Pergamon

Tetrahedron: Asymmetry, Vol. 8, No. 9, pp. 1487–1490, 1997

Printed in Great Britain
PII: S0957-4166(97)00149-3 0957-4166/97 $17.00 + 0.00

Convenient enantioselective preparation of salsolinol-1-carboxylic acid

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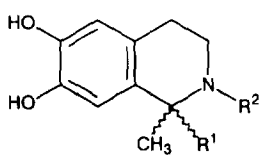
Abstract: Pictet–Spengler condensation of dopamine with (+)-menthyl pyruvate afforded a diastereomeric mixture of menthyl salsolinol-1-carboxylate, from which pure diastereomer was isolated by repeated recrystallizations in *ca.* 20% yield. Acid hydrolysis of the menthyl ester furnished (−)-(*R*)-salsolinol-1-carboxylic acid in good yield. © 1997 Elsevier Science Ltd

A dopamine-derived alkaloid salsolinol **1** (6,7-dihydroxy-1-methyl-1,2,3,4-tetrahydroisoquinoline) is enzymatically *N*-methylated into *N*-methylsalsolinol **2**.[1] Endogenous **2** was proposed as a candidate neurotoxin specific for dopaminergic neurons. The biological activities of these alkaloids are enantiospecific; only (*R*)-**2** proved to be a potent dopaminergic neurotoxin and to induce Parkinsonism.[2] In the human brain, only the (*R*)-enantiomers of **1** and **2** are detected.[3,4] Two biosynthetic pathways were proposed to produce Sal; one is the Pictet–Spengler condensation of dopamine with acetaldehyde, and the other is *via* salsolinol-1-carboxylic acid **3** (6,7-dihydroxy-1-methyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid), produced from the condensation of dopamine with pyruvic acid, followed by decarboxylation and reduction.[5] Recently, a novel enzyme was isolated from the human brain, which was found to catalyze the condensation of dopamine with acetaldehyde and with pyruvic acid to produce predominantly (*R*)-**2** and (*R*)-**3**, respectively.[3] Stereochemically pure samples are required to study the enzymatic reactions. Dostert *et al.* reported optical resolution of (*RS*)-**3** consisting of benzyl protection, selective deprotection, separation of enantiomers *via* diastereomeric salts, and final deprotection.[6] In this paper we describe a very convenient enantioselective synthesis of **3** consisting of only two steps.



	R^1	R^2
1	H	H
2	H	CH_3
3	CO_2H	H

Results and discussion

The reaction sequence for the enantioselective synthesis of (−)-(*R*)-salsolinol-1-carboxylic acid is shown in Scheme 1. In Scheme 1, recrystallizations of the diastereomeric ester formed by Pictet–Splengler condensation[7] of dopamine with optically active menthyl pyruvate furnishes a stereochemically pure isoquinoline alkaloid derivative **4**.

A mixture of dopamine and (+)-menthyl pyruvate[8] prepared from (+)-(1*S*,3*S*,4*R*)-menthol and pyruvic acid was stirred in MeOH–H_2O (5:1 *v/v*) for five days at room temperature. The Pictet–Spengler condensation product, (*R/S*)-salsolinol-1-carboxylic acid (1*S*,3*S*,4*R*)-menthyl ester hydrochloride, obtained in 85% yield, was found to be a 56:44 diastereomeric mixture[9] by the ^{1}H NMR spectrum

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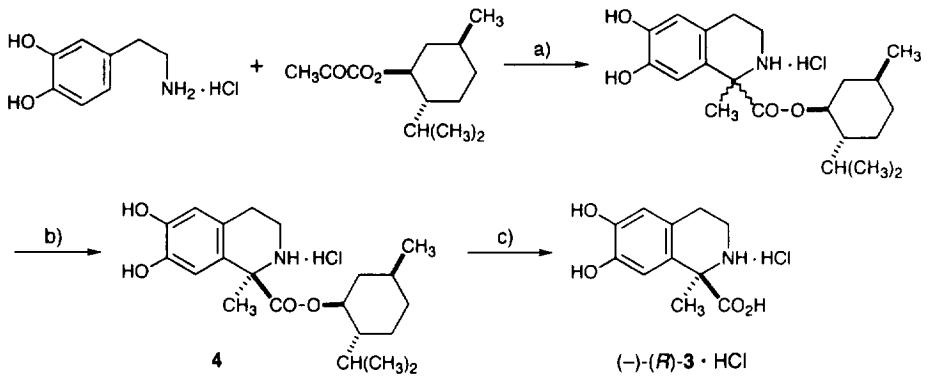

Scheme 1. Enantioselective synthesis of (−)-(*R*)-salsolinol-1-carboxylic acid hydrochloride. a) MeOH–H_2O, room temperature. b) Recrystallization. c) AcOH–conc HCl, 125°C.

measured in CD_3OD. Recrystallization from MeOH–2-propanol–benzene was found to improve the *d.e.* value markedly. Usually two to three recrystallizations gave a pure menthyl ester **4** (mp 247–249.5°C, $[\alpha]_D^{20}$ +11.7 in MeOH; *d.e.* >99%) in *ca.* 20% yield based on the starting dopamine hydrochloride. Although attempted saponification resulted in a complex mixture, removal of the menthyl group from the menthyl ester **4** was successfully achieved by acid hydrolysis in AcOH–conc HCl (1:1 *v/v*) at 125°C for 18 h. The hydrolyzate was subjected to Sephadex G-10 column chromatography and fractions containing pure **3** were collected and lyophilized to yield (−)-(*R*)-**3**·HCl as a colorless powder in 82% yield; $[\alpha]_D^{20}$ −76, *c* 0.27 in MeOH (lit.,[6] $[\alpha]_D^{24}$ −71.6, *c* 0.30 in MeOH). The absolute configuration was based on the assignment given by Dostert *et al.*[6]

The present method for preparing **3** is excellent in the following points: i) Both enantiomers of **3** can be prepared since both (+)- and (−)-menthol are commercially available. ii) The reaction sequence is simple consisting of only two steps. iii) No sophisticated purifications are required; only repeated recrystallizations in addition to routine gel filtration chromatography give reproducible results. iv) The enantiomeric purity can be determined easily and accurately by the ^1H NMR analysis of the intermediate menthyl ester **4**. v) The precursor **4** is quite stable and can be stored at room temperature over months without any detectable deterioration. Therefore, it is advisable to hydrolyze the necessary amount of **4** just before the use of **3** since the hydrolysis yield is high and only gel filtration and lyophilization give the pure sample.

Experimental

General

Reactions were monitered by silica gel TLC (Merck $60F_{254}$) with the solvent system butanol–AcOH–H_2O (4:1:1 *v/v/v*). ^1H NMR spectra were recorded on a Varian Gemini-200 spectrometer. Optical rotations were determined using a JASCO DIP-4 digital polarimeter.

Synthesis

(+)-(1S,3S,4R)-Menthyl (R)-salsolinol-1-carboxylate hydrochloride **4**

A mixture of dopamine hydrochloride (341 mg; 1.8 mmol) and (+)-(1*S*,3*S*,4*R*)-menthyl pyruvate[7] (456 mg; 2 mmol) in 2.4 ml of MeOH–H_2O (5:1 *v/v*) was stirred at room temperature (*ca.* 25°C) under nitrogen. Initially, dopamine hydrochloride partially dissolved; however, after one day complete dissolution was observed. After five days, when precipitates of the condensation product became prominent, the mixture was evaporated in vacuo. The residue, dissolved in MeOH, was subjected to Sephadex LH-20 column chromatography using MeOH as an eluent to afford a diastereomeric mixture of the menthyl esters of (*R*)- and (*S*)-**3** hydrochloride (645 mg, yield 85%; *d.e.* 12%). Recrystallization

of the above mixture (200 mg) from MeOH–2-propanol–benzene yielded 55 mg of crystals with 90% *d.e.*; and from the mother liquor a further 63 mg of crystals with 69% *d.e.* was obtained. Further recrystallizations gave the pure diastereomer **4** in *ca.* 20% yield based on the starting dopamine hydrochloride.

Colorless needles from MeOH–2-propanol–benzene, mp 247–249.5°C, $[\alpha]_D^{20}$ +11.7 (*c* 0.43 in MeOH), ^{1}H NMR δ (CD_3OD) 0.78 (3H, *d*, *J*=7 Hz, *sec*-Me), 0.90 (3H, *d*, *J*=7 Hz, *sec*-Me), 0.93 (3H, *d*, *J*=7 Hz, *sec*-Me), 1.0–1.9 (9H, m, $3CH_2$ and 3CH in menthyl), 1.89 (3H, *s*, *tert*-Me), *ca.* 2.95 (2H, *m*, C^4H_2), *ca.* 3.55 (2H, *m*, C^3H_2), 4.78 (1H, *td*, *J*=11 and 4 Hz, CHOCO), 6.61 (1H, *s*, C^5H), 6.95 (1H, *s*, C^6H). Anal: Found C 63.08, H 7.95, N 3.54% ($C_{21}H_{32}ClNO_4$ requires C 63.38, H 8.10, N 3.52%).

From the ^{1}H NMR spectra of diastereomeric mixtures, the chemical shift values of the minor diastereomer, (1*S*,3*S*,4*R*)-menthyl (*S*)-salsolinol-1-carboxylate hydrochloride, were determined as follows: δ (CD_3OD) 0.54 (3H, *d*, *J*=7 Hz, *sec*-Me), 0.74 (3H, *d*, *J*=7 Hz, *sec*-Me), 0.96 (3H, *d*, *J*=6 Hz, *sec*-Me), 1.91 (3H, *s*, *tert*-Me), *ca.* 2.95 (2H, *m*, C^4H_2), *ca.* 3.55 (2H, *m*, C^3H_2), 4.83 (1H, *td*, *J*=11 and 4 Hz, CHOCO), 6.60 (1H, *s*, C^5H), 7.01 (1H, *s*, C^6H).

(−)-(R)-Salsolinol-1-carboxylic acid **3** *hydrochloride*

The pure ester **4** (19.9 mg, 0.05 mmol) in 2 ml of AcOH–conc HCl (1:1 *v/v*) was refluxed for 18 h under nitrogen. The solvent was evaporated, the residue was dissolved in 0.02 M HCl and the insoluble menthol was filtered off. The crude hydrolyzate was subjected to Sephadex G-10 column chromatography using 0.02 M HCl as eluent and the eluate was analyzed by silica gel TLC or HPLC described below. Fractions containing pure **3** were collected and lyophilized to yield (−)-(*R*)-**3**·HCl as a colorless powder (10.7 mg, yield 82%), $[\alpha]_D^{20}$ −76, *c* 0.27 in MeOH (lit.,[6] $[\alpha]_D^{24}$ −71.6, *c* 0.30 in MeOH).

Determination of chemical and diastereomeric purity

^{1}H NMR spectral d.e. *determination*

The *d.e.* value of **4** was determined by comparing the peak heights of the most deshielded aromatic singlets (δ 6.95 *vs.* 7.01), the most shielded secondary methyl doublets (δ 0.78 *vs.* 0.54), and/or the tertiary methyl singlets (δ 1.89 *vs.* 1.91) measured in CD_3OD.

HPLC analysis

The diastereomeric ratio was also determined by HPLC; column: Inertosil ODS-3 (4.6 mm i.d. × 250 mm), mobile phase: 25 mM phosphate buffer (pH 3.0) containing 12 mM β-cyclodextrin, 1 mM sodium heptanesulfonate, and 10% acetonitrile, detecter: Coulochem-II. The major diastereomer **4** was eluted faster than the minor one.

A slightly modified mobile phase containing 2% acetonitrile instead of 10% was used for determining the purity of **3**.

Acknowledgements

We are grateful to Dr P. Dostert for the kind gift of authentic samples of (−)-(*R*)- and (+)-(*S*)-**3**.

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9. The reaction at higher temperature (85°C) resulted in lower stereoselectivity (*d.e.* 4%).

(Received in Japan 20 February 1997; accepted 24 March 1997)