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# NEW ASYMMETRIC SYNTHESIS OF DEXECADOTRIL AND ECADOTRIL STARTING FROM A SINGLE PRECURSOR

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#### SYNTHETIC COMMUNICATIONS, 31(2), 211-218 (2001)

## NEW ASYMMETRIC SYNTHESIS OF DEXECADOTRIL AND ECADOTRIL STARTING FROM A SINGLE PRECURSOR

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#### ABSTRACT

We describe herein a method providing access to both enantiomers of 3-acetylthio-2-benzylpropionic acid via enzymatic desymmetrization of 2-benzyl-1,3-propanediol. These compounds are respectively the starting materials for the synthesis of ecadotril, and dexecadotril, which are powerful inhibitors of NEP (EC 3.4.24.11) and have been developed as therapeutic agents.

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Racecadotril (**RS**)-1 (previously named acetorphan) is used as a therapeutic agent against diarrhea, and was launched in France in 1993 (1–3). Actually, it plays the role of a prodrug of thiorphan (N-[(RS)-1-oxo-2-(mercaptomethyl)-3-phenypropyl]-glycine), which acts as a powerful inhibitor of NEP (EC 3.4.24.11). It has been shown that the two enantiomers of thiorphan have a strong and equipotent *in vitro* affinity on the considered enzyme (4). However, the corresponding prodrugs display different pharmaceutical profiles. Indeed, the (R) enantiomer (dexecadotril (R)-1) is under phase 3 clinical evaluation as an intestinal antisecretatory agent, while the (S) enantiomer (ecadotril (S)-1) is useful in the cardiovascular field (6) (Fig. 1).

The industrial synthesis of both enantiomers of racecadotril relies on the peptidic coupling of benzyl glycinate with the optically pure 3-acetylthio-2-benzylpropionic acid **2** of the required configuration, which thus constitutes the key intermediate for the synthesis of (**S**) and (**R**)-**1**. Presently, the only described entries to the enantiomers are based either on a resolution process (4,5,7), or a catalytic asymmetric synthesis by means of an enantioselective hydrogenation of a prochiral precursor (8). Alternatively, the Evans oxazolidinone method leads to a closely related precursor in which the sulfur atom is benzylated instead of acetylated (9). In this paper we describe our results in the preparation of both enantiomers starting from the same prochiral precursor. The key step of the present work was the desymmetrization of 2-benzyl-1,3-propanediol **3** by means of a lipase catalyzed transesterification (Scheme 1). Indeed, the known (R)-2-benzyl-1-hydroxypropylacetate (**R**)-**4** (10–13) was readily prepared from the prochiral compound **3** using either the lipase PS Amano or the lipase P Fluka.

The optimal conditions for the use of both enzymes were realized after a systematic study (see Table 1).

Varying the source of the enzyme and experimental conditions allowed us to improve the transformation up to 91% (LPF, entry 5) and 86% yield (PS, entry 9), respectively. Comparison of the optical rotations of the obtained product with the highest reported value indicated that compound (**R**)-4 was generated in high ee

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a: Lipase PS Amano, vinylacetate; b: Jones reagent; c: LiOH, THF/water=75/25; d: PPh3, DIAD, thioacetic acid, THF; e: Novozym 435, vinyl acetate; f: Lipase P Fluka, 0.1 M KPB (pH7)/acetone (30%)

#### Scheme 1.

(>94%) (10–13). We observed that the lipase PS allowed us to carry out the transesterification at RT with good yield and a reasonable reaction time (entry 9). After Jones oxidation, hydrolysis by means of aqueous lithium hydroxide provided the corresponding hydroxy acid (**S**)-**5**. Thioacetylation of this compound was carried

Entry	Lipase <sup>a</sup> (%) <sup>b</sup>	Reaction Temp. (°C)	Reaction Time	Yield (%) <sup>c</sup>	$[\alpha]_{D}^{d}$
1	LPF (2.5)	23	17 h	83	+27.6
2	LPF (1)	23	73 h	85	+28.9
3	LPF (0.5)	25	11 d	88	+26.7
4	LPF (0.5)	37	44 h	89	+27.6
5	LPF (0.25)	40	72 h	91	+27.7
6	LPF (0.1)	45	11 d	86	+20.7
7	PS (1)	20	24 h	64	+28.0
8	PS (0.5)	21	21 h	78	+26.8
9	PS (0.25)	25	42 h	86	+28.5
10	LCA (0.5)	29	4 h	43	+2.2
11	LCA (10)	29	20 h	$0^{e}$	_

Table 1. Monoacetylation of 2-Benzyl-1,3-Propanediol 3 into (R)-4

<sup>a</sup>LPF: lipase P from *Pseudomonas fluorescens* (31.5 U/mg) purchased from Fluka; PS: lipase PS Amano kindly provided to us by Amano; LCA: lipase Novozym 435 from *Candida antartica* (7 U/mg) kindly provided to us by Novo Nordisk.

<sup>b</sup>The indicated % represents the massic amount of enzyme with respect to the substrate **3** (entries 1–7: 0.36 M in vinyl acetate; entries 8–11: 0.56 M in vinyl acetate).

<sup>c</sup>After purification by flash chromatography.

 $^{d}20^{\circ}$ C, c = 1, CHCl<sub>3</sub>, lit. +28.6 (>94% ee) (11).

<sup>e</sup>In this experiment, only the corresponding diacetate **6** was obtained in a quantitative yield.



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out by dropwise addition of thioacetic acid (1.5 equiv.) and of (S)-5 (1 equiv.) in THF at -10°C to the preformed salt of triphenylphosphine and DIAD (1.5 equiv.) in THF (14). This one-step substitution provided simple access with high yield to (**R**)-2, directly starting from the parent  $\beta$ -hydroxyacid.

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For the access to (S)-2, we first tried to achieve the monoacetylation of the same precursor **3** using lipase LCA, because this enzyme had been reported to give opposite enantioselectivity compared to other lipases, starting from closely related prochiral diols (15). Unfortunately, in our case, LCA yielded (**R**)-4 with almost no enantioselectivity (entry 10). We then turned to another strategy, in which the first step consisted of the diacetylation of compound **3** by means of LCA as the catalyst in vinyl acetate to afford the new prochiral compound **6** (entry 11). (S)-2-Benzyl-1-hydroxypropyl acetate (**S**)-4 was obtained via an enantioselective hydrolysis using lipase LPF. A similar synthetic pathway as above allowed the transformation of (**S**)-4 into (**S**)-2.

In conclusion, we describe herein the first convenient access to both enantiomers of 3-acetylthio-2-benzylpropionic acid 2 by an enzymatic process starting from a single prochiral precursor 3. The low amount of catalyst needed and the efficiency of most of the synthetic steps allowed the method to be used on a multigram scale.

#### EXPERIMENTAL

#### Synthesis of 3

To a THF (200 mL) suspension of LiAlH<sub>4</sub> (15 g, 395 mmol) was added at room temperature a THF (30 mL) solution of dimethylbenzylmalonate (22.5 g, 101 mmol). The mixture was stirred for 3 h at reflux. The reaction was cooled at 5°C, diluted with THF (140 mL), then quenched by addition of water (15 mL), 15% NaOH aqueous solution (15 mL), and water (45 mL). After stirring for 30 min, the reaction mixture was filtered. The solid residue was washed with diethylether (300 mL). The organic layers were combined, dried over magnesium sulfate, then evaporated to give 16 g of compound **3** as a white solid. After treatment by cold petroleum ether (200 mL), the residue was filtered and dried *in vacuo* to give pure **3** (15 g, 89% yield), m.p.:  $68^{\circ}$ C. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz): 7.4–7.0 (m, 5H); 3.9–3.5 (m, 4H); 3.1 (s broad, 2H); 2.55 (d, 2H, J = 7 Hz); 2.1–1.9 (m, 1H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 50 MHz): 139.7; 128.9; 128.3; 126.0; 65.0; 43.7; 34.1.

#### Synthesis of (R)-4

A suspension of **3** (4 g, 24 mmol) in vinylacetate (40 mL) was stirred at  $50^{\circ}$ C for 15 min, then cooled to  $25^{\circ}$ C. Lipase PS Amano (10 mg) was added at this

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temperature. After 48 h of stirring, the mixture was filtered on Celite. The filtrate was concentrated *in vacuo* to give (**R**)-4 (4.3 g, 86% yield, see Table 1, entry 9) as a colorless oil. Physical and spectral data were in agreement with reported values (11-13).

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<sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz): 7.35–7.10 (m, 5H); 4.25–4.0 (m, 2H); 3.65– 3.40 (m, 2H); 2.75–2.50 (m, 2H); 2.20–2.00 (m, 2H); 2.05 (s, 3H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 50 MHz): 171.6; 138.1; 128.9; 128.4; 126.2; 63.6; 61.9; 42.5; 34.2; 20.8.  $[\alpha]_{\rm D} = +28.5$  (20°C, c = 1.15, CHCl<sub>3</sub>).

#### Synthesis of (S)-5

To a solution of compound (**R**)-4 (4 g, 19.2 mmol) in acetone (80 mL), Jones reagent was added dropwise at 0°C (22.8 mL). After stirring for 10 min at 0°C, the mixture was quenched by addition of isopropanol (10 mL). After additional stirring for 1 h, the mixture was filtered, then diluted with water (40 mL) and acetone was removed by concentration *in vacuo*. The resulting aqueous layer was adjusted to pH9 by addition at 5°C of solid sodium hydrogenocarbonate, washed with ethylacetate (3 × 15 mL), then acidified with concentrated HCl (pH1). After extraction with ethylacetate (3 × 15 mL), the organic layer was washed with water (10 mL), dried over magnesium sulfate, filtrated, and concentrated *in vacuo* to give (S)-2-benzyl-3-acetoxypropanoic acid (2.8 g, 65%).

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz): 10.4 (s broad, 1H); 7.35–7.10 (m, 5H); 4.30–4.15 (m, 2H); 3.15–2.95 (m, 2H); 2.95–2.75 (m, 1H); 2.05 (s, 3H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 50 MHz): 178.5; 170.6; 137.4; 128.7; 128.5; 126.7; 63.4; 46.1; 34.3; 20.8. [α]<sub>D</sub> = +11.5 (20°C, c = 1, CHCl<sub>3</sub>).

(S)-2-benzyl-3-acetoxypropanoic acid (3.52 g, 15.8 mmol) was saponified at 0°C by lithine (2.64 g, 62.9 mmol) in a mixture of THF and water (75/25, 35 mL). After 1 h, the reaction mixture was acidified by a 3M aqueous HCl solution (22 mL), then extracted by diethylether (50 mL, then  $2 \times 15$  mL). The organic layers were combined, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The solid residue was treated with cold petroleum ether, filtrated, and dried *in vacuo* to give the  $\beta$ -hydroxy acid (S)-5 (2.45 g, 86%). m.p.:  $63^{\circ}-65^{\circ}C$ .

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz): 7.40–7.10 (m, 5H); 5.85 (s broad, 2H); 3.85– 3.60 (m, 2H); 3.15–2.95 (m, 1H); 2.95–2.75 (m, 2H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 50 MHz): 178.3; 138.2; 128.8; 128.5; 126.5; 61.9; 48.8; 33.9.  $[\alpha]_D = -14.3$  (20°C, c = 1.15, CHCl<sub>3</sub>); lit. (**R**)-5,  $[\alpha]_D = +13.9$  (20°C, c = 0.97, CHCl<sub>3</sub>), <sup>11H</sup> and  $[\alpha]_D = +14.9$ (20°C, c = 1.11, CHCl<sub>3</sub>) (16).

#### Synthesis of (R)-2

A mixture of (S)-5 (1.45 g, 8.05 mmol) and thioacetic acid (0.92 g, 12.05 mmol) in THF (10 mL) was added dropwise at  $-10^{\circ}$ C to a stirred suspension

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of the preformed adduct of triphenylphoshine (3.16 g, 12.05 mmol) and DIAD (2.44 g, 12.05 mmol) in THF (30 mL). The mixture was then stirred at  $-10^{\circ}$ C for 1 h, then 2 h at RT. The solution was concentrated and the residue was dissolved in ethyl acetate (15 mL), then extracted with an aqueous solution of sodium hydrogenocarbonate (3×20 mL). After washing with ethyl acetate (10 mL), the aqueous phase was acidified with concentrated hydrochloric acid (3 mL) and extracted with ethyl acetate (2×15 mL). The organic layer was dried over magnesium sulfate, then evaporated to give the (**R**)-**2** acid as a light yellow oil (82%).

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz): 9.5 (broad s, 1H); 7.4–7.1 (m, 5H); 3.2–2.8 (m, 5H); 2.3 (s, 3H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 50 MHz): 195.1; 179.3; 137.3; 128.8; 128.4; 126.6; 46.8; 37.3; 30.3; 29.4.  $[\alpha]_D = +33.7$  (25°C, c = 1, MeOH), lit.  $[\alpha]_D = +35.3$  (25°C, c = 1.3, MeOH) (5). The enantiomeric excess was determined to be 94% ee by means of HPLC analysis (retention time: 22.14 min; Chiralpack AD, 250 × 4.6 mm, 5  $\mu$ m, n-heptane/iPrOH/TFA = 90/10/0.1; detection: 240 nm; flow rate: 0.5 mL/mn).

#### Synthesis of (R)-1

To a solution of (**R**)-2 (2 g, 8.4 mmol) in THF (14 mL) were successively added at 5°C a solution of benzylglycinate *p*-toluenesulfonic salt (2.83 g, 8.4 mmol) and triethylamine (0.85 g, 8.4 mmol) in dichloromethane (15 mL), then a solution of hydroxybenzotriazole (1.28 g, 8.4 mmol) in THF (14 mL), then a solution of DCC (1.73 g, 8.4 mmol) in dichloromethane (14 mL). The reaction mixture was stirred overnight at room temperature, filtrated then concentrated *in vacuo*. After evaporation, the residue was diluted in ethylacetate (10 mL), filtrated, and successively washed with water, aqueous sodium hydrogenocarbonate, and brine. The organic layer was dried, filtrated, and concentrated *in vacuo*. The residue was chromatographied over silicagel (EP/diethylether: 60/40) to give pure (**R**)-**1** as a white solid (2.1 g, 65%). m.p.: 69°C.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz): 7.40–7.10 (m, 10H); 6.15 (broad t, 1H); 5.25 (s, 2H); 4.10–3.50 (m, 2H); 3.10–2.55 (m, 5H); 2.30 (s, 3H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 50 MHz): 195.8; 172.9; 169.2; 138.4; 135.0; 128.7; 128.4; 128.2; 126.5; 66.9; 49.1; 41.2; 38.2; 31.0; 30.4.  $[\alpha]_D = +24.5$  (20°C, c = 1, MeOH).

#### Synthesis of 6

To a suspension of compound 3(1.89 g, 11.37 mmol) in vinylacetate (10 mL) was added at 29°C the enzyme Novozym 435 (100 mg). The mixture was stirred for 24 h at 29°C. After filtration and concentration, the diacetate **6** was obtained as an oil (2.79 g, 98%).

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<sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz): 7.35–7.10 (m, 5H); 4.15–3.90 (m, 4H); 2.75–2.60 (m, 2H); 2.40–2.25 (m, 1H); 2.05 (s, 6H).

#### Synthesis of (S)-4

To a solution of **6** (0.25 g, 1 mmol) in a mixture of acetone (9.9 mL) and phosphate buffer (pH 7, 23.1 mL) was added lipase LPF (0.13 g). The reaction medium was warmed to 30°C for 48 h. The solution was then extracted with diethyl ether (2×20 mL). The combined organic layers were dried over magnesium sulfate, then evaporated to give (**S**)-**4** (0.08 g, 38% yield,  $[\alpha]_D = -27.7, 20^\circ$ C, c = 1.04, CHCl<sub>3</sub>; lit. (10–13):  $[\alpha]_D = -28.1, 20^\circ$ C, c = 1.01, CHCl<sub>3</sub>), as a colorless oil. All spectral data were identical to that of the enantiomer (**R**)-**4**.

Compounds (S)-2 and (S)-1 were prepared using same experimental conditions as described above for the enantiomeric series.

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