Asymmetric Synthesis of Stereodefined 7-(Alk-1-enyl)-5,6,7,8-tetrahydronaphthalene-2-carboxylic Acids and Their Precursors, Bearing a Polar Group in the 8-Position, by the 3-Sulfonyl-1,3-oxazolidine Method

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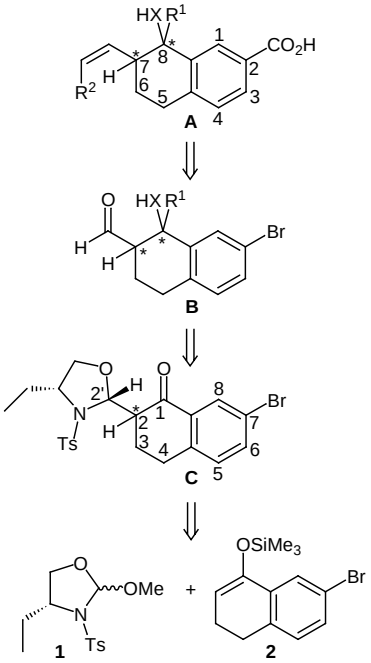
Dedicated to Professor H. J. Bestmann on the occasion of his 75th birthday

Abstract: 7-Bromo-1-(trimethylsilyloxy)-naphthalene **2** was subjected to asymmetric formylation by means of (*R*)-4-ethyl-2-methoxy-3-tosyl-1,3-oxazolidine (**1**). The enantiomerically pure 1-tetralones *u*-**3** and *l*-**3**, bearing a masked formyl group, were elaborated diastereoselectively to achieve the title compounds **11**, **13** and **23** by transformation of the 1-oxo group to a tertiary methyl carbinol moiety or a hydroxymethyl group. Subsequently, the formyl group was converted to a long-chain alkene moiety and, finally, the carboxyl group was introduced via bromine-lithium exchange and carboxylation. Difficulties arose from the high dehydration tendencies of the intermediate tertiary alcohols and by facile epimerisation of the free hydroxyaldehydes. With examples for further application of similar strategies it is demonstrated how these problems could be solved.

Key words: asymmetric electrophilic formylation, chiral β-oxo aldehydes, 3-arenesulfonyl-1,3-oxazolidines, chiral tetrahydro-naphthalenes

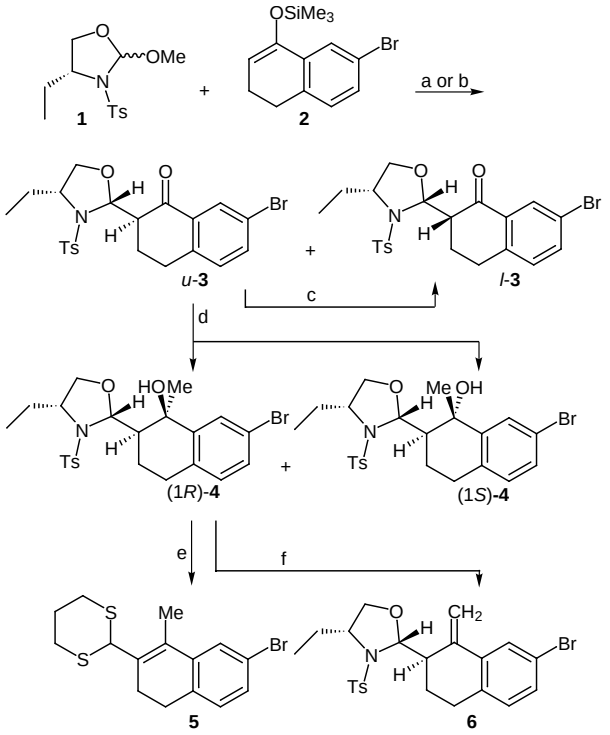
In the search for structurally simple inhibitors of protein phosphatases PP1 and PP2A we became interested in a flexible synthesis of structurally defined 5,6,7,8-tetrahydronaphthalene-2-carboxylic acids **A**, bearing a polar group XH (OH or CH_2OH) in position 8 and possessing a long-chain 1-alkenyl residue in the 7-position.[1] 7-Bromo-1,2,3,4-tetrahydronaphthalene-2-carbaldehydes **B** were aimed as intermediates which should be accessible from the protected β-ketoaldehydes **C** via diastereoselective nucleophilic attack at the oxo group, directed by the chiral auxiliary in 2-position,[2-4] and a subsequent reductive bromo-carboxyl exchange. Compounds **C** are expected to be formed by our method of asymmetric electrophilic formylation[5] of silyl enol ether **2** by means of a readily available, enantiomerically pure *N*-arenesulfonyl-2-methoxy-1,3-oxazolidine such as **1**.[3a,4,5]

Silyl enol ether **2** was prepared from 7-bromo-1-tetralone[6] by the usual method[7] (LDA, Me_3SiCl) and condensed with oxazolidine **1**[5e,8] under the influence of $ZnCl_2 \cdot OEt_2$ to give the epimeric mixture *u*-**3** and *l*-**3** in a ratio of 70:30 and in 50% yield (Scheme 2). The diastereomeric ratio (d.r.) could be improved to 87:13, and yield to 63%, when $TiCl_4$ was used and the trichlorotitanium enolate was allowed to be formed before **1** was added.[9] The d.r. is inverted to 15:85 by refluxing the original mixture with K_2CO_3 in acetone via the corresponding enolate.[8a] The same ratio was achieved by TMS triflate-mediated epimerisation,[5a,5e] although severe decomposition was observed. Separation of the pure major diastereomer *u*-**3** or *l*-**3** was possible by LC on silica gel.



Scheme 1

An X-ray crystal structure analysis of *u*-**3**/*l*-**3**[10] (Figures 1 and 2[11]) confirmed their [2*S*,2(2*R*,4*R*)]- and [2*R*,2(2*R*,4*R*)]-configuration, respectively. Since *u*-**3** already has the thermodynamically favoured 2,4-*cis*-configuration at the oxazolidine ring, it is converted to an even more stable diastereomer under Lewis acidic and basic conditions, this one must differ in the ketone part of the molecule and, thus, was assigned to be *l*-**3**.



Reagents and conditions: a) $ZnCl_2$•OEt_2 (1.15 equiv)/CH_2Cl_2, 0 °C, 2 h, 50%, d.r. 70:30; b) i. **2**+$TiCl_4$ (1.0 equiv)/CH_2Cl_2, −78 °C to r.t., 1 h, ii. **1** (1.1 equiv)/CH_2Cl_2, −90 °C to 0 °C, 14 h, 63%, d.r. 87:13; c) K_2CO_3 (7.2 equiv)/acetone, reflux, 24 h, 80%, d.r. 15:85; d) MeMgCl (3 equiv)/THF, −78 °C to r.t., 24 h, 89%, d.r. 80:20; e) $HS(CH_2)_3SH$ (2.1 equiv), $MeSO_3H$ (0.4 equiv)/CH_2Cl_2, r.t., 24 h, 93%; f) DMAP (0.5 equiv), Ac_2O, Et_3N, 100 °C, 24 h, 90%.

Scheme 2

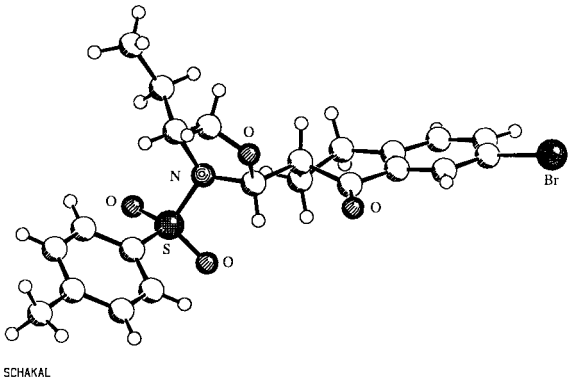


Figure 1 X-ray crystal structure of *u*-**3**.[11]

The addition of methylmagnesium chloride to ketone *u*-**3** gave rise to the formation of two epimeric tertiary alcohols (1*R*)-**4** and (1*S*)-**4** (ratio 80:20, yield 89%). The assignment of the relative configurations is based on the γ-effect in the ^{13}C NMR spectra[12] (Scheme 2).

All attempts of deblocking the masked hydroxy aldehydes led to elimination reactions. When using 1,3-propanedithiol the achiral dihydronaphth-2-yl-1,3-dithiane **5**

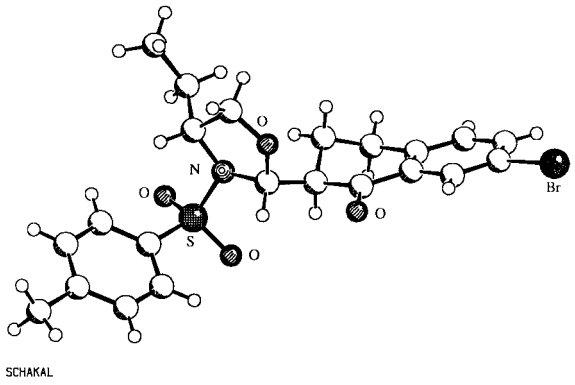


Figure 2 X-ray crystal structure of *l*-**3**.[11]

was isolated in good yields. Interestingly, when heating the tertiary alcohol (1*R*)-**4** with acetic anhydride/4-(*N*,*N*-dimethylamino)pyridine (DMAP) in triethylamine,[13] an elimination to form the 1-methylene-2-decaline **6** with 90% yield occurred. Most probably, the reaction proceeds through the tertiary acetate which undergoes ester pyrolysis at heating to 100 °C. In such a pericyclic reaction, due to steric reasons, proton removal at the exocyclic methyl group is predicted.[14]

It turned out that cleavage of the oxazolidine ring in tetralols (1*R*)-**4** and (1*S*)-**4** could not be accomplished without dehydration. Thus, the aldehyde protecting group had to be exchanged at the stage of ketone *u*-**3**.[15] Thiolysis with 1,3-propanedithiol gave the 1,3-dithiane *R*-**7** without detectable racemisation (Scheme 3). The absolute configuration of *R*-**7** was confirmed by anomalous X-ray dispersion of suitable crystals[16] (Figure 3).

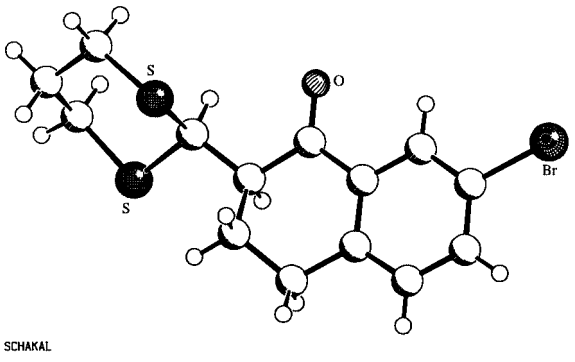
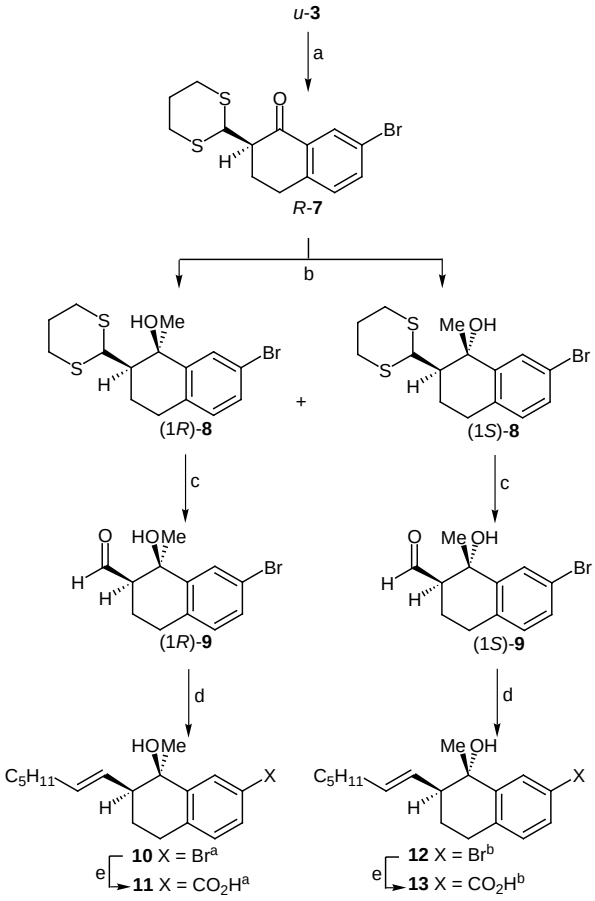


Figure 3 X-ray crystal structure of *R*-**7**.

Addition of methylmagnesium chloride in THF furnished the epimeric tertiary alcohols (1*R*)-**8** and (1*S*)-**8** in a d.r. of 79:21 (yield 80%). As expected, the dithiane ring occupies a pseudoequatorial position in the tetralone *R*-**7** shielding the *Re*-face of the carbonyl group and directing the nucleophile to enter predominantly from the *Si*-face (at the rear) leading to the major diastereomer (1*R*)-**8**. Here, the analysis of the γ-effects[12] in the ^{13}C NMR spec-

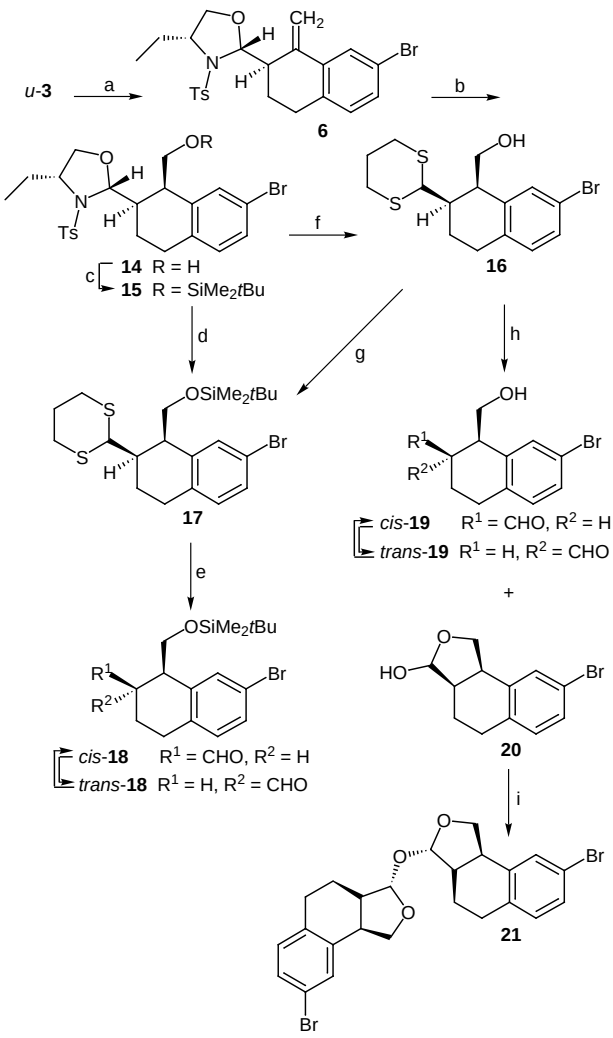


[a] Mixture of 3 isomers, only the main product is shown.

[b] The product was only prepared as the racemate.

Reagents and conditions: a) $HS(CH_2)_3SH$ (1.5 equiv), $BF_3{\bullet}OEt_2$ (1.5 equiv)/CH_2Cl_2, 0 °C, 5 h, 88%, ee >90%; b) MeMgCl (3 equiv)/THF, −78 °C to r.t., 24 h, 80%, d.r. 79:21; c) MeI (20 equiv), $CaCO_3$ (15 equiv)/acetone:H_2O (4:1), 60 °C, 24 h, (1*R*)-**9**: 98%; (1*S*)-**9**: 95%; d) *n*-$C_6H_{13}PPh_3Br$ (2.10 equiv), *n*-BuLi (2.05 equiv)/THF, 0 °C, 4 h, **10**: 50%, *E*-*cis*:*Z*-*cis*:*E*-*trans*:*Z*-*trans* = 57:31:12:0; **12**: 52%, *E* only; e) i. MeLi·LiBr (1.0 equiv)/THF, −78 °C, 30 min, ii. *tert*-BuLi (2.5 equiv)/THF, −78 °C, 10 min, iii. CO_2, −78 °C to r.t., 30 min, **11**: 91%, *E*-*cis*:*Z*-*cis*:*E*-*trans*:*Z*-*trans* = 56:28:16:0; **13**: 29%, *E* only.

Scheme 3



Reagents and conditions: a) Tebbe reagent (1.06 equiv)/THF, r.t., 4 h, 75%; b) i. $BH_3{\cdot}THF$ (5.0 equiv)/THF, r.t. 3 h, ii. H_2O_2, $NaOH/H_2O$, r.t., 3 h, 82%, d.r. > 95:5; c) i. NaH (1.5 equiv)/THF, r.t., 2 h, ii. TBDMSCl (2.5 equiv)/THF, r.t., 24 h, 90%; d) $HS(CH_2)_3SH$ (1.5 equiv), $MeSO_3H$ (0.3 equiv)/CH_2Cl_2, r.t., 3 h, 29%; e) MeI (20 equiv), $CaCO_3$ (15 equiv)/acetone:H_2O (4:1), 60 °C, 24 h, 84%, d.r. 85:15; f) **14**, $HS(CH_2)_3SH$ (2 equiv), $BF_3{\bullet}OEt_2$ (2 equiv)/CH_2Cl_2, 0 °C, 2 h, 87%; g) i. NaH (2 equiv)/THF, r.t. 2 h, ii. TBDMSCl (2 equiv)/THF, r.t., 24 h, 80%; h) MeI (20 equiv), $CaCO_3$ (15 equiv)/acetone:H_2O (4:1), 60 °C, 24 h, **19**: 43%, d.r. 23:77, and **20** (only from *cis*-**19**), 36%; i) crystallization, Et_2O/petroleum ether, r.t., 5 d.

Scheme 4

tra supports a (pseudo)equatorial position of the 1-CH_3 group in (1*R*)-**8**.

The deprotection of separated epimers (1*R*)-**8** and (1*S*)-**8** to form the corresponding labile β-hydroxy aldehydes (1*R*)-**9** and (1*S*)-**9** was accomplished without epimerisation or competing elimination of water by refluxing the 1,3-dithianes with a large excess of methyl iodide/calcium carbonate in acetone/water.[4,5d,5f] Almost quantitative yields (98% and 95%) resulted, when a special, non-aqueous work-up was applied (see Experimental).

A (*Z*)-1-heptenyl side chain, taken as a model for structurally more complicated alkenyl residues, was elaborated from the formyl groups. Aldehyde (1*R*)-**9**, without protection of the hydroxy group, was reacted with 2 equivalents of *n*-hexylidenetriphenylphosphorane. Surprisingly, a mixture of (*E*)-(1*R*)-**10**, the corresponding (*Z*)-alkene and the 1-epimer (*E*)-(1*S*)-**10** (50%, 57:31:12) was isolated. Obviously, an epimerisation of the aldehyde (1*R*)-**9** takes place under the basic reaction conditions. From another experiment, a pure sample of racemic (*E*)-(1*R**)-**10** could be separated, the vicinal coupling constants of the olefinic protons (15.5 Hz and 10.9 Hz) support the *E*- and *Z*-assignment, respectively. A racemic sample of (1*S**)-**9** provided the racemic diastereomerically pure (*E*)-**12**.

Table 1 Prepared Compounds **3**-**5**, **7**-**13**.

Product[a]	Yield [%]	Ratio (*dr*)	Mp [°C][b]	$[\alpha]_D^{20}$ (*c*, CH_2Cl_2)	Configuration
u-**3** +	50[c], 63[d]	70:30[c], 87:13[d]	180−182	+97.4 (0.92)	2*S*,2(2*R*,4*R*)
l-**3**			199−201	+37.3 (1.00)	2*R*,2(2*R*,4*R*)
R-**7**	88	–	131−132	–23.6 (1.96)	2*R*
(1*R*)-**8** +	80	79:21	118−120	–77.4 (0.95)	1*R*,2*R*
(1*S*)-**8**			105−106	+30.1 (0.76)	1*S*,2*R*
(1*R*)-**9**	98	>95:5	oil	–[e]	1*R*,2*R*
(1*S*)-**9**	95	>95:5	oil	–[e]	1*S*,2*R*
10	50[f]	g	oil	−15.3 (0.79)	(1*R*,2*RS*)-2*EZ*
rac-**12**	52	*E*-*trans*	oil	–	*trans*-(1*RS*,2*RS*)-2*E*
11	91[f]	h	wax	−6.8 (0.65)	(7*RS*,8*R*)-7*EZ*
rac-**13**	29	*E*-*trans*	wax	–	*trans*-(7*RS*,8*RS*)-7*E*
(1*R*)-**4** +	89	80:20	172−173	+37.1 (0.63)	1*R*,2*R*,2(2*R*,4*R*)
(1*S*)-**4**[i]			–[e]	–[e]	1*S*,2*R*,2(2*R*,4*R*)
5	93	–	oil	–	–

[a] Satisfactory microanalysis, C ±0.4, H ±0.4, N ±0.4, or HRMS were obtained.
[b] From Et_2O/petroleum ether.
[c] Method A.
[d] Method B.
[e] Not determined.
[f] Diastereomeric mixture, which was not separable by flash chromatography.
[g] *E*(1*R*,2*S*):*Z*(1*R*,2*S*):*E*(1*R*,2*R*) = 57:31:12.
[h] *E*(7*S*,8*R*):*Z*(7*S*,8*R*):*E*(7*R*,8*R*) = 56:28:16.
[i] (1*S*)-**4** could not be obtained as a diastereomerically pure sample by flash chromatography.

After reductive lithiation of the mixture of (*E*)- and (*Z*)-**10** and carboxylation, a mixture of the carboxylic acids (1*R*)- and (1*S*)-**11** were formed in a ratio, which corresponds to the starting material. Similarly, (*E*)-**12** provided pure (*E*)-**13**. Although the conditions have not been fully optimised, it is evident, that the double bond and the stereogenic centers at C-1 and C-2 are not attacked during the lithiation-carboxylation process.

The alkene **6** was also produced directly from ketone *u*-**3** by the action of Tebbe reagent,[17] yield 75% (Scheme 4). Hydroboration of the *exo*-methylene derivative **6** (with BH_3 in THF) and the usual work-up gave the crystalline, diastereomerically pure primary alcohol **14**. The crystal structure analysis of **14**[18] (Figure 4) reveals, as expected, that borane had approached from the less hindered rear-face. Cleavage of the oxazolidine ring in the *O*-TBDMS ether **15** to form the dithiane **17** proceeded only with low yield (29%). It turned out to be more advantageous to convert the alcohol **14** directly to dithiane **16** (yield 87%), followed by *O*-silylation to produce **17** (80%). Dethioacetalisation of **17** (MeI/$CaCO_3$ in wet acetone) was accompanied by partial epimerisation in 2-position of the aldehyde **18**, a *cis*-**18**/*trans*-**18** ratio of 85:15 was observed. The dethioacetalisation of the free alcohol **16** by the same method delivered, besides an inseparable mixture of the *cis*, *trans*-aldehydes **19** (*cis*-**19**/*trans*-**19**, ratio 23:77), the *cis*-lactol **20**. After having kept a sample for several weeks, from a solution of **20** in Et_2O, crystals separated which proved to consist of the stereohomogeneous "dimeric" acetal **21**, formed by connecting two identical moieties by an *exo*,*exo*-oxygen bridge (Figure 5).[19]

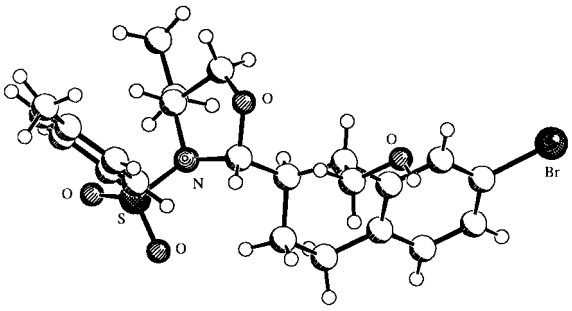


Figure 4 X-ray crystal structure of **14**.

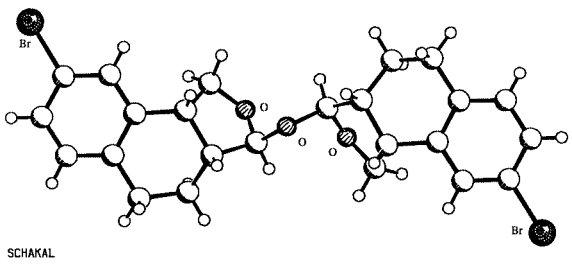
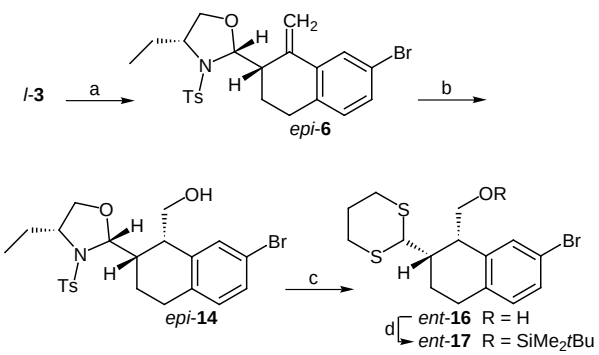


Figure 5 X-ray crystal structure of **21**.

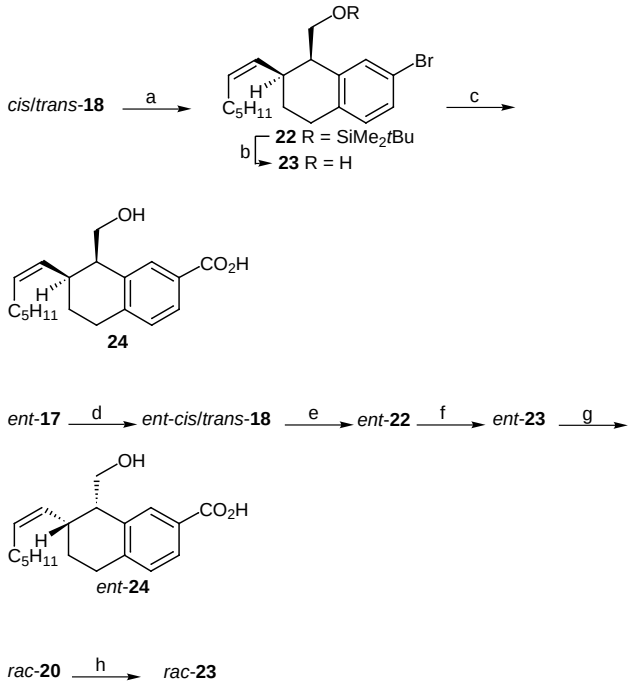
Similarly, the protected enantiomeric hydroxyaldehyde *ent*-**17** was prepared from the ketone *l*-**3** via the methylene compound *epi*-**6** and the alcohol *epi*-**14** (Scheme 5).

From the Wittig reaction of *cis*-**18**/*trans*-**18** (ratio 85:15) with *n*-hexyltriphenylphosphonium bromide,[20] a homogeneous pure sample[21] (33%) of *Z*-alkene **22** was isolated (Scheme 6). Fluoride-induced deprotection of **22** led to



Reagents and conditions: a) Tebbe reagent (1.06 equiv)/THF, r.t., 4 h, 74%; b) i. BH_3·THF (5.0 equiv)/THF, r.t. 3 h, ii. H_2O_2, NaOH/H_2O, r.t., 3 h, 60%, d.r. > 95:5; c) $HS(CH_2)_3SH$ (2.8 equiv), BF_3•OEt_2 (2.8 equiv)/CH_2Cl_2, 0 °C, 3 h, 83%; d) i. NaH (2 equiv)/THF, r.t., 2 h, ii. TBDMSCl (2 equiv)/THF, r.t., 24 h, 83%.

Scheme 5



Reagents and conditions: a) *n*-$C_6H_{13}PPh_3Br$ (1.10 equiv), *n*-BuLi (1.08 equiv)/THF, 0 °C, 4 h, 33%; b) TBAF (2 equiv)/THF, r.t., 24 h, 57%; c) i. MeLi·LiBr (1.0 equiv)/THF, −78 °C, 30 min, ii. *tert*-BuLi (2.5 equiv)/THF, −78 °C, 10 min, iii. CO_2, −78 °C to r.t., 30 min, 37%; d) MeI (20 equiv), $CaCO_3$ (15 equiv)/acetone:H_2O (4:1), 60 °C, 24 h, 92%, d.r. 70:30; e) *n*-$C_6H_{13}PPh_3Br$ (1.10 equiv), *n*-BuLi (1.08 equiv)/THF, 0 °C, 4 h; f) TBAF (2 equiv)/THF, r.t., 24 h, 78% (over 2 steps); g) i. MeLi·LiBr (1.0 equiv)/THF, −78 °C, 30 min, ii. *tert*-BuLi (2.5 equiv)/THF, −78 °C, 10 min, iii. CO_2, −78 °C to r.t., 30 min, 54%; h) *n*-$C_6H_{13}PPh_3Br$ (2.10 equiv), *n*-BuLi (2.05 equiv)/THF, 0 °C, 4 h, 34%.

Scheme 6

the free alcohol **23**.[22] Starting from *ent*-**17**, the identical sequence gave the enantiomer *ent*-**23**. Nearly identical specific rotations of opposite sense give evidence that no uncontrolled epimerisation reactions are involved in the final steps. A (racemic) sample of lactol *rac*-**20** was directly converted to pure alkene *rac*-**23**, illustrating that two protecting group manipulations could be saved. Finally, **23** and *ent*-**23**, via bromine-lithium exchange, followed by carboxylation, provided the carboxylic acids **24** and *ent*-**24**, respectively.

We have demonstrated that the asymmetric formylation by means of chiral *N*-arenesulfonyl-2-alkoxy-1,3-oxazolidines provides a powerful and versatile tool for the asymmetric introduction of vicinal carbon substituents, starting from ketones. Even in problematic situations, such as the presence of reactive benzylic positions, which can give rise to side reactions, the method can be applied advantageously. In addition, the high tendency of the intermediate sulfonyloxazolidines for crystallisation facilitates structure determinations during the synthesis.

All reactions, which are sensitive to moisture, were carried out under Ar. All solvents were purified by distillation and dried, if necessary, prior to use. ^1H and ^{13}C NMR spectra were recorded on Bruker WM300, AM360 or U600 spectrometers. HRMS was recorded on a Finnigan MAT 8230 mass spectrometer (EI, 70 eV). Optical rotations were recorded on a Perkin−Elmer polarimeter 241 at 20 °C. Mps were obtained on Gallenkamp melting point apparatus MFB-595 and are uncorrected. Microanalyses were performed at the Organisch-Chemisches Institut der WWU Münster with a Perkin−Elmer Analyser 240. Products were purified by flash column chromatography on silica gel (40−63 µm). Tebbe reagent was purchased from Fluka.

7-Bromo-3,4-dihydro-1-trimethylsilyloxynaphthalene (2)

According to the general method[7] a solution of LDA (38.4 mmol) in THF (50 mL) was prepared from diisopropylamine (5.74 mL, 40.3 mmol) and 1.6 M *n*-BuLi in hexane (24.0 mL, 38.4 mmol). 7-Bromo-1-tetralone[6] (8.24 g, 36.6 mmol), dissolved in anhyd THF (30 mL), was added dropwise during a period of 20 min at −78 °C, the mixture was stirred for 2 h at −78 °C, and Me_3SiCl (5.56 mL, 44.0 mmol) slowly added. After stirring at −78 °C for 1 h, the reaction mixture was allowed to warm to r.t. (approx. 1 h). The solvents were evaporated in vacuo, light petroleum ether (PE) (50 mL) was added to the remaining residue, the solids were filtered off, and the solvents again removed. Distillation afforded **2** (10.0 g, 92%), as a slightly yellow oil.

R_f 0.71 (Et_2O/PE, 1:4); bp 115−117 °C, 0.05 Torr.

IR (film): ν = 2860, 2810, 1615, 1580, 1545, 1410, 1230, 1175, 830, 750 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.25 (s, 9H), 2.25−2.32 (m, 2H), 2.65−2.73 (m, 2H), 5.15−5.21 (m, 1H), 6.92−6.96 (m, 1H), 7.23 (dd, 1H, ^4J = 2.13 Hz, ^3J = 7.86 Hz), 7.50 (d, 1H, ^4J = 2.13 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 0.2, 22.0, 27.6, 106.1, 120.0, 124.9, 128.5, 130.0, 135.5, 135.8, 147.1.

[2*S*,2(2*R*,4*R*)]- and [2*R*,2(2*R*,4*R*)]-7-Bromo-2-{4-ethyl-3-[(4-methylbenzene)sulfonyl-1,3-oxazolidin-2-yl}-1,2,3,4-tetrahydro-1-naphthalenone (*u*-3 and *l*-3)

Method A: To a solution of silyl enol ether **2** (2.97 g, 10.0 mmol) and 2-methoxy-1,3-oxazolidine[5e,23] **1** (3.14 g, 11.0 mmol) in anhyd CH_2Cl_2 (20 mL) at 0 °C was added 2.2 M $ZnCl_2$·OEt_2 in CH_2Cl_2 (5.23 mL, 11.5 mmol). The mixture was stirred at 0 °C for 2 h. After addition of sat. NaCl (10 mL), the aqueous layer was separated, extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic extracts

Table 2 Prepared Compounds **6**, **14**–**24**.

Product[a]	Yield [%]	Ratio (*dr*)	Mp [°C][b]	$[\alpha]_D^{20}$ (*c*, CH_2Cl_2)	Configuration
6	90[c], 75[d]	>95:5	137−138	−7.1 (0.54)	2*R*,2(2*R*),4*R*
epi-**6**	74	>95:5	138−140	+108.0 (0.48)	2*R*,2(2*S*),4*R*
14	82	>95:5	159−161	+50.9 (0.51)	1*R*,2*R*,2(2*R*,4*R*)
epi-**14**	60	>95:5	142−144	+45.3 (0.23)	1*S*,2*S*,2(2*R*,4*R*)
15	90	>95:5	oil	+48.7 (0.46)	2*R*,2(1*R*,2*R*),4*R*
16	87	-	51−53	+60.7 (110)	1*R*,2*R*
ent-**16**	83	-	51−53	−64.4 (0.95)	1*S*,2*S*
17	80	-	81−82	+51.3 (1.42)	1*R*,2*R*
ent-**17**	83	-	81−82	−52.1 (1.05)	1*S*,2*S*
cis-**19** + *trans*-**19**	43[e]	23:77	oil	–[f]	1*R*,2*R* 1*R*,2*S*
20	36	>95:5	127−129	−108.0 (0.64)	3*R*,3a*R*,9b*R*
cis-**18** + *trans*-**18**	84[e]	85:15	oil	–[f]	1*R*,2*R* 1*R*,2*S*
ent-*cis*-**18** *ent*-*trans*-**18**	92[e]	70:30	oil	–[f]	1*S*,2*S* 1*S*,2*R*
22	33	>95:5	oil	+61.8 (0.82)	1*R*,2*S*,2*Z*
ent-**22**	–[f]	>95:5	oil	–[f]	1*S*,2*R*,2*Z*
23	57	>95:5	oil	+65.2 (0.33)	1*R*,2*S*,2*Z*
ent-**23**	78[g]	>95:5	oil	−66.1 (0.12)	1*S*,2*R*,2*Z*
24	37	>95:5	wax	+70.6 (0.17)	7*S*,8*R*,7*Z*
ent-**24**	54	>95:5	wax	150.0 (0.40)[h]	7*R*,8*S*,7*Z*

[a] Satisfactory microanalysis, C ±0.4, H ±0.4, N ±0.4, or HRMS were obtained.
[b] From Et_2O/petroleum ether.
[c] Method A.
[d] Method B.
[e] Diastereomeric mixture, which was not separable by flash chromatography.
[f] Not determined.
[g] Yield over 2 steps.
[h] In $CDCl_3$.

dried (Na_2SO_4). The solvent was removed in vacuo and the residue (*u*-**3**:*l*-**3**, 70:30) purified on silica gel by flash chromatography with Et_2O/PE (1:4 to 1:2) to afford pure oxazolidine *u*-**3** (0.36 g, 7%) and a mixture of *u*-**3**:*l*-**3** (2.06 g, 43%, d.r. 65:35); combined yield 50%.

Method B: To a solution of silyl enol ether **2** (2.97 g, 10.0 mmol), dissolved in anhyd CH_2Cl_2 (80 mL), $TiCl_4$ (1.09 mL, 10.0 mmol) was added dropwise below −78 °C. The mixture was stirred at −78 °C (15 min) and at r.t. (25 min), chilled to −90 °C and 2-methoxy-1,3-oxazolidine **1** (2.58 g, 10.9 mmol) in anhyd CH_2Cl_2 (20 mL) was slowly added during 1.5 h. The reaction mixture was first allowed to warm slowly to −50 °C during 5 h and then to 0 °C during 9 h. After addition of aq 2N HCl (10 mL) and sat. NaCl (10 mL), the aqueous layer was separated, extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic extracts dried (Na_2SO_4). The solvent was removed in vacuo and the residue (*u*-**3**:*l*-**3**, d.r. 87:13) purified on silica gel by flash chromatography with Et_2O/PE (1:4 to 1:2) to afford pure oxazolidine *u*-**3** (1.91 g, 40%) and a mixture of *u*-**3**:*l*-**3** (1.12 g, 23%, d.r. 70:30); combined yield 63%.

An attempt to separate the epimers by crystallisation from Et_2O/PE, resulted in twin crystals of *l*-**3** and *u*-**3** (50:50).

Compound *u*-3

Colourless crystals; R_f 0.35 (Et_2O/PE, 1:1); mp 180−182 °C (Et_2O/PE); $[\alpha]_D$ = +97.4 (*c* 0.92, CH_2Cl_2).

Anal. Calcd for $C_{22}H_{24}BrNO_4S$ (478.4): C, 55.23; H, 5.06; N, 2.93. Found: C, 55.51; H, 5.05; N, 2.98.

^1H, ^{13}C NMR and IR data: Tables 3 and 4.

Isomerization of *u*-3 into *l*-3

A mixture of ketones *u*-**3** and *l*-**3** (478 mg, 1.00 mmol, d.r. 70:30) and K_2CO_3 (1.0 g, 7.2 mmol) in acetone (10 mL) was refluxed for 24 h. The salt was filtered off, the solvent removed in vacuo and the residue (*u*-**3**:*l*-**3**, d.r. 15:85) separated by flash chromatography on silica gel (Et_2O/PE, 1:4) to afford pure *l*-**3** (287 mg, 60%) and a mixture of *u*-**3**:*l*-**3** (96 mg, 20%, d.r. 60:40); combined yield 80%.

Compound *l*-3

Colourless crystals; R_f 0.38 (Et_2O/PE, 1:1); mp 199−201 °C (Et_2O/PE).

$[\alpha]_D$ = +37.3 (*c* 1.00, CH_2Cl_2).

^1H, ^{13}C NMR and IR data: see Tables 3 and 4.

(2*R*)-7-Bromo-2-(1,3-dithian-2-yl)-1,2,3,4-tetrahydro-1-naphthalenone [*R*-7]

To a solution of oxazolidine *u*-**3** (1.23 g, 2.56 mmol) in anhyd CH_2Cl_2 (20 mL) at 0 °C was added 1,3-propanedithiol (0.29 mL, 3.84 mmol) and BF_3•OEt_2 (0.48 mL, 3.84 mmol). After stirring for 5 h, sat. $NaHCO_3$ (20 mL) was introduced and the reaction mixture was stirred for 20 min. The two phases were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic phases were dried (Na_2SO_4) and the solvent was removed in vacuo. The residue was flash chromatographed on silica gel (Et_2O/PE, 1:19 to 1:4) to give dithiane *R*-**7** (774 mg, 88%).

Colourless crystals; R_f 0.33 (Et_2O/PE, 1:4); mp 131−132 °C (Et_2O/PE).

$[\alpha]_D$ = −23.6 (*c* 1.96, CH_2Cl_2).

HRMS (EI): *m/z* calcd for (M^+): 341.97476. Found: 341.97555.

Table 3 Selected Data of Compounds **3**, **4**, **7**-**9** (IR, ^{1}H NMR).

Product	IR (KBr/film) ν [cm^{-1}]	^{1}H-NMR (300 MHz, $CDCl_3$), δ, J (Hz)[a]				
		2′-H ($^3J_{2',2}$)	2-H	1-CH_3	1-OH	2-CHO
u-**3**	1685, 1340, 1160	5.57 (d, 4.53)	2.77–3.02 (m)	–	–	–
l-**3**	1685, 1340, 1160	5.56 (d, 2.13)	3.30 (ddd)	–	–	–
R-**7**	1670	4.95 (d, 3.33)	2.31–2.40 (m)	–	–	–
(1*R*)-**8**	3490, 1580, 1260	4.50 (d, 4.26)	2.15–2.20 (m)	1.49 (s)	3.23 (s)	–
(1*S*)-**8**	3490, 1580, 1260	4.42 (d, 4.47)	2.29–2.37 (m)	1.49 (s)	2.75–3.01 (m)	–
(1*R*)-**9**	3400, 1700, 1340		2.69–2.77 (m)	1.60 (s)	2.69–2.77 (m)	9.82 (d)
(1*S*)-**9**	3450, 1705, 1345	–	2.64–2.88 (m)	1.46 (s)	2.64–2.88 (m)	10.01 (s)
(1*R*)-**4**	3482, 1165	5.22 (d, 10.26)	2.01–2.07 (m)	1.46 (s)	4.17 (s)	–
(1*S*)-**4**	–[b]	5.47 (d, 9.99)	–[b]	–[b]	–[b]	–[b]

[a] s = singlet, d = doublet, t = triplet, m = multiplet.
[b] Not determined. (1*S*)-**4** could not be obtained as a diastereomerically pure sample by flash chromatography.

^{1}H, ^{13}C NMR and IR data: Tables 3 and 4.

(1*R*,2*R*)- and (1*S*,2*R*)-7-Bromo-2-(1,3-dithian-2-yl)-1-methyl-1,2,3,4-tetrahydro-1-naphthol [(1*R*)-8 and (1*S*)-8]

MeMgCl (3 M) in THF (2.4 mL, 7.13 mmol) in anhyd THF (5 mL) was cooled to −78 °C and dithiane *R*-**7** (816 mg, 2.38 mmol), dissolved in anhyd THF (15 mL), was added dropwise. The reaction mixture was allowed to warm up to r.t. overnight and then hydrolysed with sat. NaCl (5 mL). The aqueous layer was separated and extracted with Et_2O (3 × 30 mL). The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. Purification of the residue by flash chromatography (Et_2O/PE, 1:9) afforded the diastereomers (1*R*)-**8** (535 mg, 63%) and (1*S*)-**8** (140 mg, 17%) in a ratio of 79:21 and some starting material *R*-**7** (42 mg, 5%).

Compound (1*R*)-8

White solid; R_f 0.15 (Et_2O/PE, 1:9); mp 118−120 °C (Et_2O/PE).

$[\alpha]_D$ = −77.4 (*c* 0.95, CH_2Cl_2).

HRMS (EI): *m/z* calcd for (M^+): 358.00607. Found: 358.00652.

Compound (1*S*)-8

White solid; R_f 0.12 (Et_2O/PE, 1:9); mp 105−106 °C (Et_2O/PE).

$[\alpha]_D$ = +30.1 (*c* 0.76, CH_2Cl_2).

^{1}H, ^{13}C NMR and IR data of (1*R*)-**8** and (1*S*)-**8**: Tables 3 and 4.

Table 4 Selected Data of Compounds **3**, **4**, **7**–**9** (^{13}C NMR).

Product	^{13}C-NMR (75 MHz, $CDCl_3$), δ					
	C-2′	C-2	C-1	C-3	1-CH_3	2-CHO
u-**3**	90.7	51.4	194.9	24.1	–	–
l-**3**	91.0	51.3	195.7	21.2	–	–
R-**7**	52.5	48.0	193.9	25.1	–	–
(1*R*)-**8**	49.9	49.0	72.2	22.5	31.7	–
(1*S*)-**8**	47.7	51.0	74.5	23.9	26.9	–
(1*R*)-**9**	–	56.6	70.9	20.3	30.9	204.6
(1*S*)-**9**	–	57.4	72.6	20.4	27.4	204.4
(1*R*)-**4**	93.4	46.2	72.6	20.9	32.7	–
(1*S*)-**4**	–[a]	49.1	73.1	23.0	27.0	–

[a] Not determined.

(1*R*,2*R*,2(2*R*,4*R*)) and (1*S*,2*R*,2(2*R*,4*R*))-7-Bromo-2-{4-ethyl-3-[(4-methylbenzene)sulfonyl]-1,3-oxazolidin-2-yl}-1-methyl-1,2,3,4-tetrahydro-1-naphthol [(1*R*)-4 and (1*S*)-4]

MeMgCl (3 M) in THF (0.6 mL, 1.8 mmol) in anhyd THF (10 mL) was cooled to −78 °C and oxazolidine *u*-**3** (287 mg, 0.60 mmol), dissolved in anhyd THF (10 mL) was added dropwise. The reaction mixture was allowed to warm up to r.t. overnight and then hydrolysed with sat. NaCl (10 mL). The aqueous layer was separated and extracted with Et_2O (3 × 25 mL). The combined organic phases were dried (Na_2SO_4) and evaporated to leave a residue (1*R*)-**4**:(1*S*)-**4** (80:20) whose purification by flash chromatography (Et_2O/PE, 1:2 to 1:1) furnished diastereomerically pure (1*R*)-**4** as a white foam (158 mg, 53%) and a mixture of (1*R*)-**4** and (1*S*)-**4** (82 mg, 28%) as a white solid, d.r. 41:59.

Compound (1*R*)-4

White foam; R_f 0.29 (Et_2O/PE, 1:1); mp 171−172 °C (Et_2O/PE).

$[\alpha]_D$ = +37.1 (*c* 0.63, CH_2Cl_2).

Anal. Calcd for $C_{23}H_{28}BrNO_4S$ (494.44): C, 55.87; H, 5.71; N, 2.83. Found: C, 55.97; H, 5.88; N, 2.99.

^{1}H, ^{13}C NMR and IR data of (1*R*)-**4**: Tables 3 and 4.

2-(7-Bromo-3,4-dihydro-1-methyl-2-naphthyl)-1,3-dithiane (5)

To a solution of Grignard adduct (1*R*)-**4** (340 mg, 0.69 mmol) in anhyd CH_2Cl_2 (15 mL) were added 1,3-propanedithiol (0.15 mL, 1.50 mmol) and $MeSO_3H$ (0.02 mL, 0.30 mmol). After stirring for 24 h at r.t., solid K_2CO_3 (100 mg, 0.72 mmol) was added and the mixture was stirred for 10 min. The solid materials were filtered off and washed with CH_2Cl_2 (10 mL). The filtrate was concentrated in vacuo. The crude product was purified by flash chromatography (Et_2O/PE, 1:9) to give **5** (240 mg, 93%).

Colourless oil; R_f 0.23 (Et_2O/PE, 1:9);

IR (film): ν = 2920, 2890, 1580, 1475 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.84−1.94 (m, 1H), 2.09−2.15 (m, 1H), 2.18 (s, 3H), 2.44−2.48 (m, 2H), 2.74−2.79 (m, 2H), 2.85−3.00 (m, 4H), 4.74 (s, 1H), 6.98 (d, 1H, ^3J = 7.80 Hz), 7.22 (dd, 1H, ^4J = 1.98 Hz, ^3J = 7.80 Hz), 7.40 (d, 1H, ^4J = 1.98 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.6, 24.7, 25.2, 26.5, 31.1, 51.0, 120.0, 126.7, 128.5, 129.5, 130.7, 133.5, 135.0, 138.4.

(2*R*,2(2*R*),4*R*) and (2*R*,2(2*S*),4*R*)-2-[7-Bromo-1-methylene-1,2,3,4-tetrahydro-2-naphthyl]-4-ethyl-3-[(4-ethyl-3-[(4-methylbenzene)sulfonyl]-1,3-oxazolidine (6 and *epi*-6)

Method A: A mixture of Grignard adduct (1*R*)-**4** (2.00 g, 4.04 mmol), DMAP (240 mg, 2.00 mmol) acetic anhydride (20

mL), and Et_3N (40 mL) was refluxed at 100 °C for 24 h. The reaction mixture was cooled to r.t. and poured into a mixture of ice (200 g) and 2N HCl (200 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (5 × 50 mL) and the combined organic phases were washed with sat. $NaHCO_3$, dried (Na_2SO_4) and evaporated in vacuo. Flash chromatography of the residue on silica gel (Et_2O/PE, 1:2) afforded **6** (1.73 g, 90%) as a white solid.

Method B: A solution of ketone *u*-**3** (5.63 g, 11.8 mmol) in anhyd THF (40 mL) was cooled to 0 °C and treated dropwise with Tebbe reagent (0.5 M) in toluene (25.0 mL, 12.5 mmol), stirred at r.t. for 4 h and hydrolysed with 0.1 N NaOH (1 mL). The reaction mixture was dried (Na_2SO_4) and filtered using Celite. The resulting filter cake was washed with CH_2Cl_2 (3 × 50 mL), and the filtrate was concentrated in vacuo. Purification of the residue by flash chromatography (Et_2O/PE, 1:9 to 1:4) yielded analytically pure alkene **6** (4.15 g, 75%).

Compound 6

White solid; R_f 0.35 (Et_2O/PE, 1:2); mp 137−138 °C (Et_2O/PE).

$[\alpha]_D$ = −7.1 (*c* 0.54, CH_2Cl_2).

Anal. Calcd for $C_{23}H_{26}BrNO_3S$ (476.43): C, 57.98; H, 5.50; N, 2.94. Found: C, 57.93; H, 5.39; N, 3.05.

Compound *epi*-6

Method B, from *l*-**3** (134 mg, 0.30 mmol); yield 105 mg (74%).

Colourless crystals; R_f 0.32 (Et_2O/PE, 1:2); mp 138−140 °C (Et_2O/PE)

$[\alpha]_D$ = +108.0 (*c* 0.48, CH_2Cl_2).

^1H, ^{13}C NMR and IR data of **6** and *epi*-**6**: Tables 5 and 6.

(1*R*,2*R*,2(2*R*,4*R*))- and (1*S*,2*S*,2(2*R*,4*R*))-7-Bromo-2-{4-ethyl-3-[(4-methylbenzene)sulfonyl]-1,3-oxazolidin-2-yl}-1,2,3,4-tetrahydro-1-naphthyl)methanol (14 and *epi*-14)

To a solution of alkene **6** (1.50 g, 3.15 mmol) in anhyd THF (20 mL) was added dropwise 1 M BH_3·THF in THF (16.0 mL, 16.00 mmol) at 0 °C. The solution was stirred for 3 h at r.t. and then cooled again to 0 °C. NaOH (1.2 g), dissolved in H_2O (6 mL), and H_2O_2 (30%, 4.5 mL) were added to the mixture and stirring was continued for 3 h at r.t. The two layers were separated and the aqueous phase was extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with sat. $FeSO_4$, dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash chromatography (Et_2O/PE, 1:3) to yield diastereomerically pure **14** (1.27 g, 82%).

Compound 14

Colourless crystals; R_f 0.16 (Et_2O/PE, 1:1); mp 159−161 °C (Et_2O/PE).

$[\alpha]_D$ = +50.9 (*c* 0.51, CH_2Cl_2).

Anal. Calcd for $C_{23}H_{28}BrNO_4S$ (494.44): C, 55.87; H, 5.71; N, 2.83. Found: C, 56.02; H, 5.89; N, 3.12.

Compound *epi*-14

From *epi*-**6** (100 mg, 0.21 mmol); yield 62 mg (60%).

Colourless crystals; R_f 0.19 (Et_2O/PE, 1:1); mp 142−144 °C (Et_2O/PE).

$[\alpha]_D$ = +45.3 (*c* 0.23, CH_2Cl_2).

^1H, ^{13}C NMR and IR data of **14** and *epi*-**14**: Tables 5 and 6.

(2*R*,2(1*R*,2*R*),4*R*)-2-{7-Bromo-1-[(*tert*-butyl-dimethylsilyloxy)-methyl]-1,2,3,4-tetrahydro-2-naphthyl}-4-ethyl-3-[(4-methylbenzene)sulfonyl]-1,3-oxazolidine (15)

To a suspension of NaH (60% in mineral oil, 6.0 mg, 0.15 mmol) in THF (1 mL) was added dropwise a solution of alcohol **14** (50 mg, 0.10 mmol) in THF (5 mL) at 0 °C. After stirring for 2 h at r.t. TBDMSCl (38 mg, 0.25 mmol) in THF (1 mL) was introduced with a syringe and the reaction mixture was stirred at r.t. for 24 h. After hydrolysis with H_2O (2 mL) the aqueous layer was separated and extracted with Et_2O (3 × 10 mL). The combined organic phases were dried (Na_2SO_4) and the solvents were evaporated in vacuo. Purification of the residue by flash chromatography (Et_2O/PE, 1:4) afforded the silyl ether **15** (55 mg, 90%) as a colourless oil.

R_f 0.32 (Et_2O/PE, 1:4); $[\alpha]_D$ = +48.7 (*c* 1.46, CH_2Cl_2).

^1H, ^{13}C NMR and IR data of **15**: Tables 5 and 6.

(1*R*,2*R*)- and (1*S*,2*S*)-[7-Bromo-2-(1,3-dithian-2-yl)-1,2,3,4-tetrahydro-1-naphthyl]methanol (16 and *ent*-16)

To a solution of alcohol **14** (314 mg, 0.64 mmol) in CH_2Cl_2 (20 mL) were added 1,3-propanedithiol (0.12 mL, 1.2 mmol) and BF_3•OEt_2 (0.15 mL, 1.2 mmol) at 0 °C. After stirring for 2 h, sat. $NaHCO_3$ (20 mL) was introduced and the mixture was stirred at r.t. for 20 min. The aqueous layer was separated and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. Purification of the residue by flash chromatography (Et_2O/PE, 1:99 to 1:1) afforded **16** (197 mg, 87%).

White foam; R_f 0.32 (Et_2O/PE, 1:1); mp 51−53 °C (Et_2O/PE).

$[\alpha]_D$ = +60.7 (*c* 1.10, CH_2Cl_2).

HRMS (EI): *m/z* calcd for (M^+): 358.006068. Found: 358.00510.

Compound *ent*-16

From *epi*-**14** (353 mg, 0.72 mmol); yield 214 mg (83%).

$[\alpha]_D$ = −64.4 (*c* 0.95, CH_2Cl_2).

^1H, ^{13}C NMR and IR data of **16** and *ent*-**16**: Tables 5 and 6.

(1*R*,2*R*)- and (1*S*,2*S*)-{7-Bromo-1-[(*tert*-butyl-dimethylsilyl-oxy)-methyl]-2-(1,3-dithian-2-yl)}-1,2,3,4-tetrahydronaphthalene (17 and *ent*-17)

To a suspension of NaH (60% in mineral oil, 104 mg, 2.60 mmol) in anhyd THF (10 mL) at r.t. was added dropwise a solution of alcohol **16** (462 mg, 1.30 mmol) in THF (5 mL). After stirring for 2 h at r.t. TBDMSCl (392 mg, 2.60 mmol) in THF (5 mL) was introduced with a syringe and the reaction mixture was stirred for 24 h. After hydrolysis with H_2O (3 mL) the aqueous layer was separated and extracted with Et_2O (3 × 25 mL). The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. Purification of the residue by flash chromatography (Et_2O/PE, 1:19) afforded **17** (491 mg, 80%).

White solid; R_f 0.68 (Et_2O/PE, 1:1); mp 81−82 °C (Et_2O/PE).

$[\alpha]_D$ = +51.3 (*c* 1.42, CH_2Cl_2).

HRMS (EI): *m/z* calcd for (M^+−*tert*-butyl):. 415.02213. Found: 415.02160.

Compound *ent*-17

From *ent*-**16** (214 mg, 0.60 mmol); yield 236 mg (83%).

$[\alpha]_D$ = −52.1 (*c* 1.05, CH_2Cl_2).

^1H, ^{13}C NMR and IR data of **17** and *ent*-**17**: Tables 5 and 6.

Preparation of 17 from 15

To a solution of silyl ether **15** (609 mg, 1.00 mmol) in anhyd CH_2Cl_2 (10 mL) were added 1,3-propanedithiol (0.15 mL, 1.50 mmol) and $MeSO_3H$ (0.02 mL, 0.3 mmol). After stirring for 3 h at r.t., solid

Table 5 Selected Data of Compounds **6**, **14**-**18** (IR, ^{1}H NMR)

Product	IR (KBr/film), ν [cm^{-1}]	^{1}H-NMR (300 MHz, $CDCl_3$), δ, J (Hz)[a]				
		2′-H ($^3J_{2',2}$)	2-H	1-H	11-H	2-CHO
6	1595, 1340, 1160	5.14 (d, 7.41)	2.87–2.93 (m)	-	5.14 (s), 5.57 (s)	–
epi-**6**	1595, 1340, 1160	5.09 (d, 5.25)	2.82–2.92 (m)	-	5.16 (s), 5.59 (s)	–
14	3410, 1590, 1165	5.53 (d, 9.78)	2.60–2.80 (m)	2.91–2.99 (m)	3.67 (dd), 3.96 (dd)	–
epi-**14**	3410, 1590, 1165	5.21 (d, 3.57)	2.71–2.75 (m)	2.71–2.57 (m)	3.85–3.92 (m)	–
15	2920, 1590, 1345, 1160	5.39 (d, 9.54)	3.42–3.60 (m)	1.66–1.95 (m)	3.68 (dd), 3.85 (dd)	–
16, *ent*-**16**	3400, 1585, 1270	4.31 (d, 9.30)	2.25–2.32 (m)	3.29–3.35 (m)	3.72–3.78 (m), 3.92–3.98 (m)	–
17, *ent*-**17**	1585, 1250	4.16 (d, 10.36)	2.22–2.31 (m)	3.19–3.24 (m)	3.76 (dd), 3.93 (dd)	–
cis-**18** +	1715, 1450, 1245	–	2.53–2.57 (m)	3.53–3.67 (m)	3.53–3.67 (m)	9.83 (s)
trans-**18**[b]	–	–	2.65–2.70 (m)	3.53–3.67 (m)	3.53–3.67 (m)	9.71 (d)

[a] s = singlet, d = doublet, t = triplet, m = multiplet.
[b] Diastereomeric mixture of *cis*-**16** and *trans*-**16** (85:15), which was not separable by flash chromatography; IR and NMR data from the mixture.

K_2CO_3 (100 mg, 0.73 mmol) was added and the mixture was stirred for 10 min. The solid materials were filtered off, washed with CH_2Cl_2 (10 mL), and the filtrate was concentrated in vacuo. The crude product was purified by flash chromatography (Et_2O/PE, 1:19) to give **17** (137 mg, 29%, data see above).

Preparation of Aldehydes; General Procedure
To dithiane (1.0 mmol) and $CaCO_3$ (1.5 g, 15 mmol), suspended in acetone (16 mL) and H_2O (4 mL), MeI (1.25 mL, 20.0 mmol) was added. The reaction mixture was heated at 60 °C for 24 h, cooled to r.t. and diluted with CH_2Cl_2 (10 mL). The mixture was dried (Na_2SO_4), the solid materials were filtered off and washed with CH_2Cl_2 (10 mL). The filtrate was concentrated in vacuo (T < 35 °C). All aldehydes were used in the following Wittig reactions without further purification because of their lability.

(1*R*,2*R*)- and (1*S*,2*R*)-7-Bromo-1-hydroxy-1-methyl-1,2,3,4-tetrahydro-naphthalene-2-carbaldehyde [(1*R*)-9 and (1*S*)-9]
Compound (1*R*)-9
From (1*R*)-**8** (359 mg, 1.00 mmol); yield 264 mg (98%).

Light yellow oil; R_f 0.32 (Et_2O/PE, 1:1).

Compound (1*S*)-9
From (1*S*)-**8** (140 mg, 0.39 mmol); yield 100 mg (95%).

Light yellow oil; R_f 0.11 (Et_2O/PE, 1:4).

^{1}H, ^{13}C NMR and IR data of (1*R*)-**9** and (1*S*)-**9**: Tables 3 and 4.

Table 6 Selected Data of Compounds **6**, **14**–**18** (^{13}C NMR)

Product	^{13}C-NMR (75 MHz, $CDCl_3$), δ					
	C-2′	C-2	C-1	C-3	C-11	2-CHO
6	93.2	45.0	136.4	24.7	113.8	–
epi-**6**	94.2	44.3	137.2	22.1	112.6	–
14	93.7	41.8[a]	41.9[a]	20.2	64.8	–
epi-**14**	94.0	44.4	41.4	16.9	65.1	–
15	93.7	41.3[a]	41.8[a]	20.5	64.7	–
16, *ent*-**16**	51.3	43.2[a]	41.7[a]	22.1	64.7	–
17, *ent*-**17**	50.3	42.0[a]	41.1[a]	22.5	64.2	–
cis-**18** +	–	42.5	49.2	16.7	65.8	201.4
trans-**18**[a]	–	39.9	47.8	14.2	67.0	203.6

[a] NMR data are interchangeable.
[b] Diastereomeric mixture of *cis*-**16** and *trans*-**16** (85:15), which was not separable by flash chromatography; data from the mixture.

(1*R*,2*RS*)- and (1*S*,2*RS*)-7-Bromo-1-[(*tert*-butyldimethylsilyl-oxy)-methyl]-1,2,3,4-tetrahydro-naphthalene-2-carbaldehyde (18 and *ent*-18)
Compound 18
From **17** (491 mg, 1.04 mmol); yield 335 mg (84%).

Colourless oil; *cis*-**18**:*trans*-**18** d.r. 85:15; R_f 0.55 (Et_2O/PE, 1:4).

Compound *ent*-18
From *ent*-**17** (236 mg, 0.50 mmol); yield 176 mg (92%).

Ent-cis-**18**:*ent-trans*-**18** d.r. 70:30.

^{1}H, ^{13}C NMR and IR data of **18** and *ent*-**18**: Tables 5 and 6.

(1*R*,2*RS*)-7-Bromo-1-(hydroxymethyl)-1,2,3,4-tetrahydro-naphthalene-2-carbaldehyde (19) and (3*R*,3a*R*,9b*R*)-1,3,3a,4,5,9b-Hexahydrobenzo[*e*]isobenzofuran-3-ol (20)
As described above, dithiane **16** (186 mg, 0.52 mmol) was treated with MeI and $CaCO_3$. The work up, followed by flash chromatography on silica gel (Et_2O/PE, 1:1) gave lactol **20** (51 mg, 36%) and a mixture of aldehydes **19** (60 mg, 43%, d.r. 23:77).

Compound 19
Colourless oil; *cis*-**19**:*trans*-**19** d.r. 23:77; R_f 0.53 and 0.56 (Et_2O/PE, 1:1).

IR (film): ν = 3450, 2920, 2870, 1700, 1585, 1475, 1070 cm^{-1}.

Compound 20
Colourless crystals; R_f 0.24 (Et_2O/PE, 1:9); mp 127−129 °C (Et_2O/PE); $[\alpha]_D$ = −108.0 (*c* 0.64, CH_2Cl_2).

IR (KBr): ν = 3380, 2930, 2870, 1585, 1470, 1070 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.48−1.65 (m, 1H), 1.86−1.95 (m, 1H), 2.39−2.46 (m, 1H), 2.50−2.75 (m, 2H), 3.20 (s, 1H), 3.62−3.75 (m, 2H), 4.44−4.52 (m, 1H), 5.34 (s, 1H), 6.97 (d, 1H, ^3J = 8.10 Hz), 7.20−7.26 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$): δ =22.6, 27.8, 39.3, 44.5, 73.8, 103.9, 119.6, 129.2, 130.4, 131.8, 135.4, 138.2.

HRMS (EI): *m/z* calcd for (M^+): 268.00989. Found: 268.00676.

3,3‘-Oxido-bi-[(3*R*,3a*R*,9b*R*)-1,3,3a,4,5,9b-hexahydrobenzo[*e*-isobenzofuran] (21)
Crystallisation of **20** from Et_2O/PE afforded colourless crystals of the acetal **21**.

R_f 0.50 (Et_2O/PE, 1:1); mp 135−136 °C (Et_2O/PE).

IR (KBr): ν = 2920, 2860, 1580, 1475 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.48−1.65 (m, 2H), 1.86−1.95 (m, 2H), 2.39−2.46 (m, 2H), 2.50−2.75 (m, 4H), 3.62−3.75 (m, 4H), 4.44−4.52 (m, 2H), 5.34 (s, 2H), 6.97 (d, 2H, ^3J = 8.10 Hz), 7.20−7.26 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.6, 27.8, 39.3, 44.5, 73.8, 103.9, 119.6, 129.2, 130.4, 131.8, 135.4, 138.2.

Wittig Reaction of Aldehydes 9 (1*R*,2*RS*)-7-Bromo-2-[(*EZ*)-1-heptenyl]-1-methyl-1,2,3,4-tetrahydro-1-naphthol (10)

To a suspension of *n*-hexyltriphenylphosphonium bromide (855 mg, 2.00 mmol) in THF (10 mL) was added dropwise *n*-BuLi (1.6 M) in hexane (1.12 mL, 1.80 mmol) at −78 °C. After stirring for 10 min at 0 °C, the mixture was cooled again to −78 °C and aldehyde (1*R*)-**9** (183 mg, 0.68 mmol) in THF (8 mL) was introduced slowly with a syringe. The reaction mixture was stirred for 4 h at 0 °C and then hydrolyzed with sat. NH_4Cl (10 mL). The two layers were separated and the aqueous phase was extracted with Et_2O (3 × 25 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash chromatography (Et_2O/PE, 1:19) to afford a mixture of three diastereomers **10** (101 mg, 50%); d.r. [*E*-(1*R*,2*S*)]:[*Z*-(1*R*,2*S*)]:[*E*-(1*R*,2*R*)]:[*Z*-(1*R*,2*R*)] = 57:31:12:0.

Colourless oil; R_f 0.26 (Et_2O/PE, 1:19).

$[\alpha]_D$ = −15.3 (*c* 0.79, CH_2Cl_2).

HRMS (EI): *m/z* for calcd (M^+): 336.10889. Found: 336.10954.

***trans*-(1*RS*,2*RS*)-7-Bromo-2-[*(E)*-1-heptenyl]-1-methyl-1,2,3,4-tetrahydro-1-naphthol (12)**

From *rac*-(1*S**)-**9** (46 mg, 0.17 mmol); yield 30 mg (52%).

Colourless oil; R_f 0.21 (Et_2O/PE, 1:19); only 1 diastereomer (*E*-*trans*) was detected.

^{1}H, ^{13}C NMR and IR data of **10** and **12**: Tables 7 and 8.

Wittig Reaction of Lactol *rac*-20 (1*RS*,2*SR*)-{7-Bromo-2-[*(Z)*-1-heptenyl]-1,2,3,4-tetrahydro-1-naphthyl}methanol (*rac*-23)

As described above, lactol *rac*-**20** (50 mg, 0.19 mmol) was treated with 2 equiv *n*-hexyltriphenylphosphonium bromide/*n*-BuLi. The work-up (as above), followed by flash chromatography on silica gel (Et_2O/PE, 1:9) gave pure *Z*-*cis* alkene *rac*-**23** (22 mg, 34%; data Tables 7, 8) besides some starting material *rac*-**20** (20 mg, 40%).

Wittig Reaction of Aldehydes 18 and *ent*-18 (1*R*,2*S*)- and (1*S*,2*R*)-{7-Bromo-1-(*tert*-butyldimethylsilyloxy)-methyl-2-[*(Z)*-1-heptenyl]-1,2,3,4-tetrahydronaphthalene (22 and *ent*-22)

To a suspension of *n*-hexyltriphenylphosphonium bromide (342 mg, 0.80 mmol) in THF (10 mL) was added dropwise *n*-BuLi (1.6 M) in hexane (0.49 mL, 0.79 mmol) at −78 °C. After stirring for 10 min at 0 °C, the mixture was cooled again to −78 °C and aldehyde **18** (203 mg, 0.53 mmol) in THF (7 mL) was added. The reaction mixture was stirred for 4 h at 0 °C and then hydrolysed with sat. NH_4Cl (10 mL). The two layers were separated and the aqueous phase was extracted with Et_2O (3 × 25 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash chromatography (Et_2O/PE, 1:99) to afford **22** (79 mg, 33%).

Colourless oil; R_f 0.29 (Et_2O/PE, 1:99).

$[\alpha]_D$ = +61.8 (*c* 0.82, CH_2Cl_2).

HRMS (EI): m/z calcd for (M^+−*tert*-butyl): 393.124926. Found: 393.1236.

^{1}H, ^{13}C NMR and IR data of **22**: Tables 7 and 8.

Compound *ent*-22

The crude product *ent*-**22** (40 mg, 89%) obtained from *ent*-**18** (38 mg, 0.10 mmol) was desilylated without further purification (see below).

(1*R*,2*S*)- and (1*S*,2*R*)-{7-Bromo-2-[*(Z)*-1-heptenyl]-1,2,3,4-tetrahydro-1-naphthyl}methanol (23 and *ent*-23)

To a solution of silyl ether **22** (79 mg, 0.18 mmol) in THF (3 mL) was added 1 M TBAF in THF (0.4 mL, 0.40 mmol). The mixture was stirred for 24 h at r.t. and then hydrolysed with H_2O (1 mL). The aqueous layer was separated and extracted with Et_2O (3 × 10 mL). The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. Purification of the residue by flash chromatography (Et_2O/PE, 1:9) afforded alcohol **23** (27 mg, 57%).

Colourless oil; R_f 0.25 (Et_2O/PE, 1:9).

$[\alpha]_D$ = +65.2 (*c* 0.33, CH_2Cl_2).

HRMS (EI): *m/z* calcd for (M^+): 336.10889. Found: 336.10749.

Compound *ent*-23

From crude *ent*-**22** (40 mg, 0.09 mmol); yield 23 mg (78% over two steps).

$[\alpha]_D$ = −66.1 (*c* 0.12, CH_2Cl_2).

^{1}H, ^{13}C NMR and IR data of **23** and *ent*-**23**: Tables 7 and 8.

Table 7 Selected Data of Compounds **10**–**13**, **22**–**24** (IR, ^{1}H NMR)

Product	IR (KBr/film), *v* [cm^{-1}]	^{1}H-NMR (300 MHz, $CDCl_3$), δ, *J* (Hz)[a]				
		1-H	2-H	11-H	21-H ($^3J_{21,22}$)	22-H
10[b]	3430, 1580, 1460	–	2.42–2.48 (m)	1.50 (s)	5.40 (ddt, 15.49)	5.71 (dt)
rac-**12**	3250, 1580	–	2.31–2.43 (m)	1.32 (s)	5.49 (dd, 15.49)	5.60 (dt)
11[c,d]	3700, 1680	–	2.45–2.51 (m)	1.56 (s)	5.40 (ddt, 15.52)	5.69, (dt)
rac-**13**[d]	3400, 1685	–	2.42–2.48 (m)	1.26–1.42 (m)	5.49–5.67 (m, 15.20)	5.49–5.67 (m)
22, *ent*-**22**	1585, 1090	2.67–2.90 (m)	2.67–2.90 (m)	3.74–3.86 (m)	5.32–5.42 (m, 10.90)	5.32–5.42 (m)
23, *ent*-**23**	3320, 1580, 1470	2.69–3.00 (m)	2.69–3.60 (m)	3.82 (dd), 3.92 (dd)	5.39–5.55 (m, 11.94)	5.39–5.55 (m)
24, *ent*-**24**[d]	3360, 1665, 1600	2.84–3.07 (m)	2.84–3.07 (m)	3.91 (dd), 3.99 (dd)	5.43–5.57 (m, 8.78)	5.43–5.57 (m)

[a] s = singlet, d = doublet, t = triplet, m = multiplet.
[b] Data of *E*(1*R*,2*S*)-**10** from the diastereomeric mixture of *E*(1*R*,2*S*):*Z*(1*R*,2*S*):*E*(1*R*,2*R*) (57:31:12), which was not separable by flash chromatography.
[c] Data of *E*(7*S*,8*R*)-**11** from the diastereomeric mixture of *E*(7*S*,8*R*):*Z*(7*S*,8*R*):*E*(7*R*,8*R*) (56:28:16), which was not separable by flash chromatography.
[d] The numbering is not following the IUPAC nomenclature.

Table 8 Selected Data of Compounds **10**–**13**, **22**–**24** (^{13}C NMR)

Product	^{13}C-NMR (75 MHz, $CDCl_3$), δ						
	1-C	2-C	11-C	21-C	22-C	7-C	71-C
10[a]	71.1	49.1	30.5	127.9	136.3	119.9	–
rac-**12**[b]	–	–	–	–	–	–	–
11[c,d]	71.2	49.1	32.7	127.7	136.0	129.2	171.9
rac-**13**[d]	71.7	43.2	27.8	127.7	136.0	129.2	171.9
22, *ent*-**22**	44.8	34.3	64.9	130.7	130.8	118.7	–
23, *ent*-**23**	44.9	34.1	64.9	130.7	131.7	119.2	–
24, *ent*-**24**[d]	44.8	34.1	65.0	131.0	132.1	126.7	171.3

[a] Data of *E*(1*R*,2*S*)-**10** from the diastereomeric mixture of *E*(1*R*,2*S*):*Z*(1*R*,2*S*):*E*(1*R*,2*R*) (57:31:12), which was not separable by flash chromatography.
[b] Not determined.
[c] Data of *E*(7*S*,8*R*)-**11** from the diastereomeric mixture of *E*(1*R*,2*S*):*Z*(1*R*,2*S*):*E*(1*R*,2*R*) (56:28:16), which was not separable by flash chromatography.
[d] The numbering is not following the IUPAC nomenclature.

Conversion of Bromides into Carboxylic Acids; General Procedure

To a solution of bromoarene (1.0 mmol) in THF (10 mL) was added dropwise 1.5 M MeLi·LiBr in Et_2O (1.0 mL, 1.5 mmol) at −78 °C. Stirring was continued for 30 min and then 1.5 M *tert*-BuLi in pentane (1.66 mL, 2.50 mmol) was added dropwise to the mixture. After stirring for 10 min, anhyd CO_2 was bubbled through the reaction mixture with a stainless steel needle and the mixture was allowed to warm up to r.t. over 30 min. After addition of 2N HCl (4 mL) the aqueous layer was separated and extracted with EtOAc (5 × 10 mL). The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. Purification of the residue by flash chromatography (Et_2O/PE, 1:1 to 1:1+5% MeOH) afforded the carboxylic acid.

(7*RS*,8*R*)-7-[(*EZ*)-1-Heptenyl]-8-hydroxy-8-methyl-5,6,7,8-tetrahydro-naphthalene-2-carboxylic Acid (11)

From **10** (101 mg, 0.30 mmol); yield 83 mg (91%).

Colourless wax; d.r. [*E*-(7*S*,8*R*)]:[*Z*-(7*S*,8*R*)]:[*E*-(7*R*,8*R*)]:[*Z*-(7*R*,8*R*)] = 56:28:16:0; R_f 0.51 (Et_2O/PE; 1:1+5% MeOH).

$[\alpha]_D$ = −6.8 (*c* 0.65, CH_2Cl_2).

HRMS (EI): *m/z* calcd for (M^+): 302.18820. Found: 302.18923.

^{1}H, ^{13}C NMR and IR data: Tables 7 and 8.

***trans*-(7*RS*,8*RS*)-7-[(E)-1-Heptenyl]-8-hydroxy-8-methyl-5,6,7,8-tetrahydro-naphthalene-2-carboxylic Acid (13)**

From **12** (30 mg, 0.09 mmol); yield 8 mg (29%).

Colourless wax; R_f 0.22 (Et_2O/PE, 1:1+5% MeOH).

HRMS (EI): *m/z* calcd for (M^+): 302.18820. Found: 302.18607.

^{1}H, ^{13}C NMR and IR data: Tables 7 and 8.

(7*S*,8*R*)- and (7*R*,8*S*)-8-(Hydroxymethyl)-7-[*(Z)*-1-heptenyl]-5,6,7,8-tetrahydro-naphthalene-2-carboxylic Acid (24 and *ent*-24)

From **23** (27 mg, 0.08 mmol); yield 9 mg (37%).

Colourless wax; R_f 0.41 (Et_2O/PE, 1:1+5% MeOH); $[\alpha]_D$ = +70.6 (*c* = 0.17, CH_2Cl_2).

HRMS (EI): m/z calcd for (M^+): 302.18820. Found: 302.18822.

Compound *ent*-24

From *ent*-**23** (23 mg, 0.07 mmol); yield 11 mg (54%).

$[\alpha]_D$ = −105.0 (*c* 0.40, $CDCl_3$).

^{1}H, ^{13}C NMR and IR data of **24** and *ent*-**24**: Tables 7 and 8.

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(18) X-ray crystal structure analysis of **14**: formula $C_{23}H_{28}BrNO_4S$, *M* = 494.43, colourless crystal 0.3 × 0.25 × 0.20 mm, *a* = 9.099(1), *b* = 10.236(1), *c* = 12.653(1) Å, β = 102.25(1)°, V = 1151.6(2) Å^3, ρ_{calcd} = 1.426 gcm^{-1}, μ = 35.16 cm^{-1}, empirical absorption correction via ψ scan data (0.758 ≤ *C* ≤ 0.999), *Z* = 2, monoclinic, space group $P2_1$ (No. 4), λ = 1.54178 Å, *T* = 223 K, ω/2 θ scans, 4961 reflections collected (±h, −k, ±l), [(sin θ)/λ] = 0.62 Å^{-1}, 2484 independent and 2437 observed reflections [$I \geq 2\,\sigma(I)$], 275 refined parameters, *R* = 0.032, Rw^2 = 0.086, max. residual electron density 0.64 (−0.48) eÅ^{-3}, Flack parameter 0.03(2), hydrogens calculated and refined as riding atoms.
(19) X-ray crystal structure analysis of **21**: formula $C_{24}H_{24}Br_2O_3$, *M* = 520.25, colourless crystal 0.30 × 0.30 × 0.10 mm, *a* = 12.398(1), *b* = 6.662(1), *c* = 13.092(1) Å, β = 99.70(1)°, V = 1065.9(2) Å^3, ρ_{calcd} = 1.621 gcm^{-1}, μ = 50.07 cm^{-1}, empirical absorption correction via ψ scan data (0.796 ≤ *C* ≤ 1.000), *Z* = 2, monoclinic, space group $P2_1$ (No. 4), λ = 1.54178 Å, *T* = RT, ω/2 θ scans, 2487 reflections collected (−h, +k, ±l), [(sin θ)/λ] = 0.62 Å^{-1}, 2377 independent and 2332 observed reflections [$I \geq 2\,\sigma(I)$], 263 refined parameters, *R* = 0.036, Rw^2 = 0.105, max. residual electron density 0.84 (−0.42) eÅ^{-3}, Flack parameter 0.03(3), hydrogens calculated and refined as riding atoms.
Data sets were collected with an Enraf Nonius CAD4 diffractometer. Programs used: data reduction MolEN, stucture solution SHELXS-97, structure refinement SHELXL-97, graphics SCHAKAL-92.
Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCSD-141914 (**3**), CCSD 141915 (*R*-**7**), CCSD 141916 (**14**) and CCSD 141917 (**21**). Copies of the data can be obtained free of charge on application to The Director CCDC, 12 Union Road, CambridgeCB2 1EZ, UK [fax:+44(1223)336033, e-mail: deposit@ccdc.cam.ac.uk].
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