Tetrahedron Letters, Vol.31, No.52, pp 7583-7586, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

PREPARATION OF 1-BENZOYL-4-(AMINO)-1,2,2a,3,4,5-HEXAHYDROBENZ[*CD*]INDOLES FROM L-TRYPTOPHAN

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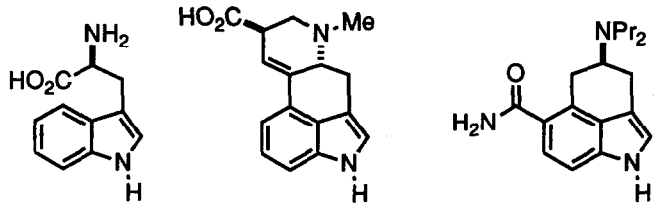
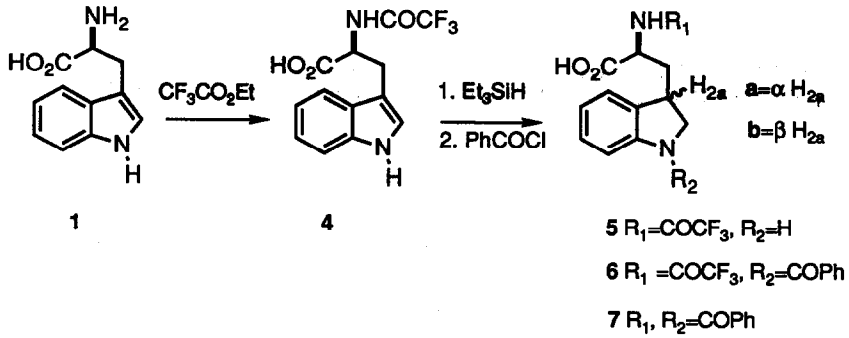
*Summary: Acid **6a**, derived from L-tryptophan, has been shown to be a useful precursor to partial ergot structures such as **3**. Optically pure amine **(+)-13**, a key intermediate in the synthesis of **3**, was prepared in 45% overall yield from **6a** via a four step sequence employing an intramolecular Friedel-Crafts cyclization and a C-5 deoxygenation procedure.*

Naturally occurring amino acids are attractive starting materials for the synthesis of optically active molecules. Readily available L-tryptophan (**1**) has been successfully converted to lysergic acid (**2**) by Rebek and coworkers.[1a] Based on this precedent and the fact that L-tryptophan contains an appropriately positioned stereocenter (with the desired absolute configuration[2]) needed for the $5HT_{1a}$ agonist **3**,[3] we found it to be an appealing potential precursor to **3**. This paper describes the formal total synthesis of **3** from L-tryptophan.



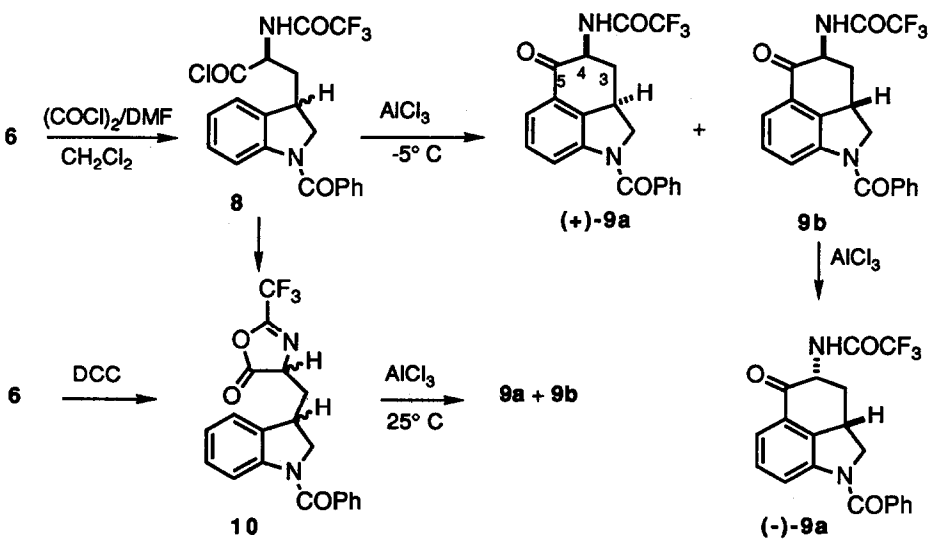
1 **2** **3**

The key bond-forming reaction was envisioned to be an intramolecular Friedel-Crafts cyclization.[1,4,5] This strategy required reduction of the indole double bond (to avoid cyclization onto the 2-position) and protection of both nitrogen atoms, preferably with groups that could be differentially removed later in the synthesis. The preferred cyclization precursor was found to be 1-benzoyl-4-trifluoroacetamido indoline **6**, prepared by trifluoroacetylation of L-tryptophan,[6] followed by indole reduction,[7] and benzoylation of N-1. Compound **6** was isolated in 67% yield from **4** as a 45:55 mixture of epimers at C-2a (HPLC assay). Crystallization of **6** from $CHCl_3$ gave a 21% yield of the minor epimer with greater than 99% diastereomeric purity.[8] Based on conversion of this compound to the dibenzoyl derivative **7a** prepared by Rebek,[1a] it was assigned the α H_{2a} configuration (**6a**).



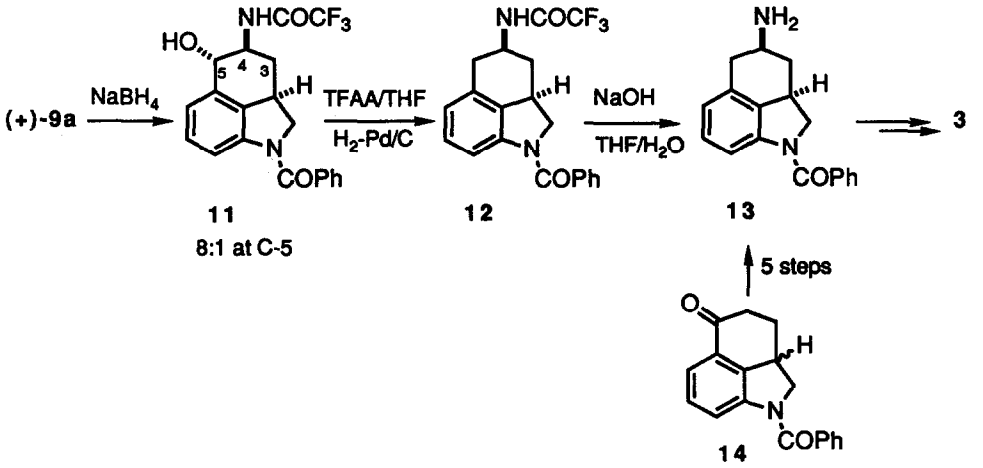
The Friedel-Crafts cyclizations of **6** and **6a** proved quite sensitive to reaction conditions. Optimal conditions were: Formation of acid chloride **8** ($(COCl)_2$/DMF/CH_2Cl_2) at -5° C, followed by the addition of four equivalents of $AlCl_3$. Diastereomeric ketones **9a** and **9b** as well as azlactone **10** were formed in 2-4 hours. Warming the reaction mixture to 25° C converted **10** to **9a** and **9b** after 24 hours. Azlactone **10** was isolated from reaction mixtures as a 50:50 mixture of diastereomers (HPLC assay), and its structure confirmed by elemental analysis and the characteristic IR band at 1809 cm^{-1}. This material was indentical to the product obtained when **6** (or **6a**) was treated with dicyclohexylcarbodiimide (DCC). Cyclization of isolated **10** with $AlCl_3$ was much slower than the cyclization of acid chloride **8**; only 50% of **10** was converted to **9a** and **9b** after 24 hours at 25° C. The formation of **10** from acid chloride **8** could be limited to less than 10% by carefully maintaining the cyclization reaction temprature at -10° C.

SCHEME.



Critical to the success of this approach was the preservation of configuration at C-4 during the cyclization reaction. It had been hoped that the mixture of acid **6** diastereomers could be used since the C-2a stereocenter would eventually be destroyed. Cyclization of the diastereomer mixture **6** at -5° C afforded a 45:55 ratio of **(+)-9a** and **9b** (HPLC assay) after one hour, indicating no epimerization had occurred. However, during the course of the reaction (24 hours), the ratio of **9a:9b** increased to 75:25. This change in diastereomer ratio is believed to be due to epimerization of **9b** to (-)-**9a**, the enantiomer of **(+)-9a** (see Scheme). Support for this rests on the large decrease in optical activity of **9a** prepared from **6** compared to **9a** prepared from **6a** (specific rotations of +30° and +180° in $CHCl_3$, respectively). It was found that any mixture of **9a** and **9b** could be converted to a 98:2 equilibrium mixture of **9a:9b** by extended treatment with $AlCl_3$ in CH_2Cl_2. Epimerization of **9b** to **(-)-9a** was quite rapid (2 hours, 25° C) in the presence of triethylamine. Clearly, in order to maintain the desired configuration at C-4 during the cyclization reaction, a single diastereomer of **6** was required.[9] Using the optimal cyclization reaction conditions described above, acid **6a** was converted to a 98:2 mixture of **(+)-9a:9b**. Recrystallization of the crude product from n-butanol gave **(+)-9a** as a single diastereomer (melting point 211-13° C) in 69% yield from **6a**.

Direct reduction of **(+)-9a** to **12** was accomplished with hydrogen and 10% Pd/C in trifluoroacetic acid in 47% yield. A variety of known methods[5b,5c,10] for aryl ketone to methylene reductions gave less satisfactory results. A two step reduction sequence was then employed. Treatment of **(+)-9a** with $NaBH_4$ (MeOH/THF/0° C) gave alcohol **11** in 90% yield as an 8:1 mixture of epimers at C-5. Based on the C-4,5 proton coupling constants (8 Hz for the major epimer, 4.2 Hz for the minor epimer) the major epimer of **11** was presumed to result from hydride delivery from the β face. Alcohol **11** was especially resistant to hydrogenolysis. An 85% yield of **12** was obtained by *in situ* preparation (trifluoroacetic anhydride/THF) of the trifluoroacetyl ester[11] of **11** under reducing conditions (10% Pd/C, 50psi hydrogen). Simple base hydrolysis of the trifluoroacetamide of **12** (THF/H_2O/NaOH) gave primary amine **13** in 86% yield which was identical[12] in all respects to **13** prepared from ketone **14**.[2] As the conversion of **13** to **3** has previously been described,[2] total synthesis of **3** from L-tryptophan has been achieved.



In conclusion, the successful cyclization and carbonyl reduction of masked L-tryptophan derivative **6**, offers a useful extension of the known synthetic methodology. The synthesis of **3** described illustrates the potential of L-tryptophan as a precursor for the convenient preparation of a variety of compounds having partial ergot structures.

Acknowledgements: The author is indebted to Drs. T. J. Kress, M. J. Martinelli, and M. K. Peters for numerous helpful discussions.

References and Notes

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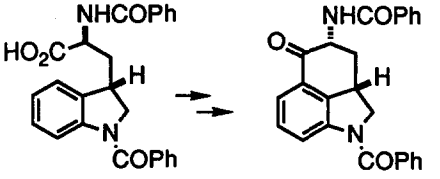
8. Data for **6a**: Melting point 185-7 °C. $[\alpha]_D$= -39.6 ° (MeOH, c=1.0). IR (KBr) 3250, 3070, 1707, 1700, 1612, 1568,1560, 1485, 1461 cm^{-1}. ^1H NMR (DMSO-d_6) δ13.2 (1H, bs), 9.85 (1H, d, J=9Hz), 7.55 (6H, m), 7.25 (2H, m), 7.1 (1H, m), 4.4 (1H, m), 4.15 (1H, t, J=10 Hz), 3,76 (1H, m), 3.4 (1H, m), 2.3 (1H, m), 2.0 (1H, m).
9. The azlactone derived from **7b** cyclized at 80 °C with $AlCl_3$ to give exclusively (I) having inverted configuration at C-4 (ref. 1a).



7b **I**

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12. Data for **13**: Melting point 146-8 °C. $[\alpha]_D$= +61.6° (THF, c=1.0). ^1H NMR ($CDCl_3$) δ7.55 (3H, m), 7.45 (4H, m), 6.8 (1H, bs), 4.25 (1H, bs), 3.65 (1H, t, J=11 Hz), 3.33 (2H, m), 3.14 (1H, dd, J=16.8, 6 Hz), 2.43 (1H, dd, J=16.8, 10.5 Hz), 2.20 (1H, m), 2.00 (2H, s), 1.35 (1H, q, J=11.5 Hz).

(Received in USA 1 October 1990)