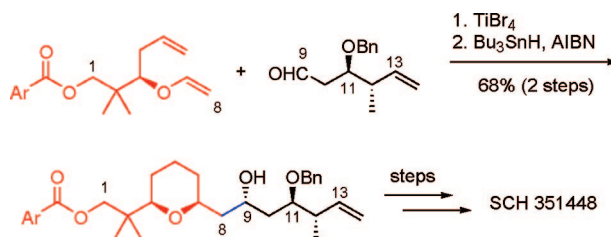


Assignment of Absolute Configuration
to SCH 351448 via Total Synthesis[†]Lael L. Cheung, Shinji Marumoto, Christopher D. Anderson, and Scott
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ABSTRACT



The synthesis and absolute configuration of SCH 351448, an interesting ionophoric natural product, are reported herein. Mukaiyama aldol–Prins and segment-coupling Prins reactions were employed to construct the constituent tetrahydropyrans of SCH 351448. Efforts to assemble the C₂-symmetric core of the natural product by a templated olefin metathesis strategy are described; however, a stepwise fragment assembly was ultimately utilized to complete the target molecule.

In 2000, Hegde and co-workers from Schering-Plough Research Institute and Duke University reported the isolation of the dimeric sodiated polyketide SCH 351448 (**1**) from an unspecified *Micromonospora* sp.¹ Compound **1** was found to be a selective activator of the low-density lipoprotein receptor (LDLR) promoter, a genetic sequence responsible for modulating expression of the surface receptor for LDL. Increased expression of LDLR has been shown to decrease blood serum cholesterol levels, thereby offering a potential therapy for hypercholesterolemia.²

Compound **1** is the only known small-molecule activator of the LDLR promoter and has drawn appreciable scrutiny, as evinced by several total^{3–6} and partial^{7,8} syntheses of the (+)-enantiomer. In addition to completing the first total synthesis, Lee noted the high binding affinity of compound

1 for Ca²⁺ ion at near-physiological pH. This affinity for calcium may be pertinent to the biological activity of compound **1**.⁹ We report a new synthesis of compound **1** using Mukaiyama aldol–Prins (MAP) and segment-coupling Prins reactions to prepare the constituent tetrahydropyrans. Furthermore, we have determined the heretofore unknown absolute stereochemistry of the natural enantiomer.

The monomeric subunits of compound **1** were dissected into the tetrahydropyranyl fragments **2** and **3** (Figure 1). Fragment **2** would be prepared by a MAP reaction between the homoallylic enol ether **4** and aldehyde **5**.¹⁰ Fragment **3** would be derived from tetrahydropyran **6**, which would be

[†] This paper is dedicated to Professor Madeline Joullie at the University of Pennsylvania for her inspirational and unwavering commitment to chemical research and education.

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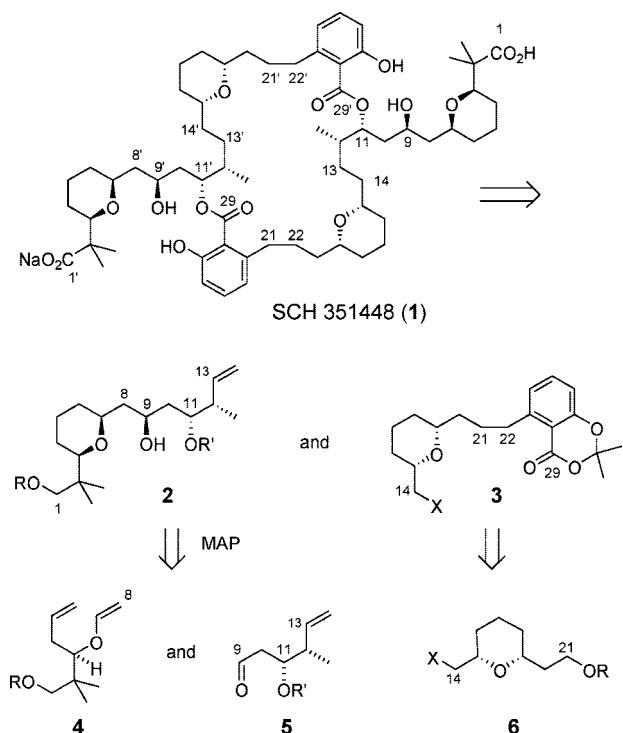
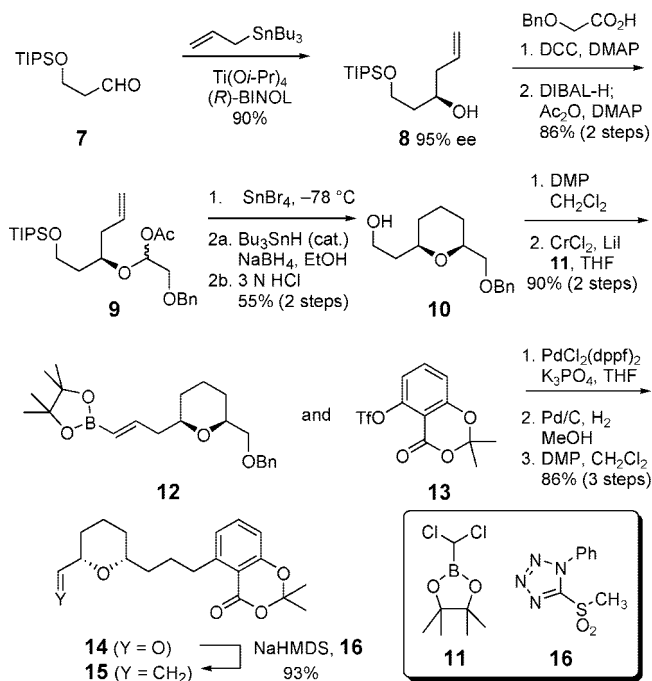


Figure 1. Retrosynthetic analysis of SCH 351448 (**1**)

prepared by segment-coupling Prins reaction.¹¹ Departing from other reported strategies, we envisioned that a one-pot cross-metathesis/ring-closing metathesis (CM/RCM) event would unite two identical C1–C29 monomers and form the macrocycle of compound **1**.¹² The appropriate chemo- and regioselectivities would be dictated by a Ca^{2+} template^{12c} in the dimerization/macrocyclization cascade.

Synthesis of the C14–C29 fragment of compound **1** began with asymmetric allylation¹³ of aldehyde **7**¹⁴ to yield alcohol **8** (Scheme 1). Conversion of alcohol **8** to α -acetoxy ether **9**, followed by segment-coupling Prins reaction with SnBr_4 , furnished an epimeric mixture of C17-bromotetrahydropyrans, which was homogenized into alcohol **10**. Oxidation of alcohol **10** to an intermediate aldehyde and subsequent olefination through Takai's procedure provided vinyl boronate **12**.¹⁵ Suzuki coupling of vinyl boronate **12** with aryl

Scheme 1. Synthesis of Tetrahydropyranyl Fragments **13** and **14**



triflate **13**¹⁶ provided a provisional C14–C29 segment containing a benzyl ether and an *E*-alkene. Hydrogenation revealed a primary alcohol that was later oxidized to aldehyde **14**. Julia–Kociński olefination of aldehyde **14** gave alkene **15**.³ Both aldehyde **14** and alkene **15** were used in subsequent studies.

Synthesis of the C1–C13 fragment of compound **1** began with alcohol **17**,¹⁷ prepared by asymmetric crotylation¹⁸ of aldehyde **7** (Scheme 2). Benzyl ether formation, TIPS deprotection, and oxidation provided aldehyde **18**, the electrophilic component for the MAP reaction. Asymmetric allylation¹⁹ of aldehyde **19** furnished alcohol **20**. Vinyl exchange²⁰ catalyzed by $\text{Hg}(\text{TFA})_2$ converted alcohol **20** to homoallylic enol ether **21**, the nucleophilic component for the MAP reaction.

Enol ether **21** and aldehyde **18** were subjected to TiBr_4 -promoted MAP reaction in the presence of 2,6-di-*tert*-butylmethylpyridine (2,6-DTBMP), a hindered base, at -78°C (Scheme 2). The resultant adduct was isolated in 76% yield as a mixture of C9,C11-*anti/syn* epimers favoring the desired *anti* disposition by ca. 3:1. The superfluous bromide was removed by radical-mediated reduction and the C9,C11-*anti/syn* epimers were separated by flash chromatography. The C9 alcohol was protected as the SEM ether **22**. Hydrolysis and a stepwise oxidation of intermediate **22** gave

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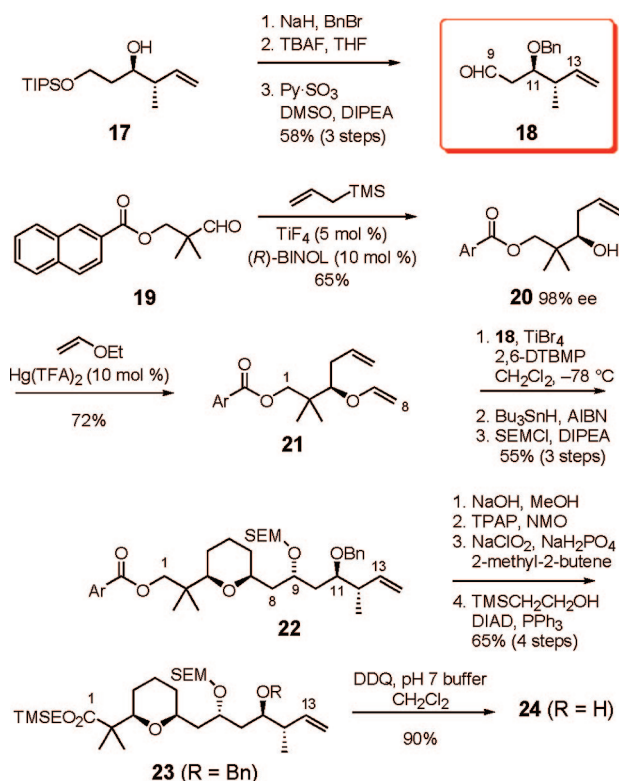
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Scheme 2. Synthesis of the C1–C13 Ester **22** Using a Mukaiyama Aldol–Prins Reaction



the acid, which was protected as a TMSE ester **23** by Mitsunobu reaction. DDQ deprotection of benzyl ether **23** yielded alcohol **24**, poised for coupling.

To expedite macrodiolide formation, an ion-templated CM/RCM cascade was examined (Scheme 3). We proposed that a Ca^{2+} complex comprised of two monomeric ligands would be predisposed toward a synthetically convergent dimerization/cyclization cascade. Hence, alcohol **24** was esterified with the dioxinone of alkene **14**. Global deprotection with TFA furnished the free acid, which was then treated with stoichiometric CaO in CH_2Cl_2 to yield Ca^{2+} salt **25**.²¹ Unfortunately, treatment of salt **25** with a variety of metathesis catalysts²² never led to the dimeric product **27** (Table 1). The CM/RCM cascade was further attempted using Hovey's relay tactic²³ to ensure alkene activation, but substrate **26** led only to compound **25** upon treatment with metathesis

(21) The most drastic change upon formation of calcium salt **25** from the free acid is found in their ^{13}C NMR spectra, wherein the signal for the C1 carbon of the acid (δ 180.8 ppm) disappears after exposure to CaO . Furthermore, there are noticeable changes in peak patterns for the 60–90 ppm region: the free acid exhibits six signals whereas the calcium complex **25** exhibits only five (two of the peaks have become coincident). The differences seen in the ^1H NMR spectra are subtle, consisting primarily of broadening of three peaks appearing between 2.5 and 4.0 ppm. Both compounds show an identical parent molecular ion ($M + \text{Na}^+$) by ES-MS. For references regarding NMR studies of calcium coordination complexes please see: (a) Chen, C.-S.; Wu, S.-H.; Wu, Y.-Y.; Fang, J.-M.; Wu, T. H. *Org. Lett.* **2007**, *9*, 2985–2988. (b) Akine, S.; Taniguchi, T.; Nabeshima, T. *J. Am. Chem. Soc.* **2006**, *128*, 15765–15774. (c) Akine, S.; Taniguchi, T.; Saiki, T.; Nabeshima, T. *J. Am. Chem. Soc.* **2005**, *127*, 540–541. (d) Nabeshima, T.; Takahashi, T.; Hanami, T.; Kikuchi, A.; Kawabe, T.; Yano, Y. *J. Org. Chem.* **1998**, *63*, 3802–3803.

Scheme 3. Attempted Template-Directed CM/RCM To Form Macrodiolide Chelate **27** from Ca^{2+} salts **25** and **26**

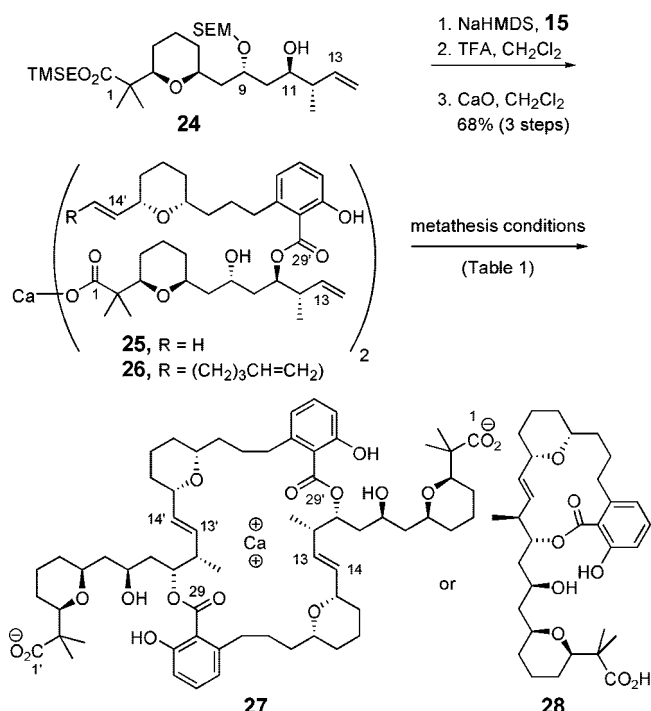


Table 1. Screen of Conditions for Templated CM/RCM

substrate	catalyst ^a	conditions ^b	outcome ^c
25	Grubbs I	23 °C, 12 h	25
25	Grubbs I	60 °C, 6 h	25 + 28
25	Grubbs II	23 °C, 12 h	25
25	Grubbs II	60 °C, 8 h	25 + 28
25	Grubbs–Hoveyda	45 °C, 8 h	25
25	Grubbs Variant ^c	45 °C, 8 h	25
26	Grubbs II	23 °C, 12 h	25
26	Grubbs–Hoveyda	23–45 °C, 12 h	25

^a For the catalyst structures, see ref 21. ^b All reactions were run in CH_2Cl_2 . ^c All reactions were monitored by mass spectrometry.

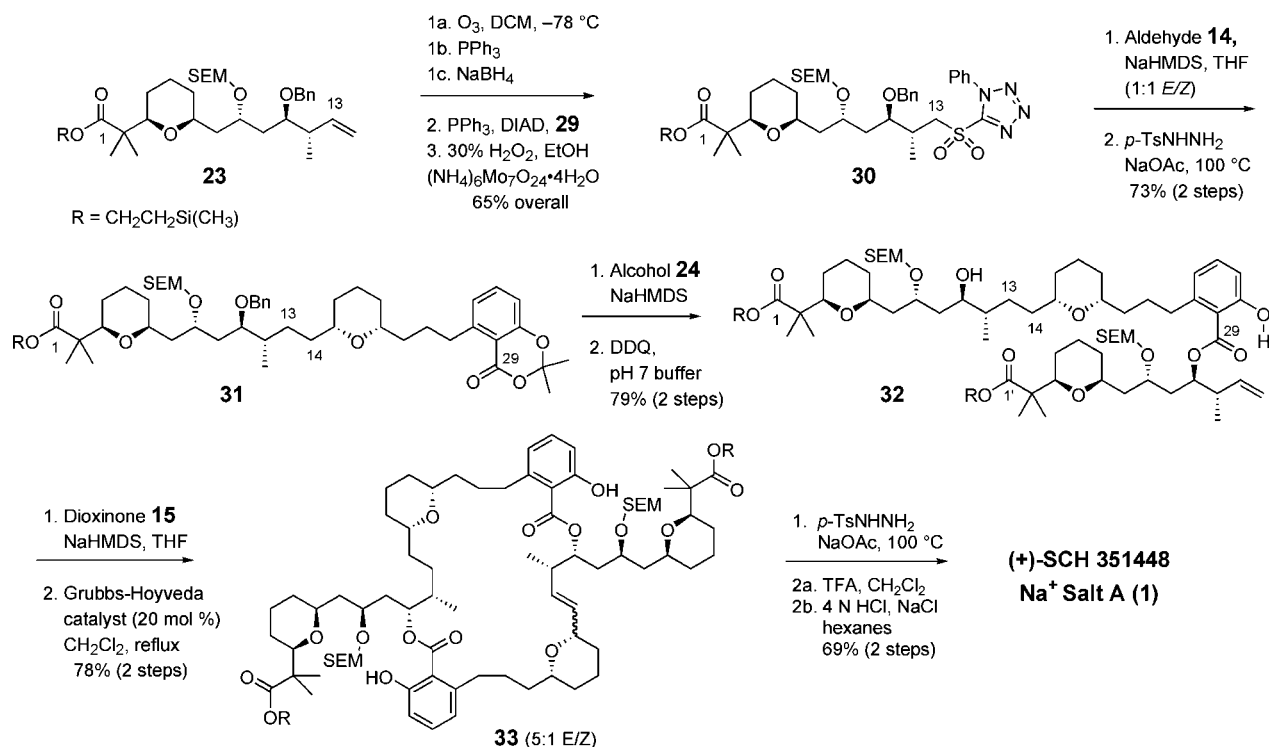
catalysts. While these experiments confirmed that substrate **26** underwent relay metathesis to extrude cyclopentene, the resultant ruthenium–alkylidene funneled to the unreactive complex **25**. After these disappointing results, we redirected our efforts to a more conventional strategy for completing the synthesis of compound **1**.

The sequence that ultimately proved fruitful mirrored Lee's route to the macrocycle of compound **1** (Scheme 4). Ozonolysis of the terminal alkene in THP **23** followed by

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Scheme 4. Assembly of (+)-SCH 351448 (**1**) by Sequential Esterification and RCM



reductive workup provided an intermediate alcohol, which was substituted with 1-phenyl-1*H*-tetrazole-5-thiol (**29**) and then oxidized to sulfone **30**. Julia–Kociński coupling with aldehyde **14** using NaHMDS gave an inconsequential 1:1 *E/Z* mixture of alkenes, which was reduced with diimide to furnish dioxinone **31**. Esterification with alcohol **24** and subsequent benzyl deprotection with DDQ gave the alcohol **32**. Esterification with dioxinone **15** afforded the acyclic diene, which underwent ring-closing metathesis upon treatment with the Grubbs–Hoveyda catalyst to produce macrocycle **33** in 93% yield. Diimide reduction, global deprotection, and metalation delivered SCH 351448 (**1**) as the (+)-enantiomer of sodium salt A described by Lee.

The absolute configuration of the natural enantiomer of compound **1** had remained unknown. Through the generous gift from the Schering-Plough Research Institute of an authentic sample of compound **1**, the absolute configuration of the natural product could then be established. Proton and carbon data for synthetic **1** (sodium salt A) were identical to that reported for the natural product.¹ The specific rotations of the synthetic and natural compounds **1** (sodium salts A) were both positive.²⁴ Because of the limited quantity of

authentic material, the identity of natural and synthetic (+)-SCH 351448 was further confirmed by comparison of their CD spectra.²⁵

The synthesis of (+)-SCH 351448 was achieved by using MAP and segment-coupling Prins reactions to construct the two pairs of THPs. A templated CM/RCM cascade proved to be a nonviable strategy, and thus the macrodiolide was assembled by iterative esterifications followed by RCM. The absolute configuration of natural SCH 351448 was determined to be identical to that of the (+)-enantiomer. This synthesis illustrates the utility of Prins cyclizations in natural product synthesis.

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Supporting Information Available: Characterization data and experimental procedures for all compounds described are included. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(25) CD spectra are provided in the Supporting Information.

(24) Synthetic (+)-SCH 351448: [α]_D²³ = +80 (*c* = 1.0, CHCl₃). Natural SCH 351448: [α]_D²³ = +26 (*c* = 1.0, CHCl₃). Both of these rotations were obtained from newly acid-equilibrated samples (ref 1). The reported rotation of synthetic (+)-SCH 351448 has varied from +22.4 to +79.9.