Tetrahedron: *Asymmetry* 22 (2011) 1591–1593

Contents lists available at SciVerse ScienceDirect

Tetrahedron: *Asymmetry*

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

Concise, efficient and highly selective asymmetric synthesis of (+)-(3*S*,4*R*)-cisapride

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ARTICLE INFO

Article history:
Received 18 August 2011
Accepted 25 August 2011
Available online 6 October 2011

ABSTRACT

A concise asymmetric synthesis of the gastroprokinetic agent (+)-(3*S*,4*R*)-cisapride {(+)-(3*S*,4*R*)-*N*(1)-[3′-(4″-fluorophenoxy)propyl]-3-methoxy-4-(2‴-methoxy-4‴-amino-5‴-chlorobenzamido)piperidine} from commercially available starting materials has been developed. The key step of this synthesis employs the diastereoselective conjugate addition of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide to *tert*-butyl 5-[*N*-3′-(4″-fluorophenoxy)propyl-*N*-allylamino]pent-2-enoate and in situ enolate oxidation with (−)-camphorsulfonyloxaziridine to set the (3*S*,4*R*)-configuration found within the piperidine ring of the product. This synthesis proceeds in 9 steps from commercially available 1-(4′-fluorophenoxy)-3-bromopropane with an overall yield of 19%.

1. Introduction

(±)-(*RS*,*SR*)-Cisapride {(±)-(*RS*,*SR*)-*N*(1)-[3′-(4″-fluorophenoxy)propyl]-3-methoxy-4-(2‴-methoxy-4‴-amino-5‴-chlorobenzamido)piperidine} is a gastroprokinetic agent[1] that was developed by Janssen Pharmaceutica in the 1980s[2] (Fig. 1). The racemate was marketed (from 1993 onwards) under the trade name Propulsid® as a treatment for gastroesophageal reflux disease,[3] although it has also been used successfully in the treatment of other gastrointestinal diseases such as chronic bowel constipation and irritable bowel syndrome.[4] However, the adverse gastrointestinal (e.g., abdominal pain and diarrhoea) and cardiovascular effects associated with the drug can be severe.[5] Between 1993 and 1999 there were 341 cases of cardiac dysrhythmia attributed to the use of Propulsid®, as well as 80 reported deaths, which ultimately led to the voluntary withdrawal of the drug from market in the USA in 2000, pending further research.[6] It has been reported that administration of the (+)-(3*S*,4*R*)-eutomer substantially reduces the adverse effects associated with the racemate,[7] and the biological screening of compounds related to cisapride is still an active area of research.[8] As such, there is continued interest in the development of methods to enable the efficient syntheses of analogues of cisapride. Herein we report a concise and efficient asymmetric synthesis of (+)-(3*S*,4*R*)-cisapride[9] in 19% yield over 9 steps from commercially available starting materials that should be readily amenable to diversification. The key step of this synthesis employs the diastereoselective conjugate addition of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide to *tert*-butyl 5-[*N*-3′-(4″-fluorophenoxy)propyl-*N*-allylamino]pent-2-enoate and in situ enolate oxidation with (−)-camphorsulfonyloxaziridine [(−)-CSO] to set the (3*S*,4*R*)-configuration found within the piperidine ring of the final product.

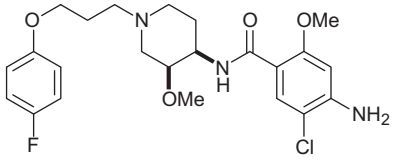
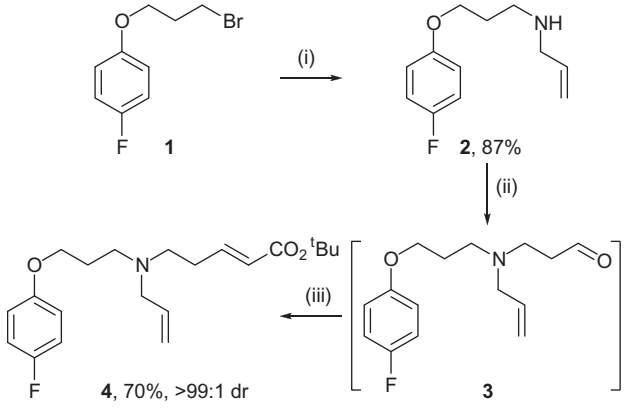


Figure 1. Structure of (+)-(3*S*,4*R*)-cisapride.



Scheme 1. Reagents and conditions: (i) allylamine, K_2CO_3, NaI, THF, rt, 16 h; (ii) acrolein, DBU, THF, −15 °C, 40 min; (iii) $Ph_3P{=}CHCO_2{}^tBu$, THF, −15 °C to rt, 16 h.

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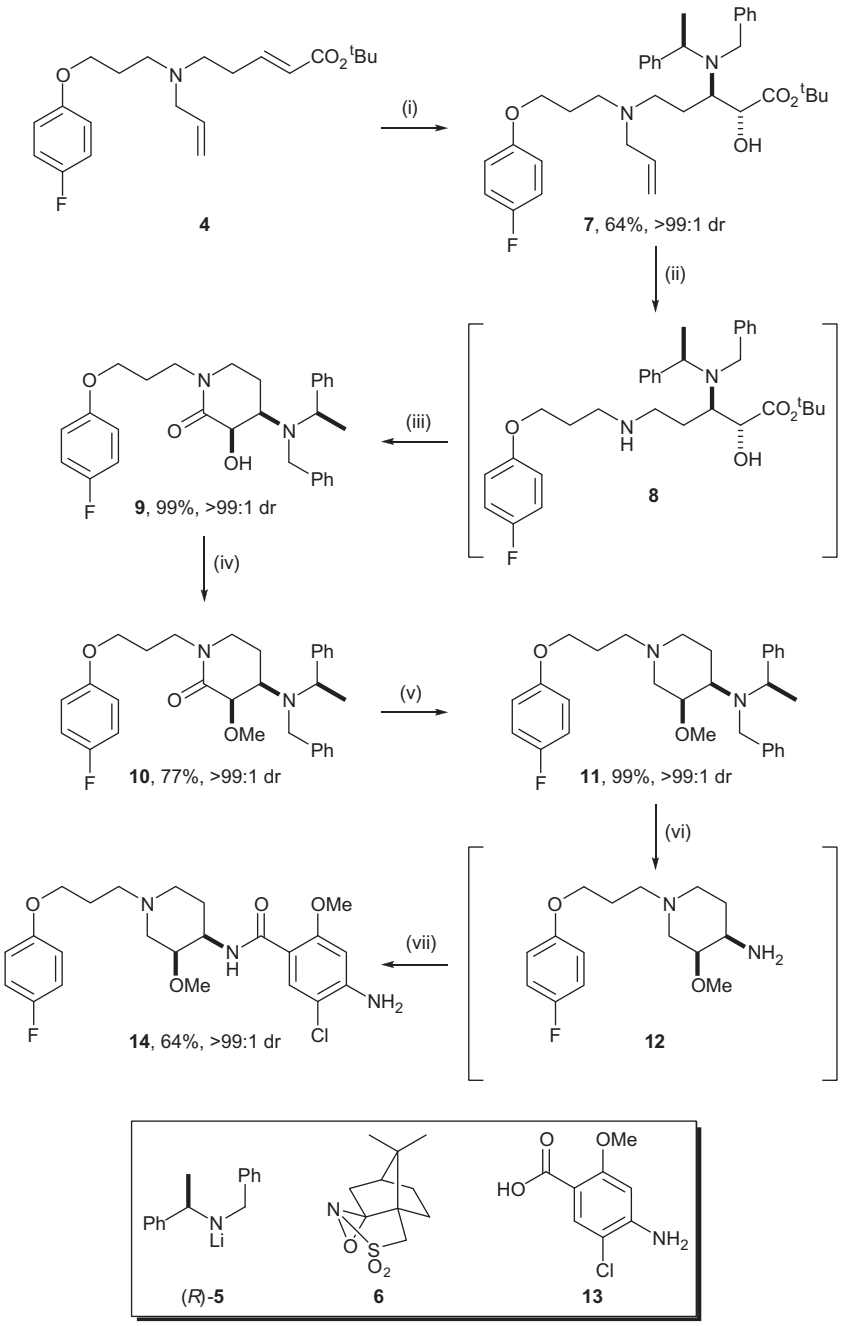
doi:10.1016/j.tetasy.2011.08.020

2. Results and discussion

Treatment of 1-(4′-fluorophenoxy)-3-bromopropane **1** with allylamine gave secondary amine **2** in 87% yield.[10] Subsequent conversion of **2** into α,β-unsaturated ester **4** was achieved by following the procedure of Chesney and Marko,[11] which involved conjugate addition of **2** to acrolein at −15 °C to give β-amino aldehyde **3** that was trapped by in situ Wittig reaction with *tert*-butyl (triphenylphosphoranylidene)acetate to give a 77:23 mixture of (*E*):(*Z*) olefin isomers. Purification gave the diastereoisomerically pure (*E*)-isomer **4** ($J_{2,3}$ = 16.2 Hz) in 70% yield (Scheme 1).

Diastereoselective conjugate addition of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide **5** (99% ee)[12] to α,β-unsaturated ester **4**[13] was followed by in situ enolate oxidation upon treatment with (−)-CSO **6**[14] to give α-hydroxy-β-amino ester **7** as a single diastereoisomer which was isolated in 64% yield after chromatography. The absolute (*R*,*R*,*R*)-configuration within **7** was assigned by analogy to the well established stereochemical outcome of our aminohydroxylation process.[14,15] The deallylation and cyclisation of **7** to give the corresponding piperidin-2-one **9** was achieved by sequential treatment with $Pd(PPh_3)_4$ in the presence of *N*,*N*-dimethylbarbituric acid as an allyl cation scavenger,[16] followed by heating a solution of the crude reaction mixture (containing **8**) in PhMe at reflux in the presence of $PhCO_2H$. Chromatographic purification gave the desired piperidin-2-one **9** in 99% yield over 2 steps. *O*-Methylation of **9** was achieved upon treatment with



Scheme 2. Reagents and conditions: (i) lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide **5**, THF, −78 °C, 2 h, then (−)-CSO **6**, −78 °C to rt, 12 h; (ii) $Pd(PPh_3)_4$, *N*,*N*-dimethylbarbituric acid, CH_2Cl_2, 35 °C, 3 h; (iii) $PhCO_2H$, PhMe, 80 °C, 16 h; (iv) NaH, THF, 0 °C, 1 h, then MeI, 0 °C to rt, 16 h; (v) $LiAlH_4$, THF, 60 °C, 16 h; (vi) H_2, $Pd(OH)_2$/C, MeOH, rt, 16 h; (vii) **13**, $ClCO_2Et$, Et_3N, THF, rt, 16 h.

NaH then MeI, which gave **10** in 77% isolated yield, with subsequent reduction of piperidin-2-one **10** with $LiAlH_4$ in THF at reflux giving piperidine **11** in 99% isolated yield. Hydrogenolytic *N*-debenzylation of **11** gave primary amine **12**. Subsequent *N*-acylation of **12** with 2-methoxy-4-amino-5-chlorobenzoic acid **13** was achieved via the mixed anhydride method,[2] upon treatment of **13** with ethyl chloroformate and Et_3N, and subsequent addition of **12** to the reaction flask.[17] Chromatographic purification gave (+)-(3*S*,4*R*)-cisapride **14** in 64% isolated yield over the 2 steps (Scheme 2).

3. Conclusion

In conclusion, a concise asymmetric synthesis of the gastroprokinetic agent (+)-(3*S*,4*R*)-cisapride {(+)-(3*S*,4*R*)-*N*(1)-[3′-(4″-fluorophenoxy)propyl]-3-methoxy-4-(2‴-methoxy-4‴-amino-5‴-chlorobenzamido)piperidine} from commercially available starting materials has been developed. The key step of this synthesis employs the diastereoselective conjugate addition of lithium (*R*)-*N*-benzyl-*N*-(-methylbenzyl)amide to *tert*-butyl 5-[*N*-3′-(4″-fluorophenoxy)propyl-*N*-allylamino]pent-2-enoate and in situ enolate oxidation with (−)-camphorsulfonyloxaziridine to set the (3*S*,4*R*)-configuration found within the piperidine ring of the product. This synthesis proceeds in 9 steps from commercially available 1-(4′-fluorophenoxy)-3-bromopropane with an overall yield of 19%.

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