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Syntheses of Conformationally Restricted Analogues of an Angiotensin II Receptor Antagonist. General Synthetic Approach to Functionalized Imidazo[1,5-*a*]pyridine Derivatives.

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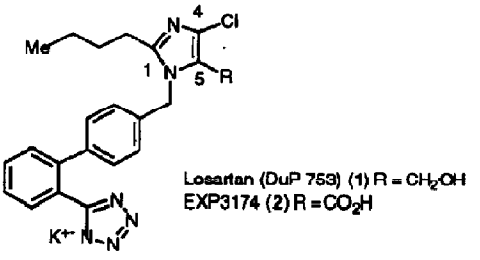
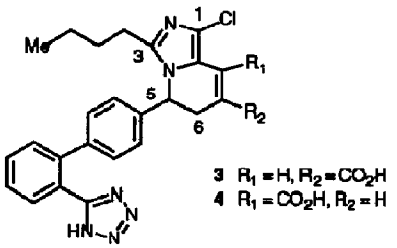
Abstract: Syntheses of two conformationally restricted analogues **3** and **4** of the angiotensin II receptor antagonistst losartan (**1**) are described. Michael addition of imidazole-5-carboxaldehyde **8** to biphenylpropiolate **7** provides an efficient method for the skeletal construction of imidazo[1,5-*a*]pyridine derivatives.

As expressed in recent patent literature, losartan (**1**) (DuP 753), a nonpeptide angiotensin II (AII) receptor antagonist, is currently undergoing advanced clinical study for the treatment of hypertension and serves as a leading design model for numerous drug research programs.[1] Closely related to losartan (**1**) is its acid metabolite EXP 3174 (**2**), a potent, selective and noncompetitive AII receptor antagonist.[2] So far the structural modifications of **1** have evolved mostly in two directions. The first involves side chain variations on the imidazole nucleus with the most important contribution from optimization of the 4-position of imidazole. The second reflects the efforts directed toward substitution of the imidazole nucleus with imidazo(4,5)-fused heterocyclic variants.

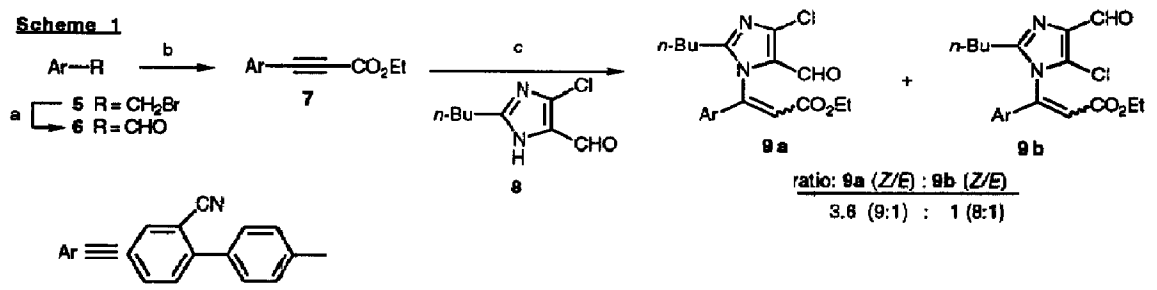
In order to obtain a better understanding of the active conformation of losartan (**1**) at the receptor site, we decided to introduce a bridge between the position 5 of imidazole and the benzylic position. Introduction of such a linker would add to a conformational rigidity of the biphenyl moiety, hindering its rotation around the C-N bond. To test the effect of such structural changes on pharmacological activity we undertook the syntheses of two closely related losartan analogues **3** and **4**, wherein the biphenyl group is forced to assume a rigid pseudoaxial orientation.





Schemes 1-3 summarize our synthetic routes to **3** and **4**, respectively. We envisaged a Michael addition of imidazole-5-carboxaldehyde **8** to the corresponding 4-biphenylpropiolate **7** as a crucial step in the synthesis. Assuming that the proper conditions were to be found for the 1,4-conjugated addition of **8**,[3] the questions of the regiochemistry (*vide infra*) would remain to be addressed.

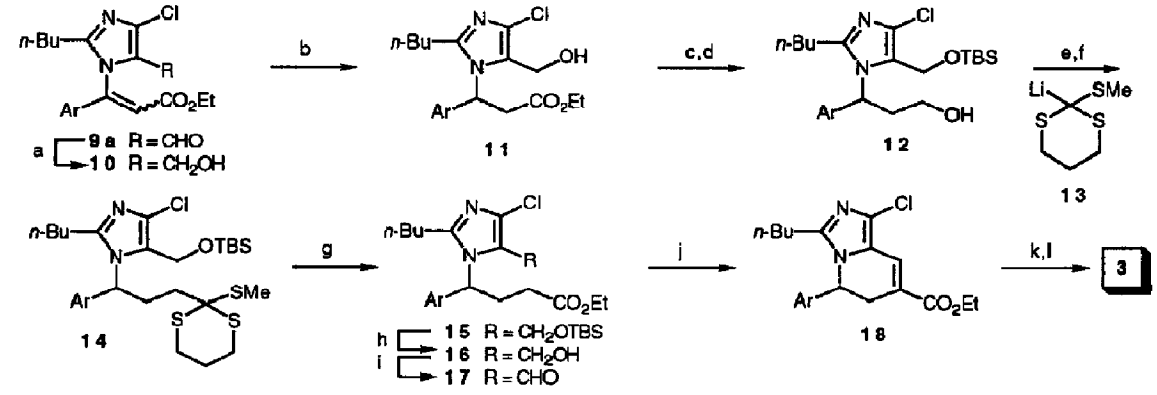
Scheme 1



Reagents and conditions: (a) $(CH_2)_6N_4$, AcOH-H_2O (1:1), 120°C, 1 h, (67%); (b) (i) $(EtO)_2P(O)CH_2CO_2Et$, NaH, DME, 0 °C; (ii) I_2, NaH, 25-40 °C (40%); (c) Li_2CO_3, DMF, 80°C, 16 h, (92%).

The starting aldehyde **6** was prepared by exposure of 4'-(bromomethyl)-2-biphenylcarbonitrile (**5**)[4] to Sommelet conditions: heating at reflux with hexamethylenetetramine in AcOH-H_2O (67%) (**Scheme 1**). It was subsequently transformed by Horner-Wadsworth-Emmons reaction of *in situ* generated iodophosphonate $(EtO)_2P(O)CHICO_2Et$[5] to ethyl propiolate **7**. Studies of conjugate addition of aldehyde **8**[4,6] to propiolate **7** gave encouraging results with Cs_2CO_3, which has been used as an efficient base for the intramolecular Michael addition of cyclic β-ketoesters on ynones.[7] Comparative trials with other alkaline metal carbonates lead to the conclusion that Li_2CO_3 gave the best results regarding the yields of the coupling products and distribution of the regioisomers.[8] The key synthetic intermediate **9a** was prepared as a *ca* 9:1 mixture of *Z*- and *E*-isomers,[9] respectively, in 72% isolated yield, on heating the aldehyde **8** with propiolate **9** in DMF at 80°C in the presence of Li_2CO_3 (3 eq). Condensation afforded also a *Z*- / *E*-diastereoisomeric mixture (8:1, respectively) of the regioisomer **9b** (20% isolated yield), which could be easily separated from **9a** by flash chromatography (hexane-EtOAc 4:1).

Scheme 2

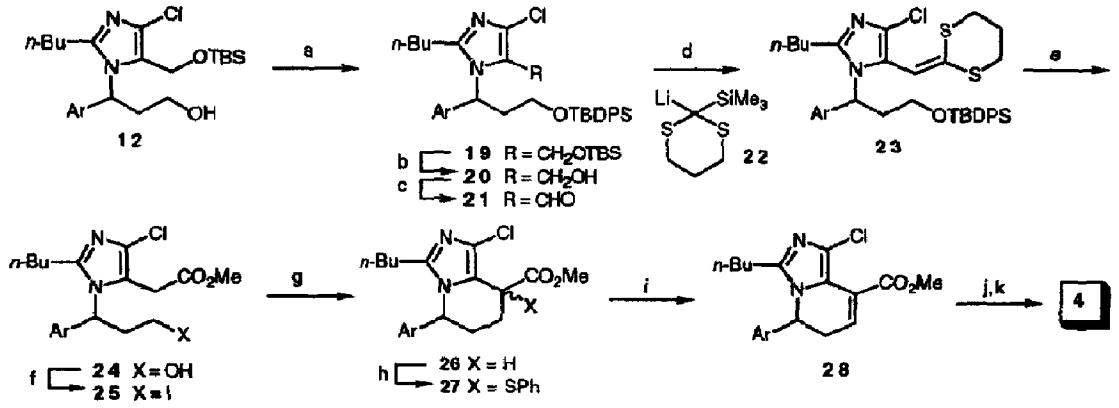


Reagents and conditions: (a) $NaBH_4$, MeOH, -10 °C, 1 h; (b) NaHTe, EtOH, rt, 3 h, (90%, from **9a**); (c) TBSCl, Im, DMF, rt,3 h; (d) $CeCl_2$, $NaBH_4$, *i*-PrOH, rt, 22 h, (90%, from 11); (e) I_2, PPh_3, Py, THF, rt, 48 h, (92%); (f) **13**, THF, -78 °C, 1 h, (92%); (g) I_2, $NaHCO_3$, EtOH-H_2O 95:5, 0 °C, 2 h, (72%); (h) Bu_4NF, THF, -10 °C, 1 h, (90%); (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C, (86%); (j) NaH, *t*-BuOK, THF, -10 °C, 45 min, (48%); (k) *n*-Bu_3SnN_3, xylene, 110 °C, 24 h, (61%); (l) NaOH, MeOH-H_2O 1:1, 45 °C, 2.5 h, (95%).

Having succesfully constructed the N-C bond in the biphenylcinnamate **9a**, we turned our attention to reduction of the olefinic bond in the same (**Scheme 2**). A number of available methods for 1,4-reduction of conjugated systems were explored.[10] Success was achieved with NaHTe reagent in EtOH (80%) as described by

Yamashita et. *al.*[11] Under these conditions the aldehyde **9a** was simultaneously reduced to alcohol **10**. A slightly better yield (90%) could be obtained from a two step sequence: reduction of aldehyde **9a**, as a 9:1 *Z/E*-mixture, with $NaBH_4$ in MeOH, followed by reduction of the isolated alcohol **10** with NaHTe. At this point the stage was set for one-carbon elongation of the side chain in **11**, which calls for conversion of the ester either to aldehyde or to CH_2X (X=leaving group). Taking into account that 3–(imidazo-1-yl)propanals might have a tendency to undergo retro-Michael addition of the imidazole moiety under basic conditions and thus limit the the conditions for condensation of aldehyde with masked carboxyl anion, we chose to explore the second approach. First, the primary hydroxyl group was protected as the TBS ether and the ester subsequently reduced selectively in the presence of cyano group with $Ca(BH_4)_2$ in *i*-PrOH to afford **12** (90% from **11**). Exposure of the resulting alcohol **12** to I_2-PPh_3 reagent in THF smoothly afforded the primary iodide (92%), which was alkylated with 2-lithio-2-methylthio-1,3-dithiane (**13**)[12] to provide orthotrithiocarboxylate **14** in 92% yield. The coresponding ester **15** could be obtained by hydrolysis of **14** under the mild conditions usually applied for deprotection of thioacetals: I_2+$NaHCO_3$ (71%). Removal of the TBS group (90%) and subsequent oxidation of the primary alcohol **16** under Swern conditions provided the corresponding aldehyde **17** (86%). Disappointingly, intramolecular aldol condensation of the aldehyd **17** with sterically hindered lithium bases that are routinely used for ester enolate formation (LDA, LICA, LHMDS) afforded only decomposition of the aldehyde. With NaH or *t*-BuOK starting material was recovered from the reaction mixture. However, aldol condensation was accomplished with the combination of these two bases (*ca* 1:1 molar ratio) in THF and the 5,6-dihydroimidazo[1,5-*a*]pyridine system **18** was isolated in 48% yield. Treatment of **18** with excess *n*-Bu_3SnN_3 (9 eq) in xylene at 110°C and flash chromatography of the reaction mixture with Et_2O-EtOAc-AcOH (90:10:1) afforded directly the 5-(biphenyl-2'-yl)tetrazole derivative. In the final step of the synthesis of analogue **3**, the ester was hydrolysed easily with NaOH in MeOH-H_2O (95%).

Scheme 3



Reagents and conditions: (a) *t*-$BuPh_2SiCl$, Im, DMF, rt, (94%); (b) HCOOH-H_2O 1:1-THF, rt, 18 h, (69%); (c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C, (96%); (d) **22**, THF, -78 °C, 30 min, (56%); (e) $HgCl_2$, MeOH-H_2O 9:1, HCl (1M, 1 eq), reflux, 17 h, (84%); (f) I_2, PPh_3, Py, THF, rt, 9 h, (91%); (g) LDA, THF-HMPA, -78 °C, 30 min, (quant); (h) (i) LDA, THF-HMPA, -78 °C, 45 min; (ii) $PhSO_2SPh$, -78 °C, 1 h, (80 %) ; (i) (i) MCPBA, CH_2Cl_2, -78 °C, 1 h; (ii) reflux, 1 h (54%); (j) *n*-Bu_3SnN_3, xylene, 110 °C, 24 h, (71%); (k) NaOH, H_2O, rt, 4 h, (83%).

Based on the retrosynthetic analysis aimed at a synthesis of analogue **4**, the intermediate alcohol **12** was subjected to the following transformations (**Scheme 3**). Silylation of **12** with the TBDPSCl afforded bis-silylated protected derivative **19** in which the TBS group was selectively cleaved with HCO_2H-H_2O to give 5-

hydroxymethylimidazole **20**. Swern oxidation of **20** furnished the aldehyde **21** (96%), for which a similar two-step one-carbon elongation sequence was applied as for the preparation of ester **15** (**Scheme 2**). The Peterson-type olefination of **21** with 2-lithio-2-trimethylsilyl-1,3-dithiane (**22**)[13] provided ketene thioacetal **23** in 56% yield. Mercuric ion catalysed hydrolysis of **23** in MeOH-H_2O 9:1 in the presence of HCl, effected simultaneously cleavage of the TBDPS group to afford the corresponding methyl acetate **24** which was easily converted to a primary iodide **25** with I_2-PPh_3 reagent. Quantitative intramolecular cyclization of **25** was achieved with LDA in THF-HMPA solution at -78°C to afford 5,6,7,8-tetrahydroimidazo[1,5-*a*]pyridine derivative **26** as a *ca* 1:1 mixture of two diastereoisomers. This mixture was subjected, without separation, to Trost sulfenylating conditions,[14] lithiation with LDA in THF-HMPA at -78°C for 45 min and quenching of the reaction with $PhSO_2SPh$ furnished again a 1:1 diastereoisomeric mixture of thiophenyl derivatives **27**. Oxidation of this mixture with MCPBA in CH_2Cl_2 at -78°C and thermal elimination of phenylsulfenic acid in CH_2Cl_2 at reflux gave rise to the 5,6-dihydroimidazo[1,5-*a*]pyridine **28** (54%). This system was transformed into analogue **4** through procedures already established for the synthesis of **3** from **18**.

In conclusion, an efficient methodology has been introduced for the construction of losartan analogues with elaborated benzylic side chain as well as the methodology for a design of conformationally restricted analogues **3** and **4**. The IC_{50}'s of **3** and **4** (10 nM and 50 nM, respectively) were similar to that of losartan, but were however an order of magnitude higher than EXP3174 (0.2 nM).[15] The complete pharmacological evaluation of these analogues will be reported in due course.

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8. The preponderance of the regioisomer **9a** could be well correlated with the distribution of regioisomers obtained upon alkylation of imidazole-5-carboxaldehyde **8** with 4'-(bromomethyl)biphenyl derivatives under similar reaction conditions.[4]
9. The ratio *Z*/*E* was determined from the ^1H NMR spectra. In the *Z*-isomers **9a** the olefinic proton is shifted more downfield (200 MHz, $CDCl_3$, 6.77 ppm) as compared to the *E*-isomer **9a** (6.12 ppm). In the case of **10**, the *Z*- and *E*-isomers were separated by preparative TLC chromatography (4% MeOH-CH_2Cl_2). ^1H NMR NOE experiments (irradiation of the olefinic proton and protons of the phenyl ring) established that the major product had the *Z*-configuration.
10. We have investigated both the hydride reductions of the enoates **9a** and **10** as well as catalytic reduction. Following conditions afforded either decomposition or recovery of the starting material: Red-Al-Cu_2Br_2, Semmelhack M. F., Stauffer R. D., Yamashita A., *J. Org. Chem.*, **1977**, *42*, 3180-3188; MeLi-CuI-DIBAL-H, Tsuda T., Hayashi T., Satomi H., Kawamoto T., Saegusa. T, *J. Org. Chem.* **1986**, *51*, 537-540; $NaBH_4$-$NiCl_2$, Satoh T., Nanba K., Suzuki S., *Chem. Pharm. Bull.*, **1971**, *19*, 817-820; $NaHFe_2(CO)_8$-AcOH, Collman J. P., Finke R. G., Matlock D. L., Wahren R., Brauman J. I., *J. Am. Chem. Soc.*, **1976**, *98*, 4685-4687; $NaBH_3CN$/acids effected only reduction of aldehyde. Catalytic reduction with Pd-C/10%, MeOH, 50 atm, did produced **11** (30%), however, its difficult separation from the unreacted **10** made this approach unattractive.
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15. Pharmacological tests were performed against [^{125}I]AII (0.01 nM), on rat liver membranes in the absence of BSA.

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