Enantioselective Total Synthesis of 13,14,15-Isocrambescidin 800

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Crambe crambe, a bright red encrusting sponge commonly found at shallow depths along the rocky coast of the Mediterranean, is a rich source of structurally novel, bioactive alkaloids.[2] Rinehart and co-workers[3] and later Braekman and his group,[4] described a series of complex guanidinium alkaloids, including 13,14,15-isocrambescidin 800 (**1**), crambescidin 800 (**2**), and crambescidin 816 (**3**), from *C. crambe*. The related alkaloid, ptilomycalin A (**4**), was reported earlier by Kashman, Kakisawa, and co-workers from sponges collected in the Caribbean and Red Sea.[5] Ptilomycalin A[5,6] and several of the crambescidins[3,4] show substantial antitumor, antiviral, and antifungal activities. As a result of its low abundance, 13,14,15-isocrambescidin 800 has not been extensively screened, although it is reported to be less cytotoxic to L-1210 cells than other crambescidins.[3b] The defining structural feature of the crambescidin alkaloids is a pentacyclic guanidine linked by a straight chain ω-hydroxycarboxylic acid spacer to a spermidine or hydroxyspermidine unit. Extensive NMR studies demonstrated that the relative stereochemistry of the pentacyclic cores of **2**−**4** is identical,[3,4] while 13,14,15-isocrambescidin 800 (**1**) is epimeric at C13, C14, and C15.[3b,4b] The absolute configuration of the guanidine moieties of **1** and **3** was established by oxidative degradation of the oxepene rings of these alkaloids to yield (*S*)-2-hydroxybutanoic acid,[3b] while the absolute configuration of the hydroxyspermidine unit of **3** was assigned using Mosher's method.[4b,7] Since ¹H NMR and ¹³C NMR chemical shifts in the hydroxyspermidine fragments of **1** are nearly identical to those of **2** and **3**, it has been assumed that the stereochemistry at C43 is the same for all crambescidins.[4b]

In 1995 we reported an enantioselective total synthesis of (−)-ptilomycalin A (**4**), which was the first (and to date only) total synthesis of a member of the crambescidin alkaloid family.[8,9] Herein, we disclose an enantioselective total synthesis of 13,14,15-isocrambescidin 800 (**1**) which for the first time makes this rare
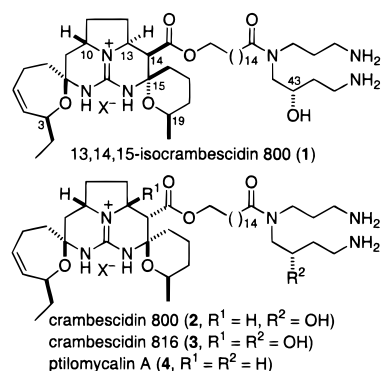
member of the crambescidin family available for detailed pharmacological screening. The defining reaction of the synthesis is a tethered-Biginelli condensation[10,11] of guanidino aminal **14** with β-ketoester **15**; this reaction unites all of the atoms of the guanidine core of **1** and sets the pivotal C10−C13 stereorelationship.[10b]

Diene **13**, the precursor of the C1−C13 guanidino aminal, was prepared from 3-butyne-1-ol (**5**) as summarized in Scheme 1. The C3 stereocenter was introduced by the method of Weber and Seebach[12] through condensation of ynal **6** with Et₂Zn in the presence of (−)-TADDOL (20 mol %) and Ti(O*i*-Pr)₄ to give (*S*)-**7** in 94% yield and >98% ee. Standard manipulations yielded iodide **8** which was converted to the corresponding lithium reagent and coupled with **9**[13−15] to generate dienone **10** in 60−70% yield. Ketalization of **10** with ortho ester **11**[16] and 1,3-propanediol in the presence of Amberlyst-15 provided **12** in 80% yield. Mitsunobu displacement of the secondary alcohol with azide, reduction to the primary amine, and condensation with 1*H*-pyrazole-1-carboxamidine hydrochloride[17] furnished guanidine **13** in ~30% overall yield from **6**.

Selective dihydroxylation of the trisubstituted double bond of **13**,[18] followed by cleavage of the vicinal diol with Pb(OAc)₄ in toluene containing several equiv of morpholinium acetate, yielded **14** (Scheme 2).[19] Biginelli condensation of **14** with β-ketoester **15**[10b] under Knoevenagel conditions took place with modest (3:1) diastereoselectivity in ethanol. Fortunately, diastereoselection was improved to 7:1 in 2,2,2-trifluoroethanol, and, after chromatographic separation of the minor C13 epimer, the major isomer **16** was isolated in 49% yield for the 3 steps.

The silyl-protecting groups of **16** were next discharged with TBAF to provide the corresponding guanidine diol. After considerable experimentation, we found that exposure of this intermediate to 3 equiv of anhydrous HCl in ethyl acetate at 23 °C gave a *single* pentacyclic product **17**, which was isolated in 62% yield from **16**. Since the spirohydropyran evolves from trans-addition of the C19 alcohol to the C14−C15 double bond

(1) Current Address: Elan Pharmaceuticals, 800 Gateway Boulevard, South San Francisco, CA 94080.

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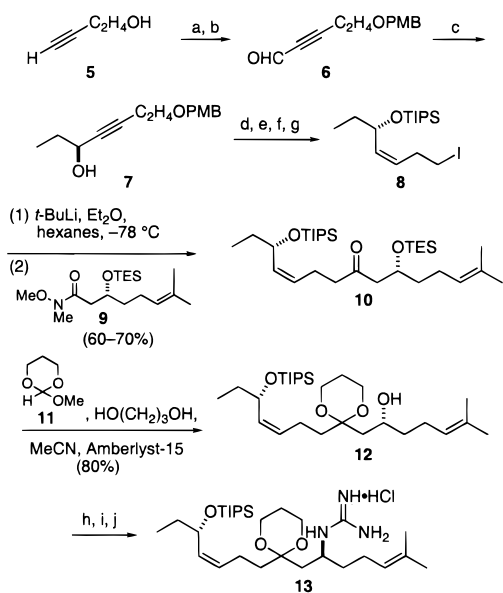
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(13) Prepared by treating the known β-hydroxyester[14] with Me(MeO)NH·HCl and Me₃Al,[15] followed by TES-Cl and *i*-PrNEt₂.

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(19) This intermediate is a mixture of several components as judged by ¹H and ¹³C NMR data.

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Scheme 1[a]

[a] Reagents: (a) TfOH, PMBOC(N=H)CCl₃, Et₂O, 0 °C; (b) *n*-BuLi, THF, −40 °C; DMF, −40 °C to rt, 90% (2 steps); (c) Et₂Zn, Ti(O*i*-Pr)₄, (−)-TADDOL (20 mol%), Et₂O, −30 °C, 94%, >98% ee; (d) TIPS-OTf, 2,6-lutidine, CH₂Cl₂; (e) H₂, Pd/CaCO₃/PbO, quinoline, hexanes; (f) DDQ, CH₂Cl₂, H₂O, 95% (3 steps); (g) Ph₃P, I₂, imidazole, Et₂O, MeCN, 95%; (h) HN₃, Ph₃P, DEAD, THF, 88%; (i) LiAlH₄, Et₂O, 88%; (j) 1*H*-pyrazole-1-carboxamidine hydrochloride, *i*-Pr₂NEt, DMF, 99%.

(signaled by the 11.8 Hz ¹H NMR coupling constant of H14), the ester side chain is epimeric to that of **1**. Epimerization at C14 was best accomplished after removal of the allyl-protecting group[20] by heating the resulting acid with 10 equiv of Et₃N (MeOH, 60 °C) to furnish **18** in 60% yield.[21]

The synthesis of 13,14,15-isocrambescidin 800 (**1**) was completed as follows. The (*S*)-7-hydroxyspermidine fragment **19** was prepared from (*R*)-epichlorohydrin[22] and coupled with pentacycle **18** using benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP)[23] to provide **20** in 71% yield. Removal of the BOC groups with 2 M HCl in ethyl acetate[24] and purification of the crude product by reverse-phase HPLC provided the trihydrochloride salt of 13,14,15-isocrambescidin 800 (**1**), [α]²³_D −67.7 (*c* 0.7 MeOH),[25] in 70% yield. Synthetic **1**, and triacetate derivative **21**, showed ¹H NMR and ¹³C NMR spectra consistent with those reported for natural **1**[3b] and **21**;[4b] synthetic **1** was indistinguishable from a natural sample by HPLC comparisons using three eluents. Moreover, ¹⁹F NMR studies demonstrated that the Mosher derivative **22** prepared from synthetic **1** was indistinguishable from a sample of this derivative prepared from natural **1**, and different from the identical derivative of the C43 epimer of **1**, which we synthesized from **18** and *ent*-**19**.

In conclusion, the first total synthesis of 13,14,15-isocrambescidin 800 (**1**) was accomplished in convergent fashion with the longest linear sequence from commercially available material

(20) Deziel, R. *Tetrahedron Lett.* **1987**, *28*, 4371−4372.

(21) A diagnostic d, *J* = 3.0 Hz is observed for H14. In contrast to precursors of **4**,[8] the axial ester is highly favored at equilibrium in the 13,14,15-isocrambescidin series.

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(23) Castro, B.; Dormoy, J. R.; Evin, G.; Selve, C. *Tetrahedron Lett.* **1975**, 1219−1222.

(24) Stahl, G. L.; Walter, R.; Smith, C. W. *J. Org. Chem.* **1978**, *43*, 2285−2286.

(25) A rotation of [α]²³_D −48 (*c* 0.5 MeOH) is reported for natural 13,14,15-isocrambescidin 800 (**1**). Since the counterion of natural **1** was not described, the significance, if any, of the small discrepancy in rotation magnitude is unknown.

Scheme 2[a]

20: R¹ = H, R² = BOC
g →
1: R¹ = H, R² = H•HCl (13,14,15-isocrambescidin 800)
h →
21: R¹ = R² = Ac
22: R¹ = R² = (*S*)-COC(CF₃)(OMe)Ph
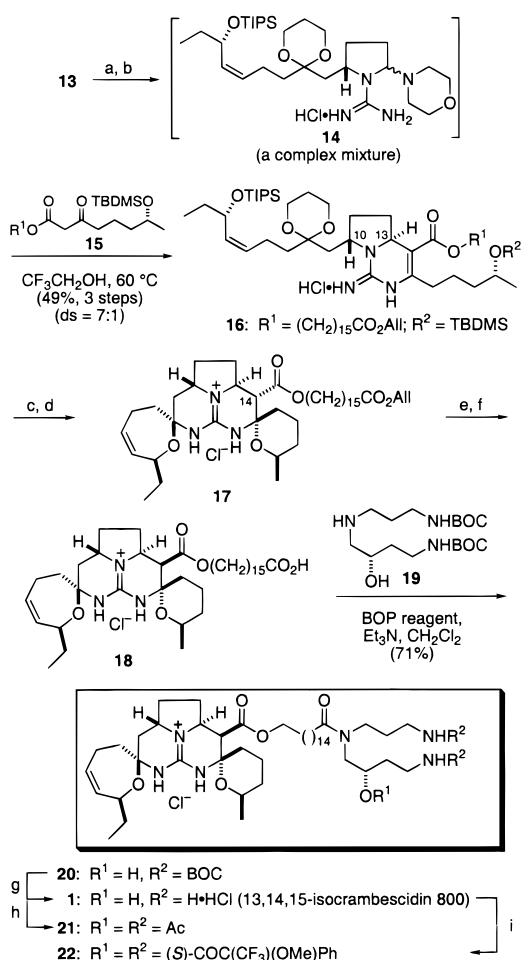
[a] Reagents: (a) OsO₄ (2 mol %), NMO, THF, H₂O; (b) Pb(OAc)₄, morpholinium acetate, toluene; (c) TBAF, DMF, 80%; (d) HCl, EtOAc, 78%; (e) (Ph₃P)₄Pd, morpholine, MeCN; (f) Et₃N, MeOH, 60 °C, 60% (2 steps); (g) 2 M HCl, 70%; (h) Ac₂O, pyridine, 70%; (i) (*R*)-MPTA-Cl, Et₃N, DMAP.

being 21 steps. These investigations confirm the stereochemical assignment of **1** and rigorously establish that the absolute configuration of its hydroxyspermidine side chain is *S*. This enantioselective total synthesis demonstrates for the first time that: (a) our tethered Biginelli strategy can be extended to guandine intermediates, (b) the key Biginelli condensation can be accomplished under sufficiently mild conditions that fragments containing the full functionality of the crambescidin core can be employed, and (c) that the spiroaminal units in the isocrambescidin series assemble with high stereochemical fidelity.

Supporting Information Available: Characterization data for new compounds; detailed experimental procedures for the preparation of **16**, **17**, **20**, **21**, and **1**; copies of ¹H and ¹³C NMR spectra for synthetic **1** and **21** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.