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AN IMPROVED SYNTHESIS OF THE UNIQUE ANTI-MIGRAINE AGENT CP-122,288: A BROMINE ATOM PASSENGER IN AN INTRAMOLECULAR HECK REACTION

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Abstract: *Utilizing a 2,6-dibromoaniline (**6b**) in place of the original monobromo aniline in the indole-forming intramolecular Heck reaction allows for a greater than two-fold improvement in the overall yield of CP-122,288. The second bromine is carried through unmolested, forming a 7-bromoindole analog of CP-122,288 (**1b**). This result might represent a novel approach to 7-substituted indole derivatives.*

The discovery and success of the novel anti-migraine drug, sumatriptan (Imigran®)[2] has prompted additional study in the area of migraine research. The focus of these efforts has been the synthesis and discovery of new agents which will either improve on the action of sumatriptan or shed more light on the pathogenesis of the disease. Along these lines of investigation, we discovered CP-122,288 (Scheme 1),[3] a conformationally restricted analog of sumatriptan, which was resistant to the major metabolic pathway of sumatriptan, i.e., degradation by the enzyme MAO (*monoamine oxidase*). More importantly, however, CP-122,288 possessed a unique potency in a crucial model of migraine: namely CP-122,288 was 7000-fold more potent than sumatriptan in its ability to inhibit the neurogenic inflammation thought responsible for the precipitation of a migraine attack.[4] This unique activity of CP-122,288, coupled with its otherwise identical pharmacology with sumatriptan, made this compound a highly desirable agent for additional studies. These studies should determine the advantages of CP-122,288 over sumatriptan and shed light on the exact etiology of migraine headaches.

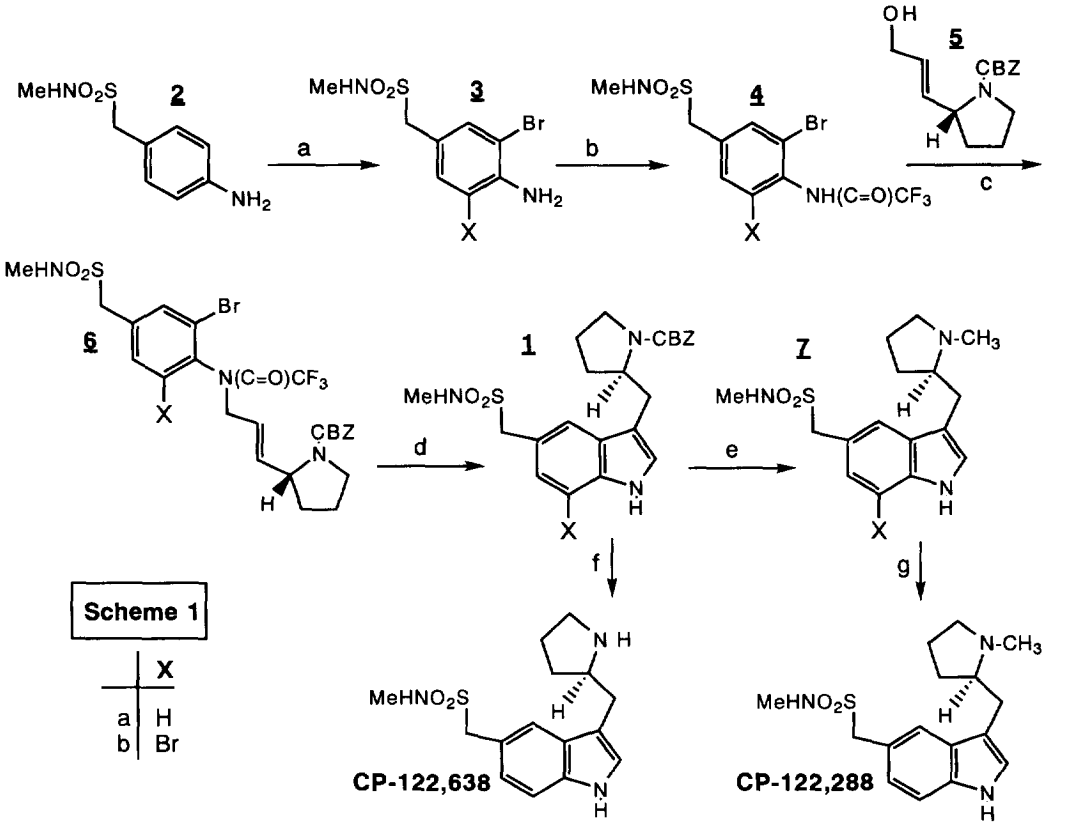
With this in mind, large quantities of CP-122,288 were sought, and examination of the initial synthesis[3] of the compound was undertaken. This convergent synthesis centered on an intramolecular Heck reaction to form the fully functionalized 3,5-disubstituted indole (**1a**, X=H) which was reduced to CP-122,288 (Scheme 1). While the length of the original sequence was somewhat daunting, all reactions proceeded in good to excellent yields with the exception of one early process: bromination of the requisite aniline derivative (**2**).[3] This reaction was consistently low yielding

regardless of conditions, and usually a statistical mixture of returned starting material (**2**), desired monobromo species (**3a**, X=H), and the dibrominated aniline (**3b**, X=Br, Scheme 1) was isolated. Since the next step in the sequence was the formation of a trifluoroacetamide [needed for NH activation in the subsequent Mitsunobu coupling with the alcohol (**5**)], we reversed the sequence. However, attempted monobromination of the trifluoroacetamide of **2** also gave large amounts of returned starting material and the dibromotrifluoroacetanilide (**4b**, X=Br).

Since it appeared that high yield of a monobrominated species was difficult to achieve, we sought to explore the possibility of utilizing the dibromo species (**3b**, X=Br), which could be obtained in almost quantitative yield (96%) utilizing two equivalents of bromine in methanol with sodium bicarbonate as an acid scavenger. However, there was little evidence in the literature which suggested that the second bromine would be ignored in the palladium catalyzed intramolecular Heck reaction, which was the cornerstone of the synthesis of CP-122,288. However, a single report by Hegedus and co-workers[5] in which they were able to differentiate between an aryl iodide over an aryl bromide in an intermolecular Heck coupling provided the incentive to proceed. Following the path of the previous synthesis, the dibromoaniline (**3b**, X=Br) was reacted with trifluoroacetic anhydride to form the trifluoroacetanilide (**4b**, X=Br, 84%, Scheme 1). This step both protected the aromatic amine and activated it for the subsequent Mitsunobu reaction with the 3-(pyrrolidin-2-yl)prop-2-enol (**5**).[3] This Mitsunobu coupling formed the key intermediate (**6b**, X=Br, 92%) for the Heck reaction. It should be noted that the presence of the second bromine atom on the benzene ring had no deleterious effect on the efficiency of these transformations when compared to the original synthesis.[3]

The intramolecular reaction of **6b** (X=Br) employed relatively standard Heck reaction conditions (i.e., 10 mol% palladium acetate, excess triethylamine in DMF/DME with heating at 80 °C until reaction was complete as determined by TLC, usually 1h). The cyclization of **6b** (X=Br) proceeded in essentially equivalent yield [76% of **1b** (X=Br)] when compared with the reaction of the monobromo analog [**6a** (X=H)] in the original synthesis [81% of **1a** (X=H)]. However, the reaction of the dibromo species (**6b**, X=Br) seemed to produce a darker crude reaction mixture. Purification of the 7-bromoindole derivative (**1b**, X=Br) was aided by the increased crystallinity of the compound, presumably resulting from the heavy atom found in the product (**1b**, X=Br). Accordingly, silica gel filtration (4% acetone in chloroform) followed by crystallization in CH_2Cl_2/ether (1:5) afforded crystalline product (**1b**, Scheme 1). Clearly, the presence of the second bromine (the bromine "passenger") was not significantly deleterious to the Heck reaction, and we believe that a small amount of the 7-bromoindole (**1b**, X=Br) was sacrificed at the end of the reaction to consume the active palladium catalyst. The ability to perform this type of intramolecular Heck reaction in the presence of a "passenger" bromine atom could find additional use in

the synthesis of other 7-substituted indole derivatives. Accordingly, our approach to **1b** (X=Br) could provide a general method of accessing 7-bromoindoles (a rare class of indole derivatives), which then could be further manipulated for the synthesis of more complex 7-substituted indoles.



Scheme 1

	X
a	H
b	Br

a) Br_2, $NaHCO_3$, MeOH, rt (96%)
b) trifluoroacetic anhydride, pyridine, CH_2Cl_2 (84%)
c) **5** (from reference 3), Ph_3P, DEAD, THF (92%)
d) $Pd(OAc)_2$, NBu_4Cl, TEA, DMF/DME, Δ (76%)
e) lithium aluminum hydride, THF, rt (56%)
f) palladium hydroxide (20% on carbon), H_2, EtOH (68%)
g) Pd (10%) on carbon, H_2, EtOH (80%)

Direct catalytic reduction of **1b** (X=Br) afforded the secondary pyrroldine, CP-122,638 (68%, Scheme 1), which itself is 70,000-fold more potent than sumatriptan in its ability to inhibit neurogenic inflammation.[4] This approach to CP-122,638 required no more steps than the original synthesis,[3] since both the CBZ group and bromine were removed concomitantly. Furthermore, in the present synthesis, the

overall yield from the aniline (**2**) to CP-122,638 was 38% compared to 11% in the original synthesis using the monobromoaniline (**3a**, X=H).[3]

In the same vein, reduction of the CBZ group in **1b** (X=Br) to the N-methyl group in **7b** (X=Br) using lithium aluminum hydride at room temperature afforded the 7-bromo analog of CP-122,288 (**7b**, X=Br, 56%).[6,7] Heating this reaction led to some reduction of the bromine, forming CP-122,288 directly, but this was not an efficient transformation. Rather, catalytic hydrogenation smoothly removed the bromine atom forming CP-122,288 in high yield (80%, Scheme 1). While the present synthesis added an additional step to the original scheme, the use of the dibromoaniline (**3b**, X=H) gave an overall yield of CP-122,288 from **2** of 25% compared to an overall yield of 11% in the original synthesis using the monobromoaniline (**3a**, X=H).

In conclusion, we have found that the original synthesis of the novel anti-migraine agent CP-122,288 can be improved via the use of a dibromoaniline derivative (**1b**, X=Br) in the intramolecular, indole-forming Heck reaction. The greater than two-fold improvement in overall yield results primarily from a corresponding three-fold improvement in the efficiency of forming the requisite dibromoaniline precursor (**3b**, X=Br) versus the monobromoaniline precursor (**3a**, X=H) used in the original synthesis. The ability to carry a second bromine atom unscathed through the Heck reaction represents a unique approach to 7-bromoindoles, and specifically to a unique precursor of CP-122,288. We are presently exploring the scope of the methodology for its application to a novel, general approach to 7-bromoindoles.

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6) The spectral and physical properties of **7b** were as follows: white solid, mp 58 °C; ^{1}H NMR (CD_3OD) δ 7.59 (d, J=1.3 Hz, 1H), 7.36 (d, J=1.3 Hz, 1H), 7.18 (s, 1H), 4.88 (s, 2 exchangeable H), 4.39 (s, 2H), 3.21-3.06 (m, 2H), 2.65-2.52 (m, 2H), 2.61 (s, 3H), 2.45 (s, 3H), 2.28 (dd, J=9.3 and 18.5 Hz, 1H), 1.86-1.50 (m, 4H); ^{13}C NMR (DMSO-d_6) δ 134.0, 129.1, 125.8, 124.9, 121.9, 120.6, 113.8, 103.7, 66.0, 56.9, 55.6, 40.5, 30.8, 29.3, 28.9, 21.6; LRMS (m/z, relative intensity) 401 ([M^+ with ^{81}Br], 1), 399 ([M^+ with ^{79}Br], 1), 223 (4), 221 (4), 84 (100); HRMS calculated for $C_{16}H_{22}BrN_3O_2S$ 399.0618, found 399.0585 [-1.5 σ deviation); $[\alpha]^{25}$ = +43° (MeOH, c=1). Anal. calc for $C_{16}H_{22}BrN_3O_2S \cdot 0.25$ ethyl acetate: C, 48.34; H, 5.73; N, 9.95. Found: C, 48.20; H, 5.70; N, 9.85.
7) It should be noted by the reader that **7a** (X=H) is, in fact, CP-122,288.

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