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A Formal Synthesis of SCH 351448

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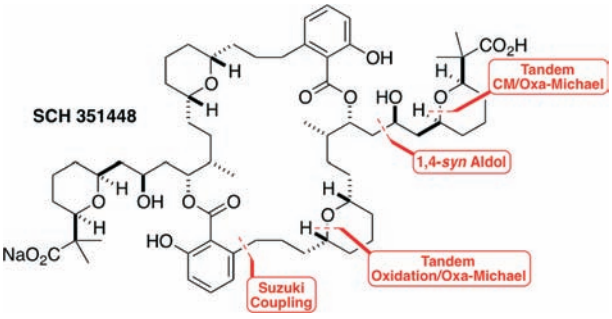
ABSTRACT



An efficient formal synthesis of SCH 351448 was accomplished through the tandem cross-metathesis (CM)/oxa-Michael, the 1,4-*syn* aldol, the tandem oxidation/oxa-Michael, and the Suzuki coupling reaction.

Low-density lipoprotein receptor (LDL-R) is a membrane-anchored, transmembrane receptor that plays an important role in regulating plasma cholesterol levels.[1] Increased levels of LDL-R leads to reduced cholesterol levels and, therefore, is a promising strategy to treat hypercholesterolemia. Hedge and co-workers screened microbial fermentation broths and reported the isolation and structure elucidation of SCH 351448 (**1**, Scheme 1), an activator of the LDL-R obtained from a microorganism belonging to *Micromonospora* sp.[2] Due to its potential for treating hypercholesterolemia, the synthesis of **1** has attracted considerable interest from a number of groups,[3,4] culminating in the first total synthesis by Lee and co-workers.[3a] Herein, we report an efficient formal synthesis of **1** using a combination of the tandem cross-metathesis (CM)/oxa-Michael reaction and the tandem oxidation/oxa-Michael reaction.

Our retrosynthetic plan for **1** relies on the tandem CM/oxa-Michael reaction and the tandem oxidation/oxa-Michael reaction for the synthesis of the 2,6-*cis*-tetrahydropyrans embedded in **1** (Scheme 1). We envisioned that the Suzuki coupling reaction of **3** and **4** would complete the monomeric unit **2**, which would constitute a formal synthesis of **1**. The tandem oxidation/oxa-Michael reaction in conjuction with the dithiane coupling reaction was expected to afford 2,6-*cis*-tetrahydropyran **4** with excellent stereoselectivity. The requisite epoxide **6** could be prepared by the 1,4-*syn* aldol reaction of tetrahydropyran aldehyde **8** and ketone **9**. We envisioned that the tandem CM/oxa-Michael reaction of hydroxy alkene **10** and (*E*)-crotonaldehyde would smoothly proceed to provide 2,6-*cis*-tetrahydropyran aldehyde **8** under mild thermal conditions.

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(1) Goldstein, J. L.; Brown, M. S. *Arterioscler. Thromb. Vasc. Biol.* **2009**, *29*, 431–438.

(2) 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.

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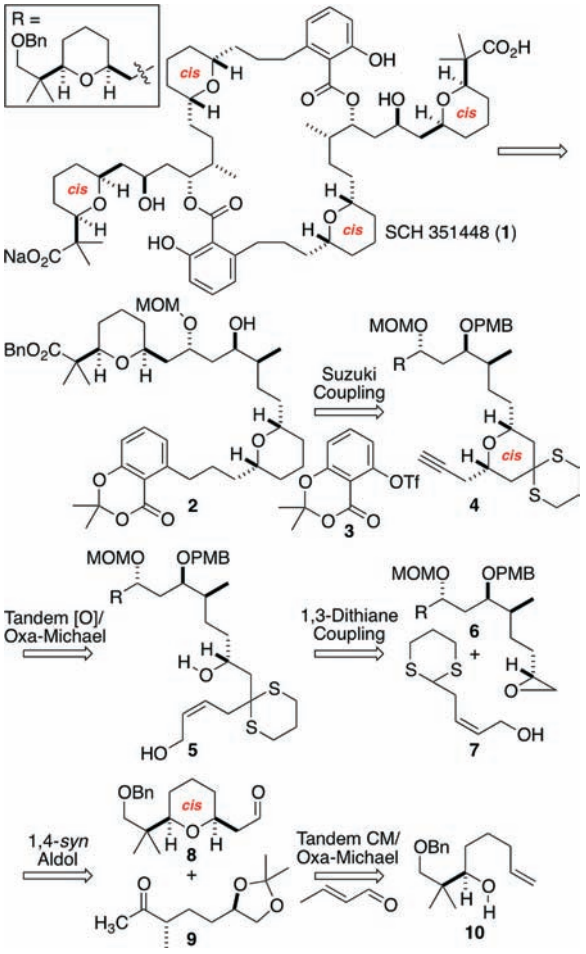
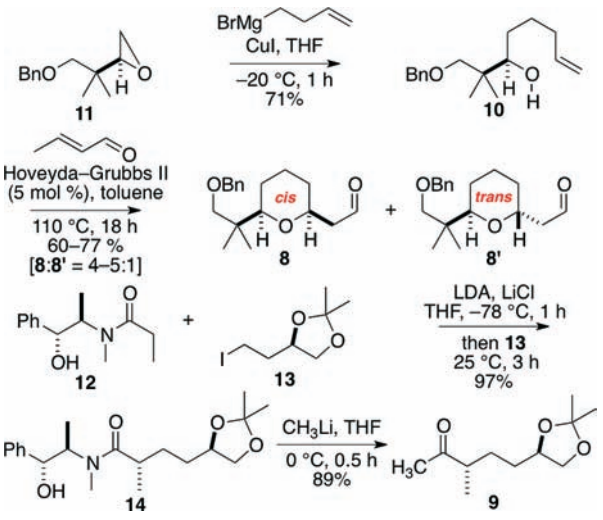
Scheme 1. Retrosynthetic Plan for SCH 351448 (**1**)

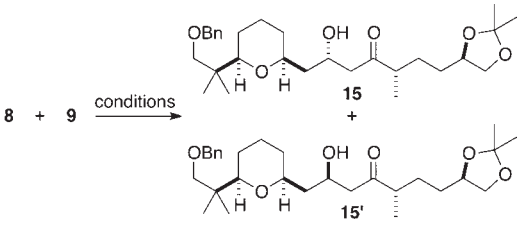


Scheme 2. Synthesis of 2,6-*cis*-Tetrahydropyran Aldehyde **8** through the Tandem CM/Oxa-Michael Reaction



The formal synthesis of SCH 351448 (**1**) started with the preparation of 2,6-*cis*-tetrahydropyran aldehyde **8** and ketone **9** (Scheme 2). Opening of the chiral epoxide **11**[5] with 3-butenylmagnesium bromide provided hydroxy alkene **10**. The CM reaction of **10** and (*E*)-crotonaldehyde in the presence of Hoveyda–Grubbs II catalyst[6] and the subsequent oxa-Michael reaction smoothly proceeded to provide the desired 2,6-*cis*-tetrahydropyran aldehyde **8** (60–77%, dr = 4–5:1).[7–11] The conjugate addition step required no activation by base or microwave[7] and proceeded under mild thermal conditions. To the best of our knowledge, this is the *first successful* example of the tandem CM/Michael reaction with aldehyde substrates. The Myers' asymmetric alkylation reaction[12] of **12**[12] and **13**[13] afforded the desired alkylation product **14** as a single disastereomer in 97% yield. Treatment of **14** with CH_3Li afforded the corresponding methyl ketone **9** in 89% yield.

Table 1. 1,4-*syn*-Aldol Reaction of **8** and **9**



entry	reagents	enolization conditions	reaction conditions	yield (%)[a]	dr[b]
1	*c*-Hex_2BCl, Et_3N, Et_2O	0 °C, 1 h	−78 °C, 1 h; −20 °C, 14 h	55	1.5:1
2	(−)-Ipc_2BCl, Et_3N, Et_2O	0 °C, 2 h	−78 °C, 5 h	70	3:1
3	(−)-Ipc_2BCl, Et_3N, Et_2O	0 °C, 1 h	−78 °C, 1 h; −20 °C, 3 h	62	4:1
4	(−)-Ipc_2BCl, Et_3N, Et_2O	0 °C, 1 h	−78 °C, 2 h; −20 °C, 16 h	72	9:1

[a] Combined yield of the isolated **15** and **15′**. [b] The diastereomeric ratio (**15**:**15′**) was determined by integration of the ^1H NMR of the mixture.

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(9) For the analogous tandem CM/S_N2' reaction, see: Lee, K.; Kim, H.; Hong, J. *Org. Lett.* **2009**, *11*, 5202–5205.

(10) The tandem CM/oxa-Michael reaction of **10** and (*E*)-crotonaldehyde in the presence of Grubbs II catalyst (5 mol %, toluene, 110 °C, 14 h) provided a mixture of **8** and **8′** (75%, dr = 1.5:1).

(11) The relative stereochemistry was determined to be *cis* by extensive 2D NMR studies (see the Supporting Information for details).

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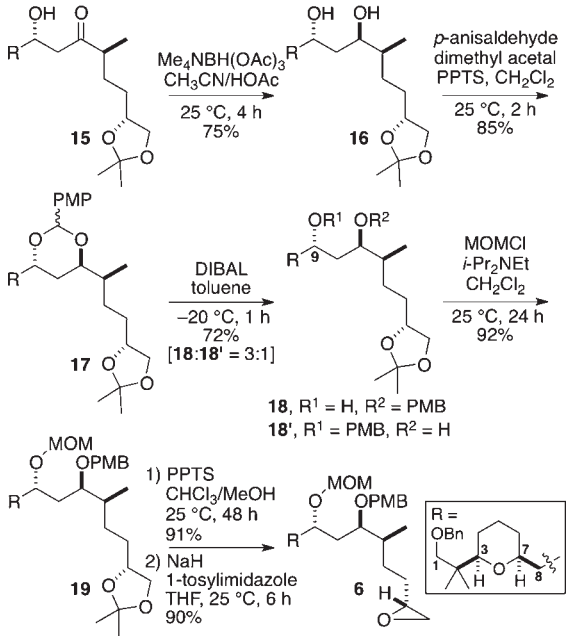
With efficient routes to **8** and **9** in hand, we next examined the coupling of **8** and **9** through the 1,4-*syn* aldol reaction (Table 1). The aldol addition of **9** to **8** (*c*-Hex_2BCl, Et_3N, Et_2O)[14] provided the desired β-hydroxy ketone **15** (55%), but with poor stereoselectivity (dr = 1.5:1, entry 1). The 1,4-*syn* aldol reaction of **8** and **9** at −78 °C in the presence of (−)-Ipc_2BCl[14] improved the stereoselectivity of the reaction (dr = 3:1, entry 2). Surprisingly, a higher reaction temperature and prolonged reaction time further improved the stereoselectivity of the 1,4-*syn* aldol reaction (dr = 9:1, entry 4).[15] Despite the broad utility, the 1,4-*syn* aldol reaction has rarely been applied in the stereoselective synthesis of natural products.[15,16]

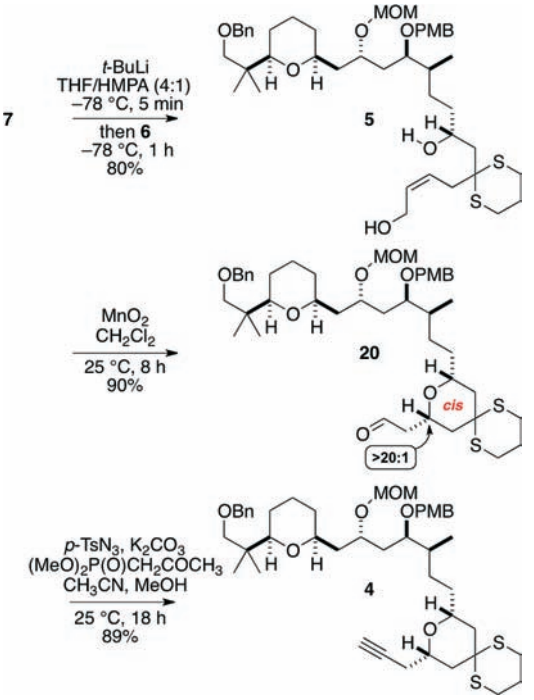
1,3-*anti* Reduction,[17] PMB-acetal protection, and DIBAL-reduction provided a mixture of **18** and **18′** (3:1, Scheme 3).[11,18] MOM-protection, acetonide deprotection, and epoxide formation[19] set the stage for the installation of the second 2,6-*cis*-tetrahydropyran moiety.

Scheme 3. Synthesis of Epoxide **6**



The coupling reaction of epoxide **6** and dithiane **7**[20] proceeded smoothly to provide allyl alcohol **5** for the key tandem oxidation/oxa-Michael reaction (Scheme 4). The tandem oxidation/oxa-Michael reaction[20,21] of **5** (MnO_2, CH_2Cl_2, 25 °C, 8 h) stereoselectively provided the desired 2,6-*cis*-tetrahydropyran aldehyde **20** with excellent yield and stereoselectivity (90%, dr >20:1).[11] One-carbon homologation of aldehyde **20** was achieved by the Bestmann reagent.[22]

Scheme 4. Synthesis of 2,6-*cis*-Tetrahydropyran Aldehyde **20** through the Tandem Oxidation/Oxa-Michael Reaction



Having successfully assembled both the 2,6-*cis*-tetrahydropyran moieties in **1**, we embarked on the final stage of the synthesis of **1** (Scheme 5). The Suzuki coupling reaction[23] of alkyne **4** with triflate **3**[24] provided the

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(18) The configuration of the C9 stereocenter of **18** was determined using the Kakisawa's procedure, see: Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092–4096.
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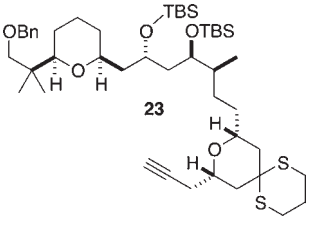
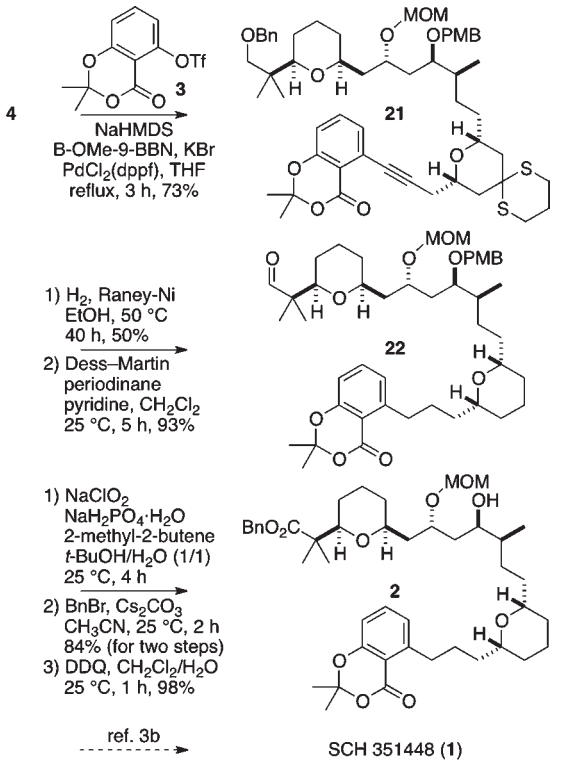
(25) The Sonogashira reaction of alkyne **23** and triflate **3** provided only the homocoupling product of **23**. Other coupling reactions (the Negishi, the Stille, and the Heck reaction) did not provide the desired coupling product.



Scheme 5. Completion of a Formal Synthesis of SCH 351448 (**1**)



corresponding coupling product **21**.[25] Simultaneous Bn-deprotection, desulfurization, and reduction of alkyne **21** were accomplished by treatment with Raney-Ni. Oxidation to carboxylic acid, formation of Bn ester, and PMB-deprotection completed the synthesis of **2**, which proved identical in all respects with the known synthetic **2** reported by De Brabander and co-workers (see the Supporting Information for details).[3b]

In summary, the utility of the tandem CM/oxa-Michael reaction and the tandem oxidation/oxa-Michael reaction was demonstrated for the efficient formal synthesis of SCH 351448 (**1**). The tandem reactions proceeded under mild reaction conditions and required no activation of oxygen nucleophiles and/or aldehydes. It was also shown that the 1,4-*syn* aldol reaction and the Suzuki coupling reaction were effective for the efficient construction of the monomeric unit of **1**. It is noteworthy that all seven of the stereogenic centers in **2** was derived from three simple fragments **11**–**13** and substrate-controlled reactions. The convergent route should be broadly applicable to the synthesis of a diverse set of analogues of **1** for further biological studies.

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Supporting Information Available. General experimental procedures including spectroscopic and analytical data along with copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.