ORGANIC LETTERS

2005
Vol. 7, No. 16
3437−3440

Enantioselective Synthesis of a Highly Potent Selective Serotonin Reuptake Inhibitor. An Application of Imidazolidinone Catalysis to the Alkylation of Indoles with an α,β-Disubstituted α,β-Unsaturated Aldehyde

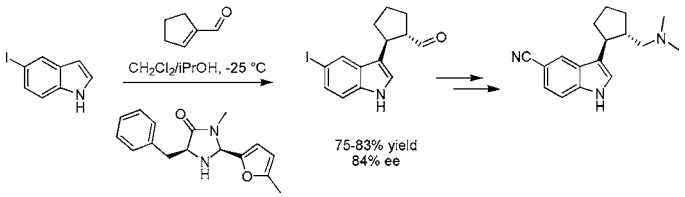
H. Dalton King,* Zhaoxing Meng,* Derek Denhart, Ronald Mattson, Roy Kimura, Dedong Wu, Qi Gao, and John E. Macor

Bristol Myers Squibb, 5 Research Parkway, Wallingford Connecticut 06492

dalton.king@bms.com

Received May 2, 2005

ABSTRACT



The synthesis of the highly potent and selective serotonin reuptake inhibitor 1 (BMS-594726) is described. In the key construction step, an enantioselective alkylation of the indole nucleus with an α-branched α,β-unsaturated aldehyde 7 was accomplished utilizing MacMillan's imidazolidinone catalyst 3b. A rationale is presented for the unexpected stereochemical result, as well as the novel reactivity of the α-branched substrate.

Selective serotonin reuptake inhibitors (SSRIs) have widespread utility in the treatment of depression and other mental illnesses, even though current therapies suffer from several pharmacological disadvantages such as delayed onset of antidepressant action and sexual dysfunction.[1] An alternate therapeutic application for SSRIs that has been proposed is the treatment of premature ejaculation in men.[2] Such a drug should have high potency, a rapid onset of action, and a short pharmacological half-life ($t_{1/2}$). Our research efforts in this area have focused on conformationally restrained analogues of 5-hydroxytryptamine (5-HT, serotonin), especially homotryptamines such as **1** (BMS-505130).[3] Conformational restriction of the side chain has been shown to be an effective tool to optimize potency and selectivity in a number of SSRI scaffolds.[3−6] As an extension of this approach we investigated

(1) (a) Baldwin, D. S. *Hum. Psychopharmacol.* **2001**, *16*, S93−S99. (b) Spinks, D.; Spinks, G. *Curr. Med. Chem.* **2002**, *9*, 799−810.

(2) (a) Rosen, R. C.; Lane, R. M.; Menza, M. *J. Clin. Psychopharmacol.* **1999**, *19*, 67−85. (b) Waldingeri, M. D.; Berendsen, H. H. G.; Blok, B. F. M.; Olivier, B.; Holstege, G. *Behav. Brain Res.* **1998**, *92*, 111−118.

(3) Taber, M. T.; Wright, R. N.; Molski, T. F.; Clarke, W. J.; Brassil, P. J.; Denhart, D. J.; Mattson, R. J.; Lodge, N. J. *Pharmacol. Biochem. Behav.* **2005**, *80*, 521−528.

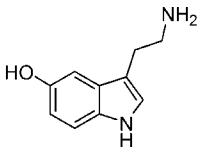
(4) Schmitz, W. D.; Denhart, D. J.; Brenner, A. B.; Ditta, J. L.; Mattson, R. J.; Mattson, G. K.; Molski, T. F.; Macor, J. E. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1619−1621.

(5) Boy, K. M.; Dee, M.; Yevich, J.; Torrente, J.; Gao, Q.; Iben, L.; Stark, A.; Mattson, R. J. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4467−4470.

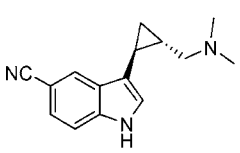
(6) Toda, N.; Tago, K.; Marumoto, S.; Takami, K.; Ori, M.; Yamada, N.; Koyama, K.; Naruto, S.; Abe, K.; Yamazaki, R.; Hara, T.; Aoyagi, A.; Abe, Y.; Kaneko, T.; Kogen, H. *Bioorg. Med. Chem.* **2003**, *11*, 4389−4415.

10.1021/ol051000c CCC: $30.25
Published on Web 07/08/2005

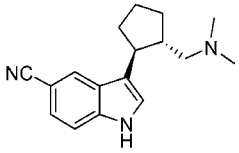
the construction of other cyclic side chain analogues related to **1**. This effort resulted in the discovery of the highly potent 1,2-disubstituted cyclopentane **2** (BMS-594726).[7]



5-hydroxytryptamine



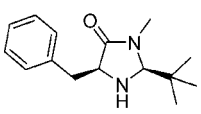
1



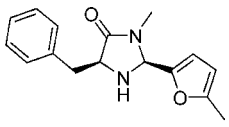
2

As **2** was advanced into later stage toxicological studies, we were required to synthesize large quantities of this compound. The original synthesis,[7] with an overall yield of only 3%, was not capable of producing the large quantities of **2** needed. Thus, it was necessary to develop an alternate synthetic procedure.

MacMillan and Austin have recently published a new method to generate a variety of chiral 3-(indol-3-yl)-propionaldehydes from β-substituted α,β-unsaturated aldehydes.[8] Using the imidazolidinone catalyst **3a**, they achieved high product yields with ee's >90%. This methodology was limited to the use of indoles without strong electron-withdrawing groups, as well as α,β-unsaturated aldehydes that had no α-substituents. A related imidazolidinone catalyst **3b**, originally developed for enantioselective Diels−Alder reactions,[9] was recently used for our synthesis of simple homotryptamine SSRIs from indoles and acrolein.[10] In this example, electron-deficient indoles were successfully alkylated albeit in low yield. We postulated that an analogous approach might be applied to the synthesis of **2**. Since **2** carries both an electron-withdrawing cyano group on the indole nucleus and an alkyl substituent α to the amino group, we studied a series of model reactions with both catalysts in the absence of these factors before proceeding.



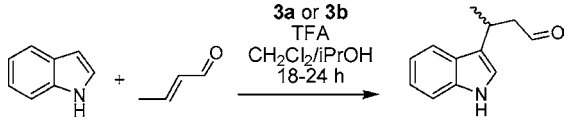
3a



3b

We initially screened the reaction of indole **4** with (*E*)-crotonaldehyde **5** using both **3a** and **3b** as catalysts (Scheme 1). We corroborated the previously reported results[8] with **3a**

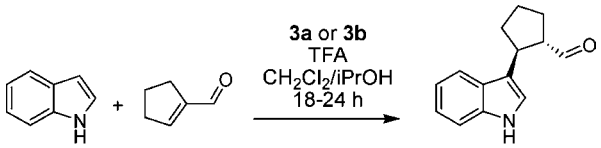
Scheme 1. Screening Reactions Using Catalysts **3a** and **3b**



4 **5** **6**

at −80 °C to give (*R*)-**6** in 93% ee. Though **3b** provided good yields of alkylated indole product (85−87%), it was a far less enantioselective catalyst than **3a**, yielding only 23−32% ee. More importantly though, the favored enantiomer obtained with **3b** was the unexpected (*S*)-**6**. Extending to the α-branched substrate **7** (Table 1), **3a** was completely

Table 1. Reaction of **4** and α,β-Unsaturated Aldehyde **7** at Various Conditions with Catalysts **3a** or **3b**



4 **7** **8**

catalyst	temp (°C)	yield (%)	ee (%)
3a	−80	NR[a]	
3a	−25	NR	
3b	−25	39[b]	85[c]

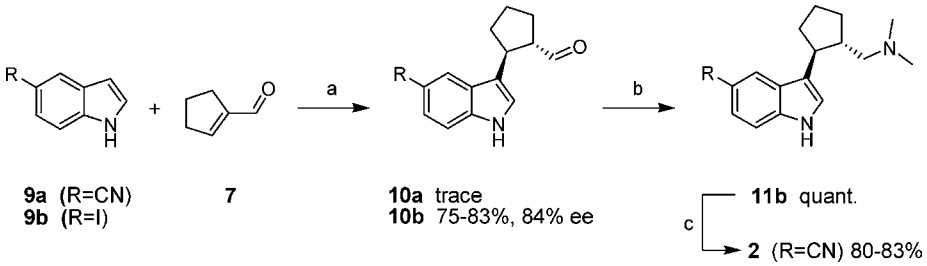
[a] No reaction noted. [b] Unoptimized. [c] *trans*-**8**. Absolute configuration not determined.

ineffective as a catalyst at either −80 or −25 °C over 24 h. By contrast, catalyst **3b** gave **8** in 39% yield, 85% ee after 18 h at −25 °C. Though yield and ee of this cyclic product were relatively modest, we were encouraged that **3b** might provide the desired *S* stereocenter in the synthesis of **2**.

Reaction of 5-cyanoindole **9a** with **7** at −25 °C in the presence of **3b** gave only trace amounts of **10a**, even after 3−4 days (Scheme 2).[11] Increasing the reaction temperature to 0 °C resulted in decomposition of the reaction mixture. We then tried a more reactive halogen-substituted indole, since those derivatives may be later cyanated by numerous methods.[12,13] Using 5-iodoindole **9b**, this approach proved successful: **10b** was obtained in good yield (75−83%) with 84% ee.[14] The absolute configuration of **10b** was determined to be 1*S*,2*S* by X-ray crystallography.

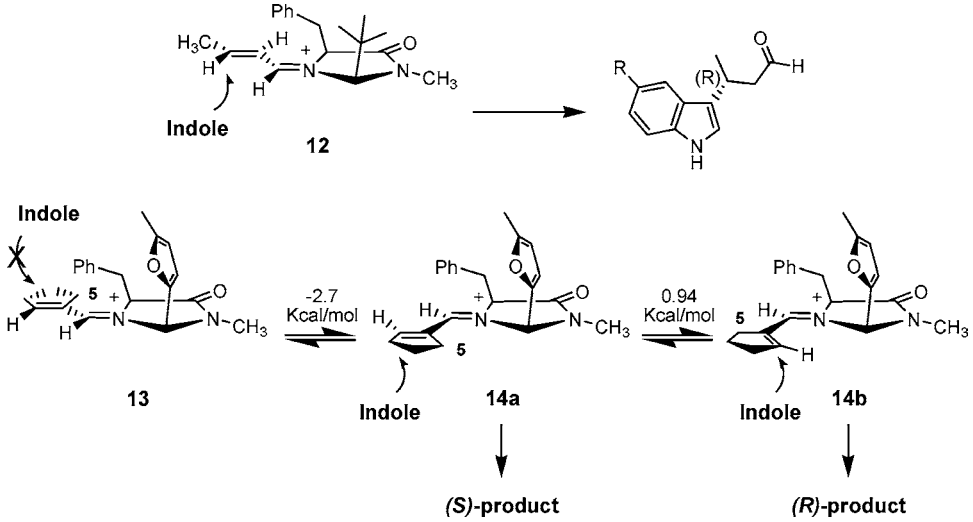
(7) Denhart, D.; Ditta, J.; King, D.; Macor, J.; Marcin, L.; Mattson, R.; Meng, Z. WO 026237, 2004; *Chem. Abstr.* **2004**, *140*, 303528.
(8) Austin, J. F.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 1172−1173.
(9) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 2458−2460.
(10) Denhart, D. J.; Mattson, R. J.; Ditta, J. L.; Macor, J. E. *Tetrahedron Lett.* **2004**, *45*, 3803−3805.
(11) Catalyst **3a** gives no detectable **10a** in the analogous reaction. However, it is reported in ref 10 that 5-cyanoindole reacts with acrolein at −25 °C in the presence of **3a** to give the corresponding 3-substituted propionaldehyde product in modest yield.
(12) Ellis, G. P.; Romney-Alexander, T. M. *Chem. Rev.* **1987**, *87*, 779−794.
(13) Zanon, J.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 2890−2891.
(14) The *cis* isomer of **10b** was detected in the crude product by ^{1}H NMR (*trans*/*cis* ratio 24:1). After $NaBH_4$ reduction, the *cis* alcohol was isolated and characterized. Details are supplied in Supporting Information.

Scheme 2. Synthesis of **2** Using Catalyst **3b**[a]



[a] Reaction conditions: (a) 10−20 mol % **3b**, 10−20 mol % TFA, −25 °C, 24 h; (b) Me_2NH, $NaBH(OAc)_3$, MeOH, rt; (c) NaCN, 10% CuI, $MeNHCH_2CH_2NHMe$, toluene, 100 °C, 18 h.

Scheme 3. Proposed Mechanisms Leading to Enantiospecific Indole Alkylation Products



Reductive amination of the aldehyde **10b** afforded **11b** in quantitative yield. Using cyanation methodology recently developed by Buchwald,[13] **11b** was converted to **2** in 80−83% yield. Stereochemical integrity was maintained throughout these two steps. Recrystallization of the final product as a HCl salt brought the ee of **2** to 100%. Confirmation of the absolute configuration of **2** as 1*S*,2*S* was accomplished by X-ray crystallography of the HCl salt. This synthesis has been scaled to produce over 20 g of **2** without reductions in either overall yield or enantiomeric purity.

In the earlier work MacMillan and Austin proposed that catalyst **3a** forms an iminium intermediate **12**, in which the olefin orients itself as the *E*-isomer in order to avoid nonbonding interactions with the *tert*-butyl group (Scheme 3). *si*-Face approach by the indole to this intermediate is effectively blocked by the benzyl group. Predominant *re*-face addition in this case leads to products with *R* configuration and the high levels of enantioselectivity.[8] In contrast, we observe *S* stereochemistry at the analogous reaction center in the synthetic intermediate **10b**. Thus, the indole must attack the opposite face of the cyclopentene as in either *E*-iminium **13** or *trans*-*Z*-iminium **14a** (Scheme 3). In **13**, the required face (*si*) is sterically blocked by the benzyl group. Our results are best explained by **14a**, in which the required *re*-face attack is unimpeded. Our molecular modeling studies confirm this argument: **14a** represents a global minimum and is conformationally preferred by 2.7 kcal/mol over *E*-iminium **13**.[15]

We postulate that **14a** is formed preferentially because (i) significant steric interactions between the cyclopentene C-5 methylene group and the imidazolidinone benzyl group of **13** are avoided, and (ii) the 5-methylfuryl group of catalyst **3b** presents a minimal steric obstacle to the cyclopentene group as in **14a**. An alternate conformation, *cis*-*Z* isomer **14b**, is found to be 0.94 kcal/mol higher in energy than the global minimum. This conformation would present the opposite face of the cyclopentene to the attacking indole and thus may contribute to the lower ee values observed with **3b**. In a recent report, Taggi et al.[16] used a similar molecular mechanics approach to predict stereochemical induction in

(15) Conformational searches were performed with MacroModel (Schrodinger Inc.) MCMM (Monte Carlo Multiple Minima method), and the MM3 force-field using Generalized Born treatment of $CHCl_3$ solvent.

(16) Taggi, A. E.; Hafez, A. M.; Dudding, T.; Lectka, T. *Tetrahedron* **2002**, *58*, 8351−8356.

a model system involving the cycloaddition reaction of an imino ester and zwitterionic intermediates derived from ketenes and chiral nucleophilic catalysts. The calculated energy differences for the global minima of their intermediates correlated well with enantioselectivity observed in the experimental systems. For example, calculated ΔE values of 1.40−2.64 kcal/mol corresponded to 73−99% ee. Assuming that the transition state energies for the addition of indole to the intermediates are equal in our system, the calculated 0.94 kcal/mol energy preference for **14a**, though relatively small, is consistent with the observed 84% ee of the *S* product isomer.

In conclusion, we have developed a very efficient synthesis of **2** and demonstrated its utility by performing the reaction on a 20 g scale. These results represent the first example of enantioselective alkylation of indoles with an α-branched α,*β*-unsaturated aldehyde utilizing imidazolidinone catalysis. We have also demonstrated that asymmetric induction in this system yielded the unexpected opposite stereocenter in our indole alkylation product. Further studies are in progress to probe the generalities of these initial observations in other α-branched α,*β*-unsaturated aldehydes.[17]

Acknowledgment. The authors thank Professor D. W. C. MacMillan and Joel F. Austin for their helpful discussions and the initial suggestion to attempt the alkylation reaction with **3b**.

Supporting Information Available: Experimental procedures and spectral data are for all compounds, as well as X-ray crystallographic structures for **10b** and **2** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

OL051000C

(17) Preliminary experiments with other simple α-branched enals show that this reaction is very sensitive to steric effects. In the reaction of an acyclic substrate, *trans*-2-methyl-2-butenal, and indole under identical conditions with catalyst **3b**, product 3-(3-indoyl)-2-methylbutanal was obtained in only 33% yield, 10−19% ee after 4 days. In this case we reason that there is a greater degree of rotational freedom in the iminium intermediate leading to a lack of facial discrimination in the attack of indole. Expanding the cyclic enal system to 1-cyclohexene-1-carboxaldehyde, reaction with indole under identical conditions requires 7 days to obtain only a 13% yield of *trans*-2-(3-indoyl)-cyclohexanecarboxaldehyde. Enantioselectivity, though, was equivalent to that of **8** (80% ee), indicating similar facial discrimination. The combination of variable stereoselectivity and low reactivity in these model systems suggests that the general utility of catalysis with **3b** in other branched systems may be limited.