Synthesis of (+)-(4*S*,5*S*)-Muricatacin *via* Pd-Catalyzed Stereospecific Hydroxy Substitution Reaction of γ,δ-epoxy α,β-Unsaturated Ester with $B(OH)_3$

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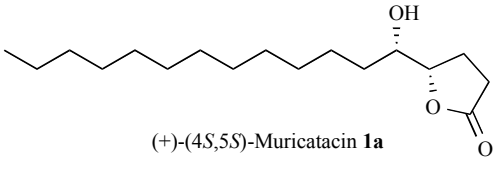
Abstract: The stereoselective synthesis of (+)-(4*S*,5*S*)-muricatacin has been achieved involving the palladium-catalyzed stereospecific hydroxy substitution reaction of γ,δ-epoxy α,β-unsaturated ester with $B(OH)_3$.

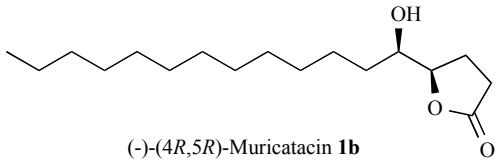
Keywords: γ-Lactone, Pd-catalyzed, γ,δ-epoxy α,β-unsaturated ester, muricatacin, stereospecific.

INTRODUCTION

Muricatacin **1** was isolated by McLaughlin *et al*. from the seeds of the tropical fruit, *Annona muricata* [1]. Interestingly, it was found that the isolated material was a mixture of enantiomers, and both (+)- and (−)-muricatacins exhibit potent cytotoxicity (~1 to 10 μg/mL) toward several human tumor cell lines, immunosuppressant, antimalarial and pesticidal activities [2]. Muricatacins served as precursors in the synthesis of several bioactive natural products [3]. Owing to its interesting biological properties, muricatacin **1** has become a popular target for organic chemists. Although many synthetic approaches [4] to this biologically important molecule have been reported, there is still a need for a new type of methodology that allows the stereospecific synthesis of muricatacin. We herein report a novel method for the synthesis of (+)-muricatacin using the palladium-catalyzed stereospecific hydroxy substitution reaction of γ,δ-epoxy α,β-unsaturated ester with Boric acid as a key step.



(+)-(4*S*,5*S*)-Muricatacin **1a**



(-)-(4*R*,5*R*)-Muricatacin **1b**

Fig. (1). Structures of (+)- and (−)- muricatacins (**1a** and **1b**).

Retrosynthetic analysis is depicted in Scheme **1**. The target molecule **1a** was realized from γ,δ-epoxy α,β-unsaturated ester **2** by Pd-catalyzed stereospecific hydroxy substitution reaction with $B(OH)_3$. The epoxy ester **2** was in turn prepared from aldehyde by simple transformations.

The synthesis of target molecule started from commercially available aldehyde **4** (Scheme **2**). The required allylic alcohol **3** was prepared in 87% overall yield (for 2 steps) from aldehyde **4** as reported [4g] by Wittig olefination/DIBAL-H reduction sequence. Then, **3** was converted in to γ,δ-epoxy α,β-unsaturated ester **2** by a two-step reaction sequence: a) Katsuki-Sharpless asymmetric epoxidation [5] with L-(+)-DIPT, $Ti(O^iPr)_4$ and TBHP in CH_2Cl_2 at –20 °C, leading to epoxy alcohol **5** with 95% ee. b) TEMPO-BAIB oxidation [6] followed by Wittig olefination. The γ,δ-dihydroxy α,β-unsaturated ester **6** (*syn* diol) was obtained with double inversion of configuration (i.e., with retention of configuration) at the γ-position in 92% yield by the reaction of epoxide **2** with boric acid in the presence of palladium catalyst, $Pd(PPh_3)_4$ in THF [7]. The reaction was very fast and completed in 10 min at room temperature. After catalytic hydrogenation of the double bond in **6** over Pd/C in EtOAc, treatment of the crude ester with PTSA in MeOH afforded target (+)-muricatacin **1a** in 62% yield (for two steps). (−)-Muricatacin should also be readily available using L-(-)-DIPT by this route. The synthetic material spectral data and optical rotation value match with the reported data [4b].

In summary, we have applied a palladium-catalyzed reaction of unsaturated epoxy esters to the stereospecific synthesis of muricatacin in excellent yields. Further investigations into the synthetic applications of this methodology are ongoing.

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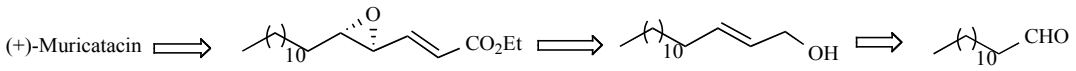
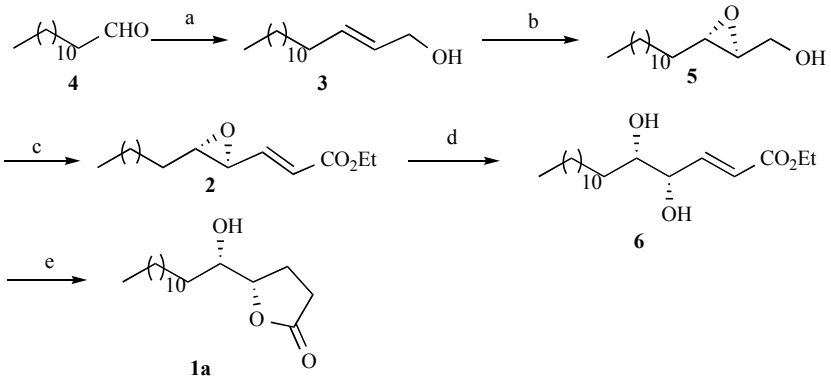


Scheme 1. Retrosynthetic analysis for **1a**.



Scheme 2. Reagents and conditions a) ref 4g, overall yield 87%; b) (+)-DIPT, Ti(^{i}OPr)$_4$, TBHP, dry CH_2Cl_2, -20 ^{o}C, 5 h, 90%, 95% ee; c) (i) TEMPO, BAIB, CH_2Cl_2, 0 ^{o}C – r. t, 1 h; (ii) PPh_3=$CHCO_2Et$, benzene, reflux, 1 h, (76% yield from two steps); d) $B(OH)_3$, $Pd(PPh_3)_4$, dry THF, r. t, 10 min, 92%; e) (i) Pd/C, H_2, dry EtOAc, 3 h; (ii) *p*-TsOH, MeOH, r. t, 5 h (62% yield from two steps).

EXPERIMENTAL SECTION

Reactions were conducted under N_2 in anhydrous solvents such as CH_2Cl_2, THF and EtOAc. All reactions were monitored by TLC (silica-coated plates and visualizing under UV light). *n*-Hexane (bp 60–80 °C) was used. Yields refer to chromatographically and spectroscopically (^{1}H and ^{13}C NMR) homogeneous material. Air sensitive reagents were transferred by syringe or double-ended needle. Evaporation of solvents was performed at reduced pressure on a Buchi rotary evaporator. ^{1}H and ^{13}C NMR spectra of samples in $CDCl_3$ were recorded on Bruker UXNMR FT-300 MHz (Avance) and 500MHz (Inova) spectrometers. Chemical shift δ is reported relative to TMS (δ = 0.0) as an internal standard. Mass spectra were recorded E1 conditions at 70 eV on LC-MSD (Agilent technologies) spectrometers. All high resolution spectra were recorded on QSTAR XL hybrid MS/MS system (Applied Biosystems/MDS sciex, foster city, USA), equipped with an ESI source (IICT, Hyderabad). Column chromatography was performed on silica gel (60-120 mesh) supplied by Acme Chemical Co., India. TLC was performed on Merck 60 F-254 silica gel plates. Melting points were determined in open glass capillaries on a fischer-johns melting point apparatus and are incorrect. Optical rotations were measured with a JASCO DIP-370 Polarimeter at 25 °C. The % ee of the products was determined using Chiral HPLC, DIONEX (chromeleon, PDA).

[(2*S*,3*S*)-3-dodecyloxiran-2-yl]methanol (5)

In a 50 mL two neck round bottomed flask, 5 mL of anhydrous CH_2Cl_2 was added to 4 A^o powdered activated molecular sieves and suspension mixture was cooled to –20 ^{o}C, Ti(O*i*Pr)$_4$ (0.1 mL,0.30 mmol) and L-(+) DIPT (0.06 g, 0.30 mmol) in anhydrous CH_2Cl_2 (1 mL) were added subsequently with stirring and the resulting mixture was stirred for 0.5 h at –24 ^{o}C. Compound **3** (0.33 g, 1.46 mmol) in anhydrous CH_2Cl_2 (5 mL) was then added and the resulting mixture was stirred for another 0.5 h at –24 ^{o}C followed by addition of TBHP (5M solution in CH_2Cl_2, 0.4 mL, 2.04 mmol) and the resulting mixture was stirred at the same temperature for 4 h. It was then warmed to 0 ^{o}C, quenched with 0.2 mL of water and stirred for 1 h at room temperature. After that 30% aqueous NaOH solution saturated with NaCl (0.5 mL) was then added and the reaction mixture was stirred vigorously for another 0.5 h at room temperature. The resulting mixture was then filtered through *Celite* rinsing with CH_2Cl_2. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2. Combined organic phases were washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and purified by silica gel column chromatography (eluent: PE–EtOAc, 8.5:1.5) to afford **5** (0.31 g, 90%) as a white solid; **mp** = 60-62 °C; **[α]$_D^{25}$**: −19.6 (c = 1, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 3. 97-3.88 (m, 1H), 3.68-3.58 (m, 1H), 2.99-2.90 (m, 2H), 1.71 (t, -OH, *J* = 6.2 Hz), 1.56 (t, 1H, *J* = 6.0 Hz), 1.49-1.39 (m, 1H), 1.37-1.22 (m, 20H), 0.89 (t, 3H, *J* = 6.9 Hz); **^{13}C NMR** ($CDCl_3$, 75 MHz): 61.7, 58.4, 55.9, 31.8, 31.5, 29.6(5C), 29.4, 29.3, 25.9, 22.6, 14.0; **IR (KBr)**: 3282, 2918, 1461, 1035 cm^{-1}; **ESI-MS:** *m/z*: 265 [M+Na]$^+$; **HRMS** calcd for $C_{15}H_{30}O_2Na$: 265.21380; found: 265.21451.

(*E*)-ethyl 3-((2*S*,3*S*)-3-dodecyloxiran-2-yl)acrylate (2)

BAIB (0.4g, 1.23 mmol) was added to a solution of alcohol **5** (0.25 g, 1.03 mmol) and TEMPO (0.03 g, 0.20 mmol) in 1 ml of CH_2Cl_2. The reaction mixture was stirred until the alcohol was no longer detectable (TLC), and then it was diluted with CH_2Cl_2 (20 mL). The mixture was washed with a saturated aqueous solution of $Na_2S_2O_3$ (10 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The unstable crude aldehyde was immediately used for the next reaction.

To a solution of above crude aldehyde in C_6H_6 (10 mL) was added Ph_3P=CHCOOEt (0.31 g, 0.90 mmol) and the reaction mixture was stirred for 1 h at reflux condition. After completion of the reaction, monitored by TLC, C_6H_6 was removed under reduced pressure, residue was dissolved in ether, and petroleum ether was added to it. The triphenylphosphine oxide crystallized out was filtered off and the filtrate was concentrated to dryness. The crude product was purified by column chromatography (eluent: PE–EtOAc, 9.5:0.5) to afford the pure α,β-unsaturated ester **2** (0.19 g, 76% yield from two steps) as a colorless liquid; $[\alpha]_D^{25}$: −5.0 (c = 1, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 6.68 (dd, 1H, *J* = 8.1, 16.3 Hz), 6.12 (d, 1H, *J* = 16.3 Hz), 4.20 (q, 2H, *J* = 7.0, 14.0 Hz), 3.20 (d, 1H, *J* = 7.0 Hz), 2.88 (t, 1H, *J* = 4.6 Hz), 1.51-1.38 (m, 2H), 1.36-1.22 (m, 23H), 0.88 (t, 3H, *J* = 7.0 Hz); **^{13}C NMR** ($CDCl_3$, 75 MHz):165.6, 144.8, 123.3, 61.4, 60.4, 56.3, 31.8(2C), 29.6, (5C), 29.4, 29.3, 25.7, 22.6, 14.1, 14.0; **IR (Neat)**: 2925, 1723, 1462, 1261, 1039 cm^{-1}; **ESI-MS:** *m/z*: 333 $[M+Na]^+$.

(4*S*,5*S*,*E*)-ethyl 4,5-dihydroxyheptadec-2-enoate (6)

To a solution of 2 (0.14 g, 0.45 mmol) in anhydrous THF (5 mL) was added $B(OH)_3$ (0.036 g, 0.58 mmol) and $Pd(PPh_3)_4$ (0.026 g, 0.02 mmol) and the reaction mixture was stirred at room temperature for 10 min. The reaction mixture was passed through a silica gel column by the aid of EtOAc and the elute was concentrated in vacuo to leave the crude diol. The crude product was purified by silica gel column chromatography (eluent: PE–EtOAc, 8.0:2.0) to give the **6** ***syn*** diol (0.13 g, 92%) as a white solid; **mp** = 69°C; $[\alpha]_D^{25}$: −19 (c = 1, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 6.94 (dd, 1H, *J* = 5.0, 15.0 Hz), 6.14 (d, 1H, *J* = 16.0 Hz), 4.21 (q, 2H, *J* = 7.0, 14.0 Hz), 4.15-4.11 (m, 1H), 3.59-3.53 (m, 1H), 2.48 (brs-OH, 1H), 2.11 (brs-OH, 1H), 1.57-1.45 (m, 2H), 1.39-1.21 (m, 20H,), 1.30 (t, 3H, *J* = 8.0 Hz), 0.88 (t, 3H, *J* = 7.0 Hz); **^{13}C NMR** ($CDCl_3$, 75 MHz): 166.4, 147.0, 122.3, 74.1, 74.0, 60.6, 33.0, 31.9, 29.6(5C), 29.5, 29.3, 25.6, 22.6, 14.1, 14.0; **IR (KBr)**: 3518, 3294, 2919, 1712, 1465, 1276, 1040 cm^{-1}; **ESI-MS:** *m/z*: 351 $[M+Na]^+$; **HRMS** calcd for $C_{19}H_{36}O_4Na$: 351.25058; found: 351.25077.

(*S*)-5-((*S*)-1-hydroxytridecyl)dihydrofuran-2(3*H*)-one [(+)-Muricatacin] (1a)

To a solution of compound **6** (0.08 g, 0.24 mmol) in anhydrous EtOAc (3 mL) was added catalytic amount of 10% Palladium adsorbed on carbon and stirred under H_2 atmosphere for 3h. The reaction mixture was filtered through *Celite* and the filtrate was concentrated under reduced pressure.

To a solution of above crude product in methanol (3 mL) was added catalytic amount of *p*-TsOH. The reaction mixture was stirred at room temperature for 5 h. Methanol was removed under reduced pressure. The crude residue was purified by silica gel column chromatography to afford **1a** (0.05 g, 62% yield from two steps) as a colorless solid; **mp** = 66-68 °C; $[\alpha]_D^{25}$: +24.4 (c = 1.5, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 4.41-4.37 (m, 1H), 3.54-3.50 (m, 1H), 2.63-2.43 (m, 2H), 2.29-2.08 (m, 2H,), 1.58-1.47 (m, 2H), 1.40-1.22 (m, 20H), 0.89 (t, 3H, *J* = 7.1 Hz); **^{13}C NMR** ($CDCl_3$, 75 MHz): 177.1, 82.9, 73.6, 32.9, 31.9, 29.6 (4C), 29.5, 29.4, 29.3, 28.6, 25.4, 24.0, 22.6, 14.0; **IR (KBr)**: 3405, 2923, 1747, 1465, 1191 cm^{-1}; **ESI-MS:** *m/z*: 307 $[M+Na]^+$; **HRMS** calcd for $C_{17}H_{32}O_3Na$: 307.22437; found: 307.22542.

CONFLICT OF INTEREST

None declared.

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SUPPLEMENTARY MATERIAL

Supplementary material is available on the publishers web site along with the published article.

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