Studies toward the Total Synthesis of Sorangicins: Asymmetric Synthesis of the Key Fragments

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Received 5 August 2004

Dedicated to Professor Johann Mulzer on the occasion of his 60th birthday.

Abstract: Efficient synthesis of the key fragments of the complex antibiotics class of sorangicins (Scheme 1) is described. Starting from simple compounds fragments I, II, and IV can be synthesized. For fragment III we chose an approach via L-glucal.

Key words: sorangicin, asymmetric synthesis, tetrahydropyran, bicyclic ether, macrolide, antibiotic activity

In 1985, the research groups of G. Höfle and H. Reichenbach at the Gesellschaft für Biotechnologische Forschung (GBF) in Braunschweig, Germany, reported the isolation of the novel antibiotic sorangicin A (Scheme 1) from the gliding bacteria *Sorangium cellulosum*.[2] It has proved highly active against a broad spectrum of Gram-positive and -negative bacteria, including slow-growing or intracellular bacteria and methicillin- or polyresistant clinical isolates, e.g. mycobacteria, staphylococci, pseudomonades, enterococci and neisseria. The minimal inhibitory concentration (MIC) values against Gram-negative bacteria range from 2 to >32 μg/mL. For Gram-positive bacteria the MIC may be less than values of 10 ng/mL. At values of 2–5 times the MIC bactericidal action is observed. Sorangicin A has proved effective against experimental staphylococcal infections in rats. The mechanism of action has been shown to be the inhibition of the DNA-dependent RNA polymerase in *Staphylococcus aureus* and *Escherichia coli*. Eukaryotic cells are completely resistant. In addition, sorangicin A is active in vitro against several tumor cell lines.[3]

Its structure was determined by extensive use of ^{1}H NMR and ^{13}C NMR, MS and UV data. Our interest in the synthesis of sorangicin A and its natural variants is connected to its unique macrolide-polyether structure. A flexible and convergent synthetic route might open the possibility for the synthesis of derivatives, which could improve the biological efficacy in order to modify the pharmaceutical and biological properties, and to gain insight into structure–activity relationships.

In this article we present our recent investigations towards the synthesis of the key building blocks for the total synthesis of sorangicins. A highly convergent, stereoselective synthesis of four subunits is described.

SYNLETT 2004, No. 15, pp 2689–2692
Advanced online publication: 10.11.2004
DOI: 10.1055/s-2004-835661; Art ID: G31204ST
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Retrosynthetic Analysis

The structure of sorangicins is characterized by a 31-membered macrocyclic polyether with either 14 or 15 stereocenters. Disconnection gives four key fragments, which can be assembled in a convergent manner: tetrahydropyran fragment **I**, bicyclic ether fragment **II**, dihydropyran fragment **III** and side chain fragment **IV** containing the carboxylic acid. The tetrahydropyran rings in fragments **I** and **II** have similar structures with differing absolute configurations at C-27 and C-31. So, it is possible to prepare them from the same starting material. A ring-closing–epoxide-opening strategy by attack of a hydroxy group on an epoxide should create the tetrahydropyran rings.[4]

Tetrahydropyran Fragment I

Scheme 2 summarizes the synthesis of tetrahydropyran fragment **I** starting from 1,3-propanediol. Aldehyde[5] **2** was obtained after selective protection of one of the hydroxy groups, followed by Swern oxidation.[6] Asymmetric crotylboration using the *Z*-alkene[7] of **2**, followed by silylation[8] with TIPSOTf in the presence of 2,6-lutidine furnished the silyl ether. After dihydroxylation[9] of the terminal alkene moiety with OsO_4, both diastereomers **4** and **5** could be isolated, which later on could be used for the synthesis of the tetrahydropyran fragments. The use of the Sharpless protocol with AD-mix-α or AD-mix-β[10] for this step gave no noteworthy advantage in selectivity compared to OsO_4. Protection of the diol as the acetonide and selective deprotection of the primary hydroxy group was achieved simultaneously using *p*-TsOH, acetone and copper sulfate at room temperature. The resulting alcohol was oxidized using Ley's procedure (TPAP/NMO/MS)[11] yielding aldehyde **6** in 80% yield. A *Z*-selective Horner–Wadsworth–Emmons reaction of aldehyde **6** and Still–Gennari reagent[12] gave **7** as a single diastereoisomer in 92% yield, which after reduction with DIBAL[13] was converted into alcohol **8** in 99% yield. Selective epoxidation of allylalcohol **8** by the Sharpless protocol[14] gave epoxide, which after protection of the primary alcohol with BnBr[15] gave **9**. It was then converted into **10** by a ring-closing–epoxide-opening sequence via attack of the hydroxy group on the protonated epoxide in 52% yield. Fragment **I** could be synthesized using the same procedure starting

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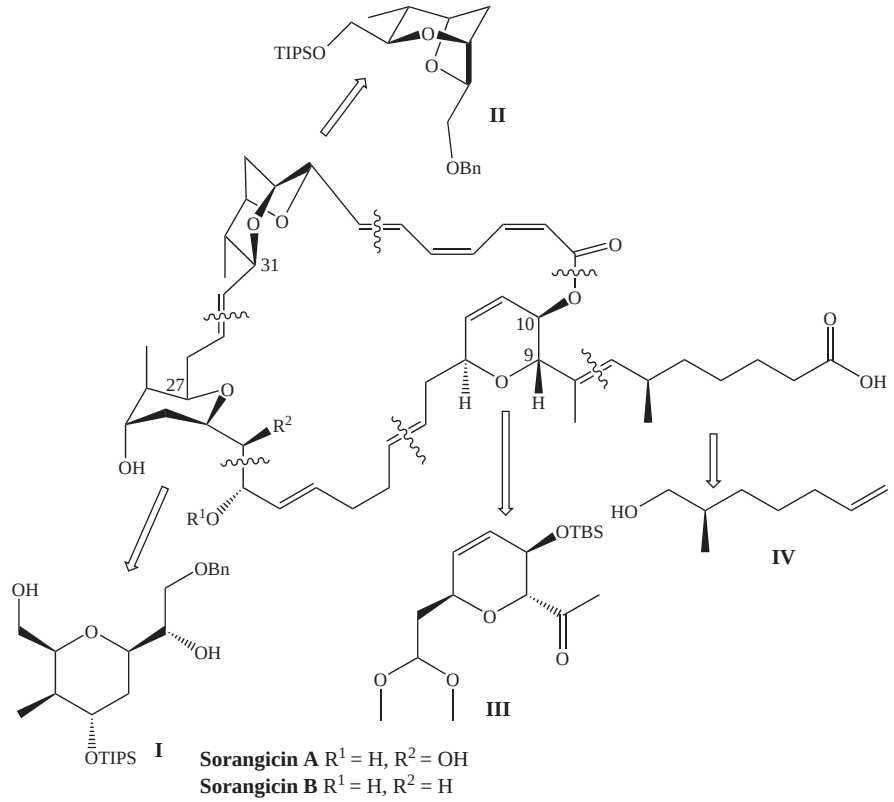

Scheme 1 Retrosynthetic analysis.

from diol **5**. The ring-closing–epoxide-opening sequence gave fragment **I** (tetrahydropyran **11**) in 82% yield.

Approach to the Bicyclic Ether II

The synthesis of bicyclic fragment[16] **II** was accomplished as shown in Scheme 3. A selective protection of primary alcohol **10** with TIPSCl followed by secondary alcohol with PMBCl furnished after deprotection of the silyl ethers with TBAF in THF, the primary alcohol **12**. It was selectively protected with TIPSCl and after mesylation[17] gave a mixture of bicyclic ether **15** (28%) and mesylate **13** (59%), which could then be converted to the desired bicyclic ether **15**[18] in two steps and an overall yield of 1% after 19 steps.

Dihydropyran Fragment III

Scheme 4 shows the synthesis of the dihydropyran fragment **III**. For this subunit we favored a precursor from the 'chiral pool', namely L-glucose, which bears the suitable stereochemistry at C-9 and C-10. In the one-pot, three-step procedure of Koreeda et al.,[19] it can be converted to a tri-*O*-acetyl-L-glucal, which was deprotected with Et_3N–MeOH–H_2O and finally underwent a carbon Ferrier-rearrangement[20] with allylsilane and TMSOTf to give a single diastereomer **16** in 84% yield. After protection of both hydroxy groups as silyl ethers, it was converted into aldehyde **17** by dihydroxylation of the terminal alkene moiety with AD-mix-β[21] making use of the greater selectivity of the chiral reagent. Protection of aldehyde **167** with orthoformic acid dimethyl ester[22] gave the acetal **18** in 94% yield. Selective desilylation of the primary alcohol was achieved by the action of CSA in MeOH–CH_2Cl_2[23] leading to hydroxy compound **19**, which was oxidized under Swern conditions in THF, followed by a one-pot Grignard addition with MeMgBr. Further oxidation with Dess–Martin periodinane[24] gave the desired key fragment **20 (III)**.

Side Chain Fragment IV

The construction of side chain fragment **IV** proceeded from 6-heptenoic acid chloride (**21**), which was coupled with the Seebach auxiliary[25] to obtain **22**. Diastereoselective alkylation with MeI at –78 °C (de >99%) furnished **23** (Scheme 5). Reductive removal of the auxiliary gave alcohol **24**. The use of Seebach auxiliary for the preparation of the known alcohol 24,[26] which we used in our epothilone synthesis, gave better stereoselectivity (>99%) in comparison to Evans auxiliary (92%). The enantiomeric excess was determined by chiral GC analyses.[27]

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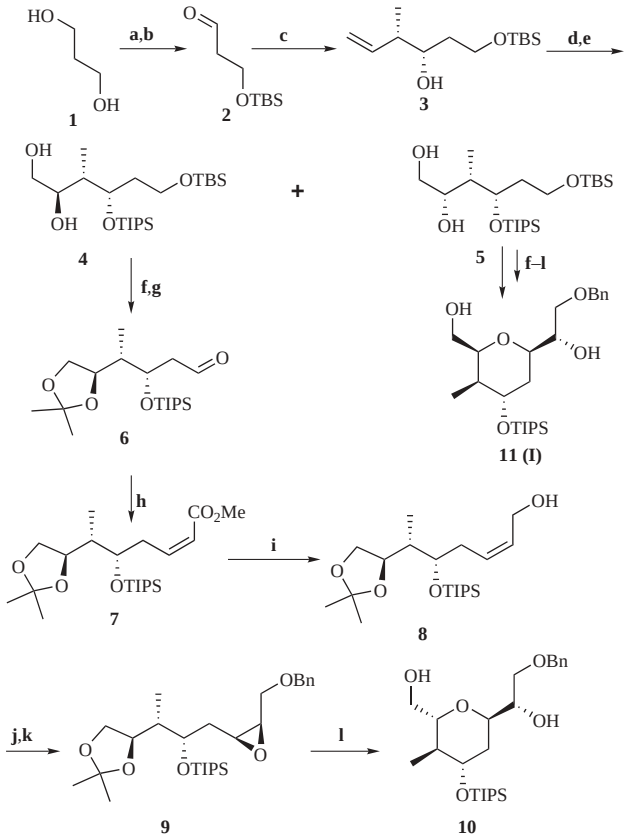
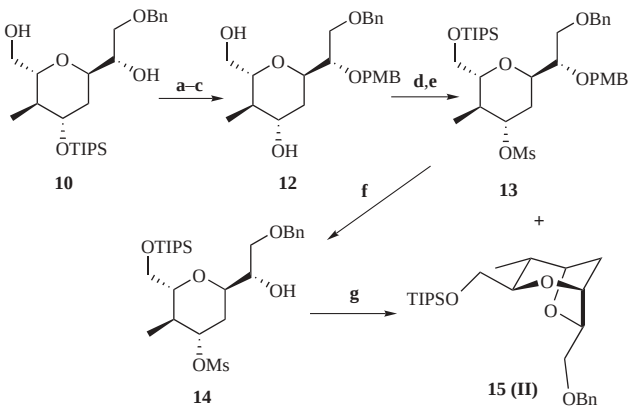
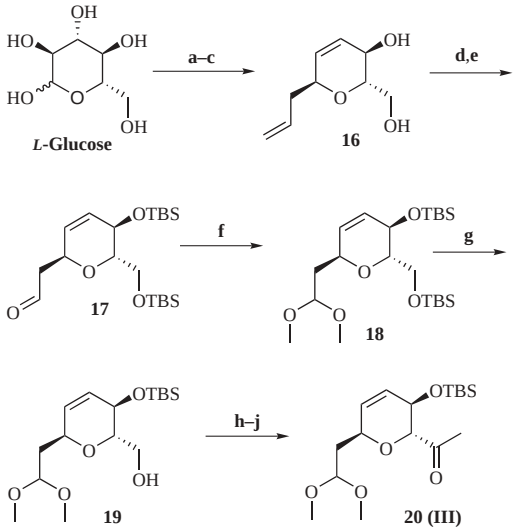


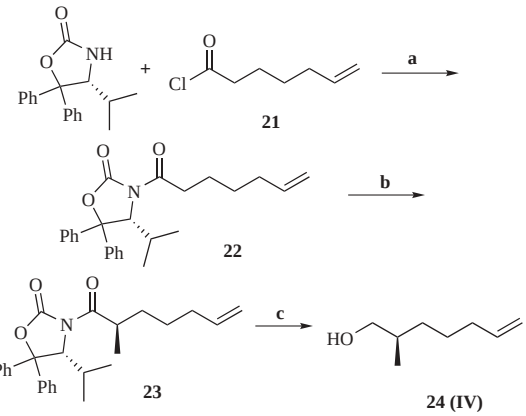
Scheme 2 *Reagents and conditions*: a) TBSCl, NaH, THF, 95%; b) Swern oxidation, 83%; c) 2-$^{d}Ipc_2B$-*Z*-($CH_2CH{=}CHCH_3$), $BF_3{\cdot}Et_2O$, THF, –78 °C, 62%; d) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 97%; e) OsO_4, NMO, THF, H_2O, 48% of **4**, 24% of **5**; f) *p*-TsOH, $CuSO_4$, acetone, 81%, 76% precursor for **11**; g) TPAP/NMO, CH_2Cl_2, molecular sieves, 80%, 81% precursor for **11**; h) $(CF_3CH_2O)_2POCH_2CO_2Me$, 18-crown-6, KHMDS, THF, –78 °C, 92%, 91% precursor for **11**; i) DIBAL-H, CH_2Cl_2, –78 °C, 99% for both diastereomers; j) D-DET, $Ti(O\textit{i}\text{-}Pr)_4$, *t*-BuOOH, molecular sieves, 67%, 56% precursor for **11**; k) BnBr, NaH, Bu_4NI, 80% for both diastereomers; l) CSA, CH_2Cl_2:*i*-PrOH (30:1), 52% of **10**, 82% of **11**.



Scheme 3 *Reagents and conditions*: a) TIPSCl, imidazole, DMF, 91%; b) PMBCl, NaH, Bu_4NI, 71%; c) TBAF, THF, 83%; d) TIPSCl, imidazole, DMF, 91%; e) MsCl, pyridine, DMAP, CH_2Cl_2; f) DDQ, CH_2Cl_2–H_2O, 48%; g) KHMDS, THF, –78 °C, 93%.



Scheme 4 *Reagents and conditions*: a) HBr–HOAc–Ac_2O, Zn/HOAc, 81%; b) Et_3N–MeOH–H_2O, 100%; c) allylsilane, TMSOTf, CH_2Cl_2–MeCN (2:1), 84%, de >99%; d) TBSCl, pyridine, 100%; e) AD-mix-β, *t*-BuOH–H_2O (1:1), NMO, $NaIO_4$, 70%; f) $HC(OMe)_3$, CH_2Cl_2, r.t., 94%; g) CSA, CH_2Cl_2–MeOH (1:1), 73%; h) Swern oxidation in THF; i) MeMgBr, THF, 82% after two steps; j) Dess–Martin periodinane, 95%.



Scheme 5 *Reagents and conditions:* a) *n*-BuLi, THF, 89%; b) NaHMDS, MeI, 74% (de >99%); c) LAH, Et_2O, 95%.

Conclusion

In this paper we have demonstrated and used a convergent approach to synthesize the key fragments **I**, **II**, **III** and **IV** of the novel sorangicin antibiotics. The coupling of the key fragments and the final steps in total synthesis is under investigation and will be reported in due course.

Acknowledgment

This work was supported by the Fonds der Chemischen Industrie. O. K. thanks the state of Sachsen-Anhalt for a fellowship.

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(18) **Procedure for the Preparation of (1*R*,3*R*,4*R*,5*R*,7*R*)-7-Benzyloxymethyl-4-methyl-2,6-dioxa-5,1-bicyclo[3.2.1]oct-3-yl-methoxytriisopropylsilane (15):** To a stirred solution of **13** (12 mg, 0.023 mmol) in 1.5 mL THF cooled to –78 °C was added dropwise KHMDS (0.52 µL of 0.5 M solution in hexane, 0.026 mmol). After stirring at this temperature for 2 h, 0.6 mL sat. NH_4Cl solution was added and the mixture was allowed to warm to r.t. The product was then extracted with Et_2O, and the organic layer washed with brine and dried. The solvent was removed on a rotary evaporator, and the residue was flash-chromatographed (pentane–methyl-*tert*-butylether, 3:1) to give 7 mg of 15 (93%) as a colorless oil. Analytical data for **15**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.26 (m, 5 H, H-11), 4.65–4.57 (m, 2 H, H-10), 4.36–4.34 (m, 1 H, H-7), 4.22 (d, *J* = 6.5 Hz, 1 H, H-5), 4.08 (dt, *J* = 2.3, 6.5 Hz, 1 H, H-8), 3.84–3.76 (m, 2 H, H-9), 3.71 (dq, *J* = 3.2, 11 Hz, 2 H, H-1), 3.47 (dt, *J* = 3.2, 7.1 Hz, 1 H, H-2), 1.99–1.94 (m, 1 H, H-6), 1.81 (dd, *J* = 1.5, 11.5 Hz, 1 H, H-6), 1.76–1.68 (m, 1 H, H-3), 1.05 (s, 21 H, H-12), 0.94 (d, *J* = 6.7 Hz, 3 H, H-4). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.34 (s, C-11), 128.32 (d, C-11), 127.69 (d, C-11), 81.71 (d, C-8), 79.52 (d, C-5), 79.16 (d, C-2), 74.52 (d, C-7), 73.27 (t, C-10), 68.39 (t, C-9), 65.22 (t, C-10), 38.15 (t, C-6), 37.00 (d, C-3), 17.99 (dq, C-12), 16.04 (q, C-4), 12.02 (dq, C-12). IR (neat): 2927, 2866, 1496, 1463, 1380, 1258, 1129, 1100, 1066, 1017, 883, 661 cm^{-1}. MS (CI): *m*/*z* = 435.1 (100) $[M + H]^+$, 391.2 (89), 357.2 (7), 309.2 (10), 261.2 (50), 243.2 (10), 191.1 (6), 119.1 (10), 91.1 (28). HRMS: *m*/*z* calcd for $C_{25}H_{42}O_4Si$ $[M]^+$: 434.2852. Found: 434.2853.

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