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

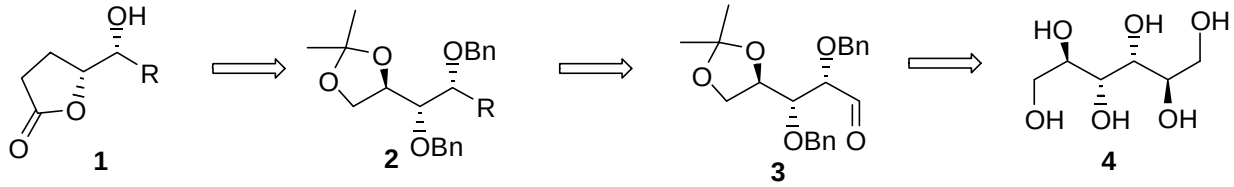
Introduction

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 activity[1] 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 quernica*[4] and *Streptomyces 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 muricata 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

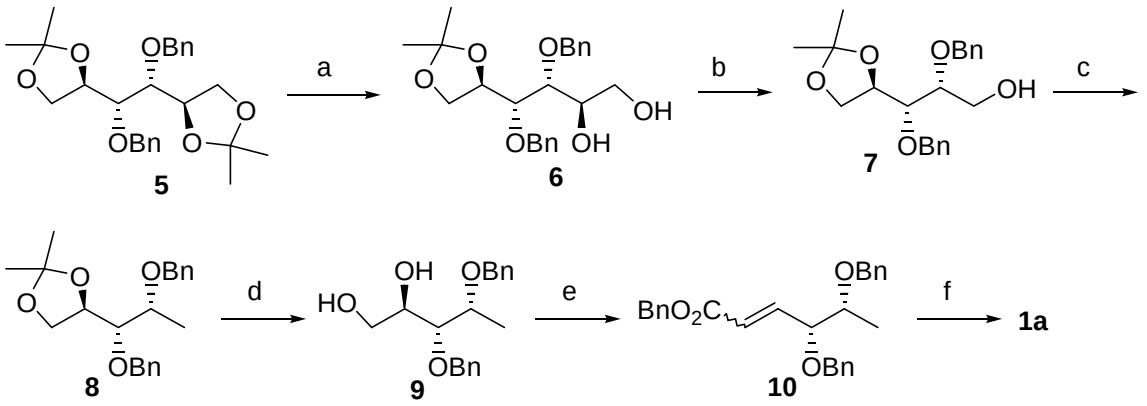
While working on total synthesis of (-)-boronolide[13] and hexadecanolide, a pheromone[14] we realized that 5-hydroxyalkylbutan-4-olides **1** type natural products can also easily be synthesized from D-mannitol. The retrosynthetic analysis for our approach is shown in Scheme 1. The γ-lactone unit can 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).



a: R = CH_3; **b**: R = C_4H_9; **c**: R = C_5H_{11}; **d**: R = $C_{12}H_{25}$; **e**: R = CH_2CH_2Ph

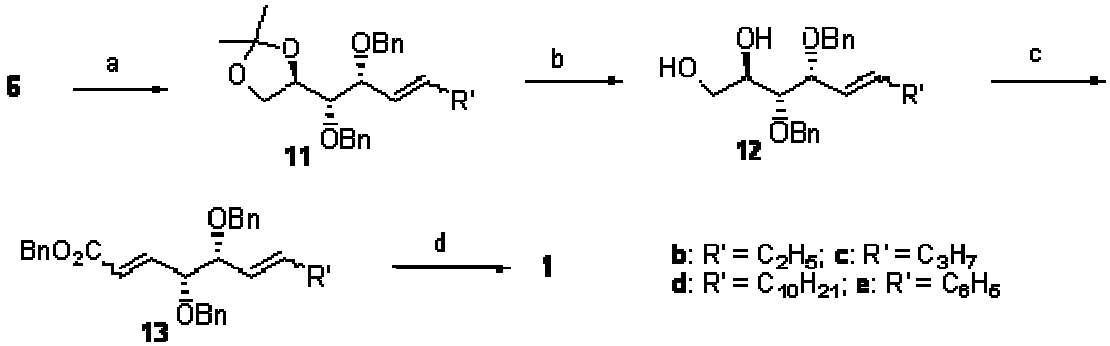
Scheme 1. Retrosynthetic analysis.

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 CH_2Cl_2 and the crude aldehyde was reduced with $NaBH_4$ to provide the alcohol **7**. The alcohol was then tosylated, and the crude tosylate was reduced with $NaBH_4$ 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) $Pb(OAc)_4$, CH_2Cl_2, rt, 3 h. (ii) $NaBH_4$, EtOH, 0 °C, 2 h (96 % yield). c: (i) TsCl, Et_3N, CH_2Cl_2, 14 h; (ii) $NaBH_4$, DMSO, 160 °C, 7 min (73 % yield). d: TFA, THF-H_2O (4:1), 65 °C, 6 h (86 % yield). e: (i) $Pb(OAc)_4$, CH_2CL_2, rt, 3 h; (ii) $BnO_2CCH_2P^+PhBr^-$, *n*-BuLi, THF, 0 °C-rt, 12 h (74 % yield). f: (i) H_2, 10% Pd/C, EtOH, rt, 12 h; (ii) *p*- TSA, toluene, 70 °C, 1 h (95 % yield)

Scheme 2. Synthesis of **1a**.



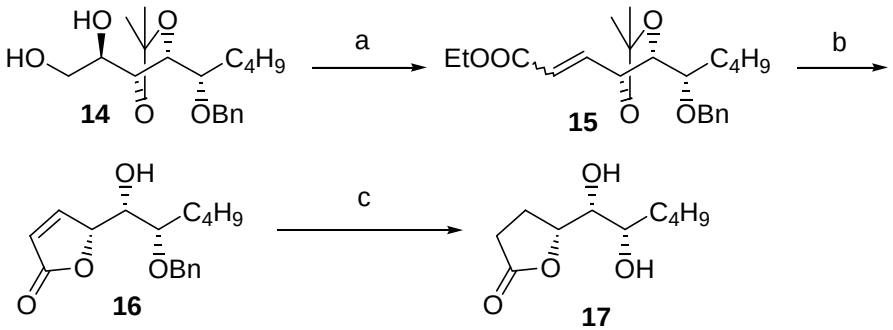
a: (i) $Pb(OAc)_4$, CH_2Cl_2, rt, 3 h; (ii) $R'CH_2Ph_3Br^-$, *n*-BuLi, THF, 0 °C-rt, 12 h (65-75 % yield). b: TFA, THF-H_2O (4:1), 65 °C, 6 h (85-95 % yield). c: (i) $Pb(OAc)_4$, CH_2Cl_2, rt, 3 h; (ii) $BnO_2CCH_2P^+Ph_3Br^-$, *n*-BuLi, THF, 0 °C-rt, 12 h (70-80 % yield). d: (i) H_2, 10% Pd/C, EtOH, 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**,[13] 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 $CuCl_2.2H_2O$[16] 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).



a. (i) $Pb(OAc)_4$, CH_2Cl_2, rt, 3 h; (ii) $EtO_2CCH{=}PPh_3$, MeOH, rt, 12 h (75 % yield);
b. $CuCl_2.2H_2O$, MeCN, rt, 12 h (65 % yield); c. H_2, 10% Pd/C, EtOH, rt, 12 h.

Scheme 4. Synthesis of **17**.

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 CH_2Cl_2 (5 ml/mmol), 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 $NaHCO_3$ solution. The solids were removed by filtration through celite pad. The aqueous layer was

extracted with CH_2Cl_2 and the combined organic layers were washed with water and brine. The organic layer was then dried over anhydrous Na_2SO_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_2SO_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_2SO_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 Na_2SO_4. 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); R_f 0.45 (50 % EtOAc in petroleum ether); $[\alpha]^{25}_D$ + 24.8 (c 1.0, $CHCl_3$); IR (thin film) 3430, 3040, 1450 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 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 $C_{23}H_{30}O_6$: 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, $NaBH_4$ (142 mg, 3.74 mmol) was added and stirred for 1 h. The reaction mixture was quenched by an addition of saturated NH_4Cl 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 Na_2SO_4, concentrated in vacuo and the residue was chromatographed over silica gel to give an alcohol **7** as a colorless oil; Yield 920 mg (99 %), R_f 0.28 (20 % EtOAc in petroleum ether); ^1H NMR (400 MHz, $CDCl_3$) 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), 4.63 (s, 2H), 4.73 (m, 2H), 7.31 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{22}H_{28}O_5$: 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 Et_3N (730µl, 5.2 mmol) in CH_2Cl_2 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 Na_2SO_4 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 $NaBH_4$ (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 Na_2SO_4. It was concentrated and the residue was chromatographed over silica gel to give **8** as a colorless oil; Yield 628 mg (73 %); R_f 0.71 (10 % EtOAc in petroleum ether); IR (thin film): 3031, 2976, 1495 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz,

$CDCl_3$) 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 $C_{22}H_{28}O_4$: 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; R_f 0.40 (40 % EtOAc in petroleum ether); $[\alpha]^{25}_D$ – 2.4 (c 0.5, $CHCl_3$); IR (thin film): 3394, 3031, 1494, 1495 cm^{-1}; ^1H NMR (400MHz, $CDCl_3$) 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). ^{13}C NMR (100MHz, $CDCl_3$) 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 $C_{19}H_{24}O_4$: 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; R_f 0.32 (50 % EtOAc in petroleum ether); $[\alpha]^{25}_D$ – 48.6 (c 0.9, $CHCl_3$); IR (thin film) 3459, 2982, 1771cm^{-1}; ^1H NMR (400MHz, $CDCl_3$) 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). ^{13}C NMR (100MHz, $CDCl_3$) δ 18.5, 24.0, 28.7, 69.9, 84.2, 177.1. MS (FAB): 131 (M+1). Anal. Calcd. for $C_6H_{10}O_3$: 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; R_f 0.49 (10 % EtOAc in petroleum ether); $[\alpha]^{25}_D$ –11.1 (c 0.9, $CHCl_3$); IR (thin film): 3029, 2930, 1495, 1455 cm^{-1}; ^1H NMR (400MHz, $CDCl_3$) δ 0.89 (t, *J* = 7.6Hz, 3H); 1.29 (s, 3H); 1.35 (s, 3H); 1.89 – 1.98 (m, 2H); 3.67 (dd, *J* = 4.2, 3.9Hz, 1H); 3.93 (m, 2H); 4.18 (m, 2H); 4.26 (d, *J* = 12Hz, 1H); 4.54 (d, *J* = 12Hz, 1H); 4.68 (m, 2H); 5.37 (m, 1H); 5.59, (td, *J* = 11, 7.1Hz, 1H); 7.25 (m, 10H). ^{13}C NMR (100MHz, $CDCl_3$) δ 14.1, 21.1, 25.3, 26.4, 65.4, 70.0, 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 $C_{25}H_{32}O_4$: 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 79 % for two steps) of the olefin **11c** as a colorless oil; R_f 0.55 (10 % EtOAc in petroleum ether); $[\alpha]^{25}_D$ -7.74 (c 0.9, $CHCl_3$); IR (thin film): 3029, 2958, 1495, 1455 cm^{-1}; ^1H NMR (400MHz, $CDCl_3$) δ 0.84 (t, *J* = 6.4Hz, 3H), 1.29 (s, 3H), 1.33 (m, 2H), 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). ^{13}C NMR (100MHz, $CDCl_3$) 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 $C_{26}H_{32}O_4$: 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; R_f 0.65 (10 % EtOAc in petroleum ether); $[\alpha]^{25}_D$ – 14.1 (c 1.8 , $CHCl_3$); IR (thin film): 3029, 2926, 1495. 1456 cm^{-1}; ^1H NMR (400MHz, $CDCl_3$): 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, 3.9Hz, 1H), 3.92 (m, 2H), 4.19 (m, 2H), 4.27 (d, *J* = 12Hz, 1H), 4.55 (d, *J* = 12Hz, 1H), 4.68 (m, 2H), 7.25 (m, 10H), 5.40 (dd, *J* = 11.2, 9.5Hz, 1H), 5.60 (td, *J* = 11.2, 7.3Hz, 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); $[\alpha]^{25}_D$ –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, 138.3; 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); $[\alpha]^{25}_D$ – 2.8 (c 1.4, $CHCl_3$); IR (thin film): 3461, 2928, 1495, 1494 cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$) δ 0.98 (t, *J* = 7.6Hz, 3H), 2.04 (m, 2H), 3.66 (m, 3H), 3.84, (m, 1H), 4.33 (d, *J* = 12Hz, 1H), 4.44 (dd, *J* = 9.8, 4.9Hz, 1H), 4.58 (d, *J* = 11.2Hz, 1H), 4.66 (d, *J* = 12Hz, 1H), 4.72 (d, *J* = 11.2Hz, 1H), 5.49 (m, 1H), 5.77 (td, *J* = 11.2, 7.3Hz, 1H), 7.30 (m, 10H). ^{13}C NMR (100MHz, $CDCl_3$) 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); $[\alpha]^{25}_D$ – 3.9 (c 0.9, $CHCl_3$); IR (thin film): 3442, 2930, 1495, 1454 cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.3Hz, 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* = 12Hz, 1H), 4.43 (dd, *J* = 9.5, 4.1Hz, 1H), 4.60 (m, 1H), 4.69 (d, *J* = 11.6Hz, 1H), 5.52 (dd, *J* = 11, 9.5Hz, 1H), 5.74 (td, *J* = 11, 7.6Hz, 1H), 7.27 (m, 10H). ^{13}C NMR (100MHz, $CDCl_3$) 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); $[\alpha]^{25}_D$ – 4.4 (c 0.9, $CHCl_3$); IR (thin film): 3441, 2925, 1495, 1455 cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$) δ 0.88 (t, *J* = 6.6Hz, 3H), 1.26 (bs, 16H), 2.00 (m, 2H), 3.66 (m, 3H), 3.83 (m, 1H), 4.33 (d, *J* = 12Hz, 1H), 4.44 (dd, *J* = 9.8, 4.9Hz, 1H), 4.59 (d, *J* = 11.2Hz, 1H), 4.63 (d, *J* = 12Hz, 1H), 4.72 (d, *J* = 11.2Hz, 1H), 5.51 (dd, *J* = 11, 9.8Hz, 1H), 5.77 (td, *J* = 11.2, 7.3Hz, 1H), 7.30

(m, 10H); ^{13}C NMR (100MHz, $CDCl_3$) 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); $[\alpha]^{25}_D$ – 29.6 (c 0.9, $CHCl_3$); IR (thin film): 3434, 3029, 1494, 1452 cm^{-1}; ^{1}H NMR (400 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, 126.87, 127.9, 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 α,β-unsaturated ester **13b** gave 157 mg (80 % yield) of the lactone **1b** as a viscous liquid; Rf 0.43 (40% EtOAc in petroleum ether); $[\alpha]^{25}_D$ –35.0 (c 0.7, $CHCl_3$); IR (thin film) 3441. 2931, 1768 cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$) δ 0.92 (t, *J* = 7.1Hz, 3H), 1.26 – 1.58 (m, 6H), 2.13 (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 $C_9H_{16}O_3$: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 α,β-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); $[\alpha]^{25}_D$ –35.9 (c 1.9, $CHCl_3$) {lit[17] – 33.1 (c 1.6, $CHCl_3$)}; 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); ^{13}C 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 α,β-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); $[\alpha]^{25}_D$ -23.5 (c 0.43, $CHCl_3$) {lit[8] $[\alpha]^{25}_D$ -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 (100MHz, $CDCl_3$) 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 α,β-unsaturated ester provided 185 mg (81% yield) of the lactone **1e**; R_f 0.37 (40% EtOAc in petroleum ether); $[\alpha]^{25}_D$ –2.38 (c 0.8, $CHCl_3$); IR (thin film) 3434, 1767 cm^{-1}; 1H NMR (400 MHz, CDCl3) 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-Benzyloxy-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 CH_2Cl_2, $Pb(OAc)_4$ (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)triphenyphosphorane (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); R_f 0.65 (10% EtOAc in petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{22}H_{32}O_5$: 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 $NaHCO_3$ solution and extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4 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; R_f 0.17 (40% EtOAc in petroleum ether); $[\alpha]^{25}_D$ – 39.0 (c 0.51 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 22.6, 24.0, 27.7, 28.3, 33.3, 71.7, 75.1, 81.5, 177.4. Anal. Calcd. for $C_{10}H_{18}O_4$: C, 59.39; H, 8.97. Found: C, 59.31; H, 8.89.

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