ORGANIC LETTERS

2011
Vol. 13, No. 17
4652–4655

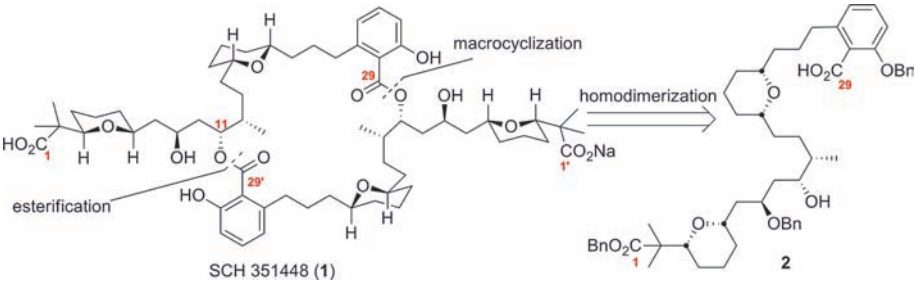
# Total Synthesis of (+)-SCH 351448

**Kaicheng Zhu and James S. Panek***

*Department of Chemistry and Center for Chemical Methodology and Library Development, Metcalf Center for Science and Engineering, Boston University, 590 Commonwealth Avenue, Boston, Massachusetts 02215, United States*

*panek@bu.edu*

**Received July 11, 2011**




**A convergent synthesis of (+)-SCH 351448 (1), a monosodium salt of a $C_2$-symmetric macrodiolide, is described. Our approach is based on a [4 + 2] annulation with a chiral allyl silane (*anti*-5c) to assemble the pyran subunits. Homodimerization was carried out in a stepwise fashion; initial esterification at C29′ followed by macrocyclization at C29 afforded the desired macrodiolide.**

In 2000, Hedge and co-workers reported the bioassay-guided isolation of a microbial metabolite, named SCH 351448 (**1**), from the organic extract of *Micromonospora sp.*[1] SCH 351448 is a novel activator ($ED_{50}$ = 25 $\mu$M) for a low-density lipoprotein receptor promoter, which is important for the treatment of hypercholesterolemia.[2]

The structure of SCH 351448 (**1**) was determined by single-crystal X-ray analysis and exhibited a hepta-coordinated sodium ion positioned in the interior cavity of the hydrophobic skeletal array.[1] Its structure consisted of a 28-membered macrodiolide comprised of two identical hydroxy carboxylic acid monomeric subunits. The intriguing structure and unique bioactivity of **1** have led to several total synthesis programs being initiated by the synthetic community.[3]

Our retrosynthetic analysis of this target (Figure 1) began with a disconnection of the C29/C29′ ester bonds to yield the monomeric subunit **2**. The latter was envisioned to come from an olefin cross metathesis of fragments **3** and **4**. Fragment **3** could arise from an asymmetric allylation and crotylation of the *cis*-2,6-dihydropyran core, which would be formed from a [4 + 2] annulation reaction[4] of allylsilane *anti*-**5c** with aldehyde **6a**. Similarly, fragment **4** would be derived from silane *anti*-**5c** and aldehyde **6b**.

We have previously reported a highly diastereo- and enantioselective [4 + 2] annulation between aldehydes and *syn* allylsilanes.[4] However, early experiments at applying the annulation to form dihydropyran products **7** from silanes *syn*-**5b**/*syn*-**5c** and aldehyde **6a** (Scheme 1, eq 1) gave inconsistent results and thus were not synthetically useful. Previously, Roush had reported the construction of *cis*-2,6-disubstituted dihydropyrans using *anti*-allylsilanes derived from the asymmetric $\gamma$-silyl allylboration of an aldehyde.[5] In that report, the favored pathway was thought to proceed *via* a boat-like TS-A which fashioned the *cis*-isomer as the major product, while the *trans*-isomer was suggested to form *via* the unfavored chairlike TS-B

(1) Hegde, V. R.; Puar, M. S.; Dai, P.; Patel, M.; Gullo, V. P.; Das, P. R.; Bond, R. W.; McPhail, A. T. *Tetrahedron Lett.* **2000**, *41*, 1351–1354.

(2) (a) Brown, M. S.; Goldstein, J. L. *Science* **1986**, *232*, 34–47. (b) Brown, M. S.; Goldstein, J. L. *Cell* **1997**, *89*, 331–340.

(3) For previous total syntheses, see: (a) Kang, E. J.; Cho, E. J.; Lee, Y. E.; Ji, M. K.; Shin, D. M.; Chung, Y. K.; Lee, E. *J. Am. Chem. Soc.* **2004**, *126*, 2680–2681. (b) Kang, E. J.; Cho, E. J.; Ji, M. K.; Lee, Y. E.; Shin, D. M.; Choi, S. Y.; Chung, Y. K.; Kim, J.-S.; Kim, H.-J.; Lee, S.-G.; Lah, M.; Lee, E. *J. Org. Chem.* **2005**, *70*, 6321–6329. (c) Soltani, O.; De Brabander, J. K. *Org. Lett.* **2005**, *7*, 2791–2793. (d) Bolshakov, S.; Leighton, J. L. *Org. Lett.* **2005**, *7*, 3809–3812. (e) Crimmins, M. T.; Vanier, G. S. *Org. Lett.* **2006**, *8*, 2887–2890. (f) Cheung, L. L.; Rychnovsky, S. D. *Org. Lett.* **2008**, *10*, 3101–3104. For the partial syntheses, see: (g) Backes, J. R.; Koert, U. *Eur. J. Org. Chem.* **2006**, *12*, 2777–2785. (h) Chan, K.-P.; Ling, Y. H.; Loh, T.-P. *Chem. Commun.* **2007**, 939–941. (i) Park, H.; Kim, H.; Hong, J. *Org. Lett.* **2011**, *13*, 3742–3745.

(4) Su, Q.; Panek, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 2425–2430.

(5) Roush, W. R.; Dilley, G. J. *Synlett* **2001**, *SI*, 955–959.

10.1021/ol201863b 
**Published on Web 08/11/2011**

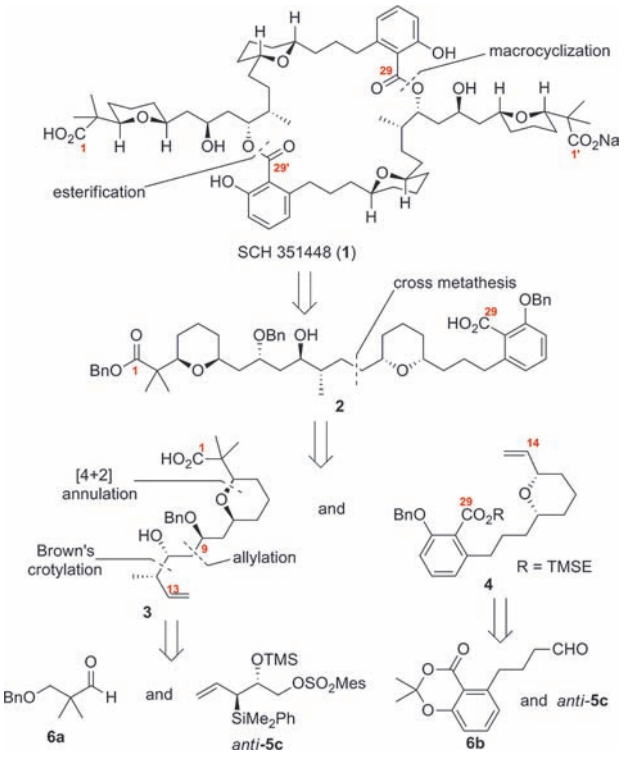
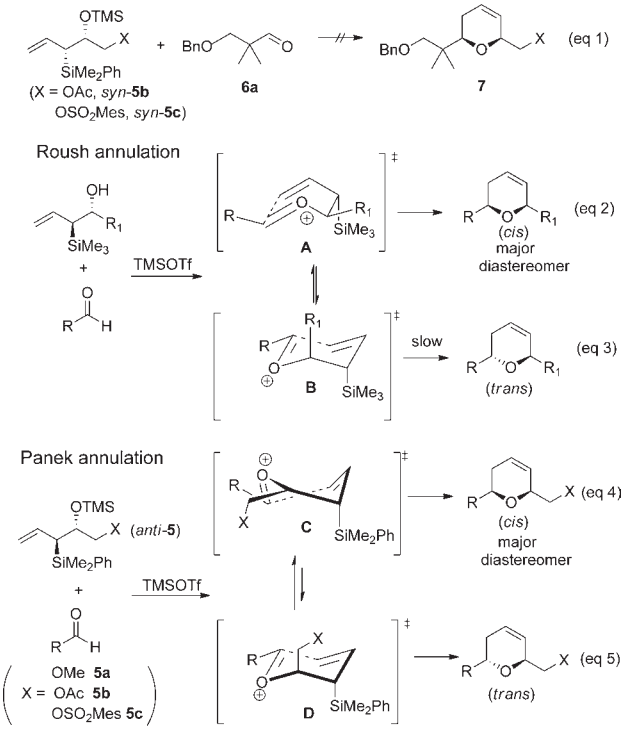


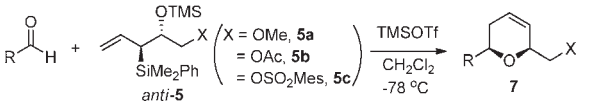

**Figure 1.** Retrosynthetic analysis of SCH 351448 (**1**).

**Scheme 1.** Possible Transition States for the [4 + 2] Annulation




(Scheme 1). In that context, we have observed that *anti*-silanes such as **5** participate in a [4 + 2]-annulation with aldehydes to produce 2,6-*cis* dihydropyrans **7**; the results are summarized in Table 1. One proposed mechanism that accounts for the stereochemical course of the annulation involves the equilibration between a twist boat-like TS-C and a chairlike TS-D, where TS-C avoids the steric destabilizing *trans*-diaxial orientation versus TS-D (Scheme 1, eqs 4 and 5).

**Table 1.** Synthesis of *cis*-Dihydropyrans *via* [4 + 2] Annulation

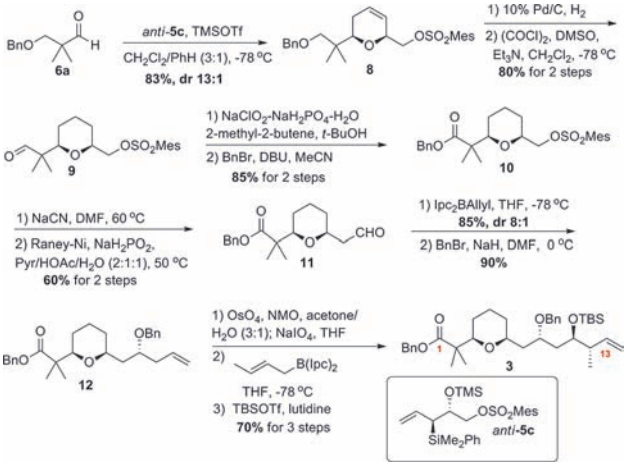



| entry | aldehyde | *anti*-silane | major isomer[a] | yield (%)[b] | dr (*cis*/*trans*)[c] |
|---|---|---|---|---|---|
| 1 | R = $PhCH_2$ | **5a** | **7a** | 30 | 10:1 |
| 2 | R = $PhCH_2$ | **5b** | **7b** | 46 | 13:1 |
| 3 | R = $PhCH_2$ | **5c** | **7c** | 83 | 17:1 |
| 4 | R = *n*-$C_4H_9$ | **5a** | **7d** | 25 | 10:1 |
| 5 | R = *n*-$C_4H_9$ | **5b** | **7e** | 58 | 12:1 |
| 6 | R = *n*-$C_4H_9$ | **5c** | **7f** | 81 | 18:1 |

[a] Stereochemistry of the dihydropyrans was assigned by NOE experiments. [b] Yields were based on pure materials isolated by chromatography on $SiO_2$. [c] The product ratios were determined by $^1H$ NMR (400 MHz).

Synthesis of the C1−C13 fragment began with the known α,α′-dimethyl aldehyde **6a**[6] (Scheme 2). Annulation of silane *anti*-**5c** and aldehyde **6a** proceeded smoothly in the presence of TMSOTf to afford the desired dihydropyran **8** in 83% yield (dr 13:1). Hydrogenation of **8** afforded a primary alcohol which was later oxidized to aldehyde **9** in 80% yield over two steps. Further oxidation under Pinnick oxidation conditions[7] and protection afforded benzyl ester **10**. An $S_N2$ displacement of the mesitylate in compound **10** with NaCN followed by Raney-nickel mediated partial reduction[8] of the resulting nitrile afforded aldehyde **11** in 60% yield, after hydrolysis of the intermediate imine.

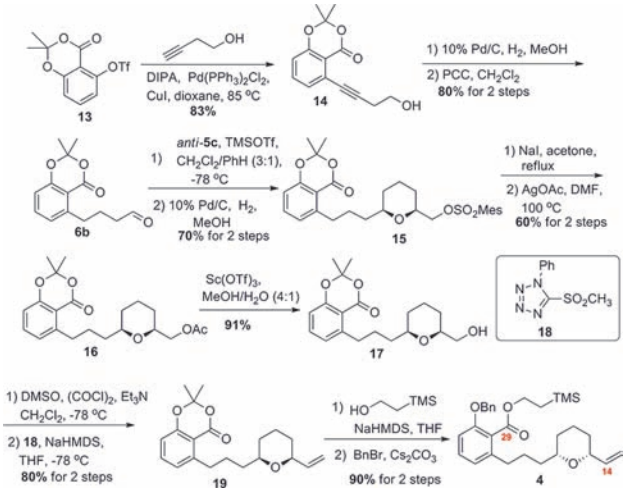
**Scheme 2.** Synthesis of C1−C13 Fragment



Asymmetric allylation of **11** using Brown's protocol[9]-furnished the desired secondary homoallylic alcohol, which was subsequently protected as benzyl ether **12**. Oxidative cleavage of alkene **12** followed by asymmetric crotylation of the resulting aldehyde using Brown's (*E*)-crotyl borane[10] afforded the *anti*-homoallylic alcohol, which was protected as its TBS ether to provide olefin **3** as one of the coupling partners in 60% yield over three steps.

Synthesis of the C14−C29 fragment (Scheme 3) began with aryl triflate **13**,[11] which was subjected to a Sonogashira cross-coupling to afford propargylic alcohol **14** in 85% yield. Catalytic hydrogenation of alkyne **14** in the presence of Pd/C followed by PCC oxidation provided aldehyde **6b**.

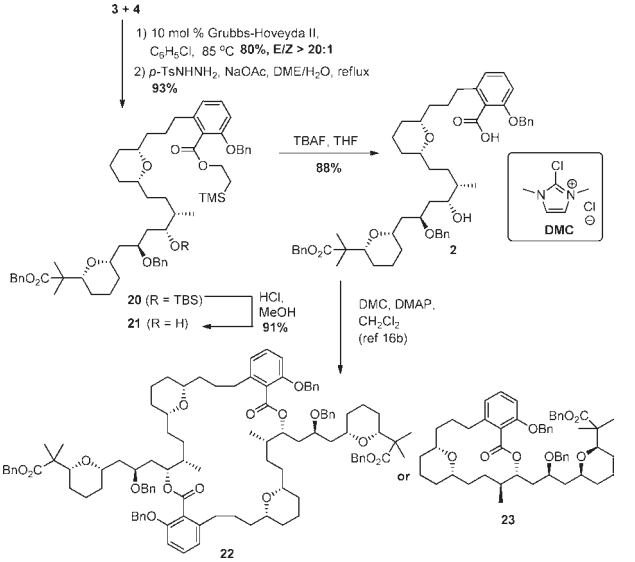
**Scheme 3.** Synthesis of C14−C29 Fragment




Annulation between aldehyde **6b** and silane *anti*-**5c** furnished the desired dihydropyran, which was hydrogenated to give **15** in 70% yield over two steps. Subsequent $S_N2$ displacement of the mesitylate in **15** yielded an iodide, which was further converted to acetate **16** in 60% yield over two steps. A $Sc(OTf)_3$ catalyzed hydrolysis[12] of acetate **16** provided primary alcohol **17** in 91% yield, which was then subjected to a Swern oxidation, followed by a Julia−Kociénski olefination[3e] with sulfone **18**,[13] to give alkene **19** in 80% yield. Opening of the dioxinone ring in **19** afforded the intermediate phenol, which was converted to the $\beta$-silyl ester **4**.

With advanced intermediates **3** and **4** available in useful amounts, we were now positioned to investigate methods for their union. Cross metathesis between **3** and **4** (Scheme 4) proceeded smoothly using the Grubbs−Hoveyda second generation catalyst,[14] which delivered the (*E*)-olefin. This material was then subjected to diimide reduction[3a] to afford advanced intermediate **20**. Deprotection of **20** provided seco acid **2**, which was poised for the homodimerization experiments.

**Scheme 4.** Attempted Template-Directed Macrodimerization

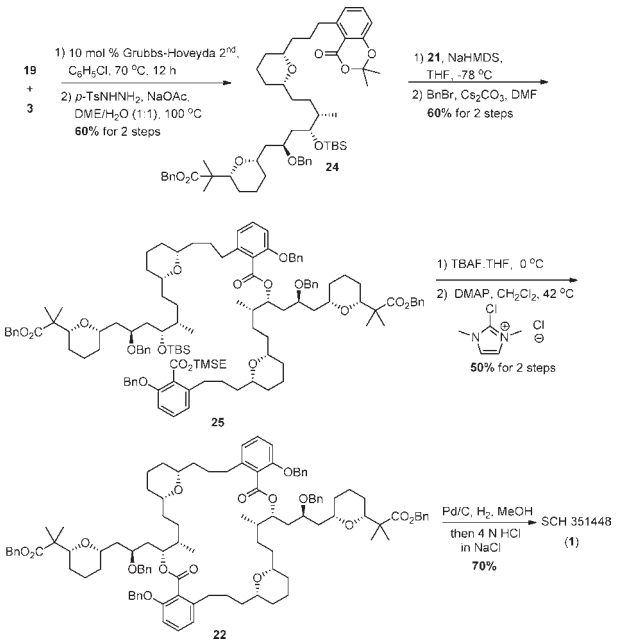



A synthetic strategy to construct the $C_2$-symmetrical macrodiolide core of cycloviracin $B_1$ has been described by Fürstner.[15] It involved a template-directed macrodilactonization reaction promoted by 2-chloro-1,3-dimethylimidazolinium chloride (DMC).[16] Inspired by this work, we investigated a similar strategy for macrodiolide formation. Unfortunately, treatment of seco acid **2** with DMC/DMAP and suitable additives[17] only led to the undesired 14-membered lactone **23**[18] without formation of dimeric product **22**. After these disappointments, we evaluated a

(6) Yang, Y.; Wang, J.; Kayser, M. *Tetrahedron: Asymmetry* **2007**, *18*, 2021–2025.
(7) Bal, B. S.; Childers, W. E.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091–2096.
(8) Ghosh, A. K.; Moon, D. K. *Org. Lett.* **2007**, *9*, 2425–2427.
(9) Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc.* **1983**, *105*, 2092–2093.
(10) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 5919–5923.
(11) Uchiyama, M.; Ozawa, H.; Takuma, K.; Matsumoto, Y.; Yonehara, M.; Hiroya, K.; Sakamoto, T. *Org. Lett.* **2006**, *8*, 5517–5520.
(12) Kajiro, H.; Mitamura, S.; Mori, A.; Hiyama, T. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 1553–1560.
(13) Leburn, M. −E.; Le Marquand, P.; Berthelette, C. *J. Org. Chem.* **2006**, *71*, 2009–2013.
(14) (a) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168–8179. (b) Chatterjee, A. K.; Choi, T. L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360–11370.
(15) Fürstner, A.; Albert, M.; Mlynarski, J.; Matheu, M.; DeClercq, E. *J. Am. Chem. Soc.* **2003**, *125*, 13132–13142.
(16) (a) Isobe, T.; Ishikawa, T. *J. Org. Chem.* **1999**, *64*, 5832–5835. (b) Isobe, T.; Ishikawa, T. *J. Org. Chem.* **1999**, *64*, 6984–6887. (c) Isobe, T.; Ishikawa, T. *J. Org. Chem.* **1999**, *64*, 6989–6992. (d) Fujisawa, T.; Mori, T.; Fukumoto, K.; Sato, T. *Chem. Lett.* **1982**, *11*, 1891–1895.
(17) (a) Fürstner, A. In *Templated Organic Synthesis*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 2000; pp 249−273. (b) Typical procedure: the additive (2.0 equiv) is added at 0 °C to a solution of seco acid **2** (20 mg, 0.023 mmol) and 2-chloro-1,3-dimethylimidazolinium chloride (10 mg, 0.059 mmol) in $CH_2Cl_2$ (1.1 mL), and the resulting mixture is stirred for 1 h at that temperature. DMAP (7.2 mg, 0.059 mmol) is then introduced, and stirring is continued for 16 h at ambient temperature; additives: NaH, KH, $CaH_2$, $Na_2CO_3$, $Cs_2CO_3$.
(18) Similar 14-membered lactones were also reported in the previous syntheses by Lee and Rychnovsky.

stepwise pathway to complete the synthesis, as illustrated in Scheme 5.

**Scheme 5.** Assemly of **1** by Dioxinone Ring-Opening and Macrocyclization




The reaction sequence that ultimately proved successful utilized Lee's method of esterification,[3a] which was facilitated by dioxinone ring opening. Cross metathesis between **19** and **3** afforded the intermediate alkene, which was reduced with diimide to deliver dioxinone **24**. TBS deprotection of **20** gave alcohol **21** in 91% yield (Scheme 4). Deprotonation of alcohol **21** with NaHMDS and addition of dioxinone **24** led to the desired monoester product, which was protected to afford **25** in 60% yield over two steps. Deprotection of the monoester provided the seco acid, which was subjected to a DMC/DMAP-promoted esterification[16] reaction to achieve macrocycle formation; **22** was obtained in 50% yield over two steps. Lastly, deprotection followed by workup with 4 M HCl saturated with NaCl[3a] delivered SCH 351448 (**1**) as its monosodium salt in 70% yield. The spectral data for our synthetic material matched those reported for the natural product.[3]

In summary, we have described a convergent, enantioselective total synthesis of (+)-SCH 351448 that proceeds in 2.3% overall yield from readily available allylsilane *anti*-**5c**. Synthetic highlights of our route include a [4 + 2] annulation strategy using silane *anti*-**5c** to ultimately construct the tetrahydropyran ring systems in fragments **3** and **4**. Olefin cross metathesis was utilized in the union of two advanced fragments to generate the monomeric subunit. A metal-template directed macrodilactonization strategy proved unsuccessful. Thus, the macrodiolide was assembled through a two-step sequence involving dioxinone ring opening with concomitant esterification followed by DMC/DMAP-mediated macrocyclization.

**Acknowledgment.** Financial support was obtained from NIH CA 53604. We are grateful to Prof. John Snyder, Dr. Paul Ralifo, and Dr. Norman Lee (Chemical Instrumentation Center at Boston University) for helpful discussions and assistance with NMR and HRMS experiments.

**Supporting Information Available.** Experimental details and selected spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.