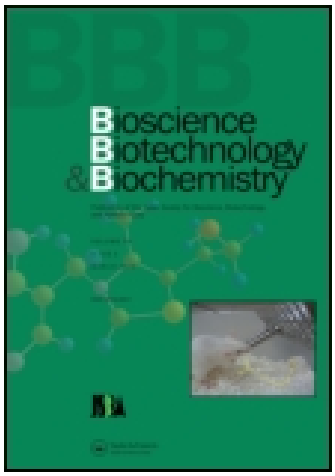

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Synthesis of (-)-Muricatacin

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Note

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The synthesis of (−)-muricatacin starting from 1-bromododecane and 2-pentyn-1-ol is described. 2-Pentadecyn-1-ol (4), which was prepared from 1-bromododecane (2) and 2-pentyn-1-ol (3), was converted to epoxy alcohol 6 through a two-step reaction sequence, 6 being successively submitted to tosylation, iodination, chain extension with *tert*-butyl lithioacetate, and acid-catalyzed cyclization to give (−)-muricatacin (1a). Recrystallization afforded optically pure 1a.

Muricatacin, an acetogenin derivative that has shown cytotoxicity toward human tumorial cell lines, has recently been isolated by McLaughlin and co-workers from seeds of the tropical fruit, *Annona muricata*.[1] The isolated material was determined to be a mixture of enantiomers (−)-(4*R*,5*R*) (**1a**), and (+)-(4*S*,5*S*) (**1b**), with a slight predominance of the former. Until now, six reports on the synthesis of **1a** and/or **1b** have appeared in the literature.[2–7] In this paper, we describe an enantioselective synthesis of (−)-muricatacin (**1a**) in seven steps.

2-Pentadecyn-1-ol (**4**) was prepared by alkylating 2-propyn-1-ol (**3**) with **2**, employing lithium amide in liquid ammonia. Catalytic hydrogenation of **4** over Lindlar catalyst gave (*Z*)-allyl alcohol **5**. Asymmetric epoxidation of **5** by the improved Sharpless procedure[8] with L-(+)-diethyl tartrate afforded epoxy alcohol **6**, which showed 84% *e.e.* by a ^{1}H-NMR analysis of the corresponding Mosher ester.

Transformation of **6** into iodide **8** was effected in two steps through tosylate **7**. Epoxy iodide **8** was then subjected to alkylation with the lithium enolate of *tert*-butyl acetate[9] in tetrahydrofuran to yield **9** in a good yield. Finally, **9** was treated with camphorsulfonic acid to afford **1a**, which after two recrystallization steps gave optically pure (about 100% *e.e.*) (−)-muricatacin (**1a**). The optical rotation, ^{1}H- and ^{13}C-NMR spectra, and the melting point of synthetic **1a** are in good agreement with the reported values.[3]

Fig. 1.

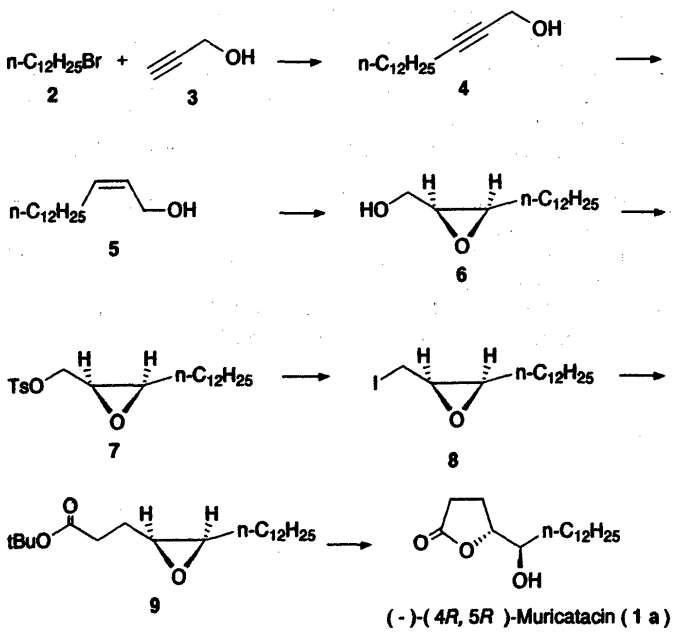

Fig. 2.

Experimental

All melting point (mp) values are uncorrected. Optical rotation was measured with a JASCO DIP-4 spectrometer. IR spectra were taken with a JASCO IR-810 infrared spectrometer, and ^{1}H- and ^{13}C-NMR spectra were measured with JEOL GSX-270 (270 MHz) and GSX-400 (400 MHz) spectrometers. MS spectra were recorded with a JEOL JMS-DX-300 instrument.

2-Pentadecyn-1-ol (**4**). To a $LiNH_2$ solution, which had been prepared from Li (7.0 g, 1.01 mol) and liq NH_3 (450 ml), was added gradually a solution of 2-propyn-1-ol (**3**, 28 g, 0.45 mol) in Et_2O (50 ml) over 30 min. After stirring for 2 h, a solution of 1-bromododecane (**2**, 74.8 g, 0.30 mol) in Et_2O (50 ml) was added to the solution over 1 h. After stirring had been continued for a further 1 h, dry DMSO (85 ml) was added, and the ammonia was allowed to evaporate overnight. Ether (300 ml) and water (300 ml) were then added, before the aqueous layer was extracted with ether (3 × 50 ml). After the usual work-up, the crude product was chromatographed over silica gel, and elution with hexane–AcOEt (3 : 1) gave **4** (47.1 g, 71%) as colorless needles, mp 41–42.5°C. IR (KBr) ν_{max} cm^{-1}: 3340, 3200, 2950, 2930, 2850, 2290, 2230, 1470, 1130, 1020, 720. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6.6 Hz), 1.26–1.47 (20H, m), 1.54 (1H, br. OH), 2.20 (2H, tt, J=7.1, 2.2 Hz), 4.25 (2H, t, J=2.2 Hz). HREIMS: Found, 224.2134; Calcd. for $C_{15}H_{28}O$, 224.2140.

(*Z*)-*2-Pentadecen-1-ol* (**5**). A solution of **4** (2.95 g, 14.5 mmol) in MeOH (25 ml) was hydrogenated over 5% palladium on $CaCO_3$ (50 mg) for 6 h. Filtration and evaporation of the reaction mixture provided an oil, which was chromatographed on silica gel with hexane–AcOEt (3 : 1) as the eluent to give **5** (2.71 g, 91%) as a colorless oil. IR (film) ν_{max} cm^{-1}: 3330, 3020, 2960, 2930, 2850, 1655, 1465, 1375, 1020, 720. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6.7 Hz), 1.20 (1H, br. OH), 1.26–1.47 (20H, m), 2.08 (2H, m), 4.20 (2H, m), 5.57 (2H, m). HREIMS: Found, 226.2289; Calcd. for $C_{15}H_{30}O$, 226.2297.

(*2S,3R*)-*2,3-Epoxypentadecanol* (**6**). A mixture of powdered, activated 4A molecular sieves (1.95 g) in CH_2Cl_2 (100 ml) was cooled to 0°C. L-(+)-diethyl tartrate (0.99 g, 4.8 mmol) and Ti(Oiso-Pr)$_4$ (0.82 g, 2.87 mmol) were added sequentially to the stirred mixture. After the mixture had been cooled to −20°C, *tert*-butyl hydroperoxide (37.6 ml, 113 mmol, 3.0 M in toluene) was added, and the resulting mixture was stirred for 20 min, whereupon **5** (13.0 g, 57.5 mmol) was added. After an initial 0.5 h period of stirring at −20°C, the reaction mixture was refrigerated (*ca.* −12°C) for 1 wk. After the reaction was completed, the mixture was warmed to 0°C, the catalyst was quenched with water (14 ml), and the

usual work-up afforded **6**, which upon recrystallization from hexane, gave pure **6** (10.55 g, 76%) as colorless needles (84% *e.e.* by a ^{1}H-NMR analysis of the ester derived from the (+)-MTPA chloride), mp 66–67°C. $[\alpha]_D^{24}$ −4.2° (c=2.2, $CHCl_3$). IR (KBr) ν_{max} cm^{-1}: 3400, 3300, 2950, 2920, 2850, 1470, 1035, 900, 875, 850, 715. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6.6 Hz), 1.26–1.58 (22H, m), 1.74 (1H, br. OH), 3.04 (1H, ddd, J=6.6, 5.6, 4.4 Hz), 3.15 (1H, ddd, J=6.8, 4.4, 4.2 Hz), 3.68 (1H, dd, J=12.2, 4.2 Hz), 3.84 (1H, dd, J=12.2, 6.8 Hz). HREIMS: Found, 242.2247; Calcd. for $C_{15}H_{30}O_2$, 242.2246.

(2S,3R)-1-Iodo-2,3-epoxypentadecane (**8**). To an ice-cooled mixture of **6** (4.84 g, 20 mmol), Et_3N (2.43 g, 24 mmol) and 4-dimethylaminopyridine (10 mg) in CH_2Cl_2 (200 ml) was added *p*-TsCl (4.57 g, 24 mmol). After being stirred in an ice bath for 1 h and then at room temperature for 5 h, the mixture was diluted with CH_2Cl_2 and washed with water. Drying and subsequent evaporating gave crude tosylate **7** as a colorless oil, which was used in the next step without further purification. Tosylate **7** was dissolved in acetone (200 ml), and NaI (30 g, 200 mmol) was added. After being stirred at room temperature for 2 d, the mixture was filtered, and the filtrate was evaporated. The residue was chromatographed over silica gel, and elution with hexane–AcOEt (20:1) gave **8** (6.84 g, 97%) as a colorless oil, $[\alpha]_D^{26}$ +41° (c=1.39, $CHCl_3$). IR (film) ν_{max} cm^{-1}: 2920, 2850, 1470, 1420, 1265, 1180, 1145, 1115, 1020, 955, 850, 835, 820, 720, 610. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6.7 Hz), 1.26–1.58 (22H, m), 2.95–3.11 (2H, m), 3.26–3.37 82H, m). HREIMS: Found, 352.1257; Calcd. for $C_{15}H_{29}OI$, 352.1263.

(4S,5R)-tert-Butyl-4,5-epoxyheptadecanoate (**9**). To a solution of isopropylcyclohexylamine (3.39 g, 24 mmol) in THF (50 ml) was added an *n*-BuLi solution in hexane (1.56 M, 15.4 ml, 24 mmol) at −78°C, after which the mixture was stirred for 60 min. Subsequently, a solution of *tert*-butyl acetate (2.79 g, 24 mmol) in THF (5 ml) was added, and the mixture was stirred for another 60 min. Then **8** (7.04 g, 20 mmol) dissolved in HMPA (5.2 ml, 30 mmol) was added, and the mixture was allowed to warm to room temperature. The reaction mixture was poured into sat. NH_4Cl and extracted with Et_2O. The usual work-up gave pure **9** (5.53 g, 81%) after column chromatography (hexane–AcOEt=5:1), $[\alpha]_D^{24}$ −2.8° (c=1.33, $CHCl_3$). IR (film) ν_{max} cm^{-1}: 2975, 2950, 2920, 2850, 1730, 1465, 1455, 1390, 1360, 1255, 1150, 850. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6.7 Hz), 1.26 (20H, br.), 1.45 (9H, s), 1.50 (2H, m), 1.69–1.88 (2H, m), 2.40 (2H, m), 2.94 (2H, m). HREIMS: Found, 340.2964; Calcd. for $C_{21}H_{40}O_3$, 340.2977.

(4R,5R)-5-Hydroxyheptadecan-4-olide[(−)-*Muricatacin*] (**1a**). To a solution of **9** (128 mg, 0.38 mmol) in CH_2Cl_2 (5 ml) was added camphorsulfonic acid (44.1 mg, 0.19 mmol) at 0°C, and the mixture was stirred for 15 h at this temperature. The reaction mixture was filtered through silica gel, and the filtrate was concentrated. The residue was recrystallized from hexane–Et_2O to give **1a** (75 mg, 70%) as colorless needles (84% *e.e.* by a ^{1}H-NMR analysis of the ester derived from the (+)-MTPA chloride). Two more recrystallizations gave optically pure **1a** (about 100% *e.e.*), mp 73°C (lit.,[3] 72°C), $[\alpha]_D^{24}$ −23.5° (c=1.00, $CHCl_3$), {lit.,[3] $[\alpha]_D^{24}$ −22.9° (c=1.1, $CHCl_3$)}. IR (KBr) ν_{max} cm^{-1}: 3400, 2950, 2920, 2850, 1750, 1470, 1375, 1360, 1220, 1190, 1100, 1020, 980, 900, 830, 720. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6.7 Hz), 1.26–1.53 (22H, m), 1.84 (1H, br. OH), 2.12 (1H, ddt, $J_{3a,4}$=7.3 Hz, $J_{3a,3b}$=12.7 Hz), 2.24 (1H, ddt, $J_{3b,4}$=7.3 Hz), 2.54 (1H, dt, $J_{2a,3a}$=$J_{2a,3b}$=10.0 Hz, $J_{2a,2b}$=17.8 Hz), 2.63 (1H, dt, $J_{2b,3a}$=10.0 Hz, $J_{2b,3b}$=5.4 Hz), 3.57 (1H, m), 4.41 (1H, dt, $J_{3,4}$=7.3 Hz, $J_{4,5}$=4.6 Hz). ^{13}C-NMR ($CDCl_3$) δ: 14.0, 22.6, 24.0, 25.4, 28.6, 29.2, 29.4, 29.5, 31.8, 32.9, 73.4, 82.9, 177.4. *Anal.* Found: C, 71.76; H, 11.27. Calcd. for $C_{17}H_{32}O_3$: C, 71.78; H, 11.34%.

References

1) M. J. Rieser, J. F. Kozlowski, K. V. Wood, and J. L. McLaughlin, *Tetrahedron Lett.*, **32**, 1137–1140 (1991).
2) B. Figadère, J.-C. Harmange, A. Laurens, and A. Cavé, *Tetrahedron Lett.*, **32**, 7539–7542 (1991).
3) G. Scholz and W. Tochtermann, *Tetrahedron Lett.*, **32**, 5535–5538 (1991).
4) W. Tochtermann, G. Scholz, G. Bunte, C. Wolff, E.-M. Peters, K. Peters, and H. G. von Schnering, *Liebigs Ann. Chem.*, **1992**, 1069–1080.
5) S.-K. Kang, H.-S. Cho, H.-S. Sim, and B.-K. Kim, *J. Carbohydr. Chem.*, **11**, 807–812 (1992).
6) J. A. Marshall and G. S. Welmaker, *Synlett.*, **1992**, 537–538.
7) Z.-M. Wang, X.-L. Zhang, K. B. Sharpless, S. C. Sinha, A. Sinha-Bagchi, and E. Keinan, *Tetrahedron Lett.*, **33**, 6407–6410 (1992).
8) Y. Gao, R. M. Hanson, J. M. Klunder, S. Y. Ko, H. Masamune, and K. B. Sharpless, *J. Am. Chem. Soc.*, **109**, 5765–5780 (1987).
9) I. Paterson, I. Boddy, and I. Mason, *Tetrahedron Lett.*, **28**, 5205–5208 (1987).