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Conformationally Restricted Peptide Isosteres. 2.[1] Synthesis and In Vitro Potency of Dipeptide Renin Inhibitors Employing a 2-Alkylsulfonyl-3-phenylcyclopropane Carboxamide as a P_3 Amino Acid Replacement

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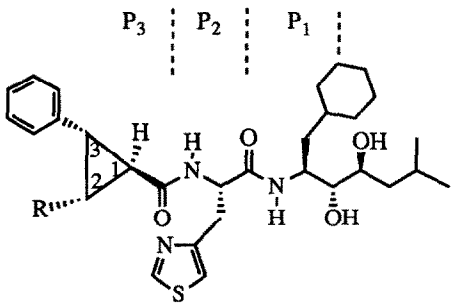
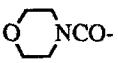
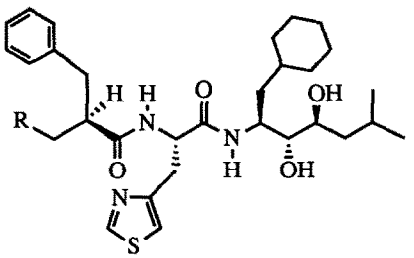
Abstract: *A series of dipeptide renin inhibitors employing a 2,3-disubstituted cyclopropane carboxamide at the P_3 position of the molecule were prepared by coupling racemic(1S,2R,3R) 2-alkylsulfonyl-3-phenyl(or cyclohexyl)cyclopropanecarboxylic acid with the amino acid derivatives* ***11a-d.*** *The individual diastereomers were separated and tested for in vitro potency. IC_{50} values ranged from 0.37 to 1.4 nM and 5.8 to 29 nm against purified, pH 6.0 and plasma, pH 7.4 human renin, respectively. In all examples, the more polar diastereomer was the most potent.*

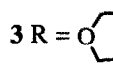
We have recently described a novel series of dipeptide renin inhibitors which incorporated a 1,2,3-trisubstituted cyclopropane at the P_3 position of the molecule.[1] The 1,2,3-trisubstituted cyclopropane served as an isosteric replacement for phenylalanine and the most potent inhibitor in the series contained a 4-morpholinocarbonyl and a phenyl substituent at the C(2) and C(3) position of the cyclopropane ring. Maximum inhibitory potency was achieved when the C(2) and C(3) substituents on the ring were cis to each other and trans to the C(1) carboxylate. In addition, two diastereomeric series were independently synthesized and evaluated. The (1R,2R,3R) diasteromer



1 R =  NCO-

2 R = RSO_2



3 R =  NCO-

4 R = RSO_2

1 which correlated at C(1) with the natural or S-configuration of phenylalanine was more potent than the (1S,2S,3S) diastereomer. The potency of inhibitor **1** against purified human renin (pH 6.0) and plasma human renin (pH 7.4)

was 0.7 and 20 nanomolar, respectively, and comparable to the acyclic analogue **3**.[3] We concluded that the substituted cyclopropane closely mimicked the biologically active conformation of the P_3 amino acid phenylalanine by enforcing an extended (β-strand) conformation and fixing the orientation of the phenyl ring relative to the backbone.

Structure-activity relationship (SAR) studies have shown that the in vitro potency of dipeptide renin inhibitors was increased when alkyl sulfones and sulfonamides were incorporated at the N-terminal position.[4a-c] For example, the in vitro potencies of inhibitors **4** (R = t-butylSO_2 and 4-morpholinosulfonyl) in the plasma human renin assay (pH 7.4) were 0.87 and 1.4 nM, respectively.[5] The six to nine-fold increase in potency over inhibitor **3** was attributed to the sulfonyl group. These results encourged us to synthesize a series of alkylsulfonylcyclopropane-containing dipeptide renin inhibitors **2** and determine if the alkyl sulfone moiety would impart increased potency. In addition, we were also interested in modifing inhibitor **2** by substituting other lipophilic and polar amino acids at the P_2 position. Preliminary results from our study are now reported.

The synthesis of the sulfonylcyclopropane analogues **2** required a general method for the preparation of racemic (1S,2R,3R) 2-alkylsulfonyl-3-phenylcyclopropane carboxylic acids **13**. Our strategy for the preparation of carboxylic acids **13**, involved as the key step, a stereoselective metallation of a 1,1-dibromo-2-hydroxymethyl-3 phenylcyclopropane ether **5** and subsequent protonation of the configurationally stable cyclopropyllithium to give the syn diastereomer **6**. This approach demanded that the hydroxymethyl ether substituent direct the metallation reaction.

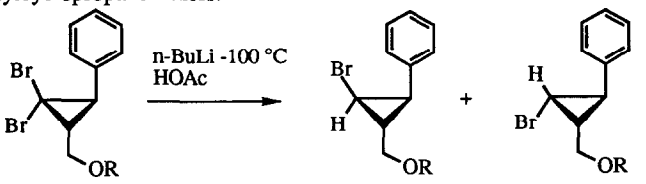
1,1-Dibromo-2-hydroxymethyl-3-phenylcyclopropane t-butyldimethylsilyl ether **5a**, prepared by cyclpropanation of cinnamyl alcohol t-butyldimethylsilyl ether with dibromocarbene[6] was metallated with n-BuLi at -100 °C to furnish the monobromocyclopropanes **6a/7a** in excellent yield (Table 1). However, two diastereomers were formed. The ^{1}H NMR ($CHCl_3$, 300 MHz) of the crude cyclopropylbromide mixture **6a/7a** exhibited two resonances at δ 2.14 (doublet of doublets, J = 4 and 6 Hz) and δ 2.31 (doublet of doublets, J = 8 Hz) for the proton on the cyclopropyl carbon bearing the phenyl group in a ratio of 3:2. The stereochemistry of **6a** and **7a** was assigned by metallation of the crude cyclopropylbromide mixture with n-BuLi (-75 °C, THF) and addition of phenyl disulfide. The crude phenyl sulfides were oxidized to the sulfones with MCPBA (rt, CH_2Cl_2, 18h) and the TBDMS ether was cleaved with tetrabutylammonium fluoride (TBAF). Two crystalline sulfone carbinols **11** and **12** (R = R_1 = Ph) were isolated by silica gel chromatography (1:1 ethyl acetate-hexane). The ^{1}H NMR (CD_3OD, 500 MHz) of the more polar diastereomer (R*f* 0.11, 1:1 EtOAc-hexane, mp 85-86 °C, minor isomer) displayed a doublet of doublets (J = 5 and 10Hz) at δ 2.97 for the proton on the cyclopropyl carbon bearing the phenyl sulfone and a doublet of doublets (J = 8Hz) at δ 2.68 for the benzylic methine proton. The less polar diastereomer ($CDCl_3$, 500 MHz, mp 118-119 °C, major isomer) exhibited a doublet of doublets (J = 5 and 10 Hz) at δ 2.77 and a triplet (J = 8Hz) at δ 3.03 for the proton on the cyclopropyl carbon bearing the phenyl sulfone and benzylic methine, respectively. The proton NMR data suggested that the more polar phenyl sulfone diastereomer was compound **12** and the less polar phenyl sulfone diastereomer was **11**. The structure of the less polar diastereomer was confirmed by single crystal X-ray analysis and, as predicted from the ^{1}H NMR data, was compound **11** (R = R_1 = Ph).[7] Therefore, the more polar and minor diastereomer was assigned structure **12** (R = R_1 = Ph). Since carbinol **11** was obtained as the major product from the bromocyclopropane mixture **6a/7a**, then the proton resonances at δ 2.14 and δ 2.31 were assigned to anti **7a** and syn **6a** diastereomers, respectively.

In order to improve the metallation reaction and maximize the syn:anti ratio of monobromocyclopropanes, a series of experiments were conducted in which the solvent and ether protecting group were varied and the ratio of

6a/7a was determined by integration of protons on the cyclopropane carbon bearing bromine and the phenyl group (Table 1). The TBDMS and TBDPS ethers favored the formation of the anti diastereomer in all solvents examined. However, when the metallation was performed using the nonpolar solvent mixture (5:1) hexane-THF and benzyl or benzyloxymethyl (BOM) ethers as the protecting groups, the syn diastereomer was slightly favored by a ratio of 5-3 to 2. In THF and ether no selectivity was observed and the syn:anti ratio was unchanged. These results may be interpereted in the following manner. There are two groups capable of complexing the n-butyllithium and directing the metallation reaction, the phenyl group[8] and the benzyl or BOM ether. The complexation of n-butyllithium and substrate **5** was maximized in nonpolar solvents. Thus, the phenyl ring directed the metallation more effectively than the stericly demanding and weakly chelating TBDMS and TBDPS ethers. However, the benzyl ether group was able to compete with the phenyl ring in directing the metallation reaction and the syn isomer **6c** was favored in (5:1) hexane-THF.

Having developed optimum conditions for the metallation of cyclopropane **5**, the synthesis of the racemic sulfonylcyclopropane carboxylic acids **13** was completed (Scheme). Alkylsulfonylcyclopropane carbinols **11** and **12** (R_1 = Me, Et, Ph, $CH_3OCH_2O(CH_2)_2$, and isopropyl) were prepared by metalating **10a,b** with n-butyllithium and trapping the resultant cyclopropyllithium intermediates with an alkyl disulfide. The crude cyclopropyl sulfides were oxidized to the sulfones with MCPBA. Hydrogenolysis of the benzyl ether, separation of the more polar alcohol diastereomer **12**, and Jones oxidation completed the synthesis of acids **13a-f**. Inhibitors **15a-i** and **16a-i** were prepared by coupling acids **13a-f** with the amino acid derivatives **14a-d**[1,9ab] using standard peptide coupling procedures (EDC, HOBT). Except for inhibitor **15c**, the cyclopropane dipeptide inhibitors were separated by silica

Table 1. The Effect of Solvent and Protecting Group on the Metallation of (2R,3R) 1,1-Dibromo-2-hydroxymethyl-3-phenylcyclopropane Ethers.



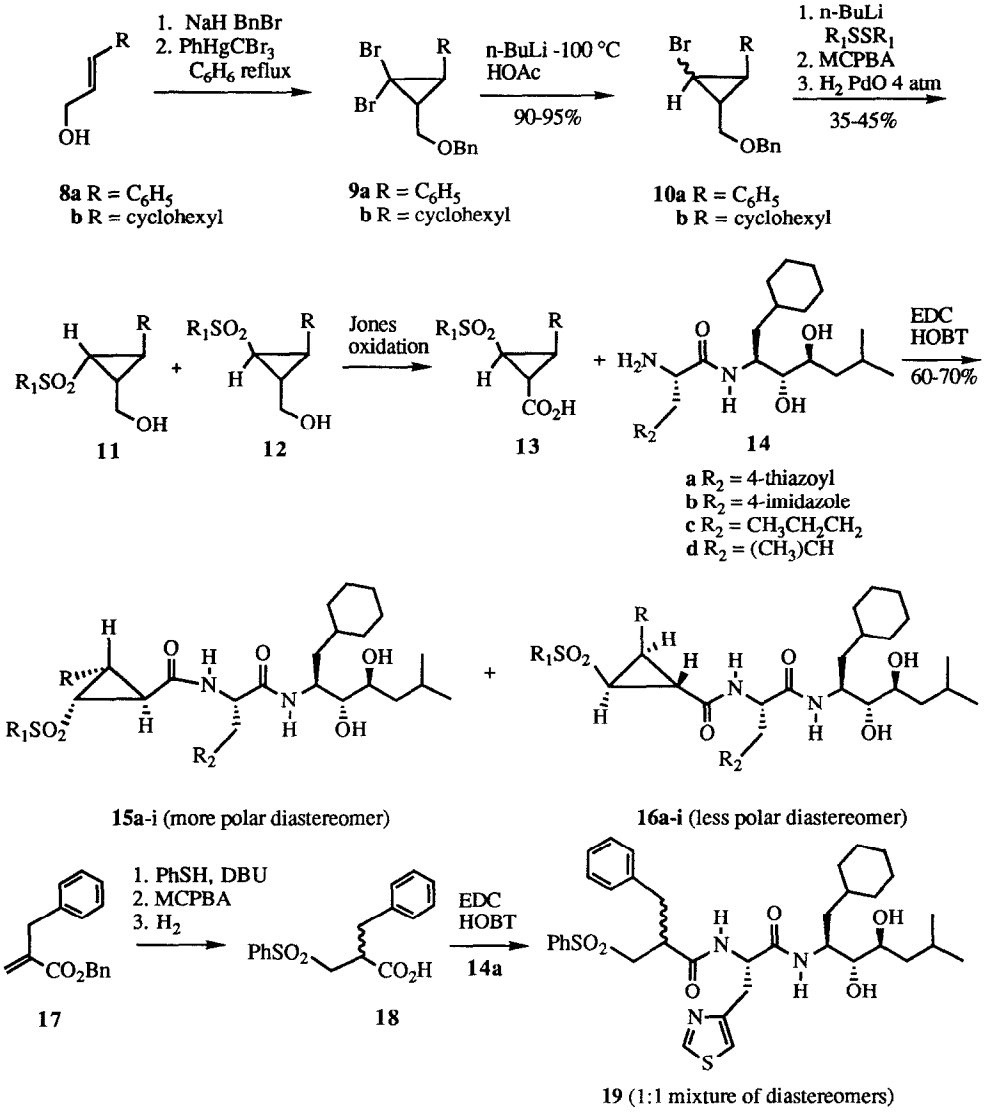
5 **6** syn **7** anti

R	syn:anti ratio[a] (5:1) hexane-THF	(1:1) hexane-ether	ether	THF
a. TBDMS[b]	1:4	1:3	1:2	1:2
b. TBDPS[c]	1:5	1:4	1:2	2:3
c. $PhCH_2$	5:2	2:1	1:1	1:1
d. $PhCH_2OCH_2$	3:2	5:4	1:1	1:1

[a] The diastereomeric ratios (syn:anti) were determined by ^1H NMR (300 MHz, $CHCl_3$) integration of the methine protons (CHBr, PhCH) in the crude reaction mixture. [b] TBDMS = t-butyldimethylsilyl. [c] TBDPS = t-butyldiphenylsilyl

gel chromatography and tested as individual diastereomers. The absolute stereochemistry of the more polar diastereomers was tentatively assigned by TLC comparison to the 4-morpholinocarbonyl series. Thus, inhibitor **1** (1R,2R,3R) which was prepared in optically pure form was more polar by TLC (R_f 0.29 5:95 methanol-CH_2Cl_2)

Scheme



than the less polar (1S,2S,3S) diastereomer (R*f* 0.34 5:95 methanol-dichloromethane). By analogy, the absolute stereochemistry for the more polar alkylsulfonylcyclopropane diastereomers was assigned to structures **15a,b,d-i** and the less polar diastereomers structures **16a,b,d-i**. For comparison to inhibitor **15c**, the acyclic inhibitor **19** was synthesized from benzyl 2-benzyl acrylate as shown in the Scheme and was tested as a 1:1 mixture of diastereomers.

Data for the in vitro potency of sulfonylcyclopropane dipeptide renin inhibitors against purified and plasma

renin are shown in Table 2. Five substituents at the R_1 position of the inhibitor were evaluated with the R (phenyl) and R_2 (4-thiazoyl) groups remaining constant (entries **15a-e**). The data revealed that the alkyl sulfone substitution, like the acyclic analogues **4**, produced potent inhibitors of purified human renin. Inhibitors employing the 2-(methoxymethoxy)ethyl sulfone **15d** and the isopropyl sulfone **15e** were more potent than the 4-morpholinocarbonyl-containing inhibitor **1**. The data also showed that the sulfonylcyclopropane isostere mimicked its acyclic counterpart (compare **15c** and **19**). The most noticeable effect on potency was the isopropyl sulfone substitution. Inhibitor **15e** was the most potent compound tested in the purified assay (pH 6.0) with an IC_{50} value of 0.38 nM. However, inhibitors **15a-e** were 20-40-fold less potent in the plasma renin assay. This drop in potency between the two assays was also noted in the 4-morpholinocarbonyl series.[1] The cyclohexyl analogue **15f** was only 2-fold less potent than the most potent inhibitor **15e**. This result was not surprising since the acyclic renin inhibitor, TBA-(cyclohexyl)Ala-His-ACDH, with the cyclohexyl group at the P_3 position was two-fold less potent in the purified renin assay (pH 6.0) than inhibitor TBA-Phe-His-ACDH with a phenyl group at the same position.[10] The 2-isopropylsulfonyl-3-phenylcyclopropane isostere with the 4-thiazol-1-yl substitution at P_2 produced the most potent inhibitors. We were interested in evaluating the effect of the 2-isopropylsulfonyl-3-phenylcyclopropane moiety with other P_2 amino acids. Three inhibitors were prepared which contained histidine **15g**, norleucine **15h**, and leucine **15i** at the P_2 position. The leucine and norleucine analogues, **15h** and **15i**, exhibited subnanomolar potency with IC_{50} values of 0.37 and 0.59 nM, respectively. The histidine-containing inhibitor **15g** was the least potent of the series. However, inhibitor **15g** was the most potent analogue tested in the plasma renin assay

Table 2. In Vitro Potency of Dipeptide Renin Inhibitors Employing a 2-Alkylsulfonyl-3-phenyl(or cyclohexyl)cyclopropane carboxamide at the P_3 Position.

				IC_{50}, nM[a]			
	R_1	R_2	R	pH 6.0[b]		pH 7.4[c,d]	
				15	**16**	**15**	**16**
a	CH_3	4-thiazol-1-yl	C_6H_5	0.63	18	23	nd
b	C_2H_3	4-thiazol-1-yl	C_6H_5	0.63	7.2	17	27
c	C_6H_5	4-thiazol-1-yl	C_6H_5	1.2[e]		29[e]	
d	$(CH_2)_2OCH_2OCH_3$	4-thiazol-1-yl	C_6H_5	0.48	1.0	16	33
e	i-propyl	4-thiazol-1-yl	C_6H_5	0.38	7	7.9	85
f	i-propyl	4-thiazol-1-yl	cyclohexyl	0.79	14	15	nd
g	i-propyl	4-imidazol-1-yl	C_6H_5	1.4	2.5	5.8	15
h	i-propyl	$(CH_2)_2CH_3$	C_6H_5	0.37	1.9	13	160
i	i-propyl	$CH(CH_3)_2$	C_6H_5	0.59	4.4	14	370
19				0.77[e]		18[e]	

[a] IC_{50} values were determined against human renin. [b] Purified renin. [c] Plasma renin.
[d] Compounds were selected for IC_{50} determinations against plasma renin at pH 7.4 if their IC_{50} value in the purified assay, pH 6.0 was 10 nM or less. [e] The diastereomers were not separated. The IC_{50} value was obtained on a 1:1 mixture.

(pH 7.4) with an IC_{50} value of 5.8 nM. These data suggested that at 7.4 pH a polar substituent at the P_2 position

is required for maximum binding to the S_2 domain of renin. The less polar diastereomers **16a-i** possessed weaker inhibitory activity than the more polar isomers **15a-i** in both renin assays.

In conclusion, we have extended our SAR studies on conformationally restricted dipeptide renin inhibitors to include 2-alkylsulfonyl-3-phenylcyclopropanes as isosteric replacements for phenylalanine. The 2-isopropyl sulfonyl substituent at the C(2) position of the cyclopropyl ring produced the most potent inhibitors of purified human renin at pH 6.0. In addition, improved in vitro potency in the plasma renin assay (pH 7.4) was achieved by substituting histidine for the more lipophilic amino acids leucine, norleucine, and 4-thiazoylalanine.

References and Notes

1. For part 1, see: Martin, S. F.; Austin, R. E.; Oalmann, C. J.; Baker, W. R.; Condon, S. L.; deLara, E.; Rosenberg, S. H.; Spina, K. P.; Stein, H. H.; Cohen, J.; Kleinert, H. D. *J. Med. Chem.* **1992**, *35*, 1710-1721.
2. (a) Abbott Laboratories. (b) University of Texas.
3. The IC_{50} value for compound **3** against purified renin (pH 6.0) and plasma renin (pH 7.4) was 0.36 and 8.3 nM, respectively.
4. (a) Buhlmayer, P.; Caselli, A.; Fuhrer, W.; Goschke, R.; Rasetti, V.; Rueger, H.; Stanton, J. L.; Criscione, L.; Wood, J. M. *J. Med Chem.* **1988**, *31*, 1839-1846. (b) Doherty, A. M.; Kaltenbronn, J. S.; Hudspeth, J. P.; Repine, J. T.; Roark, W. H.; Sircar, I.; Tinney, F. J.; Connolly, C. J.; Hodges, J. C.; Taylor, M. D.; Batley, B. L.; Ryan, M. J.; Essenburg, A. D.; Rapundalo, S. T.; Weishaar, R. E.; Humblet, C.; Lunney, E. A. *J. Med. Chem.* **1991**, *34*, 1258-1271. (c) Repine, J. T. Himmelsbach, R. J.; Hodges, J. C.; Kaltenbronn, J. S.; Sircar, I.; Skeean, R. W.; Brennan, S. T.; Hurley, T. R.; Lunney, E. A.; Humblet C. C.; Weishaar, R. E.; Rapundalo, S.; Ryan, M. J.; Taylor Jr., D. G.; Olson, S. C.; Michniewicz, B. M.; Kornberg, B. E.; Belmont, D. T.; Taylor, M. D*J. Med. Chem.* **1991**, *34*, 1935-1943.
5. Unpublished results.
6. Dibromocarbene was generated from the thermal decomposition of phenyl(tribromomethyl)mercury which was prepared according to the procedure of Seyferth and Lambert, *J. Organomet. Chem.* **1969**, *16*, 21-26.
7. X-ray crystallographic data for compound **11** ($R = R_1 = Ph$) is available upon request.
8. The directing effect of a phenyl ring on the metalation of 1,1-dibromocyclopropanes has been observed, see: Danheiser, R. L.; Morin, J. M.; Yu, M.; Basak, A.; *Tetrahedron Lett.* **1981**, *42*, 4205-4208.
9. (a) For the synthesis of **11b**, see: Plattner. J. J.; Marcotte, P. A.; Kleinert, H. D.; Stein, H. H.; Greer, J.; Bolis, G.; Fung, A. K. L.; Bopp, B. A.; Luly, J. R.; Sham, H. L.; Kempf, D. J.; Rosenberg, S. H.; Dellaria, J. F.; De, B.; Mertis, I.; Perun, T. *J. Med. Chem.* **1988**, *31*, 2277-2288. (b) The amino acid derivatives **11c** and **11d** were prepared according to the procedure cited in reference 1 for the preparation of **11a** with the modification that N-(tert-butyloxycarbonyl)-L-norluecine and N-(tert-butyloxycarbonyl)-L-luecine were substituted for N-(tert-butyloxycarbonyl)-3-(4-thiazoyl)-L-alanine.
10. The IC_{50} value for TBA-(cyclohexyl)Ala-His-ACDH was 1.8 nM (purified renin, pH 6.0) and 11 nM (plasma renin, pH 7.4) and TBA-Phe-His-ACDH was 1 nM (purified renin, pH 6.0) and 9 nM (plasma renin, pH 7.4), see: Luly et. al *J. Med. Chem.* **1988**, *31*, 2264-2276. TBA = t-butylacetyl. ACDH = (2S,3R,4S) 2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane.