Formal synthesis of (+)-SCH 351448: the Prins cyclization approach†

Kok-Ping Chan, Yvonne Hui Ling and Teck-Peng Loh*

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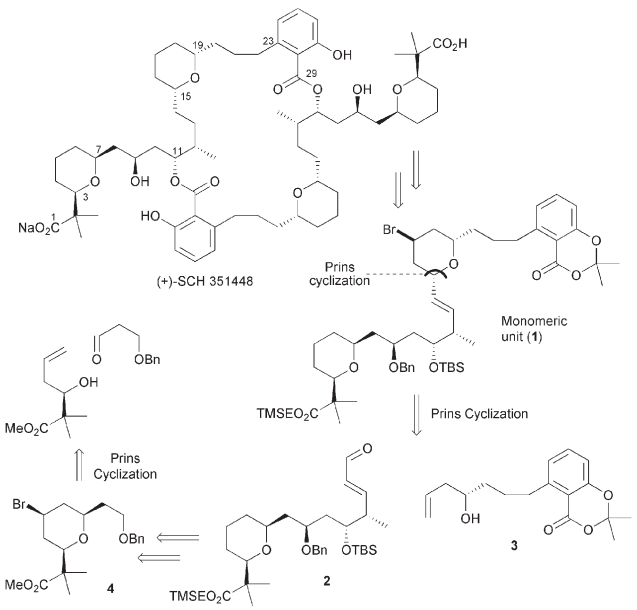
The formal synthesis of (+)-SCH 351448 has been accomplished with the catalytic Prins cyclization strategy, yielding the monomeric unit as a single isomer.

(+)-SCH 351448[1] is a novel activator of low density lipoprotein receptor promoter with an IC_{50} of 25 μM isolated from *Micromonospora sp*. To date, (+)-SCH 351448 is the first small molecule activator of the LDL-R promoter identified, thus its chemical synthesis[2] is of significant value to many scientists engaged in serum cholesterol research.

(+)-SCH 351448 possesses a very interesting and unique structure. It features a 28-membered macrodiolide consisting of two identical hydroxyl carboxylic acid units, and comprises four *cis*-2,6-disubstituted tetrahydropyran rings with opposite relative stereochemistry on each half of the molecule. Such symmetrical architecture allows a highly convergent disconnection approach into a monomeric unit **1** as depicted in Scheme 1. This is also the target molecule in our formal synthesis of (+)-SCH 351448 using the Prins cyclization[3] approach, demonstrating a pioneer strategy to conjoin two complex molecular fragments with concomitant formation of a THP ring in natural product synthesis.



Scheme 1 Retrosynthetic analysis of the Prins cyclization approach to (+)-SCH 351448.

Division of Chemistry and Biological Chemistry, Nanyang Technological University, Singapore 637616. E-mail: teckpeng@ntu.edu; Fax: (+65) 6316 6984; Tel: (+65) 6790 3733

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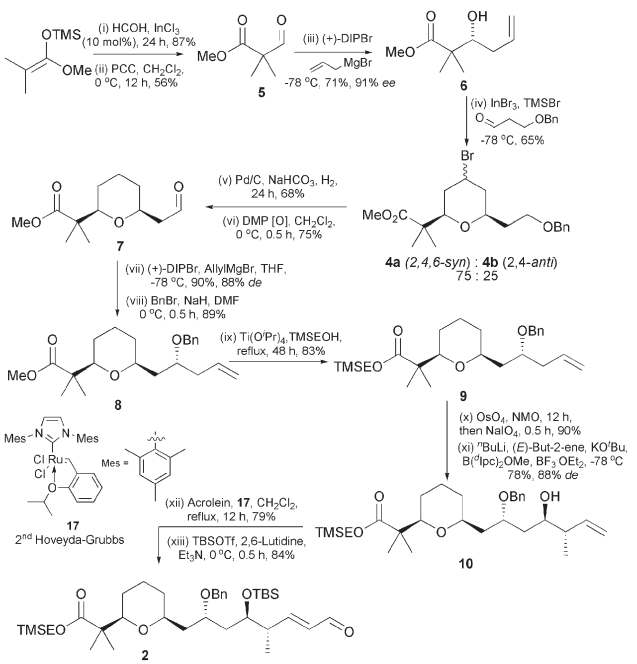
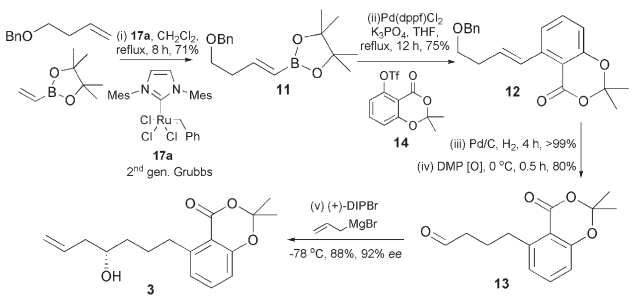
The monomeric unit **1** can be disconnected into two fragments, namely a conjugated aldehyde **2** and an acetonide homoallylic alcohol **3**, using the established Prins cyclization strategy. Further disconnection of **2** with olefin metathesis and a series of asymmetric crotylation and allylation can lead to a THP-ester intermediate **4**, which can also be assembled from synthetical viable aldehyde and homoallylic alcohol *via* Prins cyclization.

The synthesis of **2** commenced with aqueous Mukaiyama aldol[4] reaction of silylenol ether and formaldehyde catalyzed by $InCl_3$, followed by PCC oxidation to form an aldehyde **5**. After purification by vacuum distillation, we subjected **5** to Brown allylation[5] using (+)-DIPBr to afford the desired homoallylic alcohol[6] **6** in 71% yield and 91% *ee* (Scheme 2). Catalytic Prins cyclization[3j] of **6** with 3-benzoxypropanal using $InBr_3$ and TMSBr as additive yielded two isomers of the 4-bromo-THP intermediate (overall yield 65%), with the 2,4,6-*syn*-isomer (**4a**) as the major product. HPLC analysis of the major isomer revealed a complete retention of enantiomeric excess from the homoallylic alcohol **6**. The formation of isomeric products of **4** did not discourage the use of our Prins cyclization strategy, since the bromide functionality would be removed in the next step. A one-pot hydrodehalogenation[7] followed by Dess–Martin periodinane oxidation afforded the THP aldehyde **7**. Brown's allylation of **7** was carried out to install a homoallylic fragment, which was then followed by benzyl



Scheme 2 Synthesis of intermediate **2**.



Scheme 3 Synthesis of intermediate **3**.

protection to form the benzyl-ether alkene **8** in 90% yield and 88% diastereomeric excess. Transesterification[8] of **8** with trimethylsilylethanol resulted in 83% conversion of the methylester protecting group to the fluoride-cleavable silylethylester alkene **9**. The aldehyde precursor to **10** was accomplished with osmium tetraoxide dihydroxylation on **9**, followed by periodate oxidation. The purified aldehyde was immediately subjected to Brown crotylation[9] to yield 78% of the *anti*-α-methylhomoallylic alcohol **10** in 88% diastereomeric excess. The final intermediate **2** was accomplished by olefin metathesis with acrolein using 2nd generation Hoveyda–Grubbs[10] catalyst followed by *tert*-butyldimethylsilyl protection, with a yield of 67% over two steps.

The synthesis of **3** commenced with olefin metathesis of 4-benzyloxybut-1-ene with vinylborolane pinacolate to form the oxoborolane **11** (Scheme 3) in 71% yield. Suzuki coupling[11] of **11** with an acetonide triflate[12] **14** catalyzed by $PdCl_2$(dppf) afforded 75% of the desired acetonide alkene **12**. The final intermediate **3** was accomplished by a series of functional group interconversions followed by Brown allylation in an overall 70% yield and 92% *ee*.

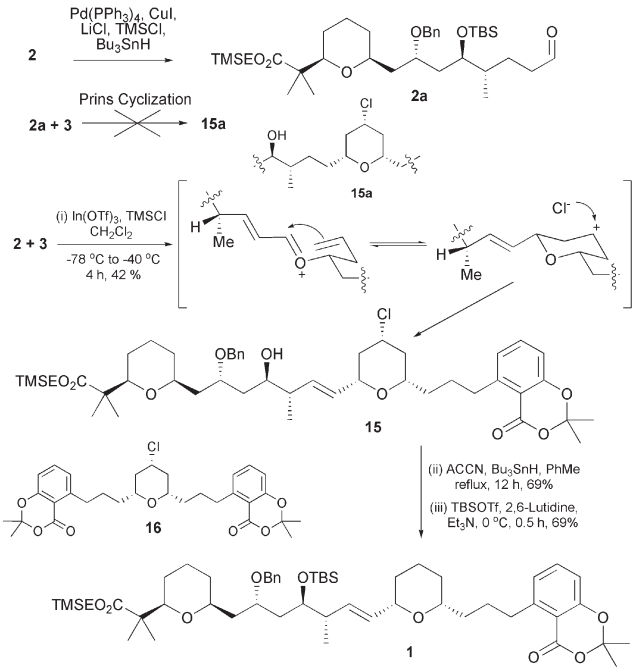
Prins cyclization has achieved much success with the condensation of relatively simple homoallylic alcohols and aldehydes. In the synthesis of the monomeric unit, we attempt to pioneer the demonstration of the coupling of two complex molecular fragments. From our experience, we expected **2a** to be a better substrate for Prins cyclization. Hence, we carried out Prins cyclization of **2** or **2a** with **3** under various conditions (Table 1). To our surprise, Prins cyclization of **2a**[13,16] with **3** at varying temperatures was unsuccessful (entries 6 to 8), yielding numerous side products with no sign of the desired THP monomeric unit

Table 1 Optimization of reaction conditions for Prins cyclization

2 (2a) + 3 → 15 (15a) + 16

Entry	Aldehyde	Catalyst	Conditions for Prins cyclization	Yields (%) **15** or **15a**	**16**
1	**2**	$In(OTf)_3$	−78 °C, 24 h	12	33
2	**2**	$In(OTf)_3$	0 °C, 4 h	23[a]	58
3	**2**	$In(OTf)_3$	25 °C, 4 h	< 5	71
4	**2**	$In(OTf)_3$	−78 °C to −40 °C, 4 h	42	18
5	**2**	$InCl_3$	−78 °C to 25 °C, 48 h	6	—[b]
6	**2a**	$In(OTf)_3$	−78 °C to −40 °C, 4 h	—	36[c]
7	**2a**	$In(OTf)_3$	0 °C, 4 h	—	41[c]
8	**2a**	$InCl_3$	−78 °C to 25 °C, 48 h	—	25[c]

[a] A mixture of inseparable isomers of **15** was isolated, indicating significant racemization of **15**. [b] 79% of unreacted homoallylic alcohol **3** was recovered. [c] No trace of **2a** was recovered.[14]



Scheme 4 Formal synthesis of (+)-SCH 351448.

(Scheme 4). Hence, we attempted the direct cyclization with conjugated aldehyde **2**.

The initial attempt at Prins cyclization of **2** and **3** using $InBr_3$ and TMSBr at −78 °C resulted in the deprotection of the acetonide group without formation of any THP products. However, a combination of $In(OTf)_3$ and a milder additive (TMSCl) at −78 °C resulted in the formation of the THP unit **15** in low yield (Table 1), accompanied by a significant amount of *meso*-acetonide **16** (Scheme 4). At first glance, this seemed to imply that a considerable degree of racemization had taken place in this reaction, resulting in **16** as the major product. However, it was found that only one isomer of the desired THP product **15** was isolated. After several attempts (entries 1 to 5), an optimized reaction condition of stirring at −40 °C raised the yield of **15** significantly to 42%, with considerable yield reduction of the *meso*-product **16**. The use of $In(OTf)_3$ at low temperature was crucial in suppressing the formation of **16**, whereas $InCl_3$ appeared sluggish in catalyzing the cyclization effectively. The product **15** was then subjected to radical dehalogenation using ACCN[15] with tributyltin hydride, followed by TBS protection under basic conditions to afford the desired monomeric unit **1** which completes the formal synthesis of (+)-SCH 351448.

In conclusion, a formal synthesis of (+)-SCH 351448 has been accomplished with the condensation of two complex fragments using catalytic Prins cyclization. The accomplishment of Prins cyclization from readily synthesized conjugated aldehydes without significant racemization set forth a new strategy in which total synthesis of THP containing natural products can be realized. Further demonstration of this novel strategy in the total synthesis of other natural products is in progress.

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13 Palladium catalyzed reduction[16] of **2** *via* a radical mechanism resulted in an incomplete conversion to unconjugated aldehyde **2a**. The failure to separate the **2** and **2a** rendered spectroscopic analysis very difficult.

14 A significant amount of unreacted homoallylic alcohol **3** was recovered in the three entries (6 to 8) in Table 1. There are possibly other competing reactions which degrade this reactive aldehyde **2a** in the presence of a Lewis acid before Prins cyclization can take place.

15 ACCN denotes 1,1′-azobis(cyclohexane) carbonitrile, a synthetic equivalent to AIBN.

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