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Studies toward the Total Synthesis of Sorangiolides and Their Analogues. A Convergent Stereoselective Synthesis of the Macrocyclic Lactone Precursors

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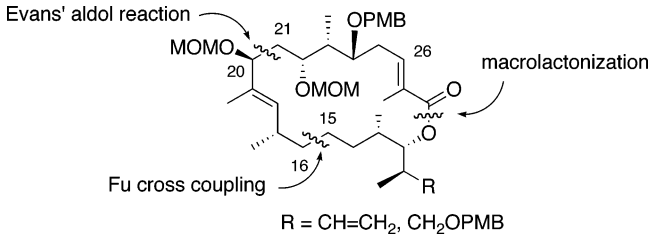
ABSTRACT



Stereoselective synthesis of the fully protected 18-membered macrocyclic lactones as the immediate precursors of the natural products, sorangiolides A and B, is described. The key steps used in the synthesis include the sp^3-hybridized carbon–carbon Fu cross coupling, the stereoselective Evans' aldol reaction with 1,5-*anti* induction, the 1,3-diastereoselective *syn* reduction of a β-hydroxyketone intermediate, and Mukaiyama macrolactonization reactions.

Sorangiolides A and B (**1a**,**b**) are 18-membered macrocyclic lactones isolated from *Sorangium cellulosum*, strain So ce12.[1] They possess a weak antibiotic activity (MIC 5−20 μg/mL) against Gram-(+) bacteria, e.g., *Staphylococcus aureus*. Although the structure of these compounds was confirmed by an X-ray analysis of **1a**, no synthetic studies have so far been reported. Moreover, the relative or absolute stereochemistry of the hydroxy function in **1b** at C-6 is yet to be determined. Therefore, to synthesize the naturally occurring sorangiolides as well as their analogues for the biological evaluations, we designed and studied a general synthetic strategy. Here, we report the results of this study leading to the stereoselective synthesis of 18-membered macrolide precursors, enroute to the proposed synthesis of **1a**, **1b**, and their analogues.

Scheme 1 outlines the retrosynthesis of the naturally occurring sorangiolides A and B, **1a** and **1b**, and their analogues, which would possess the identical 18-membered macrocyclic ring. We envisaged that the macrocyclic lactones **IIIa** or **IIIb** could serve as the key precursors of **1a**,**b** and their analogues. Intermediate **IIIa** could undergo Fu coupling[2] with **I** to form the immediate precursors of the title compounds. Alternatively, these precursors could be prepared by cross metathesis[3] of **IIIb** with **II** followed by a regioselective hydrogenation of the resulting disubstituted alkene. Macrolides **IIIa** and **IIIb** could be prepared by the intramolecular esterification of the appropriately protected hydroxy acids **IVa** and **IVb**. The latter compounds would arise from the 1,3-*syn* reduction of the aldol compounds **Va** and **Vb**, respectively. The 1,5-*anti* diastereoselectivity in the aldol

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(2) Netherton, M. R.; Dai, C.; Neuschütz, K.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 10099.

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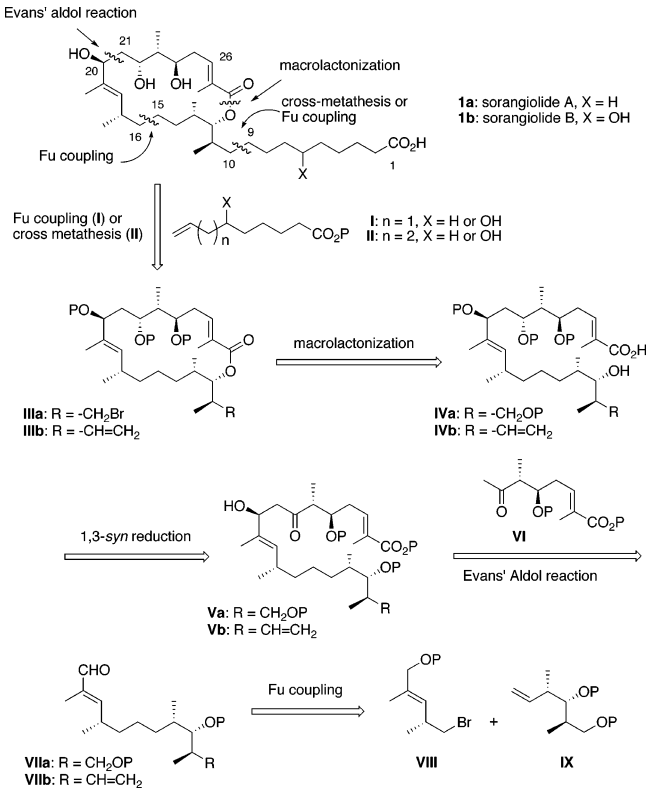
Scheme 1. Retrosynthesis of Sorangiolides A and B and Their Analogues (P = a Protecting Group)



products could be achieved by Evans' methodology,[4] using ketone **VI** and aldehydes **VIIa** and **VIIb**. Finally, these aldehydes could be easily derived from the Fu coupling product of bromide **VIII** and alkene **IX**.

Synthesis of the First Key Intermediate with Use of the Fu Coupling Reaction. Obviously, among all five key steps listed in the retrosynthesis of sorangiolides (Scheme 1), Fu coupling has been the least studied methodology. In fact, most compounds prepared by this method with use of a bromide and the 9-BBN derivative of an alkene were devoid of any complexity. In contrast, the proposed starting materials, **VIII** and **IX**, for the Fu coupling reaction were highly functionalized. Nevertheless, we prepared intermediates **4** and **5a** (**VIII** and **IX** in Scheme 1) as shown in Scheme 2A. Compound **4** was synthesized from the commercially available methyl (*S*)-(+)-3-hydroxy-2-methyl propionate via compound **2**,[5] which was converted to bromide **4** in four steps. First the alcohol function in **2** was protected as a TBS ether and the PMB group was removed under the oxidizing conditions to yield alcohol **3**. The latter was then mesylated with MsCl and Et_3N, and the product was reacted with LiBr in refluxing THF. Compound **5a** was prepared from methyl (*R*)-(−)-3-hydroxy-2-methyl propionate via compound **5**, using the identical set of reactions as reported by Roush[6] with the exception that Brown's method[7] (*trans*-2-butene and (−)-Ipc_2BOMe) was used for crotylboration. The resulting alcohol **5** was then protected as its TIPS ether to give **5a**.

Next, we examined the Fu coupling reaction of bromide **4** with alkene **5a**. Thus, alkene **5a** was first treated with 9-BBN for 6 h at room temperature and the hydroborated product was then reacted with bromide **4** in the presence of $Pd(OAc)_2/PCy_3/K_3PO_4 \cdot H_2O$. The desired coupling product **6** was obtained in a moderate yield. We also attempted Fu coupling between different bromide and alkene partners, such as **4** and **9**, **5a** and **10**, or **9** and **10**, but to our surprise no coupling products were obtained. Without going into further depth, we focused on compound **6** and converted it to aldehydes **7a** and **7b** (viz., **VIIa** and **VIIb** in Scheme 1). For this, the TBS ether in **6** was selectively removed by an acid treatment, and the resulting alcohol was oxidized by TPAP-catalyzed oxidation to give **7a**. In another set of experiments, the PMB group in **6** was removed by oxidative cleavage, and the corresponding alcohol was oxidized to aldehyde and then olefinated by Wittig reaction. The resulting product underwent TBS cleavage and TPAP-catalyzed oxidation as above to give **7b**.

Synthesis of the Key Hydroxy Acid via Evans' Aldol and 1,3-*Syn* Reduction Steps. Moving ahead with the synthesis, we prepared ketone **14** from aldehyde **11** via the previously reported compound **12**[8] in three steps (Scheme 2B). Here, the primary alcohol in **12** was oxidized to aldehyde and olefinated by Wittig reaction with (carbethoxyethylidene)triphenylphosphorane to afford the unsaturated ester **13**, and the terminal alkene was oxidized by using the modified Wacker process.[9] Next we carried out the Evans' aldol reaction of ketone **14** with aldehydes **7a** and **7b** using Bu_2BOTf. As expected, the aldol compounds **15a** and **15b** were obtained in good yields and diastereoselectivities. These compounds underwent the proposed stereoselective 1,3-*syn* reduction[10] with use of $Et_2BOMe-NaBH_4$ to afford the corresponding diols, **16a** and **16b**, which were protected as their MOM ethers with $MOMCl/iPr_2EtN$ to yield **17a** and **17b**. The ester function in compounds **17a** and **17b** was next hydrolyzed and the TIPS group was removed to give the hydroxy acids **18a** and **18b** (intermediates **IVa** and **IVb** in Scheme 1).

Here, stereochemistry of the newly generated hydroxyl functions in the aldol products **15a** and **15b**, as well as the diol functions in the reduced products, **16a** and **16b**, was forwarded on the basis of the reported precedence. We also gained credence for the assigned stereochemistry of compounds **15a**,**b** and **16a**,**b** using acetonides **23**, **25**, and **26**, which were prepared from diol **22** (Scheme 2C). Compound **22** was synthesized by Evans' aldol reaction of aldehyde **19**[11] with ketone **20**[12] followed by 1,3-*syn* reduction, as described

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(5) Smith, A. B., III; Adams, C. M.; Lodise Barbosa, S. A.; Degnan, A. P. *J. Am. Chem. Soc.* **2003**, *125*, 350.

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(8) Drouet, K. E.; Theodorakis, E. A. *Chem. Eur. J.* **2000**, *6*, 1987.

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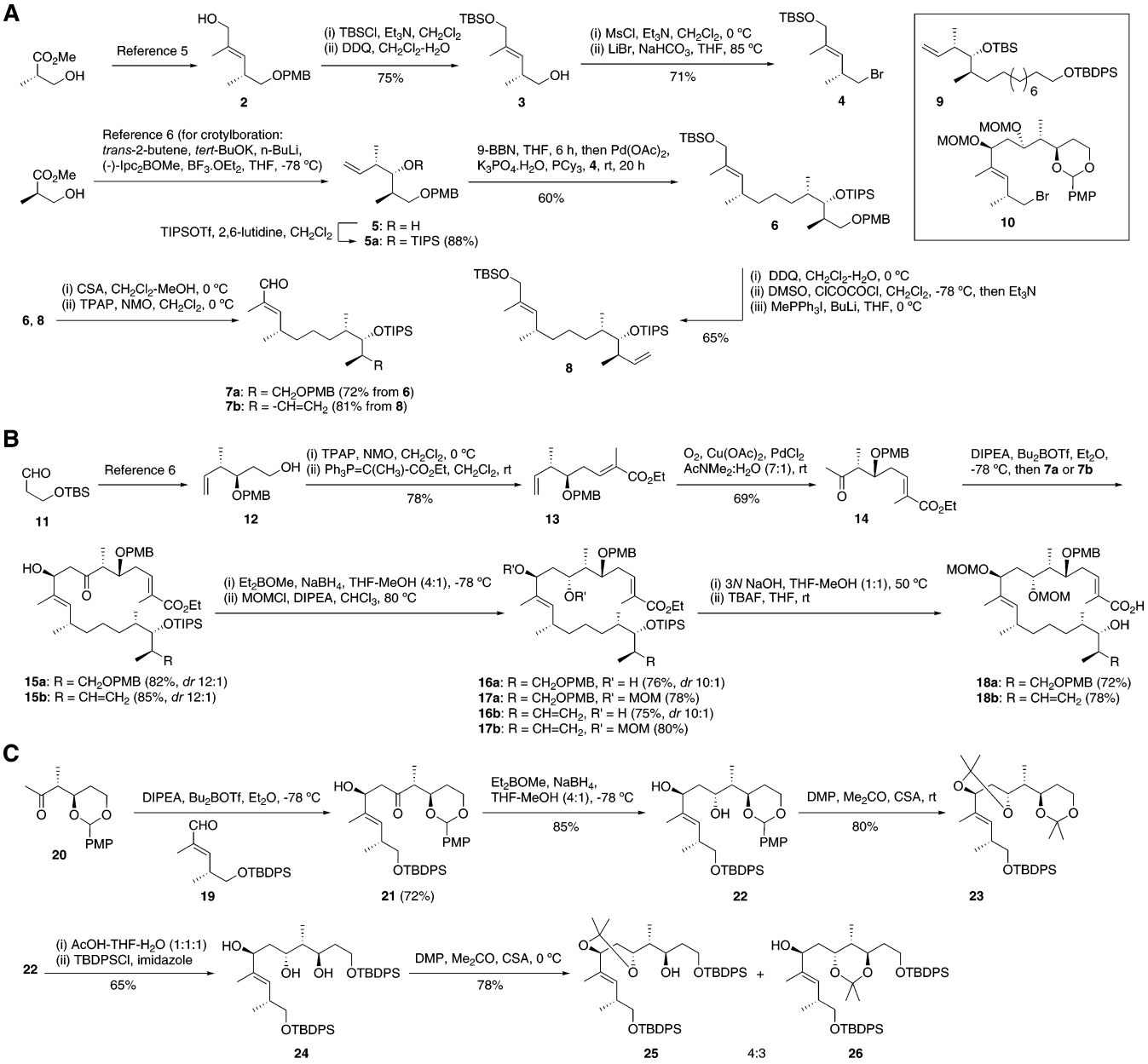
(10) Chen, K.-M.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Tetrahedron Lett.* **1987**, *28*, 155.

Scheme 2. Synthesis of the (A) First Key Intermediate Using Fu Coupling and (B) Key Hydroxy Acids via Evans' Aldol and 1,3-Syn Reduction Steps and (C) Determination of the Stereochemistry of Evans' Aldol Addition and $Et_2BOMe/NaBH_4$ Reduction Steps



above for compounds **15a**,**b** and **16a**,**b**. Diacetonide **23** was prepared by reacting **22** with an excess of 2,2-dimethoxypropane (DMP) in the presence of a catalytic amount of CSA. Separately, the PMP group in **22** was removed and the resulting tetrol was monoprotected as TBDPS ether on the primary alcohol affording compound **24**. The latter was transformed into the regioisomeric monoacetonides **25** and **26** by using DMP and a catalytic amount of CSA. An analysis of the ^{13}CNMR spectra of compounds **23**, **25**, and **26** revealed the following facts: Compound **23** showed δ_C at 98.3 and 98.4 for the ketal carbons and at 19.33, 19.25 and 30.0, 30.2 for the acetonide methyl groups. Similarly, the ketal and two methyl carbons in **25** appeared at 98.6, 19.7, and 30.2 ppm, respectively. These ^{13}C NMR signals in compounds **23** and **25** were in agreement with a *syn* acetonide.[13] In contrast, compound **26** showed the respective signals at 100.9, 23.7, and 25.1 ppm, as expected for an *anti* acetonide.

The Macrolide Formation. Next, we carried out macrolactonization of hydroxy acid **18a** using the Yamaguchi

(11) Compound **19** was prepared from the corresponding alcohol, which was obtained from the commercially available methyl (*S*)-(+)-3-hydroxy-2-methyl propionate in a series of reactions as described for its enantiomer (see: Diez-Martin, D.; Kotecha, N. R.; Ley, S. V.; Mantegani, S.; Menendez, J. C.; Organ, H. M.; White, A. D. *Tetrahedron* **1992**, *48*, 7899).

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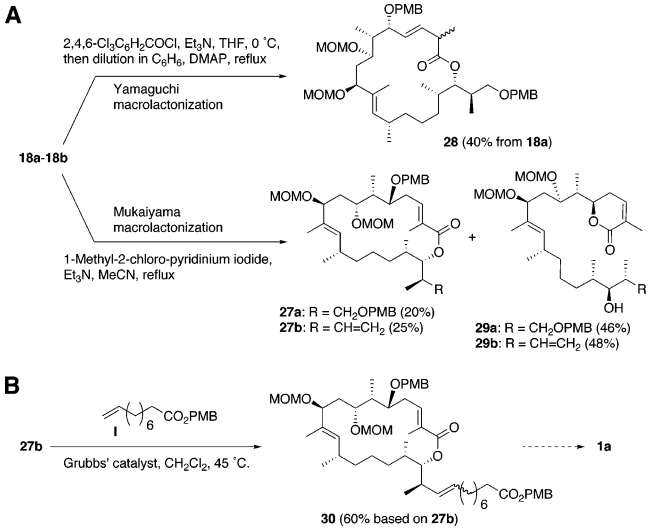
(13) (a) Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945. (b) Evans, D. A.; Rieger, D. L.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 7099.

reaction.[14] Here, though the macrolactonization proceeded smoothly, the product obtained was not the expected lactone **27a** but the corresponding double bond isomerized compound **28** (Scheme 3A). Probably the expected product **27a** was rapidly isomerized under the reaction conditions to the energetically favored compound **28**.[15] Thereafter, using hydroxy acid **18a** and/or **18b** we examined a series of macrolactonization reactions, including the Mukaiyama method,[16] the modified Yamaguchi reaction,[17] the EDC reaction,[18] and the Corey−Nicolaou double activation strategy.[19] Surprisingly, none of these methods except Mukaiyama macrolactonization gave the desired products **27a** and **27b**, albeit in low yields (20−25%). The major products isolated in the Mukaiyama macrolactonization were found to be the δ lactones, **29a** and **29b**, respectively. Presumably, the δ lactones was produced by Et_3N-mediated isomerization of the α,β-unsaturated pyridinium ester intermediate followed by a nucleophilic attack on the ester function by the OPMB and facilitated by the quinomethide generation.

Scheme 3. (A) Macrolactonization of the Hydroxy Acids to the Expected Macrocyclic Lactones and the Unexpected Products and (B) an Attempted Synthesis of **1a** by the Cross-Metathesis Approach



Finally, we examined the conversion of compounds **27a** and **27b** to sorangiolides. Because the selective deprotection of the primary PMB group in **27a** was unsuccessful, we quickly moved to **27b**. The cross metathesis of **27b** was carried out with alkene **Ia** in the presence of Grubbs' second generation catalyst ($RuCl_2$[imid-H_2-Mes_2][CHPh]PCy_3) (Scheme 3B). As expected, product **30** was obtained in good yield. However, the preliminary experiments for the conversion of compound **30** to **1a**, including removal of the protecting groups or the dimide-mediated hydrogenation, were unsuccessful.

In summary, macrocyclic lactones **27a**,**b** were prepared via hydroxy acids **18a**,**b** by using the carbon−carbon bond formation by the Fu cross coupling reaction, the 1,5-*anti* induction by using Evans' aldol reaction, and the Mukaiyama macrolactonization process as the key steps. Interestingly, macrolactonization of hydroxy acids **18a**,**b** was not trivial, as the Mukaiyama reaction afforded the isomeric δ lactones **29a**,**b** as the major side products, whereas Yamaguchi macrolactonization of **18a** yielded mainly the double bond isomerized macrocyclic lactone **28**. Further studies to ascertain the reasons for these abnormalties and synthesize the macrocyclic lactones **27a**,**b** and the title compounds with improved yields are in progress.

Acknowledgment. We thank the Skaggs Institute for Chemical Biology and NIH (R01 GM063914) for their financial support.

Supporting Information Available: Typical experimental procedure and analytical data for selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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