Synthesis of the Cyclopentyl Nucleoside (−)-Neplanocin A from D-Glucose *via* Zirconocene-Mediated Ring Contraction

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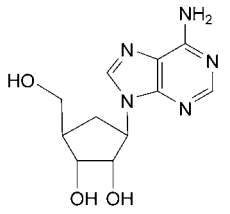
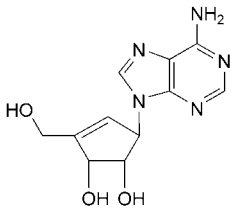
It is a pleasure to honor Professor *Rolf Huisgen* on the occasion of his 85th birthday. His pioneering mechanistic and synthetic studies in organic chemistry are exemplary of some of the most creative work in the field.

Two approaches for the conversion of D-glucose to (−)-neplanocin A (**2**), both based on the zirconocene-promoted ring contraction of a vinyl-substituted pyranoside, are herein evaluated (*Scheme 1*). In the first pathway (*Scheme 2*), the substrate possesses the α-D-*allo* configuration (see **6**) such that ultimate introduction of the nucleobase would require only an inversion of configuration. However, this precursor proved unresponsive to Cp_2Zr (= $[ZrCl_2(Cp)_2]$), an end result believed to be a consequence of substantive nonbonded steric effects operating in a key intermediate (*Scheme 5*). In contrast, the C(2) epimer (see **7**) experienced the desired metal-promoted conversion to an enantiomerically pure polyfunctional cyclopentane (see **5** in *Scheme 3*). The substituents in this product are arrayed in a manner such that conversion to the target nucleoside can be conveniently achieved by a double-inversion sequence (*Scheme 4*). Recourse to palladium(0)-catalyzed allylic alkylation did not provide an alternate means of generating **2**.

Introduction. – The era of carbocyclic nucleoside synthesis [1] was ushered in by the isolation from *Streptomyces citricolor* of the metabolite named (−)-aristeromycin (**1**) in 1968 [2], and was significantly advanced by the discovery in 1981 that (−)-neplanocin A (**2**) is produced by *Ampullariella regularis* [3]. The cytotoxicity of **2** is so elevated that its use as an effective antiviral agent is precluded [4]. The antiviral properties of **2** have been attributed to the inhibition of *S*-adenosylhomocystine (AdoHcy) hydrolase [5]. Since the latter serves as a potential feedback inhibitor of cellular transmethylation by involving *S*-adenosyl-L-methionine as the methyl donor, mRNA maturation is arrested [6].



1 (–)-aristeromycin



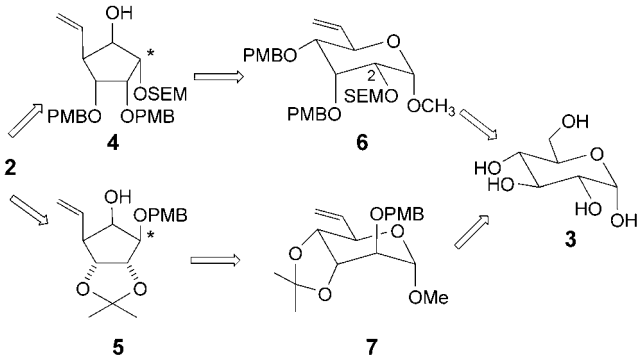
2 (–)-neplanocin A

Many synthetic analogs of **1** and **2**, including abacavir [7] and carbovir [8], have demonstrated potent anti-HIV activity. (−)-Neplanocin A itself has served as a target

of opportunity for evaluating new synthetic routes to carbocyclic nucleosides [1][9], particularly involving modern synthetic tactics of an organometallic nature. Recent select examples include the application of a carbene chromium complex [10], Pd^0-catalyzed enantioselective allylic amination [11], and scandium(III) triflate promoted ring expansion [12] as useful approaches. In continuation of our program to utilize the zirconocene-mediated ring contraction [13] of vinyl-substituted pyranosides and furanosides as a key synthetic transformation [14], we herein define a means for transforming D-glucose (**3**) into enantiomerically pure natural neplanocin A.

Results. – To secure the stereogenic centers in **2**, it is necessary that the particular vinyl-substituted pyranoside derived from D-glucose (**3**) possesses an α-D-allopyranoside configuration. Beyond that, the option exists to project the C(2)–O bond either equatorially as in **6** or axially as in **7** (*Scheme 1*). The first of these choices was on the attractive path to return **4** following exposure to zirconocene ($Cp_2Zr = [ZrCl_2(Cp)_2]$) and requires only configurational inversion at the asterisked carbon to arrive at the carbanucleoside target. Application of the same retrosynthetic analysis to **7** takes one back to **5**, where attachment of the base must necessarily be accomplished with retention or, more likely, double inversion. Both routes have been investigated, with success awaiting only one of the alternatives.

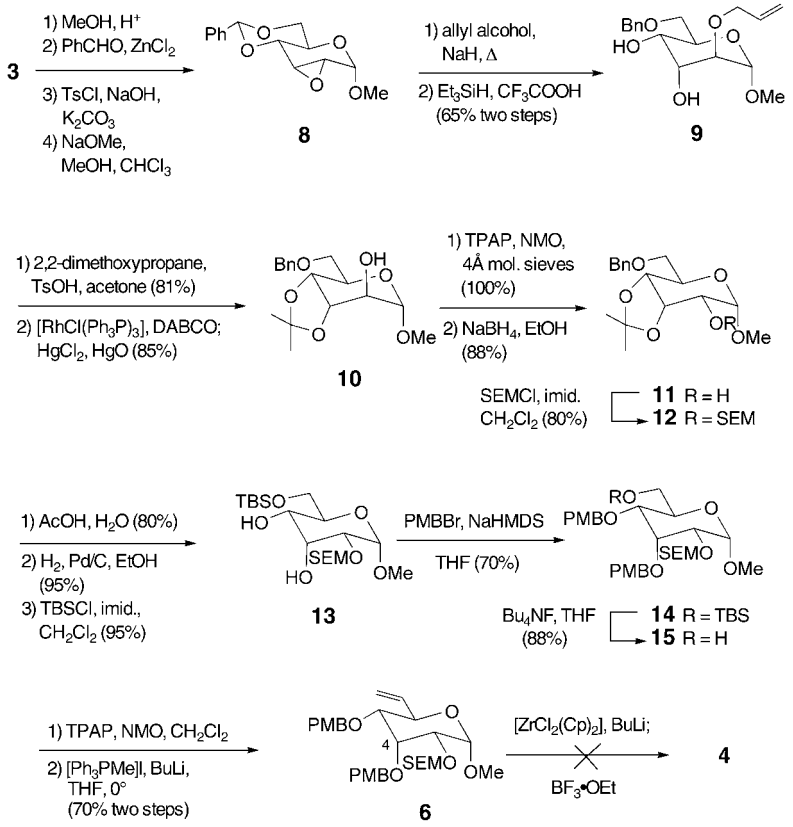
Scheme 1



PMB = 4-$MeOC_6H_4CH_2$, SEM = $Me_3SiCH_2CH_2OCH_2$

Since 4-methoxybenzyl (PMB) and [2-(trimethylsilyl)ethoxy]methyl (SEM) protecting groups have been found to survive the deoxygenative ring-contraction conditions reasonably well [14], they were therefore relied upon for deployment in the present context. Progress in the forward direction was initiated by executing the known four-step conversion of D-glucose to the 2,3-anhydropyranoside **8** [15][16] (*Scheme 2*). The heating of **8** in boiling allyl alcohol that had first been treated with sodium hydride resulted in regioselective *trans*-diaxial opening of the oxirane ring as determined by NMR analysis. In preparation for configurational inversion at C(2), the obtained intermediate was directly treated in unpurified form with triethylsilane and CF_3COOH [14b][16]. Whereas these conditions afforded **9** in 65% yield for the two steps, we note that comparable cleavage of the benzylidene acetal with $LiAlH_4/AlCl_3$

Scheme 2



Ts = 4-$MeC_6H_4SO_2$, Bn = $PhCH_2$, DABCO = 1,4-diazabicyclo[2.2.2]octane, TPAP = $(Pr_4N)RuO_4$, NMO = 4-morpholine 4-oxide, SEM = $Me_3SiCH_2CH_2OCH_2$, TBS = $^tBuMe_2Si$, PMB = 4-$MeOC_6H_4CH_2$, NaHMDS = $Me_3SiN(Na)SiMe_3$

[17], $NaBH_3CN \cdot HCl$ [18], and others [19–21] is not feasible because of the presence of a free OH group.

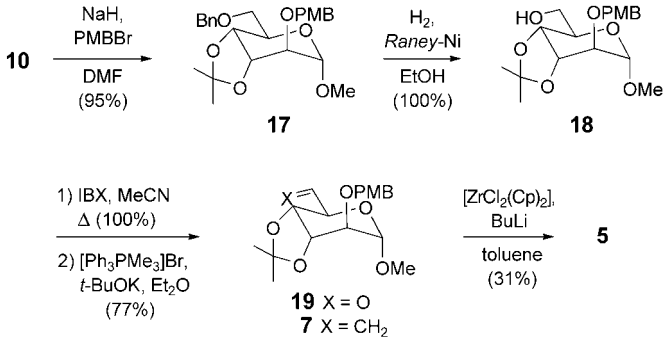
Following the conversion of **9** to its acetonide, the allyl protecting group was removed by treatment with *Wilkinson*'s catalyst to isomerize the C=C bond [22] in advance of oxymercuration [23]. The resulting axial alcohol **10** was subjected to perruthenate oxidation [24], this maneuver generating the ketone in quantitative yield. The targeted conversion to **11** was completed by fully stereocontrolled reduction with $NaBH_4$ [25]. At this juncture, the SEM functionality [26] was introduced to provide **12** (*Scheme 2*). To achieve maximum efficiency in this step, it was imperative that the potassium hydride be free of oil. After reaching **12**, we took advantage of an ability to cleave the acetonide in 80% acetic acid without adversely affecting the SEM substituent. Close monitoring of the reaction progress was necessary to avoid overreaction. Arresting progress after 4 h irrespective of scale ultimately became the standard protocol. A third OH group was unmasked by conventional hydrogenolysis of

the *O*-benzyl substituent. The resulting polar product was conveniently monosilylated in selective fashion. With **13** in hand, it proved an easy matter to accomplish dual PMB protection as in **14** provided that recourse was made to an amide base such as sodium hexamethyldisilazide. The involvement of other bases resulted in the formation of monoalkylation mixtures as well as products of silyl migration. The last hurdle prior to arrival at **6** involved sequential removal of the TBS group from **14** with Bu_4NF ($\rightarrow$**15**), perruthenate oxidation to generate the aldehyde, and *Wittig* olefination. This reaction sequence proved challenging to monitor by TLC because of the instability of the aldehyde toward silica gel or alumina. However, direct filtration of the oxidation mixture through a *Florisil* plug after 2 h and subsequent addition of methylenetriphenylphosphorane in THF at 0° successfully furnished **6** in 70% yield over the two steps.

With conversion of D-glucose to **6** now complete, probe experiments designed to produce **4** were undertaken. When general conditions involving initial treatment with the zirconocene reagent $[ZrCl_2(Cp)_2]$ and subsequent addition of boron trifluoride etherate and hydrochloride acid [14b] were screened, no evidence for the operation of a ring contraction was found. Only epimerization at the anomeric center in **6** occurred. Since a comparable chemical event did not materialize when **6** was admixed with either $[ZrCl_2(Cp)_2]$ or $BF_3 \cdot OEt_2$ alone, this finding was interpreted to mean that the vinyl-substituted pyranoside in question was undergoing initial conversion to a nine-membered zirconacycle [13]. However, further advance along the reaction pathway was either very slow or none at all, with the consequence of ultimate nonstereoselective regeneration of the pyranoside. Alternative precedent for this phenomenon is lacking.

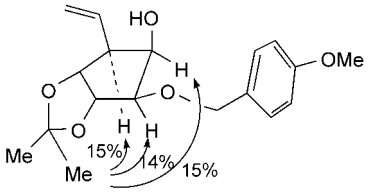
It seemed reasonable to suppose that the failure on the part of **6** to undergo ring contraction might originate from steric consequences arising from *cis* orientation of the oxygenated substituents at C(2), C(3), and C(4) on the α-face. Therefore, we next addressed the consequences of inverting the configuration at C(2). To this end, **10** was treated with sodium hydride and freshly prepared 4-methoxybenzyl bromide [27] to give the globally protected ether **17** (*Scheme 3*). Selective debenzylation was subsequently effected with carefully washed commercial *W-2 Raney*-Ni as catalyst under 1 atm of H_2 [28]. Frequent TLC monitoring of the reaction progress was necessary to obtain **18** efficiently and in a high state of purity. The oxidative conversion of **18** to aldehyde **19** proved initially to be problematic. Several protocols based on the use of dimethyl sulfoxide, hypervalent iodine reagents, perruthenate as tetrapropylammonium perruthenate (TPAP), or chromates as pyridinium chlorochromate (PCC) proved to be too inefficient. In contrast, recourse to *o*-iodoxybenzoic acid (=2-iodylbenzoic acid; IBX) in refluxing MeCN [29] and direct addition of the unstable **19** to methylenetriphenylphosphorane in the dark furnished the targeted **7** in 77% overall yield. As before, $[ZrBu_2(Cp)_2]$ was generated *in situ* from $[ZrCl_2(Cp)_2]$ and BuLi at $-78°$. Following the addition of **7** at this temperature, the reaction mixture was allowed to warm to 20° prior to workup. These conditions brought about high levels of acetonide deprotection, presumably induced by one or more zirconocene species serving as a *Lewis* acid. One possibility was that formation of the Cp_2Zr intermediate had not occurred prior to the addition of **7**. Accordingly, the mixture was allowed to warm to 0° and maintained at 0° for 20 min. During this time period, an intense brown coloration developed. To continue the process, this reactive species was added to **7** at

Scheme 3



PMB = 4-MeOC$_6$H$_4$CH$_2$, Bn = 1 PhCH$_2$, IBX = 2-iodoxybenzoic acid

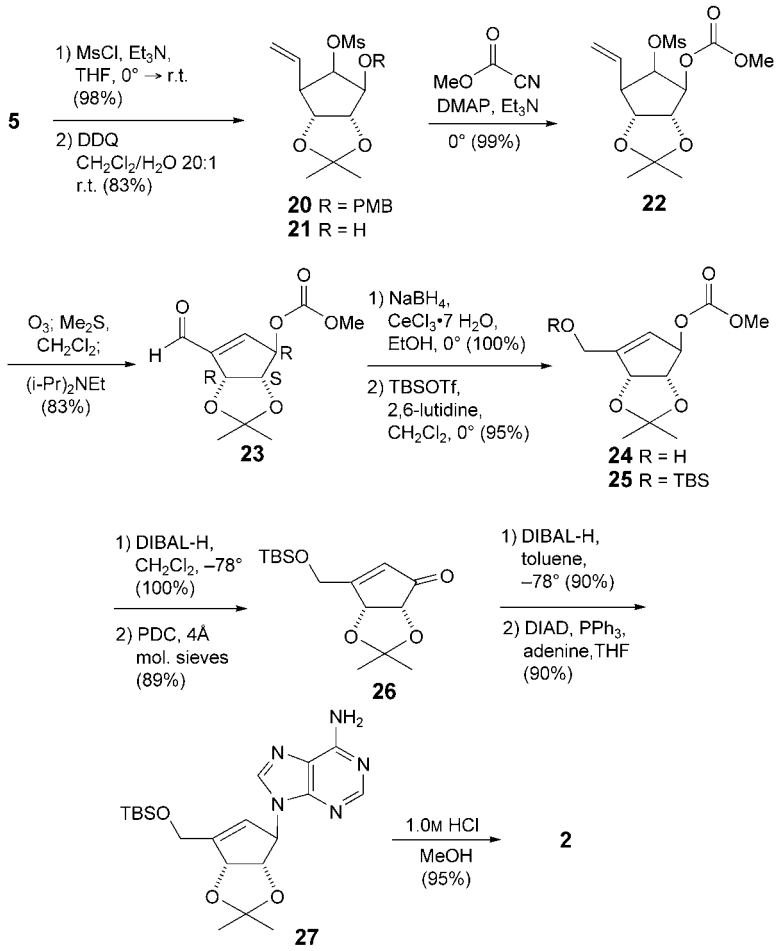
$-78°$, warmed to $0°$ for 2–3 h, and treated with boron trifluoride etherate at $-25°$. After conventional workup, **5** was isolated in 31% yield. Although the efficiency of this conversion proved to be modest, it represents the first time that an acetonide group has been successfully deployed in the Zr-catalyzed ring contraction. Noteworthy is the fact that a single diastereoisomer was produced, the configuration of which was established by COSY, NOSY, and NOE spectroscopy (see **A**) to be as depicted in **5**.



A

We were now in a position to exploit the interesting finding made by several research groups [30–34], who demonstrated that carbocyclic nucleosides are amenable to assembly by Pd-catalyzed allylic alkylation. To apply this reaction, **5** was first mesylated (→**20**) and freed of its PMB protecting group by treatment with 4,5-dichloro-3,6-dioxocyclohexadiene-1,2-dicarbonitrile (DDQ) [35] to generate **21** (*Scheme 4*). Protection of the remaining OH group was achieved by acylation with methyl carbonocyanidate [36] in the presence of *N*,*N*-dimethylpyridin-4-amine (DMAP). As events unfolded, the ozonolysis of **22** [37] and β-elimination in the presence of *Hünig*'s base was carried out in a single flask to deliver the α,β-unsaturated aldehyde **23** in 83% yield. Chemoselective *Luche* reduction [38] followed by *O*-silylation with *tert*-butyldimethylsilyl triflate [39] led to **25** without difficulty and set the stage for the impending allylic substitution. Rather unexpectedly, **25** proved to be totally unreactive to Pd^0 catalysis in the specific instances where adenine and 6-chloropurine served as the nucleobases of choice. Examples of ineffective couplings of this type have been reported [40][41]. Since triethylaluminium can serve to assist these

Scheme 4



Ms = $MeSO_2$, DDQ = 4,5-dichloro-3,6-dioxocyclohexadiene-1,2-carbonitrile, PMB = 4-$MeOC_6H_4CH_2$, DMAP = *N*,*N*-dimethylpyridin-4-amine, TBSOTf = $CF_3SO_2SiMe_2{}^tBu$, 2,6-lutidine = 2,6-dimethylpyridine, DIBAL-H = diisopropylaluminium hydride, PDC = pyridinium dichromate, DIAD = diisopropyl azodicarboxylate

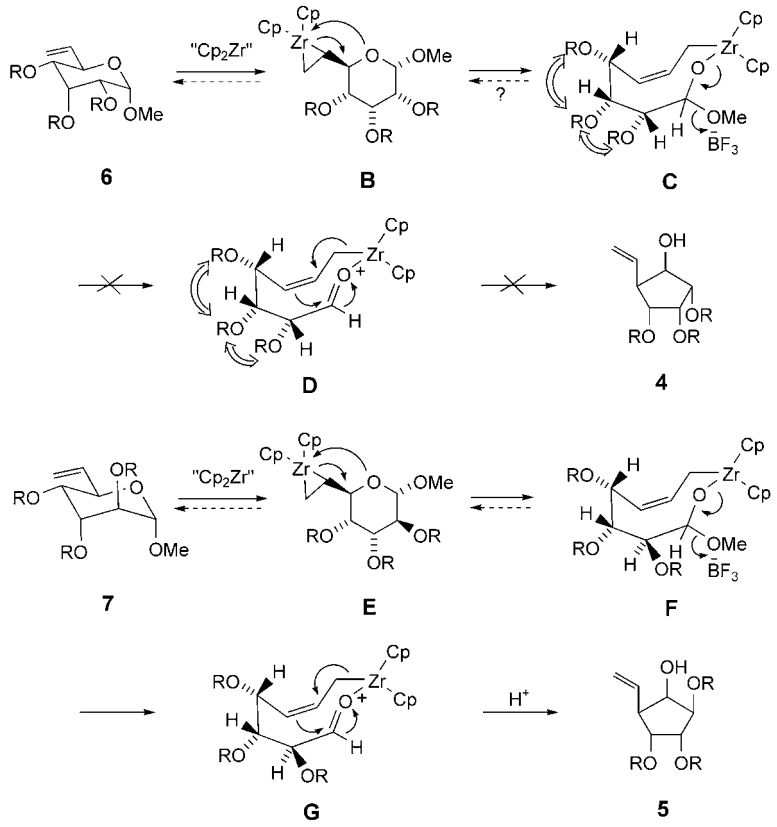
reactions in certain cases [41], the possible efficacy of this co-additive was also explored, but to no avail. Unreacted **25** was readily retrieved.

Despite this setback, the availability of **25** did play a crucial role in our quest of (−)-neplanocin A (**2**). In the hope that the *Mitsunobu* reaction [42] would serve our purposes, configurational inversion at the carbonate-bearing C-atom first had to be accomplished. Sequential reduction with diisopropylaluminium hydride (DIBAL-H) and oxidation with pyridinium dichromate (PDC) [43] under conditions of catalysis by 4-Å molecular sieves [44] furnished ketone **26** efficiently. Installation of the α-hydroxyl group was secured by DIBAL-H reduction in toluene, thus setting the stage for reaction with adenine, diisopropyl azodicarboxylate, and triphenylphosphine [43] to form the

penultimate intermediate **27** (90%). Final treatment with 1.0M HCl in aqueous MeOH [43] gave rise to **2**, the physical and spectral properties [43] of which proved essentially identical to literature data [43][45][46].

Discussion. – Successful use was made of the zirconocene-promoted vinylpyranoside ring contraction as a device for producing enantiomerically pure multiply functionalized cyclopentanes. Where **5** is concerned, further chemical modification to give (−)-neplanocin A was feasible by way of a double-inversion protocol. An interesting stereochemical dependence to the metal-mediated O-extrusion reaction was noted. The unreactivity of **6** and its tendency to experience anomerization in the presence of Cp_2Zr suggests that ligand exchange to generate **B** operates, and that further conversion to **C** may even occur [47] (*Scheme 5*). Seemingly, more-advanced progression to oxocarbenium ion **D** does not operate due to the extensive nonbonded steric repulsion generated as a consequence of the *cis* orientation of the three OR substituents on the periphery of the nine-membered ring. In contrast, the advancement from **7** to **5** is not similarly complicated by steric congestion, with the result that **E** can

Scheme 5



isomerize *via* **F** and **G** to produce **5**. The cyclic nature of the chair-like transition state depicted in **G** serves to deliver **5** with excellent diastereoselective placement of the *cis*-oriented vinyl and OH substituents in **5**.

Cyclopentane **5** is a highly versatile optically active intermediate that can be further transformed in numerous directions. The scheme outlined here leads in 12 steps to natural levorotatory neplanocin A. Hopefully the lessons learned in this undertaking can be fruitfully applied to other synthetic targets.

This research was supported in part by an unrestricted grant from the *Yamanouchi USA Foundation*, for which we are grateful. Details for the generation of **26** from the (4*R*)-alcohol and its conversion to **27** were kindly supplied by Prof. *Kunio Ogasawara*, Tohoku University, whom we thank.

Experimental Part

General. CC = Column chromatography. IR Spectra: in cm^{-1}. NMR Spectra: δ in ppm, J and $\Delta\nu$ in Hz. Mass spectra: in m/z.

Methyl 2-O-*Allyl 6*-O-*benzyl-α*-D-*altropyranoside* (**9**). Epoxide **8** (10.00 g, 37.8 mmol) was dissolved in allyl alcohol (500 ml), treated with NaH (1.36 g, 56.8 mmol), and heated to reflux for 48 h. The soln. was cooled, and excess allyl alcohol was removed by evaporation. The residue was dissolved in AcOEt (200 ml), and sat. NH_4Cl soln. (150 ml) was added. The aq. layer was extracted with AcOEt (3 × 75 ml) and the combined org. phase washed with brine (75 ml), dried, and evaporated. The crude material was dissolved in CH_2Cl_2 (500 ml), cooled to 0°, and treated with Et_3SiH (30.0 ml, 189 mmol, 5 equiv.) and CF_3COOH (14.6 ml, 189 mmol). The resulting soln. was stirred at 0° for 1 h, warmed to r.t. for 2 h, and quenched slowly with sat. $NaHCO_3$ soln. (300 ml). The aq. layer was extracted with AcOEt (3 × 75 ml), the combined org. phase washed with brine (75 ml), dried, and evaporated, and the residue purified by column chromatography (CC; silica gel, hexane/Et_2O 1:2): **9** (7.95 g, 65%). Colorless oil. $[\alpha]_D^{18} + 56.3$ ($c = 5.0$, $CHCl_3$). IR (neat): 3476, 1737. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.37–7.26 (*m*, 5 H); 5.92–5.85 (*m*, 1 H); 5.31–5.26 (*m*, 1 H); 5.21–5.19 (*m*, 1 H); 4.75 (*s*, 1 H); 4.62 (*s*, 2 H); 4.08–4.07 (*m*, 2 H); 3.99 (br. *s*, 1 H); 3.88–3.84 (*m*, 2 H); 3.79–3.73 (*m*, 2 H); 3.63–3.62 (*m*, 1 H); 3.42 (*s*, 3 H); 3.02 (br. *s*, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 138.8; 134.6; 128.7 (2C); 128.0 (2 C); 127.9; 118.1; 99.8; 76.0; 73.9; 71.7; 70.9; 69.3; 68.5; 65.7; 55.7. ES-HR-MS: 347.1451 ($[M + Na]^+$, $C_{17}H_{24}NaO_6^+$; calc. 347.1465).

Methyl 6-O-*Benzyl-3,4*-O-*isopropylidene-α*-D-*altropyranoside* (**10**). Diol **9** (1.27 g, 4.27 mmol) was dissolved in acetone (12 ml) and 2,2-dimethoxypropane (0.57 ml, 4.65 mmol) and treated with a catalytic amount of TsOH (0.012 g). The soln. was stirred for 1 h and evaporated. After CH_2Cl_2 (50 ml) was added, the org. layer was washed with sat. $NaHCO_3$ soln. (10 ml), dried, and evaporated and the residue subjected to CC (silica gel, hexane/Et_2O 2:1): acetonide of **9** (1.27 g, 81%). Colorless oil. $[\alpha]_D^{18} = +46.8$ ($c = 1.0$, $CHCl_3$). IR (neat): 1454, 1382, 1213. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.41–7.36 (*m*, 4 H); 7.34–7.30 (*m*, 1 H); 6.02–5.94 (*m*, 1 H); 5.35 (*ddd*, $J = 1.6, 3.2, 17.3$, 1 H); 5.23 (*dd*, $J = 1.4, 10.4$, 1 H); 4.66 (*s*, 2 H); 4.64 (*d*, $J = 4.7$, 1 H); 4.30–4.19 (*m*, 4 H); 3.92–3.89 (*m*, 1 H); 3.78 (*dd*, $J = 2.5, 10.9$, 1 H); 3.68–3.65 (*m*, 1 H); 3.57 (*dd*, $J = 4.7, 7.2$, 1 H); 3.48 (*s*, 3 H); 1.52 (*s*, 3 H); 1.39 (*s*, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 138.6; 135.1; 128.8 (2 C); 128.0 (2 C); 127.9; 117.8; 110.6; 102.1; 79.9; 76.9; 73.8; 72.6; 72.3; 70.9; 70.4; 55.7; 28.0; 25.8. ES-HR-MS: 387.1772 ($[M + Na]^+$, $C_{20}H_{28}NaO_6^+$; calc. 387.1778).

To a soln. of the acetonide of **9** (1.00 g, 1.9 mmol) in a EtOH/benzene/H_2O 7:4:1 (92 ml), DABCO (0.09 g, 0.84 mmol) and *Wilkinson*'s catalyst (0.23 g, 0.25 mmol) were added. The soln. was heated to reflux for 18 h, cooled to r.t., and evaporated. The residue was dissolved in acetone/H_2O 9:1 (40 ml). Yellow mercury(II) oxide (0.90 g) was first added followed by the slow addition of mercury (II) chloride (0.90 g). After 30 min of stirring, the mixture was filtered through *Celite*, and the filtrate was evaporated. The residue was taken up in Et_2O (100 ml), washed with sat. KI soln., dried, and evaporated. The residue was purified by CC (silica gel, hexane/Et_2O 3:2): **10** (0.52 g, 85%). Light yellow oil. $[\alpha]_D^{18} = +26.7$ ($c = 2.4$, $CHCl_3$). IR (neat): 3462, 1497, 1454. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.37–7.28 (*m*, 5 H); 4.62 (*s*, 2 H); 4.56 (*d*, $J = 5.4$, 1 H); 4.31 (*dd*, $J = 7.2, 8.7$, 1 H); 4.13 (*t*, $J = 7.5$, 1 H); 3.92–3.80 (*m*, 1 H); 3.78–3.72 (*m*, 2 H); 3.62 (*dd*, $J = 5.4, 10.9$, 1 H); 3.54 (*s*, 3 H); 2.69 (*d*, $J = 4.4$, 1 H); 1.48 (*s*, 3 H); 1.35 (*s*, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 138.4; 128.8 (2 C); 128.0 (2 C); 127.9; 111.0; 102.3; 77.2; 73.9; 73.4; 72.6; 70.9; 70.8; 56.0; 27.9; 25.7. ES-HR-MS: 347.1450 ($[M + Na]^+$, $C_{17}H_{24}NaO_6^+$; calc. 347.1465).

*Methyl 6-*O*-Benzyl-3,4-*O*-isopropylidene-α-*D*-allopyranosede* (**11**). To a soln. of **10** (0.40 g, 1.2 mmol) in CH_2Cl_2 (10 ml), 4-Å molecular sieves (0.60 g) were added, followed by 4-methylmorpholine 4-oxide (0.22 g, 1.8 mmol) and tetrapropylammonium perruthenate (0.021 g, 0.06 mmol). The mixture was stirred for 1 h and filtered through a plug of silica gel (elution with CH_2Cl_2/Et_2O 1:1): ketone (0.40 g, quant.). $[\alpha]_D^{18} = +9.8$ ($c = 0.8$, $CHCl_3$). IR (neat): 1794, 1759, 1673. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.37–7.31 (*m*, 5 H); 4.90 (*s*, 1 H); 4.77–4.64 (*m*, 4 H); 3.97–3.91 (*m*, 1 H); 3.82–3.70 (*m*, 2 H); 3.50 (*s*, 3 H); 1.47 (*s*, 3 H); 1.38 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 201.8; 137.7; 128.4 (2 C); 127.8; 127.6 (2 C); 112.7; 99.0; 77.6; 74.7; 73.5; 72.7; 69.7; 55.9; 27.1; 25.5. ES-HR-MS: 345.1302 ($[M+Na]^+$, $C_{17}H_{22}NaO_6^+$; calc. 345.1309).

The above ketone (0.40 g, 1.2 mmol) was dissolved in EtOH (10 ml), cooled to 0°, and treated with $NaBH_4$ (0.07 g, 2.0 mmol). After 30 min, the reaction was quenched by the addition of acetone (3 ml), and the solvent was evaporated. The residue was taken up in Et_2O (30 ml), washed with brine (10 ml), dried, and evaporated prior to purification by CC (silica gel, hexane/Et_2O 3:2): **11** (0.35 g, 88%). Light yellow oil. $[\alpha]_D^{18} = +92.4$ ($c = 1.0$, $CHCl_3$). IR (neat): 3490, 1451. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.37–7.30 (*m*, 5 H); 4.76 (*d*, $J = 4.7$, 1 H); 4.60 (*d*, $J = 1.8$, 2 H); 4.45 (*t*, $J = 4.9$, 1 H); 4.11 (*dd*, $J = 5.1$, 9.6, 1 H); 3.89–3.79 (*m*, 2 H); 3.73 (*dd*, $J = 2.2$, 10.8, 1 H); 3.61 (*dd*, $J = 5.4$, 10.8, 1 H); 3.46 (*s*, 3 H); 1.50 (*s*, 3 H); 1.36 (*s*, 3 H); OH not observed. ^{13}C-NMR (125 MHz, $CDCl_3$): 138.6; 128.8 (2 C); 128.0 (3 C); 110.6; 98.7; 74.6; 74.0; 72.1; 69.9; 67.3; 67.0; 56.4; 28.7; 26.6. ES-HR-MS: 347.1474 ($[M+Na]^+$, $C_{17}H_{24}NaO_6^+$; calc. 347.1465).

*Methyl 6-*O*-Benzyl-3,4-*O*-isopropylidene-2-*O*-{[2-(trimethylsilyl)ethoxy]methyl}-α-*D*-allopyranoside* (**12**). To a soln of **11** (0.35 g, 1.08 mmol) in THF (20 ml), oil-free KH (0.09 g, 2.16 mmol) was added followed by SEMCl (0.38 ml, 2.16 mmol). After 1 h, the mixture was quenched with H_2O (10 ml), and the aq. layer was extracted with Et_2O (2 × 20 ml). The combined org. phase was washed with brine (10 ml), dried, and evaporated and the residue purified by CC (silica gel, hexane/Et_2O 2:1): **12** (0.39 g, 80%). Colorless oil. $[\alpha]_D^{18} = +40.8$ ($c = 2.4$, $CHCl_3$). IR (neat): 1497, 1454. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.40–7.30 (*m*, 5 H); 4.90–4.84 (*m*, 3 H); 4.65 (*AB′q′*, $J = 12.2$, $\Delta\nu_{AB} = 10.6$, 2 H); 4.57 (*t*, $J = 4.6$, 1 H); 4.15 (dd, $J = 4.9$, 9.6, 1 H); 3.92–3.89 (*m*, 2 H); 3.79–3.73 (*m*, 3 H); 0.99–0.95 (*m*, 2 H); 0.05 (*s*, 9 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 138.6; 128.8 (2 C); 128.0 (2 C); 127.9; 110.9; 98.2; 95.1; 74.0; 73.8; 72.4; 72.2; 69.9; 67.2; 66.2; 56.3; 29.0; 26.6; 18.7; −1.0 (3 C). ES-HR-MS: 477.2250 ($[M+Na]^+$, $C_{23}H_{38}SiNaO_7^+$; calc. 477.2279).

*Methyl 6-*O*-[(*tert*-Butyl)dimethylsilyl]-2-*O*-{[2-(trimethylsilyl)ethoxy]methyl}-α-*D*-allopyranoside* (**13**). A soln. of **12** (1.20 g) in 80% AcOH/H_2O (30 ml) was stirred at r.t. for 4.5 h, after which the AcOH was evaporated, and the H_2O was removed by azeotropic distillation with benzene (2 × 50 ml). The residue was purified by CC (silica gel, hexane/Et_2O 1:1): diol (0.88 g, 80%). Colorless glass. $[\alpha]_D^{18} = +21.9$ ($c = 2.6$, $CHCl_3$). IR (neat): 3487, 1057. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.40–7.35 (*m*, 4 H); 7.32–7.29 (*m*, 1 H); 4.92 (*d*, $J = 3.5$, 1 H); 4.84 (*AB′q′*, $J = 7.1$, $\Delta\nu_{AB} = 26.2$, 2 H); 4.65 (*s*, 2 H); 4.24–4.21 (*m*, 1 H); 3.88–3.85 (*m*, 1 H); 3.80–3.59 (series of *m*, 6 H); 3.49 (*s*, 3 H); 3.40 (*d*, $J = 8.8$, 1 H); 2.77 (*d*, $J = 10.3$, 1 H); 1.01–0.95 (*m*, 2 H); 0.05 (*s*, 9 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 138.6; 128.8 (2 C); 128.0; 127.9 (2 C); 100.0; 94.2; 74.0; 73.1; 70.5; 69.9; 68.1; 67.4; 66.1; 56.2; 18.6; −1.0. ES-HR-MS: 437.1955 ($[M+Na]^+$, $C_{20}H_{34}SiNaO_7^+$; calc. 437.1966).

To the above diol in abs. EtOH (75 ml), 10% Pd/C (0.05 g) was added. H_2 Gas was bubbled through the mixture for 5 min, and the mixture was stirred under a H_2-filled balloon for another hour. After filtration through a pad of *Celite*, solvent evaporation gave 0.57 g (84%) of crude triol, which was directly dissolved in CH_2Cl_2 (30 ml) and treated with 1*H*-imidazole (0.16 g, 1.3 equiv.) and ^{t}BuMe$_2$SiCl (0.29 g, 1.1 equiv.). The mixture was stirred for 1 h and quenched with sat. NH_4Cl soln. (10 ml). The aq. layer was extracted with CH_2Cl_2 (10 ml), the combined org. phase was dried and evaporated and the residue subjected to CC (silica gel, hexane/Et_2O 1:1): **13** (0.69 g, 90%). Colorless oil. $[\alpha]_D^{18} = +24.9$ ($c = 0.8$, $CHCl_3$). ^{1}H-NMR (500 MHz, $CDCl_3$): 4.90 (*d*, $J = 3.4$, 1 H); 4.86 (*AB′q′*, $J = 7.2$, $\Delta\nu_{AB} = 25.2$, 2 H); 4.22 (br. *s*, 1 H); 4.01 (*dd*, $J = 2.4$, 11.2, 1 H); 3.88 (*dd*, $J = 5.4$, 11.2, 1 H); 3.77–3.62 (*m*, 4 H); 3.52–3.49 (*m*, 4 H); 0.99–0.94 (*m*, 11 H); 0.13 (*s*, 6 H); 0.06 (*s*, 9 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 199.8; 94.3; 73.3; 70.6; 69.3; 69.3; 67.6; 66.1; 63.5; 56.0; 26.4 (3 C); 18.8; 18.6; −1.0 (3 C); −4.9 (2 C). ES-HR-MS: 461.2381 ($[M+Na]^+$, $C_{19}H_{42}NaO_7Si_2^+$; calc. 461.2361).

*Methyl 6-*O*-[(*tert*-Butyl)dimethylsilyl]-3,4-bis-*O*-(4-methoxybenzyl)-2-*O*-{[2-(trimethylsilyl)ethoxy]methyl}-α-*D*-allopyranoside* (**14**). Diol **13** (0.40 g, 0.91 mmol) was dissolved in THF (20 ml), cooled to 0°, and treated with sodium hexamethyldisilazanide (2.70 ml, 2.70 mmol). After 1 h, 4-methoxybenzyl bromide (0.46 g, 2.3 mmol) and a cat. amount of Bu_4NI were added. The ice bath was removed, and the mixture was stirred for 3 d and quenched by the addition of H_2O (10 ml). The aq. layer was extracted with Et_2O (3 × 10 ml), the combined org. soln. dried and evaporated, and the residue subjected to CC (silica gel, hexane/Et_2O 3:1): **14** (0.43 g, 70%). Colorless oil. $[\alpha]_D^{18} = +34.8$ ($c = 2.3$, $CHCl_3$). IR (neat): 1613, 1514. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.30 (*d*, $J = 8.7$, 2 H); 7.20 (*d*, $J = 8.7$, 2 H); 6.85 (*d*, $J = 8.7$, 2 H); 6.79 (*d*, $J = 8.7$, 2 H); 4.78 (*d*, $J = 3.6$, 2 H); 4.73 (*d*, $J = 4.0$, 1 H); 4.66 (*AB′q′*, $J = 7.1$, $\Delta\nu_{AB} = 13.1$, 2 H); 4.43 (*ABX*, $J = 11.3$, $\Delta\nu_{AB} = 23.7$, 2 H); 4.12–4.05 (*m*,

2 H); 3.89–3.69 (series of *m*, 10 H); 3.61–3.56 (*m*, 2 H); 3.42 (*s*, 3 H); 0.90 (br. *s*, 11 H); 0.06 (*s*, 6 H); 0.02 (*s*, 9 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 159.1 (2 C); 131.4; 130.5; 129.3 (2 C); 129.0 (2 C); 113.7 (2 C); 113.4 (2 C); 98.6; 93.2; 74.9; 74.0; 73.3; 72.3; 71.0; 67.2; 65.4; 62.5; 55.6; 55.2 (2 C); 26.0 (3 C); 18.3; 18.1; −1.5 (3 C); −5.2; −5.4. ES-HR-MS: 701.3470 ($[M+Na]^+$, $C_{35}H_{58}NaO_9Si_2^+$; calc. 701.3512).

Methyl 3,4-Bis-O-*(4-methoxybenzyl)-2*-O-*{[2-(trimethylsilyl)ethoxy]methyl}-α-*D-*allopyranoside* (**15**). To a soln. of **14** (0.10 g, 0.15 mmol) in THF (10 ml), 1M Bu_4NF in THF (0.15 ml) was added, and the soln. was stirred at r.t. for 2 h. The mixture was quenched by the addition of H_2O (5 ml), the aq. phase extracted with Et_2O (2 × 10 ml), the combined org. phase dried (Na_2SO_4) and evaporated, and the residue subjected to CC (silica gel, hexane/Et_2O 3:2): **15** (0.07 g, 88%). Colorless oil. $[\alpha]_D^{18} = +37.0$ ($c = 3.1$, $CHCl_3$). IR (neat): 3493, 1613, 1514. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.32 (*d*, $J = 8.6$, 2 H); 7.20 (*d*, $J = 8.7$, 2 H); 6.85 (*d*, $J = 8.7$, 2 H); 6.81 (*d*, $J = 8.6$, 2 H); 4.85–4.64 (series of *m*, 5 H); 4.40 (*AB′q′*, $J = 11.5$, $\Delta\nu_{AB} = 42.5$, 2 H); 4.15–4.10 (*m*, 2 H); 3.85–3.61 (*m*, 10 H); 3.61–3.53 (*m*, 1 H); 3.44–3.39 (*m*, 4 H); 1.87 (*dd*, $J = 5.4$, 7.4, 1 H); 0.96–0.89 (*m*, 2 H); 0.01 (*s*, 9 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 159.3; 158.9; 131.3; 129.4 (3 C); 129.3 (2 C); 113.8 (2 C); 113.5 (2 C); 98.9; 93.5; 74.9; 74.2; 73.3; 72.0; 70.7; 66.4; 65.5; 62.2; 55.9; 55.3; 55.2; 18.2; −1.4 (3 C). ES-HR-MS: 587.2688 ($[M+Na)^+$, $C_{29}H_{44}NaO_9Si^+$; calc. 587.2647).

*{2-{[6-Ethenyl-tetrahydro-2-methoxy-4,5-bis[(4-methoxybenzyl)oxy]-2*H*-pyran-3-yl}oxy}methoxy}ethyl}-trimethylsilane* (**6**). A soln. of **15** (0.20 g, 0.35 mmol) in CH_2Cl_2 (5 ml) was treated with 4 Å molecular sieves (0.20 g), NMO (0.06 g, 0.53 mmol), and TPAP (0.006 g, 0.02 mmol). The mixture was stirred for 2 h, filtered through a plug of *Florisil*, and evaporated. The aldehyde was dissolved in dry THF (5 ml), and cooled to 0°. Into the cold soln. was cannulated a soln. prepared from methyltriphenylphosphonium iodide (0.36 g, 0.89 mmol) and BuLi (0.7 ml, 0.89 mmol) in THF (5 ml), which had been stirred for 1 h at 0°. The mixture was warmed to r.t., and quenched with H_2O after 3 h. The aq. layer was extracted with Et_2O (2 × 10 ml), the combined org. phase dried and evaporated, and the residue subjected to CC (silica gel, hexane/Et_2O 2:1): **6** (0.10 g, 48%). Colorless syrup. $[\alpha]_D^{18} = +34.0$ ($c = 0.6$, $CHCl_3$). ^{1}H-NMR (500 MHz, $CDCl_3$): 7.36 (*d*, $J = 8.5$, 2 H); 7.23 (*d*, $J = 8.5$, 2 H); 6.89 (*d*, $J = 8.6$, 2 H); 6.85 (*d*, $J = 8.6$, 2 H); 6.02–5.95 (*m*, 1 H); 5.50–5.46 (*m*, 1 H); 5.30–5.28 (*m*, 1 H); 4.84 (*s*, 2 H); 4.78 (*d*, $J = 4.1$, 1 H); 4.70 (*ABX*, $J = 7.1$, $\Delta\nu = 26.6$, 2 H); 4.60–4.57 (*m*, 1 H); 4.43 (*AB′q′*, $J = 11.5$, $\Delta\nu_{AB} = 34.1$, 2 H); 4.15–4.14 (*m*, 1 H); 3.85 (*s*, 3 H); 3.82 (*s*, 3 H); 3.80–3.74 (*m*, 1 H); 3.69–3.67 (*m*, 1 H); 3.63–3.56 (*m*, 1 H); 3.47 (*s*, 3 H); 3.20 (*dd*, $J = 2.6$, 9.7, 1 H); 1.02–0.94 (*m*, 2 H); 0.05 (*s*, 9 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 159.6; 159.3; 136.1; 131.7; 130.6; 129.9 (2 C); 129.6 (2 C); 117.8; 114.1 (2 C); 113.9 (2 C); 99.2; 93.7; 79.4; 74.3; 73.7; 72.7; 71.6; 67.3; 65.9; 56.4; 55.7; 31.3; 18.6; −1.0 (3 C). ES-HR-MS: 583.2690 ($[M+Na)^+$, $C_{30}H_{44}NaO_8Si^+$; calc. 583.2698).

*(3a*R*,4*R*,6*S*,7*S*,7a*R*)-4-[(Benzyloxy)methyl]-tetrahydro-6-methoxy-[(7-(4-methoxybenzyl)oxy]-2,2-dimethyl-4*H*-1,3-dioxolo[4,5-*c*]pyran* (**17**). To a soln. of **10** (200 mg, 062 mmol) in DMF (6.0 ml) was added NaH (52 mg, 60% in mineral oil, 1.30 mmol) at 0°. The mixture was stirred for 15 min before 4-methoxybenzyl bromide (186 mg, 0.93 mmol) was added dropwise. The cold bath was removed after 20 min, the suspension allowed to warm to r.t., and stirring continued until unreacted **10** was no longer detected by TLC. The mixture was quenched by the careful addition of H_2O (8 ml) and extracted with CH_2Cl_2 (3 × 8 ml), the combined org. layer washed with brine and dried, and the residue subjected to flash chromatography (silica gel, hexane/Et_2O 5:1 → 3:1): **17** (260 mg, 95%). Colorless oil. $[\alpha]_D^{20} = +6.9$ ($c = 0.42$, $CHCl_3$). IR (neat): 1654, 1616, 1559. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.37–7.26 (*m*, 7 H); 6.87 (*m*, 2 H); 4.73–4.62 (*m*, 5 H); 4.28–4.17 (*m*, 2 H); 3.86 (*m*, 1 H); 3.80 (*s*, 3 H); 3.74 (*m*, 1 H); 3.60 (*m*, 2 H); 3.45 (*s*, 3 H); 1.43 (*s*, 3 H); 1.35 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 159.2; 138.1; 130.1; 129.6 (3 C); 128.3 (2 C); 127.5 (2 C); 113.6 (2 C); 110.1; 101.6; 79.1; 77.0; 76.4; 73.3; 72.5; 72.0; 70.3; 69.9; 55.2; 27.5; 25.4. ES-HR-MS: 467.2038 ($[M+Na)^+$, $C_{25}H_{32}NaO_7^+$; calc. 467.2040).

*(3a*R*,4*R*,6*S*,7*S*,7a*R*)-Tetrahydro-6-methoxy-7-[(4-methoxybenzyl)oxy]-2,2-dimethyl-4*H*-1,3-dioxolo[4,5-*c*]pyran-4)methanol* (**18**). To a soln. of **17** (64.3 mg, 0.15 mmol) in EtOH (3 ml) was added *W-2 Raney* Ni (from 0.12 ml rinsed with EtOH) in EtOH (2.0 ml) at 0°. The mixture was stirred under 1 atm of H_2 for 2 days (TLC monitoring was very important) before it was filtered through a pad of *Celite*. Evaporation of the filtrate under vacuum gave **18** (52 mg, quant.). Colorless oil. $[\alpha]_D^{20} = +31.5$ ($c = 0.74$, $CHCl_3$). IR (neat): 3435, 1652, 1637. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.30 (*m*, 2 H); 6.88 (*m*, 2 H); 4.70 (*d*, $J = 11.4$, 1 H); 4.63 (*d*, $J = 11.4$, 1 H); 4.60 (*d*, $J = 4.4$, 1 H); 4.21 (*m*, 2 H); 3.88 (*m*, 1 H); 3.84 (*s*, 3 H); 3.73 (*m*, 2 H); 3.59 (*m*, 1 H); 3.40 (*s*, 3 H); 1.90 (br. *s*, 1 H); 1.43 (*s*, 3 H); 1.34 (s, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 159.2; 130.0; 129.6 (2 C); 113.7 (2 C); 110.2; 101.5; 78.6; 76.1; 72.6; 71.6; 70.5; 63.3; 55.3 (2 C); 27.4; 25.4. ES-HR-MS: 377.1570 ($[M+Na]^+$, $C_{18}H_{26}NaO_7^+$; calc. 377.1571).

*(3a*S*,4*S*,6*S*,7*S*,7a*R*)-Tetrahydro-6-methoxy-7-[(4-methoxybenzyl)oxy]-2,2-dimethyl-4*H*-1,3-dioxolo[4,5-*c*]pyran-4-carboxaldehyde* (**19**). A suspension of **18** (460 mg, 1.30 mmol) and IBX (1.196 g, 4.27 mmol) in MeCN (13 ml) was refluxed for 28 min. After the mixture was allowed to cool to r.t., it was further cooled in an ice/salt

bath. The mixture was then filtered through a pad of silica gel and the solvent evaporated: **19**. Colorless oil. (458 mg, quant.). $[\alpha]_D^{20} = +17.6$ ($c = 0.49$, $CHCl_3$). IR (film): 3500 (br.), 1740, 1612. ^{1}H-NMR (300 MHz, $CDCl_3$): 9.76 (*s*, 1 H); 7.28 (*m*, 2 H); 6.87 (*m*, 2 H); 4.69 (*d*, $J = 4.0$, 1 H); 4.64 (*d*, $J = 3.5$, 2 H); 4.38 (*dd*, $J = 6.6$, 6.6, 1 H); 4.21 (*m*, 2 H); 3.80 (*s*, 3 H); 3.59 (*m*, 1 H); 3.45 (*s*, 3 H); 1.47 (*s*, 3 H); 1.37 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 198.3; 159.1; 129.4; 129.3 (2 C); 113.5 (2 C); 110.5; 102.5; 76.4; 75.4; 74.1; 72.4; 70.3; 55.6; 55.0; 27.3; 25.3. ES-HR-MS: 375.1404 ($[M + Na]^+$, $C_{18}H_{24}NaO_7^+$; calc. 375.1414).

*(3a*R,*4*R,*6*S,*7*S,*7a*R*)-4-Ethenyl-tetrahydro-6-methoxy-7-[(4-methoxybenzyl)oxy]-2,2-dimethyl-4*H*-1,3-dioxolo[4,5-*c*]pyran* (**7**). At 0°, methyltriphenylphosphonium bromide (639 mg, 1.75 mmol) in dry Et_2O (13 ml) was treated with sublimed KO^{t}Bu (195 mg, 1.74 mmol) for 30 min with stirring. A soln. of freshly prepared **19** (458 mg, 1.30 mmol) in Et_2O (8.2 ml was introduced *via* cannula and stirred for 20 min before the cooling bath was removed. The mixture was stirred for another hour at r.t., at which point H_2O (5 ml) and sat. $NaHCO_3$ soln. (5 ml) were slowly added at 0°. The aq. phase was extracted with Et_2O (3 × 8 ml), the combined org. soln. dried and evaporated, and the residue submitted to CC (silica gel, hexane/Et_2O 5 :1): 351 mg (77% yield for two steps) of **7**. White solid. M.p. 68°. $[\alpha]_D^{20} = +25.0$ ($c = 0.28$, $CHCl_3$). IR (film): 1613, 1514, 1457. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.30 (*m*, 2 H); 6.87 (*m*, 2 H); 5.99–5.88 (*m*, 1 H); 5.42 (*dd*, $J = 1.0$, 16.3, 1 H); 5.27 (*dd*, $J = 1.0$, 16.3, 1 H); 4.71 (*d*, $J = 11.4$, 1 H); 4.65 (*d*, $J = 11.4$, 1 H); 4.60 (*d*, $J = 4.7$, 1 H); 4.21 (*m*, 1 H); 4.13 (*m*, 1 H); 3.80 (*s*, 3 H); 3.60 (*dd*, $J = 4.7$, 6.0, 1 H); 3.41 (*s*, 3 H); 1.44 (*s*, 3 H); 1.35 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 159.3; 135.6; 130.1; 129.7 (2 C); 117.2; 113.7 (2 C); 110.1; 101.5; 89.0;79.2; 76.5; 75.8; 72.6; 70.6; 55.3; 27.5; 25.3. ES-HR-MS: 373.1622 ($[M + Na]^+$, $C_{19}H_{26}NaO_6^+$ calc. 373.1622).

*(3a*R,*4*S,*5*R,*6*R,*6a*R*)-4-Ethenyl-tetrahydro-4-[(4-Methoxybenzyl)oxy]-2,2-dimethyl-4*H*-cyclopenta[*d*]-1,3-dioxol-5-ol* (**5**). BuLi (1.9M in hexane; 2.5 ml, 4.80 mmol) was slowly added to a soln. of $[ZrCl_2](Cp)_2$ (729 mg, 2.50 mmol) in toluene (26 ml) at −78°. The mixture was stirred for 40 min at −78° and for 20 min at 0°, during which time the color changed from yellow to bright brown. This brown soln. was slowly cannulated into a soln. of **7** (350 mg, 1.00 mmol) in toluene (19.5 ml) at −78°. After the mixture had been stirred for 25 min at −78° and an added 3 h at 0°, the temp. was lowered to −25°, at which point freshly distilled $BF_3 \cdot OEt_2$ (278 µl, 2.2 mmol) was slowly introduced, and stirring was continued for 25 min at −25° before 1M HCl (20 ml) was added dropwise. The aq. layer was extracted with AcOEt (3 × 10 ml), the combined org. layer washed with sat. $NaHCO_3$ soln. and brine and evaporated, and the residue subjected to CC (silica gel, hexane/Et_2O 5 :1): **5** (87.5 mg, 31% based on 89% conversion). Colorless oil. $[\alpha]_D^{20} = +46.9$ ($c = 1.4$, $CHCl_3$). IR (film): 3498, 1613, 1586. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.28 (*m*, 2 H); 6.89 (*m*, 2 H); 5.99–5.87 (*m*, 1 H); 5.26–5.18 (*m*, 2 H); 4.71–4.64 (*m*, 3 H); 4.50 (*d*, $J = 11.3$, 1 H); 4.26 (*m*, 1 H); 3.88 (*m*, 1 H); 3.81 (*s*, 3 H); 2.67 (*m*, 1 H); 2.39 (*d*, $J = 4.3$, 1 H); 1.43 (*s*, 3 H); 1.31 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 134.5; 129.6 (2 C); 129.5; 118.2; 113.9 (2 C); 112.4; 110.1; 84.8; 83.1; 82.8; 75.8; 71.7; 55.3; 52.9; 30.3; 24.4. ES-HR-MS: 343.1516 ($[M + Na]^+$, $C_{18}H_{24}NaO_5^+$; calc. 343.1516).

*(3a*R,*4R,5*R,*6S,6a*R*)-4-Ethenyl-tetrahydro-4-[(4-methoxybenzyl)oxy]-2,2-dimethyl-4*H*-cyclopenta[*d*]-1,3-dioxol-5-ol Methanesulfonate* (**20**). To a stirred soln. of **5** (76.3 mg, 0.24 mmol) and Et_3N (167.3 µl, 1.20 mmol) in THF (3.8 ml) was slowly added methanesulfonyl chloride (64.7 µl, 0.84 mmol) at 0°. The mixture was allowed to reach r.t. before being quenched with H_2O (2.0 ml). The aq. layer was extracted with Et_2O (3×) and the combined org. phase washed with brine and evaporated: **20** (95 mg, 98%). Pale yellow oil. $[\alpha]_D^{20} = +11.2$ ($c = 0.59$, $CHCl_3$). IR (film): 1614, 1514, 1359. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.29 (*m*, 2 H); 6.89 (*m*, 2 H); 5.97–5.89 (*m*, 1 H); 5.32–5.17 (*m*, 3 H); 4.68–4.55 (*m*, 4 H); 4.02 (*m*, 1 H); 3.79 (*s*, 3 H); 2.96 (*s*, 3 H); 2.83 (*m*, 1 H); 1.51 (*s*, 3 H); 1.33 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 133.0; 129.6; 129.3 (2 C); 127.0; 113.8 (2 C); 113.7; 105.6; 86.9; 83.6; 82.9; 82.3; 72.0; 55.3; 51.3; 39.0; 26.9; 24.5. ES-HR-MS: 421.1310 ($[M + Na]^+$, $C_{19}H_{26}NaO_7S^+$; calc. 421.1291).

*(3a*S,*4*S,*5*R,*6*R,*6a*R*)-6-Ethenyl-tetrahydro-2,2-dimethyl-4*H*-cyclopenta[*d*]-1,3-dioxole-4,5-diol 5-Methanesulfonate* (**21**). To a soln. of **20** (58 mg, 0.15 mmol) in CH_2Cl_2 (10 ml) was added H_2O (0.5 ml) followed by DDQ (83 mg, 0.37 mmol). The mixture was stirred for 7 h prior to the introduction of sat. $NaHCO_3$ soln. (5.0 ml). The aq. layer was extracted with AcOEt (3 × 3 ml), the combined org. phase dried and evaporated, and the residue purified by CC (silica gel, hexane/Et_2O 2 :1): **21** (41 mg, 83%). White solid. M.p. 110°. $[\alpha]_D^{20} = +18.8$ ($c = 0.17$, $CHCl_3$). IR (film): 3648, 1445, 1423. ^{1}H-NMR (300 MHz, $CDCl_3$): 6.00–5.88 (*m*, 1 H); 5.29–5.21 (*m*, 2 H); 5.13 (*m*, 1 H); 4.63–4.55 (*m*, 2 H); 4.32 (*m*, 1 H); 3.09 (*s*, 3 H); 3.01 (*m*, 1 H); 2.39 (*d*, $J = 4.0$, 1 H); 1.48 (*s*, 3 H); 1.30 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 133.5; 119.2; 112.6; 84.5; 83.5; 82.3; 77.2; 51.6; 38.6; 26.6; 24.1. ES-HR-MS: 301.0713 ($[M + Na]^+$, $C_{11}H_{18}NaO_6S^+$; calc. 301.0716).

*(3a*R,*4*S,*5*R,*6*R,*6a*R*)-6-Ethenyl-tetrahydro-2,2-dimethyl-4*H*-cyclopenta[*d*]-1,3-dioxole-4,5-diol 5-Methanesulfonate 4-(Methyl Carbonate)* (**22**). Alcohol **21** (20.0 mg, 0.072 mmol) was mixed with Et_3N (73.8 µl, 0.53 mmol) and a catalytic amount of DMAP in CH_2Cl_2 (1.2 ml) and placed in an ice-water bath. Methyl

carboncyanidate (20.0 µl, 0.25 mmol) was then added, after which the bath was removed, and stirring was continued until the starting material was not detected by TLC (*ca.* 20 min). The mixture was diluted with CH_2Cl_2 (5 ml), washed with 5% $NaHCO_3$ soln. and brine, dried, and evaporated and the residue subjected to CC (silica gel, hexane/Et_2O 2.2 :1): **22** (24 mg, 99%). Colorless oil. $[\alpha]_D^{20} = -16.4$ ($c = 1.6$, $CHCl_3$). IR (film): 1757, 1648, 1637. ^{1}H-NMR (300 MHz, $CDCl_3$): 5.89 (*m*, 1 H); 5.33 (*m*, 1 H); 5.27 (*m*, 2 H); 5.09 (*t*, $J = 3.9$, 1 H); 4.71 (*m*, 1 H); 4.63 (*m*, 1 H); 3.82 (*s*, 3 H); 3.02 (*s*, 3 H); 3.00–2.94 (*m*, 1 H); 1.55 (*s*, 3 H); 1.33 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 154.6; 132.2; 119.4; 113.8; 84.0; 81.7; 81.5; 80.9; 55.4; 51.3; 38.6; 26.8; 24.3. ES-HR-MS: 359.0771 ($[M + Na]^+$, $C_{13}H_{20}NaO_8S^+$; calcd 359.0771).

*(3a*S*,4*R*,6a*R*)-3a,6a-Dihydro-4-[(methoxycarbonyl)oxy]-2,2-dimethyl-4*H*-cyclopenta[*d*]-1,3-dioxole-6-carboxaldehyde* (**23**). A soln. of **22** (23.9 mg, 71.0 µmol) in CH_2Cl_2 (3.2 ml) was purged with O_3 at $-78°$ for a few minutes until the soln. became blue, at which point N_2 was introduced to remove the remaining O_3. Me_2S (13.0 µl, 178 µmol) was added, the mixture allowed to reach r.t., and stirring maintained for 4 h followed by co-evaporation with benzene. The residue was dissolved in CH_2Cl_2 (3 ml), cooled to 0° in an ice-water bath, and treated with ^{i}Pr$_2$EtNH (18.6 µl, 107 µmol). This soln. was stirred for 10 min in the cold and evaporated. The residue was purified by CC (silica gel, hexane/Et_2O 2 :1): **23** (14 mg, 83%). Colorless oil: IR (film): 1754, 1693. ^{1}H-NMR (300 MHz, $CDCl_3$): 9.90 (*s*, 1 H); 6.78 (*m*, 1 H); 5.66 (*m*, 1 H); 5.46 (*dd*, $J = 1.6, 5.9$, 1 H); 4.76 (*d*, $J =$ 5.9, 1 H); 3.84 (*s*, 3 H); 1.43 (*s*, 3 H); 1.37 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 188.7; 154.8; 148.6; 144.4; 113.4; 85.0; 83.3; 80.3; 55.3; 26.9; 25.0. ES-HR-MS: 265.0680 ($[M + Na]^+$, $C_{11}H_{14}NaO_6^+$; calc. 265.0683).

*(3a*S*,4*R*,6a*R*)-3a,6a-Dihydro-4-[(methoxycarbonyl)oxy]-2,2-dimethyl-4*H*-cyclopenta[*d*]-1,3]-dioxole-6-methanol* (**24**). A soln. of **23** (37.6 mg, 155 µmol) and $CeCl_3 \cdot 7\,H_2O$ (69.3 mg, 186 µmol) in EtOH (7.9 ml) was cooled in an ice/salt bath, treated with $NaBH_4$ (7.0 mg, 186 µmol) in one portion, and stirred for 40 min before the introduction of sat. NH_4Cl soln. After extraction with AcOEt, the combined org. layer was, washed with sat. $NaHCO_3$ soln., dried, and evaporated an the residue purified by CC (silica gel, hexane/Et_2O 2.2 :1): **24** (38 mg, quant.). Colorless oil. $[\alpha]_D^{20} = -84.6$ ($c = 0.76$, $CHCl_3$). IR (film): 3216, 1745. ^{1}H-NMR (300 MHz, $CDCl_3$): 5.80 (*t*, $J << 1$, 1 H); 5.48 (br. *s*, 1 H); 5.19 (*d*, $J = 5.7$, 1 H); 4.68 (*d*, $J = 5.7$, 1 H); 4.34 (*m*, 2 H); 3.80 (*s*, 3 H); 1.82 (*t*, $J = 4.6$, 1 H); 1.42 (*s*, 3 H); 1.35 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 158.0; 151.2; 123.7; 112.8; 85.3; 83.6; 83.5; 60.2; 55.0; 27.3; 25.8. ES-HR-MS: 267.0852 ($[M + Na]^+$, $C_{11}H_{16}NaO_6^+$; calc. 267.0839).

*(3a*S*,4*R*,6a*R*)-6-{[[(1,1-Dimethylethyl)dimethylsilyl]oxy}methyl]-3a,6a-dihydro-2,2-dimethyl-4*H*-cyclopenta[*d*]-1,3-dioxol-4-ol Methyl Carbonate* (**25**). To a cold (0°) soln. of **24** (41.5 mg, 170 µmol) in CH_2Cl (6.0 ml) was added 2,6-dimethylpyridine (49.5 µl, 425 µmol) followed by ^{t}BuMe$_2$SiOTf (78 µl, 340 µmol). The mixture was stirred for 10 min, quenched with sat. $NaHCO_3$ soln., and extracted with Et_2O. The combined org. layer was washed in turn with 1M HCl and sat. $NaHCO_3$ soln., dried, and evaporated and the residue subjected to CC (silica gel, hexane/Et_2O 7 :1): 49 mg (95%) of **25**. Colorless oil. $[\alpha]_D^{20} = -48.2$ ($c = 3.8$, $CHCl_3$). IR (film): 1750, 1442, 1372. ^{1}H-NMR (300 MHz, $CDCl_3$): 5.77 (br. *s*, 1 H); 5.47 (*m*, 1 H); 5.09 (*m*, 1 H); 4.66 (*d*, $J = 5.7$, 1 H); 4.31 (*m*, 2 H); 3.79 (*s*, 3 H); 1.39 (*s*, 3 H); 1.34 (*s*, 3 H); 0.90 (*s*, 9 H); 0.07 (*s*, 6 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 152.5; 125.6; 122.5; 112.5; 85.4; 83.9; 82.9; 60.3; 54.9; 27.3; 25.9; 25.8 (3 C); 18.3; −5.5 (2 C).

*(3a*S*,4*R*,6a*R*)-6-{[[(1,1-Dimethylethyl)dimethylsilyl]oxy}methyl]-3a,6a-dihydro-2,2-dimethyl-4*H*-cyclopenta[*d*]-1,3-dioxol-4-ol.* To a soln. of **25** (55.8 mg, 0.16 mmol) in CH_2Cl_2 (3.1 ml) was added 1M DIBAL-H in hexane (0.59 ml, 0.59 mmol) at $-78°$. The mixture was stirred at $-78°$ for 15 min before MeOH (1.5 ml) and sat. *Roschelle*'s salt soln. (20 ml) as well as AcOEt (30 ml) were added sequentially. After the two layers became clear, the aq. layer was extracted with AcOEt (3 × 10 ml), the combined org. layer washed with brine (2 ml × 2), dried, and evaporated, and the crude product purified by CC (silica gel, hexane/Et_2O 5 :1): (4*R*)-alcohol (47 mg, quant.). Colorless oil. $[\alpha]_D^{20} = -13.5$ ($c = 0.26$, $CHCl_3$). IR (film): 3385, 1659, 1462. ^{1}H-NMR (300 MHz, $CDCl_3$): 5.75 (*d*, $J < 1$, 1 H); 5.12 (*dd*, $J = 5.3$, < 1, 1 H); 4.73 (*d*, $J < 1$, 1 H); 4.55 (*d*, $J = 5.6$, 1 H); 4.32 (*d*, $J = 15.8$, 1 H); 4.27 (*d*, $J = 15.8$, 1 H); 1.34 (*s*, 3 H); 1.30 (*s*, 3 H); 0.91 (*s*, 9 H); 0.09 (*s*, 6 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 149.8; 126.5; 111.9; 86.7; 83.1; 79.9; 60.3; 27.3; 25.9; 25.8 (3C); 18.4; −5.4; −5.5.

*(3a*R*,6a*R*)-6-{[[(1,1-Dimethylethyl)dimethylsilyl]oxy}methyl]-3a,6a-dihydro-2,2-dimethyl-4*H*-cyclopenta[*d*]-1,3-dioxol-4-one* (**26**). Pyridinium dichromate (152 mg, 0.41 mmol) was added in several portions to a stirred suspension of the above (4*R*)-alcohol (49 mg, 0.16 mmol) and 4-Å molecular sieves (109 mg) in CH_2Cl_2 (10.8 ml). After an additional hour, Et_2O (20 ml) was added, and the mixture was stirred for 45 min prior to filtration through a pad of *Celite* and washing with Et_2O. The combined filtrate and washings were evaporated, and the residue was subjected to CC (silica gel, hexane/Et_2O 6 :1): **26** (42 mg, 89%). Colorless oil. $[\alpha]_D^{20} = -7.5$ ($c = 0.81$, $CHCl_3$). IR (film): 1726, 1630, 1443. ^{1}H-NMR (300 MHz, $CDCl_3$): 6.16 (*m*, 1 H); 5.05 (*d*, $J = 5.6$, 1 H); 4.66 (*dd*, $J = 1.9, 18.8$, 1 H); 4.51 (*d*, $J = 5.6$, 1 H); 4.47 (*dd*, $J = 1.2, 18.8$, 1 H); 1.40 (*s*, 6 H); 0.91 (*s*, 9 H); 0.10 (*s*, 6 H); ^{13}C-NMR (75 MHz, $CDCl_3$): 201.6; 177.2; 127.7; 115.4; 78.0; 77.6; 61.6; 27.4; 26.2; 25.7 (3 C); 18.2; −5.5 (2 C).

*(3aS,4S,6aR)-6-{[[(1,1-Dimethylethyl)dimethylsilyl]oxy}methyl]-3a,6a-dihydro-2,2-dimethyl-4*H-*cyclopenta[*d*]-1,3-dioxol-4-ol.* A soln. of **26** (42.1 mg, 0.14 mmol) in toluene (3.0 ml) was treated with 1.0M DIBAL-H in toluene (0.35 ml, 0.35 mmol) dropwise at $-78°$, stirred for 1.5 h, and quenched with MeOH (5 ml) and H_2O (5 ml). The aq. layer was extracted with $CHCl_3$ (3×3 ml), the combined org. extract washed with brine (5 ml), dried, and evaporated, and the residue purified by CC (silica gel, 0–10% Et_2O/CH_2Cl_2): (4*S*)-alcohol (38 mg, 90%). Colorless oil. $[\alpha]_D^{20} = +22.5$ ($c = 0.53$, $CHCl_3$). IR (film): 3504, 1513, 1472. ^{1}H-NMR (300 MHz, $CDCl_3$): 5.72 (*d*, *J* = 0.9, 1 H); 4.89 (*d*, *J* = 5.6, 1 H); 4.75 (*t*, *J* = 5.5, 1 H); 4.54 (*m*, 1 H); 4.34 (*dd*, *J* = 15.1, < 1, 1 H); 4.23 (*dd*, *J* = 15.1, < 1, 1 H); 2.68 (*d*, *J* = 10.0, 1 H); 1.41 (*s*, 3 H); 1.38 (*s*, 3 H); 0.91 (*s*, 9 H); 0.07 (*s*, 6 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 145.6; 129.2; 112.5; 82.7; 77.9; 73.2; 59.9; 27.6; 26.6; 25.9 (3 C); 18.3; −5.4; −5.5.

*9-{(3aS,4R,6aR)-6-{[[(1,1-Dimethylethyl)dimethylsilyl]oxy}methyl}-3a,6a-dihydro-2,2-dimethyl-4*H-*cyclopenta[*d*]-1,3-dioxol-4-yl}-9*H-*purin-6-amine* (**27**). A soln. of the above (4*S*)-alcohol (38 mg, 0.13 mmol), triphenylphosphine (140 mg, 0.53 mmol), and adenine (72 mg, 0.51 mmol) in THF (24 ml) was cooled at an ice-water bath, and diisopropyl diazocarboxylate (105 µl, 0.53 mmol) was slowly introduced. The mixture was allowed to warm to r.t., and stirring was continued overnight. The volatiles were evaporated, and the residue was subjected to CC (silica gel, hexane/AcOEt 1:2 containing 1% MeOH): **27** (48 mg, 90%). Thick oil. $[\alpha]_D^{20} = -30.0$ ($c = 0.33$, $CHCl_3$). IR (film): 3331, 1652, 1635. ^{1}H-NMR (300 MHz, $CDCl_3$): 8.38 (*s*, 1 H); 7.67 (*s*, 1 H); 5.90 (*s*, 2 H); 5.78 (*s*, 1 H); 5.59 (*s*, 1 H); 5.30 (*d*, *J* = 5.7, 1 H); 4.71 (*d*, *J* = 5.7, 1 H); 4.42 (*m*, 2 H); 1.48 (*s*, 3 H); 1.35 (*s*, 3 H); 0.92 (*s*, 9 H); 0.10 (*s*, 6 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 153.1; 152.6; 150.0; 138.5; 132.2; 128.6; 121.0; 112.7; 84.8; 83.6; 64.4; 60.4; 27.4; 25.9; 25.8 (3 C); 14.2; −5.4 (2 C).

*(−)-Neplanocin A (=(1S,2R,5R)-5-(6-Amino-9*H-*purin-9-yl)-3-(hydroxymethyl)cyclopent-3-ene-1,2-diol*; **2**). A soln. of **27** (48 mg, 0.12 mmol) in MeOH (5 ml) was treated with 1.0M HCl (5 ml) and stirred at r.t. for 3.5 h. The solvent was evaporated and the residue purified by ion exchange (*Dowex 50WX4-400*; H^+ form), aq. ammonia: **2** (29 mg, 95%). White solid. M.p. 217–219°. $[\alpha]_D^{20} = -155.5$ ($c = 0.20$, H_2O). IR (film): 3326, 3151, 1649, 1643. ^{1}H-NMR (300 MHz, (D_6)DMSO/D_2O): 8.10 (*s*, 1 H); 8.05 (*s*, 1 H); 5.68 (*d*, *J* = 1.3, 1 H); 5.33 (br. *s*, 1 H); 4.41 (*d*, *J* = 5.5, 1 H); 4.25 (*t*, *J* = 5.5, 1 H); 4.09 (*s*, 2 H). ^{13}C-NMR (300 MHz, (D_6)DMSO/D_2O): 56.1; 152.8; 150.2; 149.9; 140.2; 124.0; 119.2; 76.9; 72.5; 64.7; 58.8.

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