Synthesis of pseudo saccharide precursors through 'off template site' Michael –Wittig reaction on sugar derived enal[#]

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Dedicated to Dr. A V Rama Rao on his 70th birthday April 2, 2005
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Abstract
[3+3] Annulation protocol at an'off template site' on the sugar derived enal synthon effectively resulted in the formation of C-C linked pseudo saccharide precursors. Thus, the enolate of phosphorane generated from ethyl acetoacetate first undergoes a Michael reaction on the enal followed by a Wittig reaction to furnish the target saccharides, where the chirality is very effectively translated from the parent sugar.

Keywords: 'Off template site', pseudo saccharide precursors, Michael Wittig reaction, [3+3] annulation, nuclear Overhauser effect, molecular mechanics

Introduction

Several antibiotics and compounds of biological interest incorporate glycosides of pseudo-sugars[1-3] or carba-sugars[4], since, they are endowed with relatively greater stability towards glycosidase-induced hydrolysis. Besides the application as enzyme inhibitors, the carba-sugars are discussed as synthetic intermediates for the preparation of more efficient drugs in order to substitute carbohydrate moieties[5]. Thus, development of novel and efficient methods for the enantioselective or enantiospecific construction of carbocycles[6] resulted in a variety of useful routes such as Diels-Alder approaches, the double Michael cyclisation, 1,3-dipolar cycloaddition and free radical-induced C-C bond formation. As part of our ongoing efforts on the transformation of monosaccharides into new glycosubstances[7-15], herein we describe the synthesis of C-C linked pseudo saccharide precursors **1-5** (Figure 1), adopting a Michael-Wittig reaction on sugar-derived enal.

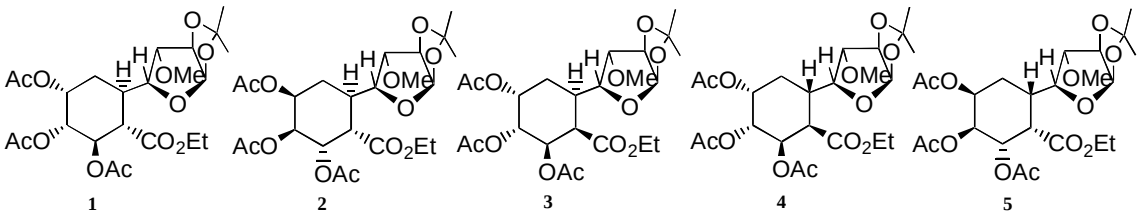
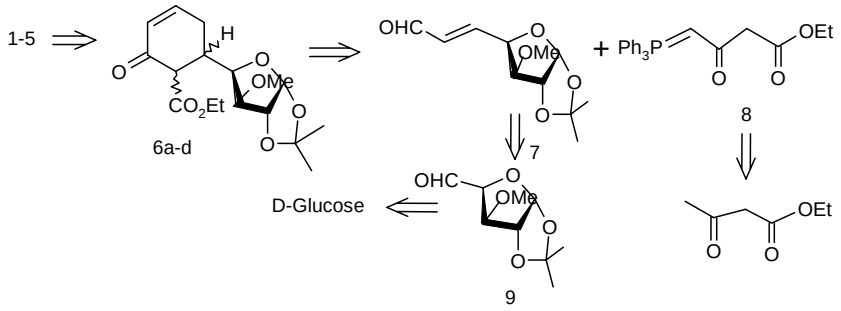


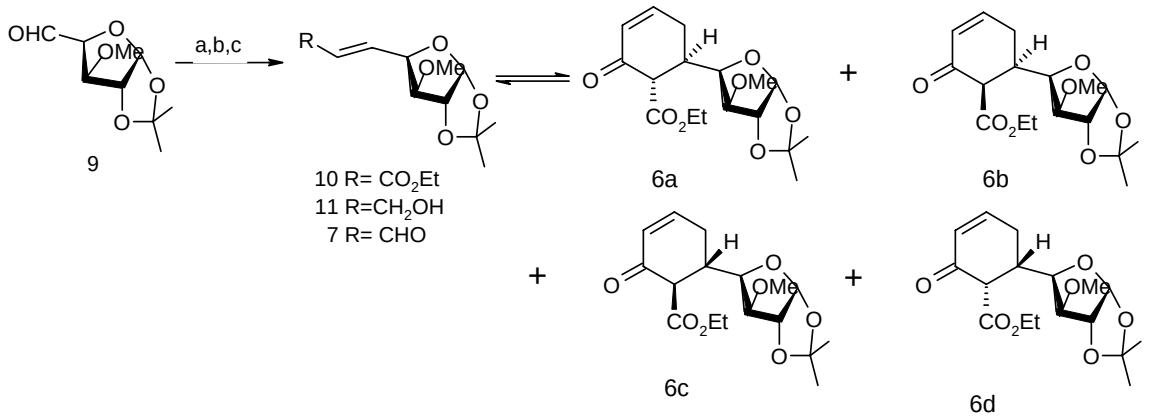
Figure 1

Results and Discussion

From the retro synthetic analysis of **1**-**5** (Scheme 1), it was envisaged that, the enones **6a-d** are appropriate late stage intermediates, which could be realized from the condensation of α, β-unsaturated aldehyde **7** and Wittig ylide **8** by a Michael-Wittig reaction. The enal **7** in turn could be made from D-glucose through aldehyde **9**, while **8** could be prepared from ethyl acetoacetate.



Scheme 1

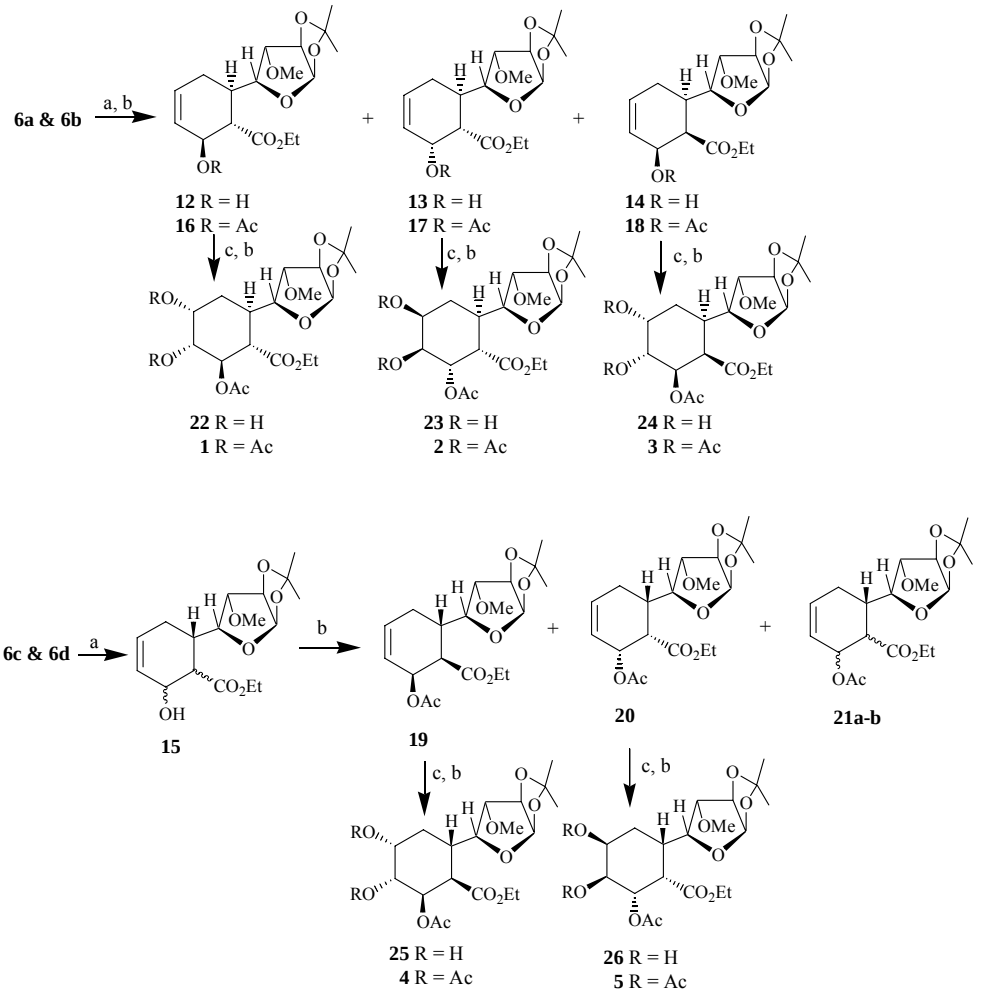


Scheme 2. a) $Ph_3=CHCO_2Et$, C_6H_6, reflux, b) DIBAL-H, CH_2CL_2, -23 ^oC, c)PDC CH_2CL_2, reflux, d) $Ph_3P=CHCOCH_2CO_2Et$, NaH, 2 drops water, THF, 50 ^oC.

Aldehyde **9**[16] was subjected to Wittig olefination (Scheme 2) with (ethoxycarbonyl methylene)triphenylphosphorane in benzene at reflux to give the ester **10**, which on reduction with DIBAL-H in CH_2Cl_2 afforded **11** in 86**%** yield. Oxidation of **11** with PDC in CH_2Cl_2 at reflux gave enal **7** (95%), which on reaction with **8**[17] in the presence of NaH and two drops of

water[18] in THF at 50 ^{0}C for 10 min., resulted in the formation of **6a-d** as a partially separable mixture of diastereoisomers in (6:1.5:1.5:1) 75% overall yield. The stereochemical outcome of each of the annulated products was unambiguously determined by ^{1}H NMR spectra. The formation of **6a** as major product, in the present study, indicates that the initial Michael-addition of nucleophile (sodium enolate of **8**) on the γ-alkoxy enal system **7** results in the formation of a *syn* product[19] and the aldehyde moiety of the adduct concomitantly undergoes a Wittig reaction in affording the cyclohexenone derivatives **6a-d**.

The mixture of diastereoisomers **6a** and **6b** were separated from **6c** and **6d** by column chromatography and both the mixtures were independently treated with $NaBH_4$ in ethanol (Scheme 3) in the presence of $CeCl_3.7H_2O$ under Luche's reaction conditions[20]. **6a** and **6b** afforded a mixture of alcohols **12** (major), **13** (minor) and **14** (single isomer) in the ratio of 4:1:2 respectively in a combined yield of 88%, while **6c** and **6d** furnished **15** as an inseparable mixture of alcohols. Acetylation of alcohols **12-14** with acetic anhydride in pyridine independently gave the corresponding acetates **16**, **17** and **18** respectively, while **15** gave **19**, **20** and **21a-b**. All the acetates were thoroughly identified by spectral data.



Scheme 3. a) $NaBH_4$, $CeCl_3.H_2O$, Et OH, 0 ^{o}C to RT, b) Ac_2O-Py, c) OsO_4-NMO, CH_3COCH_3:H_2O (3:1).

Stereoselective *cis*-hydroxylation of the olefins **16-20** was affected using OsO_4-NMO in acetone-water (3:1) system to afford the diols **22-26**. The stereochemical outcome, *anti*-to the -OAc group, is in accordance with literature[21] precedence. Acetylation of diols **22-26** with acetic anhydride in pyridine afforded the corresponding pseudo saccharide precursors **1-5** in quantitative yields.

The structures of **1-5** were fully confirmed with the help of detailed NMR analysis using the vicinal couplings (J) as well as the data from the NOESY experiments. For compound **1**, the characteristic NOE cross peaks (Figure 2) H6-H8, H6-H10a, H8-H10a and H7-H5 and $J_{5,6}$, $J_{6,7}$, $J_{7,8}$ and $J_{5,10a}$ values of about 10 Hz are in consensus with a chair conformation, $^8C_5$, for the carbocycle ring. Interestingly, most of the substituents in this conformation take energetically favored equatorial position. For compound **2**, the structure and conformation are supported by strong NOE cross peaks between H5-H9 and H6-H10a as well as large value of about 10 Hz for $J_{5,6}$, $J_{5,10a}$ and $J_{9,10a}$ whereas large NOE cross peaks between H5-H7 as well as $J_{5,10a}$ 13.0 Hz and $J_{7,8}$ 10.8 Hz confirm the structure of compound **3**.

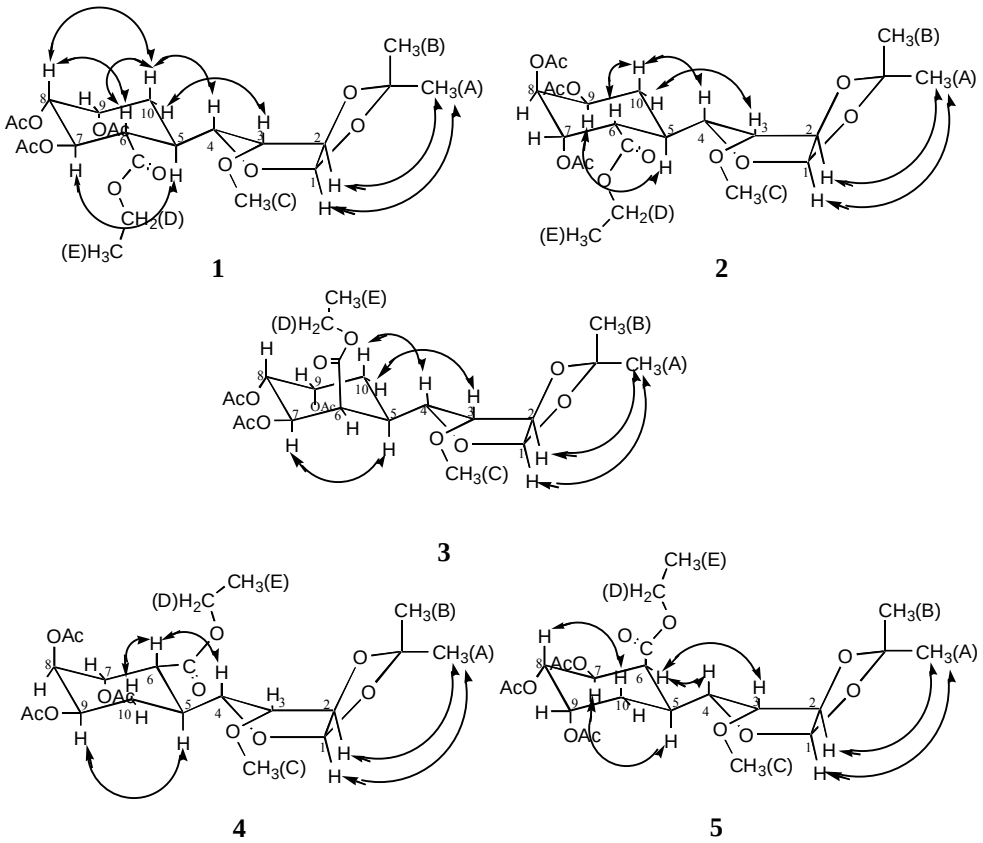


Figure 2. Diagramatic representation of NOEs.

Such a conformation for the carbocycle ring is again energetically favored, as apart from substituent at C-6 and C-9, all the substituents are placed equatorial. For compound **4** the characteristic NOE cross peaks H6-H10a and H5-H9 as well as large value of about 10 Hz for $J_{9,10a}$ and $J_{5,10a}$ and 9.8 Hz for $J_{5,6}$ are in conformity with a chair conformation, while for **5**, the

structure and conformation are supported by strong NOE cross peaks between H5-H7, H8-H10a and $J_{5,\ 10a}$ and $J_{7,\ 8}$ of about 10 Hz. The six membered rings in all these molecules take $^{8}C_{5}$ chair conformation. The five membered ring is puckered in all the compounds. Small values of $J_{1,2}$, $J_{2,3}$ and $J_{3,4}$ point out to a twist conformation for the sugar ring. The presence of NOE cross peaks between H1-Me (A), H2-Me (A) and H4-Me (B) implies an envelop conformation for the five membered ring containing isopropylidine group. The relative orientation of the carbocycle and sugar rings is derived with the help of NOESY experiments. For **1-3** the strong NOE cross peaks between H3-H10e, H4-H10a, and weak NOE cross peaks between H3-H10a and H4-H10e and H10e-OMe confirm the structures shown in Figure **2**. For **4** and **5**, on the other hand, there is change in configuration at C5 and the NOE cross peak between H3-H6 and H4-H6 support relative orientation of the rings. Molecular mechanics study is carried out on **1-5** using Sybyl[22] and the results obtained agree with the experimental data. Dihedral angle H4-C4-C5-H5 of about 170° for **1-3** and **5** (Figure 3) is consistent with large $J_{4,5}$ of about 10 Hz. For **4** the calculated dihedral angle H4-C4-C5-H5 of -129° is conformity in experimentally observed $J_{4,5}$ 4.3 Hz.

These observations are in agreement with the experimental data supporting the *trans* stereochemistry across the rings.

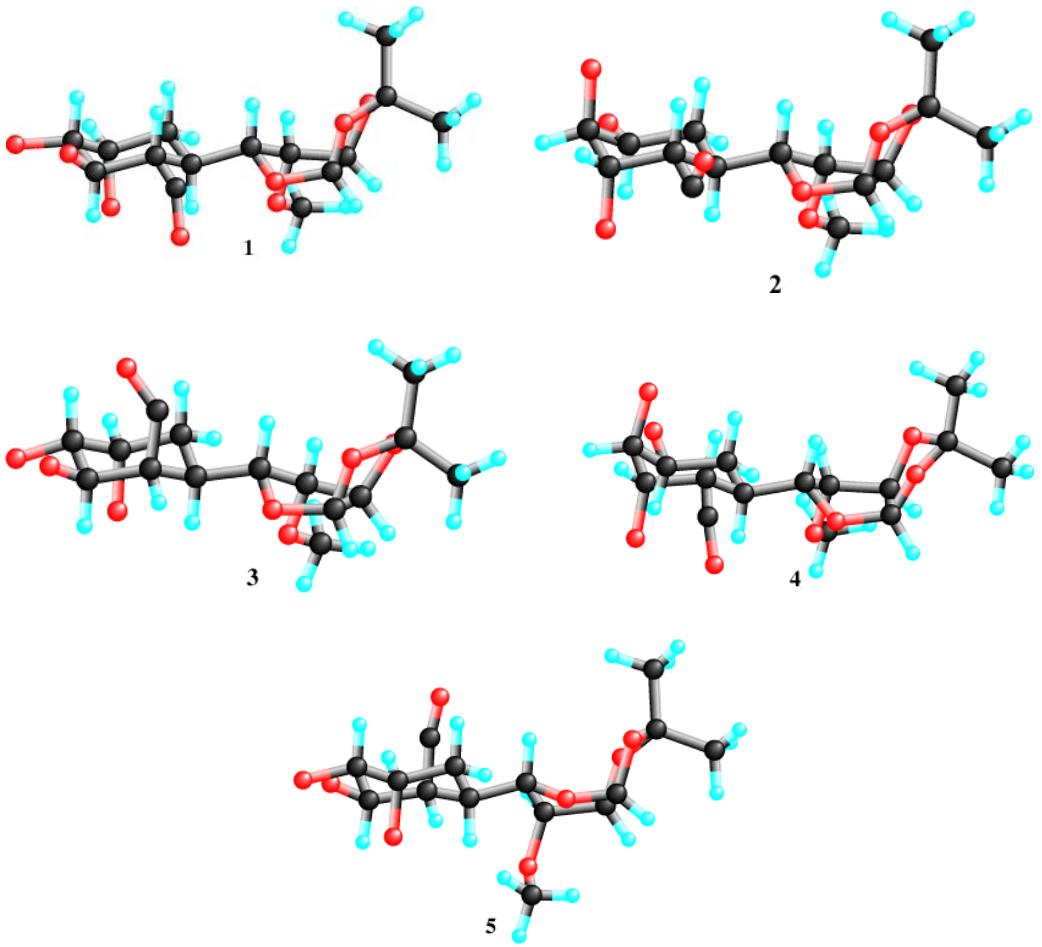


Figure 3. Structures obtained from energy minimization for **1-5**. (Note: For clarity in visualization the protecting groups are not shown in the figure).

Thus, pseudo saccharide precursors **1-5** were synthesised by adopting an 'off template site' stereoselective [3+3] annulation approach, where the chirality of the carbocycle is induced from the sugar template. In this present [3+3] annulation protocol, Michael-Wittig reaction was exploited for the first time in carbohydrate chemistry for the installation of carbocycle ring system at C-5 of sugar synthon. Due to the ready availability of reagents and simple reaction conditions, the present protocol and the pseudo saccharide precursors **1-5** should find a wide use in the synthesis of several C-glycoside mimics towards the bioactive carbohydrates.

Experimental Section

General Procedures. Solvents were dried over standard drying agents and freshly distilled prior to use. ^{1}H NMR (200 MHz, 400 MHz, 500 MHz) and ^{13}C NMR (50 MHz, 100 MHz, 125 MHz) spectra were recorded in deuteriochloroform solution with tetramethylsilane as an internal reference on Varian Gemini-200 MHz, Unity-400 MHz and INOVA-500 MHz spectrometers and J values are given in Hz. Optical rotations were measured with a JASCO DIP-370 instrument and $[\alpha]_D$ values are in units of 10^{-1}deg cm^{2}g^{-1}. Organic solutions were dried over anhydrous Na_2SO_4 and concentrated below 40°C in *vacuo*. HRMS were recorded on V G Autospec Mass Spectrometer at 5 or 7 K resolution using perfluoro kerosene as an internal reference. Infrared (IR) are reported in wavenumbers (cm^{-1}). The nomenclature mentioned in the experimental section was adopted from ACD/Name version 1.0β, ACD Inc., Toronto, Canada.

Synthesis

Ethyl 3-[6-methoxy-2,2-dimethyl-(3a*R*,5*R*,6*S*,6a*R*)-perhydrofuro[2,3-*d*][1,3]dioxol-5-yl]-(*E*)-2-propenoate (10). A mixture of **9** (5.0 g, 24.75 mmol) and (ethoxycarbonylmethylene) triphenylphosphorane (10.3 g, 29.60 mmol) in benzene (50 mL) was heated at reflux temperature for 4 h. The reaction mixture was brought to room temperature and solvent evaporated under reduced pressure. The crude product was purified by column chromatography (60-120 mesh Si-gel, Ethyl acetate: Pet. ether 1:9) to give the title compound **10** (5.5 g) in 82% yield as a light yellow syrup. $[\alpha]_D^{20}$ -125.38 (*c* 1.30, $CHCl_3$); ν_{max} (Neat): 3020, 1200, 1160, 1080 cm^{-1}; δ_H(200 MHz, $CDCl_3$): 6.36-6.22 (m, 1H, H-5), 5.96-5.85 (m, 2H, H-1,6), 5.62-5.52 (m, 1H, H-4), 4.55 (d, 1H, $J_{1,2}$ 4.4 Hz, H-2), 4.18 (q, 2H, -OCH_2CH_3), 4.02 (d, 1H, $J_{3,4}$ 4.0 Hz, H-3), 3.32 (s, 3H, -OMe), 1.52 (s, 3H, CH_3), 1.30 (t, 6H, CH_3); m/z (FABMS) 273 (100 MH$^+$), 272 (9), 271 (26), 257 (39), 227 (64).

3-[6-Methoxy-2,2-dimethyl- (3a*R*,5*R*,6*S*,6a*R*)- perhydrofuro [2,3-*d*][1,3] dioxol-5-yl]-(*E*)-2-propen-1-ol (11). To a stirred solution of **10** (4.0 g, 14.70 mmol) in dry CH_2Cl_2 (30 mL), DIBAL-H (29.4 mL, 29.41 mmol, 1M solution in hexane) was added dropwise at –23 °C (CCl_4 + solid CO_2) under nitrogen atmosphere for 15 min. After 3 h, methanol (15 mL) was added, stirred for 1 h and brought to room temperature. The separated solid was filtered off and washed with CH_2Cl_2 (2 x 50 mL). The combined organic layers were washed with brine (50 mL) and

dried (Na_2SO_4). Solvent was evaporated under reduced pressure and purification of the residue by column chromatography (60-120 mesh Si-gel, Ethyl acetate: Pet. ether 1:4) gave the title compound **11** (2.9 g) in 86% yield as a colorless syrup $[\alpha]_D^{20}$ -84.57 (*c* 1.40, $CHCl_3$); ν_{max} (Neat): 3500, 2980, 1760, 1420, 1140 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 5.98-5.83 (m, 2H, H-1,5), 5.75-5.62 (m, 1H, H-6), 4.92 (dd, 1H, $J_{3,4}$ 3.6 $J_{4,5}$ 8.6 Hz, H-4), 4.56 (d, 1H, $J_{1,2}$ 4.0 Hz, H-2), 4.40-4.10 (m, 2H, H-7, 7'), 3.61 (d, 1H, $J_{3,4}$ 3.6 Hz, H-3), 3.40 (s, 3H, -OMe), 1.95 (br. t, 1H, -OH), 1.50, 1.32 (2s, 6H, CH_3); m/z (FABMS) 253 (15 M^++23), 231 (57), 215 (18), 213 (100).

Michael-Wittig reaction on enal 7 (preparation of 6a-d). A solution of **11** (2.5 g, 10.86 mmol) in dry CH_2Cl_2 (25 mL) was treated with PDC (4.9 g, 13.04 mmol) and heated at reflux for 2 h. The reaction mixture was brought to room temperature; CH_2Cl_2 was removed under reduced pressure and filtered through silica gel bed using ether as eluent. Evaporation of solvent gave the title compound **3-[6-methoxy-2,2-dimethyl-(3aR,5R,6S,6aR)-perhydrofuro[2,3-d][1,3]di-oxol-5-yl]-(E)-2-propenal** (**7**; 2.36 g) in 95% yield as a light yellow syrup. $[\alpha]_D^{20}$ -61.91 (*c* 2.40, $CHCl_3$); δ_H (200 MHz, $CDCl_3$): 9.55 (d, 1H, $J_{6,CHO}$ 8.8 Hz, -CHO), 6.72 (dd, 1H, $J_{4,5}$ 5.8, $J_{5,6}$ 17.6 Hz, H-5), 6.32 (dd, 1H, $J_{5,6}$ 17.6, $J_{6,CHO}$ 8.8 Hz, H-6), 5.88 (d, 1H, $J_{1,2}$ 4.4 Hz, H-1), 4.85-4.76 (m, 1H, H-4), 4.56 (d, 1H, $J_{1,2}$ 4.4 Hz, H-2), 3.75 (d, 1H, $J_{3,4}$ 4.0 Hz, H-3), 3.35 (s, 3H, -OMe), 1.45, 1.28 (2s, 6H, CH_3).

To a stirred solution of **7** (2.0 g, 8.77 mmol) and ylide **8** (3.42 g, 8.77 mmol) in dry THF (25 mL), NaH (0.8 g, 17.54 mmol, 60% suspension in paraffin oil) was added in portions at 50 °C under nitrogen atmosphere followed by 2 drops of water and stirred for 15 min. at the same temperature. The reaction mixture was brought to room temperature, acidified with 5% aq. HCl solution (pH~6) and extracted into ether (2 × 50 mL). The organic layer was washed with water (50 mL), brine (50 mL) and dried (Na_2SO_4). Evaporation of solvent under reduced pressure and purification of the residue by column chromatography (finer than 200 mesh Si-gel, Ethyl acetate: Pet. ether 1:4) gave the title compounds **6a-d** (2.23 g) in 75% yield as partially separable mixtures **6a**, **b** (1.66 g, 56%) and **6c**, **d** (0.56 g, 19%). However, the mixture was separated by HPLC (ODS-preparative column, MeOH: H_2O, 7:3, UV: 225 nm) to afford **6a-d** in 6:1.5:1.5:1 ratio respectively. First eluted was **ethyl 6-[6-methoxy-2,2-dimethyl-(3aR,5R,6S,6aR)-perhydro-furo[2,3-d][1,3]dioxol-5-yl]-2-oxo-(1S,6R)-3-cyclohexene-1-carboxylate (6a)** as a light yellow syrup. $[\alpha]_D^{20}$ -88.55 (*c* 1.16, $CHCl_3$); δ_H (200 MHz, $CDCl_3$): 7.00-6.86 (m, 1H, H-9), 6.14-6.02 (m, 1H, H-8), 5.81 (d, 1H, $J_{1,2}$ 4.6 Hz, H-1), 4.52 (d, 1H, $J_{1,2}$ 4.6 Hz, H-2), 4.20 (q, 2H, $-OCH_2CH_3$), 4.02 (dd, 1H, $J_{3,4}$ 4.4, $J_{4,5}$ 9.3 Hz, H-4), 3.62 (d, 1H, $J_{3,4}$ 4.4 Hz, H-3), 3.45 (d, 1H, $J_{5,6}$ 9.3 Hz, H-6), 3.40 (s, 3H, -OMe), 3.12-2.96 (m, 1H, H-5), 2.70-2.51 (m, 1H, H-10), 2.34-2.14 (m, 1H, H-10'), 1.42 (s, 3H, CH_3), 1.30-1.20 (m, 6H, CH_3); m/z (FABMS) 341 (29 MH^+), 295 (43), 133 (85), 87 (100), 43 (94); HRMS(FAB): MH^+ found 340.150527. $C_{17}H_{24}O_7$ required 340.152203.

Second eluted was *ethyl* **6-[6-methoxy-2,2-dimethyl-(3aR,5R,6S,6aR)-perhydrofuro[2,3-d][1,3]dioxol-5-yl]-2-oxo-(1R,6R)-3-cyclohexene-1-carboxylate (6b)** as a pale yellow syrup. $[\alpha]_D^{20}$ -60.24 (*c* 0.80, $CHCl_3$); δ_H (200 MHz, $CDCl_3$): 7.05-6.92 (m, 1H, H-9), 6.12-6.00 (m, 1H, H-8), 5.82 (d, 1H, $J_{1,2}$ 4.0 Hz, H-1), 4.55 (d, 1H, $J_{1,2}$ 4.0 Hz, H-2), 4.20 (q, 2H, $-OCH_2CH_3$), 4.18

(dd, 1H, $J_{3,4}$ 4.0, $J_{4,5}$ 8.5 Hz, H-4), 3.62 (d, 1H, $J_{3,4}$ 4.0 Hz, H-3), 3.45-3.35 (m, 4H, H-6, -OMe), 3.15-3.00 (m, 1H, H-5), 2.75-2.62 (m, 1H, H-10), 2.32-2.10 (m, 1H, H-10'), 1.44 (s, 3H, CH_3), 1.35-1.20 (m, 6H, CH_3); m/z (FABMS) 363 (M^++23, 28), 341 (42), 295 (44), 55 (100), 41 (85); HRMS (FAB): MH^+, found 340.151054. $C_{17}H_{24}O_7$ requires 340.152203.

Third eluted was **ethyl 6-[6-methoxy-2,2-dimethyl-(3aR,5R,6S,6aR)-perhydrofuro[2,3-d][1,3]dioxol-5-yl]-2-oxo-(1R,6S)-3-cyclohexene-1-carboxylate (6c)** as a light yellow syrup. $[\alpha]_D^{20}$ +94.40 (*c* 0.70, $CHCl_3$); δ_H (200 MHz, $CDCl_3$): 7.00-6.90 (m, 1H, H-9), 6.12-6.03 (m, 1H, H-8), 5.82 (d, 1H, $J_{1,2}$ 3.7 Hz, H-1), 4.54 (d, 1H, $J_{1,2}$ 3.7 Hz, H-2), 4.21 (q, 2H, $-OCH_2CH_3$), 4.00 (dd, 1H, $J_{3,4}$ 3.2, $J_{4,5}$ 9.3 Hz, H-4), 3.60 (d, 1H, $J_{3,4}$ 3.2 Hz, H-3), 3.41 (s, 3H, -OMe), 3.30 (d, 1H, $J_{5,6}$ 6.9 Hz, H-6), 3.10-2.95 (m, 1H, H-5), 2.85-2.50 (m, 2H, H-10, 10'), 1.44 (s, 3H, CH_3), 1.36-1.22 (m, 6H, CH_3), m/z (FABMS): 341 (17 MH^+), 295 (35), 133 (100). 55 (45); HRMS (FAB) MH^+, found 340.154248. $C_{17}H_{24}O_7$ requires 340.152203.

Fourth eluted was **ethyl 2-hydroxy-6-[6-methoxy-2,2-dimethyl-(3aR,5R,6S,6aR)-perhydrofuro[2,3-d][1,3]dioxol-5-yl]-(1S,2R,6S)-3-cyclohexene-1-carboxylate (6d)** as a colorless solid, m. p. 105-107 ^oC; $[\alpha]_D^{20}$ +72.64 (*c* 0.65, $CHCl_3$); ν_{max} (Neat): 3040, 1680, 1080 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 7.15-7.02 (m, 1H, H-9), 6.12-6.02 (m, 1H, H-8), 5.82 (d, 1H, $J_{1,2}$ 3.7 Hz, H-1), 4.55 (d, 1H, $J_{1,2}$ 3.7 Hz, H-2), 4.18 (q, 2H, $-OCH_2CH_3$), 4.05 (dd, 1H, $J_{3,4}$ 3.2, $J_{4,5}$ 9.3 Hz, H-4), 3.80 (d, 1H, $J_{3,4}$ 3.2 Hz, H-3), 3.42 (s, 3H, -OMe), 3.29 (d, 1H, $J_{5,6}$ 4.6 Hz, H-6), 2.75-2.55 (m, 3H, H-5, 10, 10'), 1.45 (s, 3H, CH_3), 1.32-1.20 (m, 6H, CH_3); m/z (FABMS) 363 (19 M^++23), 341 (13 MH^+), 133 (57), 43 (100); HRMS(FAB): MH^+, found 340.153724. $C_{17}H_{24}O_7$ requires 340.152203.

Reduction of enones 6a and 6b. Preparation of 12-14. To a stirred solution of **6a-b** (0.8 g, 2.35 mmol) and $CeCl_3.7H_2O$ (1.75 g, 4.70 mmol) in ethanol (10 mL), $NaBH_4$ (0.08 g, 2.35 mmol) was added in portions at 0 ^oC. The reaction mixture was brought to room temperature and stirred for 1h. Ethanol was removed under reduced pressure, diluted with water (25 mL) and extracted into ether (3 × 25 mL). The combined ether layers were washed with water (50 mL), brine (50 mL) and dried (Na_2SO_4). Solvent was evaporated under reduced pressure and residue purified by column chromatography (finer than 200 mesh Si-gel, Ethyl acetate: Pet. ether 1:4) gave a mixture of title diastereoisomers **12**, **13** and **14** (0.7 g) in 88% yield in 4:1:2 ratio respectively. First eluted was **ethyl 2-hydroxy-6-[6-methoxy-2,2-dimethyl-(3aR,5R,6S,6aR)-perhydrofuro[2,3-d][1,3]dioxol-5-yl]-(1S,2R,6R)-3-cyclohexene-1-carboxylate** (**13**; 0.1 g) in 13% yield as a colorless solid, m. p. 84-86 ^oC. $[\alpha]_D^{20}$ -123.22 (*c* 1.30, $CHCl_3$), ν_{max} (Neat) 3560, 2960, 1140 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 5.92-5.70 (m, 3H, H-1,8,9), 4.50 (d, 1H, $J_{1,2}$ 4.5 Hz, H-2), 4.40-4.05 (m, 3H, H-7, $-OCH_2CH_3$), 4.00 (dd, 1H, $J_{3,4}$ 4.2, $J_{4,5}$ 8.5 Hz, H-4), 3.56 (d, 1H, $J_{3,4}$ 4.2 Hz, H-3), 3.40 (s, 3H, -OMe), 2.86-2.62 (m, 2H, H-5,6), 2.32-2.14 (m, 1H, H-10), 1.84-1.66 (m, 1H, H-10'), 1.46 (s, 3H, CH_3), 1.35-1.25 (m, 6H, CH_3); m/z (FABMS): 365 (15 M^++23), 343 (14 MH^+), 325 (28), 281 (29), 221 (50), 147 (100), 109 (75); HRMS (FAB): MH^+, found 343.175791. $C_{17}H_{27}O_7$ requires 343.175679.

Second eluted was **ethyl 2-hydroxy-6-[6-methoxy-2,2-dimethyl-(3aR,5R,6S,6aR)-perhydrofuro[2,3-d][1,3]dioxol-5-yl]-(1R,2S,6R)-3-cyclohexene-1-carboxylate** (**14**; 0.2 g) in

25% yield as a colorless solid, m. p. 103-105 ^{0}C. $[\alpha]_D^{20}$ -37.20 (*c* 2.20, $CHCl_3$), δ_H (200 MHz, $CDCl_3$): 5.78 (d, 1H, $J_{1,2}$ 4.0 Hz, H-1), 5.70-5.62 (m, 2H, H-8,9), 4.48 (d, 1H, $J_{1,2}$ 4.0 Hz, H-2), 4.40-4.25 (m, 2H, H-4,7), 4.14 (q, 2H, -OCH_2CH_3), 3.49 (d, 1H, $J_{3,4}$ 3.7 Hz, H-3), 3.35 (s, 3H, -OMe), 3.15 (dd, 1H, $J_{5,6}$ 6.2,$J_{6,7}$ 4.1 Hz, H-6), 2.48-2.30 (m, 1H, H-5), 1.95-1.86 (m, 2H, H-10,10'), 1.42 (s, 3H, CH_3), 1.30-1.20 (m, 6H, CH_3); m/z (FABMS) 343 (75 MH^+), 342 (45, M^+), 325 (100), 221 (70), 154 (89), 136 (86); HRMS(FAB): MH^+, found 343.176421. $C_{17}H_{27}O_7$ requires 343.175679.

Third eluted was **ethyl 2-hydroxy-6-[6-methoxy-2,2-dimethyl-(3aR,5R,6S,6aR)-perhydrofuro[2,3-d][1,3]dioxol-5-yl]-(1S,2S,6R)-3-cyclohexene-1-carboxylate** (**12**; 0.4 g) in 50% yield as a colorless solid, m. p. 78-80 ^{0}C. $[\alpha]_D^{20}$ -56.80 (*c* 2.00, $CHCl_3$); ν_{max} (Neat): 3540, 2950, 1120 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 5.79 (d, 1H, $J_{1,2}$ 4.4 Hz, H-1), 5.68 (br. s, 2H, H-8,9), 4.62-4.52 (m, 1H, H-7), 4.48 (d, 1H, $J_{1,2}$ 4.4 Hz, H-2), 4.28-4.05 (m, 2H, -OCH_2CH_3), 3.98 (dd, 1H, $J_{3,4}$ 4.0, $J_{4,5}$ 9.5 Hz, H-4), 3.55 (d, 1H, $J_{3,4}$ 4.0 Hz, H-3), 3.36 (s, 3H, -OMe), 2.42-2.26 (m, 2H, H-5,6), 2.20-2.00 (m, 1H, H-10), 1.95-1.76 (m, 1H, H-10'), 1.46 (s, 3H, CH_3), 1.35-1.22 (m, 6H, CH_3); m/z (FABMS): 343 (52 MH^+), 327 (18), 325 (100), 297 (31), 221 (70); HRMS(FAB): MH^+, found 343.176149. $C_{17}H_{27}O_7$ requires 343.175679.

6-Ethyloxycarbonyl-5-[6-methoxy-2,2-dimethyl-(3a*R*,5*R*,6*S*,6a*R*)-perhydrofuro[2,3-*d*] [1,3] dioxol-5-yl]-(1*S*,5*R*,6*S*)-2-cyclohexenyl acetate (16). A solution of **12** (0.075 g, 0.219 mmol) in pyridine (0.5 mL) containing DMAP (catalytic) was treated with Ac_2O (0.02 g, 0.219 mmol) at 0 ^{o}C and stirred for 1 h at room temperature. The reaction mixture was diluted with sat. aq. $NaHCO_3$ solution (15 mL) and extracted into CH_2Cl_2 (2 × 15 mL). The combined organic layers were washed with sat. $CuSO_4$ solution (10 mL), water (10 mL), brine (15 mL) and dried (Na_2SO_4). Solvent was evaporated under reduced pressure and residue purified by column chromatography (60-120 mesh Si-gel, Ethyl acetate: Pet. ether 1:4) to give the title compound **16** (0.075 g) in 90% yield as a colorless solid, m. p. 86-88 ^{o}C. $[\alpha]_D^{20}$ -19.90 (*c* 0.75, $CHCl_3$); ν_{max} (Neat): 2960, 1730, 1230 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 5.84 (d, 1H, $J_{1,2}$ 4.0 Hz, H-1), 5.83-5.81 (m, 1H, H-8), 5.74-5.70 (m, 1H, H-9), 5.64-5.61 (m, 1H, H-7), 4.54 (d, 1H, $J_{1,2}$ 4.0 Hz, H-2), 4.20-4.10 (m, 3H, H-4, -OCH_2CH_3), 3.60 (d, 1H, $J_{3,4}$ 3.2 Hz, H-3), 3.38 (s, 3H, -OMe), 2.84 (dd, 1H, $J_{5,6}$ 8.4, $J_{6,7}$ 6.8 Hz, H-6), 2.59-2.51 (m, 1H, H-5), 2.25-2.18 (m, 1H, H-10), 2.04 (s, 3H, -OAc), 1.91-1.84 (m, 1H, H-10'), 1.48, 1.30 (2s, 6H, CH_3), 1.26 (t, 3H, CH_3); δ_C NMR (50 MHz, $CDCl_3$): 172.54, 170.36, 128.68, 125.27, 111.19, 104.63, 83.68, 80.65, 80.54, 69.67, 60.76, 57.26, 47.34, 33.57, 26.62, 26.20, 25.62, 21.03, 13.94; m/z (FABMS): 385 (6 MH^+), 325 (84), 221 (50), 173 (72), 115 (95), HRMS(FAB): MH^+, found 385.184093. $C_{19}H_{29}O_8$ requires 385.186243.

6-Ethyloxycarbonyl-5-[6-methoxy-2,2-dimethyl-(3a*R*,5*R*,6*S*,6a*R*)-perhydrofuro[2,3-*d*] [1,3] dioxol-5-yl]-(1*S*,5*R*,6*R*)-2-cyclohexenyl acetate (17). A solution of **13** (0.02 g, 0.058 mmol) in pyridine (0.3 mL) containing DMAP (catalytic) was treated with Ac_2O (0.006 g, 0.058 mmol) at 0 ^{o}C, worked up and purified as described for **16**, gave **17** (0.021 g) in 94% yield as a pale yellow syrup. $[\alpha]_D^{20}$ -144.60 (*c* 1.65, $CHCl_3$); δ_H (400 MHz, $CDCl_3$): 5.96-5.91 (m, 1H, H-8); 5.86 (d, 1H, $J_{1,2}$ 4.0 Hz, H-1), 5.77-5.72 (m, 1H, H-9), 5.56 (br. t, 1H, H-7), 4.52 (d, 1H, $J_{1,2}$ 4.0 Hz, H-2), 4.15-4.06 (m, 3H, H-4, -OCH_2CH_3), 3.57 (d, 1H, $J_{3,4}$ 2.8 Hz, H-3), 3.37 (s, 3H, -OMe),

2.92 (dd, 1H, $J_{5,6}$ 9.2, $J_{6,7}$ 7.2 Hz, H-6), 2.74-2.69 (m, 1H, H-5), 2.45-2.38 (m, 1H, H-10), 2.04 (s, 3H, -OAc), 1.96-1.89 (m, 1H, H-10'), 1.46, 1.30 (2s, 6H, CH_3), 1.24 (t, 3H, CH_3), δ_c (50 MHz, $CDCl_3$): 171.48, 170.43, 131.00, 123.75, 111.31, 104.87, 84.38, 80.87, 80.45, 65.65, 60.47, 57.28, 45.28, 31.18, 26.73, 26.20, 25.80, 21.10, 14.05; m/z (FABMS): 369 (7), 325 (29), 301 (18), 221 (100); HRMS (FAB): MH^+, found 385.186374. $C_{19}H_{29}O_8$ requires 385.186243.

6-Ethyloxycarbonyl-5-[6-methoxy-2,2-dimethyl-(3a*R*,5*R*,6*S*,6a*R*)-perhydrofuro[2,3-*d*] [1,3] dioxol-5-yl]-(1*R*,5*R*,6*S*)-2-cyclohexenyl acetate (18). A solution of **14** (0.05 g, 0.14 mmol) in pyridine (0.5 mL) containing DMAP (catalytic) was treated with Ac_2O (0.014 g, 0.14 mmol) at 0 ^oC, worked up and purified as described for **16**, to give the title compound **18** (0.044 g) in 79% yield as a colorless solid, m. p. 102-104 ^oC. $[\alpha]_D^{20}$ -32.14 (*c* 1.40, $CHCl_3$); δ_H (400 MHz, $CDCl_3$): 5.94-5.89 (m, 1H, H-8), 5.86 (d, 1H, $J_{1,2}$ 4.0 Hz, H-1), 5.59-5.57 (m, 2H, H-7,9), 4.56 (d, 1H, $J_{1,2}$ 4.0 Hz, H-2), 4.20-4.00 (m, 2H, $-OCH_2CH_3$), 3.92 (dd, 1H, $J_{3,4}$ 2.8, $J_{4,5}$ 9.0 Hz, H-4), 3.57 (d, 1H, $J_{3,4}$ 2.8 Hz, H-3), 3.49 (dd, 1H, $J_{5,6}$ 7.2, $J_{6,7}$ 3.6 Hz, H-6), 3.40 (s, 3H, -OMe), 2.47-2.40 (m, 1H, H-5), 2.34-2.24 (m, 1H, H-10), 2.04 (s, 3H, -OAc), 2.00-1.93 (m, 1H, H-10'), 1.42, 1.31 (2s, 6H, CH_3), 1.26 (t, 3H, CH_3); δ_C NMR (50 MHz, $CDCl_3$): 170.85, 170.07, 129.38, 124.43, 111.38, 104.58, 83.30, 80.88, 80.52, 69.33, 60.08, 57.48, 42.28, 33.38, 26.83, 26.30, 24.10, 20.92, 14.31; m/z (FABMS): 407 (M^++23, 17), 385 (MH^+, 17), 370 (13), 326 (72), 173 (100), 135 (68); HRMS (FAB): MH^+, found 385.186289. $C_{19}H_{29}O_8$ requires 385.186243.

Reduction of enones 6c and 6d. A solution of **6c-d** (0.40 g, 1.17 mmol) and $CeCl_3.7H_2O$ (0.87 g, 2.35 mmol) in ethanol (5 mL), was treated with $NaBH_4$ (0.04 g, 1.17 mmol), worked up and purified as described for **12-14** to give **15** (0.31 g) in 78% yield as an inseparable mixture of isomers.

A solution of above alcohols **15** (0.20 g, 0.58 mmol) in pyridine (0.5 mL) was treated with Ac_2O (0.05 g, 0.58 mmol), worked up and purified as described for **16**, to give **19**, **20** and **21a-b** (0.20 g) in 89% yield in 1:1:1.7 ratio respectively, after purification by column chromatography (finer than 200 mesh Si-gel, Ethyl acetate: Pet. ether 1:9). First eluted was **6-ethyloxycarbonyl-5-[6-methoxy-2,2-dimethyl-(3aR,5R,6S,6aR)-perhydrofuro[2,3-d][1,3]-dioxol-5-yl]-(1R,5S,6S)-2-cyclohexenyl acetate** (**20**; 0.054 g) in 24% yield as a pale yellow syrup. $[\alpha]_D^{20}$ +116.33 (*c* 0.60, $CHCl_3$); δ_H (400 MHz, $CDCl_3$): 6.00-5.96 (m, 1H, H-8), 5.85 (d, 1H, $J_{1,2}$ 4.0 Hz, H-1), 5.73-5.68 (m, 1H, H-9), 5.51-5.49 (m, 1H, H-7), 4.54 (d, 1H, $J_{1,2}$ 4.0 Hz, H-2), 4.17 (dd, 1H, $J_{3,4}$ 3.6, $J_{4,5}$ 5.0 Hz, H-4), 4.14-4.08 (m, 2H, $-OCH_2CH_3$), 3.75 (d, 1H, $J_{3,4}$ 3.6 Hz, H-3), 3.43 (s, 3H, -OMe), 2.96 (dd, 1H, $J_{5,6}$ 4.8, $J_{6,7}$ 9.2 Hz, H-6), 2.63-2.53 (m, 1H, H-5), 2.50-2.48 (m, 1H, H-10), 2.32-2.25 (m, 1H, H-10'), 2.03 (s, 3H, -OAc), 1.43, 1.31 (2s, 6H, CH_3), 1.24 (t, 3H, $-OCH_2CH_3$); δ_c (50 MHz, $CDCl_3$): 171.52, 170.38, 132.48, 122.38, 111.35, 104.38, 85.62, 81.61, 79.78, 67.00, 60.49, 57.62, 45.88, 30.83, 26.71, 26.29, 25.14, 21.01, 14.12; m/z (FABMS): 385 (14 MH^+), 383 (18), 369 (46), 325 (97), 173 (100), 147 (50); HRMS (FAB): MH^+, found 385.186112. $C_{19}H_{29}O_8$ requires 385.186243.

Second eluted was **6-ethyloxycarbonyl-5-[6-methoxy-2,2-dimethyl-(3aR,5R,6S,6aR)–perhydro- furo[2,3-d][1,3]dioxol-5-yl]-(1S,5S,6R)-2-cyclohexenyl acetate** (**19**; 0.054 g) in 24% yield as a pale yellow syrup. $[\alpha]_D^{20}$ +215.99 (*c* 0.65, $CHCl_3$); δ_H (400 MHz, $CDCl_3$): 5.98-

5.948 (m, 1H, H-8), 5.87 (d, 1H, $J_{1,2}$ 3.6 Hz, H-1), 5.58-5.55 (m, 2H, H-7,9), 4.58 (d, 1H, $J_{1,2}$ 3.6 Hz, H-2), 4.24-4.08 (m, 2H, -OCH_2CH_3), 3.90 (dd, 1H, $J_{3,4}$ 3.2, $J_{4,5}$ 6.6 Hz, H-4), 3.77 (d, 1H, $J_{3,4}$ 3.2 Hz, H-3), 3.45 (s, 3H, -OMe), 3.09 (dd, 1H, $J_{5,6}$ 3.6, $J_{6,7}$ 7.2 Hz, H-6), 2.48-2.41 (m, 1H, H-5), 2.39-2.29 (m, 2H, H-10,10'), 2.06 (s, 3H, -OAc), 1.44, 1.31 (2s, 6H, CH_3), 1.26 (t, 3H, -OCH_2CH_3); δ_c (50 MHz, $CDCl_3$): 170.47, 170.04, 130.37, 123.63, 111.30, 104.57, 83.28, 81.80, 80.96, 69.68, 60.22, 57.57, 42.70, 33.60, 26.61, 26.19 (2C), 21.05, 14.31; m/z (FABMS): 385 (10 MH^+), 383 (14), 369 (29), 325 (100), 173 (63), 133 (49); HRMS(FAB): MH^+, found 385.186972. $C_{19}H_{29}O_8$ requires 385.186243.

Further eluted was **21a-b** (0.092 g) in 41% yield as an inseparable mixture.

Ethyl 3,4-dihydroxy-6-[6-methoxy-2,2-dimethyl-(3a*R*,5*R*,6*S*,6a*R*)-perhydrofuro-[2,3–*d*][1,3] dioxol-5-yl]2-methylcarbonyloxy-(1*S*,2*R*,3*R*,4*R*,6*R*)-cyclohexane-1-carboxylate (22). To a stirred solution of **16** (0.059 g, 0.15 mmol) and NMO (0.036 g, 0.30 mmol, 50% aq. solution) in acetone: water (3:1, 4 mL), OsO_4 in toluene (catalytic) was added and stirred for 12 h at room temperature in dark. Excess solid $NaHSO_3$ (100 mg) was added, stirred for 20 min., diluted with water (10 mL) and extracted into ethyl acetate (2 × 15 mL). The combined ethyl acetate layers were washed with brine (15 mL) and dried (Na_2SO_4). Evaporation of solvent under reduced pressure and purification of residue by column chromatography (60-120 mesh Si-gel, Ethyl acetate: Pet. ether, 1:1) gave the title compound **22** (0.052 g) in 82% yield as a colorless solid, m. p. 158-160 ^{0}C. $[\alpha]_D^{20}$ -82.35 (*c* 0.85, $CHCl_3$); δ_H (200 MHz, $CDCl_3$): 5.74 (d, 1H, $J_{1,2}$ 4.0 Hz, H-1) , 5.30 (dd, 1H, $J_{6,7}$ 12.0, $J_{7,8}$ 12.0 Hz, H-7), 4.45 (d, 1H, $J_{1,2}$ 4.0 Hz, H-2), 4.20-4.00 (m, 3H, H-9, -OCH_2CH_3), 3.82 (dd, 1H, $J_{3,4}$ 3.6, $J_{4,5}$ 10.0 Hz, H-4), 3.55 (d, 1H, $J_{3,4}$ 3.6 Hz, H-3), 3.46 (dd, 1H, $J_{7,8}$ 12.0, $J_{8,9}$ 4.0 Hz, H-8), 3.40 (s, 3H, -OMe), 2.80-2.55 (m, 1H, H-5), 2.38 (dd, 1H, $J_{5,6}$ 12.0, $J_{6,7}$ 10.5 Hz, H-6), 2.20-2.07(m, 1H, H-10), 2.05 (s, 3H, -OAc), 1.98-1.82 (m, 1H, H-10'), 1.45 (s, 3H, CH_3), 1.31-1.18 (m, 6H, CH_3); m/z (FABMS): 419 (26 MH^+), 375 (17), 373 (100); HRMS(FAB): MH^+, found 419.190253. $C_{19}H_{31}O_{10}$ requires 419.191723.

Ethyl 3,4-dihydroxy-6-[6-methoxy-2,2-dimethyl-(3a*R*,5*R*,6*S*,6a*R*)-perhydrofuro [2,3-*d*][1,3] dioxol-5-yl]-2-methylcarbonyloxy-(1*S*,2*S*,3*S*,4*S*,6*R*)-cyclohexane-1-carboxylate (23). To a stirred solution of **17** (0.02 g, 0.05 mmol) and NMO (0.012 g, 0.10 mmol, 50% aqueous solution) in acetone: water (3:1, 4 ml), OsO_4 in toluene (catalytic) was added, worked up and purified as described for **22**, to give the title compound **23** (0.018 g) in 86% yield as a pale yellow syrup. $[\alpha]_D^{20}$ -36.00 (*c* 0.80, $CHCl_3$); δ_H (200 MHz, $CDCl_3$): 5.75 (d, 1H, $J_{1,2}$ 4.4 Hz, H-1), 5.25 (dd, 1H, $J_{6,7}$ 9.0, $J_{7,8}$ 4.4 Hz, H-7), 4.45 (d, 1H, $J_{1,2}$ 4.4 Hz, H-2), 4.10-3.90 (m, 5H, H-4,8,9, -OCH_2CH_3), 3.60 (d, 1H, $J_{3,4}$ 4.0 Hz, H-3), 3.40 (s, 3H, -OMe), 2.90 (dd, 1H, $J_{5,6}$ 4.5, $J_{6,7}$ 9.0 Hz, H-6), 2.52-2.36 (m, 1H, H-5), 2.05 (s, 3H, -OAc), 1.92-1.72 (m, 2H, H-10, -OH), 1.60-1.45 (m, 1H, H-10'), 1.40 (s, 3H, CH_3), 1.30-1.15 (m, 6H, CH_3); m/z (FABMS): 419 (100 MH^+), 375 (17), 373 (84), 185 (13); HRMS (FAB): MH^+ found 419.192092. $C_{19}H_{31}O_{10}$ requires 419.191723.

Ethyl 3,4-dihydroxy-6-[6-methoxy-2,2-dimethyl-(3a*R*,5*R*,6*S*,6a*R*)-perhydrofuro [2,3-*d*][1,3] dioxol-5-yl]-2-methylcarbonyloxy-(1*R*,2*R*,3*R*,4*R*,6*R*)-cyclohexane-1-carboxylate (24). To a stirred solution of **18** (0.044 g, 0.11 mmol) and NMO (0.026 g, 0.22 mmol, 50% aq. solution) in acetone: water (3:1, 4 mL), OsO_4 in toluene (catalytic) was added, worked up and purified as

described for **22**, gave the title compound **24** (0.039 g) in 83% yield as a colorless solid, m. p. 154-156 ^{o}C. $[\alpha]_D^{20}$ -73.90 (*c* 2.20, $CHCl_3$); ν_{max} (Neat): 3470, 2960, 1725, 1230, 1080 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 5.76 (d, 1H, $J_{1,2}$ 4.4 Hz, H-1), 5.10 (dd, 1H, $J_{6,7}$ 6.0, $J_{7,8}$ 10.0 Hz, H-7), 4.45 (d, 1H, $J_{1,2}$ 4.4 Hz, H-2), 4.20-4.00 (m, 4H, H-8,9, -OCH_2CH_3), 3.72 (dd, 1H, $J_{3,4}$ 4.0, $J_{4,5}$ 11.3 Hz, H-4), 3.50 (d, 1H, $J_{3,4}$ 4.0 Hz, H-3), 3.45-3.30 (m, 4H, H-6, -OMe), 2.75-2.50 (m, 1H, H-5), 2.15-1.86 (m, 4H, H-10, -OAc), 1.65-1.50 (m, 1H, H-10'), 1.35 (s, 3H, CH_3), 1.32-1.20 (m, 6H, CH_3); m/z (FABMS) 419 (100 MH^+), 403 (6), 373 (86), 87 (32), 43 (57); HRMS(FAB): MH^+ found 419.194050. $C_{19}H_{31}O_{10}$ requires 419.191723.

Ethyl 3,4-dihydroxy-6-[6-methoxy-2,2-dimethyl-(3a*R*,5*R*,6*S*,6a*R*)-perhydrofuro [2,3-*d*][1,3]-dioxol-5-yl]-2-methylcarbonyloxy-(1*R*,2*R*,3*R*,4*R*,6*S*)-cyclohexane-1-carboxylate (25). To a stirred solution of **19** (0.035 g, 0.09 mmol) and NMO (0.021 g, 0.18 mmol, 50% aq. solution) in acetone: water (3:1, 4 mL), OsO_4 in toluene (catalytic) was added, worked up and purified as described for **22**, to give the title compound **25** (0.03 g) in 79% yield as a colorless solid, m. p. 140-142 ^{0}C. $[\alpha]_D^{20}$ +21.90 (*c* 1.05, $CHCl_3$); ν_{max} (Neat): 3490, 1735, 1230, 1070 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 5.82 (d, 1H, $J_{1,2}$ 4.0 Hz, H-1), 5.15 (dd, 1H, $J_{6,7}$ 5.5, $J_{7,8}$ 9.3 Hz, H-7), 4.55 (d, 1H, $J_{1,2}$ 4.0 Hz, H-2), 4.32 (dd, 1H, $J_{3,4}$ 3.7, $J_{4,5}$ 9.3 Hz, H-4), 4.24-4.04 (m, 3H, H-8, -OCH_2CH_3), 3.78-3.68 (m, 2H, H-3,9), 3.45 (s, 3H, -OMe), 3.05 (dd, 1H, $J_{5,6}$ 5.5, $J_{6,7}$ 7.0 Hz, H-6), 2.74-2.40 (m, 1H, H-5), 2.19-1.86 (m, 5H, H-10,10', -OAc), 1.42 (s, 3H, CH_3), 1.34-1.22 (m, 6H, CH_3); m/z (FABMS): 419 (135 MH^+), 373 (47), 361 (33), 154 (100); HRMS(FAB): MH^+ found 419.190928. $C_{19}H_{31}O_{10}$ requires 419.191723.

Ethyl 3,4-dihydroxy-6-[6-methoxy-2,2-dimethyl-(3a*R*,5*R*,6*S*,6a*R*)-perhydrofuro[2,3-*d*][1,3] dioxol-5-yl]-2-methylcarbonyloxy-(1*S*,2*S*,3*S*,4*S*,6*S*)-cyclohexane-1-carboxylate (26). To a stirred solution of **20** (0.05 g, 0.13 mmol) and NMO (0.03 g, 0.25 mmol, 50% aq. solution) in acetone: water (3:1, 4 mL), OsO_4 in toluene (catalytic) was added, worked up and purified as described for **22**, to give the title compound **26** (0.05 g) in 93% yield as a colorless solid, m. p. 136-138 ^{o}C. $[\alpha]_D^{20}$ -34.46 (*c* 0.65, $CHCl_3$); δ_H (200 MHz, $CDCl_3$): 5.81 (d, 1H, $J_{1,2}$ 4.0 Hz, H-1), 5.28 (br. t, 1H, H-7), 4.51 (d, 1H, $J_{1,2}$ 4.0 Hz, H-2), 4.28-3.94 (m, 5H, H-4,8,9, -OCH_2CH_3), 3.68 (d, 1H, $J_{2,3}$ 3.6 Hz, H-3), 3.42 (s, 3H, -OMe), 3.00 (dd, 1H, $J_{5,6}$ 4.0, $J_{6,7}$ 8.1 Hz, H-6), 2.56-2.38 (m, 1H, H-5), 2.08 (s, 3H, -OAc), 2.04-1.80 (m, 2H, H-10,10'), 1.45 (s, 3H, CH_3), 1.34-1.18 (m, 6H, CH_3); m/z (FABMS): 419 (100 MH^+), 401 (10), 373 (95), 154 (31); HRMS(FAB): MH^+, found 419.191573. $C_{19}H_{31}O_{10}$ requires 419.191723.

Ethyl 6-[6-methoxy-2,2-dimethyl-(3a*R*,5*R*,6*S*,6a*R*)-perhydrofuro[2,3-*d*][1,3]dioxol-5-yl]-2, 3,4-tri(methylcarbonyloxy)-(1*S*,2*R*,3*R*,4*R*,6*R*)-cyclohexane-1-carboxylate (1). Ac_2O (0.016 g, 0.16 mmol) was added to a stirred solution of diol **22** (0.036 g, 0.086 mmol) in pyridine (0.32 mL) containing DMAP (catalytic), worked up and purified as described for **16**, gave the title compound **1** (0.03 g) in 75% yield as a colorless solid, m. p. 95-97 ^{o}C. $[\alpha]_D^{20}$ -53.41 (*c* 1.70, $CHCl_3$); δ_H (400 MHz, $CDCl_3$): 5.80 (d, 1H, $J_{1,2}$ 3.9 Hz, H-1), 5.60 (t, 1H, H-7), 5.33 (m, 1H, $J_{9,10a}$ 2.3, $J_{9,10e}$ 4.2 Hz, H-9), 4.88 (dd, 1H, $J_{7,8}$ 9.9, $J_{8,9}$ 3.1 Hz, H-8), 4.51 (d, 1H, $J_{1,2}$ 3.9 Hz, H-2), 4.13 (q, 2H, J 7.1 Hz, -OCH_2CH_3), 3.93 (dd, 1H, $J_{3,4}$ 2.9, $J_{4,5}$ 8.8 Hz, H-4), 3.60 (d, 1H, $J_{3,4}$ 2.9 Hz, H-3), 3.35 (s, 3H, -OMe), 2.65 (m, 1H, $J_{5,10e}$ 3.5 Hz, H-5), 2.56 (dd, 1H, $J_{5,6}$ 11.3, $J_{6,7}$ 10.5

Hz, H-6), 2.13 (s, 3H, -OAc), 2.02 (dt, 1H, H-10e), 1.99 (s, 3H, -OAc), 1.98 (s, 3H, -OAc), 1.52 (ddd, 1H, $J_{5,10a}$ 12.4, $J_{10a,10e}$ 13.6, $J_{9,10a}$ 2.3 Hz, H-10a), 1.45 (s, 3H, CH_3), 1.28 (s, 3H, CH_3),1.25 (t, 3H, J 7.1 Hz, -OCH_2CH_3); δ_c(50 MHz, $CDCl_3$): 170.88, 170.24, 170.18, 168.11, 111.38, 104.56, 85.32, 81.06, 80.85, 72.32, 70.37, 68.62, 60.38, 57.20, 47.08, 33.16, 29.53, 28.02, 26.83, 26.17, 20.98, 20.64,13.31; m/z (FABMS): 503 (36 MH^+), 487 (12), 457 (100), 443 (27); HRMS(FAB): $MOEt^+$, found 457.169200. $C_{21}H_{29}O_{11}$ requires 457.170987.

Ethyl 6-[6-methoxy-2,2-dimethyl-(3a*R*,5*R*,6*S*,6a*R*)-perhydrofuro[2,3-*d*][1,3]dioxol-5-yl]-2,3, 4-tri(methylcarbonyloxy)-(1*S*,2*S*,3*S*,4*S*,6*R*)-cyclohexane-1-carboxylate (2). Ac_2O (0.006 g, 0.06 mmol) was added to a stirred solution of diol **23** (0.014 g, 0.033 mmol) in pyridine (0.3 mL) containing DMAP (catalytic), worked up and purified as described for **16**, to give the title compound **2** (0.012 g) in 75% yield as a pale yellow syrup. $[\alpha]_D^{20}$ +3.20 (*c* 0.50, $CHCl_3$); δ_H (400 MHz, $CDCl_3$): 5.83 (d, 1H, $J_{1,2}$ 3.8 Hz, H-1), 5.42 (dd, 1H, $J_{6,7}$ 3.5, $J_{7,8}$ 6.0 Hz, H-7), 5.34 (dd, 1H, $J_{7,8}$ 6.0, $J_{8,9}$ 3.2 Hz, H-8), 5.30 (ddd, 1H, $J_{8,9}$ 3.2, $J_{9,10a}$ 9.9, $J_{9,10e}$ 4.2 Hz, H-9), 4.55 (d, 1H, $J_{1,2}$ 3.8 Hz, H-2), 4.11 (dd, 1H, $J_{3,4}$ 3.0, $J_{4,5}$ 9.1 Hz, H-4), 4.10 (qd, 2H, J 7.1 Hz, -OCH_2CH_3), 3.57 (d, 1H, $J_{3,4}$ 3.0 Hz, H-3), 3.40 (s, 3H, -OMe), 2.92 (dd, 1H, $J_{5,6}$ 9.1, $J_{6,7}$ 3.5 Hz, H-6), 2.67 (dq, 1H, $J_{5,10e}$ 4.8 Hz, H-5), 2.10, 2.08, 2.03 (3s, 9H, -OAc), 1.99 (dt, 1H, $J_{10a,10e}$ 13.2, $J_{9,10e}$ 4.2, $J_{5,10e}$ 4.8 Hz, H-10e), 1.64 (dt, 1H, $J_{5,10a}$ 9.8, $J_{9,10a}$ 9.9, $J_{10a,10e}$ 13.2 Hz, H-10a), 1.49 (s, 3H, CH_3), 1.31 (s, 3H, CH_3), 1.24 (t, 3H, J 7.1 Hz, -OCH_2CH_3); δ_c (50 MHz, $CDCl_3$): 171.18, 160.80, 160.33 (2C), 111.54, 104.50, 83.73, 81.30, 80.66, 68.59, 68.21, 67.70, 60.81, 57.32, 44.71, 32.85, 28.62, 26.74, 26.27, 26.21, 20.83, 20.77, 13.85; m/z (FABMS): 503 (100), 457 (52), 443 (22); HRMS (FAB): MH^+, found 503.210874. $C_{23}H_{35}O_{12}$ requires 503.212852.

Ethyl 6-[6-methoxy-2,2-dimethyl-(3a*R*,5*R*,6*S*,6a*R*)-perhydrofuro[2,3-*d*][1,3]dioxol-5-yl]-2,3, 4-tri(methylcarbonyloxy)-(1*R*,2*R*,3*R*,4*R*,6*R*)-cyclohexane-1-carboxylate (3). Ac_2O (0.018 g, 0.18 mmol) was added to a stirred solution of diol **24** (0.04 g, 0.095 mmol) in pyridine (0.3 mL) containing DMAP (catalytic), worked up and purified as described for **16**, to give the title compound **3** (0.04 g) in 83% yield as a colorless solid, m. p. 95-97 ^oC. $[\alpha]_D^{20}$ -54.54 (*c* 2.30, $CHCl_3$), δ_H (400 MHz, $CDCl_3$): 5.85 (d, 1H, $J_{1,2}$ 3.8 Hz, H-1), 5.60 (dd, 1H, $J_{7,8}$ 10.8, $J_{8,9}$ 3.3 Hz, H-8), 5.44 (m, 1H, $J_{8,9}$ 3.3 Hz, H-9), 5.36 (dd, 1H, $J_{7,8}$ 10.8 Hz, H-7), 4.54 (d, 1H, $J_{1,2}$ 3.8 Hz, H-2), 4.25-4.11 (m, 2H, -OCH_2CH_3), 3.83 (dd, 1H, $J_{3,4}$ 2.9, $J_{4,5}$ 10.5 Hz, H-4), 3.54 (d, 1H, $J_{3,4}$ 3.0 Hz, H-3), 3.53 (t, 1H, H-6), 3.36 (s, 3H, -OMe), 2.58 (m, 1H, $J_{4,5}$ 10.5, $J_{5,6}$ 4.2, $J_{5,10e}$ 3.3 Hz, H-5), 2.23 (m, 1H, $J_{9,10e}$ 2.5, $J_{5,10a}$ 13.0 Hz, H-10a), 2.00, 2.01, 2.09 (3s, 9H, -OAc), 1.64 (dt, 1H, $J_{9,10e}$ 5.8, $J_{5,10e}$ 3.3, $J_{10a,10e}$ 14.2 Hz, H-10e), 1.41, 1.31 (2s, 6H, CH_3), 1.28 (t, 3H, J 7.1 Hz, -OCH_2CH_3); δ_c (50 MHz, $CDCl_3$): 171.30, 170.19, 169.97, 169.75, 111.48, 104.60, 83.23, 80.97, 79.93, 69.68, 69.57, 69.16, 60.60, 57.66, 45.15, 31.30, 29.64, 26.61, 26.40, 26.25, 20.76, 20.69, 14.31; m/z (FABMS): 503 (36 MH^+), 457 (52), 279 (100); HRMS(FAB): MH^+ found 503.214328. $C_{23}H_{35}O_{12}$ requires 503.212852.

Ethyl 6-[6-methoxy-2,2-dimethyl-(3a*R*,5*R*,6*S*,6a*R*)-perhydrofuro[2,3-*d*][1,3]dioxol-5-yl]-2,3, 4-tri(methylcarbonyloxy)-(1*R*,2*R*,3*R*,4*R*,6*S*)-cyclohexane-1-carboxylate (4). Ac_2O (0.009 g, 0.09 mmol) was added to a stirred solution of diol **25** (0.02 g, 0.048 mmol) in pyridine (0.3 mL) containing DMAP (catalytic), worked up and purified as described for **16**, to give the title

compound **4** (0.022 g) in 94% yield as a colorless solid, m. p. 150-152 ^{o}C. $[\alpha]_D^{20}$ +185.71 (*c* 0.35, $CHCl_3$); δ_H (400 MHz, $CDCl_3$): 5.85 (d, 1H, $J_{1,2}$ 3.8 Hz, H-1), 5.36 (dd, 1H, $J_{6,7}$ 3.5, $J_{7,8}$ 5.6 Hz, H-7), 5.32 (dd, 1H, $J_{7,8}$ 5.6, $J_{8,9}$ 2.7 Hz, H-8), 5.25 (dt, 1H, $J_{8,9}$ 2.7 Hz, H-9), 4.53 (d, 1H, $J_{1,2}$ 3.8 Hz, H-2), 4.18-4.13 (m, 3H, H-4, -OCH_2CH_3), 3.71 (d, 1H, $J_{3,4}$ 3.5 Hz, H-3), 3.43 (s, 3H, -OMe), 3.01 (dd, 1H, $J_{5,6}$ 9.8, $J_{6,7}$ 3.5 Hz, H-6), 2.65 (tt, 1H, $J_{4,5}$ 4.3, $J_{5,6}$ 9.8 Hz, H-5), 2.13 (dt, 1H, $J_{5,10e}$ 4.4, $J_{9,10e}$ 4.2 Hz, H-10e), 2.10, 2.08, 2.01 (3s, 9H, -OAc), 1.97 (dt, 1H, $J_{5,10a}$ 10.3, $J_{9,10a}$ 10.3, $J_{10a,10e}$ 13.6 Hz, H-10a), 1.45, 1.32 (2s, 6H, CH_3), 1.24 (t, 3H, -OCH_2CH_3); δ_c (100 MHz, $CDCl_3$): 171.49, 170.14, 169.46, 169.37, 111.29, 104.45, 85.76, 81.36, 79.83, 69.20, 68.90, 67.77, 60.94, 57.68, 45.14, 31.73, 26.68, 26.15, 24.90, 20.98, 20.81, 20.74, 14.05; m/z (FABMS): 525 (10 M^++23, 10), 445 (18), 207 (35), 73 (61), 57 (100), 55 (96); HRMS(FAB): MH^+, found 503.213914. $C_{23}H_{35}O_{12}$ requires 503.212852.

Ethyl 6-[6-methoxy-2,2-dimethyl-(3a*R*,5*R*,6*S*,6a*R*)-perhydrofuro[2,3-*d*][1,3]dioxol-5-yl]-2,3,4-tri(methylcarbonyloxy)-(1*S*,2*S*,3*S*,4*S*,6*S*)-cyclohexane-1-carboxylate (5). Ac_2O (0.02 g, 0.2 mmol) was added to a stirred solution of diol **26** (0.045 g, 0.107 mmol) in pyridine (0.3 mL) containing DMAP (catalytic), worked up and purified as described for **16**, to give the title compound **5** (0.052 g) in 98% yield as a pale yellow syrup. $[\alpha]_D^{20}$ -27.12 (*c* 2.50, $CHCl_3$); δ_H (400 MHz, $CDCl_3$): 5.86 (d, 1H, $J_{1,2}$ 4.0 Hz, H-1), 5.69 (dd, 1H, $J_{7,8}$ 10.7, $J_{8,9}$ 3.5 Hz, H-8), 5.57 (m, 1H, $J_{8,9}$ 3.5 Hz, H-9), 5.32 (dd, 1H, $J_{6,7}$ 6.1, $J_{7,8}$ 10.7 Hz, H-7), 4.59 (d, 1H, $J_{1,2}$ 4.0 Hz, H-2), 4.25, 4.14 (2dq, 2H, -OCH_2CH_3), 3.77 (dd, 1H, $J_{3,4}$ 3.1, $J_{4,5}$ 9.6 Hz, H-4), 3.74 (d, 1H, $J_{3,4}$ 3.1 Hz, H-3), 3.46 (s, 3H, -OMe), 3.18 (t, 1H, $J_{5,6}$ 4.7, $J_{6,7}$ 6.1 Hz, H-6), 2.56 (tt, 1H, $J_{4,5}$ 9.6, $J_{5,6}$ 4.7 Hz, H-5), 2.16 (m, 1H, $J_{5,10a}$ 12.7, $J_{9,10a}$ 2.5 Hz, H-10a), 2.10 (s, 3H, -OAc), 2.09 (dt, 1H, $J_{5,10e}$ 4.3, $J_{9,10e}$ 3.1, $J_{10a,10e}$ 14.8 Hz, H-10e), 2.03, 1.98 (2s, 6H, -OAc), 1.43, 1.31 (2s, 6H, CH_3), 1.29 (t, 3H, -OCH_2CH_3); δ_c (100 MHz, $CDCl_3$): 170.46, 170.12, 170.10, 169.97, 111.34, 104.44, 83.24, 80.93, 80.69, 69.72, 69.28, 68.58, 60.91, 57.59, 45.15, 31.44, 28.16, 26.50, 26.06, 21.06, 20.82, 20.74,14.27; m/z (FABMS): 503 (12 MH^+), 457 (20), 154 (50), 133 (79), 89 (68), 77 (100); HRMS (FAB): MH^+ found 503.211435. $C_{23}H_{35}O_{12}$ requires 503.212852.

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References

1. Higton, A.; Roberts, D. *Dictionary of Antibiotics and Related Substances.* Bycroft, B. W. Ed., Chapman & Hall: London 1988.
2. Bach, G.; Breiding-Mack, S.; Grabley, S.; Hammann, P.; Hutter, K.; Thiericke, R.; Uhr, H.; Wink, J.; Zeeck, A. *Liebigs Ann. Chem*. **1993**, 241.

3. McCasland, G. E.; Furuta, S.; Durham, L. J. *J. Org. Chem.* **1996**, *61***,** 1516.
4. Suami, T.; Ogawa, S. *Adv. Carbohydr. Chem. Biochem*. **1990**, *48*, 22.
5. Cookson, R. C.; Dudfield, P. J. *J. Chem. Soc., Perkin Trans. 1* **1986**, 393.
6. Ferrier, R. J.; Middleton, S.; *Chem. Rev*. **1993**, *93*, 2779.
7. Sharma, G. V. M.; Chander, A. S.; Krishnudu, K.; Krishna, P. R. *Tetrahedron Lett*. **1997**, *38,* 9051.
8. Sharma, G. V. M.; Chander, A. S.; Krishnudu, K.; Krishna, P. R. *Tetrahedron Lett*. **1998**, *39,* 6957.
9. Sharma, G. V. M.; Hymavathi, L.; Krishna, P. R. *Tetrahedron Lett*. **1997**, *38,* 6929.
10. Sharma, G. V. M.; Reddy, V. G.; Krishna, P. R. *Tetrahedron Lett*. **1999**, *40,* 1783.
11. Sharma, G. V. M.; Prasad, T. R.; Krishna, P. R.; Krishnudu, K.; Rao, M. H. V. R.; Kunwar, A. C. *Tetrahedron: Asymm*etry **2000**, *11*, 4499.
12. Sharma, G. V. M.; Chander, A. S.; Reddy, V. G.; Krishnudu, K.; Rao, M. H. V. R.; Kunwar, A. C. *Tetrahedron Lett.* **2000,** *41*, 1997.
13. Sharma, G. V. M.; Chander, A. S.; Krishna, P. R. *Tetrahedron*: *Asymm*etry **2001**, *12*, 539.
14. Krishna, P. R.; Lavanya, B.; Ilangovan, A.; Sharma, G. V. M. *Tetrahedron*: *Asymm*etry **2000,** *11*, 4463.
15. Sharma, G. V. M.; Chander, A. S.; Krishna, P. R.; Krishnudu, K.; Rao, M. H. V. R.; Kunwar, A. C. *Tetrahedron*: *Asymm*etry **2000**, *11*, 2643.
16. Tronchet, J. M. J.; Baehler, B. J.; Eder, H.; Le Hong, F.; Perret, N.; Poncet, J.; Zumbwald, B. J. *Helv. Chem. Acta* **1973**, *56*, 1310.
17. *Chem. Abstr.* **1967,** *66*, 2623f.
18. Pietrusiewicz, K. M.; Monkiewicz, J.; Bodalski, R. *J. Org. Chem*. **1983**, *48*, 788.
19. Leonard, J.; Mohialdin, S.; Redd, D.; Ryan, G.; Jones, M. F. *J. Chem. Soc., Chem. Commun*. **1993**, 23.
20. Luche, J. L.; Hahn, L. R.; Crabbe, P. *J. Chem. Soc., Chem. Commun*. **1978**, 601.
21. Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron* **1984**, *40*, 2247.
22. The energy minimization was carried out using Sybyl 6.8 with default Tripose force field Parameters. Minimization was done first with steepest descent followed by conjugate gradient methods for a maximum of 2000 iteration each or RMS deviation of 0.005 Kcal/mole which ever was earlier.

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