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Highly diastereoselective hetero-Diels–Alder reaction of buta-1,3-diene with *N*-glyoxyloyl-(2*R*)-bornane-10,2-sultam: an efficient synthesis of homochiral (*S*)-3-[2-{(methylsulfonyl)oxy}ethoxy]-4-(triphenylmethoxy)-1-butanol methanesulfonate

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Abstract—The influence of Lewis acid on the diastereoselectivity of [4+2] cycloaddition of buta-1,3-diene to *N*-glyoxyloyl-(2*R*)-bornane-10,2-sultam was investigated and high levels of asymmetric induction were achieved. (*S*)-3-[2-{(Methylsulfonyl)oxy}ethoxy]-4-(triphenylmethoxy)-1-butanol methanesulfonate were synthesized in 15% overall yield, applying as a crucial step the above-mentioned [4+2] cycloaddition catalyzed by $ZnBr_2$.

1. Introduction

Naturally occurring indolocarbazoles, such as staurosporine **1**[1] and rebeccamycin **2**[2] are known to be inhibitors of protein kinase C (PKC), which regulates vascular function.[3] Recently, Jirousek et al.[4] have identified a family of macrocyclic bisindolylmaleimides of type **3** that are competitive, reversible inhibitors of PKC. The promising biological and pharmacological properties of compounds **3** encouraged Faul et al.[5] to synthesize them in enantiomerically pure form. A retrosynthetic analysis (Scheme 1) shows that the crucial intermediate for the synthesis is homochiral compound **4**,[4,5] which could be readily obtained from (*S*)-trityloxymethyl-3,6-dihydro-2*H*-pyran **5** via ozonolysis.[6] Compound (*S*)-**5** could be synthesized via enantioselective hetero-Diels–Alder reaction of buta-1,3-diene **6** with trityloxyacetaldehyde **7** or in its diastereoselective version using, for example, *N*-glyoxyloyl-(2*R*)-bornane-10,2-sultam **8**[7] a highly activated heterodienophile containing the efficient chiral auxiliary **11**.[8] Unfortunately, the reaction of **6** with nonactivated heterodienophile **7** failed, even when it was carried out under very high pressure.[9] Thus, we examined the diastereoselective reaction of **6** with **8**, as a potential route to enantiomerically pure (*S*)-3-[2-{(methylsulfonyl)oxy}ethoxy]-4-(triphenylmethoxy)-1-butanol methanesulfonate **4**.

2. Results

Our preliminary studies concerning the diastereoselective [4+2] cycloaddition of buta-1,3-diene **6** to chiral glyoxylates[10] suggested that this process requires optimization. We first studied *N*-glyoxyloyl-(2*R*)-bornane-10,2-sultam **8** as a chiral heterodienophile (Scheme 2) in an effort to assess the influence of Lewis acids on this reaction.

The hetero-Diels–Alder reactions of **6** with **8** were carried out in methylene chloride at room temperature in the presence of several Lewis acids: $BF_3{\cdot}Et_2O$, $AlCl_3$, $TiCl_4$, $SnCl_4$, $ZnCl_2$ and $ZnBr_2$. The results are collected in Table 1.

In all cases a mixture of distereoisomers (2′*S*)-**9** and (2′*R*)-**9** was obtained. The highest diastereoselectivity and the best yields were obtained when the reaction was

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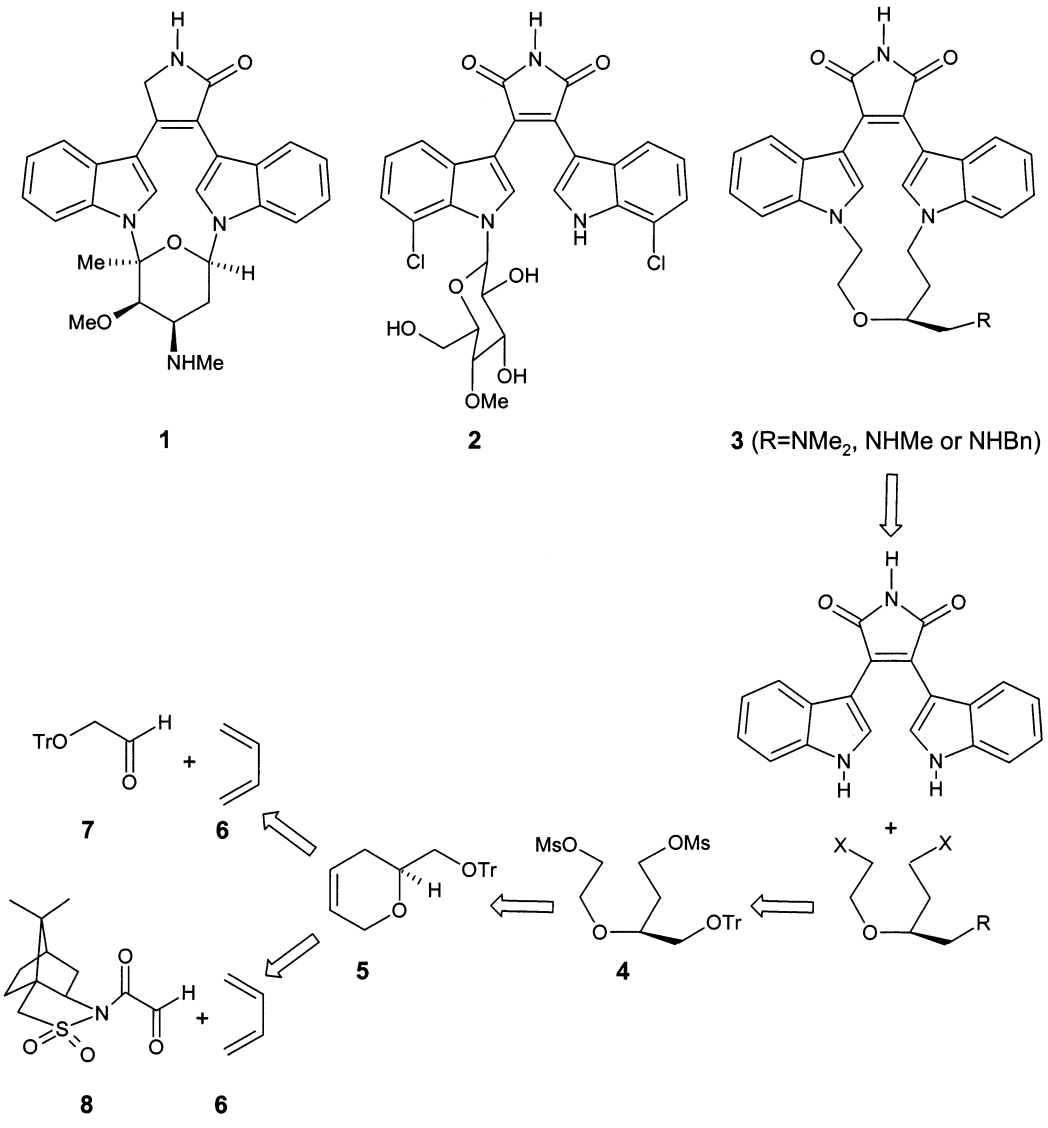


Scheme 1.

carried out in the presence of $ZnBr_2$ (Table 1, entry 6). Similar diastereoselectivity was found for $ZnCl_2$ and for the high-pressure experiment[11] (Table 1, entries 5 and 7, respectively) but in both cases, the yields were slightly lower. Separation of the diastereoisomers was successfully executed using flash silica chromatography. X-Ray structural analysis (Fig. 1) showed that the configuration of the newly formed stereogenic center at C-2′ was (2′*S*) for the major diastereoisomer.

Table 1. Asymmetric [4+2]cycloaddition of **6** to **8**

Entry	Lewis acid	Pressure (bar)	Yield (%)	Diastereoisomeric ratio (2′*S*)-**9**:(2′*R*)-**9**
1	$BF_3{\cdot}Et_2O$	1	64	7:3
2	$AlCl_3$	1	57	7:3
3	$TiCl_4$	1	51	8:2
4	$SnCl_4$	1	57	8:2
5	$ZnCl_2$	1	57	9:1
6	$ZnBr_2$	1	66	9:1
7	–	10 000	50	9:1

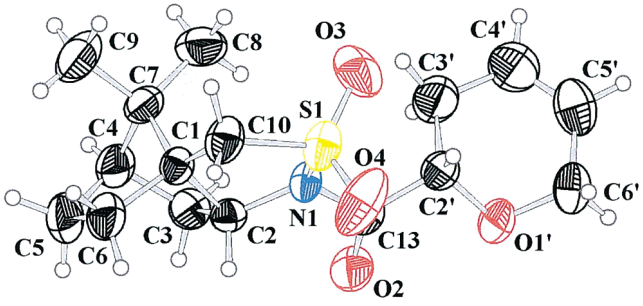
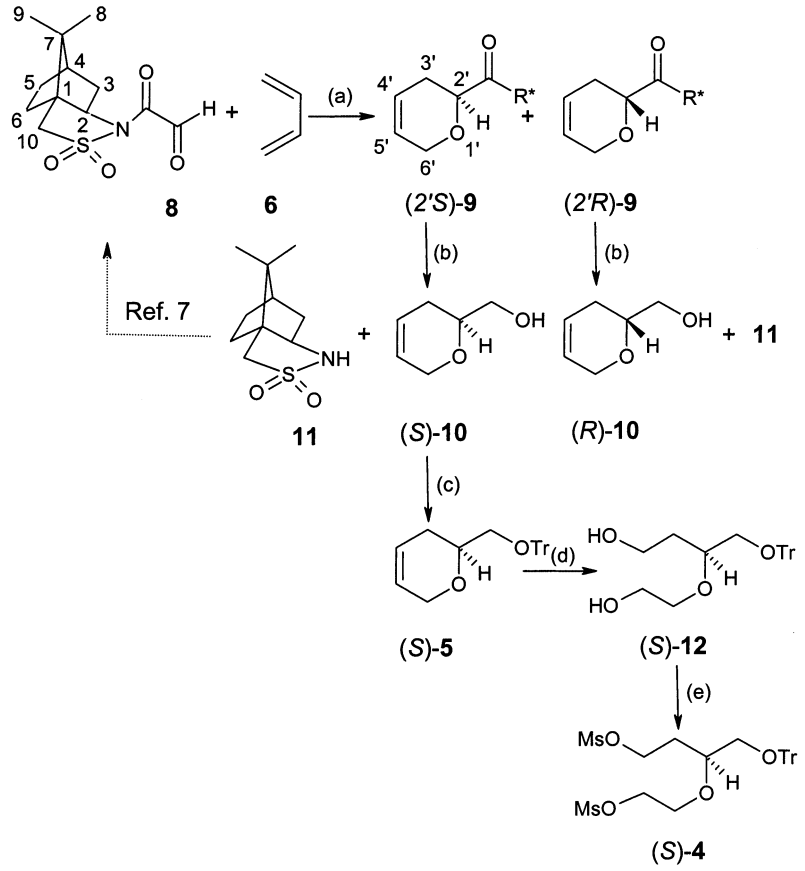


Figure 1. ORTEP diagram of (2′*S*)-**9**.

Having in hand a very good method for the synthesis of diastereoisomerically pure compound (2′*S*)-**9**, we pursued the synthesis of (*S*)-3-[2-{(methylsulfonyl)oxy} ethoxy]-4-(triphenylmethoxy)-1-butanol methanesulfonate (**4**). Separate reduction of diastereoisomers (2′*S*)-**9** and (2′*R*)-**9** with lithium aluminum hydride afforded the respective enantiomerically pure (>99% ee) alcohols (*S*)-**10** and (*R*)-**10** in a good yield. Then enantiomeric



Scheme 2. *Reagents and conditions*: (a) i. $ZnBr_2$ (cat), CH_2Cl_2, −78°C→rt, 24 h; ii. Chromatographic separation; (b) $LiAlH_4$, Et_2O, 0°C→rt, 2 h; (c) TrCl, CH_2Cl_2, DMAP (cat), Et_3N, 0°C, 12 h; (d) i. O_3, CH_2Cl_2:MeOH (1:1 v/v), −50°C, 1 h; ii. $NaBH_4$, 0.05 N $NaOH_{aq}$; (e) MsCl, Et_3N, CH_2Cl_2, 0°C, 2 h.

purities were confirmed by GC experiments using a chiral column. Protection of the (*S*)-**10** hydroxy group using trityl chloride, gave (*S*)-**5** in excellent yield; its configuration was established by X-ray structural analysis (Fig. 2). Compound (*S*)-**5** was then subjected to ozonolysis, followed by reduction with sodium borohydride to afford diol (*S*)-**12**. Treatment of diol (*S*)-**12** with methanesulfonyl chloride gave the desired compound (*S*)-**4** in 15% overall yield.

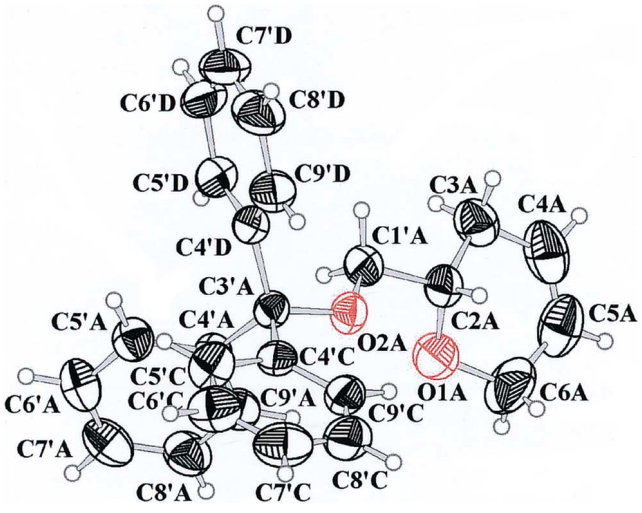


Figure 2. ORTEP diagram of (*S*)-**5**.

3. Conclusions

The highly stereoselective synthesis of (*S*)-3-[2-{(methylsulfonyl)oxy}ethoxy]-4-(triphenylmethoxy)-1-butanol methanesulfonate **4** proceeds in 15% yield over five steps, starting from *N*-glyoxyloyl-(2*R*)-bornane-10,2-sultam **8**. During the course of our studies we found that the [4+2]cycloaddition of buta-1,3-diene **6** to **8** is Lewis acid dependent. The best results were obtained for $ZnBr_2$ as the catalyst. We also found that the [4+2]cycloaddition of **6** to **8** can be successfully conducted under high-pressure conditions in the absence of a Lewis acid.

4. Experimental

4.1. General

Melting points were determined on a Kofler hot-stage apparatus with a microscope, and are uncorrected. All reported NMR spectra were recorded with a Varian Unity plus spectrometer at 500 (^{1}H NMR) and 125 (^{13}C NMR) MHz. Chemical shifts are reported as δ values relative to TMS peak defined at $\delta = 0.00$ (^{1}H NMR) or $\delta = 0.0$ (^{13}C NMR). IR spectra were obtained on a Perkin–Elmer 1640 FTIR spectrometer. Mass spectra were obtained on an AMD 604 Intectra instrument using the EI or LSIMS techniques, or on a Mariner

BioSystem unit using the ESI technique. Optical rotations were recorded using a Perkin–Elmer 241 polarimeter with a thermally jacketed 10 cm cell. X-Ray analysis was performed on a Kuma KM4CCD κ-axis diffractometer with graphite-monochromated Mo Kα radiation. Elemental analysis (C, H, and N) were performed by the 'in-house' analytical service. Analytical TLC was carried out on commercially prepared plates coated with 0.25 mm of Merck Kieselgel 60. Preparative flash silica chromatography was performed using Merck Kieselgel 60 (230–400 mesh). GC experiments were carried out on a Hewlett–Packard 5890 apparatus equipped with a FID detector and β-Dex 225 chiral column (30 m×0.25 mm I.D.).

All chemicals were used as received unless otherwise noted. Reagents grade solvents were dried and distilled prior to use. *N*-Glyoxyloyl-(2*R*)-bornane-10.2-sultam was prepared according to the literature procedure.[7]

4.2. [4+2]Cycloaddition of buta-1,3-diene (6) to *N*-glyoxyloyl-(2*R*)-bornane-10,2-sultam (8)

4.2.1. Lewis acid-catalyzed reaction, typical procedure. The heterodienophile **8** (0.1 mol) was dissolved in dry CH_2Cl_2 (100 mL) and added to a suspension of $ZnBr_2$ (0.1 mol) in CH_2Cl_2 (100 mL), and the mixture was stirred for 1 h at room temperature. Then the mixture was cooled to −78°C and buta-1,3-diene (**6**, 0.3 mol) was added dropwise, and it was stirred for additional 24 h at rt. After evaporation of solvents, the residue was chromatographed on a silica-gel column using a hexane/acetone/ethyl acetate (2.5:3:1 v/v/v) system to give two diastereoisomerically pure products (2′*S*)-**9** and (2′*R*)-**9** in a ratio of 9:1 with 69% overall yield.

4.2.2. High-pressure reaction, typical procedure.[11] In a Teflon ampoule was placed a solution of buta-1,3-diene (**6**, 2 mmol) and heterodienophile **8** (1 mmol) in dry CH_2Cl_2 (2 mL). The ampoule was subjected to a high-pressure apparatus and compressed up to 10 kbar for 48 h. After decompression, the post-reaction mixture was purified on a silica-gel column as in Section 4.2.1 to afford two pure diastereoisomers (2′*S*)-**9** and (2′*R*)-**9** in a 9:1 ratio with 50% overall yield.

4.2.3. Diastereoisomer (2′*R*)-9. Mp 144–145°C; $[\alpha]_D^{20}=-32$ (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 27°C, TMS): $\delta=0.99$ (s, 3H), 1.21 (s, 3H), 1.32–1.43 (m, 2H), 1.85–1.97 (m, 3H), 2.09 (dd, 1H, $J_1=8$ Hz, $J_2=13.5$ Hz), 2.14–2.19 (m, 1H), 2.24–2.31 (m, 1H), 2.47–2.55 (m, 1H), 3.47 (AB, 2H, $J_1=13.5$ Hz), 3.95 (dd, 1H, $J_1=5$ Hz, $J_2=7.75$ Hz), 4.23–4.33 (m, 2H), 4.60 (dd, 1H, $J_1=3.25$ Hz, $J_2=10.5$ Hz), 5.71–5.75 (m, 1H, $J_1=$ 10 Hz), 5.83–5.88 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, 27°C, TMS): $\delta=19.9$, 21.3, 26.3, 26.4, 33.3, 38.6, 45.0, 47.8, 48.6, 53.3, 65.8, 66.1, 72,7, 123.2, 125.7, 170.2; IR (KBr): $\nu=1080$, 1138, 1332, 1691 cm^{-1}; MS (EI LR) $m/z=325$ $(M)^+$ (2.0%), 244 (10.3%), 177 (10.6%), 135 (21.9%), 93 (15.3%), 83 (100%), 82 (31.3%), 55 (51.6%), 41 (13.6%). Anal. calcd for $C_{16}H_{23}NSO_4$: C, 59.05; H, 7.12; N, 4.30; S, 9.85. Found: C, 59.02; H, 7.16; N, 4.27; S, 9.70%.

4.2.4. Diastereoisomer (2′*S*)-9. Mp 189–191°C; $[\alpha]_D^{20}=-193.3$ (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 27°C, TMS): $\delta=0.97$ (s, 3H), 1.13 (s, 3H), 1.34–1.47 (m, 2H), 1.85–1.96 (m, 3H), 1.99–2.04 (m, 1H), 2.10–2.14 (dd, 1H, $J_1=8$ Hz, $J_2=14$ Hz), 2.27–2.35 (m, 1H), 2.41–2.47 (m, 1H, $J_1=1.5$ Hz, $J_2=3.5$ Hz, $J_3=15$ Hz), 3.47 (AB, 2H, $J_1=13.5$ Hz), 3.96 (dd, 1H, $J_1=4.75$ Hz, $J_2=7.75$ Hz), 4.27–4.39 (m, 2H), 4.71 (dd, 1H, $J_1=3$ Hz, $J_2=10.25$ Hz), 5.74–5.77 (m, 1H, $J_1=1.5$ Hz, $J_2=$ 10.5 Hz), 5.81–5.85 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, 27°C, TMS): $\delta=19.9$, 20.7, 26.4, 28.6, 32.7, 38.1, 44.5, 47.9, 48.7, 53.1, 65.0, 65.8, 72.8, 122.7, 126.1, 170.63; IR (KBr): $\nu=1054$, 1135, 1337, 1713, cm^{-1}; MS (EI LR) $m/z=325$ $(M)^+$ (1.6%), 244 (10.9%), 177 (15.0%), 135 (23.4%), 93 (15.5%), 83 (100%), 82 (32.8%), 75 (48.1%), 55 (51.6%), 41 (10.8%). Anal. calcd for $C_{16}H_{23}NSO_4$: C, 59.05; H, 7.12; N, 4.30; S, 9.85. Found: C, 58.79; H, 7.25; N, 4.14; S, 9.65%.

4.3. Transformation of (2′*S*)-9 into (*S*)-5

To a solution of $LiAlH_4$ (0.03 mol) in diethyl ether (80 mL), the enantiomerically pure (2′*S*)-**9** (0.06 mol) dissolved in dry CH_2Cl_2 (10 mL) was added dropwise, and a reaction mixture was stirred for 2 h. After usual work-up, a post-reaction mixture was filtered, and filtrate was dried with $MgSO_4$. After evaporation of CH_2Cl_2, addition of hexane to the residue caused precipitation of sultam **11** which was filtered off, and hexane was removed by distillation. The residue was diluted with dry CH_2Cl_2 (500 mL) and treated with trityl chloride (0.07 mol) in the presence of catalytic amount of DMAP. A solution was cooled (0°C) and Et_3N (0.07 mol) was added in a stream of argon. After 12 h stirring, a post-reaction mixture was washed with brine (100 mL), dried with Na_2SO_4, and solvents were evaporated. The residue was then directly subjected to flash silica chromatography using hexane/ethyl acetate (30:1) as an eluent. Overall yield of (*S*)-**5** counted on (2′*S*)-**9** was 60%.

4.3.1. Alcohol (*S*)-10. $[\alpha]_D^{20}=-147.4$ (*c* 1.02, $CDCl_3$); >99% ee (determined by GC on chiral column β-dex 225); ^{1}H NMR (500 MHz, $CDCl_3$, 27°C, TMS): $\delta=$ 1.87–1.93 (m, 1H), 2.06–2.14 (m, 1H), 2.18–2.53 (m, 1H; –OH), 3.56–3.60 (m, 1H), 3.65–3.69 (m, 1H), 3.67–3.70 (m, 1H), 4.22–4.24 (m, 2H), 5.67–5.76 (m, 1H), 5.80–5.85 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, 27°C, TMS): $\delta=26.5$, 65.6, 65.7, 74.1, 123.7, 126.2; IR (film): $\nu=1641$, 3393 cm^{-1}; MS (ESI HR): calcd for $[C_6H_{10}O_2Na]^+$ 137.0573, found 137.0579.

4.3.2. Alcohol (*R*)-10. $[\alpha]_D^{15}=+140.7$ (*c* 1, $CDCl_3$); >99% ee (determined by GC on chiral column β-dex 225); ^{1}H NMR and ^{13}C NMR were the same as in Section 4.3.1.

4.3.3. Compound (*S*)-5. Mp 124–126°C; $[\alpha]_D^{21}=-74.2$ (*c* 1, $CDCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 25°C, TMS): $\delta=2.00$–2.11 (m 2H), 3.02–3.05 (m, 1H), 3.27 (dd, 1H, $J_1=6$ Hz, $J_2=10$ Hz), 3.77 (sextet, 1H), 4.18–4.26 (m, 2H), 5.67–5.74 (m, 1H), 5.79–5.83 (m, 1H), 7.23 (q, 3H, $J_1=7.5$ Hz), 7.29 (t, 6H, $J_1=7.5$ Hz), 7.47 (d, 6H, $J_1=7.5$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$, 25°C, TMS):

$\delta = 28.1$, 65.9, 66.7, 73.0, 86.4, 123.9, 126.3, 126.9, 127.8, 128.7, 144.1; IR (KBr) $\nu = 1595$ cm^{-1}; MS (ESI HR): calcd for $[C_{25}H_{24}O_2Na]^+$ 379.1674, found 379.1674.

4.4. (*S*)-3-(2-Hydroxyethoxy)-4-(triphenylmethoxy)-1-butanol (12)

Compound (*S*)-**5** was subjected to ozonolysis which was carried out at −50°C in a mixture of solvents CH_2Cl_2/MeOH (1:1 v/v), and in the presence of Sudan indicator. After 2 h of ozonolysis, when the color of the indicator was changed, the reaction mixture was treated with cooled (0–5°C) solution of $NaBH_4$ (2.2 equiv.) in 0.05N $NaOH_{aq}$. When the addition was completed, the temperature of the reaction mixture was allowed to rise to rt, and was stirred for an additional 12 h. After that a post-reaction mixture was concentrated and washed with water. An organic layer was dried with $MgSO_4$ and solvents were evaporated to give (*S*)-**12** as an oil with 50% yield.

Compound (*S*)-**12**: $[\alpha]_D^{21} = -20.7$ (*c* 1.01, $CDCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 25°C, TMS): $\delta = 1.76$ (q, 2H, $J_1 = 6.0$ Hz), 2.47 (br s, 2H; -OH), 3.15 (dd, 1H, $J_1 = 4.25$ Hz, $J_2 = 10$ Hz), 3.21 (dd, 1H, $J_1 = 6.0$ Hz, $J_2 = 10.0$ Hz), 3.64–3.60 (m, 1H), 3.68–3.75 (m, 4H), 3.73–3.82 (m, 2H), 7.22–7.26 (m, 3H), 7.28–7.31 (m, 6H), 7.43–7.46 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$, 25°C, TMS): $\delta = 34.4$, 60.3, 62.3, 66.2, 71.8, 78.5, 86.9, 127.1, 127.8, 128.7, 143.9; IR (film CH_2Cl_2) $\nu = 1597$, 3370 cm^{-1}; MS (LSIMS HR): calcd for $[C_{25}H_{28}O_4Na]^+$ 415.18853, found 415.18901.

4.5. (*S*)-3-[2-{(Methylsulfonyl)oxy}ethoxy]-4-(triphenylmethoxy)-1-butanol methanesulfonate (4)

Diol (*S*)-**12** was dissolved in 50 mL of dry CH_2Cl_2, the solution was cooled to 0°C, and after addition of Et_3N (0.03 mol), mesyl chloride (0.03 mol) was added. After additional stirring at 0–5°C for 2 h, the reaction mixture was washed with water (2×20 mL), and treated with brine (20 mL). An organic layer was dried with $MgSO_4$, and solvents were evaporated. The solid residue was recrystallized from a mixture of heptane/ethyl acetate, to afford the pure product (*S*)-**4** in 80% yield, which is thermally unstable.[5] ^{1}H and ^{13}C NMR spectra are identical with those obtained by Lilly Research Laboratories.[5]

4.6. X-Ray structure determination of (2′*S*)-9 and (*S*)-5

All measurements of crystal were performed on a Kuma KM4CCD κ-axis diffractometer with graphite-monochromated MoKα radiation. The crystal was positioned at 62.2 mm from the KM4CCD camera. 796 frames were measured at 1.6° intervals with a counting time of 15 s. The data were corrected for Lorentz and polarization effects. No absorption correction was applied. Data reduction and analysis were carried out with the Kuma Diffraction (Wrocław) programs.

The structure was solved by direct methods[12] and refined using SHELXL.[13] The refinement was based on F^2 for all reflections except those with very negative F^2. Weighted *R* factors *wR* and all goodness-of-fit *S* values are based on F^2. Conventional *R* factors are based on *F* with *F* set to zero for negative F^2. The $Fo^2 > 2s(Fo^2)$ criterion was used only for calculating *R* factors and is not relevant to the choice of reflections for the refinement. The *R* factors based on F^2 are about twice as large as those based on *F*. All hydrogen atoms were located from a differential map and refined isotropically. Scattering factors were taken from Tables 6.1.1.4 and 4.2.4.2 in Ref. 14.

Crystallographic data (excluding structural factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre under the deposition numbers CCDC 194388 and 194387 for (2′*S*)-**9** and (*S*)-**5**, respectively.

Compound (2′*S*)-**9**: $C_{16}H_{23}NSO_4$, $M = 325.41$, orthorhombic, $a = 7.921(2)$, $b = 12.786(3)$, $c = 16.148(3)$ Å, space group $P2_12_12_1$, $V = 1635.4(6)$ Å^3, $Z = 4$, $D_c = 1.322$ Mg m^{-3}, μ(Mo Kα) = 0.215 mm^{-1}, $T = 293$ K, 16501 reflections measured, 16501 unique reflections ($R_{int} = 0.1285$), which were used in all calculations. Data/parameters: 16501/202. The final $R_1 = 0.0639$ (all data). Residual electron density: 0.201 and −0.172 e Å^3.

Compound (*S*)-**5**: $C_{25}H_{24}O_2$, $M = 356.44$, monoclinic, $a = 9.5656(19)$, $b = 10.602(2)$, $c = 19.905(4)$ Å, space group $P2_1$, $V = 1963.1(7)$ Å^3, $Z = 4$, $D_c = 1.206$ Mg m^{-3}, μ(Mo Kα) = 0.075 mm^{-1}, $T = 293$ K, 25391 reflections measured, 25391 unique reflections ($R_{int} = 0.1220$), which were used in all calculations. Data/parameters: 25391/488. The final $R_1 = 0.0563$ (all data). Residual electron density: 0.137 and −0.153 e Å^3.

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