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A Two-step Asymmetric Synthesis of Pure *Trans-(R,R)*-Diaryl-epoxides.

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Abstract : Pure *trans*-(*R,R*)-diaryl-epoxides are obtained in two steps and under aprotic conditions using Eliel's oxathiane as the chiral auxiliary. The enantiomeric excesses, determined by chiral HPLC, are 97.9% to 99.9% and the oxathiane is recovered in 78% to 92% yield and may thus be re-used. Copyright © 1996 Elsevier Science Ltd

Johnson and coll. in 1961[1] were the first to report that sulfur-ylides could react with substituted benzaldehydes to give epoxides. Since then the method has been extensively developed[2-4] and enantiomerically enriched diaryl-epoxides were prepared from sulfur-ylides[5] using either biphasic solid/liquid conditions[6], phase transfer conditions[7,8,9a] or aprotic Rh(II) catalyzed conditions[9b] in either 43-47% ee[6], 64-96% ee[7], 0%-100% ee[8], 12%-42% ee[9a] and 11% ee[9b], depending on the nature of the substituents and on the chiral auxiliary.

During our work on a short synthesis of adrenergic drugs having the desired *R* configuration[10] we have found that oxathiane **1** under aprotic conditions could provide monoaryl-epoxides of high enantiomeric purities (92%-98% ee)[11]. We therefore, decided to extend this method to diaryl-epoxides as intermediates for the syntheses of diaryl chiral ligands and report here highly enantioselective synthesis of pure *trans*-(*R,R*)-diaryl-epoxides **4a-4e**.

Results

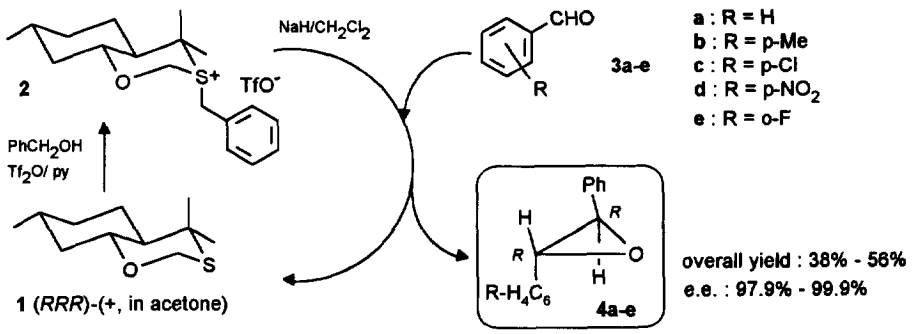
Enantioselective synthesis of trans-R,R-epoxides **4a-4e**

The chiral auxiliary, the (*R,R,R*)-(+)-oxathiane **1**, was prepared in 30% yield from inexpensive technical (+)-(*R*)-pulegone using the known literature procedure[12] and the enantiomeric purity was determined (by chiral GC on FS-Lipodex E) to be 100%. It must be noted that, in the synthesis described below, the auxiliary is recovered.

The sulfonium salt **2** was obtained from (*R,R,R*)-(+)-1,3-oxathiane **1** in high yield (90% crude and 67% after

crystallization from AcOEt) using the triflate method.[13] Using 200 MHz ^{1}H NMR one may conclude that only one isomer was formed and that the configuration of the benzyl group is axial in accord with previous results.[14] Reaction of the sulfonium salt **2** with various *para*- and *ortho*-substituted benzaldehydes under aprotic conditions, Scheme 1, then afforded the desired epoxides **4a-4e** in 76% to 84% isolated yields, Table 1. Somewhat lower yield (56%) was obtained for epoxide **4b**, due to non-optimized chromatographic conditions as indicated by the 82% yield in recovered oxathiane and the 90% of conversion determined (^{1}H NMR) on the crude product of the reaction. The chiral auxiliary **1** was recovered in high yield (78%-90%) and could thus be re-used.

Scheme 1



It is worth noting that the *cis*-epoxides, which are usually formed in up to 6%-20%,[7,9] were not observed under these conditions. The enantiomeric purities, determined using ^{1}H NMR and chiral HPLC, ranged between 97.9% and 99.9% (*cf.* below and Table 1)

Table 1 : Asymmetric synthesis of **4a-e** from the sulfonium salt **2** and aldehydes **3a-e**.

3 R	Epoxides : 4 e.e.% Y%	HPLC	NMR	oxathiane : 1 Y%	$[\alpha]_D^{22°}$, EtOH	Conf.	Comp.
H	80%	99.0%	a	87%	+ 296 (1.01)	*RR*	**4a**
p-Me	56%	99.6%	a	82%	+303 (1.16)	*RR*	**4b**
p-Cl	76%	99.0%	a	78%	+ 274 (1.19)	*RR*	**4c**
p-NO_2	77%	97.9%	> 97%	90%	+ 303 (1.03)	*RR*	**4d**
o-F	84%	99.9%	a	92%	+218 (1.06)	*RR*	**4e**

a) Only one enantiomer detected in the ^{1}H NMR spectra.

Determination of the enantiomeric purities and of the configuration

NMR : Through progressive additions of small amounts of $Eu(hfc)_3$ into $CDCl_3$ solutions of the racemic[15] epoxide **4a**, the singlet corresponding to the two isochronous ring-protons was split into two A_2 systems but,

the non-equivalence being small (0.02 ppm), the determination of the enantiomeric ratio (Table 1) was difficult. In racemic[15] epoxides **4b**, **4c**, **4d** and **4e** the two ring-protons are already anisochronous (AB system), upon addition of $Eu(hfc)_3$ the AB system splitted into two AB systems or one AB and one A2. The non-equivalences observed between the two systems were small, respectively 0.07 ppm (two AB systems), 0.06 ppm (one AB system and one A_2 system), 0.08 ppm (two AB systems), 0.05 ppm (two AB systems), and the determination of the enantiomeric ratios (Table 1) were possible but difficult. The enantiomeric purities were thus estimated to be very high on the basis of the symetrical shapes of the lines, only in the case of epoxide **4d** was the other enantiomer observed as a small shoulder. Confronted by these difficulties chiral HPLC was used.

HPLC : All the samples obtained from the asymmetric syntheses were HPLC pure. The enantiomers of epoxides **4a-e** were successfully separated on Chiralcel OD columns and comparison with racemic samples[15] allowed unambiguous determination of the enantiomeric purities which happened to be very high, ranging between 97.9% and 99.9%, Table 1. The conditions used are given on Table 2.

Table 2 : HPLC results, conditions and properties for compounds **4a-4e** obtained with chiracel OD column at room temperature

Compound	**4a**	**4b**	**4c**	**4d**	**4e**
% e.e.	99.0	99.6	99.0	97.9	99.9
Mobile phase	10% i-PrOH 90% n hexane	10% i-PrOH 90% n hexane	5% i-PrOH 90% n hexane	10% i-PrOH 90% n hexane	10% i-PrOH 90% n hexane
Flow rate (mL/min)	0.5	0.5	0.5	0.5	0.5
Rt (R,R), min	20.5	15.9	20.2	23.5	16.7
Rt (S,S), min	13.5	12.8	18.0	18.5	11.4
K'_1	1.25	1.13	2.00	2.08	0.90
K'_2	2.42	1.65	2.37	2.92	1.78
α	1.94	1.46	1.19	1.40	1.98
Rs	7.51	3.66	2.60	5.36	5.69

Configuration : The *R,R* configuration was assigned to the epoxides **4a-4e** on the basis of the positive sign of their rotation in EtOH as compared with literature results.[16] However large variations of the rotations have been observed with the nature of the solvent (as expected) but also with the solvent specifications, Table 3. This last behaviour (although expected, because of differences in additives) is usually not considered and leads to false optical purities when determined from calculated $[\alpha]_D$Max (Table 3). As an example : the calculated $[\alpha]_D$Max of **4a** in various EtOH ranges between +235 and +342.

Table 3 : Changes of [α] values of **4a-4e** with the solvent and specifications of the solvent.

Solvent		R = H **4a**	R = Me **4b**	R = Cl **4c**	R = NO_2 **4d**	R = o-F **4e**
EtOH (unspecified) from ref. 6,16	$[\alpha]_D$	+342 (1.11)		+ 362 (1.36)	+ 278 1.01)	
	e.e. %	100%		100%	100%	
	$[\alpha]_D$ Max	+342		+362	+278	
EtOH absol. (1% MeOH, 0.3% iPrOH) from ref. 8	$[\alpha]_D$	+169 (1.10)	+92 (0.7) [b]	+223 (1.35) [b]		
	e.e. %	72% [a]				
	$[\alpha]_D$ Max	+235				
EtOH anhyd. (5% iPrOH)	$[\alpha]_D$	+296 (1.01)	+302 (1.16)	+274 (1.19)	+303 (1.03)	+218 (1.06)
	e.e. %	99% [c]	99.6 [c]	99% [c]	97.9% [c]	99.9% [c]
	$[\alpha]_D$ Max	+299	+303	+277	+309	+218
PhH	$[\alpha]_D$	+205 (1.01)	+361 (1.01)	+337 (1.02)	+344 (1.00)	+258 (1.01)
	$[\alpha]_D$Max	+207	+362	+340	+351	+258

a) Determined by ^1H NMR with $Eu(hfc)_3$, *cf.* ref.[8]. b) Determined from literature $[\alpha]_D$ Max, *cf.* ref.[16]. c) Determined by HPLC (this work).

Conclusion

Pure *trans-(R,R)*-diaryl-epoxides having 97.9% to 99.9% e.e. may be synthesized in two steps and in high isolated yields (~ 56% overall yield) from Eliel's oxathiane **1**, provided NaH was used as base in CH_2Cl_2. The chiral auxiliary **1** is recovered in high yield (78-92%) and may thus be re-used.

Experimental Section

For ^1H (200 MHz when not specified) and ^{13}C (50 MHz) NMR spectra δ, in ppm, are referenced to TMS. Melting points are uncorrected. All starting materials were commercially available research-grade chemicals purchased from Aldrich and used without further purification. Et_2O was distilled from $LiAlH_4$ and CH_2Cl_2 from CaH_2. All reactions were run under argon. Silica gel 60 F_{254} was used for TLC and the spots were detected with UV. Flash chromatography was performed using silica gel 70-330 mesh from Merck. Microanalyses were performed in our Department. HPLC was performed with a Knauer HPLC pump 64 and Knauer Variable wavelength monitor, estimated at 254 nm, using an analytical chiral column : Chiralcel OD (25 cm x 4.6 mm I.D., Diacel, Japan). GC was performed with a Hwlett-Packard 5890 using a chiral column : FS-Lipodex E (0.25 mm I.D. x 25 m)

(+)-(*R,R,R*)-Oxathiane, 1 : White solid, mp. 32-35 °C. 30% overall yield from pulegone[12].$[\alpha]_D$ = +12 (c = 2, acetone), e.e. = 100% (using chiral GC, FS-Lipodex E)

Preparation of the sulfonium Triflate, 2

To a solution of pyridine (0.8 mL, 9.84 mmol) in CH_2Cl_2 (20 mL) cooled at -20°C, was added trifluoromethane

sulfonic anhydride (1.6 mL, 9.51 mmol). After stirring at -20°C for 15 mn., benzyl alcohol (0.5 mL, 4.83 mmol) was added dropwise, and stirring was maintained for 1h. A solution of oxathiane (1g, 4.99 mmol) in CH_2Cl_2 (4 mL) was, then, added, and the mixture stirred at -10°C for 4h. After addition of cold water (100 mL), the mixture was extracted with CH_2Cl_2 (5 x 20 mL). The combined organic layers were dried over $MgSO_4$, and the solvent was evaporated under vacuum. The residu was rinsed with anhydrous Et_2O : 95% yield of a **2/1** mixture (95/5) which could be used without purification.

Sulfonium salt, 2 : yield 67% after recrystallization from AcOEt ; white powder, m.p. 136-139°C. $[\alpha]_D$ = -222 (c = 1.04, $CHCl_3$). ^1H NMR ($CDCl_3$), one diastereomer, δ : 0.95 (d, J = 6.5, 3H), 1.1 (br t, J = 11, 2H), 1.3 (q, J = 11, 1H), 1.5 (m, 1H), 1.68 (s, 3H), 1.74 (s, 3H), 1.8 (m, 2H), 2.01 (br m, 1H), 3.8 (td, J = 10.5, 10.5, 4.5, 1H), 4.66 (br s, 2H), 4.8 (A of AB, d, J_{AB} = 12, 1H), 5.6 (B of AB, d, J_{AB} = 12, 1H), 7.38 (m, 3H), 7.48 (m, 2H). ^{13}C NMR ($CDCl_3$), δ : 21, 22, 23.5, 24, 31, 33.5, 36, 40, 43, 58, 71, 78, 127, 129.8, 130.1, 130.7. Anal. Calcd for $C_{19}H_{27}F_3S_2O_4$: C, 51.79 ; H, 6.18. Found : C, 51.53 ; H, 6.19.

Synthesis of Epoxides 4a-4e

To a suspension of NaH (73.5 mg, 3.06 mmol) in CH_2Cl_2 (10 mL) was added dropwise at -40°C a solution of the desired sulfonium salt (1g ; 2.27 mmol) in CH_2Cl_2 (5 mL). After 1h at -40°C, the desired aldehyde (359.7 mg, 2.38 mmol) in CH_2Cl_2 (5 mL) was added, and the mixture was stirred at -40°C for 24h or 48h. After addition of cold water (100 mL) the resulting mixture was extracted with CH_2Cl_2 (5 x 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The resulting pale yellow oil was analyzed by ^1H NMR before and after purification. The epoxides were then separated from the oxathiane by column chromatography.

Epoxide 4a : Y. 80% . White solid, mp. 61-63°C. Rf = 0.31 (hexane/CH_2Cl_2 7/3). $[\alpha]_D$ = + 296 (c = 1.01, EtOH) ; e.e = 99% (99.48/0.52, HPLC). ^1H NMR ($CDCl_3$), δ : 3.9 (s, 2H), 7.4 (m, 10H). ^{13}C NMR ($CDCl_3$), δ : 63, 125.5, 128.3, 128.5, 137. Anal. Calcd for $C_{14}H_{12}O$: C, 86.68 ; H, 6.16. Found : C, 86.45 ; H ; 6.32.

Epoxide 4b : Y. 56%. White solid, mp. 72-73°C. Rf = 0.50 (hexane/CH_2Cl_2 7/3). $[\alpha]_D$ = + 302 (c = 1.16, EtOH) ; e.e = 99.6% (99.8/0.2, HPLC). ^1H NMR ($CDCl_3$) , δ : 2.4 (s, 3H), 3.8 (AB, $\Delta\nu_{AB}$ = 5, J_{AB} = 2, 2H), 7.25 (m, 9H). ^{13}C NMR ($CDCl_3$), δ : 21.5, 62.9, 63, 125.5, 128.3, 128.6, 129.5, 134, 137.5, 138. Anal. Calcd for $C_{15}H_{14}O$: C, 85.68 ; H, 6.71. Found : C, 85.38 ; H, 6.55.

Epoxide 4c : Y. 76% (hexane/CH_2Cl_2 6/4 to 5/5). Colorless oil. Rf = 0.29 (hexane/CH_2Cl_2 6/4). $[\alpha]_D$ = + 274 (c = 1.19, EtOH) ; e.e. = 99% (99.50/0.50, HPLC). ^1H NMR ($CDCl_3$), δ : 3.8 (AB, $\Delta\nu_{AB}$ = 5, J_{AB} = 2, 2H), 7.35 (m, 9H) ; ^{13}C NMR ($CDCl_3$), δ : 62.3, 63, 125.5, 127, 128.6, 128.7, 129, 134, 135.5, 137. Anal. Calcd for $C_{14}H_{11}ClO$: C, 76.54 ; H, 5.03. Found : C, 76.31 ; H, 5.03.

Epoxide 4d : Y. 77% (hexane/Et_2O, 95/5 to 70/30). White solid, m.p = 73-75°C. Rf = 0.29 (hexane/Et_2O, 9/1). $[\alpha]_D$ = + 303 (c = 1.03, EtOH) ; e.e = 97.9% (98.97/1.03, HPLC). ^1H NMR ($CDCl_3$), δ : 3.8 (A of AB, d, J_{AB} = 1.5, 1H), 3.9 (B of AB, d, J_{AB} = 1.5, 1H), 7.36 (m, 5H), 7.5 (A of AB, d, J_{AB} = 8.5, 2H), 8.25 (B of AB, d, J_{AB}

= 8.5, 2H). ^{13}C NMR ($CDCl_3$), δ : 61.5, 63.5, 124, 125.5, 126.5, 128.8, 128.9, 136, 144.5, 148. Anal. Calcd. for $C_{14}H_{11}NO_3$: C, 69.69 ; H, 4.59 ; N, 5.80. Found : C, 69.60 ; H, 4.85 ; N, 5.69.

Epoxide 4e : Y. 84% Colorless oil. Rf = 0.37 (hexane/CH_2Cl_2 7/3). $[\alpha]_D$ = + 218 (c = 1.06, EtOH) ; e.e = 99.9% (99.93/0.07, HPLC). ^1H NMR ($CDCl_3$), δ : 3.8 (A of AB, d, J_{AB} = 2, 1H), 4.2 (B of AB, d, J_{AB} = 2, 1H), 7.3 (m, 9H). ^{13}C NMR ($CDCl_3$), δ : 57.6, 115.5 (d, $^2J_{CF}$ = 21, 1H), 124.5 (d, $^3J_{CF}$ = 4, 1H), 125, 125.7, 126. (d, $^3J_{CF}$ = 3.5, 1H), 128.7, 129.7 (d, $^3J_{CF}$ = 8, 1H), 137. Anal. Calcd. for $C_{14}H_{11}FO$: C, 78.48 ; H, 5.17. Found : C, 78.53 ; H, 5.3.

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