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Enantioselective Total Synthesis of (+)-SCH 351448

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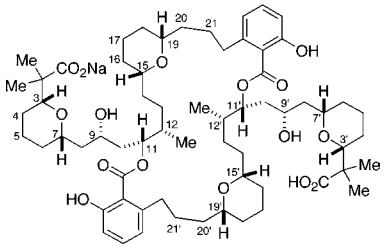
ABSTRACT



SCH 351448 (1)

A stereoselective synthesis of SCH 351448 has been completed. Twelve of the fourteen stereogenic centers were established through chiral enolate reactions, and six key C–C bonds were formed by metathesis reactions.

Hedge and co-workers at the Schering-Plough Research Institute recently reported the bioassay-guided isolation of a microbial metabolite, designated SCH 351448 (**1**), from the extracts of *Micromonospora* sp.[1] SCH 351448 (**1**) selectively activates (ED_{50} = 25 μM) transcription from the low-density lipoprotein receptor (LDL-R) promoter. Uptake of low-density lipoprotein (LDL) from the blood serum is controlled by the LDL-R, and regulation of the LDL-R promoter transcription can allow for control of cholesterol levels.[2] SCH 351448 is the only known agent that is a selective activator of LDL-R. The biological potential as well as the remarkably novel diolide structure of SCH 351448 have marked it as an important synthetic target with three total syntheses already recorded.[3−5]

Our strategy for the synthesis of SCH 351448 centered on the use of chiral enolate technology to establish 12 of the 14 required stereocenters and the utilization of olefin metathesis for the formation of six C−C bonds (C4−C5, C4′−C5′, C16−C17, C16′−C17′, C20−C21, C20′−C21′). Thus, SCH 351448 could be derived from subunits **2**, **3**, and **4** (Scheme 1) by esterification of the C11 and C11′ hydroxyls, cross metathesis to form the C20′−21′ bond, hydrogenation of the double bonds, and final adjustment of the C1 oxidation state. This strategy provided substantial flexibility in determining the optimal order of the operations for the assembly of the key fragments. Subunits **2** and **3** would be derived from polyene **5**, which would be prepared by a diastereoselective aldol reaction to construct the C11−C12 bond and establish the required stereochemical configuration at C11 and C12.

The synthesis began with the preparation of the C1−C11 subunit **6** as illustrated in Scheme 2. Addition of acrolein to a solution of the chlorotitanium enolate of *N*-propionyl thiazolidinethione **7** provided the aldol adduct **8** (97%, >98:2 dr).[6] Direct transesterification of the thioimide with isobutanol gave the isobutyl ester, which was alkylated under Frater−Seebach conditions[7] to deliver ester **9**. The ester **9** was reduced, and the resultant diol was selectively protected

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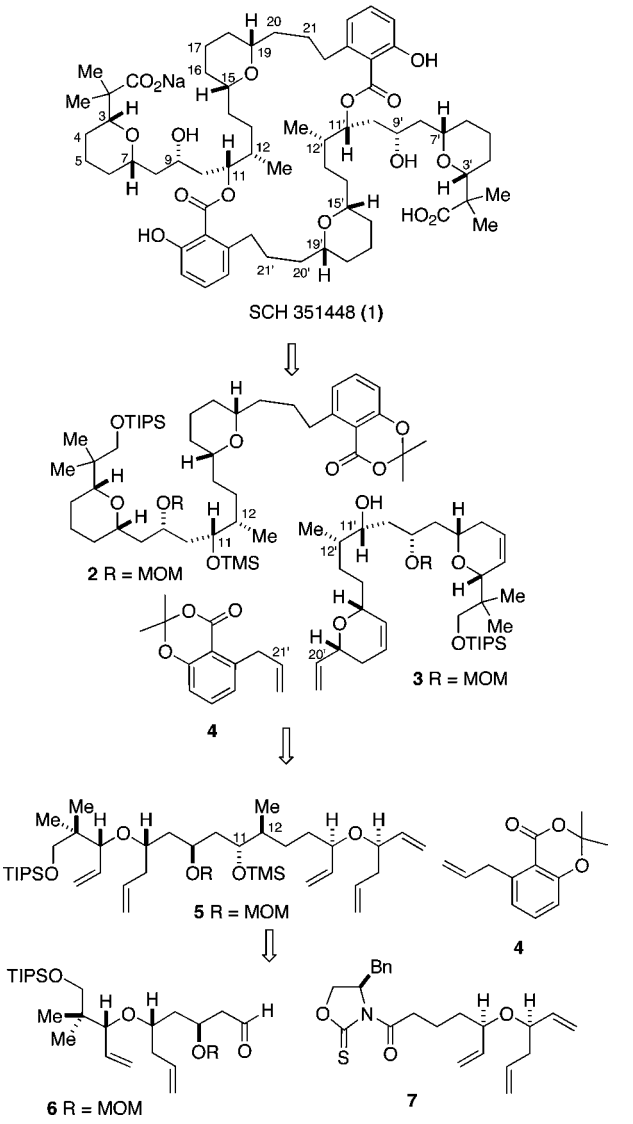
Scheme 1



as the corresponding primary TIPS ether **10**. The secondary alcohol **10** was alkylated with sodium bromoacetate, whereupon the glycolic acid obtained was converted to the *N*-acyl oxazolidinone **12** via the mixed anhydride. The C7 stereocenter was established by alkylation of the sodium enolate of imide **12** with allyl iodide.[8] Reductive removal of the auxiliary provided the alcohol **13** as a single diastereomer. One carbon homologation of alcohol **13** to aldehyde **14** was efficiently achieved by direct conversion of the alcohol **13** to the nitrile[9] followed by reduction of the nitrile to the aldehyde with *i*-Bu_2AlH. The C9 stereocenter was incorporated by exploiting the Phillips[10] *N*-acetyloxazolidinethione **15** in an aldol addition to aldehyde **14**. Immediate protection of the alcohol of the aldol adduct as its MOM ether gave the imide **16** in 84% yield over two steps (10:1 dr). The C1−C11 fragment was completed by reductive removal of the auxiliary and subsequent oxidation of the alcohol under Swern[11] conditions to provide the aldehyde **6** in good yield.

The C12−C20 subunit was constructed as shown in Scheme 3. Allylic alcohol **17** was readily available in large quantities in high enantiomeric purity through a Sharpless kinetic resolution[12] of the corresponding racemic alcohol. The alcohol **17** was converted in the usual manner to the glycolic acid, which was transformed to the *N*-acyloxazolidinone **19** in excellent yield by acylation of (*S*)-lithio-4-benzyl-2-oxazolidinone with the mixed anhydride of the glycolic acid. Alkylation of the sodium enolate of imide **19** with allyl iodide[8] served to selectively establish the C19 stereocenter providing alcohol **20** after reductive removal of the auxiliary. Oxidation of the primary alcohol **20** to the aldehyde was followed by a Wittig methylenation to produce the triene **21**. Completion of the C12−C20 fragment was accomplished in three steps by removal of the TIPS ether, Jones oxidation of the primary alcohol to the corresponding acid, and formation of the *N*-acyloxazolidinethione **7** via acylation of (*R*)-lithio-4-benzyl-2-oxazolidinethione with the intermediate acid chloride.

The C1−C11 fragment **6** and the C12−C20 subunit **7** were joined as illustrated in Scheme 4. The critical C11−C12 bond was formed with excellent stereocontrol by execution of a diastereoselective syn aldol addition[6] between the chlorotitanium enolate of thioimide **7** and aldehyde **6**. The reaction proceeded in 81% yield and >15:1 diastereoselectivity for the required isomer **22**, thus introducing the remaining two stereogenic centers of each monomeric unit of the diolide. The C12 methyl group was introduced by reduction of the carbonyl group of the *N*-acyloxazolidinethione to the methyl group in an efficient sequence. The aldol adduct was protected as the TMS ether, whereupon the *N*-acyloxazolidinethione was reduced with sodium borohydride to give a primary alcohol. The alcohol was deoxygenated by conversion to its mesylate followed by reduction with $LiEt_3BH$ to give the desired C1−C20 fragment **5**. The polyene **5** contains C1−C20 of each of the monomeric halves of SCH 351448.

With a workable route to polyene **5**, we turned to the issue of attaching the salicylic acid unit and assembling the monomers. An ambitious tandem metathesis reaction was envisioned at this point to complete the monomer by forming three carbon−carbon double bonds in a single operation: the closure of both the hydropyran rings and attachment of the salicylic acid unit of SCH 351448. In the event, exposure of polyene **5** to the Grubbs catalyst[13] (10 mol %, 0.05 M in CH_2Cl_2) in the presence of dioxenone **4** (10 equiv) provided an excellent yield (88%) of the triene **23** containing all the required carbons for the diolide monomer. This double-ring

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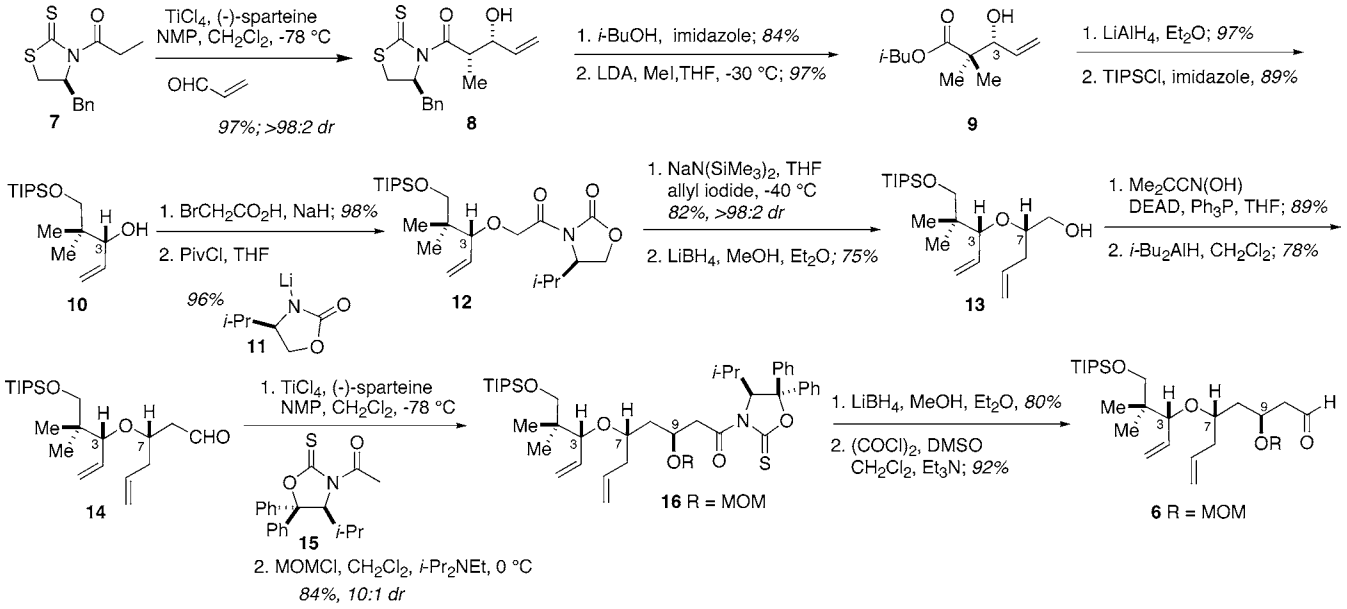
Scheme 2



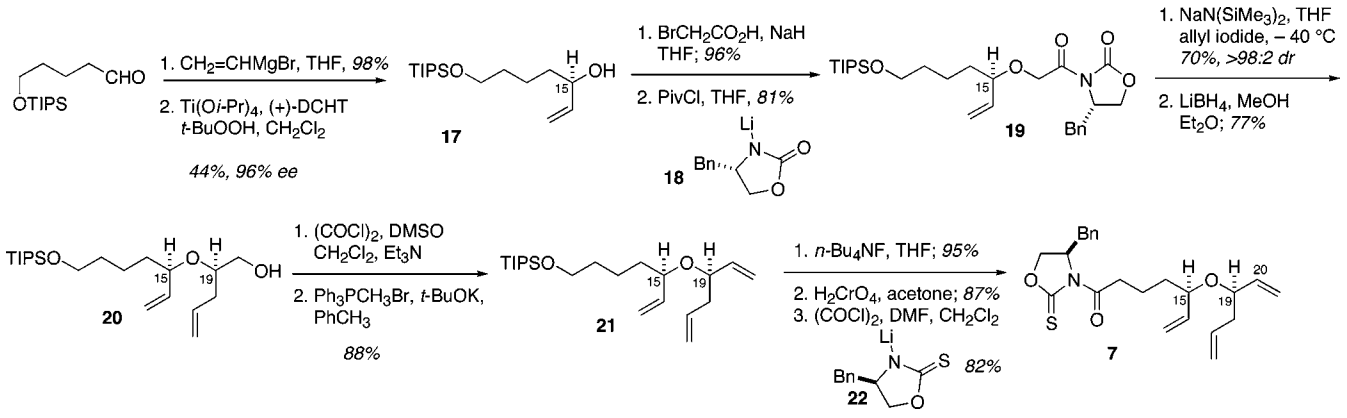
closing metathesis−cross metathesis demonstrates the remarkable selectivity accessible in metathesis reactions. Hydrogenation of the triene with Rh/Al_2O_3 delivered the saturated monomer **2**.

Although it would be desirable at this point to assemble the two monomers into the macrodiolide, all attempts to accomplish the transformation directly have been unsuccessful. This has clearly been a problem in other approaches as well.[3−5] As an alternative, assembly of the diolide in a stepwise manner was investigated. To this end, silyl ether **5** was converted the alcohol by removal of the TMS ether with mild acid, whereupon the polyene was exposed to the Grubbs catalyst [$Cl_2(PCy_3)_2Ru{=}CHPh$, 10 mol %, 0.001 M in CH_2Cl_2] in the absence of dioxenone **4** to produce the bishydropyran **3**. When alcohol **3** and dioxenone **2** were exposed to $NaN(SiMe_3)_2$ in THF, esterification at the C11 hydroxyl occurred in good yield. Subsequent exposure of the product to the Grubbs catalyst[13] (10 mol %, 0.05 M in CH_2Cl_2) in the presence of dioxenone **4** gave the dioxenone **24** in good yield, albeit somewhat lower than in the conversion of polyene **5** to dioxenone **23**.

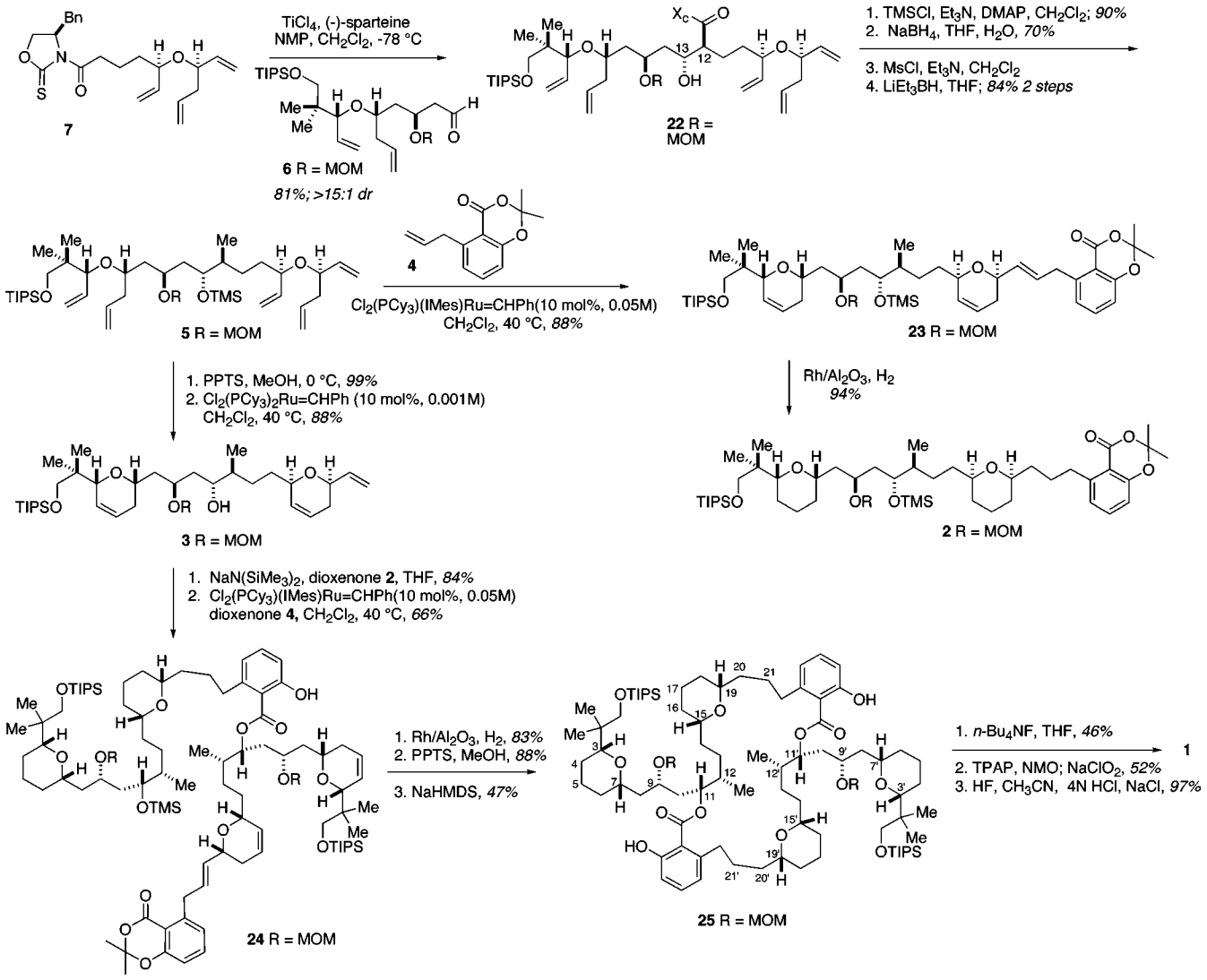
With the two monomers joined, it remained only to close the macrocycle and adjust the oxidation states at C1 and C1′. Hydrogenation of the three isolated alkenes was readily achieved by catalysis with Rh/Al_2O_3, whereupon the C11 TMS ether was removed. Macrolactonization was accomplished under basic conditions to provide the macrolide **25**. Removal of the TIPS ethers, two-stage oxidation of the primary alcohols to the carboxylic acids, and cleavage of the MOM ethers provided SCH 351448, identical to that previously reported.[1,3−5]

To summarize, a stereoselective synthesis of SCH 351448 has been completed (30 steps; longest linear sequence) relying on the use of titanium enolates of *N*-acylthioimides to establish eight of the required stereocenters and alkylation of glycolyloxazolidinones to incorporate four stereogenic

Scheme 3



Scheme 4



centers. Additionally, six carbon−carbon bonds were constructed through olefin metathesis reactions.

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Supporting Information Available: Experimental details and spectral data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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