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Extending Pummerer Reaction Chemistry. Application to the Oxidative Cyclization of Tryptophan Derivatives

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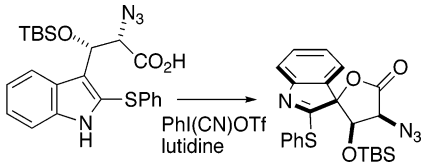
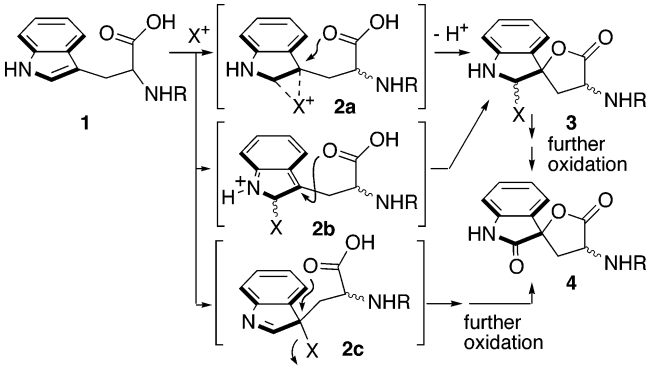
ABSTRACT



The diastereoselective oxidative cyclization of a β-oxygenated tryptophan derivative is reported. This process, which utilizes a new variant of the Pummerer reaction, may have application in TMC-95A synthesis.

The stereoselective oxidative cyclization of tryptophan derivatives to form spirocyclic butyrolactone oxindole products, **1** → **4**, Scheme 1,[1] has remained an enduring problem in alkaloid synthesis, primarily in response to the structural challenges posed by toxins within the tryptoquivaline family of mycotoxin metabolites.[1e,f,i,j] With a singular exception,[1e] diastereoselectivity is scarcely seen upon formation of oxindoles **4**. Identification of the structural/stereoelectronic factors that might influence the stereochemical outcome of this cyclization is complicated by lack of a clear mechanistic understanding. For example, three distinct species, the three-membered ring-bearing **2a**,[1a,d,g] the orthoquinone iminium ion **2b** (this work), and the C(3) oxidized indoline **2c**,[1b,c,i,j] have all been postulated by different authors to occupy central roles in the process. Arguments that link the resident stereochemistry at the α-position to the forming C(3) stereogenic center have not been forthcoming, perhaps because of the discouragingly poor diastereoselectivity typically observed. Introduction of additional stereochemical control elements might favorably influence the diastereoselectivity of these cyclizations, but a lack of appropriately functionalized target molecules (≠ tryptoquivalines) did little to motivate such pursuits.

Scheme 1. Mechanistic Speculation Governing the Oxidative Cyclization of Tryptophan Derivatives



(1) (a) Lawson, W. B.; Patchornik, A.; Witkop, B. *J. Am. Chem. Soc.* **1960**, *82*, 5918−5923. (b) Hinman, R. L.; Bauman, C. P. *J. Org. Chem.* **1964**, *29*, 1206−1214. (c) Hinman, R. L.; Bauman, C. P. *J. Org. Chem.* **1964**, *29*, 2431−2437. (d) Nagasaka, T.; Ohki, S. *Chem. Pharm. Bull.* **1971**, *19*, 545−551. (e) Büchi, G.; DeShong, P. R.; Katsumura, S.; Sugimura, Y. *J. Am. Chem. Soc.* **1979**, *101*, 5084−5086. (f) Ohnuma, T.; Kimura, Y.; Ban, Y. *Tetrahedron Lett.* **1981**, *22*, 4969−4972. (g) Palla, G.; Marchelli, R.; Casnati, G.; Dossena, A. *Gazz. Chim. Ital.* **1982**, *112*, 535−536. (h) Ohnuma, T.; Kasuya, H.; Kimura, Y.; Ban, Y. *Heterocycles* **1982**, *17*, 377−380. (i) Nakagawa, M.; Taniguchi, M.; Sodeoka, M.; Ito, M.; Yamaguchi, K.; Hino, T. *J. Am. Chem. Soc.* **1983**, *105*, 3709−3710. (j) Nakagawa, M.; Sodeoka, M.; Yamaguchi, K.; Hino, T. *Chem. Pharm. Bull.* **1984**, *32*, 1373−1384. (k) Labroo, R. B.; Labroo, V. M.; King, M. M.; Cohen, L. A. *J. Org. Chem.* **1991**, *56*, 3637−3642.

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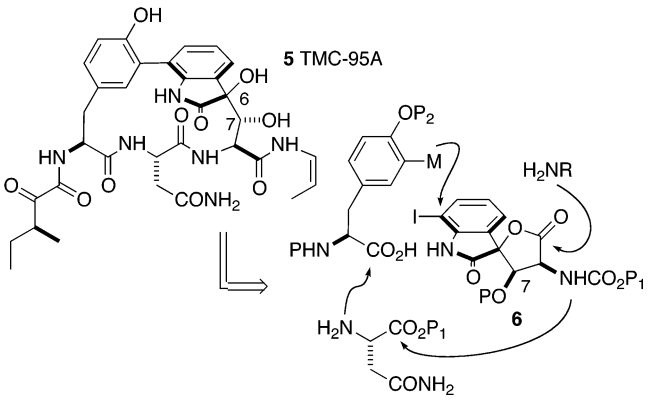
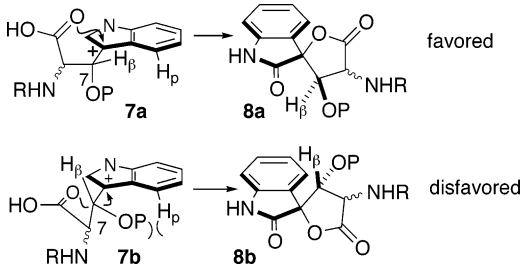
However, the recent report describing the structure of the 20S proteosome inhibitor TMC-95A (**5**) (and congeners),[2] with its C(3) oxidized oxindole core, simulated a reinvestigation of this dormant area of tryptophan chemistry. One approach to the synthesis of this microbial metabolite might pass through the spirocyclic butyrolactone oxindole construct **6** as part of the fragment coupling strategy summarized in Scheme 2.

Scheme 2. Retrosynthetic Analysis for TMC-95A



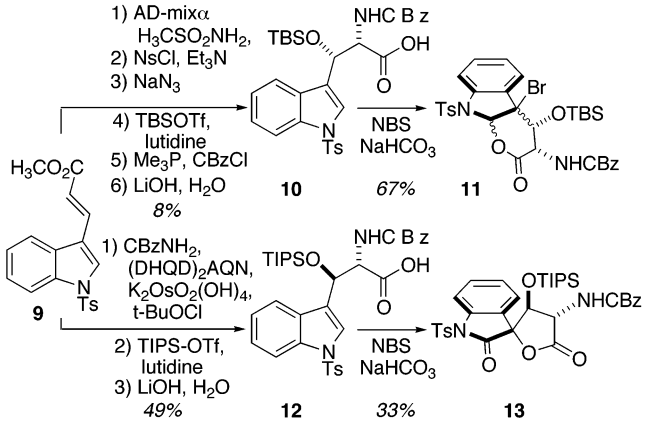
The synthesis sub-goal **6** bears a C(7) ether moiety (TMC-95A numbering) that may be the missing stereochemical determinant in tryptophan oxidative cyclizations. Two diastereotopic transition states can be envisioned, **7a** and **7b**, for the cyclization of a C(7) functionalized tryptophan derivative (Scheme 3). In these models, a generic C(3) sp^2-hybridized electrophile is indicated since the mechanistic uncertainty described with Scheme 1 makes further refinement impossible. In particular, a burgeoning steric interaction (cf. **7b**) between the C(7) ether substituent and the peripositioned hydrogen H_p might serve to steer the cyclization of **7** down an alternate pathway favoring formation of the diastereomer **8a**. Transition state construct **7a** also may enjoy an additional energetic benefit via Felkin−Ahn-type LUMO−LUMO mixing between σ^*_{C-O} and the p orbital of the electrophile, an advantage that is not available in the diastereomeric species **7b**. On the basis of the results with the simple tryptophan derivatives highlighted in Scheme 1, the influence of the α-stereogenic (NHR) center is not expected to overwhelm any of these putative control elements. The test of this hypothesis is described below.

Scheme 3. Model for Diastereoselective Cyclization of Tryptophan Derivatives Bearing an Ether Substituent at the Indolic Position



The initial attempt to probe this strategy for introducing stereoselectivity into tryptophan oxidative cyclizations relied on the normally dependable brominative cyclization procedure[1a,b,g,i] to convert a C(β)-oxidized tryptophan derivative into the desired oxindole, Scheme 4. Construction of the

Scheme 4. Model Brominative Cyclizations



C(α)-(*S*)/C(β)-(*S*) diastereomer **10** followed from known enoate **9**[3] by application of a protocol developed by Boger et al.[4] The Sharpless bishydroxylation[5] of indole derivative **9** provided a diol product in ≥99% ee (HPLC, OJ-H column). The low yield for this sequence can be attributed to a problematical azide reduction/acylation step, but a disappointing cyclization outcome provided little reason to pursue optimization studies. Treatment of tryptophan derivative **10** under a variety of bromonium ion initiated oxidative cyclization procedures afforded varying amounts of a single cyclization product. Under the most favorable conditions (NBS, $NaHCO_3$), yields as high as 67% could be obtained. Spectroscopic analysis (e.g., IR 1764 cm^{-1}; compare 1800 cm^{-1} for structures of the type **4**)[1g] of this diastereomerically pure tricycle led to the conclusion that incorporation of the

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C(β)-(*S*) ether substituent diverted the reaction down an unexpected channel, and a C(2) rather than a C(3) cyclized product resulted. The stereochemical relationship between the ring fusion and the C(α)/C(β) stereogenic centers was not determined. It is possible that an intermediate related to **2c** preceded nucleophilic acid addition to C(2) of the oxidized indole core.

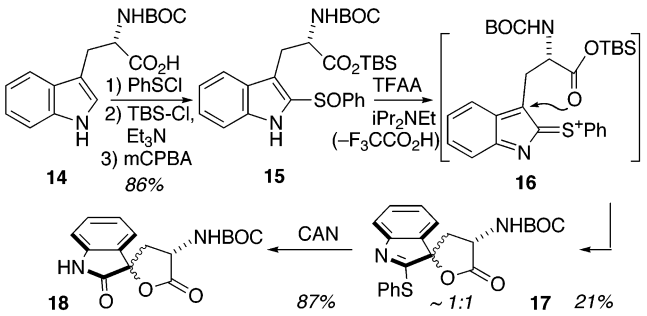
This unexpected turn was rendered even more curious by the cyclization results obtained upon exposing the diastereomeric species **12** (OTIPS instead of OTBS) to the same brominative reaction conditions. Oxidative cyclization substrate **12** was prepared by a strategy similar to that used for the synthesis of **10**, and the Sharpless amidohydroxylation procedure[6] provided hydroxyamide product in ≥99% ee (HPLC, OJ-H column) and 10:1 regiochemical selectivity. In this instance, the only cyclized material isolated from a relatively more complex reaction mixture was the butyrolactone-containing oxindole **13** (IR 1810 cm^{-1}). Despite the modest yield, the formation of a single stereoisomeric product was encouraging, especially since the specific stereochemical relationship between the C(β) OTIPS moiety and the oxindole's spirocyclic center corresponded to that expected from application of the cyclization model shown in Scheme 3. Unfortunately, this diastereomeric relationship does not match the one desired for TMC-95A (**10** might have led to that species).

The basis for the regiochemically disparate cyclization outcomes with **10** and **12** remains uncertain, but it is apparent that the C(α) group NHCBz must be exerting some influence after all. Possible eclipsing steric interactions between the OTBS and NHCBz groups in the cyclization transition state derived from **10**, which are absent (or at least minimized) in the alternative transition state extending from **12**, may play a role in raising the energy of the former process. In this view, alternative, normally higher energy cyclization modes (e.g., → **11**) then may have a chance to be expressed. Whatever the reason, these divergent cyclization results bring into focus a more general problem with oxidative cyclizations of these C(β)-functionalized tryptophan constructs—a lack of predictable regiochemical control.

An approach to solving the problem of regiochemical control in indole oxidative cyclizations has been described recently.[7] This methodology uses a variant of the Pummerer reaction to effect C(3)-selective oxidative cyclization of pendant carbon nucleophiles to furnish spirocyclic 2-thioimidate and/or derived oxindole products. The extension of this chemistry to the tryptophan series requires successful participation of a carboxylic acid derivative as the nucleophile, Scheme 5.

Initial attempts to effect cyclization with 2-thiophenyl tryptophan derivatives featuring either a free carboxylic acid or its derived methyl ester were not productive. However, switching to a silyl ester **15** did provide the first evidence that this transformation was possible. Cyclization substrate

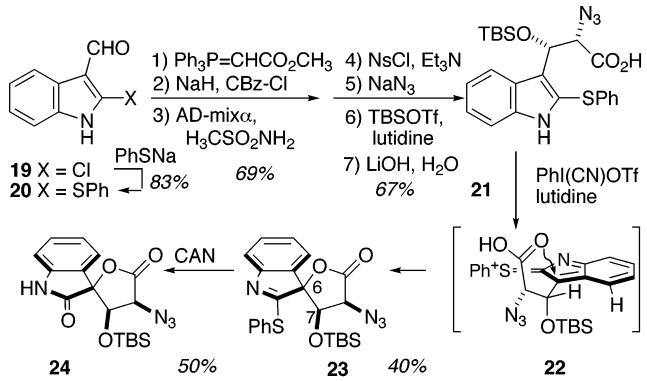
Scheme 5. Pummerer-Based Oxidative Cyclization of a Simple Tryptophan Derivative



15, readily available via completely regioselective C(2) sulfenylation of NBOC tryptophan **14**,[8] was treated with the standard Pummerer trigger trifluoroacetic anhydride (TFAA) to furnish modest amounts of the spirocyclic butyrolactone **17** (IR 1798 cm^{-1}) as a 1:1 mixture of diastereomers. This transformation may pass through the reactive, electrophilic orthoquinone imine sulfonium ion **16**, a species that resembles the bromonium ion generated orthoquinone iminium ion **2b**. The product thioimidate **17** could be hydrolyzed in good yield to afford the desired oxindole **18**. No better cyclization diastereoselectivity attends this cyclization procedure than typically is observed with other oxidants in the tryptophan series.[1] Yield optimization studies, in which the Pummerer initiator (trifluoroacetic anhydride, triflic anhydride, TBSOTf) and base (*i*-Pr_2NEt, pyridine, 2,6-lutidine, Et_3N) were varied (solvent = CH_2Cl_2, −78 °C), did not lead to improvements over the example shown in Scheme 5. Nevertheless, formation of the desired spirocycle attested to the feasibility of this approach to using tryptophan oxidative cyclizations for selective spiro butyrolactone oxindole synthesis and prompted attempts to apply this methodology to the TMC-95A problem.

Assembly of the key cyclization precursor **21** began with 2-chloroindole-3-carboxaldehyde (**19**)[9] and used a nucleophilic sulfur source to introduce the requisite Pummerer functionality, Scheme 6. Sharpless dihydroxylation provided

Scheme 6. Pummerer-Based Oxidative Cyclization of a Functionalized TMC-95A Core Model



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a chiral diol intermediate (ee ≥ 99%, HPLC, OJ-H column) that could be processed on to the azido silyl ether **21** using chemistry similar to that described for the preparation of **10**. Surprisingly, treatment of the sulfoxide derived from **21** (not shown) with a variety of electrophilic Pummerer triggers did not lead to any butyrolactone spirocyclic product, nor were related attempts with the analogous silyl ester or methyl ester rewarded. These disappointing results, in contrast to the simpler system **15**, point to unexpected complications engendered by introduction of the β-silyloxy substituent.

Fortunately, use of the unconventional Pummerer initiator PhI(CN)OTf[7b,10] with *sulfide* **21** did lead to a productive cyclization that furnished a single butyrolactone thioimidate product **23** in moderate yield. With this particular substrate, use of functional variants such as the silyl or methyl esters, or an NHBOC group in place of the azide, did not improve the yield shown. In fact, participation of the $NHCO_2t$-Bu substrate's carbonyl in bond formation to C(3) provided a glimpse of some of the difficulties that can hamper this cyclization. The butyrolactone product **23** was formed with a diastereomeric relationship between C(6) and C(7) that is both consistent with the cyclization model described in Scheme 3 and on track for TMC-95A synthesis. As with the simpler system **17**, ready hydrolysis of the thioimidate unit delivered the desired oxindole **24**.

These studies demonstrate that, for the first time, possibly biomimetic oxidative cyclization of a tryptophan derivative to form a butyrolactone product can be achieved with both high and predictable stereochemical control. This advance is tied to the use of a hypervalent iodine reagent in a Pummerer-based oxidative cyclization protocol.

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Supporting Information Available: Spectral data including ^{1}H NMR, ^{13}C NMR, IR, and MS for **10**−**13**, **15**, **17**, **18**, **20**, **21**, **23**, and **24**. This material is available free of charge via the Internet at http://pubs.acs.org.

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