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Catalytic Asymmetric Synthesis of the Central Tryptophan Residue of Celogentin C

Steven L. Castle* and G. S. C. Srikanth

Department of Chemistry and Biochemistry, Brigham Young University, Provo, Utah 84602

scastle@chem.byu.edu

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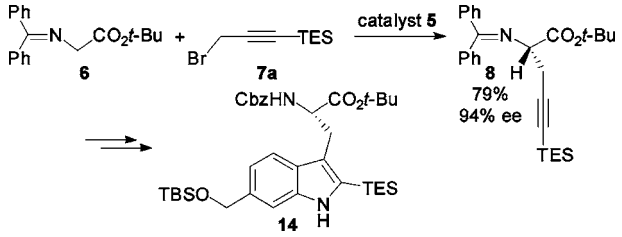
ABSTRACT



Chiral phase-transfer catalyst 5 containing an electron-deficient trifluorobenzyl moiety promoted the alkylation of glycine derivative 6 with propargyl bromide 7a in good yield and excellent ee. The resulting propargyl glycine 8 was converted to 14, the central tryptophan residue of Celogentin C, in two steps, with the Pd-catalyzed heteroannulation as the key transformation. This method promises to be an efficient route for the preparation of tryptophan derivatives possessing substitution on the indole ring.

Celogentin C (**1**, Figure 1) is a bicyclic octapeptide isolated from the seeds of *Celosia argentea*.[1] It is the most potent member of the moroidin family of natural products, a group of structurally similar bicyclic peptides characterized by their inhibition of the polymerization of tubulin.[2] The unusual architecture of **1** is derived from two cross-links, one joining the leucine β-carbon with the indole C-6 of tryptophan, and the other connecting the tryptophan indole C-2 with the imidazole N-1 of histidine. Synthetic studies of moroidin natural products are limited to the work of Moody resulting in the preparation of the right-hand macrocycle of moroidin.[3] Clearly, any synthesis of **1** will need to address the preparation of a tryptophan derivative with functionality at the indole C-2 and C-6 positions that is appropriate for constructing the aforementioned strategic bonds. Herein, we report our synthesis of such a molecule as well as our parallel investigations in the area of phase-transfer-catalyzed asymmetric alkylation.

Although several processes have been developed for the synthesis of optically active tryptophan derivatives possessing substituted indoles,[4] we were attracted to the recent report by Cook and co-workers.[5] They have disclosed a versatile synthesis of tryptophans (Scheme 1) in which the indole

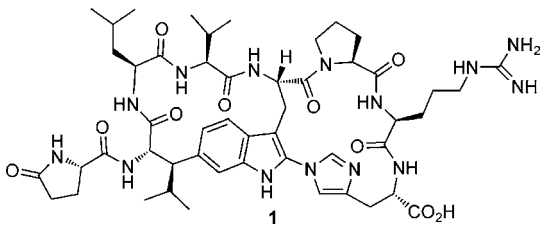


Figure 1. Celogentin C (**1**).

(1) Kobayashi, J.; Suzuki, H.; Shimbo, K.; Takeya, K.; Morita, H. *J. Org. Chem.* **2001**, *66*, 6626.

(2) (a) Leung, T.-W. C.; Williams, D. H.; Barna, J. C. J.; Foti, S.; Oelrichs, P. B. *Tetrahedron* **1986**, *42*, 3333. (b) Kahn, S. D.; Booth, P. M.; Waltho, J. P.; Williams, D. H. *J. Org. Chem.* **1989**, *54*, 1901. (c) Morita, H.; Shimbo, K.; Shigemori, H.; Kobayashi, J. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 469.

(3) (a) Harrison, J. R.; Moody, C. J. *Tetrahedron Lett.* **2003**, *44*, 5189. (b) Comber, M. F.; Moody, C. J. *Synthesis* **1992**, 731.

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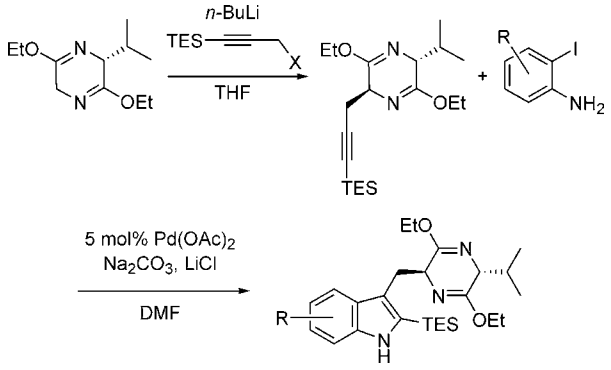
Scheme 1. Cook Tryptophan Synthesis



moiety is formed via the palladium-catalyzed heteroannulation chemistry of Larock.[6] This process permits functionality at C-6 of the indole product, and it results in the presence of a triethylsilyl (TES) group at the indole C-2. Thus, the Cook method would appear to be ideal for our purposes; however, it suffers from its reliance on a stoichiometric amount of the Schöllkopf chiral auxiliary.[7] It occurred to us that we could rectify this shortcoming of an otherwise useful protocol by employing the chiral phase-transfer-catalyzed alkylation of a glycinate Schiff base[8] in place of the diastereoselective alkylation of the Schöllkopf reagent.

Although selected examples exist of highly enantioselective phase-transfer-catalyzed alkylations of glycinate Schiff bases with propargylic electrophiles,[9] we were unsure of the prospects for obtaining suitable enantioselectivity in our case. In alkylations of the Schöllkopf reagent with TMS-propargylic electrophiles, Cook observed dramatic variations in diastereoselectivities (2.5:1 to 46:1) with respect to the leaving group. The propargyl bromide provided the lowest levels of selectivity, and the analogous diphenyl phosphate delivered the best results.[5] Additionally, Ley's chiral glycine equivalent affords high levels of diastereoselectivity (≥10:1) in alkylations with several electrophiles but gives significantly reduced selectivity (3:1) with propargyl bromide.[10] With these results in mind, we initiated a study of the

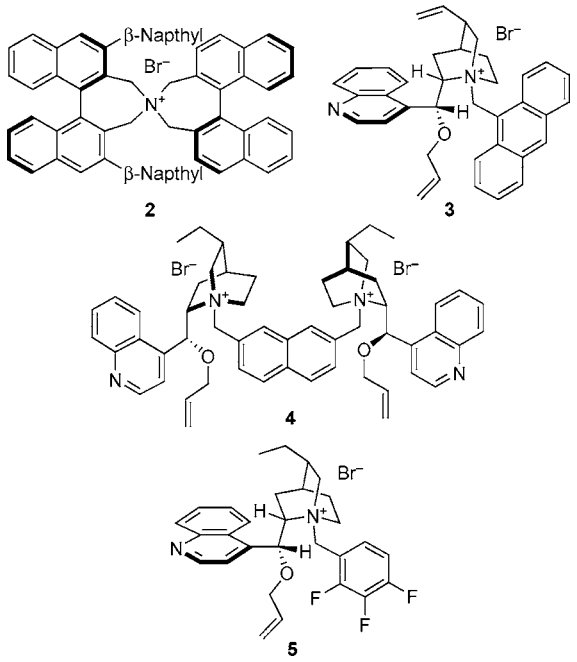
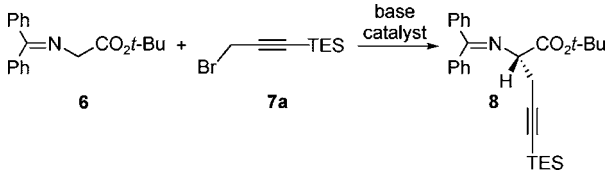


Figure 2. Phase-transfer catalysts surveyed.

enantioselective alkylation of glycinate Schiff base **6**[11] with TES-propargyl bromide (**7a**) using chiral phase-transfer catalysts **2**−**5** (Figure 2, Table 1).

Table 1. Phase-Transfer-Catalyzed Alkylation of **6** with **7a**[a]



catalyst	conditions[b]	yield (%)	ee (%)[c]
2	A	65	79[d]
3	B	54	84
4	C	80	81
5	D	80	90

[a] Data are the average of two runs. [b] A: 0.01 equiv of **2**, toluene−50% aq KOH 3.25:1, 0 °C, 1 h. B: 0.1 equiv of **3**, 10 equiv of CsOH·H_2O, CH_2Cl_2, −78 °C, 22 h. C: 0.04 equiv of **4**, (toluene/$CHCl_3$ 7:3)−50% aq KOH 3:1, 0 °C, 3 h. D: 0.1 equiv **5**, (toluene/$CHCl_3$ 7:3)−50% aq KOH 3:1, 0 °C, 2 h. 5 equiv of **7a** was used in all cases. [c] Determined by HPLC (Chiralcel OD-H, 99.8:0.2 hexanes:*i*-PrOH, 1 mL/min). [d] *ent*-**8** was obtained.

In this survey of catalysts for the preparation of propargyl glycine **8** from **6** and **7a**, we employed the optimized reaction conditions reported for each catalyst. Our suspicions were confirmed, as BINOL-derived catalyst **2**[9b] and cinchonidine-derived catalysts **3**[9a] and **4**[9c] all delivered **8** in moderate ee.

(4) (a) Wang, W.; Xiong, C.; Zhang, J.; Hruby, V. J. *Tetrahedron* **2002**, *58*, 3101. (b) Yokoyama, Y.; Osanai, K.; Mitsuhashi, M.; Kondo, K.; Murakami, Y. *Heterocycles* **2001**, *55*, 653. (c) Drury, W. J., III; Ferraris, D.; Cox, C.; Young, B.; Lectka, T. *J. Am. Chem. Soc.* **1998**, *120*, 11006. (d) Zembower, D. E.; Ames, M. M. *Synthesis* **1994**, 1433. (e) Lee, M.; Phillips, R. S. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 1563. (f) Sato, K.; Kozikowski, A. P. *Tetrahedron Lett.* **1989**, *30*, 4073.

(5) Ma, C.; Liu, X.; Li, X.; Flippen-Anderson, J.; Yu, S.; Cook, J. M. *J. Org. Chem.* **2001**, *66*, 4525.

(6) Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689.

(7) Schöllkopf, U.; Groth, U.; Deng, C. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 798. The precursor to the antipode of the Schöllkopf reagent necessary for the preparation of natural amino acids, (*R*)-(−)-3-isopropyl-2,5-piperazinedione, is available from Aldrich at a cost of $34.80/g. Alternatively, the reagent can be synthesized via a four-step procedure[5] employing the pulmonary toxin phosgene.

(8) O'Donnell, M. J. *Aldrichim. Acta* **2001**, *34*, 3.

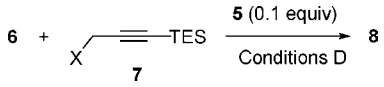
(9) (a) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414. (b) Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 5139. (c) Park, H.-g.; Jeong, B.-S.; Yoo, M.-S.; Lee, J.-H.; Park, M.-k.; Lee, Y.-J.; Kim, M.-J.; Jew, S.-s. *Angew. Chem., Int. Ed.* **2002**, 41, 3036. (d) Jew, S.-s.; Yoo, M.-S.; Jeong, B.-S.; Park, I.-Y.; Park, H.-g. *Org. Lett.* **2002**, *4*, 4245. (e) Park, H.-g.; Jeong, B.-S.; Yoo, M.-S.; Lee, J.-H.; Park, B.-s.; Kim, M. G.; Jew, S.-s. *Tetrahedron Lett.* **2003**, *44*, 3497.

(10) Dixon, D. J.; Harding, C. I.; Ley, S. V.; Tilbrook, D. M. G. *Chem. Commun.* **2003**, 468.

Additionally, modest yields due to competitive hydrolysis of the imine moiety of **6** were observed in reactions with catalysts **2** and **3**. Fortunately, the electron-poor catalyst **5** recently disclosed by Park and Jew[9d] provided **8** in good yield and ee.

With the selection of **5** as the optimal catalyst, we next investigated the effect of the propargylic leaving group on the enantioselectivity (Table 2).[12] In contrast to Cook's study

Table 2. Effect of Leaving Group on Alkylation[a]



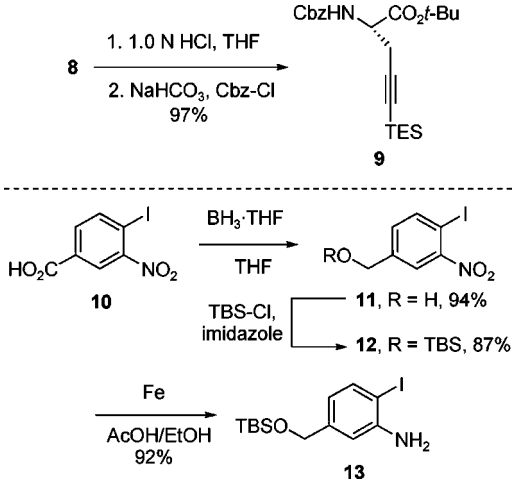
electrophile	X	yield (%)	ee (%)
7a	Br	80	90
7b	I	71	92
7c	Cl	13	85
7d	OMs	35	81
7e	OTs	NR[b]	
7f	$OPO(OPh)_2$	NR	
7a[c]	Br	79	94

[a] Data are the average of two runs. [b] No reaction observed. [c] Reaction performed at −20 °C.

with the Schöllkopf reagent, our investigations of the phase-transfer-catalyzed alkylation of **6** revealed only a modest variation in ee with respect to leaving group. Among the propargyl halides, iodide **7b** provided **8** with slightly better ee but lower yield than did bromide **7a**, presumably due to the instability of **7b**. Alkylations with chloride **7c** were characterized by poor yields and moderate ee values. Of the non-halogen leaving groups examined, only mesylate **7d** delivered **8**, albeit in low yield and moderate ee. Fortunately, when the alkylation of **6** with **7a** was performed at −20 °C, **8** was obtained in 94% ee with essentially no sacrifice in yield.

As we turned our attention to performing the alkylation on a scale more suited to preparative work, we desired to reduce the number of equivalents of **7a** used in the reaction. Unfortunately, this led to a significant decrease in the reaction rate. We were hesitant to allow the reaction to proceed for long periods of time due to the likelihood of increased levels of imine hydrolysis of **6**. We were pleased to find an acceptable compromise by performing the reaction on a ca. 1 mmol scale with 2.5 equiv of **7a** at −20 °C for 7 h. Using these conditions, we isolated **8** in 66% yield (75% based on recovered **6**) along with 11% of **6** and 53% of **7a**. Thus, although excess **7a** is required in the alkylation to ensure a useful rate, the unreacted bromide can be almost completely recovered from the reaction. Moreover, the ability to recover the phase-transfer catalyst from the reaction mixture[9a] makes this process quite economical and attractive for large-scale synthesis.

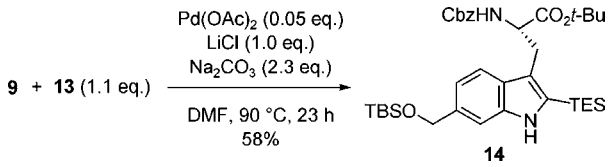
Scheme 2. Synthesis of Heteroannulation Partners



With ample quantities of **8** in hand, we next addressed the preparation of the coupling partners for the heteroannulation reaction (Scheme 2). Exchange of the rather labile benzophenone imine moiety for the more robust Cbz protecting group provided alkyne **9**. Iodoaniline **13** was synthesized from 4-iodo-3-nitrobenzoic acid (**10**)[13] via a high-yielding three-step sequence.

The palladium-catalyzed heteroannulation of alkyne **9** and iodoaniline **13** to form tryptophan **14** is illustrated in Scheme 3. A variety of conditions were examined,[6,14] and the best

Scheme 3. Synthesis of Tryptophan **14**



results were obtained from a slight modification of Cook's protocol.[5] In each case, varying amounts of unreacted **9** were observed, whereas **13** was never recovered even in cases where it was used in excess. This suggests that decomposition of **13** may be responsible for the attenuated yield. Comparison of the chiral HPLC profile (Chiralcel OD-H) of **14** with that of a racemic sample indicated that no racemization occurred under the basic heteroannulation conditions.

In conclusion, we have discovered that the trifluorobenzyl phase-transfer catalyst **5** is uniquely effective among the catalysts studied for the alkylation of glycinate Schiff base **6** with propargyl bromide **7a**. This catalyst may prove useful in other demanding alkylations. Variation of the propargylic leaving group resulted in relatively small changes in enantioselectivity compared to the large changes in diastereoselectivity observed by Cook in alkylations of the Schöllkopf

(11) O'Donnell, M. J.; Polt, R. L. *J. Org. Chem.* **1982**, *47*, 2663.

(12) The electrophiles for this study were synthesized by the following procedures. **7a**: Jones, G. B.; Wright, J. M.; Plourde, G. W., II; Hynd, G.; Huber, R. S.; Mathews, J. E. *J. Am. Chem. Soc.* **2000**, *122*, 1937. **7b**: Rigby, J. H.; Cuisiat, S. V. *J. Org. Chem.* **1993**, *58*, 6286. **7c**: Marshall, J. A.; Wallace, E. M.; Coan, P. S. *J. Org. Chem.* **1995**, *60*, 796. **7d**: Magnus, P.; Exon, C.; Albaugh-Robertson, P. *Tetrahedron* **1985**, *41*, 5861. **7e**,**f**: ref 5.

(13) Collini, M. D.; Ellingboe, J. W. *Tetrahedron Lett.* **1997**, *38*, 7963.

(14) Gathergood, N.; Scammells, P. J. *Org. Lett.* **2003**, *5*, 921.

reagent. Finally, we were able to convert the alkylation product **8** into the functionalized tryptophan derivative **14**, thereby demonstrating that phase-transfer-catalyzed asymmetric alkylation can be used to increase the efficiency of the Cook tryptophan synthesis by eliminating the need for a stoichiometric chiral auxiliary. Studies involving the incorporation of **14** into a total synthesis of **1** are currently in progress.

Acknowledgment. We thank Brigham Young University for support of this work and Sashikumar Mettath for assistance in catalyst preparation. This Letter is dedicated to Professors Dale L. Boger and Larry E. Overman on the occasion of their 50th and 60th birthdays, respectively.

Supporting Information Available: Spectral data for **7a**−**f**, and experimental procedures and spectral data for **8**, **9**, and **11**−**14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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