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An Efficient Synthesis Strategy to the Core Structure of 6–5–6–5–6-Membered Epipolythiodiketopiperazines

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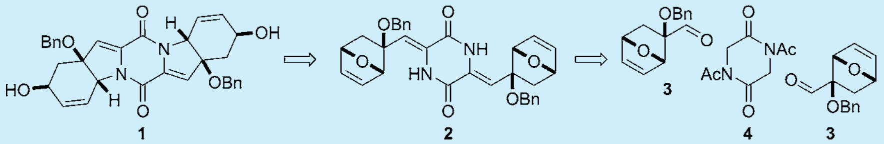
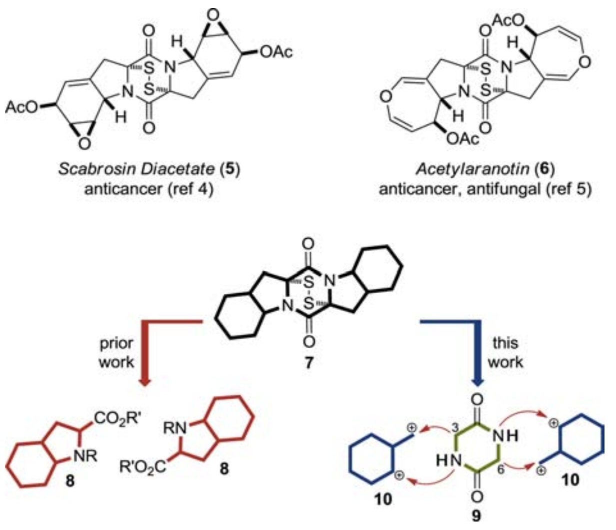
S *Supporting Information*



ABSTRACT: A concise route to the core structure **1** of 6–5–6–5–6-membered epipolythiodiketopiperazines is described. The strategy relies on construction of the pyrrolines by double nucleophilic opening of a *bis*(oxabicyclo[2.2.1]heptene) **2**, obtained after bidirectional condensation of *N,N*′-diacetyldiketopiperazine (**4**) with aldehyde **3**.

The 2,5-diketopiperazine structural motif is found in a wide variety of natural products and therapeutic agents.[1] Among the myriad of natural products constructed around this core, the 6–5–6–5–6- and 7–5–6–5–7-membered epipolythiodiketopiperazines (ETPs) are particularly intriguing. Their structural complexity along with their anticancer, antiviral, and antifungal activity provide compelling reasons for considerable interest in this class of natural products (Scheme 1).[2,3]

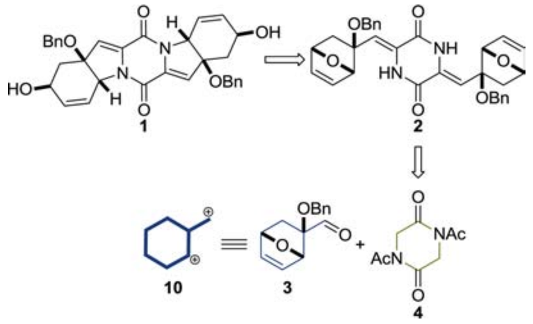
Scheme 1. Strategies towards 6–5–6–5–6-Membered Epipolythiodiketopiperazines



The published syntheses of members of this hexacyclic subgroup are characterized by late-stage assembly of a central diketopiperazine core.[3] We became interested in examining an alternative approach in which the unsubstituted diketopiperazine **9** serves as a preassembled linchpin. In such a strategy, installation of the C3 and C6 substituents and subsequent bidirectional ring-forming reactions would allow rapid access to the embedded fused pyrrolidines. Herein, we document the realization of such an approach which demonstrates an efficient entry into the full core structure of 6-5-6-5-6-membered ETPs. The modular approach of this strategy also enables access to analogues of ETP natural products, which are of interest in the context of SAR studies.[6]

Diketopiperazine **1** was chosen as a target compound on which to examine the viability of the synthetic strategy, as it would enable late-stage diversification into a wide series of ETP natural and non-natural products (Scheme 2). In this approach, **1** was envisioned to be accessible by Lewis acid-mediated nucleophilic opening of the *bis*(oxabicyclo[2.2.1]heptene) **2** using methods recently developed in our group.[7,8] Cyclization precursor **2** was disconnected to diketopiperazine **4** and α-oxygenated aldehyde **3**.

Scheme 2. Retrosynthetic Strategy



Oxabicyclic α-oxygenated aldehydes such as **3** have not been subjected to study; in fact, to the best of our knowledge, there is only one reported synthesis of such a compound.[9a] Initial thoughts on the preparation of *endo*-aldehyde **3** by Diels–Alder-

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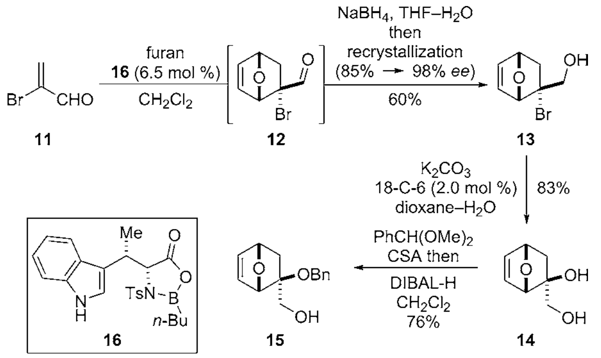
cycloaddition of an α-oxygenated acrolein derivative were set aside, because furan Diels−Alder reactions are generally known to have varying degrees of *exo*-selectivity.[10] In addition, the Lewis acid catalyzed reaction of α-silyloxy acrolein derivatives with furan furnishes (4 + 3)-, rather than (4 + 2)-cycloadducts.[9b−e] We were intrigued by the findings of Corey and Loh who prepared diol **14** starting from bromoacrolein **11** (Scheme 3).[11]

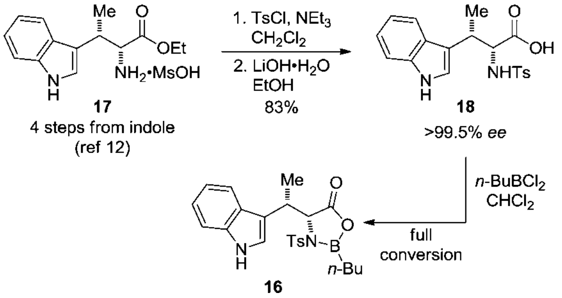
Scheme 3. Synthesis of Alcohol 15



In their key step, the Diels−Alder cycloaddition reaction of bromoacrolein **11** with furan, 10 mol % of oxazaborolidinone **16** were used to prepare α-bromoaldehyde **12**. Inspired by this direct approach, we decided to thoroughly examine the entire reaction sequence in the context of scalability as well as the transformation of diol **14** into aldehyde **3**.

Catalyst precursor **18** was easily prepared in two steps from known β-methyltyrosine ethyl ester **17** which can be prepared as either enantiomer in four steps from indole (Scheme 4).[12]

Scheme 4. Synthesis of Catalyst 16



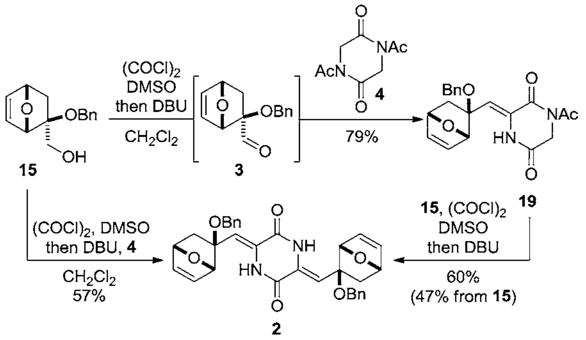
Overall, it was possible to obtain more than 50 g of **18** in >99.5% *ee* in one batch, in a process without chromatographic purification throughout the entire sequence.[13] The published procedure for the formation of oxazaborolidinone catalyst **16** describes refluxing a mixture of acid **18** and n-$BuB(OH)_2$ in toluene−THF with azeotropic removal of water at 110 °C over the course of 20 h. We decided to investigate a modification of this procedure commencing with n-$BuBCl_2$. In the event, the reaction of **18** and 1.0 equiv of n-$BuBCl_2$ in CH_2Cl_2 proceeded to completion at ambient temperature within 1 h to give **16**.[14]

Attention was then turned to the Diels−Alder reaction of bromoacrolein **11** with furan (Scheme 3). We were pleased to find that the reaction could be conducted with only 6.5 mol % of **16** to achieve full conversion to **12** as noted by thin layer chromatography. Due to its tendency to undergo cycloreversion, bromoaldehyde **12** was reduced immediately by adding the reaction mixture to a solution of $NaBH_4$ in THF−H_2O. The corresponding alcohol **13** could thus be obtained in 85% *ee*, which was determined by conversion to its benzoate and analysis by SFC on a chiral stationary phase. Recrystallization from ether−pentane furnished material in 60% overall yield and 98% *ee*.

Treatment of **13** with K_2CO_3 in dioxane−H_2O yielded diol **14**. Upon scale-up of the reported procedure, reaction time and yield were found to be highly variable, presumably due to the biphasic reaction mixture. It was found that addition of 2.0 mol % of 18-crown-6 as a phase transfer catalyst allowed the reaction to proceed reliably within 20 h and in 83% yield. Selective protection of the tertiary alcohol was then achieved by formation of the benzylidene acetal followed by one-pot reduction with DIBAL-H to give alcohol **15**. This route enabled the preparation of more than 20 g of alcohol **15** in a single batch.

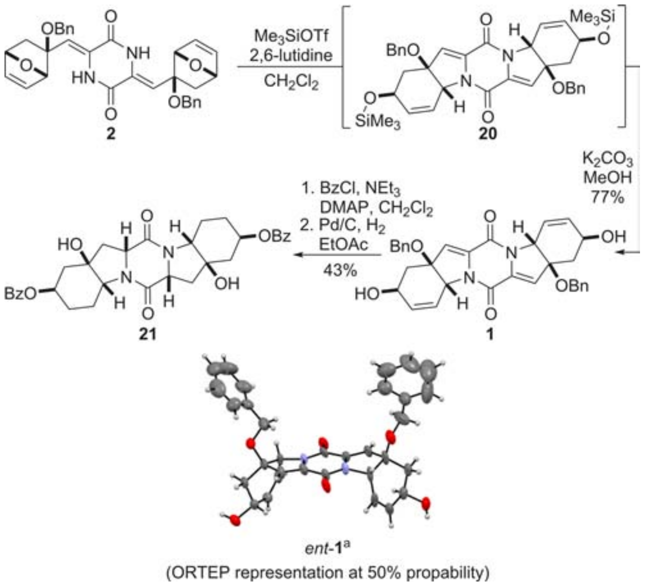
All attempts to isolate sensitive aldehyde **3** failed under a variety of oxidation conditions. Presumably, its instability arises from its tendency to undergo a retro-Diels−Alder reaction.[15] In order to circumvent this issue, we trapped aldehyde **3** *in situ* and at low temperature by condensation with diketopiperazine **4** (Scheme 5).[16] Swern oxidation of alcohol **15** yielded aldehyde **3** at −78 °C, which was directly subjected to condensation with *N,N′*-diacetyldiketopiperazine (**4**) to give olefin **19** in 79% yield. A second condensation with *in situ* prepared aldehyde **3** then yielded the desired cyclization precursor **2** in 47% yield over two steps. In the optimized procedure, the reaction sequence was performed in a one-pot operation by Swern oxidation of 2.6 equiv of alcohol **15** followed by the addition of one equivalent of diketopiperazine **4** to give *bis*(alkylidene)diketopiperazine **2** in an improved 57% yield. Careful control of the reaction temperature throughout the sequence was crucial in order to obtain high yields without decomposition of the sensitive aldehyde **3**.[15] Initial attempts with an $SiMe_2$*t*-Bu protected tertiary alcohol instead of a benzyl protecting group only gave a monocondensed product, and when reaction times were prolonged only decomposition was observed.

Scheme 5. Synthesis of Cyclization Precursor 2



The next step in the desired reaction sequence was the double intramolecular opening of the oxabicyclo[2.2.1]heptenes in **2** (Scheme 6). The transformation was found to proceed smoothly under slightly modified conditions from those originally reported, wherein triethyl amine was replaced with 2,6-lutidine.[7,8] The resulting silyl ether **20** was then directly deprotected with K_2CO_3 in MeOH to give **1** in 77% yield over two steps. The transformation proved to be robust and allowed the convenient preparation of more than 5 g of **1** in a single batch. X-ray crystallographic analysis unambiguously established the correct assignment of the structure. With **1** in hand, the core structure of 6−5−6−5−6−membered ETPs was completed. Because ETP

Scheme 6. Double Nucleophilic Opening of 2

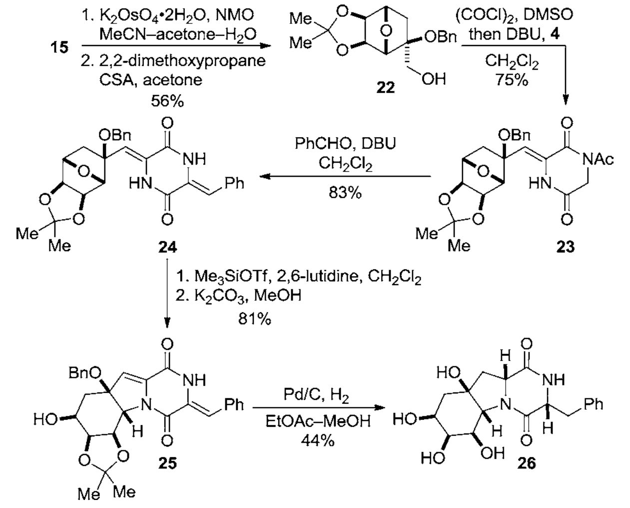


[a]X-ray crystal structure was obtained for *ent*-**1**. See Supporting Information for details.

natural products (see Scheme 1) incorporate pyrrolidines, the reduction of the pyrrolines was examined. Subjection of **1** to hydrogenation with Pd/C allowed the reduction of the enamides to furnish **21** in 43% yield over two steps as a single diastereoisomer, as determined by ^{1}H NMR spectroscopic analysis.

As a consequence of the interesting potential uses of ETPs in pharmacology, we sought to demonstrate the approach to implementation of the synthesis of structural analogues.[2] Therefore, alcohol **15** was subjected to dihydroxylation followed by protection to afford acetonide **22** (Scheme 7). Swern oxidation and *in situ* condensation with *N*,*N*′-diacetyldiketopiperazine (**4**) then gave olefin **23**. A second condensation with benzaldehyde, as a truncated mimic for other 5−6 ring systems, yielded **24** in 83% yield.[17] Me_3SiOTf-mediated ring opening of the oxabicyclo[2.2.1]heptane **24** proceeded uneventfully and delivered **25** in an excellent 81% yield after desilylation. Hydrogenation of **25** with concomitant acetonide cleavage led to completion of the synthesis of polyol **26** as a highly functionalized diketopiperazine.

Scheme 7. Application to the Synthesis of Analogue 26



It is quite remarkable that the presence of an acid sensitive acetonide is tolerated during the Me_3SiOTf-mediated annulation reaction, highlighting the practicality of the approach, even on highly functionalized molecules.

In summary, we have achieved a concise synthesis of the core structure of 6−5−6−5−6-membered ETPs in six steps from bromoacrolein **11**, allowing the synthesis of gram amounts of diketopiperazine **1** and thus successfully demonstrating the new synthetic strategy. Pentacycle **1** is a highly functionalized intermediate that can serve as a platform for the synthesis of a wide range of ETP natural products as well as synthetic analogues.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and characterization data for all reactions and products, including ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Borthwick, A. D. *Chem. Rev.* **2012**, *112*, 3641−3716.

(2) (a) Waring, P.; Eichner, R. D.; Müllbacher, A. *Med. Res. Rev.* **1988**, *8*, 499−524. (b) Waring, P.; Beaver, J. *Gen. Pharmacol. - Vascular System* **1996**, *27*, 1311−1316. (c) Gardiner, D. M.; Waring, P.; Howlett, B. J. *Microbiology* **2005**, *151*, 1021−1032.

(3) Selected syntheses of 6(7)−5−6−5−6(7)-membered ETPs: (a) Nicolaou, K. C.; Totokotsopoulos, S.; Giguère, D.; Sun, Y.-P.; Sarlah, D. *J. Am. Chem. Soc.* **2011**, *133*, 8150−8153. (b) Codelli, J. A.; Puchlopek, A. L. A.; Reisman, S. E. *J. Am. Chem. Soc.* **2012**, *134*, 1930−1933. (c) Fujiwara, H.; Kurogi, T.; Okaya, S.; Okano, K.; Tokuyama, H. *Angew. Chem., Int. Ed.* **2012**, *51*, 13062−13065. (d) Nicolaou, K. C.; Lu, M.; Totokotsopoulos, S.; Heretsch, P.; Giguére, D.; Sun, Y.-P.; Sarlah, D.; Nguyen, T. H.; Wolf, I. C.; Smee, D. F.; Day, C. W.; Bopp, S.; Winzeler, E. A. *J. Am. Chem. Soc.* **2012**, *134*, 17320−17332.

(4) (a) Williams, D. E.; Bombuwala, K.; Lobkovsky, E.; De Silva, E. D.; Karunaratne, V.; Allen, T. M.; Clardy, J.; Andersen, R. J. *Tetrahedron Lett.* **1998**, *39*, 9579−9582. (b) Ernst-Russell, M. A.; Chai, C. L. L.; Hurne, A. M.; Waring, P.; Hockless, D. C. R.; Elix, J. A. *Aust. J. Chem.* **1999**, *52*, 279−283. (c) Chai, C. L. L.; Elix, J. A.; Huleatt, P. B.; Waring, P. *Bioorg. Med. Chem.* **2004**, *12*, 5991−5995.

(5) (a) Nagaraja, R.; Huckstep, L. L.; Lively, D. H.; Delong, D. C.; Marsh, M. M.; Neuss, N. *J. Am. Chem. Soc.* **1968**, *90*, 2980−2982. (b) Nagaraja, R.; Neuss, N.; Marsh, M. M. *J. Am. Chem. Soc.* **1968**, *90*, 6518−6519. (c) Cosulich, D. B.; Nelson, N. R.; Van den Hende, J. H. *J. Am. Chem. Soc.* **1968**, *90*, 6519−6521. (d) Murdock, K. C. *J. Med. Chem.* **1974**, *17*, 827−835. (e) Choi, E. J.; Park, J.-S.; Kim, Y.-J.; Jung, J.-H.;

Lee, J. K.; Kwon, H. C.; Yang, H. O. *J. Appl. Microbiol.* **2011**, *110*, 304−313.

(6) (a) Combinatorial approach to substituted 2,5-diketopiperazines for SAR studies: Loughlin, W. A.; Marshall, R. L.; Carreiro, A.; Elson, K. E. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 91−94. (b) For a review of the importance of non-natural analogues of natural products, see: Szpilman, A. M.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 9592−9628. For work in our own laboratories along these lines, see: (c) Szpilman, A. M.; Cereghetti, D. M.; Wurtz, N. R.; Manthorpe, J. M.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4335−4338. (d) Szpilman, A. M.; Manthorpe, J. M.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4339−4342.

(7) Schindler, C. S.; Diethelm, S.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 6296−6299.

(8) Application of the methodology in total synthesis: (a) Diethelm, S.; Schindler, C. S.; Carreira, E. M. *Org. Lett.* **2010**, *12*, 3950−3953. (b) Diethelm, S.; Schindler, C. S.; Carreira, E. M. *Chem.—Eur. J.* **2014**, *20*, 6071−6080.

(9) (a) Zinser, H.; Henkel, S.; Föhlisch, B. *Eur. J. Org. Chem.* **2004**, 1344−1356. For Lewis acid catalyzed (4 + 3)-cycloadditions of α-silyloxy acrolein derivatives with furan, see: (b) Sasaki, T.; Ishibashi, Y.; Ohno, M. *Tetrahedron Lett.* **1982**, *23*, 1693−1696. (c) Harmata, M.; Sharma, U. *Org. Lett.* **2000**, *2*, 2703−2705. (d) Aungst, R. A., Jr.; Funk, R. L. *Org. Lett.* **2001**, *3*, 3553−3555. (e) Harmata, M.; Huang, C. *Tetrahedron Lett.* **2009**, *50*, 5701−5703.

(10) (a) Brion, F. *Tetrahedron Lett.* **1982**, *23*, 5299−5302. (b) Schindler, C. S.; Carreira, E. M. *Chem. Soc. Rev.* **2009**, *38*, 3222−3241.

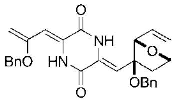
(11) Corey, E. J.; Loh, T.-P. *Tetrahedron Lett.* **1993**, *34*, 3979−3982.

(12) Sawai, Y.; Mizuno, M.; Ito, T.; Kawakami, J.-i.; Yamano, M. *Tetrahedron* **2009**, *65*, 7122−7128.

(13) The optical purity of **18** was determined from its corresponding ethyl ester by SFC analysis on a chiral stationary phase (see Supporting Information).

(14) Because catalyst **16** is moisture-sensitive, it was prepared just prior to its use in the Diels−Alder reaction.

(15) If the temperature of the reaction **15**→**2** was not carefully controlled, varying amounts of **27** were obtained. This suggests that a retro-Diels−Alder reaction is a possible decomposition pathway for aldehyde **3**, because *bis*(alkylidene)diketopierazine **2** is stable at ambient temperature and under the reaction conditions.



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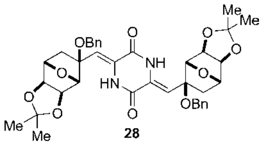
(16) Selected publications on condensation reactions of *N,N*′-diacetyldiketopiperazine with aldehydes: (a) Hendrix, J. A.; Strupczewski, J. T.; Bordeau, K. J.; Brooks, S.; Hemmerle, H.; Urmann, M.; Zhao, X.-Y.; Mueller, P. J. Novel Heterocyclic Urea Derivatives and their use as Dopamine D3 Receptor Ligands. U.S. Patent 2003/229066 A1, Dec 11, 2003. (b) González, J. F.; de la Cuesta, E.; Avendaño, C. *Synth. Commun.* **2004**, *34*, 1589−1597. (c) Balducci, D.; Conway, P. A.; Sapuppo, G.; Müller-Bunz, H.; Paradisi, F. *Tetrahedron* **2012**, *68*, 7374−7379.

(17) It was also possible to condense 2 equiv of the corresponding aldehyde of **22** with *N,N*′-diacetyldiketopiperazine (**4**) to yield (80%) compound **28** (see Supporting Information). Nucleophilic opening of **28** proceeded quickly on one side, but upon prolongation of the reaction time, a complex mixture was obtained.



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