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(+)-Sorangicin A Synthetic Studies. Construction of the C(1–15) and C(16–29) Subtargets

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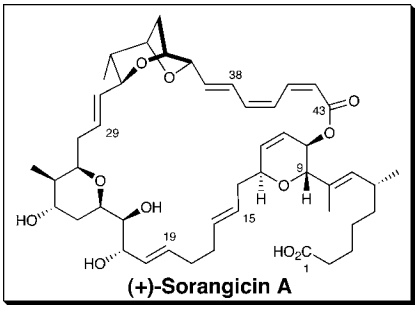
ABSTRACT



Effective stereocontrolled syntheses of subtargets (–)-2 and (–)-4, comprising respectively the C(16–29) and C(1–15) tetrahydropyran and dihydropyran moieties of the potent antibiotic (+)-sorangicin A (1), have been achieved. The cornerstone for the synthesis of (–)-2 involved an aldol tactic exploiting 1,4-induction, followed in turn by an acid-mediated cyclization/ketalization and hydrosilane reduction promoted by TMSOTf, while construction of (–)-4 entailed a stereoselective conjugate addition/α-oxygenation sequence.

In 1985, the laboratories of Höfle and Reichenbach reported the isolation and structural determination of the sorangicins, a new class of macrolide natural products produced by *Sorangium cellulosum*.[1] Importantly, (+)-sorangicin A, the most potent congener, demonstrated extraordinary antibiotic activity against a broad panel of both Gram-positive and Gram-negative bacteria, displaying average MIC values of 10 ng/mL and 10 μg/mL, respectively. Subsequent mechanistic examination revealed that the selective biological response induced by the sorangicins in prokaryotic cells arises from the inhibition of RNA polymerase in both *Escherichia coli* and *Staphylococcus aureus*.[2]

The sorangicin class of natural products and, in particular, sorangicin A (**1**) comprise timely synthetic targets[3] given both the novel architecture, including the signature dioxabicyclo[3.2.1]octane moiety, the *cis*,*cis*,*trans*-trienoate, and the 31-membered macrolide ring, and the significant biological properties. In this Letter, we disclose our overall synthetic strategy (Scheme 1), in conjunction with effective, stereocontrolled assemblies of subtargets **2** and **4**, comprising respectively the C(16−29) and C(1−15) fragments of (+)-sorangicin A. A viable approach to the signature element, the C(30)−C(38) dioxabicyclo[3.2.1]-octane subtarget (−)-**3**, was previously reported from this laboratory.[4]

A central tenet of our synthetic analysis of sorangicin A (**1**), taking into careful consideration the reported significant instability of the natural product to a variety of reagents (e.g., fluoride ion, DDQ, and the dissolving metal sodium amalgam),[5] entailed development of a viable protecting group

(1) (a) Jansen, R.; Wray, V.; Irschik, H.; Reichenbach, H.; Höfle, G. *Tetrahedron Lett.* **1985**, *26*, 6031. (b) Jansen, R.; Irschik, H.; Reichenbach, H.; Schomburg, D.; Wray, V.; Höfle, G. *Liebigs Ann. Chem.* **1989**, 111.

(2) Irschik, H.; Jansen, R.; Gerth, K.; Höfle, G.; Reichenbach, H. *J. Antibiot.* **1987**, *40*, 7.

(3) For other synthetic approaches, see: Schinzer, D.; Schulz, C.; Krug, O. *Synlett* **2004**, *15*, 2689.

(4) Smith, A. B., III; Fox, R. J. *Org. Lett.* **2004**, *6*, 1477.

(5) Schummer, D.; Irschik, H.; Höfle, G. *Liebigs Ann. Chem.* **1993**, 293.

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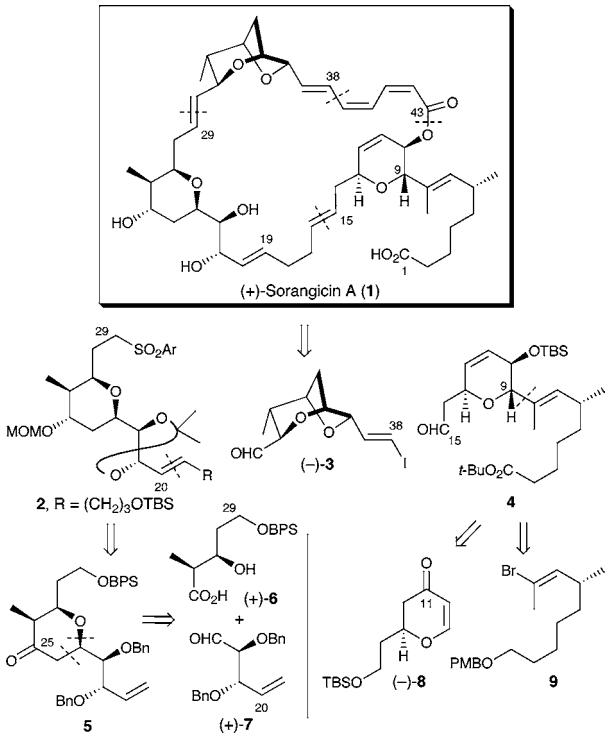
Scheme 1



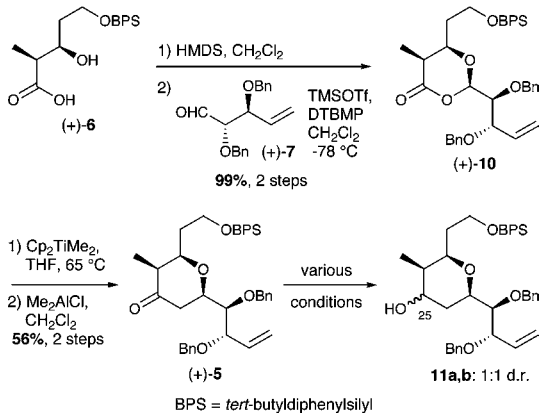
scenario. Fortunately, Höfle had demonstrated the potential utility of an acetonide for the C(21,22) diol system, in particular with removal by TFA treatment.[6] With this information in mind, we envisioned disconnections at the macrocyclic lactone, the C(38)−C(39) σ-bond, and both the C(15−16) and C(29−30) *trans*-disubstituted olefins to reveal subtargets **2**, (−)-**3**,[4] and **4**.

Recognition of the 2,6-*cis*-disubstituted tetrahydropyran in **2** initially suggested the powerful Petasis−Ferrier union/rearrangement[7] tactic developed in our laboratory exploiting known β-hydroxy acid (+)-**6**[7c] and aldehyde (+)-**7**.[8] This strategy, however, was not without significant risk: first, the Petasis−Ferrier rearrangement had not been explored with an α-oxygenated aldehyde; second, to the best of our knowledge, there are no examples of selective reductions of a C(4) carbonyl to the corresponding axial alcohol in a 2,3,6-*cis*-*cis*-trisubstituted tetrahydropyranone (cf. **5**).

For aldehyde **4**, our synthetic plan (Scheme 1) called for a conjugate addition of a cuprate derived from vinyl bromide **9** to known enone (−)-**8**,[9] followed in turn by α-oxygenation and Pd-catalyzed tin hydride reduction of the kinetic enol triflate derived from the C(11) ketone. Stereo- and regioselectivity in these transformations would derive from substrate control.

With this overview in mind, we began construction of **2**, exploiting the Petasis−Ferrier union/rearrangement. Silylation of known β-hydroxy acid (+)-**6**[7c] (Scheme 2), followed by condensation with aldehyde (+)-**7**,[8] promoted by TMSOTf,[10] afforded dioxanone (+)-**10**.

Scheme 2



Petasis−Tebbe methylenation[11] and in turn exposure of the derived enol ether to Me_2AlCl to trigger the Petasis−Ferrier rearrangement furnished tetrahydropyranone (+)-**5** both in good yield and as a single diastereomer.[12] Importantly, this transformation comprises the first example of the use of an α-oxygenated aldehyde in a Petasis−Ferrier union/rearrangement sequence.[13] However, despite the clear success of the Petasis−Ferrier union/rearrangement tactic, selective reduction of the derived ketone (+)-**5** to the requisite C(25) axial alcohol proved unattainable. A wide variety of reduction conditions including K- and L-selectride, $NaBH_4/CeCl_3$, CBS employing both (*R*) and (*S*) enantiomers, and DIBAL-H furnished at best a mixture (ca. 1:1) of the C(25) axial and equatorial alcohols. Equally daunting, Mitsunobu inversion of the undesired diastereomer resulted only in elimination. A nearly identical observation, including Mitsunobu elimination, was recently reported by Funk and Cossey for an analogous 2,3,6-*cis*-*cis*-trisubstituted tetrahydropyranone.[14] We therefore turned to an aldol construction tactic between methyl ketone (+)-**14** and aldehyde (+)-**16** (Scheme 3),

(6) Jansen, R.; Schummer, D.; Irschik, H.; Höfle, G. *Liebigs Ann. Chem.* **1990**, 975.

(7) (a) Ferrier, R. J.; Middleton, S. *Chem. Rev.* **1993**, *93*, 2779. (b) Petasis, N. A.; Lu, S.-P. *Tetrahedron Lett.* **1996**, *37*, 141. For examples exploiting the Petasis−Ferrier union/rearrangement tactic in natural product synthesis, see: (c) Smith, A. B., III; Minbiole, K. P.; Verhoest, P. R.; Schelhaas, M. *J. Am. Chem. Soc.* **2001**, *123*, 10942. (d) Smith, A. B., III; Verhoest, P. R.; Minbiole, K. P.; Lim, J. J. *Org. Lett.* **1999**, *1*, 909. (e) Smith, A. B., III; Minbiole, K. P.; Verhoest, P. R.; Beauchamp, T. J. *Org. Lett.* **1999**, *1*, 913. (f) Smith, A. B., III; Sfouggatakis, C.; Gotchev, D. B.; Shirakami, S.; Bauer, D.; Zhu, W.; Doughty, V. A. *Org. Lett.* **2004**, *6*, 3637. (f) Smith, A. B., III; Safonov, I. G.; Corbett, R. M. *J. Am. Chem. Soc.* **2002**, *124*, 11102. (g) Smith, A. B., III; Safonov, I. G.; Corbett, R. M. *J. Am. Chem. Soc.* **2001**, *123*, 12426. For more recent modifications, see: (h) O'Neil, K. E.; Kingree, S. V.; Minbiole, K. P. C. *Org. Lett.* **2005**, *7*, 515.

(8) Redlich, H.; Bruns, W.; Francke, W.; Schurig, V.; Payne, T. L.; Vite, J. P. *Tetrahedron* **1987**, 2029.

(9) Keck, G. E.; Li, X.-Y.; Krishnamurthy, D. *J. Org. Chem.* **1995**, *60*, 5998.

(10) Seebach, D.; Imwinkelried, R.; Stucky, G. *Helv. Chim. Acta* **1987**, *70*, 448.

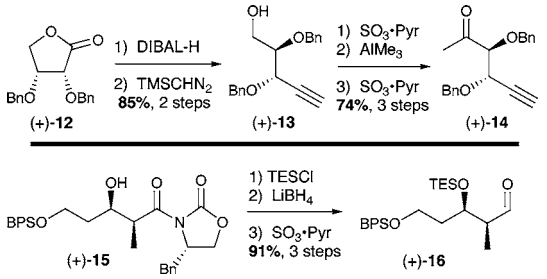
(11) Petasis, N. A.; Bzowej, E. I. *J. Am. Chem. Soc.* **1990**, *112*, 6392.

(12) The stereochemistry in (+)-**5** was established on the basis of NMR nOe measurements observed between the C(23) and C(27) hydrogens.

(13) Although dioxanone formation and methylenation proceeded smoothly, attempts to perform the rearrangement with an acetonide at C(21,22) led to decomposition.

(14) Cossey, K. N.; Funk, R. L. *J. Am. Chem. Soc.* **2004**, *126*, 12216.

Scheme 3



calling upon 1,4-stereoinduction[15] to install the C(25) hydroxyl prior to pyran ring formation.

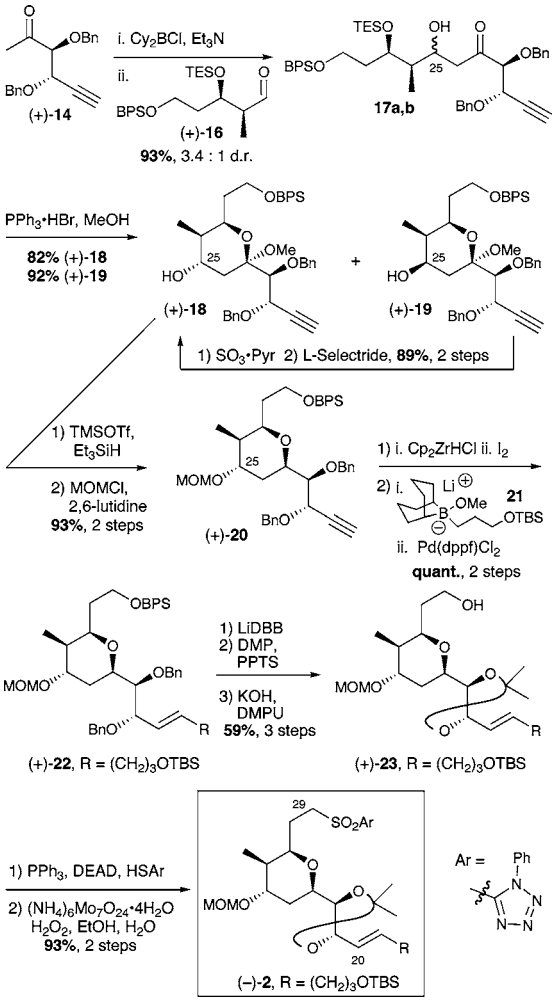
Ketone (+)-**14** and aldehyde (+)-**16** proved readily accessible as outlined in Scheme 3. Notable here was the two-step construction of (+)-**13** via DIBAL reduction of lactone (+)-**12**,[16] followed by exposure of the resulting lactol to trimethylsilyldiazomethane.[17]

For the aldol, treatment of the boron enolate derived from (+)-**14** with aldehyde (+)-**16** furnished a separable mixture (ca. 3.4:1) of C(25) diastereomers (Scheme 4).[15] Removal of the TES group in **17a** and **17b**, accompanied by cyclization and methyl ketal formation,[18] furnished mixed methyl ketals (+)-**18** and (+)-**19** in excellent yield. Although the aldol diastereoselectivity proved only modest, this route held considerable appeal since the minor diastereomer could be *completely* converted in excellent yield to (+)-**18** via oxidation and reduction of (+)-**19**.[18]

Continuing with construction of **2**, Et_3SiH reduction promoted by TMSOTf and MOM protection of the C(25) hydroxyl afforded tetrahydropyran (+)-**20** in excellent yield as a single diastereomer.[19]

Hydrozirconation/iodination,[20] followed by Suzuki–Miyaura coupling[21] with alkyl boronate **21**,[22] next furnished olefin (+)-**22** as a single *E*-isomer possessing the full carbon skeleton of subtarget **2**. Removal of the benzyl groups employing dissolving metal conditions, followed in turn by conversion of the resulting diol to the acetonide, and selective removal of the *tert*-butyldiphenylsilyl (BPS) group with hydroxide[23] led to alcohol (+)-**23** in 59% yield for the three steps. Thioether formation via a Mitsunobu reaction,[24] and oxidation of the derived sulfide to the sulfone completed construction of (−)-**2**. Sulfone (−)-**2** was thus prepared in 17 steps (longest linear sequence) from commercially available starting materials; the overall yield was 17%.

Scheme 4



We next turned to construction of aldehyde **4**, beginning with enone (−)-**8**, exploiting a conjugate addition/α-oxygenation sequence (Scheme 5). Synthesis of the requisite vinyl bromide (−)-**9** entailed a Myers alkylation[25] between (+)-**24** and **25** (Scheme 5) to furnish amide (+)-**26**, both in excellent yield and with high diastereoselectivity (>20:1).[26] Reduction to the aldehyde,[25,27] followed by Corey–Fuchs homologation[28] and hydrozirconation/bromination[20] led to vinyl bromide (−)-**9** as a single stereoisomer.

Enone (−)-**8**[9] (Scheme 5) was readily prepared enantioselectively via cyclocondensation between the Danishefsky

(15) For a similar example proceeding with 1,4-anti selectivity, see: Crimmins, M. T.; Katz, J. D.; Washburn, D. G.; Allwein, S. P.; McAtee, L. F. *J. Am. Chem. Soc.* **2002**, *124*, 5661.

(16) Marshall, J. A.; Seletsky, J. A.; Boris, M.; Luke, G. P. *J. Org. Chem.* **1994**, *59*, 3413.

(17) Myers, A. G.; Goldberg, S. D. *Angew. Chem., Int. Ed.* **2000**, *29*, 2732 and references therein.

(18) For selectivity precedent, see: Heathcock, C. H.; McLaughlin, M.; Medina, J.; Hubbs, J. L.; Wallace, G. A.; Scott, R.; Claffey, M. M.; Hayes, C. J.; Ott, G. R. *J. Am. Chem. Soc.* **2003**, *125*, 12844.

(19) The stereochemistry of (+)-**20** was verified upon semi-hydrogenation to afford material identical to that prepared through the Petasis–Ferrier rearrangement sequence.

(20) Hart, D. W.; Blackburn, T. F.; Schwartz, J. *J. Am. Chem. Soc.* **1975**, *97*, 679.

(21) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

(22) Alkyl boronate **21** was prepared from 1,3-propanediol; see Supporting Information.

(23) Shekhani, M. S.; Khan, K. M.; Mahwood, K.; Shah, P. M.; Malik, S. *Tetrahedron Lett.* **1990**, 1669.

(24) Mitsunobu, O. *Synthesis* **1981**, 1.

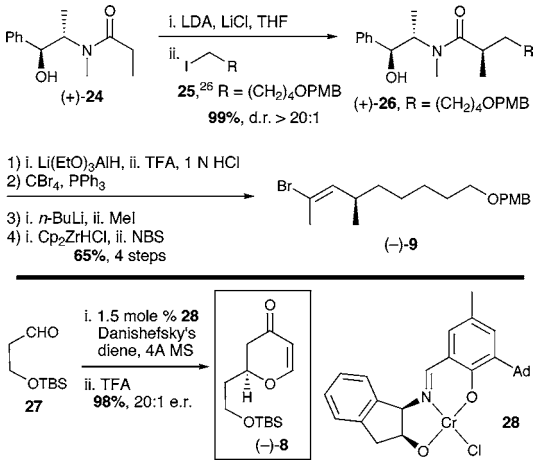
(25) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496.

(26) Iodide **25** was prepared in two steps from 1,5-pentanediol; see Supporting Information.

(27) The absolute stereochemistry of the aldehyde was verifed via chemical correlation; see Supporting Information.

(28) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *36*, 3769.

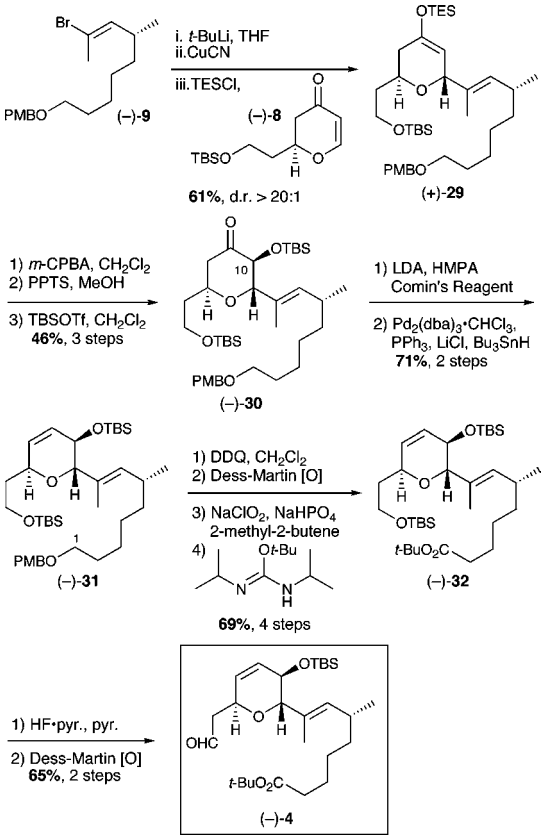
Scheme 5



diene and aldehyde **27**,[29] catalyzed by chromium(III) complex **28**.[30] Both the yield and enantioselectivity proved excellent (ca. 98%; 20:1 er).

Pleasingly, treatment of the higher-order cuprate derived from (−)-**9** with enone (−)-**8** (Scheme 6), in the presence of chlorotriethylsilane, led to enol ether (+)-**29** as a single diastereomer. Chemo- and stereoselective C(10) oxidation of (+)-**29** employing the Rubottom protocol,[31] followed by conversion of the derived α-TES ether to the α-TBS ether, next furnished (−)-**30** in 46% yield for the three steps.[32,33] Kinetic enolate formation (LDA/HMPA), followed in turn by formation of the enol triflate with Comin's reagent [*N*-(5-chloro-2-pyridyl)triflimide][34] and palladium-catalyzed reduction,[35] led to diene (−)-**31**. A two-step oxidation[36] and *tert*-butyl ester formation,[37] after removal of the PMB protecting group, next furnished (−)-**32**. Elaboration of aldehyde (−)-**4** was then achieved by chemoselective removal of the primary TBS group and Dess−Martin

Scheme 6



oxidation.[38] Overall, the synthesis of (−)-**4** entailed a longest linear sequence of 19 steps and proceeded in 5% overall yield.

In summary, syntheses of advanced intermediates (−)-**2** and (−)-**4**, comprising respectively the C(16−29) and C(1−15) backbone of sorangicin A (**1**), have been achieved in 17 and 19 steps. The cornerstone of the synthetic strategy for (−)-**2** entailed an aldol tactic, followed in turn by an acid-mediated cyclization/ketalization and hydrosilane reduction, whereas (−)-**4** arose via a highly stereoselective conjugate addition/α-oxygenation sequence. Studies to complete the total synthesis of (+)-sorangicin A (**1**) will be reported in due course.

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

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(29) Aldehyde **27** was prepared in two steps from 1,3-propanediol; see Supporting Information.

(30) (a) Dossetter, A. G.; Jamison, T. F.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2398. (b) Gademann, K.; Chavez, D. E.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2002**, *41*, 3059.

(31) RuBottom, G. M.; Vazquez, M. A.; Pelegrina, D. R. *Tetrahedron Lett.* **1974**, *49*, 4319.

(32) Conversion of the corresponding TBS-enol ether to (−)-**30** or the enol acetate to the α-hydroxy ketone were significantly less efficient.

(33) (a) The absolute stereochemistry of C(10) was verified via Mosher ester analysis; see Supporting Information. (b) The observed *J* value of 8.3 Hz between the C(9) and C(10) hydrogens of (−)-**30** verified the relative stereochemistry. For the conformation of substituted tetrahydropyranones, see: (c) Goodwin, T. E.; Crowder, M.; White, R. B.; Swanson, J. S. *J. Org. Chem.* **1983**, *48*, 376.

(34) Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1992**, *33*, 6299.

(35) Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 3033.

(36) Bal, B. S.; Childers, W. E., Jr.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091.

(37) Mathias, L. J. *Synthesis* **1979**, 561.

(38) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4156.