An approach towards chiral 5-hydroxyalkyl butan-4-olides: total synthesis of (-)-muricatacin and related natural products

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Dedicated with respect to Professor S. V. Kessar on his 70th birthday
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Abstract
A general approach towards synthesis of 5-hydroxyalkylbutan-4-olides from D-mannitol has been described. The approach has been used successfully for total synthesis of (-)-muricatacin, an anti-tumour natural product. Other related natural and unnatural compounds were also synthesized.

Keywords: D-Mannitol, (-)-muricatacin, 5-hydroxyalkyl butan-4-olides

Introduction

Chiral hydroxylactones occupy an important position as bio-active molecules and useful synthetic intermediates in total synthesis. One such group of hydroxylactones is 5-hydroxyalkylbutan-4-olides 1. These are found widely in nature and show diverse biological properties. Some of these compounds are known to have insect antifeedant activity1 and are cytotoxic to human tumor cells.2 The short chain homologues are important flavor constituents in wine, sherry, and tobacco smoke.3 These are also found in microbial metabolite cultures of Erwinia quernica4 and Streptomycetes griseus.5 Many of these butanolides are often used as synthons in the synthesis of complex and biologically important natural products.6 These have been used as precursors to HIV-1 protease inhibitors.7 One such molecule that has attracted much attention since its isolation was (-)-muricatacin 1d. It was isolated from the seeds of Anona muriicata L. ( annonaceae),8 commonly known as sour group or guanabana, and is grown commercially as a fruit crop throughout the tropical regions of the world. This plant, as well as others in the family of annonaceae, are a source of many annonaceous acetogenins that are known to have anti-tumor properties.2 Both the enantiomers of 1d are found in nature. The isolated material is a mixture of the two, the (-)-(R,R)-1d being predominant (ee of ca. 25 % based on optical rotation). It is shown to be cytotoxic towards human tumor cells. Biological
studies revealed that the length of the side chain is very crucial. Decreasing the length of the alkyl side chain led to decreased activity and increasing the chain length did not show any increase in the activity. Both (+)- and (-)-muricatacin (threo) have the same activity. The biological activity of muricatacin and other related compounds prompted many syntheses of this type of molecule.9-11 Most of the known syntheses are target oriented. In this paper we describe a general approach towards hydroxy lactones from D-mannitol.12 We have also synthesized (-)-muricatacin and related natural products.

**Results and Discussion**

While working on total synthesis of (-)-boronolide13 and hexadecanolide, a pheromone14 we realized that 5-hydroxyalkylbutan-4-olides type natural products can also easily be synthesized from D-mannitol. The retrosynthetic analysis for our approach is shown in Scheme 1. The γ-lactone unit can be constructed from the corresponding hydroxy acid, which can come from the acetonide 2. The appropriate alkyl group can be added on the aldehyde of 3 (Scheme 1).

![Scheme 1. Retrosynthetic analysis.](image)

The synthesis commences with diacetonide benzyl ether 5, which was subjected to selective hydrolysis using acetyl chloride in MeOH at 0 °C to give a diol 6 in 88 % yield.15 The diol 6 was subjected to oxidative cleavage using LTA in CH2Cl2 and the crude aldehyde was reduced with NaBH4 to provide the alcohol 7. The alcohol was then tosylated, and the crude tosylate was reduced with NaBH4 in DMSO to give 8, whose acetonide group was cleaved using trifluoroacetic acid in THF-water mixture (4:1). The diol 9, thus obtained, was cleaved to aldehyde by using LTA. The aldehyde, without any purification, was subjected to Wittig olefination reaction with (benzyloxycarbonylmethylene)triphenylphosphorane to obtain α,β-unsaturated ester 10, which was converted into the target compound 1a by hydrogenation over Pd/C followed by treatment of the resulting crude hydroxy acid with p-TsOH (Scheme 2).
a: AcCl (5 equivalents), MeOH, 0 °C, 5 min (88 % yield). b: (i) Pb(OAc)₄, CH₂Cl₂, rt, 3 h. (ii) NaBH₄, EtOH, 0 °C, 2 h (96 % yield). c: (i) TsCl, Et₃N, CH₂Cl₂, 14 h; (ii) NaBH₄, DMSO, 160 °C, 7 min (73 % yield). d: TFA, THF-H₂O (4:1), 65 °C, 6 h (86 % yield). e: (i) Pb(OAc)₄, CH₂Cl₂, rt, 3 h; (ii) BnO₂CCH₂P⁺PhBr⁻, n-BuLi, THF, 0 °C-rt, 12 h (74 % yield). f: (i) H₂, 10% Pd/C, EtOH, rt, 12 h; (ii) p-TSA, toluene, 70 °C, 1 h (95 % yield).

Scheme 2. Synthesis of 1a.

a: (i) Pb(OAc)₄, CH₂Cl₂, rt, 3 h; (ii) R’CH₂Ph₃Br⁻, n-BuLi, THF, 0 °C-rt, 12 h (65-75 % yield). b: TFA, THF-H₂O (4:1), 65 °C, 6 h (85-95 % yield). c: (i) Pb(OAc)₄, CH₂Cl₂, rt, 3 h; (ii) BnO₂CCH₂P⁺Ph₃Br⁻, n-BuLi, THF, 0 °C-rt, 12 h (70-80 % yield). d: (i) H₂, 10% Pd/C, EtOH, rt, 12 h; (ii) p-TSA, toluene, 70 °C, 1 h (92-95 % yield).

Scheme 3. Synthesis of 1b-e.

We extended the above approach to compounds with different alkyl groups in the side chain. For alkyl groups other than methyl, the scheme was modified. The aldehyde, obtained from the diol 6, was treated with ylides, prepared from phosphonium salts with different alkyl groups to provide olefins 11. The acetonide group of 11 was cleaved, as described earlier. The diol 12, thus obtained, was converted into the olefinic compound 13 using the aforementioned...
Wittig chemistry. Conversion of 13 into target compounds such as 1b, 1c, 1d, and 1e was carried out as described for 1a. In this way, we were able to synthesize several hydroxyalkyl γ-lactones in ~45 % overall yield (Scheme 3).

In order to show some more versatility in our approach, we set out to synthesise some analogues having extra hydroxy groups. This was accomplished from the known diol 14, which was subjected to oxidative cleavage with LTA, and the aldehyde obtained was then allowed to react with the ylide prepared from (ethoxycarbonylmethylene)triphenylphosphorane to provide α,β-unsaturated ester 15 as a mixture of cis and trans isomers (ratio 70:30). The mixture, on treatment with CuCl2.2H2O gave the lactone after cleaving the acetonide group. Only the cis isomer lactonized, and the trans isomer remained unreacted. The unsaturated lactone 16 was hydrogenated to provide a saturated lactone 17 which could be an important precursor in synthesis (Scheme 4).


Conclusions

We have developed a simple and flexible strategy for the synthesis of hydroxyalkylbutan-4-olides from D-mannitol. Using the above strategy, a total synthesis of (-)-muricatacin and related compounds was accomplished.

Experimental Section

General procedure for oxidative cleavage of diols (6, 9, 12, or 14) using Pb(OAc)4
To a solution of a diol in dry CH2Cl2 (5 ml/mmole), LTA (1.1 eq.) was added at 0 °C and the reaction was allowed to proceed with gradual warming to rt. After all the diol was consumed (by tlc, usually 4 h), the reaction mixture was quenched by an addition of saturated aqueous NaHCO3 solution. The solids were removed by filtration through celite pad. The aqueous layer was
extracted with CH$_2$Cl$_2$ and the combined organic layers were washed with water and brine. The organic layer was then dried over anhydrous Na$_2$SO$_4$ and concentrated in vacuo to give an aldehyde in quantitative yield, which was used as such in the next step.

**General procedure for the synthesis of olefins (11)**

To a suspension of a Wittig salt (1.3 eq with respect to aldehyde) in anhydrous THF (5 mL/mmol) at 0 °C, n-BuLi (1.3 eq., 1.43 M in hexanes) was added under N$_2$ atmosphere and was stirred for 30 min at the same temperature. To the resulting orange red solution, the crude aldehyde (obtained by an oxidative cleavage of the diol 6) in anhydrous THF (1 ml/mmol) was added slowly over a period of 10 min. The reaction mixture was stirred for 6 h with gradual warming to rt. All the solids were removed by filtration and the organic layer was concentrated and chromatographed over silica gel to give the olefins as a mixture of cis-trans isomers.

**General procedure for cleavage of acetonide (8 or 11) with TFA**

To a solution of acetonide (8 or 11) in THF and water (4:1) was treated with trifluoroacetic acid (1.5 equivalent) at 65 °C. After all the starting material was consumed (by tlc, usually 6 h), THF was removed in vacuo and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with saturated aqueous NaHCO$_3$ solution, water, and brine. The organic layer was finally dried over anhydrous Na$_2$SO$_4$, concentrated in vacuo and chromatographed over silica gel to give the diol 9 or 12.

**General procedure for synthesis of α,β-unsaturated esters (10 or 13)**

To a suspension of a Wittig salt (1.3 eq. with respect to a diol, obtained by treatment of benzyl bromoacetate with triphenylphosphine) in anhydrous THF (5 mL/mmol) at 0 °C was added n-BuLi (1.3 eq. with respect to diol) under N$_2$ atmosphere and stirred for 30 min. To this clear solution was added the crude aldehyde (obtained by oxidative cleavage of the corresponding diol) in anhydrous THF (1 ml/mmol) and stirred over night with gradual warming to rt. THF was removed in vacuo and the residue was chromatographed over silica gel to give the α,β-unsaturated esters. The α,β-unsaturated ester was subjected to lactonization without purification and characterization.

**General procedure for the synthesis of lactones (1)**

The α,β-unsaturated ester (10 or 13) was dissolved in EtOH (3mL/mmol) and 50 – 60 mg of 10 % Pd on activated charcoal was added to it. The flask was evacuated and purged with H$_2$ gas and the reaction was allowed to proceed for 12 h at rt under a balloon filled with H$_2$ gas. The reaction mixture was filtered through celite, washed with little EtOH, and concentrated in vacuo. The residue was taken in benzene (5 ml/mmol) and 5 – 10 mg of p-TSA was added and refluxed for 1 h. It was diluted with EtOAc and washed successively with water and brine. Finally the organic layer was dried over Na$_2$SO$_4$, concentrated and chromatographed over silica gel to give the lactone.
3,4-Di-O-benzyloxy-5,6-O-isopropylidene-D-mannitol (6). A solution of mannitol derivative 5 (15 g, 34 mmol) in dry MeOH (135 mL) was treated by a drop wise addition of AcCl (12.1 mL, 170 mmol) at 0 °C and the reaction mixture was stirred for 5 min. It was quenched by an addition of KOH solution (19.1 g, 340 mmol in 1:1 MeOH-water, 60 mL). Most of the MeOH was removed in vacuo, the solid residue was taken in water and extracted with EtOAc. The combined organic layers were washed with water, brine, and finally dried over anhydrous Na2SO4. It was concentrated in vacuo and the residue was chromatographed over silica gel to give the diol 6 as a yellow oil; Yield 7.5 g (55 %; but 88 % after recovery of starting material); Rf 0.45 (50 % EtOAc in petroleum ether); [α]25D + 24.8 (c 1.0, CHCl3); IR (thin film) 3430, 3040, 1450 cm⁻¹; 1H NMR (300 MHz, CDCl3) δ 1.36 (s, 3H), 1.47 (s, 3H), 2.05 (bs, 1H, -OH); 2.93 (s, 1H, -OH); 3.63 (m, 4H), 3.94 (m, 2H), 4.07 (m, 1H), 4.31 (q, J = 6.6 Hz, 1H), 4.64 (ABd, J = 11.4 Hz, 2H), 4.77 (ABd, J = 11. 4 Hz, 2H); 7.33 (m, 10H); MS (FAB): 403 (M+1). Anal. calcd. for C23H30O6: C, 68.64; H, 7.51. Found: C, 68.70; H, 7.60.

2,3-Bis-benzyloxy-3-(2,2-dimethyl-[1,3]dioxolan-4-yl)-propan-1-ol (7). The crude aldehyde obtained by oxidative cleavage of the diol 6 (1 g, 2.48 mmol) was taken in dry EtOH and cooled to 0 °C. To this cooled solution, NaBH₄ (142 mg, 3.74 mmol) was added and stirred for 1 h. The reaction mixture was quenched by an addition of saturated NH₄Cl and EtOH was removed in vacuo. The aqueous layer was extracted with EtOAc, the combined organic layer was washed with water and brine. The organic layer was finally dried over Na₂SO₄, concentrated in vacuo and the residue was chromatographed over silica gel to give an alcohol 7 as a colorless oil; Yield 920 mg (99 %), Rf 0.28 (20 % EtOAc in petroleum ether); 1H NMR (400 MHz, CDCl3) δ 1.35 (s, 3H), 1.44 (s, 3H), 3.59 – 3.68 (m, 2H), 3.75 (dd, J = 11.1, 5.1 Hz, 1H), 3.82 (t, J = 4.6 Hz, 1H), 3.97 (m, 1H), 4.05 (dd, J = 8.3, 6.4 Hz, 1H), 4.24 (m, 1H), 4.31 (q, J = 6.6 Hz, 1H), 4.73 (m, 2H), 7.31 (m, 10H); 13C NMR (100 MHz, CDCl3) δ 25.4, 26.8, 61.8, 66.5, 73.0, 75.0, 76.7, 79.6, 80.3, 108.9, 128.2, 128.25, 128.3, 128.5, 128.8, 138.3; MS (FAB): 373 (M+1); Anal. Calcd. for C22H28O5: C, 70.94; H, 7.58. Found: C, 70.88; H, 7.54.

4-(1,2-Bis-benzyloxy-propyl)-2,2-dimethyl-[1,3]dioxolane (8). A solution of the alcohol 7 (656 mg, 1.76 mmol) and Et₃N (730µl, 5.2 mmol) in CH₂Cl₂ was treated with tosyl chloride (369mg, 1.93 mmol) and stirred for 12 h at rt. The reaction mixture was diluted with large excess of ether and organic layer was washed with water and brine. The organic layer was finally dried over Na₂SO₄ and concentrated in vacuo. The crude tosylated product was then subjected to reduction as such. The tosylate solution in dry DMSO (10ml) was treated with NaBH₄ (665 mg, 17.6 mmol) for 7 min at 160 °C. The flask was cooled, and the reaction mixture was quenched by careful addition of water and extracted with ether. The combined organic layers were washed with water, brine and finally dried over Na₂SO₄. It was concentrated and the residue was chromatographed over silica gel to give 8 as a colorless oil; Yield 628 mg (73 %); Rf 0.71 (10 % EtOAc in petroleum ether); IR (thin film): 3031, 2976, 1495 cm⁻¹; 1H NMR (400 MHz, CDCl3) δ 1.17 (d, J = 6.6 Hz, 3H), 1.35 (s, 3H), 1.43 (s, 3H), 3.61 – 3.70 (m, 2H), 4.00 (d, J = 7.1 Hz, 2H), 4.26 (m, 1H), 4.44 (ABd, J = 11.7 Hz, 1H), 4.58 (ABd, J = 11.7 Hz, 1H), 4.67 (ABd, J = 11.5 Hz, 1H), 4.78 (ABd, J = 11.5 Hz, 1H), 7.30 (m, 10 H); 13C NMR (100 MHz,
CDCl₃) δ 15.9, 25.1, 26.5, 65.6, 71.2, 74.7, 74.9, 76.8, 81.1, 108.0, 127.5, 127.6, 127.8, 128.0, 128.2, 128.3, 138.41, 138.46; MS (FAB): 357 (M+1); Anal. Calcd. for C₂₂H₂₈O₄: C, 74.13; H, 7.92. Found: C, 74.08; H, 7.87.

3,4-Bis-benzyloxy-pentane-1,2-diol (9). 600 mg of the acetonide 8 provided 458 mg (yield 86 %) of the diol 9 as per the general procedure; Rᵣ 0.40 (40 % EtOAc in petroleum ether); [α]²⁵ D - 2.4 (c 0.5, CHCl₃); IR (thin film): 3394, 3031, 1494, 1495 cm⁻¹; ¹H NMR (400MHz, CDCl₃) δ 1.32 (d, J = 6.3Hz, 3H); 3.36 (bs, -OH, 2H); 3.63 (dd, J = 7.8, 4.2Hz, 1H); 3.75 (dABq, J = 11.5, 4.6, 3.2Hz, 2H); 3.90 ( m, 2H); 4.50 (d, J = 11.7Hz, 1H), 4.63 (m, 3H), 7.32 (m, 10H). ¹³C NMR (100MHz, CDCl₃) δ 14.4, 63.2, 70.91, 70.96, 73.3, 74.7, 78.4, 127.6, 127.8, 128.2, 128.23, 137.5, 137.8. MS (FAB): 317 (M+1); Anal. Calcd. for C₁₉H₂₄O₄: C, 72.13; H, 7.65. Found: C, 72.07; H, 7.56.

5-(1-Hydroxy-ethyl)-dihydro-furan-2-one (1a). 400 mg of the α,β-unsaturated ester 10 gave 118 mg (95 % yield) of 1a as a colorless oil; Rᵣ 0.32 (50 % EtOAc in petroleum ether); [α]²⁵ D – 48.6 (c 0.9, CHCl₃); IR (thin film) 3459, 2982, 1771cm⁻¹; ¹H NMR (400MHz, CDCl₃) δ 1.26 (d, J = 6.6Hz, 3H), 2.00 – 2.10 (m, 1H), 2.22 – 2.30 (m, 1H), 2.50 – 2.66 (m, 2H), 3.79 (m, 1H), 3.35 (dt, J = 7.3, 5.4Hz, 1H). ¹³C NMR (100MHz, CDCl₃) δ 18.5, 24.0, 28.7, 69.9, 84.2, 177.1. MS (FAB): 131 (M+1). Anal. Calcd. for C₆H₁₀O₃: C, 55.37; H, 7.74. Found: C, 55.40; H, 7.73.

4-(1,2-Bis-benzyloxy-hex-3-enyl)-2,2-dimethyl-[1,3]dioxolane (11b). 1 g of the diol 6 provided 758 mg (yield 77 % for two steps) of the olefin 11b as a colorless oil; Rᵣ 0.49 (10 % EtOAc in petroleum ether); [α]²⁵ D –11.1 (c 0.9, CHCl₃); IR (thin film): 3029, 2958, 1495, 1455 cm⁻¹; ¹H NMR (400MHz, CDCl₃) δ 0.89 (t, J = 7.6Hz, 3H); 1.29 (s, 3H); 1.35 (s, 3H); 1.89 – 1.98 (m, 2H); 3.67 (t, J = 3.9Hz, 1H), 3.92 (m, 1H), 4.18 (m, 1H), 4.27 (d, J = 12Hz, 1H), 4.54 (d, J = 12Hz, 1H), 5.42 (m, 1H), 5.61 (td, J = 11.6, 11.2Hz, 1H), 7.25 (m, 10H). ¹³C NMR (100MHz, CDCl₃) δ 13.8, 22.7, 25.3, 26.4, 65.4, 70.4, 74.3, 75.1, 76.6, 81.5,108.1, 126.5, 127.38, 127.44, 127.6, 127.9, 128.1, 128.3, 136.5, 138.3, 138.5. MS (FAB): 397 (M+1). Anal. Calcd. for C₂₅H₃₂O₄: C, 75.73; H, 8.13. Found: C, 75.65; H, 8.09.

4-(1,2-Bis-benzyloxy-hept-3-enyl)-2,2-dimethyl-[1,3]dioxolane (11c). 1g of the diol 6 provided 780 mg (yield 77 % for two steps) of the olefin 11c as a colorless oil; Rᵣ 0.49 (10 % EtOAc in petroleum ether); [α]²⁵ D -7.74 (c 0.9, CHCl₃); IR (thin film): 3029, 2958, 1495, 1455 cm⁻¹; ¹H NMR (400MHz, CDCl₃) δ 0.84 (t, J = 6.4Hz, 3H), 1.29 (s, 3H), 1.35 (s, 3H), 1.93 (m, 2H), 3.67 (t, J = 3.9Hz, 1H), 3.92 (m, 1H), 4.18 (m, 1H), 4.27 (d, J = 12Hz, 1H), 4.54 (d, J = 12Hz, 1H), 4.68 (m, 2H), 5.42 (m, 1H), 5.61 (td, J = 11.6, 11.2Hz, 1H), 7.25 (m, 10H). ¹³C NMR (100MHz, CDCl₃) δ 13.8, 22.7, 25.3, 26.4, 29.8, 65.4, 70.1, 74.4, 75.1, 76.7, 81.5, 108.1, 127.3, 127.4, 127.47, 127.8, 127.9, 128.14, 128.16, 134.8, 138.4, 138.5. Anal. Calcd. for C₂₆H₃₂O₄: C, 76.06; H, 8.35. Found: C, 76.00; H, 8.32.

4-(1,2-Bis-benzyloxy-tetradec-3-enyl)-2,2-dimethyl-[1,3]dioxolane (11d). 1g of the diol 6 provided 884 mg (yield 70 % for two steps) of the olefin 11d as a colorless oil; Rᵣ 0.65 (10 % EtOAc in petroleum ether); [α]²⁵ D - 14.1 (c 1.8 , CHCl₃); IR (thin film): 3029, 2926, 1495, 1456 cm⁻¹; ¹H NMR (400MHz, CDCl₃): δ 0.83 (t, J = 6.6Hz, 3H), 1.20 (bs, 16H), 1.29 (s, 3H),
1.35 (s, 3H), 1.91 (m, 2H), 3.67 (dd, $J = 4.2, 3.9$ Hz, 1H), 3.92 (m, 2H), 4.19 (m, 2H), 4.27 (d, $J = 12$ Hz, 1H), 4.55 (d, $J = 12$ Hz, 1H), 4.68 (m, 2H), 7.25 (m, 10H), 5.40 (dd, $J = 11.2, 9.5$ Hz, 1H), 5.60 (dd, $J = 11.2, 7.3$ Hz, 1H); $^{13}$C NMR (100MHz, CDCl$_3$) δ 22.7, 25.3, 26.5, 27.9, 29.3, 29.4, 29.5, 29.6, 31.9, 65.5, 70.1, 74.4, 75.2, 76.7, 81.5, 108.1, 127.1, 127.4, 127.5, 127.8, 128.0, 128.2, 128.21, 135.2, 138.4, 138.5; MS (FAB): 509 (M+1). Anal. Calcd. for C$_{33}$H$_{48}$O$_4$: C, 77.91; H, 9.51. Found: C, 77.86; H, 9.42.

4-(1,2-Bis-benzyloxy-4-phenyl-but-3-enyl)-2,2-dimethyl-[1,3]dioxolane (11e). 1 g of the diol 6 provided 950 mg (86 % for two steps) of 11e as a colorless oil; $R_f$ 0.55 (10 % EtOAc in petroleum ether); [α]$^{25}_D$ –54.2 (c 1.5, CHCl$_3$); IR (thin film): 3029, 2985, 1494, 1453 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 1.32 (s, 0.9H), 1.34 (s, 2.1H), 1.40 (s, 0.9H), 1.42 (s, 2.1H), 3.81 – 4.80 (m, 9H), 5.80 (dd, $J = 11.5, 9.9$ Hz, 0.29H), 6.22 (dd, $J = 16.1, 7.8$ Hz, 0.71H), 6.58 (d, $J = 16.1$ Hz, 0.71H), 6.75 (d, $J = 11.5$ Hz, 0.29H), 7.16 – 7.38 (m, 15H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 25.1, 25.3, 26.5, 65.5, 65.8, 70.3, 70.7, 74.0, 75.07, 75.1, 76.6, 80.2, 81.5, 81.8, 108.2, 126.5, 126.8, 127.2, 127.4, 127.5, 127.6, 127.9, 128.1, 128.24, 128.29, 128.6, 130.1, 133.1, 133.5, 136.3, 136.4, 137.9, 138.1, 138.2; MS (FAB): 445 (M+1). Anal. Calcd. for C$_{29}$H$_{32}$O$_4$: C, 78.35; H, 7.26. Found: C, 78.26; H, 7.18.

3,4-Bis-benzyloxy-oct-5-ene-1,2-diol (12b). 740 mg of the acetonide 11b provided 631 mg (yield 95 %) of the diol 12b as a viscous liquid; $R_f$ 0.50 (40 % EtOAc in petroleum ether); [α]$^{25}_D$ –2.8 (c 1.4, CHCl$_3$); IR (thin film): 3461, 2928, 1495, 1494 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 0.98 (t, $J = 7.6$ Hz, 3H), 2.04 (m, 2H), 3.66 (m, 3H), 3.84 (m, 1H), 4.33 (d, $J = 12$ Hz, 1H), 4.44 (dd, $J = 9.8, 4.1$ Hz, 1H), 4.58 (d, $J = 11.2$ Hz, 1H), 4.66 (d, $J = 12$ Hz, 1H), 5.49 (m, 1H), 5.77 (td, $J = 11.2, 7.3$ Hz, 1H), 7.30 (m, 10H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 14.1, 21.3, 63.4, 70.1, 71.1, 74.36, 74.43, 80.8, 124.9, 127.8, 127.9, 128.1, 128.4, 128.5, 137.79, 137.84, 138.2; MS (FAB): 357 (M+1). Anal. Calcd. for C$_{22}$H$_{28}$O$_4$: C, 74.13; H, 7.92. Found: C, 74.06; H, 7.88.

3,4-Bis-benzyloxy-non-5-ene-1,2-diol (12c). 780 mg of the acetonide 11c provided 675 mg (yield 96 %) of the diol 12c; $R_f$ 0.51 in (40 % EtOAc in petroleum ether); [α]$^{25}_D$ –3.9 (c 0.9, CHCl$_3$); IR (thin film): 3442, 2930, 1495, 1454 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 0.88 (t, $J = 7.3$ Hz, 3H), 1.36 (m, 2H), 1.98 (m, 2H), 2.61 (bs, 1H), 3.37 (bs, 1H), 3.64 (m, 3H), 3.83 (m, 1H), 4.32 (d, $J = 12$ Hz, 1H), 4.43 (dd, $J = 9.5, 4.1$ Hz, 1H), 4.60 (m, 1H), 4.69 (d, $J = 11.6$ Hz, 1H), 5.52 (dd, $J = 11.9, 5.9$ Hz, 1H), 5.74 (td, $J = 11, 7.6$ Hz, 1H), 7.27 (m, 10H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 13.7, 22.6, 29.8, 63.2, 69.9, 71.1, 74.2, 74.3, 80.9, 125.8, 127.6, 127.64, 127.69, 127.9, 128.2, 128.23, 136.1, 137.77, 137.82; Anal. Calcd. for C$_{23}$H$_{30}$O$_4$: C, 74.56; H, 8.16. Found: C, 74.50; H, 8.12.

3,4-Bis-benzyloxy-hexadec-5-ene-1,2-diol (12d). 865 mg of the acetonide 11d provided 733 mg (92% yield) of the diol 12d as a viscous liquid; $R_f$ 0.64 (40 % EtOAc in petroleum ether); [α]$^{25}_D$ –4.4 (c 0.9, CHCl$_3$); IR (thin film): 3441, 2925, 1495, 1455 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 0.88 (t, $J = 6.6$ Hz, 3H), 1.26 (bs, 16H), 2.00 (m, 2H), 3.66 (m, 3H), 3.83 (m, 1H), 4.33 (d, $J = 12$ Hz, 1H), 4.44 (dd, $J = 9.8, 4.9$ Hz, 1H), 4.59 (d, $J = 11.2$ Hz, 1H), 4.63 (d, $J = 12$ Hz, 1H), 4.72 (d, $J = 11.2$ Hz, 1H), 5.51 (dd, $J = 11, 9.8$ Hz, 1H), 5.77 (td, $J = 11.2, 7.3$ Hz, 1H), 7.30
(m, 10H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 22.7, 28.1, 29.3, 29.4, 29.5, 29.6, 31.9, 63.4, 70.1, 71.2, 74.4, 74.6, 80.9, 125.5, 127.8, 127.9, 127.92, 128.2, 128.4, 128.5, 136.9, 137.85, 137.89; MS (FAB): 469 (M+1); Anal. Calcd. for C$_{30}$H$_{44}$O$_4$: C, 76.88; H, 9.46. Found: C, 76.73; H, 9.31.

3,4-Bis-benzyloxy-6-phenyl-hex-5-ene-1,2-diol (12e). 930 mg of the acetonide 11e provided 753 mg (89% yield) of the diol 12e as a viscous liquid; R$_f$ 0.63 (40% EtOAc in petroleum ether); [α]$^2$$_D$ = −29.6 (c 0.9, CHCl$_3$); IR (thin film): 3434, 3029, 1494, 1452 cm$^{-1}$; $^1$H NMR (100 MHz, CDCl$_3$) δ 2.60 (bs, 2H, -OH), 3.57 – 4.71 (m, 9H), 5.88 (dd, $J$ = 12.0, 10.0 Hz, 0.29H), 6.29 (dd, $J$ = 16.1, 7.6 Hz, 0.71H), 6.63 (d, $J$ = 16.1 Hz, 0.71H), 6.87 (d, $J$ = 12.0 Hz, 0.29), 7.17 – 7.40 (m, 15H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 63.3, 63.4, 70.1, 70.7, 71.2, 73.5, 74.08, 74.13, 80.1, 80.5, 125.5, 126.6, 127.3, 127.8, 127.86, 128.0, 128.09, 128.13, 128.14, 128.28, 128.31, 128.35, 128.39, 128.48, 128.5, 128.6, 134.2, 134.9, 136.1, 136.3, 137.4, 137.5, 137.8; MS (FAB): 405 (M+1); Anal. Calcd. for C$_{26}$H$_{28}$O$_4$: C, 77.20; H, 6.98. Found: C, 77.11; H, 6.87.

5-(1-Hydroxy-pentyl)-dihydro-furan-2-one (1b). 520 mg of $\alpha$, $\beta$-unsaturated ester 13b gave 157 mg (80 % yield) of the lactone 1b as a viscous liquid; R$_f$ 0.43 (40% EtOAc in petroleum ether); [α]$^2$$_D$ –35.0 (c 0.7, CHCl$_3$); IR (thin film) 3441, 2931, 1768 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 0.92 (t, $J$ = 7.1Hz, 3H), 1.26 – 1.58 (m, 6H), 2.1 3 (m, 1H), 2.25 (m, 1H), 2.49 – 2.67 (m, 2H), 3.57 (m, 1H), 4.43 (dt, $J$ = 7.3, 4.4Hz, 1H). $^{13}$C NMR (100MHz, CDCl$_3$) δ 13.9, 22.5, 24.0, 27.6, 28.7, 32.6, 73.6, 82.9, 177.2. MS (FAB): 173 (M+1); Anal. Calcd. for C$_9$H$_{16}$O$_3$: C, 62.77; H, 9.36. Found: C, 62.68; H, 9.37.

5-(1-Hydroxy-hexyl)-dihydro-furan-2-one (1c). 520 mg of the $\alpha$, $\beta$-unsaturated ester gave 185 mg (yield 90 %) of the lactone 1c as a viscous liquid (previously it was reported as low melting solid, mp 42 °C); 17 R$_f$ 0.43 (50 % EtOAc in petroleum ether); [α]$^2$$_D$ –35.9 (c 1.9, CHCl$_3$); IR (thin film) 3446, 2954, 1780 cm$^{-1}$; $^1$H NMR (400MHz, CDCl$_3$) δ 0.90 (t, $J$ = 7.1Hz, 3H), 1.26 – 1.39 (m, 6H), 1.54 (m, 2H), 2.13 (m, 1H), 2.25 (m, 1H), 2.38 (bs, 1H), 2.59 (m, 2H), 3.57 (m, 1H), 4.43 (dt, $J$ = 7.3, 5.4Hz, 1H); 13C NMR (CDCl$_3$) δ 13.9, 22.5, 23.9, 25.1, 28.6, 31.6, 32.8, 73.5, 82.9, 177.4.

(-)-Muricatacin (1d). 581 mg of the $\alpha$, $\beta$-unsaturated ester gave 276 mg (yield 95 %) of (-)-muricatacin 1d as a white solid; mp: 65 °C (lit 9d mp 71 °C); R$_f$ 0.51 (40% EtOAc in petroleum ether); [α]$^2$$_D$ -23.5 (c 0.43, CHCl$_3$) {lit8 [α]$^2$$_D$ -23.3 (c 1.8, CHCl$_3$)}; IR (CDCl$_3$ solution) 3570, 1765 cm$^{-1}$; $^1$H NMR (400MHz, CDCl$_3$) δ 0.88 (t, $J$ = 6.6Hz, 3H), 1.26 (bs, 22H), 1.99 (bs, 1H), 2.13 (m, 1H), 2.26 (m, 1H), 2.57 (m , 2H), 3.57 (m, 1H), 4.42 (dt, $J$ = 7.3, 4Hz, 1H); $^{13}$C NMR (CDCl$_3$) δ 28.7, 29.3, 29.5, 29.6, 29.6, 31.9, 32.9, 73.6, 82.9, 177.1; MS (FAB): 285 (M+1).

5-(1-Hydroxy-3-phenyl-propyl)-dihydro-furan-2-one (1e). 525 mg of the $\alpha$, $\beta$-unsaturated ester provided 185 mg (81% yield) of the lactone 1e; R$_f$ 0.37 (40% EtOAc in petroleum ether); [α]$^2$$_D$ –2.38 (c 0.8, CHCl$_3$); IR (thin film) 3434, 1767 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 1.75 – 1.94 (m, 2H), 2.07 (m, 1H), 2.19 (m, 1H), 2.44 – 2.61 (m, 2H), 2.70 (m, 1H), 2.86 (m, 1H), 3.55 (dt, $J$ = 9.5, 3.9 Hz, 1H), 4.40 (td, $J$ = 7.3, 4.4 Hz, 1H), 7.26 (m, 5H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 23.8, 28.5, 31.5, 34.4, 72.5, 83.1, 125.9, 128.4, 141.3, 177.5; MS (FAB): M+1 221. Anal. Calcd. for C$_{13}$H$_{16}$O$_3$: C, 70.89; H, 7.32. Found: C, 70.83; H, 7.30.
3-[5-(1-Benzylloxy-pentyl)-2,2-dimethyl-[1,3]dioxolan-4-yl]-acrylic acid ethyl ester 15. To the diol 14 (224 mg, 0.67 mmol) in 3 ml dry CH₂Cl₂, Pb(OAc)₄ (350 mg, 0.73 mmol) was added at 0 °C and the reaction mixture was stirred for 4 h and worked up as earlier. The crude aldehyde was then taken in MeOH and to it (ethoxycarbonylmethylene)triphenylphosphorane (255 mg, 0.73 mmol) was added and stirred for 12 h at rt. All the MeOH was removed in vacuo and the residue was chromatographed over silica gel to provide the α,β-unsaturated ester 15 (211 mg, 85 % yield for two steps); Rₓ 0.65 (10% EtOAc in petroleum ether); ¹H NMR (400 MHz, CDCl₃) δ 0.78 (t, J = 6.8 Hz, 2.3H), 0.82 (t, J = 6.8 Hz, 0.7H), 1.19 (t, J = 7.2 Hz, 2.3H), 1.21 (t, J = 7.2 Hz, 0.7H), 1.24 – 1.33 (m, 4H), 1.37 (s, 3H), 1.38 (s, 3H), 1.43 – 1.58 (m, 2H), 3.45 (m, 1H), 3.81 (m, 1H), 4.08 (q, J = 7.1 Hz, 1.4H), 4.12 (q, J = 7.1 Hz, 0.6H), 4.40 (m, 0.3H), 4.54 (m, 1.4H), 4.70 (ABd, J = 11.5 Hz, 0.6H), 5.50 (m, 0.7H), 5.90 (m, 1H), 6.06 (dd, J = 9.3, 4.6 Hz, 0.7H), 6.76 (dd, J = 15.6, 5.6 Hz, 0.3H), 7.28 (m, 5H); ¹³C NMR (100 MHz, CDCl₃) δ 13.94, 13.99, 14.1, 14.2, 22.6, 22.7, 26.7, 26.93, 26.98, 27.2, 27.7, 27.9, 30.1, 30.5, 72.4, 72.5, 72.8, 76.1, 77.2, 78.9, 81.8, 83.6, 109.8, 122.4, 123.3, 127.3, 127.7, 127.9, 128.1, 128.1, 128.2, 128.4, 138.2, 138.9, 144.7, 145.2, 165.3, 166.0. Anal. Calcd. for C₂₂H₃₂O₅: C, 70.18; H, 8.57. Found: C, 70.14; H, 8.48.

5-(1,2-Dihydroxy-hexyl)-dihydro-furan-2-one (17). The α,β-unsaturated ester 15 (196 mg, 0.52 mmol) was taken in distilled MeCN (3 ml) and to it cupric chloride dihydrate (222 mg, 1.30 mmol) was added and stirred overnight at rt. The reaction was then quenched by addition of saturated aqueous NaHCO₃ solution and extracted with EtOAc. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated in vacuo. The residue was chromatographed over silica gel to give α,β-unsaturated lactone. This was subjected to hydrogenation as earlier using Palladium on activated charcoal to give the 17 as white solid; Yield 46 mg (70 % for two steps) as colorless white solid; Rₓ 0.17 (40% EtOAc in petroleum ether); [α]²⁵ D = 39.0 (c 0.51 in CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 0.39 (t, J = 7.0 Hz, 3H), 0.72 – 1.05 (m, 6H), 1.76 (m, 2H), 1.99 (m, 1H), 2.13 (m, 1H), 2.91 (m, 1H), 3.20 (m, 1H), 4.10 (dt, J = 6.8, 3.6 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 13.9, 22.6, 24.0, 27.7, 28.3, 33.3, 71.7, 75.1, 81.5, 177.4. Anal. Calcd. for C₁₀H₁₈O₄: C, 59.39; H, 8.97. Found: C, 59.31; H, 8.89.

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References


