Tetrahedron Letters, Vol. 33, No. 52, pp. 8011-8014, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

THE SYNTHESIS OF A CONFORMATIONALLY RESTRICTED ANALOG OF THE ANTI-MIGRAINE DRUG SUMATRIPTAN

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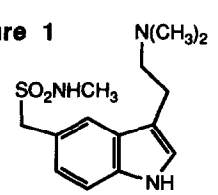
Abstract: The synthesis of 5-N-Methylaminosulfonylmethyl-3-(N-methylpyrrolidin-2-ylmethyl)indole (1), a conformationally restricted analog of the anti-migraine drug, sumatriptan, is described. To incorporate our novel stereogenic replacement for the aminoethyl sidechain in sumatriptan, a convergent synthesis of the 3,5-disubstituted indole (1) was employed which utilized an intramolecular Heck reaction as the cornerstone reaction.

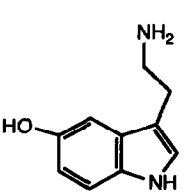
Through an ever increasing understanding of the pharmacology of the neurotransmitter serotonin (5-hydroxytryptamine, 5-HT, Figure 1),[1] novel therapies for the treatment of neuronal dysfunction within this receptor family have been found. For example, using pharmacological insights about the 5-HT_{1A} receptor, Buspar® was developed for the treatment of generalized anxiety disorders.[2] Recently, workers at Glaxo developed a novel approach for the treatment of migraine via agonism of a new 5-HT"$_{1\text{-like}}$" receptor. This work led to the identification of the tryptamine, sumatriptan (Figure 1), as a novel anti-migraine drug.[3]

Our studies in the area of serotonin neurochemistry have focused on the synthesis of conformationally and rotationally restricted analogs of the natural substrate to be used as probes within the individual serotonin receptor subtypes.[4] Via this synthesis of "unnatural products," we hoped to define molecular recognition elements specific for individual serotonin receptors, and then use this information to develop novel therapies for serotonin receptor dysfunction. Recently in Groton, we discovered that the aminoethyl sidechain of serotonin and other tryptamines could be successfully replaced by the (R)-(pyrrolidin-2-ylmethyl) group without loss of affinity for serotonin receptors (Figure 1).[5] The resulting conformationally restricted analog of serotonin (CP-108,509, Figure 1) has led us to a better understanding of the recognition phenomena of serotonin in 5-HT receptors. Additionally, since tryptamines are very susceptible to metabolism by monoamine oxidase (MAO), and since α-methylphenethylamines are not substrates for MAO,[6] the (R)-(pyrrolidin-2-ylmethyl) replacement should afford a more metabolically-stable molecule, which should allow for a better understanding of the *in vivo* effects of tryptamines in living systems.

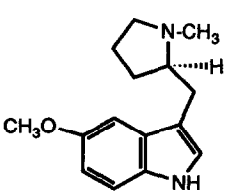
Figure 1



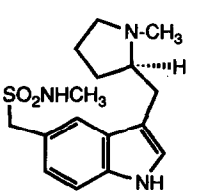
Sumatriptan



Serotonin



CP-108,509

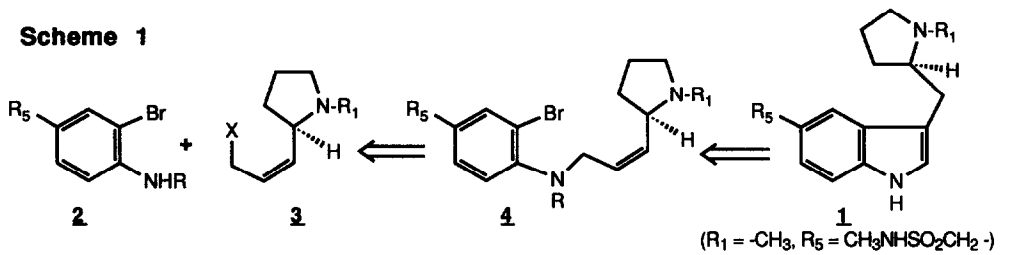


1

Because of the novel pharmacology of sumatriptan, the conformationally restricted analog (**1**) of this drug was seen as a highly desirable target. However, there are few generalized approaches in the literature for the synthesis of complex 3,5-disubstituted indoles. Attempted Fischer Indolization routes to **1** were entirely unsuccessful. Equally disappointing were efforts to functionalize C3 of 5-(N-methylaminosulfonylmethyl)-indole using either acylation or alkylation chemistry common to indoles. Therefore, we embarked on a general approach to 3,5-disubstituted indole derivatives, and this communication outlines the application of that approach to a conformationally restricted analog of the anti-migraine drug, sumatriptan.

The cornerstone of our methodology utilized the palladium catalyzed cyclization (Heck Reaction) of 2-bromo-N-(2-propenyl)anilines which has been demonstrated by Hegedus and others[7] on simple indole systems. In convergent fashion, we sought to couple an appropriately substituted aniline (**2**) with a properly substituted 2-propenyl alcohol or halide (**3**, Scheme 1), followed by the key cyclization step of the resulting olefin (**4**). Scheme 2 shows the successful application of this strategy in the synthesis of **1**.[8]

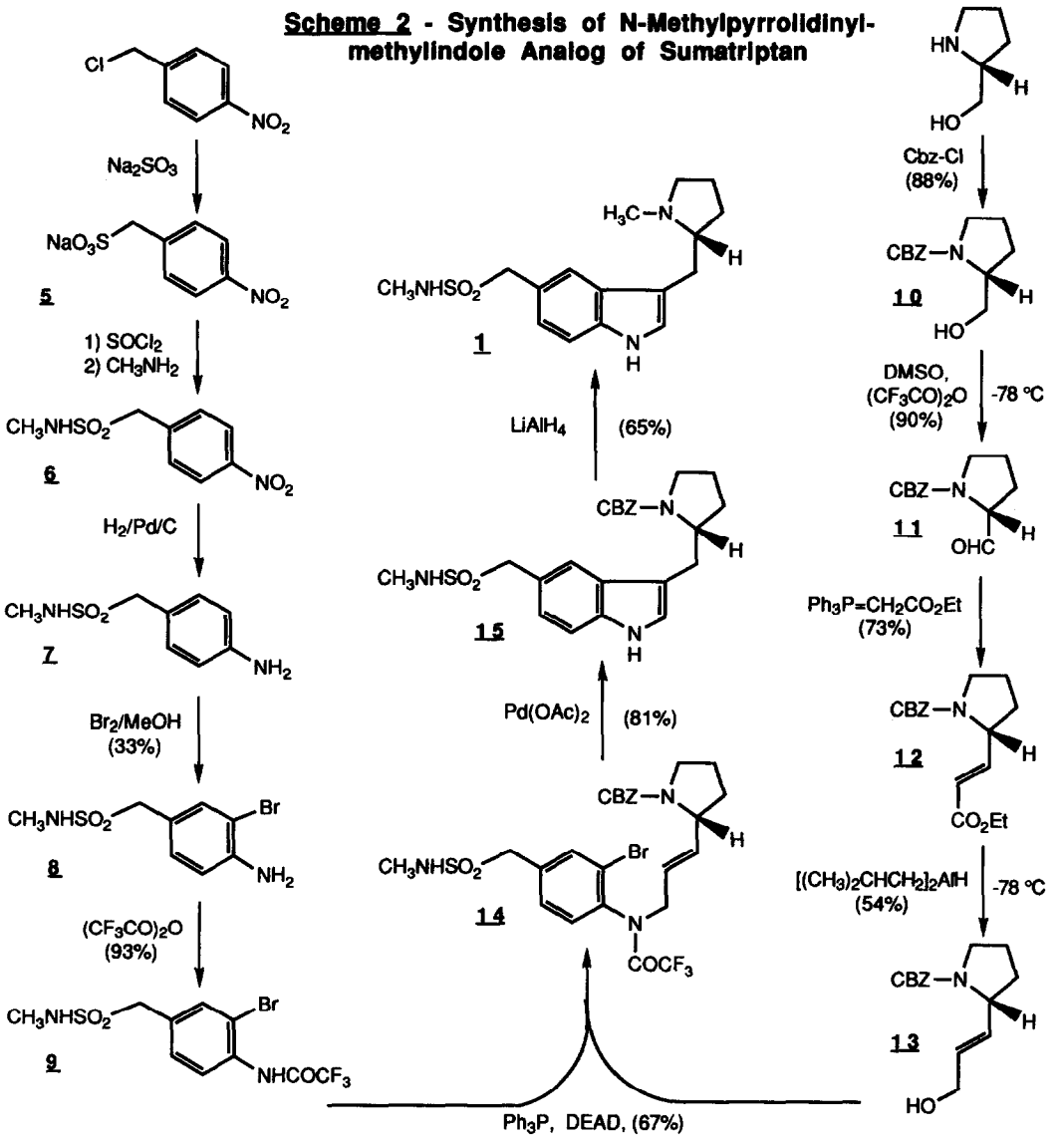
Scheme 1



Starting with the aniline derivative (**7**) available in three steps from *p*-nitrobenzyl chloride,[9] incorporation of the necessary aryl bromide *ortho* to the amine was accomplished with the simple conditions of bromine in methanol (Scheme 2). The yield of this reaction (33%) reflected the fact that significant amounts of the dibromo derivative were also obtained. Protection and activation of the resulting aniline derivative (**8**) resulted from the high yielding formation of the trifluoroacetamide derivative (**9**, 93%). It should be noted at this point in the synthesis that we have recently reversed these last two steps, i.e. bromination of a trifluoroacetamide, in other similar total syntheses and have greatly improved the yield for the bromination (always greater than 60%). While not yet attempted in this total synthesis, this modification represents an important area for possible optimization of this synthesis. While there are few (if any) reports of the use of an aryl trifluoroacetamide as the acid component in a Mitsunobu coupling reaction, we felt that the amide in **9** would be a suitable candidate for such a coupling reaction.

The propenyl alcohol component in our convergent synthesis required the incorporation of the stereogenic pyrrolidine ring. Therefore, protection of the amine in commercially available (R)-2-hydroxymethyl-pyrrolidine was easily accomplished via reaction with benzyl chloroformate in the presence of triethylamine to afford **10** (88%, Scheme 2). The choice of nitrogen protecting group was arbitrary, and the use of a BOC or other carbamate protecting group should not have any deleterious effects on this reaction sequence. Standard Swern oxidation of the pyrrolidinemethanol (**10**) afforded the stereogenic aldehyde (**11**) in excellent yield (90%). Reaction of **11** with (carbethoxymethylene)triphenylphosphorane in a typical Wittig reaction led to the *trans* olefin (**12**, 73%). Finally, the α,β-unsaturated ester in **12** was smoothly and selectively reduced to the allyl alcohol derivative (**13**, 54%) with diisobutylaluminum hydride (DIBAH) at -78 ° C.

Scheme 2 - Synthesis of N-Methylpyrrolidinyl-methylindole Analog of Sumatriptan



Mitsunobu coupling of the trifluoroacetamide (**9**) with the 3-hydroxypropene (**13**) using triphenylphosphine and diethylazodicarboxylate (DEAD) afforded our key intermediate (**14**, 67%) in good yield. Key to the efficiency of this reaction was the order of addition of the reactants. Our best results were achieved when the alcohol (**13**) was added last to a solution of the preformed Ph_3P/DEAD complex and the acidic component (**9**). When the DEAD was added last to a solution of Ph_3P/**9**/**13**, full consumption of the starting materials (**9** and **13**) was not achieved, and significantly lower yields of the product (**14**) were obtained. These results are entirely consistent with recent observations we have made concerning the

mechanism of the Mitsunobu reaction.[10] Treatment of **14** with $Pd(OAc)_2$ in Heck reaction fashion (Et_3N, DMF, Δ) afforded an excellent yield of our desired N-protected analog of sumatriptan (**15**, 81%). This cyclization reaction was straightforward, and convergently incorporated multifunctional pieces into a complex 3,5-disubstituted indole heterocycle. A bonus of this reaction was the concomitant loss of our trifluoroacetyl group. This strategy confirms the utility of this intramolecular (Heck reaction) approach to complex, multifunctional indoles derivatives.

Reduction of the N-benzyl carbamate directly to our desired tertiary amine (**1**, 65%)[11] was simply and smoothly effected using lithium aluminum hydride in refluxing tetrahydrofuran. Alternately, removal of the Cbz-protecting group to afford the secondary amine could be accomplished using standard hydrogenation conditions (i.e. H_2, Pd on C, ethanol). The *in vitro* and *in vivo* characteristics of **1** are presently under study, but initial results suggest that **1** is analogous to sumatriptan in its *in vitro* characteristics. More details on the pharmacology of **1**, a conformationally restricted analog of the anti-migraine drug sumatriptan, will be reported in due course in an appropriate forum.

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3) Hopkins, S.J. Drugs of Today, **1992**, 28, 155, and references cited within.

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6) Biel, J.H.; Bopp, B.; Mitchell, B.D. Chemistry and Structure Activity Relationships of Psychotropic Drugs in *Principles of Psychopharmacology*, 2nd ed. (Clark, W.G. and del Guidice, J. eds.), Academic Press, **1978**, pp.140-168.

7) Hegedus, L.S. Angewandte Chemie (Int. Ed.), **1988**, 27, 1113, and references cited within.

8) All new compounds disclosed in this communication have been thoroughly characterized including ^1H NMR, ^{13}C NMR, IR, LRMS, HRMS and/or elemental analysis.

9) As per UK patent Application No. 2124210 A (**1983**), p-nitrobenzyl chloride was reacted with sodium sulfite to form (**5**, 86%, Scheme 2). The sulfonyl chloride was then formed using thionyl chloride (79%), which was reacted with methylamine. The resulting 4-(N-methylaminosulfonylmethyl)-nitrobenzene (**6**, 82%) was reduced using catalytic hydrogenation (Pd/C) to afford the aniline (**7**, 87%, 48% overall from p-nitrobenzyl chloride).

10) Addition of the alcohol component last in a Mitsunobu reaction avoids unwanted interactions of the alcohol and triphenylphosphine, leading to a more direct course of reaction. For a preliminary report of this study, see: Macor, J.E.; Wehner, J.M. Tetrahedron Letters, **1991**, 32, 7195.

11) The physical and spectral characteristics of **1** are: mp, 213.0-214.0 °C; ^1H NMR (DMSO-d_6) δ 10.85 (br s, indole NH), 7.50 (s, 1H), 7.31 (d, J=8.3 Hz, 1H), 7.15 (d, J=1.9 Hz, 1H), 7.07 (dd, J=2.5 and 8.3 Hz, 1H),6.8 (br q, J=4.9 Hz, sulfonamide NH), 4.34 (s, 2H), 3.04 (dd, J=3.0 and 13.8 Hz, 1H), 3.00-2.95 (m, 1H), 2.54 (d, J=4.7 Hz, 2H), 2.51-2.43 (m, 1H), 2.43-2.34 (m, 1H), 2.35 (s, 3H), 2.10 (dd, J= 8.8 and 17.0 Hz, 1H), 1.72-1.44 (m, 4H); ^{13}C NMR (DMSO-d_6) δ 135.8, 127.5, 123.7, 123.5, 120.8, 119.7, 112.1, 111.1, 66.3, 56.9, 56.6, 40.4, 30.9, 29.2, 28.9, 21.6; LRMS (m/z, relative intensity, EI [70 eV]) 321 (M^+, 1), 227 (3), 143 (37), 142 (17), 85 (45), 84 (100); $[\alpha]^{25}$ = +89° [DMSO-d_6, c=1]; $[\alpha]^{25}$ = +70° [MeOH, c=1]; Anal. calcd for $C_{16}H_{23}N_3O_2S$: C, 59.79; H, 7.21; N, 13.07. Found: C, 59.66; H, 7.29; N, 12.81.

(Received in USA 28 July 1992; accepted 30 September 1992)