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A convergent synthesis approach towards CGP60536B, a non-peptide orally potent renin inhibitor, via an enantiomerically pure ketolactone intermediate

Heinrich Rüeger,[a] Stefan Stutz,[a] Richard Göschke,[a] Felix Spindler[b] and Jürgen Maibaum[a,*]

[a]*Novartis Pharma AG, Metabolic and Cardiovascular Diseases, Klybeckstrasse 220, CH-4002 Basel, Switzerland*
[b]*Novartis Services AG, CH-4002 Basel, Switzerland*

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Abstract

We report a convergent synthesis of the potent orally active non-peptide renin inhibitor CGP60536B. The key reaction employs the coupling of the enantiopure Grignard species derived from chloride **13** with the diastereomerically pure γ-lactone **9b**. The stereoselective reduction of the resulting ketone **14b** has been thoroughly investigated.

Keywords: renin inhibitor; Grignard reaction; γ-butyrolactone derivatives; keto-lactone; stereoselective hydrogenation.

The highly potent, orally active human renin inhibitor CGP60536B (**1**), one of a novel class of dipeptide transition state mimetics, exerted a pronounced and long-lasting blood-pressure reduction in marmoset monkeys and has been selected for clinical investigation.[1]

The initial synthetic route to the hydroxyethylene isostere **1**, which followed the classical protocol[2] via a non-proteinogenic *N*-BOC α-amino acid intermediate, had major disadvantages such as a high number of linear steps and insufficient stereoselectivity for key reaction steps, and thus was not amenable for scale-up.[1] Aiming at a more convergent approach, the Grignard addition of the readily accessible fragment **A** to a suitable γ-butyrolactone precursor **B** was envisaged as an attractive route resulting from retrosynthetic cleavage of the C5–C6 bond of **1** (Scheme 1). We report here the synthesis of the keto-lactone precursor **14b** as single diastereoisomer,[3] as well as our studies on its stereoselective reduction and subsequent conversion to **1**.

* Corresponding author. E-mail: juergen_klaus.maibaum@pharma.novartis.com

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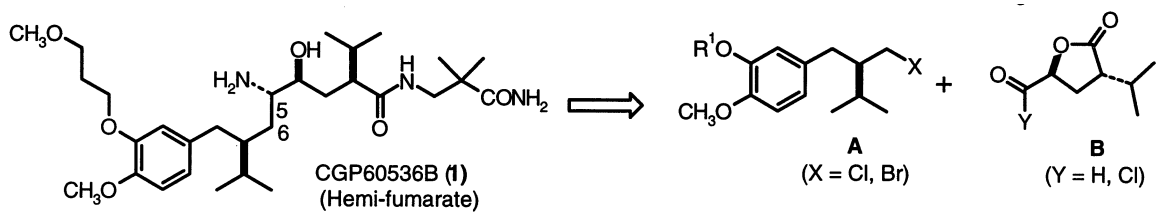
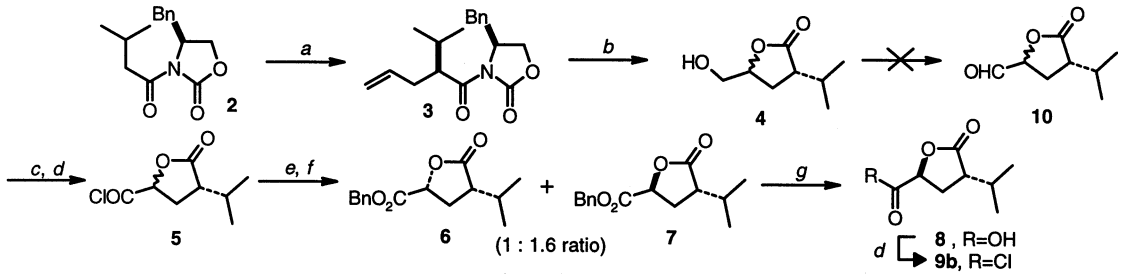


Scheme 1.

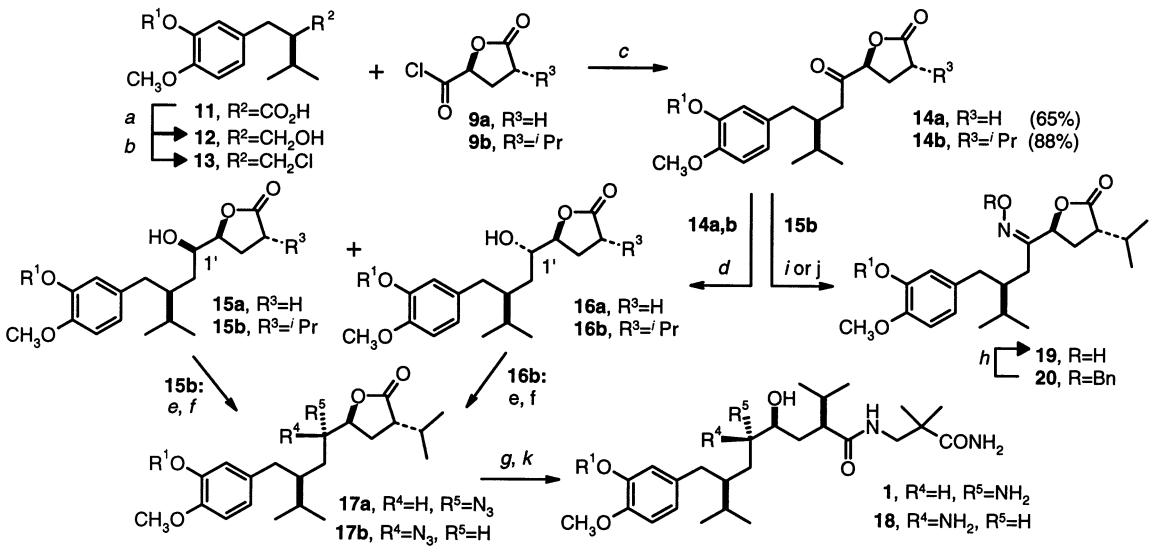
For initial rapid exploration of this alternative synthetic pathway we devised a practical method for the preparation of the diastereopure γ-butyrolactone acid **8** on a multi-gram scale (Scheme 2). Dihydroxylation,[4] of the oxazolidinone **3**,[5] cleavage of the auxiliary and lactonisation provided alcohol **4** as a 1.6:1 ratio of the inseparable 2(*R*),4(*S*):2(*R*),4(*R*)-diastereomers. Sharpless oxidation was employed to convert **4** to the benzylic esters **6** and **7**, which were easily separated by SC chromatography. Hydrogenation of the more polar **7** afforded the desired acid **8** and subsequently **9b**, which was purified by distillation (bp 64–65°C, 0.06 mbar) without detectable epimerisation.[6] Attempts to prepare aldehyde **10** by various oxidation methods were unsuccessful.[3]



Scheme 2. Reagents: (a) LiHMDS, allyl bromide, THF, −78°C, 94%; (b) OsO_4 (cat.), NMMO, *tert*-BuOH–acetone–H_2O (1:1:1), 88%; (c) $NaIO_4$, $RuCl_3{\cdot}H_2O$, CCl_4–MeCN–H_2O (1:1:2), 6 h, >78%; (d) $(COCl)_2$, toluene, DMF (cat.), 1 h, 80–85%; (e) BnOH, NEt_3, CH_2Cl_2, 82% (combined yield); (f) flash chromatography on silica gel; (g) **7**, H_2, Pd/C 10%, EtOAc, 100%

Alkyl chloride **13**, readily synthesized from enantiopure acid **11**[1] after reduction to the alcohol **12** and chlorination with $SOCl_2$/pyridine, was transformed smoothly into the Grignard reagent which reacted with the enantiomeric acid chloride **9a**[8] to provide the keto-lactone **14a** (Scheme 3) in good yield. In case of **9b** bearing the 2(*R*)-isopropyl group, improved yields (ca. 90%) were obtained by addition of an excess of the Grignard species (1.5 equiv.) to afford **14b** as crystalline solid after chromatographic removal of the homo-coupling side product. No epimerisation[9] at the carbon adjacent to the keto group was observed.[10]

The diastereoselective reduction of the ketones **14** to the desired alcohols 1′(*R*)-**15** as the key step was thoroughly investigated (Table 1). The initial results from the standard reaction of **14a** with $NaBH_4$ giving an appreciable (3:1)-diastereoselectivity for 1′(*R*)-**15a** versus 1′(*S*)-**16a** (chelation control, cf. Ref. 9) were promising (entry 1). However, in the case of **14b** bearing the 2(*R*)-isopropyl group (entry 2, vide infra for configurational assignment) diastereofacial differentiation was only minor and opposite under the same conditions. On the other hand, excellent diastereoselectivities were observed with the bulky K-selectride®[9] affording almost exclusively 1′(*R*)-**16a**, as well as the undesired 1′(*R*)-**16b** (Felkin-Ahn products, entries 3, 4). Also, pressure



Scheme 3. Reagents: $R^1 = CH_3O(CH_2)_3$–: (a) $NaBH_4$, I_2, THF, 4 days rt, 90%; (b) $SOCl_2$, Py, $CHCl_3$, 70%; (c) **13**, Mg, $BrCH_2CH_2Br$, THF, rt; (d) see Table 1 for details; (e) MsCl, NEt_3, CH_2Cl_2, 82–99%; (f) NaN_3, 15-crown-5, DMPU, 85%; (g) $H_2NCH_2C(Me)_2CONH_2$ (**21**), 2-OH-pyridine, NEt_3, 59%; (h) H_2, Pd/C MeOH, 74%; (i) $NH_2OH{\cdot}HCl$, $NaHCO_3$, MeOH, rt, 81%; (j) $NH_2OBn{\cdot}HCl$, $NaHCO_3$, 89%; (k) H_2, Pd/C, 1N HCl, MeOH

Table 1
Diastereoisomeric ratios for the reduction of keto-lactones **14a**,**b**

Entry	Substrate	Reducing agent/catalyst[a]	Reaction conditions	Ratio[b] **15a/b**:**16a/b**	% Yield[c]
1	**14a**	$NaBH_4$	THF/EtOH 1:2, rt	3:1	98
2	**14b**	$NaBH_4$	MeOH, rt	1:1.1	89
3	**14a**	K-Selectride	THF, −78→0°C	3:97[d]	84
4	**14b**	K-Selectride	THF, −78°C	3:97	70–80
5	**14a**	BH_3, Me_2S	THF, rt	1:1	35
6	**14a**	BH_3/(*S*)-Oxazaborolidine	THF, −10→0°C	1:3	64
7	**14b**	Rh°/bppfoh	H_2, MeOH, 50 bar, rt	No reaction	–
8	**14b**	Rh°/(*R*)-(*S*)-cy_2PF–Pcy_2	H_2, toluene, 50 bar, rt	1.3:1	Nd[e]
9	**14b**	Rh°/(*S*)-(*R*)-cy_2PF–Pcy_2	H_2, toluene, 50 bar, rt	1.1:1	Nd
10	**14b**	Rh°/(*R*)-(*S*)-PPF–Pcy_2	H_2, toluene, 80 bar, rt	1.5:1	Nd
11	**14b**	Rh°/(*R*)-(*S*)-PPF–$P(xyl)_2$	H_2, toluene, 80 bar, rt	1:1	Nd
12	**14b**	Rh°/(*R*)-(*S*)–PPF–P(*tert*-Bu)$_2$	H_2, toluene, 80 bar, 40°C	1:1	Nd
13	**14b**	$[Ru_2Cl_4$((*S*)-BINAP)]NEt_3	H_2, MeOH, 50 bar, 40 h	1:100	41
14	**14b**	$[Ru_2Cl_4$((*R*)-BINAP)]NEt_3	H_2, MeOH, 50 bar	1:1.5	Nd

[a] see Ref. 16.
[b] Determined by RP-HPLC, Nucleosil C18, 5 μm, MeCN (Gradient 20–100% within 20 min)–water.
[c] Isolated yields, conditions not optimized.
[d] Stereochemical assignment according to Ref. 9.
[e] Not determined.

hydrogenation using Noyori's Ru-BINAP catalyst[11] (entry 13) provided exclusively **16b** when the (*S*)-complex was used (matched stereodifferentiation). In contrast, the (*R*)-BINAP complex (entry 14) was non-selective. The Rh–PP chiral complexes in entries 8, 10 were the only Rh catalysts leading to the desired **15b** in slight excess, however, the observed minor stereoinduction was not promising for further optimisation.

Assignment of the absolute configuration of the pure epimers **15b** and **16b**, obtained both in gram quantities from $NaBH_4$ reduction of **14b** and separation by silica gel flash chromatography, was established by their straightforward conversion to **1** and the 5(*R*)-isomer **18**, respectively (Scheme 3). Thus, displacement of the corresponding mesylates of **15b** and **16b** with sodium azide in the presence of catalytic 15-crown-5 occurred with complete inversion to provide 1′(*S*)-configured azido-lactone **17a** and its 1′(*R*)-epimer **17b**. Direct opening of lactone 1′(*S*)-**17a** with amine **21**, which turned out to be only a weak nucleophile, required addition of stoichiometric 2-OH-pyridine.[12,13] Final reduction of the azide group afforded a product which was identical by proton NMR with the target compound **1**, and which was clearly distinguishable from epimer **18** obtained from **17b**.

We also sought to introduce the nitrogen group stereoselectively via the oximes **19** and **20**, both obtained from **14a** as *E*/*Z* isomers (1:1) in high yields (Scheme 3). All attempts to reduce **19** with borohydrides or by catalytic hydrogenation under neutral or acidic conditions failed, and hydrogenation (Pd/C) of **20** led exclusively to *O*-debenzylation.[14] Also, **20** was inert towards $NaBH_4$ under standard conditions, and in the presence of a large excess of the reagent concomitant reduction to the *O*-benzyl hydroxylamine and of the lactone to the lactol was observed.[15]

In summary, a convergent practical synthesis of the stereoisomerically pure keto-lactone **14b** as precursor of the novel renin inhibitor CGP60536B (**1**) has been devised. Attempts to reduce **14b** stereoselectively to the desired alcohol 1′(*R*)-**15b**, which was transformed with complete inversion to azide **17a**, remained unsuccessful. On the other hand, reduction with K-selectride® or hydrogenation in presence of $[Ru_2Cl_4((S)\text{-BINAP})]NEt_3$ proceeded in a highly diastereofacial manner to give alcohol 1′(*S*)-**16b** which could potentially provide access to **1** via a double-inversion protocol. Moreover, the present work and continued efforts to establish a stereoselective synthesis of γ-butyrolactone **9b** led to a new efficient large-scale synthesis of **1** which is reported elsewhere.[3]

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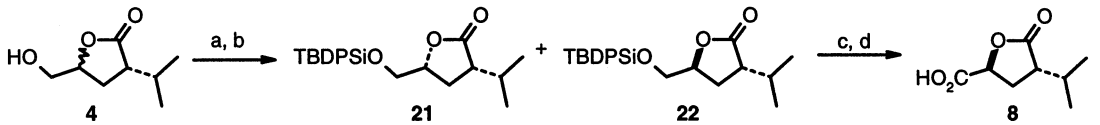
6. Assignment of the absolute configuration of **8** and **9b** was accomplished by derivatizing **4** to the known silyl ethers **21** and **22**.[7] Compound **8** prepared from the less polar **22** (R_f=0.53, hexane–methyl *tert*-butyl ether 3:1) was identical by NMR to the material obtained according to Scheme 2: Colorless oil, $[\alpha]_D^{22}=-9.6$ ($c=1$, CH_2Cl_2), ^{1}H NMR ($CDCl_3$): δ 8.0 (br. s, 1H), 4.92 (dd, $J=11.3$, 7.5 Hz, 1H), 2.73–2.58 (m, 1H), 2.46–2.34 (m, 2H), 2.20 (m, 1H), 1.04 (d, $J=12$ Hz, 3H), 0.94 (d, $J=12$ Hz, 3H) ppm. The ^{1}H NMR of the 1(*R*),3(*R*)-epimeric acid prepared from **6** showed a signal at 4.86 ppm (dd, $J=15.1$, 11.3 Hz) for the C1 methine.



Reagents: (a) TBDPSiCl, imidazole, DMF, rt, 12 h, 97%; (b) separation of diastereomers on silica gel; (c) **22**, TBAF, THF, 73%; (d) $NaIO_4$, $RuCl_3H_2O$, CCl_4–MeCN–H_2O (1:1:2), 6 h, 96%.

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