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A convergent synthesis of the renin inhibitor SPP-100 using a nitrone intermediate

Alessandro Dondoni,* Geert De Lathauwer and Daniela Perrone

Dipartimento di Chimica, Laboratorio di Chimica Organica, Università di Ferrara, Via L. Borsari 46, I-44100 Ferrara, Italy

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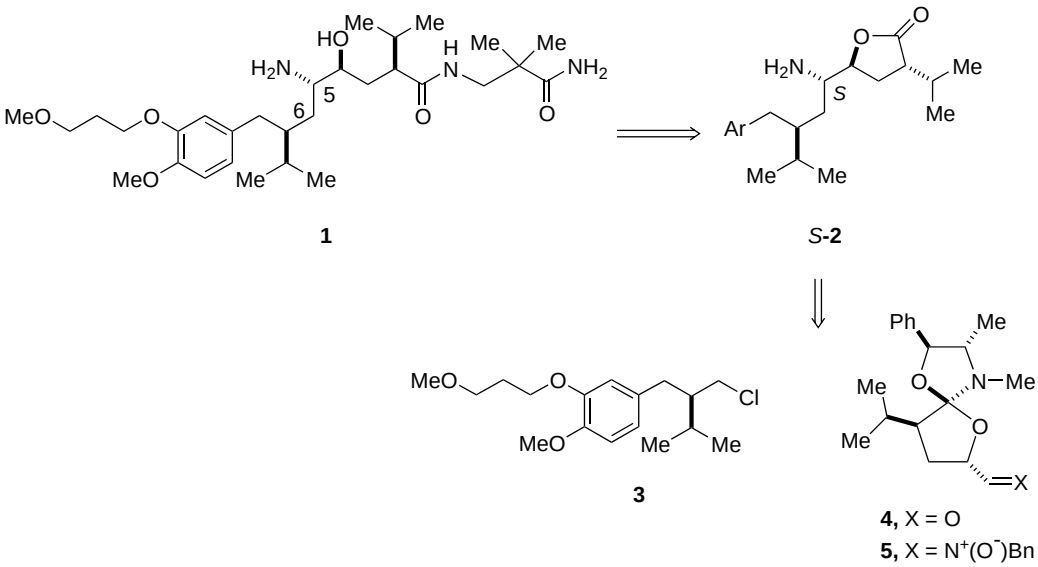
Abstract—The total synthesis of SPP-100 and its C-5 epimer involves the construction of the β-amino alcohol segment via addition of the Grignard reagent derived from 3-aryl-2-isopropyl-1-chloropropane to the nitrone functional group installed at C-4 of the pseudoephedrine spiroanellated γ-butyrolactone derivative.

The hydroxyethylene dipeptide isostere **1** represents a novel class of dipeptide transition state mimetics exerting a pronounced and long-lasting blood-pressure reduction in laboratory animals.[1] Compound **1** employed as the hemi-fumarate[2] proved to be a highly potent human renin inhibitor and therefore, was selected for clinical investigation. The synthesis of **1** has been very recently reported by research groups at Novartis by two convergent methods,[3,4] the more efficient one[4] involving the functionalized chiral amino lactone *S*-**2** as a key intermediate (Scheme 1). The precursor of *S*-**2** was the corresponding azido derivative. Hence, the amino group in *S*-**2** was introduced by coupling the cerium reagent derived from 3-aryl-2-isopropyl-1-chloropropane **3** and the (1*S*,2*S*)-(+)-pseudoephedrine spiroanellated γ-lactone-aldehyde **4**, followed by the removal of the pseudoephedrine residue, substitution of the hydroxyl by the azido group via brosylation and reaction with NaN_3, and reduction of N_3 to NH_2. The pseudoephedrine residue played a double role in this synthesis as it served as a chiral auxiliary in the asymmetric synthesis of **4** starting from



Scheme 1. Retrosynthetic analysis of SPP-100, **1**.

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* Corresponding author. E-mail: adn@dns.unife.it

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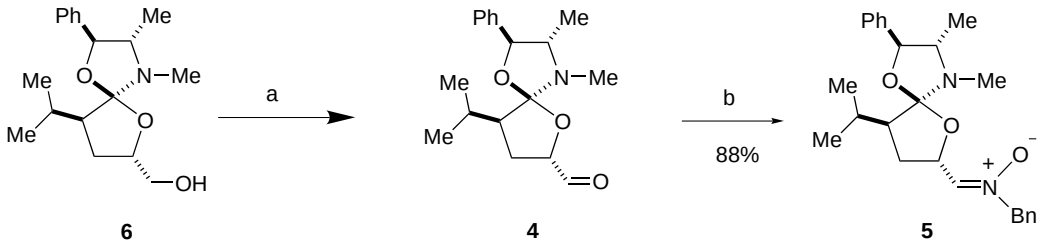
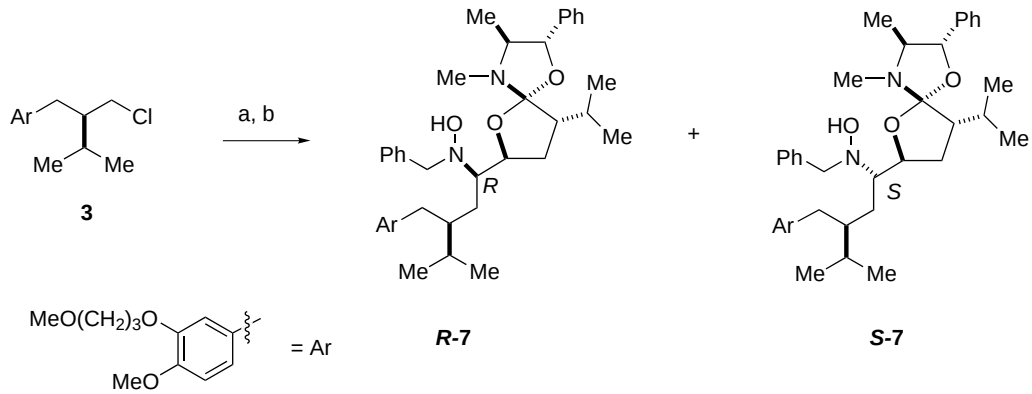
isovaleryl chloride[5] via the Myers amide-based asymmetric alkylation methodology[6] and as a protective group of the lactone carbonyl in the organometallic addition to the formyl group. This key step afforded a mixture of diastereomeric *R*- and *S*-alcohols in 85:15 ratio and 51% overall yield. A higher selectivity (96:4) but a substantially lower yield (33%) was registered by carrying the reaction in the presence of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA). The instability of the aldehyde **4** constitutes an additional drawback in this synthesis.[7] Hence, we would like to report here a new convergent synthesis of the amino lactone *S*-**2** and its epimer *R*-**2** using the stable and crystalline *N*-benzyl nitrone **5** derived from the aldehyde **4**. We sought this method as a more straightforward entry to the β-amino alcohol moiety of **1**, avoiding the three-step reaction sequence through the azide intermediate. This new synthetic route evolved from our recent work on the use of chiral aldonitrones in synthetic approaches to aminated systems.[8,9] The convenient introduction of the amino functionality via addition of nucleophiles to nitrones relies in general on the superior properties of nitrones, such as their ease of preparation, stability, and high reactivity, over other imino compounds. This methodology appears to be highlighted below as well as in the synthetic approach to SPP-100, the hemifumarate (SPP-100B) of which is a potential drug against a disease of great human relevance.[2]

Starting from the readily available and enantiomerically pure (1*S*,2*S*)-(+)-pseudoephedrine protected lactone-alcohol **6** (three steps from (+)-pseudoephedrine isovaleramide, 40% yield),[4] the nitrone **5** was prepared through the aldehyde **4** in 88% isolated yield (Scheme 2). Crude **4** was transformed into **5** via the standard nitrone synthesis[8] involving condensation with *N*-benzylhydroxylamine in the presence of anhydrous sodium sulfate. This nitrone was easily purified by crystallization and stored for several days at room temperature without appreciable decomposition.[10] The assigned *Z*-



Scheme 2. *Reagents and conditions:* (a) SO_3·pyridine, Et_3N, DMSO/CH_2Cl_2 (2:1), 0°C to rt, 1 h; (b) $PhCH_2NHOH$, Na_2SO_4 (anhydrous), CH_2Cl_2, rt, 2 h.



Scheme 3. *Reagents and conditions:* (a) Mg, 1,2-dibromoethane, THF, 45°C, 1 h; (b) nitrone **5**, THF (see Table 1).

Table 1. Addition of the grignard reagent derived from **3** to the nitrone **5** in THF

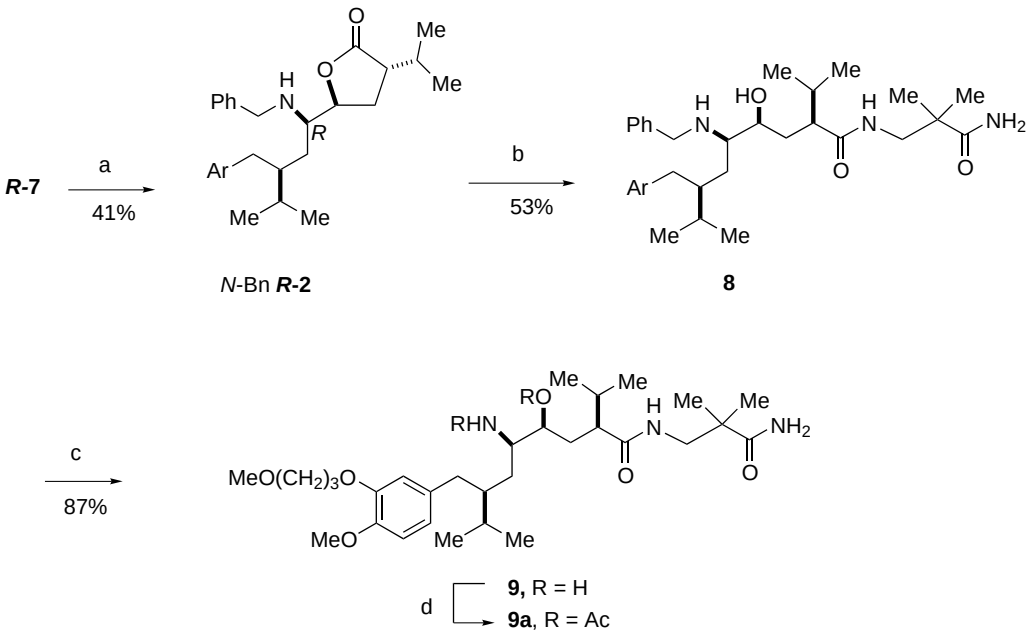
Run	Additive	Temp. (°C)	Time (h)	Grignard reagent (2 equiv.)	Ratio[a] *R*-**7**:*S*-**7**	Overall yield[b] *R*-**7**+*S*-**7** (%)
1	–	−10	15	–	70:30	77
2	–	−40	15	–	85:15	62
3	–	−10	6	+$CeCl_3$[c]	80:20	51
4	TMEDA	−10	15	–	65:35	32
5	DMPU	−10	15	–	45:55	47

[a] Determined by NMR analysis of the isolated mixture of products.
[b] Isolated products by chromatography.
[c] Prepared by addition of 4 equiv. of $CeCl_3$ to the preformed Grignard reagent.

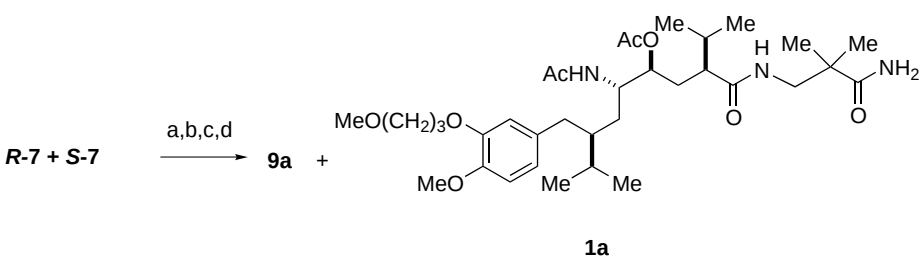
configuration based on the nuclear Overhauser effect between C*H*=N and C*H*$_2$Ph signals,[8a] was confirmed by X-ray crystallography.[11]

The key step in the new convergent approach to **1** was carried out by coupling nitrone **5** and the Grignard reagent prepared from the chiral alkyl chloride[12] **3** (Scheme 3). As opposed to the unsuccessful addition[4] of organometallic reagents to imines derived from the aldehyde **4**, the Grignard reagent prepared from **3** reacted readily with **5** between −10 and −40°C to give mixtures of *N*-alkyl,*N*-benzylhydroxylamines *R*-**7** and *S*-**7** in satisfactory overall yields and diastereoselectivity in favor of the former isomer (Table 1, runs 1 and 2). The use of the cerium reagent obtained from the Grignard reagent by transmetallation with cerium chloride gave a similar mixture of products but in lower yield (run 3). Also the use of TMEDA as an additive concurred to reduce the overall yield of isolated products (run 4). A tendency toward inversion of diastereoselectivity was observed by the use of the chelate complex-destroying agent 1,3-dimethyl-3,4,5-tetrahydro-2(1*H*)-pyrimidinone (DMPU) (run 5). However, a substantial predominance of the desired *S*-epimer could not be achieved.[13] The absolute configuration at the newly created stereocenter of compounds *R*-**7** and *S*-**7** was established following their transformation into the target product **1** and its C-5 epimer.

The stereomers *R*-**7** and *S*-**7** obtained as in run 1 were separated by medium-pressure column chromatography (6 bar, silica, cyclohexane–acetone 9:1, plus 0.5% Et_3N) and the major product *R*-**7** was subjected to suitable elaborations.[14] Guided by our earlier work on the deoxygenation of nitrone–organometal adducts,[8c,15] *R*-**7** was treated with Zn/Cu(OAc)$_2$ in AcOH–H_2O (Scheme 4). In addition to the desired transformation of the N(OH)Bn to the NHBn group induced by the zinc–copper couple, the mild acid conditions caused the cleavage of the amide spiroacetal, giving rise to the formation of the *N*-benzylamino lactone *R*-**2** in a single step. Hence, the implementation of the direct introduction of the amino group via nitrone chemistry appeared to have been demonstrated. Next, opening of the lactone ring by 3-amino-2,2-dimethylpropionamide (ADPA) afforded compound **8**, thus, completing the construction of the hydroxyethylene dipeptide isostere skeleton. This compound was debenzylated by hydrogenolysis over Pd/C to give the amino-free product **9**, the C-5 epimer of **1**. The product **9** was



Scheme 4. *Reagents and conditions:* (a) Zn/Cu(OAc)$_2$, AcOH–H_2O; rt, 55 h; (b) ADPA, 2-OH-pyridine, Et_3N, 80°C, 72 h; (c) H_2, Pd/C, MeOH, rt, 3 h; (d) Ac_2O, pyridine, rt 5 h.



Scheme 5. *Reagents and conditions*: a, b, c and d, see Scheme 4.

isolated and characterized as the bis-acetyl derivative **9a**.

The same reaction sequence described above was repeated starting from a mixture of the adducts *R*-**7** and *S*-**7** (70:30). Each reaction (Scheme 5) was carried out using the crude reaction mixture obtained in the previous step. The major final isolated product was **9a** while the minor product was identical to compound **1a**, obtained by acetylation of an authentic sample of **1**.

In conclusion, a new synthetic approach to **1**, the substrate for the preparation of the antihypertensive drug SPP-100B, and its C-5 epimer **9** has been disclosed. The use of the stable and crystalline nitrone **5** as a key intermediate permits a rapid entry to the β-amino alcohol moiety, thus reducing the number of steps and the troublesome manipulation of an unstable compound such as the γ-lactone-aldehyde **4**. Hence, this new and operatively simple synthetic route appears to be quite attractive, particularly in a large-scale synthesis. However, the search for conditions giving a more favorable stereoselectivity of the key coupling reaction toward the desired product *S*-**7** is a crucial issue which is actively addressed in our laboratory.

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2. The hemifumarate of **1** was originally assigned the identification number CGP60536B by Novartis (see Refs. 3 and 4). This compound has been renamed as SPP-100B (generic name: Aliskiren) by Speedel Pharma AG, a licensee of Novartis.
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7. In our hands the aldehyde **4** appeared to be a sticky oil which decomposed substantially under chromatographic purification.
8. (a) Dondoni, A.; Franco, S.; Junquera, F.; Merchan, F. L.; Merino, P.; Tejero, T.; Bertolasi, V. *Chem. Eur. J*. **1995**, *1*, 505; (b) Dondoni, A.; Perrone, D. *Aldrichimica Acta* **1997**, *30*, 35; (c) Dondoni, A. *Synthesis* **1998**, 1691; (d) Dondoni, A.; Perrone, D.; Rinaldi, M. *J. Org. Chem*. **1998**, *63*, 9252; (e) Dondoni, A.; Perrone, D. *Tetrahedron Lett*. **1999**, *40*, 9375; (f) De Risi, C.; Dondoni, A.; Perrone, D.; Pollini, G. P. *Tetrahedron Lett*. **2001**, *42*, 3033.
9. For a recent and comprehensive review on nucleophilic additions to nitrones, see: Lombardo, M.; Trombini, C. *Synthesis* **2000**, 759.
10. Compound **5**: mp 123–124°C (from cyclohexane); $[\alpha]_D = +27$ (*c* 0.8, $CHCl_3$). ^1H NMR (selected, 300 MHz, $CDCl_3$): δ 7.47–7.30 (10H, m), 6.86 (1H, d, $J=4.8$ Hz), 5.24 (1H, m), 4.92 (2H, s), 4.49 (1H, d, $J=8.6$ Hz), 2.85 (1H, dq, $J=6.4$, 8.6 Hz), 2.35 (1H, ddd, $J=9.6$, 12.2, 12.4 Hz), 2.28 (3H, s), 2.17 (1H, ddd, 3.8, 8.4, 12.2 Hz), 1.86 (1H, dqq, $J=3.8$, 6.0, 6.2 Hz), 1.73 (1H, dt, $J=8.4$, 12.4 Hz), 1.13 (3H, d, $J=6.0$ Hz), 1.05 (3H, d, $J=6.2$ Hz), 0.92 (3H, d, $J=6.4$ Hz).
11. Private communication from Professor V. Bertolasi (Centro di Strutturistica Diffrattometrica, Dipartimento di Chimica, Università di Ferrara, I-44100 Ferrara, Italy, e-mail: m38@unife.it) to whom enquiries regarding the X-ray crystal structure analysis should be addressed.
12. Also the preparation of this building block was centered on the Myers asymmetric alkylation of a pseudoephedrine derived amide followed by removal of the chiral auxiliary (see Ref. 4). A stock solution of the Grignard reagent for various experiments (Table 1) was prepared by slow addition of **3** (mp 56–57°C (MeOH); $[\alpha]_D = +48$ (*c* 1.0, $CHCl_3$)) and catalytic 1,2-dibromoethane in THF to a suspension of Mg powder (dried by heating for 8 h at 120°C under moderate vacuum (1 mmHg)) in THF at 40–45°C containing a few crystals of I_2. The mixture was heated at the same temperature for one additional hour. Afterward, a sample was quenched with water and analyzed by ^1H NMR spectroscopy. Mixtures containing a substantial amount (more than 10%) of the Wurtz-type side-product were discarded.
13. Given the complexity of the chiral moiety of the nitrone **5**, the stereochemical outcome of the organometallic addition is open to various conjectures. Tunable *syn*/*anti* selectivity was reported in addition reactions of organometallic reagents to chiral α-alkoxy nitrones by complexation with Lewis acids. Stereochemical models such as Felkin–Anh–Houk, and similar ones, appeared to give a satisfactory explanation for reactions of rather simple compounds while exceptions were reported in the case of nitrones bearing complex chiral substituents (see Ref. 8a).
14. Unlike *R*-**7**, the epimer *S*-**7** could not be isolated in a pure form. Compound *R*-**7**: oil, $[\alpha]_D = +54$ (*c* 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.48–7.23 (10H, m), 6.77–6.75 (3H, m), 4.99 (1H, bs), 4.59 (1H, dt, $J=4.1$, 6.8 Hz), 4.50 (1H, d, $J=8.8$ Hz), 4.08 (1H, dt, $J=6.4$, 9.5 Hz), 4.00 (1H, dt, $J=6.6$, 9.5 Hz), 3.82 (3H, s), 3.80 (1H, d, $J=13.7$ Hz), 3.72 (1H, d, $J=13.7$ Hz), 3.54 (2H, t, $J=6.2$ Hz), 3.33 (3H, s), 2.94 (1H, dt, $J=4.1$, 8.0 Hz), 2.86 (1H, dq, $J=6.1$, 8.8 Hz), 2.70 (1H, dd, $J=5.4$, 13.7 Hz), 2.34 (1H, dd, $J=9.0$, 13.7 Hz), 2.26 (3H, s), 2.07 (2H, ddt, $J=6.2$, 6.4, 6.6 Hz), 2.05–1.43 (8H, m), 1.12 (3H, d, $J=5.8$ Hz), 1.08 (3H, d, $J=5.1$ Hz), 1.06 (3H, d, $J=6.6$ Hz), 0.96 (3H, d, $J=6.1$ Hz), 0.92 (3H, d, $J=6.6$

Hz). Compound *S*-**7**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.52–7.26 (10H, m), 6.86–6.72 (3H, m), 5.58 (1H, bs), 4.54 (1H, d, $J=8.4$ Hz), 4.48 (1H, m), 4.28 (1H, d, $J=12.9$ Hz), 4.09 (1H, t, $J=6.3$ Hz), 3.99 (1H, d, $J=12.9$ Hz), 3.86 (3H, s), 3.56 (2H, t, $J=6.3$ Hz), 3.36 (3H, s), 3.02–2.88 (2H, m), 2.66 (1H, dd, $J=5.4$, 13.7 Hz), 2.49 (1H, dd, $J=9.0$, 13.7 Hz), 2.34 (3H, s), 2.12–2.03 (2H, m), 1.92–1.51 (8H, m), 1.14 (3H, d, $J=6.3$ Hz), 1.06 (3H, d, $J=5.6$ Hz), 0.96 (3H, d, $J=6.3$ Hz), 0.91 (6H, d, $J=7.0$ Hz).

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