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Assignment of Absolute Configuration to SCH 351448 via Total Synthesis∫

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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 C_2-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 coworkers 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[3,4,5,6] 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 Ca^{2+} 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 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 allylation[13] of aldehyde **7**[14] to yield alcohol **8** (Scheme 1). Conversion of alcohol **8** to α-acetoxy ether **9**,

∫This paper is dedicated to Professor Madeline Joullié at the University of Pennsylvania for her inspirational and unwavering commitment to chemical research and education.

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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 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-Kocieński 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 crotylation[18] of aldehyde **7** (Scheme 2). Benzyl ether formation, TIPS deprotection, and oxidation provided aldehyde **18**, the electrophilic component for the MAP reaction. Asymmetric allylation[19] of aldehyde **19** furnished alcohol **20**. Vinyl exchange[20] catalyzed by $Hg(TFA)_2$ 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 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 catalysts[22] never led to the dimeric product **27** (Table 1). The CM/RCM cascade was further attempted using Hoye's relay tactic[23] to ensure alkene activation, but substrate **26** led only to compound **25** upon treatment with metathesis 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). Ozonlysis of the terminal alkene in THP **23** followed by reductive workup provided an intermediate alcohol, which was substituted with 1-phenyl-1*H*-tetrazol-5-thiol (**29**) and then oxidized to sulfone **30**. Julia-Kocieński 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 metallation 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

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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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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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 to 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 ^{1}H 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 ($M + Na^+$) by ES-MS. For references regarding NMR studies of calcium coordination complexes please see: a Chen CS, Wu SH, Wu YY, Fang JM, Wu TH. Org Lett 2007;9:2985–2988. [PubMed: 17629283] b Akine S, Taniguchi T, Nabeshima T. J Am Chem Soc 2006;128:15765–15774. [PubMed: 17147386] c Akine S, Taniguchi T, Saiki T, Nabeshima T. J Am Chem Soc 2005;127:540–541. [PubMed: 15643875] d Nabeshima T, Takahashi T, Hanami T, Kikuchi A, Kawabe T, Yano Y. J Org Chem 1998;63:3802–3803.

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24. Synthetic (+)-SCH 351448: $[\alpha]^{23}_{D} = +80$ (c = 1.0, $CHCl_3$); Natural SCH 351448: $[\alpha]^{23}_{D} = +26$ (c = 1.0, $CHCl_3$). 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 + 80.0.

25. CD spectra are provided in the supporting information.

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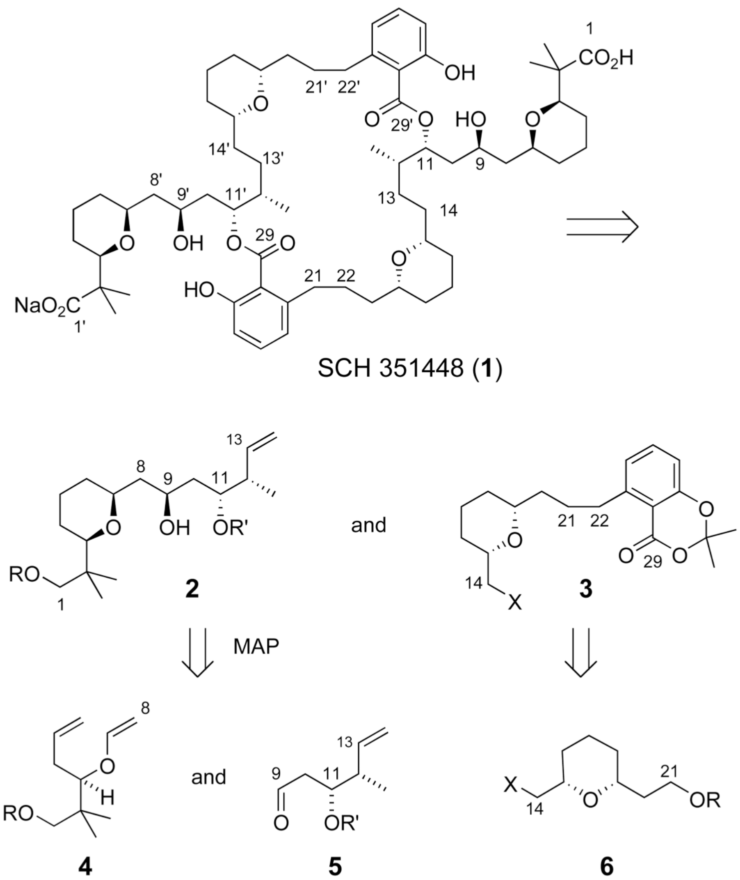
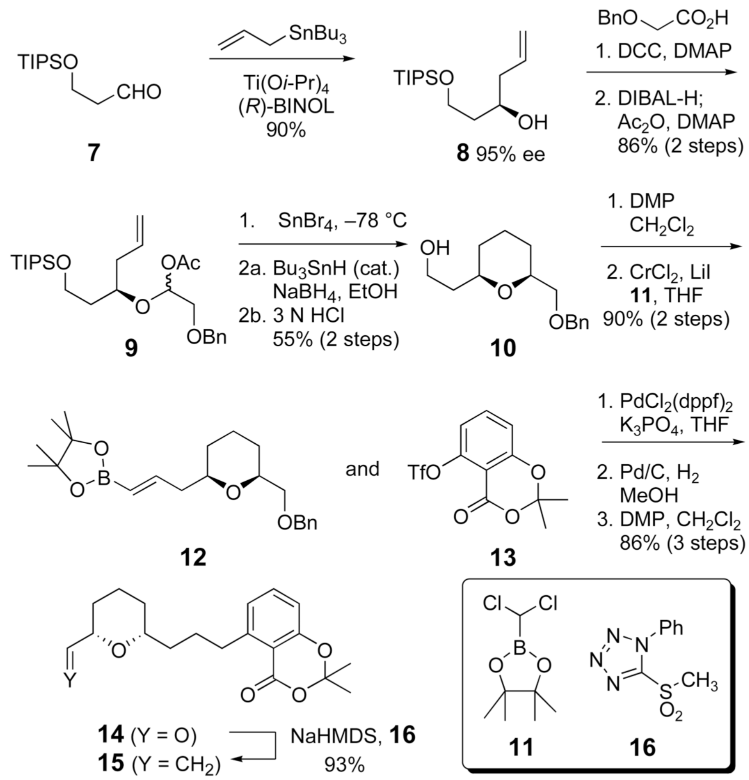
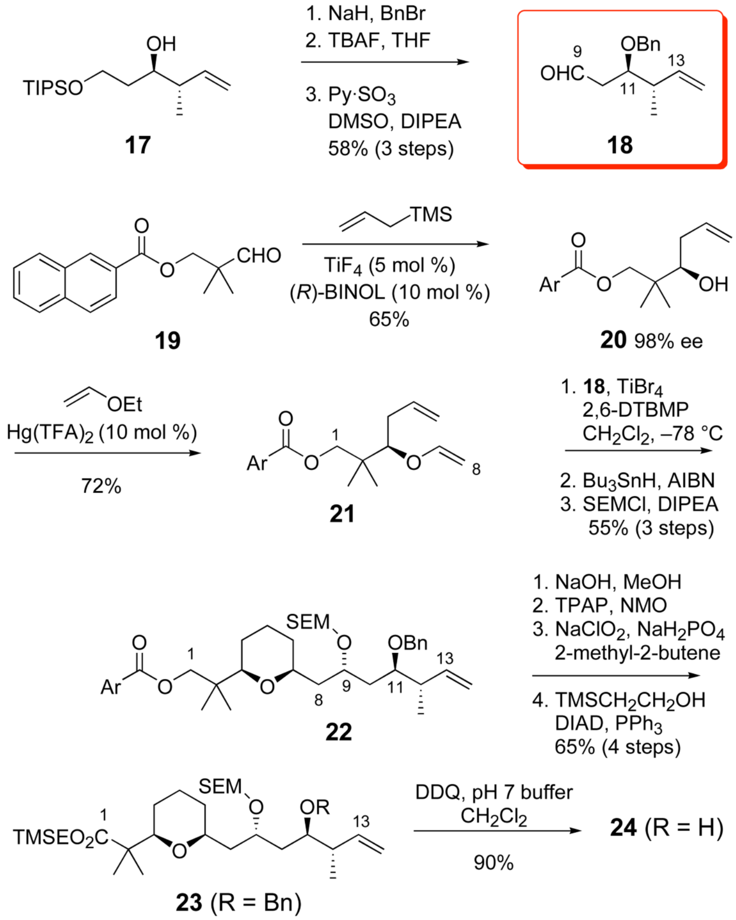


Figure 1.
Retrosynthetic analysis of SCH 351448 (**1**)



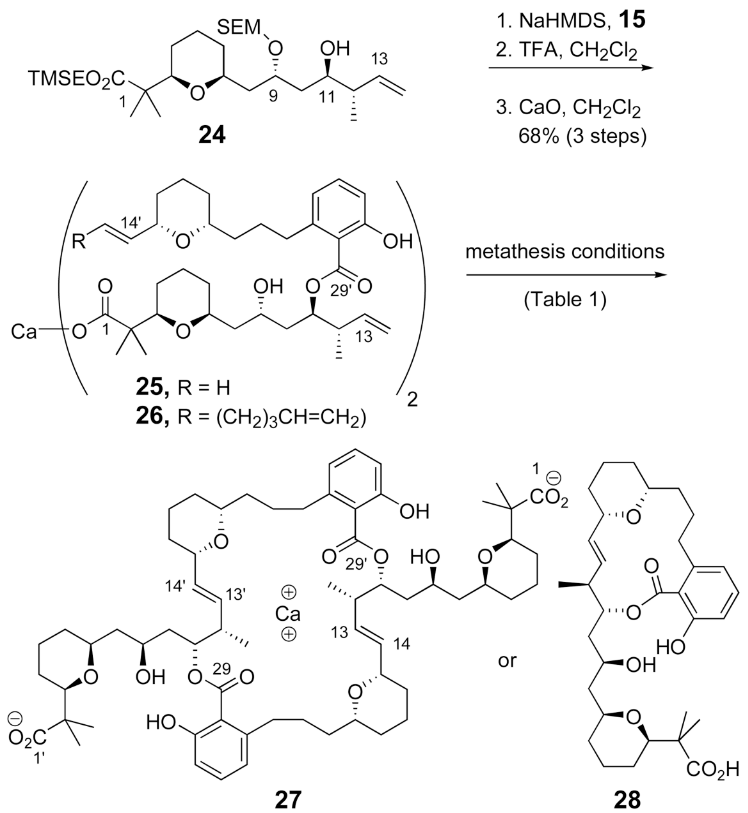
Scheme 1.

Synthesis of tetrahydropyranyl fragments **13** and **14**

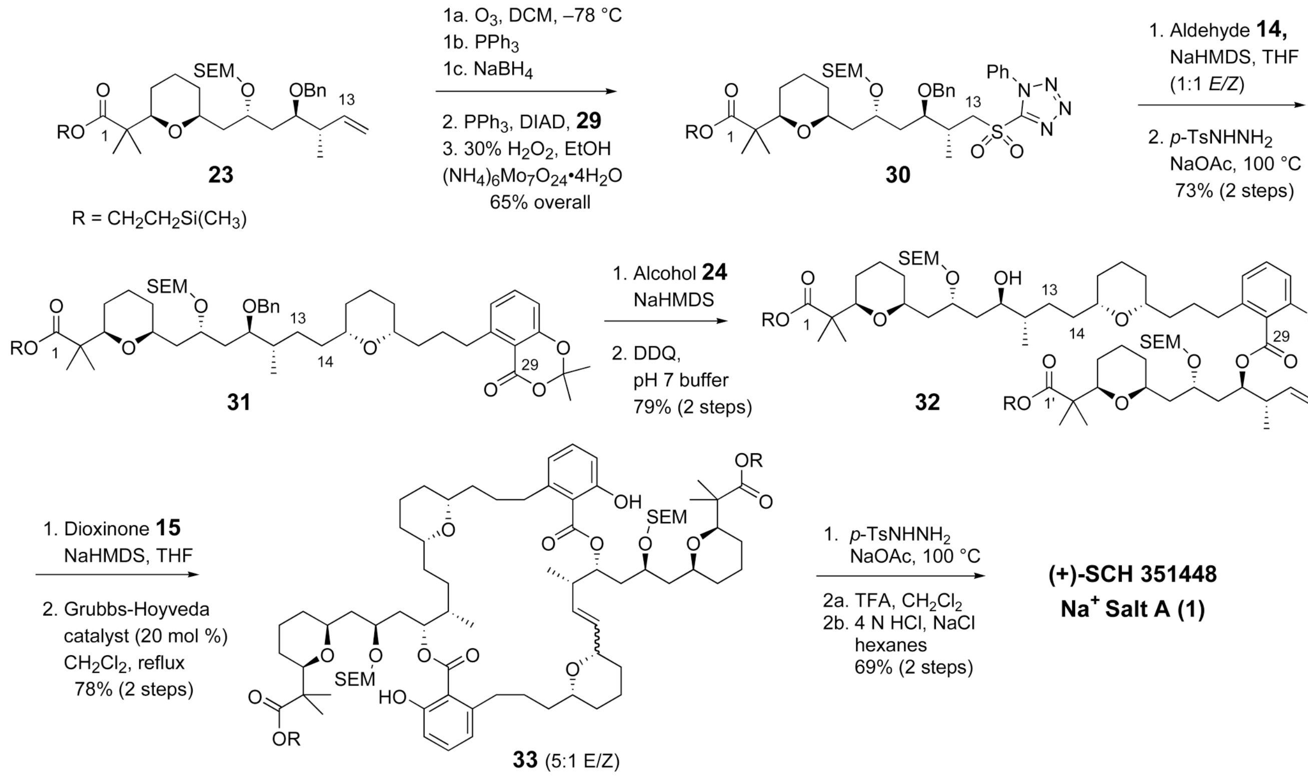


Scheme 2.

Synthesis of the C1-C13 ester **22** using a Mukaiyama aldol-Prins reaction



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



Scheme 4.

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

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 reference [21].

[b]All reactions were run in CH_2Cl_2.

[c]All reactions were monitored by mass spectrometry.