Synthesis of cyclobutane fused γ-butyro lactones through intramolecular [2+2] photocycloaddition. Application in a formal synthesis of grandisol

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Dedicated to Professor T. R. Govindachari on the occasion of his 85th birthday
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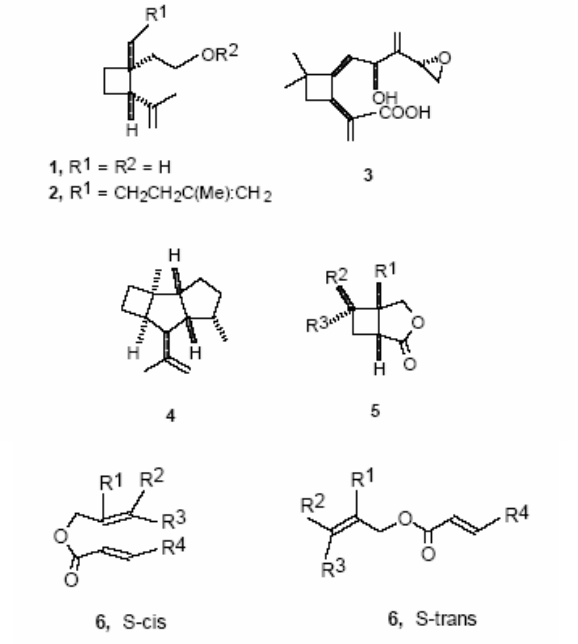
Abstract
An approach to the synthesis of cyclobutane fused γ-butyrolactones is described. The key step involves a Cu(I) catalysed intramolecular [2+2] photocycloaddition of 1,6-dienes in which the two alkene units are tethered through acetal oxygen. The resulting bicyclic lactols were then oxidised to provide the title compounds. The synthetic potential of these lactones is illustrated by a formal synthesis of grandisol.

Keywords: Cyclobutane fused butyrolactones, intramolecular, [2+2]photocycloaddition, bicyclic lactols, grandisol

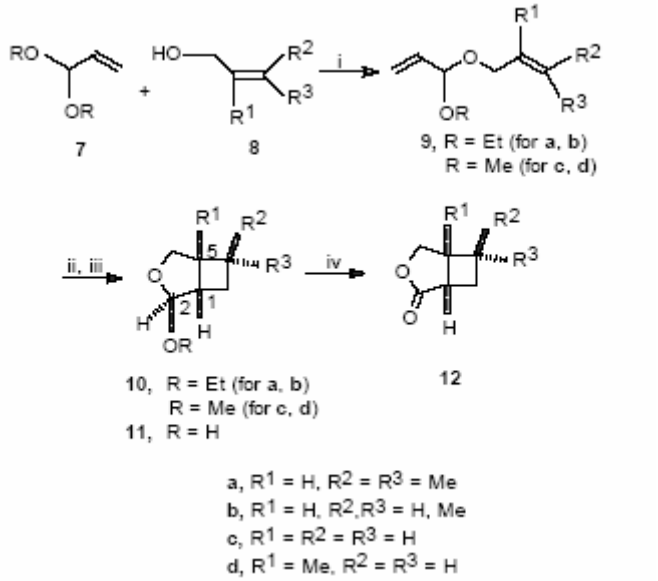
Introduction

The cyclobutane ring is present in many naturally occurring molecules. Grandisol **1**,[1] the pheromone **2**,[2] hebellophyllene **3**[3] and kelsoene **4**[4] are a few representative examples. Cyclobutane derivatives are also extensively used as synthetic intermediates[5] taking advantage of their inherent ring strain that renders them to undergo facile ring enlargement and ring cleavage. Thus development of methodologies for the synthesis of highly functionalised four membered rings is of continued interest.[6] We envisaged that cyclobutane fused γ-butyro lactones represented by the general structure **5** may lead to access to the natural products **1-4**. We herein, report[7] a general protocol for the synthesis of the cyclobutane fused γ-butyro lactones and its application in a formal synthesis of grandisol **1**.



Results and Discussion

Retrosynthetically, the bicyclic lactone **5** should, in principle, be available through intramolecular [2+2] photocycloaddition of the dienes **6**. However, UV irradiation of the diene **6**

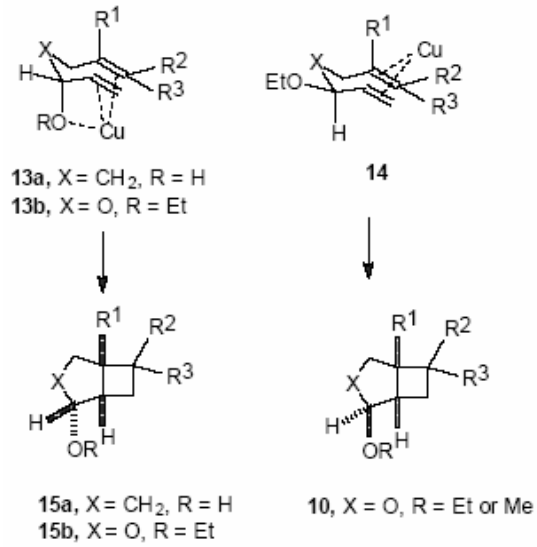


a, R^1 = H, R^2 = R^3 = Me **b,** R_1 = H, R_2,R_3 = H, Me **c,** R^1 = R^2 = R^3 = H **d,** R^1 = Me, R^2 = R^3 = H

Scheme -1 *Reagents and Conditions* : i, PPTS, C_6H_6, reflux, 1 h, (68-74%); ii, hn, CuOTf, Et 2O, 5-6 h, (50-69%); iii, 80% AcOH, 80 o C, 3.5 h, (56-77%); iv, Jones Reagent, 0 ^{o} C -rt, 1 h, (60-72%) (R^1 = R^2 = R^3 = H, R^4 = CH_3)

failed to induce stylization even in the presence of sanitizers or metal catalysts, probably because the diene **6** exists in the most stable S-trans conformation[8] rather than the less stable S-cis conformation required for cycloaddition. Salomon *et. al*[9] has demonstrated that diallyl ether derivatives undergo smooth photobicyclisation to produce 3-oxabicyclo[3.2.0]heptanes in the presence of Cu(I) catalyst which brings the diene in the required S-cis conformation through formation of Cu(I) complex. Based on this observation we anticipated that photobicyclisation of the diene **9** (Scheme 1) in which the two π-units are tethered through an acetal oxygen, would produce the bicyclic lactol **10**. Oxidation of the lactol **10** will then provide the desired lactone **11**.

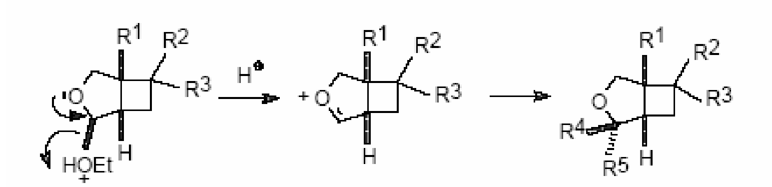
To begin, the diene **9a** was prepared (Scheme 1) in 68% yield through transacetalisation of acrolein diethyl acetal **7** (R=Et) with the allyl alcohol **8a** in benzene under reflux with azeotropic removal of ethanol in the presence of PPTS as catalyst. Cycloaddition of the diene **9a** was carried out in diethyl ether solution in the presence of cuprous trifluoromethane sulfonate (CuOTf) as catalyst by irradiating with quartz filtered light. The photoadduct **10a** was isolated in 50% yield. The gross structure of the photoadduct **10a** was established through its ^{1}H and ^{13}C NMR spectra.



The exo-stereochemical assignment to the photoadduct **10a** was based on comparison of the coupling constant of the C_2-H with those reported[10] for analogous exo and endo-2-substituted-3-oxabicyclo[3.2.0]heptanes. It has been reported that in exo-2-substituted-3-oxabicyclo[3.2.0]heptanes, the C_2-H which is trans to C1-H exhibits a coupling constant of 1.5 Hz, while the C_2-H which is cis to C_1-H in the corresponding endo structure exhibits a higher coupling constant of 5.5 Hz. The C_2-H in the photoadduct **10a** was found to appear at δ 4.82 as a singlet i.e. with J =0. Thus C_2- and C_1-hydrogens bear a trans relationship in the photo adduct **10a**.

The formation of the adduct **10a** with OEt group occupying an exo position is in contrast to the formation of the endo-adduct **15a** from Cu(I) catalyzed photo cycloaddition of 3-hydroxy-1,6-heptadiene. The latter reaction is believed[11] to proceed through a tricordinated Cu(I) complex **13a**. However, an analogous Cu(I) complex **13b** with the bulkier OEt group occupying an endo

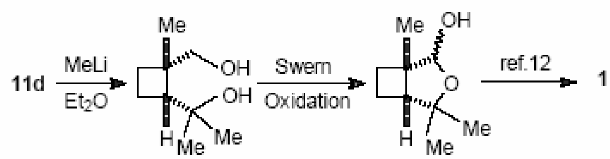
position, necessary for formation of the endo-adduct **15b**, would be highly sterically crowded. Thus cycloaddition of the diene **3a** takes place through the less crowded Cu(I) complex **14** resulting in exo adduct **10a**.



16, R^1 = H, R^2 = R^3 = Me
17, R^1= Me, R^2 = R^3 = H

11a, R^1 = R^5 = H,
R^2 = R^3 = Me, R^4 = OH
18, R^1 = Me, R^5 = OH R^2 R^3 R^4 H

The photoadduct **10a** was then treated with hot 80% aqueous acetic acid to afford the lactol **11a** in 71% yield. Retention of configuration at C2-centre during deprotection was indicated by the appearance of the C_2-H at δ5.19 as a singlet and is attributed to be the result of addition of H2O to the intermediate oxonium ion **16** from the least hindered exo face. Oxidation of the lactol **11a** finally afforded the lactone **12a** in 68% yield. The generality of this four-step protocol was established by the synthesis of the lactones **10bd** in very good yields. The diene **9b,** prepared from transacetalisation of acrolein diethyl acetal with crotyl alcohol, afforded the photoadduct **10b** as a mixture of two diastereoisomers in 1:2.5 ratio as determined from the integration of the C2-H singlets at δ 4.79 (minor isomer) and 4.90 (major isomer). The adduct **10b** was converted to the lactone mixture **12b** through oxidation of the corresponding lactols **11b**.



19 **20**

Scheme -2

The dienes **9c** and **9d** were prepared from transacetalisation of acrolein dimethyl acetal **7** (R = OMe) with allyl alcohol and methyallyl alcohol respectively. UV irradiation of these dienes in the presence of CuOTf afforded cycloadducts which underwent partial *in situ* demethylation, possibly through catalysis by TfOH generated from CuOTf during irradiation, to produce a mixture of the adducts **10c**, **11c** and **10d, 18** respectively. These lactols without characterisation, were directly treated with acid and the resulting products were oxidised with Jones reagent to provide the known lactones **12c** and **12d**. It is worth mentioning that in the lactol **18** the stereochemistry at C_2 is opposite to those of the lactols **11a,b** as indicated by the coupling constant of the C_2-H which appeared as a doublet at δ 4.89 (J = 9.9 Hz). The reversal of stereochemistry at C_2 may be attributed to the addition of H_2O to the oxonium ion **17** from the endo face as addition from the exo face is blocked by the C_5-Me.

The synthetic potential of the cyclobutane fused γ-butyro lactone is demonstrated by a formal synthesis of grandisol **1** (Scheme 2). The lactone **12d**, on reaction with excess of MeLi, afforded the diol **19** in 71% yield. Swern oxidation of the diol **19** afforded the known diastereomeric mixture of the lactols **20**. The mixture of lactols **20** has already been transformed[12] to grandisol, thus accomplishing its formal synthesis.[13]

In conclusion transacetalisation of an acrolein acetal with allyl alcohol in conjunction with photocycloaddition and oxidation offers an excellent route to cyclobutane fused γ-butyro lactones. An application of this synthetic protocol has been demonstrated by a formal synthesis of grandisol.

Experimental Section

General Procedures. Compounds described here are all racemates. All reactions were carried out under an atmosphere of N_2. Column chromatography was performed on silica gel (60-120 mesh). Petroleum refers to the fraction of petroleum ether bp 60-80 ^oC. Ether refers to diethyl ether. Organic extracts were dried over anhydrous Na_2SO_4. IR spectra were recorded in thin film. Unless otherwise stated, ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution at 300 MHz and 75 MHz respectively. Elemental analyses were carried out at the microanalytical laboratory of this laboratory.

3-Ethoxy-7-methyl-4-oxa-1,6-octadiene (9a). A mixture of 3-methyl-but-2-ene-1-ol (1g, 11.6 mmol), acrolein diethyl acetal (3.7 g, 29 mmol), PPTS (5 mg) and benzene (12 mL) was heated under reflux in an oil bath for 1 h with azeotropic removal of ethanol (Dean-Stark apparatus). On cooling, the reaction mixture was washed with aqueous $NaHCO_3$ (2x3 mL, 5%), dried and concentrated carefully in vacuum. The residual mass was chromatographed (ether-petroleum, 1:19) to afford the diene **9a** in 68% yield; ^1H NMR (60 MHz) δ (CCl_4) 1.05 (t, J = 7 Hz, Me), 1.66 (s, Me), 1.73 (s, Me), 3.44 (q, J = 7 Hz, 1H), 3.49 (q, J = 7 Hz, 1H), 3.89 (d, J = 7 Hz, 2H), 4.80 (m, 1H), 5.06-6.10 (m, 4H).

3-Ethoxy-4-oxa-1,6-octadiene (9b). Following the above procedure, the diene **9b** was prepared in 74% yield; ^1H NMR δ 1.20 (t, J = 6 Hz, 3H), 1.68 (d, J = 6 Hz, 3H), 3.4-3.6 (m, 4H), 3.9-4.0 (m, 2H), 4.9 (d, J = 3 Hz, 1H), 5.2-5.8 (m, 5H).

3-Methoxy-4-oxa-1,6-heptadiene (9c). The diene **9c** was obtained in 72% yield from the reaction of allyl alcohol and acrolein dimethyl acetal using the above procedure; ^1H NMR (60 MHz) (CCl_4) δ 3.33 (s, 3H), 4.08 (d, J = 6 Hz, 2H), 4.83-6.03 (m, 7H).

3-Methoxy-6-methyl-4-oxa-1,6-heptadiene (9d). The diene **9d** was prepared in 68% yield from the reaction of methallyl alcohol and acrolein dimethyl acetal following the above procedure. ^1H NMR (60 MHz) (CCl_4) δ 1.73 (s, 3H), 3.23 (s, 3H), 3.88 (s, 2H), 4.80-6.23 (m, 6H). Purification of these volatile dienes for microanalysis led to rapid decomposition.

General procedure for [2+2] photocycloaddition

exo-2-Ethoxy-6,6-dimethyl-3-oxa-bicyclo[3.2.0]heptane (10a). A solution of the diene **9a** (600 mg, 3.5 mmol) in ether (250 mL) containing CuOTf (0.2 g) was irradiated internally with a 450 W medium pressure mercury vapor lamp (Hanovia) through a double walled water cooled quartz immersion well for 5 h. The reaction mixture was then washed with ice-cold aqueous NH_4OH (2x20 mL, 35%), dried and concentrated in vacuum. The residual oil was chromatographed (ether-petroleum, 1:19) to afford the cyclobutane derivative **10a** (300 mg, 50%) as a colorless liquid; ^{1}H NMR δ 0.93 (s, 3H), 1.13 (s, 3H), 1.16 (t,*J* = 7.2 Hz, 3H), 1.73 (m, 2H), 2.45 (m, 1H), 2.77 (m, 1H), 3.41 (q, *J* = 6.9 Hz, 2H), 3.74 (dd, *J* = 6.3 and 9.6 Hz, 1H), 3.96 (d, *J* = 9.6 Hz, 1H); ^{13}C NMR δ15.3 (CH_3), 23.9 (CH_3), 31.3 (CH_3), 32.6 (C), 35.5 (CH_2), 38.5 (CH), 46.6 (CH), 62.1 (CH_2), 67.1 (CH_2), 107.4 (CH). Anal. Calcd. for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found, C, 70.87; H, 10.56.

exo-2-Ethoxy-6-methyl-3-oxabicyclo[3.2.0]heptane (10b). Obtained as a mixture of two diastereoisomers in 69% yield as a colorless liquid; ^{1}H NMR δ 0.91 (d, *J* = 6.6 Hz, CH_3 for minor diastereoisomer), 1.07 (d, *J* = 7.2 Hz, CH_3 for major diastereoisomer), 1.14 (t, *J* = 7.2 Hz, 3H), 1.59 (m, 1H), 1.83 (m, 1H), 2.02 (m, 1H), 2.45 (m, 1H), 2.75 (m, 1H), 3.37-4.00 (m, 4H), 4.79 (s, C_2-H for minor diastereoisomer), 4.90 (s, C_2-H for major diastereoisomer); ^{13}C NMR δ 15.3 (CH_3), 16.1 (CH_3), 22.2 (CH_3), 27.0 (CH_3), 28.6 (CH_2), 29.5 (CH_2), 32.2 (CH), 39.5 (CH), 40.8 (CH), 41.2 (CH), 44.8 (CH), 62.1 (CH2), 66.1 (CH_2), 72.1 (CH_2), 107.5 (CH), 108.3 (CH). Anal. Calcd. for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found : C, 69.45; H, 10.02.

6,6-Dimethyl-3-oxabicyclo[3.2.0]heptan-2-one (12a). A solution of the photo adduct **10a** (500 mg, 2.9 mmol) in aqueous acetic acid (10 mL, 80%) was heated in an oil bath at 80°C for 3.5 h. Most of the acetic acid was removed from the reaction mixture in vacuum. The residual mass was dissolved in ether (20 mL). The ether layer was washed with saturated aqueous $NaHCO_3$ (2x5 mL), dried and concentrated in vacuum. The residual mass was chromatographed (ether-petroleum, 1:3) to afford the lactol **11a** (300 mg, 71%); ^{1}H NMR δ 0.87 (s, 3H), 1.09 (s, 3H), 1.67-1.74 (m, 2H), 2.45 (t, *J* = 6.6 Hz, 1H), 2.71-2.79 (m, 1H), 3.87 (dd, *J* = 6.6, 9.6 Hz, 1H), 3.96 (d, *J* = 9.6 Hz, 1H), 5.19 (s, 1H). Without further characterization, it was oxidized according to the following procedure.

To a magnetically stirred solution of the lactol **11a** (250 mg, 1.76 mmol) in acetone (2 mL) cooled to 0°C, was added drop wise Jones reagent (0.5 mL, 0.7 M). The reaction mixture was stirred at rt for 1h, diluted with water (5 mL) and extracted with ether (3x5 mL). The ether extract was washed with saturated aqueous $NaHCO_3$ (4 mL), dried and concentrated in vacuum. The residual mass was chromatographed (etherpetroleum, 1:5) to afford the lactone **12a** (170 mg, 68%); IR : 1772 cm^{-1}; ^{1}H NMR δ 1.14 (s, 3H), 1.21 (s, 3H), 1.95 (dd, *J* = 3.9, 12.3 Hz, 1H), 2.28 (dd, *J* = 10.2, 12.3 Hz, 1H), 2.76 (br t, *J* = 8.1 Hz, 1H), 3.04 (m, 1H), 4.31 (dd, *J* = 7.2, 10.2 Hz, 1H), 4.45 (dd, *J* = 4.5, 10.2 Hz, 1H); ^{13}C NMR δ 15.3 (CH_3), 23.8 (CH_3), 31.1 (CH), 35.4 (C), 37.8 (CH_2), 43.2 (CH), 69.1 (CH_2), 181.3 (CO). Anal. Calcd for $C_8H_{12}O_2$: C, 68.55; H, 8.63. Found : C, 68.32; H, 8.34.

6-Methyl-3-oxabicyclo[3.2.0]heptan-2-one (12b). Following the above procedure, the photo

adduct **10b** was transformed to the lactol **11b** in 77% yield; ^{1}H NMR (60 MHz) δ(CCl_4) 0.85 (d, *J* = 7 Hz, CH_3 for minor diastereoisomer), 1.13 (d, *J* = 7 Hz, CH_3 for major diastereoisomer), 1.68-2.90 (m, 5H), 3.85 (m, 3H), 5.10 (s, C2-H for minor diastereoisomer), 5.20 (s, C2-H for major diastereoisomer). Anal. Calcd for $C_7H_{12}O_2$: C, 65.60; H, 9.44. Found : C, 65.30; H, 9.54.

The lactol **11b** was oxidized with Jones reagent to afford the lactone **12b** in 72% yield; IR: 1770 cm^{-1}; ^{1}H NMR δ 1.14 (d, *J* = 6.9 Hz, CH_3 for minor diastereoisomer), 1.16 (d, *J* = 6.9 Hz, CH_3 for major diastereoisomer), 1.76-1.83 (m, 0.5 H), 2.0-2.1 (m, 1H), 2.29-2.53 (m, 1.5 H), 2.67-2.80 (m, 1H), 2.99-3.20 (m, 1H), 4.21-4.50 (m, 2H); ^{13}C NMR δ16.3 (CH_3), 21.2 (CH_3), 28.8 (CH), 31.4 (CH_2), 31.5 (CH_2), 34.4 (CH), 34.7 (CH), 35.1 (CH), 36.1 (CH), 42.3 (CH), 68.6 (CH_2), 73.3 (CH_2), 180.8 (CO). Anal. Calcd for $C_7H_{10}O_2$: C, 66.65; H, 7.99. Found: C, 66.49; H, 8.12.

3-Oxabicyclo[3.2.0]heptan-2-one (12c). The crude product comprising of a mixture of the adducts **10c** and **11c** obtained after irradiation of the diene **9c** on treatment with HCl (1N) for 1h in dioxane afforded after chromatography the lactol **11c** in 59% yield; ^{1}H NMR δ1.74 (m, 2H), 2.14 (m, 3H), 2.90 (m, 1H), 3.02 (m, 1H), 3.87 (d, *J* = 9 Hz, 1H), 4.07 (dd, *J* = 5.4, 9 Hz), 5.38 (s, 1H); ^{13}C NMR δ 20.6 (CH_2), 23.7 (CH_2), 36.7 (CH), 44.0 (CH), 72.9 (CH_2), 103.9 (CH). The lactol **11c** was directly oxidised with Jones reagent as before to produce the known lactone **12c**[8] in 60% yield; IR: 1763 cm^{-1}; ^{1}H NMR δ 2.09-2.23 (m, 2H), 2.4-2.65 (m, 3H), 3.13-3.24 (m, 1H), 4.26 (d, *J* = 9 Hz, 1H), 4.39 (dd, *J* = 6.3 and 9 Hz, 1H).

5-Methyl-3-oxabicyclo[3.2.0]heptane-2-one (12d). The crude photoadducts **10d, 18** obtained after irradiation of the diene **9d** was converted to the lactol **18** in 56% according to the procedure for the synthesis of the lactone **12c**; ^{1}H NMR δ 1.27 (s, 3H), 1.65-2.12 (m, 4H), 2.40 (m, 1H), 3.51-3.71 (m, 2H), 4.89 (d, J = 9.9 Hz, 1H). Without further characterization, it was oxidized with Jones reagent as above to afford the lactone **12d** in 68% yield; IR: 1774 cm^{-1}; ^{1}H NMR δ 1.35 (s, 3H), 1.93-2.13 (m, 2H), 2.22-2.28 (m, 1H), 2.47-2.60 (m, 1H), 2.69 (dt, *J* = 2.6, 9.8 Hz, 1H), 3.96 (d, *J* = 9 Hz, 1H), 4.22 (d, *J* = 9 Hz, 1H); ^{13}C NMR δ 20.5 (CH_2), 21.7 (CH_3), 31.09 (CH_2), 43.08 (CH), 79.15 (CH_2), 41.6 (C), 180.7 (CO). Anal. Calcd for $C_7H_{10}O_2$: C, 66.65; H, 7.99. Found: C, 66.45; H, 7.75.

1,4,4-Trimethyl-3-oxabicyclo[3.2.0]heptan-2-ol (19). To a magnetically stirred solution of the lactone **12d** (500 mg, 3.96 mmol) in ether (5 mL) cooled to -10^{o}C was added MeLi (9.1 mL, 11.83 mmol, 1.3 M) in ether. The reaction mixture was slowly warmed to rt and stirring was continued for 12 h. After quenching with saturated aqueous NH_4Cl (1 mL), the reaction mixture was extracted with ether (3x10 mL). The organic extract was washed with brine (2x5 mL), dried and concentrated in vacuum. The residual mass was chromatographed (ether-petroleum, 2:3) to afford the diol **19** (360 mg, 71%) as a colorless liquid; ^{1}H NMR δ 1.08 (s, 3H), 1.12 (s, 3H), 1.25 (s, 3H), 1.45-2.10 (m, 7H), 3.49 (d, *J* = 11.4 Hz, 1H), 3.72 (d, *J* = 11.4 Hz, 1H); ^{13}C NMR δ 17.3 (CH_3), 26.9 (CH_2),28.5 (CH_3), 30.3 (CH_2), 45.0 (C), 54.7 (CH_2), 67.6 (CH), 72.8 (C).

To a magnetically stirred solution of oxalyl chloride (0.06 mL, 0.69 mmol) in dichloromethane (2 mL) at –70 ^{o}C, was added DMSO (0.18 mL, 2.54 mmol). After stirring for 15 min a solution of the above diol (40 mg, 0.25 mmol) in dichloromethane (2 mL) was added to

it. After stirring for 45 min, triethylamine (0.375 mL, 2.69 mmol) was added to it and the resulting reaction mixture was stirred at rt for 3h. It was poured into water (2 mL) and extracted with dichloromethane (3x5 mL). The organic extract was dried and concentrated in vacuum. The residual mass was chromatographed to afford the lactol mixture **20** (30 mg, 63%); ^{1}H NMR δ 1.16 (s, CH_3), 1.23 (s, CH_3), 1.26 (s, CH_3), 1.27 (s, CH_3), 1.34 (s, CH_3), 1.6-2.1 (m, 5H), 5.02 (d, J = 5.4 Hz, 1H), 5.12 (s, 1H); ^{13}C δ16.7, 16.8, 20.6, 22.6, 23.9, 24.2, 24.7, 28.6, 29.9, 31.5, 49.1, 51.9, 52.9, 52.2, 52.9, 80.05, 84.05, 103.2, 104.9. ^{1}H and ^{13}C NMR data are comparable to the literature.[12]

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