Pergamon

Tetrahedron: Asymmetry Vol. 5, No. 8, pp. 1519-1524, 1994
Elsevier Science Ltd
Printed in Great Britain
0957-4166/94 $7.00+0.00

0957-4166(94)00217-7

2- AND 8- FUNCTIONALIZED 1,4,7,10-TETRAOXASPIRO[5.5]UNDECANES.

III. Resolution of a (±)-E,E structure by enzymatic and chemical methods.

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Abstract: *The optical resolution of a (±)-E,E-2,8-disubstituted-1,4,7,10-tetraoxaspiro[5.5] undecane system was carried out by lipase-catalyzed hydrolysis of a symmetrical diester and also by monosubstitution with a chiral amine. Configurations of the new products were assigned by chemical correlations.*

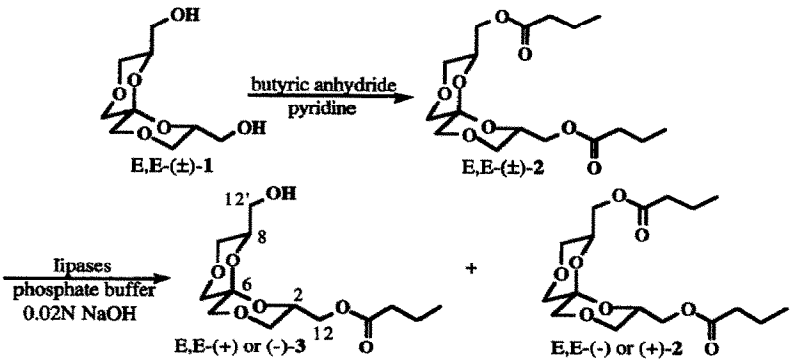
INTRODUCTION

Special interest for spiroacetal structures was prompted by the observation that many active natural compounds discovered in the last two decades contain this subunit in their skeleton, and considerable efforts have been made toward enantioselective synthesis mainly of dioxaspiro[5.5]undecane systems[1]. Recently the stereochemical features of these systems have been used for synthetic purposes, e. g. the protection of 1,2-diols as dispiroacetals has been used in the development of highly stereoselective reactions[2].

We have undertaken the study of 2,8-functionalized spirobidioxanes, especially E,E isomers which are new helical structures with a C2 symmetry for identical 2 and 8 substituents. These skeletons can be considered as resulting from a triglycerol precursor via a cyclodehydrative reaction carried out on a symmetrical ketodiol intermediate. The preparation of (±)-E,E and (±)-E,Z isomers was straightforward[3]. More recently we described the enantioselective synthesis of a (+)-E,E compound[4]. In the course of this work we subsequently investigated the optical resolution of diol E,E-(±)-**1** using known methods. Our first approach was based on the enantioselective hydrolysis of a symmetrical 2,8-diester with lipases and the second entailed the separation of diastereoisomers obtained with a chiral amine.

ENZYMATIC METHOD

We first tried transesterification on (±)-**1** with vinyl acetate[5] in different solvents using various lipases, but we did not observe any enantioselectivity in the monoacetylation step, after 50 % conversion. Furthermore kinetics of the reactions were very slow in these conditions. We therefore developed the hydrolytic pathway shown in scheme 1. The butyrate group was chosen, according to Esterman et al.[6] who tested several ester groups in similar experiments. The diester (±)-**2** was easily obtained in 96 % yield from the diol (±)-**1** with butyric anhydride in pyridine.



Scheme 1

Using commercially available enzymes we first studied the monohydrolysis of (±)-**2** to select the most efficient catalytic systems. Results are shown in table 1. All the runs were carried out with 0.2 mmol of diester in 10 ml of phosphate buffer. Yields were calculated for 50% monohydrolysis after solvent extraction, column chromatography purification and weighing. Dibutyrate was extracted more easily than highly water-soluble monobutyrate which can explain the differences observed.

Table 1. Enzyme-catalyzed monohydrolysis of (±)-**2**.

		Dibutyrate **2**		Monobutyrate **3**	
Lipase	Time	$[\alpha]_J^{25}$	Yield	$[\alpha]_J^{25}$	Yield
PPL	5h00	- 1	84 %	+ 1	38 %
CCL	3h30	+ 3	82 %	- 3	58 %
PLE	1h30	0	84 %	0	47 %
MJL	2h15	- 3	84 %	+ 3	*45 %
RAL	0h30	0	84 %	0	69 %

PPL: *Porcine pancreas* lipase, CCL: *Candida cylindricacea* lipase, PLE: *Porcine liver* esterase, MJL: *Mucor javanicus* lipase, RAL: *Rhizopus arrhyzus* lipase. * e.e. = 50 %.

Interestingly, CCL and MJL enzymes gave the highest enantiomeric excess but with opposite enantioselectivity. As we had previously synthesized (+)-**1**[4], we decided to improve the reaction with MJL which gave a positive optical rotation for the monobutyrate. The addition of cosolvents can sometimes increase the e.e. value for such kinetic resolution[7], depending on the enzyme used. We therefore examined the effects of adding cosolvents in phosphate buffer for MJL. Results are given in table 2.

Table 2. Phosphate buffer + cosolvent (ratio: 9/1).

		Dibutyrate **2**		Monobutyrate **3**	
Cosolvent	Time	$[\alpha]_J^{25}$	Yield	$[\alpha]_J^{25}$	Yield
DMF	1h00	- 2	52 %	+ 2	62 %
DMSO	3h00	- 4	74 %	+ 4	34 %
t-BuOH	3h40	- 3	64 %	+ 3	52 %

DMSO gave interesting results with improved optical rotation. As the percentage of hydrolysis could be monitored by the quantity of aqueous NaOH added, we could observe that the e.e. values decreased as the reaction progressed (table 3).

Table 3

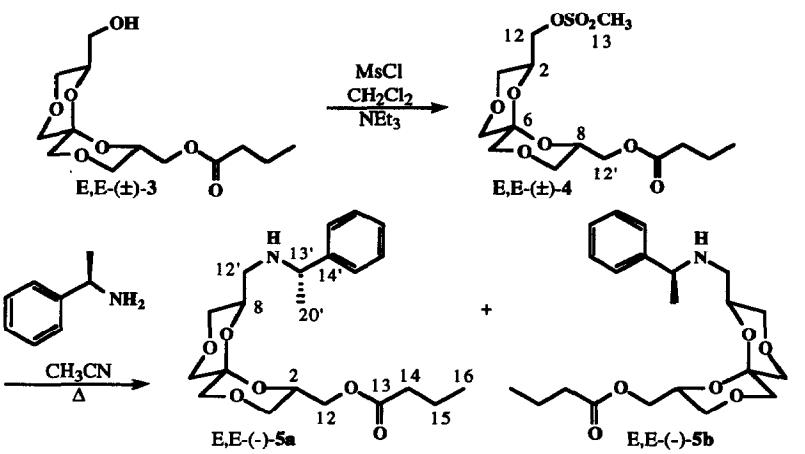
	Dibutyrate **2**		Monobutyrate **3**		
Hydrolysis	$[\alpha]_J^{25}$	Yield	$[\alpha]_J^{25}$	Yield	e.e.
75 %	- 5	44 %	+ 2	62 %	27 %
50 %	- 4	74 %	+ 4	34 %	62 %
25 %	- 2	86 %	+ 5	21 %	75 %

With 25 % hydrolysis, 75 % e.e. was obtained for (+)-**3**. This value was determined by NMR with the chiral shift reagent Eu(hfc)$_3$. In the same conditions (±)-**3**[3] gave duplicate resonance signals (^{1}H spectra) for the protons of the ester chain, especially the terminal CH_3 group, making it possible to measure e.e. by this method.

Determination of the absolute configuration of E,E-(+)-**2** and E,E-(+)-**3** was straightforward as we had previously prepared the pure corresponding enantiomers ($[\alpha]_J^{25}$ +7 for both compounds, e.e. = 98%) by total synthesis[4]. Compound E,E-(+)-**3** obtained by hydrolysis with LMJ was (2S,6S,8R).

CHEMICAL METHOD

Diastereoisomers **5a** and **5b** were prepared via the mesylate (±)-**4** and subsequent substitution with (S)-α-methylbenzylamine using spiroacetal E,E-(±)-**3** previously described[3] as starting material (scheme 2).



Scheme 2

As the spiroacetals studied were soluble in aqueous media, mesylate (±)-**4** was prepared in CH_2Cl_2/NEt_3 at O°C (yield: 95 %) instead of pyridine which required several aqueous treatments for the work up and gave

poorer yields. (±)-**4** was then refluxed for two days with (S)-α-methylbenzylamine in anhydrous acetonitrile under argon (yield: 49 %). Possible hydrogenolysis of the benzyl group to obtain the primary amine was the main reason for choosing (S)-α-methylbenzylamine, and separation of the diastereoisomers is generally possible with this chiral amine. **5a** and **5b** were easily separated by flash column chromatography giving products with respective optical rotations $[\alpha]_J^{25}$ -17 and $[\alpha]_J^{25}$ -37.

The diastereomeric excesses were directly accessible by ^1H NMR. The best separations on silica gel yielded **5a** with 90% d.e. and **5b** with 96% d.e.

Application of the above preparative method to compound (+)-**3**[4] enabled us to correlate diastereoisomers obtained with compounds of known configuration.

E,E-(2S,6S,8R)-(+)-3 $\xrightarrow{a}$ **E,E-(2S,6S,8S)-(-)-4** $\xrightarrow{b}$ **E,E-(2S,6S,8R,13'S)-(-)-5**

a : MsCl, NEt_3, CH_2Cl_2 ; **b** : (S)-α-methylbenzylamine, CH_3CN, Δ.

Scheme 3

The chiral mesylate **4** had an optical rotation of $[\alpha]_J^{25}$ -3 and a (2S,6S,8S) configuration. The corresponding amine **5** had: $[\alpha]_J^{25}$ -15 which meant diastereoisomer **5a** was similarly 2S,6S,8R for the spiroacetal part.

To conclude, we have shown that resolution of a racemic mixture prepared from the (±)-1,4,7,10-tetraoxaspiro[5.5]undecane structure can be achieved either by separation of diastereoisomers obtained with a chiral amine and a simple final chromatographic purification, in good diastereomeric excess (96%), or with lipases on diesters, when our best result was e.e. = 75 % (MJL) with fair yield .

EXPERIMENTAL

Optical rotation values were measured on a Perkin-Elmer 141 polarimeter for the mercury J line (λ = 578 nm) at 25°C (c in g/mL).Infrared (IR) spectra were obtained using a Perkin-Elmer 881 spectrometer and band are expressed in frequency units (ν cm^{-1}). NMR spectra were recorded at 300 MHz for ^1H and 75.47 MHz for ^{13}C on a Bruker MSL 300 spectrometer. All signals are expressed in ppm using tetramethylsilane as an internal standard. The following abbreviations are used: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), pseudotriplet (pt), axial (a) and equatorial (e). Mass spectra were obtained from a ZAB-SEQ (FAB^+) spectrometer. Satisfactory analytical data were obtained for all new compounds (± 0.3%) at the Service Central d'Analyse du CNRS, Solaize, France. Tris-[3-(trifluoromethylhydroxymethylene)-(+)-camphorato]-europium III ($Eu(hfc)_3$), was used as a shift reagent for enantiomeric excess determinations. Merck silica gel 60 was used for column chromatography and commercial Kieselgel 60 F254 plates were used for thin layer chromatography (TLC).

Lipases: PPL (Sigma ref. 3126, lot 67F-0270); CCL (Sigma ref. L1754, lot 43F-0043); PLE (Sigma ref. E9627, lot 121F-03351); MJL (Fluka ref. 62304, lot 275937); RAL (Sigma ref. L4384, lot 29F-04411).

General procedure for analytical enzymatic hydrolysis

A solution of diester (72 mg, 0.2 mmol) **2** in phosphate buffer (pH = 7, 0.01 M, 10 mL) or phosphate buffer/solvent 9:1 (10 mL) was treated with the required quantity of lipase (0.5 to 1 U per experiment). The suspension was stirred at room temperature. A solution of NaOH (0.02 N, 5 mL) was required to hydrolyse 50 % of an ester function (2.5 mL for 25 % and 7.5 mL for 75 %) and was added over a period indicated in table 1 or 2. After filtration of the lipase, the filtrate was extracted with ethyl acetate (3 x 4 mL). The combined extracts were dried with $MgSO_4$ and evaporated to dryness. The residue was chromatographed on silica gel with cyclohexane/ethyl acetate 50:50. Results are given in tables 1, 2 and 3.

(±)-8-Butyryloxymethyl-2-mesyloxymethyl-1,4,7,10-tetraoxaspiro[5.5]undecane 4 and (2S,6S,8S)-(-)-4

A solution of NEt_3 (0.45 mL, 3.2 mmol) and the product (±)-**3** (0.73 g, 2.5 mmol) in methylene chloride (15 mL) was stirred at 0°C. Methane sulfonyl chloride (0.37 g, 3.2 mmol) was added dropwise, and the resulting mixture was stirred at room temperature for 3 h. The solution was washed with brine (2 x 15 mL), dried over $MgSO_4$ and concentrated. The residue underwent column chromatography on silica gel with cyclohexane/ethyl acetate 70:30, to give the mesyl compound **4** in 95 % (0.875 g) yield. Colorless lac. IR (KBr) : 1060, 1540, 1650, 1740 cm^{-1}. MS (FAB^+) m/z : 369.1, 368.1, 367.1 $(M + H)^+$; 279.1 $(M-C_4H_9O_2)^+$. Anal. Calcd for $C_{14}H_{24}O_9S$ (368) : C 45.64, H 6.56. Found : C 45.37, H 6.71. ^{1}H-NMR ($CDCl_3$) δ : 4.24 (m, AB system, 2H, H12 or H12'), 4.21 (m, 1H, H2, a, $J_{2,3e}$ 2.5 Hz, $J_{2,3a}$ 11.5 Hz), 4.16 (m, 1H, H8, a, $J_{8,9e}$ 2.5 Hz, $J_{8,9a}$ 11.5 Hz), 4.08 (m, AB system, 2H, H12' or H12), 3.85 (dd, 1H, H3, e, $J_{3e,2}$ 2.5 Hz, $J_{3e,3a}$ 11.5 Hz), 3.80 (dd, 1H, H9, e, $J_{9e,8}$ 2.5 Hz, $J_{9e,9a}$ 11.5 Hz), 3.62 (d, 1H, H5, e, $J_{5e,5a}$ 11,5 Hz), 3.59 (d, 1H, H11, e, $J_{11e,11a}$ 11.5 Hz), 3.41 (pt, 1H, H9, a, $J_{9a,8}$ 11.5 Hz, $J_{9a,9e}$ 11.5 Hz), 3.37 (pt, 1H, H3, a, $J_{3a,2}$ 11.5 Hz, $J_{3a,3e}$ 11.5 Hz), 3.25 (d, 2H, H5 and H11, each a, $J_{5a,5e} = J_{11a,11e}$ 11.5 Hz), 3.07 (s, 3H, H13), 2.30 (t, 2H, H14', $J_{14',15'}$ 7.5 Hz), 1.62 (m, 2H, H15', $J_{15',14'} = J_{15',16'}$ 7.5 Hz), 0.93 (t, 3H, H16', $J_{16',15'}$ 7.5 Hz). ^{13}C-NMR ($CDCl_3$) δ : 173.2 (C13'), 91.9 (C6), 68.5 (C12), 68.3 (C5 and C11), 67.4 (C9), 66.6 (C8), 66.5 (C3), 66.3 (C2), 63.0 (C12'), 35.9 (C14'), 18.3 (C15'), 13.6 (C16').

The same procedure applied to (2S,6S,8R)-(+)-**3** yielded (2S,6S,8S)-(-)-**4** in the same yield. $[\alpha]_J^{25}$ - 3 (c = 0.017, $CHCl_3$) ; ee ≥ 98 % (by NMR).

(-)-2-Butyryloxymethyl-8-N-(α-methylbenzyl)-aminomethyl-1,4,7,10-tetraoxaspiro[5.5] undecane 5a and 5b and (2S,6S,8R,13'S)-(-)-5

A solution of product (±)-**4** (0.55 g, 1.5 mmol) and (S)-α-methylbenzylamine (0.40 g, 3 mmol) ($[\alpha]_{20}^{546}$ - 45) in dry acetonitrile (30 mL) was refluxed for 48 h under an atmosphere of argon. The solution was treated with 10 % aqueous K_2CO_3 (15 mL). The organic phase was dried over $MgSO_4$ and concentrated to give a residue which underwent column chromatography on silica gel with cyclohexane/ethyl acetate 20 : 80.

The diastereoisomer **5a** (60 mg) was first collected, and then a mixture of **5a** and **5b** (160 mg) was isolated that could be recycled for better separation. Finally, the diastereoisomer **5b** (70 mg) was collected. The three fractions (290 mg) gave the amine **5** in 49 % yield. Yellow oil. Data for **5a** and **5b** : IR ($CHCl_3$) : 1060-1090-1130, 1740, 3350 cm^{-1}. MS (FAB^+) m/z : 394.2 $(M + H)^+$ (exact mass, calcd for $C_{21}H_{32}NO_6$: 394.2229. Found : 394.2223). Anal calcd for $C_{21}H_{31}NO_6$ (393) : C 64.12, H 7.89. Found : C 64.13, H 7.84. Data for **5a** : $[\alpha]_J^{25}$ - 17 (c = 0.020, $CHCl_3$). Containing 5 % of **5b** (by NMR), ed = 90 %. ^{1}H-NMR ($CDCl_3$) δ : 7.35-7.21 (m, 5H, H aromatics), 4.25 (dtd, 1H, H2, a, $J_{2,3e}$ 3 Hz, $J_{2,12A} = J_{2,12B}$ 5 Hz, $J_{2,3a}$ 11 Hz), 4.17

(dd, AB system, 1H, H12A, $J_{12A,2}$ 5 Hz, $J_{12A,12B}$ 11.5 Hz), 4.10 (dddd, 1H, H8, a, $J_{8,9e}$ 3, $J_{8,12'B}$ 4 Hz, $J_{8,12'A}$ 7 Hz, $J_{8,9a}$ 11 Hz), 4.09 (dd, AB system, 1H, H12B, $J_{12B,2}$ 5 Hz, $J_{12A,12B}$ 11.5 Hz), 3.84 (dd, 1H, H3, e, $J_{3e,2}$ 3 Hz, $J_{3e,3a}$ 11.5 Hz), 3.76 (dd, 1H, H9, e, $J_{9e,8}$ 3 Hz, $J_{9e,9a}$ 11.5 Hz), 3.74 (q, 1H, H13', $J_{13',20'}$ 6 Hz), 3.61 (d, 1H, H11, e, $J_{11e,11a}$ 11.5 Hz), 3.58 (d, 1H, H5, e, $J_{5e,5a}$ 11.5 Hz), 3.38 (pt, 1H, H3, a, $J_{3a,2}$ 11 Hz, $J_{3a,3e}$ 11.5 Hz), 3.27 (pt, 1H, H9, a, $J_{9a,8}$ 11 Hz, $J_{9a,9e}$ 11.5 Hz), 3.24 (d, 1H, H11, a, $J_{11a,11e}$ 11.5 Hz), 3.21 (d, 1H, H5, a, $J_{5a,5e}$ 11.5 Hz), 2.55 (dd, AB system, 1H, H12'A, $J_{12'A,8}$ 7 Hz, $J_{12'A,12'B}$ 12 Hz), 2.41 (dd, AB system, 1H, H12'B, $J_{12'B,8}$ 4 Hz, $J_{12'A,12'B}$ 12 Hz), 2.34 (t, 2H, H14, $J_{14,15}$ 7.5 Hz), 1.95 (m, 1H, NH), 1.66 (m, 2H, H15, $J_{15,14} = J_{15,16}$ 7.5 Hz), 1.35 (d, 3H, H20', $J_{20',13'}$ 6 Hz), 0.97 (t, 3H, H16, $J_{16,15}$ 7.5 Hz). ^{13}C-NMR ($CDCl_3$) δ : 173.3 (C13), 145.4 (C14'), 128.5 (C15' and C19'), 127.7 (C18'), 127.6 (C16'), 127.0 (C17'), 91.7 (C6), 68.9 (C9), 68.7 (C5), 68.5 (C11), 68.0 (C8), 67.6 (C3), 66.3 (C2), 63.3 (C12), 58.5 (C13'), 48.4 (C12'), 36.0 (C14), 24.4 (C20'), 18.4 (C15), 13.7 (C16). Data for **5b** : $[\alpha]_J^{25}$ - 37 (c = 0.011, $CHCl_3$). Containing 2 % of **5a** (by NMR), d.e.= 96 %. ^{1}H-NMR ($CDCl_3$) δ : 7.38-7.26 (m, 5H, H aromatics), 4.26 (dtd, 1H, H2, a, $J_{2,3e}$ 2.5 Hz, $J_{2,12A} = J_{2,12B}$ 5 Hz, $J_{2,3a}$ 11 Hz), 4.22 (dddd, 1H, H8, a, $J_{8,9e}$ 3 Hz, $J_{8,12'A}$ 4 Hz, $J_{8,12'B}$ 6.5 Hz, $J_{8,9a}$ 11 Hz), 4.19 (dd, AB system, 1H, H12A, $J_{12A,2}$ 5 Hz, $J_{12A,12B}$ 11.5 Hz), 4.09 (dd, AB system, 1H, H12B, $J_{12B,2}$ 5 Hz, $J_{12A,12B}$ 11.5 Hz), 3.86 (m, 2H, H13' and H3, e, $J_{13',20'}$ 6 Hz and $J_{3e,2}$ 2.5 Hz, $J_{3e,3a}$ 11.5 Hz), 3.75 (dd, 1H, H9, e, $J_{9e,8}$ 3 Hz, $J_{9e,9a}$ 11.5 Hz), 3.64 (d, 1H, H5 or H11, e, $J_{5e,5a}$ 11.5 Hz), 3.62 (d, 1H, H11 or H5, e, $J_{11e,11a}$ 11.5 Hz), 3.47 (pt, 1H, H3, a, $J_{3a,2}$ 11 Hz, $J_{3a,3e}$ 11.5 Hz), 3.42 (pt, 1H, H9, a, $J_{9a,8}$ 11 Hz, $J_{9a,9e}$ 11.5 Hz), 3.28 (d, 1H, H5 or H11, a, $J_{5a,5e}$ 11.5 Hz)), 3.26 (d, 1H, H11 or H5, a, $J_{11a,11e}$ 11.5 Hz), 2.67 (dd, AB system, 1H, H12'A, $J_{12'A,8}$ 4 Hz, $J_{12'A,12'B}$ 12.5 Hz), 2.50 (dd, AB system, 1H, H12'B, $J_{12'B,8}$ 6.5 Hz, $J_{12'A,12'B}$ 12.5 Hz), 2.34 (t, 2H, H14, $J_{14,15}$ 7.5 Hz), 1.67 (m, 3H, NH and H15, $J_{15,14} = J_{15,16}$ 7.5 Hz), 1.45 (d, 3H, H20', $J_{20',13'}$ 6 Hz), 0.97 (t, 3H, H16, $J_{16,15}$ 7.5 Hz). ^{13}C-NMR ($CDCl_3$) δ : 173.4 (C13), 148.5 (C14'), 128.7 (C15' and C19'), 127.5 (C17'), 126.9 (C16' and C18'), 92.0 (C6), 68.7 (C11 or C5), 68.5 (C5 or C11), 68.5 (C9), 67.7 (C3), 66.8 (C8), 66.4 (C2), 63.3 (C12), 58.5 (C13'), 47.6 (C12'), 36.0 (C14), 23.9 (C20'), 18.4 (C15), 13.7 (C16).

The same procedure applied to (2S,6S,8S)-(-)-**4** yielded (2S,6S,8R,13'S)-(-)-**5** in the same yield. $[\alpha]_J^{25}$ - 15 (c = 0.017, $CHCl_3$).

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(*Received in UK* 3 *May* 1994; *accepted* 16 *June* 1994)