Tetrahedron Letters 54 (2013) 1449–1451

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

First asymmetric synthesis of Silodosin through catalytic hydrogenation by using Ir-SIPHOX catalysts

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ARTICLE INFO

Article history:
Received 8 November 2012
Revised 31 December 2012
Accepted 4 January 2013
Available online 10 January 2013

Keywords:
Silodosin
Asymmetric hydrogenation
Ir-SIPHOX catalyst
α,β-Unsaturated carboxylic acid

ABSTRACT

An asymmetric synthesis of Silodosin was accomplished in high yield via catalytic hydrogenation of α,β-unsaturated carboxylic acid derivatives by using chiral catalyst Ir-SIPHOX, followed by Curtius rearrangement.

Introduction

Benign prostatic hyperplasia (BPH) is a common disorder in middle-aged and elderly men which produces bladder outlet obstruction, followed by voiding dysfunction characterized by urinary frequency, nocturia, urgency, poor steam, and hesitancy in initiation of micturition. Functional response of the human prostate is predominantly mediated through α_1-adrenoceptors. The ability of α_1-adrenoceptor antagonists to improve the symptoms of BHP was first demonstrated by Caine et al., and their use in the treatment of therapy is now widely accepted.[1] α_1-Blockers (α_1-adrenoceptor antagonists) are a well-established and effective treatment for BPH-related lower urinary tract symptoms and are generally a first-line therapy for BPH management.[2]

Silodosin (Rapaflo®) was developed by Kissei and Daiichi, and was approved by the FDA in 2008. The drug works as a selective α_1-adrenergic receptor antagonist developed for the treatment of the signs and symptoms of BHP.[3] Its chemical structure is known as (*R*)-1-(3-hydroxypropyl)-5-[2-[[2-[2-(2,2,2-trifluoro-ethoxy) phenoxy]-ethyl]amino]propyl]-indoline-7-carboxamide (Fig. 1).

The synthesis of Silodosin is relatively complex, which involves multistep synthesis. The most challenging part is to construct a chiral center bearing an amino group in the molecule. The general approaches up to date are chiral resolution of the racemic amine **2**[4] and reductive amination of the adduct from ketone and chiral amine derivatives.[5,6] However, the efficiency, enantioselectivity, and atom-economy of all those approaches are low. Therefore, more efficient, economically, and environmentally benign route,

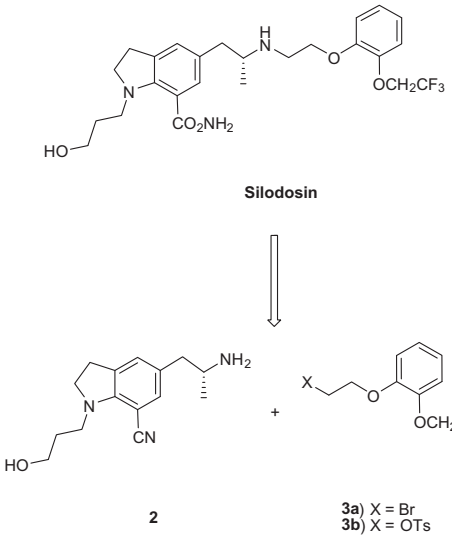

Figure 1. Retrosynthesis of Silodosin.

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http://dx.doi.org/10.1016/j.tetlet.2013.01.003

which can be used for large scale manufacture of Silodosin, is highly desired.

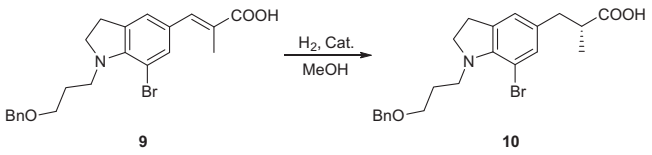
It is well known that the catalytic asymmetric hydrogenation is one of the elegant and powerful methods for the preparation of optical active compounds in atom-economic way, and has been widely used in industry. A number of efficient chiral catalysts including Ru catalysts and Rh catalysts have been reported for the asymmetric hydrogenation of α,β-unsaturated carboxylic acid to produce optical chiral carboxylic acids.[7]

The chiral Ir catalysts, which are very efficient in the hydrogenations of unfunctionalized olefins, imines, and heteroaromatic compounds,[8] however, were rarely used in the hydrogenation of unsaturated carboxylic acids[9] until a novel class of chiral spiro iridium/phosphine–oxazoline complexes (Ir-SIPHOX) was developed by Zhou and co-workers.[10] The Ir-SIPHOX catalysts have been proved to be highly efficient for the asymmetric hydrogenation of α-alkyl α,β-unsaturated carboxylic acids (ee up to 99.4%, TON up to 10,000),[11] α-aryloxy and α-alkoxy α,β-unsaturated carboxylic acids (ee up to 99.8%, TON up to 10,000)[12] under mild conditions. Herein, we report the first asymmetric synthesis of Silodosin by using Ir-SIPHOX-catalyzed asymmetric hydrogenation of α,β-unsaturated carboxylic acid as the key technology.

Synthesis

The synthesis of α,β-unsaturated carboxylic acid **9** is shown in Scheme 1. The N-alkylation of indoline (**4**) with 1-chloro benzyloxypropane produced compound **5** in 95% yield. Formylation of **5** by Vilsmeier–Haack reaction gave aldehyde **6** in 90% yield. Bromination of **6** with bromine afforded regioselectively **7** as the only product in 97% yield. Reaction of **7** with Wittig reagent $Ph_3P{=}C(Me)CO_2Et$ provided α,β-unsaturated carboxylic acid ethyl ester **8**, followed by hydrolysis with sodium hydroxide in methanol to give α,β-unsaturated carboxylic acid **9** in 86% yield.

The asymmetric hydrogenation of α,β-unsaturated carboxylic acid **9** (Scheme 2) was investigated by using Ir-SIPHOX catalysts. Three of Ir-SIPHOX catalysts (Fig. 2) were compared as they showed high reactivity and high enantioselectivity in the asymmetric hydrogenation of α,β-unsaturated carboxylic acids.[11,12] The reaction was initially performed at a substrate to catalyst mole ratio (*S*/*C*) of 400 in MeOH under 8 atm of H_2 at 70 °C for 24 h (Table 1). With catalyst (R_a,*R*)-**1a**, the hydrogenation product (**10**) was obtained in 92% ee, but with only 18% conversion (entry 1). With an addition of 1.0 equiv of triethylamine the reaction rate and enantioselectivity were significantly improved (complete conversion within 2 h in 98% ee) (entry 2). The low efficiency of the catalyst (R_a,*S*)-**1a** (entry 3) revealed that it has mis-matched configurations. In the presence of NEt_3, the catalyst (R_a)-**1b** which has no substituent on the oxazoline ring gave a result similar to that of (R_a,*R*)-**1a** (entry 4). When the reaction was performed at a lower catalyst loading, the catalyst (R_a)-**1b** showed much higher efficiency than catalyst (R_a,*R*)-**1a**, giving a full conversion and high



Scheme 2. Asymmetric hydrogenation of α,β-unsaturated carboxylic acid **9**.

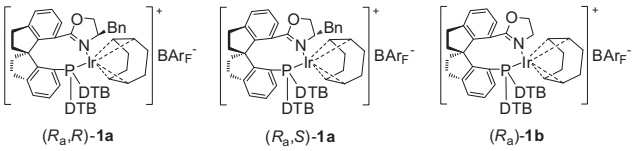
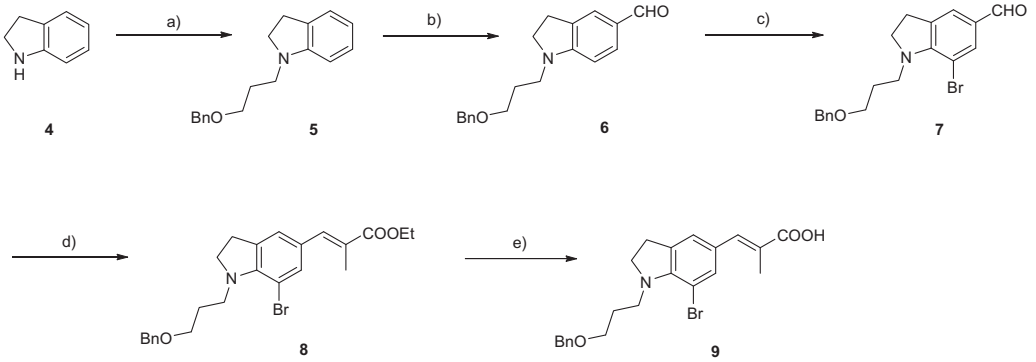


Figure 2. Ir-SIPHOX catalysts.

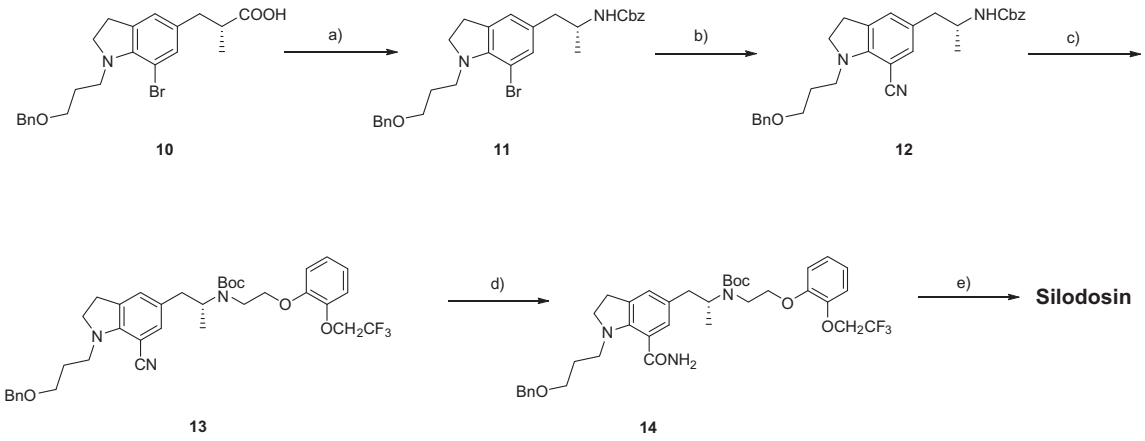
Table 1
Asymmetric hydrogenation of (*E*)-3-(1-(3-(benzyloxy)propyl)-7-bromoindolin-5-yl)-2-methylacrylic acid: optimization of reaction conditions[a]

Entry	Catalyst	*S*/*C*	Additive	Time (h)	Conv[b] (%)	ee[c] (%)
1	(R_a,*R*)-**1a**	400	None	24	18	92
2	(R_a,*R*)-**1a**	400	1 equiv of NEt_3	2	100	98
3	(R_a,*S*)-**1a**	400	1 equiv of NEt_3	24	12	n.d.[d]
4	(R_a)-**1b**	400	1 equiv of NEt_3	2	100	98
5	(R_a,*R*)-**1a**	1000	1 equiv of NEt_3	24	45	n.d.[d]
6	(R_a)-**1b**	1000	1 equiv of NEt_3	5	100	98
7	(R_a)-**1b**	2000	2 equiv of NEt_3	9	100	98
8	(R_a)-**1b**	4000	2 equiv of NEt_3	24	90	97
9	(R_a)-**1b**	4000	2 equiv of $^iPr_2NEt$	24	72	97
10	(R_a)-**1b**	4000	1 equiv of $CsCO_3$	48	57	96
11	(R_a)-**1b**	4000	3 equiv of NEt_3	20	100	97
12	(R_a)-**1b**	4000	5 equiv of NEt_3	20	100	97
13	(R_a)-**1b**	6000	3 equiv of NEt_3	50	100	97
14	(R_a)-**1b**	6000	5 equiv of NEt_3	50	100	97

[a] Reaction conditions: [substrate] = 0.5 M in MeOH, PH_2 = 8–10 atm, 70 °C.
[b] Determined by ^1H NMR analysis.
[c] Determined by HPLC analysis with a chiral column (see Supplementary data).
[d] n.d. = not determined.



Scheme 1. Synthesis of α,β-unsaturated carboxylic acid (**9**). Reaction conditions: (a) $BnOCH_2CH_2CH_2Cl$, DIPEA, NaI, DMF, 100 °C, 3.5 h, 95%; (b) $POCl_3$, DMF, 35 °C, 3 h, 90%; (c) Br_2, CH_2Cl_2, 0 °C, 2.5 h, 97%; (d) $Ph_3P{=}C(Me)CO_2Et$, toluene, 16 h, 100 °C; (e) NaOH, MeOH, 40 °C, 3 h, 86% (two steps).



Scheme 3. Synthesis route of Silodosin from chiral acid **10**. Reaction conditions: (a) Diphenylphosphoryl azide (DPPA), DIPEA, $PhCH_2OH$, 70 °C, 10 h, 76%; (b) CuCN, DMF, 120 °C, 20 h, 88%; (c) (i) H_2, Pd/C, MeOH, rt, 3 h; (ii) **3b**, toluene, reflux, 18 h; (iii) Boc_2O, $NaHCO_3$, 1,4-dioxane, rt, 2 h, 72% (for three steps); (d) H_2O_2, 5 N NaOH, DMSO, rt, 12 h, 83%; (e) H_2, Pd/C, 6 N HCl, MeOH, 90%.

enantioselectivity (98%, ee) within 9 h at $S/C = 2000$ (entries 5–7). Further investigation indicated that in the presence of 3–5 equiv of NEt_3, the catalyst (R_a)-**1b** allowed the reaction to be performed at a very low catalyst loading ($S/C = 6000$) without compromising the enantioselectivity (entries 13 and 14), albeit the reaction needs a longer time. Compared with NEt_3, other additives such as $^iPr_2NEt$ and Cs_2CO_3 gave lower conversion (entries 9 and 10). It is worthy mentioning that bromine on the aromatic ring of **9** was tolerated under hydrogenation conditions, and the product (**10**) was isolated in almost quantitative yield. A reasonable explanation raised by Yamamoto et al. is that the α,β-unsaturated carboxylate anion formed with the addition of tertiary amine is more strongly chelated to the transition-metal center than the acid itself, resulting in higher reactivity and enantioselectivity.[13]

With chiral intermediate **10** in hand, the synthesis of Silodosin was accomplished according to the route shown in Scheme 3.[14] Curtius rearrangement of **10**, followed by trapping the intermediary isocyanate with benzyl alcohol gave the amine **11** in 76% yield with 97.8% ee without loss of the enantiomeric purity. Cynation of **11** by coupling with CuCN in DMF afforded cyanide compound **12** in 85% yield. After deprotection of the Cbz group of **12** and coupling with **3b**, followed by protection of amino group with Boc, **13** was isolated in 90% yield in three steps. Oxidative hydrolysis of **13** provided amide **14** in 83% yield. Deprotection of Boc and benzyl groups simultaneously of **14** by hydrogenation with Pd/C in the presence of acid gave Silodosin in 90% yield (Scheme 3).

In summary, we have accomplished the asymmetric synthesis of Silodosin with high efficiency and high enantioselectivity by a new approach. The key step of the synthesis is the asymmetric hydrogenation of α,β-unsaturated carboxylic acid intermediate **9** by using the novel Ir-SIPHOX catalysts.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.01.003.

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