Total Synthesis of (−)-Altemicidin: A Novel Exploitation of the Potier−Polonovski Rearrangement

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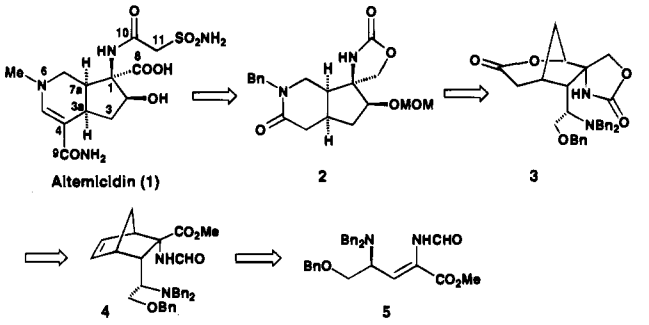
The unusual naturally occurring sulfonamide altemicidin (**1**), isolated from the actinomycete strain *Streptomyces sioyaensis* SA-1758, was first reported by investigators in Japan in 1989.[1] The relative structure of altemicidin was determined by NMR analysis,[2,3] and its absolute configuration was established through X-ray structure determination of its xanthenyl derivative.[3] Altemicidin is the first 6-azaindene monoterpene alkaloid isolated as a metabolite of microorganisms. In addition to its potent acaricidal activity, altemicidin has been shown to strongly inhibit the growth of tumor cells.[1] In this communication, we report the first total synthesis of altemicidin.

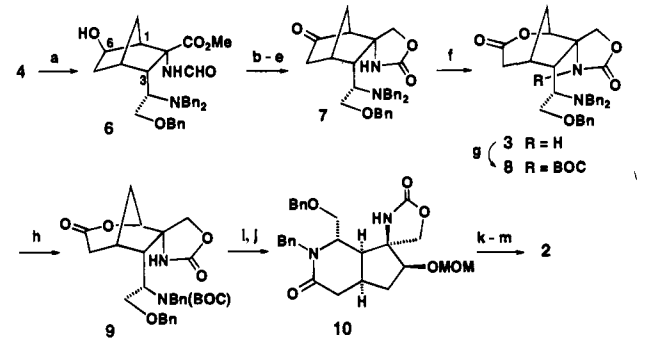
The relatively small but highly functionalized altemicidin molecule posed a formidable challenge for an enantioselective total synthesis. Our strategy, retrosynthetically represented in Scheme 1, was inspired by a Diels−Alder reaction developed by Reetz, in which an analog of dienophile **5** reacted with cyclopentadiene to produce the corresponding adduct with high diastereoselectivity.[4] The bicyclo[2.2.1]heptene derivative **4** is in principle well structured for the regiospecific functionalization of the lone double bond. *N*-Debenzylation of the lactone derivative **3** and transannular lactam formation should give a derivative of **2**, which possesses the desired altemicidin skeleton.

In direct analogy with the reported Reetz cycloaddition,[4] dienophile **5**[5] reacted with cyclopentadiene in the presence of 2.1 equiv of Et_2AlCl at 0 °C for 96 h to produce cycloadduct **4** as a single diastereomer in 87% yield. Rhodium(I)-catalyzed hydroboration of **4** employing catecholborane took place with striking regioselectivity to give exclusively the 6-*exo*-carbinol **6** in 92% yield (Scheme 2).[6] Methanolysis of **6**, followed by $LiAlH_4$ reduction, produced the amino diol in 92% yield. Oxazolidinone formation with triphosgene, then TPAP oxidation,[7] afforded ketone **7** in 85% yield. A variety of reagents under different reaction conditions were tested for the Baeyer−Villiger rearrangement of ketone **7**.[8] Among them, trifluoroperacetic acid was found to give the best result. When **7** was treated with trifluoroperacetic acid in CH_2Cl_2 at 0 °C for 1 h, a mixture of the expected bridgehead-migrated lactone **3** and the "wrong" methylene-migrated lactone was obtained in a 5:4 ratio in 85% yield. Lactone **3** was isolated by chromatography, and its structure was confirmed through single-crystal X-ray analysis.

Scheme 1



Scheme 2[a]



[a] (a) 5% $(COD)_2RhCl$, Ph_3P, catecholborane, THF, − 3 °C; H_2O_2, NaOH, 92%. (b) HCl, MeOH, room temperature, 15 h. (c) $LiAlH_4$, THF. (d) Triphosgene, CH_2Cl_2-saturated aqueous $NaHCO_3$. (e) TPAP, NMO, CH_2Cl_2, 78% from **6**. (f) CF_3CO_3H, CH_2Cl_2, 0 °C, 1 h, 45%. (g) $(BOC)_2O$, DMAP, Et_3N, CH_2Cl_2, room temperature, 15 h, 95%. (h) 20% $Pd(OH)_2/C$, cyclohexene−EtOH, reflux, 3 h, 84%. (i) CF_3CO_2H, CH_2Cl_2, 100%. (j) $CH_2(OMe)_2$, cat. pTSA, PhH, reflux, 85%. (k) 10% Pd/C, HCO_2NH_4, MeOH, reflux, 100%. (l) Dess−Martin periodinane, $CHCl_3$, 90%. (m) $(Ph_3P)_3RhCl$, PhCN, 160 °C, 5 min, 80%.

With the enantiopure lactone **3** in hand, we were able to test the feasibility of the desired transannular lactam formation implied by our retrosynthetic plan. In the presence of DMAP, **3** reacted with $(BOC)_2O$ to form derivative **8** in 95% yield. Transfer hydrogenation of **8** with Pearlman's catalyst (20% $Pd(OH)_2/C$) and cyclohexene[9] selectively cleaved only one of the *N*-benzyl groups followed by BOC migration to yield 84% of **9**. Acidic removal of the BOC group in **9** followed by basic workup triggered the transannular cyclization, leading upon OMOM formation to piperidone **10** in 85% yield.

The stereo-directing role of the CH_2OBn group had now been played out, and its removal was mandated. After considerable experimentation, we found that transfer hydrogenation with ammonium formate and 10% Pd/C in refluxing methanol resulted in the selective *O*-debenzylation of **10** to generate the primary alcohol.[10] Dess−Martin oxidation to the aldehyde,[11] then decarbonylation with Wilkinson's reagent $(Ph_3P)_3RhCl$,[12] produced the norpiperidone **2** in 72% yield from **10**.

Reduction of **2** with $LiAl(OEt)_2H_2$ afforded the *N*-benzyl piperidine derivative **11** in 85% yield (Scheme 3).[13] Subsequent *N*-debenzylation and *N*-methylation were achieved in one synthetic operation. Hydrogenolytic debenzylation using H_2/Pd−C in the presence of formaldehyde gave *N*-methylpiperidine

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(8) (a) For a review, see: Krow, G. R. *Tetrahedron* **1981**, *37*, 2697. (b) Transformation of **6** to the cyclic carbamate-**7** was dictated by our observation that the Baeyer−Villiger rearrangement of the ketone corresponding to **6** gave exclusively the undesired methylene-migrated lactone product.
(9) (a) Hanessian, S.; Liak, T. J.; Vanasse, B. *Synthesis* **1981**, 396. (b) For an example of selective *N*-debenzylation in the presence of an *O*-benzyl group, see: Bernotas, R. C.; Cube, R. V. *Synth. Commun.* **1990**, *20*, 1209.
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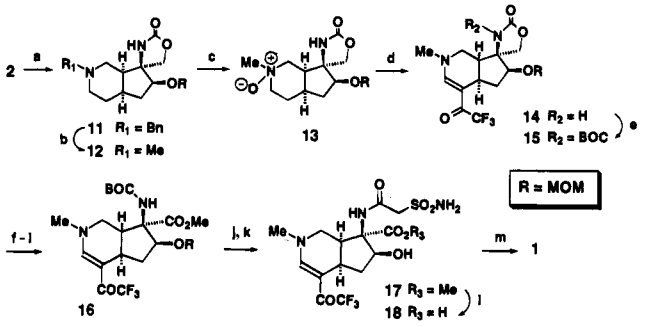
Scheme 3[a]



[a] (a) $LiAl(OEt)_2H_2$, Et_2O, 85%. (b) 10% Pd/C, H_2 (balloon), 37% aqueous HCHO, 87%. (c) H_2O_2, MeOH, 100%. (d) $(CF_3CO)_2O$, pyridine, CH_2Cl_2, 65%. (e) $(BOC)_2O$, DMAP, MeCN, 92%. (f) LiOH, THF–H_2O (3:1), 94%. (g) Dess–Martin periodinane, CH_2Cl_2. (h) $NaClO_2$, *tert*-butyl alcohol. (i) CH_2N_2, THF, 85% (three steps). (j) Catecholborane bromide, CH_2Cl_2, room temperature, 15 min, 70%. (k) (Aminosulfonyl)acetic acid, 1,1′-carbonyldiimidazole, THF, 87%. (l) LiSPr-*n*, HMPA, room temperature, 88%. (m) $NaNH_2$, DABCO, PhH, 80 °C, 40 min, 50%.

derivative **12** in 87% yield. The critical Potier–Polonovski rearrangement sequence to establish the carbamoyl enamine structure was now at hand.[14] In the event, the *N*-oxide **13**, which was generated by hydrogen peroxide oxidation of **12**, reacted with excess trifluoroacetic anhydride followed by pyridine to give in 65% yield the expected vinylogous trifluoromethyl amide **14**.[15] Treatment of **14** with $(BOC)_2O$ in the presence of DMAP afforded the *N*-BOC derivative **15** in 91% yield.[16] The activated oxazolidinone ring was then hydrolyzed with lithium hydroxide. Oxidation of the resulting alcohol with Dess–Martin periodinane produced the aldehyde, which was further oxidized by sodium chlorite to give the acid. Treatment of the acid with diazomethane afforded ester **16** in 80% overall yield.

At this juncture, we needed to construct the sulfamoylacetamide unit, truly a rare functional group among natural products. Both the BOC and MOM groups were deblocked by treatment of **16** with bromocatecholborane to afford the amino alcohol in 70% yield.[17] (Aminosulfonyl)acetic acid[18] was activated with 1,1′-carbonyldiimidazole[19] and then coupled with the amino alcohol to give amide **17** in 87% yield.

The final thrust was initiated by nucleophilic cleavage of the methyl ester, since normal aqueous alkaline hydrolysis of **17** was sluggish due to steric hindrance. Treatment of ester **17** with lithium *n*-propyl mercaptide in HMPA at room temperature for 2 h afforded acid **18** in 88% yield.[20] Transformation of the trifluoromethyl group in **18** to the amino group was achieved by a Haller–Bauer fragmentation.[21] Treatment of acid **18** with sodium amide in the presence of DABCO[22] gave in 50% yield the synthetic altemicidin (**1**) ($[\alpha]_D = -7.0°$(*c* 0.65, H_2O), mp 195–200° dec; lit.[1] $[\alpha]_D = -7.6°$(*c* 1.00, H_2O), lit.[1] mp 195–199° dec). Although we were unable to obtain a reference sample of natural **1**, the high-field ^1H and ^{13}C NMR spectra of our synthetic altemicidin were identical with those described in detail in the original literature,[1] confirming that its total synthesis has been achieved.

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Supporting Information Available: Physical and analytical data for **1**–**4**, **7**, **10**, **12**, **14**, **16**, and **17** and experimental procedures for **11**, **12**, **14**, and **1** (17 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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