Highly Functionalised Cyclobutanols by Samarium(II) Iodide Induced Radical Cyclisations of Carbohydrate-Derived Unsaturated Ketones

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Keywords: Carbocycles / Carbohydrates / Radical reactions / Samarium / Small ring systems

Certain carbohydrates have been found to be excellent precursors for the samarium diiodide-mediated 4-*exo*-*trig* cyclisation reaction of their keto-olefin derivatives, which were readily prepared in a few easy steps. The cyclisation was found to be stereoselective, affording *cis* products, the diastereoselective excesses of which were influenced by the nature of the protecting group employed at C5–O of the furanose sugar. The major chiral cyclobutane product of the cyclisation step was converted into an advanced intermediate for the synthesis of a nucleoside anti-viral analogue.

Introduction

Chiral cyclobutane derivatives are fascinating target molecules for synthetic chemists. They occur in natural products of diverse origin,[1] are desirable from a pharmaceutical/medicinal chemistry perspective (as antiviral agents[2] and sedatives[3]), and there is much current interest in the synthesis of small rings, including cyclobutane derivatives, due to their remarkable physiological activity. Some approaches to cyclobutanes make use of [2+2] cycloaddition reactions,[4] anionic cycloalkylations[5] and ring-opening reactions.[6] Accounts of cyclobutanol formation by radical-induced cyclisation onto activated alkenes are limited.[7] Few of these make use of samarium(II) iodide as the radical initiator,[8] and the preparation of some cyclobutanols through a SmI_2-mediated[9] nucleophilic acyl substitution/ketyl olefin coupling reaction has recently been reported.[10] These processes, however, do not allow easy entry to the highly functionalised, chiral cyclobutanol derivatives that are essential to physiological activity or to the total synthesis of a broad spectrum of chiral natural products.

Until relatively recently, carbohydrates had been neglected as synthetic precursors to chiral carbocyclic targets in Sm^{II}-mediated chemistry. This has been changed by our efforts,[11a–11d] and by those of others,[11e–11f] in which the SmI_2-induced conversion of carbohydrates into carbocycles, including the synthesis of some chiral cyclopentanes and cyclohexanes, has become well documented. Here we describe what is, to the best of our knowledge, the first record of a SmI_2-mediated process in which carbohydrate derivatives have been converted into cyclobutanes.[12]

With the above in mind, and in line with our continued interest in SmI_2-promoted transformations,[13] it was decided to investigate the 4-*exo*-*trig* ketyl-olefin cyclisation of a number of carbohydrate derivatives.

Results and Discussion

Synthesis of Chiral Cyclobutanols

Keto-olefin precursors **3** were readily prepared by standard chemistry in only four steps (two-pot procedure). The first two transformations involved selective acetonide protection of the *cis*-diol of the sugar,[14] followed by masking of the primary alcohol with various groups (60–80% over two steps, Scheme 1, R = TBDMS,[14] trityl,[14] pivaloyl[15]). The crux of the sequence was the Wittig reaction[16] followed by in situ Dess–Martin oxidation[17] of the resulting alcohol to afford the desired (*Z*)-α,β-unsaturated esters (Scheme 1). (Attempts to isolate the intermediate alcohols resulted in *C*-nucleoside formation due to Michael addition of the secondary hydroxy group onto the α,β-unsaturated ester, a process previously put to good use in the synthesis of functionalised tetrahydrofurans.[18]) Lactols **2** were treated with 1.2 equivalents of the triphenylphosphorane reagent in dichloromethane (DCM) for 12 h, after which the reaction mixture was diluted with DCM and 1.2 equivalents of Dess–Martin periodinane were added. This procedure altogether eliminated the unwanted Michael addition, and allowed the desired ketoalkenes **3** to be isolated in acceptable yields (40–60% over two steps).

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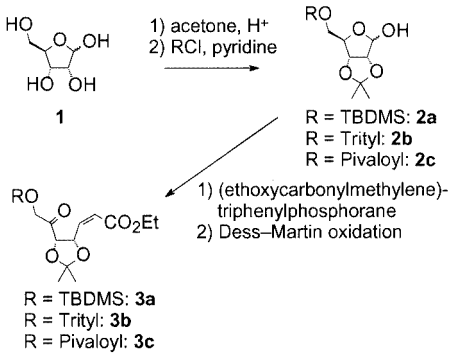
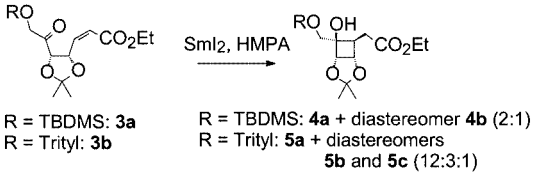
  DOI: 10.1002/ejoc.200400220



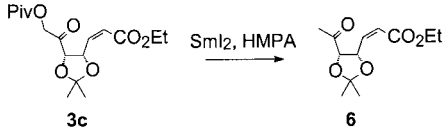
Scheme 1

The substrates **3** were dissolved in THF and added to mixtures of excess SmI_2 and HMPA at −78 °C, smoothly effecting the 4-*exo*-*trig* cyclisations to the desired cyclobutane monomers (Scheme 2).



Scheme 2

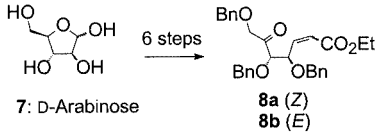
The outcomes of these reactions were dependent upon the nature of the protecting groups: substrates functionalised with *tert*-butyldimethylsilyl (TBDMS, **3a**) or with trityl (**3b**) protective groups on the primary oxygen underwent smooth cyclisation to provide the anticipated cyclobutanols. The analogous pivaloyl-protected enone **3c**, however, underwent reductive elimination to afford the Sm-enolate and thence the corresponding ketone **6** (Scheme 3), presumably because the pivaloyl moiety is a relatively good leaving group.



Scheme 3

The mechanism for this elimination step could be either a Grob-type fragmentation[19] of the cyclised product or a direct anionic or radical elimination at the ketyl radical stage. The said protective groups also played a role in the stereocontrol of the reaction: while the TBDMS-protected enone **3a** provided a 2:1 ratio of diastereomers **4a** and **4b** in a total yield of 69%, the cyclisation of the trityl analogue was more highly diastereoselective, affording **5a** and **5b** in a 4:1 ratio (total yield of 79%), along with a third cyclobutanol product **5c** in a yield of 6%. The cyclisation yielded products with *cis* selectivity[20] (with the exception of the trace product **5c**[21]), differing from the few other reported stereoselective 4-*exo*-*trig* radical cyclisations, in which *trans* selectivity was observed.[8,22] The reasons for the observed selectivity might lie in the bulky nature of the protecting groups at the primary hydroxy function dominating the orientation of the α,β-unsaturated ester moiety in the cyclisation transition state.

A study was carried out to establish whether the inclusion of a fused-ring isopropylidene moiety was a necessary constraint for cyclisation to occur, or whether use of a 2,3-*O*-dialkyl-protected D-arabinose derivative could mimic the *gem*-dialkyl effect,[23] the rotational restriction imposed on a compound due to steric effects when two alkyl groups are present on the same carbon atom. This effect has been employed to allow 4-*exo*-*trig* cyclisation of suitable non-carbohydrate precursors into cyclobutane derivatives.[8a] The substrates **8** were readily accessible by protection of the anomeric oxygen, perbenzylation, deprotection of the lactol, and subsequent Wittig- and Dess−Martin reactions (Scheme 4).



Scheme 4

Treatment of both the *E* and *Z* isomers, of the α,β-unsaturated esters **8** with SmI_2 under a variety of reaction conditions yielded, instead of the cyclobutanols, rather complex and intractable mixtures of products. These experiments showed that the cyclisation is undoubtedly facilitated by the rotational restriction imposed by the isopropylidene group. Whereas others have made use of the *gem*-dialkyl effect,[8,22] this work neatly demonstrates that such substitutionally restrictive substrates are not essential to a successful outcome of the cyclisation step.

Preparation of an Antiviral Precursor

With the cyclobutane ring formation methodology completed, an application of the work was initiated, and is currently in progress (vide infra). The design and preparation of novel nucleosides as antiviral agents from carbohydrates is well established in medicinal chemistry.[24] Examples of compounds that are active against HIV and/or herpes viruses include deoxy carbohydrate analogues such as AZT (**9**), acyclic structures such as acyclovir (**10**), and carbocyclic materials such as the cyclobutyl nucleoside BMS-180,194 (**11**), which has received quite some interest (Figure 1).[25]

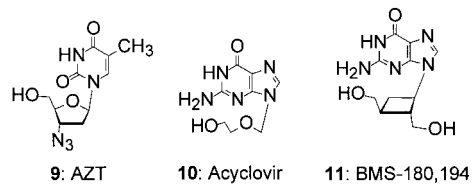
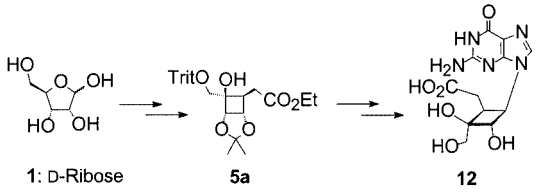


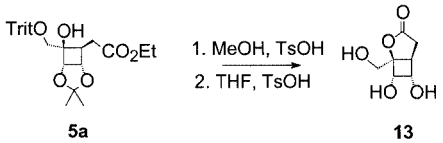
Figure 1. Examples of anti-viral materials

Preparation of the key direct precursor for the introduction of a guanine moiety, and a popular route to compounds such as BMS-180,194 (**11**), involves the selective triflation of an hydroxy group directly attached to the cyclobutane ring and subsequent coupling with a nucleoside derivative.[25] We conceived of a two-pot synthetic pathway to obtain a similar compound from the protected cyclobutane **5a**, which would then be coupled to the guanine and eventually be manipulated to form the BMS-180,194 (**11**) analogue **12** (Scheme 5).[12]



Scheme 5

Unmasking of the hydroxy groups of **5a** was achieved in acidified methanol, and the tertiary alcohol was reprotected in situ through an internal lactonisation in THF in the presence of a catalytic amount of *p*-toluenesulfonic acid, producing the triol **13** in a yield of 63% over the two steps (Scheme 6). The structure and stereochemistry of the cyclobutanetriol **13** were confirmed by single-crystal X-ray crystallography (Figure 2).[20] The key intermediate **13** is now perfectly primed for further manipulation towards the synthesis of analogues of BMS-180,194 (**11**), and results of these ongoing studies shall be reported in due course.



Scheme 6

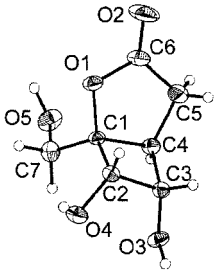


Figure 2. X-ray structure of bicyclic lactone **13**

Conclusion

The results of this project describe an efficient procedure for the conversion of D-ribose into highly functionalised, chiral, nonracemic cyclobutanes. The linchpin is a tethering protective group that affords a rotationally restricted substrate suitable for SmI_2-mediated radical cyclisation. This approach nicely complements that making use of the *gem*-dialkyl effect. The application of our methodology to the synthesis of a key intermediate towards a BMS-180,194 analogue further highlights the potential of these cyclobutane compounds in the synthesis of novel antiviral materials.

Experimental Section

General Remarks: Thin-layer chromatography (TLC) was conducted quantitatively with "Merck GF_{254} pre-coated silica gel glass plates" (0.25 layer). Aromatic derivatives were viewed under UV light (254 nm) while carbohydrate substrates were detected after spraying of the TLC plate with a chromic acid solution followed by heating. "Flash column chromatography" (FCC) refers to column chromatography under nitrogen pressure (*ca*. 50 kPa). The columns were loaded with Merck Kieselgel 60 (230−400 mesh) and eluted with appropriate solvent mixtures in volume per volume ratios. Acetone was dried over anhydrous K_2CO_3 for 24 h. The salt was then filtered off, and the solvent was subsequently distilled from over 3-Å molecular sieves and stored under N_2. Benzene and toluene were dried by heating the respective solvent over sodium-benzophenone under a N_2 atmosphere until the solution turned a deep blue colour. The solvent was freshly distilled before use. Diethyl ether and THF were pre-dried over freshly ground KOH. The KOH was then filtered off and the solvent was dried from sodium-benzophenone. The solvents were distilled under N_2 prior to use. Dichloromethane and dimethylformamide were heated over CaH_2 under N_2 with subsequent distillation. Ethanol and methanol were distilled from Mg/I_2 and stored over 3-Å molecular sieves. Ethyl acetate was distilled from K_2CO_3 through a Vigreux distillation column. Hexanes were distilled prior to use. HMPA was heated over CaH_2 under an argon atmosphere for one week prior to use. The solvent was only used if freshly distilled. Pyridine was predried over anhydrous $CaCl_2$ and was then distilled from 3-Å molecular sieves. NMR spectra were recorded on a Varian Gemini 2000, 300 MHz spectrometer. The samples were usually made up in $CDCl_3$ and for more polar samples D_2O was used. The ^1H NMR spectroscopic data are referenced to the residual solvent peak of $CDCl_3$ (δ = 7.24 ppm). The relative stereochemistry was determined after study of nuclear Overhauser effect spectra. ^{13}C NMR spectroscopic data are referenced to the solvent peak of $CDCl_3$ (δ = 77.0 ppm). The compilation of fragmentation determinations were recorded on a Finnigan Matt 8200 spectrometer at an electron impact of 70 eV, while FAB-HRMS spectra were recorded on a Varian E7070 with glycerol or nitrobenzyl alcohol as the matrix. A

Perkin−Elmer 881 spectrometer was used to record IR spectra in dry chloroform as solvent. A Jasco model DIP-730 spectropolarimeter with a cell with a 10-mm path length was used to determine optical rotations. The concentration *c.* indicates the concentration of the sample in grams per 100 mL of solution. Melting points were determined with a Reichert Thermopan microscope together with a Koffler hot-stage and are uncorrected. All reactions were performed in flamed out glass apparatus in dry solvents unless otherwise stated. All samarium diiodide reactions were carried out under argon in degassed solvents, while standard chemistry was performed under an atmosphere of nitrogen. "Room temperature" refers to a temperature ranging from 20−25 °C. The standard workup procedure involved addition of water to the reaction mixture and repeated extraction with EtOAc. The organic layer was then separated and rinsed with brine and finally with water. After separation and drying of the organic phase with anhydrous $MgSO_4$ the solvent was removed in vacuo at a temperature of ca. 40 °C. The crude product was then purified by flash column chromatography.

General Procedure for the Preparation of α,β-Unsaturated Esters 3: (Ethoxycarbonylmethylene)triphenylphosphorane (181 mg, 0.50 mmol) was added to a solution of the protected ribose derivatives **2**[14,15] (0.41 mmol) in dry CH_2Cl_2 (2 mL), and the reaction mixture was stirred at room temperature for 12 h. The mixture was diluted with CH_2Cl_2 (2 mL), treated with Dess−Martin periodinane (209 mg, 0.50 mmol) and stirred at the same temperature for 12 h. The solvent was removed in vacuo, and the residue was purified by chromatography to afford the sugar derivatives **3**.

TBDMS Derivative 3a: Colourless oil (79 mg, 0.21 mmol, 52%). R_f = 0.58 (hexanes/EtOAc, 6:1). IR ($CHCl_3$): $\tilde{\nu}$ = 3040, 2960, 1740, 1715, 1660, 1520, 1220 cm^{-1}. $[\alpha]_D^{20}$ = +5.4 (*c* = 0.4, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.03 and 0.04 (2 × s, 6 H, $SiCH_3$), 1.28 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3), 0.87 (s, 9 H, CCH_3), 1.39 (s, 3 H, isopropylidene CH_3), 1.58 (s, 3 H, isopropylidene CH_3), 4.16 (qd, *J* = 1.0, 7.2 Hz, 2 H, OCH_2), 4.26 (d, *J* = 19.1 Hz, 1 H, H7b), 4.49 (d, *J* = 19.1 Hz, 1 H, H7a), 4.92 (d, *J* = 7.8 Hz, 1 H, H5), 6.05−6.11 and 5.85−5.92 (m, 3 H, H2, H3, H4) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = −5.3 ($SiCH_3$), 14.2 (CH_2CH_3), 18.5 (CCH_3), 24.8 (isopropylidene CH_3), 25.9 (CCH_3), 26.8 (isopropylidene CH_3), 60.6 (CH_2CH_3), 68.6 (C7), 74.8 and 80.7 (C4 and C5), 110.8 (acetal C), 123.1 (C2), 142.8 (C3), 165.2 (C1), 205.5 (C6) ppm. FAB-HRMS: calcd. for $C_{18}H_{33}SiO_6$ 373.2046, found 373.2044.

Trityl Derivative 3b: Colourless oil (82 mg, 0.16 mmol, 40%). R_f = 0.73 (hexanes/EtOAc, 4:1). IR ($CHCl_3$): $\tilde{\nu}$ = 3040, 3000, 1740, 1715, 1570, 1384, 1260, 1220, 1060 cm^{-1}. $[\alpha]_D^{20}$ = +31.1 (*c* = 0.9, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.28 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3), 1.32 (s, 3 H, isopropylidene CH_3), 1.37 (s, 3 H, isopropylidene CH_3), 3.72 (d, *J* = 18.6 Hz, 1 H, H7b), 4.00 (d, *J* = 18.6 Hz, 1 H, H7a), 4.13 (q, *J* = 7.2 Hz, 2 H, CH_2CH_3), 4.84 (d, *J* = 7.8 Hz, 1 H, H2), 5.77−5.89 (m, 3 H, H3, H4, H5), 7.22−7.31 (m, 9 H, H3′, H4′), 7.42−7.46 (m, 6 H, H2′) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2 (CH_2CH_3), 24.8 (isopropylidene CH_3), 26.4 (isopropylidene CH_3), 60.6 (CH_2CH_3), 69.0 (C7), 75.2 and 81.0 (C4, C5), 87.0 (*C*Ph), 110.8 (acetal C), 123.1 (C2), 127.1 (C4′), 127.9 (C3′), 128.4 (C2′), 142.6 (C1′), 143.2 (C3), 165.1 (C1), 203.6 (C6) ppm. FAB-HRMS:, calcd. for $C_{31}H_{33}O_6$ 501.2277, found 501.2277.

Pivaloyl Derivative 3c: Colourless oil (86 mg, 0.25 mmol, 61%). R_f = 0.5 (hexanes/EtOAc, 5:1). IR ($CHCl_3$): $\tilde{\nu}$ = 3040, 2960, 1740, 1715, 1490, 1384, 1220 cm^{-1}. $[\alpha]_D^{20}$ = +84.0 (*c* = 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.27 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3), 1.40 (s, 3 H, isopropylidene CH_3), 1.61 (s, 3 H, isopropylidene CH_3), 4.16 (qd, *J* = 0.5, 7.2 Hz, 2 H, CH_2CH_3), 4.75 (d, *J* = 18.2 Hz, 1 H, H7b), 4.83 (d, *J* = 7.7 Hz, 1 H, H5), 4.84 (d, *J* = 18.2 Hz, 1 H, H7a), 5.90 (td, *J* = 1.7, 7.7 Hz, 1 H, H4), 5.95 (dd, *J* = 1.7, 11.5 Hz, 1 H, H2), 6.20 (dd, *J* = 7.7, 11.5 Hz, 1 H, H3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2 (CH_2CH_3), 24.6 (isopropylidene CH_3), 26.6 (isopropylidene CH_3), 27.2 (CCH_3), 38.7 (CCH_3), 60.6 (CH_2CH_3), 67.4 (C7), 75.5 and 81.2 (C4, C5), 111.0 (acetal C), 123.2 (C2), 142.3 (C3), 165.4 (C1), 177.6 (Piv−C=O), 201.4 (C6) ppm. FAB-HRMS: calculated for $C_{17}H_{27}O_7$ 343.1757, found 343.1756.

General Cyclisation Procedure: Keto ester **3** (0.21 mmol) was dissolved in degassed THF (5 mL), and the solvent was removed by vacuum distillation to ensure an oxygen-free system. The residue was then dissolved in THF (20 mL) and was added dropwise over 20 minutes with stirring to a freshly prepared solution of SmI_2 in THF (6.3 mL of a 0.1 M solution, 0.63 mmol, 3.0 equiv.) and HMPA (0.21 mL, 1.43 mmol, 6.8 equiv.) at −78 °C. The mixture was stirred at −78 °C for 2 h, after which it was diluted with EtOAc (20 mL) and filtered through a thin pad of silica gel. The solvent was removed in vacuo, and the residue was purified by column chromatography.

Major Isomer 4a: Colourless oil (36 mg, 0.097 mmol, 46%). R_f = 0.59 (hexanes/EtOAc, 4:1). IR ($CHCl_3$): $\tilde{\nu}$ = 3040, 2960, 2880, 1790, 1740, 1715, 1660, 1560, 1390, 1270, 1220 cm^{-1}. $[\alpha]_D^{20}$ = −41.1 (*c* = 0.9, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.06 and 0.07 ppm(2 × s, 6 H, $SiCH_3$), 0.88 (s, 9 H, CCH_3), 1.23 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3), 1.23 (s, 3 H, isopropylidene CH_3), 1.51 (s, 3 H, isopropylidene CH_3), 2.34 (ddd, *J* = 2.1, 7.2, 9.0 Hz, 1 H, H1′), 2.45 (dd, *J* = 7.2, 16.0 Hz, 1 H, H2b), 2.57 (dd, *J* = 9.0, 16.0 Hz, 1 H, H2a), 3.03 (s, 1 H, OH, D_2O exchange), 3.51 (d, *J* = 9.8 Hz, 1 H, $CH_aH_bOTBDMS$), 3.84 (d, *J* = 9.8 Hz, 1 H, CH_aH_b-OTBDMS), 4.10 (q, *J* = 7.2 Hz, 2 H, CH_2CH_3), 4.37 (s, 1 H, H2′), 4.38 (s, 1 H, H3′) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = −5.29 ppm and −5.32 (2 × $SiCH_3$), 14.2 (CH_2CH_3), 18.4 (CCH_3), 25.86 (isopropylidene CH_3), 25.9 (CCH_3), 26.7 (isopropylidene CH_3), 31.7 (C2), 43.2 (C1′), 60.5 (CH_2CH_3), 64.7 ($CH_2OTBDMS$), 73.2 (C4′), 75.8 (C2′), 80.7 (C3′), 114.5 (acetal C), 172.4 (C1) ppm. MS: *m/z* = 375 (75) [M^+ + 1], 359 (7), 167 (100). FAB-HRMS: calcd. for $C_{18}H_{35}O_6Si$ 375.2203, found 375.2202.

Minor Isomer 4b: Colourless oil (18 mg, 0.048 mmol, 23%). R_f = 0.38 (hexanes/EtOAc, 4:1). IR ($CHCl_3$): $\tilde{\nu}$ = 3040, 2960, 2890, 1780, 1740, 1715, 1540 cm^{-1}. $[\alpha]_D^{20}$ = −79.6 (*c* = 0.5, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.07 (s, 3 H, $SiCH_3$), 0.89 (s, 9 H, CCH_3), 1.23 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3), 1.31 (s, 3 H, isopropylidene CH_3), 1.58 (s, 3 H, isopropylidene CH_3), 2.54−2.71 (m, 3 H, H4, H2a, H2b), 2.93 (s, 1 H, OH, D_2O exchange), 3.59 (d, *J* = 10.1 Hz, 1 H, $CH_aH_bOTBDMS$), 3.64 (d, *J* = 10.1 Hz, 1 H, CH_aH_b-OTBDMS), 4.04 (t, *J* = 4.8 Hz, 1 H, H2′), 4.12 (q, *J* = 7.2 Hz, 2 H, CH_2CH_3), 4.59 (d, *J* = 4.8 Hz, 1 H, H3′) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = −5.6 ($SiCH_3$), 114.3 (acetal C), 14.3 (CH_2CH_3), 18.2 (CCH_3), 25.8 (CCH_3), 26.4 (isopropylidene CH_3), 27.4 (isopropylidene CH_3), 31.9 (C2), 52.6 (C1′), 60.6 (CH_2CH_3), 64.2 ($CH_2OTBDMS$), 69.0 (C4′), 73.6 (C2′), 79.4 (C3′), 172.4 (C1) ppm. MS: *m/z* = 375 (60) [M^+ + 1], 359 (4), 167 (100). FAB-HRMS: calcd. for $C_{18}H_{35}O_6Si$ 375.2203, found 375.2203.

Major Isomer 5a: Colourless oil (67 mg, 0.13 mmol, 64%). R_f = 0.54 (hexanes/EtOAc, 3:1). IR ($CHCl_3$): $\tilde{\nu}$ = 3560, 3040, 2960, 1740, 1715, 1660, 1550, 1460, 1380, 1220, 1080 cm^{-1}. $[\alpha]_D^{20}$ = −40.0 (*c* = 1.5, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.15 (t, *J* =

7.2 Hz, 3 H, CH_2CH_3), 1.23 (s, 3 H, isopropylidene CH_3), 1.32 (s, 3 H, isopropylidene CH_3), 2.24−2.31 (m, 1 H, H1′), 2.45 (dd, J = 6.9, 15.9 Hz, 1 H, H2b), 2.55 (dd, J = 9.2, 15.9 Hz, 1 H, H2a), 3.03 (d, J = 9.3 Hz, 1 H, CH_aH_bOTrit), 3.12 (s, 1 H, OH, D_2O exchange), 3.52 (d, J = 9.3 Hz, 1 H, CH_aH_bOTrit), 3.98 (qd, J = 3.6, 7.2 Hz, 1 H, $CH_aH_bCH_3$), 4.05 (qd, J = 3.6, 7.2 Hz, 1 H, $CH_aH_bCH_3$), 4.38 (dd, J = 3.3, 6.0 Hz, 1 H, H2′), 4.51 (dd, J = 1.1, 6.0 Hz, 1 H, H3′), 7.23−7.29 (m, 9 H, H3′′, H4′′), 7.43−7.46 (m, 6 H, H2′′) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2 (CH_2CH_3), 25.9 (isopropylidene CH_3), 26.4 (isopropylidene CH_3), 32.0 (C2), 43.3 (C1′), 60.5 (CH_2CH_3), 65.4 (CH_2OTrit), 73.6 (C4′), 76.0 (C2′), 80.8 (C3′), 86.7 (*C*Ph), 114.5 (acetal C), 127.0 (C4′′), 127.7 (C3′′), 128.7 (C2′′), 143.7 (C1′′), 172.3 (C1′) ppm. MS: m/z = 502 (7) [M^+], 243 (100). FAB-HRMS: calcd. for $C_{31}H_{34}O_6$ 502.2355, found 502.2361.

Minor Isomer 5b: Colourless oil (16 mg, 0.32 mmol, 15%). R_f = 0.46 (hexanes/EtOAc, 3:1). IR ($CHCl_3$): ṽ = 3040, 1740, 1715, 1660, 1520, 1220, 1080 cm^{-1}. $[\alpha]_D^{20}$ = −74.0 (c = 0.5, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.14 (t, J = 7.2 Hz, 3 H, OCH_2CH_3), 1.32 (s, 3 H, isopropylidene CH_3), 1.60 (s, 3 H, isopropylidene CH_3), 2.29 (dd, J = 8.7, 16.4 Hz, 1 H, H2b), 2.43 (dd, J = 7.5, 16.4 Hz, 1 H, H2a), 2.57 (td, J = 5.1, 8.7 Hz, 1 H, H1′), 3.05 (s, 1 H, OH, D_2O exchange), 3.09 (d, J = 9.5 Hz, 1 H, CH_aH_bOTrit), 3.22 (d, J = 9.5 Hz, 1 H, CH_aH_bOTrit), 3.99 (dq J = 3.6, 7.2 Hz, 2 H, $CH_aH_bCH_3$), 4.11 (t, J = 5.0 Hz, 1 H, H2′), 4.58 (dd, J = 0.6, 5.0 Hz, 1 H, H3′), 7.23−7.29 (m, 9 H, H3′′, H4′′), 7.41−7.44 (m, 6 H, H2′′) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2 (CH_2CH_3), 26.5 (isopropylidene CH_3), 27.3 (isopropylidene CH_3), 32.1 (C2), 52.4 (C1′), 60.5 (CH_2CH_3), 64.5 (CH_2OTrit), 69.1 (C4′), 73.8 (C2′), 78.7 (C3′), 87.1 (*C*Ph), 114.6 (acetal C), 127.1 (C4′′), 127.9 (C3′′), 128.6 (C2′′), 143.3 (C1′′), 172.1 (C1) ppm. MS: m/z = 503 (10) [M^+ + 1], 243 (100). FAB-HRMS: calcd. for $C_{31}H_{35}O_6$ 503.2434, found 503.2439.

Lactone 13: The cyclobutane derivative **5a** (100 mg, 0.199 mmol) was dissolved in methanol (5 mL), and TsOH (20 mg, 20% m/m) was added. The reaction mixture was stirred at ambient temperature for 24 h. Triethylamine (5 drops) was added to neutralise the reaction (pH paper), and the methanol was then removed in vacuo. Toluene (5 mL) was added and then removed under reduced pressure to ensure that no trace of triethylamine remained. THF (5 mL) and H_2O (3 drops) were added together with TsOH (20 mg), and the reaction mixture was stirred for a further 24 h. The neutralisation process was repeated as before, and all the solvents were removed. The crude product was subjected to column chromatography. White solid (27 mg, 0.155 mmol, 78%). R_f = 0.18 (EtOAc). IR ($CHCl_3$): ṽ = 3040, 2960, 1745, 1720, 1660, 1520 cm^{-1}. $[\alpha]_D^{20}$ = +4.16 (c = 0.5, H_2O). M.p. 140−142 °C (EtOAc). ^1H NMR (300 MHz, D_2O): δ = 2.60 (dd, J = 3.3, 17.7 Hz, 1 H, H4b), 2.66 (dddd, 1 H, J = 1.2, 2.7, 3.3, 9.3 Hz, H5), 2.82 (dd, J = 9.3, 17.7 Hz, 1 H, H4a), 3.77 (d, J = 12.9 Hz, 1 H, H1′b), 3.88 (d, J = 12.9 Hz, 1 H, H1′a), 4.10 (dd, J = 2.7, 6.3 Hz, 1 H, H6), 4.24 (dd, J = 1.2, 6.3 Hz, 1 H, H7) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 34.6 (C4), 42.2 (C5), 61.1 (C1′), 70.5 (C6), 73.5 (C7), 92.9 (C1), 181.9 (C=O) ppm. MS: m/z = 174 (3) [M^+], 137 (100). FAB-HRMS: calcd. for $C_7H_{10}O_5$ 174.0528, found 174.0528.

Acknowledgments

We gratefully recognise the financial support for this project by the National Research Foundation (GUN2053664), South Africa and the Rand Afrikaans University.

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Received April 2, 2004

