THE CHEMISTRY OF CYCLIC TAUTOMERS OF TRYPTOPHAN: HIGHLY DIASTEREOSELECTIVE ALDOL CONDENSATIONS

David Crich,[a,*] Isaura Pastrana-Gress,[b] Leticia Quintero-Cortes,[b] and Jesús Sandoval-Ramirez[b,*]

a) Department of Chemistry, University of Illinois at Chicago (M/C 111), 845 W. Taylor St., Chicago, Il 60607-7061, USA

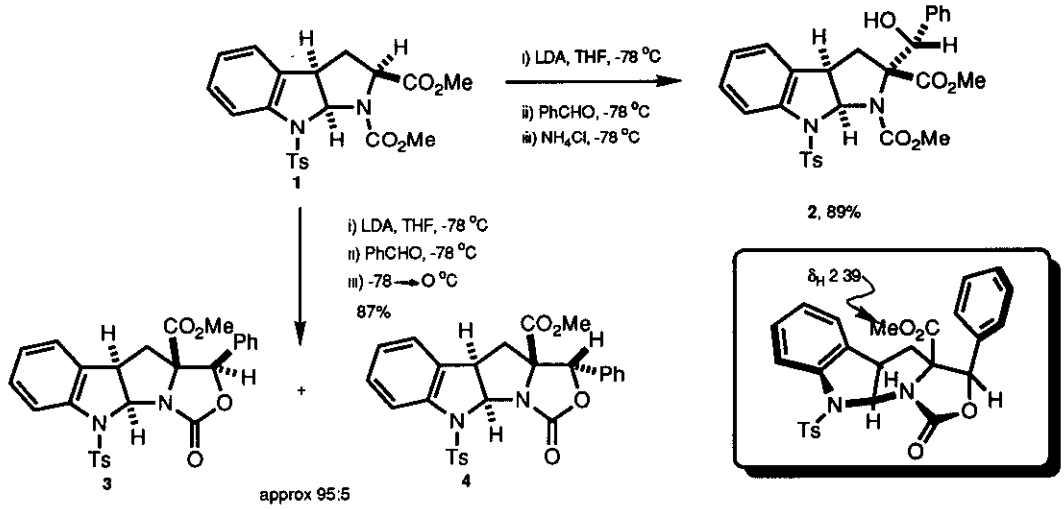
b) Unidad de Investigación en Síntesis Orgánica, Escuela de Ciencias Químicas, Universidad Autónoma de Puebla, Puebla, México

Abstract- Highly diastereoselective aldol reactions of a cyclic tryptophan tautomer (**1**) are reported, together with stereochemical assignments of the products and a possible rationale for the selectivity.

In this laboratory we have been interested in the chemistry of cyclic tautomers of tryptophan and in particular in their use as precursors to diastereoisomerically and enantiomerically pure α- and β-substituted derivatives of tryptophan[1,2] of interest to the pharmaceutical industry due to restrictions on conformation that they impart to their derivatives.[3] β-Alkylated derivatives of tryptophan have also found use as chiral ligands in asymmetric Lewis acid catalysed Diels-Alder reactions.[4] In this letter we describe the extension of our methodolgy to encompass the reaction of enolates of cyclic tryptophan tautomers with aldehydes resulting in highly diastereoselective aldol reactions.

Treatment of the hexahydropyrroloindole (**1**) with lithium diisopropylamine (LDA) in THF at -78 °C followed reaction of the ensueing enolate with benzaldehyde and subsequent quenching with ammonium chloride, at that temperature, resulted in the isolation, in 89% yield, of a single crystalline aldol (**2**). The diastereoselectivity in this experiment was excellent with the crude reaction mixture only containing traces of a

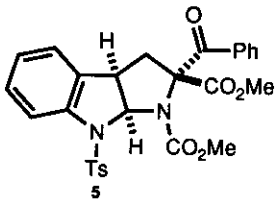
possible second diastereoisomer (Scheme 1). The configuration at C-2 was readily assigned on the basis of the upfield chemical shift (δ_H 3.21) of the methyl ester group, typical of its *endo*-location where it is shielded by the ring current of the aromatic system,[1,5] and indicated that attack had occurred as anticipated with high selectivity on the *exo*-face of the bicyclic system. The configuration at the adjacent and new stereogenic center was assigned on the basis of subsequent observations. Thus, similar reaction of **1** with LDA and then benzaldehyde in THF at -78 °C followed by warming to 0 °C before quenching gave not **2**, but the tetracyclic species (**3**) resulting from displacement of methoxide from the carbamate moiety by the lithium salt of the aldol.



Scheme 1

The oxazolidinone (**3**) was characterized by a strong ir carbonyl absorption at υ 1777 cm^{-1} (and 1739 for the ester) and by an extremely shielded methyl ester group as evidenced by its chemical shift of δ_H 2.39. This latter observation prompted the hypothesis that the methyl ester group was sandwiched between the hexahydropyrroloindole and the newly introduced benzene ring and so shielded by both. This is not unlike the system (**6**) prepared by Zimmerman in which the ester has δ 1.71.[6] Substantiation of this hypothesis was achieved by oxidation of **2** with Ley's[7] tetrapropylammonium perruthenate (TPAP) *N*-methylmorpholine *N*-oxide (NMNO) system to the ketone (**5**) in quantitative yield followed by reduction with $NaBH_4$ in methanol resulting in a 1.55:1 mixture of **3** and its C-2' epimer (**4**) whose methyl ester group resonates at the typical δ_H 3.10 for the 2-*endo*-carbomethoxyhexahydropyrroloindole system. Isolation and characterization of **4**

enabled its identification as a minor component (~ 5%) in the crude reaction mixture resulting from the above aldol reaction with quenching at 0 °C enabling the de of the aldol reaction to be set at 90%. It appears evident that, as outlined in Scheme 1, aldol condensation occurs with high selectivity and chemical yield at -78 °C. Quenching at low temperature enables the isolation of the aldol in excellent yield whereas warming to 0 °C before quenching enables cyclization of the lithium salt of the aldol onto the carbamate group.



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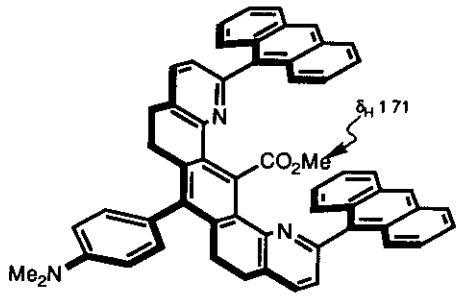

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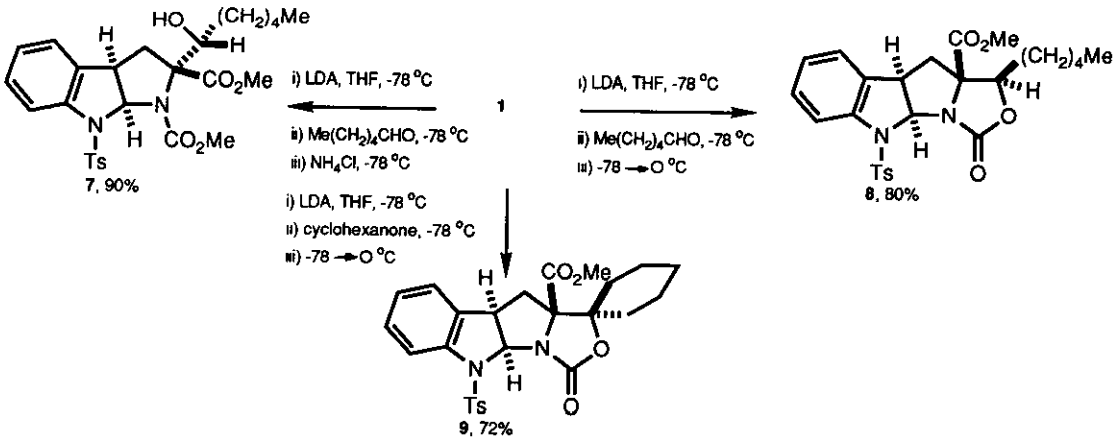
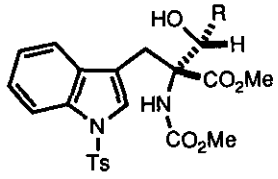
The reaction is not limited to benzaldehyde. Treatment of the lithium enolate of **1** at -78 °C with n-hexanal enabled the isolation of the aldol (**7**) in 90% yield following the low temperature quench or the oxazolidinone (**8**) in 80% yield when the reaction was allowed to come to room temperature before quenching (Scheme 2). Use of cyclohexanone as electrophile and quenching at room temperature gave **9** in 72% isolated yield (Scheme 2). Each of these reactions were highly diastereoselective (≥ 95:5) and the configurations of the various stereogenic centers are assigned by analogy with the above benzaldehyde adducts.

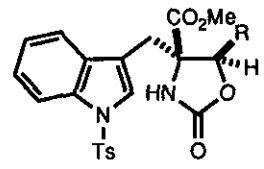


Scheme 2

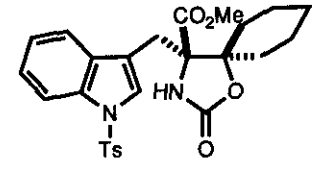
Brief treatment of each of the above adducts with trifluoroacetic acid at room temperature resulted in the isolation of the corresponding tryptophan derivatives (**10** - **14**) each in essentially quantitative yield. In **12** the ester had δ_H 3.20 indicating shielding by a single aromatic group and confirming its *cis*-relationship to the phenyl group.



10, R = *Ph*
11, R = $(CH_2)_4Me$



12, R = *Ph*
13, R = $(CH_2)_4Me$



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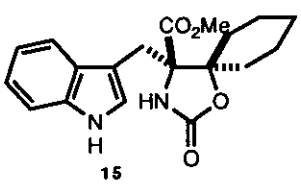
We also note that the toluenesulfonamide group is readily removed from the tryptophan derivatives, after ring opening, by photolysis with anisole and ascorbic acid according to Yonemitsu[8] and as previously employed by ourselves[1] in our preparation of β-alkylated tryptophans. The transformation of **14** to **15** in 92% isolated yield in this manner is illustrative.

It is interesting to compare the diastereoselectivities obtained in this study with those recorded by Seebach in conjunction with the exploitation of his self reproduction of chirality method. Thus fused systems, as for example the cysteine derivative (**16**), in which following deprotonation with LDA the enolate geometry is fixed give high diastereoselectivities on reaction with aldehydes which may be explained by chair like chelation controlled transition states.[9] On the other hand when the enolate double bond is exocyclic to the ring, as in the threonine derivative (**17**), aldol stereoselectivity at the newly introduced stereogenic center is negligable[10] which might be taken to imply poor control of enolate geometry.[11] Clearly, the results outlined above are in contrast to those predicted by simple analogy with the kinetic aldol reactions of **17**. The observed results appear to be satisfactorily rationalized by a chair like transition state as depicted in **18**. This then implies that a single enolate (**19**) is largely formed on deprotonation of **1** with LDA. The high preference for this enolate geometry is probably best explained in terms of minimization of dipole dipole repulsion between the enolate and the N-1 carbamate group as indicated in **19**.[12]



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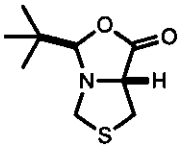

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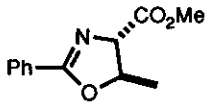

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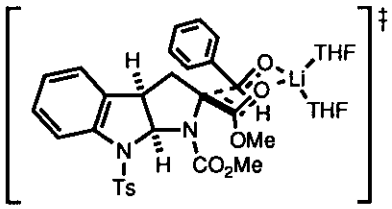

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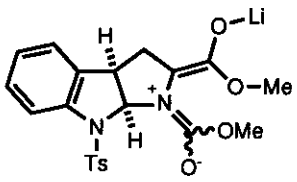

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ACKNOWLEDGEMENTS

We thank CONACYT for financial support (Research grant No. 481100-5-1801E).

REFERENCES

1. G.T. Bourne, D. Crich, J.W. Davies, and D.C. Horwell, *J. Chem. Soc., Perkin Trans. 1,* 1991, 1693; D. Crich and S. Natarajan, *Tetrahedron Lett.*, 1992, **33,** 3405; M. Bruncko and D. Crich, *Tetrahedron Lett.*, 1992, **33**, 6251; D. Crich and L.B.L. Lim, *Heterocycles*, 1993, **36**, 1199; C.-O. Chan, C.J. Cooksey, and D.Crich, *J. Chem. Soc., Perkin Trans. 1,* 1992, 777. Also see: D.E. Zembower, J.A. Gilbert, and M.M. Ames, *J. Med. Chem.,* 1992, **36**, 305.
2. For an alternative approach to β–substituted tryptophans see: L.W. Botejn, K. Wegner, and V.J. Hruby, *Tetrahedron Lett.*, 1992, **33**, 7491.
3. For a recent overview see: D.C. Rees, in *Ann. Rep. Med. Chem.*, ed. J.A. Bristol, Academic, San Diego, 1993, **28**, 59.
4. E.J. Corey, T.-P. Loh, T.D. Roper, M.D. Azimioara, and M.C. Noe, *J. Am. Chem. Soc.,* 1992, **114**, 8290; E.J. Corey and T.-P. Loh, *Tetrahedron Lett.*, 1993, **34**, 3979.
5. In the corresponding *exo*-isomer the ester has δ_H 3.75; M. Bruncko and D. Crich, unpublished results.
6. S.C. Zimmerman and W. Wu, *J. Am. Chem. Soc.,* 1989, **111**, 8054.
7. W.P. Griffith and S.V. Ley, *Aldrichimica Acta,* 1990, **23**, 13.
8. T. Hamada, A. Nishida, and O. Yonemitsu, *J. Am. Chem. Soc.,* 1986, **108**, 140.

9. D. Seebach and T. Weber, *Helv. Chim. Acta,* 1984, **67**, 1650. Also see: D. Seebach, E. Juaristi, D.D.Miller, C. Schickli, and T. Weber, *Helv. Chim. Acta,* 1987, **70**, 237; D. Blaser, S.Y. Ko, and D.Seebach, *J. Org. Chem.,* 1991, **56**, 6230; C. Lowe, Y. Pu, and J.C. Vederas, *J. Org. Chem.,* 1992, **57**, 10.

10. D. Seebach, J.D. Aebi, M. Gandor-Coquoz, and R. Naef, *Helv. Chim. Acta,* 1987, **70**, 1194. For an exception see: E.J. Corey and G.A. Reichard, *J. Am. Chem. Soc.,* 1992, **114**, 10677.

11. Indeed, in ref. 10 the authors repeatedly point out that the enolate geometry is uncertain.

12. All new compounds gave satisfactory spectroscopic and/or microanalytical data.

Received, 5th November, 1993