Total Synthesis of (+)-Ambruticin

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Ambruticin (**1**) is a novel antifungal agent that was isolated from fermentation extracts of the myxobacterium *Polyangium cellulosum* by Warner-Lambert scientists in 1977.[1] This natural product exhibits pronounced activity against systemic medical pathogens such as *Coccidioides immitis*, *Histoplasma capsulatum*, and *Blastomyces dermatitidis*.[1] It also displays potent inhibitory activity against the yeast strain *Hansenula anomala* with an MIC of 0.03 μg/mL.[2] Recently, the mechanism of action of ambruticin has been shown to be analogous to that of pyrrolnitrin, in that its lethality to cells is achieved through interference with osmoregulation.[3] The relative and absolute stereochemistry of **1** have been established through a combination of spectroscopic studies,[4] chemical degradation, and single-crystal X-ray analysis.[5] This structurally intriguing molecule incorporates 10 stereocenters and 3 *E*-olefins within a relatively small framework bearing a dihydropyran, a tetrahydropyran diol, and a trisubstituted divinylcyclopropane unit unique to this family of natural products.[6] The diverse structural features of ambruticin, in conjunction with its potentially valuable biological activities, have stimulated considerable interest in the synthetic community[7] and to date two total syntheses have been documented.[8,9] We report herein our synthetic efforts in this area, which have led to a concise and highly stereocontrolled total synthesis of **1**.

From a retrosynthetic standpoint, ambruticin can be viewed as consisting of four distinct chiral subunits serially linked through the three double bonds. The strategy underlying our synthetic plan was to apply efficient, enantioselective reactions to generate each of the stereochemical elements independently, as this would offer maximum flexibility for the preparation of stereoisomeric and structural analogues. Cleavage of the C8−C9 olefin bond revealed two fragments **2** and **3** (Figure 1), union of which was envisaged via a Kocieński−Julia olefination.[10] We anticipated that the two pyran systems could be fashioned efficiently employing the highly enantio- and diastereoselective chromium-catalyzed hetero-Diels−Alder (HDA) methodologies reported recently from our laboratories.[11] Construction of the central ring would present a challenging test to state-of-the-art asymmetric cyclopropanation methodologies. Finally, although it is certainly not obvious, we envisaged installing the isolated C15 stereocenter by means of an asymmetric carbonylation reaction on an appropriate conjugated diene precursor.

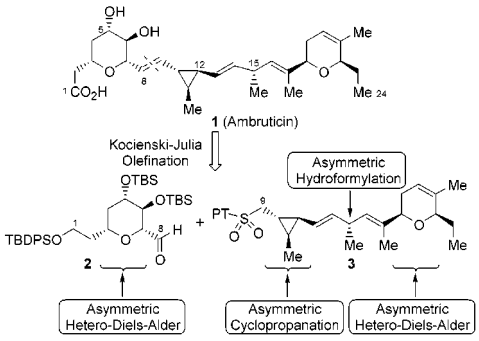
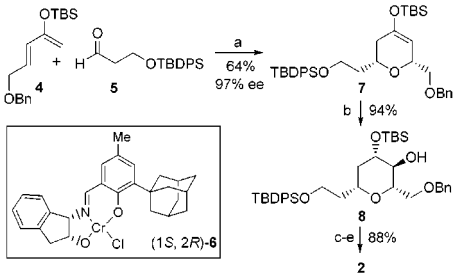


Figure 1. Retrosynthetic analysis (PT = phenyltetrazolyl).

Scheme 1. Synthesis of the C1−C8 Fragment (**2**)[a]



[a] Conditions: (a) (1*S*,2*R*)-**6** (10 mol %), room temperature. (b) BH_3·THF, THF, 0 °C; then 30% H_2O_2, 3 N NaOH, 0 °C → room temperature. (c) TBSOTf, 2,6-lutidine, CH_2Cl_2, −30 °C. (d) Pd/C, H_2. (e) cat. TPAP, NMO, CH_2Cl_2, room temperature.

The synthesis of **2** was initiated with a HDA reaction between diene **4**[12] and aldehyde **5** catalyzed by (1*S*,2*R*)-**6**,[11] which provided dihydropyran **7** in 97% ee (Scheme 1). A highly regio- and diastereoselective hydroboration/oxidation[13] of **7** generated **8** as a single diastereoisomer, thereby establishing all four stereocenters in the left-hand pyran of **1**. Protection of the secondary hydroxyl and debenzylation/oxidation of the primary alcohol afforded the C1−C8 fragment **2** in an overall yield of 53% for the 5-step sequence.

The carbon framework of the right-hand dihydropyran was accessed through the asymmetric HDA reaction between diene **12**, derived from α,β-unsaturated ketone **11**, and aldehyde **13**. In the presence of (1*R*,2*S*)-**6**, **14** was generated in high yield and greater than 99% ee (Scheme 2). Removal of the triethylsilyloxy group was effected by hydroboration and acid-catalyzed elimination,[14] and this operation also liberated the primary alcohol. Oxidation to aldehyde **16** followed by homologation with TMSC-

(1) Ringel, S. M.; Greenough, R. C.; Roemer, S.; Connor, D.; Gutt, A. L.; Blair, B.; Kanter, G.; von Strandtmann, M. *J. Antibiot*. **1977**, *30*, 371−375.
(2) Gerth, K.; Washausen, P.; Höfle, G.; Irschik, H.; Reichenbach, H. *J. Antibiot*. **1996**, *49*, 71−75.
(3) Knauth, P.; Reichenbach, H. *J. Antibiot*. **2000**, *53*, 1182−1190.
(4) Connor, D. T.; von Strandtmann, M. *J. Org. Chem*. **1978**, *43*, 4606−4607.
(5) (a) Connor, D. T.; Greenough, R. C.; von Strandtmann, M. *J. Org. Chem*. **1977**, *42*, 3664−3669. (b) Just, G.; Potvin, P. *Can. J. Chem*. **1980**, *58*, 2173−2177.
(6) The Höfle group isolated ambruticin and six new analogues bearing an amino group at the C5 position from myxobacterium *Sorangium cellulosum*. See: Höfle, G.; Steinmetz, H.; Gerth, K.; Reichenbach, H. *Liebigs Ann. Chem*. **1991**, 941−945.
(7) For earlier synthetic studies on ambruticin, see: (a) Michelet, V.; Adiey, K.; Bulic, B.; Genêt, J.-P.; Dujardin, G.; Rossignol, S.; Brown, E.; Toupet, L. *Eur. J. Org. Chem*. **1999**, *64*, 2885−2892. (b) Wakamatsu, H.; Isono, N.; Mori, M. *J. Org. Chem*. **1997**, *62*, 8917−8922. (c) Liu, L.; Donaldson, W. A. *Synlett* **1996**, 103−104. (d) Markó, I. E.; Bayston, D. J. *Synthesis* **1996**, 297−304. (e) Markó, I. E.; Bayston, D. J. *Tetrahedron* **1994**, *50*, 7141−7156. (f) Markó, I. E.; Bayston, D. J. *Tetrahedron Lett.* **1993**, *34*, 6595−6597. (g) Nagasawa, T.; Handa, Y.; Onoguchi, Y.; Ohba, S.; Suzuki, K. *Synlett* **1995**, 739−741. (h) Davidson, A. H.; Eggleton, N.; Wallace, I. H. *J. Chem. Soc., Chem. Commun*. **1991**, 378−380. (i) Burke, S. D.; Armistead, D. M.; Schoenen, F. J.; Fevig, J. M. *Tetrahedron* **1986**, *42*, 2787−2801. (j) Barnes, N. J.; Davidson, A. H.; Hughes, L. R.; Procter, G. *J. Chem. Soc., Chem. Commun*. **1985**, 1292−1294. (k) Barnes, N. J.; Davidson, A. H.; Hughes, L. R.; Procter, G.; Rajcoomar, V. *Tetrahedron Lett.* **1981**, *22*, 1751−1754. (l) Sinay, P. In *Bioorganic Heterocycles 1986*: *Synthesis, Mechanism and Bioactivity*; Elsevier: Amsterdam, The Netherlands, 1986; pp 59−70.
(8) (a) Kende, A. S.; Fujii, Y.; Mendoza, J. S. *J. Am. Chem. Soc*. **1990**, *112*, 9645−9646. (b) Kende, A. S.; Mendoza, J. S.; Fujii, Y. *Tetrahedron* **1993**, *49*, 8015−8038.
(9) Martin has presented a total synthesis of ambruticin, see: Kirkland, T. A.; Martin, S. F.; Colucci, J.; Marx, M.; Geraci, L. *Paper Abstracts*; 220th National Meeting of the American Chemical Society, 2000; American CHemical Society: Washington, DC, 2000; ORGN-126.
(10) (a) Blakemore, P. R.; Cole, W. J.; Kocieński, P. J.; Morley, A. *Synlett* **1998**, 26−28. (b) Julia, M.; Paris, J.-M. *Tetrahedron Lett*. **1973**, 14, 4833−4836.
(11) Dossetter, A. G.; Jamison, T. F.; Jacobsen, E. N. *Angew. Chem., Int. Ed*. **1999**, *38*, 2398−2400.
(12) Li, L.-S.; Wu, Y.; Hu, Y.-J.; Xia, L.-J.; Wu, Y.-L. *Tetrahedron: Asymmetry* **1998**, *9*, 2271−2277.
(13) Larson, G. L.; Prieto, J. A. *Tetrahedron* **1983**, *39*, 855−860.
(14) Larson, G. L.; Hernandez, E.; Alonso, C.; Nieves, I. *Tetrahedron Lett*. **1975**, *16*, 4005−4008.

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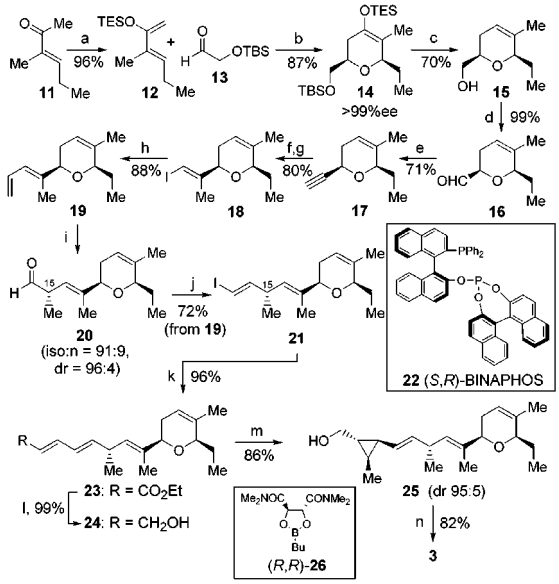
Scheme 2. Synthesis of the C9−C24 Fragment (**3**)[a]

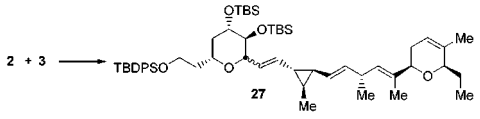


[a] Conditions: (a) TESOTf, Et_3N, Et_2O, 0 °C. (b) (1*R*,2*S*)-**6** (5 mol %), room temperature. (c) BH_3·THF, THF, 0 °C → room temperature; then 10% HCl, reflux. (d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C → room temperature. (e) TMSC(Li)N_2, THF, −78 °C → room temperature. (f) $Bu_3SnCu(Bu)CNLi_2$, CH_3I, THF/DMPU, −78 °C → room temperature. (g) I_2, Et_2O, 0 °C. (h) CH_2=CHMgBr, $Pd(PPh_3)_4$ (5 mol %), PhH, 70 °C. (i) H_2/CO (1:1), 20 atm, $Rh(acac)(CO)_2$ (0.5 mol %), (*S*,*R*)-**22** (2 mol %), PhH, 30−35 °C. (j) $CrCl_2$, CHI_3, THF, 0 °C → room temperature. (k) ethyl acrylate, $Pd(OAc)_2$ (10 mol %), Ag_2CO_3, CH_2Cl_2, room temperature. (l) DIBAL-H, PhMe, −78 °C. (m) $Zn(CH_3CHI)_2$·DME, (*R*,*R*)-**26**, CH_2Cl_2, −10 °C. (n) PPh_3, PTSH, DEAD, THF, room temperature; then Mo(VI)/H_2O_2, EtOH, 0 °C → room temperature.

(Li)N_2[15] afforded alkyne **17**. Addition of $Bu_3SnCu(Bu)(CN)Li_2$[16] to **17** followed by trapping of the intermediate alkenyl cuprate with MeI and stannane−iodine exchange provided vinyl iodide **18**, which was converted to conjugated diene **19** with use of a Kumada coupling.[17]

The C15 stereocenter represents one of the most interesting challenges to the synthesis of **1**. While a number of classical approaches (e.g. [3,3]-sigmatropic rearrangement or a S_N2-type allylic displacement) might be adaptable to this task, such methods would rely on indirect installation of the C15 center in a multistep manner. Regioselective hydroformylation of 1,3-dienes affords β,γ-unsaturated α-methyl-substituted aldehydes directly, and Nozaki has applied the BINAPHOS catalyst system in an enantioselective variant with simple model dienes.[18] Diene **19** was subjected to the Nozaki hydroformylation conditions, providing aldehyde **20** in high diastereoselectivity. This represents the first application of the Takaya−Nozaki catalytic asymmetric hydroformylation in target-oriented synthesis, and it highlights a powerful and efficient approach to stereochemically defined α-substituted β,γ-unsaturated aldehydes. Aldehyde **20** was converted to tetraene **24** by a three-step sequence consisting of a Takai olefination[19]/Heck reaction/DIBAL-H reduction. Ethylidenation of the allylic alcohol of **24** was accomplished by using the asymmetric Simmons−Smith reaction developed by Charette and co-workers.[20] This transformation afforded the central cyclopropane ring with high diastereoselectivity, thereby establishing the complete carbon framework of the C9−C24 fragment. Finally,

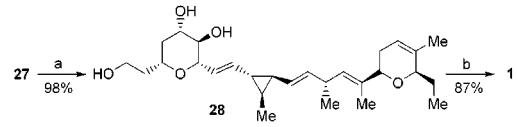
Table 1. Fragment Coupling



entry	conditions[a,b]	*E*/*Z* ratio[c]
1	NaHMDS, THF, −78 °C	1:8
2	NaHMDS, THF, −35 °C	1:6
3	KHMDS, DMF, −60 °C	1:1
4	KHMDS, DME, 18-crown-6, −60 °C	1:3
5	LiHMDS, THF/HMPA (4:1 v/v), −60 °C	3:1
6	LiHMDS, DMF/HMPA (4:1 v/v), −35 °C	>30:1
7	LiHMDS, DMF/DMPU (1:1 v/v), −35 °C	>30:1

[a] Reactions were set up at the indicated temperatures and then allowed to warm to room temperature. [b] In all cases, yields were greater than 90%. [c] *E*/*Z* ratios were determined by ^{1}H NMR analysis of crude product mixtures.

Scheme 3. Completion of the Synthesis[a]



[a] Conditions: (a) TBAF, THF, room temperature. (b) Pt, O_2, H_2O/acetone, 50 °C.

a one-pot Mitsunobu/oxidation process[21] completed the synthesis of sulfone **3**.

With **2** and **3** in hand, a careful survey of conditions for the crucial fragment coupling was conducted (Table 1). It was found that high selectivity for either double bond isomer could be obtained in the Kocieński−Julia olefination, with the use of NaHMDS in THF providing *Z* alkene (entries 1 and 2) and LiHMDS in polar solvents affording the desired *E* isomer almost exclusively (entries 6 and 7). While similar trends have been linked previously to solvent effects, the attainment of very high *E* selectivity with LiHMDS is unprecedented and potentially of considerable broader significance.[10a]

The synthesis was completed by global deprotection and selective oxidation[22] of the primary alcohol to the carboxylic acid (Scheme 3). The physical and spectroscopic properties of synthetic **1** thus obtained were found to be identical with those of natural material (^{1}H NMR, ^{13}C NMR, IR, and $[\alpha]_D$).[8,23]

This total synthesis of ambruticin was accomplished in 16 steps and 12% yield in the longest linear sequence (21 steps, overall). Each of the stereochemical challenges was met in a highly selective manner, with recently developed enantioselective C−C bond-forming reactions applied to the direct introduction of 8 of the 10 stereocenters. As such, this route provides a versatile and flexible route to **1**, and a compelling illustration of the impact modern asymmetric catalysis can have on target-oriented synthesis.

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Supporting Information Available: Experimental procedures, physical and spectral data; ^{1}H NMR and ^{13}C NMR spectra of synthetic **1**; and comparison of ^{1}H NMR spectra between synthetic **1** and natural **1** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Miwa, K.; Aoyama, T.; Shioiri, T. *Synlett* **1994**, 107−108.
(16) Lipshutz, B. H.; Ellsworth, E. L.; Dimock, S. H.; Reuter, D. C. *Tetrahedron Lett*. **1989**, *30*, 2065−2068.
(17) Dang, H. P.; Linstrumelle, G. *Tetrahedron Lett*. **1978**, *19*, 191−194.
(18) (a) Horiuchi, T.; Ohta, T.; Nozaki, K.; Takaya, H. *J. Chem. Soc., Chem. Commun*. **1996**, 155−156. (b) Horiuchi, T.; Ohta, T.; Shirakawa, E.; Nozaki, K.; Takaya, H. *Tetrahedron* **1997**, *53*, 7795−7804.
(19) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc*. **1986**, *108*, 7408−7410.
(20) (a) Charette, A. B.; Lemay, J. *Angew. Chem., Int. Ed*. **1997**, *36*, 1090−1092. (b) Charette, A. B.; Juteau, H.; Lebel, H.; Molinaro, C. *J. Am. Chem. Soc*. **1998**, *120*, 11943−11952.
(21) Bellingham, R.; Jarowicki, K.; Kocieński, P.; Martin, V. *Synthesis* **1996**, 285−296.
(22) Fried, J.; Sih, J. C. *Tetrahedron Lett*. **1973**, *14*, 3899−3902.
(23) Hölscher, A. Ph.D. Thesis, GBF, Braunschweig, Germany, 1996, pp 210−211.