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Construction of Epidithiodioxopiperazines by Directed Oxidation of Hydroxyproline-Derived Dioxopiperazines

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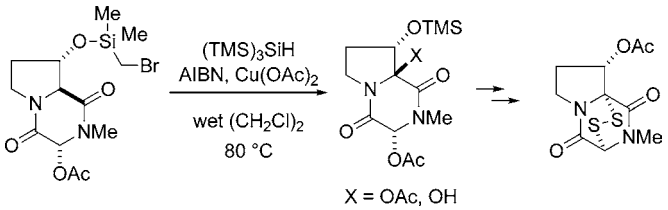
ABSTRACT



Functionalization of the angular methine carbon of hydroxyproline-derived dioxopiperazines by a radical-promoted C–H bond oxidation, which is directed by a proximal (bromomethyl)silyl group, is described. This regioselective oxidation is the key step in a new synthesis of epidithiodioxopiperazines.

Epipolythiodioxopiperazines (ETPs) are toxic secondary metabolites made by fungi.[1] The varied biological effects of ETP natural products are attributed to the bridged disulfide, which can directly conjugate to cysteine residues or generate reactive oxygen species by redox cycling.[1] The largest number of natural ETPs are derived from tryptophan and contain an ETP ring fused to a cyclotryptamine fragment. Leptosins D (**1**) and K (**2**), which were isolated by Numata and co-workers, are exemplary of this subclass of ETP natural products (Figure 1).[2,3]

The synthesis of ETP compounds received much attention in the 1970s and 1980s,[4] culminating in the landmark total synthesis of (+)-gliotoxin by Kishi and co-workers.[4i] As a step toward developing total syntheses of the cyclotryptophan group of ETP metabolites, we report a method for constructing tricyclic epidithiodioxopiperazines from dioxopiperazines containing a hydroxyproline unit. The development of a protecting-group-directed, regioselective C−H bond oxidation was critical to implementing this sequence.

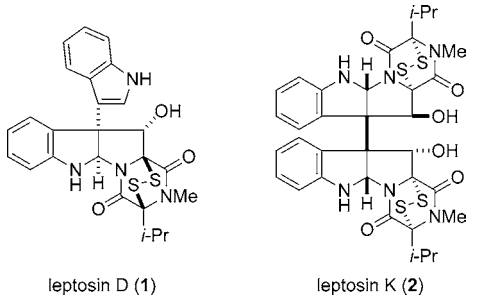


Figure 1. Representative ETP natural products containing cyclotryptophan fragments.

(1) For reviews, see: (a) Waring, P.; Eichner, R. D.; Müllbacher, A. *Med. Res. Rev.* **1988**, *8*, 499−524. (b) Gardiner, D. M.; Waring, P.; Howlett, B. J. *Microbiology* **2005**, *151*, 1021−1032.

(2) Takahashi, C.; Numata, A.; Ito, Y.; Matsumura, E.; Araki, H.; Iwaki, H.; Kushida, K. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1859−1864.

(3) Takahashi, C.; Minoura, K.; Yamada, T.; Numata, A.; Kushida, K.; Shingu, T.; Hagishita, S.; Nakai, H.; Sato, T.; Harada, H. *Tetrahedron* **1995**, *51*, 3483−3498.

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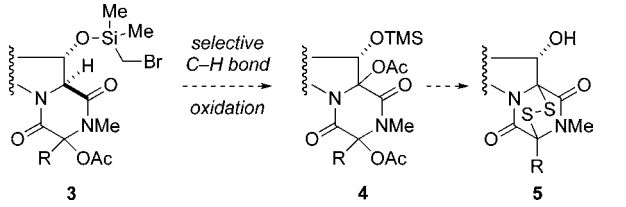
The high reactivity of the disulfide bridge is a critical consideration in designing synthetic routes to ETP natural products. The disulfide bridge is known to be extremely labile under reductive, basic, and strongly acidic conditions.[1,4i] Accordingly, we plan to install the disulfide bridge at a late stage in the synthesis of cyclotryptophan-containing ETPs from precursors such as dioxopiperazine diacetate **4** (Scheme 1).[5,6] Most ETP natural products of this type contain a hydroxyl substituent adjacent to the disulfide bridge (e.g., **1** and **2**). Thus, we hoped to engage this substituent to direct selective, late-stage oxidation of the adjacent angular carbon of a hexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione fragment.

Scheme 1

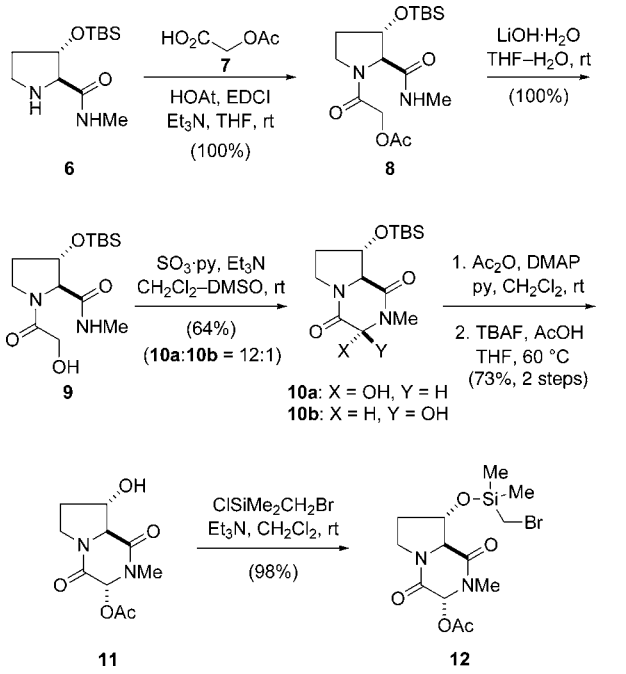


3 **4** **5**

The sequence we ultimately developed employs a silyl group on the secondary alcohol to initiate a radical chain oxidation reaction (**3** → **4**, Scheme 1).[7] The (bromomethyl)-dimethylsilyl-protecting/radical-translocating group was chosen because it should be possible to introduce it into complex molecules under mild conditions, and the resulting trimethylsiloxy product should be easily transformed to the parent alcohol. Radical-promoted C−H bond oxidation is appreciated as a technique for remote functionalization of alcohol derivatives; however, these directed oxidations typically take place at carbons α or δ to the hydroxyl group.[8,9] Some transformations of radicals translocated to the β-carbon of an alcohol derivative have been documented; however, oxidation of such translocated radicals apparently has not been reported previously.[10]

Our investigation commenced with the coupling of 3-hydroxyproline derivative **6**[11] and acetylglycolic acid **7** (Scheme 2). After hydrolytic cleavage of the acetate of diamide **8**, Parikh−Doering oxidation[12] and attendant cyclization gave a mixture of dioxopiperazines **10a** and **10b** (12:1 ratio, 64% yield), from which the crystalline epimer **10a** was isolated in 59% overall yield from aminoamide **6**. After acetylating the hydroxyl group of **10a**, the TBS group was removed at

Scheme 2



6 **8** **9** **10a**: X = OH, Y = H **10b**: X = H, Y = OH **11** **12**

(4) (a) Trown, P. W. *Biochem. Biophys. Res. Commun.* **1968**, *33*, 402−407. (b) Hino, T.; Sato, T. *Tetrahedron Lett.* **1971**, *12*, 3127−3129. (c) Öhler, E.; Poisel, H.; Tataruch, F.; Schmidt, U. *Chem. Ber.* **1972**, *105*, 635−641. (d) Öhler, E.; Tataruch, F.; Schmidt, U. *Chem. Ber.* **1973**, *106*, 165−176. (e) Yoshimura, J.; Nakamura, H.; Matsunari, K.; Sugiyama, Y. *Chem. Lett.* **1974**, 559−560. (f) Kishi, Y.; Fukuyama, T.; Nakatsuka, S. *J. Am. Chem. Soc.* **1973**, *95*, 6490−6492. (g) Kishi, Y.; Fukuyama, T.; Nakatsuka, S. *J. Am. Chem. Soc.* **1973**, *95*, 6492−6493. (h) Kishi, Y.; Nakatsuka, S.; Fukuyama, T.; Havel, M. *J. Am. Chem. Soc.* **1973**, *95*, 6493−6495. (i) Fukuyama, T.; Nakatsuka, S.; Kishi, Y. *Tetrahedron* **1981**, *37*, 2045−2078. (j) Strunz, G. M.; Kakushima, M. *Experientia* **1974**, *30*, 719−720. (k) Ottenheijm, H. C. J.; Herscheid, J. D. M.; Kerkhoff, G. P. C.; Spande, T. F. *J. Org. Chem.* **1976**, *41*, 3433−3438. (l) Herscheid, J. D. M.; Nivard, R. J. F.; Tijhuis, M. W.; Ottenheijm, H. C. J. *J. Org. Chem.* **1980**, *45*, 1885−1888. (m) Williams, R. M.; Rastetter, W. H. *J. Org. Chem.* **1980**, *45*, 2625−2631. (n) Srinivasan, A.; Kolar, A. J.; Olsen, R. K. *J. Heterocycl. Chem.* **1981**, *18*, 1545−1548. (o) Shimazaki, N.; Shima, I.; Hemmi, K.; Tsurumi, Y.; Hashimoto, M. *Chem. Pharm. Bull.* **1987**, *35*, 3527−3530. (p) Jiang, H.; Newcombe, N.; Sutton, P.; Lin, Q. H.; Müllbacher, A.; Waring, P. *Aust. J. Chem.* **1993**, *46*, 1743−1754. (q) Wu, Z.; Williams, L. J.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 3866−3868. (r) Aliev, A. E.; Hilton, S. T.; Motherwell, W. B.; Selwood, D. L. *Tetrahedron Lett.* **2006**, *47*, 2387−2390.

(5) For synthetic studies toward cyclotryptophan-containing ETPs by other groups, see: (a) Crich, D.; Fredette, E.; Flosi, W. J. *Heterocycles* **1998**, *48*, 545−547. (b) Yamada, F.; Goto, A.; Somei, M. *Heterocycles* **2000**, *53*, 1255−1258.

(6) For the recent total synthesis of a related, structurally simpler cyclotryptophan alkaloid, see: Overman, L. E.; Shin, Y. *Org. Lett.* **2007**, *9*, 339−341.

(7) For an early example of 1,5-radical translocation from a protecting group, see: Curran, D. P.; Kim, D.; Liu, H. T.; Shen, W. *J. Am. Chem. Soc.* **1988**, *110*, 5900−5902.

(8) For examples of C−H bond oxidation α to oxygen of alcohol derivatives, see: (a) Lewin, A. H.; Dinwoodie, A. H.; Cohen, T. *Tetrahedron* **1966**, *22*, 1527−1537. (b) Curran, D. P.; Yu, H. *Synthesis* **1992**, 123−127. (c) Han, G.; McIntosh, M. C.; Weinreb, S. M. *Tetrahedron Lett.* **1994**, *35*, 5813−5816.

(9) For examples of C−H bond oxidation δ to oxygen of alcohol derivatives, see: (a) Barton, D. H. R.; Beaton, J. M.; Geller, L. E.; Pechet, M. M. *J. Am. Chem. Soc.* **1960**, *82*, 2640−2641. For recent reviews, see: (b) Majetich, G.; Wheless, K. *Tetrahedron* **1995**, *51*, 7095−7129. (c) Reese, P. B. *Steroids* **2001**, *66*, 481−497. (d) Togo, H.; Katohgi, M. *Synlett* **2001**, 565−581. (e) Čeković, Ž. *Tetrahedron* **2003**, *59*, 8073−8090.

(10) Intramolecular hydrogen atom abstraction β to a protected alcohol, followed by C−C bond formation or trapping with hydrogen has been described; see: (a) Brunckova, J.; Crich, D.; Yao, Q. *Tetrahedron Lett.* **1994**, *35*, 6619−6622. (b) Yamazaki, N.; Eichenberger, E.; Curran, D. P. *Tetrahedron Lett.* **1994**, *35*, 6623−6626. (c) Curran, D. P.; Xu, J. *J. Am. Chem. Soc.* **1996**, *118*, 3142−3147. (d) Moenius, T.; Andres, H.; Acemoglu, M.; Kohler, B.; Schnelli, P.; Zueger, C. *J. Labelled Compd. Radiopharm.* **2000**, *43*, 113−120. (e) Sukeda, M.; Matsuda, A.; Shuto, S. *Tetrahedron* **2005**, *61*, 7865−7873. (f) Sakaguchi, N.; Hirano, S.; Matsuda, A.; Shuto, S. *Org. Lett.* **2006**, *8*, 3291−3294.

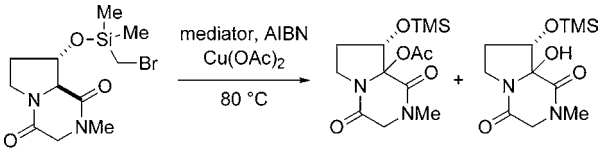
(11) Synthesis of 3-hydroxyproline derivative **6** is described in the Supporting Information.

(12) Parikh, J. R.; Doering, W. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505−5507.

60 °C with TBAF buffered with acetic acid to provide dioxopiperazine alcohol **11** in 73% yield (over two steps).[13] To allow selective oxidation at the angular position, this secondary alcohol was transformed in high yield to (bromomethyl)dimethylsiloxy ether **12** by reaction at room temperature with (bromomethyl)chlorodimethylsilane and Et_3N.[14]

The crucial radical-promoted functionalization of the angular carbon was initially developed with the more readily available bromomethylsilyl acetal **13** (Table 1).[15] Conditions

Table 1. Radical-Promoted Selective Oxidation of Bromomethylsilyl Ether **13**[a,b]



13 14 15

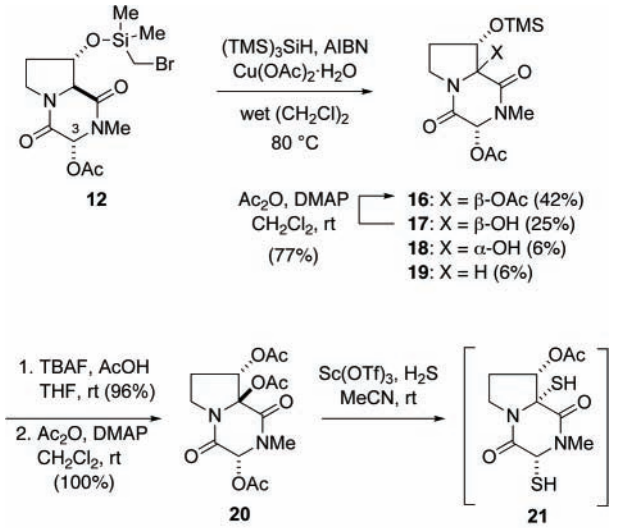
			yield (%)		
entry	mediator	solvent	**14**	**15**	**13**
1	Bu_3SnH	benzene	0	0	53
2	Bu_3GeH	benzene	16	0	40
3	$(TMS)_3SiH$	benzene	29	0	0
4	$(TMS)_3SiH$	MeCN	15	0	0
5	$(TMS)_3SiH$	DME	30	0	38
6	$(TMS)_3SiH$	$(CH_2Cl)_2$	37	27	23

[a] Conditions: 40 μmol of **13**, 3 equiv of mediator, 3 equiv of AIBN, 10 equiv of $Cu(OAc)_2$, solvent (0.02 M), 80 °C. [b] The relative configurations of **14** and **15** were not determined.

that favor oxidative termination were examined, on the assumption that single-electron transfer from the primary radical derived from **13** would be slower than oxidation of the more electron-rich captodative radical produced upon 1,5-hydrogen atom transfer.[16] Attempted reaction of **13** with 3 equiv of Bu_3SnH and 3 equiv of AIBN in benzene at 80 °C in the presence of a large excess of $Cu(OAc)_2$ led only to recovered starting material, as tributyltin hydride and $Cu(OAc)_2$ reacted rapidly under these conditions (entry 1). However, when the weaker reducing agent tributylgermanium hydride was employed, the desired acetate **14** was isolated in 16% yield, together with recovered starting material (entry 2). Tris(trimethylsilyl)silane proved to be the best radical mediator, providing **14** in 29% yield (entry 3). The nature of the solvent had some effect on reaction efficiency (entries 3−6). Best results were obtained in $(CH_2Cl)_2$, wherein acetate **14** (37% yield) and alcohol **15** (27% yield) were the major products produced (entry 6), corresponding to 64% efficiency in selectively oxidizing the angular carbon. A large excess of $Cu(OAc)_2$ and excess AIBN and tris(trimethylsilyl)silane are required because of competing redox side reactions between these reagents.

Encouraged by the success in selectively oxidizing the angular carbon of model substrate **13**, we turned our attention to 3-acetoxyhydropyrrolopyrazine-1,4-dione **12** (Scheme 3).

Scheme 3



X-ray model of **23**

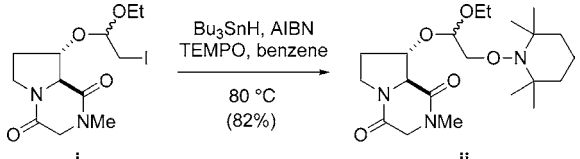
Radical-promoted oxidation of this substrate using the conditions optimized with bromide **13** (Table 1, entry 6) provided acetate **16** and alcohols **17** and **18** as major products. Also produced in significant amounts was the reduced product **19**. Modifying the procedure slightly by adding a solution of tris(trimethylsilyl)silane and AIBN to acetoxy substrate **12** and incorporating a trace amount of water[17] led to products of selective oxidation of the angular

(13) Attempted cleavage of the TBS group under several other conditions (TBAF, HF/pyridine, or MeOH in HCl) led to significant decomposition.

(14) For pioneering studies of the use of (bromomethyl)dimethylsiloxy ethers in free radical chain reactions, see: (a) Nishiyama, H.; Kitajima, T.; Matsumoto, M.; Itoh, K. *J. Org. Chem.* **1984**, *49*, 2298−2300. (b) Stork, G.; Kahn, M. *J. Am. Chem. Soc.* **1985**, *107*, 500−501.

(15) The synthesis of α-bromomethylsilyl **13** is described in the Supporting Information.

(16) In an early calibration experiment, the reaction of iodoacetal **i** with tributyltin hydride, AIBN, and TEMPO in benzene at 85 °C resulted only in substitution at the acetal substituent to provide TEMPO adduct **ii**. This result showed that the primary radical derived from **i** was trapped with TEMPO faster than it underwent 1,5-hydrogen atom transfer.



i ii

carbon being isolated in 73% combined yield: β-acetate **16** (42%), β-alcohol **17** (25%), and α-alcohol **18** (6%).[18,19]

The major products of angular oxidation were transformed to epidithiodioxopiperazine congeners **22** and **23** as follows. First, alcohol **17** was converged with acetate **16** by reaction with acetic anhydride in the presence of DMAP (Scheme 3). Next, the trimethylsiloxy group of intermediate **16** was converted to an acetate in two standard steps in high yield. Finally, reaction of triacetate **20** with excess hydrogen sulfide and a catalytic amount of scandium triflate in acetonitrile provided dithiol **21**, which upon exposure to oxygen gave a single epidithiodioxopiperazine product **22** in 37% yield.[20] The success of this transformation was highly dependent upon the choice of solvent for the first step; the desired dithiol was not isolated when CH_2Cl_2, benzene, Et_2O, or $MeNO_2$ were substituted for acetonitrile. Extensive NMR analysis failed to conclusively establish the relative configuration of the disulfide bridge. Therefore, the acetyl group of epidithiodioxopiperazine **22** was removed by reaction with 1 equiv of scandium triflate in MeOH/MeCN at room temperature to give the crystalline alcohol **23**, mp 198−199 °C (dec), in quantitative yield.[21] Single-crystal X-ray analysis of this product established that the hydroxyl substituent and the disulfide bridge are cis,[22] indicating the absence of acetate participation in the addition of H_2S to the angular carbon. The observed 1,2-cis stereoselectivity in this addition step is in accord with the Woerpel model for stereoselection in the addition of nucleophiles to five-membered oxocarbenium ions (and related *N*-acyliminium ions) containing oxygen substituents adjacent to the electrophilic carbon.[23]

In summary, a procedure for selective oxidation of the angular methine carbon of hydroxyproline-derived dioxopiperazines to allow a dithio bridge to be introduced into such heterocyclic frameworks is reported. The protecting-group-directed C−H bond oxidation that is a key step in this sequence likely will be useful for the regioselective oxidative elaboration of other polyfunctional organic molecules.

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Supporting Information Available: Experimental procedures and copies of ^1H and ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) These modifications were developed during contemporaneous studies of the oxidation of an analogue of **12** having an isopropylidene substituent at C3.

(18) The relative configuration of these products was determined by NOESY NMR experiments; see the Supporting Information for details.

(19) Experiments aimed at decreasing the excess of reagents employed showed that the amount of $Cu(OAc)_2$ could be reduced to 7 equiv; however, yields of angular oxidation were maximized by using an equal excess of the silane.

(20) The construction of epidithiodioxopiperazines from dioxopiperazines that contain two leaving groups by $ZnCl_2$-promoted reaction of H_2S has been reported; see refs 4d, 4e, 4k, and 4l.

(21) More conventional conditions for removing the acetate group were not compatible with the disulfide bridge.

(22) CCDC 663428. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(23) Larsen, C. H.; Ridgway, B. H.; Shaw, J. T.; Smith, D. M.; Woerpel, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 10879−10884.