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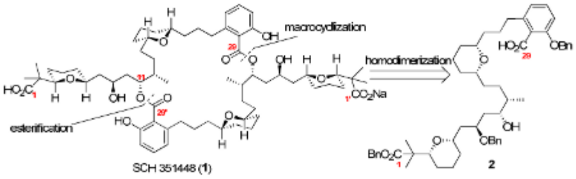
Total Synthesis of (+)-SCH 351448

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

James S. Panek: panek@bu.edu

Abstract



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 coworkers 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 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** has 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 enantio-selective [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**

Correspondence to: James S. Panek, `panek@bu.edu`.

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.

(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 *γ*-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 chair-like TS-B (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 chair-like TS-D, where TS-C avoids the steric destabilizing *trans*-diaxial orientation *versus* TS-D (Scheme 1, eq 4 and eq 5).

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. 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**. 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 *β*-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.

A synthetic strategy to construct the C_2-symmetrical macrodiolide core of cycloviracin B_1 has been described by Furstner. [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 stepwise pathway to complete the synthesis, as illustrated in Scheme 5.

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 mono-ester 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 mycrocycle **22** in 50% yield over two steps. Lastly, deprotection followed by work up 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 with a 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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17. (a)Fürstner A. Templated Organic Synthesis. Diederich F, Stang PJ. Wiley-VCHWeinheim2000:249–273.(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.

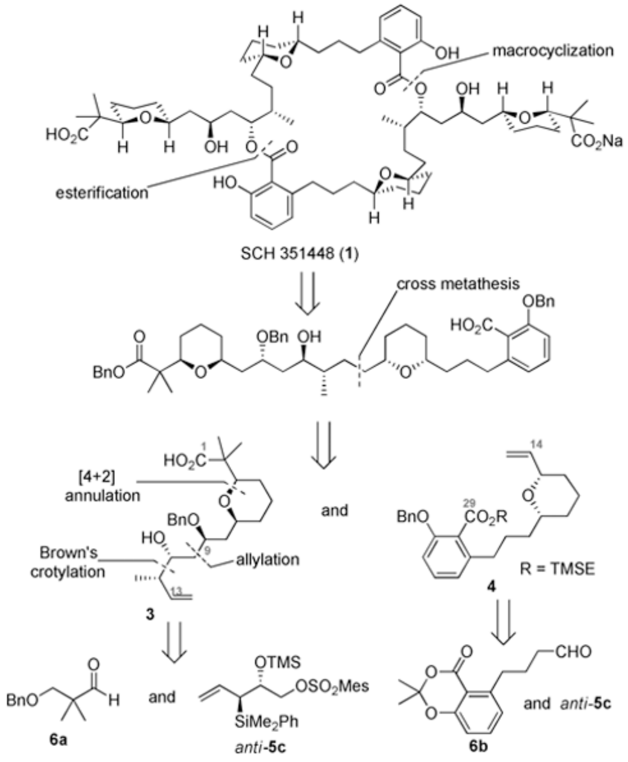
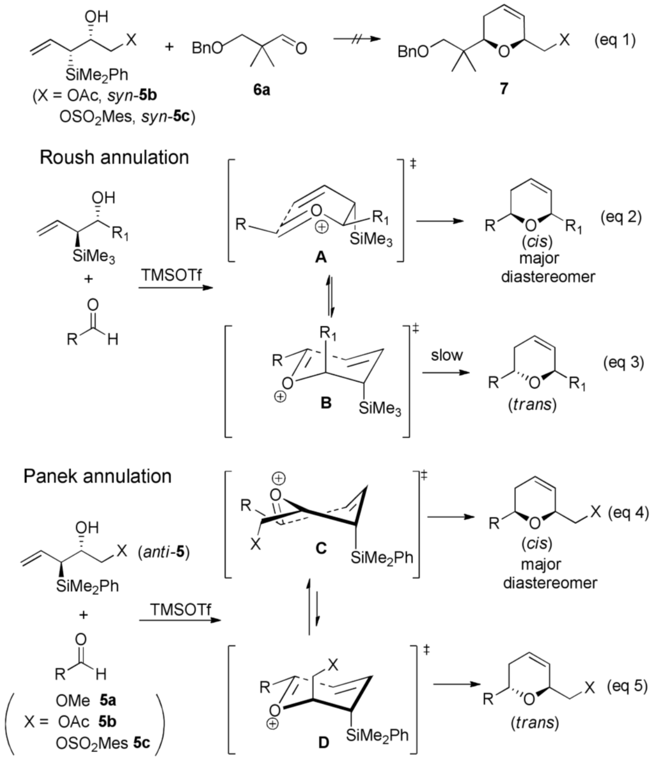
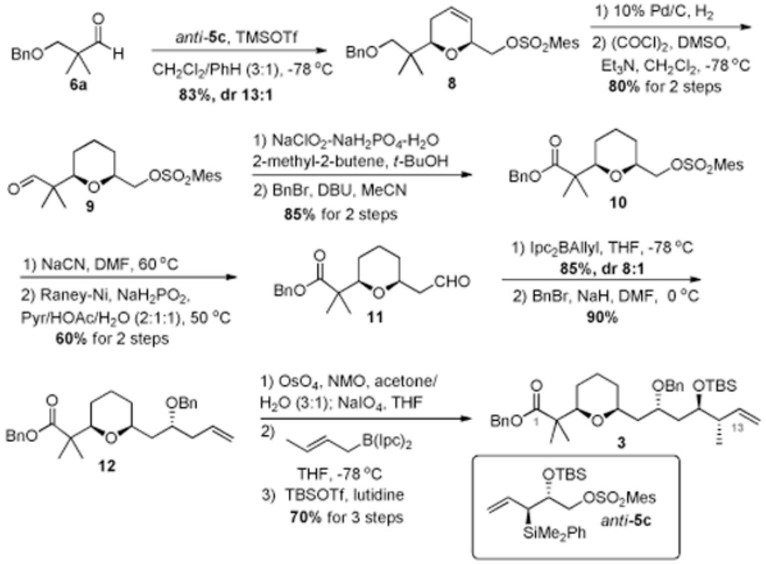


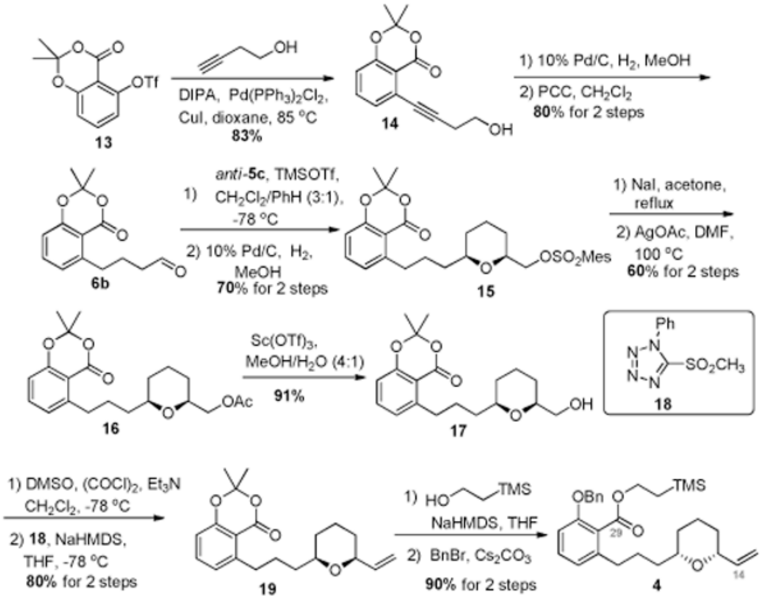
Figure 1. Retro synthetic analysis of SCH 351448 (1)



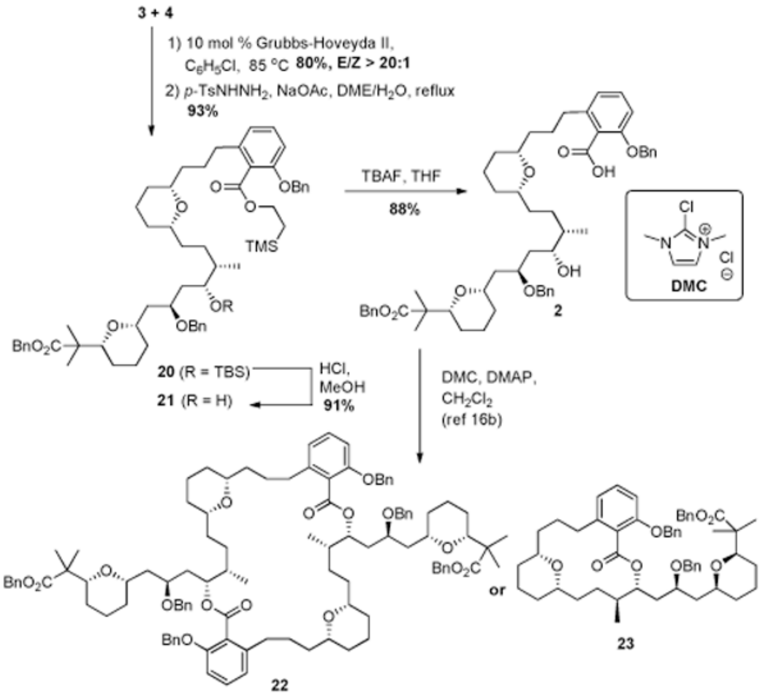
Scheme 1. Possible transition states for the [4+2] annulation



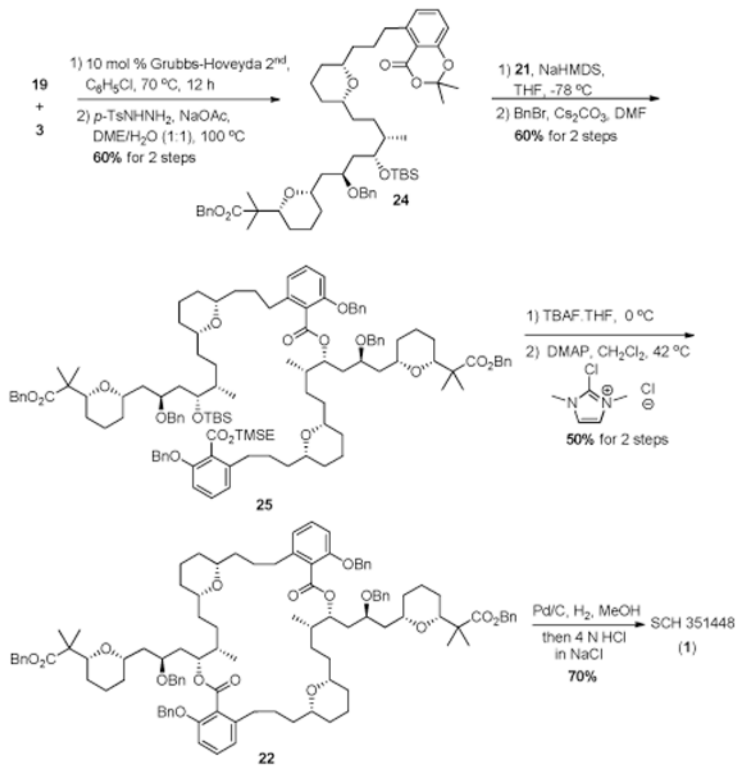
Scheme 2. Synthesis of C1-C13 fragment



Scheme 3. Synthesis of C14-C29 fragment



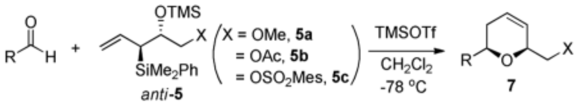
Scheme 4. Attempted template-directed macrodimerization



Scheme 5. Assemly of 1 by dioxinone ring-opening and macrocyclization

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**	60	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).