Concise total synthesis of cytotoxic natural products (+) and (-)-muricatacin

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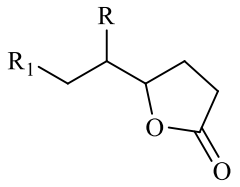
Abstract
A short and efficient total synthesis of antitumor natural products (+) and (-)-muricatacin is described in four steps with an overall yield of 47%. The key reactions involved in the synthesis are Ph_3P mediated isomerization and asymmetric dihydroxylation.

Keywords: Triphenylphosphine mediated isomerization, natural product, butyrolactone, dihydroxylation, total synthesis, muricatacin

Introduction

γ-Butyrolactones (Figure 1) are an important class of natural products with intriguing biological activities[1] such as antitumor,[1d, 1i] antiparasitic,[1e] antibacterial[1f] and pesticidal. Muricatacin **1, 2**, a simple biologically active γ-butyrolactone derivative, belongs to acetogenin class of natural products and was isolated from seeds of the plant *Annona muricata* in 1991 by McLaughlin *et al.*,[2] as a mixture of both enantiomers, with (-) enantiomer as the predominant enantiomer (ca 25%). Interestingly, both isomers show potent cytotoxic activity against a variety of human tumor cell lines.[2] Further, their structure activity relationship studies revealed that the antitumor activities depend mainly upon the length of the alkyl side chains and stereochemistry.[3] Several groups have published total synthesis of (+) or (-)-muricatacin or both[4] and their epi-or aza analogues.[5] Recently Popsavin *et al*., reported that some of the muricatacin analogues are several fold more potent than the original molecule.[6] During the course of our ongoing research related to toxic shock syndrome,[7] we have examined natural products containing long chain alkyl groups with free hydroxyl groups as possible antibacterial agents due to their similarities with glycerol monolaurate.[7] In continuation of our interest in the synthesis of this class of natural products, herein we report a concise total synthesis of (+) and (-)-muricatacin. This method enables the

preparation of a variety of side chain analogues of the natural product for extensive microbiological screening.

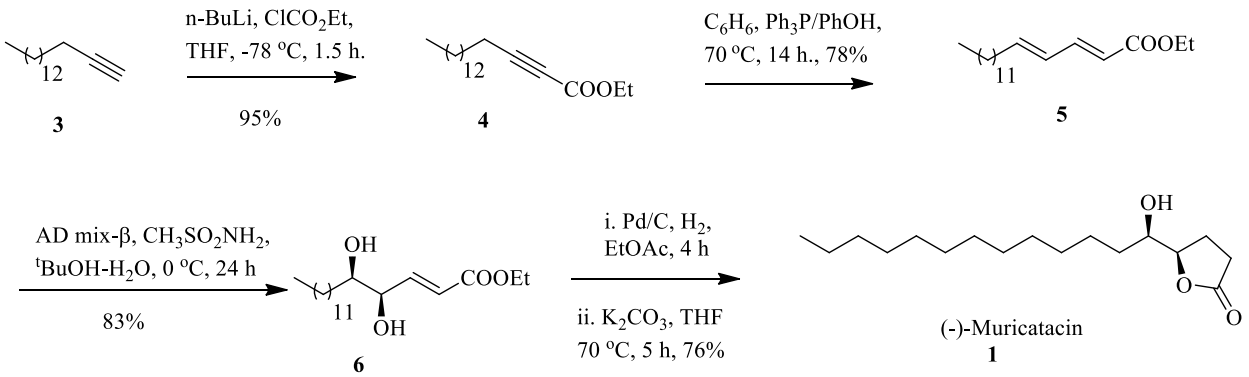


R=H, γ-butyrolactones
R=OH, hydroxy–γ-butyrolactones
R_1=alkyl/aryl

Figure 1

Results and Discussion

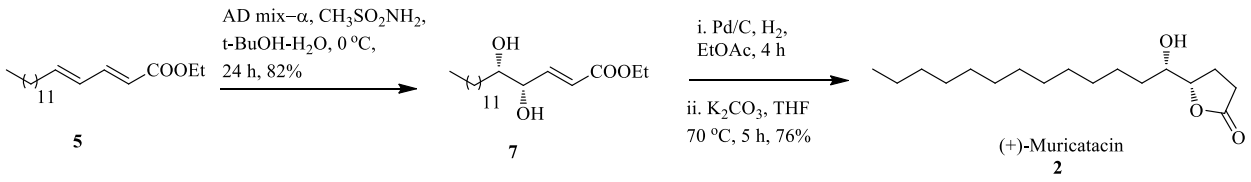
Our synthetic plan was based on our earlier work,[8e] namely the triphenylphosphine-mediated isomerization of acetylenic esters to the corresponding (*E,E*)-αβ-γδ-diene esters, which has attracted considerable attention in the total synthesis of many other natural products.[8] Sharpless Asymmetric Dihydroxylation (SAD)[9] on diene ester is employed as the next key reaction to complete the synthesis of (+) and (-)-muricatacin.[4a] A similar dihydroxylation on diene ester was reported by O'Doherty *et al.*[4u] However, the advantage of our method is a two step synthesis of (*E,E*)-αβ-γδ-diene ester from the alkyne with improved yields whereas the same diene ester synthesis was achieved in five steps starting from the corresponding alcohol.



Scheme 1. Synthesis of (-) muricatacin.

As shown in the Scheme 1, the synthesis of both enantiomers of muricatacin commenced with the commercially available 1-hexadecyne **3**. This was lithiated using *n*-butyllithium at –78

^{o}C, and treated with ethyl chloroformate to form the alkyne-ester **4** in 95% yield. This alkyne ester was ready to form the requisite key intermediate (diene ester) **5** for the synthesis of both enantiomers of the target natural product under modified Trost isomerization conditions.[8] Thus, alkynoate **4,** was treated with Ph_3P/PhOH in benzene at room temperature for 14 h to obtain exclusively (*E,E*)-αβ-γδ -diene esters **5** in 78% yield. Enantio- and regio-selective Sharpless dihydroxylation of diene ester **5** with AD mix β- gave (γδ)-dihydroxy, (αβ)-unsaturated esters **6** as a single product in 83% yield in 24 h.[9] Hydrogention of diol **6** with Pd/C in ethyl acetate for 4 h, followed by refluxing with K_2CO_3 in THF for 5 h furnished (-)- muricatacin **1** in 76% yield. In the similar manner (+)-muricatacin **2** was also synthesized from diene ester **5** (Scheme 2), SAD of **5** with AD-mix α furnished diol **7** in 82% yield which was subjected to Pd/C catalyzed hydrogenation (ethyl acetate, 4 h) followed by refluxing with K_2CO_3 (THF, 5 h) gave (+)-muricatacin **2** in 76 % overall yield for two steps. The spectral and physical data of our synthetic (-) and (+)-muricatacin were in agreement with published literature.[4u]



Scheme 2. Synthesis of (+) muricatacin.

Conclusions

In conclusion, an efficient total synthesis for both enantiomers of antitumor natural product muricatacin was described in four steps using triphenylphosphine mediated isomerization of alkynoate ester to diene ester and Sharpless asymmetric dihydroxylation as key steps. We expect this method to be useful for the synthesis of a variety of side chain analogues and also applicable for large scale synthesis.

Experimental Section

General. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ solvent on BRUKER-400 MHz spectrometer at ambient temperature. Chemical shifts δ are given in ppm, coupling constant *J* are in Hz. The chemical shifts are reported in ppm on scale downfield from TMS as internal standard and signal patterns are indicated as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad peak. FTIR spectra were recorded as NaCl thin films. Optical rotations were measured on digital polarimeter (Autopol V) using a 2 mL cell with a 100 mm path length. For low (MS) and High (HRMS) resolution, *m/z* ratios are reported as values in atomic mass units (Waters,

Micromass). All reagents and solvents were reagent grade and used without further purification unless specified otherwise. Column chromatography was carried out using silica gel (230-400 mesh) packed in glass columns. All reactions were performed under an atmosphere of nitrogen in flame-dried or oven-dried glassware with magnetic stirring.

Ethyl heptadec-2-ynoate (4). To a stirred solution of hexadecyne **3** (0.8 g, 3.6 mmol) in dry THF (10 mL) at -78 ^{o}C was added *n*-BuLi (2.25 mL, 1.6 M in hexanes, 3.6 mmol) slowly under N_2 atmosphere and stirred for 15 min at same temperature. Ethyl chloroformate (0.28 mL, 3.6 mmol) was added to the reaction mixture and stirring was continued for 1 h at the same temperature. Saturated NH_4Cl (5 mL) was added to the reaction mixture at -78 ^{o}C and slowly warmed to rt, ethyl acetate (10 mL) was added to the reaction mixture and organic layer was seperated. The aqueous layer was extracted with EtOAc (2x10 mL), and the combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was purified by silica gel column chromatography using hexanes and ethyl acetate as the eluents (19:1) to get ester **4** as pale yellow oil in 95% yield.
^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.14 (q, *J*= 14.3, 7.1 Hz, 2H), 2.25 (t, *J*= 7.1 Hz, 2H), 1.55-1.46 (m, 2H), 1.37-1.28 (m, 2H), 1.27-1.61 (m, 23H), 0.81 (t, *J*= 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 153.8, 89.4, 73.1, 61.7, 31.9, 29.66, 29.63, 29.61, 29.56, 29.4, 29.3, 29.0, 28.8, 27.5, 22.6, 18.6, 14.1, 14.0; IR (film) ν_{max}: 2925, 2854, 2235, 1714, 1465, 1366, 1249, 1074 cm^{-1}; Mass (ESI, *m/z*): 295.4 $(M+H)^+$.
Ethyl (2*E*,4*E*)-heptadeca-2,4-dienoate (5). A mixture of ester **4** (1.0 g, 3.4 mmol) and Triphenylphosphine (1.34 g, 5.1 mmol) was refluxed in benzene (10 mL) with a catalytic phenol (0.5 mL) for 14 h. After completion of the reaction (monitored by TLC), the solvent was removed under vacuum and the crude product was purified on a silica gel column (eluted with 4% ethyl acetate in hexanes), furnished *(E, E)*-αβ-γδ-unsaturated ester **5** as a colorless oil in 78% yield.
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.21-7.15 (m, 1H), 6.13-6.00 (m, 2H), 5.70 (d, *J*= 15.4 Hz, 1H), 4.03 (q, *J*= 7.1, 2.0 Hz, 2H), 2.08 (q, *J*= 13.2, 6.7 Hz, 2H), 1.62-1.53 (m, 1H), 1.39-1.28 (m, 3H), 1.27-1.15 (m, 19 H), 0.86 (t, *J*= 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.3, 145.1, 144.7, 128.3, 119.1, 60.1, 33.0, 31.9, 30.7, 29.6, 29.58, 29.4, 29.3, 29.2, 28.7, 22.6, 14.3, 14.1; IR (film) ν_{max}: 2925, 2854, 1725, 1660, 1642, 1466, 1302, 1265, 1178 cm^{-1}; Mass (ESI, m/z): 295.2 $(M+H)^+$; HRMS (ESI, *m/z*): calculated for $C_{19}H_{35}O_2$ $(M+H)^+$ 295.2481, found – 295.2479.
Ethyl (4*S*,5*S*,*E*)-4,5-dihydroxyheptadec-2-enoate (6). ADmix-β $K_2OsO_2(OH)_4$ + $K_3Fe(CN)_6$ + K_2CO_3+ ((DHQD)$_2$PHAL] (4.76 g, 1.4 g for 1 mmol of olefin) was dissolved in *t*-BuOH (5 mL) and H_2O (5 mL). Methanesulfonamide (325 mg, 3.4 mmol) and diene **5** (1.0 g, 3.4 mmol) were then added at 0 ^{o}C and the reaction vigorously stirred for 24 h at same temperature. After complete consumption of the starting material, Na_2SO_3 (1 g) was then added and the solution stirred for 1 h after which the reaction was poured into water (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organics were washed with brine (10 mL), and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to yield the crude diol which was

purified by silica gel column chromatography using EtOAc/hexanes (1:4) to yield pure diol **6** in 83% yield as a white solid.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.93 (dd, *J*= 15.6, 5.0 Hz, 1H), 6.13 (dd, *J*= 15.6, 1.5 Hz, 1H), 4.20 (q, *J*= 14.3, 7.1 Hz, 2H), 4.12 (t, *J*= 4.5 Hz, 1H), 3.57-3.53 (m, 1H), 2.59 (s, 1H), 2.20 (s, 1H), 1.59-1.41 (m, 3H), 1.40-1.17 (m, 22H), 0.87 (t, *J*= 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 166.4, 146.9, 122.5, 74.1, 74.0, 60.6, 33.1, 31.9, 29.7, 29.66, 29.61, 29.59, 29.3, 25.6, 22.7, 14.2, 14.1; IR (film) ν_{max}: 3277, 2955, 2917, 2846, 1708, 1665, 1464, 1276 cm^{-1}; Mass (ESI, m/z): 329.2 $(M+H)^+$; HRMS (ESI, m/z): calculated for $C_{19}H_{37}O_4$ $(M+H)^+$ 329.2535, found 329.2521; white solid, mp 77-79 ºC.

Ethyl (4*R*,5*R*,*E*)-4,5-dihydroxyheptadec-2-enoate (7). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.93 (dd, *J*= 15.6, 5.0 Hz, 1H), 6.13 (dd, *J*= 15.6, 1.6 Hz, 1H), 4.20 (q, *J*= 14.3, 7.1 Hz, 2H), 4.10 (t, *J*= 7.1 Hz, 1H), 3.57-3.53 (m, 1H), 2.59 (s, 1H), 2.20 (s, 1H), 1.59-1.41 (m, 3H), 1.40-1.17 (m, 22H), 0.87 (t, *J*= 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 166.2, 146.7, 122.5, 74.1, 74.0, 60.6, 33.1, 31.9, 29.7, 29.66, 29.61, 29.59, 29.3, 25.6, 22.7, 14.2, 14.1; IR (film) ν_{max}: 3277, 2955, 2917, 2846, 1708, 1665, 1464, 1276 cm^{-1}; Mass (ESI, m/z): 329.2 $(M+H)^+$; HRMS (ESI, m/z): calculated for $C_{19}H_{37}O_4$ $(M+H)^+$ 329.2535, found 329.2519; white solid, mp 77-79 ºC.

(*R*)-5-((*R*)-1-Hydroxytridecyl)dihydrofuran-2(3*H*)-one {(-)-muricatacin} (1):[4] $[\alpha]_D^{20}$= -19.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.40 (dt, *J*= 7.6, 4.8 Hz, 1H), 3.59-3.51 (m, 1H), 2.65-2.47 (m, 2H), 2.28-2.18 (m, 1H), 2.18-2.07 (m, 1H), 1.89-1.87 (m, 1H), 1.62-1.49 (m, 3H), 1.45-1.19 (m, 19H), 0.86 (t, *J*= 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 177.1, 82.9, 73.6, 32.9, 31.9, 29.61, 29.60, 29.5, 29.4, 29.3, 28.7, 25.5, 24.1, 22.6, 14.1; IR (neat) ν_{max}: 3400, 2955, 2918, 2849, 1742, 1472, 1453, 1190 cm^{-1}; Mass (ESI, m/z): 285.2 $(M+H)^+$. HRMS (ESI, m/z): calculated for $C_{17}H_{32}O_3$ $(M+H)^+$ 285.2430, found 285.2434; white solid, mp 68-70 °C .

(*S*)-5-((*S*)-1-Hydroxytridecyl)dihydrofuran-2(3*H*)-one {(+)-muricatacin} (2):[4] $[\alpha]_D^{20}$= +19.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.40 (dt, *J*= 7.6, 4.8 Hz, 1H), 3.59-3.51 (m, 1H), 2.65-2.47 (m, 2H), 2.28-2.18 (m, 1H), 2.18-2.07 (m, 1H), 1.89-1.87 (m, 1H), 1.62-1.49 (m, 3H), 1.45-1.19 (m, 19H), 0.86 (t, *J*= 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 177.1, 82.9, 73.6, 32.9, 31.9, 29.61, 29.60, 29.5, 29.4, 29.3, 28.7, 25.5, 24.1, 22.6, 14.1; IR (neat) ν_{max} : 3400, 2955, 2918, 2849, 1742, 1472, 1453, 1190 cm^{-1}; Mass (ESI, m/z): 285.2 $(M+H)^+$. HRMS (ESI, m/z): calculated for $C_{17}H_{33}O_3$ $(M+H)^+$ 285.2430, found 285.2427; white solid, mp 68-70 °C.

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References and Notes

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