Two-Directional Chain Synthesis: An Application to the Synthesis of (+)-Mycoticin A

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Two-directional synthesis involves the simultaneous, stereoselective homologation of the termini of a nascent chain.[2] The potential for efficiency associated with double processing is best realized when the problem of terminus differentiation is solved effectively. This is required for synthetic targets that lack overall symmetry. The strategies for achieving differentiation of chain termini are linked to the symmetry properties of the two-directionally synthesized intermediates. Enantiotopic termini were selectively differentiated in intermediates used in the syntheses of (+)-KDO[3] and (−)-riboflavin[3] and in the stereochemical assignment of (+)-mycoticins A and B.[4] Diastereotopic termini were selectively differentiated in intermediates used in the syntheses of (−)-FK506[5] and the ansa chain of streptovaricin A,[6] whereas homotopic termini were differentiated in a synthesis of (−)-hikizimycin.[7] We now report the two-directional synthesis of a C_2-symmetric fragment of the skipped polyol chain in the oxopolyene[8,9] macrolide antibiotics mycoticins A and B.[10] Differentiation and sequential homologation of the chain's homotopic termini have resulted in the first synthesis of a member of the oxopolyene macrolide family,[9,11] (+)-mycoticin A (**1**) (Figure 1).

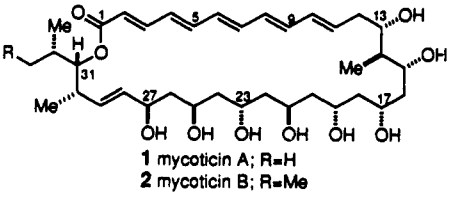

Figure 1

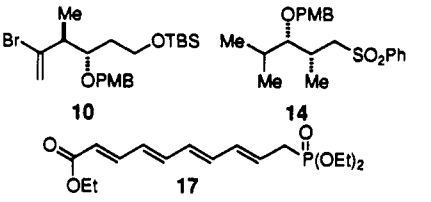

Figure 2

The C_{17}–C_{27} fragment of mycoticin A was prepared in enantiomerically pure form using the class B two-directional chain synthesis strategy[2] (Scheme I). Thus, acylation of the sodium anion of α-keto sulfone **3**[12,13] with anhydride **4**[12] followed by zinc metal reduction[14] gave the diketone **5** in 64% overall yield. Two-directional catalytic asymmetric reduction using the Noyori–Akutagawa catalyst[15] and protection followed by dissolving metal reduction and ozonolysis[16] afforded the bis-β-keto ester **6**. The conversion of **6** to the tris-acetonide **7** was achieved in four steps (30% overall yield), including a second double catalytic asymmetric reduction[17] and a one-pot sequence involving a double reduction and a two-directional Grignard addition.[18] Double ozonolysis of **7** followed by base-catalyzed epimerization[19] and sodium borohydride reduction furnished a C_2-symmetric diol. Terminus differentiation was accomplished via monoprotection of the homotopic alcohols with 1 equiv of TBSCl to give a statistical mixture of products from which alcohol **8** could be isolated directly in 49% yield and in 67% yield with one round of recycling. A Sharpless oxidation[20] of **8** followed by an amidation using benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate[21] afforded the amide **9**.

Coupling of **9** (Scheme II) with the vinyllithium reagent derived from **10**[12] (Figure 2) followed by a Luche reduction,[22] ozonolysis, and protection provided two diastereomeric α-mesyloxy ketones **11** (ca. 1:1). Although attempts to reductively cleave the α-keto mesylates using SmI_2 failed,[23] a novel dissolving metal reduction sequence was developed that accomplished several goals. Treatment of **11** with lithium in buffered ammonia resulted in the cleavage of the mesyloxy and *p*-methoxy benzyl groups and the stereoselective (>15:1 syn:anti)[24] reduction of the ketone. Acetalization of the resultant diol yielded tetrakis-acetonide **12**, which was identical in all respects to material obtained by degradation of **1**.[25]

Compound **12** was converted to **13** in three steps: deprotection

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(25) Compound **12** was derived from natural mycoticins by the following sequence: isolation from *Streptomyces ruber*,[10b] protection of the mycoticins as their tetraacetonides, ozonolysis followed by $NaBH_4$ workup and bisprotection of the diol with excess TBSCl.

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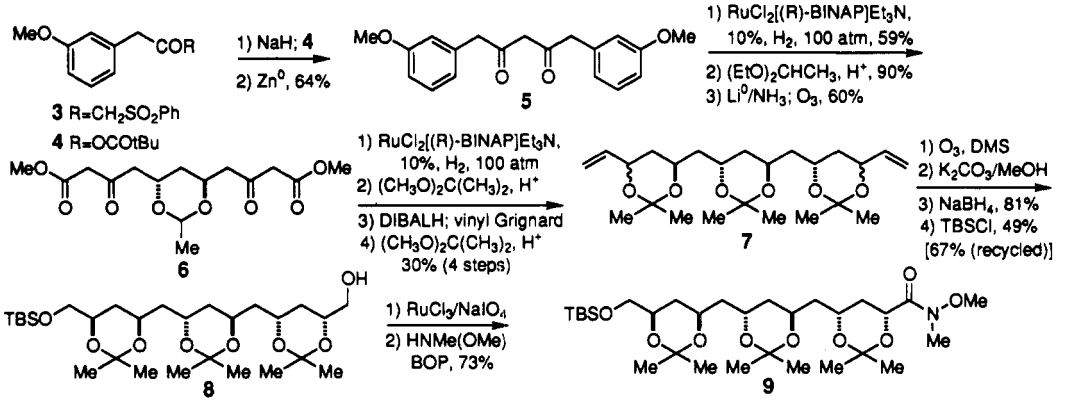
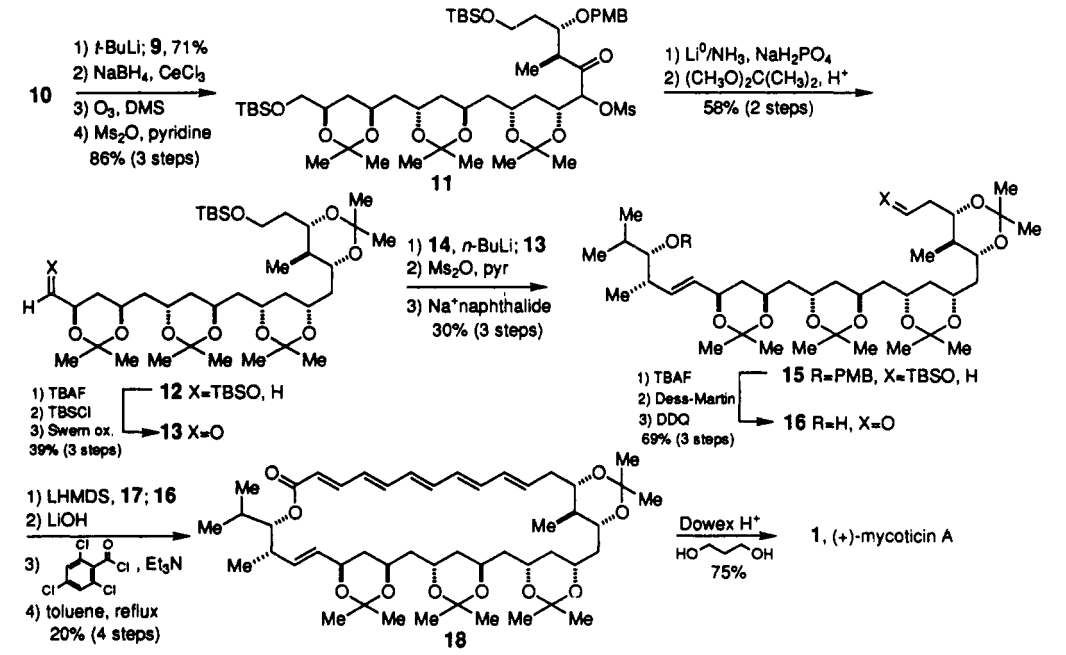
Scheme I



Scheme II



of the two TBS groups, monoprotection, and Swern oxidation.[26] Aldehyde **13**[27] was coupled with sulfone **14**[12] under Julia's conditions[28] to furnish the differentially protected diol **15**. After a deprotection, Dess–Martin oxidation,[29] deprotection sequence that provided aldehyde **16**, the polyene was introduced by condensation with the lithium salt of phosphonate **17**.[12,30] Hydrolysis of the ethyl ester and macrolactonization using Yamaguchi's protocol[31] gave the tetrakis-acetonide of (+)-mycoticin A, **(18)**,[32,33] which was identical to material derived from natural mycoticin A. Final deprotection of **18** produced (+)-mycoticin A (**1**) in 75% yield.

The synthesis of (+)-mycoticin A confirms the earlier stereochemical assignment that was based upon synthetic and spectroscopic analyses of degradation products from the oxopolyene.[4] These and other synthetic studies[3-7] and the work described herein relied heavily upon the efficient material processing that can be achieved using two-directional chain synthesis strategies.[2]

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Supplementary Material Available: Complete spectral data for compounds **1**, **3**, **5–10**, **12–18**, and (+)-mycoticin A; ^{1}H NMR and ^{13}C NMR spectra of natural and synthetic compounds **12** and **18** are included (8 pages). Ordering information is given on any current masthead page.

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(32) Natural and synthetic (+)-mycoticin A, tetraacetonide, and (+)-mycoticin A produce five olefinic isomers upon light exposure as studied by HPLC (Rainin Microsorb column, 10.0 × 250.0 mm^2, 15% EtOAc/hexane, 4 mL/min) and ^{1}H NMR. The major (all-trans) isomer reconverts into the five-component mixture after a few hours of light exposure; in addition, the four minor isomers individually convert to the five-component mixture under the same conditions.
(33) Compound **18** was isolated as a mixture of olefin isomers. The major isomer ($[\alpha]_D$ = +182.3° (c = 0.32, $CHCl_3$)) was identical to **18** derived from natural material ($[\alpha]_D$ = +261.9° (c = 1.09, $CHCl_3$)) in all respects except optical rotation. This difference is attributed to a small amount of olefin isomers present in the synthetic material. Mycoticin A itself has been reported to yield a range of optical rotations from +63.4° to −41.3°, depending upon the duration of light exposure.[19b]