## Formal Total Synthesis of Mycoticin A

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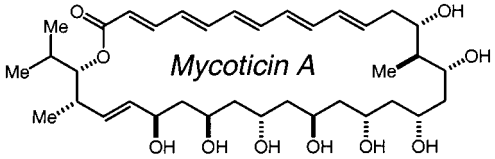
The polyene macrolide antibiotics (e.g., the clinically used amphotericin B) commonly contain a (1,3,5,...) polyol section as a recurring structural motif.[1] We have been engaged in the development of carbonylation-based approaches to the synthesis of such structures, and the results of these studies include the tandem intramolecular silylformylation/allylsilylation,[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.

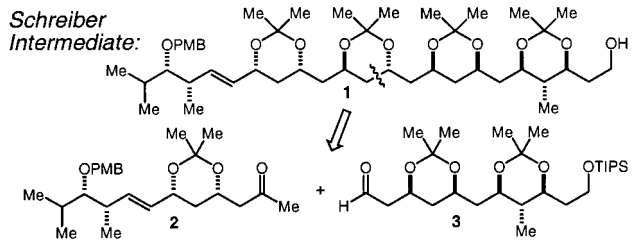



There has been one total synthesis of mycoticin A, reported by Schreiber and co-workers in 1993.[4,5] We chose as our synthetic target the fragment **1**, a late stage intermediate in Schreiber's synthesis which comprises the entire polyol region of mycoticin A (Scheme 1). In seeking a maximally convergent 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.

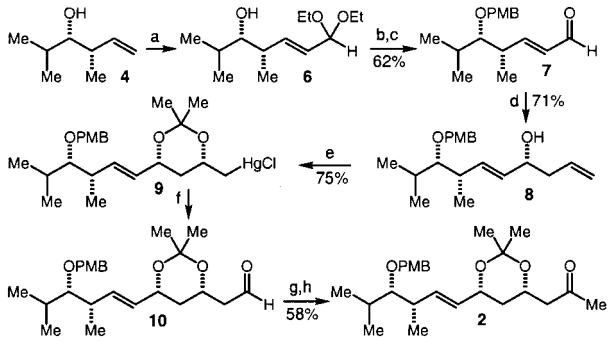
The synthesis of ketone **2** (Scheme 2) commenced with subjection of the known alkene **4**[6] to intermolecular olefin cross-metathesis with diethoxyacrolein,[7] catalyzed by 1,3-dimesityl-4,5-dihydroimidazol-2-ylideneRu(=CHPh)($Pcy_3$)$Cl_2$ **5**[8] (4 mol %, $CH_2Cl_2$, reflux, 4h), to give the desired (*E*)-alkene **6** with >20:1 *E*:*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 *p*-toluenesulfonate (PPTS), acetone, $H_2O$, reflux) to give aldehyde **7** in 62% overall yield from **4** (three steps). Aldehyde **7** was subjected to Brown's asymmetric allylation methodology[9] 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)$_3$[10] 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-2,4-di-*t*-BuPh)$_3$, 0.50 equiv 1,4-diazabicyclo[2.2.2]-octane (DABCO), 800 psi 1/1 CO/$H_2$, 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 ($Et_2O$, 0 °C). The resulting alcohols (1:1 mixture of diastereomers) could be easily purified and were subjected to oxidation using the Dess−Martin periodinane[11] 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]

**Scheme 1**




**Scheme 2**[a]




[a] (a) 4 mol % **5**, 3,3-diethoxy-1-propene, $CH_2Cl_2$, reflux. (b) KH, PMBBr, THF. (c) PPTS, acetone, $H_2O$, reflux. (d) $CH_2$=$CHCH_2MgBr$, (+)-B-methoxydiisopinocampheylborane, $Et_2O$, −78 °C; **7**, −90 to 23 °C; NaOH, $H_2O_2$. (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-*tert*-butylphenyl)phosphite, 0.50 equiv DABCO, 800 psi 1/1 $H_2$/CO, EtOAc, 50 °C. (g) MeMgBr, $Et_2O$, 0 °C. (h) Dess−Martin periodinane, $CH_2Cl_2$.

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(10) For this complex diene substrate **8**, optimal results were achieved using a lower temperature and a higher catalyst loading than recommended (5 mol%) for most substrates. See ref. 3b.

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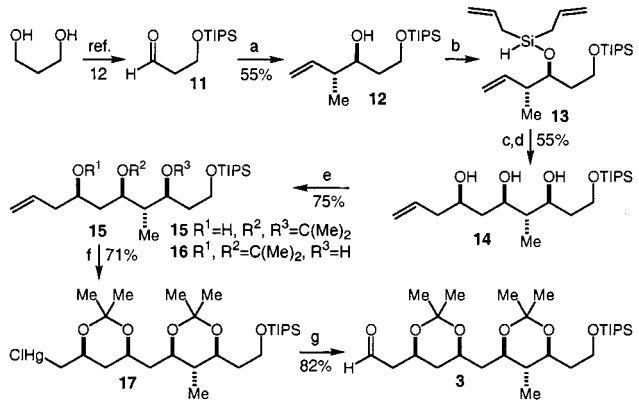
**Scheme 3**[a]

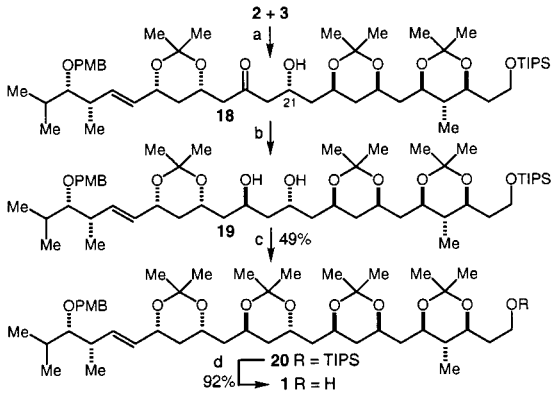


[a] (a) KO-*t*-Bu, *n*-BuLi, (*E*)-2-butene, THF, −78 °C; (+)-B-methoxydiisopinocampheylborane, $BF_3{\cdot}OEt_2$, **11**, −78 to −30 °C; NaOH, $H_2O_2$. (b) *n*-BuLi, $HSiCl_3$, AllylMgBr, THF, −78 to 0 °C. (c) 3 mol % $Rh(acac)(CO)_2$, PhH, 1000 psi CO, 60 °C. (d) $H_2O_2$, $NaHCO_3$, THF, MeOH, reflux. (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(2,4-di-*tert*-butylphenyl)phosphite, 0.50 equiv DABCO, 1000 psi 1/1 $H_2/CO$, EtOAc, 60 °C.

alcohol **12** was treated with *n*-BuLi followed by $HSiCl_3$ 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 ($H_2O_2$, $NaHCO_3$, 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**:Σ 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 $CO/H_2$, EtOAc, 60 °C)[3c] afforded the desired aldehyde **3** in 82% yield. The synthesis of aldehyde **3** proceeds in nine steps and 13% overall yield from 1,3-propanediol.

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*-$Pr_2NEt$ ($CH_2Cl_2$, −78 to 0 °C), and the resultant enol

**Scheme 4**[a]



[a] (a) i. **2**, TMSOTf, *i*-$Pr_2NEt$, $CH_2Cl_2$, −78 to 0 °C. ii. **3**, $BF_3{\cdot}OEt_2$, $CH_2Cl_2$, −78 °C. (b) $Me_4NBH(OAc)_3$, AcOH, THF, $CH_3CN$, −78 to −20 °C. (c) PPTS, 2,2-dimethoxypropane, $CH_2Cl_2$. (d) *n*-$Bu_4NF$, THF, 0 to 23 °C.

silane was treated with aldehyde **3** (1.0 equiv) and $BF_3{\cdot}OEt_2$ (1.05 equiv) in $CH_2Cl_2$ 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 $Me_4NBH(OAc)_3$ (AcOH, THF, $CH_3CN$, −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, $CH_2Cl_2$) 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*-$Bu_4NF$ in THF provided the target compound **1** in 92% yield. Full spectral comparison ($^1H$ and $^{13}C$ NMR, IR, MS, optical rotation) with the Schreiber intermediate[18] 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**.

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**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.

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