Total Syntheses of Thiocoraline and BE-22179: Establishment of Relative and Absolute Stereochemistry

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Thiocoraline (**1**, Figure 1) is a potent antitumor antibiotic[1] isolated from *Micromonospora* sp. L-13-ACM2-092. It constitutes the newest member of the 2-fold symmetric bicyclic octadepsipeptides which include BE-22179[2] (**2**), triostin A[3] (**3**), and echinomycin[4] (**4**), which bind to DNA with bisintercalation.[5,6] Unlike BE-22179, thiocoraline does not inhibit DNA topoisomerase I or II, but it does inhibit DNA polymerase α at concentrations that inhibit cell cycle progression and clonogenicity.[7] It was found to unwind double-stranded DNA,[7] and thus it may bisintercalate DNA analogous to triostin, echinomycin, and members of the larger cyclic decadepsipeptides including sandramycin,[8,9] luzopeptins,[9,10] and quinoxapeptins.[11] Studies on thiocoraline as well as BE-22179 have established their two-dimensional structures but not their relative and absolute stereochemistry.[1,2] Triostin and echinomycin possess a D-stereochemistry at the α-position of the amide linkage to the quinoxaline chromophore (D-Ser) and L-stereochemistry at the remaining stereogenic centers. We have shown that the analogous centers of sandramycin[8] and the quinoxapeptins,[11] like the luzopeptins,[10] also incorporate D-Ser. Thus, we anticipated that **1**, as well as **2**, might possess a similar stereochemistry with incorporation of an unusual chromophore bearing D-Cys. Herein, we report the first total syntheses of thiocoraline and BE-22179, the determination of their relative and absolute stereochemistry, and the preparation of sufficient material with which further studies may be conducted.

Key elements of the approach include the late stage introduction of the chromophore, symmetrical tetrapeptide coupling, macrocyclization of the 26-membered octadepsipeptide conducted at the single secondary amide site following disulfide formation, and a convergent assemblage of the tetradepsipeptide with introduction of the labile thiol ester linkage in the final coupling reaction under near racemization free conditions. By virtue of the late stage introduction of the chromophore and despite the challenges this imposes in the synthesis because of a potential cleavage of the macrocyclic thiol ester, this approach provides ready access of a range of chromophore analogues.

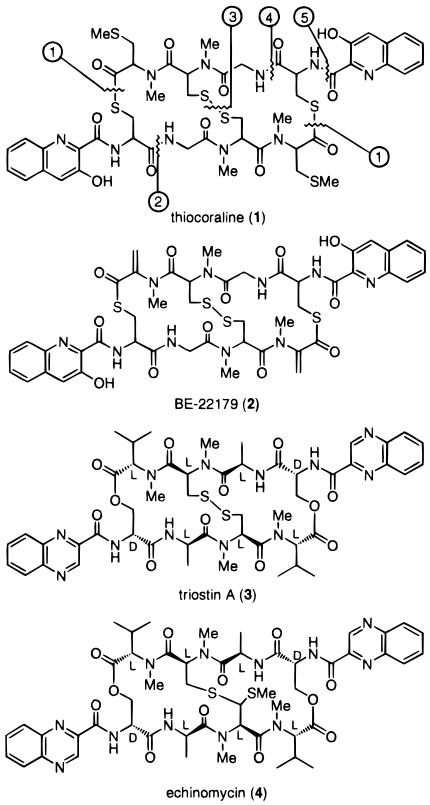

Figure 1.

The assemblage of tetradepsipeptide **16** from tripeptide **15** and *N*-Cbz-D-Cys-OTce (**12**) along with the preparation of the three suitably functionalized Cys residues found in **1** are summarized in Scheme 1. Sequential *S*- and *N*-protection of *N*-Me-Cys-OH (**5**)[12] with an acetamidomethyl (Acm) group (1.5 equiv of *N*-hydroxymethylacetamide, H_2SO_4, H_2O, 25 °C, 12 h) and BOC group (1.2 equiv of BOC_2O, NaOH, THF−H_2O, 25 °C, 12 h, 62%) gave **6**, the precursor to the bridging disulfide Cys residue. Selective *S*-methylation of *N*-Me-Cys-OH (**5**,[12] 1.0 equiv of MeI, 2.0 equiv of $NaHCO_3$, THF−H_2O, 25 °C, 3 h) followed by BOC protection (1.2 equiv of BOC_2O, NaOH, THF−H_2O, 25 °C, 12 h, 73%) provided **7**. Esterification of **7** (1.0 equiv of $TMSCHN_2$, 89%) followed by BOC deprotection of **8** (3 M HCl−AcOEt, 91%) provided **9**, the precursor to the second L-Cys residue.

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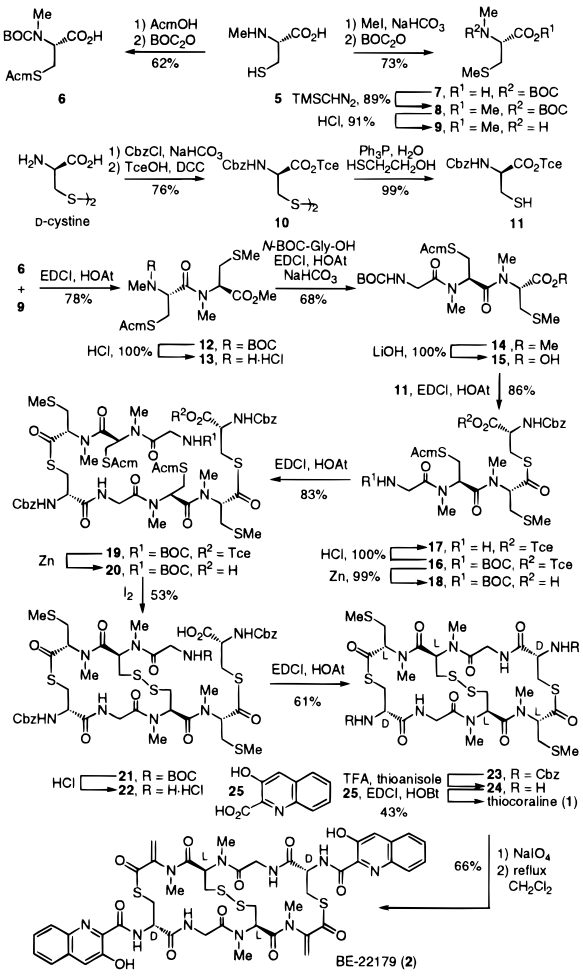
Scheme 1



Compound **11**, the chromophore bearing D-Cys residue, was prepared by the reduction of its disulfide precursor **10** (1.0 equiv of Ph_3P, 2-mercaptoethanol, H_2O, THF, 50 °C, 6 h, 99%) which in turn was obtained by stepwise Cbz (2.1 equiv of CbzCl, 4.0 equiv of $NaHCO_3$, THF−H_2O, 0−25 °C) and Tce (2.5 equiv of trichloroethanol, 3.0 equiv of DCC,[13] HOBt,[13] pyridine, −20 °C, 48 h, 76%) protection of D-cystine. Coupling of **6** with **9** (1.0 equiv of EDCI,[13] HOAt,[13] $NaHCO_3$, CH_2Cl_2, 0 °C, 12 h, 78%) provided **12**. BOC deprotection of **12** (3 M HCl−AcOEt, 100%), coupling with *N*-BOC-Gly-OH (1.5 equiv of EDCI, HOAt, $NaHCO_3$, CH_2Cl_2, 0 °C, 12 h, 68%), and methyl ester hydrolysis of **14** (3 equiv of LiOH, THF−MeOH−H_2O, 25 °C, 1.5 h, 100%) provided **15**.

The key thiol esterification reaction linking the D-cysteine derivative **11** and the tripeptide **15** was accomplished under near racemization free conditions with use of EDCI−HOAt (1.2 equiv of EDCI, HOAt, DMF, −20 °C, 4 h, 83%) in the absence of added base to afford **16** (de 95:5). Much lower conversions were observed using DPPA[14] or DEPC[14] and Et_3N due in part to competitive base-catalyzed formation of disulfide **10**. Analogous to prior reports,[14] near complete racemization was observed (**16**: *epi*-**16** = 58:42) when the nonpolar solvent CH_2Cl_2 was used. The use of base in all reactions following formation of the thiol ester **16** was found to lead to competitive β-elimination or cleavage of the thiol ester and was avoided. Linear octadepsipeptide formation was accomplished by deprotection of the amine (3 M HCl−AcOEt, 100%) and carboxylic acid (Zn, 90% aqueous AcOH, 0 °C, 1.5 h, 99%) of **16** to provide **17** and **18**, respectively, which were coupled with formation of the secondary amide in the absence of added base (1.2 equiv of EDCI, HOAt, CH_2Cl_2, 0 °C, 4 h, 83%) to obtain **19**. Cyclization of **19** to provide the 26-membered cyclic octadepsipeptide **23** with ring closure conducted at the single secondary amide site was accomplished by sequential Tce ester deprotection (Zn, 90% aqueous AcOH, 0 °C, 1.5 h), disulfide bond formation[15] (I_2, CH_2Cl_2−MeOH, 25 °C, 0.001 M, 53% for 2 steps), and BOC deprotection (3 M HCl−dioxane) followed by treatment with EDCI−HOAt (5.0 equiv of EDCI, HOAt, 0.001 M CH_2Cl_2, −20 °C, 6 h, 61% for 2 steps). Reversing the *N*-BOC deprotection and disulfide bond formation steps in this 4-step sequence resulted in lower conversions (13% overall). To date, all attempts to effect ring closure followed by disulfide bond formation have not been successful. Even though the 26-membered-ring macrocyclization reaction proceeds exceptionally well (>50%), the subsequent disulfide bond formation (I_2, CH_2Cl_2−MeOH, 25 °C) fails to occur. Thus, the order of steps enlisted for formation of **23** was not to improve macrocyclization via the constrained disulfide, but rather to permit disulfide bond formation. While it is possible this may be due to constraints within the macrocycle destabilizing the disulfide, the lack of similar observations with **3** suggests the origin of the difficulties may lie with competitive cleavage of the adjacent thiol ester by the liberated bridging thiol within the 26-membered macrocycle. Removal of the Cbz protecting group under mild conditions[16] (TFA-thioanisole, 25 °C, 4 h) and coupling of **24** with 3-hydroxyquinoline-2-carboxylic acid (**25**,[17,18] 5.0 equiv of EDCI, DMAP, CH_2Cl_2, 25 °C, 24 h, 43%) without protection of the chromophore phenol provided (−)-**1**, $[\alpha]^{25}_D$ −180 (*c* 0.11, $CHCl_3$) [lit.[1] $[\alpha]^{25}_D$ −191 (*c* 1.1, $CHCl_3$)], identical in all respects with the properties reported for natural material.[1] Under these conditions, a problematic intramolecular *S*−*N* acyl migration to the liberated amine with cleavage of the thiol ester was minimized.[19] Treatment of **1** with $NaIO_4$ (10 equiv, acetone−H_2O, 25 °C, 12 h) served to provide the bis-sulfoxide as a mixture of diastereomers which was warmed in CH_2Cl_2 (reflux, 6 h, 66% overall) to promote elimination and provide BE-22179, identical in all respects with the properties reported for natural material.[2] Thus, the correlations of synthetic and natural **1** and **2** confirm the two-dimensional structure assignments and establish the relative and absolute stereochemistries as those shown in Scheme 1. Sufficient synthetic material (14 steps, >5% overall for **1**) was assembled to permit further studies on the natural products and their results will be disclosed in due course.

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Supporting Information Available: Full experimentals and characterization of **1**, **2**, **6**−**12**, **14**, **16**, **19**, and **23** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) DCC = dicyclohexylcarbodiimide; EDCI = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; HOBt = 1-hydroxybenzotriazole; HOAt = 1-hydroxy-7-azabenzotriazole.

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(19) Preliminary efforts enlisting Fmoc and basic deprotection conditions vs Cbz protecting groups on **23** failed to provide **24** or **1**. In addition, effort to first form the symmetrical disulfide of **16** followed by simultaneous formation of both secondary amides of the macrocycle led to a complex mixture of products.