimethylcuprate. The reaction was monitored by TLC (silica gel; ethyl acetate/n-hexane 2/8) The reaction mixture was worked up in the usual manner after 4 hr. the crude reaction mixture was flash-chromatographed (silica gel; ethyl acetate/n-hexane 2/8) and afforded **6** (0.07 g, 0.23 mmol, 53%, diastereoisomeric ratio 70/30).

6a (major diastereoisomer): ^{1}H NMR ($CDCl_3$): δ 1.33 (d, 3H, J=7.3 Hz), 2.05 (s, 1H, disappears with D_2O), 2.62 (dd, 1H, J=15.4, J=6.9 Hz), 2.65 (m, 2H), 2.76 (dd, 1H, J=15.4, J=6.9 Hz), 3.18 (dd, 1H, J=15.4, J=7.8 Hz), 3.18 (dd, 1H, J=15.4, J=5.8 Hz), 3.3 (m, 1H) 3.86 (ddd, 1H, J=6.9, J=5.8, J=5.8 Hz), 4.92 (ddd, 1H, J=7.8, J=6.9, J=5.8, Hz), 6.9–7.5 (m, 9H); ^{13}C NMR: 22.10 (q), 33.9 (d), 36.21 (t), 36.8 (t), 42.5 (t), 69.2 (d), 77.0 (d), 127.0 (d), 2×127.3 (d), 2×127.8 (d), 2×128.8 (d), 2×129.5 (d), 2×133.0 (s), 145.8 (s), 172.5 (s); MS, m/z: 310 (M^+), 293 (M^+−OH), 146.

6b (minor diastereoisomer): see **5a**

Reduction of 4 to (S)-3-methyl heptanol

A solution of **4** (0.4 g, 1.37 mmol) in tetrahydrofuran (5 ml) was added to a stirred suspension of $LiAlH_4$ in dry tetrahydrofuran (15 ml). After 2 hr at room temperature the reaction mixture was cautiously treated with icy-water, 0.1 N HCl and extracted with ethyl acetate (3×5 ml). The combined organic phases were washed with water, dried (Na_2SO_4) and the solvent was removed at atmospheric pressure. Bulb-to-bulb distillation of the crude residue under reduced pressure (18 mmHg) gave pure (*S*)-3-methyl heptanol (0.117 g, 0.89 mmol). Colorless oil; $[\alpha]_D=-2.62$ (c=0.1, CH_2Cl_2) { lit.[2]: $[\alpha]_D=-3.07$, neat}; IR (neat): 3350, 2960, 1460, 1380, 1060cm^{-1}; ^{1}H NMR ($CHCl_3$): δ 0.89 (t, 3H, J=6.6, 6.6 Hz), 0.89 (d, 3H, J=6.6 Hz), 1.12–1.4 (m, 7H), 1.45–1.65 (m, 2H), 3.67 (m, 2H); MS, m/z: 112 (M^+-H_2O).

Typical procedure for the preparation of the acetals of (2R,3R)-dihydroxy-1,2,3,4-tetrahydronaphthalene

A mixture of methyl 2-oxocyclopentanecarboxylate (0.5 g, 3.5 mmol) in dry methanol (10 ml), Dowex 50 (acid form, 0.3 g) and triethyl orthoformate (6 mol eq) was shaken at room temperature for 4 hr. The resin was filtered off, and the solution was treated with Amberlist IRA 900 (10 g). The resin was filtered off, the solvent and the excess of orthoformate were distilled under reduced pressure and afforded 2-carbomethoxy cyclopentanone di-methyl acetal (0.46 g, 2.47 mmol, 70% yield): colorless oil; IR ($CHCl_3$): 1720, 1220, 1200 cm^{-1}; ^1H NMR: δ, 1.6 (m, 1H), 1.86–1.90 (m, 3H), 1.88 (dd, 1H, J=6.0, J=3.0 Hz),2.02 (dd, J=6.0, J=3.0 Hz), 2.98 (dd, 1H, J=9.0, J=6.0 Hz), 3.20 (s, 3H), 3.22 (s,3H), 3.67 (s, 3H); ^{13}C NMR: 21.73 (t), 27.33 (t), 34.08 (t), 48.41 (d), 49.80 (q), 50.20 (q), 51.32 (q), 112.13 (s), 173.30 (s); MS, m/z: 188 (M^+), 156 (M^+-OCH_3), 126 (M^+-2OCH_3), 98 ($M^+-COOMe$, $-OCH_3$), 68 ($97-OCH_3$).

To (2*R*,3*R*)-dihydroxy-1,2,3,4-tetrahydronaphthalen (0.47 g, 2.86 mmol) in dry dichloromethane (10 ml), methyl 2-oxocyclopentanecarboxylate dimethyl acetal was added (0.98 g, 5.21 mmol), followed by a catalytic amount of p-toluenesulphonic acid. The reaction mixture was shaken at room temperature for 4 hr, till an aliquot showed no starting (2*R*,3*R*)-dihydroxy-1,2,3,4-tetrahydronaphthalene by TLC analysis (silica gel, n-hexane/ethyl acetate 7/3). The reaction mixture was filtered over an Amberlist IRA 900 column (2 g), and the solvent was removed under reduced pressure. the crude material was purified by flash chromatography and afforded **8** (0.58 g, 2.01 mmol, 70% yield) as a mixture of two diastereoisomers: IR ($CHCl_3$): 1725cm^{-1}; ^1H NMR: δ, 1.6–2.4 (m, 6H), 2.84 (dd, 1H, J=15.0, J=12 Hz), 2.88 (dd, 1H, J=15.0, J=12.0 Hz), 3.06 (dd, 1H, J=9.0, J=9.0 Hz), [other diastereoisomer 3.03 (dd, 1H, J=9.0, J=9.0 Hz] 3.22 (dd, 1H, J=15, J=5.4 Hz) 3.25 (dd, 1H, J=15.0, J=5.0 Hz), [3.27 (dd, 1H, J=15.0, J=5.0 Hz)] 3.7 (m, 2H), [3.7 (m, 1H), 3.9 (ddd, 1H, J=12.0, J=11.0, J=5.4 Hz)] 3.69 (s, 3H) 7.19–7.22 (m, 4H); ^{13}C NMR: 22.22 [21.99] (t) 27.61 [27.06] (t) 34.55 [34.27] (t) 38.62 (t), 38.26 (t) 50.54 (q) [50.74] 57.83 (d) 75.56 (d) 78.73 (d), 119.63 (s), 2×129.79 (d), 2×130.21 (d), 2×133.68 (s), 174.32 (s); MS, m/z: 288 (M^+), 201 ($M^+- CH_2CH_2COOCH_3$), 146, 129 (146 – OH). Calcd for $C_{17}H_{20}O_4$: C, 70.83%; H, 6.94%. Found: C, 71.12%; H, 7.12%.

Treatment of ethyl 2-methyl acetoacetate with triethyl orthoformate as described above afforded the corresponding dimethyl acetal [68% yield; IR ($CHCl_3$): 1723, 1222, 1200 cm^{-1};^1H NMR: δ, 1.10 (d, 3H, J=7.5 Hz), 1.21 (t, 3H, J=6.0 Hz), 1.31 (s, 3H), 2.90 (q, 1H, J=7.5 Hz), 3.12 (s, 3H), 3.17 (s, 3H), 4.10 (q, 2H, J=6.0, J=13.5 Hz); ^{13}C NMR: 12.59 (q), 12.88 (q), 14.03 (q), 44.77 (d), 47.77 (q), 48.35 (q), 60.25 (t), 102.24 (s), 173.59 (s); MS m/z: 175 (M^+-CH_3), 159 (M^+-OCH_3), 145 ($159-CH_3$), 113 ($145-OCH_3$), 99 ($113-CH_3$)] which was directly reacted with (2*R*,3*R*)-dihydroxy-1,2,3,4-tetrahydronaphthalene

9: IR: 1735cm^{-1}; ^1H NMR: δ 1.26 [other diastereoisomer: 1.28] (t, 3H, J=6.0 Hz), 1.28 [1.28] (d, 3H, J=6.0), 1.34 [1.36] (s, 3H), 2.82 [2.88] (q, 1H, J=6.0Hz), 2.96 (dd, 2H, J=15.0, J=12.0 Hz), 2.96 (dd, 2H, J=15.0, J=12.0 Hz), 3.25 (dd, 2H, J=15.0, J=4.5 Hz), 3.25 (dd, 2H, J=15.0, J=4.5 Hz), 3.73 (m, 1H), 3.80 m (m, 1H), 4.14 [4.16] (q, 2H, J=6.0 Hz), 7.15 (m, 4H); ^{13}C NMR: 12.82 [13.24] (q), 14.22 (q), 22.65 [23.23] (q), 34.17 (t), 34.55 [34.67] (t), 49.11 [49.27] (d), 50.41 (t), 76.60 [77.02] (d), 77.59 [78.13] (d), 111.21 (s), 2×126.56 (d), 2×130.13 (d), 2×133.65 (s), 173.20 (s); MS m/e: 290 (M^+), 275 (M^+-CH_3), 245 (M^+-CH_3, $-CH_2CH_3$). Calcd for $C_{17}H_{22}O_4$: C, 70.34%; H, 7.59%. Found: C, 69.88%; H, 7.20%.

Typical alkylation procedure of the acetals 8 and 9

To a solution of lithium diisopropylamide (5 mmol) in dry tetrahydrofuran (15 ml) at −50°C, dry HMPT (0.9 ml), and **8** (0.27 g, 0.94 mmol) in dry tetrahydrofuran (1.6 ml) were added successively at −50°C. The reaction mixture was stirred for 15 min, then methyl iodide (5 mmol) was added, and the stirring was continued for 4 hr at −50°C. The reaction mixture was treated with an aqueous saturated NH_4Cl solution (30 ml) and extracted with ethyl acetate. The organic phase was dried (Na_2SO_4) and the solvent removed at reduced pressure. The residue was purified by flash chromatography (silica gel; n-hexane/ethyl acetate 8/2) to afford **11** as a colorless solid (65% yield, 98/2 diastereoisomeric ratio).

11a (major diastereoisomer): IR: 1718, 1210 cm^{-1}; ^1H NMR: δ 1.4 (s, 3 H), 1.82 (m, 1H), 2.3–2.4 (m, 3H), 2.82 (dd, 1H, J=16.5, 10.5 Hz), 2.87 (dd, 1H, J=16.5, J=10.5 Hz), 3.22 (dd, 1H, J=16.5, J=6.0 Hz), 3.3 (dd, 1H, J=16.5, J=6.0 Hz), 3.7 (s, 3H), 3.85 (s, 1H, exchanges with D_2O), 4.02 (ddd, 1H, J=10.5, J=10.5, J=6.0 Hz), 4.2 (ddd, 1H, J=10.5, J=10.5, J=6.0 Hz), 4.7 (dd, 1H, J=1.6, J=1.6 Hz), 7.05– 7.15 (m, 4H); ^{13}C NMR: 20.38 (t), 21.01 (q), 34.65 (t), 35.82 (t), 38.10 (t), 52.07 (q), 55.69 (s), 78.74 (d), 78.81 (d), 86.32 (d), 120.36 (s), 2×127.14 (d), 2×130.74 (d), 2×134.4 (s), 175.74 (s); MS, m/z: 302 (M^+), 243 (M^+−COOMe), 156 (M^+−diol **1**−OH), 147 (M^+−2methyl-2 carbomethoxy cyclopentanone), 129 (147−H_2O). Calcd for $C_{18}H_{22}O_4$: C, 71.52%; H, 7.28%. Found: C, 71.35%; H, 7.15%.

Alkylation of **8** with 1-bromo-nonane gave **12** (70% yield, 97/3 diastereoisomeric ratio).

12a (major diastereoisomer): IR: 1735cm^{-1}; ^1H NMR: δ, 0.88 (t, 3H, J=6.8 Hz), 1.2–1.35 (m, 14H), 167 (m, 1H), 1.85 (m, 2H), 2.25–2.35 (m, 3H), 2.85 (dd,,1H, J=17.5, J=8.6 Hz), 2.88 (dd, 1H, J=17.5, J=8.6 Hz), 3.25 (dd, 1H, J=17.5, J=5.5 Hz), 3.31 (dd, 1H, J=17.2, J=5.5 Hz), 3.72 (s, 3H), 3.85 (s, 1H, exchanges with D_2O), 4.05 (ddd, 1H, J=8.6, J=8.6, J=5.5 Hz), 4.15 (ddd, 1H, J=8.6, J=8.6, J=5.5 Hz), 4.71 (dd, 1H, J=1.9, J=1.9 Hz),7.05–7.15 (m, 4H); ^{13}C NMR: 14.08 (q), 20.12 (t), 22.65 (t), 24.43 (t), 26.34 (t), 29.29 (t), 29.50 (t), 2×29.93 (t), 31.89 (t), 32.47 (t), 35.29 (t), 35.92 (t), 52.16 (q), 58.05 (s), 70.30 (d), 80.45 (d), 97.48 (d), 126.22 (d), 126.39 (d), 128.75 (d), 128.99 (d), 133.33 (s), 133.90 (s), 157.12 (s), 177.2 (s); MS, m/z: 414 (M^+), 355 (M^+−COOMe). Calcd for $C_{26}H_{38}O_4$: C, 75.36%; H, 9.18%. Found: C, 74.98%; H, 8.92%.

Alkylation of **9** with benzyl bromide, under the conditions reported above, gave **13** (75% yield, 96/4 diastereoisomeric ratio).

13a (major diastereoisomer): IR: 1718cm^{-1}; ^1H NMR: δ, 1.15 (s, 3H), 1.23 (t, 3H, J=7.0 Hz), 1.61 (s, 3H), 2.72 (d, 1 H, J=12.4 Hz), 2.92 (dd, J=14.3, J=11.1 Hz), 3.05 (dd, J=14.3, J=11.1 Hz), 3.31 (dd, J=14.3, J=4.1 Hz), 3.33 (dd, J=14.3, 4.1 Hz), 3.58 (d, 1H, J=12.4 Hz), 3.78 (ddd, 1H, J=11.1, J=10.0, J=4.1 Hz), 3.90 (ddd, 1H, J=11.1, J=10.0, J=4.1 Hz), 4.18 (q, 2H, J=7.0, J=7.0, J=7.0 Hz), 7.1–7.2 (9H); ^{13}C NMR: 14.73 (q), 17.64 (q), 23.05 (q), 34.54 (t), 35.93 (t), 40.38 (t), 57.02 (s), 61.29 (t), 77.88 (d), 79.60 (d), 114.11 (s), 126.8 (d), 127.0 (d), 128.6 (d), 2×128.7 (d), 2×131.0 (d), 2×131.3 (d), 2×134.3 (s), 139.2 (s), 174.2 (s); MS m/z: 380 (M^+), 365 (M^+−CH_3), 335 (M^+−2CH_3), 289 (M^+−CH_2Ph). Calcd for $C_{24}H_{28}O_4$: C, 75.79%; H, 7.37% Found: C, 76.19%; H, 7.41%.

Typical procedure for the hydrolysis of the enol ethers 11–13

To a solution of **11** (0.08 g, 0.3 mmol) in methanol (4 ml) and water (0.6 ml) a 3 N HCl solution in methanol (1.5 meq) was added dropwise at room temperature. After completition of the reaction (30 min), the mixture was treated with Amberlist IRA 900 (4 g). The resin was filtered off, the solvent removed under reduced pressure, and the residue distilled (bulb-to-bulb) under vacuum (15 mmHg) to afford (*S*)-2-methyl-2-carbomethoxy cyclopentanone; colorless oil; $[\alpha]_D$=+10.15 (c=1.3, $CHCl_3$) [lit.[9]: $[\alpha]_D$=+10.6 (c=5.8, $CHCl_3$)]; IR ($CHCl_3$): 1749, 1722cm^{-1}; ^1H NMR:δ 1.31 (s, 3H), 1.80–1.90 (m, 3H), 2.30–2.40 (m, 3H), 3.69 (s, 3H); ^{13}C NMR: 19.52 (q), 19.52 (t), 36.13 (t), 37.60 (t), 47.92 (s), 52.44 (q), 172.78 (s), 212.31 (s); MS m/z: 156 (M^+), 141 (M^+−CH_3), 97, (M^+−COOMe), 82 (97−CH_3).

The compound **12**, treated as described above, afforded (*S*)-2-nonyl-2-carbomethoxy cyclopentanone $[\alpha]_D$=−19.46 (c=3.4, $CHCl_3$) [lit.[9]: $[\alpha]_D$=−20.90 (c=1.3, $CHCl_3$)]; ^1H NMR: δ, 0.88 (t, 3H, J=6.0, J=6.0 Hz), 1.18–1.99 (m, 14 H), 1.46–1.63 ppm (m, 1H), 1.8 –2.1 (m, 4 H), 2.2–2.6 (m, 3H), 3.71 (s, 3H); ^{13}C NMR: 13.98 (q), 19.52 (t), 22.58 (t), 24.83 (t), 29.28 (t), 29.40 (t), 29.61 (t), 29.80 (t), 31.82(t), 32.63 (t), 33.96 (t), 37.90 (t), 50.81 (s), 52.33 (q), 171.50 (s), 214.66 (s); MS m/z: 268 (M^+), 254 (M^+−CH_3), 237 (M^+−2CH_3), 142 (M^+−C_9H_{19}), 110 (142−OCH_3).

The compound **13**, treated as described above, afforded ethyl 2-benzyl-2-methyl acetoacetate; $[\alpha]_D$=+58.51 (c=2.6, $CHCl_3$) [lit.[11]: $[\alpha]_D$=+63.26 (c=3.2, $CHCl_3$)]; ^1H NMR ($CHCl_3$): δ, 1.28 (s, 3H), 1.24 (t, 3H, J=7.5), 2.17 (s, 3H), 3.04 and 3.27 (AB system, 2H, J=13.5 Hz), 4.13 and 4.20 (ABX system, 2H, J_{AB}=10.5, J_{AX}=J_{BX}=7.5 Hz), 7.08–7.3 (m, 5H); ^{13}C NMR ($CDCl_3$): 15.16 (q), 19.04 (q), 26.45 (q), 40.47 (t), 60.82 (s), 61.35 (t), 126.79 (d), 126.79 (d), 128.18 (d), 130.14 (d), 130.14 (d), 136.48 (s), 172.38 (s), 205.27 (s). MS, m/z: 234 (M^+), 191 (M^+-CH_3CO), 145 (191−EtOH), 118 (145−CO), 91 ($PhCH_2$), 78 (Ph).

Typical procedure for the hydrolysis of esters 5–7

A solution of **5** (0.120 g, 0.387 mmol) and potassium hydroxide (0.05 g, 0.78 mmol) in ethanol (3 ml) was refluxed for 4 hr. The reaction mixture was cooled to room temperature and diluted with 5% aqueous HCl (1.2 ml) and extracted with ethyl acetate (3×3 ml). The combined organic extracts were washed twice with a saturated Na_2CO_3 solution (2×2 ml), water, dried (Na_2SO_4) and the solvent removed under reduced pressure to afford (2*R*,3*R*)-dihydroxy-1,2,3,4-tetrahydronaphthalene (0.54 g, 0.33 mmol). The aqueous layer was acidified with 15% HCl and extracted three times with ethyl acetate (3×3 ml). The combined organic extracts were washed with water, dried (Na_2SO_4), and the solvent removed under reduced pressure to afford (*R*)-3-phenylbutyric acid: $[\alpha]_D$=−50.64 (c=1.1, benzene) [lit.[5]: $[\alpha]_D$=−57.1 (c=5, benzene)]; ^1H NMR ($CDCl_3$): δ, 1.32 (d, 3H, J=6.9 Hz), 2.55 (dd, 1H, J=15.5, J=8.3 Hz), 2.66 (dd, 1H, J=15.5, J=6.8Hz), 3.25 (m, 1H), 7.23 (m, 5H); MS, m/z: 164 (M^+), 118, 105, 77.

The compound **7**, obtained from cinnamate **3** and lithium dibutylcuprate in Et_2O–DMF, was treated as described above and afforded (*S*)-3-phenyl heptanoic acid; $[\alpha]_D$=23.5 (c=7, benzene) [lit.[7]: $[\alpha]_D$=37.05 (c=8, benzene)]; ^1H NMR ($CDCl_3$+D_2O): δ, 0.9 (t, 3H, J=6.8 Hz), 1.05–1.35 (m, 4 H), 1.5–1.7 (m, 2H), 2.53 (dd, 1H, J=15.5, J=8.3 Hz), 2.65 (dd, 1H, J=15.5, J=6.8 Hz), 3.2 (m, 1H), 7.2 (m, 5H).

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