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An Efficient, Second-Generation Synthesis of the Signature Dioxabicyclo[3.2.1]octane Core of (+)-Sorangicin A and Elaboration of the (*Z*,*Z*,*E*)-Triene Acid System

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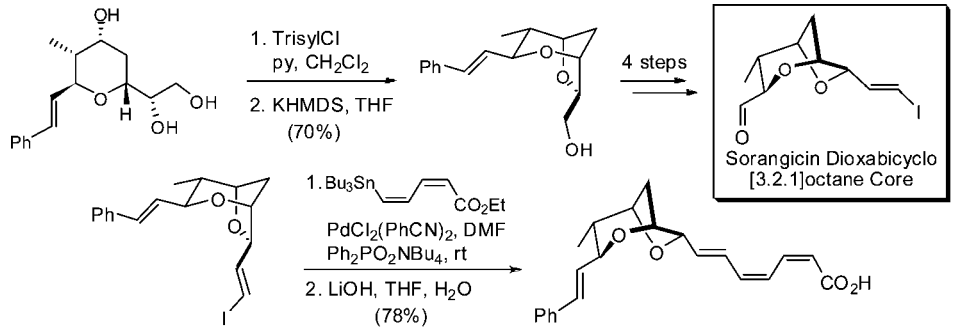
ABSTRACT



An efficient, second-generation synthesis of the signature dioxabicyclo[3.2.1]octane core of (+)-sorangicin A (1), in conjunction with an effective, stereocontrolled protocol to arrive at the requisite (*Z*,*Z*,*E*)-triene acid system has been developed. Highlights of the core construction entail a three-component union, a KHMDS-promoted epoxide ring formation−ring opening cascade, a Takai olefination, and a chemoselective Sharpless dihydroxylation. Assembly of the triene acid system was then achieved via Stille cross-coupling with the ethyl ester of (*Z*,*Z*)-5-tributylstannyl-2,4-pentadienoic acid, followed by mild hydrolysis preserving the triene configuration.

The sorangicins comprise a family of architecturally complex macrolide antibiotics isolated from a fermentation broth of the myxobacteria *Sorangium cellulosum* (strain So ce 12).[1] The most potent and prevalent congener, (+)-sorangicin A (**1**), was found to be highly effective against a spectrum of both Gram-positive (MIC 0.01−0.3 μg/mL) and Gram-negative bacteria (MIC 3−25 μg/mL). Subsequent studies revealed that (+)-sorangicin A (**1**) inhibits bacterial RNA-polymerase in both *E. coli* and *S. aureus*, while not affecting eukaryotic cells.[2]

The structure of (+)-sorangicin A (**1**; Scheme 1),[3] endowed with a highly unsaturated 31-membered macrolactone, a rare (Z,*Z*,*E*)-trienoate linkage, and the signature dioxabicyclo[3.2.1]octane, in conjunction with the important biological properties, has engendered considerable interest

(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) The stereocenter at C(10) in (+)-sorangicin A, as confirmed by R. Jansen (Helmholtz Center for Infection Research, Braunschweig, Germany) is *S*, not *R* as depicted in ref 4b. We thank R. Jansen for this clarification.

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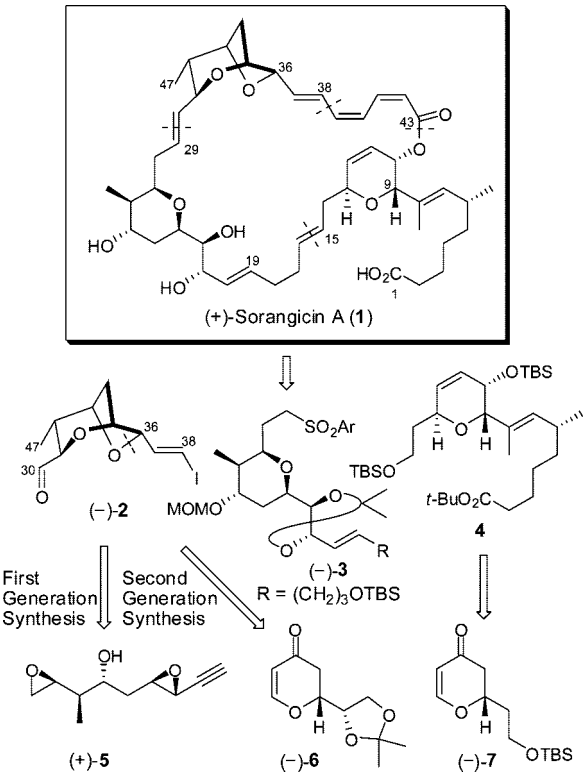
Scheme 1



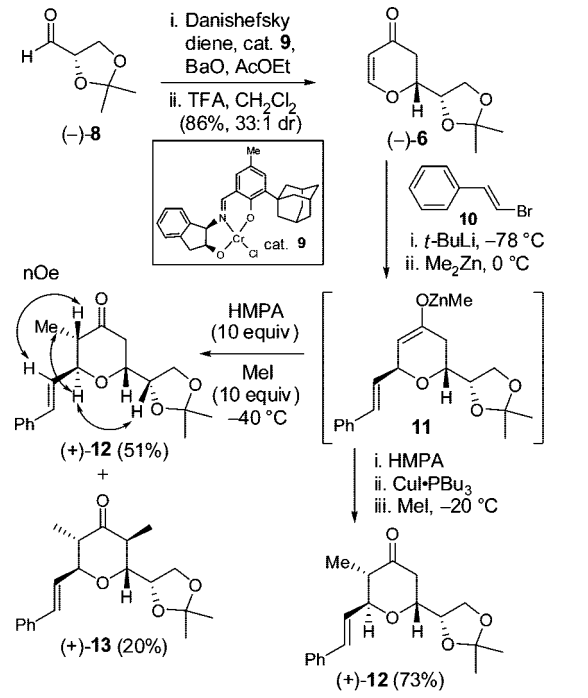
within the synthetic and biomedical communities.[4] Indeed, significant progress toward the total synthesis of (+)-sorangicin A has been recorded by the Schinzer[5] and Crimmins[6] groups, in addition to our laboratory.[7]

From the outset, our synthetic analysis of (+)-sorangicin A (**1**) called for disconnections at the macrocyclic lactone, the C(38−39) σ-bond, and both the C(15−16) and C(29−30) *trans*-disubstituted olefins to yield three advanced subtargets: bicyclic ether (−)-**2**, tetrahydropyran (−)-**3**, and dihydropyran **4** (Scheme 1).[7] To construct the dioxabicyclo[3.2.1]octane core of (−)-**2**, our first-generation route featured an acid-promoted intramolecular cascade of epoxide openings, the first facilitated and controlled chemoselectively by a $Co_2(CO)_6$-alkyne complex of bis-epoxide (+)-**5** and the second mediated by $BF_3{\bullet}OEt_2$.[7a] Although effective, the route was not highly efficient vis-à-vis material advancement. We now report a second-generation synthesis of (−)-**2**, in conjunction with the development of an effective, highly stereocontrolled protocol to elaborate the C(37−43) (*Z*,*Z*,*E*)-triene acid unit.

Reanalysis of the structure of (−)-**2** led to the observation that disconnection of the bicyclic ether fragment at the C(36)−O bond would lead to a tetrahydropyran,[8] sharing the same 2,6-*trans*-relationship as **4**, and thus potentially available via a similar substrate-controlled stereoselective conjugate addition of a Michael donor to a similar dihydropyrone as employed to construct **4**.[7b]

Toward this end, dihydropyrone (−)-**6** was readily prepared in 86% yield (33:1 dr) via a hetero Diels−Alder (HDA) reaction between the Danishefsky diene and aldehyde (−)-**8**,[9] catalyzed by the chromium(III)-Schiff base **9**, the same Jacobsen catalyst employed for our earlier synthesis of dihydropyrone (−)-**7** (Scheme 2).[10]

Scheme 2



Attention next turned to the three-component union of dihydropyrone (−)-**6** with MeI and a suitable Michael donor, the latter corresponding to a surrogate aldehyde. The literature however is not rich with such examples, due presumably to deactivation of the enone by the ring oxygen.[11,7b] In fact, dihydropyrone (−)-**6** proved to be a reluctant Michael acceptor. For example, use of the cuprate derived from $BnOCH_2SnBu_3$ displayed no reactivity. This result may however be a donor problem, given the low reactivity of this type of organometallic addend toward Michael addition as observed by Fuchs et al.[12]

We turned next to the commercially available β-bromostyrene (**10**) as a prospective nucleophile progenitor, with a view

(4) (a) Jansen, R.; Schummer, D.; Irschik, H.; Höfle, G. *Liebigs Ann. Chem.* **1990**, 975. (b) Schummer, D.; Irschik, H.; Höfle, G. *Liebigs Ann. Chem.* **1993**, 293. (c) Campbell, E. A.; Pavlova, O.; Zenkin, N.; Leon, F.; Irschik, H.; Jansen, R.; Severinov, K.; Darst, S. A. *EMBO J.* **2005**, *24*, 674.

(5) Schinzer, D.; Schulz, C.; Krug, O. *Synlett* **2004**, *15*, 2689.

(6) Crimmins, M. T.; Haley, M. W. *Org. Lett.* **2006**, *8*, 4223.

(7) (a) Smith, A. B., III; Fox, R. J. *Org. Lett.* **2004**, *6*, 1477. (b) Smith, A. B., III; Fox, R. J.; Vanecko, J. A. *Org. Lett.* **2005**, *7*, 3099.

(8) A similar disconnection was elegantly employed by the Crimmins laboratory in an efficient approach to (−)-**18**; see ref 6.

(9) Aldehyde (−)-**8**, although commercially available, was prepared in two steps from L-gulonic acid γ-lactone; see: Hubschwerlen, C.; Specklin, J.-L.; Higelin, J. *Org. Synth.* **1995**, *72*, 1.

(10) Joly, G. D.; Jacobsen, E. N. *Org. Lett.* **2002**, *4*, 1795.

(11) Paterson, I.; Steven, A.; Luckhurst, C. A. *Org. Biomol. Chem.* **2004**, *2*, 3026.

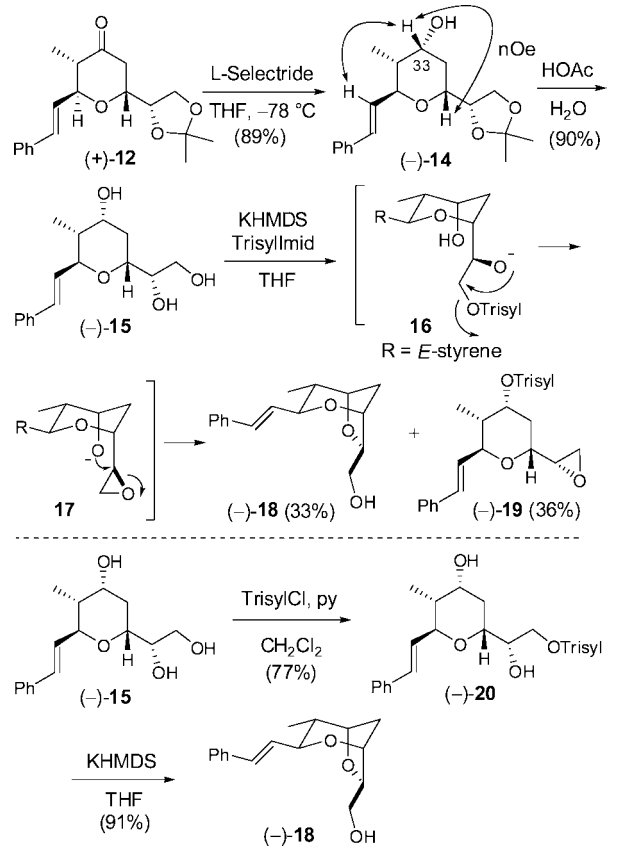
(12) Hutchinson, D. K.; Fuchs, P. L. *J. Am. Chem. Soc.* **1987**, *109*, 4930.

to achieving olefin cleavage at a later stage to access the C(30) aldehyde. Application of the Noyori three-component prostaglandin coupling protocol,[13] involving Li halogen exchange of the bromine in **10** with *t*-BuLi at −78 °C,[14] followed in turn by addition of Me_2Zn, warming to 0 °C to furnish a mixed zincate, and then addition of dihydropyrone (−)-**6** at −78 °C effectively led to conjugate addition.[15] Although forcing conditions (ca. 10 equiv of MeI and HMPA at −40 °C) were required to quench the resultant enolate (**11**), a single diastereomer (+)-**12** was obtained in modest yield (51%), along with the formation of a significant amount of α,α′-bismethylated product (+)-**13** (20%). This result is not without precedent. Alexakis et al. observed unusual reactivity of a Zn-methyl group with an enolate similar to **11** upon trapping with allyl bromide.[16] We reasoned that during the slow enolate capture process **11**, possessing the Zn-methyl group, is sufficiently basic in the presence of excess HMPA to deprotonate (+)-**12**, and in turn lead via methylation to (+)-**13**. Lowering the alkylation temperature from −40 to −60 °C only led to longer reaction times and an increase of (+)-**13** (38%). Higher temperature (−20 °C) however did have a beneficial effect on the yield of (+)-**12**; the same trend was observed by Alexakis et al. In the end, we discovered that the reactivity of the zinc enolate (**11**) could be successfully down-regulated by addition of CuI•PBu_3 just prior to the addition of MeI, which led to a slower, but more selective reaction to furnish (+)-**12** in 73% yield. Confirmation of the requisite 2,3,6-*trans*-*cis*-configuration was obtained by NOESY studies (Scheme 2).

Final elaboration to (−)-**2** began with L-Selectride reduction of (+)-**12** to furnish (−)-**14** as a single diastereomer (Scheme 3); confirmation of the requisite configuration at C(33) was again achieved by NOESY correlations. The acetonide moiety was then removed with aqueous acetic acid to furnish triol (−)-**15**.

With (−)-**15** in hand, we turned to the critical task of generating the two-atom bridge. Triol (−)-**15** was treated with KHMDS (1 equiv), followed by slow addition of the bulky *N*-triisopropylbenzenesulfonylimidazole (TrisIm; 1 equiv) to effect regioselective sulfonylation of the least hindered hydroxyl. In analogy with the work of Crimmins et al.,[6] treatment of the resultant trisylate (**16**) with an additional 2 equiv of KHMDS then promoted a reaction cascade involving epoxide ring formation, followed by ring opening to generate the bridged bicycle.[17] Although this "one-pot" protocol delivered the desired product (−)-**18**, the yield was disappointing (ca. 33%), due to oversulfonylation to form (−)-**19** (ca. 36%). Lower reaction temperatures or the use of potassium *tert*-butoxide did not improve the

Scheme 3



situation. A less elegant, two-step protocol was thus explored. The primary hydroxyl of (−)-**15** was first selectively sulfonylated with triisopropylbenzenesulfonyl chloride (TrisylCl) employing pyridine/CH_2Cl_2 (2:3) as solvent at room temperature.[18] Under these conditions, sulfonylation of the secondary hydroxyl was suppressed; in addition, the resultant sulfonate (−)-**20** proved stable to purification and handling. The primary sulfonate was then treated with 1 equiv of KHMDS to furnish bicyclic ether (−)-**18** in high yield, possessing spectral data in complete accord with the data reported by the Crimmins laboratory.[6] Bicycle (−)-**18**, comprising the signature dioxabicyclo[3.2.1]octane core of (+)-sorangicin A (**1**), was thus available in 6 steps and 35% overall yield from (−)-**8**.

To arrive at (−)-**2** (Scheme 4), (−)-**18** was oxidized employing Parikh−Doering conditions,[19] and the resultant sensitive aldehyde **21** immediately subjected to Takai olefination without purification.[20] Initial experiments on small scale employing THF as solvent afforded an *E*/*Z* diastereomeric mixture (3.2:1); the olefin configurations were assigned, respectively, based on ^{1}H NMR coupling constants

(13) Suzuki, M.; Morita, Y.; Koyano, H.; Koga, M.; Noyori, R. *Tetrahedron* **1990**, *46*, 4809.

(14) It is critical to add *β*-bromostyrene to *t*-BuLi; the inverse addition led to low conversion.

(15) Commercial *β*-bromostyrene is a *trans*/*cis* mixture (ca. 9:1); interestingly only one geometric product was observed. This result could be attributed to unproductive 1,4-addition of the *cis*-isomer, cf.: Fürstner, A.; Grela, K.; Mathes, C.; Lehmann, C. W. *J. Am. Chem. Soc.* **2000**, *122*, 11799.

(16) Rathgeb, X.; March, S.; Alexakis, A. *J. Org. Chem.* **2006**, *71*, 5737.

(17) Dounay, A. B.; Florence, G. J.; Saito, A.; Forsyth, C. J. *Tetrahedron* **2002**, *58*, 1865.

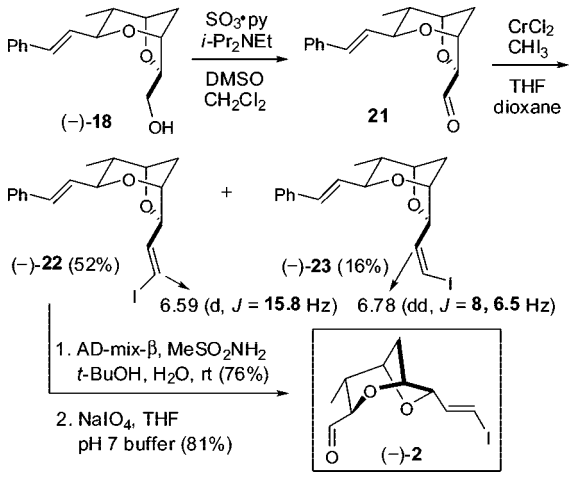
(18) Kojima, N.; Maezaki, N.; Tominaga, H.; Asai, M.; Yanai, M.; Tanaka, T. *Chem. Eur. J.* **2003**, *9*, 4980.

(19) Parikh, J.; Doering, W. V. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505.

(20) Takai, K. R.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408.

(15.8 Hz vs 8 Hz).[21] The observed low *E*/*Z* selectivity was unexpected given that α-alkoxy-aldehydes in general exhibit near complete (*E*)-selectivity.[22] Larger-scale reactions also proved problematic, furnishing the vinyl iodides in significantly lower yield. Recourse to a mixture of dioxane/THF (4:1; v/v) as solvent system,[23] although not significantly improving the selectivity, did improve the scale-up issue to furnish (−)-**22** and (−)-**23** in 52 and 16%, respectively, on half gram reaction scale.

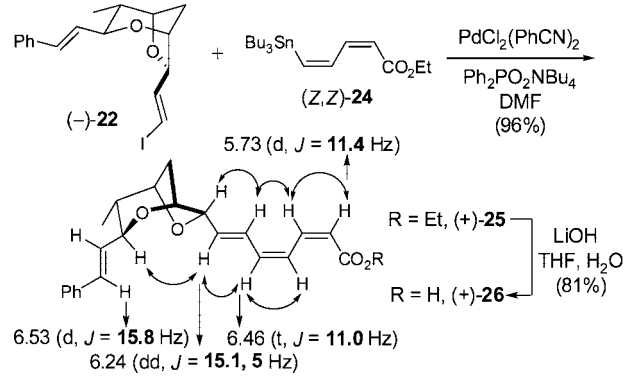
Scheme 4



Required at this stage was differentiation of the two olefins present in (−)-**22** to access aldehyde (−)-**2**. We reasoned that the electron-withdrawing and -donating biases, respectively, of the iodide and phenyl substituents would permit chemoselective functionalization of the more electron-rich olefin. Gratifyingly, Sharpless dihydroxylation of (−)-**22** at room temperature proceeded only at the styrene moiety to generate the corresponding diol,[24] which upon reaction with $NaIO_4$ employing buffered conditions furnished (−)-**2** identical in all respects to material prepared previously in our laboratory.[7a]

Having achieved an effective, second-generation synthesis of (−)-**2**, we turned next to explore possible tactics to construct the sensitive (*Z*,*Z*,*E*)-triene acid fragment. Vinyl iodide (−)-**22** was selected as a model system. Stille cross-coupling with known (*Z*,*Z*)-dienoate **24** led to (+)-**25** (Scheme 5).[25] Best results were obtained using bis(benzonitrile)-dichloropalladium(II) as catalyst in DMF, along with excess $Ph_2PO_2NBu_4$ (6 equiv) as a tin scavenger[26] to suppress *Z*/*E* isomerization. Under these conditions, (+)-**25** was produced in 96% yield as a single isomer (>20:1). Correlations derived from NOESY studies, as well as coupling constants, confirmed the desired (Z,*Z*,*E*)-configuration of (+)-**25** (Scheme 5). Hydrolysis of trienoate (+)-**25** was then achieved with LiOH in aqueous THF to furnish acid (+)-**26** in 81% yield, with complete preservation of the olefin configuration.

Scheme 5



In summary, an effective, scalable route to (−)-**2** possessing the C(30−38) signature core of (+)-sorangicin A (**1**) has been achieved in 10 steps from (−)-**8**. In addition, an effective protocol has been developed for prospective elaboration of the C(37−43) (*Z*,*Z*,*E*)-triene acid functionality, required for any successful (+)-sorangicin A (**1**) endgame. Progress toward the total synthesis of (+)-sorangicin A (**1**) will be reported in due course.

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Supporting Information Available: Experimental procedures and full spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) *Z*-Vinyl iodide (−)-**23** could be useful for the synthesis of (+)-Sorangicin A_1.

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