Biomimetic Total Syntheses of (+)-Cephalostatin 7, (+)-Cephalostatin 12, and (+)-Ritterazine K[1]

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Cephalostatin 7 (**12**)[2] is a potent member of a family of 28 trisdecacyclic pyrazines, characterized by the groups of Pettit at Arizona State University and Fusetani at the University of Tokyo.[3] These materials have been isolated from the marine tube worm *Cephalodiscus gilchristi* and, more recently, from the tunicate *Ritterella tokioka.* In particular, cephalostatin 7 (**12**) exhibits an average toxicity of ~1 nM in the 60 *in vitro* cancer screens of the NCI.[2] In his seminal contribution detailing the structure of cephalostatin 1, Pettit hypothesized that the pyrazine core structure was assembled via dimerization and oxidation of steroidal α-amino ketones,[4] a well-known reaction in the laboratory.[5]

An intriguing biosynthetic question relates to the timing of the dimerization step. In principle, several scenarios can be envisaged. The first of these postulates processing a single precursor steroid via selective oxidations to individual "North" and "South" α-amino ketones **9** and **10** which undergo dimerization to the unsymmetrical pyrazine cephalostatin 7 (**12**).[2] A consequence of this mechanistic variant is the expectation that the C_2 symmetrical dimers cephalostatin 12[6] (**11**) and the recently discovered ritterazine K (**13**)[3b] would also be formed (Scheme 1). While one would expect a 1:2:1 ratio of **11**:**12**:**13** to be formed if precursors **9** and **10** were present at the same concentration and if dimerization rates for all α-amino ketones were approximately the same, it is clear that isolation of **11** and **12** to the virtual exclusion of **13** would occur if the "North spiroketal" precursor **9** was present in substantially greater concentration. Such a picture is consistent with the fact that the "North spiroketal" appears in most of the 15 known cephalostatins isolated from *C. gilchristi* and is also in accord with the finding that cephalostatin 7 (**12**) is isolated in 10-fold lower yields than cephalostatin 12 (**11**).[2,6]

Although the random-coupling conjecture is satisfying in the context described above, it appears to break down in relation to the relative amounts of the unsymmetrical cephalostatin 1 (structure not shown) and C_2 symmetrical cephalostatin 12 (**11**), since cephalostatin 1 was isolated in 100-fold greater yield than cephalostatin 12 (**11**). Therefore, one can postulate a second pathway for biosynthesis of the cephalostatins of Scheme 1 involving biological deoxygenation of symmetrical cephalostatin 12 (**11**) to C-23 monodeoxy cephalostatin 12 (**11**, Z = H, currently unknown) followed by acid-catalyzed rearrangement[7] of the South 5/5 spiroketal to the 6/5 spiroketal present in cephalostatin 7 (**12**). A third possibility would be C-23 oxidative monofunctionalization of ritterazine K (**13**) followed by acid-catalyzed spiroketal rearrangement to cephalostatin 7 (**12**).

As pertains to total synthesis of cephalostatin 7 (**12**), a biomimetic approach would convert appropriately protected α-azido ketones **7** and **8** to α-amino ketones **9** and **10** followed by statistical combination to produce cephalostatins 12[6] (**11**) and 7[2] (**12**) and ritterazine K[3b] (**13**). The specific synthetic strategy adopted involved transformation of the commercially available steroidal spiroketal hecogenin acetate **1** (not shown) to dihydrofuran−aldehyde **2**,[8] which served as the common intermediate for preparation of both hemispheres (**3**[9] and **4**[10]) of the target pyrazines (Scheme 1).

Reaction of the North ketone **3** (R_{12} = Ac, R_{17} = H, R_{23} = TBDPS, R_{26} = TBDMS)[9] with phenyltrimethylammonium tribromide (PTAB, 1.25 equiv) in THF at 0 °C for 8 min followed by quenching with sodium bisulfite affords North bromoketone **5** (R_{12} = Ac, R_{17} = H, R_{23} = TBDPS, R_{26} = TBDMS) in 72% yield. *Successful conversion of* **5** *to North azido ketone* **7** *was crucially dependent upon the correct choice of solvent.* While treatment of **5** with tetramethylguanidinium azide (TMGA) in methylene chloride[11] or sodium azide in DMF gives mixtures of **7** and α-aminoenone **14** (via base-catalyzed nitrogen elimination[5,12] from **7**), reaction of TMGA in nitromethane[13] delivers North azido ketone **7** (R_{12} = Ac, R_{17} = H, R_{23} = TBDPS, R_{26} = TBDMS) in quantitative yield.

Synthesis of the South azido ketone **8** began with South ketone **4** ($R_{12'}$ = Ac, $R_{17'}$ = TMS, $R_{25'}$ = CH_2SMe).[10] Bromination of this substrate using 1.3 equiv of PTAB in THF at 0 °C for 20 min affords a 76% yield of South bromo ketone **6** ($R_{12'}$ = Ac, $R_{17'}$ = TMS, $R_{25'}$ = H) which has suffered concomitant deprotection of the C-25 MTM moiety.[14] As with the North series, use of 4 equiv of TMGA in nitromethane[13] at 25 °C for 4 h was the key to avoiding competitive decomposition (to **15**) of the initially-formed α-azido ketone **8**. In this instance, the isolated yield of **8** was 95% using nitromethane, as compared to 30−40% when employing acetonitrile or dichloromethane.

Pyrazine formation was accomplished by treating a 1:1 mixture of azido ketones **7** and **8** in ether with 6 equiv of an ethanolic solution of NaHTe[15] for 1 h at 25 °C, followed by adding silica gel as a mild acid catalyst and stirring the mixture in ethyl acetate with exposure to the air for 18 h. Chromatography of the reaction mixture afforded the protected pyrazines **11** (R_{12} = Ac, R_{17} = H, R_{23} = TBDPS, R_{26} = TBDMS), **12** (R_{12} = Ac, R_{17} = H, R_{23} = TBDPS, R_{26} = TBDMS, $R_{12'}$ = Ac, $R_{17'}$ = TMS, $R_{25'}$ = H), and **13** ($R_{12'}$ = Ac, $R_{17'}$ = TMS, $R_{25'}$ = H) in 14%, 35%, and 23% isolated yields, respectively. Azide-cleaved ketones **3** (R_{12} = Ac, R_{17} = H, R_{23} = TBDPS, R_{26} = TBDMS) and **4H** ($R_{12'}$ = Ac, $R_{17'}$ = TMS, $R_{25'}$ = H) were also recovered in 36 and 15% yields from this reaction. Since the reductive cleavage reaction of **7** and **8** with NaHTe disturbed the 1:1 ratio of α-amino ketones **9** and **10**, it is

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(14) Bromination of a South ketone devoid of the C-25 MTM protecting group generates a mixture of α-bromo ketone **6** and an α-bromo ketone bearing a rearranged 5/5 spiroketal (for acid-catalyzed rearrangements in this series, see refs 7 and 10).

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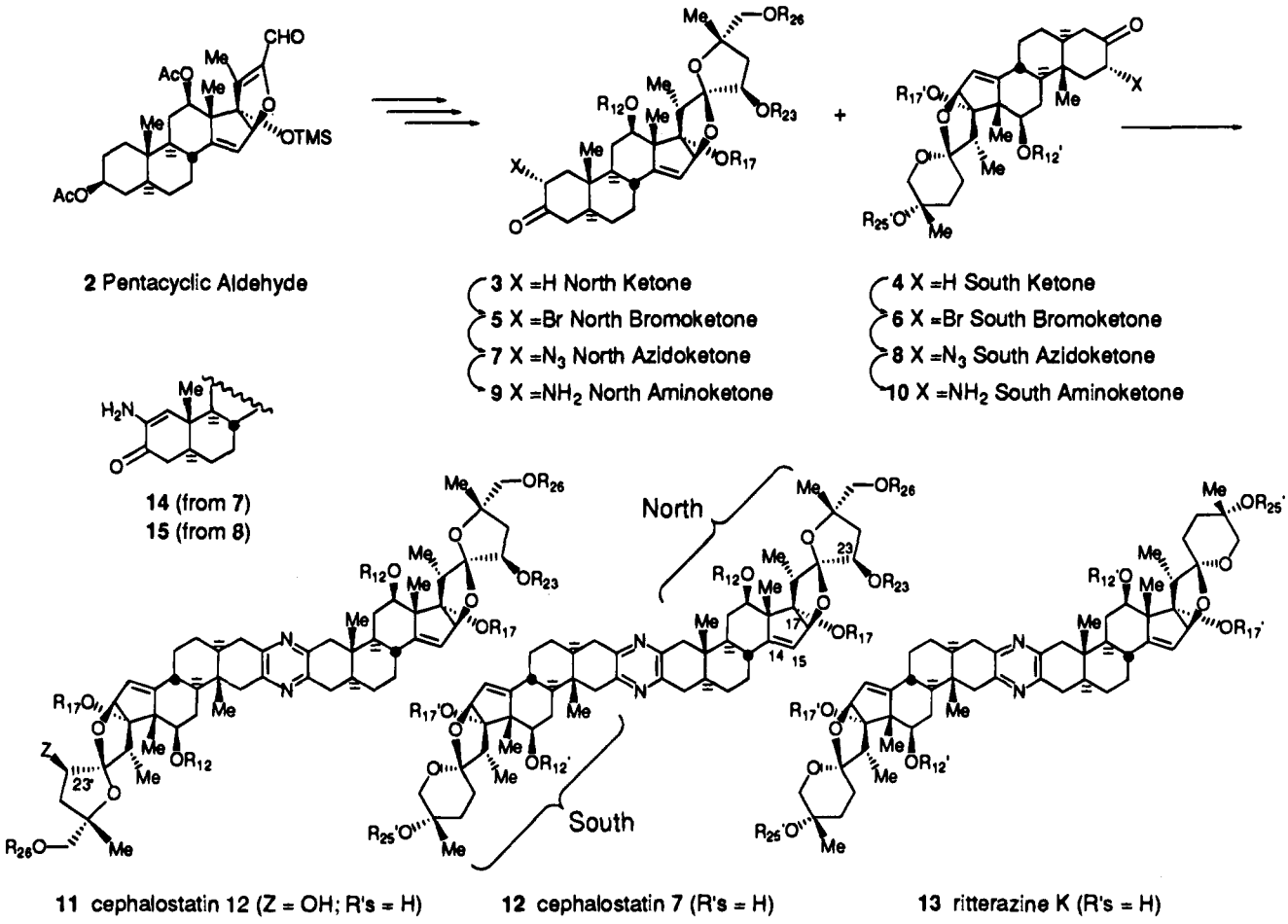
Scheme 1



reasonable that the coupling reaction was slightly biased toward favoring ritterazine K (**13**). Individual treatment of protected **11**–**13** with 15 equiv of TBAF in THF at reflux for 1 h provides the first synthetic samples of cephalostatin 12 (**11**,[16] all R's = H) and cephalostatin 7 (**12**, all R's = H), and ritterazine K (**13**, all R's = H), each in approximately 80% yield. Samples of each of the three synthetic materials were provided to Professor Pettit, who confirmed the identity of cephalostatins 7 and 12 by direct NMR and chromatographic comparison. A search of the residual materials accumulated by the Pettit group in the course of identification of the growing stock of natural cephalostatins revealed a substance having a chromatographic profile identical to that of synthetic ritterazine K (**13**).[17] Unfortunately it was present in only microgram quantities and a definitive NMR could not be secured at this time.[18]

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Supporting Information Available: An experimental procedure for the synthesis of **11**–**13** as well as ^{1}H and ^{13}C NMR spectra and tabular comparison of all new compounds (28 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(16) Rotations of synthetic compounds **11**–13 were as follows: **11** (+151° ± 20°; *c* 0.025 in MeOH; *cf.* natural cephalostatin 12 (**11**) (+157.5°, *c* 0.40 in MeOH; ref 6)); **12** (+97° ± 10°, *c* 0.03 in MeOH; *cf.* natural cephalostatin 7 (**12**) (+ 106°, *c* 0.244 in MeOH; ref 2)); **13** (+117° ± 10°; *c* 0.225 in MeOH; *cf.* natural ritterazine K (**13**) (+74°, *c* 0.1 in MeOH; ref 3b)).

(17) Pyridine-d_5 proton and carbon NMR data for compound **13** are identical to those reported by Fusetani for ritterazine K (see ref 3b and supporting information).

(18) We are grateful to Dr. Jun-Ping Xu for conducting these comparisons.