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# Enantioselective synthesis of (1*R*,2*S*,4*S*)-7-oxabicyclo[2.2.1]heptan-2-*exo*-carboxylic acid

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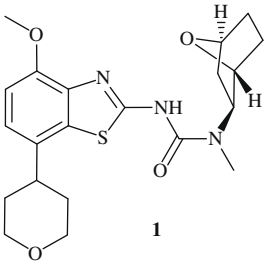
ABSTRACT

A scalable enantioselective access to (1*R*,2*S*,4*S*)-7-oxabicyclo[2.2.1]heptan-2-*exo*-carboxylic acid **7**, a key precursor in the synthesis of A2a receptor antagonist **1** by means of an enzymatic resolution of the respective butyl ester with lipase A from *Candida antarctica*, is described.

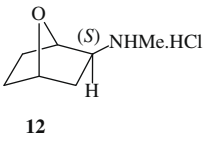


## 1. Introduction

Adenosine is a key modulator of many neurophysiological processes and the high concentration of A2a-receptors present in the dopamine-rich regions of the brain are intimately involved in the control of emotion, reward and pleasure. Benzothiazole derivative **1** was under evaluation as a A2a receptor antagonist candidate for the treatment of major depression,[1] and in view of clinical studies, a scalable synthesis had to be developed. Among several alternative approaches evaluated, only the convergent assembly from two key components, the bicyclic methylamine **12** and aminobenzothiazole **2** (via an activated carbamate, cf. Scheme 1) turned out to be viable on a larger scale.



**1**



**12**

## 2. Results and discussion

Several potential routes to building block **12** based on various cycloaddition reactions followed by enzymatic or classical resolution steps were considered and partially evaluated. However, none of them really revealed sufficient practical promise in terms of yield, cost or selectivity to warrant further thorough investigation. Instead, under relatively tight time constraints, an existing published, non-patented route to compound **12** as the racemate[2] was chosen and adapted accordingly. Essentially it comprised the uncatalyzed cycloaddition of furan to methyl acrylate, affording a 6:1 *endo*-/*exo*-mixture of *rac*-ester adducts which were separated by chromatography after hydrogenation. The remaining steps paralleled those shown in Scheme 1. Since the cycloaddition reactions were unselective and the isomer separation was impractical, a more manageable synthesis was essential for the preparation of enantiopure **12**, especially for scale-up purposes. The Diels–Alder reaction was significantly ameliorated by implementing instead a $ZnCl_2$-mediated cycloaddition (0.3 equiv, rt/16 h) of furan with acrylonitrile, generating the bicyclic eneether **3** as a 1:1 mixture of *endo*- and *exo*-isomers[3] which after hydrogenation to the saturated nitrile isomers **4**[3a] were hydrolyzed under alkaline conditions (aq KOH/EtOH, 75 °C/2 h) exclusively to the racemic *exo*-acid **5** (95% from **3**) thus solving the initial selectivity issue. Enantioselective enzymatic hydrolysis of the respective racemic *exo*-butylester **6b** gave rise to the (*S*)-acid **7** which was re-esterified to the ethyl ester **8** required for successful conversion in the subsequent reaction sequence. In a one-pot, three-step process, successive hydrazinolysis, treatment of the acylhydrazide **9** with $NaNO_2$/aq HCl and *Curtius* rearrangement in EtOH of the acylazide **10** intermediate created in situ produced the carbamate **11**. Reduction with LAH furnished the bicyclic methylamine **12**, isolated as the HCl-salt in an overall yield of 15% (Scheme 1).[4]

### 2.1. Evaluation of chemoenzymatic routes

In the course of route evaluation, the potential of an array of enzyme-catalyzed resolution reactions was cursorily screened (see below); only the kinetic resolution of the racemic *exo*-ester

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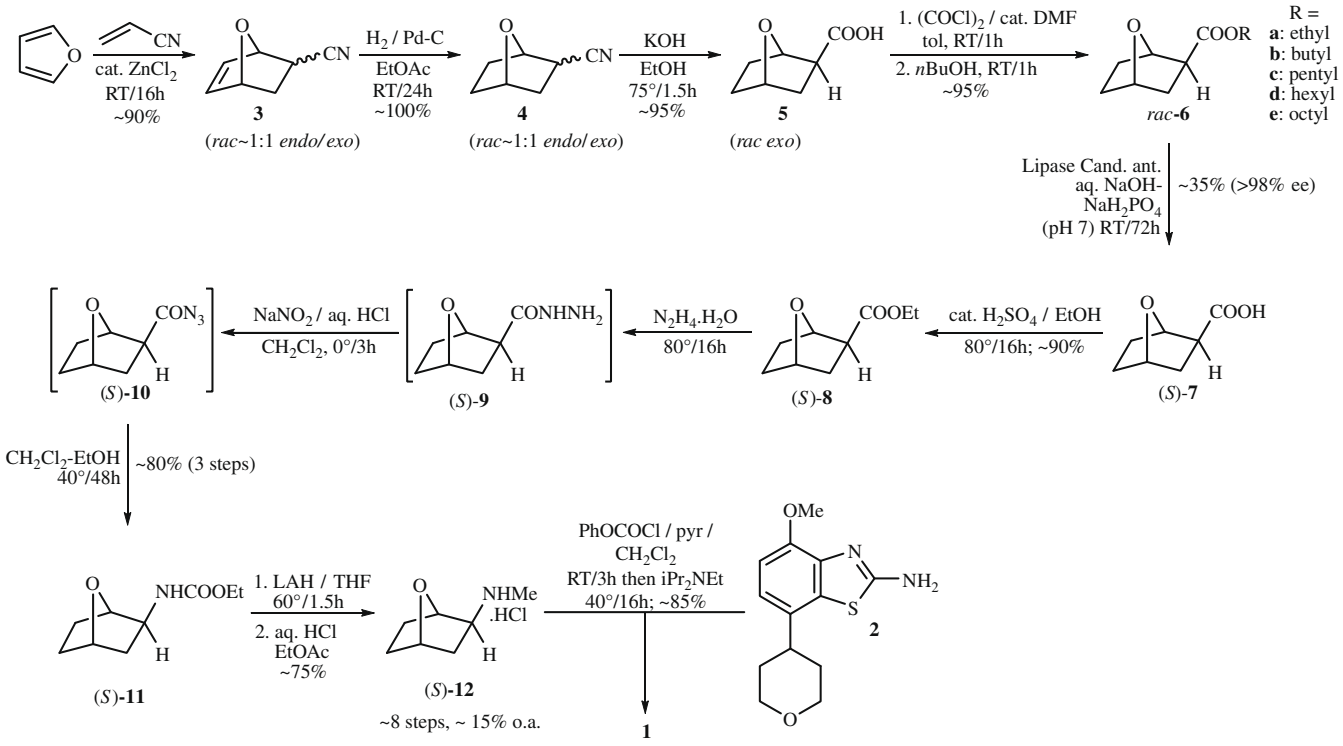
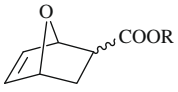



**Scheme 1.** Chemoenzymatic route to A2a receptor antagonist **1**.

**6** delivered results with practical relevance (see next section). Resolution of the structurally related esters **13** derived from the unsaturated compound *exo*-7-oxabicyclo[2.2.1]hept-5-ene-2-carboxylic acid has been described in the literature.[5] However, both the methyl ester (using *Candida rugosa*[5a]) and the ethyl ester (using lipase from *Candida antarctica,* form B[5b]) were resolved only with moderate selectivity ($E$ <15), insufficient for large-scale preparation of the formed (*S*)-configured acid in high enantiomeric excess. In addition, problems due to concomitant retro Diels–Alder reaction were observed during workup of the product.[5b]



**13**

A more direct enantioselective access to acid **7** was attempted by the stereoselective action of nitrilases on nitrile **4** prepared with an improved *exo*/*endo*-ratio of 9:1 when employing 1 equiv of $ZnCl_2$, 50 °C, 72 h in the Diels–Alder reaction.[6] However, screening of microbial strains containing nitrilase activity as well as a panel of commercially available nitrilases afforded only modest selectivities ($E$ <14).[7] Likewise, no appreciable reaction was observed in the attempted hydroxylaminolysis of the pentyl ester **6c** with lipase A and B from *C. antarctica* in various solvents, as well as in the enzymatic formation of hydroxamic acid from acid **5**.

## 2.2. Enantioselective hydrolysis of bicyclic ester 6

In an extensive enzyme screening for the enantioselective hydrolysis of ethyl ester **6a**, none of the enzymes showed appreciable preference for retention of the (1*R*,2*S*,4*S*)-configurated ester which would have provided a short and robust route to ester **8**. Therefore, the pathway had to proceed via the formed (1*R*,2*S*,4*S*)-acid **7** which required a high selectivity ($E$ >100).[8] With the butyl ester **6b** only lipase from *C. antarctica* form A—a commercial source of which is Chirazyme L-5 (Roche Diagnostics) or the bulk enzyme Novocor AD L (Novozymes)—exhibited moderate selectivity ($E$ ≈35). The longer chain alkyl esters **6c**–**e** exhibited *E*-values >90 at rt, nevertheless the reaction had to be stopped before reaching 50% conversion in order to obtain the acid in >97% ee which was mandatory owing to the modest enantiomeric enrichment attainable in the subsequent steps.

Employing the pentyl ester **6c** at a technically acceptable substrate concentration of 5%, acid **7** was obtained in ~98% ee at ~41% conversion ($E \geqslant 180$) using the liquid enzyme formulation Novocor AD L (*s*/*e* 5) in 0.1 M NaCl and 4 mM sodium phosphate buffer pH 7.0 at 28 °C.[4] At higher substrate concentrations the selectivity deteriorated significantly. Since on a kg-scale the preparation of the pentyl ester suffered from thermal stress in the removal of excess pentanol, the butyl ester **6b** was favoured. Optimization of reaction parameters for **6b** revealed the positive effect of elevated phosphate ion concentration (100 mM; pH 7.0) on the reaction rate (~1.4-fold acceleration). This in turn permitted the reaction temperature to be lowered to 10 °C, improving selectivity. Finally, at a butyl ester concentration of 5%, the product was obtained in 98% ee at 40% conversion ($E \geqslant 180$).[9] Since the enzyme did not act upon the *endo*-ester, present in only a very small amount in the substrate, the *endo*-form was easily removed together with the retained ester and the fairly water-soluble product acid **7** was isolated by repeated extraction with organic solvent at acidic pH. Acid **7** was obtained in 98% ee and 36% yield and could be enantiomerically enriched to >99.5% ee by means of digestion from MTBE-heptane 1:2 (32% yield). The procedure[9] was successfully scaled-up to a multi-kg-scale.

## 3. Conclusion

The present enzymatic resolution procedure of **6b** enabled a scalable enantioselective synthesis of the enantiopure bicyclic moiety **12** (eight steps, ~15% o.a.) with technical potential for

the large scale access to the A2a receptor antagonist **1** devoid of chromatographic purifications, extreme conditions and toxic/exotic reagents.

Route assessment including several enzyme screenings indicated the enzymatic kinetic resolution of racemic 7-oxa-bicyclo[2.2.1]heptan-2-*exo*-carboxylic acid ester **6** as the favoured option and work on a larger scale indicated the butyl ester **6b** as the substrate of choice. The screening of various chemical and physical reaction parameters revealed an enhanced reaction rate at elevated phosphate buffer concentration. The increased reaction rate in turn allowed a reduction of the reaction temperature, enhancing enzyme selectivity. The enzymatic procedure established was scaled-up to a multi-kg level.

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7. Personal communication Steven Paul Hanlon and Hans Iding, Hoffmann-La Roche Ltd.
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9. Butyl ester **6b** (100 g, 504 mmol, 99%) was emulsified in 2 L 100 mM sodium phosphate buffer pH 7. The pH was adjusted to 7.1 with 5.7 ml aq NaOH (32%) and the temperature lowered to 10 °C. Hydrolysis was started with 15 ml *C. antarctica* A lipase Novocor AD L (Novozymes, Bagsvaerd, Denmark) and the pH was maintained at 7.0 by the controlled addition of 1 M NaOH solution under vigorous stirring. After a consumption of 200.3 ml (40% conversion; 72 h; 97.9% ee) the reaction was stopped by the addition of 350 ml dichloromethane, followed by 40 g filter aid dicalite. The mixture was stirred for 0.3 h, filtered and extracted with 1.2 L and 0.5 L MTBE. The organic phases were washed separately with 100 ml deionized water and the combined aqueous phases acidified with 55 ml hydrochloric acid (25%) to pH 2. Then 40 g of Dicalite were added, and after stirring for 0.3 h and filtering, the filtrate was saturated with 800 g NaCl and extracted four times with 0.8 L MTBE. The combined extracts were dried over $Na_2SO_4$, filtered and evaporated at 50 °C/440-280 mbar, yielding 26 g (36%) of a white solid (GLC purity: 97.5%, ee: 98.3%, $[\alpha]_D = -28.8$ (*c* 1.00, EtOH). For further purification, a main portion of the crude material (24.6 g) was suspended in 25 ml MTBE and heated to 50 °C. The partial solution attained was treated after 0.2 h with 50 ml heptane at the same temperature. The white suspension was cooled to rt and stirred for 3 h. The product was filtered, washed three times with 2.5 ml MTBE/heptane 1:2 and dried for 4 h at 50 °C/30 mbar providing 21.8 g **7** (89% recovery, 32% step yield based on assay for entire amount) as a white crystalline solid. Analysis: 99.6% GLC; 99.6% ee; EI-MS: 143.2 ($M+H^+$), 142.2 (M); IR (nujol): 2923, 1720, 1230, 1192 (COOH), 1140 (C–O–C) $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ (ppm) 10.6 (s br, 1H, COOH), 4.86 (d, *J* = 5.1 Hz, 1H, H-1), 4.69 (t, *J* = 5.0 Hz, 1H, H-4), 2.67 (dd, *J* = 9.1, 4.6 Hz, 1H, H-2), 2.06–2.22 (m, 1H, H-3′), 1.69–1.85 (m, 3H, H-3″, H-5′, H-6′), 1.43–1.60 (m, 2H, H-5″, H-6″).