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De Novo Asymmetric Syntheses of Muricatacin and Its Analogues via Dihydroxylation of Dienoates

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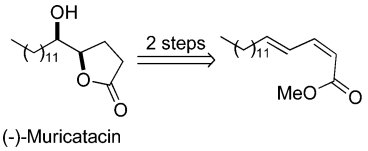
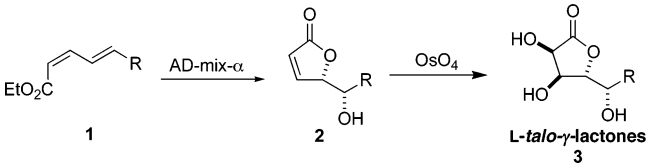


A short and highly efficient route to both enantiomers of muricatacin as well as the C-5-epimer has been developed. The key to the overall transformation is the highly regio- and enantioselective Sharpless asymmetric dihydroxylation of an (*E*,*Z*)-dienoate. The highly efficient stereoselective synthesis prepares (−)-muricatacin in seven steps and 66% overall yield.

The muricatacins are a class of naturally occurring 5-hydroxy-γ-butyrolactones with potent cytotoxicity (~1 to 10 μg/mL) against several human tumor cell lines. Various SAR studies of the muricatacin showed that its activity is influenced significantly by the nature of the side chain.[1] In 1991, muricatacin was isolated by McLaughlin et al. from the seeds of the tropical fruit, *Annona muricata* as a quasi-racemic component (ca. 25% ee), with the (−)-enantiopode being the predominate form.[2] In addition to their potent biological activity, muricatacin and related γ-butyrolactones have served as precursors in syntheses of complex bioactive natural products.[3] Although, numerous synthetic approaches to this class of molecule have been reported,[4] the development of a flexible and efficient route for the preparation of 5-hydroxy-γ-butyrolactone natural products still remains exigent.

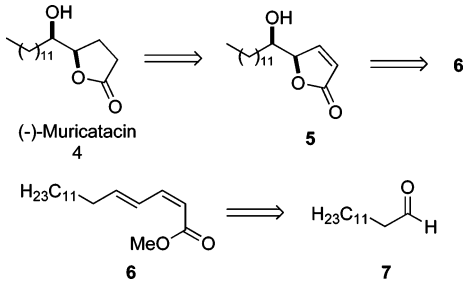
As part of a program aimed at the synthesis of a library of anticancer compounds, we were interested in the access to large amounts of muricatacin and its stereoisomers. In particular, we desired access to the α,β-unsaturated variants, which we envisioned would be amenable to a palladium-catalyzed dimerization of these stereoisomers, toward acetogenin analogues.

SCHEME 1. An Iterative Dihydroxylation Approach to Various Talose Sugars



Previously, we have had significant success at the synthesis of various carbohydrates by means of the iterative dihydroxylation of dienoates.[5] Thus establishing the C-2 to C-5 tetrol stereochemistry of the hexoses from dienoates (e.g., **3** from **1**).[6] As part of our efforts to apply this methodology to *talo*-sugars (**3**) (Scheme 1), we discovered a simple approach to enantioenriched 5-hydroxy-γ-butylrolactones (**2**). Thus we decided to explore the potential to use this approach toward muricatacin and eventually dimeric acetogenin analogues.[7] Herein, we would like to report a very short and highly efficient approach for the synthesis of either enantiomer of muricatacin (**4**) and its 5-*epi*-muricatacin (**12**) via a regioselective asymmetric Sharpless dihydroxylation (Scheme 2).

SCHEME 2. Retrosynthetic Analysis of Muricatacin



Retrosynthetically, we targeted the *Z*,*E*-dienoate **6**, which we envisioned preparing by means of a Still−Gennari olefination[8] of enal **10**. Similarly, the enal **10** could be prepared from

(1) Cave, A.; Chaboche, C.; Figadere, B.; Harmange, J. C.; Laurens, A.; Peyrat, J. F.; Pichon, M.; Szlosek, M.; Cotte-Laffite, J.; Quero, A. M. *Eur. J. Med. Chem.* **1997**, *32*, 617−623.

(2) Rieser, M. J.; Kozlowski, J. F.; Wood, K. V.; McLaughlin, J. L. *Tetrahedron Lett.* **1991**, *32*, 1137−1140.

(3) (a) Kumar, P.; Naidu, S. V.; Gupta, P. *J. Org. Chem.* **2005**, *70*, 2843−2846. (b) Hu, Y.; Brown, R. C. D. *Chem. Commun.* **2005**, *69*, 5636−5637. (c) Yoshimitsu, T.; Makino, T.; Nagaoka, H. *J. Org. Chem.* **2005**, *69*, 1993−1998. (d) Avedissain, H.; Sinha, S. C.; Yazhak, A.; Neogi, P.; Sinha, S. C.; Keinan, E. *J. Org. Chem.* **2000**, *65*, 6035−6051. (e) Ha, J. D.; Cha, J. K. *J. Am. Chem. Soc.* **1999**, *121*, 10012-6028. (f) Towne, T. B.; McDonald, F. E. *J. Am. Chem. Soc.* **1997**, *119*, 6022−6028.

(4) For recent synthesis of muricatacin, see the following: (a) Dhotare, B.; Chattopadhyay, A. *Tetrahedron Lett.* **2005**, *46*, 3103−3105. (b) Quinn, K. J.; Isaacs, A. K.; Arvary, R. A. *Org. Lett.* **2004**, *6*, 4143−4145. (c) Yoshimitsu, T.; Makino, T.; Nagaoka, H. *J. Org. Chem.* **2003**, *68*, 7548−7550. (d) Bernard, A. M.; Frongia, A.; Piras, P. P.; Secci, F. *Org. Lett.* **2003**, *5*, 2923−2926. (e) Popsavin, V.; Krstic, I.; Popsavin, M. *Tetrahedron Lett.* **2003**, *44*, 8897−8900. (f) Raghavan, S.; Joseph, S. C. *Tetrahedron: Asymmetry* **2003**, *14*, 101−105. (g) Carda, M.; Rodriguez, S.; Gonzalez, F.; Castillo, E.; Villanueva, A.; Marco, J. A. *Eur. J. Org. Chem.* **2002**, *15*, 2649−2655. (h) Chandrasekhar, M.; Chandra, K. L.; Singh, V. K. *Tetrahedron Lett.* **2002**, *43*, 2773−2775. (i) Konno, H.; Hiura, N.; Yanura, M. *Heterocycles* **2002**, *57*, 1793−1797. (j) Baylon, C.; Prestat, G.; Heck, M. P.; Mioskowski, C. *Tetrahedron Lett.* **2000**, *41*, 3833−3835. (k) Trost, B. M.; Rhee, Y. H. *J. Am. Chem. Soc.* **1999**, *121*, 11680−11683. (l) Solladie, G.; Hanquet, G.; Izzo, I.; Crumbie, R. *Tetrahedron Lett.* **1999**, *40*, 3071−3074. (m) Couladouros, E. A.; Mihou, A. P. *Tetrahedron Lett.* **1999**, *40*, 4861−4862. (n) Marshall, J. A.; Welmaker, G. S. *J. Org. Chem.* **1994**, *59*, 4122−4125. (o) Wang, Z.-M.; Zhang, X.-L.; Sharpless, K. B. *Tetrahedron Lett.* **1992**, *33*, 6407−6410. (p) Wright, A. E.; Schafer, M.; Midland, S.; Munnecke, D. E.; Slims, J. J. *Tetrahedron Lett.* **1989**, *30*, 5699. (q) Kotsuki, H.; Miyazaki, A.; Ochi, M.; Slims, J. J. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 721.

(5) (a) Ahmed, Md. M.; O'Doherty, G. A. *Tetrahedron Lett.* **2005**, *46*, 3015−3019. (b) Ahmed, Md. M.; Berry, B. P.; Hunter, T. J.; Tomcik, D. J.; O'Doherty, G. A. *Org. Lett.* **2005**, *7*, 745−748.

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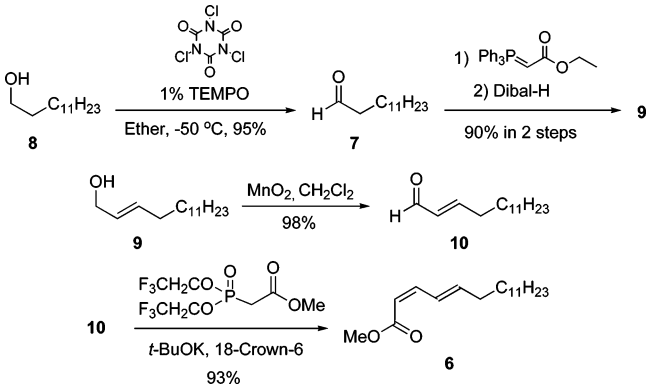
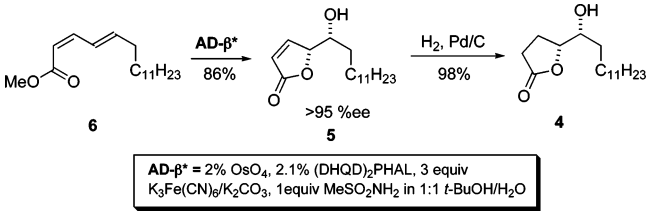
SCHEME 3. Synthesis of *Z,E*-Dienoate 6



commercially available aldehyde **7** (Scheme 3). In practice, we found it was significantly cheaper and procedurally easy to prepare aldehyde **7** from 13-carbon alcohol **8** via a TEMPO oxidation (95% yield).[9] The aldehyde **7** was homologated to the allylic alcohol **9** by a stablized Wittig olefination/DIBALH reduction sequence (90%). Allylic oxidation of **9** with MnO_2 afforded the enal **10** in excellent yield (98%), which coupled smoothly under the typical Still−Gennari conditions to give the desired *Z,E*-dienoate **6** in good yield and stereoselectivity (>20:1, *Z,E* to *E,E*). This five-step procedure allowed for the preparation of multigram quantities of dienoate **6** in excellent overall yield from alcohol **8** (78%).

We next investigated the dihydroxylation/lactonization of the dienoate **6** (Scheme 4). Simply exposing the (2*Z*,4*E*)-

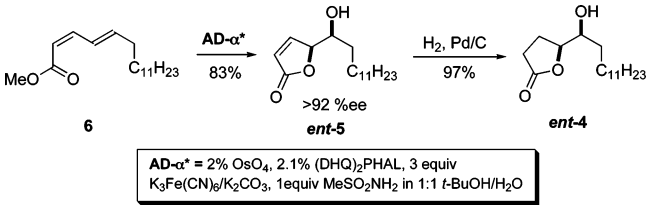
SCHEME 4. Enantioselective Synthesis of (−)-Muricatacin



dienoate **6** to the typical Sharpless AD-mix procedure (2% OsO_4/2.1% $(DHQD)_2PHAL$, 3 equiv $K_3Fe(CN)_6/K_2CO_3$, 1 equiv $MeSO_2NH_2$), afforded lactone **5** in good yield (86%) and excellent enantiomeric excess (>95% ee).[10] Finally the natural product (−)-muricatacin **4** was prepared by hydrogenation (1 atm H_2, 5% Pd/C in MeOH) of the butenolide double bond, which gave synthetic material (98%) with identical physical and spectral data to that of the isolated natural product[2] (^{1}H NMR, ^{13}C NMR, optical rotation,[11] and melting point).

By a nearly identical protocol the (+)-muricatacin *ent*-**4** could also be synthesized from dienoate **6** (Scheme 5). All

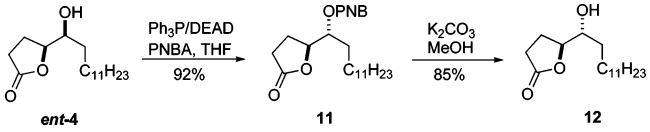
SCHEME 5. Enantioselective Synthesis of (+)-Muricatacin



that was required was simply switch to the pseudoenantiomeric AD-mix catalyst system (2% OsO_4/2.1% $(DHQ)_2PHAL$, 3 equiv $K_3Fe(CN)_6/K_2CO_3$, 1 equiv $MeSO_2NH_2$). Thus exposing (2*Z*,4*E*)-dienoate **6** to the pseudoenantiomeric AD-mix catalyst (AD-α*) yielded the enantiomeric lactone *ent*-**5** in a similarly good yield (83%) and enantiopurity (>92% ee). As with it enantiomer, *ent*-**5** could be converted to (+)-muricatacin *ent*-**4** via hydrogenation of a methanol solution of lactone *ent*-**5** with Pd/C in an excellent yield of 97%.

We could also easily access the C-5 epimer of muricatacin by means of the Mitsunobu reaction (Scheme 6). Thus, exposing

SCHEME 6. Enantioselective Synthesis of 5-*Epi*-Muricatacin



(+)-muricatacin *ent*-**4** to the typical Mitsunobu reaction condition afforded the *p*-nitro-benzoic ester **11** in excellent yield (92%). Hydrolysis of the ester **11** with K_2CO_3 in MeOH yielded the C-5-*epi*-muricatacin **12** in good yield (85%).

In conclusion, short, flexible, and highly efficient syntheses of either enantiomer of muricatacin and its C-5 epimer have been developed. This highly enantio- and diastereocontrolled route illustrates the utility of the Sharpless dihydroxylation and Mitsunobu reaction. This approach provides both enantiomers of muricatacin (**4** and *ent*-**4**) in 66% and 63% overall yields from commercially available 13-carbon alcohol **8**, respectively. This route was also amenable to C-5 epimer of muricatacin **12** in 49% overall yields from alcohol **8**. Further application of this approach toward the synthesis of acetogenin analogues is ongoing.

Experimental Section[12]

***(E)*-Pentadec-2-en-1-ol (9).** A solution of (*E*)-ethyl pentadec-2-enoate (1.8 g, 6.72 mmol) in THF (80 mL) was cooled to −78 °C, and then Dibal-H (1M, 16.8 mL, 16.8 mmol) was added dropwise. After the mixture was stirred for 30 min, the reaction mixture was quenched with 2 mL acetone. Bulk THF was removed under reduced pressure, and the residue was treated with 30 mL 1 N HCl solution and then extracted with ether (3 × 30 mL). The organic extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by flash chro-

(6) To control the double selectivity in the oxidation, we chose to take advantage of both the differing double bond reactivity in dienoates and the Sharpless reagent systems preference of trans-double bonds. See ref 5 as well as (a) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483−2547. (b) Zhang, Y.; O'Doherty, G. A. *Tetrahedron* **2005**, *61*, 6337−6351.

(7) Previously, Sharpless has shown that muricatacin can be prepared by the asymmetric dihydroxylation of a partially saturated **6** ((4*E*)-ethyl heptadeca-4-enoate), see ref 4o. Because we were also interested in access to an unsaturated form of muricatacin (**5**), we decided to pursue this dienoate oxidation approach.

(8) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405−4408.

(9) Luca, L. D.; Giacomelli, G.; Porcheddu, A. *Org. Lett.* **2001**, *3*, 3041−3043.

(10) All enantiomeric excesses were determined by chiral HPLC (for details see Supporting Information).

(11) Because natural muricatacin was isolated in low enantiopurity, we compared our optical rotation data ($[\alpha]^{25}_D$ −22.3 (*c* 1.8, $CHCl_3$)) with that of synthetic material ($[\alpha]^{25}_D$ −22.9 (*c* 1.84, $CHCl_3$)), see ref 4b and 4n.

(12) Presented in this text are the experimental procedures for the preparation of compounds **9**−**12**. Complete experimental procedures and spectral data for all compounds are presented in the Supporting Information.

matography on silica gel (20:1 (v/v) hexane/EtOAc) to yield (*E*)-pentadec-2-en-1-ol **9** (1.5 g, 96% yield) as a white solid: mp: 31−33 °C; R_f (20% EtOAc/ hexanes) = 0.52. IR (thin film, cm^{-1}): 3288, 2955, 2917, 2848, 1472, 1462, 1081, 1001, 961, 719, 666. ^1H NMR ($CDCl_3$, 600 MHz): δ 5.69 (m, 1H), 5.63 (m, 1H), 4.0 (d, J = 6 Hz, 2H), 2.0 (tdd, J = 7, 7, 1.2 Hz, 2H), 1.25 (m, 20H), 0.88 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 133.6, 128.8, 63.8, 32.2, 31.9, 29.66, 29.65, 29.63, 29.60, 29.4, 29.3, 29.2, 29.1, 22.6, 14.0; HRMS(ESI): calcd for $[C_{15}H_{30}ONa]^+$, 249.2194; found, 249.2189.

(*E*)-Pentadecthyl-2-enal (10). To a solution of (*E*)-pentadec-2-en-1-ol **9** (1.0 g, 4.58 mmol) in 30 mL hexane was added manganese(IV) oxide (4.8 g, 55 mmol). The mixture was stirred for 24 h at room temperature and then filtrated. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography on silica gel (hexane) to yield (*E*)-pentadecthyl-2-enal **10** (0.97 g, 98% yield) as a colorless oil: R_f (10% EtOAc/ hexanes) = 0.7. IR (thin film, cm^{-1}): 2923, 2853, 2732, 1694, 1638, 1466, 1378, 1138, 974, 722. ^1H NMR ($CDCl_3$, 600 MHz): δ 9.48 (dd, J = 7.8, 1.2 Hz, 1H), 6.82 (dtd, J = 15.6, 6.6, 1.2 Hz, 1H), 6.1 (ddt, J = 15.6, 7.8, 1.2 Hz, 1H), 2.3 (dtd, J = 7.8, 6, 1.2 Hz, 2H), 1.48 (tt, J = 7.2, 7.2 Hz, 2H), 1.26−1.24 (m, 20H), 0.85 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 193.4, 158.8, 132.9, 32.6, 31.8, 29.58, 29.56, 29.54, 29.4, 29.29, 29.28, 29.1, 27.8, 22.6, 14.0. HRMS(ESI): calcd for $[C_{15}H_{28}ONa]^+$, 247.2038; found, 247.2032.

(2*Z*,4*E*)-Methyl Heptadeca-2,4-dienoate (6). A solution of $(CF_3CH_2O)_2P(O)CH_2CO_2CH_3$ (1.03 g, 4.58 mmol) and 18-crown-6 (5.13 g, 19.4 mmol) in THF (100 mL) was cooled to −78 °C and treated with *t*-BuOK (0.62 g, 5.5 mmol). After the mixture was stirred for 15 min, a solution of the (*E*)-pentadecthyl-2-enal **10** (1.03 g, 4.58 mmol) in THF (10 mL, plus 5 mL of rinse) was added by cannula. The resulting mixture was stirred at −78 °C for 2.5 h, and the reaction mixture was quenched by the addition of saturated aqueous NH_4Cl. The bulk of THF was removed under reduced pressure. The residue was extracted with ether (3 × 30 mL), and the organic extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by flash chromatography on silica gel (hexane) to yield (2*Z*,4*E*)-methyl heptadeca-2,4-dienoate **6** (1.2 g, >20:1 *Z, E*/*E, E* ratio, 93% yield) as a viscous oil. Major isomer (**6**): R_f (10% EtOAc/hexanes) = 0.85. IR (thin film, cm^{-1}): 2922, 2853, 1719, 1639, 1437, 1192, 1074, 999, 962, 895, 816, 721. ^1H NMR ($CDCl_3$, 600 MHz): δ 7.34 (ddt, J = 15.0, 11.4, 1.2 Hz, 1H), 6.54 (dd, J = 11.4, 11.4 Hz, 1H), 6.07 (dt, J = 15.0, 7.2 Hz, 1H), 5.56 (d, J = 11.4, 1H), 3.71 (s, 3H), 2.2 (m, 2H), 1.25 (m, 20H), 0.87 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 166.9, 146.0, 145.6, 126.8, 114.9, 51.0, 33.0, 31.9, 29.65, 29.62 (2C), 29.5, 29.4, 29.3, 29.2, 28.8, 22.6, 14.0. MS(EI): calcd for $[C_{18}H_{32}O_2]^+$, 280; found, 280.[13]

(*R*)-5-((*R*)-1′-hydroxytridecyl)furan-2(5*H*)-one (5). Into a 10 mL round-bottom flask was added 1 mL of *t*-BuOH, 1 mL of water, $K_3Fe(CN)_6$ (1.6 g, 4.7 mmol), K_2CO_3 (0.6 g, 4.7 mmol), $MeSO_2NH_2$ (0.2 g, 1.57 mmol), $(DHQD)_2PHAL$ (26 mg, 34 μmol, 2.1 mol %), and OsO_4 (4 mg, 16 μmol, 1 mol %). The mixture was stirred at room temperature for about 15 min and then cooled to 0 °C. To this solution was added (2*Z*,4*E*)-methyl heptadeca-2,4-dienoate **6** (0.4 g, 1.57 mmol), and the reaction was stirred vigorously at 0 °C overnight. The reaction was quenched with solid sodium sulfite (10 mg) at room temperature. Ethyl acetate (5 mL) was added to the reaction mixture, and after separation of the layers, the aqueous phase was further extracted with the ethyl acetate (2 × 5 mL). The combined organic layers were washed with brine and dried over anhydrous sodium sulfate. After removal of the solvents in vacuo, flash chromatography on silica gel (5:1 (v/v) hexanes/EtOAc) afforded 379 mg (86% yield) of (*R*)-5-((*R*)-1′-hydroxytridecyl)furan-2(5*H*)-one **5** as a white solid: mp 89−91 °C; R_f (50% EtOAc/hexanes) = 0.55; $[\alpha]^{25}_D$ 69 (*c* 1.8, CH_2Cl_2). IR (thin film, cm^{-1}): 3370, 2952, 2913, 2849, 1715, 1603, 1471, 1179, 1108, 1020, 919, 866, 836, 827, 801, 718, 658 cm^{-1}. ^1H NMR ($CDCl_3$, 600 MHz): δ 7.45 (dd, J = 6, 1.8 Hz, 1H), 6.18 (dd, J = 6, 1.8 Hz, 1H), 4.98 (ddd, J = 5.6, 1.8, 1.8 Hz, 1H), 3.75 (ddd, J = 12, 6, 6 Hz, 1H), 2.1 (m, 1H), 1.59 (m, 2H), 1.52 (m, 2H), 1.32−1.25 (m, 20H), 0.87 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 172.7, 153.5, 122.7, 86.0, 71.9, 33.2, 31.9, 29.63, 29.60 (2C), 29.5, 29.46, 29.40, 29.3, 25.4, 22.6, 14.0. HRMS-(ESI): calcd for $[C_{17}H_{30}O_3Na]^+$, 305.2093; found, 305.2086.

(*R*)-Dihydro-5-((*R*)-1′-hydroxytridecyl)furan-2(3*H*)-one (4). Into a 10 mL round-bottom flask was added (*R*)-5-((*R*)-1′-hydroxytridecyl)furan-2(5*H*)-one **5** (52 mg, 0.18 mmol), 4 mL of MeOH and 10 mg 10 wt % Pd on activated carbon. The reaction was stirred under 1 atm of H_2 for 24 h. Filtration and evacuation under reduced pressure afforded 51 mg (98% yield) (−)Muricatacin as white solid: mp 68−70 °C; R_f (50% EtOAc/hexane) = 0.55; $[\alpha]^{25}_D$ −19 (*c* 1.8, CH_2Cl_2). IR (thin film, cm^{-1}): 3394, 2953, 2916, 2849, 1743, 1471, 1364, 1319, 1189, 1099, 975, 810, 720. ^1H NMR ($CDCl_3$, 600 MHz): δ 4.41 (ddd, J = 7.2, 7.2, 4.2 Hz, 1H), 3.55 (ddd, J = 8.4, 4.8, 4.8 Hz, 1H), 2.60 (dd, J = 18, 9.6, 1H), 2.52 (dd, J = 18, 9.6 Hz, 1H), 2.22 (m, 1H), 2.12 (m, 1H), 1.52 (m, 2H), 1.28−1.24 (m, 20H), 0.86 (t, J = 7.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 177.1, 82.9, 73.6, 32.9, 31.8, 29.63, 29.61-(2C), 29.5, 29.49, 29.48, 29.3, 28.6, 25.4, 24.0, 22.6, 14.0. HRMS-(ESI): calcd for $[C_{17}H_{32}O_3Na]^+$, 307.2249; found, 307.2243.

(*S*)-5-((*S*)-1′-hydroxytridecyl)furan-2(5*H*)-one (*ent*-5). Into a 25 mL round-bottom flask was added 2 mL of *t*-BuOH, 2 mL of water, $K_3Fe(CN)_6$ (2.4 g, 7.26 mmol), K_2CO_3 (1.0 g, 7.26 mmol), $MeSO_2NH_2$ (0.23 g, 1.57 mmol), $(DHQ)_2PHAL$ (39 mg, 50 μmol, 2.1 mol %), and OsO_4 (6 mg, 24 μmol, 1 mol %). The mixture was stirred at room temperature for about 15 min and then cooled to 0 °C. To this solution was added (2*Z*,4*E*)-methyl heptadeca-2,4-dienoate **6** (0.68 g, 2.42 mmol), and the reaction was stirred vigorously at 0 °C overnight. The reaction was quenched with solid sodium sulfite (15 mg) at room temperature. Ethyl acetate (10 mL) was added to the reaction mixture, and after separation of the layers, the aqueous phase was further extracted with the organic solvent (2 × 10 mL). The combined organic layers were washed with brine and dried over anhydrous sodium sulfate. After removal of the solvents in vacuo, flash chromatography on silica gel (5:1 (v/v) hexanes/EtOAc) afforded 557 mg (83% yield) of (*S*)-5-((*S*)-1′-hydroxytridecyl)furan-2(5*H*)-one *ent*-**5** as a white solid: mp 89−91 °C; R_f (50% EtOAc/hexanes) = 0.55; $[\alpha]^{25}_D$ −68 (*c* 1.2, CH_2Cl_2). IR (thin film, cm^{-1}): 3393, 3358, 3080, 2914, 2849, 1714, 1702, 1604, 1471, 1360, 1225, 1180, 1073, 1021, 919, 867, 838, 830, 803, 718, 656 cm^{-1}. ^1H NMR ($CDCl_3$, 600 MHz): δ 7.45 (dd, J = 6, 1.8 Hz, 1H), 6.18 (dd, J = 6, 1.8 Hz, 1H), 4.98 (ddd, J = 5.6, 1.8, 1.8 Hz, 1H), 3.75 (ddd, J = 12, 6, 6 Hz, 1H), 2.1 (m, 1H), 1.59 (m, 2H), 1.52 (m, 2H), 1.32−1.25 (m, 20H), 0.87 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 172.7, 153.6, 122.7, 86.0, 71.8, 33.2, 31.8, 29.63, 29.60, 29.59, 29.52, 29.45, 29.40, 29.3, 25.4, 22.6, 14.0.[14]

(*S*)-Dihydro-5-((*S*)-1′-hydroxytridecyl)furan-2(3*H*)-one (*ent*-4). Into a 50 mL round-bottom flask was added (*S*)-5-((*S*)-1′-hydroxytridecyl)furan-2(5*H*)-one *ent*-**5** (200 mg, 0.69 mmol), 20 mL of CH_3OH, and 20 mg 10 wt % Pd on activated carbon. The reaction was stirred under 1 atm of H_2 for 24 h. Filtration and evacuation under reduced pressure afforded 195 mg (97% yield) *ent*-**4** (+)-muricatacin as a white solid: mp 68−70 °C; R_f (50% EtOAc/hexane) = 0.55; $[\alpha]^{25}_D$ 19.7 (*c* 1.5, CH_2Cl_2). IR (thin film, cm^{-1}): 3394, 2952, 2915, 2848, 1742, 1471, 1362, 1268, 1186, 1101, 1019, 998, 977, 902, 832, 721. ^1H NMR ($CDCl_3$, 600 MHz):

(13) While we were able to generate a molecular ion for dienoate **6** using electron impact ionization, we were unable to generate a molecular ion using electrospray ionization techniques, thus we were unable to obtain any high-resolution mass data.

(14) High-resolution MS data was not obtained for the enantiomers of compounds **4** and **5**.

δ 4.41 (ddd, J = 7.2, 7.2, 4.2 Hz, 1H), 3.55 (ddd, J = 8.4, 4.8, 4.8 Hz, 1H), 2.60 (dd, J = 18, 9.6, 1H), 2.52 (dd, J = 18, 9.6 Hz, 1H), 2.22 (m, 1H), 2.12 (m, 1H), 1.52 (m, 2H), 1.28−1.24 (m, 20H), 0.86 (t, J = 7.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 177.2, 82.9, 73.5, 32.9, 31.8, 29.6, 29.57 (2C), 29.51, 29.4 (2C), 29.2, 28.6, 25.4, 24.0, 22.6, 14.0.[14]

(*S*)-1′-((*R*)-Tetrahydro-5″xofuran-2″-yl)tridecyl 4-Nitrobenzoate (11). Into a 50 mL round-bottom flask was added 20 mL THF. The mixture was cooled to 0 °C, and then triphenylphosphine (440 mg, 1.89 mmol) and DEAD(330 mg, 1.89 mmol) were added, followed by (*S*)-dihydro-5-((*S*)-1′-hydroxytridecyl)furan-2(3*H*)-one (*ent*-**4**) (180 mg, 0.63 mmol) and *p*-nitro-benzoic acid (127 mg, 0.76 mmol). The mixture was stirred at room temperature for 2 h. The solvent was removed under reduced pressure and the residue was purified by chromatography on silica gel (20:1 (v/v) hexanes/EtOAc) to afford 255 mg (92% yield) of (*S*)-1′-((*R*)-tetrahydro-5″-oxofuran-2″-yl)tridecyl 4-nitrobenzoate **11** as a light yellow solid: mp 42−44 °C; R_f (30% EtOAc/hexane) = 0.75; $[\alpha]^{25}_D$ 8.1 (c 1.0, CH_2Cl_2). IR (thin film, cm^{-1}): 2924, 2854, 1781, 1726, 1608, 1528, 1465, 1348, 1268, 1179, 1115, 1102, 1014, 921, 873, 783, 719. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.29 (m, 2H), 8.18 (m, 2H), 5.38 (ddd, J = 9, 4.8, 4.8 Hz, 1H), 4.68 (ddd, J = 7.8, 7.8, 4.2 Hz, 1H), 2.58 (m, 2H), 2.36 (dddd, J = 13.2, 9.6, 7.8, 6.0 Hz, 1H), 2.21 (dddd, J = 12.6, 9.6, 8.4, 7.2 Hz, 1H), 1.80 (m, 1H), 1.73 (m, 2H), 1.28−1.22 (m, 20H), 0.86 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 176.0, 164.0, 150.7, 135.0, 130.7, 128.8, 123.6, 123.5, 79.8, 75.2, 31.8, 29.8, 29.57, 29.56, 29.52, 29.4, 29.3, 29.29, 29.28, 27.9, 25.1, 23.1, 22.6, 14.0. HRMS(ESI): calcd for $[C_{24}H_{35}NO_6Na]^+$, 456.2362; found, 456.2357.

(*S*)-Dihydro-5-((*R*)-1′-hydroxytridecyl)furan-2(3*H*)-one (12). Into a 5 mL round-bottom flask was added 3 mL CH_3OH, then potassium carbonate (289 mg, 2.1 mmol) and (*S*)-1′-((R)-tetrahydro-5″-oxofuran-2″-yl)tridecyl 4-nitrobenzoate **11** (180 mg, 0.42 mmol). The mixture was stirred for 10 min at room temperature and then filtered through a pad of Celite. The solvent was removed under reduced pressure, and the residue was purified by chromatography on silica gel (4:1 (v/v) hexanes/EtOAc) to afford 100 mg (85% yield) of (*S*)-dihydro-5-((*R*)-1′-hydroxytridecyl)furan-2(3*H*)-one **10** as solid: mp 70−72 °C; R_f (50% EtOAc/hexane) = 0.50; $[\alpha]^{25}_D$ 14 (c 1.2, CH_2Cl_2). IR (thin film, cm^{-1}): 3415, 2956, 2917, 2849, 1783, 1471, 1462, 1268, 1206, 1191, 1082, 1071, 1011, 729, 720. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 4.40 (ddd, J = 7.2, 7.2, 3 Hz, 1H), 3.92 (m, 1H), 2.58 (dd, J = 18, 9.6, 1H), 2.50 (m, 1H), 2.25 (m, 1H), 2.13 (m, 1H), 1.51 (m, 2H), 1.41(m, 2H), 1.31−1.25 (m, 18H), 0.87 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 177.4, 82.8, 71.3, 31.90, 31.88, 29.62, 29.60, 29.59, 29.53, 29.50, 29.47, 29.3, 28.6, 25.6, 22.6, 21.0, 14.0; HRMS(ESI): calcd for $[C_{17}H_{32}O_3Na]^+$, 307.2249; found, 307.2243.

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Supporting Information Available: Complete experimental procedures and spectral data for all new compounds can be found in the Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

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