36. Enantioselective Synthesis of Both Enantiomers of a Isoproterenol Analogue and of Di-*O*-pivaloylepinephrine

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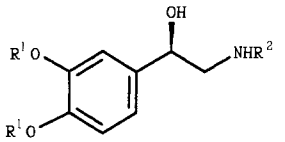
An asymmetric synthesis of the analogue **4a** of isoproterenol and of di-*o*-pyvaloylepinephrine **3** which provides both enantiomers in optically pure state is reported. The key step of the method is the highly diastereoselective reduction (using DIBAL or DIBAL/$ZnCl_2$) of a β-ketosulfoxide **7** which leads, as desired, to the (*S*)- or the (*R*)-configuration at C(1) (*Schemes 4* and *5*).

1. Introduction. – (−)-(*R*)-Isoproterenol ((−)-**2**[1]) and (−)-(*R*)-3′,4′-di-*O*-pivaloyl derivative (−)-**3**[2]) of (*R*)-epinephrine (**1**) are well known β-adrenoreceptor agonist used in the treatment of asthma and glaucoma [4].



1 $R^1 = H$, $R^2 = Me$; (*R*)-epinephrine
2 $R^1 = H$, $R^2 = i\text{-Pr}$; (−)-(*R*)-isoproterenol
3 $R^1 = t\text{-BuCO}$, $R^2 = Me$; (−)-(*R*)-3′,4′-Di-*O*-pivaloylepinephrine
4a $R^1\text{–}R^1 = -CH_2-$, $R^2 = i\text{-Pr}$

No asymmetric synthesis of these compounds have been performed until now. Optically pure isoproterenol analogues have been obtained from optically pure epoxide **5** [5] which was prepared from the resolved dibenzyl derivative of 3,4-dihydroxymandelic acid (*Scheme 1*). Di-*O*-pivaloylepinephrine **3** has been synthesized in its racemic form by catalytic reduction of aminoketone **6** and has then been resolved into its enantiomers [2] [3].

We want to report here an asymmetric synthesis which can afford both enantiomers of **4a** and **3** [6]. The key step of the method is the highly diastereoselective reduction of a β-keto sulfoxide **7** [7] [8] which leads *via* **8**, as desired, to (*R*)- or (*S*)-configuration at C(1) (*Scheme 2*).

2. Results. – Keto sulfoxides **7** are obtained by addition of the anion **9′** of (+)-(*R*)-methyl *p*-tolyl sulfoxide **9**, which is synthesized in the usual way [9] from (*S*)-methyl sulfinate (*Scheme 3*), onto a suitable aromatic substrate.

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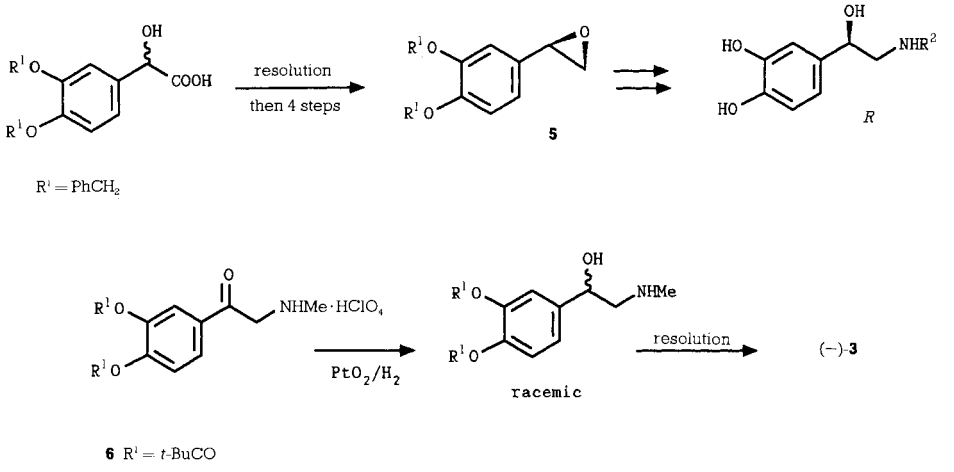
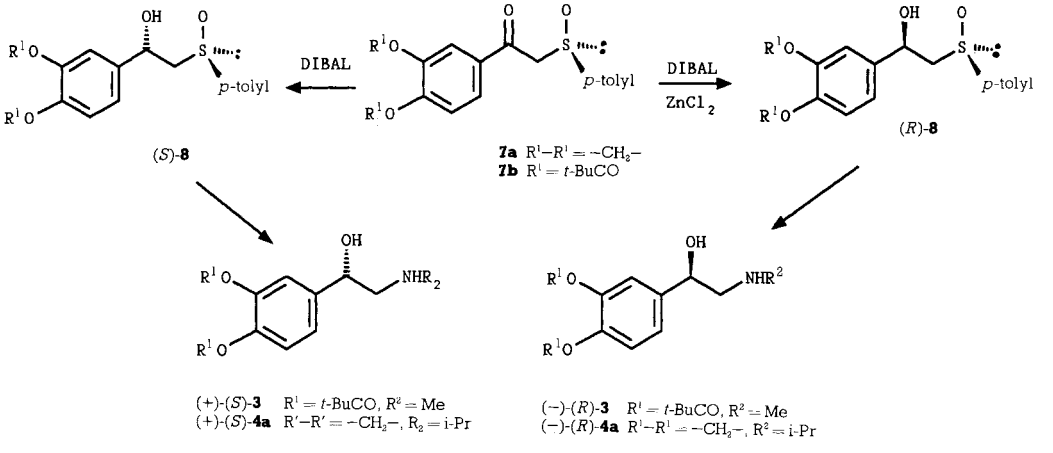
[1]) The (*R*)-configuration of (−)-isoproterenol ((−)-**2**) has been unambiguously assigned [1].

[2]) The configuration of (−)-3′,4′-di-*O*-pivaloylepinephrine ((−)-**3**) has not been assigned [2] [3], but by analogy with similar compounds ((−)-(*R*)-adrenaline, (−)-(*R*)-isoproterenol ((−)-**2**)), one could postulate it to be (*R*), which is confirmed by the results presented here.

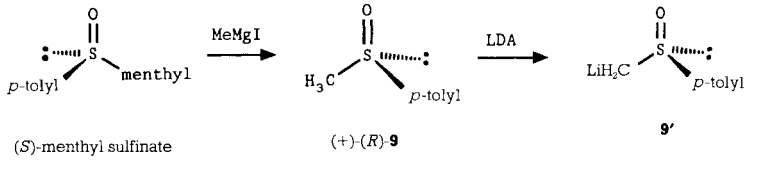
Scheme 1



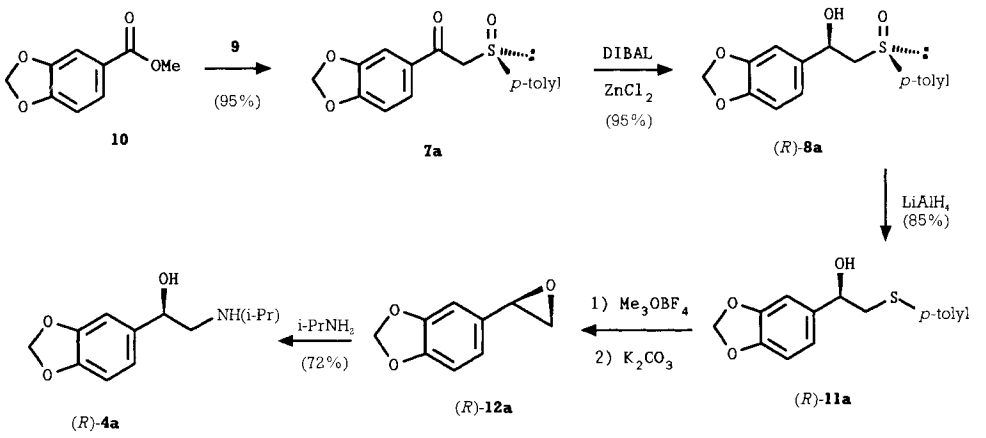
Scheme 2



Scheme 3



Scheme 4

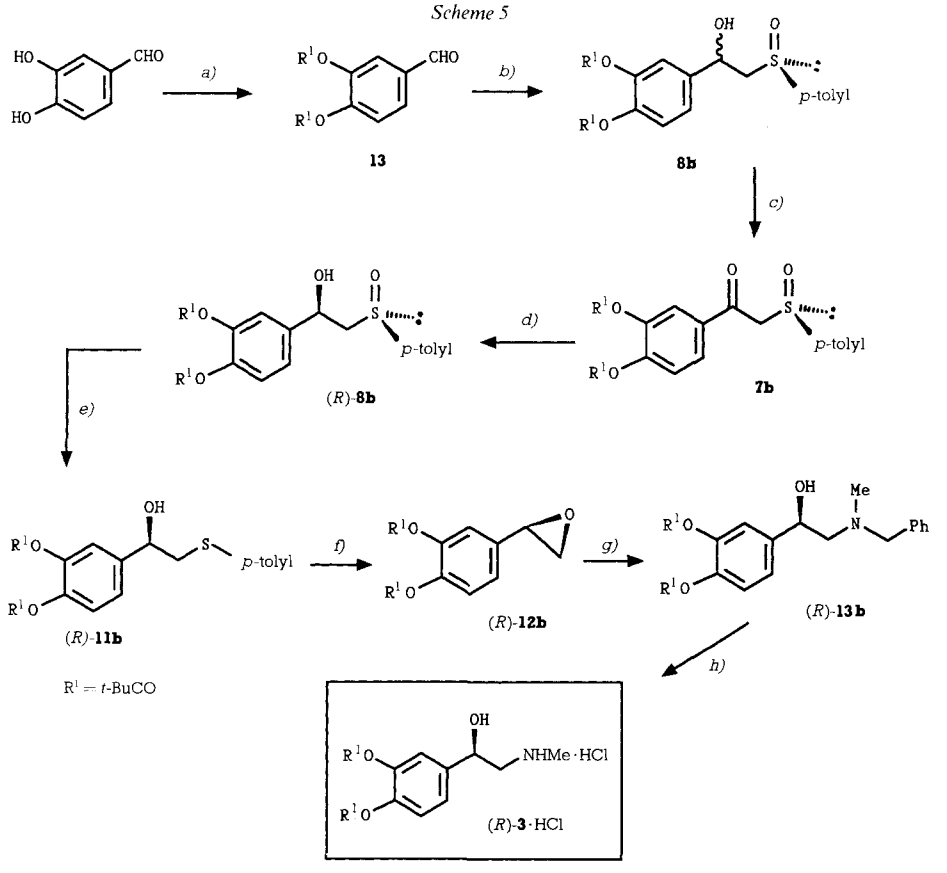


10 7a (*R*)-**8a** (*R*)-**11a** (*R*)-**12a** (*R*)-**4a**

Isoproterenol Analogue **4a**. Thus, **7a** is obtained in one step and 95% yield [10] on displacement of the MeO group of aromatic ester **10** by anion **9′** (*Scheme 4*). Reduction of **7a** with diisobutylaluminium hydride (DIBAL) at −78° in the presence of 1 equiv. of dry $ZnCl_2$ then affords the (1*R*,*R*)-hydroxy sulfoxide (*R*)-**8a** in 95% yield and with a diastereoselectivity of at least 98% (200-MHz ^{1}H-NMR spectrum: only 1 diastereoisomer). According to [7] [8], one can anticipate that the configuration at C(1) is (*R*). After reduction of (*R*)-**8a** into hydroxy sulfide (*R*)-**11a** using $LiAlH_4$ (85% yield), the oxirane (*R*)-**12a** is obtained in the usual way by treatment of (*R*)-**11a** with Me_3OBF_4 in $MeNO_2$ (0°) followed, after evaporation of $MeNO_2$, by addition of K_2CO_3 (1–2 equiv.) in MeOH/H_2O 1:4 and CH_2Cl_2. After 12 h, the crude oxirane (*R*)-**12a** is obtained as a 1:1 mixture with the methyl *p*-tolyl sulfide and is used directly for the condensation with i-$PrNH_2$. In MeOH as solvent, the desired regioisomer (*R*)-**4a** is the main product (72%) and has thus been obtained in optically pure state in 6 steps and 50% overall yield. Its enantiomer (*S*)-**4a** is available from hydroxy sulfoxide (*S*)-**8a** obtained in turn by DIBAL reduction of **7a**.

*Di-O-pivaloylepinephrine (−)-***3**. Because of the presence of the two pivaloyloxy groups on the aromatic ring, the desired keto sulfoxide **7b** had to be synthesized in 2 steps as follows. Addition of anion **9′** to aromatic aldehyde **13** affords hydroxy sulfoxide **8b** in 85% yield as a 3:2 mixture of the two diastereoisomers (*Scheme 5*). Therefore, they are oxidized using freshly prepared MnO_2 in CH_2Cl_2 to the desired keto sulfoxide **7b** (90% yield) which is then reduced diastereoselectively with DIBAL at −78° in the presence of 1 equiv. of dry $ZnCl_2$ to (1*R*,*R*)-hydroxy sulfoxide (*R*)-**8b** in 85% yield and with a diastereoselectivity of at least 98% (200-MHz ^{1}H-NMR spectrum only one diastereoisomer). The (*R*)-configuration at C(1) is again assigned according to known results [7] [8]. Because of the presence of the two ester groups in (*R*)-**8b**, reduction is achieved with Al-Hg amalgam in THF/H_2O at room temperature providing hydroxy sulfide (*R*)-**11b** in 75% yield. Using the usual method (see above), oxirane (*R*)-**12b** is then obtained in 2 steps and 90% yield. As the regioselectivity observed upon condensation of i-$PrNH_2$ on oxirane (*R*)-**12a** in the above synthesis was not high enough (72% of the desired regioisomer (*R*)-**4a** and 28% of the other), we decided to increase the steric demand of the amine

Scheme 5



a) *t*-BuCOCl/Et_3N. *b*) **9**', THF, −78 to −50°. *c*) MnO_2, CH_2Cl_2. *d*) DIBAL/$ZnCl_2$, THF. *e*) Al-Hg, THF/H_2O. *f*) Me_3OBF_4, $MeNO_2$; K_2CO_3, MeOH/H_2O/CH_2Cl_2. *g*) Me(PhCH_2)NH, THF. *h*) 10% Pd/C, EtOH/HCl.

and, therefore, to use *N*-methylbenzylamine instead of $MeNH_2$. Under these conditions, crude oxirane (*R*)-**12b** afforded 88% of the desired regioisomer (*R*)-**4b**. Poor regioselectivity has already been observed in the case of condensation of an amine upon aromatic epoxides [11]. After debenzylation, using Pd/C and H_2, di-*O*-pivaloylepinephrine (*R*)-**3** was obtained.

The (1*S*,*R*)-diastereoisomer (*S*)-**8b** is obtained from **7b** like (*R*)-**8b** in identical yield and diastereoselectivity (85% and 98%) using DIBAL at −78° (without $ZnCl_2$). Analogous transformations *via* (*S*)-**11b** (75%), (*S*)-**12b**, and (*S*)-**4b** (84%) then gave (*S*)-**3**. Therefore, the described method leads to (−)-(*R*)- or (+)-(*S*)-di-*O*-pivaloylepinephrine in 8 steps and a total yield of 20%.

We wish to thank *Pos-Alcon*, France, and *Alcon-R&D*, USA, for financial support.

Experimental Part

General. All reactions were performed under Ar. $LiAlH_4$ was purchased from *Janssen* and BuLi soln. from *Merck AG*. THF was distilled from Na/benzophenone and Et_2O from $LiAlH_4$. $MeNO_2$ and amines were distilled over $CaSO_4$ and KOH, resp. and then stored over molecular sieves. Reagent-grade MeOH from *Carlo Erba* was used without purification, and CH_2Cl_2 (*Carlo Erba*) was distilled over CaH_2 and stored over molecular sieves. Piperonylic acid (= 3,4-(methylenedioxy)benzoic acid) and 3,4-dihydroxybenzaldehyde were purchased from *Aldrich* and used without purification. $ZnCl_2$ from *Fluka* was dried under vacuum before use. Column chromatography: silica gel (230–400 mesh) from *Merck*; FC = flash chromatography. M.p.: uncorrected; *Reichert* microscope. $[\alpha]_D^{25}$: *Perkin-Elmer-241-MC* polarimeter; *c* in g/100 ml. IR spectra: *Perkin Elmer 257*; in cm^{-1}. ^{1}H- and ^{13}C-NMR spectra: *Bruker WP-200SY* (200 MHz) and *AC 200* (200 MHz); δ values in ppm rel. to internal TMS, coupling constants (*J*) in Hz.

1. *(R)-Methyl* p-*Tolyl Sulfoxide* (**9**) is prepared following the known procedure [9].

2. *(R)-1-[3',4'-(Methylenedioxy)phenyl]-2-(*p-*tolylsulfinyl)ethan-1-one* (**7a**). BuLi in hexane (1.43M; 4.66 ml, 6.6 mmol) is added slowly at −50° to a soln. of anh. $(i\text{-}Pr)_2NH$ (1.03 ml, 6.6 mmol) in anh. THF (12 ml). After 20 min stirring, the temp. is allowed to reach −35°, and **9** (513 mg, 3.3 mmol) in anh. THF (8 ml) is added dropwise. The resulting mixture is stirred for 1 h and the temp. allowed to reach 0°. After cooling again to −35°, methyl piperonylate (900 mg, 5 mmol) in anh. THF (10 ml) is added dropwise. The resulting mixture is stirred for 4 h and the temp. allowed to reach r.t. After addition of sat. NH_4Cl soln. (50 ml), the org. phase is separated, the aq. phase acidified (pH 3–4) and extracted with CH_2Cl_2 (3 × 30 ml), and the combined phase dried ($MgSO_4$) and evaporated. Filtration over activated charcoal gave crude **7a** (700 mg, 90%). Pale yellow amorphous solid. ^{1}H-NMR (200 MHz, $CDCl_3$): 2.4 (*s*, CH_3); 4.35 (*AB*, $J_{AB} = 14$, $\Delta\nu = 60$, 2 H); 6.05 (*s*, CH_2); 6.82 (*d*, *A* of *AMX*, $J_{AM} = 8$, 1 H); 7.3 (*d*, *A* of $(AB)_2$, $J_{AB} = 9$, 2 H); 7.33 (*d*, *X* of *AMX*, $J_{MX} = 1.5$, 1 H); 7.47 (*dd*, *M* of *AMX*, $J_{AM} = 8$, $J_{MX} = 15$, 1 H); 7.55 (*d*, *B* of $(AB)_2$, $J_{AB} = 9$, 2 H).

3. *(R,R)-1-[3',4'-(Methylenedioxy)phenyl]-2-(*p-*tolylsulfinyl)ethan-1-ol* ((*R*)-**8a**). To a soln. of crude **7a** (1 g, 3.3 mmol) in anh. THF (15 ml) at r.t. is added a soln. of anh. $ZnCl_2$ (540 mg, 1.2 equiv.) in anh. THF (15 ml), and the mixture is stirred for 30 min at r.t. After cooling to −78°, 1M DIBAL (4,6 ml, 4.6 mmol) is added dropwise. After addition, the mixture is stirred for 1 h at −78°. Then, MeOH (40 ml) is added and the temp. allowed to reach r.t. After addition of H_2O (200 ml) and extraction with CH_2Cl_2 (5 × 50 ml), the combined org. phases are dried ($NaSO_4$) and evaporated: crude (*R*)-**8a** (930 g, 93%). ^{1}H-NMR (200 MHz, $CDCl_3$): only 1 diastereoisomer is detected. 2.42 (*s*, CH_3); 3.02 (*AB* of *ABX*, $J_{AB} = 13$, $J_{AX} \approx 2$, $J_{BX} \approx 9$, $\Delta\nu = 50$, 2 H); 4.25 (br. *s*, OH); 5.3 (*dd*, *X* of *ABX*, 1 H); 5.95 (*s*, CH_2); 6.8 (*m*, 3 arom. H); 7.32 (*d*, *A* of $(AB)_2$, $J = 9$, 2 H); 7.67 (*d*, *B* of $(AB)_2$, 2 H).

Diastereoisomer (*S*)-**8a** from **7a** by DIBAL reduction (without $ZnCl_2$): ^{1}H-NMR (200 MHz, $CDCl_3$): 2.75 (*A* of *ABX* no overlap); 5.15 (*X* of *ABX* no overlap); 6.05 (*s*, CH_2).

4. *(R)-1-[3',4'-(Methylenedioxy)phenyl]-2-(*p-*tolylthio)ethan-1-ol* ((*R*)-**11a**). To a suspension of $LiAlH_4$ (420 mg, 1.1 mmol) in anh. THF (10 ml) at 0° is added dropwise a soln. of (*R*)-**8a** (167 mg, 0.5 mmol) in anh. Et_2O (5 ml). Stirring is maintained for 6 h at 0°. When no (*R*)-**8a** remains (TLC), a sat. NH_4Cl soln. (20 ml) is added, and the aq. phase is extracted with Et_2O (4 × 20 ml). The combined org. phase is dried ($MgSO_4$) and evaporated. Crude (*R*)-**11a** is purified by chromatography (Et_2O/hexane 1:1): 108 mg, 75%. Colorless oil. $[\alpha]_D = +62.8$ (*c* = 8.03, acetone). ^{1}H-NMR (200 MHz, $CDCl_3$): 2.32 (*s*, CH_3); 2.85 (*d*, OH); 3.07 (*AB* of *ABX*, $J_{AB} = 12$, $J_{AX} \approx 10$, $J_{BX} \approx 3$, $\Delta\nu_{AB} = 23$, 2 H); 4.55 (*dt*, *X* of *ABX*, 1 H); 5.95 (*s*, CH_2); 6.72 (*s*, 2 arom. H); 6.82 (*s*, 1 arom. H); 7.1 (*d*, *A* of $(AB)_2$, $J_{AB} = 9$, 2 H); 7.35 (*d*, *B* of $(AB)_2$, 2 H). Anal. calc. for $C_{16}H_{16}O_3S$ (288.35): C 66.64, H 5.59; found: C 66.88, H 5.79.

5. *(R)-2-[3',4'-(Methylenedioxy)phenyl]oxirane* ((*R*)-**12a**). To a soln. of (*R*)-**11a** (181 mg, 0.6 mmol) in anh. $MeNO_2$ (5 ml) is added at 0° Me_3OBF_4 (112 mg, 0.8 mmol; weighted under Ar). The mixture is stirred for 1 h at 0°. When no (*R*)-**11a** remains (TLC), the mixture is evaporated. To the residue, dissolved in CH_2Cl_2 (15 ml), is added dropwise 0.4M K_2CO_3 in MeOH/H_2O 1:4 (1.9 ml, 1.2 equiv.). The mixture is stirred overnight at r.t. The aq. phase is extracted with CH_2Cl_2 (4 × 10 ml) and the combined org. phase dried (Na_2SO_4) and evaporated. The crude product is a 1:1 mixture of the desired (*R*)-**12a** and of methyl *p*-tolyl sulfide and is rapidly used without purification. ^{1}H-NMR (200 MHz, $CDCl_3$): (*R*)-**12a**: 2.75 (*dd*, *A* of *AMX*, $J_{AM} = 5$, $J_{AX} = 2$, 1 H); 3.1 (*dd*, *M* of *AMX*, $J_{MA} = 5$, $J_{MX} = 4$, 1 H); 3.78 (*dd*, *X* of *AMX*, $J_{XM} = 4$, $J_{XA} = 2$, 1 H); 5.95 (*s*, CH_2); 6.7 (*m*, 3 arom. H); sulfide: 2.3 (*s*, CH_3); 2.45 (*s*, CH_3); 7.15 (*AB*, 4 arom. H).

6. *(R)-(Isopropylamino)-1-[3',4'-(methylenedioxy)phenyl]ethan-1-ol* ((*R*)-**4a**). To a soln. of crude (*R*)-**12a**/methyl *p*-tolyl sulfide (175 mg, 0.57 mmol of (*R*)-**12a**) in MeOH (10 ml) is added an excess of $i\text{-}PrNH_2$ (1 ml). The

mixture is refluxed for 4 h. After evaporation, the crude product is acidified (50 ml of 10% HCl soln.) and extracted with AcOEt (2 × 10 ml). Solid Na_2CO_3 is then added to the aq. phase which is extracted with AcOEt (5 × 10 ml). The last five combined org. phases are dried (Na_2SO_4) and evaporated: 110 mg (87%) of pale brown liquid, consisting of (*R*)-**4a**/regioisomer 73:27 (^{1}H-NMR: *X* of *ABX* of (*R*)-**4a** is deshielded relative to regioisomer, while the reverse happens to *AB*). ^{1}H-NMR (200 MHz, $CDCl_3$): (*R*)-**4a**: 1.02 (*d*, $(CH_3)_2CH$); 2.7 (*m*, *AB* of *ABX*, overlapped with with *sept.* $J_{AB} = 12$, $J_{AX} \approx 9$, $J_{BX} \approx 3$, $\Delta\nu_{AB} = 30$, 2 H, $(CH_3)_2CH$); 3 (br., OH); 4.6 (*dd*, *X* of *ABX*, 1 H); 5.95 (*s*, CH_2); 6.77 (*s*, 2 arom. H); 6.85 (*s*, 1 arom. H); regioisomer: 0.95 (*d*, $(CH_3)_2CH$); 2.7 (*sept.*, $(CH_3)_2CH$, overlapped with (*R*)-**4a**); 3.5 (*AB* of *ABX*, $J_{AB} = 10$, $J_{AX} \approx 8$, $J_{BX} \approx 4$, $\Delta\nu_{AB} = 35$, 2 H); 3.75 (*dd*, *X* of *ABX*, 1 H); 5.95 (*s*, CH_2, overlapped with (*R*)-**4a**); 6.7 (*m*, 3 arom. H).

7. *3,4-Bis[(pivaloyl)oxy]benzaldehyde* (**13**). To a soln. of 3,4-dihydroxybenzaldehyde (4.4 g, 92 mmol) in anh. THF (75 ml) are added an excess of Et_3N (75 ml) and then, dropwise, 2 equiv. of pivaloyl chloride (7.8 ml, 63 mmol). The temp. is maintained at 25°, and after addition, the mixture is stirred 3 h. After filtration of the precipitate and evaporation, the crude product is purified by FC (Et_2O/hexane 1:1): 8.8 g (90%) of **13**. Yellow oil. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.36 (*s*, *t*-Bu); 1.37 (*s*, *t*-Bu); 7.34 (*d*, *A* of *ABX*, $J_{AB} = 8.5$, 1 H); 7.68 (*d*, *X* of *ABX*, $J_{BX} = 2$, 1 H); 7.77 (*dd*, *B* of *ABX*, $J_{AB} = 8.5$, $J_{BX} = 2$, 1 H); 9.97 (*s*, CHO).

8. *(RS,R)-1-{3',4'-Bis[(pivaloyl)oxy]phenyl}-2-(*p*-tolylsulfinyl)ethan-1-ol* (**8b**; 2 Diastereoisomers). To a soln. of lithium diisopropylamide (16.7 mmol), prepared at −60° from anh. $(i\text{-Pr})_2NH$ (2.35 ml), anh. THF (30 ml), and BuLi (1.6M; 10.4 ml) is added dropwise at −40° a soln. of **9** (2.34 g, 15.2 mmol) in anh. THF (30 ml). The temp. is rised to 0° and the mixture stirred for 1 h. After cooling to −78°, this mixture is added dropwise, through a canula, into a soln. (cooled at −78°) of **13** (5.6 g, 15.2 mmol) in anh. THF (35 ml). The mixture is then stirred for 4 h and the temp. allowed to reach −50°. Then, a sat. NH_4Cl soln. (50 ml) is added dropwise and the temp. allowed to reach r.t. After evaporation of the THF, the remaining aq. phase is extracted with CH_2Cl_2 (5 × 50 ml), the combined org. phase dried ($NaSO_4$) and evaporated, and the residue purified by FC (Et_2O/hexane 7:3): white powder (5.2 g, 75%). M.p. 105–106°. IR ($CHCl_3$): 3600, 3400, 1750. ^{1}H-NMR (200 MHz, $CDCl_3$); 2 diastereoisomers I/II, ratio 65:35): 1.33 (1*s*, 2*t*-Bu); 2.43 (2*s*, arom. CH_3); 3.10 (2 *AB* of 2 *ABX*); 4.22 (*d*, OH, diast. II); 4.45 (*d*, OH, diast. I); 5.35 (*dt*, *X* of *ABX*, diast. II); 5.44 (*dt*, *X* of *ABX*, diast. I); 7.1–7.6 (*m*, 7 arom. H). Anal. calc. for $C_{25}H_{32}O_6S$: C 65.19, H 7.01; found: C 64.98, H 6.83.

9. *(R)-1-{3',4'-Bis[(pivaloyl)oxy]phenyl}-2-(*p*-tolylsulfinyl)ethan-1-one* (**7b**). Activated MnO_2 is freshly prepared according to [12]. To a soln. of **8b** (see *Exper. 8*; 7.4 g, 16 mmol) in CH_2Cl_2 (250 ml) are added 10 equiv. of MnO_2 (14 g, 160 mmol). The suspension is stirred for 2 h. If necessary, more MnO_2 must be added until no **8b** remains (TLC). After filtration over a 1-mm layer of silica gel, the precipitate is carefully rinsed with Et_2O. The combined org. phase is evaporated and the crude product purified by FC (Et_2O/CH_2Cl_2 3:1): colorless liquid (5.9 g, 80%). IR ($CHCl_3$): 1710, 1750. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.35 (*s*, *t*-Bu); 1.36 (*s*, *t*-Bu); 2.40 (*s*, CH_3); 4.39 (*AB*, $J_{AB} = 14$, $\Delta\nu = 49$, 2 H); 7.24 (*d*, *A* of *ABX*, $J_{AB} = 8.5$, 1 H); 7.31 (*A* of $(AB)_2$, $J_{AB} = 8$, 2 H of *p*-tolyl); 7.57 (*B* of $(AB)_2$, $J_{AB} = 8$, 2 H); 7.63 (*d*, *X* of *ABX*, $J = 2$, 1 H); 7.75 (*dd*, *B* of *ABX*, $J = 8.5$, 2, 1 H).

10. *(R,R)-1-{3',4'-Bis[(pivaloyl)oxy]phenyl}-2-(*p*-tolylsulfinyl)ethan-1-ol* ((*R*)-**8b**): *Reduction with $ZnCl_2$.* As described in *Exper. 3*, but with 13 mmol (6.1 g) of **7b**. Crude (*R*)-**8b** is purified by FC (Et_2O/CH_2Cl_2 3:1): colorless liquid (5.4 g, 90%). $[\alpha]_D = +40.8$ ($c = 3.31$, acetone). IR ($CHCl_3$): 3600, 3400, 1750. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.33 (*s*, *t*-Bu); 1.34 (*s*, *t*-Bu); 2.42 (*s*, CH_3); 3.05 (*AB*, of *ABX*, $J_{AB} = 13$, $J_{AX} \approx 2.5$, $J_{BX} \approx 10$, $\Delta\nu_{AB} = 39$, 2 H); 4.5 (*d*, $J = 1.5$, OH); 5.41 (*X* of *ABX*, 1 H); 7.1–7.6 (*m*, 7 arom. H). Anal. calc. for $C_{25}H_{32}O_6S$: C 65.19, H 7.01; found: C 64.48, H 6.79.

11. *(S,R)-1-{3',4'-Bis[(pivaloyl)oxy]phenyl}-2-(*p*-tolylsulfinyl)ethan-1-ol* ((*S*)-**8b**): *Reduction without $ZnCl_2$.* To a soln. of **7b** (13 g, 28.5 mmol) in anh. THF (200 ml) at −78° is added dropwise 1M DIBAL (57 ml, 57 mmol). Then the mixture is stirred for 1 h more, and MeOH (50 ml) is added followed by H_2O (300 ml). The temp. is allowed to reach r.t. After extraction with CH_2Cl_2 (5 × 200 ml), the combined phase is dried (Na_2SO_4) and evaporated. Crude (*S*)-**8b** is purified by FC (Et_2O/CH_2Cl_2 3:1): colorless liquid (11.2 g, 90%). $[\alpha]_D = +105.3$ ($c = 1.01$, acetone). IR ($CDCl_3$): 3600, 3400, 1750. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.32 (*s*, *t*-Bu); 1.33 (*s*, *t*-Bu); 2.44 (*s*, CH_3); 3.00 (*AB* of *ABX*, $J_{AB} = 13.5$, $J_{AX} \approx 17$, $J_{BX} \approx 10.5$, $\Delta\nu = 78$, 2 H); 4.45 (*d*, $J = 2.8$, OH); 5.23 (*X* of *ABX*, 1 H); 7.0–7.6 (*m*, 7 arom. H). Anal. calc. for $C_{25}H_{32}O_6S$: C 65.19, H 7.01; found: C 65.08, H 7.04.

12. *(R)-1-{3',4'-Bis[(pivaloyl)oxy]phenyl}-2-(*p*-tolylthio)ethan-1-ol* ((*R*)-**11b**). Commercially available Al foil is cut in pieces (*ca.* 1 cm^2). Each of them is dipped in 1.2N HCl, abundantly rinsed with H_2O, dipped in an $HgCl_2$ soln. (2% in weight) for 15 s, rinsed with H_2O, then in Et_2O, and immediately used. A mixture of (*R*)-**8b** (4.5 g, 9.8 mmol), THF (270 ml), H_2O (30 ml), and Al-Hg amalgam (13 g, 50 equiv.) is stirred at r.t. for 12 h. The reaction is

followed by TLC, and more amalgam is added if necessary. After filtration of the grey precipitate, the filtrate is evaporated. The aq. phase is then extracted with Et_2O (5 × 30 ml) and the org. phase dried (Na_2SO_4) and evaporated. Crude (*R*)-**11b** was purified by FC (Et_2O/hexane 1:1): pale yellow oil (2.8 g, 65%). IR ($CDCl_3$): 3600, 3400, 1750. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.34 (*s*, *t*-Bu); 1.35 (*s*, *t*-Bu); 2.35 (*s*, CH_3); 2.99 (*s*, OH); 3.1 (*AB* of *ABX*, $J_{AB} = 14$, $J_{AX} \approx 10$, $J_{BX} \approx 3.5$, $\Delta\nu_{AB} = 55$, 2 H); 4.65 (*X* of *ABX*, 1 H); 7.75 (*m*, 7 arom. H).

13. *(S)-1-{3',4'-Bis[(pivaloyl)oxy]phenyl}-2-(p-tolylsulfinyl)ethan-1-ol* ((*S*)-**11b**) is obtained as described in *Exper. 12* from (*S*)-**8b**. Yield 65%.

14. *(R)-2-{3',4'-Bis[(pivaloyl)oxy]phenyl}oxirane* ((*R*)-**12b**) is obtained as described in *Exper. 5*, but with 1.5 mmol (655 mg) of (*R*)-**11b**. The 1:1 mixture (*R*)-**12b**/methyl *p*-tolyl sulfide is clearly identified by the $J_{AB} = 5.5$ and is rapidly used for the next step. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.35 (*s*, 2 *t*-Bu); 2.76 (*A* of *ABX*, $J_{AB} = 5.5$, $J_{AX} \approx 2.5$, $\Delta\nu = 75$, 1 H); 3.14 (*B* of *ABX*, $J_{AB} = 5.5$, $J_{BX} \approx 4$, $\Delta\nu_{AB} = 75$, 1 H); 3.86 (*X* of *ABX*, 1 H); 7.10 (*m*, 3 arom. H).

15. *(S)-2-{3',4'-Bis[(pivaloyl)oxy]phenyl}oxirane* ((*S*)-**12b**) is obtained as described in *Exper. 14*.

16. *(R)-2-(N-Benzyl-N-methylamino)-1-{3',4'-bis[(pivaloyl)oxy]phenyl}ethan-1-ol* ((*R*)-**13b**.) To a soln. of crude (*R*)-**12b**/methyl *p*-tolyl sulfide (870 mg, 19 mmol of (*R*)-**12b**) in THF (2 ml) is added ($PhCH_2$)MeNH (0.3 ml, 235 mmol, 1.2 equiv.), and the mixture is refluxed for 6 h. After evaporation, the crude product is purified by chromatography (CH_2Cl_2 to eliminate methyl *p*-tolyl sulfide, then CH_2Cl_2/Et_2O 4:1): colorless liquid (587 mg, 70%). $[\alpha]_D = -26.7$ ($c = 4.13$, acetone). ^{1}H-NMR (200 MHz, $CDCl_3$); 12% of regioisomer present; (*R*)-**13b**: 1.34 (*s*, *t*-Bu); 1.35 (*s*, *t*-Bu); 2.31 (*s*, CH_3N); 2.57 (*AB*, of *ABX*, 2 H); 3.56 (*AB*, $J_{AB} = 13$, $\Delta\nu = 37$, $PhCH_2$); 4.74 (*X* of *ABX*, 1 H); 7–7.5 (*m*, 8 arom. H).

17. *(S)-2-(N-Benzyl-N-methylamino)-1-{3',4'-bis[(pivaloyl)oxy]phenyl}ethan-1-ol* ((*S*)-**13b**) is obtained as described in *Exper. 16* from (*S*)-**12b**. Yield 70%. Colorless liquid. $[\alpha]_D = +20.4$ ($c = 4{,}48$, acetone). ^{1}H-NMR: 16% of regioisomer present; other data identical to the one of (*R*)-**13b**.

18. *(R)-3,4-Di-O-pivaloylepinephrine Hydrochloride* (= *(R)-1-{3',4'-Bis[(pivaloyl)oxy]phenyl}-2-(methylamino)ethan-1-ol Hydrochloride*; (*R*)-**3**·HCl). To a soln. of (*R*)-**13b** (560 mg, 1.27 mmol) in EtOH (25 ml) and 1 equiv. of 1.2N HCl (1.06 ml, 1.27 mmol) is added a small spatula of 10% Pd/C. The stirred mixture is hydrogenated overnight under 15 atm H_2. Filtration and evaporation give a white powder (443 mg, 90%). $[\alpha]_D = -19.2$ ($c = 1.56$, acetone). ^{1}H-NMR (200 MHz, (D_6)acetone/D_2O): 5% of regioisomer present; (*R*)-**3**·HCl: 1.30 (*s*, *t*-Bu); 1.31 (*s*, *t*-Bu); 2.85 (*s*, CH_3N); 3.31 (*AB* of *ABX*, $J_{AB} = 12.5$, $J_{AX} \approx 10$, $J_{BX} \approx 3$, $\Delta\nu_{AB} = 40$, 2 H); 5.24 (*X* of *ABX*, 1 H); 7.17 (*d*, *A* of *ABX*, $J_{AB} = 8.5$, 1 H); 7.31 (*d*, *X* of *ABX*, $J_{BX} = 2$, 1 H); 7.40 (*dd*, *B* of *ABX*, $J_{AB} = 8.5$, $J_{AX} = 2$, 1 H).

19. *(S)-3,4-Di-O-pivaloylepinephrine Hydrochloride* ((*S*)-**3**·HCl) is obtained as described in *Exper. 18* from (*S*)-**13b**. White powder. $[\alpha]_D = +13.5$ ($c = 1.40$, acetone). ^{1}H-NMR (200 MHz, (D_6)acetone/D_2O): 16% of regioisomer present.

REFERENCES

[1] A. La Manna, P. Zaffaroni, *Farmace (Pavia)* **1960,** *15,* 3.
[2] A. Hussain, S. E. Truelove, Patent No. 7331597 (August 31, 1973).
[3] N. S. Bodor, S. S. Yuan, Patent No. 7721171 (July 8, 1977).
[4] 'Medical Chemistry, a Biochemical Approach', Ed. T. Nogrady, Oxford University Press, Oxford, 1985.
[5] H. P. Märki, Y. Crameri, R. Eigenmann, A. Krasso, H. Ramuz, K. Bernauer, M. Goodman, K. L. Melmon, *Helv. Chim. Acta* **1988,** *71,* 320.
[6] M. C. Simon-Wermeister, thèse, Strasbourg, 1990.
[7] G. Solladié, C. Greck, G. Demailly, A. Solladié-Cavallo, *Tetrahedron Lett.* **1982,** *23,* 5047.
[8] G. Solladié, G. Demailly, G. Greck, *Tetrahedron Lett.* **1985,** *26,* 435.
[9] G. Solladié, *Synthesis* **1981,** 185; G. Solladié, J. Hutt, A. Girardin, *ibid.* **1987,** 173.
[10] G. Solladié, G. Demailly, C. Greck, *J. Org. Chem.* **1985,** *50,* 1552.
[11] M. Chini, P. Crotti, F. Macchia, *Tetrahedron Lett.* **1990,** *31,* 5641.
[12] J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen, T. Walker, *J. Chem. Soc.* **1952,** 1104.