J|A|C|S
COMMUNICATIONS

Published on Web 02/14/2004

Total Synthesis of (+)-SCH 351448

Eun Joo Kang, Eun Jin Cho, Young Eun Lee, Mi Kyung Ji, Dong Mok Shin, Young Keun Chung, and Eun Lee*

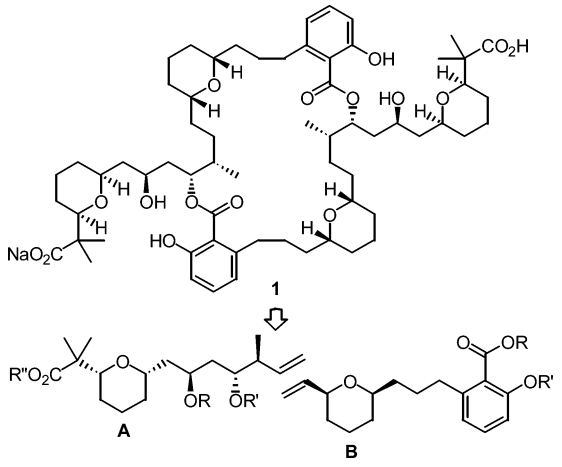
School of Chemistry and Molecular Engineering, Seoul National University, Seoul 151-747, Korea

Received December 5, 2003; E-mail: eunlee@snu.ac.kr

SCH 351448 (**1**) is a novel activator of low-density lipoprotein receptor (LDL-R) promoter with an IC_{50} of 25 μM, which was discovered from the organic extract of the fermentation broth of a *Micromonospora* microorganism.[1]

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).

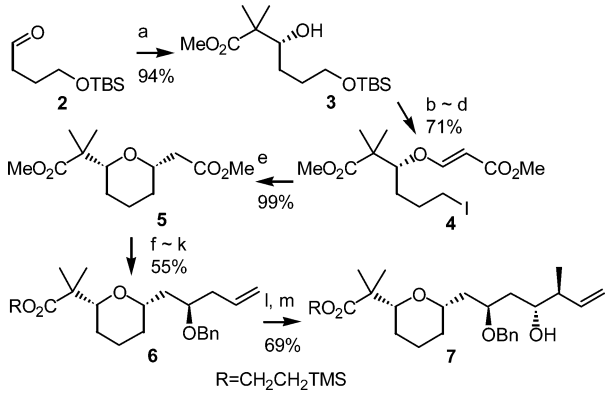
Scheme 1. Retrosynthetic Analysis



Synthesis of the **A** fragment started with Mukaiyama aldol reaction of the aldehyde **2**[3] mediated by a chiral borane reagent.[4] The secondary alcohol **3** obtained was converted into the β-alkoxyacrylate **4** via reaction with methyl propiolate, TBS deprotection, and iodide substitution. Radical cyclization[5] in the presence of hypophosphite and triethylborane in ethanol[6] proceeded efficiently to yield the diester **5**. Basic hydrolysis of **5** provided a monocarboxylic acid, and the corresponding aldehyde was converted into the correct 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[7] (Scheme 2).

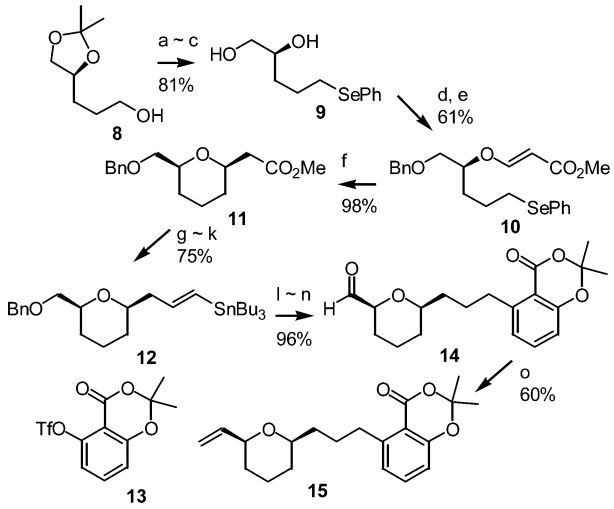
For the synthesis of the fragment **B**, the selenide **9** obtained from **8**[8] was converted into **10** via regioselective benzylation and reaction with methyl propiolate. Radical cyclization of **10** proceeded smoothly in the presence of tributylstannane and AIBN to provide the ester **11** in good yield. The aldehyde obtained from the ester **11** was converted into the homologous vinylstannane **12** via a modified Corey−Fuchs protocol[9] and hydrostannylation. Efficient Stille coupling[10] of **12** and **13**[11] 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[a]



[a] (a) *N*-tosyl-(*S*)-valine, BH_3·THF, DCM; **2**, $Me_2CC(OMe)(OTMS)$, −78 °C; (b) $CHCCO_2Me$, NMM, MeCN; (c) concentrated HCl, MeOH; (d) I_2, Ph_3P, imidazole, THF, 0 °C; (e) H_3PO_2, 1-ethylpiperidine, Et_3B, EtOH; (f) KOH, THF−H_2O−MeOH (3:1:1); (g) BH_3·DMS, $B(OMe)_3$, THF, 0 °C; (h) SO_3·Pyr, TEA, DMSO−DCM (1:1), 0 °C; (i) $CH_2CHCH_2B(^{i}Ipc)_2$, ether, −78 °C; NaOH, H_2O_2, reflux; (j) NaHMDS, BnBr, THF−DMF (4:1), 0 °C to room temperature; (k) $Ti(O^{i}Pr)_4$, $TMSCH_2CH_2OH$, DME, 120 °C; (l) OsO_4, NMO, acetone−H_2O (3:1); $NaIO_4$; (m) (E)-$CH_3CHCHCH_2B(^{d}Ipc)_2$, THF, −78 °C; NaOH, H_2O_2, −78 °C to room temperature.

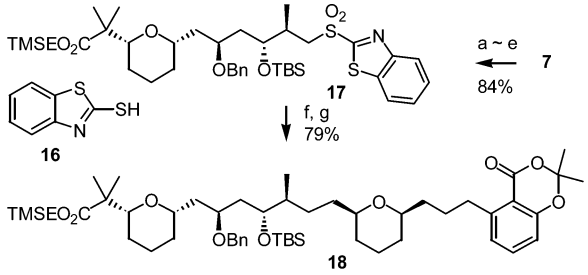
Scheme 3. Preparation of the **B** Fragment[a]



[a] (a) TsCl, TEA, DCM, 0 °C; (b) PhSeSePh, $NaBH_4$, EtOH; (c) concentrated HCl, MeOH; (d) Bu_2SnO, benzene, reflux (−H_2O); BnBr, TBAI, benzene, reflux; (e) $CHCCO_2Me$, NMM, MeCN; (f) n-Bu_3SnH, AIBN, benzene (0.01 M), reflux; (g) LAH, THF, 0 °C; (h) SO_3·Pyr, TEA, DMSO−DCM (1:1), 0 °C; (i) CBr_4, HMPT, THF, −30 °C; (j) n-BuLi, THF, −78 °C; (k) n-Bu_3SnH, AIBN, benzene (0.02 M), reflux; (l) $PdCl_2(PPh_3)_2$, **13**, LiCl, Ph_3P, DMF (0.1 M), 120 °C; (m) H_2, Pd/C, MeOH; (n) SO_3·Pyr, TEA, DMSO−DCM (1:1), 0 °C; (o) $Ph_3PCH_3^+Br^-$, n-BuLi, THF, 0 °C; **14**, −78 °C to room temperature.

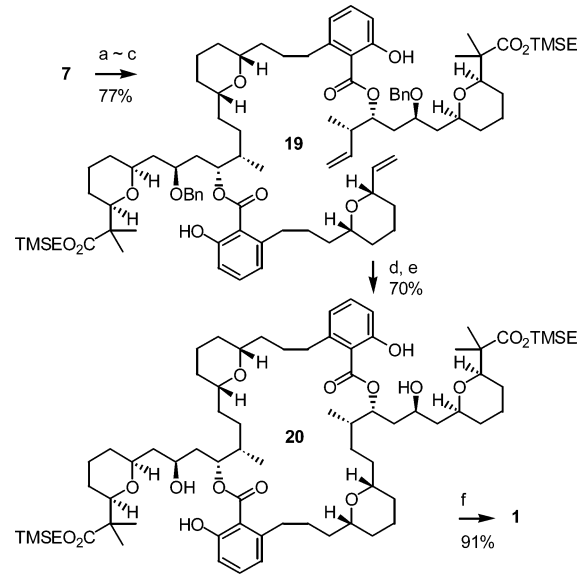
10.1021/ja0315309 CCC: $27.50

Scheme 4. Preparation of the **A**−**B** Fragment[a]



[a] (a) TBSOTf, 2,6-lutidine, DCM, 0 °C; (b) OsO_4, NMO, acetone−H_2O (3:1); $NaIO_4$; (c) $NaBH_4$, EtOH; (d) **16**, DIAD, Ph_3P, THF, 0 °C; (e) $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$, H_2O_2, EtOH, 0 °C to room temperature; (f) NaHMDS, ether, −78 °C; **14** (syringe pump, 30 min), −78 °C to room temperature; (g) $TsNHNH_2$, NaOAc, DME−H_2O (1:1), reflux.

Scheme 5. Synthesis of SCH 351448[a]



[a] (a) NaHMDS, THF, 0 °C; **18**; (b) concentrated HCl, MeOH; (c) NaHMDS, THF, 0 °C; **15**, 0 °C; (d) 10 mol % Grubbs' catalyst (2nd generation), DCM (3 mM), 80 °C; (e) H_2, Pd/C, MeOH−EtOAc (3:1); (f) TBAF, THF; 4 N HCl (saturated with NaCl).

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[12] proceeded smoothly, and the macrodiolide **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[13] (Scheme 5).

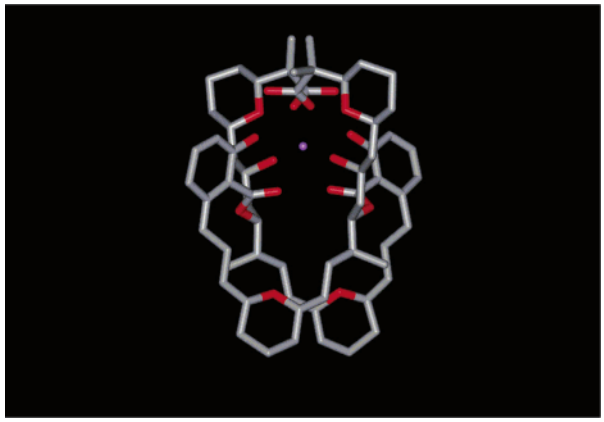


Figure 1. X-ray crystal structure of **1**.

Compound **1** appears to be a remarkable sodiophile. The crystallographic data reveal a pseudo-C_2-symmetric structure in which the sodium cation is surrounded by eight oxygen atoms (Figure 1).

Acknowledgment. This paper is dedicated to Prof. A. I. Scott on the occasion of his 75th birthday. The authors thank the Ministry of Science and Technology, Republic of Korea, and KISTEP for a NRL grant (1999). BK21 graduate fellowship grants to E. J. Kang, E. J. Cho, and Y. E. Lee are gratefully acknowledged. The authors also thank Dr. V. R. Hegde (Schering Plough Research Institute) for providing spectroscopic data of the natural sample.

Supporting Information Available: Selected experimental procedures, ^1H and ^{13}C 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

(1) 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.
(2) For previous synthetic efforts, see: Bhattacharjee, A.; Soltani, O.; De Brabander, J. K. *Org. Lett.* **2002**, *4*, 481−484.
(3) Danishefsky, S. J.; Pearson, W. H. *J. Org. Chem.* **1983**, *48*, 3865−3866.
(4) Kiyooka, S.; Kaneko, Y.; Komura, M.; Matsuo, H.; Nakano, M. *J. Org. Chem.* **1991**, *56*, 2276−2278.
(5) For recent examples of β-alkoxyacrylate radical cyclization, see: (a) Song, H. Y.; Joo, J. M.; Kang, J. W.; Kim, D.-S.; Jung, C.-K.; Kwak, H. S.; Park, J. H.; Lee, E.; Hong, C. Y.; Jeong, S.; Jeon, K.; Park, J. H. *J. Org. Chem.* **2003**, *68*, 8080−8087. (b) Jeong, E. J.; Kang, E. J.; Sung, L. T.; Hong, S. K.; Lee, E. *J. Am. Chem. Soc.* **2002**, *124*, 14655−14662. (c) Lee, E.; Choi, S. J.; Kim, H.; Han, H. O.; Kim, Y. K.; Min, S. J.; Son, S. H.; Lim, S. M.; Jang, W. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 176−178.
(6) Lee, E.; Han, H. O. *Tetrahedron Lett.* **2002**, *43*, 7295−7296.
(7) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 5919−5923.
(8) Rodriguez, E. B.; Scally, G. D.; Stick, R. V. *Aust. J. Chem.* **1990**, *43*, 1391−1405.
(9) Drouet, K. E.; Theodorakis, E. A. *J. Am. Chem. Soc.* **1999**, *121*, 456−457.
(10) Saá, J. M.; Martorell, G.; García-Raso, A. *J. Org. Chem.* **1992**, *57*, 678−685.
(11) Fürstner, A.; Konetzki, I. *Tetrahedron* **1996**, *52*, 15071−15078.
(12) Sanford, M. S.; Love, J. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 6543−6554.
(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: $[\alpha]^{13}_D$ +31.2 (*c* 0.73, $CHCl_3$). The specific rotation of the natural sample is unknown.

JA0315309