An enantiospecific total synthesis of (+)-muricatacin

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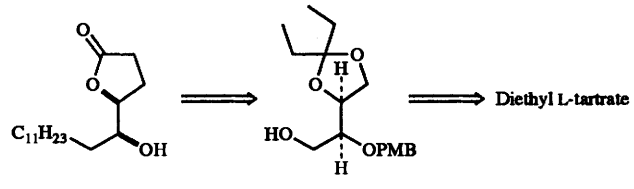
This paper describes an enantiospecific total synthesis of (+)-muricatacin **1** from the L-threitol derivative **2**, itself easily prepared from diethyl L-tartrate.

Muricatacin **1**, an acetogenin related γ-lactone, was recently isolated from the seeds of *Annona muricata*.[1] Interestingly, it was found that the isolated material was a mixture of enantiomers, and by comparison with a synthetic analogue it could be shown that the (4*R*,5*R*) isomer was present in excess (*ent*-**1**, ≈25% ee). Owing to its interesting biological properties, cytotoxic activity against various tumour cell lines, as well as those of the more complex, structurally related acetogenins,[2] muricatacin **1** has become a popular target for organic chemists. To date four total syntheses of **1** have been reported,[3] all of which yielded the title compound in high enantiomeric excess. Recently we described the preparation of the enantiomerically pure protected D-threitol derivative *ent*-**2** in four steps and 83% yield from diethyl D-tartrate[4a] and also demonstrated its utility as a versatile four-carbon unit by incorporating it in our total syntheses of D-*erythro*-sphingosine[4a] and (+)-altholactone.[4b] Subsequent to our initial study, Yonemitsu and co-workers have described a somewhat different preparation of **2**[5a] and, furthermore, used it as a chiral starting material for the synthesis of the C(27)–C(36) subunit of halichondrin B.[5b] As a continuation of our previous investigation we now wish to report on the enantiospecific total synthesis of (+)-muricatacin **1** starting from the readily available derivative **2** (Scheme 1).



(+)-Muricatacin **1** **2**

Scheme 1

Results and discussion

The undecyl side-chain required for (+)-muricatacin was introduced into the alcohol **2** by an efficient two-step procedure previously used by us, as shown in Scheme 2.[4b] Thus, when **2** was treated with toluene-*p*-sulfonyl chloride in pyridine the corresponding tosylate was formed in high yield and the crude product was normally used in the subsequent step. When this material was subjected to a copper-catalysed[6] addition of freshly prepared undecylmagnesium bromide in THF at −30 °C a rapid reaction ensued delivering compound **3** in 82% yield for two steps. Unmasking of the acetal protective group was then effected by exposure to dilute sulfuric acid in methanol furnishing the diol **4** in 91% yield.[7] In order to set the stage for the two-carbon homologation and lactone formation, **4** was converted into the epoxide **5**. Thus, selective tosylation of **4** at the primary hydroxy group and then subjecting the crude reaction product to potassium carbonate in methanol gave **5** in high yield (83% from **4**).

Schreiber and co-workers have developed an efficient protocol for the conversion of a terminal epoxide into the corresponding γ-lactone.[8] Opening of the epoxide with the lithium anion of ethoxyacetylene gives the corresponding hydroxy alkynyl ether which is then treated with mercury(II) chloride and toluene-*p*-sulfonic acid to effect hydrolysis and lactone formation. In a subsequent study, MaGee has shown that lactones can be formed by intramolecular trapping of ketenes, themselves available from the corresponding hydroxy alkynyl ethers by a retro-ene reaction.[9] Of these two methods the latter one seemed more appealing since it would omit the use of heavy metal salts.

Thus, addition of the lithium anion of ethoxyacetylene to the epoxide **5** in THF at −78 °C gave the alkyne **6** in 79% yield. Slow addition of this material to carefully dried refluxing xylenes resulted in the smooth formation of the lactone **7** (79% yield) as the only detectable product. Finally, removal of the PMB-group (DDQ, CH_2Cl_2, H_2O)[10] gave (+)-muricatacin (89% yield), its spectroscopic data being in excellent accord with published values.[1,3]

In conclusion, we have developed an efficient and enantiospecific total synthesis of (+)-muricatacin in 8 steps and 34% overall yield from the readily available L-threitol derivative **2**.

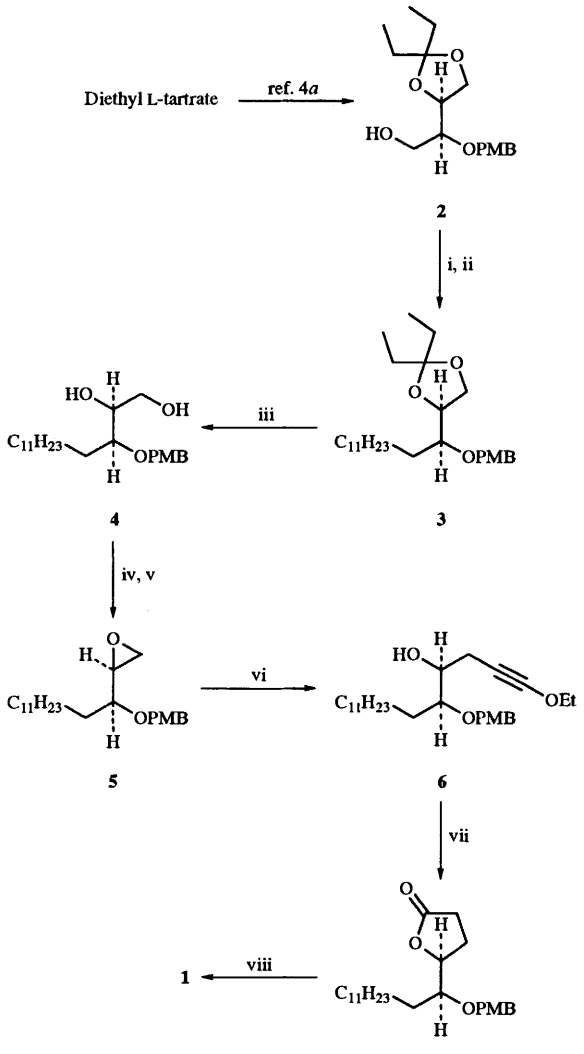
Experimental

^1H and ^{13}C NMR spectra were obtained on a Varian XL-300 spectrometer using $CDCl_3$ ($CHCl_3$ δ 7.26) as solvent. *J* Values are given in Hz. IR spectra were run on a Perkin-Elmer 298 spectrophotometer and only the strongest/structurally most important peaks are listed. Optical rotations ($[\alpha]_D$), measured on a Perkin-Elmer 141 polarimeter at the sodium D line and at ambient temperatures, are recorded in units of 10^{-1} deg cm^2 g^{-1}. Flash chromatography employed Grace Amicon silica gel 60 (0.035–0.070 mm). Pyridine was distilled from calcium hydride immediately before use; tetrahydrofuran (THF) and xylenes were distilled from sodium benzophenone ketyl. All reactions were run in septum-capped, oven-dried flasks under atmospheric pressure of nitrogen, solvents, reactant solutions and liquid reagents being transferred *via* oven-dried syringes.

(1′*S*,4*S*)-2,2-Diethyl-4-[1′-(4-methoxybenzyloxy)tridecyl]-1,3-dioxolane 3

The alcohol **2** was converted into the corresponding tosylate as described in ref. 4*b*.

To a slurry of CuI (0.712 g, 3.730 mmol) in THF (50 cm^3) at −30 °C was added a solution of freshly prepared undecylmagnesium bromide [from 1-bromoundecane (8.790 g, 37.38 mmol) and Mg (0.980 g, 37.38 mmol) in THF (50 cm^3)]. After the resultant mixture had been stirred for 10 min the above-mentioned tosylate (3.469 g, 7.477 mmol) in THF (5 cm^3) was added dropwise to it. The mixture was kept at −30 °C for 90



Scheme 2 *Reagents, conditions and yields:* i, *p*-TsCl, pyridine, 0 °C; ii, $C_{11}H_{23}MgBr$, CuI, THF, −30 °C, 82%; iii, 2% aq. H_2SO_4, MeOH, 91%; iv, *p*-TsCl, pyridine, 0 °C; v, K_2CO_3, MeOH, 83%; vi, ethoxyacetylene, BuLi, BF_3·Et_2O, THF, −78 °C, 79%; vii, heat, xylenes, 79%; viii, DDQ, CH_2Cl_2, H_2O, 89%

min and then poured into Et_2O and aq. NH_4Cl/NH_4OH with rapid stirring. The organic layer was separated and the aqueous phase was extracted twice with Et_2O. The combined organic phases were washed once with brine, dried ($MgSO_4$) and concentrated. Flash chromatography (EtOAc–heptane 1:19 ⟶ 1:4) of the residue gave the title compound **3** (2.116 g, 82%) as an oil (Found: C, 74.9; H, 11.0. $C_{28}H_{48}O_4$ requires C, 74.9; H, 10.8%); $[\alpha]_D$ −3.25 (*c* 2.95 in $CHCl_3$); ν(film)/cm^{-1} 2940 and 1610; δ_H(300 MHz; $CDCl_3$) 7.29 (2 H, *J* 8.9, Ar), 6.86 (2 H, *J* 8.9, Ar), 4.74 (1 H, d, *J* 11.2, O*H*CHAr), 4.56 (1 H, d, *J* 11.2, OHC*H*Ar), 4.15 (1 H, m, O*H*CCHOPMB), 3.97 (1 H, dd, *J* 7.8 and 6.1, *H*CHO), 3.79 (3 H, s, OMe), 3.56 (1 H, t, *J* 7.8, HC*H*O), 3.39 (1 H, m, C*H*OPMB), 1.71–1.59 [4 H, m, OC(CH_2CH_3)], 1.46–1.13 (22 H, m, 2′-H_2–12′-H_2) and 0.98–0.82 [9 H, m, OC(CH_2CH_3) and 13′-H_3]; δ_C(75 MHz; $CDCl_3$) 159.1, 131.2, 129.6, 113.7, 113.2, 79.5, 79.4, 72.6, 66.8, 55.2, 31.9, 31.0, 29.8, 29.7, 29.6, 29.5, 29.4, 25.5, 22.6, 14.1, 8.3 and 8.1 (Found: M^+, 448.3564. Calc. for $C_{28}H_{48}O_4$: M^+, 448.3553).

(2*S*,3*S*)-3-(4-Methoxybenzyloxy)pentadecane-1,2-diol 4

To a stirred solution of compound **3** (2.017 g, 4.502 mmol) in MeOH (50 cm^3) was added 2% aq. H_2SO_4 (0.5 cm^3). After 2 d solid K_2CO_3 was added to the solution and the resultant heterogeneous mixture was stirred for an additional 30 min. The solvents were removed and the residue was dissolved in Et_2O–H_2O. The organic layer was separated and the aqueous phase was extracted twice with Et_2O. The combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated. Flash chromatography (EtOAc–heptane 2:3 ⟶ 1:1) of the residue gave the title compound **4** (1.557 g, 91%) as an oil (Found: C, 72.9; H, 10.6. $C_{23}H_{40}O_4$ requires C, 72.6; H, 10.6%); $[\alpha]_D$ +26.0 (*c* 1.08 in $CHCl_3$); ν(film)/cm^{-1} 3400, 2910 and 1615; δ_H(300 MHz; $CDCl_3$) 7.25 (2 H, d, *J* 9.0, Ar), 6.88 (2 H, d, *J* 9.0, Ar), 4.60 (1 H, d, *J* 10.7, *H*CHAr), 4.39 (1 H, d, *J* 10.7, HC*H*Ar), 3.79 (3 H, s, OMe), 3.72–3.55 (3 H, m, CH_2OH and C*H*OH), 3.44 (1 H, m, C*H*OPMB), 2.58 (1 H, m, OH), 2.23 (1 H, m, OH), 1.61–1.49 (2 H, m, 4-H_2), 1.41–1.07 (20 H, m, 5-H_2–14-H_2) and 0.88 (3 H, m, 15-H_3); δ_C(75 MHz; $CDCl_3$) 159.4, 130.2, 129.6, 114.0, 79.4, 72.7, 71.8, 64.1, 55.3, 31.9, 30.2, 29.9, 29.7, 29.6, 29.4, 25.1, 22.7 and 14.1 (Found: M^+, 380.2925. Calc. for $C_{23}H_{40}O_4$: M^+, 380.2927.

(2*S*,3*S*)-3-(4-Methoxybenzyloxy)-1,2-epoxypentadecane 5

To a solution of compound **4** (1.584 g, 4.169 mmol) in pyridine (5 cm^3) at 0 °C was added toluene-*p*-sulfonyl chloride (0.874 g, 4.586 mmol). The resultant mixture was stirred at 0 °C for 13 h and then poured into Et_2O–aq. $CuSO_4$. The layers were separated and the aqueous layer was extracted once with Et_2O. The combined organic phases were washed once with water and once with brine, dried ($MgSO_4$) and concentrated. To the above crude tosylate in MeOH (20 cm^3) at 0 °C was added K_2CO_3 (4.03 g, 29.18 mmol). After the mixture had been stirred for 30 min at 0 °C the solvents were removed and the residue was dissolved in Et_2O–H_2O. The layers were separated and the aqueous phase was extracted once with Et_2O. The combined organic phases were washed once with brine, dried ($MgSO_4$) and concentrated. Flash chromatography (EtOAc–heptane 1:4 ⟶ 1:3) of the residue gave the title compound **5** (1.255 g, 83%) as an oil (Found: C, 76.1; H, 10.7. $C_{23}H_{38}O_3$ requires C, 76.2; H, 10.6%); $[\alpha]_D$ −19.9 (*c* 1.53 in $CHCl_3$); ν(film)/cm^{-1} 2930 and 1615; δ_H(300 MHz; $CDCl_3$) 7.29 (2 H, d, *J* 8.9, Ar), 6.87 (2 H, d, *J* 8.9, Ar), 4.76 (1 H, d, *J* 11.2, *H*CHOAr), 4.52 (1 H, d, *J* 11.2, HC*H*OAR), 3.69 (3 H, s, OMe), 3.10 (2 H, m, HCO and HCOPMB), 2.77 (1 H, m, *H*CHO), 2.48 (1 H, dd, *J* 5.0 and 2.1, HC*H*O), 1.72–1.38 (2 H, m, 4-H_2), 1.37–1.16 (20 H, m, 5-H_2–14-H_2) and 0.88 (3 H, t, *J* 6.7, 15-H_3); δ_C(75 MHz; $CDCl_3$) 159.1, 130.8, 129.4, 113.7, 80.1, 71.3, 55.3, 55.2, 43.2, 32.4, 31.9, 29.7, 29.6, 29.5, 29.4, 25.5 and 14.1 (Found: M^+, 362.2817. Calc. for $C_{23}H_{38}O_3$: M^+, 362.2821).

(4*S*,5*S*)-1-Ethoxy-5-(4-methoxybenzyloxy)heptadec-1-yn-4-ol 6

To a solution of ethoxyacetylene (1.0 g, 6.757 mmol, 50% wt. in hexanes) in THF (10 cm^3) at −78 °C was added BuLi (1.35 mol dm^{-3} in hexanes; 4.17 cm^3, 5.630 mmol). After the solution had been stirred for 20 min BF_3·Et_2O (0.692 cm^3, 5.630 mmol) was added to it followed by a dropwise addition of compound **5** (0.815 g, 2.252 mmol) in THF (10 cm^3). The resultant mixture was stirred for 1 h at −78 °C and then aq. Na_2CO_3 was added to it. The layers were separated and the aqueous phase was extracted once with Et_2O. The combined organic phases were washed once with water and once with brine, dried ($MgSO_4$) and concentrated. Flash chromatography (EtOAc–heptane 1:4 ⟶ 1:3) of the residue gave **6** (0.744 g, 79%) as a slightly greenish oil, $[\alpha]_D$ +26.5 (*c* 1.03 in $CHCl_3$); ν(film)/cm^{-1} 3460, 2930, 2270 and 1610; δ_H(300 MHz; $CDCl_3$) 7.27 (2 H, d, *J* 8.8, Ar), 6.88 (2 H, d, *J* 8.8, Ar), 4.59 (1 H, d, *J* 10.6, *H*CHAr), 4.48 (1 H, d, *J* 10.6, HC*H*Ar), 4.11 (2 H, q, *J* 12.5, OC$H_2$$CH_3$), 3.80 (3 H, s, OMe), 3.62 (1 H, m, C*H*OH), 3.51 (1 H, m, C*H*OPMB), 2.41–2.32 (2 H, m, CHCC), 1.69–1.52 (2 H, m, 4-H), 1.42–1.17 (23 H, m, 5-H_2–14-H_2 and OCH_2CH_3) and 0.88 (3 H, t, *J* 6.7,

15-H_3); δ_C(75 MHz; $CDCl_3$) 159.3, 130.6, 129.5, 113.8, 90.4, 79.8, 74.1, 72.3, 71.8, 55.2, 33.7, 31.9, 30.5, 29.8, 29.7, 29.6, 29.4, 25.4, 22.7, 22.7, 14.4 and 14.1 (Found: M^+, 432.3238. Calc. for $C_{27}H_{44}O_4$: M^+, 432.3240).

(5*S*,1′*S*)-5-[1′-(4-Methoxybenzyloxy)tridecyl]tetrahydrofuran-2-one 7

A solution of compound **6** (0.539 g, 1.248 mmol) in xylenes (10 cm^3) was added dropwise to refluxing xylenes (30 cm^3) over 30 min. After refluxing the resultant mixture for an additional 2 h it was cooled to room temperature and the solvents were removed. Flash chromatography (EtOAc–heptane 1:4 ⟶ 2:3) of the residue gave the title compound **7** (0.398 g, 79%), mp 51–53 °C (Found: C, 74.3; H, 9.8. $C_{25}H_{40}O_4$ requires C, 74.3; H, 10.0%); $[\alpha]_D$ +10.6 (*c* 0.92 in $CHCl_3$); ν(film)/cm^{-1} 2929, 1750 and 1615; δ_H(300 MHz; $CDCl_3$) 7.27 (2 H, d, *J* 8.7, Ar), 6.87 (2 H, d, *J* 8.7, Ar), 4.59–4.48 (3 H, m, OCH_2Ar and *H*COOC), 3.79 (3 H, s, OMe), 3.38 (1 H, m, HCOPMB), 2.63–2.48 (2 H, m, CH_2COO), 2.19 (1 H, m, *H*$CHCH_2COO$), 1.95 (1 H, m, HC*H*CH_2COO), 1.54 (2 H, m, 2′-H_2), 1.47–1.11 (20 H, m, 3′-H_2–12′-H_2) and 0.88 (3 H, m, 13′-H_3); δ_C(75 MHz; $CDCl_3$) 177.4, 159.3, 130.4, 129.5, 113.8, 81.9, 80.1, 72.3, 55.2, 31.9, 29.8, 29.7, 29.7, 29.6, 29.4, 28.5, 25.3, 24.4, 22.7 and 14.1 (Found: M^+, 404.2926. Calc. for $C_{25}H_{40}O_4$: M^+, 404.2927).

(+)-Muricatacin 1

To a solution of compound **7** (0.052 g, 0.129 mmol) in CH_2Cl_2 (5 cm^3) was added water (2 drops) and DDQ (0.044 g, 0.193 mmol). The resultant mixture was stirred for 45 min and then poured into Et_2O–H_2O. The layers were separated and the aqueous phase was extracted once with Et_2O. The combined organic phases were washed twice with water and once with brine, dried ($MgSO_4$) and concentrated. Flash chromatography (EtOAc–heptane 1:3 ⟶ 2:3) of the residue gave **1** (0.033 g, 89%) as a crystalline solid, mp 72 °C (lit.,[3b] 65 °C, lit.,[3c] 73–74 °C); $[\alpha]_D$ +23.6 (*c* 1.50 in $CHCl_3$) [lit.,[3b] +25 (*c* 1.7 in MeOH), lit.,[3c] +23.02 (*c* 1.26 in $CHCl_3$), lit.,[3d] +22.6]; ν(KBr)/cm^{-1} 3440, 2905 and 1740; δ_H(300 MHz; $CDCl_3$) 4.42 (1 H, dt, *J* 7.4 and 3.9, HCOOC), 3.56 (1 H, m, C*H*OH), 2.69–2.47 (2 H, m, CH_2COO), 2.31–2.04 (2 H, m, CH_2CH_2COO), 1.97 (1 H, br s, OH), 1.68–1.42 (2 H, m, 2′-H_2), 1.40–1.18 (20 H, m, 3′-H_2–12′-H_2) and 0.87 (3 H, m, 13′-H_3); δ_C(75 MHz; $CDCl_3$) 177.2, 82.9, 73.6, 32.9, 31.9, 29.6, 29.6, 29.5, 29.3, 28.7, 25.4, 24.1, 22.7 and 14.1 (Found: M^+, 284.2352. Calc. for $C_{17}H_{32}O_3$: M^+, 284.2351).

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