Formal Total Synthesis of Mycoticin A

Spencer D. Dreher and James L. Leighton*

Department of Chemistry, Columbia University New York, New York, 10027

Received September 27, 2000

The polyene macrolide antibiotics (e.g., the clinically used amphotericin B) commonly contain a (1,3,5,...) polyol section as a recurring structural motif.1 We have been engaged in the development of carbonylation-based approaches to the synthesis of such structures, and the results of these studies include the tandem intramolecular silvlformylation/allylsilvlation,² and the oxymercuration/formylation of homoallylic alcohol-derived hemiketals.³ Herein we report the application of these reactions to an efficient formal total synthesis of the polyene macrolide antibiotic mycoticin A.



There has been one total synthesis of mycoticin A, reported by Schreiber and co-workers in 1993.^{4,5} We chose as our synthetic target the fragment 1, a late stage intermediate in Schreiber's synthesis which comprises the entire polyol region of mycoticin A (Scheme 1). In seeking a maximally convergent approach, our retrosynthetic analysis envisioned cutting the target 1 roughly in half to methyl ketone 2 and aldehyde 3, each of which might efficiently be constructed using our carbonylation methodology. Diastereoselective aldol coupling of these fragments followed by functional group manipulation would give the completed polyol fragment 1, and thereby complete a formal total synthesis of mycoticin A.

The synthesis of ketone 2 (Scheme 2) commenced with subjection of the known alkene 4^6 to intermolecular olefin crossmetathesis with diethoxyacrolein,⁷ catalyzed by 1,3-dimesityl-4,5-dihydroimidazol-2-ylideneRu(=CHPh)(Pcy₃)Cl₂ 5⁸ (4 mol %, CH₂Cl₂, reflux, 4h), to give the desired (*E*)-alkene 6 with > 20:1E:Z selectivity. Following protection of the alcohol as its p-methoxybenzyl (PMB) ether (KH, PMBBr, THF), the acetal was hydrolyzed under mildly acidic conditions (pyridinium Scheme 1







(a) 4 mol % 5, 3,3-diethoxy-1-propene, CH₂Cl₂, reflux. (b) KH, PMBBr, THF. (c) PPTS, acetone, H₂O, reflux. (d) CH₂=CHCH₂MgBr, (+)-B-methoxydiisopinocampheylborane, Et₂O, -78 °C; 7, -90 to 23 °C; NaOH, H₂O₂. (e) HgClOAc, acetone, 20 mol % Yb(OTf)₃, -78 to 0 °C. (f) 6 mol % Rh(acac)(CO)2, 6 mol % tris(2,4-di-tertbutylphenyl)phosphite, 0.50 equiv DABCO, 800 psi 1/1 H₂/CO, EtOAc, 50 °C. (g) MeMgBr, Et₂O, 0 °C. (h) Dess-Martin periodinane, CH₂Cl₂.

p-toluenesulfonate (PPTS), acetone, H₂O, reflux) to give aldehyde 7 in 62% overall yield from 4 (three steps). Aldehyde 7 was subjected to Brown's asymmetric allylation methodology⁹ to produce a 10:1 mixture of diastereomers, from which the desired homoallylic alcohol 8 could be isolated in 71% yield. Treatment of a solution of 8 in acetone with HgClOAc and 20 mol % Yb-(OTf)₃¹⁰ led to smooth oxymercuration to afford organomercury chloride 9 (>20:1 ds) in 75% yield.^{3b} Formylation of organomercury chloride 9 (6 mol % Rh(acac)(CO)₂, 6 mol % P(O-2,4di-t-BuPh)₃, 0.50 equiv 1,4-diazabicyclo[2.2.2]-octane (DABCO), 800 psi 1/1 CO/H₂, EtOAc, 50 °C)^{3c} gave aldehyde 10, along with small amounts of aldehyde byproducts attributable to hydroformylation of the internal alkene. This mixture was treated with MeMgBr (Et₂O, 0 °C). The resulting alcohols (1:1 mixture of diastereomers) could be easily purified and were subjected to oxidation using the Dess-Martin periodinane¹¹ to give the desired ketone 2 in 58% overall yield from 9 (three steps). The synthesis of ketone 2 proceeds in nine steps and 14% overall yield from isobutyraldehyde.

The synthesis of aldehyde 3 (Scheme 3) began with subjection of known aldehyde 11^{12} to Brown's *anti*-diastereoselective asymmetric crotylation to afford homoallylic alcohol 12 in 55% overall yield (three steps from 1,3-propanediol).¹³ In anticipation of a tandem intramolecular silylformylation/allylsilylation,^{2b}

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Scheme 3^a



^{*a*} (a) KO-*t*-Bu, *n*-BuLi, (*E*)-2-butene, THF, -78 °C; (+)-B-methoxydiisopinocampheylborane, BF₃·OEt₂, **11**, -78 to -30 °C; NaOH, H₂O₂. (b) *n*-BuLi, HSiCl₃, AllylMgBr, THF, -78 to 0 °C. (c) 3 mol % Rh(acac)(CO)₂, PhH, 1000 psi CO, 60 °C. (d) H₂O₂, NaHCO₃, THF, MeOH, reflux. (e) Acetone, 10 mol % CSA. (f) HgClOAc, acetone, 10 mol % Yb(OTf)₃, 0 °C. (g) 8 mol % Rh(acac)(CO)₂, 8 mol % tris(2,4di-*tert*-butylphenyl)phosphite, 0.50 equiv DABCO, 1000 psi 1/1 H₂/CO, EtOAc, 60 °C.

alcohol 12 was treated with *n*-BuLi followed by HSiCl₃ and then allylmagnesium bromide to give diallylsilane 13. Subjection of diallylsilane 13 to the action of 3 mol % Rh(acac)(CO)₂ in benzene under 1000 psi CO at 60 °C in a stainless steel pressure reactor, followed by evaporation of solvent and subjection of the residue to the conditions of the Tamao oxidation (H₂O₂, NaHCO₃, THF/ MeOH, reflux) led to the isolation of triol 14 in 55% overall yield (three steps from 12).^{2b} Isolation of all products revealed that the diastereoselectivity was > 10:1 for $14:\Sigma$ all other diastereomers. Triol 14 was then protected as its acetonide under equilibrating conditions (camphorsulfonic acid (CSA), acetone, 16 h) to afford a 7:1 mixture of the desired homoallylic alcohol 15 and the isomeric acetonide 16, from which 15 could be isolated in 75% yield. Subjection of homoallylic alcohol 15 to the hemiketal oxymercuration (10 mol % Yb(OTf)₃, HgClOAc, acetone, 0 °C) gave organomercury chloride 17 in 71% yield and >20:1 diastereoselectivity.3b Finally, formylation of organomercury chloride 17 (8 mol % Rh(acac)(CO)₂, 8 mol % P(O-2,4-di-t-BuPh)₃, 0.50 equiv DABCO, 1000 psi 1/1 CO/H₂, EtOAc, 60 °C)^{3c} afforded the desired aldehyde $\overline{3}$ in 82% yield. The synthesis of aldehyde 3 proceeds in nine steps and 13% overall yield from 1,3propanediol.

In the aldol union of methyl ketone **2** with aldehyde **3**, the desired product is that resulting from 1,3-*anti* induction with respect to the aldehyde, and 1,5-*syn* induction with respect to the ketone. Ample precedent has established that β -alkoxy aldehydes exhibit a preference for the 1,3-*anti* product in aldol addition reactions with methyl ketone enolates and enol silanes.¹⁴ Remarkable levels of 1,5-*anti* induction have been observed in the aldol reactions of β -alkoxy methyl ketone dialkylboron enolates.¹⁵ However, it has also been shown that the 1,5-*anti* induction is not expressed using enol silanes, and in these cases the aldehyde dominates.^{15c} Informed by the comprehensive work of Evans, therefore, we focused on the Mukaiyama variant of the aldol coupling.¹⁶ Thus, methyl ketone **2** was treated with TMSOTf and *i*-Pt₂NEt (CH₂Cl₂, -78 to 0 °C), and the resultant enol





^{*a*} (a) i. **2**, TMSOTF, *i*-Pr₂NEt, CH₂Cl₂, -78 to 0 °C. ii. **3**, BF₃·OEt₂, CH₂Cl₂, -78 °C. (b) Me₄NBH(OAc)₃, AcOH, THF, CH₃CN, -78 to -20 °C. (c) PPTS, 2,2-dimethoxypropane, CH₂Cl₂. (d) *n*-Bu₄NF, THF, 0 to 23 °C.

silane was treated with aldehyde 3 (1.0 equiv) and $BF_3 \cdot OEt_2$ (1.05) equiv) in CH₂Cl₂ at -78 °C to afford aldol **18** and the C(21) epimer in a ratio of 6:1 (Scheme 4). This inseparable mixture was then subjected to *anti*-diastereoselective β -hydroxy ketone reduction with Me₄NBH(OAc)₃ (AcOH, THF, CH₃CN, -78 to -20 °C) to give diol **19** and a diastereomer in a 6:1 ratio.¹⁷ Although we could not quantitatively determine the diastereoselectivity of the reduction, the fact that the product was a 6:1 mixture of diastereomers is certainly suggestive of a very selective (>95:5) reaction. Protection of the mixture of diols as acetonides (PPTS, 2,2-dimethoxypropane, CH₂Cl₂) provided a separable 6:1 mixture of tetraacetonides from which 20 could be isolated in 49% overall yield (from 2 and 3). Finally, cleavage of the TIPS group with n-Bu₄NF in THF provided the target compound **1** in 92% yield. Full spectral comparison (¹H and ¹³C NMR, IR, MS, optical rotation) with the Schreiber intermediate¹⁸ established the structure of our material and confirmed the completion of the formal synthesis.

The synthesis of mycoticin A polyol fragment 1 was accomplished with a longest linear sequence of 14 steps from isobutyraldehyde and with an overall yield of 6%. This highlights both the convergent nature of the present approach and the efficiency of the carbonylation-based methodology used to prepare the polyol fragments 2 and 3.

Acknowledgment. We thank the National Institutes of Health (National Institute of General Medical Sciences - R01 GM58133) and the Research Corporation (Cottrell Scholar Award to J.L.L.) for financial support of this work. We thank Merck Research Laboratories and DuPont Pharmaceuticals for generous financial support. J.L.L. is a recipient of a Sloan Research Fellowship, a Camille Dreyfus Teacher—Scholar Award, a Bristol-Myers Squibb Unrestricted Grant in Synthetic Organic Chemistry, an Eli Lilly Grantee Award, an AstraZeneca Excellence in Chemistry Award, and a GlaxoWellcome Chemistry Scholar Award.

Supporting Information Available: Experimental procedures and spectral data for 1-3, 7-10, 12-15, 17, and 20 (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA0035102

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