mixture was stirred for 2 h at 0 °C and for 4 h at 25 °C and then quenched with saturated ammonium chloride. The mixture was diluted with ether and filtered through Celite. The organic layer was washed with water, dried, concentrated, and flash chromatographed to provide 530 mg (71%) of cyclopentenone 4.

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Lipase-Catalyzed Transesterification in the Synthesis of a New Chiral Unlabeled and Carbon-14 Labeled Serotonin Uptake Inhibitor

Robert J. Cregge, Eugene R. Wagner, Jules Freedman,† and Alexey L. Margolin*

Merrell Dow Research Institute, Indianapolis Center, 9550 Zionsville Rd., Indianapolis, Indiana 46268

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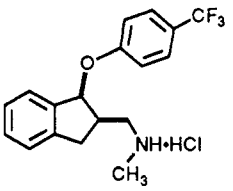
Summary: The synthesis of a new chiral unlabeled and carbon-14 labeled serotonin uptake inhibitor via lipase-catalyzed resolution is described.

The synthesis of chiral drugs is a major challenge in medicinal chemistry[1] since enantiomers may have different biological activities and be responsible for toxic side effects.[2] Currently, there is a widespread consensus that a racemic drug should be considered, not as an individual compound, but as a combination of drugs.[3] However, many synthetic pharmaceuticals are still being developed and marketed as racemates.[4] The development of efficient methods of resolution, asymmetric synthesis,[5] and new chiral analytical techniques[6] will change this situation.

Enzyme-catalyzed kinetic resolution, both in aqueous[7] and nonaqueous[8] media, has emerged as a versatile technique for the synthesis of chiral compounds. Enzymatic catalysis in organic solvents has become increasingly popular among organic chemists[9] and has been found to be especially useful for the synthesis of some unique chiral intermediates and pharmaceuticals.[10]

The indanamine derivative MDL 27777A (1) is a new serotonin uptake inhibitor.[11] Preliminary studies show that (+)-1 (MDL 28618A) is at least 10 times more active in inhibiting serotonin uptake both in vitro and in vivo than (−)-1.[12] The resolution of the racemic alcohol (±)-4



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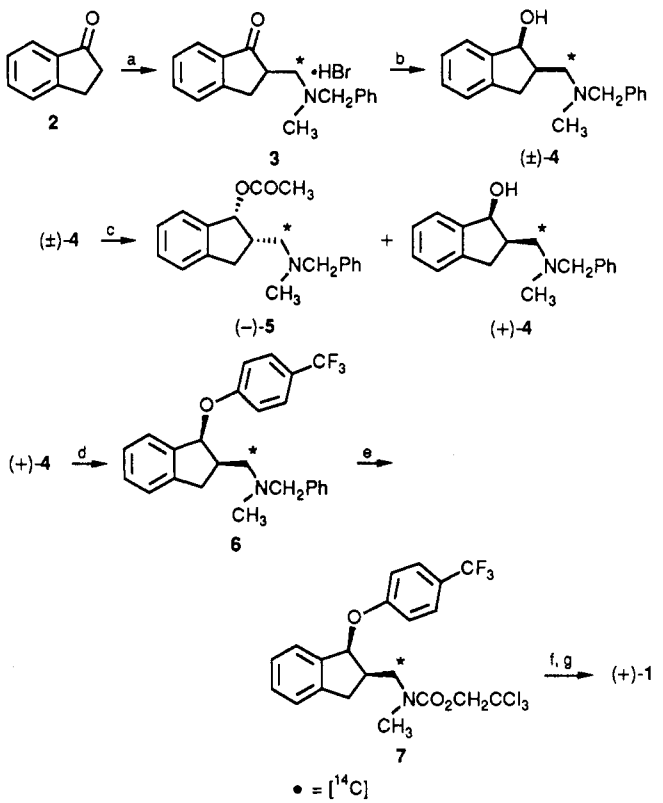
via lipase-catalyzed acylation of (−)-4 allowed the synthesis of [^{14}C]-(+)-1, the first example of the application of enzyme-catalyzed reactions in organic solvents for the synthesis of a radiolabeled compound.

Scheme I outlines the synthetic route to (+)-1.[13,14] Paraformaldehyde was condensed in a Mannich reaction with 1-indanone (2) and *N*-benzylmethylamine hydrobromide in refluxing acetonitrile to form 3. Reduction of ketone 3 with L-Selectride (Aldrich) gave alcohol 4 (cis/trans, 20/1); after chromatography, pure 4 was obtained in 88% yield. Lipase from *Pseudomonas fluorescens* (50 mg/mL) was suspended in a solution of alcohol 4 (2.2 g) and vinyl acetate (2.3 equiv) in *tert*-butyl methyl ether (50

Scheme I[a]



[a] (a) [^{14}C]CH_2O, $PhCH_2NHCH_3$·HBr (CH_3CN) reflux, 2 h; (b) 2 equiv of L-Selectride (THF) 0 °C → 22 °C, 16 h; (c) 2 equiv of H_2C=CHOAc, Lipase P (*t*-BuOMe) 22 °C, 4 days; (d) *p*-$FC_6H_4CF_3$, NaH (DMF), 90 °C, 30 min; (e) $ClCO_2CH_2CCl_3$ ($PhCH_3$), reflux, 30 min; (f) Zn (90% HOAc), 23–25 °C, 30 min; (g) HCl(Et_2O).

† Merrell Dow Research Institute, 2110 East Galbraith Road, Cincinnati, OH 45215.

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mL), and the mixture was stirred at room temperature for 4 days. After silica gel chromatography (EtOAc/hexane), 1.23 g (43% yield; 97% ee) of the ester (-)-5 and 1.02 g (46% yield, 98% ee) of the alcohol (+)-4 were obtained.[15] The excellent optical purity of both enantiomers is due to the high selectivity of the catalyst. Indeed, separate measurements of the initial rates of transesterification of (-)-4 and (+)-4 gave a ratio of 90:1.

Introduction of the 4-(trifluoromethyl)phenyl group was accomplished by alkylation of the alcohol (+)-4 with 4-fluorobenzotrifluoride using sodium hydride in DMF to give ether (+)-6 in 95% yield. The dealkylation of the *N*-benzyl group of (+)-6 was achieved via a two-step sequence. Reaction with 2,2,2-trichloroethyl chloroformate in refluxing toluene gave carbamate (+)-7 in 95% yield after filtration through silica gel. Then removal of the carbamate group of (+)-7 with zinc dust in 90% acetic acid[16] gave (+)-1, after treatment with ethereal HCl, in 61% yield. A single crystallization from 2-propanol gave (+)-1 (43% overall yield from (+)-4) with excellent optical purity (>99% ee). The enantiomer (-)-1 was similarly prepared in 62% yield (>99% ee) from (-)-4, the product of saponification of ester (-)-5 with NaOH in ethanol (96% yield).

The reaction conditions, developed first for the unlabeled synthesis, were employed for the synthesis of [^{14}C]MDL 28618A. Thus, 96 mg (3.20 mmol) of unlabeled paraformaldehyde and 46.8 mg (1.56 mmol, 95.1 mCi, 61 mCi/mmol as CH_2O) of [^{14}C]paraformaldehyde were condensed with 628 mg (4.75 mmol) of indane 2 and 959 mg (4.75 mmol) of benzylmethylamine hydrobromide to give 928 mg of [^{14}C]-3 (2.68 mmol, 39.1 mCi, 14.6 mCi/mmol). Reduction with L-Selectride gave 630 mg of [^{14}C]-(±)-4 (2.36 mmol, 34.5 mCi) after chromatography.

The enzymatic resolution of [^{14}C]-(±)-4, as conducted for the unlabeled material above, gave a 43% yield (272 mg, 1.02 mmol, 14.9 mCi) of the [^{14}C]-(+)-4 after column chromatography. The optical purity of this material was shown to be >99% ee.[15] Also recovered was 253 mg (1.22 mmol) of the [^{14}C]-(-)-5.

Conversion of [^{14}C]-(+)-4 to [^{14}C]-(+)-1 was accomplished according to the scheme. In the synthesis of the radioactive material, a low yield (44%) was obtained in the final deprotection step ((+)-7 → (+)-1), resulting in an overall radiochemical yield of 5%. A total of 4.8 mCi (117 mg) of [^{14}C]-(+)-1 was obtained with a specific activity of 14.6 mCi/mmol and radiochemical purity of 99.8%.[17]

Supplementary Material Available: Elemental analyses, $[\alpha]^{20}_D$, and spectral data (MS, NMR) for compounds 1-7 and chiral HPLC chromatograms for compounds 1 and 4 (6 pages). Ordering information is given on any current masthead page.

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(13) All compounds have been fully characterized by ^{1}HMR, MS, and elemental analyses and also melting points and $[\alpha]^{20}_D$ have been determined. Determination of the absolute configurations of these compounds is under investigation. Only one possible option is shown here for clarity. Selected data are cited: (-)-1: mp 205-206 °C; $[\alpha]^{20}_D$ -180° (*c* 0.91, MeOH). (+)-1: mp 204.5-206 °C; $[\alpha]^{20}_D$ +181° (*c* 1.01, MeOH); $C_{18}H_{18}F_3NO\cdot HCl$ [*m/z* 322 (M^+ + 1)]. Calcd: C, 60.42; H, 5.35; N, 3.92. Found: C, 60.17; H, 5.35; N, 3.83. ^{1}H NMR (300 MHz, CD_3OD): δ 2.77 (s, 3 H), 3.1-3.3 (m, 5 H), 3.43 (dd, *J* = 12.8 Hz, 1 Hz), 7.17 (t, *J* = 7 Hz, 1 H), 7.25-7.37 (m, 5 H), 7.6 (d, *J* = 8.5 Hz, 2 H).

(14) The resolution of (±)-4 can be achieved by hydrolysis of its *O*-acetyl derivative in water, catalyzed by porcine liver esterase. However, the moderate selectivity of this enzyme combined with the instability of (±)-4 esters in water makes the hydrolytic pathway less attractive.

(15) Lipase P was supplied by Amano Pharmaceutical Co. Enantiomeric excess was determined by HPLC using Chiralcel OD column (Daicel) with a mobile phase of hexane-2-propanol-diethylamine (80:20:0.1). t_R in min (+)-1, 9.33; (-)-1, 14.06; (+)-4, 10.75; (-)-4, 11.42. The ee for (-)-5 has been measured on the alcohol (-)-4 from saponification of (-)-5.

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(17) Radiochemical purity was analyzed by HPLC. Fifty 15-s fractions were collected and counted by liquid scintillation.

Use of Reaction Cubes for Generation and Display of Multiple Mechanistic Pathways

Paul H. Scudder

Division of Natural Sciences, New College, Sarasota, Florida 34243

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Summary: Reaction cubes in which one face represents the charge types of reactants and the opposite face represents the corresponding charge types of products can be used for displaying coherently the multiple mechanistic paths of familiar reactions and for generating systematically mechanistic hypotheses for new reactions.

Three-dimensional energy diagrams and their two-dimensional projections have found extensive use in the analysis of complex reactions, especially eliminations and carbonyl addition reactions.[1] These More O'Ferrall diagrams have also found extensive qualitative use in instruction at the graduate level.[2] They help explain the

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