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Synthesis of (−)-Muricatacin via α- and α′-C−H Bond Functionalization of Tetrahydrofuran

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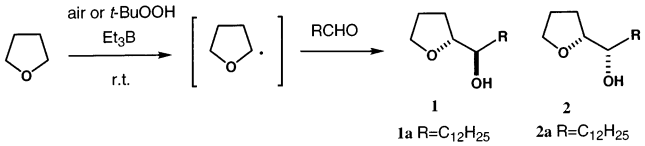
Abstract: (−)-Muricatacin, a potent cytotoxic (4*R*,5*R*)-5-hydroxyheptadecan-4-olide, has been synthesized through α-C−H hydroxyalkylation and α′-C−H oxidation of tetrahydrofuran. This study presents a novel method for C−H bond functionalization as a means for preparing γ-(hydroxyalkyl)-γ-butyrolactones.

Functionalization of unreactive carbon−hydrogen (C−H) bonds of organic molecules has attracted considerable attention.[1−3] Carbon−carbon (C−C) bond formation via C−H functionalization is particularly important in the construction of molecular frameworks. Radical translocation reactions[4] as well as the photolysis of carbonyl compounds[5] have been generally applied to this type of chemical transformation,[6] while metal-mediated C−H activation reactions have significant potential for transforming C−H to C−C bonds.[7,8]

Recently, we established a novel α-C−H hydroxyalkylation of tetrahydrofuran (THF) with aldehydes, in which triethylborane−air[9] or triethylborane−*tert*-butyl hydroperoxide (TBHP)[10] as the radical source is used (Scheme 1).[11] The synthesis of (−)-muricatacin (**6**) in this study presents a novel route to γ-(hydroxyalkyl)-γ-butyrolactones via α-C−H hydroxyalkylation and α′-C−H oxidation of THF.

SCHEME 1



(−)-Muricatacin (**6**) was isolated as a quasi-racemic constituent (ca. 25% ee) from seeds of the tropical fruit, *Annona muricata L.*[12] This simple acetogenin has been shown to exert cytotoxicity toward human tumor cell lines and accordingly has prompted intense synthetic studies.[13−15]

The present synthesis was initiated with α-substituted tetrahydrofuran **1a**, prepared by *the direct assembly of THF with tridecanal via α-hydrogen abstraction from THF under triethylborane−TBHP condition* (Scheme 2).[10,16,17] α-C−H hydroxyalkylation of THF with tridecanal using triethylborane−TBHP provided alcohols **1a** and **2a** (64% yield) whose subsequent acetylation gave acetates **3** and **4** in 84% yield (**3**/**4** 65:35). Acetate **4** was transformed into **3** in 75% overall yield via reduction with

(1) Reviews for metal-promoted C−H activation of organic molecules see: (a) Arndtsen, B. A.; Bergman, R. G.; Mobley, T. A.; Peterson, T. H. *Acc. Chem. Res.* **1995**, *28*, 154. (b) Shilov, A. E.; Shulpin, G. B. *Chem. Rev.* **1997**, *97*, 2879. (c) Dyker, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1698. (d) Guari, Y.; Sabo-Etienne, S.; Chaudret, B. *Eur. J. Inorg. Chem.* **1999**, 1047. (e) Kakiuchi, F.; Murai, S. In *Activation of Unreactive Bonds and Organic Synthesis*; Murai, S., Ed.; Springer: Berlin, Germany, 1999; p 47. (f) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633. (g) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731. (h) Labinger, J. A.; Bercaw, J. E. *Nature* **2002**, *417*, 507.

(2) (a) Crabtree, R. H. *Pure Appl. Chem.*, **1995**, *67*, 39. (b) Hill, C. L. *Synlett* **1995**, 127. (c) Fokin, A. A.; Schreiner, P. R. *Chem. Rev.* **2002**, *102*, 1551.

(3) (a) Olah, G. A.; Molnár, A. *Hydrocarbon Chemistry*; Wiley: New York, 1995. (b) Sommer, J.; Bukala, J. *Acc. Chem. Res.* **1993**, *26*, 370.

(4) Robertson, J.; Pillai, J.; Lush, R. K. *Chem. Soc. Rev.* **2001**, *30*, 94.

(5) (a) Horspool, W. M. *Photochemistry* **2001**, *32*, 49. (b) Wagner, P. J. *Acc. Chem. Res.* **1971**, *4*, 168. (c) Coyle, J. D.; Carless, H. A. J. *Chem. Soc. Rev.* **1972**, *1*, 465.

(6) For recent development of radical chemistry, see: Renaud, P.; Sibi, M. P., Eds. *Radicals in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2001.

(7) Selected examples of intramolecular C−H functionalization in natural product synthesis: (a) Dangel, B. D.; Godula, K.; Youn, S. W.; Sezen, B.; Sames, D. *J. Am. Chem. Soc.* **2002**, *124*, 11856. (b) Feldman, K. S.; Saunders, J. C. *J. Am. Chem. Soc.* **2002**, *124*, 9060. (c) Taber, D. F.; Neubert, T. D.; Rheingold, A. L. *J. Am. Chem. Soc.* **2002**, *124*, 12416. (d) Bradley, D. M.; Mapitse, R.; Thomson, N. M.; Hayes, C. J. *J. Org. Chem.* **2002**, *67*, 7613. (e) Doyle, M. P.; Hu, W.; Valenzuela, M. V. *J. Org. Chem.* **2002**, *67*, 2954. (f) Kurosawa, W.; Kan, T.; Fukuyama, T. *J. Am. Chem. Soc.* **2003**, *125*, 8112.

(8) For intermolecular C−H insertions, see: (a) Davies, H. M. L.; Venkataramani, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 2197. (b) Davies, H. M. L.; Gregg, T. M. *Tetrahedron Lett.* **2002**, *43*, 4951. (c) Davies, H. M. L.; Walji, A. M.; Townsend, R. J. *Tetrahedron Lett.* **2002**, *43*, 4981. For reviews, see: (d) Davies, H. M. L. *J. Mol. Catal. A* **2002**, *189*, 125. (e) Davies, H. M. L.; Antoulinakis, E. G. *J. Organomet. Chem.* **2001**, *617−618*, 45.

(9) Yoshimitsu, T.; Tsunoda, M.; Nagaoka, H. *Chem. Commun.* **1999**, 1745.

(10) Yoshimitsu, T.; Arano, Y.; Nagaoka, H. *J. Org. Chem.* **2003**, *68*, 625.

(11) For reviews of radical reactions with organoborane, see: (a) Ollivier, C.; Renaud, P. *Chem. Rev.* **2001**, *101*, 3415. (b) Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Synlett*, **2002**, 674. (c) Oshima, K.; Utimoto, K. *J. Synth. Org. Chem., Jpn.* **1989**, 40.

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

(13) Figadere, B.; Cave, A. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: New York, 1996; Vol. 18; p 193.

(14) Syntheses of muricatacin (after 1998): (a) Raghavan, S.; Joseph, S. C. *Tetrahedron: Asymmetry* **2003**, *14*, 101. (b) Carda, M.; Rodriguez, S.; González, F.; Castillo, E.; Villanueva, A.; Marco, J. A. *Eur. J. Org. Chem.* **2002**, *15*, 2649. (c) Chandrasekhar, M.; Chandra, K. L.; Singh, V. K. *Tetrahedron Lett.* **2002**, *43*, 2773. (d) Konno, H.; Hiura, N.; Yanaru, M. *Heterocycles* **2002**, *57*, 1793. (e) Baylon, C.; Prestat, G.; Heck, M.-P.; Mioskowski, C. *Tetrahedron Lett.* **2000**, *41*, 3833. (f) Trost, B. M.; Rhee, Y. H. *J. Am. Chem. Soc.* **1999**, *121*, 11680. (g) Solladie, G.; Hanquet, G.; Izzo, I.; Crumbie, R. *Tetrahedron Lett.* **1999**, *40*, 3071. (h) Couladouros, E. A.; Mihou, A. P. *Tetrahedron Lett.* **1999**, *40*, 4861. (i) Yoon, S.-H.; Moon, H.-S.; Hwang, S.-K.; Choi, S. R.; Kang, S.-K. *Bioorg. Med. Chem.* **1998**, *6*, 1043. (j) Szlosek, M.; Franck, X.; Figadère, B.; Cavé, A. *J. Org. Chem.* **1998**, *63*, 5169. (k) Chang, S.-W.; Hung, C.-Y.; liu, H.-H.; Uang, B.-J. *Tetrahedron: Asymmetry* **1998**, *9*, 521.

(15) Addition of 2-[(trimethylsilyl)oxy]furan to aldehydes providing muricatacin building blocks, see: Rassu, G.; Pinna, L.; Spanu, P.; Zanardi, F.; Battistini, L.; Casiraghi, G. *J. Org. Chem.* **1997**, *62*, 4513. See also ref 14j.

(16) A ketone−THF coupling mediated by iodobenzene−SmI_2, see: (a) Inanaga, J.; Ishikawa, M.; Yamaguchi, M. *Chem. Lett.* **1987**, 1485. (b) Kagan, H. B.; Namy, J. L.; Girard, P. *Tetrahedron*, **1981**, *37*, 175.

(17) Radical aminoalkylation of THF with use of Me_2Zn: (a) Yamada, K.; Fujihara, H.; Yamamoto, Y.; Miwa, Y.; Taga, T.; Tomioka, K. *Org. Lett.* **2002**, *4*, 3509. (b) Yamada, K.; Yamamoto, Y.; Tomioka, K. *Org. Lett.* **2003**, *5*, 1797. Also see: (c) Torrente, S.; Alonso, R. *Org. Lett.* **2001**, *3*, 1985. (d) Fernández, M.; Alonso, R. *Org. Lett.* **2003**, *5*, 2461.

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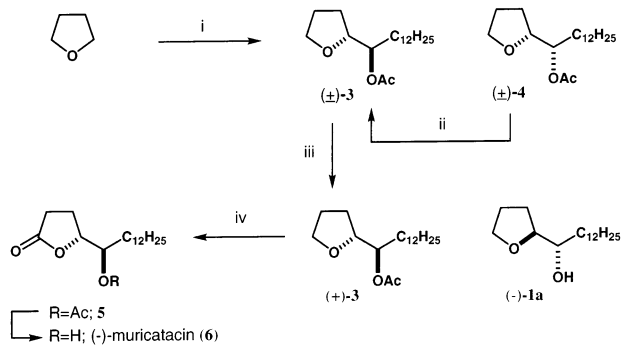
SCHEME 2[a]



[a] Reagents and conditions: (i) (a) tridecanal, Et_3B, *tert*-butyl hydroperoxide, 0 °C to room temperature, 64%, (b) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt, 84% (**3**/**4** 65/35). (ii) (a) LAH, THF, 0 °C to room temperature, 99%, (b) DEAD, Ph_3P, acetic acid, toluene, −15 °C, 76%. (iii) PLE, MeCN, phosphate buffer (pH 8), rt, (+)-**3** (49%, 79% ee), (−)-**1a** (47%, 90% ee). (iv) $RuCl_3 \cdot nH_2O$, $NaHCO_3$, $NaIO_4$, CCl_4, MeCN, H_2O, rt, 66%. (v) K_2CO_3, EtOH, rt, then PPTS, benzene, reflux, 94%, recrystallization.

lithium aluminum hydride in THF followed by Mitsunobu reaction [DEAD, Ph_3P, AcOH, toluene, −15°C].[18] Enzymatic resolution of racemic acetate **3** with PLE (porcine liver esterase) in acetonitrile−phosphate buffer (pH 8.0) at 25 °C afforded enantiomerically enriched acetate (+)-**3** (79% ee, 49% yield) and alcohol (−)-**1a** (90% ee, 47% yield). α′-C−H oxidation of (+)-**3** with ruthenium tetroxide under a modified Sharpless condition[19] gave (−)-acetyl muricatacin (**5**) (66%) along with 4-keto-5-acetoxyheptadecanoic acid (32%). Ethanolysis of **5** followed by acid treatment of the crude mixture produced (−)-muricatacin (**6**) in 94% yield and subsequent recrystallization from diethyl ether/pentane provided optically pure (−)-(**6**): mp 71−73°C [lit.[20] mp 73−74°C, lit.[14a] mp 72°C], $[\alpha]^{28}_D$ −23.2 (*c* 1.5, $CHCl_3$) [lit.[20] $[\alpha]^{28}_D$ −23.1 (*c* 2.36, $CHCl_3$), lit.[14a] $[\alpha]^{28}_D$ −22.8 (*c* 1.0, $CHCl_3$)].

Alternatively, (−)-muricatacin (**6**) (>97% ee) was obtained via chromatographic separation of diastereomeric carbonates **7** and **8** derived from (±)-**1a** (Scheme 3): (±)-**1a** was transformed into **7** and **8** upon treatment with (+)-menthyl chloroformate in pyridine. Oxidation of **7** with ruthenium tetroxide[19] and subsequent removal of the menthoxycarbonyl group of **9** with K_2CO_3 in MeOH afforded (−)-**6** (>97% ee) in 58% overall yield.

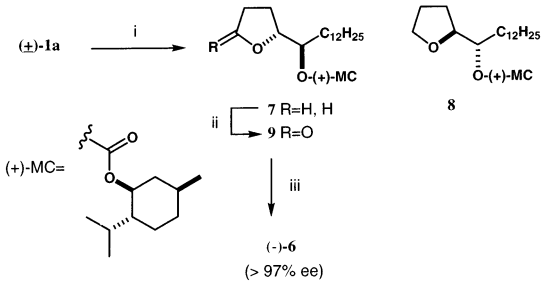
In conclusion, the present mode of functionalization of THF makes possible the unprecedented chemical transformation of the common cyclic ether into (−)-muricatacin (**6**). In considering the availability of starting materials and simple transformations, this synthesis should constitute an efficient alternative to the previous ones which require rather functionalized substrates and reagents. The strategy presented in this study should prove applicable to the synthesis of various γ-(hydroxyalkyl)-γ-butyrolactones that may serve as bioactive compounds as well as useful building blocks in organic synthesis.

(18) (a) Mitsunobu, O. *Synthesis* **1981**, 1. (b) Hughes, D. L.; Reamer, R. A. *J. Org. Chem.* **1996**, *61*, 2967 and references therein.

(19) (a) Han, J.-S.; Lowary, T. L. *J. Org. Chem.* **2003**, *68*, 4116. (b) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.

(20) Wang, Z.-M.; Zhang, X.-L.; Sharpless, K. B.; Shinha, S. C.; Shinha-Bagchi, A.; Keinan, E. *Tetrahedron Lett.* **1992**, *33*, 6407.

SCHEME 3[a]



[a] Reagents and conditions: (i) (+)-menthyl chloroformate, pyridine, 0°C to room temperature, **7** (50%), **8** (50%). (ii) $RuCl_3 \cdot nH_2O$, $NaHCO_3$, $NaIO_4$, $NaHCO_3$, CCl_4, MeCN, H_2O, rt, 61%. (iii) K_2CO_3, MeOH, rt, then PPTS, benzene, reflux, 95%.

Studies on the synthesis of more complex acetogenins, in which the uniqueness of the C−H functionalization strategy will become more imposing, are presently underway.

Experimental Section

General. For details, see the Supporting Information.

***threo*-α-Dodecyltetrahydrofurfuryl Acetate (3)/*erythro*-α-Dodecyltetrahydrofurfuryl Acetate (4).** To a solution of tridecanal (2.0 g, 10.0 mmol) in THF (57 mL, 700 mmol) at 0 °C was added Et_3B (8.7 mL, 5.88 g, 60.0 mmol). At 8 min, 6.24 M *tert*-butyl hydroperoxide in nonane (12.8 mL, 80.0 mmol) was added *dropwise* to the reaction mixture over a period of 30 min. [**Caution:** *Triethylborane, a liquid pyrophoric toward oxygen, should be handled so as to avoid exposure to air. The addition of tert-butyl hydroperoxide to the reaction mixture results in exothermic reaction and gas evolution. No violent reaction by the present procedures has occurred but still, special care is advised.*] After being stirred at room temperature for 1 h, the reaction mixture was allowed to cool to 0 °C and treated with 28% NH_4OH and then sat. $Na_2S_2O_3$. The mixture was extracted with Et_2O and washed with brine, and the organic extracts were dried over $MgSO_4$. Following solvent evaporation in vacuo, the residue was purified by silica gel chromatography (AcOEt/hexane 1:4) to give alcohols **1a**/**2a** (1.47 g, 64% based on tridecanal (0.3 g recovery)) as colorless oil. Spectroscopic data (^1H and ^{13}C NMR, IR, mass) of **1a** and **2a** were identical with those reported (see ref 10). To a solution of **1a**/**2a** (1.47 g, 5.44 mmol) in CH_2Cl_2 (15 mL) at room temperature were added Et_3N (2.3 mL, 16.2 mmol), Ac_2O (0.76 mL, 8.1 mmol), and DMAP (131 mg, 1.08 mmol). After being stirred at room temperature for 13 h, the mixture was extracted with Et_2O and washed with water and the extracts were dried over $MgSO_4$. The solvent was removed in vacuo and the residue was filtered through silica gel pad (Et_2O/hexane 1:3) to provide acetates **3**/**4** (1.43 g, 84%) as a colorless oil. The ratio **3**/**4** was determined to be 65:35 by ^1H NMR analysis. Further purification of the acetates by silica gel chromatography afforded pure *threo*-acetate **3** and *erythro*-acetate **4**. ***threo*-Acetate 3:** IR (neat) ν_{max} 2930, 1738, 1464, 1373, 1244 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.88 (dt, 1H, J = 6.8, 5.8 Hz), 3.93−3.70 (m, 3H), 2.08 (s, 3H), 1.98−1.81 (m, 3H), 1.61−1.50 (m, 3H), 1.35−1.20 (m, 20H), 0.87 (t, 3H, J = 6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 79.6, 75.3, 68.2, 31.9, 31.2, 29.68, 29.65, 29.59, 29.55, 29.52, 29.4, 28.0, 26.0, 25.4, 22.7, 21.2, 14.1; HRMS (FAB) calcd for $C_{19}H_{37}O_3$ (MH^+) 313.2744, found 313.2752. ***erythro*-Acetate 4:** IR (neat) ν_{max} 2926, 2855, 1744, 1464, 1371, 1238, 1076 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.95 (m, 1H), 3.93−3.73 (m, 3H), 2.06 (s, 3H), 1.96−1.79 (m, 3H), 1.75−1.66 (m, 1H), 1.60−1.53 (m, 2H), 1.35−1.20 (m, 20H), 0.88 (t, 3H, J = 6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 79.8, 75.0, 68.5, 31.9, 30.7, 29.6, 29.58, 29.52, 29.48, 29.45, 29.3, 27.3, 25.7, 25.3, 22.6, 21.1, 14.0; HRMS (FAB) calcd for $C_{19}H_{37}O_3$ (MH^+) 313.2744, found 313.2736.

Transformation of *erythro*-Acetate 4 into *threo*-Acetate 3. To a solution of *erythro*-acetate **4** (1.86 g, 5.96 mmol) in THF (40 mL) at 0 °C was added LAH (248 mg, 6.55 mmol). The mixture was stirred at 0 °C for 10 min and additionally at room temperature for 1 h. The mixture, cooled to 0 °C, was treated with 28% NH_4OH and stirred at room temperature for 30 min. Following Celite addition, the mixture was stirred at room temperature for 30 min and filtered. Subsequent solvent evaporation and purification of the residue by silica gel chromatography (AcOEt/hexane 1:4) afforded *erythro*-alcohol **2a** (1.6 g, 99%) as a colorless waxy solid. To a solution of **2a** (1.03 g, 3.82 mmol) in toluene (130 mL) at −15 °C were added Ph_3P (5.0 g, 19.1 mmol) and diethyl azodicarboxylate (8.3 mL, 19.1 mmol). At 15 min, AcOH (0.22 mL, 3.82 mmol) was added and the mixture was stirred at the same temperature for 7 h during which time additional AcOH (0.11 mL, 1.91 mmol) was added three times. The mixture was poured into sat. $NaHCO_3$, extracted with Et_2O and the extracts were dried over $MgSO_4$. Solvent evaporation in vacuo and purification of the residue by silica gel chromatography (AcOEt/hexane 1:7) gave acetate **3** (0.91 g, 76%) as a colorless oil.

Enzymatic Resolution of (±)-3. To a solution of (±)-acetate **3** (98 mg, 0.31 mmol) in MeCN−0.1 M pH 8 phosphate buffer (1:4 v/v, 4.4 mL) at 25 °C was added PLE (65 mg; 41 units/mg solid; SIGMA). The mixture was stirred at 25 °C for 12 days and filtered through Celite pad to remove solid materials. The filtrate was extracted with Et_2O and washed with water and the organic extracts were dried over $MgSO_4$. Following solvent evaporation in vacuo, the residue was purified by silica gel chromatography (AcOEt/hexane 1:6) to give (+)-**3** (48 mg, 49% yield, 79% ee) and (−)-**1a** (40 mg, 47% yield, 90% ee). Enantiomeric excess was determined by ^{1}H NMR of MTPA esters derived from (+)-**3** and (−)-**1a**. Optical rotation for (+)-**3**: $[\alpha]^{28}_D$ +5.5 (*c* 0.766, $CHCl_3$) (79% ee). Optical rotation for (−)-**1a**: $[\alpha]^{28}_D$ −11 (*c* 0.146, $CHCl_3$) (90% ee).

(−)-Acetyl Muricatacin (5). To a solution of acetate (+)-**3** (312 mg, 1.0 mmol, 79% ee) in CCl_4−MeCN−H_2O (1:1:1 v/v, 18 mL) at room temperature were added $NaHCO_3$ (546 mg, 6.5 mmol), $NaIO_4$ (855 mg, 4.0 mmol), and $RuCl_3 \cdot nH_2O$ (83 mg, 0.4 mmol). After 3.5 h of stirring, the mixture was poured into aq $Na_2S_2O_3$ and extracted with AcOEt. The aqueous layer was acidified with 1 N HCl and extracted with AcOEt. The organic extracts were combined and dried over $MgSO_4$. Following solvent evaporation in vacuo, the residue was purified by column chromatography on silica gel (AcOEt/hexane 1:2) to give **5** (214 mg, 66%) as a colorless waxy solid along with 4-keto-5-acetoxyheptadecanoic acid (108 mg, 32%; methanol as eluent); $[\alpha]^{28}_D$ −3.0 (*c* 0.202, $CHCl_3$) (79% ee); IR (neat) ν_{max} 2924, 2855, 1784, 1744, 1464, 1371, 1236, 1171 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.98 (m, 1H), 4.58 (m, 1H), 2.53 (dd, 1H, J = 7.5, 1.5 Hz), 2.50 (d, 1H, J = 7.5 Hz), 2.28 (ddd, 1H, J = 16, 13, 7.8 Hz), 2.09 (s, 3H), 2.02−1.87 (m, 1H), 1.70−1.60 (m, 2H), 1.30−1.25 (m, 20H), 0.87 (t, 3H, J = 6.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.5, 170.3, 79.8, 74.2, 31.8, 30.4, 29.51, 29.50, 29.47, 29.39, 29.28, 29.23, 29.21, 28.1, 25.0, 23.9, 22.5, 20.8, 14.0; HRMS (FAB) calcd for $C_{19}H_{35}O_4$ (MH^+) 327.2537, found 327.2515.

(−)-Muricatacin (6). To a solution of **5** (93 mg, 0.284 mmol, 79% ee) in EtOH (5 mL) at room temperature was added K_2CO_3 (117 mg, 0.85 mmol). The mixture was stirred for 3.5 h and concentrated in vacuo. The residue was poured into 1 N HCl. The mixture was extracted with Et_2O and the organic extracts were dried over $MgSO_4$. Following solvent evaporation in vacuo, the residue was dissolved in benzene (3 mL). To this was added PPTS (10.6 mg, 0.042 mmol) at room temperature and the mixture was heated under reflux with Dean−Stark apparatus for 35 min. The reaction mixture was poured into sat. $NaHCO_3$, extracted with Et_2O and the organic extracts were dried over $MgSO_4$. The solvent was removed in vacuo to give the crude product, which was purified by column chromatography on silica gel (AcOEt/hexane 2:3) to give (−)-muricatacin **6** (76 mg, 94%) as a colorless solid. Enantiomerically pure (−)-**6** was obtained by recrystallization from Et_2O/pentane. Mp 71−73 °C (Et_2O/pentane). Spectroscopic data of the synthetic **6** were in agreement with those reported;[14,20] $[\alpha]^{28}_D$ −23.2 (*c* 1.5, $CHCl_3$) (>99% ee determined by ^{1}H NMR of MTPA ester); IR (neat) ν_{max} 3402, 2918, 2847, 1745, 1470, 1190 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.41 (dt, 1H, J = 7.3, 4.6 Hz), 3.57 (m, 1H), 2.66−2.49 (m, 2H), 2.30−2.20 (m, 1H), 2.17−2.07 (m, 1H), 1.81 (m, 1H), 1.60−1.45 (m, 2H), 1.45−1.20 (m, 20H), 0.88 (t, 3H, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.3, 82.9, 73.4, 32.9, 31.9, 29.6, 29.54, 29.48, 29.3, 28.6, 25.5, 24.0, 22.6, 14.1; HRMS (EI) calcd for $C_{17}H_{32}O_3$ (M^+) 284.2353, found 284.2358.

Chromatographic Separation of Carbonates 7 and 8 Derived from (±)-1a. To a solution of (±)-**1a** (2.45 g, 9.07 mmol) in pyridine (50 mL) at 0 °C was added (+)-menthyl chloroformate (2.9 mL, 13.6 mmol). The mixture was stirred at 0 °C for 10 min and then at room temperature for 3 h. The mixture was extracted with Et_2O and washed with 1 N HCl and sat. $NaHCO_3$, and the extracts were dried over $MgSO_4$. The solvent was removed in vacuo and the residue was purified by silica gel chromatography (Et_2O/hexane 1:7) to give **7** (2.04 g, 50%) and **8** (2.04 g, 50%) as a colorless oil. **7**: $[\alpha]^{28}_D$ +41 (*c* 1.042, $CHCl_3$); IR (neat) ν_{max} 2926, 1738, 1464, 1261 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.68 (m, 1H), 4.53 (dt, 1H, J = 10.7, 4.1 Hz), 3.93 (m, 1H), 3.84 (m, 1H), 3.74 (m, 1H), 2.07−1.83 (m, 5H), 1.70−0.86 (m, 39H), 0.80 (d, 3H, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.2, 79.6, 79.3, 78.1, 68.2, 47.1, 40.8, 34.2, 32.0, 31.5, 31.0, 29.7, 29.67, 29.6, 29.5, 29.49, 29.4, 27.8, 26.2, 25.7, 25.5, 23.5, 22.7, 22.0, 20.7, 16.4, 14.2; HRMS (FAB) calcd for $C_{28}H_{53}O_4$ (MH^+) 453.3946, found 453.3949. **8**: $[\alpha]^{28}_D$ +27.4 (*c* 1.01, $CHCl_3$); IR (neat) ν_{max} 2926, 1738, 1458, 1261 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.70 (ddd, 1H, J = 9.5, 5.9, 4.1 Hz), 4.53 (dt, 1H, J = 11, 4.4 Hz), 3.92 (m, 1H), 3.86 (m, 1H), 3.78−3.72 (m, 1H), 2.10−2.04 (m, 1H), 2.03−1.80 (m, 4H), 1.70−0.86 (m, 39H), 0.79 (d, 3H, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.2, 79.7, 79.2, 78.1, 68.2, 47.1, 40.8, 34.2, 32.0, 31.5, 31.1, 29.7, 29.68, 29.6, 29.55, 29.5, 29.4, 27.9, 26.2, 26.0, 25.4, 23.5, 22.7, 22.0, 20.7, 16.3, 14.2; HRMS (FAB) calcd for $C_{28}H_{53}O_4$ (MH^+) 453.3946, found 453.3949.

Transformation of Carbonate 7 into (−)-Muricatacin (6). With the procedure similar to that used for the transformation of (+)-**3** into **5**, α′-C−H oxidation of **7** (300 mg, 0.664 mmol, >97% ee) was carried out to afford **9** (189 mg, 61%) as a colorless solid along with 4-keto-5-menthoxycarbonyloxyheptadecanoic acid (106 mg, 33%). **(+)-Menthoxycarbonyl muricatacin (9):** mp 34−35 °C; $[\alpha]^{28}_D$ +39.5 (*c* 0.876, $CHCl_3$) (>97% ee); IR (neat) ν_{max} 2924, 1790, 1738, 1462, 1259 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.81 (m, 1H), 4.59 (ddd, 1H, J = 9.8, 5.9, 3.9 Hz), 4.52 (dt, 1H, J = 10.7, 4.4 Hz), 2.61−2.44 (m, 2H), 2.35−2.26 (m, 1H), 2.07−1.88 (m, 3H), 1.78−0.86 (m, 38H), 0.80 (d, 3H, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1, 154.7, 79.7, 78.7, 78.1, 46.9, 40.6, 34.0, 31.9, 31.4, 30.3, 29.6, 29.57, 29.55, 29.4, 29.36, 29.3, 29.2, 27.9, 26.3, 25.1, 23.8, 23.4, 22.6, 21.9, 20.6, 16.3, 14.1; HRMS (FAB) calcd for $C_{28}H_{51}O_5$ (MH^+) 467.3738, found 467.3730. Methanolysis of **9** (189 mg, 0.406 mmol) with K_2CO_3 (224 mg, 1.62 mmol) in MeOH (5 mL) at room temperature for 11 h and subsequent lactonization as described above provided (−)-**6** (109 mg, 95% yield, >97% ee).

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of new compounds **3**, **4**, **5**, **7**, **8**, **9**, and (−)-muricatacin (**6**). This material is available free of charge via the Internet at http://pubs.acs.org.

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