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THE SYNTHESIS OF [^{3}H]-LOSARTAN, [^{3}H]-L-158,641 AND [^{3}H]-L-158,809.

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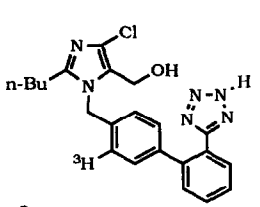
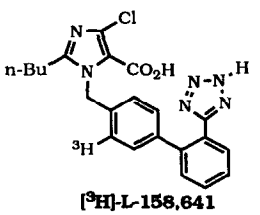
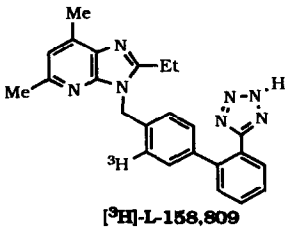
Abstract: Selective radioligands of the angiotensin II AT_1 receptor subtype have been prepared. Radiolabeled Losartan (DuP 753)[1,2], L-158,641 (EXP3174)[3] and L-158,809[4,5] were prepared from a common bromobiphenyl intermediate. The key step in the synthesis is the selective aromatic monobromination of 2-cyano-4'-methylbiphenyl.



[^{3}H]-Losartan (DuP 753)



[^{3}H]-L-158,641



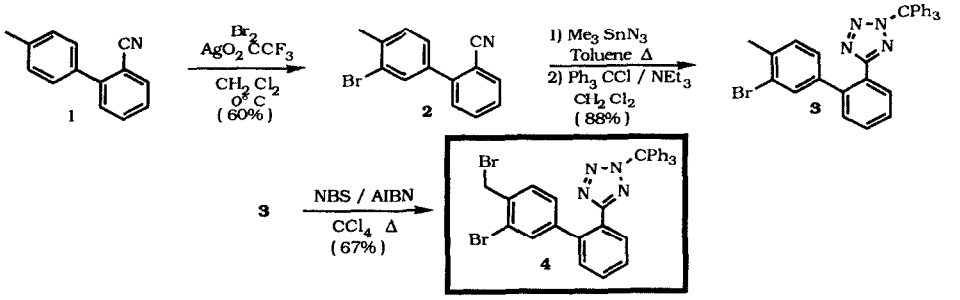
[^{3}H]-L-158,809

Angiotensin II, an intermediate in the renin-angiotensin cascade, plays a critical role in the regulation of blood pressure and fluid and electrolyte balance. The remarkable success achieved by angiotensin converting enzyme inhibitors for the treatment of hypertension and congestive heart failure has generated considerable interest in the development of novel pharmacological agents to intervene in the renin-angiotensin system.[6] During the past several years there have been extraordinary advances in the development of potent nonpeptide angiotensin II receptor antagonists. The biphenyl tetrazole moiety is a common feature to many of these antagonists.[7] During our evaluation of Losartan (DuP 753)[8], L-158,641 (EXP 3174)[8] and L-158,809 it became clear that in order to facilitate attaining pharmacokinetic data, radiolabeled analogs would be necessary. Toward this end, we have developed an efficient synthesis of *N*-triphenylmethyl-5-(3'-bromo-4'-bromomethyl-biphen-2-yl)tetrazole, a common intermediate which could be used for the synthesis of the desired labeled compounds.

A reasonable precursor for tritiation is a bromobiphenyl derivative. Since selective monobromination of the intact antagonists was, as anticipated, problematic and provided complex mixtures, it became necessary to introduce the bromine prior to appending the heterocycle. Introduction of the bromine atom into a common intermediate would allow for the facile preparation of all three labeled antagonists. As is illustrated in Scheme I this was best accomplished starting with 2-cyano-4'-methylbiphenyl.[4] Treatment of **1** in CH_2Cl_2 at 0°C with one equivalent of both silver trifluoroacetate[9] and bromine cleanly afforded monobromide **2** in 60% yield after purification.[10] The trityl protected tetrazole was efficiently constructed by heating the nitrile at reflux with 3-5 equivalents of Me_3SnN_3 in toluene, followed by reaction

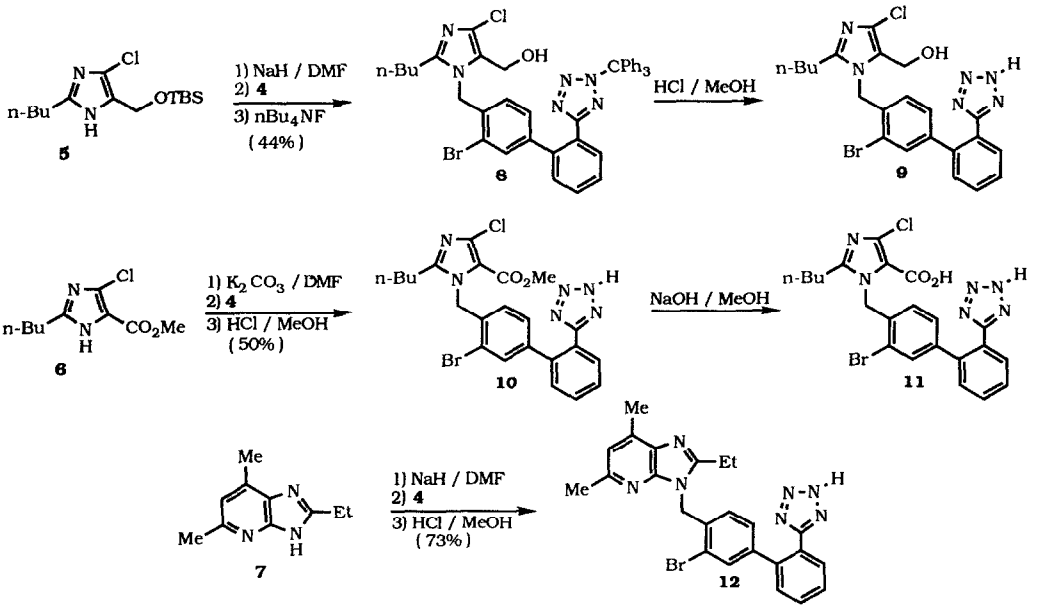
with trityl chloride in the presence of triethylamine. Activation of the methyl group, necessary for coupling, was accomplished with N-bromosuccinamide in refluxing CCl_4 using AIBN as catalyst to afford a 67% yield of dibromide **4**, *N*-triphenylmethyl-5-(3'-bromo-4'-bromomethyl-biphen-2-yl)tetrazole.[11]

SCHEME I



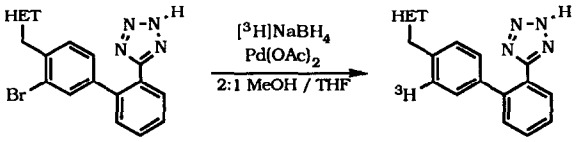
Coupling of dibromide **4** to the respective heterocycles is illustrated in Scheme II. Alkylation of heterocycles **5**, **6** using NaH and K_2CO_3 in DMF, respectively, afforded, after deprotection and chromatographic separation of the undesired regioisomers, compounds **8** and **10** in 44 and 50% yield, respectively.[12] A second deprotection step then afforded the desired tritiation precursors **9** and **11**. Alkylation of heterocycle **7** using NaH in DMF followed by deprotection afforded tritiation precursor **12** in 73% yield.[11]

SCHEME II



A general procedure, illustrated in scheme III, for the reductive dehalogenation of aromatic bromides[13] utilizing sodium borotritide and $Pd(OAc)_2$[14] was adapted to complete the synthesis of [^{3}H]-Losartan[15] (DUP 753), [^{3}H]-L-158,641[16] (EXP3174) and [^{3}H]-L-158,809[16] from bromo derivatives **9**, **11** and **12**, respectively. A solution of aromatic bromide (3-3.5 mM) and $Pd(OAc)_2$ (3-5 mM) in 2:1 methanol-THF is added in one portion to [^{3}H]$NaBH_4$[18] with stirring. After 1 hour, the reaction mixture is diluted with methanol, filtered, concentrated, and the products purified by semipreparative HPLC.[19]

SCHEME III



In summary, we have outlined a general procedure for the synthesis of radiolabelled angiotensin II AT_1 receptor antagonists which contain a biphenyl tetrazole fragment. This procedure utilizes the key dibromo intermediate, *N*-triphenylmethyl-5-(3'-bromo-4'-bromomethyl-biphen-2-yl)tetrazole (**4**). Following alkylation of the desired heterocycle and deprotection, tritiation of the bromo-precursor was carried out using a mild tritiation protocol. This newly developed protocol is compatible with a variety of functionality.

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9. Silver trifluoroacetate has been used for the iodination of aromatic rings. Janssen, D. E.; Wilson, C. V. *Org. Syn., Coll Vol.* **1963**, 4, 547.

10. The dibromide was conveniently purified by recrystallization from a mixture of hexane/ethyl acetate (5:1).

11. The structure assigned to each new compound is in accord with its mass spectrum (FAB) and high field (300 or 400 MHz) NMR spectrum.
    4: H^1 NMR (400 MHz, $CDCl_3$) δ 4.48 (s, 2H), 6.85-6.95 (comp m, 8H), 7.21-7.32 (comp m, 11 H), 7.49 (dd, 2H), 8.00 (dd, 1H). FAB MS (MH^+ calcd for $C_{33}H_{24}N_4Br_2$) 635, found (MH^+) 635, (MH^++2) 637, (MH^++4) 639.
    9: H^1 NMR (400 MHz, CD_3OD) δ 0.91 (t, 3H), 1.36 (m, 2H), 1.59 (m, 2H), 2.57 (t, 2H), 4.48 (s, 2H), 5.35 (s, 2H), 6.45 (d, 1H), 7.10 (dd, 1H), 7.44 (dd, 1H), 7.49-7.60 (comp m, 3H), 7.63 (t, 1H). FAB MS (MH^+ calcd for $C_{22}H_{22}N_6OBrCl$) 501, found (MH^+) 501, (MH^++2) 503, (MH^++4) 505.
    11: H^1 NMR (300 MHz, CD_3OD) δ 0.90 (t, 3H), 1.32 (m, 2H), 1.57 (m, 2H), 2.61 (t, 2H), 5.69 (s, 2H), 6.41 (d, 1H), 7.08 (dd, 1H), 7 41 (s, 1H), 7.52 (m, 2H), 7.68 (m, 2H). FAB MS (MH^+ calcd for $C_{22}H_{20}N_6O_2BrCl$) 515, found (MH^+) 515, (MH^++2) 517, (MH^++4) 519.
    12: H^1 NMR (400 MHz, CD_3OD) δ 1.41 (t, 3H), 2.68 (s, 3H), 2.73 (s, 3H), 3.22 (q, 2H), 5.88 (s, 2H), 6.88 (d, 1H), 7.02 (dd, 1H), 7.43 (s, 1H), 7.61 (m, 2H), 7.67 (d, 1H), 7 72 (m, 2H). FAB MS (MH^+ calcd for $C_{24}H_{22}N_7Br$) 488, found (MH^+) 488, (MH^++2) 490.

12. In the alkylation of imidazoles **4** and **6** the undesired regioisomers were produced in less than 30% yield. Separation, prior to deprotection, was carried out using flash chromatography.

13. Bromine is more reactive than chlorine to catalyzed hydrodehalogenation with $NaBH_4$. For examples see, Eglic, R. A. *Helv Chem. Acta.* **1968**, 51, 2090.

14. Adapted from Satoh, T.; Mitsuo, N.; Nishiki, M.; Nanba, K.; Suzuki, S. *Chem Lett.* **1981**, 1029.

15. HPLC purification afforded 1.52 mCi, specific activity 6.90 Ci/mmol and having a radiochemical purity of 98.9% by HPLC analysis.

16. HPLC purification afforded 4.99 mCi, specific activity 8.08 Ci/mmol and having a radiochemical purity of 99.7% by HPLC analysis

17. HPLC purification afforded 6.88 mCi, specific activity 8.76 Ci/mmol and having a radiochemical purity of 99.5% by HPLC analysis.

18. For precautions involving tritium handling see: E. A. Evans, "Tritium and Its Compounds", 2nd ed., Wiley, NY, **1974**, pg. 190-237.

19. In the general procedure of reference 14 a large excess (10 molar equivalents) of $NaBH_4$ is used for the hydrohalogenation in the presence of a palladium catalyst. The effective reducing agent may be an unstable borohydride-palladium complex as evidenced by rapid gas evolution upon mixing. The percentage of tritium incorporation in the products depends on the specific activity of the sodium borotritide. The specific activity of the sodium borotritide (40-50 Ci/mmol) is reflected in the activity of the products