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A convergent synthesis of the renin inhibitor CGP60536B

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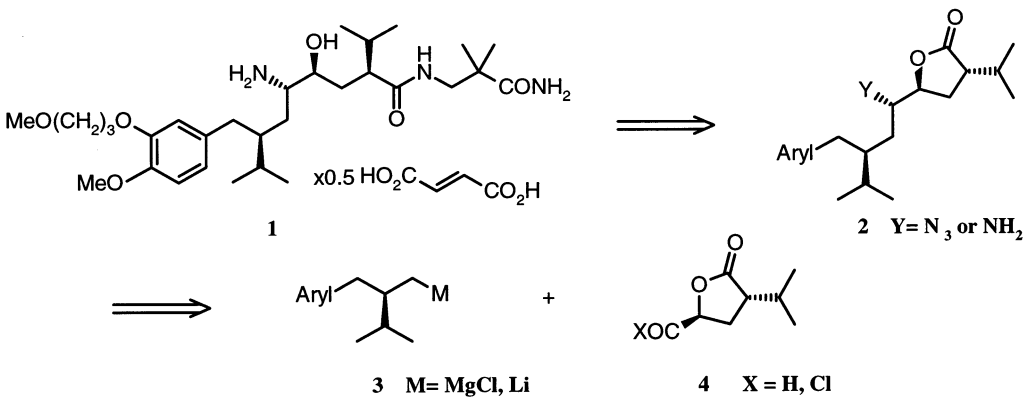
Abstract

Pseudoephedrine serves as a dual purpose chiral auxiliary and protecting group in the synthesis of the novel orally active renin inhibitor CGP60536B.

Keywords: alkylation; asymmetric synthesis; lactonisation; renin inhibitor; spiro compounds.

CGP60536B **1** is a potent non-peptidic inhibitor of human renin, the discovery and synthesis of which has been described elsewhere.[1–3] The report by Dragovich et al. on the use of pseudoephedrine amides for the synthesis of simple dipeptide isosteres[4] prompts us to disclose a similar application of this methodology as an alternative convergent synthesis of **1**. We planned to prepare lactone **2** (Scheme 1) by the union of left- and right-hand fragments **3** and **4**.[3] For assembly of both fragments we envisaged application of Myers' pseudoephedrine amide alkyla-



Scheme 1. Strategy for the synthesis of CGP60536B

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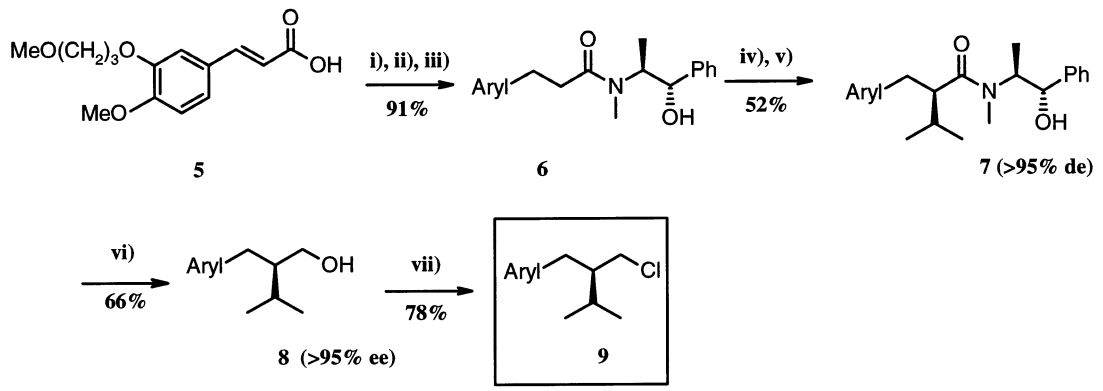
tion methodology,[5] in conjunction with the known *trans* selectivity in halolactonisation of *N*,*N*-substituted 4-alkenyl amides.[6–8]

The approach to the left-hand moiety **3** (Scheme 2) began with cinnamic acid **5**, which was obtained by Knoevenagel condensation of the isovanillin-derived aldehyde with malonic acid in 82% yield. Hydrogenation and amidation with (+)-pseudoephedrine delivered amide **6**, which was then deprotonated and alkylated with 2-iodopropane *in refluxing THF* to afford **7** as a single diastereomer. Reduction of the amide functionality in **7** proceeded without epimerisation,[5] as confirmed by the formation of Mosher's ester derivatives of **8** and its enantiomer. The chiral auxiliary could also be efficiently recovered at this stage. Chlorination furnished **9** as the organometallic precursor.[3]

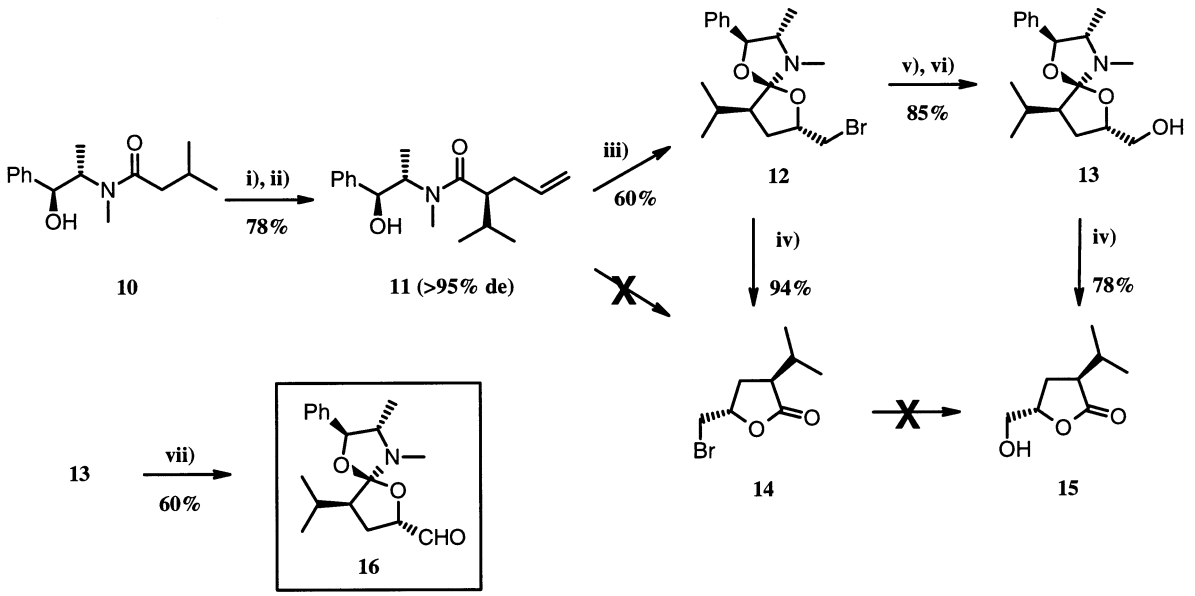


Scheme 2. Preparation of the left-hand fragment. Reagents: (i) H_2, Pd/C, EtOAc, rt; (ii) $(COCl)_2$, DMF, rt; (iii) (+)-pseudoephedrine, NaOH, PhMe–H_2O, rt; (iv) LDA, LiCl, THF, 0°C; (v) 2-iodopropane, rt-reflux; (vi) $BH_3{\cdot}NH_3$, *n*-BuLi, THF, rt; (vii) $POCl_3$, DMF, PhMe, 80°C

Synthesis of the right-hand fragment **4** (Scheme 3) commenced with (+)-pseudoephedrine isovaleramide **10**, which was efficiently deprotonated and alkylated using allyl bromide; diastereomerically pure **11** could be obtained on crystallisation of the crude reaction mixture. Attempted bromolactonisation of this material did not provide lactone **14**, instead, *in the absence of acetic acid*, amide acetal **12** was cleanly formed with a single configuration at the spirocentre and a 6:1 mixture of *trans*:*cis* ring substituents. Crystallisation delivered diastereomerically pure **12**,[9] assigned as (*R*) at the spirocentre on the basis of NOE studies. This is in contrast to the stereochemistry proposed by Dragovich et al. for their related amide acetal.[4]

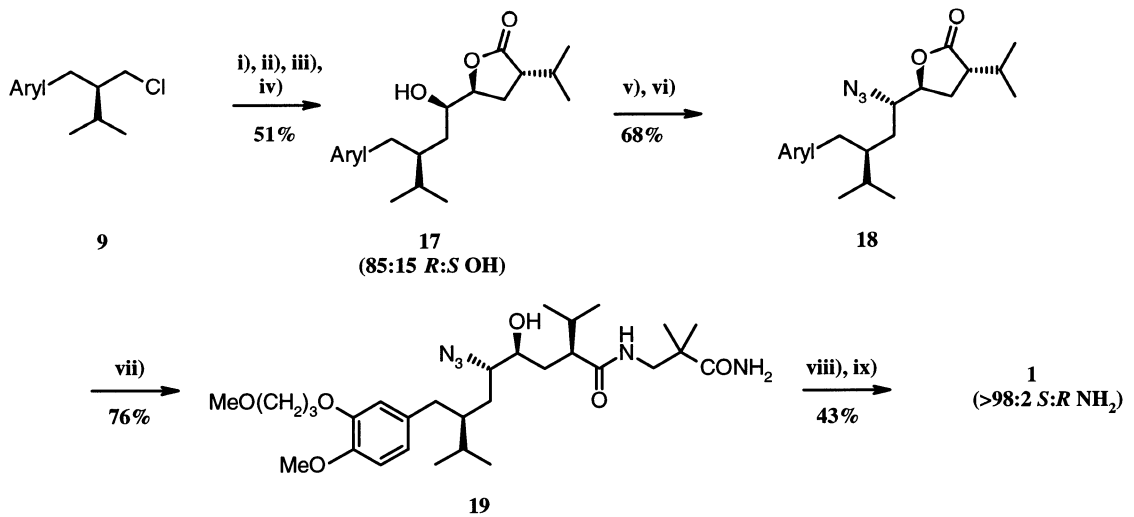
Mild acidic hydrolysis of **12** did provide the desired bromolactone **14**, along with recovered pseudoephedrine. However, attempted conversion to hydroxylactone **15** by treatment with a variety of nucleophilic oxygen sources resulted in competing lactone ring opening. Instead, we were able to exploit the amide spiroacetal functionality in **12** as an effective protecting group, with acetate displacement and in situ basic hydrolysis efficiently providing alcohol **13**. Acidic hydrolysis of this material enabled chemical correlation of the *trans* stereochemistry in **15**.[10] However, oxidation of this hydroxylactone had earlier been shown to give a highly unstable aldehyde.[3] In contrast, activated DMSO oxidation of **13** proceeded without epimerisation to furnish the masked lactone aldehyde **16**.

Coupling of the two fragments (Scheme 4) was achieved by treatment of **16** with the Grignard reagent prepared from **9**[3] and transmetallated with cerium chloride. Hydrolysis of the crude spirocyclic addition product revealed that the hydroxylactone **17** had been formed as an



Scheme 3. Preparation of the right-hand fragment. Reagents: (i) LDA, LiCl, THF, 0°C; (ii) allyl bromide, 0°C; (iii) NBS, DME–H_2O, 0°C; (iv) AcOH–THF–H_2O (3:1:1), 50°C; (v) n-Bu_4NOAc, acetone, reflux; (vi) K_2CO_3, MeOH–H_2O, rt; (vii) Py·SO_3, Et_3N, DMSO–CH_2Cl_2, 0°C

inseparable epimeric mixture with a Felkin–Anh selectivity of 85:15, verified by spectroscopic comparison with an independently prepared authentic sample.[3] The use of TMEDA as an additive gave enhanced 96:4 selectivity, albeit at the expense of a reduction in the yield of **17** to 33%.



Scheme 4. Completion of the synthesis. Reagnets (i) Mg, 1,2-dibromoethane, THF, reflux; (ii) $CeCl_3$, −78°C; (iii) aldehyde **16**, −78°C; (iv) AcOH–THF–H_2O (3:1:1), 50°C; (v) p-bromobenzenesulfonyl chloride, DMAP, CH_2Cl_2, rt; (vi) NaN_3, NMP, 60°C; (vii) 3-amino-2,2-dimethylpropionamide, 2-hydroxypyridine, Et_3N, 80°C; (viii) H_2, Pd/C, ethanolamine, MeOH, rt; (ix) fumaric acid, H_2O, MeCN, MeOH

The requisite nitrogen functionality was installed via the brosylate to give azido lactone **18**. Aminolysis with the 3-amino-2,2-dimethylpropionamide moiety[3] led to formation of the open chain azido alcohol **19** in good yield. The synthesis was completed by azide hydrogenolysis and formation of the hemifumarate salt, crystallisation of which removed the residual minor (*R*)-epimer carried through from the Grignard addition step.

An alternative method for stereoselective incorporation of nitrogen utilising nucleophilic attack on an imine prepared from **16** was also investigated. Although a variety of such derivatives was readily obtained, they proved uniformly unreactive towards organometallics prepared from **9**.

In conclusion, we have described an approach to the novel renin inhibitor CGP60536B, featuring pseudoephedrine amide alkylation to incorporate two of the chiral centres in >95% ee. The formation of amide spiroacetal **12** has been exploited as a novel lactone protecting group, allowing a stereoselective Grignard addition reaction, which is the linchpin of this convergent synthesis. Moreover, the chemistry described herein is amenable to large-scale operation, underscoring the utility of pseudoephedrine as an inexpensive and versatile chiral auxiliary.

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9. Selected data for **12**: δ_H (400 MHz, $CDCl_3$) 0.85 (d, *J* 6.5, 3H), 0.97 (d, *J* 6.4, 3H), 1.03 (d, *J* 6.0, 3H), 1.70–2.0 (m, 4H), 2.27 (s, 3H), 2.81 (dq, *J* 6.9, 8.9, 1H), 3.34 (dd, *J* 6.6, 10.1, 1H), 3.39 (dd, *J* 4.2, 10.1, 1H), 4.25–4.30 (m, 1H), 4.38 (d, *J* 8.9, 1H), 7.20–7.35 (m, 5H); δ_C (100 MHz) 15.49, 21.34, 22.23, 28.64, 31.14, 32.77, 36.74, 45.33, 65.42, 72.45, 86.33, 122.25, 127.06, 127.39, 128.26, 140.39; ν_{max} 2960, 1460 cm^{-1}; mp 72–74°C (hexanes); $C_{18}H_{26}BrNO_2$ requires C, 58.70; H, 7.12; N, 3.80%, found C, 58.83; H, 7.23; N, 3.67%.
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