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A facile approach towards synthesis of verbalactone and biologically active δ-lactones using D-glucose

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ABSTRACT

A general synthetic approach has been developed for the asymmetric synthesis of chiral δ-lactones and verbalactone using D-glucose. The key intermediate used in this approach was α-diazoketone.

The biological activity of compounds having lactonic functionality is highly dependent on their configuration and optical purity, therefore, there have been considerable efforts towards the synthesis of lactones in enantiomerically pure form.[1] In general biologically active lactones are prepared by the microbial reduction of the corresponding ketoester[2] or by the enzymatic resolution[3] of the hydroxyl-acid precursor. However, these methods often suffer from serious drawbacks. Enzymatic resolution or microbial reduction is substrate specific and the use of chiral reagents often results in low enantioselectivity. Therefore, it was of interest to investigate the use of chiral synthon in the asymmetric synthesis of these compounds. We have been working in the area of natural product synthesis for the past one and a half decades, and, have synthesized many of the naturally occurring biologically active natural products utilizing the chiron source.[4] Out of the several available carbohydrate sources, we herein report a general approach where D-glucose can be crafted in a desired way to give a common diazoketone intermediate, which can be utilized further for the synthesis of naturally occurring verbalactone **1**, and other bioactive chiral δ-lactones **2**–**4** (Fig. 1).

Verbalactone[5] **1** is the first example where 1,7-dioxacyclododecane moiety was reported as the ring system of a natural product. It is obtained from roots of *Verbascum undulatum* a biennial plant of genus *Verbascum* that belongs to Schrophulariaceae family. The lactone has a novel macrocyclic dimeric structure and shows activity against three Gram-positive bacteria with optimum activity of MIC=62.5 μg/mL and five Gram-negative bacteria with optimum activity of MIC=125 μg/mL.[5,6] The structure and absolute stereochemistry of this lactone **1**, as 4*R*,6*R*,10*R*,12*R*,4,10-dihydroxy-2,8-dioxo-6,12-dipentyl-1,7- dioxacyclododecane, were determined by spectral methods and chemical correlations. The NMR profile is very similar to the monomeric lactone of (3*R*,5*R*)-dihydroxydecanoic acid. Till date, four total synthesis of the verbalactone have been reported.[7] (*R*)-Massoialactone **2** is the allomone of two species of formmicine ants of genus *Camponotus*, collected in Western Australia.[8] It was first isolated from the bark of *Cryptocaria massoia*, by Abe[9] in 1937 and later from jasmine flower[10] and cane molasses[11] where it acts as flavour component. It is also present in *Hierochloe odorata* and *Hierochloe australis* both being used in vodka production.[12] It also acts as a powerful skin irritant and produces systolic standstill in frog heart muscles.[13] (*R*)-Decalactone **3** was first observed in cashew apple product produced from

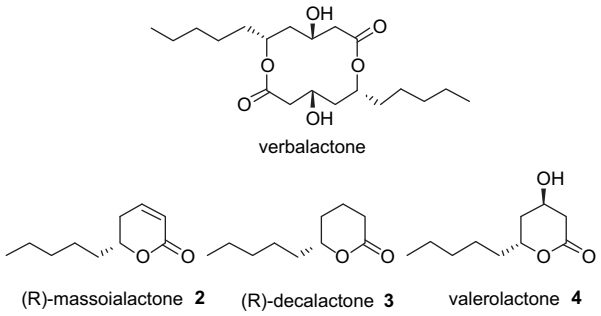

Figure 1. Verbalactone and chiral δ-lactones.

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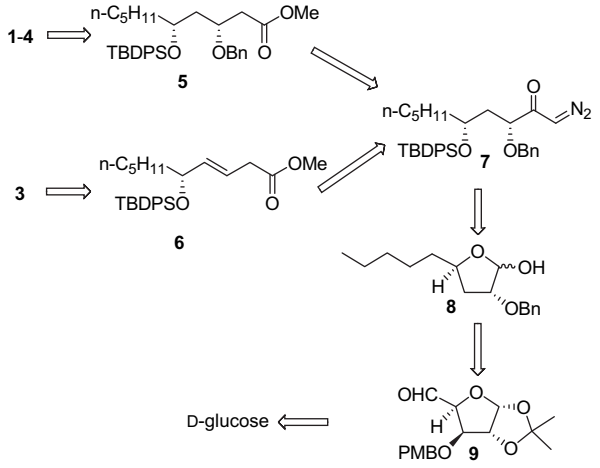
cashew tree, *Anacardium occidentale* L. an indigenous Brazilian tree found in northeastern coastal region. It is an important constituent in cheese, butter having sweet, creamy and milky odour.[14] Low threshold concentration and specific odour makes this highly important subunit to be crucial for simple synthetic approach. (+)-Valerolactone **4**, more commonly known as 3-hydroxy-5-decanolide is identical to lactone subunits present in mevinolin and compactin[15] and acts a potent inhibitor of enzyme HMG-CoA reductase. Various groups have reported both racemic as well as enantioselective synthesis of these lactones.[16,17] Although several reports for the synthesis of 6-substituted hydropyran-2-one derivatives have been reported, there is no efficient general route to these derivatives. We herein, therefore report a new route to 6-substituted hydropyran-2-one derivatives along with verbalactone.

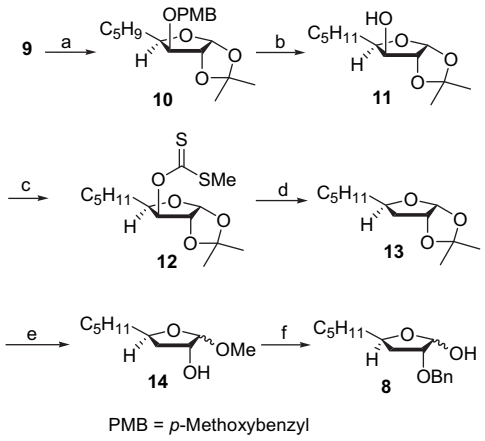
The common retrosynthetic pathway is shown in Scheme 1. It was conceived that the dimeric lactone **1** and δ-lactones **2**–**4** can be obtained from esters **5** and **6**, which were obtained by Arndt–Eistert homologation of diazoketone **7**, a common intermediate. Further this diazoketone can be derived from a hemiacetal **8**, which can be obtained from an aldehyde **9**.[18] The aldehyde **9**[18] can easily be synthesized from D-glucose using literature procedure. The chirality at C-4 and C-6 in the natural product **1** would be directly translated from D-glucose.



Scheme 1. Retrosynthetic scheme.

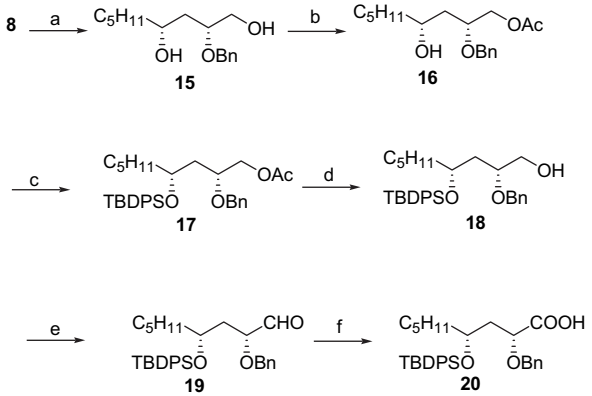
The synthesis of verbalactone **1** and chiral δ-lactones such as (*R*)-massoialactone **2**, (*R*)-decalactone **3** and valerolactone **4** involved α-D-pentodialdose **5**, which was easily synthesized from D-glucose using literature procedures.[18] The aldehyde **9** was converted into **10** using Wittig chemistry with a phosphonium salt prepared from butyl bromide and triphenylphosphine. Further oxidative cleavage of PMB ether in **10** using DDQ in aqueous DCM followed by hydrogenation of the double bond by Pd/C in MeOH gave **11** as a solid product. The C3 hydroxyl xanthate functionality in **11** was now converted to corresponding **12** by treatment with CS_2 and MeI. The xanthate **12** so obtained when exposed to *n*-Bu_3SnH in toluene under reflux conditions led to Barton–McCombie deoxygenation[19] at C3 thereby giving **13**. At this stage we decided to deprotect internal acetonide in **13** with simultaneous protection of lactal hydroxy group. Exposure of **13** to a catalytic amount of acetyl chloride in methanol afforded the methyl acetal **14**, which was successively protected as benzyl ether at α-position yielding an anomeric mixture. It was then decided to deprotect the methyl acetal and it was achieved using 60% AcOH and catalytic amount of concd HCl affording hemiacetal **8** (Scheme 2).

The hemiacetal **8** was then reduced with sodium borohydride to provide diol **15**. Selective protection of terminal hydroxyl in **15** was done using AcCl/collidine at −78 °C, to provide acetate **16** in good



Scheme 2. Reagents and conditions: (a) $Ph_3PC_4H_9Br$, *n*-BuLi, THF, 0 °C to rt, 95%; (b) (i) DDQ, DCM/H_2O (10:1); (ii) H_2, 10% Pd/C, EtOH, rt (92% for two steps); (c) NaH, CS_2, MeI, THF, 0 °C to rt, 12 h, 95%; (d) *n*-Bu_3SnH, AIBN, toluene, 110 °C, 16 h, 82%; (e) MeOH, AcCl, 60 °C, 6 h, 77%; (f) (i) NaH, BnBr, THF, 0 °C to rt, 6 h; (ii) 60% AcOH, H^+, 60 °C, 4 h (83% for two steps).

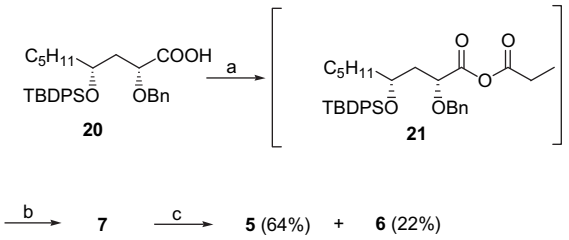
yield. Further protection of secondary hydroxyl in **16** as TBDPS ether using TBDPSCl gave **17**. The acetate group in **17** was hydrolyzed using K_2CO_3/MeOH to give **18**, which upon oxidation using Swern conditions gave an aldehyde **19**. The aldehyde **19** on further oxidation using $NaClO_2$ and NaH_2PO_4 in *t*-BuOH/H_2O (2:1) gave an acid **20** (Scheme 3). As per this stratagem, we needed one more carbon and it was achieved using Arndt–Eistert homologation protocol. The acid **20** so formed was transformed into corresponding α-diazoketone **7** via reaction of diazomethane with a mixed anhydride **21**. Wolff rearrangement[20] of α-diazoketone **7** using silver benzoate afforded a mixture of homologated ester **5** and a homologated unsaturated ester **6** as side product (Scheme 4).



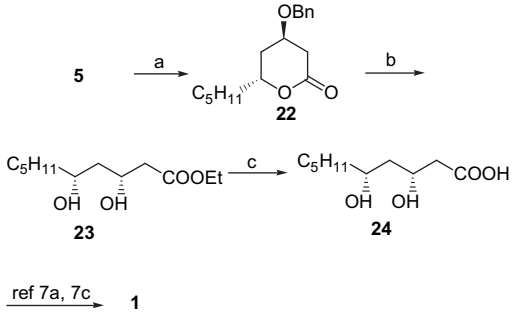
Scheme 3. Reagents and conditions: (a) $NaBH_4$, MeOH, 0 °C to rt, 6 h, 96%; (b) AcCl, collidine, DCM, −78 °C, 3 h, −40 °C, 6 h, 95%; (c) TBDPSCl, imidazole, DCM, 0 °C to rt, 4 h, 93%; (d) K_2CO_3, MeOH, 0 °C to rt, 2 h, 90%; (e) $(COCl)_2$, DMSO, DCM, Et_3N, −78 °C, 99%; (f) $NaClO_2$, $NaH_2PO_4 \cdot H_2O$, 2-methyl-2-butene, *t*-BuOH/H_2O, rt, 12 h, 92%.

With the required homologated ester **5** in hand, we first deprotected the TBDPS ether using 70% HF/Py in THF, to obtain the six-membered lactone having C-5 hydroxy protected as corresponding benzyl ether **22** (Scheme 5). The lactone upon treatment with Pd/C in ethanol led to the debenzylation as well as opening of lactone to give an ester **23**. The ester **23** was then hydrolyzed to a corresponding seco-acid **24**, which is a well known precursor for the synthesis of the natural product **1**. Since the conversion of seco-acid into verbalactone **1** is well established, this completed its formal total synthesis.[7a,c]

Further, the Arndt–Eistert products **5** and **6** obtained after Wolf rearrangement were found to be key intermediates in the synthesis

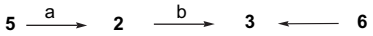


Scheme 4. Reagents and conditions: (a) (i) Et_3N, ClCOOEt, THF, 0 °C to rt, 2 h; (b) CH_2N_2, Et_2O, rt, 2 h (68% for two steps); (c) PhCOOAg, Et_3N, MeOH, −10 °C to rt, 1.5 h, 86%.



Scheme 5. Reagents and conditions: (a) 70% HF/Py, pyridine, THF, rt, 24 h, 82%; (b) H_2, Pd/C, EtOH, 40 psi, 12 h, 89%; (c) $LiOH·H_2O$, $MeOH/H_2O$ (4:1), 0 °C to rt, 4 h, 94%.

of δ-lactones. We first carried out the TBDPS cleavage in **5** using CBr_4/MeOH, which surprisingly gave the lactonized product (*R*)-massoialactone **2**, which upon hydrogenation gave (*R*)-decalactone **3**. Similarly, TBDPS deprotection in **6** with CBr_4/MeOH, followed by hydrogenation of double bond using Pd/C in MeOH gave (*R*)-decalactone **3** (Scheme 6).



Scheme 6. Reagents and conditions: (a) CBr_4, MeOH, 60 °C, 12 h; (b) H_2, Pd/C, MeOH, 1 atm, 12 h; (c) (i) CBr_4, MeOH, 60 °C, 12 h; (ii) H_2, Pd/C, MeOH, 1 atm, 12 h.

The massoialactone **2** so obtained can easily be converted into valerolactone **4** via a literature known procedure.[21]

In conclusion we have demonstrated a facile approach towards the synthesis of verbalactone **1**, (*R*)-massoialactone **2**, (*R*)-decalactone **3** and valerolactone **4** using D-glucose as a readily available chiral synthon in a simple and straight-forward manner. Infact the strategy is useful for synthesis of several other 6-substituted chiral δ-lactones present in various biologically active natural products.

1. Experimental

1.1. General methods

All reactions were carried out under an atmosphere of nitrogen in oven dried glassware with magnetic stirring. ^1H and ^{13}C NMR spectra were recorded on Joel (400 MHz) NMR or Jeol (500 MHz) spectrometer in $CDCl_3$. Chemical shifts are reported in delta (δ) units, in parts per million (ppm). Tetramethylsilane and $CDCl_3$ were used as internal standard for ^1H and ^{13}C NMR, respectively. Coupling constants were reported in hertz. Splitting patterns are designated as s for singlet; d for doublet; t for triplet; q for quartet; m for multiplet and br s for broad singlet. IR spectra were measured with Bruker FT/IR Vector 22 spectrometer. Routine monitoring of reactions was performed using precoated silica gel TLC plates from E-Merck. All the chromatographic separations were carried out by using silica gel (Acme's, 100–200 mesh). Petroleum ether used was of boiling range 60–80 °C. Melting points were determined by using Perfit apparatus and are uncorrected.

*1.1.1. (3aR,5R,6R,6aS)-6-(4-Methoxybenzyloxy)-2,2-dimethyl-5-((E)-pent-1-enyl)tetrahydrofuro[2,3-d][1,3]dioxole (**10**).* *n*-BuLi (1.6 M soln in *n*-Hexane, 19.95 mL) was added dropwise to a solution of triphenylphosphonium butyl bromide (12.78 g, 31.95 mmol) in anhydrous THF (90.0 mL) at 0 °C and allowed to stir for 15 min. Then, a solution of the aldehyde **9** (8.2 g, 26.6 mmol) in anhydrous THF (50.0 mL) was added and the mixture was stirred at room temperature for 6 h. The reaction mixture was quenched with water and filtered through Celite. The filtrate was concentrated by evaporation and taken into ethyl acetate. It was washed with water, brine and dried over Na_2SO_4. After concentration on rotavapor, the crude reaction mixture was purified over silica gel to obtain pure alkene **10** (8.3 g) as a colourless liquid; $[\alpha]_D^{25}$ −34.5 (*c* 0.60, $CHCl_3$); IR (thin film, cm^{-1}) 2934, 2890, 1173; ^1H NMR ($CDCl_3$, 500 MHz): δ 0.84 (t, *J*=5.9 Hz, 3H), 1.31 (s, 3H), 1.32–1.42 (m, 2H), 1.51 (s, 3H), 1.98–2.11 (m, 2H), 3.73 (m, 4H), 4.52 (ABq, *J*=9.4 Hz, $\Delta\nu$=34.5 Hz, 2H), 4.59 (d, *J*=3.0 Hz, 1H), 4.92 (dd, *J*=5.5, 5.9 Hz, 1H), 5.62–5.70 (m, 2H), 5.94 (d, *J*=2.9 Hz, 1H), 6.82–6.89 (m, 2H), 7.21–7.25 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 13.8, 22.7, 26.3, 26.9, 30.2, 30.4, 55.3, 71.9, 75.9, 83.1, 104.8, 111.4, 113.9, 123.9, 128.6, 129.5, 135.1, 159.4. HRMS (ESI): exact mass calcd for $C_{20}H_{28}O_5$: $[M+H]^+$: 349.1945. Found: 349.1947. Anal. Calcd for $C_{20}H_{28}O_5$: C, 68.94; H, 8.10. Found: C, 68.86; H, 8.19.

*1.1.2. (3aR,5R,6R,6aS)-2,2-Dimethyl-5-pentyltetrahydrofuro[2,3-d][1,3]dioxol-6-ol (**11**).* A solution of **10** (5.41 g, 15.24 mmol) was treated with DDQ (5.19 mg, 22.86 mmol) in CH_2Cl_2/H_2O (10:1, 60 mL) at room temperature. The reaction mixture was stirred vigorously for 4 h and quenched with an aqueous saturated sodium hydrogen carbonate. The aqueous layer was extracted with CH_2Cl_2. The organic phase was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed on a rotary evaporator and the crude mixture was chromatographed over silica gel to give 3.26 g (92% yield) of alkene, which was subjected to hydrogenation using 10% Pd/C (300 mg) in anhydrous MeOH, which afforded the **11** 3.2 g (99%) as a white solid; $[\alpha]_D^{25}$ −49.4 (*c* 6.4, $CHCl_3$); IR (thin film, cm^{-1}) 3150, 2934, 2890, 1173; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.89 (t, *J*=1.2 Hz, 3H), 1.30 (s, 3H), 1.32–1.44 (m, 5H), 1.47 (s, 3H), 1.49–1.72 (m, 3H), 4.04–4.13 (m, 3H), 4.51 (d, *J*=3.4 Hz, 1H), 5.88 (d, *J*=3.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.9, 22.5, 25.7, 26.1, 26.5, 27.5, 31.8, 75.3, 80.3, 85.2, 104.1, 111.3. HRMS (ESI): exact mass calcd for $C_{12}H_{22}O_4$: $[M+H]^+$: 231.1526. Found: 231.1529. Anal. Calcd for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63. Found: C, 62.67; H, 9.56.

*1.1.3. O-(3aR,5R,6R,6aS)-2,2-Dimethyl-5-pentyltetrahydrofuro-[2,3-d][1,3]dioxol-6-yl S-methyl carbono-dithioate (**12**).* To a suspension of NaH (3 g, 74.84 mmol) in anhydrous THF (80 mL), **11** (8.72 g, 37.42 mmol) in anhydrous THF (40 mL) was slowly added at 0 °C, stirred for 30 min followed by addition of CS_2 (3.39 mL, 56.14 mmol) and further stirred for 15 min at 0 °C. To this reaction mixture MeI (3.51 mL, 56.14 mmol) was added and left for stirring for 12 h and was quenched with acetic acid. The aqueous layer was extracted with ethyl acetate. The organic phase was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed on a rotary evaporator and the crude mixture was chromatographed over silica gel to give 11.52 g of xanthate **12**; $[\alpha]_D^{25}$ +6.4 (*c* 5.0, $CHCl_3$); IR (thin film, cm^{-1}) 2954, 1713, 1208; ^1H NMR ($CDCl_3$, 500 MHz): δ 0.86 (t, *J*=5.3 Hz, 3H), 1.24–1.30 (m, 4H), 1.32 (s, 3H), 1.41–1.49 (m, 1H), 1.52 (s, 3H), 1.60–1.74 (m, 3H), 2.59 (s, 3H), 4.32 (dt, *J*=2.2, 5.4 Hz, 1H), 4.61 (d, *J*=3.1 Hz, 1H), 5.85 (d, *J*=2.4 Hz, 1H), 5.90 (d, *J*=3.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 14.0, 19.3, 22.5,

25.8, 26.3, 26.6, 27.8, 31.8, 79.5, 83.2, 84.9, 104.5, 111.9, 215.4. Anal. Calcd for $C_{14}H_{24}O_4S_2$: C, 52.47; H, 7.55. Found: C, 52.54; H, 7.47.

*1.1.4. (3aR,5R,6aS)-2,2-Dimethyl-5-pentyltetrahydrofuro[2,3-d][1,3]-dioxole (**13**).* To a solution of *n*-Bu_3SnH (14.79 mL, 56.86 mmol) in anhydrous toluene 160 mL, **12** (11.52 g, 35.54 mmol) in anhydrous toluene 90 mL was added. To this catalytic amount of AIBN was added and the resulting reaction mixture was refluxed for 16 h. The reaction mixture was cooled to room temperature and toluene was evaporated on rotavapor to get the crude product. The crude product upon purification on silica gel gave 6.32 g of the required compound **13**; $[\alpha]_D^{25}$ −1.9 (*c* 2.6, $CHCl_3$); IR (thin film, cm^{-1}) 3150, 2934, 1173; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.86–0.88 (m, 3H), 1.31 (s, 3H), 1.39–1.46 (m, 8H), 1.51 (s, 3H), 2.11 (dd, *J*=3.8, 13.2 Hz, 2H), 4.16–4.18 (m, 1H), 4.70–4.72 (m, 1H), 5.79 (d, *J*=3.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.9, 22.5, 25.7, 26.1, 26.6, 31.9, 34.2, 38.9, 78.0, 80.5, 105.2, 110.7. HRMS (ESI): exact mass calcd for $C_{12}H_{22}O_3$: $[M+H]^+$: 215.1577. Found: 215.1572. Anal. Calcd for $C_{12}H_{22}O_3$: C, 67.26; H, 10.35. Found: C, 67.35; H, 10.26.

*1.1.5. (2S,3S,5R)-2-Methoxy-5-pentyltetrahydrofuran-3-ol (**14**).* A solution of **13** (4.6 g, 21.19 mmol) in MeOH (60.0 mL) and catalytic amount of acetyl chloride was refluxed for 6 h. The reaction mixture was neutralized with solid Na_2CO_3 and then concentrated on rotary evaporator. The residue was dissolved in EtOAc (50 mL), washed with water, brine and dried over anhydrous Na_2SO_4. The organic layer was concentrated and chromatographed over silica gel to give methyl hemiacetal **14**; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.89 (t, *J*=6.6 Hz, 3H), 1.24–1.49 (m, 5H), 1.59–2.00 (m, 5H), 3.33 (s, 3H), 4.11–4.33 (m, 2H), 4.77 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.0, 14.1, 22.7, 25.9, 31.8, 38.2, 76.3, 76.5, 79.8, 109.1. Anal. Calcd for $C_{10}H_{20}O_3$: C, 63.80; H, 10.71. Found: C, 63.71; H, 10.82.

*1.1.6. (2S,3S,5R)-3-(Benzyloxy)-5-pentyltetrahydrofuran-2-ol (**8**).* To a suspension of NaH (1.44 g, 36.12 mmol) in anhydrous THF (40 mL), the methyl acetal **14** (2.76 g, 14.45 mmol) in anhydrous THF was slowly added at 0 °C and stirred for 30 min followed by addition of benzyl bromide (2.06 mL, 17.34 mmol) and catalytic amount of TBAI. The reaction mixture was stirred at room temperature for 4 h, quenched with saturated NH_4Cl and extracted with ether. The organic layer was washed with brine and dried over anhydrous Na_2SO_4, concentrated and on purification over column chromatography gave benzyl ether. Then to a solution of benzyl ether (3.92 g, 13.95 mmol) in 60% acetic acid (70.0 mL), catalytic amount of concd HCl was added and refluxed at 80 °C for 4 h. The solution was quenched with solid $NaHCO_3$ and extracted with ethyl acetate. The organic layer was washed with water, brine and dried over anhydrous Na_2SO_4. The organic layer was concentrated and chromatographed over silica gel to give hemiacetal **8** (3.46 g, 93%); IR (thin film, cm^{-1}) 3460, 3020, 1640; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.88 (t, *J*=4.6 Hz, 3H), 1.24–2.14 (m, 10H), 3.99–4.30 (m, 2H), 4.53–4.64 (m, 2H), 5.38–5.41 (m, 1H), 7.26–7.38 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.1, 22.7, 25.9, 31.9, 35.8, 37.7, 54.4, 71.3, 80.1, 83.4, 106.8, 127.7, 127.8, 128.5, 138.1. Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.78; H, 9.08.

*1.1.7. (2R,4R)-2-(Benzyloxy)nonane-1,4-diol (**15**).* To a stirred solution of hemiacetal **8** (3.21 g, 12.02 mmol) in anhydrous MeOH was added $NaBH_4$ (1.14 g, 30.06 mmol) at 0 °C and was stirred for 6 h. The reaction mixture was quenched by addition of saturated NH_4Cl and MeOH was removed on rotary evaporator. The aqueous layer was extracted with EtOAc, the combined organic layers were washed with water, brine and dried over anhydrous Na_2SO_4, concentrated in vacuo and the residue was chromatographed over silica gel to give the diol **15** (3.10 g, 96%); IR (thin film, cm^{-1}) 3400, 2929, 1495, 1049; ^1H NMR ($CDCl_3$, 500 MHz): δ 0.88 (t, *J*=5.5 Hz, 3H), 1.26–1.37 (m, 5H), 1.38–1.48 (m, 2H), 1.68–1.79 (m, 3H), 3.59 (dd, *J*=9.3, 3.2 Hz, 1H), 3.73–3.83 (m, 3H), 4.61 (ABq, *J*=9.1 Hz, $\Delta\nu$=23.4 Hz, 2H), 7.25–7.36 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.1, 22.7, 25.3, 31.9, 37.9, 38.3, 63.8, 70.1, 71.6, 78.9, 127.9, 128.1, 128.7, 137.9. HRMS (ESI): exact mass calcd for $C_{16}H_{26}O_3$: $[M+H]^+$: 267.1890. Found: 267.1893. Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 72.23; H, 9.78.

*1.1.8. (2R,4R)-2-(Benzyloxy)-4-hydroxynonyl acetate (**16**).* To a solution of diol **15** (280 mg, 1.04 mmol) in dry DCM (5.0 mL), collidine (275 μL, 2.08 mmol) was added at −78 °C followed by acetyl chloride (81.4 μL, 1.14 mmol) under N_2 atmosphere and stirred for 3 h. The reaction mixture was warmed to −40 °C and again stirred for 6 h. The reaction mixture was quenched with saturated solution of aqueous NH_4Cl and was extracted with EtOAc. The organic layer was washed with aqueous $CuSO_4$ solution, brine and placed over anhydrous Na_2SO_4. The organic layer was concentrated under vacuo and chromatographed to give acetate **16** (306 mg, 94.6%); $[\alpha]_D^{25}$ +19.3 (*c* 3.5, $CHCl_3$); IR (thin film, cm^{-1}) 3461, 2929, 1741, 1237; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.88 (t, *J*=6.8 Hz, 3H), 1.28–1.77 (m, 10H), 2.08 (s, 3H), 3.73–3.86 (m, 2H), 4.10 (dd, *J*=4.8, 11.9 Hz, 1H), 4.29 (dd, *J*=3.6, 11.7 Hz, 1H), 4.64 (ABq, *J*=11.4 Hz, $\Delta\nu$=76.3 Hz, 2H), 7.31–7.25 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.9, 20.8, 22.5, 24.9, 31.8, 37.6, 38.7, 65.4, 70.5, 71.8, 127.8, 127.9, 128.5, 137.5, 170.8. Anal. Calcd for $C_{18}H_{28}O_4$: C, 70.10; H, 9.15. Found: C, 70.16; H, 9.09.

*1.1.9. (2R,4R)-2-(Benzyloxy)-4-(tert-butyldiphenylsilyl-oxy)nonyl acetate (**17**).* To a stirred solution of alcohol **16** (214 mg, 0.69 mmol) in anhydrous DCM (3.0 mL), imidazole (284 mg, 1.03 mmol) and TBDPSCl (93.7 mg, 1.37 mmol) were added and stirred at room temperature for 6 h. The reaction mixture was poured into water and extracted with ether. The organic layer was washed with water, brine and dried over anhydrous Na_2SO_4. The organic layer was concentrated under vacuo and chromatographed to give silyl ether **17** (351 mg, 93%); ^1H NMR ($CDCl_3$, 400 MHz): δ 0.78 (t, *J*=6.6 Hz, 3H), 1.02 (s, 9H), 1.09–1.16 (m, 3H), 1.33–1.37 (m, 3H), 1.64–1.67 (m, 1H), 1.80–1.85 (m, 3H), 2.00 (s, 3H), 3.67–3.69 (m, 2H), 3.79–3.89 (m, 2H), 4.45 (ABq, *J*=9.4 Hz, $\Delta\nu$=38 Hz, 2H), 7.19–7.71 (m, 15H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.1, 19.1, 19.4, 22.6, 24.5, 26.6, 26.7, 27.2, 31.7, 38.2, 70.4, 71.3, 73.8, 127.7, 127.9, 128.3, 128.5, 129.8, 134.3, 134.8, 134.9, 135.2, 135.9, 136.1, 138.4, 171.0. Anal. Calcd for $C_{34}H_{46}O_4Si$: C, 74.68; H, 8.48. Found: C, 74.76; H, 8.41.

*1.1.10. (2R,4R)-2-(Benzyloxy)-4-(tert-butyldiphenylsilyl-oxy)nonan-1-ol (**18**).* Acetate **17** (351.2 mg, 0.64 mmol) was dissolved in MeOH (5.0 mL) and finely powdered K_2CO_3 (132.3 mg, 0.96 mmol) at 0 °C was added. The reaction mixture was stirred for 2 h. MeOH was evaporated on rotavapor, and solid residue so obtained was dissolved in water and extracted with ether. The combined organic layers were washed with water, brine and dried over anhydrous Na_2SO_4. The organic layer was concentrated under vacuo and chromatographed to give alcohol **18** (291 mg, 90%); $[\alpha]_D^{25}$ −11.9 (*c* 1.65, $CHCl_3$); IR (thin film, cm^{-1}) 3435, 2930, 1110; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.71 (t, *J*=7.6 Hz, 3H), 1.04 (s, 9H), 1.06–1.14 (m, 10H), 3.33 (dd, *J*=1.2, 11.4 Hz, 1H), 3.52–3.60 (m, 2H), 3.80 (qn, *J*=5.3 Hz, 1H), 4.45 (ABq, *J*=11.7 Hz, $\Delta\nu$=20.5 Hz, 2H), 7.22–7.67 (m, 15H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.1, 19.4, 22.5, 24.6, 27.2, 31.8, 36.7, 37.6, 53.5, 64.2, 70.9, 71.1, 127.5, 127.6, 127.7, 127.8, 128.5, 129.8, 134.3, 136.0, 138.4. HRMS (ESI): exact mass calcd for $C_{32}H_{44}O_3Si$: $[M+H]^+$: 505.3068. Found: 505.306. Anal. Calcd for $C_{32}H_{44}O_3Si$: C, 76.14; H, 8.79. Found: C, 76.19; H, 8.71.

*1.1.11. (2R,4R)-2-(Benzyloxy)-4-(tert-butyldiphenylsilyl-oxy)-nonanal (**19**).* A solution of oxalyl chloride (254 μL, 2.96 mmol) was cautiously treated with DMSO (419.5 μL, 5.91 mmol) in CH_2Cl_2 (11.0 mL) at −78 °C under a nitrogen atmosphere. To this solution

was added a solution of the alcohol **18** (1.0 g, 1.97 mmol) in CH_2Cl_2 (3.0 mL). After the reaction mixture was stirred for 2 h at −78 °C, Et_3N (1.36 mL) was added and the resulting reaction mixture was allowed to come to 0 °C. The reaction mixture was diluted with phosphate buffer and then extracted with Et_2O. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The crude mixture was chromatographed over silica gel to give aldehyde **19** (989 mg, 99%); $[\alpha]_D^{25}$ −3.7 (*c* 1.87, $CHCl_3$); IR (thin film, cm^{-1}) 2930, 1734, 1111; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.76 (t, *J*=7.3 Hz, 3H), 1.03 (s, 9H), 1.05–1.87 (m, 10H), 3.90–3.96 (m, 2H), 4.51 (ABq, *J*=11.4 Hz, $\Delta\nu$=72.7 Hz, 2H), 7.23–7.3 (m, 10H), 7.65–7.72 (m, 5H), 9.52 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.9, 19.3, 22.4, 24.4, 27.0, 31.6, 36.1, 36.4, 69.9, 72.2, 80.4, 127.5, 127.6, 127.7, 128.4, 129.6, 134.0, 134.8, 135.2, 137.3, 202.9. Anal. Calcd for $C_{32}H_{42}O_3Si$: C, 76.45; H, 8.42. Found: C, 76.38; H, 8.49.

*1.1.12. (2R,4R)-2-(Benzyloxy)-4-(tert-butyldiphenylsilyl-oxy)-nonanoic acid (**20**).* To a solution of aldehyde **19** (1 g, 2.02 mmol) in *t*-BuOH (13.0 mL), $NaClO_2$ (3.8 g, 20.2 mmol) and $NaH_2PO_4 \cdot 2H_2O$ (2.2 g, 14.14 mmol) in H_2O (7.0 mL) was added. To this stirred solution 2-methyl-2-butene (2.0 mL) was added and left for stirring for 6 h. The reaction mixture was acidified with 1 N HCl and extracted with diethyl ether. The combined organic layers were washed with water, brine and dried over anhydrous Na_2SO_4. The organic layer was concentrated under vacuo and chromatographed to give acid **20** (972 mg, 92.3%); $[\alpha]_D^{25}$ 10.6 (*c* 7.3, $CHCl_3$); IR (thin film, cm^{-1}) 3371, 3031, 2107, 1637, 1071; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.75 (t, *J*=7.3 Hz, 3H), 1.03 (s, 9H), 1.05–2.04 (m, 10H), 3.90–3.93 (m, 2H), 4.50 (ABq, *J*=11.2 Hz, $\Delta\nu$=112.4 Hz, 2H), 7.23–7.43 (m, 11H), 7.63–7.70 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 14.0, 19.4, 22.5, 24.5, 27.1, 31.7, 35.8, 38.9, 68.6, 70.3, 72.5, 127.5, 127.6, 128.2, 128.5, 129.7, 134.3, 136.0, 136.9, 154.2. Anal. Calcd for $C_{32}H_{42}O_4Si$: C, 74.09; H, 8.16. Found: C, 74.17; H, 8.09.

*1.1.13. (3R,5R)-3-(Benzyloxy)-5-(tert-butyldiphenylsilyl-oxy)-1-diazodecan-2-one (**7**).* To acid **20** (500 mg, 0.96 mmol) in THF (4.0 mL) at 0 °C triethylamine (400 μL, 2.88 mmol) and ethylchloroformate (183.4 μL, 1.92 mmol) were added one after the other. After 15 min, the reaction mixture was brought to room temperature for 30 min and was filtered over Celite. To this filtrate a freshly prepared solution of diazomethane in diethyl ether [prepared from *N*-nitrosomethyl urea (800 mg) and KOH (1.6 g)] was added dropwise over a period of 30 min. The mixture was stirred for 1.5 h, at room temperature. The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography to give **7** (353.7 mg, 68%); $[\alpha]_D^{25}$ +8.4 (*c* 3.4, $CHCl_3$); IR (thin film, cm^{-1}) 3150, 2734, 1173; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.78 (t, *J*=7.3 Hz, 3H), 1.04 (s, 9H), 1.06–1.43 (m, 8H), 1.81–1.83 (m, 2H), 3.90 (m, 2H), 4.40 (ABq, *J*=11.4 Hz, $\Delta\nu$=78.3 Hz, 2H), 5.52–5.31 (m, 1H), 7.15–7.68 (m, 15H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.9, 19.3, 22.4, 24.1, 26.9, 31.7, 35.9, 39.8, 70.1, 72.1, 81.0, 88.5, 127.3, 127.4, 127.5, 127.7, 128.3, 129.4, 134.3, 134.7, 135.9, 137.2. HRMS (ESI): exact mass calcd for $C_{33}H_{42}N_2O_3Si$: $[M+H]^+$: 543.2973. Found: 543.2971. Anal. Calcd for $C_{33}H_{42}N_2O_3Si$: C, 73.02; H, 7.80; N, 5.16. Found: C, 73.10; H, 7.73; N, 5.19.

*1.1.14. (3R,5R)-Methyl-3-(benzyloxy)-5-(tert-butyl-diphenylsilyl-oxy) decanoate **5** and (R,E)-methyl 5-(tert-butyl-diphenylsilyl-oxy) dec-3-enoate **6**.* To a solution of α-diazoketone **7** (618 mg, 1.14 mmol) in anhydrous MeOH (10.0 mL) was added, dropwise, a solution of silver benzoate (89 mg, 0.36 mmol) in triethylamine (786 μL, 5.7 mmol) under dry N_2 at −10 °C. The reaction mixture was further stirred for 1.5 h. The solvent was evaporated and the residue was purified by column chromatography to give homologated ester **5** (401 mg, 64%) and unsaturated ester **6** (115 mg, 22%).

For **5**: $[\alpha]_D^{25}$ +3.6 (*c*, 1.15 $CHCl_3$); IR (thin film, cm^{-1}) 2930, 1738, 1111; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.78 (t, *J*=7.3 Hz, 3H), 1.02 (s, 9H), 1.04–1.95 (m, 10H), 2.31–2.43 (m, 2H), 3.63 (s, 3H), 3.79 (t, *J*=5.6 Hz, 1H), 3.97–4.00 (m, 1H), 4.54–4.55 (m, 2H), 7.18–7.47 (m, 15H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.1, 19.4, 22.6, 24.4, 26.6, 27.1, 31.8, 36.6, 39.8, 41.0, 70.6, 71.2, 73.4, 122.9, 127.5, 127.6, 127.8, 128.3, 129.7, 134.9, 136.1, 138.5, 172.1. Anal. Calcd for $C_{34}H_{46}O_4Si$: C, 74.68; H, 8.48. Found: C, 74.77; H, 8.39.

For **6**: $[\alpha]_D^{25}$ +11.8 (*c* 2.25, $CHCl_3$); IR (thin film, cm^{-1}) 2924, 1727, 1110; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.88 (t, *J*=7.3 Hz, 3H), 1.04 (s, 9H), 1.08–1.75 (m, 8H), 2.21–2.43 (m, 2H), 3.53 (s, 3H), 3.97–4.00 (m, 1H), 5.76 (d, *J*=15.1 Hz, 1H), 6.92 (d, *J*=15.4 Hz, 1H), 7.28–7.77 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.2, 19.3, 22.6, 24.4, 26.6, 27.1, 39.8, 41.0, 70.6, 71.2, 73.4, 101.4, 104.3, 122.9, 125.5, 125.6, 126.8, 128.1, 129.7, 133.9, 136.7, 138.2, 171.1. Anal. Calcd for $C_{27}H_{38}O_3Si$: C, 73.92; H, 8.73. Found: C, 73.86; H, 8.82.

*1.1.15. (4R,6R)-4-(Benzyloxy)-6-pentyltetrahydro-2H-pyran-2-one **22**.* To a solution of ester **5** (136 mg, 0.33 mmol) in THF (20.0 mL) at ambient temperature in a plastic vial was added 70% HF/Py (5.0 mL) dropwise and the yellow mixture was stirred for 24 h. The reaction mixture was quenched by the addition of saturated $NaHCO_3$ solution. The biphasic mixture was extracted with ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was purified by column chromatography to give the lactonized product **22** (53 mg, 82%); $[\alpha]_D^{25}$ +14.2 (*c* 0.8, $CHCl_3$); IR (thin film, cm^{-1}) 3171, 3031, 2107, 1698, 1071; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.89 (t, *J*=6.8 Hz, 3H), 1.25–2.17 (m, 10H), 2.69–2.75 (m, 2H), 3.63–3.74 (m, 1H), 3.98–4.00 (m, 1H), 4.52–4.63 (m, 2H), 7.26–7.37 (m, 5H). Anal. Calcd for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 73.81; H, 8.81.

*1.1.16. (3R,5R)-Ethyl-3,5-dihydroxydecanoate **23**.* To a solution of benzyl protected lactone **22** (53 mg, 0.19 mmol) in anhydrous ethanol (3.0 mL), Pd/C (15 mg) was added and left for hydrogenation at 40 psi pressure for 12 h. The reaction mixture was filtered through Celite and concentrated to give the ester **23** (34.9 mg, 89%); $[\alpha]_D^{25}$ +9.4 (*c* 0.6, $CHCl_3$); IR (thin film, cm^{-1}) 3171, 3031, 2107, 1698, 1071; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.89 (t, *J*=6.6 Hz, 3H), 1.26–1.62 (m, 13H), 2.48 (m, 2H), 3.24 (s, 1H, OH), 3.72–3.88 (m, 2H), 4.15–4.29 (m, 2H), 4.34 (s, 1H, OH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.3, 22.7, 25.1, 31.9, 37.9, 41.7, 42.3, 60.9, 69.3, 72.4, 172.7. HRMS (ESI): exact mass calcd for $C_{12}H_{24}O_4$: $[M+H]^+$: 233.1683. Found: 233.1687. Anal. Calcd for $C_{12}H_{24}O_4$: C, 62.04; H, 10.41. Found: C, 62.11; H, 10.36.

*1.1.17. (3R,5R)-3,5-Dihydroxydecanoic acid **24**.* To an ice cooled solution of **23** (50 mg, 0.24 mmol) in methanol/water (3.0 mL, 4:1) was added lithium hydroxide monohydrate (30 mg) at 0 °C. The mixture was brought to 25 °C and was further stirred for 2 h. The pH of the solution was adjusted to 7.0 by addition of aqueous NH_4Cl, the solvent was evaporated and the residue so obtained was extracted with chloroform to give seco-acid **24** (40 mg, 94%); $[\alpha]_D^{25}$ +14.3 (*c* 0.23, $CHCl_3$); IR (thin film, cm^{-1}) 3371, 3031, 2107, 1637, 1071; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.72–1.52 (m, 13H), 2.16–2.28 (m, 2H), 3.51–3.67 (m, 1H), 3.96–4.00 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.4, 21.9, 24.2, 31.1, 36.0, 42.9, 44.9, 69.7, 180.4. HRMS (ESI): exact mass calcd for $C_{10}H_{20}O_4$: $[M-H]^+$: 203.1283. Found: 203.1283. Anal. Calcd for $C_{10}H_{20}O_4$: C, 58.80; H, 9.87. Found: C, 58.89; H, 9.81.

*1.1.18. (R)-6-Pentyl-5,6-dihydro-2H-pyran-2-one **2**.* A solution of the ester **5** (100 mg, 0.182 mmol) and CBr_4 (24 mg, 0.073 mmol) in anhydrous MeOH (2.5 mL) was refluxed for 12 h. After completion of the reaction, the solvent was removed and the residue was purified by column chromatography to obtain the (*R*)-massoialactone **2** (19.2 mg, 52.2%); ^1H NMR ($CDCl_3$, 400 MHz): δ 0.89–0.91 (m, 3H), 1.00–1.04 (m, 1H), 1.32–1.42 (m, 4H), 1.52–1.81 (m, 3H), 2.32–2.34 (m, 2H), 4.42–4.44 (m, 1H), 6.03 (dd, *J*=1.4, 9.7 Hz, 1H), 6.87–6.90 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 14.1, 22.6, 24.6, 25.8, 29.5,

31.6, 34.9, 121.5, 145.2, 164.8. HRMS (ESI): exact mass calcd for $C_{10}H_{16}O_2$ $[M+H]^+$: 169.1229. Found: 169.1227. Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.48; H, 9.53.

1.1.19. (R)-6-Pentyltetrahydro-2H-pyran-2-one ***3***. A solution of the ester **6** (130 mg, 0.283 mmol) and CBr_4 (37.5 mg, 0.113 mmol) in anhydrous MeOH (3.0 mL) was refluxed for 12 h. After completion of the reaction, the solvent was removed and the residue was purified by column chromatography to obtain the 33 mg of alcohol. Now to a solution of alcohol (29 mg, 0.145 mmol) in anhydrous MeOH (3.0 mL), 10% Pd/C (15 mg) and few drops of HCl were added and hydrogenated for 6 h at 1 atm pressure under H_2 atmosphere. The solvent was filtered over Celite and filtrate was evaporated. The crude product so obtained after purification by column chromatography gave (*R*)-decalactone **3** (21 mg); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.89 (t, J=0.56 Hz, 3H), 1.25–1.31 (m, 12H), 2.46–2.56 (m, 2H), 4.14–4.29 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 14.1, 18.6, 22.6, 24.7, 27.9, 29.6, 31.7, 35.9, 80.7, 172.1. HRMS (ESI): exact mass calcd for $C_{10}H_{18}O_2$ $[M+H]^+$: 171.1386. Found: 171.1388. Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.61; H, 10.59.

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