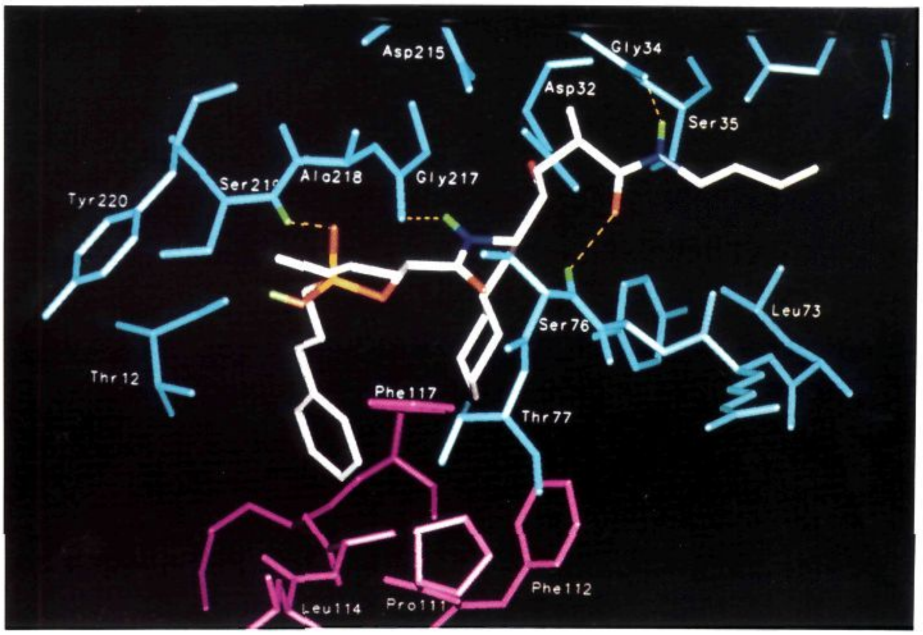

Figure 2. Compound **7b** (white; see also Table 1) in the active site of the renin model (cyan). Only those hydrogen atoms (green) involved in hydrogen bonds (yellow dashed lines) or bound to one of the phosphonate oxygens are displayed. The loop which limits pocket S3 (magenta) was taken from the X-ray structure.[14] The phenyl ring of **7b** (optimal spacer length of 3) makes contacts to the hydrophobic sidechains of Pro 111, Leu 114, and Phe 117.

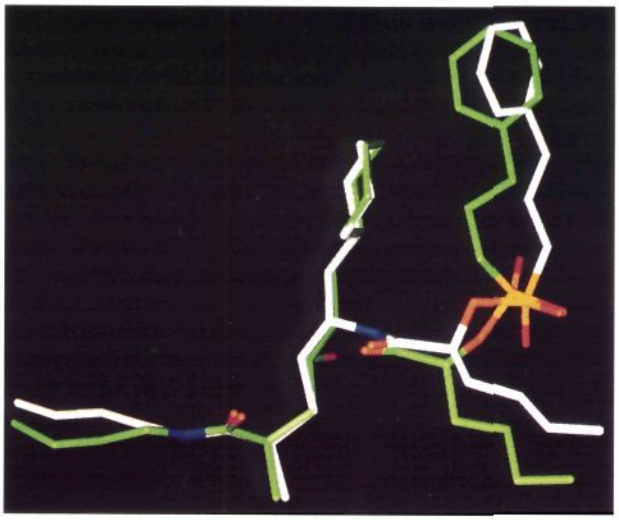

Figure 3. Compounds **7b** (*S* configuration, white) and **7f** (*R* configuration, green) superposed in their presumed receptor-bound conformation. Despite their different stereochemistry, both the phenyl rings in the highly constrained S3 site and to a lesser extent the butyl side chains in the less constrained S2 site occupy similar volumes in space. This could explain the similar activity of the stereoisomers.

stereochemistry of the phosphonate group for compounds **7k** (Figure 4a) and **7l** (Figure 4b).

A somewhat similar situation can be found for compounds **7m** and **7n** containing R′ = benzyl. The relatively good activity of inhibitor **7m** might be a consequence of the possible interaction of the benzyl moiety with Tyr 220 of binding site S4 (see Figure 4c). This edge-to-face interaction is similar to a preferred Phe–Phe interaction found in many protein structures.[21]

Enzyme Selectivity. The renin inhibitors listed in Tables 1 and 2 were assayed for their ability to inhibit other aspartic proteinases. None of these compounds showed significant inhibition of porcine pepsin (Table 3) at a concentration of 10 μM. Compound **7k**, **7m**, **8a**, **8f**, and **8h** did inhibit bovine cathepsin D albeit with very weak activity. These results demonstrate the high specificity of the inhibitors for renin in comparison to related proteinases.

In Vivo Activity. In order to evaluate effects in vivo on plasma renin activity (PRA), blood pressure, and heart rate, selected compounds were administered orally to conscious, sodium-depleted cynomolgus monkeys. Figure 5 shows the results obtained with inhibitor **7i** at an oral dose of 30 mg/kg. This dose produced a maximal hypotensive response of 15 mmHg lasting for about 180 min. PRA was suppressed by 97%, 99%, and 96% at 30, 60, and 180 min, respectivley.

Conclusion

A new series of novel renin inhibitors containing 2-(((3-phenylpropyl)phosphoryl)oxy)alkanoic acid moieties as replacements for P_2–P_3 sites was developed. Our studies resulted in highly selective compounds with inhibitory potencies in the lower nanomolar range. Small renin inhibitors, such as compounds **8c** and **8h** with low molecular weight (539 and 537, respectively), could be prepared and exhibited IC_{50} values of about 20 nM against human plasma renin. Preliminary in vivo studies with compound **7i** demonstrated moderate hypotensive effects after oral administration. Further studies are currently underway to improve the potency of the small molecular weight renin inhibitors and to evaluate their potential in vivo.

Experimental Section

Melting points were determined with a Mettler FP 62 melting point apparatus and are uncorrected. Specific rotations were measured with a Perkin-Elmer 241 MC polarimeter. IR, NMR, and mass spectra are in agreement with the structures cited and were recorded on a Bruker 85 IFS 48 IR spectrophotometer, a Bruker AC 200, WM 250 or AM 500 (TMS as internal standard), and a Vacuum Generator VG 70-70 or 70-250 at 70 eV,

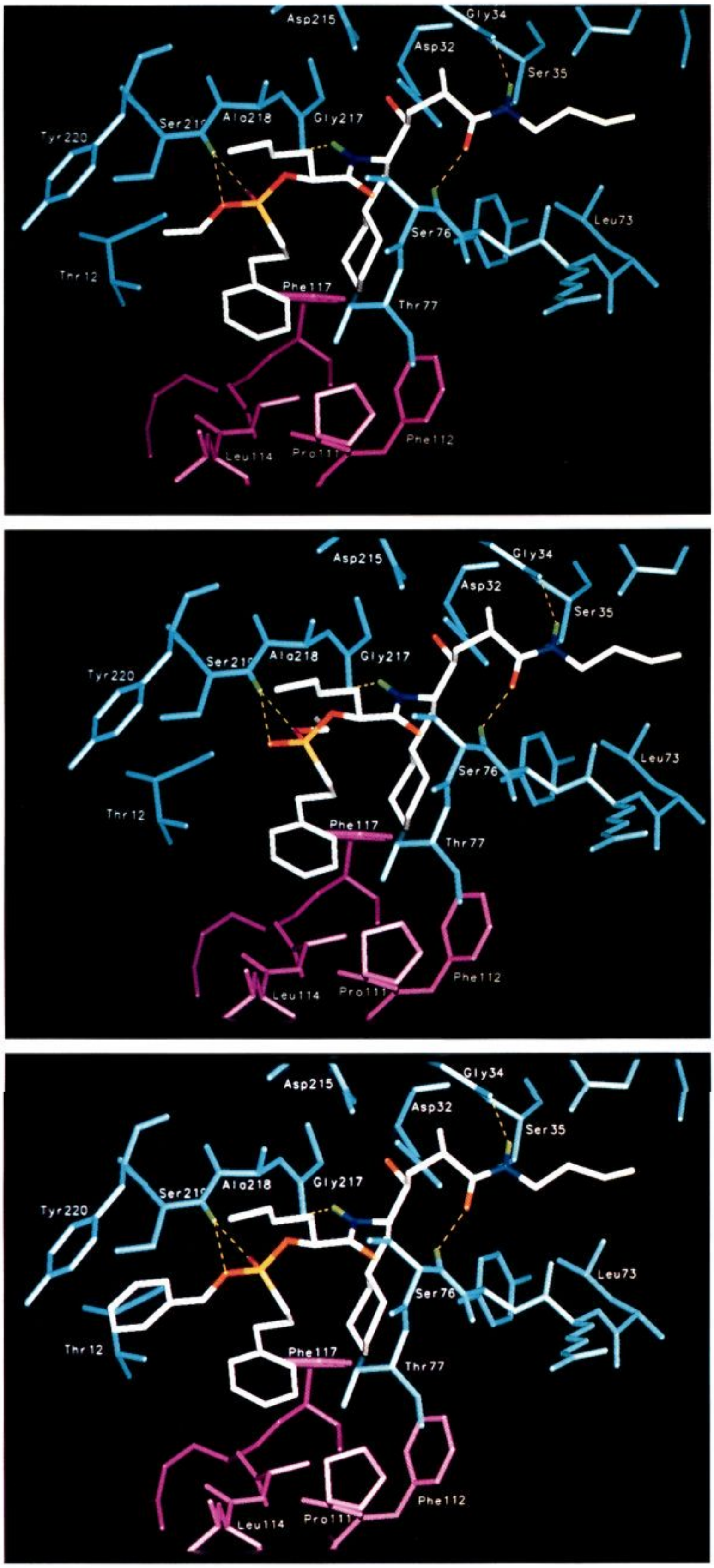

Figure 4. (a) Less polar, more active compound **7k** of the **7k**/**7l** pair in the active site of the renin model. There is ample space for the ethyl group attached to one of the two phosphonate oxygens. (b) More polar, less active compound **7l** of the **7k**/**7l** pair in the active site of the renin model. There is some steric overlap between the ethyl group attached to the other one of the two phosphonate oxygens and the protein backbone (especially the carbonyl oxygen of Gly 217). (c) Compound **7m** in the active site of the renin model. In this configuration, the phenyl group attached to one of the two phosphonate oxygens makes good edge-to-face contact to Tyr 220, which could explain the better activity of compound **7m** relative to **7n**.