Alkaloid Synthesis

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Total Synthesis of (+)-MPC1001B

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Abstract: *The first total synthesis of an epidithiodiketopiperazine alkaloid, (+)-MPC1001B, was accomplished. This synthesis features a tetra-n-butylammonium fluoride mediated intramolecular aldol reaction for forming the 15-membered macrolactone ring, and the construction of an epidithiodiketopiperazine substructure through a stepwise sulfenylation reaction involving a novel trityl trisulfide (TrSSS)-group transfer.*

Epidithiodiketopiperazines (ETPs) have attracted considerable attention owing to their broad range of biological activities and diverse structures.[1,2] This family of compounds includes MPC1001s [MPC1001B (**1**) and MPC1001 (**2a**)],[3] emestrin (**2b**),[4] acetylaranotin (**3**),[5] SCH64874 (**4**),[6] compound **5**,[7] emethallicin A (**6**),[8] and acetylapoaranotin (**7**; Figure 1).[9] These compounds possess unique seven-membered dihydrooxepines, and they display biological activities such as antiproliferative activity against the DU145 human prostate cancer cell line,[3] chemokine receptor (CCR2) antagonist activity,[4c] inhibitory activity against viral RNA polymerase,[5] epidermal growth factor receptor (EGFR) antagonist activity,[6] potent antituberculous activity,[7] inhibitory activity of histamine release,[8] and an apoptosis-inducing effect toward the HCT116 colon cancer cell line.[9] Therefore, substantial efforts have been made to develop routes to these dihydrooxepine natural products.[10] To date, only two total syntheses of acetylaranotin (**3**) have been reported, one by Reisman et al. and the other by our group.[11] Some synthetic studies of pyrrolidine-fused dihydrooxepines have also been reported.[2b,10b,c,12] No synthesis of the subfamily of dihydrooxepine natural products with a characteristic 15-membered macrolactone (**1** and **2**) has been achieved. During our work on ETPs, we became particularly interested in MPC1001B (**1**) and MPC1001 (**2a**), which were isolated by Onodera and Kanda et al. in 2004.[3] Herein, we report the first total synthesis of MPC1001B (**1**), which was accomplished through a TBAF-mediated aldol macrocyclization and the stepwise introduction of two sulfur moieties.

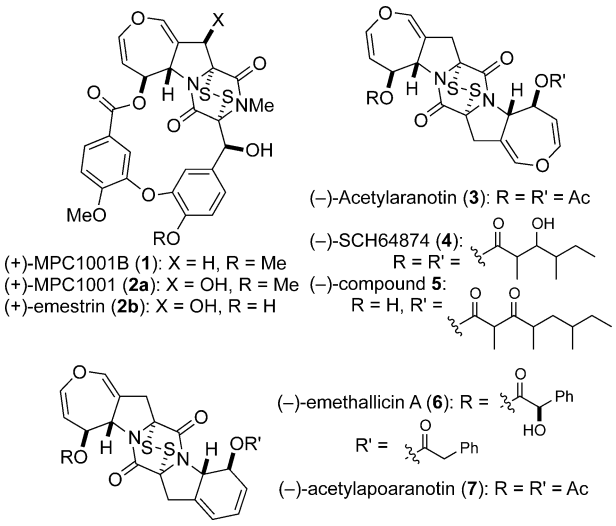
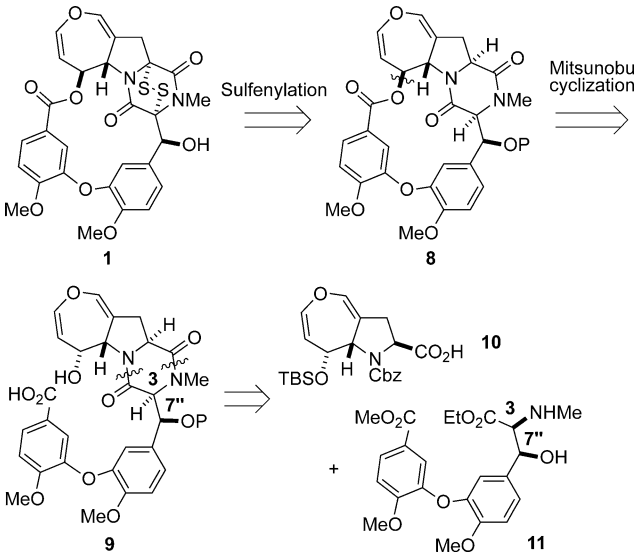


Figure 1. MPC1001 and related dihydrooxepine ETPs.

The major challenges for synthesizing MPC1001s include diastereoselective construction of the characteristic 15-membered ring, and the labile aldol substructure in dithiodiketopiperazine. Because the disulfide bond is unstable in the presence of bases, nucleophiles, and oxidants,[2a] we planned to introduce this sulfur functionality toward the end of the synthesis (Scheme 1). We envisaged that an intramolecular Mitsunobu reaction[13] could provide macrocycle **8** from seco-acid **9**. This would be prepared from dihydrooxepine unit **10**, which is a synthetic intermediate in our total synthesis of acetylaranotin (**3**),[11b] and β-hydroxy amino acid derivative **11**.



Scheme 1. Retrosynthetic analysis. TBS = *tert*-butyldimethylsilyl, Cbz = benzyloxycarbonyl.

We first prepared seco-acid **15**, which is the substrate for an intramolecular Mitsunobu reaction, from carboxylic acid

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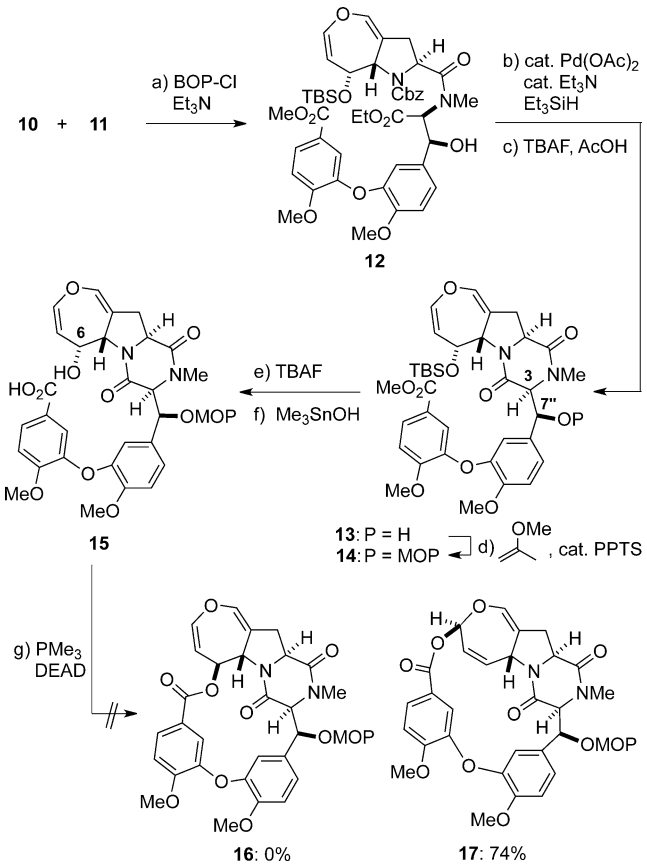
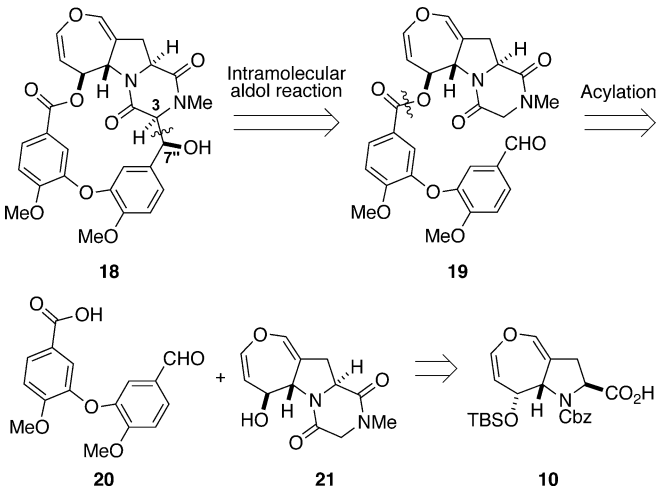


Scheme 2. Unsuccessful Mitsunobu cyclization strategy. Reagents and conditions: a) BOP-Cl, Et_3N, CH_2Cl_2, RT, 67%; b) Et_3SiH, cat. $Pd(OAc)_2$, cat. Et_3N, CH_2Cl_2, reflux; c) TBAF, AcOH, THF, RT, 71% (2 steps); d) 2-methoxypropene, cat. PPTS, CH_2Cl_2, 0°C; e) TBAF, THF, 0°C, 74% (2 steps); f) Me_3SnOH, DCE, 80°C; g) PMe_3, DEAD, THF/toluene, RT, 74%. BOP-Cl = bis(2-oxo-3-oxazolidinyl)phosphonyl chloride, MOP = 2-methoxy-2-propyl, TBAF = tetra-*n*-butylammonium fluoride, PPTS = pyridinium 4-toluenesulfonate, DEAD = diethyl azodicarboxylate, THF = tetrahydrofuran.

10[11] and a β-hydroxyphenylalanine derivative **11**[14] (Scheme 2). Carboxylic acid **10** was then condensed with amine **11** in the presence of BOP-Cl to afford the corresponding amide **12**. Diketopiperazine **13** was prepared through Pd-catalyzed hydrogenolysis of the Cbz group, which was followed by treatment with TBAF to promote cyclization. Because the unprotected benzylic alcohol **13** underwent a retro-aldol-type fragmentation of the C3–C7″ bond after treatment with TBAF, we protected alcohol **13** as a 2-methoxy-2-propyl (MOP) acetal **14**. Removal of the TBS group and subsequent hydrolysis with Me_3SnOH[15] provided the corresponding seco-acid **15**. However, the desired 15-membered macrocycle **16** was not obtained under Mitsunobu conditions; instead the regioisomer **17** was isolated in 74% yield. Note that macrolactonization of the C6-epimer of **15** under Shiina's conditions was unsuccessful.[16]

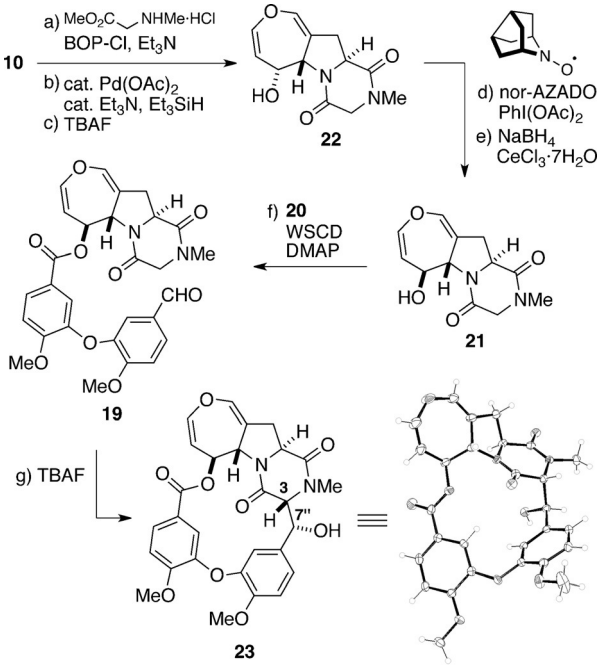
The failure of the Mitsunobu cyclization strategy led us to investigate an alternative strategy for constructing the 15-membered ring (Scheme 3). We then focused on the aldol structure in the proposed key intermediate **18** and planned to



Scheme 3. Intramolecular aldol strategy for macrocyclization.

execute an intramolecular aldol reaction to form the C3–C7″ bond. Retrosynthetic disconnection of the ester in substrate **19** leads to the anisic acid derivative **20** and dihydrooxepine **21**, which should be readily accessible from compound **10**.

The synthesis of substrate **19** for the key aldol cyclization commenced with the condensation of carboxylic acid **10** and sarcosine methyl ester by using BOP-Cl (Scheme 4). Removal of the Cbz group and the TBS group gave alcohol **22**.



Scheme 4. Construction of the 15-membered ring. Reagents and conditions: a) sarcosine (*N*-methylglycine) methyl ester·HCl, BOP-Cl, Et_3N, CH_2Cl_2, RT, 95%; b) Et_3SiH, cat. $Pd(OAc)_2$, cat. Et_3N, CH_2Cl_2, reflux, 94%; c) TBAF, THF, RT, 97%; d) cat. nor-AZADO, $PhI(OAc)_2$, CH_2Cl_2, RT, 86%; e) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, CH_2Cl_2/EtOH, −78°C, 93%; f) **20**, WSCD, cat. DMAP, CH_2Cl_2, RT, quant; g) TBAF, THF, RT, 71%. nor-AZADO = 9-azanoradamantane-*N*-oxyl, WSCD = water soluble carbodiimide, DMAP = 4-dimethylaminopyridine.

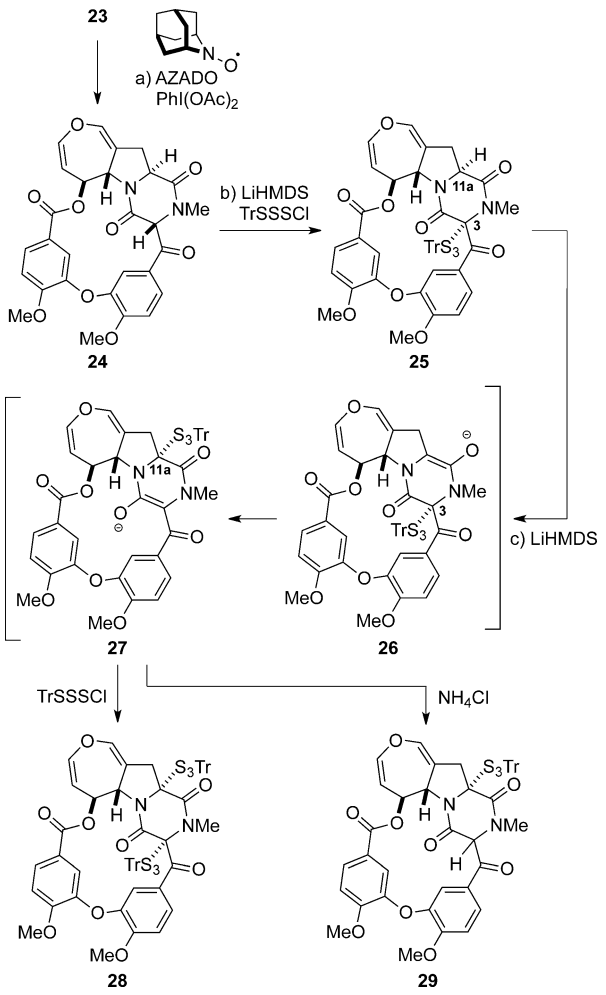
Stereochemical inversion of the hydroxy group was performed in two steps;[11b] nor-AZADO-catalyzed oxidation[17] and Luche reduction afforded **21**, which was condensed with carboxylic acid **20**[18] to provide **19**. To our delight, the crucial formation of the 15-membered ring was effected by TBAF[19,20] to afford the desired compound **23** as a single diastereomer in 71% yield. However, X-ray crystallographic analysis revealed that the stereochemistries of the C3 and C7″ positions were opposite to those of MPC1001B.[21] Nevertheless, we examined the introduction of the sulfur functionality before inversion of the stereochemistry at the C7″ position.

Based on Nicolaou's previously reported methods,[2b,22] we attempted to introduce sulfur moieties under basic conditions. However, we observed cleavage of the C3–C7″ bond of **23** through a retro-aldol reaction.[23] To prevent this undesired reaction, we planned to introduce the two requisite sulfur moieties after oxidation of the secondary alcohol **23** to the corresponding ketone (Scheme 5). Moreover, we expected a smooth deprotonation/sulfenylation reaction owing to the properties of the 1,3-ketoamide structure.[24] The secondary alcohol was oxidized by using catalytic AZADO in a CH_2Cl_2/phosphate buffer (pH 7.4) to afford the dicarbonyl compound **24**.[17,25] Consecutive treatment of diketopiperazine **24** with LiHMDS at −78 °C and TrSSSCl[26] afforded **25** in 88% yield. The desired bis(trisulfide) **28** was obtained in 60% yield through another successive cycle of LiHMDS and TrSSSCl treatments.

During our investigation on the second sulfenylation reaction, we found that the TrSSS group migrated from the C3 position to the C11a position.[27] Compound **25** was thus completely consumed when it was subjected to LiHMDS. After an acidic workup with aqueous ammonium chloride, compound **29** was isolated in 41% yield. The unexpected trisulfide migration might have proceeded via enolate **27**, because the anionic species is better stabilized by its two adjacent carbonyl groups compared to the initial enolate **26**.[28]

We finally achieved the total synthesis of MPC1001B (**1**) through reduction of the ketone and formation of the disulfide bond (Scheme 6). The carbonyl group in **28** was chemo- and diastereoselectively reduced under Luche conditions at −78 °C in CH_2Cl_2/EtOH,[11] without affecting the trisulfide moiety.[29,30] The final formation of the disulfide bond was sluggish because of concomitant C–S bond cleavage at the C3 position and retro-aldol-type fragmentation with conventional reagents such as $NaBH_4$[2b,22] or 1,3-propanedithiol.[11] Further investigation revealed that sodium 2-mercaptoethanesulfonate (MESNa),[31] which has been used in the cleavage of a disulfide bond in a complex glycopeptide, successfully facilitated the removal of the TrSS groups. The resultant dithiol was treated with oxygen to afford MPC1001B (**1**) in 33% yield.

In conclusion, we accomplished the total synthesis of (+)-MPC1001B (**1**) for the first time. This synthesis features TBAF-mediated formation of the 15-membered ring and stepwise introduction of bis-trisulfide through migration of the trisulfide group.



Scheme 5. Stepwise introduction of two TrSSS-groups. Reagents and conditions: a) cat. AZADO, $PhI(OAc)_2$, CH_2Cl_2, pH 7.4 phosphate buffer, RT, 79% (d.r. = 9:1); b) LiHMDS, TrSSSCl, THF, −78 °C, 88%; c) LiHMDS, TrSSSCl, THF, −78 °C, 60% (**25**→**28**); LiHMDS, THF, −78 °C, then aq. NH_4Cl, 41% (**25**→**29**). AZADO = 2-azaadamantane-*N*-oxyl, LiHMDS = lithium hexamethyldisilazanide, TrSSSCl = chloro(triphenylmethyl)trisulfane.

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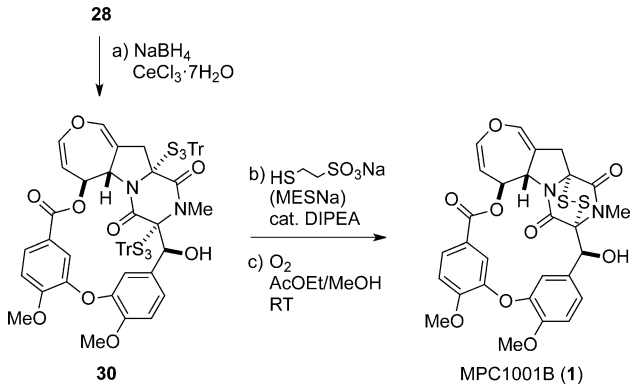

Scheme 6. Total synthesis of MPC1001B (**1**). Reagents and conditions: a) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, CH_2Cl_2/EtOH, −78 °C, quant; b) MESNa, cat. DIPEA, DMF/H_2O, RT; c) O_2, AcOEt/MeOH, RT, 33% (2 steps). MESNa = sodium 2-mercaptoethanesulfonate, DIPEA = *N*,*N*-diispropylethylamine.

Keywords: aldol reaction · alkaloids · dithiodiketopiperazine · macrolactones · total synthesis

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Angew. Chem. **2016**, *128*, 291–295

[1] For recent reviews, see: a) C.-S. Jiang, Y.-W. Guo, *Mini-Rev. Med. Chem.* **2011**, *11*, 728–745; b) E. M. Fox, B. J. Howlett, *Mycol. Res.* **2008**, *112*, 162–169; c) D. M. Gardiner, P. Waring, B. J. Howlett, *Microbiology* **2005**, *151*, 1021–1032; d) C.-J. Guo, H.-H. Yeh, Y.-M. Chiang, J. F. Sanchez, S.-L. Chang, K. S. Bruno, C. C. C. Wang, *J. Am. Chem. Soc.* **2013**, *135*, 7205–7213; e) T. R. Welch, R. M. Williams, *Nat. Prod. Rep.* **2014**, *31*, 1376–1404; f) S. Bräse, A. Encinas, J. Keck, C. F. Nising, *Chem. Rev.* **2009**, *109*, 3903–3990; g) A. D. Borthwick, *Chem. Rev.* **2012**, *112*, 3641–3716.

[2] Isolation and total synthesis of the representative ETPs: Gliotoxin: a) T. Fukuyama, S. Nakatsuka, Y. Kishi, *Tetrahedron* **1981**, *37*, 2045–2078; b) K. C. Nicolaou, M. Lu, S. Totokotsopoulos, P. Heretsch, D. Giguère, Y.-P. Sun, D. Sarlah, T. H. Nguyen, I. C. Wolf, D. F. Smee, C. W. Day, S. Bopp, E. A. Winzeler, *J. Am. Chem. Soc.* **2012**, *134*, 17320–17332; Hyalodendrin: c) G. M. Strunz, M. Kakushima, M. A. Stillwell, C. J. Heissner, *J. Chem. Soc. Perkin Trans. 1* **1973**, 2600–2602; d) R. Takeuchi, J. Shimokawa, T. Fukuyama, *Chem. Sci.* **2014**, *5*, 2003–2006; Chaetocin A: e) D. Hauser, H. P. Weber, H. P. Sigg, *Helv. Chim. Acta* **1970**, *53*, 1061–1073; f) J. Kim, M. Movassaghi, *J. Am. Chem. Soc.* **2010**, *132*, 14376–14378; g) E. Iwasa, Y. Hamashima, S. Fujishiro, D. Hashizume, M. Sodeoka, *Tetrahedron* **2011**, *67*, 6587–6599; T988C: h) Y. Feng, J. W. Blunt, A. L. J. Cole, M. H. G. Munro, *J. Nat. Prod.* **2004**, *67*, 2090–2092; i) J. E. DeLorbe, D. Horne, R. Jove, S. M. Mennen, S. Nam, F.-L. Zhang, L. E. Overman, *J. Am. Chem. Soc.* **2013**, *135*, 4117–4128.

[3] a) N. Tsumagari, R. Nakai, H. Onodera, A. Hasegawa, E. S. Rahayu, K. Ando, Y. Yamashita, *J. Antibiot.* **2004**, *57*, 532–534; b) H. Onodera, A. Hasegawa, N. Tsumagari, R. Nakai, T. Ogawa, Y. Kanda, *Org. Lett.* **2004**, *6*, 4101–4104.

[4] a) H. Seya, S. Nakajima, K. Kawai, S. Udagawa, *J. Chem. Soc. Chem. Commun.* **1985**, 657–658; b) H. Seya, K. Nozawa, S. Nakajima, K. Kawai, S. Udagawa, *J. Chem. Soc. Perkin Trans. 1* **1986**, 109–116; c) K. B. Herath, H. Jayasuriya, J. G. Ondeyka, J. D. Polishook, G. F. Bills, A. W. Dombrowski, A. Cabello, P. P. Vicario, H. Zweerink, Z. Guan, S. B. Singh, *J. Antibiot.* **2005**, *58*, 686–694.

[5] a) N. Neuss, L. D. Boeck, D. R. Brannon, J. C. Cline, D. C. DeLong, M. Gorman, L. L. Huckstep, D. H. Lively, J. Mabe, M. M. Marsh, B. B. Molloy, R. Nagarajan, J. D. Nelson, W. M. Stark, *Antimicrob. Agents Chemother.* **1968**, 213–219; b) P. W. Trown, H. F. Lindh, K. P. Milstrey, V. M. Gallo, B. R. Mayberry, H. L. Lindsay, P. A. Miller, *Antimicrob. Agents Chemother.* **1968**, 225–228; c) R. Nagarajan, L. L. Huckstep, D. H. Lively, D. C. DeLong, M. M. Marsh, N. Neuss, *J. Am. Chem. Soc.* **1968**, *90*, 2980–2982; d) N. Neuss, R. Nagarajan, B. B. Molloy, L. L. Huckstep, *Tetrahedron Lett.* **1968**, *9*, 4467–4471; e) R. Nagarajan, N. Neuss, M. M. Marsh, *J. Am. Chem. Soc.* **1968**, *90*, 6518–6519; f) D. B. Cosulich, N. R. Nelson, J. H. van den Hende, *J. Am. Chem. Soc.* **1968**, *90*, 6519–6521; g) K. C. Murdock, *J. Med. Chem.* **1974**, *17*, 827–835.

[6] V. R. Hegde, P. Dai, M. Patel, P. R. Das, M. S. Puar, *Tetrahedron Lett.* **1997**, *38*, 911–914.

[7] M. Isaka, P. Kittakoop, K. Kirtikara, N. L. Hywel-Jones, Y. Thebtaranonth, *Acc. Chem. Res.* **2005**, *38*, 813–823.

[8] N. Kawahara, S. Nakajima, M. Yamazaki, K. Kawai, *Chem. Pharm. Bull.* **1989**, *37*, 2592–2595.

[9] E. J. Choi, J.-S. Park, Y.-J. Kim, J.-H. Jung, J. K. Lee, H. C. Kwon, H. O. Yang, *J. Appl. Microbiol.* **2010**, *110*, 304–313.

[10] a) L. Wang, D. L. J. Clive, *Tetrahedron Lett.* **2012**, *53*, 1504–1506; b) J. Peng, D. L. J. Clive, *J. Org. Chem.* **2009**, *74*, 513–519; c) J. Peng, D. L. J. Clive, *Org. Lett.* **2007**, *9*, 2939–2941; d) P. T. Schuber, R. M. Williams, *Heterocycles* **2012**, *84*, 1193–1207; e) P. T. Schuber, R. M. Williams, *Tetrahedron Lett.* **2012**, *53*, 380–382.

[11] a) J. A. Codelli, A. L. A. Puchlopek, S. E. Reisman, *J. Am. Chem. Soc.* **2012**, *134*, 1930–1933; b) H. Fujiwara, T. Kurogi, S. Okaya, K. Okano, H. Tokuyama, *Angew. Chem. Int. Ed.* **2012**, *51*, 13062–13065; *Angew. Chem.* **2012**, *124*, 13239–13242.

[12] a) R. M. Goodman, *Ph. D. Thesis*, *Harvard University*, **1998**; b) R. M. Goodman, Y. Kishi, *J. Am. Chem. Soc.* **1998**, *120*, 9392–9393.

[13] a) O. Mitsunobu, *Synthesis* **1981**, 1–28; b) K. C. K. Swamy, N. N. B. Kumar, E. Balaraman, K. V. P. P. Kumar, *Chem. Rev.* **2009**, *109*, 2551–2651.

[14] For the details on preparation of **11**, see the Supporting Information. The β-hydroxyphenylalanine structure was constructed according to Boger's method. D. L. Boger, M. A. Patane, J. Zhou, *J. Am. Chem. Soc.* **1994**, *116*, 8544–8556.

[15] K. C. Nicolaou, A. A. Estrada, M. Zak, S. H. Lee, B. S. Safina, *Angew. Chem. Int. Ed.* **2005**, *44*, 1378–1382; *Angew. Chem.* **2005**, *117*, 1402–1406.

[16] For the details, see the Supporting Information.

[17] a) M. Shibuya, M. Tomizawa, I. Suzuki, Y. Iwabuchi, *J. Am. Chem. Soc.* **2006**, *128*, 8412–8413; b) M. Hayashi, Y. Sasano, S. Nagasawa, M. Shibuya, Y. Iwabuchi, *Chem. Pharm. Bull.* **2011**, *59*, 1570–1573.

[18] For the details on the preparation of **20**, see the Supporting Information.

[19] a) Y. Ito, N. Higuchi, M. Murakami, *Heterocycles* **2000**, *52*, 91–93; b) B. Xu, G. B. Hammond, *Angew. Chem. Int. Ed.* **2008**, *47*, 689–692; *Angew. Chem.* **2008**, *120*, 701–704; c) J. C. Aponte, G. B. Hammond, B. Xu, *J. Org. Chem.* **2009**, *74*, 4623–4625; d) J.-L. Zhang, Y.-F. Gong, *Org. Lett.* **2011**, *13*, 176–179; e) J. Zhang, L. Gu, Y. Gong, *Synlett* **2012**, *23*, 468–472.

[20] The reported conditions for an intramolecular aldol reaction using TBSOTf or other base did not provide a 15-membered macrocyclic compound at all. For details, see the Supporting Information.

[21] Mitsunobu reaction of alcohol **23** provided the corresponding acetate with complete retention of the stereochemistry of the alcohol. For details, see the Supporting Information.

[22] a) K. C. Nicolaou, S. Totokotsopoulos, D. Giguère, Y.-P. Sun, D. Sarlah, *J. Am. Chem. Soc.* **2011**, *133*, 8150–8153; b) K. C.

Nicolaou, D. Giguère, S. Totokotsopoulos, Y.-P. Sun, *Angew. Chem. Int. Ed.* **2012**, *51*, 728 – 732; *Angew. Chem.* **2012**, *124*, 752 – 756.

[23] Treatment of the MOP ether derived from **23** under Nicolaou's conditions resulted in E1cB elimination to provide the dehydrated compound. For details, see the Supporting Information.

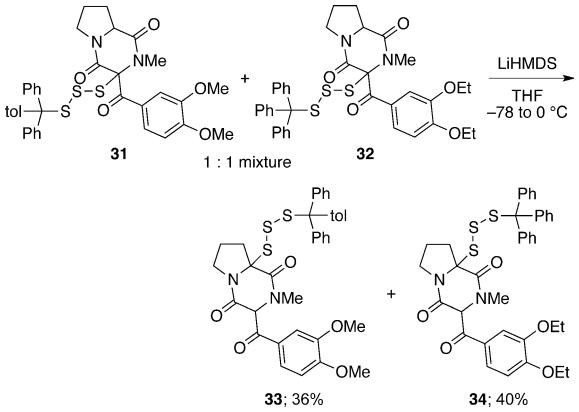
[24] a) T. Hino, T. Sato, *Chem. Pharm. Bull.* **1974**, *22*, 2866 – 2874; b) R. M. Williams, W. H. Rastetter, *J. Org. Chem.* **1980**, *45*, 2625 – 2631; c) R. Dubey, N. W. Polaske, G. S. Nichol, B. Olenyuk, *Tetrahedron Lett.* **2009**, *50*, 4310 – 4313; d) N. W. Polaske, R. Dubey, G. S. Nichol, B. Olenyuk, *Tetrahedron: Asymmetry* **2009**, *20*, 2742 – 2750 (In this paper, an intermolecular bis-sulfenylation proceeded in an *anti* fashion).

[25] The formation of epidithiodiketopiperazine in a one-pot fashion by utilizing Nicolaou's procedure was also unsuccessful in this case.

[26] C. R. Williams, J. F. Britten, D. N. Harpp, *J. Org. Chem.* **1994**, *59*, 806 – 812. Movassaghi and co-workers used diketopiperazine having TrSSS-group as the intermediate for the total synthesis of (+)-chaetocin C (See, ref. [2f]).

[27] R. M. Williams, O. P. Anderson, R. W. Armstrong, J. Josey, H. Meyers, C. Eriksson, *J. Am. Chem. Soc.* **1982**, *104*, 6092 – 6099.

[28] Because the corresponding bis(trisulfide) **28** was not observed at all under conditions without TrSSSCl (**25**→**29**), we speculated that this migration (**26**→**27**) occurs in an intramolecular fashion. Moreover, a preliminary crossover experiment with two analogous trisulfides (see below) did not afford any intermolecular sulfur transfer products upon treatment with LiHMDS, which also strongly supports an intramolecular transfer process..



[29] The stereochemistries of compounds **25**, **28**, **29**, and **30** are tentatively assigned as shown in Scheme 5 and 6 based on the fact that MPC1001B (**1**) was obtained from compound **25** through **28** and **30**.

[30] The diastereoselectivity of this reduction is discussed in the Supporting Information.

[31] M. Mandal, V. Y. Dudkin, X. Geng, S. J. Danishefsky, *Angew. Chem. Int. Ed.* **2004**, *43*, 2557 – 2561; *Angew. Chem.* **2004**, *116*, 2611 – 2615.

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