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Design of an efficient strategy for total synthesis of the microbial metabolite (—)-bactobolin

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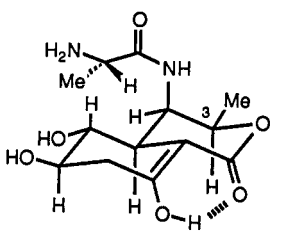
Abstract - Bactobolin (2), a broad spectrum antibiotic and antitumor agent produced by a Pseudomonas strain, has been synthesized in a completely stereoselective manner in approximately twenty steps from readily available cyclohexenol 3.

INTRODUCTION

Nearly three decades ago Haskell and Bartz isolated actinobolin (1) from a strain of Streptomyces griseoviridus (ref. 1). The unique structure of 1 was subsequently established by a combination of chemical, spectral and X-ray crystallographic methods (ref. 2). More recently, an actinobolin congener, bactobolin (2), was isolated from a Pseudomonas culture (ref. 3) and its structure was elucidated by X-ray crystallography (ref. 4). Both actinobolin and bactobolin show broad spectrum antibiotic and antitumor activity, with the latter compound being the more potent (ref. 5). The only difference



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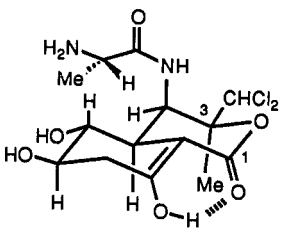


2

in the structures of 1 and 2 is at C-3, where bactobolin bears an unusual dichloromethyl group.

Both actinobolin (1) and bactobolin (2) are compact, highly functionalized molecules which pose formidable synthetic challenges. Over the past few years three total syntheses of actinobolin have appeared (ref. 6), including one from these laboratories (ref. 6b). Moreover, two syntheses of N-acetylactinobolamine have also been described (ref. 7). We now report the first total synthesis of bactobolin using an efficient variation of our successful actinobolin strategy.

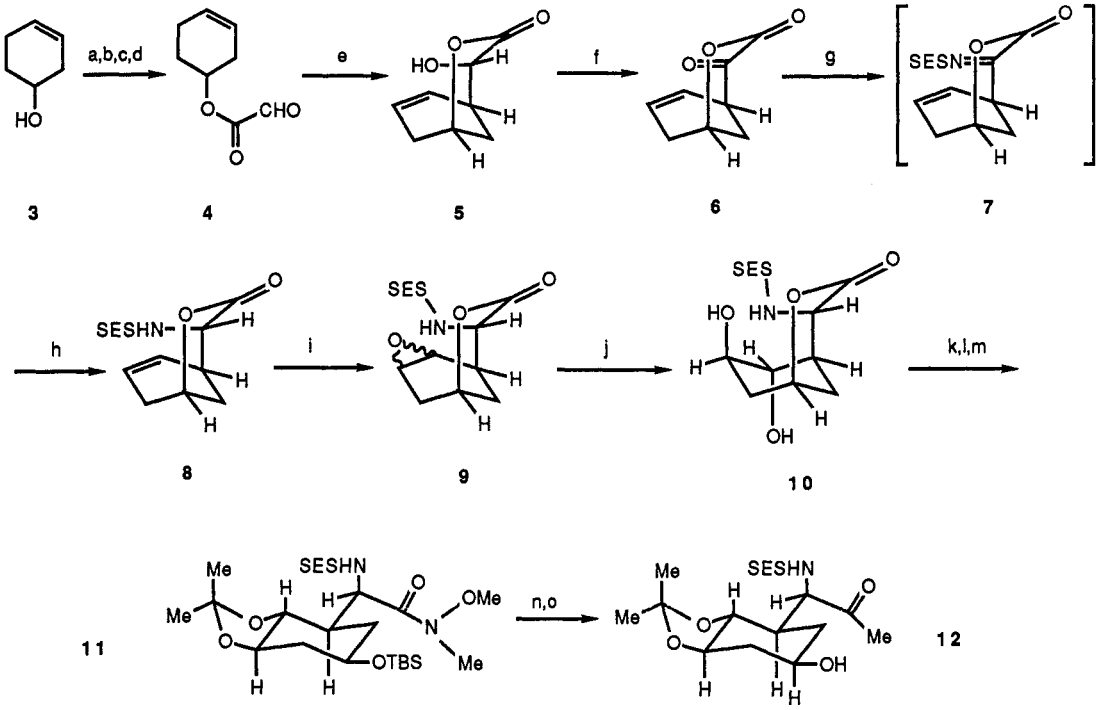
SYNTHESIS OF BACTOBOLIN

Glyoxylate 4 was prepared in 65% overall yield (ref. 8) from readily available cyclohexenol 3 (ref. 9) using the Emmons-Kornblum procedure (ref. 10) (Scheme 1). Exposure of 4 to stannic chloride in nitromethane (ref. 11) caused an intramolecular aldehyde ene reaction to occur, yielding hydroxylactone 5 (50-60%). Interestingly, other Lewis acids such as $EtAlCl_2$, $BF_3 \cdot Et_2O$, $AlCl_3$, $FeCl_3$, $ZnCl_2$ and Me_2AlCl in a variety of solvents gave no more than a trace of ene product 5. Collins oxidation of 5 afforded α-ketolactone 6 (86%).

The next stage of the synthesis involved introduction of the C-4 nitrogen in an appropriately protected form. We knew from our earlier work (ref. 8) that N-acyl protecting groups were not compatible with some of the projected synthetic transformations. Furthermore, we have found that the p-methylbenzylsulfonyl (PMS) N-protecting group used by Ohno (ref. 6a) and by us (ref. 6b) for actinobolin cannot be removed from bactobolin (ref. 12).

However, the β-trimethylsilylethanesulfonyl (SES) group (ref. 13) proved suitable for the total synthesis. Thus, treatment of 6 with the N-sulfinyl compound (ref. 14) derived from SES-NH_2 gave an intermediate N-sulfonylimine 7, which was stereoselectively reduced from the least congested face to afford sulfonamido lactone 8 (80%). Epoxidation of 8 gave a 1.8:1 mixture of isomeric epoxides 9 (100%). This mixture was then solvolyzed with anhydrous formic acid and the resulting formate esters were cleaved to give a single diaxial 1,2-diol 10 which possesses four of the five chiral centers of bactobolin.

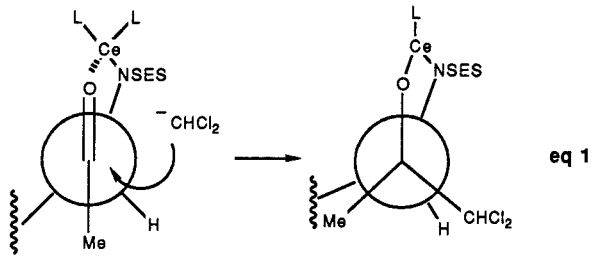
Scheme 1



a) $BrCH_2COBr$/pyr, CH_2Cl_2, 0°C b) NaI, Me_2CO c) $AgNO_3$, MeCN d) NaOAc, DMSO e) $SnCl_4$, $MeNO_2$ f) CrO_3/pyr g) $Me_3SiCH_2CH_2SO_2NSO$ (SESNSO)/$BF_3{\cdot}Et_2O$, $ClCH_2CH_2Cl$, 42°C h) $NaCNBH_3$, t-amyl alcohol i) mCPBA, CH_2Cl_2 j) HCOOH; MeOH/Et_3N k) $Me_2AlNMe(OMe)$, THF l) $Me_2C(OMe)_2$/p-TsOH, DMF m) TBSOTf/2,6-lutidine, DMF, -15°C n) MeMgBr, THF o) nBu_4NF, THF, RT

The lactone ring of 10 was cleanly opened with an aluminum reagent prepared from trimethyl aluminum and N,O-dimethylhydroxylamine (ref. 15) to give an amido triol, which was protected as silyl ether acetonide 11 (65% from epoxides 9). Addition of methyl magnesium bromide to 11 (ref. 16) afforded the desired methyl ketone, and removal of the silyl protecting group yielded ketoalcohol 12 (88%).

Studies were next conducted on introduction of the dichloromethyl group of bactobolin (2). Attempted direct addition of dichloromethyl lithium to ketone 12 gave a complex mixture of products. However, addition of one equivalent of trichlorocerium to this lithium reagent produces an organocerium species (ref. 17) which does add to 12 to afford a single stereoisomeric alcohol 13 (Scheme 2). We did find that some starting ketone 12 could be recovered (90% yield of 13, 60% conversion) presumably due to enolization towards the methyl group. The stereochemistry of 13 can be rationalized by a Cram chelation-controlled addition to the methyl ketone as outlined in eq. 1. Oxidation of the secondary hydroxyl group of 13 afforded ketoalcohol 14.



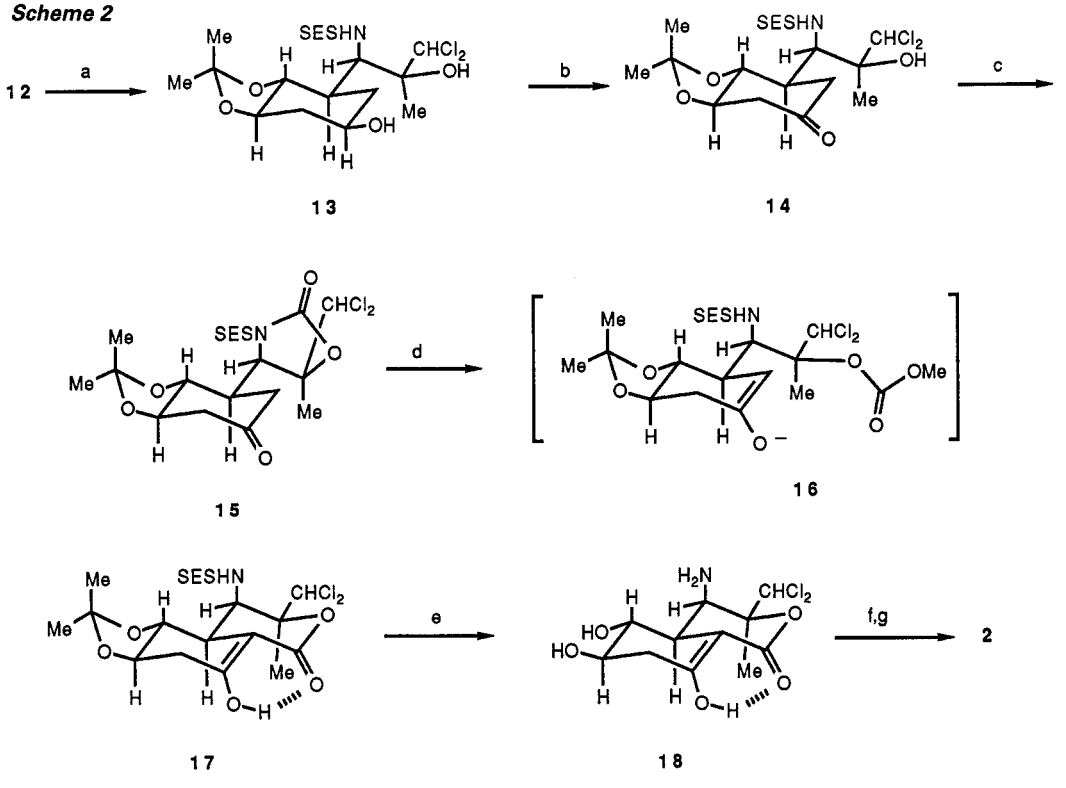
eq 1

The remaining problem in the synthesis of bactobolin involved developing a method for placement of the missing carboxylate carbon (C-1). Toward this end, several attempts were made to O-acylate the tertiary hydroxyl group of 14 with various haloformates and other phosgene-derived reagents. As one might expect, this alcohol was quite resistant to acylation. It was eventually found that treatement of 14 with methyl chloroformate in triethyl amine containing 4-pyrrolidinopyridine led to formation of cyclic carbamate 15. We believe that this compound arises via an initial N-acylation of 14 followed by a second O-acylation step. It seems clear from inspection of molecular models that an enolate derived from ketone 15 cannot directly C-acylate. We reasoned, however, that treatment of 15 with a nucleophilic alkoxide base would lead to carbamate ring opening to give a carbonate with concomitant ketone deprotonation to afford an equilibrating regioisomeric mixture of enolates. Of the two possible enolates only the one shown in 16 could undergo intramolecular acylation. In fact, exposure of 15 to methanolic sodium methoxide yielded the desired enol lactone 17 (70%).

To complete the synthesis, the SES protecting group of 17 was removed with fluoride (ref. 13) and the acetonide moiety was hydrolyzed to produce racemic amino diol 18 (45-50%). Acylation of 18 with N-Cbz-L-alanine gave a mixture of diastereomers (60% combined yield) which was separated by preparative TLC. Hydrogenolysis (80%) of the desired isomer afforded (-)-bactobolin (2) having spectral data identical with a natural sample (ref. 18).

We have therefore completed a stereoselective total synthesis of bactobolin (2) in a sequence involving approximately twenty steps starting from cyclohexenol 3.

Scheme 2



a) $Cl_2CHLi/CeCl_3$, Et_2O, -100°C b) CrO_3/pyr, CH_2Cl_2 c) MeOCOCl, Et_3N, 4-pyrrolidinopyridine
d) NaOMe, MeOH e) nBu_4NF, THF, 52°C; MeOH/HCl f) Cbz-L-alanine/DCC/Et_3N, DMF g) H_2/Pd-C, MeOH/HOAc, 0.5 N HCl

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REFERENCES

1. T.H. Haskell and Q.R. Bartz, Antibot. Ann., 505 (1958-59).
2. F.J. Antotz, D.B. Nelson, D.L. Herald and M.E. Munk, J. Am. Chem. Soc., 92, 4933 (1970) and references cited therein. J.B. Wetherington and J.W. Moncrief, Acta Crystallogr., B31, 501 (1975).
3. S. Kondo, Y. Horiuchi, M. Hamada, T. Takeuchi and H. Umezawa, J. Antibiot., 32, 1069 (1979).
4. I. Ueda, T. Munakata and J. Sakai, Acta Crystallogr., B36, 3128 (1980).
5. M. Hori, K. Suzukake, C. Ishikawa, H. Asakura and H. Umezawa, J. Antibiot., 34, 465 (1981) and references cited therein.
6. a. M. Yoshioka, H. Nakai and M. Ohno, J. Am. Chem. Soc., 106, 1133 (1984). b. R.S. Garigipati, D.M. Tschaen and S.M. Weinreb, J. Am. Chem. Soc., 107, 7790 (1985). c. A.P. Kozikowski, T.R. Nieduzak, T. Konoike and J.P. Springer, J. Am. Chem. Soc., 109, 5167 (1987).
7. M.A. Rahman and B. Fraser-Reid, J. Am. Chem. Soc., 107, 5576 (1985). D. Askin, C. Angst and S. Danishefsky, J. Org. Chem., 52, 622 (1987).
8. D.M. Tschaen, Ph.D. Thesis, The Pennsylvania State University (1984).
9. B.A. Pearlman, J. Am. Chem. Soc., 101, 6398 (1979).
10. N. Kornblum and H.W. Frazier, J. Am. Chem. Soc., 88, 865 (1966). W.D. Emmons and J.P. Freeman, J. Am. Chem. Soc., 77, 4415 (1955).
11. cf D.L. Lindner, J.B. Doherty, G. Shoham and R.B. Woodward, Tetrahedron Lett., 23, 5111 (1982).
12. R.S. Garigipati and S.M. Weinreb, Unpublished results.
13. S.M. Weinreb, D.M. Demko, T.A. Lessen and J.P. Demers, Tetrahedron Lett., 27, 2099 (1986).
14. R. Bussas, G. Kresze, H. Munsterer and A. Schwobel, Sulfur Rep., 2, 215 (1983).
15. A. Basha, M. Lipton and S.M. Weinreb, Tetrahedron Lett., 4171 (1977).
16. S. Nahm and S.M. Weinreb, Tetrahedron Lett., 22, 3815 (1981).
17. T. Imamoto, T. Kusumoto, Y. Tawarayama, Y. Sugiura, T. Mita, Y. Hatanaka and M. Yokoyama, J. Org. Chem., 49, 3904 (1984).
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