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Stereoconvergent Synthesis of Enantiopure (-)-*trans*-Lauthisan. Building Kit for Medium Ring Oxacycle Construction and Contrathermodynamic Epimerization at Allylic Carbon C(8) *via* "Invisible", E-Configurated Medium Ring Olefin.

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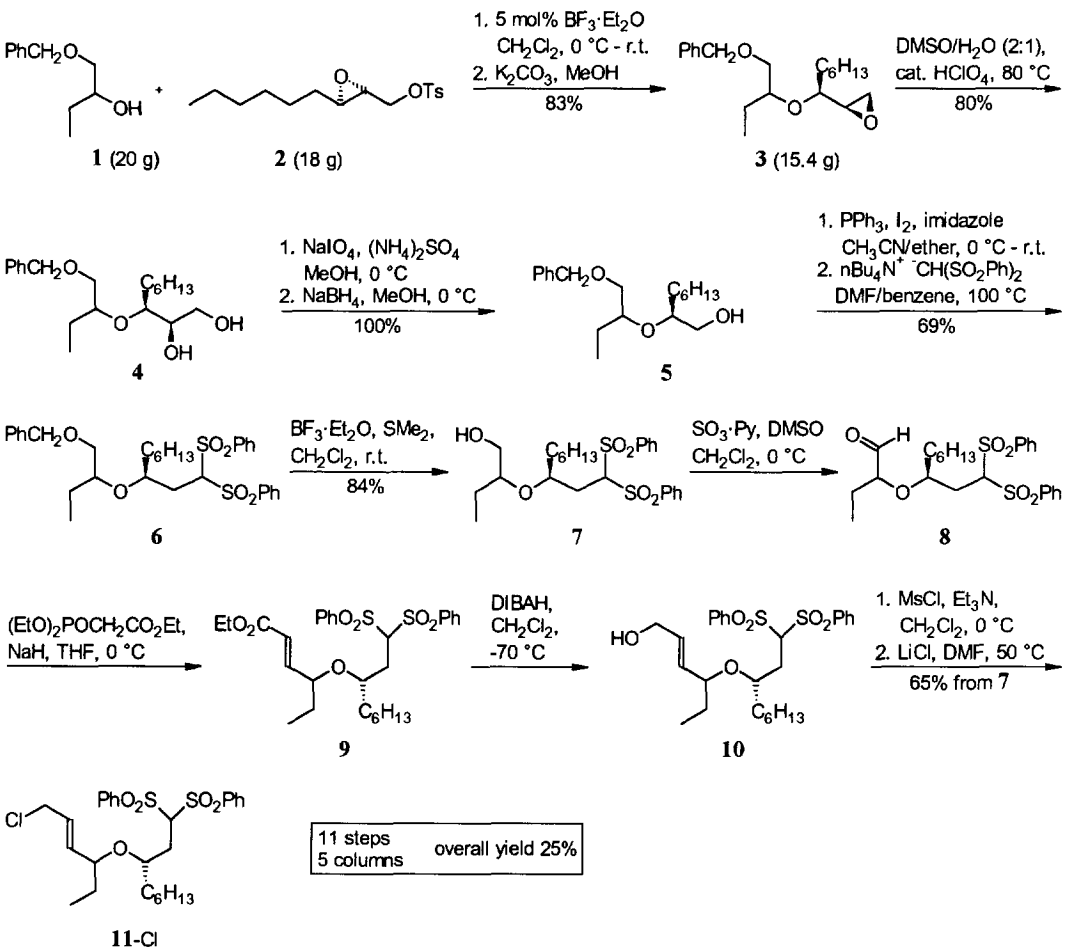
Abstract: Starting once more from simple, acyclic, functionalized α,α′-chiral, disecondary ethers we have prepared enantiomerically pure (-)-*trans*-lauthisan (which is thermodynamically less stable than its *cis*-epimer). During a Pd(0) catalyzed cyclization a strained E-configurated, 8-membered allylic ether (as an η^2 palladium complex) is believed to be a reactive intermediate, in which the oxygen of the allylic ether attains leaving group status and recloses contrathermodynamically and stereoconvergently to isolated α,α′-*trans* configurated medium ring ether. The 9-membered rings (cf. preceding paper) are suggested to be formed by an analogous sequence.

Among the variety of medium ring ethers which occur in Nature, lauthisan,§ both racemic and enantiomerically pure[1,2] has been a test case for synthetic access to this class of compounds. In continuation of previous work on a) the synthesis of acyclic α,α′-chiral disecondary ethers with full stereocontrol[3] b) successful medium ring closure *via* Pd(0)-assisted cyclization and c) controlled epimerization of the ethyl substituted allylic centre to the *less* stable, *trans* configurated diastereomer on cyclization[4] we now illustrate our approach to the 8-membered lauthisan. Modifying the synthesis of the acyclic precursor as described for the 9-membered rings[4] slightly (Scheme 1), we employed again monoprotected butane-1,2-diol (**1**), which was allowed to react under BF_3 catalysis with enantiomerically pure epoxy tosylate **2**, carrying an *n*-hexyl chain at C(3). Treatment of the intermediate alcohol tosylate with K_2CO_3 *in situ* afforded key precursor **3** (15.4 g, 83% overall) in a one pot procedure. The required excision of the terminal methylene carbon of the epoxide in **3** was carried out by chemoselective acid-catalyzed hydrolysis with an excess of water at 80 °C to the diol **4**, oxidative cleavage of the diol with $NaIO_4$ [acid buffer at 0 °C prevents racemization of the stereodefined centre at C(2)] and immediate reduction of the sensitive aldehyde with $NaBH_4$ *in situ* to the alcohol **5** (2 steps, quantitative yield).

Introduction of a good leaving group was carried out under standard conditions, giving the terminal alkyl iodide. Since S_N2 reactions on ethers bearing the leaving group β to the ether oxygen are known to be sluggish, optimization was required for the alkylation with deprotonated (pK_a ~ 11) bis(phenylsulfonyl)methane. Preparation of the neat tetra-*n*-butylammonium ion pair allowed a high concentration of nucleophile in a suitable solvent mixture (DMF/benzene, 2 : 1) and after 6 h at 100 °C we obtained bis sulfone **6** in 69% yield from **5**.

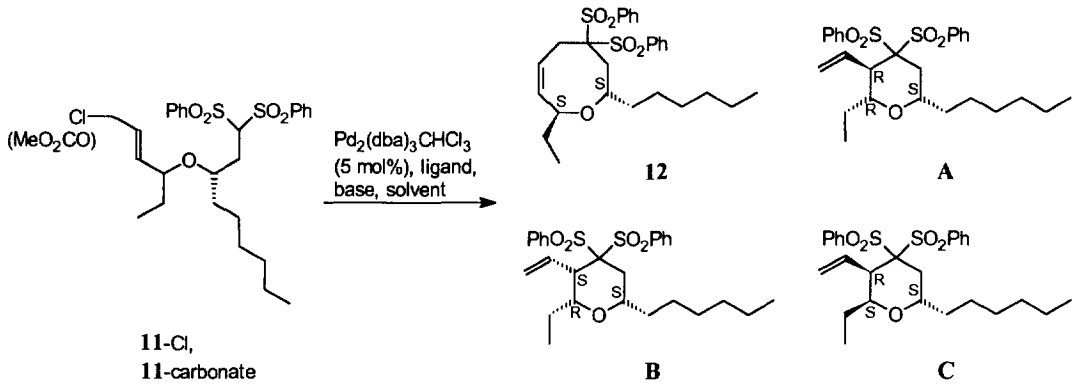


Scheme 1. Synthesis of Acyclic *Lauthisan* Precursor.

Attempted deprotection of the benzyl ether **6** with Pd/C was not successful (poisoning by sulfur). The hard/soft combination of BF_3/SMe_2 furnished alcohol **7** in satisfactory yield.

Generation of the necessary allylic moiety was carried out as described for the 9-membered ring by a) oxidation to aldehyde **8**, b) Horner-Wittig reaction of crude **8** to α,β-unsaturated ester **9**, c) reduction to allylic alco-hol **10** followed by introduction of a leaving group (65% yield overall from alcohol **7**).

Following the previous protocol[4] we used carbonate as a leaving group and only obtained 6-membered ring in poor yield (Scheme 2, entry 1). At higher temperature (refluxing dioxane, 102 °C) conversion was higher, but again only 6-membered ring was formed (entry 2), also with $P(OEt)_3$ as a ligand (entry 5). Use of a better leaving group as in **11**-Cl (entry 3) allowed cyclization at lower temperature, but again only 6-membered ring was formed. In order to improve the chances for kinetic control and formation of the less stable 8-membered ring, we decided to render the (η^3-allyl)palladium system more electrophilic by choosing a better π acceptor ligand than dppe, in combination with the better leaving group chloride.



Scheme 2. Diastereoselective Pd(0)-Cyclization of the 8-Ring Precursor.

Table 1.

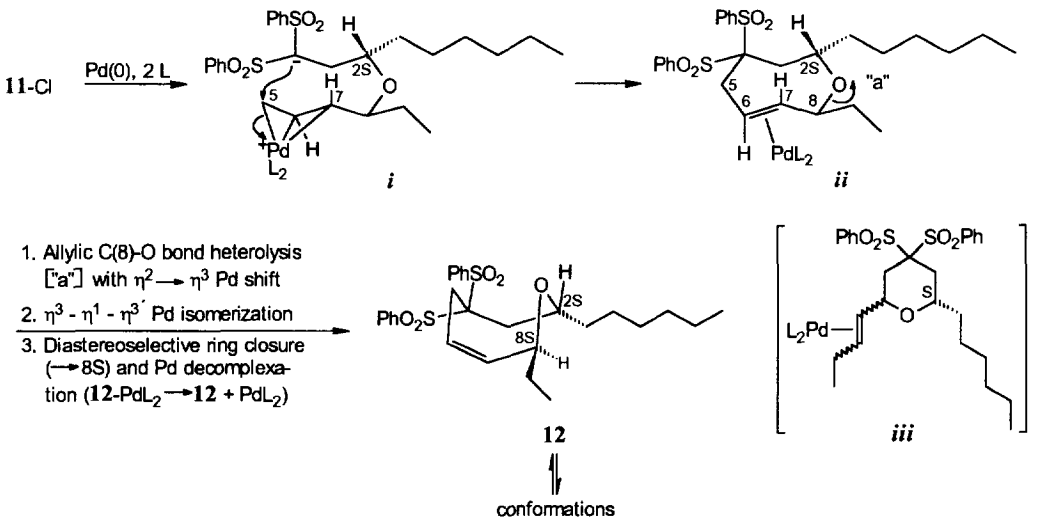
Entry	Leaving group in **11**-X	Base	Ligand	Solvent	Temp [° C]	Yield [%]	Ratio **12 : A : B : C** *8-Ring : 6-Ring*
1	Carbonate	---	dppe	THF	66	9	*0 : 1*
2	Carbonate	---	dppe	dioxane	102	59	0 : 1 : 1 : 1.15
							0 : 1
3	Chloride	NaH	dppe	THF	66	---	6-Ring only
4	Chloride	NaH	$P(OEt)_3$	THF	66	67	1.9 : 3 : 1.15 : 1
							1 : 2.7
5	Carbonate	---	$P(OEt)_3$	dioxane	102	---	6-Ring only
6	Chloride	KH	$P(OEt)_3$	THF/dioxane	80	74	4.7 : 3.5 : 1 : 1.2
				2 : 1			*1 : 1.2*
7	Chloride	KH	"biphosphite"	THF/dioxane	80	77	15.8 : 3.3 : 1.2 : 1
				2 : 1		57, **1.7 g**	*2.9 : 1*

The combination chosen in entry 4 provided 8-membered ring for the first time. In a further modification a slightly higher temperature (THF/dioxane, 2 : 1, 80 °C) and potassium hydride instead of sodium hydride as base improved the chemical yield of cyclization product (74%) and also the selectivity towards 8-membered ring (entry 6). The best result (entry 7) was achieved by adding a solution of deprotonated (with KH) bis sulfone **11**-Cl in a mixture of THF/dioxane (2 : 1) to refluxing solution of $Pd_2(dba)_3CHCl_3$ (5 mol%) and ligand "biphosphite"[5] (60 mol%) with a syringe pump over a period of 6 h at 80 °C (57% yield of **12**, 1.7 g isolated). Diastereomerically pure (which is also enantiomerically pure) lauthisane precursor **12** was isolated, although the precursor **11**-Cl had been racemic with respect to the carbon attached to the ethyl side chain!

We think that the formation of lauthisan precursor **12** might proceed as follows. The syn-configurated (η^3-allyl)palladium complex *i* is thermodynamically favoured and rendered more electrophilic by the backbonding "biphosphite" ligand and chloride leaving group. Intramolecular nucleophilic attack by the bulky bis(phenylsulfonyl) carbanion occurs at the more accessible methylene terminus in a kinetically controlled reaction. The E-configurated cyclic olefin is generated as an "invisible" intermediate, while palladium switches from η^3 complexation in *i* to η^2 complexation of the strained double bond in *ii*. The activated allylic ether

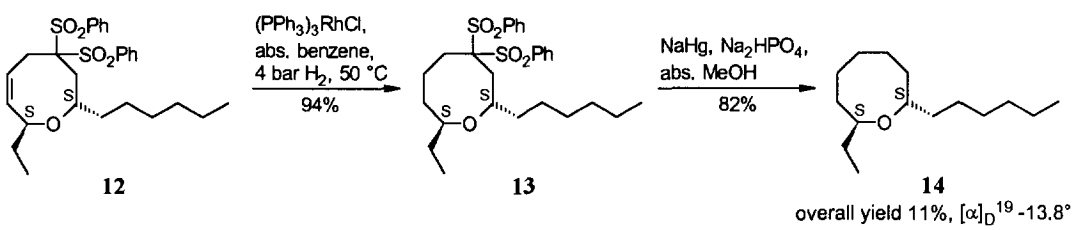
moiety in *ii* undergoes stereoelectronically favourable carbon-oxygen bond heterolysis to an entirely new (η^3-allyl)palladium complex with two *secondary* termini [C(6),C(8) instead of C(5),C(7) as in *i*]. Several stereoisomeric (η^3-allyl)palladium complexes are now accessible. In the final, irreversible ring forming step(s) palladium migrates such as to minimize nonbonded repulsions. After decomplexation (**12**-PdL_2 → **12** + PdL_2), the contrathermodynamic,[6] less stable *trans*-lauthisan precursor **12** arises in enantiomerically pure form!

It is remarkable that the 6-membered ether *iii* is not formed, in contrast to the formation of **A**, **B** and **C** (Scheme 2). However, in the formation of **A**, **B** and **C** a simple exocyclic vinyl group arises. In the case of 6-membered ring *iii* an exocyclic butenylidenyl group would have to be generated, also in the transition state leading to *iii*. Because of the additional ethyl substituent η^2 complexation by Pd(0) is sterically less favourable in *iii* than in either **A**, **B** or **C**.[7]



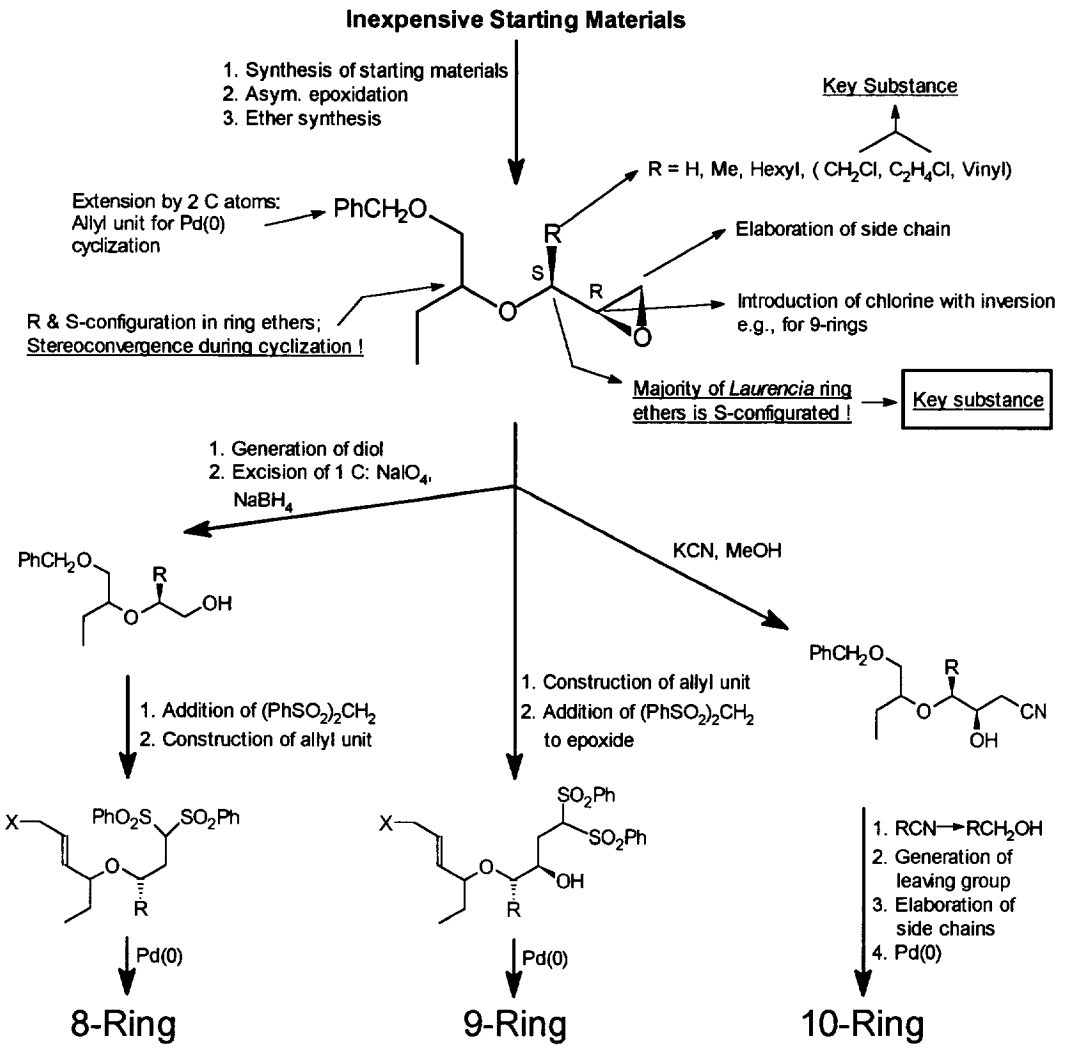
Scheme 3. From Acyclic Precursor **11**-Cl to Enantiomerically Pure 2S,8S-Pentahydrooxocin **12**. "Invisible" E-Configurated, 8-Membered Ringolefin as Postulated Reactive Intermediate.

We think that the 9-membered rings described in the preceding part[4] are formed by a similar sequence, in which the siloxy group allows additional steric control by minimizing nonbonded repulsion. Attempts to equilibrate either diastereomerically pure *cis*- or *trans*-configurated, unsaturated 9-ring ether (Scheme 4, preceding paper) under cyclization conditions were not successful. *Thus, only a strained and "invisible", E-configurated cyclic allylic ether is capable of ring opening by Pd(0).*



Scheme 4. Synthesis of Enantiopure (-)-*trans*-Lauthisan[8]

Homogenously catalyzed hydrogenation of pentahydrooxocin **12** furnished oxocan **13**, which was desulfonylated under standard conditions, yielding enantiomerically pure, unnatural (-)-*trans*-lauthisan (Scheme 4). All spectroscopic data are in excellent agreement with those of Paquette and Sweeney.[2b] Since our synthesis is *stereoconvergent* (or stereospecific)[9] and furnishes the thermodynamically less stable *trans* epimer exclusively, our overall yield of 11% compares very favourably with previous work. Many medium ring ethers in Nature are indeed *trans*-configurated.



Scheme 5. Building Kit for Medium Ring Oxacycle Construction. Building Bricks, Key Reactions and a Key Substance.

In conclusion, a readily accessible acyclic building block has been transformed into 9-membered ring ethers as well as into 8-membered rings of the *Laurencia* family. A general building kit for the stereocontrolled synthesis of 8-, 9- and possibly 10-membered oxacycles is outlined in Scheme 5. All necessary side chains emanating from the α and α′ carbon atoms of the ether can be chemodifferentiated and elaborated. Enantiomerically pure (-)-*trans*-lauthisan has been synthesized. An "invisible" E-configurated, η^2-palladium complexed, 8-membered ether and 9-membered ring is proposed as a reactive intermediate. The *stereoconvergent*, and at the same time, contrathermodynamic strategy should by applicable to the synthesis of other medium rings.

Acknowledgments. We thank the *Fonds der Chemischen Industrie* for a PhD fellowship (to A. B.) and the *Deutsche Forschungsgemeinschaft* (Graduiertenkolleg Naturstofftransformationen) for support of our work.

Experimental

General.[4]

(2R, trans*)-3-Hexyloxiranemethyl tosylate* (**2**). 2-Nonenol (21.34 g, 0.15 mmol), $Ti(OPr^i)_4$ (2.23 mL, 7.5 mmol), (-)-DET (2.27 g, 11 mmol), molecular sieves (4.5 g) and TBHP (56 mL, 5.4 M in CH_2Cl_2) in CH_2Cl_2 (300 mL) were allowed to react according to the procedure of Sharpless[10] to give (2R,*trans*)-3-hexyloxiranmethanol, 15.34 g (65%). To a solution of the epoxy alcohol (15.29 g, 96.6 mmol) and Et_3N (13.7 mL, 116 mmol) in $CHCl_3$ (200 mL) was added tosyl chloride (19.34 g, 101 mmol) at 0 °C. The mixture was stirred for 18 h at 0 °C and 24 h at r.t. Then 2 N HCl was added and the organic layer was washed with brine and dried (Na_2SO_4). After removal of the solvent the crude product was purified by chromatography (E/PE, 1 : 3) to afford **2**, 25.75 g (85%), m. p. 39.5 - 41.5 °C. $[\alpha]_D^{21} = 36.8°$ (c = 1.21, CH_2Cl_2). IR ($CHCl_3$) ν 2956, 2860, 1596, 1464, 1368, 1228, 1176, 1020, 972 cm^{-1}; ^1H NMR δ 0.87 (t, ^3J = 6 Hz, 3 H, CH_3), 1.20 - 1.63 (m, 10 H, CH_2), 2.43 (s, 3 H, arom. CH_3), 2.78 (dt, ^3J = 2, 6 Hz, 1 H, C*H*CH_2OTs), 2.93 (m, 1 H, C*H*CHCH_2OTs), 3.95 (dd, ^3J = 6 Hz, ^2J = 12 Hz, 1 H, C*H*HOTs), 4.20 (dd, ^3J = 6 Hz, ^2J = 12 Hz, 1 H, CH*H*OTs); ^{13}C NMR δ 14.04 (-, CH_3), 21.60 (-, arom. CH_3), 22.51, 25.70, 28.94, 31.29, 31.66 (+, CH_2), 54.53 (-, *C*HCH_2OTs), 56.65 (-, *C*HCHCH_2OTs), 70.40 (+, *C*H_2OTs), 127.93 (-, arom. C), 129.96 (-, arom. C), 132.81 (+, arom. C), 145.09 (+, arom. C); MS *m/z* 312 (M^+, 0), 227 (4), 155 (97), 91 (100).

(2R,3S)-3-[1-(Benzyloxy)-2-butoxy]-2-hydroxy-nonyl tosylate (**3**). A flame-dried flask was charged with epoxy tosylate **2** (18 g, 57.6 mmol) and alcohol **1** (19.6 g, 97.9 mmol) under N_2 atmosphere. CH_2Cl_2 (128 mL) was added and the mixture was cooled to 0 °C. $BF_3{\cdot}Et_2O$ (1.06 mL, 8.64 mmol) was added and the reaction mixture was allowed to reach r.t. After stirring for 20 h the solvent was removed and the crude product was dissolved in MeOH (128 mL) and treated with K_2CO_3 (15.9 g, 115 mmol). The mixture was stirred for 0.5 h, then the solvent was evaporated. The crude product was purified by chromatography to afford **3**, 15.4 g (83%), diastereomeric mixture. IR (film) ν 3848, 3740, 3660, 3369, 3032, 2929, 2858, 1605, 1455, 1310, 1205, 1103, 1029, 908 cm^{-1}; ^1H NMR δ 0.88 (m, 6 H, CH_3), 1.21 - 1.68 (m, 12 H, CH_2), 2.68 (d, ^3J = 3.6 Hz, 2 H, epoxy OCH_2), 2.85 (dt, ^3J = 3.6, 6 Hz, 1 H, epoxy OCH), 3.22 (dd, ^3J = 5, 11 Hz, 1 H, OCH), 3.34 - 3.57 (m, 3 H, OCH, PhCH_2OCH_2), 4.52 (s, 2 H, PhCH_2), 7.34 (m, 5 H, arom. H); ^{13}C NMR δ 9.63, 14.10 (-, CH_3), 22.62, 24.90, 25.14, 29.47, 31.81, 33.39 (+, CH_2), 45.93 (+, epoxy OCH_2), 53.83 (-, epoxy OCH), 72.59 (+, Ph*C*H_2), 78.12, 79.03 (-, OCH), 127.62, 128.32 (-, arom. C), 138.43 (+, arom. C); MS *m/z* 320 (M^+, 2), 289 (5), 199 (25), 179 (21), 177 (14), 159 (10), 142 (30), 107 (100).

(2R,3S)-3-[-1(Benzyloxy)-2-butoxy]-1,2-nonandiol (**4**). A solution of **3** (14.4 g, 45 mmol) and $HClO_4$ (0.9 mL, 70%) in DMSO/H_2O (2 : 1) (450 mL) was stirred for 3 h at 80 °C. E was added and the organic layer was extracted with H_2O, dried and evaporated. The crude product was purified by chromatography (E/PE) to give **4** as a diastereomeric mixture, 12.18 g (80%), clear oil. IR ($CHCl_3$) ν 3402, 3066 - 2858, 1605, 1497, 1455, 1367, 1093, 907 cm^{-1}; ^1H NMR δ 0.90 (m, 6 H, CH_3), 1.19 - 1.77 (m, 12 H, CH_2), 2.48 - 2.77 (br. m, 2 H, 2 OH), 3.41 - 4.00 (br. m, 7 H), 4.53/4.58 (2 x s, 2 H, PhCH_2), 7.34 (m, 5 H, arom. H); ^{13}C NMR δ 9.72/9.79,

14.09/14.11 (-, CH_3), 22.61/22.67, 24.73, 25.33/25.65, 29.49/29.66, 30.75/31.40, 31.79/31.86 (+, CH_2), 62.90/63.37 (+, CH_2OH), 72.14/72.64 (+, $PhCH_2OCH_2$), 72.78/72.86 (-, CHOH), 73.32/73.52 (+, $PhCH_2$), 78.72/79.86, 81.51 (-, OCH), 127.60, 127.96, 128.02, 128.32, 128.50 (-, arom. C), 137.31, 138.19 (+, arom. C); MS *m/z* 338 (M^+, 1), 200 (13), 187 (19), 116 (35), 108 (48), 91 (100).

(2R)-2-[1-Benzyloxy)-2-butoxy]-octanol (**5**). To a solution of **4** (9.82 g, 29 mmol) in MeOH (225 mL) was added a solution of $NaIO_4$ (8.70 g, 40.6 mmol) and $(NH_4)_2SO_4$ (4.98 g, 37.7 mmol) in H_2O (225 mL) at 0 °C. After 45 min H_2O (300 mL) was added and the aqueous phase was extracted with E/PE. The organic layer was dried ($MgSO_4$) and the solvent removed to give aldehyde (9 g, 100%). 7 g (22.9 mmol) of the crude product was dissolved in MeOH (50 mL) and $NaBH_4$ (1.04 g, 27.5 mmol) was added in portions at 0 °C. After 15 min MeOH was evaporated and the residue was diluted with H_2O. The aqueous layer was extracted with E and the organic layer dried ($MgSO_4$) to afford after removal of the solvent alcohol **5**, 7 g (100%), oil, diastereomeric mixture. IR ($CHCl_3$) ν 3436, 3066 - 2858, 1605, 1497, 1455, 1367, 1207, 1096, 736 cm^{-1}; ^1H NMR δ 0.90 (m, 6 H, CH_3), 1.17 - 1.69 (m, 12 H, CH_2), 2.10 (br. m, 1 H, OH), 3.35 - 3.72 (br. m, 6 H, OCH, OCH_2), 4.53/4.58 (2 x s, 2 H, $PhCH_2$), 7.33 (m, 5 H, arom. H); ^1H NMR (DMSO-d_6) δ 4.39 (t, ^3J = 4 Hz, 1 H, OH); ^{13}C NMR δ 9.79/9.93, 14.11 (-, CH_3), 22.63, 25.56, 25.76, 29.51, 31.81, 32.41 (+, CH_2), 65.66 (+, CH_2OH), 72.93 (+, $PhCH_2OCH_2$), 73.50 (+, $PhCH_2$), 79.62, 80.68 (-, OCH), 127.81, 128.46 (-, arom. C), 137.51, 138.27 (+, arom. C); MS *m/z* 308 (M^+, 1), 278 (2), 129 (14), 91 (100).

(3R)-3-[1-(Benzyloxy)-2-butoxy]-1,1-bis-(phenylsulfonyl)-nonane (**6**). To a mixture of **5** (6.77 g, 22 mol), PPh_3 (17.3 g, 66 mmol) and imidazol (4.64 g, 68.2 mmol) in E (44 mL) and CH_3CN (15 mL) was added iodine (8.66 g, 68.2 mmol) portionwise at 0 °C. The reaction mixture was heated to reflux for 1 h, then cooled to r.t. and filtered. The residue was diluted with PE, filtered, extracted with aq. $Na_2S_2O_3$ solution and brine and dried ($MgSO_4$). The solid/oil-mixture was diluted with PE, filtered and evaporated to give a mixture of iodide and PPh_3 (4 : 6 by GC). A solution of this crude product and *n*-$Bu_4NCH(SO_2Ph)_2$[11] (32.3 g, 59.4 mmol) in DMF/benzene (2 : 1) (100 mL) was heated for 6 h to 130 °C. After cooling to r.t. E was added, the organic layer extracted with 1 N HCl and brine and dried ($MgSO_4$). The solvent was removed and the crude product purified by chromatography to afford **6**, 8.85 g (69%), diastereomeric mixture. IR ($CHCl_3$) ν 3068 - 2860, 1601, 1448, 1332, 1228, 1152, 1081, 829 cm^{-1}; ^1H NMR δ 0.72 (t, ^3J = 7 Hz, 3 H, CH_3), 0.88 (t, ^3J = 6 Hz, 3 H, CH_3), 1.13 - 1.66 (m, 12 H, CH_2), 2.20 (br. m, 2 H, $CH_2CH(SO_2Ph)_2$), 3.23 (dd, ^3J = 5 Hz, ^2J = 10 Hz, 1 H, $PhCH_2OCHH$), 3.27 (m, 1 H, OCH), 3.51 (dd, ^3J = 3 Hz, ^2J = 10 Hz, 1 H, $PhCH_2OCHH$), 3.77 (m, 1 H, OCH), 4.50 (2 x s, 2 H, $PhCH_2$), 5.38 (dd, ^3J = 2.5, 8 Hz, 1 H, $CH(SO_2Ph)_2$), 7.28 - 8.10 (m, 15 H, arom. H); ^{13}C NMR δ 9.66, 14.07 (+, CH_3), 22.50/23.19, 24.43/24.85, 29.37/29.42, 31.02, 31.67/31.72, 33.86/34.91 (+, CH_2), 72.90 (+, $PhCH_2OCH_2$), 73.60 (+, $PhCH_2$), 73.62/74.76, 77.63/79.10 (-, OCH), 79.79/79.91 (-, $CH(SO_2Ph)_2$), 127.58 - 138.36 (11 signals, arom. C);FAB-MS *m/z* 588 (M^+, 4), 587 (1).

(3R)-3-[1-(Hydroxy)-2-butoxy]-1,1-bis-(phenylsulfonyl)-nonane (**7**). To an ice-cold solution of **6** (8.85 g, 15.2 mmol) and Me_2S (6.7 mL, 91.2 mmol) in CH_2Cl_2 (100 mL) was added $BF_3{\cdot}Et_2O$ (11.2 mL, 91.2 mmol) dropwise. The mixture was stirred for 16 h at r.t., then a further portion of Me_2S (6.7 mL, 91.2 mmol) and $BF_3{\cdot}Et_2O$ (11.2 mL, 91.2 mmol) was added. After stirring for 60 h at r.t. the solvent and Me_2S were removed first by a stream of N_2 and then by evaporation at 12 torr. The residue was dissolved in CH_2Cl_2 and extracted with sat. aq. $NaHCO_3$ solution (caution! exothermic reaction). The organic layer was dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude product was purified by column chromatography (E/PE) to give **7**, 6.33 g (84%), highly viscous oil, diastereomeric mixture. IR ($CHCl_3$) ν 3580, 3068 - 2860, 1448, 1332, 1228, 1152, 1080, 828 cm^{-1}; ^1H NMR δ 0.88 (m, 6 H, CH_3), 1.13 - 1.68 (m, 12 H, CH_2), 2.07 - 2.41 (m, 2 H, $CH_2CH(SO_2Ph)_2$), 3.20 - 3.42 (m, 2 H, CH_2OH), 3.51, 3.76 (m, 2 H, OCH), 4.71 - 5.33 (dd, ^3J = 2.5, 8 Hz, 1 H, $CH(SO_2Ph)_2$), 7.51 - 8.06 (m, 10 H, arom. H); ^{13}C NMR δ 9.64/9.81, 14.07 (-, CH_3), 22.56/23.18, 24.41/24.85, 29.38/29.46, 31.05, 31.69/31.73, 33.87/34.92 (+, CH_2), 33.30/34.00 (+, $CH_2CH(SO_2Ph)_2$), 63.87/63.93 (+, CH_2OH), 73.43/74.77, 77.65/79.16 (-, OCH), 79.80/79.90 (-, $CH(SO_2Ph)_2$), 128.99, 129.11, 129.37, 129.69, 129.76, 134.55, 134.72 (-, arom. C), 137.89, 137.97 (+, arom. C); FAB-MS *m/z* 497 (M^+, 27), 407 (100).

Formylated ether **8**. To a solution of **7** (6.33 g, 12.76 mmol), Et_3N (8.9 mL, 63.8 mmol) and abs. DMSO (15.1 mL) in CH_2Cl_2 (61.4 mL) was added $SO_3{\cdot}Py$ (8.12 g, 51.0 mmol) in portions at 0 °C. The mixture was stirred for 3.5 h, then diluted with CH_2Cl_2 and extracted with 2 N HCl and brine. The organic layer was dried ($MgSO_4$), the solvent removed and the sensitive crude product stored without further purification at -20 °C. Yield: 6.5 g (103%, small solvent residues), slightly cloudy oil, diastereomeric mixture. IR ($CHCl_3$) ν 3068 -

2860, 1735, 1584, 1448, 1328, 1312, 1224, 1144, 1076, 1000, 964, 632 cm^{-1}; ^1H NMR δ 0.88 (m, 6 H, CH_3), 1.10 - 1.41 (m, 10 H, hexyl CH_2), 1.81/2.40 (2 x br. m, 2 H, ethyl CH_2), 3.11/3.40 (m, 2 H, $CH_2CH(SO_2Ph)_2$), 3.71, 4.01 (m, 2 H, OCH), 4.61 (br. d, ^3J = 8 - 9 Hz, 1 H, $CH(SO_2Ph)_2$), 7.48 - 8.22 (m, 10 H, arom. H), 9.10 (d, ^3J = 5 Hz, 1 H, CHO); FAB-MS *m/z* 495 (M^+, 100), 477 (20), 295 (32), 102 (97).

4-[(3R)-1,1-Bis-(phenylsulfonyl)-3-nonoxy]-(E)-2-hexenoic acid, ethyl ester (**9**). To a suspension of NaH (428 mg, 17.8 mmol) in THF (20 mL) was added $P(OEt)_3$ (3.42 mL, 17.3 mmol) at 0 °C. After 15 min a solution of **8** (6.4 g, ca. 11.5 mmol) in THF (60 mL) was added. After a further 15 min E was added, the organic layer was extracted with H_2O, dried ($MgSO_4$) and evaporated. The residue was filtered through a column and dried under reduced pressure (0.1 torr) to afford **9**, 7.35 g (113%, solvent could not be removed completely). A small amount was purified for spectral data (diastereomeric mixture 2.6 : 1). IR ($CHCl_3$) ν 3068 - 2860, 1712, 1656, 1584, 1448, 1332, 1312, 1276, 1228, 1160, 1036, 908 cm^{-1}; ^1H NMR δ 0.88 (m, 6 H, CH_3), 1.12 - 1.65 (m, 15 H, CH_2, $CO_2CH_2CH_3$), 2.26 (dd, ^3J = 4, 6 Hz, 2 H, $CH_2CH(SO_2Ph)_2$), 3.64 - 3.92 (m, 2 H, OCH), 4.21 (q, ^3J = 7 Hz, 2 H, $CO_2CH_2CH_3$), 4.61/4.71 (dd, ^3J = 4, 6 Hz, 1 H, $CH(SO_2Ph)_2$), 5.75/5.90 (dd, ^4J = 1.5 Hz, ^3J = 16 Hz, 1 H, EtO_2CCH=CH), 6.60/6.73 (dd, ^3J = 6, 16 Hz, 1 H, EtO_2CCH=CH), 7.51 - 8.06 (m, 10 H, arom. H); ^{13}C NMR δ 9.31/9.38, 14.05, 14.25 (-, CH_3), 22.52, 24.01/24.32, 26.89/30.00, 29.25/29.40, 30.93, 31.64/31.68 (+, CH_2), 33.32/34.20 (+, $CH_2CCH(SO_2Ph)_2$), 74.02/74.67, 77.38/77.81 (-, OCH), 79.75/80.03 (-, $CH(SO_2Ph)_2$), 121.62/123.23 (-, EtO_2CCH=CH), 129.10, 129.22, 129.28, 129.41, 129.54, 134.61, 134.73 (-, arom. C), 137.86, 137.93 (+, arom. C), 147.60/148.19 (-, EtO_2CCH=CH), 165.89/166.22 (+, CO_2); FAB-MS *m/z* 565 (M^+, 5), 407 (100).

Allylic alcohol **10**. To a solution of **9** (7.1 g, 12.6 mmol, solvent-containing crude product, see above) in CH_2Cl_2 (60 mL) was added DIBAH (38.5 mL, 44.1 mmol, 1.2 M solution in hexane) dropwise at -70 °C. After stirring for 20 min at the same temperature the reaction was quenched with sat. aq. NH_4Cl solution and allowed to reach r.t. Carefully 2 N HCl was added to dissolve the solid components. The mixture was diluted with CH_2Cl_2 and extracted with H_2O and brine. The organic phase was dried ($MgSO_4$) and the solvent removed to give **10**, 5.52 g (84%), highly viscous oil, diastereomeric mixture (2.6 : 1). IR ($CHCl_3$) ν 3540, 3040 - 2860, 1448, 1332, 1152, 1080, 908 cm^{-1}; ^1H NMR δ 0.81 (m, 6 H, CH_3), 1.10 - 1.62 (m, 12 H, CH_2), 1.99 (m, 1 H, OH), 2.08 - 2.40 (m, 2 H, $CH_2CH(SO_2Ph)_2$), 3.70 (m, 2 H, OCH), 4.11 (dd, ^4J = 1 Hz, ^3J = 5 Hz, 2 H, CH_2OH), 4.70 (dd, ^3J = 4, 7 Hz, 1 H, $CH(SO_2Ph)_2$), 5.32 - 5.57 (m, 1 H, CH=CH), 5.72 (ddd, ^3J = 5, 11, 16 Hz, 1 H, CH=CH), 7.49 - 8.18 (m, 10 H, arom. H); ^{13}C NMR δ 9.69/9.75, 14.08 (-, CH_3), 22.54/24.18, 24.56/25.09, 28.20/28.52, 29.25/29.38, 30.88/31.18, 31.69 (+, CH_2), 34.38/34.66 (+, $CH_2CCH(SO_2Ph)_2$), 62.49/62.77 (+, CH_2OH), 71.80/73.82, 76.94/79.11 (-, OCH), 80.06/80.28 (-, $CH(SO_2Ph)_2$), 129.11, 129.36, 129.69, 129.85, (-, arom. C), 131.34/131.47 (-, CH=CH), 131.99/132.12 (-, CH=CH), 134.50/134.66(-, arom. C), 137.77, 137.99 (+, arom. C); FAB-MS *m/z* 523 (M^+, 1), 425 (12), 407 (100).

Allylic chloride **11**-Cl. To a solution of **10** (5.52 g, 10.6 mmol) and Et_3N (2.22 mL, 15.9 mmol) in CH_2Cl_2 (22 mL) was added slowly MsCl (0.985 mL, 12.7 mmol) at 0 °C. After 0.5 h LiCl (942 mg, 21.2 mmol) and DMF (20 mL) were added and most of the solvent (CH_2Cl_2) was evaporated. The resulting mixture was heated for 15 min to 50 °C. After cooling to r.t. E was added and the organic phase extracted with 2 N HCl and brine. After drying ($MgSO_4$) and evaporation of the solvent the crude product was purified by column chromatography (E/PE) to give **11**-Cl, 4.42 g (77%), highly viscous oil, diastereomeric mixture. IR ($CHCl_3$) ν 3068 - 2860, 1584, 1448, 1332, 1156, 1080, 972 cm^{-1}; ^1H NMR δ 0.89 (m, 6 H, CH_3), 1.13 - 1.61 (m, 12 H, CH_2), 2.23 (br. m, 2 H, $CH_2CH(SO_2Ph)_2$), 3.69 (m, 2 H, OCH), 4.02/4.08 (2 x d, ^3J = 6 Hz, 2 H, CH_2Cl), 4.69 (dd, ^3J = 4, 7 Hz, 1 H, $CH(SO_2Ph)_2$), 5.41 - 5.82 (m, 2 H, CH=CH), 7.50 - 8.05 (m, 10 H, arom. H); ^{13}C NMR δ 9.64, 14.10 (-, CH_3), 22.56, 24.03/24.56, 28.06/28.56, 29.26/29.41, 30.96, 31.72 (+, CH_2), 33.20/34.70 (+, $CH_2CCH(SO_2Ph)_2$), 44.09/44.34 (+, CH_2Cl), 72.78/74.32, 78.13/79.56 (-, OCH), 80.07/80.31 (-, $CH(SO_2Ph)_2$), 127.73 (-, CH=CH), 129.09, 129.15, 129.36, 129.81, 134.52, 134.69, 134.78 (-, arom. C), 135.79 (-, CH=CH), 137.75, 138.10 (+, arom. C); FAB-MS *m/z* 541 (M^+, 1), 425 (17), 407 (100).

4-[(3R)-1,1-Bis-(phenylsulfonyl)-3-nonoxy]-(E)-2-hexenyl methyl carbonate (**11**-carbonate). To a solution of **10** (867 mg, 1.66 mmol) and Et_3N (0.694 mL, 4.98 mmol) in CH_2Cl_2 (3.5 mL) ethyl chloroformate (0.256 mL, 3.32 mmol) was added dropwise at -20 °C. The mixture was stirred for 1 h at -20 °C, then allowed to reach r.t. and stirred for a further 1 h. CH_2Cl_2 was added and the organic layer extracted with 2 N HCl and sat. aq. $NaHCO_3$ solution. The organic phase was dried ($MgSO_4$), evaporated, and the residue chromatographed (E/PE) to afford desired **11**-carbonate (105, mg, 11%), **11**-Cl (357 mg, 40%) and starting material (258 mg, 30%). Spectrocopic data of **11**-carbonate, diastereomeric mixture. IR ($CHCl_3$) ν 3068 - 2860, 1812, 1748, 1584, 1448,

1332, 1272, 1156, 1080, 976, 948 cm^{-1}; ^1H NMR δ 0.86 (m, 6 H, CH_3), 1.11 - 1.65 (m, 12 H, CH_2), 2.22 (m, 2 H, $CH_2CH(SO_2Ph)_2$), 3.58 - 3.76 (m, 2 H, OCH), 3.80 (s, 3 H, OCH_3), 4.58 (d, ^3J = 4.5 Hz, 2 H, OCH_2), 4.67 (dd, ^3J = 4, 7 Hz, 1 H, $CH(SO_2Ph)_2$), 5.40 - 5.77 (m, 2 H, CH=CH), 7.51 - 8.05 (m, 10 H, arom. H); MS (160 °C) *m/z* 551 (M^+, 1), 407 (32), 265 (16), 157 (70), 82 (100).

(2S,8S)-4,4-Bis-(phenylsulfonyl)-8-ethyl-2-hexyl-2,3,4,5,8-pentahydro-oxocin (**12**). A flame-dried two-necked flask was charged with $Pd_2(dba)_3CHCl_3$ (297 mg, 5 mol%) and "biphosphite"[5] (1.27 g, 60 mol%). The apparatus was evacuated and refilled with N_2 (3x), to exclude any oxygen during reaction. THF/dioxane (2 : 1) (150 mL) was added and the mixture was stirred. After 10 min the colour of the dark violet solution turns to pale yellow. The colour indicates the formation of the desired Pd(0) complex. The reaction mixture was heated to reflux and deprotonated **11**-Cl {KH (755 mg, 6.61 mmol, 35% dispersion in mineral oil) was freed from oil by washing with PE. Chloride **11**-Cl (3.1 g, 5.73 mmol) in THF/dioxane (2 : 1) (100 mL) was added under N_2 and the mixture was stirred, until it was homogeneous (15 - 60 min)} was added as a clear solution *via* syringe drive over a period of 6 h. After complete addition the reaction mixture was heated to reflux for a further 1 h. The solvent was removed and the crude product was purified by chromatography to afford semi-solid **12** (1.66 g, 57%), **A** (346 mg), **B** (121 mg), and **C** (105 mg) in total 77% yield (**12 : A : B : C** = 15.8 : 3.3 : 1.15 : 1; 8-ring : 6--ring = 2.9 : 1). Spectroscopic data of **12**: IR ($CHCl_3$) ν 3072 - 2856, 1448, 1328, 1224, 1144, 1100, 1076, 996 cm^{-1}; ^1H NMR δ 0.91 (m, 6 H, CH_3), 1.20 - 1.72 (m, 12 H, hexyl CH_2, ethyl CH_2), 2.20 (br. d, ^2J = 15 Hz, 1 H, $CH_2C(SO_2Ph)_2$), 2.64 (br. m, 2 H, $CH_2C(SO_2Ph)_2$), 4.08 (br. t, ^3J = 5 Hz, 1 H, OCH), 4.19 (br. dd, ^3J = 4, 15 Hz, 1 H, $=CHCH_2C(SO_2Ph)_2$), 4.63 (m, 1 H, OCH), 5.59 (m, 2 H, HC=CH), 7.60 (m, 6 H, arom. H), 8.03 (m, 4 H, arom. H); ^1H NMR (C_6D_6) δ 0.90 (m, 6 H, CH_3), 1.10 - 1.58 (m, 12 H, hexyl CH_2, ethyl CH_2), 2.38 (dd, ^3J = 1 Hz, ^2J = 16 Hz, 1 H, $CH_2C(SO_2Ph)_2$), 2.81 (br. m, 2 H, $CH_2C(SO_2Ph)_2$), 3.88 (m, 1 H, $OCHC_6H_{13}$), 4.52 (br. dd, ^3J = 8 Hz, ^2J = 14 Hz, 1 H, $=CHCH_2C(SO_2Ph)_2$), 4.94 (m, 1 H, $OCHC_2H_5$), 5.42 (ddd, ^4J = 1 Hz, ^3J = 3, 11 Hz, 1 H, $OCHCH$=CH), 5.69 (ddt, ^4J = 1 Hz, ^3J = 8, 11 Hz, 1 H, $OCHCH$=CH), aromatic signals are not useful (solvent C_6D_6); ^{13}C NMR δ 9.56, 14.08 (-, CH_3), 22.53, 25.79, 26.38, 28.93, 29.12, 31.68 (+, hexyl CH_2, ethyl CH_2), 31.95 (+, $OCHCH_2$), 33.88 (+, $=CHCH_2$), 72.14 (-, OCH), 72.40 (-, OCH), 92.85 (+, $C(SO_2Ph)_2$), 121.04 (-, $OCHCH$=), 128.57, 131.16, 134.45 (-, arom. C), 136.78, 137.61 (+, arom. C), 137.12 (=$CHCH_2$); FAB-MS *m/z* 505 (M^+, 24), 407 (72), 363 (100). Anal. Calcd for $C_{27}H_{36}O_3S_2$: C, 64.28; H, 7.14. Found: C, 64.39; H, 7.44.

(2S,8S),-4,4-Bis-(phenylsulfonyl)-8-ethyl-2-hexyl-oxocane (**13**). A solution of **12** (250 mg, 0.496 mmol) and Wilkinson catalyst (300 mg) in abs. benzene (20 mL) was hydrogenated (4 bar) for 23 h at 40 - 50 °C. The solvent was removed and the residue chromatographed (E/PE, 1 : 4) to afford **13**, 235 mg (94%), semi-solid substance. IR ($CHCl_3$) ν 3072 - 2856, 1584, 1448, 1328, 1208, 1136, 1076, 972, 908 cm^{-1}; ^1H NMR δ 0.90 (m, 6 H, CH_3), 1.18 - 1.73 (m, 14 H, CH_2), 1.81 - 2.10 (m, 3 H, CH_2, $CH_2C(SO_2Ph)_2$), 2.24 (m, 1 H, $CH_2C(SO_2Ph)_2$), 3.12 (dd, ^3J = 8 Hz, ^2J = 16 Hz, 1 H, $CH_2C(SO_2Ph)_2$), 3.44 (m, 1 H, OCH), 3.76 (dd, ^3J = 12 Hz, ^2J = 16 Hz, 1 H, $CH_2C(SO_2Ph)_2$), 4.54 (m, 1 H, OCH), 7.48 - 8.17 (m, 10 H, arom. H); ^{13}C NMR δ 9.82, 14.07 (-, CH_3), 20.97, 25.54, 26.29, 26.54, 28.55, 29.91, 30.52, 31.68 (+, CH_2), 33.55, 34.72 (+, $CH_2C(SO_2Ph)_2$), 72.19, 73.43 (-, OCH), 93.56 (+, $C(SO_2Ph)_2$), 128.47, 131.16, 131.33, 134.34, 136.11 (-, arom. C), 136.52, 137.34 (+, arom. C); FAB-MS *m/z* 507 (M^+, 100), 251 (20), 143 (37).

(2S,8S)-Lauthisan (**14**). To a solution of **13** (215 mg, 0.425 mmol) and Na_2HPO_4 (483 mg, 3.40 mmol) in abs. MeOH (6 mL) and THF (3 mL) was added NaHg (ca. 10 g, 6%) at r.t. until the starting material was desulfonated completely. The reaction mixture was diluted with E and extracted with 1 N HCl, sat. aq. NH_4Cl solution and brine. The organic layer was dried ($MgSO_4$), the solvent evaporated and the residue purified by chromatography (E/PE) to give **14**, 79 mg (82%), oil; $[\alpha]_D^{19}$ = -13.8 (c = 0.09, $CHCl_3$) (Lit[8]: (2R,8R)-lauthisan, $[\alpha]_D^{25}$ = + 13.7°). ^1H NMR (C_6D_6) δ 0.88 - 0.98 (m, 6 H, CH_3), 1.24 - 1.78 (m, 22 H, CH_2), 3.41 - 3.61 (m, 2 H, OCH); ^{13}C NMR (C_6D_6) δ 10.65, 14.33 (CH_3), 23.07, 26.24, 26.47, 26.51, 27.12, 29.94, 30.05, 32.34, 32.56, 32.78, 37.14 (+, CH_2), 74.16, 74.86 (-, OCH); FAB-MS *m/z* 226 (M^+, 17), 225 (100); HRMS calcd. for $C_{13}H_{30}O$ 226.2297, found 226.2310.

REFERENCES AND NOTES

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§ Throughout this paper the Maehr convention is used to designate stereochemistry (Maehr, H. *J. Chem. Ed.* **1985**, *62*, 114); see preceding paper.

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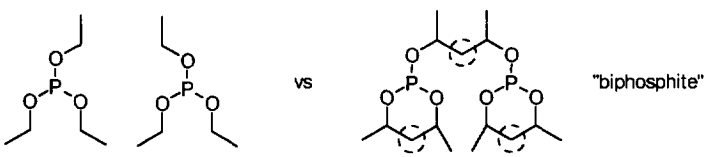
4 Preceding paper.

5 Tying up the ethyl groups of $P(OEt)_3$ by methylene groups (circled) as in the "biphosphite" reduces the steric demand of the bidentate ligand and decreases cone angles (cf. Tolman, C. A. *Chem. Rev.* **1977**, *77*, 313).



Reduced steric demand of the ligand on palladium favours the cyclization product stemming from nucleophilic attack at the simple methylene terminus of the (η^3-allyl)palladium complex; cf. Trost, B. M.; Verhoeven T. R. *J. Am. Chem. Soc.* **1980**, *102*, 4743; Trost, B. M.; Vos, B. A.; Brzezowski, C. M.; Martina, D. P. *Tetrahedron Lett.* **1992**, *33*, 717.

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7 Furthermore, it seems possible that competition between 8-membered ring complex **12**-PdL_2 and 6-membered ***iii*** is decided by kinetically controlled reductive elimination, with retention of configuration, of an oxapalladacycle. Such a reaction is, of course, different from the S_N2-like formation of **A**, **B**, **C** and opens the way to new rules of stereocontrol and stereoconvergence.

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9 The term stereospecific is often used in another sense. See Eliel, E. L. *Stereochemistry of Carbon Compounds*, McGraw Hill, New York, **1962**.

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11 Preparation of *n*-$Bu_4NCH(SO_2Ph)_2$: A suspension of bis(phenylsulfonyl)methane (7.12 g, 24 mmol), *n*-Bu_4NHSO_4 (9.78 g, 28.8 mmol) and NaOH (2.4 g, 60 mmol) in H_2O (20 mL) was heated to 120 °C for a short time, then cooled and extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$) and evaporated to give a yellow solid, which was dried under reduced pressure (0.05 torr) and pulverized (11.75 g, 91%).

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