JOC*Article*

A Formal Total Synthesis of the Salicylihalamides

Christian Herb and Martin E. Maier*

Universität Tübingen, Institut für Organische Chemie, Auf der Morgenstelle 18, 72076 Tübingen, Germany

martin.e.maier@uni-tuebingen.de

Received July 22, 2003

The synthesis of the macrolactone **23** is described. The synthesis features a diastereoselective hydroboration of the chiral alkene **17** followed by a Suzuki cross-coupling reaction with the benzoate **5**. The resulting seco acid **21** was converted to the macrolactone **23** by a Mitsunobu lactonization using immobilized triphenylphosphine. The stereogenic centers in the alkene **17** were established by a Noyori reduction of the β-keto ester **8** and an Evans aldol reaction. The synthesis illustrates the conversion of a syn aldol product to the corresponding anti product by inversion of the methyl-bearing center.

Introduction

Polyketides comprise a large group among the biologically active natural products. They are characterized by a substantial structural diversity, which is the result of various folding patterns in ring-forming reactions during biosynthesis. Thus, many polyketides contain one or more aromatic rings with a characteristic distribution of the oxygen functionality. A recently discovered group of polyketides are the benzolactone enamides (Figure 1). In addition to a benzoic acid substructure and a macrolactone ring, these natural products feature an enamide side chain. Some representative molecules from this family include the salicylihalamides,[1] the apicularens,[2] the lobatamides, the oximidines,[3] YM-75518,[4] and the macrolides CJ-12,950 and CJ-13,357.[5]

As related macrolactones that lack the enamide side chain, zearalenone,[6] radicicol,[7] C292,[8] and queenslandon[9] can be mentioned. The benzolactone enamides show potent activity against human cancer cell lines. For some of the benzolactone enamides, it could be shown that the antitumor activity is due to the inhibition of vacuolar ATPase membrane bound enzymes.[10,11] These enzymes utilize the hydrolysis of ATP to generate a potential across the membrane that can be used to transport ions and small molecules. In contrast to other known V-ATPase inhibitors, salicylihalamide A discriminates between nonmammalian and mammalian V-ATPases. There-

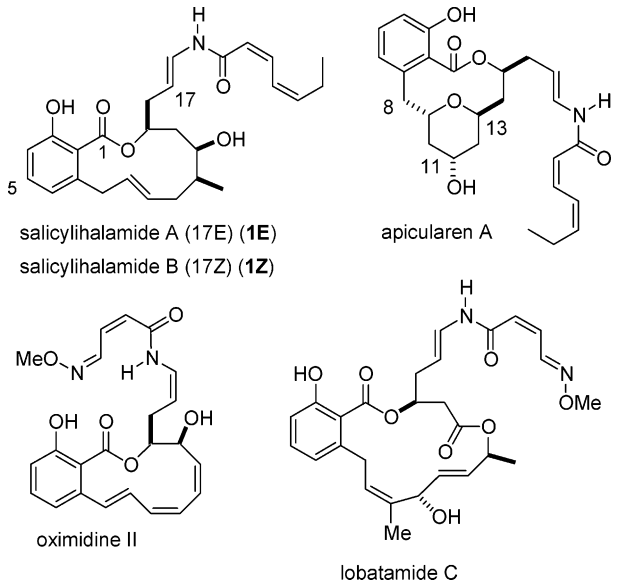


FIGURE 1. Structures of representative benzolactone enamides.

(1) Erickson, K. L.; Beutler, J. A.; Cardellina, J. H., II.; Boyd, M. R. *J. Org. Chem.* **1997**, *62*, 8188−8192.
(2) (a) Kunze, B.; Jansen, R.; Sasse, F.; Höfle, G.; Reichenbach, H. *J. Antibiot.* **1998**, *51*, 1075−1080. (b) Jansen, R.; Kunze, B.; Reichenbach, H.; Höfle, G. *Eur. J. Org. Chem.* **2000**, 913−919.
(3) Kim, J. W.; Shin-ya, K.; Furihata, K.; Hayakawa, Y.; Seto, H. *J. Org. Chem.* **1999**, *64*, 153−155.
(4) Suzumura, K.-i.; Takahashi, I.; Matsumoto, H.; Nagai, K.; Setiawan, B.; Rantiatmodjo, R. M.; Suzuki, K.-i.; Nagano, N. *Tetrahedron Lett.* **1997**, *38*, 7573−7576.
(5) Dekker: K. A.; Aiello, R. J.; Hirai, H.; Inagaki, T.; Sakakibara, T.; Suzuki, Y.; Thompson, J. F.; Yamauchi, Y.; Kojima, N. *J. Antibiot.* **1998**, *51*, 14−20.
(6) (a) Stob, M.; Baldwin, R. S.; Tuite, J.; Andrews, F. N.; Gillette, K. G. *Nature* **1962**, *196*, 1318. (b) Urry, W. H.; Wehrmeister, H. L.; Hodge, E. B.; Hidy, P. H. *Tetrahedron Lett.* **1966**, 3109−3114. (c) Hidy, P. H.; Baldwin, R. S.; Greasham, R. L.; Keith, C. L.; McMullen, J. R. *Adv. Appl. Microbiol.* **1977**, *22*, 59−82. (d) Cordier, C.; Gruselle, M.; Jaouen, G.; Hughes, D. W.; McGlinchey, M. J. *Magn. Reson. Chem.* **1990**, *28*, 835−845.
(7) (a) Mirrington, R. N.; Ritchie, E.; Shoppee, C. W.; Taylor, W. C.; Sternhell, S. *Tetrahedron Lett.* **1964**, 365−370. (b) Nozawa, K.; Nakajima, S. *J. Nat. Prod.* **1979**, *42*, 374−377. (c) Ayer, W. A.; Lee, S. P.; Tsuneda, A.; Hiratsuka, Y. *Can. J. Microbiol.* **1980**, *26*, 766−73.
(8) Sellés, P.; Lett, R. *Tetrahedron Lett.* **2002**, *43*, 4621−4625.
(9) Hoshino, Y.; Ivanova, V. B.; Yazawa, K.; Ando, A.; Mikami, Y.; Zaki, S. M.; Karam, A.-Z. A.; Youssef, Y. A.; Gräfe, U. *J. Antibiot.* **2002**, *55*, 516−519.
(10) Boyd, M. R.; Farina, C.; Belfiore, P.; Gagliardi, S.; Kim, J. W.; Hayakawa, Y.; Beutler, J. A.; McKee, T. C.; Bowman, B. J.; Bowman, E. J. *J. Pharmacol. Exp. Ther.* **2001**, *291*, 114−120.
(11) For reviews, see: (a) Nishi, T.; Forgac, M. *Nature Rev. Mol. Cell Biol.* **2002**, *3*, 94−103. (b) Beutler, J. A.; McKee, T. C. *Curr. Med. Chem.* **2003**, *10*, 787−796.

10.1021/jo035054g CCC: $25.00
Published on Web 09/23/2003

fore, these natural products are important leads for the development of drugs that target this enzyme class. The fact that the benzolactone enamides were found in various sources additionally underscores the great potential of V-ATPases as molecular targets since this mode of action seems to be an efficient defense mechanism for microorganisms. The new structural features combined with the novel mode of action rendered these natural products interesting targets for total synthesis. So far total syntheses for salicylihalamide,[12] apicularen A,[13] lobatamides,[14] and oximidine[15] have been described. In addition, synthetic studies were published.[16,17,18,19] Our group has contributed syntheses of the core structures of apicularen A,[17b,d] salicylihalamide A,[16e] and oximidine.[18a] In this paper, we disclose a formal total synthesis of salicylihalamide A featuring the tactical combination of a diastereoselective hydroboration with a Suzuki cross-coupling reaction followed by a Mitsunobu macrolactonization employing immobilized triphenylphosphine.

The macrolactone portion of salicylihalamide is unique in that it features a double bond in allylic position to the aromatic ring. Because of steric hindrance around the carboxylic group and participation of the double bond, a classical macrolactonization is difficult. So far most of the syntheses of salicylihalamide A create the macrocyclic ring by a ring-closing metathesis reaction. The Rizzacasa group constructs the macrolactone ring by a nucleophilic attack of an alkoxide on an acetal ester.[12h] Previously, we had reported formation of the macrolactone ring of the salicylihalamides by intramolecular Suzuki reaction.[16e]

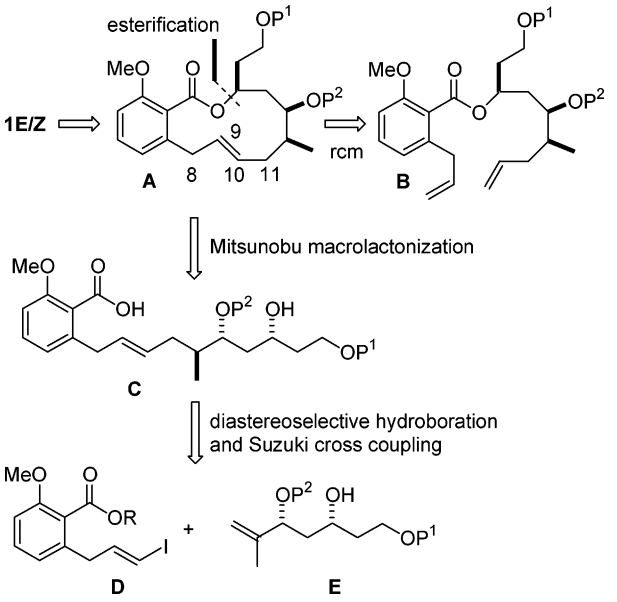
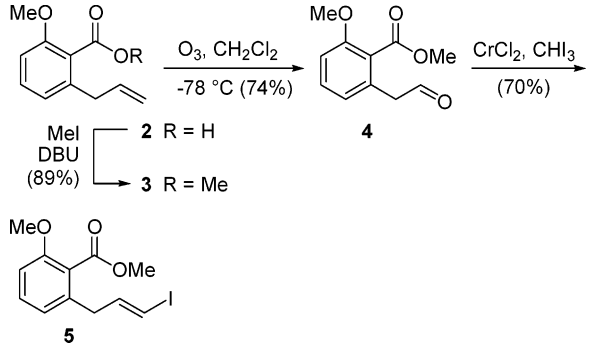


FIGURE 2. Retrosynthetic analysis for salicylihalamide featuring a Mitsunobu macrolactonization and a diastereoselective hydroboration/Suzuki cross coupling.

SCHEME 1. Synthesis of the Benzoate 5 with a 3-iodoprop-2-enyl Side Chain



In this project, we planned to invert the key reactions. That is, the Suzuki cross-coupling reaction would be intermolecular and the lactonization would be intramolecular. The retrosynthetic analysis that features a Suzuki reaction is shown in Figure 2. This analysis leads to the vinyl iodide **D** and the alkenol derivative **E**. Since macrolactonization reactions under Mitsunobu conditions are well-known,[14,16b,20] we wanted to apply this strategy for the salicylihalamide core structure.

Results and Discussion

The synthesis of the benzoate **2** carrying a propenyl side chain started with the known benzoic acid **2**.[12f] Esterification of **2** with methyl iodide and DBU[21] furnished the corresponding ester **3** (Scheme 1). The vinyl iodide was established by ozonolysis of the double bond

(12) (a) Wu, Y.; Esser, L.; De Brabander, J. K. *Angew. Chem.* **2000**, *112*, 4478−4480. (b) Fürstner, A.; Dierkes, T.; Thiel, O.; Blanda, G. *Chem.−Eur. J.* **2001**, *7*, 5286−5298. (c) Labrecque, D.; Charron, S.; Rej, R.; Blais, C.; Lamothe, S. *Tetrahedron Lett.* **2001**, *42*, 2645−2648. (d) Snider, B. B.; Song, F. *Org. Lett.* **2001**, *3*, 1817−1820. (e) Smith, A. B., III.; Zheng, J. *Synlett* **2001**, 1019−1023. (f) Smith, A. B., III.; Zheng, J. *Tetrahedron* **2002**, *58*, 6455−6471. (g) Wu, Y.; Liao, X.; Wang, R.; Xie, X.-S.; De Brabander, J. K. *J. Am. Chem. Soc.* **2002**, *124*, 3245−3253. (h) Holloway, G. A.; Hügel, H. M.; Rizzacasa, M. A. *J. Org. Chem.* **2003**, *68*, 2200−2204.

(13) (a) Bhattacharjee, A.; Seguil, O. R.; De Brabander, J. K. *Tetrahedron Lett.* **2001**, *42*, 1217−1220. (b) Lewis, A.; Stefanuti, I.; Swain, S. A.; Smith, S. A.; Taylor, R. J. K. *Tetrahedron Lett.* **2001**, *42*, 5549−5552. (c) Nicolaou, K. C.; Kim, D. W.; Baati, R. *Angew. Chem.* **2002**, *114*, 3853−3856. (d) Lewis, A.; Stefanuti, I.; Swain, S. A.; Smith, S. A.; Taylor, R. J. K. *Org. Biomol. Chem.* **2003**, *1*, 104−116.

(14) (a) Shen, R.; Lin, C. T.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2002**, *124*, 5650−5651. (b) Shen, R.; Lin, C. T.; Bowman, E. J.; Bowman, B. J.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2003,** *125*, 7889−7901.

(15) Wang, X.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2003**, *125*, 6040−6041.

(16) Salicylihalamide studies: (a) Fürstner, A.; Thiel, O. R.; Blanda, G. *Org. Lett.* **2000**, *2*, 3731−3734. (b) Feutrill, J. T.; Holloway, G. A.; Hilli, F.; Hügel, H. M.; Rizzacasa, M. A. *Tetrahedron Lett.* **2000**, *41*, 8569−8572. (c) Wu, Y.; Seguil, O.; De Brabander, J. K. *Org. Lett.* **2000**, *2*, 4241−4244. (d) Georg, G. I.; Ahn, Y. M.; Blackman, B.; Farokhi, F.; Flaherty, P. T.; Mossman, C. J.; Roy, S.; Yang, K. *J. Chem. Soc., Chem. Commun.* **2001**, 255−256. (e) Bauer, M.; Maier, M. E. *Org. Lett.* **2002**, *4*, 2205−2208.

(17) Apicularen studies: (a) Bhattacharjee, A.; De Brabander, J. K. *Tetrahedron Lett.* **2000**, *41*, 8069−8073. (b) Kühnert, S. M.; Maier, M. E. *Org. Lett.* **2002**, *4*, 643−646. (c) Hilli, F.; White, J. M.; Rizzacasa, M. A. *Tetrahedron Lett.* **2002**, *43*, 8507−8510. (d) Petri, A. F.; Kühnert, S. M.; Scheufler, F.; Maier, M. E. *Synthesis* **2003**, 940−955.

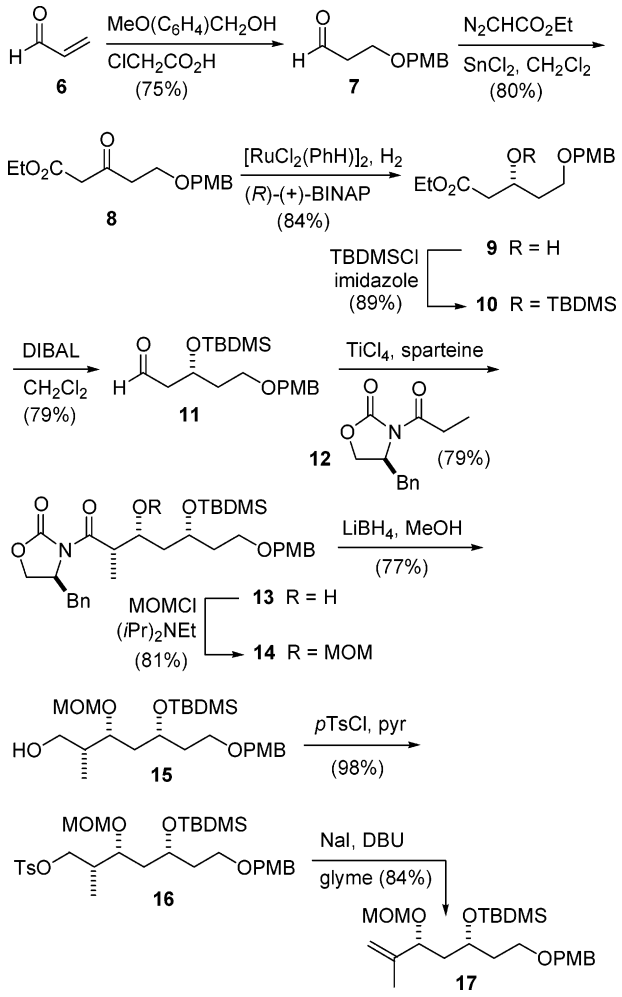
(18) Oximidine studies: (a) Scheufler, F.; Maier, M. E. *Synlett* **2001**, 1221−1224. (b) Coleman, R. S.; Garg, R. *Org. Lett.* **2001**, *3*, 3487−3490.

(19) Studies related to the enamide side chain: (a) Kuramochi, K.; Watanabe, H.; Kitahara, T. *Synlett* **2000**, 397−399. (b) Raw, S. A.; Taylor, R. J. K. *Tetrahedron Lett.* **2000**, *41*, 10357−10361. (c) Stefanuti, I.; Smith, S. A.; Taylor, R. J. K. *Tetrahedron Lett.* **2000**, *41*, 3737−3738. (d) Snider, B. B.; Song, F. *Org. Lett.* **2000**, *2*, 407−408. (e) Shen, R.; Porco, J. A., Jr. *Org. Lett.* **2000**, *2*, 1333−1336. (f) Fürstner, A.; Brehm, C.; Cancho-Grande, Y. *Org. Lett.* **2001**, *3*, 3955−3957.

(20) For some examples, see: (a) Sellés, P.; Lett, R. *Tetrahedron Lett.* **2002**, *43*, 4627−4631. (b) Liao, X.; Wu, Y.; De Brabander, J. K. *Angew. Chem.* **2003**, *115*, 1686−1690; *Angew. Chem., Int. Ed.* **2003**, *42*, 1648−1652. (c) Paterson, I.; De Savi, C.; Tudge, M. *Org. Lett.* **2001**, *3*, 213-216. (d) Smith, A. B., III.; Noda, I.; Remiszewski, S. W.; Liverton, N. J.; Zibuck, R. *J. Org. Chem.* **1990**, *55*, 3977−3979.

(21) Mal, D. *Synth. Commun.* **1986**, *16*, 331−335.

SCHEME 2. Synthesis of the 6-methylhept-6-enyl Ether 17



followed by the Takai reaction[22,12b] of the resulting aldehyde **4** providing the *E*-isomer **5** as the major product (E/Z = 5:1).

The synthesis of the aliphatic sector corresponding to **E** started with the C-3 aldehyde[23] **7** that can be attained by Michael addition of *p*-methoxy benzyl alcohol to acrolein (Scheme 2).[24] Chain extension with ethyl diazoacetate in the presence of tin(II) chloride furnished the 3-keto ester **8**.[25,26] By application of Noyori conditions and the use of (*R*)-(+)-BINAP as the chiral ligand, the keto group was reduced to the secondary alcohol **9** (84%, >90% enantiomeric excess (ee)).[27] Protection of the alcohol as *tert*-butyldimethylsilyl ether gave compound **10**. Reduction of the ester group with DIBAL secured the chiral aldehyde[12g] **11** in good overall yield. To establish the terminal alkenol subunit, the Evans strategy that we developed earlier was used.[16e,28] Accordingly, aldol reaction[29,30] of the chiral propionate **12** with aldehyde **11** using $TiCl_4$ (1.05 equiv) in the presence of sparteine (Crimmins variant)[31] (2.5 equiv) provided a high yield of the syn aldol product **13**. After protection of the resulting hydroxyl function as MOM ether, the chiral auxiliary was removed by treatment of **14** with $LiBH_4$ in methanol.[32] We found that these conditions work sometimes better than $NaBH_4$ in THF/H_2O.[33] To introduce the terminal double bond, the tosylate **16** was prepared by standard conditions. Elimination to give the alkene **17** could be smoothly accomplished by heating the tosylate **16** in glyme in the presence of NaI and DBU.

For the combination of the two fragments **5** and **17**, a Suzuki coupling[34] was employed (Scheme 3). First, the alkene was subjected to a diastereoselective hydroboration using 9-BBN (1.2 equiv) in THF. Subsequently, the solution of the intermediate borane was added to a solution of the vinyl iodide **5** in a mixture of DMF/water containing $PdCl_2$(dppf) as catalyst, Ph_3As as ligand, and $Cs_2(CO_3)$ as base.[35] Under these conditions, a 65% yield of the desired coupling product **18** could be secured. The coupling was accompanied by the iodide **19** (11%). Changing the base to NaOH and omitting Ph_3As gave similar results (63% of **18**, 9% of **19**). The stereochemical course of the hydroboration reaction was assumed to follow the Houk model (**F**, Scheme 3).[36] The hydroxy acid **21** that functions as a substrate for the macrolactonization was generated by cleavage of the silyl ether with TBAF giving the hydroxy ester **20**. Finally, basic hydrolysis of **20** provided the hydroxy acid **21**. During the workup of **21**, strong acid conditions have to be avoided. Otherwise, substantial amounts of the cyclic acetal **22** can be formed from the MOM protecting group. Initially, the Mitsunobu macrolactonization was run in solutions under high dilution (0.005 M). These conditions furnished a 25% yield of the macrolactone **23**. The yield could be improved by the use of immobilized triphenylphosphine.[37] This allowed the reaction to be run at a higher concentration (0.02 M) and led to a 43% yield. If, however, the azodicarboxylate was immobilized (5.0 equiv of polystyrene-DEAD resin, 1.3 equiv of PPh_3, THF, 0.01 M), no lactone could be observed. The NMR (^1H, ^{13}C) and other spectroscopic data are in full accord with the literature data.[12b,g]

(22) (a) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408−7410. (b) Okazoe, T.; Takai, K.; Utimoto, K. *J. Am. Chem. Soc.* **1987**, *109*, 951−953.

(23) Matsuda, F.; Kito, M.; Sakai, T.; Ojkada, N.; Miyashita, M.; Shirahama, H. *Tetrahedron* **1999**, *55*, 14369−14380.

(24) Wang, Y.; Farquhar, D. *J. Med. Chem.* **1991**, *34*, 197−203.

(25) Holmquist, C. R.; Roskamp, E. J. *J. Org. Chem.* **1989**, *54*, 3258−3260.

(26) For a related keto ester, see: Nakatsuka, M.; Ragan, J. A.; Sammakia, T.; Smith, D. B.; Uehling, D. E.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 5583−5601.

(27) (a) Kitamura, M.; Tokunaga, M.; Ohkuma, T.; Noyori, R. *Org. Synth.* **1992**, *71*, 1−13. (b) Kopecky, D. J.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2001**, *123*, 8420−8421.

(28) Phukan, P.; Bauer, M.; Maier, M. E. *Synthesis* **2003**, 1324−1328.

(29) (a) Gage, J. R.; Evans, D. A. *Org. Synth.* **1989**, *68*, 77−82. (b) Gage, J. R.; Evans, D. A. *Org. Synth.* **1989**, *68*, 83−91.

(30) For a review, see: Arya, P.; Qin, H. *Tetrahedron* **2000**, *56*, 917−947.

(31) Crimmins, M. T.; King, B. W.; Tabet, E. A.; Chaudhary, K. *J. Org. Chem.* **2001**, *66*, 894−902.

(32) Evans, D. A.; Gage, J. R.; Leighton, J. L. *J. Am. Chem. Soc.* **1992**, *114*, 9434−9453.

(33) Prashad, M.; Kim, H.-Y.; Lu, Y.; Liu, Y.; Har, D.; Repic, O.; Blacklock, T. J.; Giannousis, P. *J. Org. Chem.* **1999**, *64*, 1750−1753.

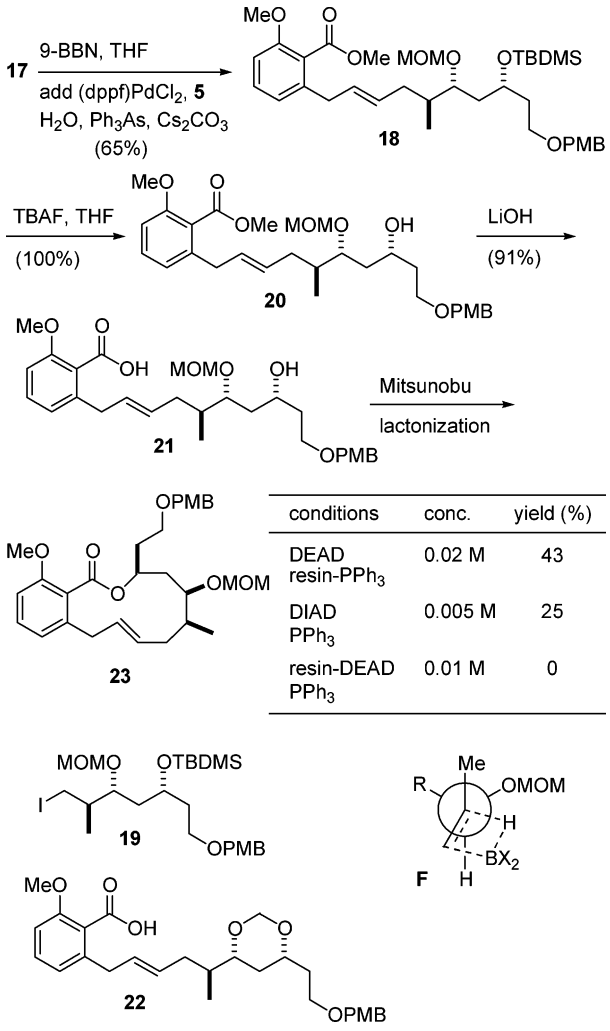
(34) (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483. (b) Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem.* **2001**, *113*, 4676−4701; *Angew. Chem., Int. Ed.* **2001**, *40*, 4544−4568.

(35) Trost, B. M.; Lee, C. *J. Am. Chem. Soc.* **2001**, *123*, 12191−12201.

(36) (a) Still, W. C.; Barrish, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 2487−2489. (b) Houk, K. N.; Rondan, N. G.; Wu, Y.-D.; Metz, J. T.; Paddon-Row, M. N. *Tetrahedron* **1984**, *40*, 2257−2274.

(37) Tunoori, A. R.; Dutta, D.; Georg, G. I. *Tetrahedron Lett.* **1998**, *39*, 8751−8754.

SCHEME 3. Combination of the Fragments 5 and 17 by Suzuki Cross-Coupling and Mitsunobu Lactonization of Hydroxy Acid 21



In summary, we present a synthesis of macrolactone **23** that represents a formal total synthesis of the salicylihalamides. Macrolactone **23** served as an advanced intermediate in the De Brabander[12a,g] and Fürstner[12b] syntheses. Our synthesis features an efficient synthesis of the chiral alkene **17**. The chiral centers were introduced by a Noyori reduction of a keto ester and an Evans aldol reaction on a derived aldehyde. This strategy also illustrates how the methyl-bearing stereocenter in a syn aldol product can be inverted by elimination and hydroboration. Finally, we demonstrated the advantage of using immobilized triphenylphosphine for the Mitsunobu lactonization in a complex setting.

Experimental Section

General. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$; chemical shifts are calibrated to the residual proton and carbon resonance of the solvent $CDCl_3$ (δ H 7.25 ppm, δ C 77.00 ppm). Atmospheric pressure ionization emission spectroscopy (API-ES) MS: Agilent 1100 Series LC/MSD. HRMS (EI): modified AMD Intectra MAT 711 A. HRMS (FT-ICR): Bruker Daltonic APEX 2 with ESI. Flash chromatography: silica gel 43−60 μm. Solvents were distilled prior to use; petroleum ether, with a boiling range of 40−60 °C, was used. The triphenylphosphine resin was obtained from Fluka.

Methyl 2-Allyl-6-methoxybenzoate (3). To a cooled (0 °C) solution of acid **2** (6.00 g, 31.2 mmol) in THF (150 mL) were added 1,8-diazabicyclo-[5.4.0]-undec-7-en (DBU) (4.70 mL, 4.75 g, 31.2 mmol) and iodomethane (5.85 mL, 13.3 g, 93.6 mmol), successively. After the mixture was stirred for 24 h at room temperature, the precipitate was removed by filtration over Celite and washed with Et_2O (100 mL). The filtrate was washed with H_2O (30 mL), dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography to yield 5.72 g (89%) of methyl ester **3** as a colorless oil. TLC (petroleum ether/EtOAc, 10:1): R_f = 0.41. IR (film): 1732, 1470, 1267 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.34 (d, J = 6.6 Hz, 2H), 3.80 (s, 3H), 3.87 (s, 3H), 5.01−5.08 (m, 2H), 5.83−5.94 (m, 1H), 6.78 (d, J = 8.3 Hz, 1H), 6.82 (d, J = 7.6 Hz, 1H), 7.27 (dd, J = 7.5, 8.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 37.6, 52.0, 55.8, 109.0 (C-5), 116.1, 121.6, 123.5, 130.4, 136.2, 138.5, 156.4, 168.5. MS (EI), m/z (%): 206 (51), 191 (24), 175 (100), 145 (26), 135 (99), 91 (27), 77 (43), 51 (17), 39 (11). HRMS (EI): $[M]^+$ calcd for $C_{12}H_{14}O_3$, 206.0943; found, 206.0928.

Methyl 2-Methoxy-6-(2-oxoethyl)benzoate (4). Ozone was passed through a solution of methyl 2-allyl-6-methoxybenzoate (**3**) (5.00 g, 31.2 mmol) in a 2:1 mixture of CH_2Cl_2/MeOH (300 mL) at −78 °C until a slight blue color persisted (∼1 h). The excess of ozone was removed by passing a stream of nitrogen gas through the solution. Subsequently, Me_2S (60 mL) was added at 0 °C and stirring was continued for 1 h at this temperature. The reaction mixture was washed with brine (2 × 100 mL), and the aqueous layer was extracted with CH_2Cl_2 (150 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated to yield 4.80 g (74%) of the crude aldehyde **4**, which was used for the Takai olefination without further purification. For analytical purposes, a small amount was purified by flash chromatography. TLC (petroleum ether/EtOAc, 1:1): R_f = 0.60. IR (film): 1729, 1586, 1268 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.61 (d, J = 2.0 Hz, 2H), 3.81 (s, 3H), 3.85 (s, 3H), 6.80 (d, J = 7.8 Hz, 1H), 6.88 (d, J = 8.3 Hz, 1H), 7.33 (dd, J = 7.8, 8.3 Hz, 1H), 9.64 (t, J = 2.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 48.3, 52.2, 55.9, 110.5, 122.8, 123.8, 131.2, 131.4, 157.2, 167.8, 198.4. MS (EI), m/z (%): 207 (3), 180 (40), 163 (9), 149 (58), 148 (100), 135 (42), 119 (11), 105 (17), 91 (22), 86 (29), 84 (48), 77 (25), 51 (28), 49 (58).

Methyl 2-[(2*E*)-3-Iodoprop-2-enyl]-6-methoxy-benzoate (5). To a vigorously stirred suspension of $CrCl_2$ (17.1 g, 139 mmol) in THF (350 mL) was added dropwise a solution of the crude aldehyde **4** (4.80 g, 23.1 mmol) and CHI_3 (18.2 g, 46.2 mmol) in THF (120 mL) at 0 °C. The red-brown mixture was stirred for another 12 h at 0 °C before it was diluted with Et_2O (250 mL) and washed with half-saturated aqueous $Na_2S_2O_3$ solution (100 mL). After separation of the layers, the aqueous phase was extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with H_2O (100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography to yield 5.37 g (70%) of the vinyl iodide **5** (E/Z = 5:1) as a slightly yellow oil. TLC (petroleum ether/Et_2O, 1:1): R_f = 0.64. IR (film): 1731, 1471, 1268 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.32 (dd, J = 1.5, 7.1 Hz, 2H), 3.80 (s, 3H), 3.88 (s, 3H), 6.08 (dt, J = 1.5, 14.4 Hz, 1H), 6.58 (dt, J = 7.1, 14.4 Hz, 1H), 6.78 (d, J = 7.8 Hz, 1H), 6.80 (d, J = 8.3 Hz, 1H), 7.28 (dd, J = 7.8, 8.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 39.6, 52.2, 55.9, 76.8, 109.5, 121, 123.4, 130.7, 136.6, 143.4, 156.7, 168.2. MS (EI), m/z (%): 332 (20), 301 (10), 205 (58), 173 (85), 127 (23), 115 (100), 77 (23), 51 (16). HRMS (EI): $[M]^+$ calcd for $C_{12}H_{13}IO_3$, 331.9910; found, 331.9921.

3-[(4-Methoxybenzyl)oxy]propanal (7). A solution of *p*-methoxybenzyl alcohol (18.0 mL, 20.0 g, 0.14 mol), monochloroacetic acid (0.82 g, 8.69 mmol), and NaOH (0.35 g, 8.69 mmol) in H_2O (1.8 mL) was added dropwise, with stirring over 5 min, to acrolein (12.0 mL, 10.2 g, 0.18 mol). Subsequently, acetic acid (3.64 mL, 3.83 g, 63.7 mmol) was added, and the

solution was maintained at 40 °C for 6 days. After the solution cooled to room temperature, the reaction mixture was diluted with CH_2Cl_2 (500 mL) and washed with H_2O (3 × 150 mL). The organic layer was dried ($MgSO_4$), filtered, and evaporated. Volatile starting materials and byproducts were removed by vacuum distillation at 120 °C (1.0 mm Hg), which left aldehyde **7** as light brown viscous oil, yielding 20.9 g (75%). Because it appeared homogeneous by TLC and NMR analysis, it was used for subsequent reactions without further purification. For analytical purposes, a small amount was purified by flash chromatography (diethyl ether). TLC (diethyl ether): $R_f = 0.68$. IR (film): 1724, 1612, 1514, 1248 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.66 (t, J = 6.1 Hz, 2H), 3.77 (t, J = 6.1 Hz, 2H), 3.79 (s, 3H), 4.45 (s, 2H), 6.87 (d, J = 8.6 Hz, 2H), 7.24 (d, J = 8.6 Hz, 2H), 9.77 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 43.8, 55.2, 63.4, 72.8, 113.7, 129.3, 129.8, 159.2, 201.2. MS (EI), *m*/*z* (%): 194 (12), 138 (8), 137 (90), 136 (6), 135 (8), 122 (10), 121 (100), 109 (14), 94 (7), 91 (8), 89 (7), 78 (8), 77 (16), 51 (4). HRMS (EI): $[M]^+$ calcd for $C_{11}H_{14}O_3$, 194.0943; found, 194.0951.

Ethyl 5-[(4-Methoxybenzyl)oxy]-3-oxopentanoate (8). Ethyl diazoacetate (617 mg, 5.41 mmol) was added with stirring at room temperature to a solution of anhydrous tin(II) chloride (98 mg, 0.52 mmol) in CH_2Cl_2 (10 mL). A few drops of aldehyde **7** (1.0 g, 5.15 mmol) in CH_2Cl_2 (5 mL) were added to the suspension. After nitrogen evolution had begun, the remaining aldehyde solution was added dropwise over 10 min. The solution continued to be stirred until the evolution of nitrogen had stopped (~1 h), and then the mixture was transferred to a separatory funnel containing saturated brine (20 mL) and diethyl ether (60 mL). After separation of the layers, the aqueous phase was extracted with diethyl ether (2 × 80 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated. Flash chromatography of the remaining oil provided the β-keto ester **8**, yielding 1.16 g (80%) of a slightly yellow oil, keto−enol mixture. TLC (petroleum ether/EtOAc, 2:1): $R_f = 0.46$. IR (film): 1744, 1717, 1514, 1248 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, data for keto isomer): δ 1.26 (t, J = 7.1 Hz, 3H), 2.81 (t, J = 6.2 Hz, 2H), 3.47 (s, 2H), 3.72 (t, J = 6.2 Hz, 2H), 3.80 (s, 3H), 4.18 (q, J = 7.1 Hz, 2H), 4.43 (s, 2H), 6.87 (d, J = 8.6 Hz, 2H), 7.24 (d, J = 8.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 43.0, 49.6, 55.2, 61.3, 64.6, 72.8, 113.7, 129.3, 129.9, 159.2, 167.0, 201.4. MS (EI), *m*/*z* (%): 262 (10), 206 (4), 205 (9), 189 (8), 176 (6), 138 (7), 137 (50), 136 (7), 135 (12), 122 (9), 121 (100), 109 (7), 99 (5), 91 (5), 78 (5), 77 (8), 73 (14), 57 (4), 45 (4). HRMS (ESI): $[M + Na]^+$ calcd for $C_{15}H_{20}NaO_5$, 303.1203; found, 303.1203.

Ethyl (3*R*)-3-Hydroxy-5-[(4-methoxybenzyl)oxy]pentanoate (9). Dry, degassed DMF (3 mL) was added to a flask containing benzeneruthenium(II) chloride dimer (45 mg, 0.09 mmol) and (*R*)-(+)-BINAP (112 mg, 0.18 mmol). The slurry was heated to 90 °C with stirring for 20 min. The reddish-brown solution was allowed to cool to room temperature and was then added via cannula to a Parr flask containing a degassed solution of β-keto ester **8** (8.4 g, 30.0 mmol) in dry ethanol (15 mL). The hydrogenation flask was flushed a few times with hydrogen and then pressurized with 4.0 bar hydrogen at 90 °C and vigorous shaking for 20 h. After the solution cooled to room temperature, the dark-red solution was concentrated in vacuo and purified by flash chromatography to provide the 3-hydroxy ester **9** (7.1 g, 84%, >90% ee) as a pale-yellow liquid. TLC (petroleum ether/EtOAc, 2:1): R_f = 0.29. $[\alpha]^{23}_D = -3.8$ (*c* 1.00, CH_2Cl_2). IR (film): 3489, 1732, 1514, 1249 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.26 (t, J = 7.1 Hz, 3H), 1.72−1.84 (m, 2H), 2.47 (d, J = 6.3 Hz, 2H), 3.36 (s, br, 1H), 3.58−3.69 (m, 2H), 3.79 (s, 3H), 4.15 (q, J = 7.1 Hz, 2H), 4.17−4.26 (m, 1H), 4.44 (s, 2H), 6.87 (d, J = 8.6 Hz, 2H), 7.24 (d, J = 8.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 36.0, 41.6, 55.2, 60.5, 67.0, 67.6, 72.8, 113.8, 129.2, 130.1, 159.2, 172.4. MS (EI), *m*/*z* (%): 176 (5), 139 (7), 138 (75), 137 (100), 135 (16), 121 (75), 109 (52), 107 (16), 105 (11), 94 (26), 91 (12), 79 (13), 78 (13), 77 (33), 65 (8), 51 (8), 39 (8). HRMS (ESI): $[M + Na]^+$ calcd for $C_{36}H_{56}NaO_8Si$, 305.1365; found, 305.1362.

The ee determination was performed by HPLC using a CHIRA-GROM 4 column, 8 μm, 60 × 2 mm, Part No. GS CH40891K0602 (corresponds to CHIRACEL AS), eluent, *n*-heptane/2-propanol (96:4); flow, 0.1 mL min^{-1}; retention times, major 35.5 min, minor 46.9 min.

Ethyl (3*R*)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-5-[(4-methoxybenzyl)oxy]pentanoate (10). A stirred solution of 3-hydroxy ester **9** (6.70 g, 23.7 mmol), imidazole (4.04 g, 59.3 mmol), and DMAP (145 mg, 1.19 mmol) in dry dimethylformamide (100 mL) was treated with *tert*-butyldimethylsilyl chloride (5.37 g, 35.6 mmol). The resulting solution was stirred at ambient temperature for 48 h, diluted with water, and extracted with ether (3 × 100 mL). The combined extracts were dried with Na_2SO_4, filtered, and concentrated. Purification of the residue by flash chromatography gave 8.33 g (89%) of the silyl ether **10** as a colorless oil. TLC (petroleum ether/EtOAc, 5:1): $R_f = 0.76$. $[\alpha]^{23}_D = -2.5$ (*c* 1.11, CH_2Cl_2). IR (film): 1737, 1514, 1250, 1097 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.03, 0.04 (2 s, 3H each), 0.85 (s, 9H), 1.24 (t, J = 7.1 Hz, 3H), 1.81 (td, J = 6.3, 6.1 Hz, 2H), 2.45 (d, J = 6.2 Hz, 2H), 3.51 (t, J = 6.3 Hz, 1H), 3.79 (s, 3H), 4.10 (q, J = 7.1 Hz, 2H), 4.28 (tt, J = 6.2, 6.1 Hz, 1H), 4.38 (d, J = 11.6 Hz, 1H), 4.42 (d, J = 11.6 Hz, 1H), 6.86 (d, J = 8.6 Hz, 2H), 7.24 (d, J = 8.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ −4.8, −4.7, 14.2, 17.9, 25.7, 37.4, 43.0, 55.2, 60.2, 66.2, 66.98, 72.5, 113.7, 129.2, 130.6, 159.1, 171.6. MS (EI), *m*/*z* (%): 196 (6), 195 (36), 143 (5), 122 (13), 121 (100), 91 (7), 77 (9), 57 (5). HRMS (ESI): $[M + Na]^+$ calcd for $C_{21}H_{36}NaO_5Si$, 419.2224; found, 419.2220.

(3*R*)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-5-[(4-methoxybenzyl)oxy]pentanal (11). To a stirred solution of ester **10** (7.06 g, 17.76 mmol) in dry CH_2Cl_2 (200 mL) was added DIBAH (1.0 M in hexane, 20.4 mL) dropwise over 30 min at −78 °C. After the mixture was stirred for 3.5 h at −78 °C, methanol (5 mL) was added, the cooling bath was removed, and the mixture was warmed to room temperature. Then water (30 mL) was added, and the mixture was extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with water (30 mL) and brine (30 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography (petroleum ether/Et_2O, 2:1) to yield 4.95 g (79%) of aldehyde **11** as a pale-yellow oil. TLC (petroleum ether/EtOAc, 5:1): $R_f = 0.70$. $[\alpha]_D = +7.1$ (*c* 1.00, CH_2Cl_2). IR (film): 1726, 1613, 1514, 1250 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.05, 0.06 (2 s, 3H each), 0.86 (s, 9H), 1.76−1.89 (m, 2H), 2.47−2.60 (m, 2H), 3.50 (t, J = 6.3 Hz, 1H), 3.79 (s, 3H), 4.33−4.39 (m, 1H), 4.37 (d, J = 11.4 Hz, 1H), 4.42 (d, J = 11.4 Hz, 1H), 6.87 (d, J = 8.6 Hz, 2H), 7.23 (d, J = 8.6 Hz, 2H), 9.78 (t, J = 2.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ −4.7, −4.6, 17.9, 25.7, 37.6, 51.0, 55.2, 65.6, 66.0, 72.6, 113.8, 129.2, 130.4, 159.2, 202.0. MS (EI), *m*/*z* (%): 137 (7), 136 (16), 135 (25), 131 (34), 122 (12), 121 (100), 101 (15), 83 (7), 77 (10), 75 (24), 59 (8). HRMS (ESI): $[M + Na]^+$ calcd for $C_{19}H_{32}NaO_4Si$, 375.1962; found, 375.1968.

(4*R*)-4-Benzyl-3-{(2*R*,3*R*,5*R*)-5-{[*tert*-butyl(dimethyl)silyl]oxy}-3-hydroxy-7-[(4-methoxybenzyl)oxy]-2-methylheptanoyl}-1,3-oxazolidin-2-one (13). To a stirred, cooled (0 °C) solution of (4*S*)-4-(phenylmethyl)-3-propanoyl-1,3-oxazolidin-2-one (**12**) (2.86 g, 12.3 mmol) in CH_2Cl_2 (100 mL) was added dropwise titanium(IV) chloride (1.42 mL, 2.44 g, 12.9 mmol), and the mixture was allowed to stir for 5 min. Subsequently, (−)-sparteine (7.04 mL, 7.19 g, 30.7 mmol) was added to the yellow slurry. The dark-red enolate solution was stirred for 20 min at 0 °C before a solution of aldehyde **11** (4.76 g, 13.5 mmol) in CH_2Cl_2 (50 mL) was added dropwise and the mixture stirred for 1 h at 0 °C. The reaction was quenched with half-saturated ammonium chloride (20 mL). After separation of the layers, the organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification of the residue by flash chromatography afforded 5.67 g (79%) of the desired product **13** as a colorless oil. TLC (petroleum ether/Et_2O, 2:3): $R_f = 0.33$. $[\alpha]^{23}_D = +44.0$ (*c* 1.00, CH_2Cl_2). IR (film): 3529, 1783, 1696, 1513 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.06, 0.07 (2

s, 3H each), 0.86 (s, 9H), 1.24 (d, J = 6.8 Hz, 3H), 1.47−1.63 (m, 1H), 1.65−1.75 (m, 1H), 1.76−1.94 (m, 2H), 2.76 (dd, J = 13.3, 9.7 Hz, 1H), 3.21−3.28 (m, 2H), 3.46−3.58 (m, 2H), 3.69−3.75 (m, 1H), 3.78 (s, 3H), 4.01−4.11 (m, 2H), 4.13−4.19 (m, 2H), 4.38 (d, J = 11.4 Hz, 1H), 4.42 (d, J = 11.4 Hz, 1H), 4.60−4.69 (m, 1H), 6.86 (d, J = 8.6 Hz, 2H), 7.16−7.21 (m, 2H), 7.21−7.29 (m, 3H), 7.29−7.36 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ −4.6, −4.5, 11.0, 17.9, 25.8, 37.1, 37.7, 40.8, 42.8, 55.2, 66.1, 66.3, 69.2, 69.8, 72.6, 113.7, 127.3, 128.9, 129.2, 129.4, 130.5, 135.1, 153.0, 159.1, 176.6. MS (EI), m/z (%): 233 (12), 148 (5), 142 (12), 122 (8), 121 (100), 91 (22), 57 (70). HRMS (ESI): $[M + Na]^+$ calcd for $C_{32}H_{47}NNaO_7Si$, 608.3014; found, 608.3024.

(4*R*)-4-Benzyl-3-[(2*R*,3*R*,5*R*)-5-{[*tert*-butyl(dimethyl)silyl]oxy}-7-[(4-methoxybenzyl)oxy]-3-(methoxymethoxy)-2-methylheptanoyl]-1,3-oxazolidin-2-one (14). To a stirred, cooled (0 °C) solution of alcohol **13** (4.01 g, 6.85 mmol) in CH_2Cl_2 (90 mL) were added *N*,*N*-diisopropylethylamine (15.4 mL, 11.6 g, 90.0 mmol), chloromethylmethyl ether (3.42 mL, 3.62 g, 45.0 mmol), and tetrabutylammonium iodide (665 mg, 1.80 mmol). The reaction mixture was protected from light and allowed to reach room temperature within 12 h. After 3 days, saturated aqueous $NaHCO_3$ solution (100 mL) was added followed by Et_2O (150 mL). The organic layer was washed with 1 N HCl (50 mL) and brine (30 mL), and the basic aqueous layer was extracted with Et_2O (2 × 50 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo. Flash chromatography of the residue provided the MOM ether **14** as a slightly yellow oil, yield 3.48 g (81%). TLC (petroleum ether/EtOAc, 2:1): R_f = 0.60. $[\alpha]^{23}_D$ = +69.8 (c 1.54, CH_2Cl_2). IR (film): 1781, 1700, 1514 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.03, 0.06 (2 s, 3H each), 0.87 (s, 9H), 1.20 (d, J = 6.8 Hz, 3H), 1.61−1.74 (m, 2H), 1.74−1.84 (m, 1H), 1.86−1.97 (m, 1H), 2.76 (dd, J = 13.3, 9.7 Hz, 1H), 3.23−3.34 (m, 4H), 3.53 (t, J = 6.32 Hz, 2H), 3.77 (s, 3H), 3.81−3.89 (m, 1H), 3.91−4.02 (m, 2H), 4.10−4.16 (m, 2H), 4.37 (d, J = 11.4 Hz, 1H), 4.42 (d, J = 11.4 Hz, 1H), 4.51−4.64 (m, 3H), 6.85 (d, J = 8.6 Hz, 2H), 7.17−7.22 (m, 2H), 7.22−7.28 (m, 3H), 7.28−7.36 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ −4.8, −4.4, 12.0, 18.0, 25.8, 36.4, 37.7, 41.3, 41.8, 55.2, 55.8, 56.2, 66.0, 66.6, 66.6, 72.5, 76.4, 96.6, 113.6, 127.3, 128.9, 129.2, 129.4, 130.7, 135.4, 153.2, 159.0, 174.7. MS (EI), m/z (%): 233 (10), 182 (7), 149 (8), 142 (16), 135 (10), 122 (17), 121 (100), 92 (16), 85 (54), 83 (78), 57 (70), 45 (41). HRMS (ESI): $[M + Na]^+$ calcd for $C_{34}H_{51}NNaO_8Si$, 652.3276; found, 652.3278.

(2*S*,3*R*,5*R*)-5-{[*tert*-Butyl(dimethyl)silyl]oxy}-7-[(4-methoxybenzyl)oxy]-3-(methoxymethoxy)-2-methylheptan-1-ol (15). To a stirred, cooled (0 °C) solution of **14** (500 mg, 0.79 mmol) in THF (10 mL) was added methanol (0.13 mL, 102 mg, 3.17 mmol) followed by $LiBH_4$ (2.0 M in THF, 1.98 mL, 3.96 mmol). The reaction mixture was stirred at 0 °C for 5 min, allowed to warm to room temperature, and stirred overnight. The reaction was quenched by addition of saturated aqueous NH_4Cl solution (10 mL), and the mixture was stirred for 1 h followed by extraction with EtOAc (3 × 20 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (15 mL) and brine (15 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude alcohol **15** was purified by flash chromatography to give 280 mg (77%) of the alcohol **15** as a colorless oil. TLC (petroleum ether/EtOAc, 2:1): R_f = 0.40. $[\alpha]^{23}_D$ = −9.4 (c 1.54, CH_2Cl_2). IR (film): 3466, 1613, 1514, 1250 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.04, 0.05 (2 s, 3H each), 0.79 (d, J = 7.1 Hz, 3H), 0.87 (s, 9H), 1.58−1.68 (m, 1H), 1.68−1.78 (m, 2H), 1.78−1.87 (m, 1H), 1.88−1.99 (m, 1H), 2.69 (dd, J = 7.5, 4.7 Hz, 1H), 3.35 (s, 3H), 3.46−3.54 (m, 3H), 3.56−3.64 (m, 1H), 3.75−3.84 (m, 4H), 3.88−3.96 (m, 1H), 4.37 (d, J = 11.4 Hz, 1H), 4.42 (d, J = 11.4 Hz, 1H), 4.59 (d, J = 6.6 Hz, 1H), 4.63 (d, J = 6.6 Hz, 1H), 6.86 (d, J = 8.6 Hz, 2H), 7.23 (d, J = 8.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ −4.6, −4.4, 11.04, 18.0, 25.9, 37.0, 37.7, 39.1, 55.3, 55.9, 65.3, 66.6, 66.9, 72.6, 76.7, 96.4, 113.7, 129.3, 130.6, 159.1. MS (EI), m/z (%): 309 (5), 279 (14), 275 (7), 247 (12), 215 (6), 199 (11), 189 (27), 176 (12), 145 (20), 137 (27), 135 (25), 131 (22), 123 (17), 122 (100), 101 (17), 99 (15), 91 (20), 89 (28), 77 (19), 75 (32), 73 (38), 59 (13), 57 (9), 45 (66). HRMS (ESI): $[M + Na]^+$ calcd for $C_{24}H_{44}NaO_6Si$, 479.2799; found, 479.2794.

(2*S*,3*R*,5*R*)-5-{[*tert*-Butyl(dimethyl)silyl]oxy}-7-[(4-methoxybenzyl)oxy]-3-(methoxymethoxy)-2-methylheptyl 4-methylbenzenesulfonate (16). To a stirred solution of alcohol **15** (1.18 g, 2.58 mmol) in pyridine (5 mL) was added *p*-toluenesulfonyl chloride (1.48 g, 7.75 mmol) at 0 °C. After the solution was stirred for 2 h, the reaction was quenched by addition of ice (0.5 g) and water (10 mL). The mixture was diluted with Et_2O (50 mL) and washed with 1 N HCl (20 mL), saturated $NaHCO_3$ solution (10 mL), and brine (10 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. Filtration of the residue over a short pad of silica gel and evaporation of the solvent gave the pure tosylate **16** as a slightly yellow oil, yield 1.54 g (98%). TLC (petroleum ether/EtOAc, 2:1): R_f = 0.76. $[\alpha]^{23}_D$ = +7.7 (c 1.46, CH_2Cl_2). IR (film): 1613, 1514, 1363, 1250, 1177 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.01, 0.02 (2 s, 3H each), 0.81 (d, J = 13.9 Hz, 3H), 0.84 (s, 9H), 1.53−1.62 (m, 2H), 1.63−1.78 (m, 2H), 2.00−2.08 (m, 1H), 2.42 (s, 3H), 3.23 (s, 3H), 3.47 (t, J = 6.3 Hz, 2H), 3.60−3.66 (m, 1H), 3.78 (s, 3H), 3.81−3.90 (m, 2H), 4.06 (dd, J = 9.4, 6.3 Hz, 1H), 4.36 (d, J = 11.4 Hz, 1H), 4.40 (d, J = 11.4 Hz, 1H), 4.46 (d, J = 6.6 Hz, 1H), 4.50 (d, J = 6.6 Hz, 1H), 6.85 (d, J = 8.6 Hz, 2H), 7.22 (d, J = 8.6 Hz, 2H), 7.31 (d, J = 8.2 Hz, 2H), 7.77 (d, J = 8.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ −4.7, −4.6, 10.9, 17.6, 21.5, 25.7, 36.1, 36.8, 38.8, 55.1, 55.6, 66.4, 66.7, 72.3, 72.5, 75.0, 96.1, 113.6, 127.8, 129.1, 129.7, 130.5, 133.0, 144.6, 159.02. MS (EI), m/z (%): 189 (16), 148 (15), 147 (100), 121 (8), 73 (9). HRMS (ESI): $[M + Na]^+$ calcd for $C_{31}H_{50}NaO_8SSi$, 633.2888; found, 633.2885.

1-({[(3*R*,5*R*)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-5-(methoxymethoxy)-6-methylhept-6-enyl]oxy}methyl)-4-methoxybenzene (17). A mixture of tosylate **16** (1.30 g, 2.13 mmol), NaI (797 mg, 5.32 mmol), and DBU (1.60 mL, 1.62 g, 10.6 mmol) in glyme (40 mL) was refluxed with stirring for 3 h. After that, the solution was cooled to room temperature, diluted with Et_2O (80 mL), and washed with saturated $NaHCO_3$ solution (15 mL), 1 N HCl (15 mL), and brine (15 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. Filtration of the residue over a short pad of silica gel gave 783 mg of the pure alkene **17** in 84% yield as a slightly yellow oil. TLC (petroleum ether/EtOAc, 5:1): R_f = 0.76. $[\alpha]^{23}_D$ = +64.7 (c 1.25, CH_2Cl_2). IR (film): 3073, 1650, 1613, 1514, 1249 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.04, 0.05 (2 s, 3H each), 0.88 (s, 9H), 1.57−1.68 (m, 4H), 1.69−1.94 (m, 3H), 3.32 (s, 3H), 3.53 (t, J = 6.6 Hz, 2H), 3.79 (s, 3H), 3.92−3.99 (m, 1H), 4.12 (dd, J = 8.3, 5.0 Hz, 1H), 4.36−4.46 (m, 3H), 4.57 (d, J = 6.6 Hz, 1H), 4.91 (s, 2H), 6.87 (d, J = 8.6 Hz, 2H), 7.24 (d, J = 8.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ −4.6, −4.4, 16.8, 18.0, 25.9, 36.7, 41.7, 55.2, 55.6, 66.6, 66.8, 72.6, 76.6, 93.4, 113.6, 114.0, 130.7, 143.9, 159.0. MS (EI), m/z (%): 389 (4), 357 (5), 245 (9), 199 (6), 189 (9), 176 (11), 147 (10), 145 (11), 137 (27), 135 (31), 131 (27), 122 (83), 121 (100), 89 (29), 75 (23), 73 (24), 59 (9), 45 (55). HRMS (ESI): $[M + Na]^+$ calcd for $C_{24}H_{42}NaO_5Si$, 461.2694; found, 461.2694.

Methyl 2-[(2*E*,5*S*,6*R*,8*R*)-8-{[*tert*-Butyl(dimethyl)silyl]oxy}-10-[(4-methoxybenzyl)oxy]-6-(methoxymethoxy)-5-methyldec-2-enyl]-6-methoxybenzoate (18). To a solution of alkene **17** (720 mg, 1.64 mmol) in THF (16 mL) was added 9-BBN (0.5 M solution in THF, 3.93 mL, 1.97 mmol), and the reaction was stirred for 4 h at room temperature. In a separate flask, to a solution of vinyl iodide **5** (653 mg, 1.97 mmol) were added Cs_2CO_3 powder (1.16 g, 3.28 mmol), $AsPh_3$ (25 mg, 0.082 mmol), $PdCl_2$(dppf) (67 mg, 0.082 mmol), and H_2O (0.88 mL, 49.1 mmol) successively under vigorous stirring. This mixture was stirred for 5 min before the borane solution was added to it. After the solution was stirred for 12 h, the reaction mixture was diluted with saturated aqueous NH_4Cl. The mixture was

extracted with CH_2Cl_2 (3 × 30 mL), and the organic layer was washed with H_2O (20 mL) and brine (10 mL), dried with $MgSO_4$, filtered, and concentrated. Purification of the residue by flash chromatography (CH_2Cl_2/acetone, 30:1) afforded coupling product **18**, yielding 687 mg (65%) as a slightly yellow oil. TLC (CH_2Cl_2/acetone, 30:1): R_f = 0.44. $[\alpha]^{23}_D$ = +20.6 (*c* 1.49, CH_2Cl_2). IR (film): 1733, 1514, 1471 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.01, 0.03 (2 s, 3H each), 0.81−0.89 (m, 12H), 1.42−1.52 (m, 1H), 1.53−1.68 (m, 2H), 1.71−1.89 (m, 2H), 1.93−2.07 (m, 2H), 3.26 (d, *J* = 6.1 Hz, 2H), 3.29 (s, 3H), 3.44−3.53 (m, 3H), 3.75 (s, 3H), 3.77 (s, 3H), 3.85 (s, 3H), 3.90−4.02 (m, 1H), 4.35 (d, *J* = 11.6 Hz, 1H), 4.39 (d, *J* = 11.6 Hz, 1H), 4.52−4.59 (m, 2H), 5.33−5.43 (m, 1H), 5.44−5.54 (m, 1H), 6.73 (d, *J* = 8.3 Hz, 1H), 6.79 (d, *J* = 7.8 Hz, 1H), 6.83 (d, *J* = 8.6 Hz, 2H), 7.18−7.26 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ −4.8, −4.4, 14.1, 18.0, 25.9, 35.7, 36.3, 36.4, 36.6, 38.2, 52.0, 55.2, 55.7, 55.9, 66.7, 67.1, 72.5, 78.1, 95.7, 108.8, 113.7, 121.5, 123.4, 129.1, 129.2, 130.4, 130.7, 130.8, 139.3, 156.4, 159.1, 168.5. MS (EI), *m*/*z* (%): 121 (8), 88 (10), 86 (64), 84 (100), 49 (13), 47 (17). HRMS (ESI): [M + Na]$^+$ calcd for $C_{36}H_{56}NaO_8$-Si, 667.3637; found, 667.3636.

As a byproduct, iodide **19** was isolated. This compound does contain some unreacted alkene **17** (123 mg, 3.9:1 molar ratio, colorless oil). TLC (petroleum ether/EtOAc, 5:1): R_f = 0.74. IR (film): 1613, 1513, 1250 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.04, 0.05 (2 s, 3H each), 0.87 (s, 9H), 0.98 (d, *J* = 6.8 Hz, 3H), 1.50−1.94 (m, 4H), 1.97−2.08 (m, 1H), 2.93−3.05 (m, 1H), 3.31−3.42 (m, 4H), 3.47−3.55 (m, 2H), 3.63−3.74 (m, 1H), 3.80 (s, 3H), 3.87−3.99 (m, 1H), 4.36−4.46 (m, 2H), 4.55−4.65 (m, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 7.24 (d, *J* = 8.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ −4.6, −4.3, 11.4, 15.3, 18.0, 25.87, 36.8, 38.8, 40.3, 55.3, 55.8, 66.5, 66.8, 72.6, 77.8, 96.4, 113.7, 129.3, 130.6, 159.1. MS (EI), *m*/*z* (%): 389 (8), 357 (9), 189 (11), 137 (29), 121 (100), 89 (18), 77 (12), 75 (14), 45 (51). MS (FD), *m*/*z* (%): 438.0 (100), 565.9 (69).

Methyl 2-[(2*E*,5*S*,6*R*,8*R*)-8-Hydroxy-10-[(4-methoxybenzyl)oxy]-6-(methoxymethoxy)-5-methyldec-2-enyl]-6-methoxybenzoate (20). To a solution of **18** (355 mg, 0.55 mmol) in THF (5.5 mL) was added TBAF (1 M in THF, 1.65 mL, 1.65 mmol) at 0 °C. After the mixture was stirred for 2 days, saturated aqueous $NaHCO_3$ solution (10 mL) was added and the mixture extracted with Et_2O (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated. Flash chromatography of the residue gave 296 mg (100%) of the desired alcohol **20** as a colorless oil. TLC (Et_2O): R_f = 0.55. $[\alpha]^{23}_D$ = +15.9 (*c* 1.27, CH_2Cl_2). IR (film): 3514, 1732, 1513, 1471 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.86 (d, *J* = 6.6 Hz, 3H), 1.43−1.53 (m, 1H), 1.53−1.66 (m, 1H), 1.66−1.75 (m, 2H), 1.75−1.90 (m, 2H), 1.91−2.02 (m, 1H), 3.27 (d, *J* = 6.1 Hz, 2H), 3.36 (s, 3H), 3.50−3.72 (m, 4H), 3.78 (s, 3H), 3.80 (s, 3H), 3.87 (s, 3H), 3.87−3.94 (m, 1H), 4.43 (s, 2H), 4.60 (d, *J* = 6.8 Hz, 1H), 4.68 (d, *J* = 6.8 Hz, 1H), 5.34−5.44 (m, 1H), 5.44−5.54 (m, 1H), 6.75 (d, *J* = 8.3 Hz 1H), 6.80 (d, *J* = 7.6 Hz, 1H) 6.86 (d, *J* = 8.6 Hz, 2H), 7.21−7.28 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7, 35.8, 36.0, 36.4, 36.4, 36.8, 52.1, 55.2, 55.9, 55.9, 67.8, 69.4, 72.8, 80.6, 95.5, 108.8, 113.8, 121.5, 123.3, 129.3, 129.4, 130.4, 130.4, 131.0, 139.2, 156.4, 159.2, 168.6. MS (EI), *m*/*z* (%): 149 (4), 135 (8), 121 (11), 109 (6), 107 (5), 77 (7), 57 (5), 44 (100). HRMS (ESI): [M + Na]$^+$ calcd for $C_{30}H_{42}NaO_8$, 553.2772; found, 553.2773.

2-[(2*E*,5*S*,6*R*,8*R*)-8-Hydroxy-10-[(4-methoxybenzyl)oxy]-6-(methoxymethoxy)-5-methyldec-2-enyl]-6-methoxybenzoic acid (21). A solution of methyl ester **20** (121 mg, 0.23 mmol) in a mixture of THF (2 mL), EtOH (4 mL), and H_2O (4 mL) was treated with $LiOH\cdot H_2O$ (96 mg, 2.28 mmol), and the mixture was stirred at 70 °C for 3 days. After the mixture cooled to room temperature, it was diluted with Et_2O (30 mL) and water (20 mL). The organic layer, containing unreacted starting material and side products, was separated. The aqueous layer was acidified (pH ∼ 3) by addition of hydrochloric acid (1 M solution, 2.2 mL) and extracted with EtOAc (3 × 25 mL). The combined extracts were washed with water (10 mL), dried ($MgSO_4$), filtered, and concentrated to give 107 mg (91%) of the desired acid **21** as a slightly yellow oil. TLC (petroleum ether /EtOAc, 1:3): R_f = 0.58. $[\alpha]^{23}_D$ = +25.4 (*c* 1.15, CH_2Cl_2). IR (film): 3447, 1726, 1584, 1512, 1472 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.83 (d, *J* = 6.1 Hz, 3H), 1.46−1.62 (m, 2H), 1.66−1.84 (m, 3H), 1.85−2.00 (m, 2H), 1.91−2.02 (m, 1H), 3.35−3.45 (m, 4H), 3.45−3.71 (m, 4H), 3.74−3.80 (m, 5H), 3.82 (s, 3H), 3.88−3.95 (m, 1H), 4.45 (s, 2H), 4.61 (d, *J* = 6.9 Hz, 1H), 4.77 (d, *J* = 6.9 Hz, 1H), 5.34−5.43 (m, 1H), 5.44−5.54 (m, 1H), 6.75−6.83 (m, 2H), 6.85 (d, *J* = 8.3 Hz, 2H), 7.22−7.26 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 35.2, 35.5, 36.4, 36.6, 37.1, 55.3, 55.7, 56.0, 67.7, 69.5, 72.8, 78.3, 94.2, 109.2, 113.8, 122.6, 122.8, 129.4, 129.6, 129.8, 130.1, 130.7, 139.8, 156.8, 159.2, 169.1. MS (EI), *m*/*z* (%): 345 (4), 199 (4), 187 (8), 177 (7), 164 (7), 162 (7), 156 (7), 137 (14), 135 (9), 122 (13), 121 (100), 77 (4), 45 (14). HRMS (ESI): [M + Na]$^+$ calcd for $C_{29}H_{40}NaO_8$, 539.2615; found, 539.2616.

Data for Acetal 22. Colorless oil, TLC (petroleum ether/EtOAc, 1:3): R_f = 0.54. IR (film): 1783, 1730 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.82 (d, *J* = 6.8 Hz, 3H), 1.29−1.38 (m, 1H), 1.44−1.55 (m, 1H), 1.58−1.69 (m, 1H), 1.69−179 (m, 1H), 1.79−1.96 (m, 2H), 2.17−2.28 (m, 1H), 1.91−2.02 (m, 1H), 3.28−3.38 (m, 1H), 3.38−3.48 (m, 2H), 3.50−3.63 (m, 2H), 3.64−3.73 (m, 1H), 3.77 (s, 3H), 3.83 (s, 3H), 4.44 (s, 2H), 4.62 (d, *J* = 6.3 Hz, 1H), 5.04 (d, *J* = 6.9 Hz, 1H), 5.32−5.48 (m, 1H), 5.48−5.63 (m, 1H), 6.78 (d, *J* = 8.1 Hz, 1H), 6.83−6.90 (m, 3H), 7.24 (d, *J* = 8.3 Hz, 2H) 7.29 (t, *J* = 8.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.4, 34.1, 35.2, 35.9, 36.6, 37.6, 55.2, 55.9, 65.6, 72.5, 73.6, 79.8, 93.3, 108.9, 113.7, 122.0, 122.3, 129.4, 129.5, 130.0, 130.2, 130.9, 140.3, 156.6, 159.1, 171.7.

(3*S*,5*R*,6*S*)-14-Methoxy-3-{2-[(4-methoxybenzyl)oxy]ethyl}-5-(methoxymethoxy)-6-methyl-3,4,5,6,7,10-hexahydro-1*H*-2-benzoxacyclododecin-1-one (23). To a cooled (0 °C) solution of hydroxy acid **21** (80 mg, 155 μmol) in THF (7.5 mL) was added polymer-bound PPh_3 (3 mmol P/g resin, 330 mg, 990 μmol). After 15 min at room temperature, the slurry was recooled to 0 °C and treated dropwise with DEAD (∼40% solution in toluene, 150 μL, 60 mg, 345 μL). Within 15 h of stirring, the reaction mixture was warmed to room temperature. The resin was filtered off and washed thoroughly with THF. After evaporation of the solvent, the residue was purified by flash chromatography (CH_2Cl_2/acetone, 20:1) to give 33 mg (43%) of the desired lactone **23** as a colorless oil. TLC (petroleum ether /EtOAc, 2:1): R_f = 0.64. $[\alpha]^{23}_D$ = −46.9 (*c* 0.85, CH_2Cl_2) (ref 12g, $[\alpha]^{20}_D$ = −49.5 (*c* 1.30, $CHCl_3$); ref 12b $[\alpha]^{20}_D$ = −21.0 (*c* 1.00, benzene)). IR (film): 1724, 1613, 1584, 1468 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.85 (d, *J* = 6.6 Hz, 3H), 1.44 (dd, *J* = 9.4, 15.4 Hz, 1H), 1.63−1.79 (m, 2H), 1.84−1.95 (m, 1H), 1.97−2.07 (m, 1H), 2.08−2.17 (m, 1H), 2.30 (d, br, *J* = 13.1 Hz, 1H), 3.31 (d, br, *J* = 16.7 Hz, 1H), 3.42 (s, 3H), 3.64 (t, *J* = 9.6 Hz, 2H), 3.69 (s, 3H), 3.67−3.76 (m, 1H), 3.78 (s, 3H), 4.14 (dd, *J* = 3.3, 9.3 Hz, 1H), 4.46 (s, 2H), 4.78 (d, *J* = 6.8 Hz, 1H), 4.87 (d, *J* = 6.8 Hz, 1H), 5.29−5.38 (m, 1H), 5.41−5.52 (m, 2H), 6.72−6.80 (m, 2H), 6.85 (d, *J* = 8.3 Hz, 2H), 7.21 (t, *J* = 8.8 Hz, 1H), 7.26 (d, *J* = 8.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.3, 34.0, 35.7, 36.4, 37.7, 37.7, 55.3, 55.3, 55.5, 66.6, 72.3, 72.6, 79.2, 96.8, 109.2, 113.7, 122.8, 124.5, 128.5, 129.0, 129.9, 130.7, 131.3, 139.1, 156.4, 159.1, 168.2. MS (EI), *m*/*z* (%): 202 (3), 176 (4), 147 (3), 130 (5), 104 (3), 84 (4), 59 (5), 45 (6), 44 (100). HRMS (ESI): [M + Na]$^+$ calcd for $C_{29}H_{38}NaO_7$, 521.2510; found, 521.2510.

Acknowledgment. Financial support by the Deutsche Forschungsgemeinschaft (Grant Ma 1012/10-1) and the Fonds der Chemischen Industrie is gratefully acknowledged.

Supporting Information Available: Copies of the ^{1}H and ^{13}C NMR spectra of all key intermediates in PDF format. This material is available free of charge via the Internet at http://pubs.acs.org.

JO035054G