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## Asymmetric synthesis of the key intermediate of an SP antagonist RPR107880 using a base-catalyzed Diels–Alder reaction

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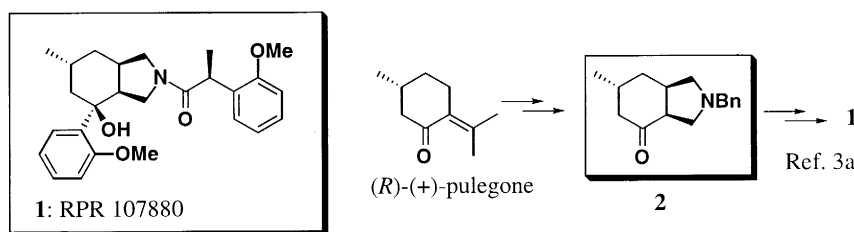
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### Abstract

An asymmetric synthesis of the key intermediate of RPR 107880, a substance P antagonist, using a base-catalyzed Diels–Alder reaction of 3-hydroxy-2-pyrone and *N*-benzylmaleimide is described. © 2000 Elsevier Science Ltd. All rights reserved.

**Keywords:** base-catalyzed Diels–Alder reaction; asymmetric synthesis; RPR 107880; substance P.

Substance P (SP) is a small peptide classified in the tachykinine family, and it behaves as a neurotransmitter.<sup>1</sup> Recent investigations into SP have disclosed its various physiological functions, such as pain transmission, vasodilatation, smooth muscle contraction, plasmatic extravasations, inflammation, and the regulation of immune response.<sup>2</sup> Therefore, such antagonists of SP are expected to be excellent drugs. Over the last 10 years vigorous research to find strong and stable antagonists was undertaken, and some compounds were reported as antagonists.<sup>3</sup> Particularly, the perhydrorisoindole derivatives (ex. **1**) were recently recognized as efficient antagonists (Scheme 1).<sup>3a–c</sup>

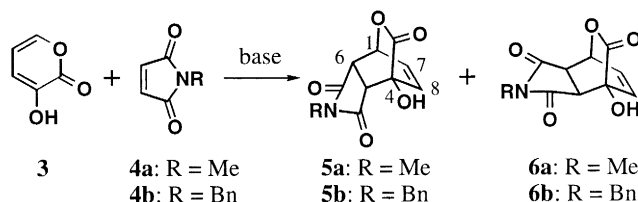


Scheme 1.

In the preceding paper, we reported the base-catalyzed Diels–Alder (DA) reaction of 3-hydroxy-2-pyrone (**3**) and *N*-methylmaleimide (**4a**),<sup>4a</sup> and its asymmetric reaction using a cinchona alkaloid

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catalyst (Scheme 2).<sup>4b</sup> Since the resulting adduct **5a** has various functionalities and a rigid cyclic structure, it seems to be an excellent building block for the synthesis of various molecules, in particular, perhydroisoindoles. Thus, we have examined the synthesis of SP antagonists RPR 107880 (**1**) and related compounds.<sup>3</sup> Although the asymmetric syntheses of these compounds were already achieved by using the chiral pool method<sup>3a</sup> or optical resolution of racemic material,<sup>3b,c</sup> no direct methods using an asymmetric reaction have been reported. In this paper, we disclose an efficient method to construct perhydroisoindole derivative using the asymmetric base-catalyzed DA reaction.



Scheme 2.

As a concrete synthetic target, we chose compound **2** which was originally derived from (*R*)-(+)-pulegone as the key intermediate of **1** (Scheme 1). Since this compound was anticipated to be synthesized from **5b**, we examined the asymmetric base-catalyzed DA reaction of **3** and *N*-benzylmaleimide (**4b**) prior to the synthesis (Table 1).

Table 1  
Asymmetric base-catalyzed DA reaction of **4** and **5b**<sup>a</sup>

entry	base (eq)	condition <sup>b</sup>	yield (%)	%ee of <b>5b</b>
1	cinchonidine (1.0)	A	99	54
2	quinine (1.0)	A	99	63
3	quinine (0.3)	A	95	55
4	quinine (0.3)	B	92	59

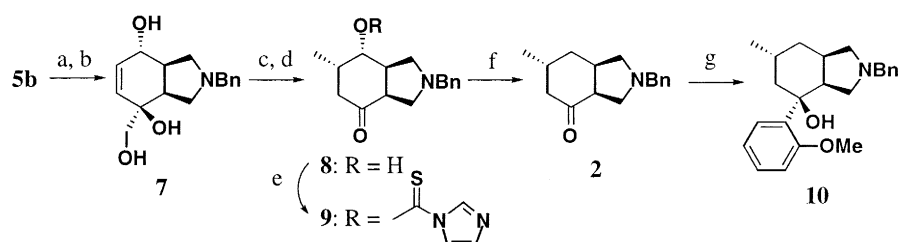
<sup>a</sup>All the reactions were carried out in CH<sub>2</sub>Cl<sub>2</sub> at -78~-20 °C for 12 h. No *exo* isomer (**6b**) was obtained. <sup>b</sup>Condition A: Crystalline **4b** (1.1 eq) was added to a CH<sub>2</sub>Cl<sub>2</sub> solution of **3** (1.0 eq) and catalyst at once; condition B: a CH<sub>2</sub>Cl<sub>2</sub> solution of **3** (1.0 eq) was slowly added to a mixture of **4b** (1.1 eq) and catalyst in CH<sub>2</sub>Cl<sub>2</sub> during the period of 5 h.

As well as the asymmetric reaction of **3** and **4a**,<sup>4b</sup> cinchona alkaloid catalyst, CH<sub>2</sub>Cl<sub>2</sub> solvent, and low temperature (-78~-20°C) were again effective to give optically active **5b**, and the highest enantioselectivity was obtained from the reaction with 1 equivalent of quinine (entry 2).<sup>5</sup> Although decreasing the amount of catalyst (entry 3) lowered the enantioselectivity, a slight improvement was achieved by the slow-addition method (condition B, entry 4). Based on several examinations, over 7 g of (-)-**5b** in 59% ee was obtained from one reaction using 0.3 equivalents of quinine (entry 4).

This insufficient optical purity of the resulting adduct prompted us to examine the purification of the enantiomer. Since the resulting product was obtained as a crystalline material, we initially attempted the purification by recrystallization, and surprisingly, *only one recrystallization from hexane/ethyl acetate afforded the complete optically pure mother liquor and racemic crystalline material*. Indeed, recrystallization of 7.0 g of (-)-**5b** (59% ee) from ca. 20 ml of hexane:ethyl acetate (1:9) afforded 2.9 g of racemate as a crystalline material and 4.1 g of the homochiral (-)-enantiomer from the mother liquor.

These weights were quite consistent with calculated quantities from the amount and purity of the starting **5b**.

With quantities of the optically pure starting material in hand, we started the synthesis of the intermediate **2** (Scheme 3). The reduction to give trihydroxylamine (**7**) was quite difficult because of the instability of **5b** under basic condition. From several examinations, compound **7** was obtained in fair yield by TMS protection of **5b** and subsequent  $\text{AlH}_3$  reduction. The oxidative cleavage of **7** followed by methylation using  $\text{MeMgBr}$  exclusively afforded the desired isomer **8**. The stereochemistry of this methyl group was presumed to be controlled by coordination between  $\text{MeMgBr}$  and the neighboring oxygen atom at the hydroxyl group. After the methylation, the hydroxyl group was removed by thiocarbonylation followed by  $n\text{-Bu}_3\text{SnH}$  reduction to give the desired intermediate **2** in good yield. To confirm its structure and stereochemistry, **2** was further converted to another intermediate **10** using a known process.<sup>3a</sup> Since the  $^1\text{H}$  NMR and  $[\alpha]_D$  value of **10** showed good agreement with those of previously reported data,<sup>3a,6,7</sup> the structure including absolute stereochemistry were confirmed as shown in Scheme 3.



Scheme 3. Reagents and conditions: (a)  $\text{TMSCl}$ , imidazole, DMF,  $60^\circ\text{C}$ , 12 h, 93%; (b)  $\text{AlH}_3$ , THF,  $-78^\circ\text{C}$ –rt, 2 days, 62%; (c)  $\text{NaIO}_4$ , aq THF,  $0^\circ\text{C}$ , 12 h, 74%; (d)  $\text{MeMgBr}$ , THF,  $-78^\circ\text{C}$ , 2 h, 48%; (e) thiocarbonyldiimidazole, THF, reflux, 2 days, 46% (26% of **10** was recovered); (f)  $n\text{-Bu}_3\text{SnH}$ , AIBN, toluene, reflux, 2 h, 93%; (g)  $o$ -anisyllithium,  $\text{LiBr}$ ,  $-78^\circ\text{C}$ , 2 h, 62%

In conclusion, we have established an efficient method to obtain a homochiral perhydroisoindole derivative using an asymmetric DA reaction. Since perhydroisoindoles are supposed to be prospects of the strong SP antagonists and potential drugs, further synthetic applications using this method are under way.

Furthermore, quite efficient recrystallization to give optically pure **5b** was also noteworthy. Detailed features of this recrystallization are also under investigation.

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- All the reactions summarized in Table 1 afforded *endo*-isomer **5b** exclusively. The enantiomeric excess of **5b** was determined on the basis of the  $^1\text{H}$  NMR signals corresponding to H-6 of the (–)- and (+)-enantiomers, which separately appeared at 3.62 and 3.54 ppm, respectively, by measurement in a saturated  $\text{CDCl}_3$  solution of (*S*)-(–)-binaphthol.

6. Spectra data for **10**:  $[\alpha]_{\text{D}}^{22} -51$  (*c* 0.59, EtOH), lit.<sup>3a</sup>  $[\alpha]_{\text{D}} -51.7$  (*c* 0.5, EtOH); IR (neat): 3283, 2951, 2913, 1597, 1582, 1483, 1454, 1235, 1028, 754, 700  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $d_6$ -DMSO with a few drops of  $\text{CD}_3\text{CO}_2\text{D}$ ):  $\delta$  0.88 (d,  $J=6.2$  Hz, 3H), 1.30 (m, 1H), 1.54 (d,  $J=12.1$  Hz, 1H), 1.75 (d,  $J=13.6$  Hz, 1H), 2.17 (t,  $J=12.1$  Hz, 2H), 2.65 (m, 1H), 2.73 (d,  $J=9.9$  Hz, 1H), 2.80–2.88 (m, 2H), 2.93 (t,  $J=9.5$  Hz, 1H), 3.18–3.23 (m, 1H), 3.80 (s, 3H), 4.10 (m, 2H), 6.95 (m, 2H), 7.23 (br t,  $J=7.7$  Hz, 1H), 7.35–7.55 (m, 5H), 7.65 (br d,  $J=7.7$  Hz, 1H);  $^{13}\text{C}$  NMR (100 MHz):  $\delta$  156.1, 128.4, 128.2, 127.6, 127.1, 120.5, 111.1, 74.5, 59.5, 56.9, 56.1, 55.0, 44.6, 41.5, 36.6, 34.5, 22.1, 21.6; HRMS  $m/z$  352.2269 ( $[\text{M}+\text{H}]^+$  calcd for  $\text{C}_{23}\text{H}_{29}\text{O}_2\text{NH}^+$ : 352.2277).
7. In the  $^1\text{H}$  NMR spectrum of **10**, the chemical shifts of the signals corresponding to the N–CH group were varied with the amount of  $\text{CD}_3\text{CO}_2\text{D}$ .