Thieme Chemistry Journal Awardees – Where Are They Now? Approaches to Tagetitoxin and its Decarboxy Analogue from D-Glucose

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Abstract: A fifteen-step route has been developed from 1,6-anhydro-β-D-glucopyranose to a *C*-alkynyl glycoside precursor of decarboxytagetitoxin. Preparation of 1,6-anhydro-5-*C*-vinyl-β-D-glucopyranose, a potential precursor of tagetitoxin, is also described.

Key words: carbohydrates, natural products, stereoselective synthesis, alkynes, organometallic reagents

Tagetitoxin, isolated from the phytopathogenic bacterium *Pseudomonas syringae* pv. *tagetis* in 1981,[1] has unique activity as a selective inhibitor of eukaryotic RNA polymerase III.[2] The bicyclic structure **1** (Figure 1) was proposed by Mitchell in 1989 on the basis of NMR and mass spectrometric measurements;[3] however, some doubts persist over the structure – in particular, the acid and amide groups of **1** may be interchanged, and the absolute configuration is unknown. More recently, a publication by Gronwald suggested that the mass spectrometric data reported previously was in error, and that tagetitoxin had a molecular weight 262 Da higher than that of structure **1**; however, neither an alternative structure nor a molecular formula was proposed.[4] Clearly a total synthesis of **1** would help to settle these structural uncertainties as well as allowing a fuller exploration of tagetitoxin's biological profile.

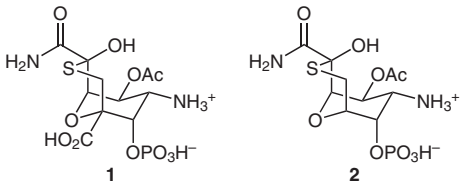

Figure 1 Tagetitoxin (**1**) and decarboxytagetitoxin (**2**)

At the commencement of our work in 1999, very little work had been published on synthetic routes towards **1**,[5] and there were no reported syntheses of the core 9-oxa-3-thiabicyclo[3.3.1]nonane ring system. Since then, we have developed two methods for the preparation of such compounds (Scheme 1). In the first route,[6] a *C*-bromoalkynyl glycoside **3** was subjected to oxidation by potassium permanganate in methanol to give an α-ketoester; subsequent hydrazinolysis of the thioacetyl group was accompanied by cyclisation of the revealed thiol onto the

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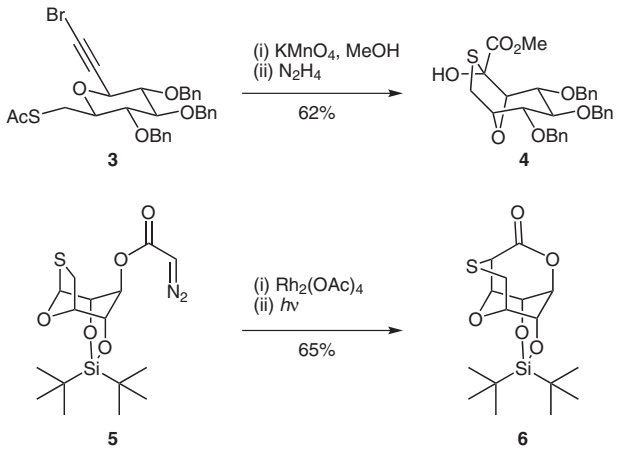
ketone to give bicycle **4**. In our second route,[7] treatment of carbohydrate-derived diazoester **5** with rhodium(II) acetate led to formation of a sulfonium ylide, which underwent 1,2-rearrangement upon irradiation to afford the tetracyclic product **6**. In this letter, we describe our efforts to apply the thiol cyclisation route to the synthesis of tagetitoxin **1** and its non-natural decarboxy analogue **2**.



Scheme 1 Previously reported routes to the tagetitoxin skeleton

Our initial target was compound **2**, and we chose D-glucose as starting material. Inversion of the stereogenic cen-

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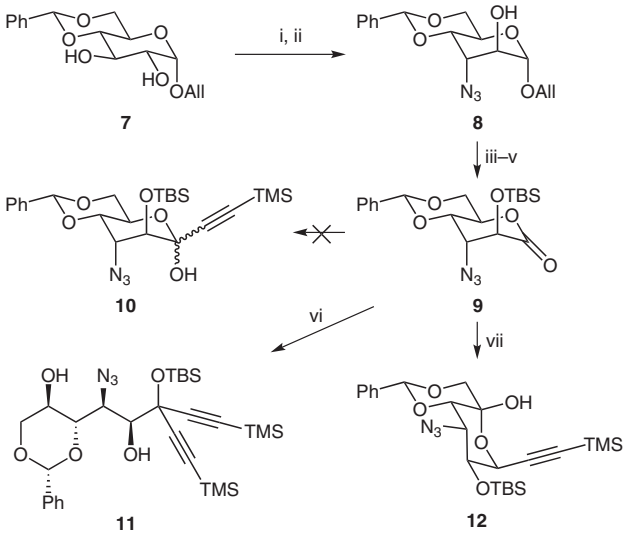
tres at positions 2 and 3 of the sugar, with installation of a nitrogen functionality at C3, was envisaged to arise through the intermediacy of a 2,3-β-epoxide.

The α-allyl glucoside **7** was prepared by literature chemistry (Scheme 2).[8] Tosylation was moderately selective for the 2-hydroxyl and was accompanied by closure to the desired β-epoxide;[9] subsequent treatment with sodium azide under acidic conditions afforded cleanly the *altro*-configured azidosugar **8**. This was silylated, then the allyl protecting group removed[10] and the resulting lactol oxidised[11] to give lactone **9**.

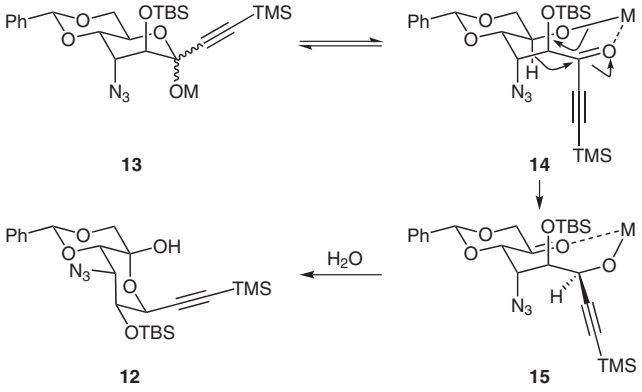
All attempts to synthesise **10** through addition of lithium trimethylsilylacetylide to the carbonyl group of **9** proved unsuccessful. Under conditions which had been successful[6] for a related sugar lactone (LiC≡CTMS, $CeCl_3$, THF, –78 °C to r.t.), the only compound which was isolated was the double addition product **11**.[12] It appears that in this case initial addition to give the lithium salt of **10** had been followed by ring opening to a ketone and a second organometallic addition. Migration of the silyl group onto the tertiary alkoxide – which is presumably relatively unhindered due to the presence of two sp-hybridised substituents – then occurred to give the observed product **11**.

We next investigated the use of ytterbium triflate[13] in place of cerium chloride as an additive in the lithium acetylide addition. To our surprise, bicycle **12**[12] was obtained in 48% yield. In this case, following addition of the acetylide to give **13** and ring opening to afford a ketone **14**, a transannular hydride shift occurred to yield a secondary alkoxide **15** (Scheme 3). Upon workup, cyclisation to the *cis*-fused bicyclic lactol **12** took place.



Scheme 2 *Reagents and conditions*: (i) NaH, DMF, r.t. then Ts-imidazole, 50 °C, 52% β-epoxide, 10% α-epoxide, 24% ditosylate; (ii) NaN_3, NH_4Cl, H_2O, 2-methoxyethanol, reflux, 92%; (iii) TBSCl, imidazole, DMF, 80 °C, 98%; (iv) Bu_3SnH, $ZnCl_2$, $Pd(PPh_3)_4$, THF, r.t., 90%; (v) DMP, pyridine, CH_2Cl_2, r.t., 88%; (vi) TMSC≡CH, BuLi, $CeCl_3$, THF, –78 °C to r.t., 32%; (vii) TMSC≡CH, BuLi, $Yb(OTf)_3$, THF, –78 °C to r.t., 48%.

Compound **12** has potential as an intermediate for the synthesis of tagetitoxin. Unfortunately, the ytterbium-mediated addition proved highly capricious, and despite numerous attempts, this product could not be obtained again; instead, starting lactone was routinely recovered.



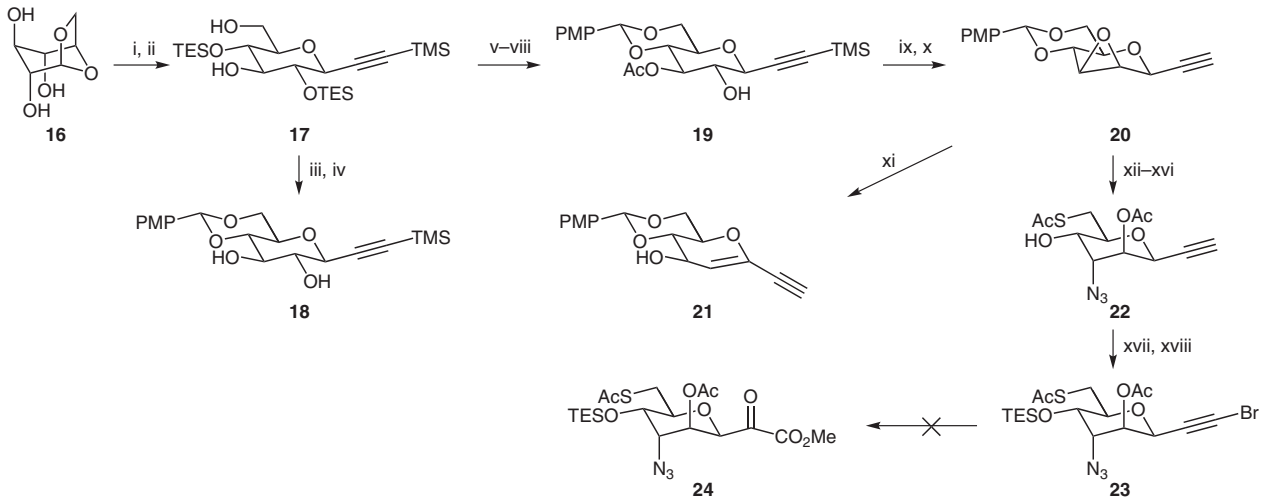
Scheme 3 Proposed mechanism for the formation of **12**

In light of the difficulties encountered in adding an acetylide to lactone **9**, we decided to introduce the alkyne moiety to a glucose derivative prior to inversion of the C2 and C3 stereogenic centres.

1,6-Anhydroglucose **16** was prepared by the method of Boons,[14] and converted to its 2,4-di-*O*-triethylsilyl derivative (Scheme 4). Vasella's method[15] was then used to stereoselectively introduce a β-configured alkynyl substituent at C1. In this procedure, lithium trimethylsilylacetylide is reacted with aluminium trichloride prior to addition of the carbohydrate substrate. In our hands, it was found essential to purify the aluminium trichloride by sublimation immediately prior to the reaction, and to subject the lithium acetylide–aluminium trichloride mixture to sonication. With these precautions, an 81% yield of diol **17** could be obtained.

Cleavage of the triethylsilyl ethers of **17** and installation of a *p*-methoxybenzylidene acetal led to bicycle **18**; however, under a variety of sulfonylation conditions (TsCl, Ts-imidazole, Ts_2O, or MsCl as reagent; NaH or pyridine as base), no selectivity was obtained for one alcohol over the other and an inseparable 1:1 mixture of sulfonates was formed.

A solution to this problem was recognised in the differential protection of O2 and O3 already present in diol **17**. Selective silylation of the primary alcohol of **17** was followed by acetylation of the remaining secondary alcohol. This acetylation proved surprisingly difficult: use of acetic anhydride with various bases, in the presence of either DMAP[16] or tributylphosphine[17] as catalyst, returned only starting material, as did the use of acetyl chloride in pyridine. However, the desired acetate was obtained on treatment of the alcohol with acetic anhydride and triethylamine in the presence of 4-(1-pyrrolidino)pyridine,[18] and acid hydrolysis of the three silyl ethers and acetal formation afforded the monoacetate **19**. Sulfonylation of the free hydroxyl of **19** also required forcing conditions: treat-



Scheme 4 *Reagents and conditions*: (i) TESCl, pyridine, 0 °C, 79%; (ii) TMSC≡CH, BuLi, $AlCl_3$, 2,4,6-collidine, toluene–THF, sonication, –15 °C to 50 °C, then add substrate, 130 °C, 81%; (iii) AcOH, MeOH, H_2O, r.t., 92%; (iv) 4-$MeOC_6H_4CH(OMe)_2$, TsOH, 4 Å MS, MeCN, reflux, 95%; (v) TESCl, pyridine, 0 °C, 92%; (vi) Ac_2O, 4-(1-pyrrolidino)pyridine, Et_3N, r.t., 70%; (vii) AcOH, THF, H_2O, 45 °C, 86%; (viii) 4-$MeOC_6H_4CH(OMe)_2$, TsOH, 4 Å MS, MeCN, 80 °C, 80%; (ix) TsCl, pyridine, 120 °C, 72%; (x) NaOMe, MeOH, CH_2Cl_2, r.t., 64%; (xi) NaN_3, DMF, 90 °C, 49%; (xii) $TMSN_3$, $Yb(OTf)_3$, LiO*i*-Pr, THF, 60 °C, 79%; (xiii) Ac_2O, DMAP, pyridine, r.t., 99%; (xiv) AcOH, THF, H_2O, 45 °C, 81%; (xv) TsCl, pyridine, r.t., 67%: (xvi) KSAc, DMF, r.t., 76%; (xvii) TESCl, pyridine, 0–40 °C, 82%; (xviii) NBS, $AgNO_3$, acetone, r.t., 73%.

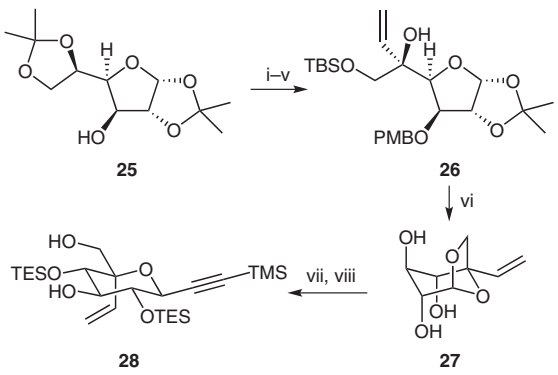
ment with tosyl chloride in refluxing pyridine afforded a rather unstable sulfonate product, which was treated immediately with sodium methoxide in methanol–dichloromethane to remove the acetate and trimethylsilyl protecting groups and effect concomitant cyclisation to the epoxide **20**.

Attempts to carry out diaxial ring opening of the epoxide under acidic conditions were thwarted by partial hydrolysis of the acetal protecting group, while heating with sodium azide in DMF gave an elimination product **21**.[19] Successful ring opening was achieved using Yamamoto's procedure,[20] in which the epoxide is treated with a combination of ytterbium triisopropoxide (formed in situ) and trimethylsilyl azide. Acetylation of the 2-hydroxyl, hydrolysis of the *p*-methoxybenzylidene acetal, selective tosylation of the primary alcohol, and tosylate displacement with potassium thioacetate led to thioester **22**.

From **22**, completion of a synthesis of decarboxytagetitoxin would require oxidation of the alkyne to an α-ketoamide, introduction of the phosphate group, reduction of the azide, and cleavage of the thioester; we chose first to investigate the alkyne oxidation. Hence the secondary alcohol of **22** was protected as a triethylsilyl ether and the alkyne brominated with *N*-bromosuccinimide/silver nitrate,[21] affording **23**.[12] However, attempted oxidation to α-ketoester **24** with potassium permanganate in methanol[22] was unsuccessful, resulting only in decomposition of the substrate.

Concurrently with our efforts to synthesise decarboxytagetitoxin, we have been investigating methods for the preparation of tagetitoxin itself. This would require the installation of an extra carbon substituent, destined to become the carboxylic acid of the natural product, at C5 of glucose. For this purpose, we chose to use the method described by Rao,[23] in which a Grignard reagent is added stereoselectively to a 5-keto derivative of glucose.

The free hydroxyl of diacetone-D-glucose **25** was protected as a *p*-methoxybenzyl ether, then selective hydrolysis of the 5,6-acetonide was effected with aqueous acetic acid (Scheme 5). Silylation of the 6-hydroxyl, Swern oxidation of the remaining secondary alcohol, and stereoselective Grignard addition afforded tertiary alcohol **26**. We were pleased to find that upon extended heating (72 h) in a mixture of aqueous acetic and trifluoroacetic acids, in the presence of thioanisole as a cation scavenger, global deprotection was accompanied by cyclisation to the desired 1,6-anhydro-5-*C*-vinylglucose **27**.[24] Extensive Fischer esterification also took place under these conditions, and so the crude material was treated with sodium



Scheme 5 *Reagents and conditions*: (i) NaH, PMBCl, THF, r.t., 86%; (ii) 60% aq AcOH, r.t., 80%; (iii) TBSCl, imidazole, DMF, r.t., 81%; (iv) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C, 79%; (v) CH_2=CHMgBr, THF, r.t., 76%; (vi) 80% aq AcOH, TFA, PhSMe, reflux then NaOMe, MeOH, r.t., 73%; (vii) TESCl, pyridine, r.t., 68%; (viii) TMSC≡CH, BuLi, $AlCl_3$, 2,4,6-collidine, toluene–THF, sonicate, –15 °C to 50 °C, then add substrate, 130 °C, 70%.

methoxide to methanolyse the mixture of acetates, affording the triol **27** in 73% yield.

Compound **27**, like its congener **16**, underwent selective disilylation followed by aluminium-mediated alkynylation[15] to give the β-*C*-glycoside **28**.[12]

In conclusion, we have developed a route from glucose to bromoalkyne **23**, which incorporates all of the carbon atoms and the correct stereochemistry for a synthesis of decarboxytagetitoxin **2**. Work towards the natural product tagetitoxin **1** has also commenced, with an efficient introduction of the additional carbon substituent in the form of a vinyl group. Efforts towards the conversion of **23** into **2**, and of **28** to **1** are ongoing in our laboratories, and the results of these studies will be reported in due course.

Acknowledgment

We thank EPSRC and UCL for funding, Dr. Abil Aliev for assistance with NMR, and Dr. Lisa Harris and Mr. John Hill for mass spectrometry.

References and Notes

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(12) **Data for Selected Compounds**
3-Azido-4,6-*O*-benzylidene-1-*O*-*tert*-butyldimethylsilanyl-3-deoxy-1,1-di-*C*-(trimethylsilanylethynyl)-D-altritol (11)
$[\alpha]_D^{20}$ –72.0 (*c* 2.35, CH_2Cl_2). IR ($CHCl_3$ cast): ν_{max} = 3444, 3055, 2121, 1706, 1421, 1361 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.48–7.43 (3 H, m), 7.36–7.28 (2 H, m), 5.49 (1 H, s), 4.35 (1 H, dd, *J* = 2.9, 0.9 Hz), 4.21 (1 H, d, *J* = 2.9 Hz), 4.33 (1 H, dd, *J* = 11.0, 5.8 Hz), 4.09 (1 H, dddd, *J* = 10.2, 8.9, 5.8, 2.9 Hz), 3.83 (1 H, dd, *J* = 9.9, 0.9 Hz), 3.74 (1 H, dd, *J* = 8.9, 2.9 Hz), 3.63 (1 H, dd, *J* = 11.0, 10.2 Hz), 3.28 (1 H, d, *J* = 9.9 Hz), 0.90 (9 H, s), 0.28 (3 H, s), 0.27 (3 H, s), 0.18 (18 H, s). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 137.4 (C), 129.0 (CH), 128.3 (CH), 126.1 (CH), 103.1 (C), 102.1 (C), 100.1 (CH), 91.6 (C), 91.5 (C), 84.4 (CH), 75.9 (CH), 70.1 (CH_2), 67.1 (C), 63.8 (CH), 60.7 (CH), 25.5 (CH_3), 18.7 (C), –0.5 (CH_3), –0.6 (CH_3), –3.5 (CH_3), –3.6 (CH_3). HRMS–FAB$^+$: *m/z* calcd for $C_{29}H_{47}O_5N_3Si_3Na$ [MNa^+]: 624.2721; found: 624.2735.
4-Azido-1,3-*O*-benzylidene-5-*O*-*tert*-butyldimethylsilanyl-4,7,8-trideoxy-8-trimethylsilanyl-β-L-*manno*-oct-7-yn-2-ulopyranose (12)
$[\alpha]_D^{20}$ –105.5 (*c* 0.4, CH_2Cl_2). IR ($CHCl_3$ cast): ν_{max} = 3445, 3053, 2304, 1633, 1421 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.47–7.42 (2 H, m), 7.33–7.24 (3 H, m), 5.56 (1 H, s), 4.76 (1 H, d, *J* = 6.2 Hz), 4.32 (1 H, dd, *J* = 10.3, 6.2 Hz), 4.23 (1 H, d, *J* = 2.8 Hz), 4.07 (1 H, dd, *J* = 10.3, 2.8 Hz), 4.03 (1 H, d, *J* = 11.9 Hz), 3.74 (1 H, s), 3.69 (1 H, d, *J* = 11.9 Hz), 0.91 (9 H, s), 0.17 (9 H, s), 0.13 (3 H, s), 0.11 (3 H, s). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 136.7 (C), 129.0 (CH), 128.2 (CH), 126.0 (CH), 103.0 (C), 100.8 (CH), 95.0 (C), 91.9 (C), 78.9 (CH), 73.5 (CH_2), 67.6 (CH), 66.3 (CH), 58.8 (CH), 25.5 (CH_3), 17.8 (C), –0.5 (CH_3), –4.7 (CH_3), –5.0 (CH_3). HRMS–FAB$^+$: *m/z* calcd for $C_{24}H_{37}O_5N_3Si_2Na$ [MNa^+]: 526.2169; found: 526.2158.
1-[2-*O*-Acetyl-6-*S*-acetyl-3-azido-3-deoxy-6-thio-4-*O*-(triethylsilanyl)-β-D-altropyranosyl]-2-bromoethyne (23)
$[\alpha]_D^{18}$ +5.1 (*c* 0.3, $CHCl_3$). IR ($CHCl_3$ cast): ν_{max} = 2947, 2110, 1755, 1693 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 4.94 (1 H, dd, *J* = 3.1, 1.5 Hz), 4.52 (1 H, d, *J* = 1.4 Hz), 3.87–3.83 (2 H, m), 3.71 (1 H, td, *J* = 9.2, 2.6 Hz), 3.60 (1 H, dd, *J* = 13.6, 2.7 Hz), 2.74 (1 H, dd, *J* = 13.6, 9.5 Hz), 2.33 (3 H, s), 2.16 (3 H, s), 0.99 (9 H, t, *J* = 8.0 Hz), 0.68–0.62 (6 H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 195.0 (C), 169.7 (C), 76.0 (CH), 74.2 (C), 71.5 (CH), 70.0 (CH), 65.9 (CH), 61.6 (CH), 47.8 (C), 31.2 (CH_2), 30.5 (CH_3), 20.7 (CH_3), 6.7 (CH_3), 4.8 (CH_2). HRMS–FAB$^+$: *m/z* calcd for $C_{18}H_{29}O_5N_3SSi^{79}Br$ [MH^+]: 506.0781; found: 506.0771.
1-(2,4-Di-*O*-triethylsilanyl-5-*C*-vinyl-β-D-glucopyranosyl)-2-trimethylsilanylethyne (28)
$[\alpha]_D^{22}$ –65.9 (*c* 0.7, $CHCl_3$). IR ($CHCl_3$ cast): ν_{max} = 3565, 2182, 1729, 1458 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 6.00 (1 H, dd, *J* = 18.0, 11.3 Hz), 5.45 (1 H, dd, *J* = 18.1, 1.4 Hz), 5.43 (1 H, dd, *J* = 11.2, 1.2 Hz), 4.21 (1 H, d, *J* = 9.5 Hz), 3.83 (1 H, d, *J* = 9.8 Hz), 3.56 (1 H, dd, *J* = 11.7, 11.0 Hz), 3.48 (1 H, dd, *J* = 9.5, 8.8 Hz), 3.39 (1 H, dd, *J* = 11.9, 2.9 Hz), 3.36 (1 H, ddd, *J* = 9.5, 8.9, 3.0 Hz), 2.19 (1 H, dd, *J* = 10.9, 3.1 Hz), 2.09 (1 H, d, *J* = 2.9 Hz), 0.99 (18 H, m), 0.71 (12 H, m), 0.20 (9 H, s). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 132.5 (CH), 119.2 (CH_2), 103.4 (C), 89.9 (C), 81.7 (C), 76.0 (CH), 75.9 (CH), 71.0 (CH), 66.7 (CH), 65.9 (CH_2), 6.9 (CH_3), 5.2 (CH_2), 5.3 (CH_2), 5.1 (CH_2), –0.2 (CH_3). HRMS (CI$^+$): *m/z* calcd for $C_{25}H_{50}O_5Si_3$ [MH^+]: 515.3044; found:515.3050.
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(24) **1,6-Anhydro-5-*C*-vinyl-β-D-glucopyranose (27)**
Thioanisole (0.17 mL, 2.1 mmol) was added to a stirred solution of glucofuranoside **26** (1.00 g, 2.08 mmol) and TFA (0.05 mL, 0.4 mmol) in 80% aq AcOH (20.8 mL). The mixture was stirred under reflux for 3 d, concentrated in vacuo, and co-evaporated with heptane (3 × 80 mL) to give a viscous black oil. MeOH (40 mL) was added and the organic solution removed from the insoluble residue using a Pasteur pipette. NaOMe (225 mg, 4.16 mmol) was added to the MeOH solution and the mixture stirred for 3 h. The solution was concentrated in vacuo and the residue purified by flash column chromatography (MeOH–CH_2Cl_2 1:99 → 10:90) to give compound **27** (284 mg, 73%) as a viscous brown oil; $[\alpha]_D^{20}$ –73.1 (*c* 1.0, EtOH). IR (neat): ν_{max} = 3368, 2901, 1646, 1416 cm^{-1}. ^1H NMR (600 MHz, CD_3OD): δ = 6.05 (1 H, dd, *J* = 17.6, 11.2 Hz), 5.44 (1 H, dd, *J* = 17.6, 1.3 Hz), 5.44 (1 H, br t, *J* = 1.6 Hz), 5.31 (1 H, dd, *J* = 11.2, 1.3 Hz), 4.32 (1 H, d, *J* = 7.0 Hz), 3.82 (1 H, br q, *J* = 1.5 Hz), 3.59 (1 H, br s), 3.45 (1 H, br q, *J* = 1.5 Hz), 3.42 (1 H, d, *J* = 7.0 Hz). ^{13}C NMR (150 MHz, CD_3OD): δ = 135.0 (CH), 115.1 (CH_2), 103.1 (CH), 82.6 (C), 74.1 (CH), 72.6 (CH), 69.6 (CH), 69.4 (CH_2). HRMS (CI^+): *m/z* calcd for $C_8H_{13}O_5$ [MH^+]: 189.0763; found: 189.0765.