

Efficient Asymmetric Synthesis of  
(+)-SCH 351448

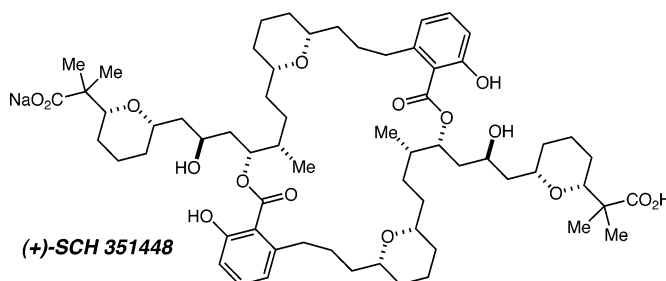
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## ABSTRACT



An efficient and stereocontrolled total synthesis of (+)-SCH 351448, a novel activator of low-density lipoprotein receptor promoter, has been achieved with a longest linear sequence of 21 steps. Key steps include applications of the recently developed asymmetric allyl- and crotylsilane reagents and a new protodesilylative version of the tandem silylformylation/allylsilylation reaction, which provides an efficient synthesis of 1,5-*syn*-diols.

In 2000, researchers at the Schering-Plough Research Institute and Duke University reported the isolation and structure elucidation of a dimeric polyketide they termed SCH 351448 (**1**).<sup>1</sup> The isolation of SCH 351448 was guided by its activation of low-density lipoprotein receptor (LDL-R) promoter. This intriguing biological activity<sup>2</sup> and the novel structure have combined to elicit attention from the synthetic community,<sup>3</sup> and two total syntheses have been recorded.<sup>4,5</sup> Our retrosynthetic analysis envisioned the coupling of alcohol **2** with ester **3** (step A, Scheme 1), followed by deprotection of the *tert*-butyldimethylsilyl (TBS) group and coupling of the resultant alcohol with ester **4**<sup>6</sup> (step B). Finally, ring-closing metathesis (RCM, step C) would be followed by hydrogenation of the alkene product accompanied by depro-

tection of the benzyl ethers and esters to provide the natural product. Fragments **2** and **3** could arise from a common intermediate **5**. Our tandem silylformylation–allylsilylation methodology<sup>7</sup> seemed well-suited to the synthesis of the 1,5-*syn*-diol in **5** but would require a previously unexplored protodesilylation workup in place of the standard oxidative procedure for triol synthesis.

Asymmetric allylation of aldehyde **6** using our recently developed silane reagent *ent*-**7**<sup>8</sup> followed by lactonization with *p*-TsOH provided lactone **8** in 72% yield (Scheme 2). The ee of the allylation product was found to be 93%. Addition of the lithium enolate derived from benzyl isobutyrate to lactone **8**, and *cis* diastereoselective (>20:1) reduction of the resulting lactol<sup>9</sup> gave tetrahydropyran **9** in 68% yield (two steps). Oxidative cleavage of the alkene to the corresponding aldehyde was followed by asymmetric allylation using Brown's protocol<sup>10</sup> (≥10:1 dr) to give alcohol

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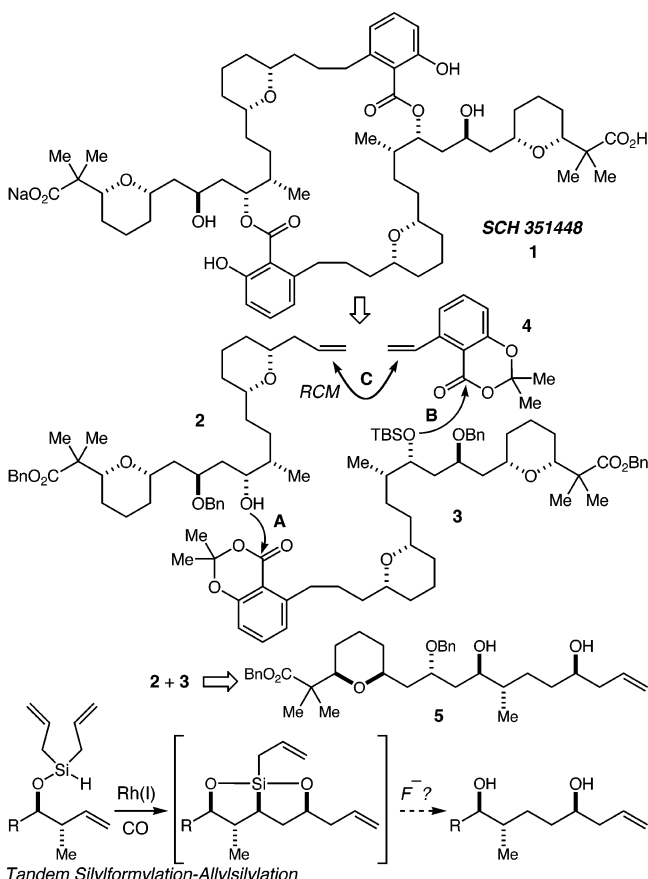
(6) Synthesis of this compound is detailed in Supporting Information.

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(8) Kubota, K.; Leighton, J. L. *Angew. Chem., Int. Ed.* **2003**, *42*, 946.

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(10) Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc.* **1983**, *105*, 2092.



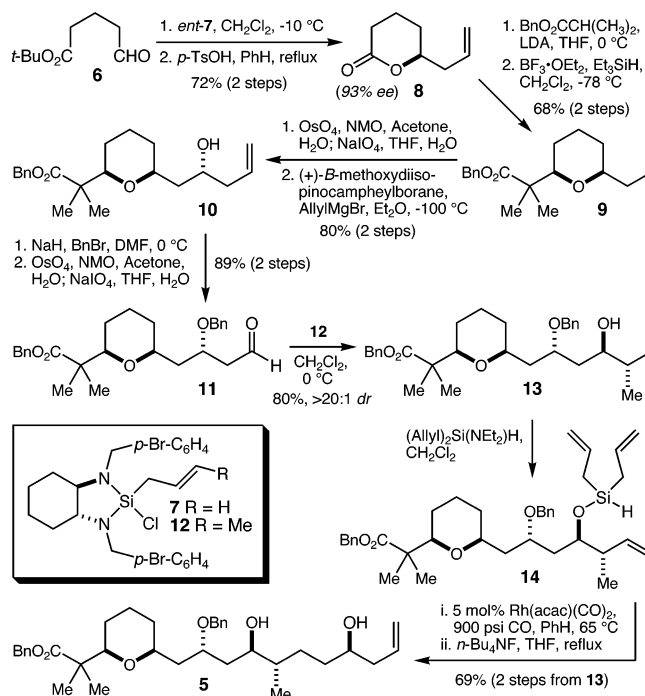
**10** in 80% yield (two steps). Protection of alcohol **10** as a benzyl ether and oxidative cleavage of the alkene gave aldehyde **11** in 89% yield (two steps). Asymmetric crotylation employing the enantiomer of crotylsilane **12**<sup>11</sup> gave alcohol **13** as a single diastereomer (>20:1) in 80% yield. Treatment of **13** with diallyl-diethylaminosilane<sup>6</sup> provided silyl ether **14**, which was immediately subjected to the rhodium-catalyzed tandem silylformylation–allylsilylation reaction (5 mol % Rh(acac)(CO)<sub>2</sub>, 900 psi CO, PhH, 65 °C).<sup>7</sup> Upon ventilation of the high-pressure reaction apparatus, the residue was treated with *n*-Bu<sub>4</sub>NF in THF (reflux) to provide diol **5** as a single diastereomer in 69% yield from **13**. While this protodesilylative version of our tandem silylformylation–allylsilylation reaction represents a relatively straightforward extension of the methodology, the difficulties encountered by Hoveyda in attempting a protodesilylation in a related  $\beta$ -hydroxysiloxane system<sup>12</sup> had given us cause for concern. That the reaction in the present system is indeed smooth provides a direct synthesis of saturated 1,5-*syn*-diols from homoallylic alcohols.

The use of the Brown allylation protocol for the synthesis of **10** is worthy of further comment. When the same allylation was performed using allylsilane *ent-7*, the diastereoselectivity

(11) Hackman, B. M.; Lombardi, P. J.; Leighton, J. L. *Org. Lett.* **2004**, 6, 4375.

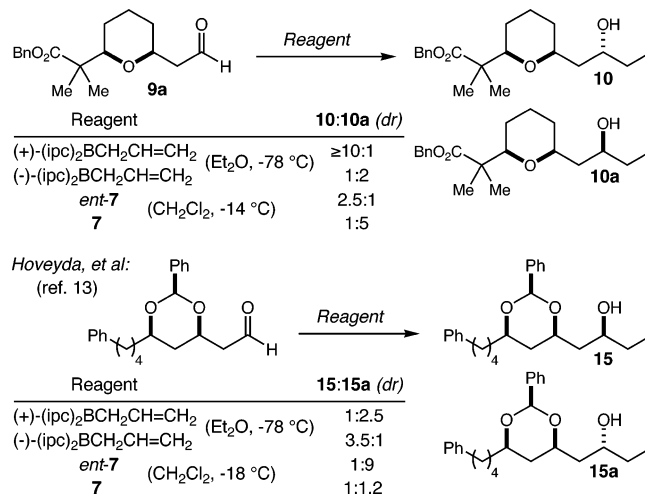
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### Scheme 2



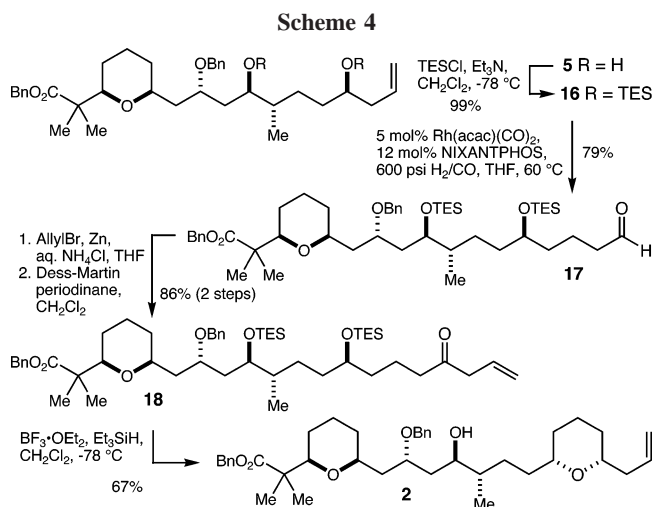
was poor (2.5:1) (Scheme 3). When the respective enantiomeric allyl reagents were employed, alcohol **10a** was the major product with 2:1 and 5:1 dr for the Brown reagent and allylsilane **7**, respectively. As shown, similar observations have been recorded by Hoveyda using a different chiral  $\beta$ -alkoxyaldehyde.<sup>13</sup> It therefore appears, at least with these two aldehydes, that the two protocols are complementary: moderate to good selectivity for the 1,3-syn product can be realized with the Brown protocol, while moderate to good selectivity for the 1,3-anti product may be secured with our allylsilane reagents. It should be noted that with  $\beta$ -benzyloxyaldehydes, the allyl- and crotylsilane reagents **7** and **12** display excellent reagent control, overwhelming any substrate

### Scheme 3



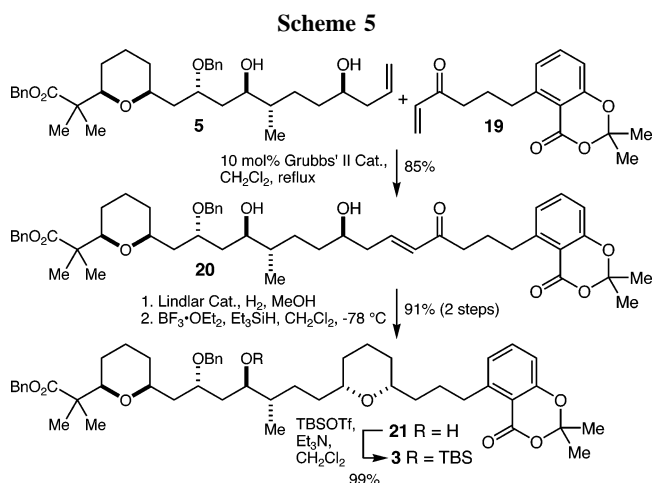
bias, as demonstrated both by the conversion of **11** to **13** and by a similar set of experiments in our earlier work.<sup>8</sup>

Protection of diol **5** as the bis-triethylsilyl (TES) ether **16** (99%) was followed by hydroformylation using the linear-selective Nixantphos ligand<sup>14</sup> to give aldehyde **17** in 79% yield (Scheme 4). Barbier-type allyl addition to **17** using the



conditions of Luche<sup>15</sup> and subsequent oxidation with the Dess–Martin periodinane<sup>16</sup> then produced allyl ketone **18** in 86% overall yield (two steps). Silyl ether deprotection and diastereoselective (>20:1) lactol reduction<sup>9</sup> were accomplished by treatment of **18** with Et<sub>3</sub>SiH and BF<sub>3</sub>·OEt<sub>2</sub>, leading to tetrahydropyran **2** in 67% yield.

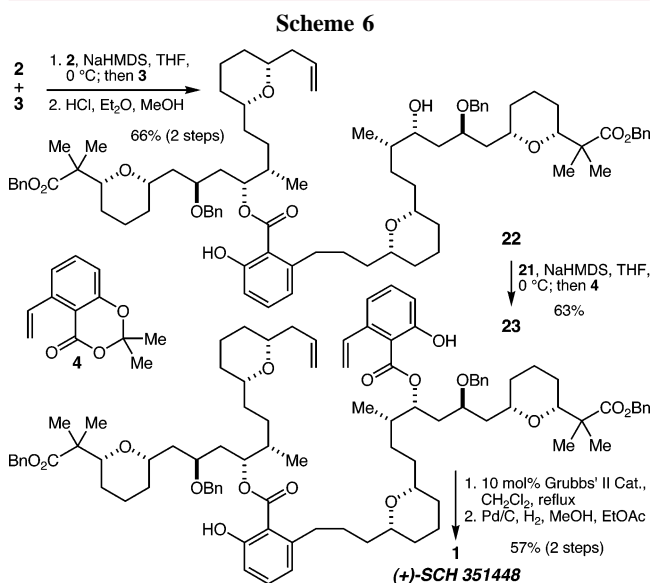
Cross metathesis<sup>17</sup> between **5** and enone **19**<sup>6</sup> proceeded smoothly using the second-generation Grubbs catalyst<sup>18</sup> to deliver enone **20** in 85% yield (Scheme 5). Conjugate



reduction was accomplished by hydrogenation over Lindlar's catalyst, and the resulting lactol was reduced with Et<sub>3</sub>SiH and BF<sub>3</sub>·OEt<sub>2</sub> to give tetrahydropyran **21** as a single diastereomer<sup>9</sup> (>20:1) in 91% yield (two steps). Finally,

protection of the alcohol as its *tert*-butyldimethylsilyl (TBS) ether proceeded to give **3** in 99% yield.

With fragments **2** and **3** in hand, we were positioned to investigate their coupling (Scheme 6). Thus, deprotonation



of alcohol **2** with sodium hexamethyldisilazide (NaHMDS) and addition of acetonide **3** led to the desired ester product, and methanolysis of the TBS ether then produced alcohol **22** in 66% yield (two steps). Deprotonation of **22** with 2.5 equiv of NaHMDS and treatment with acetonide **4**<sup>6</sup> provided bis-benzoyl ester **23** in 63% yield. RCM then proceeded smoothly using the second-generation Grubbs catalyst,<sup>18</sup> and the macrocycle product was subjected to hydrogenation over Pd/C, resulting in reduction of the alkene, both benzyl ethers, and both benzyl esters. After workup with 4 M HCl saturated with NaCl,<sup>4</sup> (+)-SCH 351448 was obtained in 57% yield (two steps). The spectral data for our synthetic material matched those of the natural compound.

The stereocontrolled synthesis of (+)-SCH 351448 was achieved in 32 total steps (including the syntheses of **4** and **19**) with a longest linear sequence of 21 steps (2.1% overall yield) from **6**. The synthesis of the stereochemistry-rich fragment **5** was accomplished in an efficient 11 steps and 19% overall yield from **6**, featured two applications of our asymmetric allyl-/crotylation reagents (**6**→**8** and **11**→**13**), and inspired the development of a simple protodesilylative

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modification of the tandem silylformylation–allylsilylation reaction for the synthesis of 1,5-*syn*-diols (**14**→**5**).

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**Supporting Information Available:** Experimental procedures, characterization data, and stereochemical proofs. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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