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A Concise Synthesis of (+)-SCH 351448

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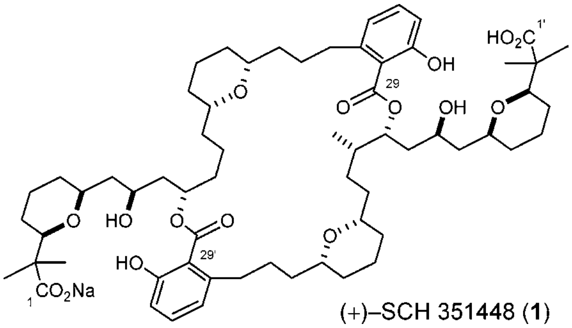
ABSTRACT

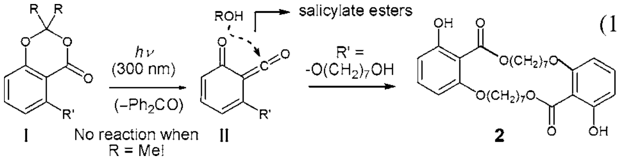


(+)–SCH 351448 (**1**)

We describe a highly convergent synthetic approach to the natural product (+)-SCH 351448 (1)—a hexane-soluble heptacoordinate monosodium salt of a *C*$_2$-symmetrical macrocyclic dilactone. Our approach implements a photochemical acylation as the key step to combine two nearly identical but orthogonal C1–C29 fragments, followed by a base-induced intramolecular acylation and deprotection to yield the natural product.

Our interest in naturally produced small molecules of structural novelty and potential biological significance led us to take note of SCH 351448 (**1**, Figure 1)—a hexane-soluble material purified from a *Micromonospora* sp. fermentation broth.[1] The reported ability of natural **1** to activate transcription from the low-density lipoprotein (LDL) receptor promoter is of mechanistic and biomedical importance.[2] The single-crystal X-ray structure of **1** shows a remarkable topology. The ionized and un-ionized carboxy groups are intramolecularly hydrogen-bonded and together with the phenol and hydroxy groups accommodate a heptacoordinate sodium ion in the interior cavity of a hydrophobic globular structure.[1] At this point, it remains unclear whether **1** functions by mediating sodium or other ion transport across membranes or whether the role of the chelated sodium ion is structural; i.e., does **1** behave as a hydrophobic small molecule ligand for a cellular receptor? To answer these and related questions, we initiated a synthetic program to provide material for future structural, physicochemical, and biological studies. Herein, we communicate a short and scalable synthesis of SCH 351448.[3,4]

Taking maximal advantage of the dimeric nature of **1**, we hoped to identify viable esterification/lactonization strategies to combine two identical or closely related C_1-C_{29} fragments (Figure 1). Recently, we reported that photolysis of 2-Ph-benzo[1,3]dioxinones (**I**, R = Ph) in the presence of alcohols is a powerful method for the synthesis of otherwise difficult to access sterically hindered salicylate esters (eq 1).[5] These studies revealed that the corresponding 2-Me-benzodioxinones (**I**, R = Me) do not photolyze to the powerful acylating quinoketene intermediate **II**.[5]



I II **2** (1)

In an ideal approach, dilactones would be accessible directly from photochemical homodimerization of a photo-

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(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) (a) Brown, M. S.; Goldstein, J. L. *Science* **1986**, *232*, 34−47. (b) Brown, M. S.; Goldstein, J. L. *Cell* **1997**, *89*, 331−340.

10.1021/ol0510769 CCC: $30.25

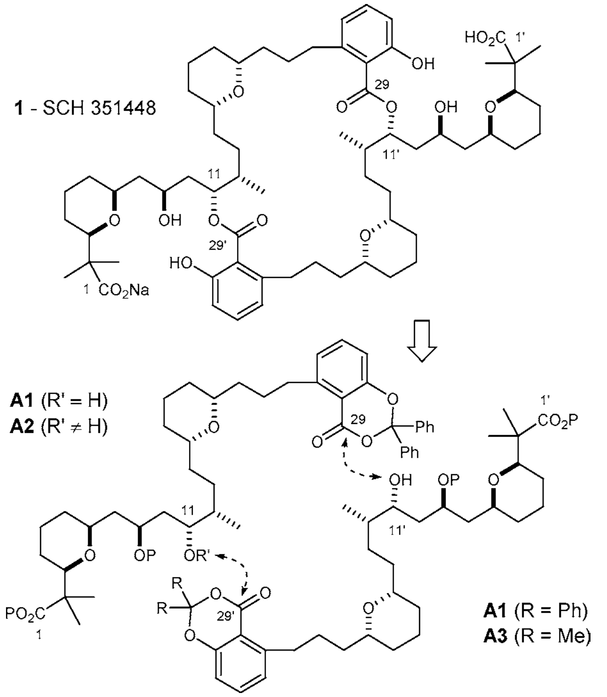
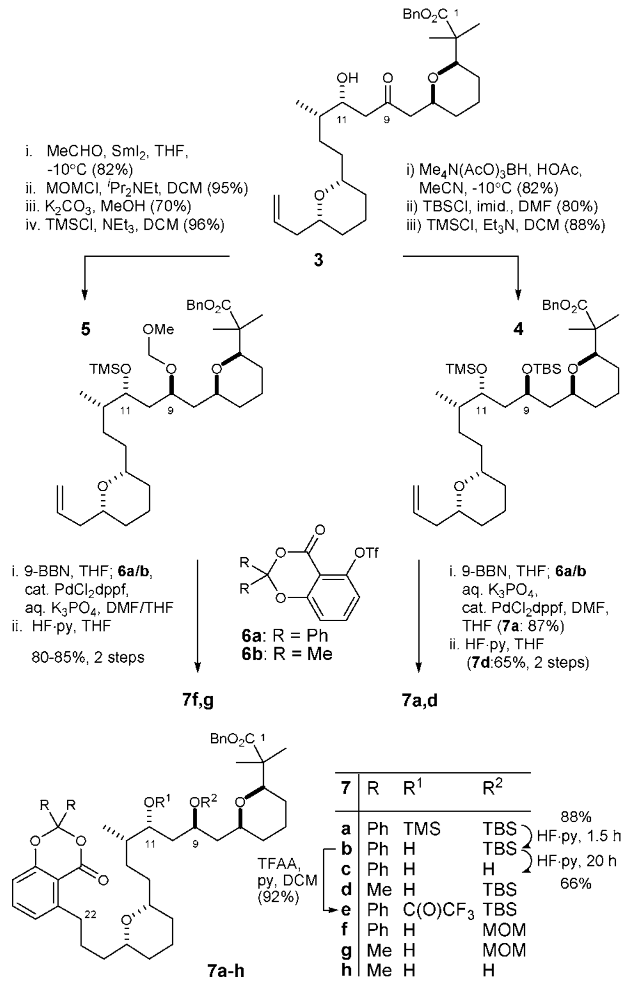


Figure 1. Symmetry-based approach for the synthesis of SCH 351448.

responsive fragment with a free C_{11}-alcohol (**A1**)—a reasonable prospectus based on our finding that photolysis of benzodioxinone **I** (R = Ph, R′ = −O(CH$_2$)$_7$OH) yielded dilactone **2** as the major product besides monolactone (eq 1).[6] Alternatively, a hydroxy-protected photoactive fragment (**A2**) would be photolyzed in the presence of an orthogonal photosilent acyl-acceptor fragment (**A3**) to yield an ester dimer, necessitating a subsequent nonphotochemical lactonization.

To fully explore the above-mentioned dimerization strategies, we prepared a series of differentially protected fragments as shown in Scheme 1. Our point of departure was the *β*-hydroxyketone **3**, prepared in multigram quantities as described previously.[4] Anti-selective reduction with Me$_4$N(AcO)$_3$BH[7] provided an *anti*-diol (82%)[4] which was differentially protected by treatment with TBSCl (80%)[4] followed by TMSCl (88%) to yield bis-silyl ether **4**. Alternatively, a C_9-OMOM-protected fragment **5** was synthesized by Evans−Tishchenko reduction of **3** (MeCHO and SmI$_2$, 82%),[8] followed by protection (→ C_9−OMOM, 95%), acetate removal (→ C_{11}−OH), and TMS protection (→ **5**, 70% for two steps). The terminal olefin of fragments **4**/**5** served as a handle for C−C bond formation with aryl triflates **6a**,**b**. Thus, palladium-catalyzed cross-coupling of in situ prepared *B*-alkyl derivatives of **4**/**5** (9-BBN, THF, 23 °C) with aryl triflates **6a**,**b** under Suzuki−Miyaura conditions (aq K$_3$PO$_4$, cat. PdCl$_2$dppf, DMF, 23 °C) provided products **7b**,**d**,**f**,**g** after removal of the C_{11}-TMS ether with HF•pyridine.[9,10]

Scheme 1



7	R	R^1	R^2
a	Ph	TMS	TBS
b	Ph	H	TBS
c	Ph	H	H
d	Me	H	TBS
e	Ph	C(O)CF$_3$	TBS
f	Ph	H	MOM
g	Me	H	MOM
h	Me	H	H

Next (Scheme 2), we performed a series of experiments designed to obtain dimeric lactones directly by ultraviolet irradiation (300 nm, 0.1 M in CH$_2$Cl$_2$, 1 h) of unprotected (C_{11}-OH) photoactive monomers **7b**, **7f**, or **7c** (from **7b** by prolonged exposure to HF•pyridine, Scheme 1). Unfortunately, intramolecular lactonization was the dominant pathway, providing C_{11}-lactone **8f** (34% yield) from alcohol **7f** (16% recovered) and a separable 2:1 mixture of regioisomeric lactones **8c** and **9c** (38% yield) from diol substrate **7c** (30% recovered). Interestingly, photolysis of the monohydroxy

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[3] Total synthesis: Kang, E. J.; Cho, E. J.; Lee, Y. E.; Ji, M. K.; Shin, D. M.; Chung, Y. K.; Lee, E. *J. Am. Chem. Soc.* **2004**, *126*, 2680−2681.

[4] For synthetic studies from our lab, see: Bhattacharjee, A.; Soltani, O.; De Brabander, J. K. *Org. Lett.* **2002**, *4*, 481−484.

[5] (a) Soltani, O.; De Brabander, J. K. *Angew. Chem., Int. Ed.* **2005**, *44*, 1696−1699. (b) García-Fortanet, J.; DeBergh, J. R.; De Brabander, J. K. *Org. Lett.* **2005**, *7*, 685−688.

[6] (a) See the Supporting Information. (b) For a similar observation with thermally generated acyclic *ω*-hydroxy-ketoketenes, see: Chen, C.; Quinn, E. K.; Olmstead, M. M.; Kurth, M. J. *J. Org. Chem.* **1993**, *58*, 5011−5014.

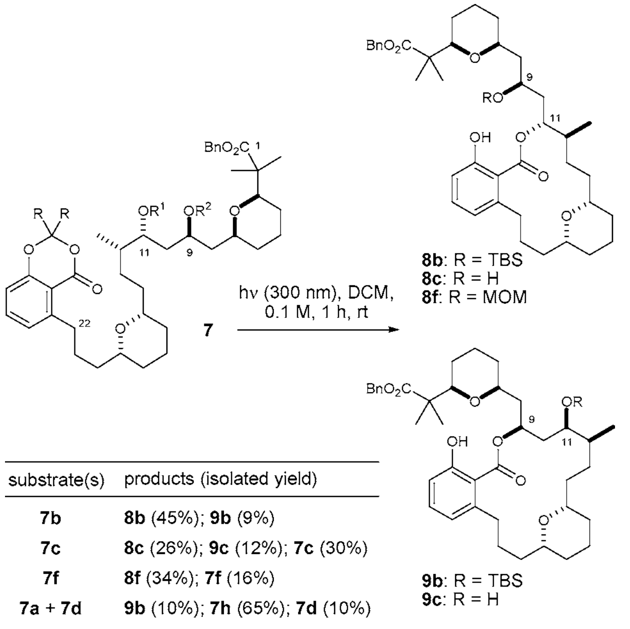
[7] Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560−3578.

[8] Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1990**, *112*, 6447−6449.

[9] Oh-e, T.; Miyaura, N.; Suzuki, A. *J. Org. Chem.* **1993**, *58*, 2201−2208.

[10] TMS protection gave optimal results for this fragment coupling.

Scheme 2



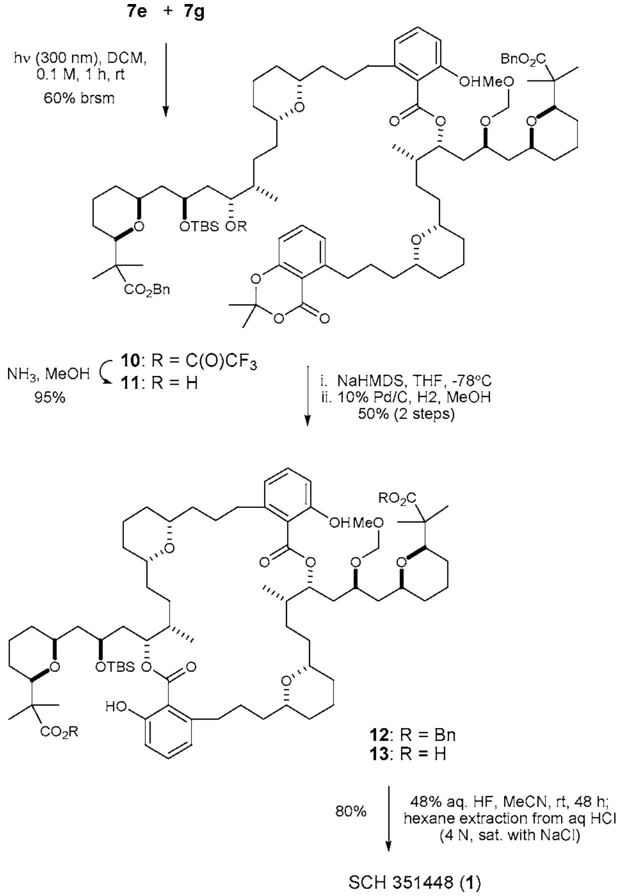
substrate(s)	products (isolated yield)
7b	**8b** (45%); **9b** (9%)
7c	**8c** (26%); **9c** (12%); **7c** (30%)
7f	**8f** (34%); **7f** (16%)
7a + **7d**	**9b** (10%); **7h** (65%); **7d** (10%)

substrate **7b** was accompanied by silyl migration to yield two regioisomeric lactones **8b** and **9b** in a ratio of 5:1 (54% yield).

The intrinsic propensity for intramolecular cyclization of **7b**,**c**,**f** necessitated a circumvention to stage an enforced heterodimerization of an orthogonal photosilent/photoactive pair. Unfortunately, irradiation (300 nm, CH_2Cl_2, 1 h) of a mixture of **7a** (1 equiv) and **7d** (3 equiv) did not provide the desired ester dimer but yielded a TBS-transposed monolactone **9b** (~10%) from intramolecular cyclization of **7a**, unreacted **7d** (10−15%) and a diol **7h** (from **7d**, 65%) as shown in Scheme 2. Based on this result, we (1) exchanged the labile C_{11}-OTMS in the photoreactive partner for a trifluoroacetate (**7e**, 92% from **7b**, Scheme 1) to eliminate intramolecular cyclization, and (2) flanked the C_{11}-alcohol in the acyl-acceptor fragment with a C_9-OMOM (i.e., **7g**) to decrease steric hindrance around the C_{11}-alcohol and increase stability.

As shown in Scheme 3, irradiation (300 nm, CH_2Cl_2, 1 h) of a mixture of **7e** (0.2 M, 1 equiv) and **7g** (2 equiv) did yield the desired ester **10** in 60% yield based on consumed **7e** (**7e,g** recovered in 50% and 80% respectively). With this key event accomplished, lactone **12** was obtained in 50% yield by treatment of alcohol **11** (from **10** by trifluoroacetate removal, 94%), with NaHMDS (THF, −78 °C).[3,11] Finally, hydrogenolytic debenzylation gave diacid **13**, which upon treatment with 48% aq HF in MeCN, followed by hexane extraction from aq HCl (4 N, saturated with NaCl),[3] yielded **1** contaminated with a minor byproduct (80%).[12] HPLC purification yielded pure material with ^{1}H and ^{13}C NMR and mass spectral data in complete agreement with those reported for natural[1] and synthetic[3] **1**.[13]

Scheme 3



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Supporting Information Available: Experimental procedures, characterization data, and copies of NMR spectra for new compounds, synthetic **1**, and natural **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Bhattacharjee A.; De Brabander, J. K. *Tetrahedron Lett.* **2000**, *41*, 8069−8073.

(12) ^{1}H NMR shifts corresponding to this byproduct were also visible in the spectrum of the natural product (from ref 3). Comparison ^{1}H NMR spectra are provided in the Supporting Information.

(13) Our material was dextrorotatory: $[\alpha]^{20}_D = +22.4$ (*c* 0.10, $CHCl_3$), similar to synthetic **1** of ref 3: $[\alpha]^{13}_D = +31.2$ (*c* 0.73, $CHCl_3$). The specific rotation and absolute configuration of the natural sample were not reported.