ORGANIC LETTERS

2007
Vol. 9, No. 3
421−424

Synthesis of the Pyrrolidinone Core of KSM-2690 B

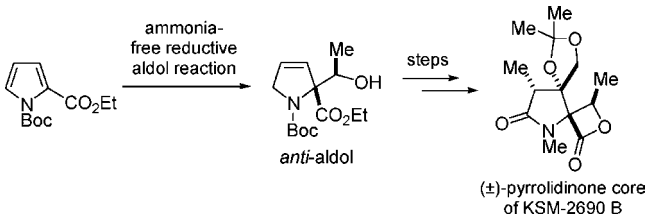
Timothy J. Donohoe,* Jessica Y. K. Chiu, and Rhian E. Thomas[†]

Department of Chemistry, University of Oxford, Chemistry Research Laboratory, Mansfield Road, Oxford OX1 3TA, U.K.

timothy.donohoe@chem.ox.ac.uk

Received November 6, 2006

ABSTRACT



The first synthesis of the pyrrolidinone core of the polyene β-lactone antibiotic KSM-2690 B is described. An ammonia-free Birch reductive aldol reaction utilizing acetaldehyde is one of the key steps, together with a ruthenium-catalyzed alkene isomerization reaction.

Isolated in 2000 from the *Streptomyces* sp. KSM-2690 strain, KSM-2690 B[1] (**1**) (Figure 1) belongs to the oxazolomycin

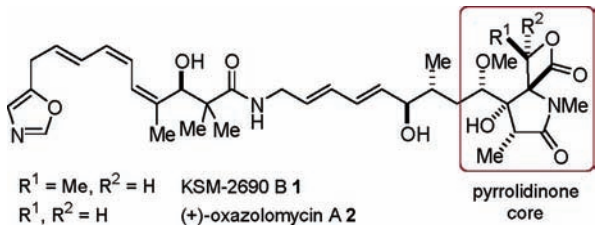


Figure 1. KSM-2690 B and oxazolomycin A.

family,[2] a class of polyene β-lactone antibiotics of which oxazolomycin A (**2**) is the parent. Compound **1** exhibits antimicrobial activity against several Gram-positive bacteria and cytotoxic activity against human bladder carcinoma T24 cells.[1] Structurally, **1** features a bicyclic β-lactone-γ-lactam pyrrolidinone core (differing from **2** by the presence of a methyl group on the β-lactone) which is linked by a diene portion to an oxazole-triene. So far, the only total synthesis reported of any of this family of compounds is that of neooxazolomycin,[3] the γ-lactone congener of **2**. To date, most studies have focused on the triene and diene fragments of **2**,[4] and reports on the synthesis of the pyrrolidinone core have predominantly been on model systems.[5]

We report, herein, our synthesis of the pyrrolidinone core of **1** which utilizes a diastereoselective ammonia-free reductive aldol reaction of a pyrrole, as previously developed within the group.[6]

Our retrosynthetic analysis is shown in Scheme 1. We felt that compound **3** was a suitable target on which to test the reductive aldol methodology. Moreover, in any subsequent

[†] Author to whom correspondence regarding the X-ray crystal structure should be addressed.

(1) Otani, T.; Yoshida, K. I.; Kubota, H.; Kawai, S.; Ito, S.; Hori, H.; Ishiyama, T.; Oki, T. *J. Antibiot.* **2000**, *53*, 1397.

(2) Moloney, M. G.; Trippier, P. C.; Yaqoob, M.; Wang, Z. *Curr. Drug Discovery Technol.* **2004**, *1*, 181 and references therein.

(3) Kende, A. S.; Kawamura, K.; DeVita, R. J. *J. Am. Chem. Soc.* **1990**, *112*, 4070.

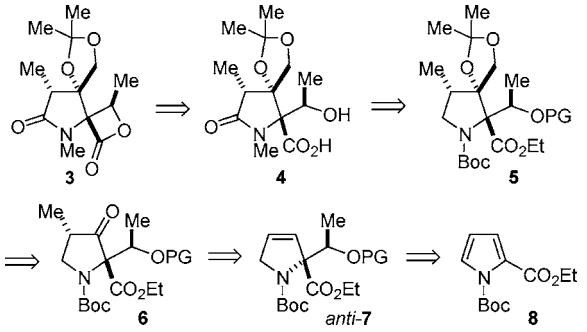
(4) (a) Henaff, N.; Whiting, A. *Org. Lett.* **1999**, *1*, 1137. (b) Wang, Z. Y.; Moloney, M. G. *Tetrahedron Lett.* **2002**, *43*, 9629. (c) Bulger, P. G.; Moloney, M. G.; Trippier, P. C. *Synlett* **2002**, 1871. (d) Bulger, P. G.; Moloney, M. G.; Trippier, P. C. *Org. Biomol. Chem.* **2003**, *1*, 3726.

(5) (a) Andrews, M. D.; Brewster, A. G.; Moloney, M. G. *Synlett* **1996**, 612. (b) Papillon, J. P. N.; Taylor, R. J. K. *Org. Lett.* **2000**, *2*, 1987. (c) Moloney, M. G.; Yaqoob, M. *Synlett* **2004**, 1631. (d) Mohapatra, D. K.; Mondal, D.; Gonnade, R. G.; Chorghade, M. S.; Gurjar, M. K. *Tetrahedron Lett.* **2006**, *47*, 6031.

(6) (a) Donohoe, T. J.; House, D. *Tetrahedron Lett.* **2003**, *44*, 1095. (b) Donohoe, T. J.; House, D.; Ace, K. W. *Org. Biomol. Chem.* **2003**, *1*, 3749.

10.1021/ol062705x CCC: $37.00
Published on Web 01/09/2007

Scheme 1. Retrosynthetic Analysis

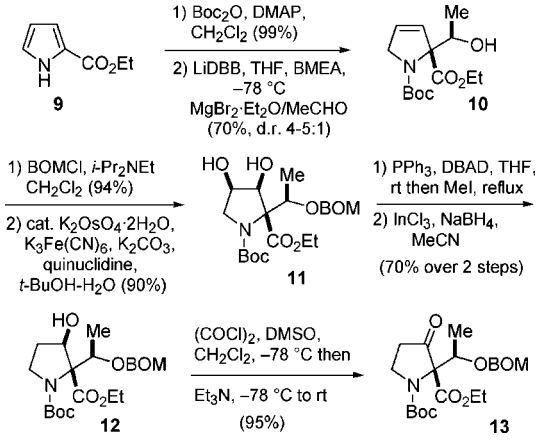


total synthesis of KSM-2690 B, deprotection of the acetonide and oxidation of the resultant primary alcohol would give an α-hydroxyaldehyde which may be used for coupling with the side chain.

The spiro lactone **3** could be derived from hydroxyacid **4** and, importantly, with the lactam moiety introduced late in the synthesis by oxidation of pyrrolidine **5** with in situ generated ruthenium tetraoxide.[7] The hydroxymethyl group at the C-3 position could be introduced by organometallic addition to the ketone functionality of β-ketoester **6** which could, in turn, be formed from manipulation of the double bond within the pyrrolidine ring of **7**. Finally, the aldol adduct could be accessed by an *anti*-selective ammonia-free reductive aldol reaction of the electron-deficient pyrrole ester **8**.

Thus, commercially available pyrrole **9** was protected to give *N*-Boc pyrrole **8** in excellent yield (Scheme 2). The latter

Scheme 2. Synthesis of β-Ketoester **13**

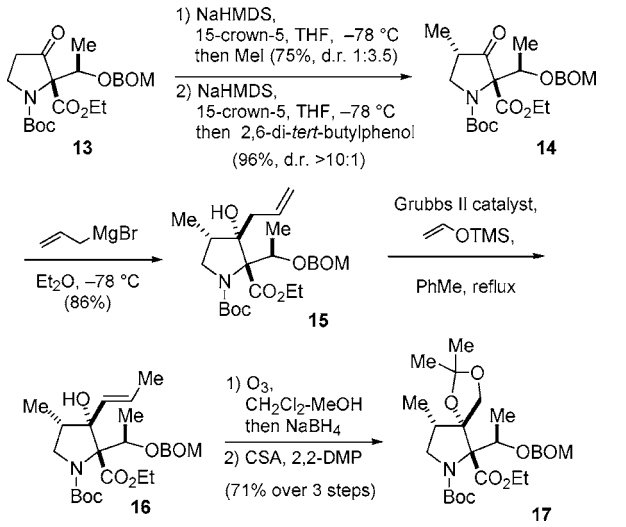


was then subjected to ammonia-free reductive aldol reaction conditions and quenched, after transmetalation with magnesium bromide, with acetaldehyde to give the aldol adduct **10** with good selectivity, favoring the (separable) *anti* diastereoisomer. This *anti* stereoselectivity is well precedented[6b] and was also key in our recent total synthesis of (±)-omuralide.[8]

A protecting group was required for aldol adduct **10** which would be stable to acid and base, as well as nucleophilic attack, and yet would also be removed with ease. The benzyloxymethyl (BOM) protecting group appeared to be ideal as it satisfied all these criteria. The protection of **10** with BOM chloride and Hünig's base occurred smoothly, and the protected aldol adduct was converted to β-hydroxyester **12** via a three-step sequence.[9] Dihydroxylation of the double bond using modified Sharpless conditions[10] led to selective attack from the face *anti* to the carbon bearing the *O*-BOM group to give *syn*-diol **11**.[11] This particular facial bias is worth noting here and becomes crucial later on in the synthesis. Regioselective Mitsunobu inversion of the less-hindered hydroxyl group at the C-4 position, with an iodide nucleophile,[12] furnished the corresponding C-4 iodohydrin, and deiodination was achieved with catalytic indium hydride generated in situ[13] to afford β-hydroxyester **12** in 70% yield over two steps. Finally, oxidation using Swern conditions provided β-ketoester **13** in excellent yield.

With ketoester **13** in hand, the next step was to address methylation at C-4 (Scheme 3). This was accomplished using

Scheme 3. Construction of the C-3 Tertiary Alcohol



sodium hexamethyldisilazide base and methyl iodide, and the methylated ketoester was obtained in good yield as an

(7) The late introduction of the lactam moiety could be advantageous. Tetramic acid derivatives (which have been used as alternative precursors to the oxazolomycin skeleton) can give problems because of the presence of an epimerizable center. See refs 2 and 5c.

(8) (a) Donohoe, T. J.; Sintim, H. O.; Sisangia, L.; Harling, J. D. *Angew. Chem., Int. Ed.* **2004**, *43*, 2293. (b) Donohoe, T. J.; Sintim, H. O.; Sisangia, L.; Ace, K. W.; Guyo, P. M.; Cowley, A.; Harling, J. D. *Chem.−Eur. J.* **2005**, *11*, 4227.

(9) Similar tactics were used en route to omuralide: see ref 8.

(10) (a) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483. (b) Eames, J.; Mitchell, H.; Nelson, A.; O'Brien, P.; Warren, S.; Wyatt, P. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1095.

(11) The relative stereochemistry of **11** was assigned by analogy to ref 8b.

(12) Schumacher, K. K.; Jiang, J.; Joullie, M. M. *Tetrahedron: Asymmetry* **1998**, *9*, 47.

(13) Inoue, K.; Sawada, A.; Shibata, I.; Baba, A. *J. Am. Chem. Soc.* **2002**, *124*, 906.

inseparable 3.5:1 mixture of diastereomers. This result is consistent with selective methylation from the less-hindered top face, anti to the *O*-BOM group, which delivers the undesired stereochemistry for the target.

To reverse the selectivity, as required for KSM-2690 B, this mixture was deprotonated and 2,6-di-*tert*-butylphenol was used as a bulky proton source to reprotonate the ketone enolate from the top face. This procedure worked as planned and gave the desired diastereomer **14** in excellent yield and >10:1 selectivity.

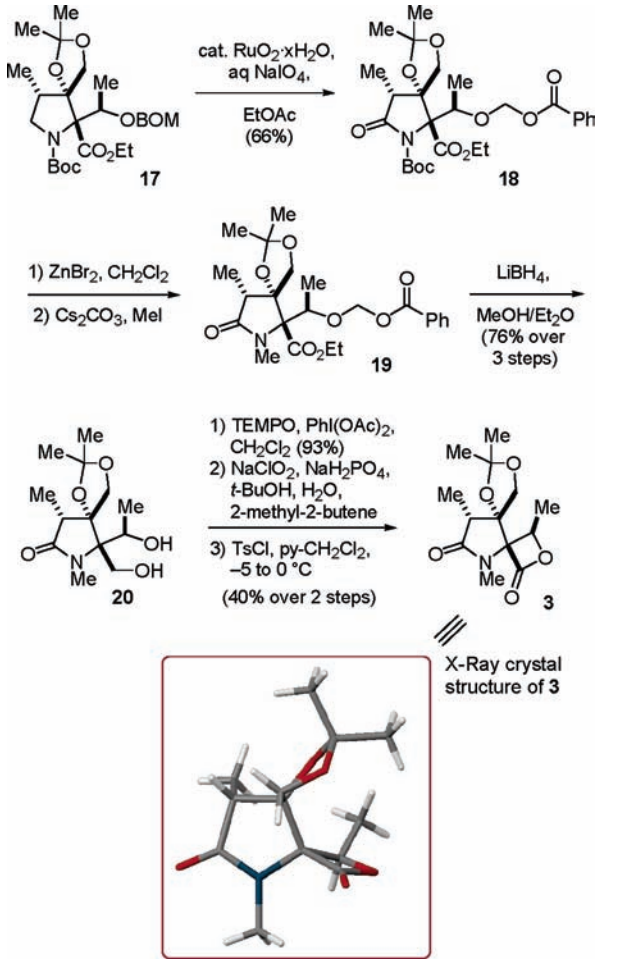
Next, we focused on the construction of the tertiary alcohol at C-3 and investigated the addition of a nucleophile that could eventually be converted to a hydroxymethyl functionality. Addition of a vinyl group to ketone **14** was attractive because a one-pot ozonolysis procedure could then be employed to give the desired 1,2-diol (using a sodium borohydride workup)[14] or a hydroxyaldehyde (through a DMS workup). Surprisingly, ketone **14** was inert to reaction with a variety of vinyl organometallic reagents and conditions that we investigated.[15]

Therefore, we sought an alternative approach. It is precedented that terminal alkenes can be isomerized to internal alkenes using Grubbs' second-generation catalyst and an excess of vinyloxytrimethylsilane.[16] Our plan was to undertake allyl organometallic addition to methylketone **14** followed by isomerization of the alkene. Pleasingly, allyl Grignard addition to methylketone **14** (again proceeding from the less-hindered top face as drawn) gave homoallyl alcohol **15** as a single diastereoisomer, and subsequent ruthenium-catalyzed isomerization to allyl alcohol **16** proceeded smoothly. Next, alcohol **16** was ozonolyzed and reduced in one pot to afford the corresponding 1,2-diol which, when stirred in 2,2-dimethoxypropane under acid catalysis, gave acetonide **17** in excellent yield over three steps.

The oxidation of acetonide **17** to lactam **18** with ruthenium tetroxide under biphasic conditions[17] proceeded in good yield and also (unavoidably) led to oxidation of the benzylic position of the BOM group (Scheme 4). We found that the oxidized BOM group was unstable to strongly acidic conditions, and therefore, the conventional method for deprotecting the Boc group, with TFA, was unsuitable. However, zinc bromide achieved the required transformation selectively from **18** under very mild conditions.[18] Treatment of the resulting lactam with cesium carbonate and methyl iodide led to smooth *N*-methylation to give the key lactam intermediate **19**.

At this point, a number of conditions were attempted for hydrolysis of the two esters within lactam **19**, but these led to either a lack of reaction or, alternatively, decomposition

Scheme 4. Endgame



of the starting material.[19] This result may be a consequence of the sterically hindered ethyl ester undergoing retro-aldol side reactions as the benzoate ester was hydrolyzed. Hence, we investigated a synthesis of the hydroxyacid via a different route.

The chemoselective reduction of esters, in the presence of amides, with lithium borohydride is well-documented.[20] It has been shown that in the presence of methanol/ether solvent steric bulk next to the acyl group has a minimal effect on the rate of reduction.[21] These reducing conditions were attempted on lactam **19**, and pleasingly, diol **20** was obtained in excellent yield over three steps from *N*-Boc lactam **18**.

The next task was to oxidize the primary hydroxyl group within diol **20** selectively in the presence of the secondary hydroxyl. Using TEMPO in conjunction with bis(acetoxy)-iodobenzene (BAIB) as the stoichiometric oxidant,[22] conver-

(14) Sousa, J. A.; Bluhm, A. L. *J. Org. Chem.* **1960**, *25*, 108.

(15) Reagents investigated included (i) vinyllithium and (ii) vinylmagnesium bromide with, or without, $CeCl_3$: (a) Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392. With $Yb(OTf)_3$: (b) Molander, G. A.; Burkhardt, E. R.; Weinig, P. *J. Org. Chem.* **1990**, *55*, 4990.

(16) Arisawa, M.; Terada, Y.; Takahashi, K.; Nakagawa, M.; Nishida, A. *J. Org. Chem.* **2006**, *71*, 4255.

(17) Yoshifuji, S.; Tanaka, K.; Kawal, T.; Nitta, Y. *Chem. Pharm. Bull.* **1986**, *34*, 3873.

(18) Nigam, S. C.; Mann, A.; Taddei, M.; Wermuth, C.-G. *Synth. Commun.* **1989**, *19*, 3139.

(19) Conditions that were unsuccessful included aqueous sodium hydroxide, sodium propanethiolate, and dimethylaluminum methyltellurate: Reddy, B. V. S.; Reddy, L. R.; Corey, E. J. *Tetrahedron Lett.* **2005**, *46*, 4589.

(20) For some recent examples, see: (a) Gheorghe, A.; Schulte, M.; Reiser, O. *J. Org. Chem.* **2006**, *71*, 2173. (b) Busque, F.; de March, P.; Figueredo, M.; Font, J.; Gallagher, T.; Milan, S. *Tetrahedron: Asymmetry* **2002**, *13*, 437.

(21) Soai, K.; Ookawa, A. *J. Org. Chem.* **1986**, *51*, 4000.

sion to the corresponding β-hydroxyaldehyde was completely selective. The crude product was very clean and did not require any purification; instead, it was oxidized immediately with sodium chlorite with sodium dihydrogenphosphate buffer[23] to β-hydroxyacid **4**. Finally, this was treated with tosyl chloride in pyridine and CH_2Cl_2[24] and we were able to isolate the target lactone (±)-**3** in 40% yield over the final two steps. The stereochemistry of the substituents was established unequivocally by X-ray crystallography on a crystal of **3** (Scheme 4).

In summary, we have developed the first synthesis of the densely functionalized pyrrolidinone core of KSM-2690 B in 20 linear steps. The key steps in this sequence include: a reductive aldol reaction of an electron-deficient pyrrole to set the relative stereochemistry at C-2 as well as that of the methyl group on the β-lactone; setting the stereochemistry of the C-4 methyl group by methylation of ketoester **13** and reprotonation from the less-hindered face with a bulky proton source; the introduction of the hydroxymethyl group at C-3 via allyl Grignard addition, alkene isomerization, and ozonolysis; and finally, access to the β-lactone via the diol obtained by reduction of the advanced intermediate diester **19**. Studies toward a synthesis of enantiopure material and a completion of the total synthesis are underway.

Acknowledgment. We wish to thank the Newton-Abraham Fund for financial support. Merck, AstraZeneca, Pfizer, and Novartis are thanked for unrestricted funding.

Supporting Information Available: Experimental and NMR spectral data and characterizations for all new compounds as well as X-ray structural data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL062705X

(22) De Mico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G. *J. Org. Chem.* **1997**, *62*, 6974.

(23) Bal, B. S.; Childers, W. E., Jr.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091.

(24) Adam, W.; Baeza, J.; Liu, J. *J. Am. Chem. Soc.* **1972**, *94*, 2000.