SCH 351448 (1) is a novel activator of low-density lipoprotein receptor (LDL-R) promoter with an IC₅₀ of 25 μM, which was discovered from the organic extract of the fermentation broth of a Micromonospora microorganism.

The structure of 1 features a 28-membered macrodiolide consisting of two identical hydroxy carboxylic acid units. We wish to report here the first total synthesis of this intriguing molecule.2 The synthetic plan called for double combination of units A and B, and the olefin metathesis reaction was envisaged for macrodiolide synthesis (Scheme 1).

**Scheme 1. Retrosynthetic Analysis**

Synthesis of the A fragment started with Mukaiyama aldol reaction of the aldehyde 23 mediated by a chiral borane reagent.4 The secondary alcohol 4 obtained was converted into the â-alkoxyacrylate 4 via reaction with methyl propiolate, TBS deprotection, and iodide substitution. Radical cyclization 5 in the presence of acrylate 4 proceeded efficiently to yield the diester 5. Basic hydrolysis of 5 provided a monocarboxylic acid, and the corresponding aldehyde was converted into the homoallylic alcohol (dr = 9.6:1) via Brown allylation. Benzyl protection and transesterification with 2-(TMS)ethanol led to a new ester 6. The aldehyde obtained via oxidative cleavage was converted into the homoallylic alcohol 7 (dr = 14.1:1) via Brown crotylation (Scheme 2).

For the synthesis of the fragment B, the selenide 9 obtained from 85 was converted into 10 via regioselective benzylisation and reaction with methyl propiolate. Radical cyclization of 10 proceeded smoothly in the presence of tributylstannane and AIBN to provide the ester 11 in good yield. The aldehyde obtained from the ester 11 was converted into the homologous vinylstannane 12 via a modified Corey–Fuchs protocol6 and hydrostannylation. Efficient Stille coupling16 of 12 and 1311 led to an olefinic intermediate which was transformed into the aldehyde 14 after hydrogenation-hydrogenolysis and oxidation. The terminal olefin 15 was prepared from 14 via the Wittig reaction (Scheme 3).

**Scheme 2. Preparation of the A Fragment**

**Scheme 3. Preparation of the B Fragment**
Scheme 4. Preparation of the A–B Fragment

```
    OMe
    /   \   OMe
   |     |   |
   O     O   O
   H   H   H

   a-e 84%  7
   f-g  79%

   (a) TBSOTf, 2,6-lutidine, DCM, 0 °C; (b) OsO4, NMO, acetone–H2O (3:1); NaOMe; (c) NaBH4, EtOH; (d) 16, DIAD, Ph3P, THF, 0 °C; (e) (NH4)6Mo7O24, H2O2, EtOH; (f) NaHMDS, THF; 4 N HCl (saturated with NaCl).
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Scheme 5. Synthesis of SCH 351448

```
    OMe
    /   \   OMe
   |     |   |
   O     O   O
   H   H   H

   a-c 77%  7
   d-e 70%
   f   91%

   (a) NaHMDS, THF, 0 °C, 18; (b) concentrated HCl, MeOH; (c) NaHMDS, THF, 0 °C, 15; (d) 10 mol % Grubbs’ catalyst (2nd generation); DCM (5 mM), 80 °C; (e) H2; Pd/C, MeOH–EtOAc (3:1); (f) TBAF, THF; 4 N HCl (saturated with NaCl).
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A five-step sequence converted the homoallylic alcohol 7 into the sulfone 17, which was efficiently coupled with the aldehyde 14 to generate the product olefin. The monomeric unit 18 was obtained from the olefin via diimide reduction (Scheme 4).

The final assembly of the fragments was initiated by reacting the sodium alkoxide derived from 7 with 18. The coupled product was then converted into another alkoxide after TBS-deprotection, which was used for the coupling with 15 to produce the diester 19. Intramolecular olefin metathesis of 19 mediated by the second-generation Grubbs catalyst proceeded smoothly, and the macrodilide 20 was obtained after hydrogenation-hydrogenolysis. (TMS)ethyl ester functionalities in 20 were removed by reaction with TBAF, and the monosodium salt 1 was obtained when the reaction mixture was equilibrated with 4 N hydrochloric acid saturated with sodium chloride (Scheme 5).

Figure 1. X-ray crystal structure of 1.

Compound 1 appears to be a remarkable sodiophile. The crystallographic data reveal a pseudo-C2-symmetric structure in which the sodium cation is surrounded by eight oxygen atoms (Figure 1).

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Supporting Information Available: Selected experimental procedures, 1H and 13C NMR spectra of synthetic and natural samples of 1, and X-ray crystallographic structure of 1 (PDF and CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(2) For previous synthetic efforts, see: Bhattacharjee, A.; Soltani, O.; De Brabander, J. K. Org. Lett. 2002, 4, 481−484.
(13) Remarkably, equilibration with highly acidic solution was required for isolation of the monosodium salt. The synthetic monosodium salt was found to be the (+)-enantiomer: [α]D25 +31.2 (c 0.73, CHCl3). The specific rotation of the natural sample is unknown.

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