Studies toward Thiostrepton Antibiotics: Assembly of the Central Pyridine−Thiazole Cluster of Micrococcins

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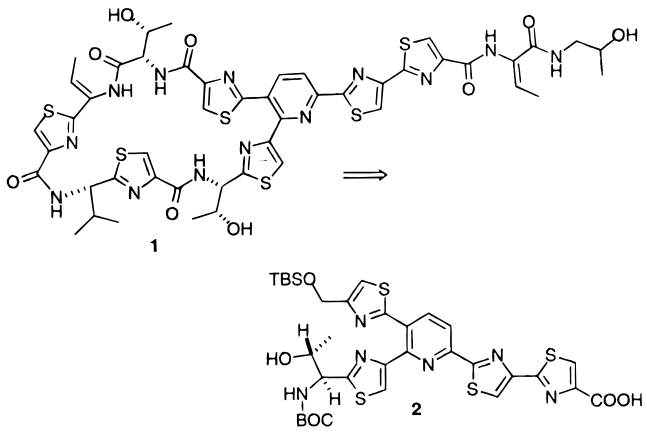
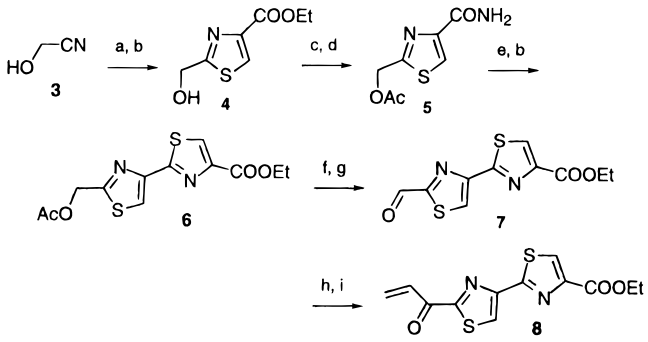
Received March 11, 1997

Micrococcin P1, **1**,[1] is a member of the thiostrepton family of antibiotics,[2] and it is a potent inhibitor of protein synthesis, seemingly as a result of interaction with ribosomal RNA.[3] Thiostrepton itself [4] and other members of the the same family[5] have been found to induce expression of various genes of unknown function in *Streptomyces* species. This property has not yet been reported for micrococcin, but because **1** and thiostrepton appear to have very similar biological properties,[3] it seems likely that **1** may also be a gene inducer. Despite these exciting reports, almost no synthetic work has been recorded in the thiostrepton area. Some of the difficulties inherent to the construction of the complex pyridine−thiazole clusters present in these substances have been addressed in the synthesis of a degradation product of **1**, termed micrococcinic acid,[6] which, however, lacks the delicate threonine-derived array evident in one of the thiazole subunits. We now describe a convergent synthesis of **2**, the complete heterocyclic core of micrococcins.



It seemed plausible that the pyridine nucleus with its full complement of thiazoles could be manufactured through the merger of fragments **8** and **15**, possibly by suitable modifications of our pyridine-forming chemistry.[7] Compounds **8** and **15** were prepared as follows. Reaction of glycolonitrile, **3**, with gaseous H_2S afforded the expected thioamide in essentially quantitative yield. In crude form, this material reacted with ethyl bromopyruvate (EBP) to furnish thiazole **4** (Scheme 1). Sequential ammonolysis, O-acetylation, treatment with the Lawesson reagent,[8] and condensation with EBP yielded bithiazole **6**. This compound was advanced to the sensitive enone **8** by selective acetate cleavage, oxidation of the resulting carbinol to an aldehyde, vinyl Grignard addition, and again oxidation with MnO_2.[9]

Scheme 1[a]



[a] Key: (a) H_2S, H_2O; (b) ethyl bromopyruvate, EtOH, heat, 95% a−b; (c) NH_3, MeOH; (d) Ac_2O, pyridine, 67% c−d; (e) Lawesson reagent, toluene, reflux; (f) K_2CO_3, EtOH; (g) PCC, CH_2Cl_2; 40% from **5**; (h) CH_2=CHMgBr; (i) MnO_2, 72% h−i.

The route to compound **15** commenced with ammonolysis of L-threonine derivative **9**[10] and chemoselective conversion of the amide into thioamide **10** with the Lawesson reagent. Best results were obtained when the thionation reaction was run in refluxing benzene (Scheme 2).[11] Condensation of **10** with EBP yielded thiazole (−)-**11**, which reacted with 3 equiv of the carbanion arising upon treatment of thiazole **14** with *n*-BuLi to form ketone **15** in high yield.[12]

The fusion of **8** and **15** into a pyridine by variants of our chemistry[7] was not straightforward, while more traditional methods were marred by technical difficulties. In particular, the formal Michael addition of the enolate of **15** into **8** was plagued by the great sensitivity of the enone to basic agents (polymerization). Numerous experiments ultimately unveiled an outstanding solution in the form of catalysis by a heterogeneous system. Thus, the long-sought Michael adduct **16** emerged in nearly quantitative yield upon reaction of **8** and **15** in ethyl acetate at room temperature in the presence of (insoluble)

(1) Structure: (a) Bycroft, B. W.; Gowland, M. S. *J. Chem. Soc., Chem. Commun.* **1978**, 256. Review: (b) Pestka, S. In *Antibiotics*; Corcoran, J. W., Hahn, F. E., Eds.; Springer-Verlag: New York, 1975; Vol. 3, p 480 ff.

(2) Review: Pestka, S.; Bodley, J. W. In *Antibiotics*; Corcoran, J. W., Hahn, F. E., Eds.; Springer-Verlag: New York, 1975; Vol. 3, p 531 ff.

(3) (a) Rosendahl, G.; Douthwaite, S. *Nucleic Acids Res.* **1994**, *22*, 357. (b) Cundliffe, E.; Thompson, J. *Eur. J. Biochem.* **1981**, *118*, 47.

(4) (a) Murakami, T.; Holt, T. G.; Thompson, C. T. *J. Bacteriol.* **1989**, *171*, 1459. (b) Holmes, D. G.; Caso, J. L.; Thompson, C. T. *EMBO J.* **1993**, *8*, 3183.

(5) Yun, B.-S.; Hidaka, T.; Furihata, K.; Seto, H. *J. Antibiot.* **1994**, *47*, 510.

(6) Kelly, T. R.; Jagoe, C. T.; Gu, Z. *Tetrahedron Lett.* **1991**, *32*, 4263.

(7) Cf. (a) Ciufolini, M. A.; Roschangar, F. *J. Am. Chem. Soc.* **1996**, *118*, 12082. (b) Ciufolini, M. A.; Shen, Y. C.; Bishop, M. J. *J. Am. Chem. Soc.* **1995**, *117*, 12460. (c) Ciufolini, M. A. In *Advances in Heterocyclic Natural Product Synthesis*; Pearson, W. H., Ed.; JAI Press: Greenwich, CT, 1996; Vol. 3, p 1.

(8) Thomsen, I.; Clausen, K.; Scheibye, S.; Lawesson, S. O. In *Organic Syntheses*; Freeman, J. P., Ed.; John Wiley & Sons: New York, NY, 1990; Collect. Vol. VII, p 372 and references cited therein.

(9) Prepared according to: Attenburrow, J.; Cameron, A. F. B.; Chapman, J. H.; Evans, R. M.; Hems, B. A.; Jansen, A. B. A.; Walker, T. *J. Chem. Soc.* **1952**, 1094. Other oxidants (PCC, PDC, Swern, TPAP/NMO) gave poor results.

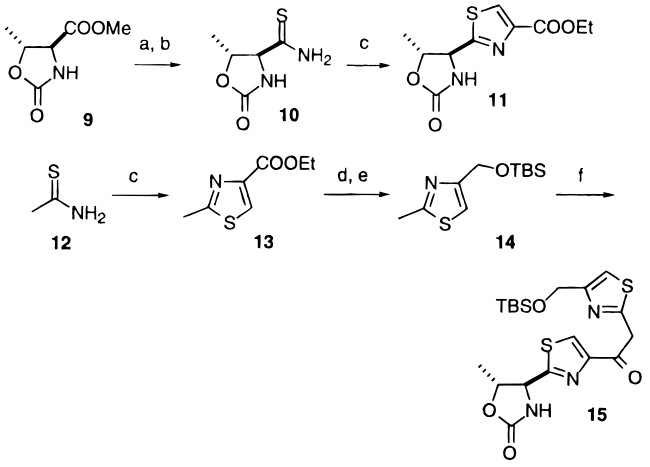
(10) Obtained from L-threonine in 97% yield by: (a) $COCl_2$, NaOH (cf. Xi, N.; Ciufolini, M. A. *Tetrahedron Lett.* **1995**, *36*, 6595); (b) MeOH, cat. H_2SO_4.

(11) A complex mixture of products was obtained when this reaction was run under standard conditions (refluxing xylenes, ca. 135 °C).

(12) This material existed as a 1:3 ratio mixture of ketone and one geometric isomer of the enol form (NMR, probably the *Z* isomer due to intramolecular H bonding).

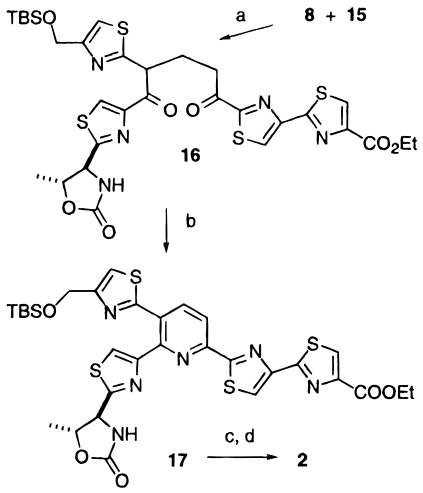
S0022-3263(97)00442-8 CCC: $14.00

Scheme 2[a]



[a] Key: (a) NH_3, MeOH; (b) Lawesson reagent, benzene, reflux; (c) ethyl bromopyruvate, EtOH, reflux, 82% a−c for **11**, 96% for **13**; (d) LAH, Et_2O, 0 °C; (e) TBS-Cl, imidazole, DMF, rt, 94% d−e; (f) 3 equiv of **14**, 3 equiv of *n*-BuLi, THF, −78 °C, then add 1 equiv of **11**, 90%.

Scheme 3[a]



[a] Key: (a) cat. Li_2CO_3, EtOAc, rt, 99%; (b) NH_4OAc, EtOH, then DDQ, $CHCl_3$, 98%; (c) BOC_2O, cat. DMAP, Et_3N, CH_2Cl_2; (d) LiOH, aqueous THF, 95% c−d.

Li_2CO_3. Conversion of **16** to a pyridine also proved to be difficult, due to its propensity to undergo retro-Michael reaction upon treatment with various sources of NH_3. Finally, an efficient conversion was realized by exposure of **16** to practically neutral NH_4OAc in EtOH, followed by DDQ oxidation of the intermediate dihydropyridine to (−)-**17** (Scheme 3). Exposure of the oxazolone *N*-BOC derivative of (−)-**17** to aqueous LiOH induced simultaneous Kunieda cleavage[13] of the cyclic carbamate and ester hydrolysis to furnish acid (−)-**2**, a substance that we believe to be suitable for incorporation into more advanced intermediates for micrococcins.

The successful creation of **2** lays the ground for further synthetic investigations in the thiostrepton area, a challenge that has remained heretofore largely unanswered. Further ramifications of this work will be described in due course.

Acknowledgment. We gratefully acknowledge the NIH (CA-55268), the NSF (CHE 95-26183), and the R. A. Welch Foundation (C-1007), for their generous support of our research program. M.A.C. is a Fellow of the Alfred P. Sloan Foundation, 1994−1998.

Supporting Information Available: Experimental procedure and spectral data for selected compounds (19 pages).

JO9704422

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