Pergamon

Tetrahedron Letters 42 (2001) 8493–8495

TETRAHEDRON LETTERS

The first asymmetric synthesis of a dopamine D1 agonist, dihydrexidine, employing asymmetric conjugate addition technology

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Received 5 September 2001; revised 25 September 2001; accepted 28 September 2001

Abstract—The first asymmetric synthesis of benzophenanthridine dopamine D1 full agonist, dihydrexidine, was accomplished employing three key processes, external chiral ligand-controlled conjugate addition of phenyllithium, Curtius conversion of a carboxylic group to an amino group, and finally Pictet–Spengler type cyclization completing skeleton construction.

Parkinson's disease is characterized by the degeneration of dopamine-secreting neurons in the nigrostriatal pathway.[1] Dopamine agonist replacement therapy with L-Dopa, which is endogenously converted to dopamine and thereby stimulates both the D1 and D2 families of receptors, remains the cornerstone of Parkinson's therapy.[2] A benzophenanthridine class compound, dihydrexidine **1**, has been designed and developed by Nichols as the first high affinity bioavailable full dopamine D1 agonist.[3] Dihydrexidine was shown to be effective in a primate model of Parkinson's disease and is reported to be in clinical development. A benzothienoquinoline, A-86929 **2**, has been developed by Abbott Laboratories as a potent and selective full agonist at the D1 receptor that is efficacious in rodent and primate models of Parkinson's disease after both acute and long-term administration.[4] Its diacetate, working as a prodrug of **2**, is in clinical development. These compounds were found to exhibit a high level of enantiospecificity in their interaction with the D1 receptor. The method by optical resolution has been the only procedure reported so far to reach these optically active compounds.[5] We describe the first asymmetric synthesis of **1** employing an asymmetric conjugate addition tech-

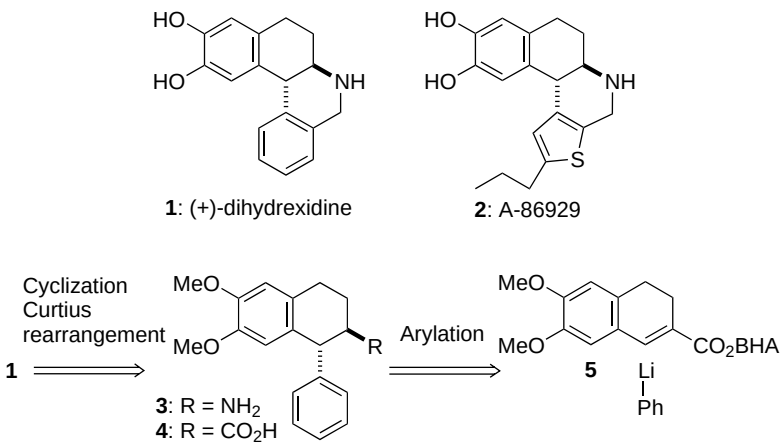

Figure 1. Asymmetric synthetic strategy for dopamine D1 agonist, dihydrexidine **1**.

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0040-4039/01/$ - see front matter
PII: S0040-4039(01)01823-8

nology.[6] The technology demonstrated here may be applicable into the asymmetric synthesis of **2** as well as their potent congeners (Fig. 1).

The synthetic pathway to **1** relies on three key processes, an external chiral ligand-controlled asymmetric conjugate addition reaction of phenyllithium with an α,β-unsaturated ester **5**,[7] Curtius rearrangement-type conversion of a carboxylic acid **4** into an amine **3**, and finally Pictet–Spengler-type cyclization of **3** completing skeleton construction. An asymmetric conjugate addition reaction of organometallic reagents with α,β-unsaturated carbonyl compounds and their equivalents is a powerful and fundamental method in forming a carbon–carbon bond[8] and has been one of targets of our research.[9]

A reaction of a BHA (2,6-di-*t*-butyl-4-methoxyphenyl) ester **5**[10] with phenyllithium was conducted in the presence of a chiral diether (*S*,*S*)-**6**[11] in toluene at −78°C for 3 h predominantly giving an addition product *cis*-**7** in 93% yield (Fig. 2). Isomerization of *cis*-**7** was possible with sodium methoxide in refluxing THF for 42 h to give a thermodynamically stable *trans*-ester in 70% yield. Attempted removal of a BHA group in *cis*- and *trans*-**7** by CAN treatment was unsuccessful giving a mixture of oxidized products.[12] Isomerization and concomitant hydrolysis of a BHA ester **7** were carried out in a one-pot procedure[13] by successive manipulation of **7** with sodium methoxide in refluxing toluene–NMP (*N*-methylpyrrolidone) for 2.5 h to give methyl ester **8** and then with water at reflux for 1 h giving a 13:1 mixture of *trans*- and *cis*-carboxylic acids **4** in 90% yield. The enantiomeric excess of *trans*-acid was then determined to be 74% by a chiral stationary phase HPLC analysis[14] of the alcohol obtained by lithium aluminum hydride reduction of **4**. Other reputable chiral external ligands were examined to improve efficiency of the asymmetric conjugate addition reaction. However, such ligands as sparteine **9** (94%, ent-42% ee), *i*-Pr-Box **10**[15] (96%, 61% ee), and phenyl-Box **11**[15] (53%, 74% ee) turned out not to be beneficial in giving **7**. Fortunately, enantioenrichment was possible by single recrystallization of dicyclohexylamine salt of **4** (74% ee) from ethanol and gave enantiomerically and diastereomerically pure *trans*-**4** in 48% overall yield from **7**.

A conversion of enantiomerically pure **4** into an amine **3** was carried out by successive reactions with ethyl chloroformate-triethylamine in acetone to a mixed anhydride, sodium azide in acetone to acyl azide, heating in refluxing toluene to isocyanate, and finally hydrochloric acid under reflux.[16] The amine **3** was then protected with tosyl chloride and triethylamine in methylene chloride giving a tosylamide **12** in 71% overall yield from a carboxylic acid **4**.

Direct cyclization of the amine **3** and its tosylamide **12** with formaldehyde or its equivalent in the presence of some acid catalysts was unsuccessful due to poor reactivity of a phenyl moiety recovering the starting material.[17] A two-step procedure overcame this problem.

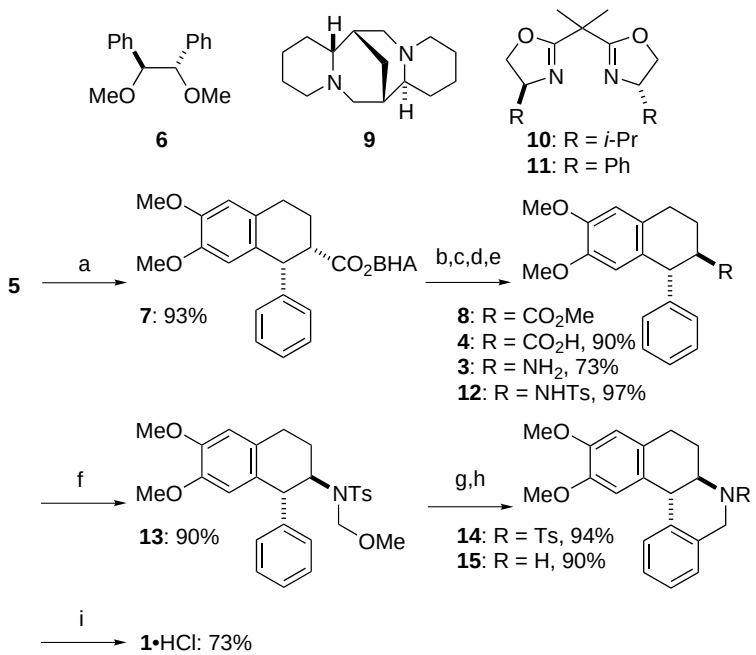

Figure 2. Asymmetric synthesis of dopamine D1 agonist, dihydrexidine **1**. (a) PhLi (2.0 equiv.)–**6** (2.8 equiv.)/toluene, −78°C, 3 h, **7** (93%); (b) i. NaOMe/toluene–NMP, reflux, 2.5 h, ii. H_2O, reflux, 1 h, **4** (90%); (c) i. $HN(c\text{-}Hex)_2$/EtOH, ii. recrystallization from EtOH, optically pure **4** (48%); (d) i. $ClCO_2Et$, Et_3N/acetone, −5 ~ 0°C, 20 min, ii. NaN_3/acetone, −5 ~ 0°C, 1 h, iii. toluene, reflux, 2 h, iv. aq. HCl, reflux, 2 h, **3** (73%); (e) TsCl, Et_3N/CH_2Cl_2, rt, 2 h, **12** (97%); (f) $CH_2(OMe)_2$, $BF_3{\cdot}OEt_2$, rt, 12 h, **13** (90%); (g) TMSOTf/CH_2Cl_2, −40 to −5°C, 3 h, **14** (94%); (h) Na, naphthalene/DME, −78°C, 0.5 h, **15** (90%); (i) i. BBr_3/CH_2Cl_2, rt, 12 h, ii. HCl/EtOH, **1**·HCl (73%).

Reaction of **12** with dimethoxymethane in the presence of boron trifluoride diethyl etherate at rt for 12 h gave a methoxymethylated tosylamide **13** in 90% yield. Treatment of **13** with trimethylsilyl triflate in methylene chloride at −40 to −5°C during 3 h afforded a cyclized tosylamide **14** in 94% conversion yield. A tosyl group in **14** was easily removed by sodium naphthalenide reduction[18] and gave an amine **15** in 90% yield.[19] The final conversion was demethylation of two methoxy groups of **15** using boron tribromide in methylene chloride at rt for 12 h and following hydrochloride formation with hydrochloric acid in ethanol afforded **1**·HCl in 73% yield. Spectroscopic data, melting point, and specific rotation were identical with those reported for the clinically potent compound.[5a]

In conclusion, an external chiral ligand-controlled asymmetric conjugate addition technology has been proved to be applicable to an asymmetric synthesis of a benzophenanthridine class of dopamine D1 full agonist, dihydrexidine **1**. The overall yield was as high as 16% from **5** and this level of performance is tolerable in process chemistry. Further studies on this field including improved strategies and an asymmetric synthesis of **2** are currently under investigation in this laboratory.

Acknowledgements

We gratefully acknowledge financial support from a Grant-in-Aid for Scientific Research on Priority Areas (A) 'Exploitation of Multi-Element Cyclic Molecules' from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

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