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Expedient conversion of D-glucose into 1,5-anhydro-D-fructose and into single stereogenic-center dihydropyranones, suitable six-carbon scaffolds for concise syntheses of the soft-coral constituents (−)-bissetone and (−)-palythazine☆

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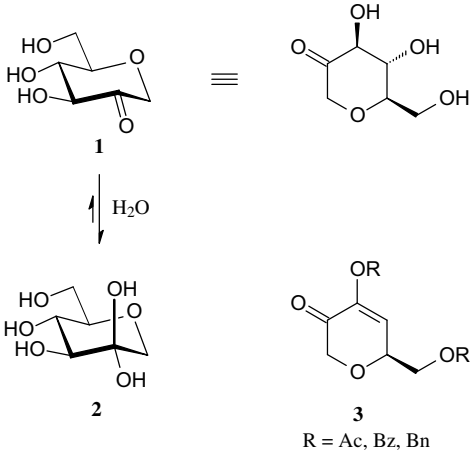
Dedicated to Professor Marek Chmielewski on the occasion of his 65th birthday

Abstract—High-yielding protocols are described to convert D-glucose—via hydroxylaminolysis of its hydroxyglucal esters, followed by deoximation and β-elimination of acid—into dihydropyranone building blocks with a single stereogenic center. Their versatility as enantiopure six-carbon scaffolds is highlighted by excellent regio- and stereocontrol in a variety of addition reactions and by their straightforward use as building blocks for the concise syntheses of the soft-coral constituents bissetone and palythazine in enantiopure form, thereby proving their absolute configuration. Moreover, several procedures are detailed to convert hydroxyglucal esters into 1,5-anhydro-D-fructose, their parent sugar, the direct low-temperature de-O-acylation being the most suitable for preparative purposes, as long as its access via enzymatic degradation of starch is not implemented on an appreciable scale.

1. Introduction

Before being encountered as a naturally occurring monosaccharide, first in fungi,[2] and then in a variety of organisms,[3] 1,5-anhydro-D-fructose **1** had been obtained by synthesis from D-glucose, requiring a sequence of six or seven steps with overall yields of 20% and 37%, respectively.[4] By the time[4,5] it was fully characterized by ^{1}H and ^{13}C NMR, the lack of a ^{13}C carbonyl resonance in D_2O and the distinct mutarotation in water indicated the presence of the hydrate form **2** in aqueous solution.[5]

Two other chemical approaches have been advanced since, comprising four steps from 1,5-anhydro-D-glucitol[6] and five from D-fructose,[7a] yet the overall yields of 27% and 36%, respectively, were not prone to improve the accessibility of **1**.[7b] Considerably more promising in this context was the discovery that 1,5-anhydro-D-fructose is generated from starch by α-1,4-glucan lyases in high yield,[8] a process



readily exploitable on a bulk scale if required. Unfortunately, the plethora of claims for applications of **1** as a powerful antioxidant,[9] an antimicrobial agent,[10] a food additive[10] or a pharmaceutical[11] obviously have not materialized since the sugar is not commercially available, not even as a research chemical. Thus, presently, the importance of 1,5-anhydro-D-fructose appears to reside in the

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highly versatile six-carbon building blocks[12] derivable from it, for example, enolones of type **3** featuring a single stereogenic center and two carbonyl functions of which one is blocked as an enol ester. The easily-crystallized dibenzoate **3** (R = Bz),[4] for example, has been used to synthesize the soft-coral constituents palythazine[14] and bissetone[15] in enantiopure form, thereby establishing their absolute configurations.

As a direct consequence of the preceeding reflections on the accessibility and utility of 1,5-anhydro-D-fructose, we herein report on the full experimental outcome and substantial improvements of our original preparative approach,[4,13,14] not only providing the hitherto most efficient chemical conversion of D-glucose into 1,5-anhydro-D-fructose, but also a convenient access to an array of six-carbon building blocks that are endowed with high stereoselectivities in ensuing reactions as to render them particularly suitable for the straightforward synthesis of a variety of non-carbohydrate natural products in enantiopure form.

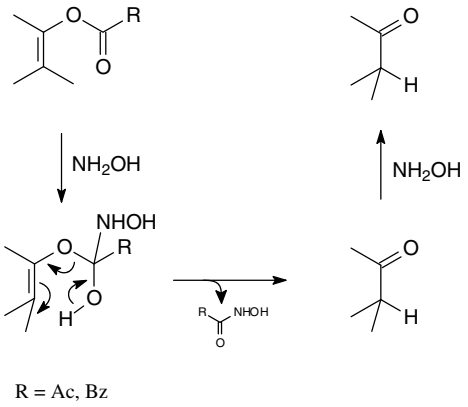
2. Results and discussion

2.1. (6*S*)-Dihydropyranone building blocks from hydroxyglucal esters

Esters of the enol form of 1,5-anhydro-D-fructose such as **4** or **5** (see Scheme 1) have been known for 80 years when they were first prepared by Maurer[15] by acetylation, respectively, benzoylation of D-glucose, subsequent anomeric bromination and base-induced elimination of HBr. This three-step sequence, upon incorporation of later improvements,[16] can be conducted on a 100 g scale in overall yields of 73% **4** and 77% **5**, (see Section 4). Acquisition of the benzylated analogue **6** requires five steps from D-glucose, performable in an overall yield of 50%.[17] Due to their ready accessibility, these hydroxyglucal esters have been used to generate a variety of six-carbon building blocks such as ulosyl bromides for the efficient generation of β-D-mannosidic linkages,[18] or dihydropyranones of the enol-lactone[19] and enolone type[20] with two stereogenic centers each, key intermediates in the syntheses of the heart poison steroid gomphoside[21] and the broad spectrum antibiotic spectinomycin.[22]

Pyranoid enolone esters with only one stereogenic center left—as compared to the five of the D-glucose starting material—are also readily accessible from hydroxyglucal esters, when exposing them to conditions that selectively cleave the enol ester function. A preparatively satisfactory means to effect this consists in the exposure of hydroxyglucal esters to hydroxylamine, which not only induces hydroxylaminolysis of the more reactive enol ester group to form the respective hydroxamic acid, but captures the keto group thus liberated in the form of its stable oxime (Scheme 1).[23]

This delightfully simple methodology is generally applicable to hydroxyglycal esters and in the case of the glucose-derived examples **4**–**6** provided ketoximes **9**–**11**, featuring such useful properties as a high tendency for crystallization, ease of isolation and stability. The yields, accordingly, are excellent (86–93%), such that the feasibility of this enol ester cleavage with semicarbazide to the semicarbazone (**4**→**7**, 83%) or with O-protected hydroxylamines (**4**→**8**, 81%) provides no preparative advantage (Scheme 2).



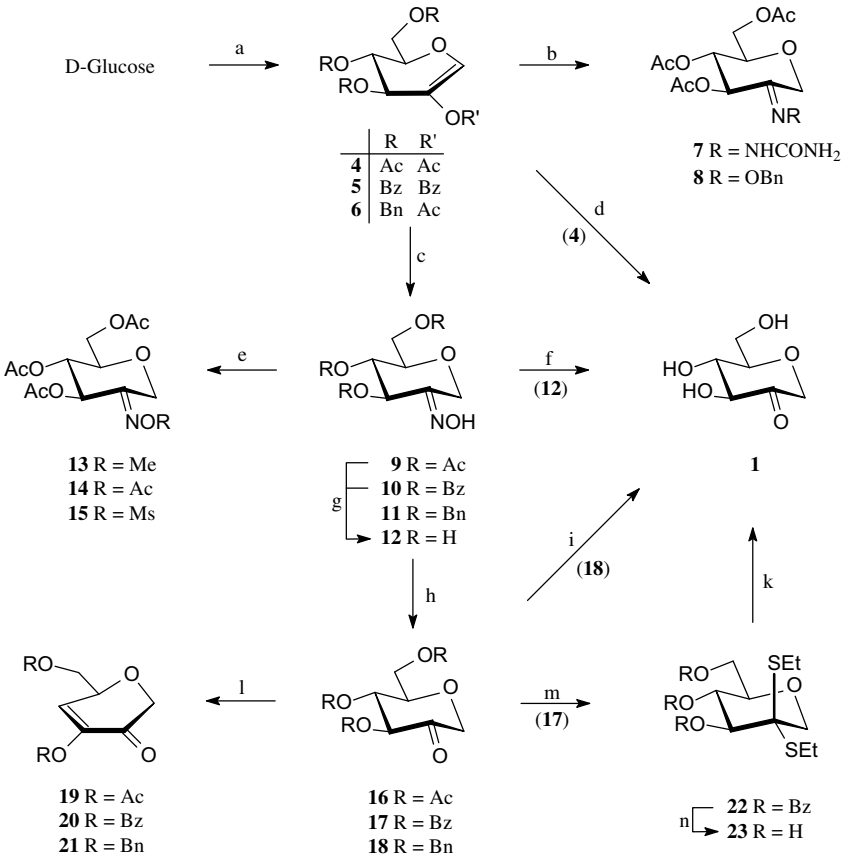
Scheme 1. Hydroxylaminolysis of enol esters.

These ketoximes can readily be derivatized as exemplified by the conversion of **9** into the *O*-methyl **13**, *O*-acetyl **14** and *O*-mesyl **15** compounds. Preparatively more important though is the fact that deoximation may be readily accomplished by any of the standard procedures, transoximation to acetaldehyde being the most convenient, providing the O-protected 1,5-anhydro-D-fructoses **16**–**18** in high yields (87–90%). Elimination of acetic or benzoic acid from **16** or **17**, respectively, can be as easily effected, by stirring with sodium acetate in acetone at ambient temperature providing the pyranoid enolone esters **19** and **20** in enantiopure form. Slightly more basic conditions are required to induce 3,4-elimination of benzyl alcohol in the tri-*O*-benzyl analogue **18**, yet exposure to K_2CO_3 in methanol for 2 d at 25 °C is sufficient to the di-*O*-benzyl enolone **21** (79%). Interestingly, the very same conditions are capable of generating dihydropyranone **21** more directly from the tri-*O*-benzyl-2-acetoxyglucal **6**, obviously through ulose **18** as the intermediate—the yield being an acceptable 75%.

The efficiency with which these six-carbon building blocks **19**–**21**, each featuring a single stereogenic center only, can be elaborated from D-glucose is noteworthy. In the case of the acylated compounds **19** and **20**, the six steps involved can be reduced to two hectogram-adaptable one-pot procedures comprising of the D-glucose → hydroxyglucal ester conversion (73% and 77%, respectively) and the one-pot sequence hydroxylaminolysis→deoximation→elimination (71% and 84%), the total yield over the six steps amounting to 52% and 65% respectively. The benzyl analog **21** requires seven steps altogether from D-glucose with an overall yield of 38%.

2.2. 1,5-Anhydro-D-fructose[24]

1,5-Anhydro-D-fructose **1**, the parent sugar underlying compounds **4**–**18** in Scheme 1, can, in principle, be liberated from any of them: directly from oxime **12** by deoximation with acetaldehyde/HCl (60%), from dithioketal **24** by

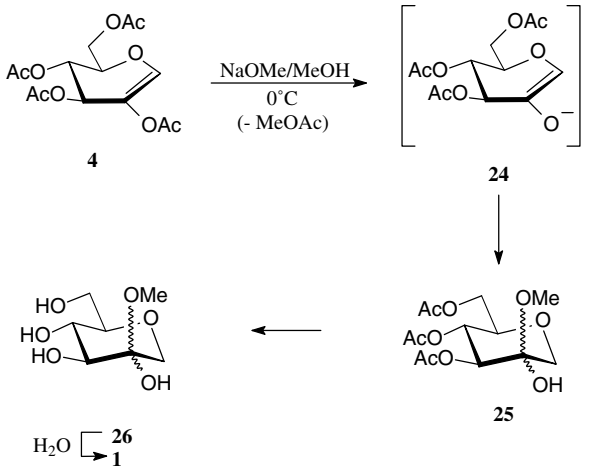


Scheme 2. Reactions and conditions: (a) **4**: $Ac_2O/HClO_4$, then P/Br_2[16a] and NaI/Et_2NH in acetone,[16e] 73%; **5**: BzCl/pyridine, then HBr/HOAc,[16b] followed by Et_2NH/NaI in acetone, 77%; **6**: $Ac_2O/HClO_4$, then P/Br_2,[16a] followed by EtOH/*s*-collidine, BnBr/KOH and reflux in C_6H_5Br,[17] 50% over five steps; (b) **7**: semicarbazide/pyridine in MeOH, 2 d, rt, 83%; **8**: $NH_2OBn{\cdot}HCl$/pyridine, 2 d, rt, 81%; (c) **9** and **11**: NH_2OH/HCl/pyridine, 16 h, rt, 86% and 91%; **10**: $NH_2OH{\cdot}HCl$/pyridine, 12 h, 70 °C, 93%; (d) **4**→**1**: NaOMe/MeOH, 10 min, 0 °C, 90%; (e) **13**: MeI/Ag_2O in Et_2O, 15 h, rt, 56%; **14**: Ac_2O/pyridine, 3 h, rt, 85%; **15**: $MeSO_2Cl$/pyridine, 15 h, rt, 93%; (f) acetaldehyde/HCl in MeCN, 5 h, rt, 60% (from **12**); (g) **12**: NaOMe/MeOH, 15 min, 1 h, 0 °C, 59% (from **9**), 64% (from **10**); (h) **16**: $TiCl_3/NH_4OAc$ in dioxane, 2 h, rt, 72%; **17** and **18**: acetaldehyde/HCl in MeCN, 5 h, rt, 90% and 87%; (i) 10% Pd, C/H_2 in EtOAc, 2 d, rt, 91%; (k) $CdCO_3/HgCl_2$ in water, 30 min, rt, 85%; (l) →**19** and **20**: NaOAc in acetone, 30 min, rt, 89% and 92%; →**21**: K_2CO_3/MeOH, 2 h, rt, 79%; (m) $EtSH/BF_3$ in $CHCl_3$, 45 min, rt, 85%; (n) NaOMe/MeOH, 6 h, 0 °C, 87%.

desulfurization with $HgCl_2/CdCO_3$ (85%), from the tri-*O*-benzyl derivative **18** by hydrogenolysis (91%) or, preparatively most straightforward, by Zemplén de-O-acetylation (NaOMe/MeOH) of hydroxyglucal tetraacetate **4** at low-temperature (90%). In each case, an amorphous product is obtained with analytical data valid for 1,5-anhydro-D-fructose **1**, yet on the basis of its complex ^1H and ^{13}C NMR spectra in DMSO-d_6 it proved to be the previously observed[3–5] mixture of several dimeric forms and its monohydrate. Only after equilibration in water, which can be followed via its mutarotation from $[\alpha]_D^{20} = -19.6$ (4 min) to −9.0 (1 h) did NMR data in D_2O, most cogently the six distinct ^{13}C resonances[5] indicate the presence of a uniform product i.e. the monohydrate **2**.

In this context, it is interesting to note that brief exposure of glucal ester **4** to Zemplén conditions (NaOMe/MeOH, 0 °C) proceeds without appreciable formation of the side products, which would be expected as the enolic ester group is apt to be saponified first, the resulting tri-*O*-acyl-ulose intermediate **16** then undergoing β-elimination to the enolone ester **19** and consecutive products. Closer inspection though reveals the reason for the clean de-O-acylation: the tri-*O*-acetyl-ketose **16** is not the actual intermediate but the monomethanolate **25** generated through methanolysis of the enol ester function and the addition of methanol to the intermediate enolate **24**, that is, **4**→[**24**]→**25**. Further deacylation then generates the free hemiacetal **26** as evidenced by ^1H and ^{13}C NMR spectra, most notably by the absence of a carbonyl resonance in CD_3OD solution (see Scheme 3).

De-O-benzoylation of tetrabenzoate **5** with sodium methoxide in methanol is less suited for releasing the parent 1,5-anhydro-D-fructose. Being scarcely soluble in methanol, methoxide-induced methanolysis of **5** is negligible at 0 °C and at ambient temperature requires about 2 h for the disappearance of **5**. The syrupy product obtained on workup revealed, aside from **1** and methyl benzoate, a slower moving component (TLC) which on the basis of NMR data is considered to be an isomer of **1**, conceivably 1,5-anhydro-D-*ribo*-hexos-3-ulose. Its formation on exposure of **1** to a weak alkali (pH 8.5—somewhat equivalent to N NaOMe/MeOH) has been conjectured previously.[3]



Scheme 3. Methanolysis of hydroxyglucal ester **4**.

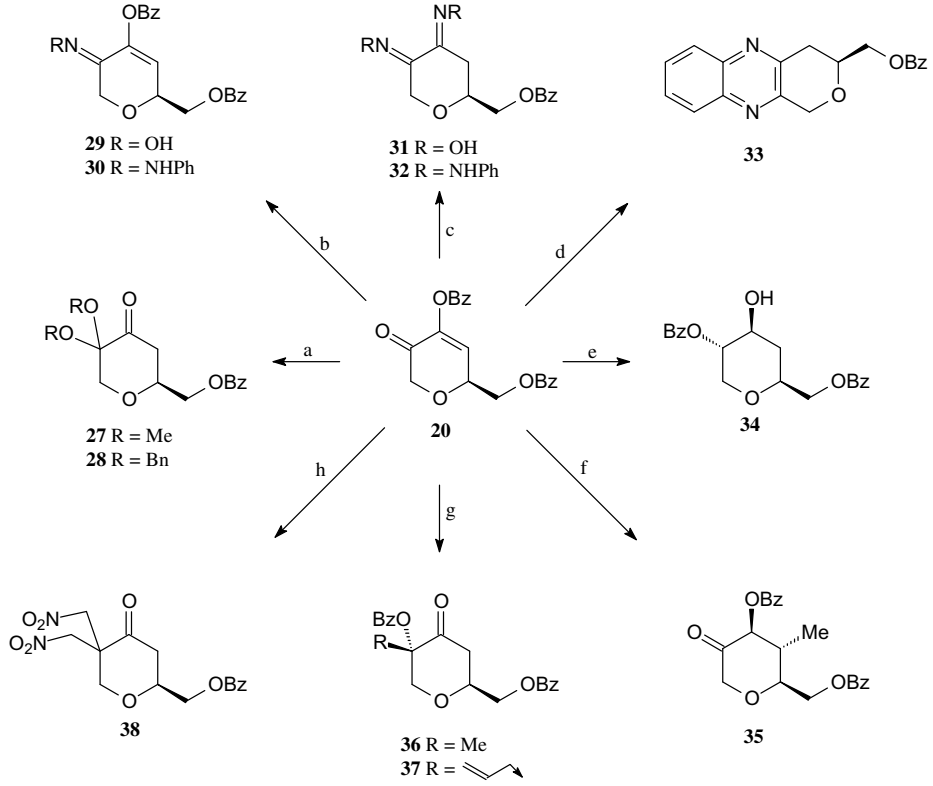
2.3. (6*S*)-Dihydropyranone 20: regio- and stereocontrol in addition reactions

Now being easily accessible, the utility of pyranoid enolone esters as enantiopure six-carbon building blocks had to be assessed with respect to the regio- and stereoselectivities attainable in addition reactions. As demonstrated with the di-*O*-benzoyl-enolone **20** (Scheme 4), a variety of synthetically useful additions are endowed with unusually high selectivities in view of the single stereogenic center present.

Brief exposure of **20** to NaOMe (5 min) or stirring with K_2CO_3 in dry methanol (20 min) not only cleaves the more reactive enol ester group but elaborates the dimethyl acetal **27** (81%), a reaction that can also be performed with alcohols less reactive than methanol, benzylalcohol, for example, providing **28** (91%), a beautifully crystalline, enantiopure diketone with one carbonyl group protected as an acetal and readily removable blocking groups.

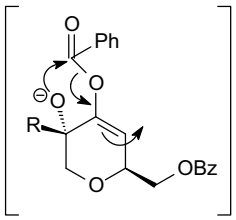
The extent with which the enolone ester function reacts with hydroxylamine or phenylhydrazine depends on the conditions used: stirring at ambient temperature in an $EtOH/CHCl_3$ solution only involves the free carbonyl group to give the mono-imino derivatives **29** and **30** in near quantitative yields, whilst heating (70 °C) or prior methanolysis of the enol ester group leads to dioxime **31** and osazone **32**, respectively. In a similar fashion, *o*-phenylenediamine smoothly gives the quinoxaline **33**.

Hydride addition to **20**, as effected with $Zn(BH_4)_2$ in ether at 0–25 °C, cleanly afforded the 1,5-anhydro-D-*xylo*-hexitol **34** (72%)—somewhat unexpectedly, as the primary addition of hydride at the carbonyl group is obviously followed by a 4-*O*→3-*O*-benzoyl group migration (arrows in intermediate **39**), thereby liberating the second carbonyl group



Scheme 4. Chemistry of (6*S*)-dihydropyranone **20**. Reagents and conditions: (a) **27**: NaOMe/MeOH, 5 min, rt, 81%; **28**: NaOBn/BnOH, 5 min, rt, 87%; (b) **29**: $NH_2OH{\cdot}HCl$/pyridine in $CHCl_3$/EtOH, 15 h, rt, 96%; **30**: $PhNHNH_2$/HOAc in EtOH, 3 min, rt, 91%; (c) **31**: $NH_2OH{\cdot}HCl$/pyridine, 3 h, 70 °C, 79%; **32**: NaOMe/MeOH, 1 min, rt, then $PhNHNH_2$/HOAc, 75%; (d) *o*-phenylenediamine/MeOH, 20 min, rt, 67%; (e) $Zn(BH_4)_2/Et_2O$, 2 h, 0→25 °C, 72%; (f) $Li_2Cu_3Me_5/Et_2O$, 30 min, −78 °C, 40%; (g) **36**: MeMgI/Et_2O, −78 °C, 15 min, 69%; **37**: $(i\text{PrO})_2TiCH_2CH{=}CH_2/CH_2Cl_2$, 15 min, −78 °C, 85%; (h) CH_3NO_2/K_2CO_3, 5 h, rt, 75%.

which then undergoes reduction. The stereoselectivities involved in the two hydride additions are remarkable.



39 R = H, Me, allyl

C-Nucleophiles similarly add with high regio- and stereocontrol: stirring enolone **20** in nitromethane in the presence of K_2CO_3, surprisingly, gives a double addition to the bis(nitromethylene)-substituted tetrahydropyranone **38**. With methyl lithium or Grignard reagents, the addition to the carbonyl group of the enolone system is the preferred reaction, exhibiting a 4:1 preference of nucleophilic attack from the upper (axial) side to yield the branched tetrahydropyranones **36** and **37**, their free 4-carbonyl groups being the result of a benzoyl group migration, as indicated by the arrows in **39**. Organocuprates, by contrast, react in the conjugate addition, yet the stereoselectivity with which lithium dimethyl cuprate elaborates the C-methyl-branched **35**, isolable in 40% yield, is not very high.

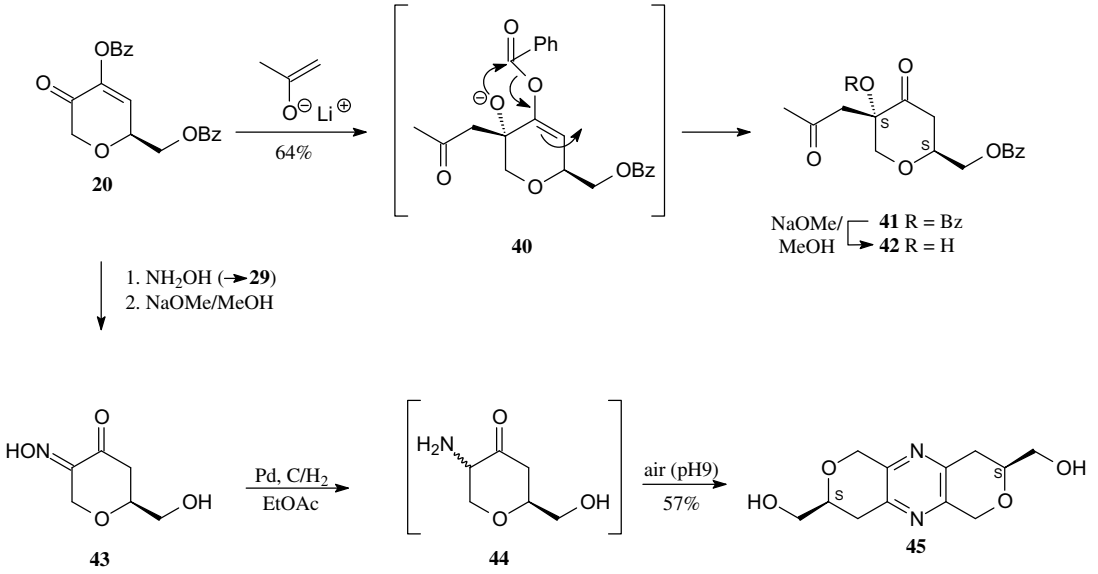
2.4. Synthesis of (*S*,*S*)-bissetone and (*S*,*S*)-palythazine

The versatility of the enantiopure six-carbon building block **20** could be further accentuated by its use for the straightforward syntheses of the marine natural products bissetone **42**, a metabolite from the Gorgonian soft coral *Briareum polyanthes*[25] and palythazine **45**, an unusual dipyranopyrazine isolated from the salt water invertebrate *Palythoa tuberculosa*.[26]

(*S*,*S*)-Bissetone **42** when traced back to building block **20**, only lacks the 3-carbon branch, that is, acetone. Indeed, the lithium enolate of acetone proved to be a suitable three-carbon synthon attacking the carbonyl function with a 4:1 preference from the proaxial side (**20**→**40**, Scheme 5). Thereby, the benzoyl group shift following the attack (arrows in **40**) directly elaborates the desired 2-oxopropyl-branched tetrahydropyranone **41**, isolable in 64% yield.

Proof for the (*S*)-configuration at the tertiary carbon was unambiguously established from the X-ray structural analysis of **41** (Fig. 1), which clearly showed the axial disposition of the acetonyl moiety. Being in fact the *O*-benzoyl derivative of bissetone, the parent compound **42** could simply be generated by de-O-benzoylation (92%) revealing IR, ^{1}H NMR and MS spectral data identical to those obtained[25] for the *B. polyanthes*-isolated product; its considerably lower $[\alpha]_D^{20}$ value (oil, −43.6, *c* 4.25, EtOH)[25] as compared with synthetic **42** (syrup, −69.4, *c* 1, EtOH) clearly indicates that the product isolated from the soft coral (73 mg from 31.3 g of water-soluble material via gel chromatography[25]) was not completely pure. Irrespective of the absolute value, the correspondence of the negative specific rotations of the synthetic and natural **42** unequivocally established the absolute configuration to be (2*S*,5*S*).

Elaboration of (*S*,*S*)-palythazine **45** from the key building block **20** was similarly effected in a high-yielding reaction sequence (Scheme 5): conversion into oxime **29**, liberation of the carbonyl function by debenzoylation (→**43**), and controlled catalytic hydrogenation to the aminoketone **44**, which dimerizes at pH 9; the concluding step is an air oxidation of the dihydropyrazine initially formed. Comparison of synthetic (*S*,*S*)-**45** with the *P. tuberculosa*-derived product[26] has mainly been confined to the melting points, since rotational data were not disclosed. Surprisingly, the melting point of synthetic **45** (223–225 °C) closely corresponds to that reported for the natural isopalythazine **46** (216–219 °C[26]), and differs markedly from that given for



Scheme 5. (6*S*)-Dihydropyranone **20** as the key building block for the elaboration of (*S*,*S*)-bissetone **42** and (*S*,*S*)-palythazine **45**.

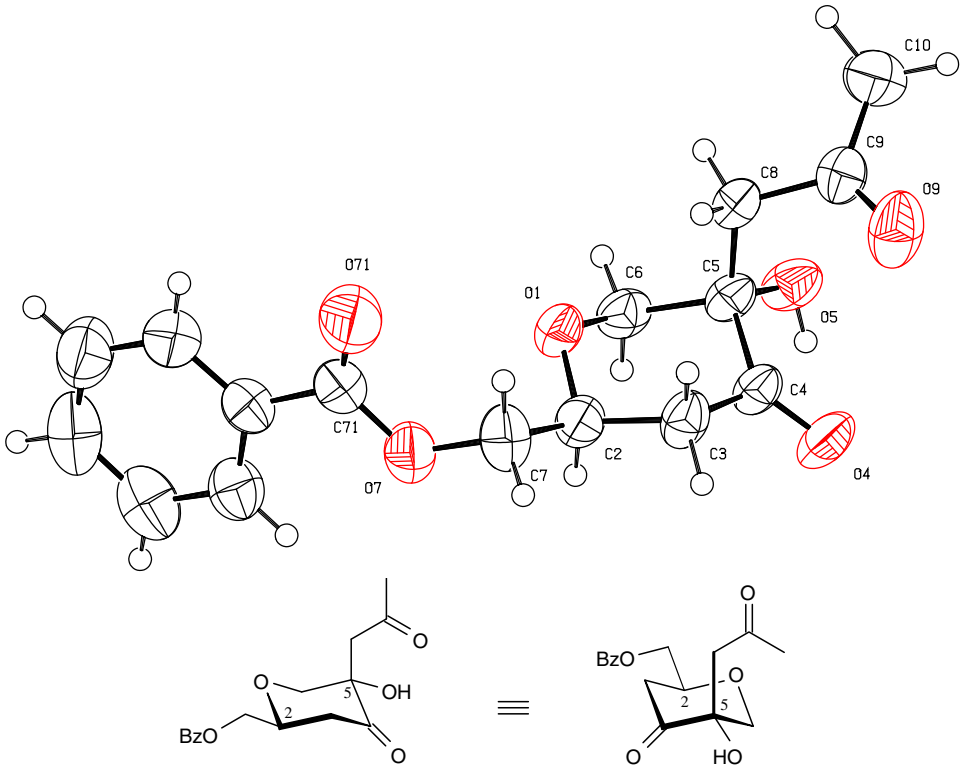
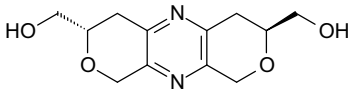


Figure 1. X-ray structure of (*S*,*S*)-7-*O*-benzoyl-bissetone **41**, providing unequivocal evidence for the axial arrangement of the oxopropyl branch. Relevant dihedral angles (°): O1–C2–C7–O7 +67.3, O1 C6–C5–O5 −178.1, O1–C6–C5–C8 +64.3, C3–C4–C5–O5 −169.4, C3–C4–C5–C8 +69.1, C3–C2–O1–C6 +62.8.

palythazine **45** (169–170 °C[26]). This indicates that the structures of the *Palythoa* pyrazines have been incorrectly assigned, that is, the high melting isomer has the structure of palythazine **45** while the low melting isomer has the structure of **46**. Support for this interpretation is derived from the fact that the ^{13}C NMR data reported for **45** and **46**[26] are so similar as to preclude unambiguous differentiation.



isopalythazine (**46**)

As bissetone **42** and palythazine **45** possess (*S*,*S*)-configuration on the basis of their synthesis from D-glucose, it is likely that the biosynthesis of both compounds proceeds from D-glucose via oxidation and elimination of water, together with transamination and C-branching, most likely through a biosynthetic equivalent of the building block **20**. If so, the highly efficient syntheses of **42** and **45** from D-glucose (yields of 38% over eight and 36% over nine steps, respectively) follow, to a significant degree, their biogeneses.

3. Conclusion

Four protocols have been described to convert hydroxyglucal esters, readily accessible from D-glucose in a three step one-pot operation, into 1,5-anhydro-D-fructose, the parent sugar. Of those, the preparatively most efficient method comprising direct low-temperature de-O-acylation of tetra-*O*-acetyl- or tetrabenzoyl-hydroxyglucal is deemed to be the method of choice for the acquisition of 1,5-anhydro-D-fructose, at least as long as its access by enzymatic degradation of starch is not implemented on an appreciable scale.

Another important facet of these hydroxyglucal esters is their straightforward convertibility into dihydropyranone building blocks with a single stereogenic center—by hydroxylaminolysis to acylated 1,5-anhydro-D-oximes, subsequent deoximation and base-induces β-elimination of acid. The versatility of these enantiopure six-carbon scaffolds, which provide excellent regio- and stereocontrol in addition reactions, is highlighted by their straightforward use as the key building blocks for the syntheses of the soft-coral constituents bissetone and palythazine in enantiopure form. This not only proved their absolute configuration but renders them available for biological investigation and allows for the synthesis of analogues.

4. Experimental

4.1. General

Melting points were determined with a Bock hot-stage microscope and are uncorrected. Optical rotations were measured on a Perkin–Elmer 241 polarimeter at 20 °C

using a cell of 1 dm path length; concentration (c) in g/100 mL and solvent are given in parentheses. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker ARX-300 spectrometer in $CDCl_3$. Mass spectra were acquired on Varian MAT 311 spectrometer. Microanalyses were determined on a Perkin–Elmer 240 elemental analyzer. Analytical thin layer chromatography (TLC) was performed on precoated Merck plastic sheets (0.2 mm Silica Gel 60 F_{254}) with detection by UV light (254 nm) and either spraying with H_2SO_4 (50%) or by dipping into sulfuric acid/anisaldehyde reagent [anisaldehyde (1 mL), concd H_2SO_4 (9 mL), HOAc (10 mL), and MeOH (85 mL)] followed by heating at 110 °C for 10 min. Column and flash chromatography were carried out on Fluka Silica Gel 60 (70–230 mesh) using the specified eluents.

4.2. 2,3,4,6-Tetra-*O*-acetyl-1,5-anhydro-D-*arabino*-hex-1-enitol 4[16a,d]

2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl bromide (124.0 g, 0.3 mol), prepared by $HClO_4$-promoted acetylation with Ac_2O and HBr/HOAc treatment according to the procedure of Lemieux[16a] (yield: 85%), was dissolved in anhydrous acetone (250 mL) containing NaI (45 g, 0.3 mol). After stirring for 15 min, diethylamine (66 g, 0.9 mol) was added in several portions and the mixture was stirred at ambient temperature for 1 h. The solution was diluted with CH_2Cl_2 (400 mL) followed by successive washings with water (2 × 250 mL), 2 M HCl (2 × 150 mL), aqueous $NaHCO_3$ (50 mL) and water. Drying over anhydrous Na_2SO_4 and removal of the solvent in vacuo gave a reddish-brown syrup, which crystallized on trituration with small amounts of EtOH. Recrystallization from EtOH afforded 76.3 g (77%) of **4**; a second crop (8.9 g) was secured by concentration and filtration of the mother liquor (total yield: 86%); mp 60–61 °C; $[\alpha]_D^{21} = -31.6$ (c 1, $CHCl_3$); lit.:[16c] mp 61–62 °C; $[\alpha]_D = -32$ (c 1, $CHCl_3$).

4.3. 2,3,4,6-Tetra-*O*-benzoyl-1,5-anhydro-D-*arabino*-hex-1-enitol 5[16b,e]

To a stirred and ice-cooled mixture of anhydrous α-D-glucose (90 g, 0.5 mol) in 250 mL (245 g, 3.1 mol) of pyridine and 400 mL of chloroform, benzoyl chloride (440 g, 3.1 mol) was added dropwise. The ice-bath was removed and the clear solution was heated to 60–70 °C for 1 h with continued stirring. Upon reaching room temperature, the mixture was diluted with chloroform (250 mL) and washed successively with water (250 mL), 2 N HCl (250 mL), saturated aqueous $NaHCO_3$ solution (2 × 250 mL), and finally water (250 mL). The organic layer was dried over Na_2SO_4, and the solvent was evaporated in vacuo below 30 °C to give a yellow syrup, which crystallized on brief refluxing with methanol (1.5 L): 332 g (95%) of D-glucose pentabenzoate as a mixture of anomers; mp 187 °C.

The product was dissolved in CH_2Cl_2 (500 mL) followed by the dropwise addition of 200 mL of 33% HBr in glacial acetic acid and stirring for 2 h at ambient temperature. The reaction mixture was then diluted with CH_2Cl_2 (250 mL), washed with ice-water (3 × 100 mL), cold saturated aqueous $NaHCO_3$ solution (2 × 250 mL), and water (3 × 100 mL). The organic layer was dried over Na_2SO_4 and the solvent evaporated in vacuo: 247 g (~90%) of crude tetra-*O*-benzoyl-α-D-glucopyranosyl bromide as a yellow-brown syrup.

The crude bromide was added to a solution of 55 g (0.37 mol) sodium iodide in 400 mL of anhydrous acetone. After stirring for 30 min, diethylamine (130 g, 1.8 mol) was added, the mixture was stirred for another 2 h at ambient temperature, and subsequently diluted with chloroform (250 mL). Washing with water (250 mL), 2 M HCl (until the solution was slightly acidic), and water (→pH 5–6), followed by drying over Na_2SO_4 and evaporation to dryness in vacuo yielded a syrup, which crystallized from methanol: 195 g of **1** (90% based on the bromide, 77% over the three steps from D-glucose); mp 121–122 °C, $[\alpha]_D^{20} = -80$ (c 1, $CHCl_3$); lit.:[15c] mp 123 °C, $[\alpha]_D = -77$ (c 2, $CHCl_3$).

4.4. 3,4,6-Tri-*O*-acetyl-1,5-anhydro-D-fructose semicarbazone 7

To a mixture of semicarbazide hydrochloride (190 mg, 2 mmol), pyridine (1 mL) and MeOH (6 mL) was added acetoxyglucal triacetate **4** (330 mg, 1 mmol), followed by stirring for 2 days at ambient temperature. Removal of the solvents in vacuo and co-distillation with toluene left a residue which was dissolved in $CHCl_3$. Washing with water (2×) and evaporation to dryness in vacuo left a residue, which crystallized on trituration with ether: 290 mg (83%) of **7**; mp 109–110 °C; $[\alpha]_D^{21} = -72.5$ (c 0.2, $CHCl_3$). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.02, 2.04, and 2.09 (three 3H-s, $3AcH_3$), 4.05 and 4.83 (two 1H-d, $J_{1,1} = 15.1$ Hz, 1-H_2), 4.12 (3H-m, 5-H, 6-H_2), 5.00 (1H-t, $J_{3,4} = J_{4,5} = 8.1$ Hz), 5.54 (1H-d, $J_{3,4} = 8.1$ Hz, 3-H). Anal. Calcd for $C_{13}H_{19}N_3O_8$ (345.31): C, 45.21; H, 5.55; N, 12.17. Found: C, 45.11; H, 5.47; N, 12.11.

4.5. 3,4,6-Tri-*O*-acetyl-1,5-anhydro-D-fructose *O*-benzyloxime 8

A solution of 3.3 g (10 mmol) of **4** and *O*-benzyl-hydroxylammonium hydrochloride (4.7 g, 20 mmol) in 20 mL of pyridine was stirred at ambient temperature for 2 days followed by dilution with chloroform. Subsequent washing with water, diluted sulfuric acid, saturated aqueous $NaHCO_3$ solution, and again water gave, upon drying over Na_2SO_4 and evaporation to dryness in vacuo, 3.2 g (81%) of a chromatographically homogeneous syrup ($R_f = 0.75$ in 5:1 CH_2Cl_2/EtOAc), which crystallized from ether: prisms of mp 48 °C, $[\alpha]_D^{21} = -39$ (c 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.10, 2.08 and 2.05 (3s, 1H each, $3AcCH_3$), 3.75 (m, 1H, H-5), 4.00 and 4.98 (two 1H-d, 1-H_2), 4.20 (d, 2H, 6-H_2), 5.07 (2H-s, $PhCH_2$), 5.08 (t, 1H, H-4), 5.48 (d, 1H, H-3), 7.33 (5H-m, C_6H_5); $J_{1,1} = 15.0$, $J_{3,4} = J_{4,5} = 7.1$, $J_{5,6} = 4.0$ Hz. Anal. Calcd for $C_{19}H_{23}NO_8$ (393.38): C, 58.01; H, 5.89; N, 3.56. Found: C, 58.10; H, 5.95; N, 3.51.

4.6. 3,4,6-Tri-*O*-acetyl-1,5-anhydro-D-fructose *E*-oxime 9

To a solution of hydroxylamine hydrochloride (6.6 g, 95 mmol) in pyridine (50 mL) was added 10.0 g (30 mmol)

of **4** and the mixture was stirred at ambient temperature for 16 h, followed by pouring into water (200 mL) and extraction with chloroform (5 × 200 mL). Washing of the combined extracts with water, drying over Na_2SO_4 and evaporation in vacuo left a syrup that crystallized on trituration with ethanol: 7.9 g (86%) of **9**; mp 89–90 °C; $[\alpha]_D^{21} = -39.0$ (*c* 0.4, $CHCl_3$). The analytical sample was purified by elution from a silica gel column (15 × 1 cm for 1 g) with CH_2Cl_2/EtOAc (10:1) to give well-shaped needles; mp 90–91 °C; $[\alpha]_D^{20} = -42.8$ (*c* 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.99, 2.02 and 2.03 (3s, 3H each, 3AcCH_3), 3.88 (ddd, 1H, 5-H), 4.05 and 4.12 (2dd, 1H each, 6-H_2), 4.04 and 4.88 (2d, 1H each, 1-H_2), 4.94 (dd, 1H, 4-H), 5.54 (d, 1H, 3-H), 11.48 (s, 1H, N–OH); $J_{1,1} = 15.0$, $J_{3,4} = 8.0$, $J_{4,5} = 8.9$, $J_{5,6} = 3.0$ and 5.5, $J_{6,6} = 12.0$ Hz. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 170.8, 169.9, 169.4 (3Ac-*C*O), 150.6 (C-2), 76.3 (C-5), 70.5 and 69.7 (C-3, C-4), 62.9 (C-1), 61.9 (C-6), 20.7–20.5 (Ac-*C*H_3). Anal. Calcd for $C_{12}H_{17}NO_8$ (303.26): C, 47.52; H, 5.65; N, 4.62. Found: C, 47.58; H, 5.58; N, 4.58.

4.7. 3,4,6-Tri-*O*-benzoyl-1,5-anhydro-D-fructose *E*-oxime 10

Hydroxylamine hydrochloride (8.3 g, 0.12 mol) was stirred into a solution of 17.5 g (40 mmol) of **5** in dry pyridine (25 mL) and kept at 70 °C (water bath) for 12 h (TLC on silica gel with 10:1 dichloromethane/EtOAc for monitoring). After cooling down, the mixture was diluted with water (100 mL), and the precipitate was filtered off and washed with water. The filtrate and washings were extracted with chloroform (3 × 30 mL) and the combined extracts were washed with water and then taken to dryness to yield the second crop. Recrystallization from ethanol gave 13.6 g (93%) of **10** as colorless needles, mp 176–177 °C, $[\alpha]_D^{22} = -52.9$ (*c* 0.5, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.08 (sept, 1H, H-5), 4.22 (dd, 1H, $J_{1,1} = 15.8$ Hz, 1-Ha), 4.55 and 4.68 (2dd, 1H each, $J_{5,6} = 3.1$ and 5.7, $J_{6,6} = 12.1$ Hz, 6-H_2), 5.17 (d, 1H, $J_{1,1} = 15.8$ Hz, 4-H), 5.72 (dd, 1H, $J_{3,4} = 7.2$, $J_{4,5} = 8.1$ Hz, 4-H), 6.02 (d, $J_{3,4} = 7.2$ Hz, 1H, 3-H), 7.40, 7.55 and 8.03 (6H-, 3H- and 6H-m, 3C_6H_5), 8.55 (1H-s, NOH). ^{13}C NMR (125.76 MHz, $CDCl_3$): 62.5 (C-1), 64.0 (C-6), 70.9 and 71.7 (C-3, C-4), 76.9 (C-5), 128.7–134.0 (3C_6H_5), 151.3 (C-2), 165.5, 165.8 and 166.7 (3Bz*C*O). Anal. Calcd for $C_{27}H_{23}NO_8$ (489.46): C, 66.25; H, 4.74; N, 2.86. Found: C, 66.19; H, 4.74; N, 2.82.

Oxime **10** was similarly obtained by adding $NH_2OH{\cdot}HCl$ (5.0 g) to a pyridine solution of **5** (5.0 g in 25 mL) stirring for 7 days at ambient temperature and processing as described above. Recrystallization from MeOH/CH_2Cl_2 provided 4.9 g (87%).

4.8. 3,4,6-Tri-*O*-benzyl-1,5-anhydro-D-fructose *E*-oxime 11

Hydroxylamine hydrochloride (1.4 g, 20 mmol) and molecular sieves (4 Å) were added to a solution of 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-D-*arabino*-hex-1-enitol **6**[17] (2.0 g, 4.2 mmol) in dry pyridine (13 mL) and the mixture was stirred at ambient temperature for 2 days, followed by stirring into water (20 mL) and extraction with CH_2Cl_2 (3 × 40 mL). The combined extracts were washed with 2 M HCl (2 × 40 mL) and water, dried over Na_2SO_4, and taken to dryness. The resulting syrup, crystallized on trituration from EtOH: 1.70 g (91%) of oxime **11** as colorless needles; mp 64–65 °C; $[\alpha]_D^{20} = -29.0$ (*c* 1.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.53 (ddd, 1H, 5-H), 3.60 (m, 2H, 6-H_2), 3.79 (dd, 1H, 4-H), 4.15 (d, 1H, 3-H), 4.31 (d, 1H, 1-Ha), 4.33, 4.49, 4.55 and 4.76 (4d, 1H each, 2 BnCH_2), 4.54 (s, 2H, BnCH_2), 4.85 (d, 1H, 1-He), 7.1–7.4 (15H-m, 3C_6H_5), 9.24 (s, 1H, NO*H*); $J_{1,1} = 16.4$, $J_{3,4} = 8.3$, $J_{4,5} = 7.2$, $J_{5,6e} = 3.9$ Hz. ^{13}C NMR (75.5 MHz, $CDCl_3$,): δ 62.8 (C-1), 70.1 (C-6), 71.4, 72.4 and 73.4 (3Bn*C*H_2), 76.4 (C-3), 78.0 (C-4), 78.6 (C-5), 154.6 (C-2), MS (FD): *m*/*z* = 448 (M^++H). Anal. Calcd for $C_{27}H_{29}NO_5$ (447.52): C, 72.48; H, 6.48; N, 3.13. Found: C, 72.54; H, 6.43; N, 3.19.

4.9. 1,5-Anhydro-D-fructose *E*-oxime 12

4.9.1. De-O-acetylation of 9. A stirred methanolic solution of sodium methoxide (prepared from 80 mg sodium and 30 mL of methanol) was cooled to 0 °C and oxime **9** (800 mg, 2.6 mmol) was added. TLC showed complete conversion of the educt within 15 min with the exclusive formation of **12** ($R_f = 0.4$ in 200:50:15:1 benzene/EtOH/water/25% aq NH_3). Cation exchange resin was then added to the mixture and after stirring for 10 min the suspension was filtered and the resin was washed with methanol. Filtrate and washings were evaporated to a syrup which crystallized from methanol: 260 mg (56%) of **10**, mp 178–180 °C; $[\alpha]_D^{21} = -43.0$ (*c* 0.3, water); ^{1}H NMR (300 MHz, D_2O): δ 3.44 (ddd, 1H, 5-H), 3.51 (dd, 1H, 4-H), 3.64 and 3.83 (2dd, 1H each, 6-H_2), 3.89 and 5.03 (2d, 1H each, 1-H_2), 4.25 (d, 1H, 3-H), 10.86 (s, 1H, NO*H*); $J_{1,1} = 14.5$, $J_{3,4} = 9.0$, $J_{4,5} = 8.0$, $J_{6,6} = 12.6$ Hz. ^{13}C NMR (75.5 MHz, D_2O): δ 61.5 (C-1), 61.8 (C-6), 72.6 and 73.3 (C-3/C-4), 80.9 (C-5), 156.1 (C-2). Anal. Calcd for $C_6H_{11}NO_5$ (177.16): C, 40.68; H, 6.26; N, 7.91. Found: C, 40.63; H, 6.29; N, 7.85.

The ^{1}H and ^{13}C NMR data for **10** correlated well with those reported for the oximation product of naturally occurring 1,5-anhydrofructose,[27] as did rotations of $[\alpha]_D^{23} = -43$ (*c* 2, water)[4] and $[\alpha]_D = -46.2$ (*c* 1.2, water)[2,27] and to a somewhat lesser degree, the melting points (155–157 °C[2] and 179–181 °C[27]).

4.9.2. De-O-benzoylation of 10. Exposure of **10** (2.95 g, 6 mmol) to 0.1 M methanolic sodium methoxide (90 mL) for 1 h at 0–5 °C and processing of the mixture as described under (a) gave 678 mg (64%) of **12**.

4.10. 3,4,6-Tri-*O*-acetyl-1,5-anhydro-D-fructose *O*-methyloxime 13

Oxime **9** (250 mg, 0.8 mmol) was added to a stirred suspension of methyl iodide (0.25 mL, 4 mmol) and Ag_2O (580 mg) in ether (8 mL) and stirring was continued for 15 h. Filtration, washing of the residue with acetone and evaporation of the filtrate and washings to dryness in vacuo left a syrup which was purified by elution from a short silica gel column with 10:1 benzene/EtOAc: 146 mg (56%) of **13** as a colorless syrup; $R_f = 0.40$ (10:1 benzene/

EtOAc); $[\alpha]_D^{21} = -29$ (*c* 1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 2.09 and 2.12 (2s, 6H and 3H, 3AcCH_3), 3.70 (m, 1H, 5-H), 3.91 (s, 3H, NOCH_3), 4.08 and 4.98 (two 1H-d, $J_{1,1} = 15.0$ Hz, 1-H_2), 4.24 (2H-m, 6-H_2), 5.13 (1H-t, $J_{3,4} = J_{4,5} = 7.0$ Hz, 4-H), 5.54 (1H-d, 3-H). Anal. Calcd for $C_{13}H_{19}NO_8$ (317.3): C, 49.21; H, 6.04; N, 4.41. Found: C, 49.22; H, 5.96; N, 4.28.

4.11. 3,4,6-Tri-*O*-acetyl-1,5-anhydro-D-fructose *O*-acetyloxime 14

A solution of oxime **9** (300 mg, 1 mmol) in a mixture of pyridine (6 mL) and acetic anhydride (4 mL) was kept at ambient temperature for 3 h, then diluted with CH_2Cl_2 (50 mL) and stirred into ice-water. The organic phase was separated and successively washed with water, 1 M H_2SO_4 solution and, again, water. Drying over Na_2SO_4 and evaporation to dryness gave a residue which crystallized on trituration with ether: 290 mg (85%) of **14**; mp 69 °C; $[\alpha]_D^{21} = -49$ (*c* 0.3, $CHCl_3$). ^1H NMR (100 MHz, $CDCl_3$): δ 2.00, 2.10 and 2.16 (3s, 3H, 6H and 3H, 4Ac CH_3), 4.00 (3H-m, 5-H and 6-H_2), 4.18 and 4.88 (two 1H-d, $J_{1,1} = 14.3$ Hz, 1-H_2), 5.04 (1H-t, $J_{3,4} = J_{4,5} = 7.9$ Hz, 4-H), 5.72 (1H-d, 3-H). Anal. Calcd for $C_{14}H_{19}NO_9$ (345.3): C, 48.69; H, 5.55; N, 4.06. Found: C, 48.65; H, 5.52; N, 3.98.

4.12. 3,4,6-Tri-*O*-acetyl-1,5-anhydro-D-fructose *O*-methanesulfonyloxime 15

Oxime **9** (606 mg, 2 mmol) was added to a mixture of methanesulfonyl chloride (0.5 mL) in pyridine (5 mL) followed by stirring overnight (~15 h). Dilution with $CHCl_3$ (50 mL), stirring into ice-water and processing of the organic phase as described for the acetylation **9**→**13** (cf. above) gave a residue, which crystallized from EtOH: 710 mg (93%); mp 95–96 °C; $[\alpha]_D^{22} = -56.6$ (*c* 0.3, $CHCl_3$). The ^1H NMR (100 MHz, $CDCl_3$) proved to be identical to that of **13** except for the mesyl-CH_3 resonance at 3.09 instead of the Ac-CH_3 at 2.16. Anal. Calcd for $C_{13}H_{19}NO_{10}S$ (381.7): C, 40.90; H, 5.11; N, 3.67. Found: C, 40.98; H, 4.93; N, 3.80.

4.13. 3,4,6-Tri-*O*-acetyl-1,5-anhydro-D-fructose 16

4.13.1. By deoximation of 9 with acetaldehyde.[28] Stirring of **9** in acetonitrile solution (3.00 g, 10 mmol, in 40 mL) with acetaldehyde (2.0 mL) and 1 M HCl (12 mL) for 6 h at ambient temperature followed by dilution with water (250 mL), extraction with EtOAc (3 × 100 mL) and removal of the solvent from the organic layer gave a syrup ($R_f = 0.15$ in 5:1 CH_2Cl_2/EtOAc), which crystallized from ether: 2.55 g (89%); prisms of mp 89–90 °C; $[\alpha]_D^{21} = -10$ (*c* 0.5, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 2.05, 2.09, and 2.13 (three 3H-s, 3Ac-CH_3), 3.98 (ddd, 1H, 5-H), 4.09 (d, 1H, 1-Heq), 4.24 (dd, 1H, 6-Ha), 4.25 (d, 1H, 1-Heq), 4.30 (dd, 1H, 6-Hb), 5.33 (dd, 1H, 4-H), 5.41 (d, 1H, 3-H); $J_{1,2} = 15.4$, $J_{3,4} = 9.9$, $J_{4,5} = 9.0$, $J_{5,6} = 2.5$ and 5.0, $J_{6,6} = 12.4$ Hz. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 20.4, 20.7 (3Ac*C*H$_3$), 62.0 (C-6), 69.2 (C-4), 72.5 (C-1), 76.1 (C-5), 76.9 (C-3), 169.2, 169.4, 170.3 (3Ac*C*O), 196.9 (C-2). Anal. Calcd for $C_{12}H_{16}O_8$ (288.25): C, 50.00; H, 5.60. Found: C, 49.98; H, 5.56.

4.13.2. By deoximation of 9 with $TiCl_3$. To a stirred solution of **9** (4.60 g, 15.2 mmol) in dioxane (100 mL) was added ammonium acetate (12.0 g) followed by the dropwise addition of a 15% aqueous solution of $TiCl_3$ (40 mL) under a nitrogen atmosphere. The mixture was then stirred for 2 h, whereafter TLC indicated the absence of educt. Extraction with dichloromethane (3 × 50 mL) and washing of the combined extracts with water, aqueous $NaHCO_3$ and water, followed by drying over Na_2SO_4, evaporation to dryness and trituration of the residue with ether afforded 3.15 g (72%) of **16** identical in all respects with the product described under (a).

4.14. 3,4,6-Tri-*O*-benzoyl-1,5-anhydro-D-fructose 17

To a suspension of 4.9 g (10 mmol) of oxime **10** in acetonitrile (50 mL) was added 1 M HCl (20 mL) and 2.5 mL (45 mmol) of acetaldehyde, and the mixture was stirred at ambient temperature for 5 h. The resulting clear solution was diluted with water (150 mL) and extracted with ethyl acetate (3 × 100 mL) followed by washing of the combined extracts with water, drying (Na_2SO_4) and evaporation to dryness. The syrup crystallized on trituration with CH_2Cl_2/*n*-hexane to yield 4.3 g (90%) of **17**, mp 126–127 °C; $[\alpha]_D^{20} = -29.2$ (*c* 0.8, $CHCl_3$). ^1H NMR (300 MHz, DMSO-d_6): δ 4.33 and 4.59 (two 1H-d, 1-H_2), 4.63 (m, 2H, 6-H_2), 4.72 (m, 1H, 5-H), 5.87 (dd, 1H, 4-H), 6.19 (d, 1H, 3-H), 7.4–8.1 (15H-m, 3C_6H_5); $J_{1,1} = 15.0$, $J_{3,4} = J_{4,5} = 9.8$ Hz. ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 62.8 (C-6), 70.3 (C-4), 72.5 (C-1), 75.0 (C-5), 77.5 (C-3), 128.5–129.5 and 133.4 (3C_6H_5), 164.6, 164.7 and 165.4 (3CO_6H_5), 197.9 (C-2). Anal. Calcd for $C_{27}H_{22}O_8$ (474.45): C, 68.35; H 4.67. Found: C, 68.26; H, 4.62.

4.15. 3,4,6-Tri-*O*-benzyl-1,5-anhydro-D-fructopyranose 18

4.15.1. Deoximation of oxime 11. Acetaldehyde (1 mL) and 2 M HCl (1.7 mL) were added to a solution of oxime **11** (1.2 g, 2.7 mmol) in acetonitrile (25 mL) and the mixture was stirred at ambient temperature for 5 h. Addition of water (100 mL), extraction with CH_2Cl_2 (4 × 40 mL), washing of the organic extracts with water (2 × 50 mL), drying over Na_2SO_4 and removal of the solvent in vacuo gave a partially crystalline residue, which was recrystallized from isopropyl ether: 1.02 g (87%) of **18**; mp 85 °C; $[\alpha]_D^{20} = -16.1$ (*c* 1.1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 3.60 (m, 3H, 5-H, 6-H_2), 3.87 (dd, 1H, 4-H, 3.95 and 4.15 (2d, 1H each, 1-H_2), 41.7 (d, 1H, 3-H), 4.50, 4.52, 4.56, 4.62, 4.82, 5.01 (6d, 1H each, 3PhCH_2), 7.14–7.41 (15H-m, 3C_6H_5); $J_{1,1} = 15.1$, $J_{3,4} = 8.8$, $J_{4,5} = 8.9$, $J_{5,6a} = 5.2$ Hz. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 69.0 (C-6), 73.1 (C-1), 73.6, 74.0 and 74.8 (3Ph*C*H$_2$), 79.0 (C-5), 79.3 (C-4), 86.0 (C-3), 203.1 (C-2). MS (FD): $m/z = 432$ [M^+], 341 [M−PhCH$_2$). Anal. Calcd for $C_{27}H_{28}O_5$ (432.51): C, 74.97; H, 6.52. Found: C, 74.91; H, 6.44.

4.15.2. De-O-acetylation of 2-acetoxy-glucal 6. A 1 M methanolic sodium methoxide solution (2.5 mL) was added

dropwise to a cooled (−40 °C) solution of **6** (1.20 g, 2.5 mmol) in 40 mL of methanol, and the mixture was stirred at −40 °C for 1.5 h. Subsequent neutralization by stirring with methanol-washed Amberlite IR 120 (H^+ form), filtration of the resin and removal of the solvent in vacuo gave a residue which crystallized on trituration with isopropyl ether: 0.92 g (85%) of **18**, identical in all respects with the product described under (a).

4.16. (6*S*)-4-Acetoxy-6-acetoxymethyl-2*H*-pyran-3(6*H*)-one 19

4.16.1. From tri-*O*-acetyl-1,5-anhydro-D-fructose 16 by NaOAc-induced β-elimination. Freshly molten NaOAc (1.5 g) was added to a solution of **16** (1.45 g, 0.5 mmol) in dry acetone (50 mL) and the mixture was stirred for 3 h at ambient temperature. Filtration and evaporation of the filtrate in vacuo, and purification of the resulting syrup on silica gel column (2 × 30 cm) by fast elution with 3:1 *n*-hexane/EtOAc afforded 1.03 g (91%) of enolone **16** as a colorless syrup; $[\alpha]_D^{20} = -42.1$ (*c* 1.2, $CHCl_3$); lit.: $[\alpha]_D^{20} = -17.7$ (*c* 0.34, CH_2Cl_2);[29] $[\alpha]_D = -43.7$ (*c* 1.7, $CHCl_3$).[30] ^1H and ^{13}C NMR data corresponded with those reported.[29,30]

4.16.2. From oxime 9 by consecutive deoximation and β-elimination. Acetaldehyde (2.4 mL, 40 mmol) and 2 M HCl (6.5 mL) was added to solution of oxime **9** (2.90 g, 10 mmol) in acetonitrile (30 mL) and the mixture was stirred for about 12 h at ambient temperature, whereafter only ulose **16** was detectable (TLC, 3:1 toluene/EtOAc). Portionwise addition of solid $NaHCO_3$ with vigorous stirring, filtration, dilution of the filtrate with water (20 mL), extraction with CH_2Cl_2 (3 × 50 mL), washings of the organic phase with water, drying over Na_2SO_4 and removal of the solvent in vacuo gave 1.87 g (82%) of syrupy enolone **18** identical in all respects with the product described under (a).

4.17. (6*S*)-4-Benzoyloxy-6-benzoyloxymethyl-2*H*-pyran-3(6*H*)-one 20

4.17.1. From 3-benzoyloxyglucal tribenzoate 5 in a 3-step, one pot conversion involving hydroxylaminolysis, deoximation and elimination of benzoic acid. A solution of **5** (115 g, 0.2 mol) and $NH_2OH{\cdot}HCl$ (55 g, 0.8 mol) in 550 mL of absolute pyridine was kept at 70 °C for 14 h and then evaporated to dryness. The residue was dissolved in CH_2Cl_2, extracted repeatedly with 2 M HCl, the aqueous $NaHCO_3$ solution, and dried over Na_2SO_4. Concentration in vacuo and crystallization from ethanol afforded 91 g of **10** (needles, mp 176–177 °C), which was suspended in a mixture of 2 M HCl (100 mL), acetaldehyde (43 mL, 0.75 mmol), and CH_3CN (500 mL) and kept at ambient temperature for 10 h. The resulting solution, containing ulose **17** only (TLC, 2:1 CCl_4/EtOAc), was stirred vigorously with 200 g of solid $NaHCO_3$ for 6 h and then poured into 1.5 L of water. Extraction with CH_2Cl_2 (2 × 300 mL), washing of the combined organic layers with water, drying over Na_2SO_4, and evaporation of the solvent left a yellowish cooling down syrup, which crystallized when dissolved in 250 mL of hot methanol: 59.4 g of **20** (84% from **5**) as colorless needles; mp 104–105 °C and $[\alpha]_D^{20} = -16.0$ (*c* 1, $CHCl_3$); lit.:[30] mp 101–102 °C and $[\alpha]_D = -16.5$ (*c* 1.3, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 4.32 (dd, 1H, $J_{2,2} = 16.4$, $J_{2,6} = 1.8$ Hz, 2-H_a), 4.54 (d, 1H, $J_{2,2} = 16.4$ Hz, 2-H_b), 4.53 and 4.63 (two 1H-dd, $J_{6,CH_2} = 4.5$ and 5.9, $J_{gem} = 11.7$ Hz, CH_2OBz), 4.97 (1H-m, 6-H), 6.86 (d, 1H, $J_{5,6} = 2.2$ Hz, 5-H), 7.45, 7.57 and 8.10 (6H-, 3H- and 6H-m, 2C_6H_5). ^{13}C NMR (125.75 MHz, $CDCl_3$): δ 67.2 (CH_2OBz), 73.8 (C-2), 75.1 (C-6), 131.0 (C-5), 130–136 (C_6H_5), 146.3 (C-4), 166.1 and 168.4 (2C_6H_5*C*O), 190.0 (C-3). Anal. Calcd for $C_{20}H_{16}O_6$ (352.33): C, 68.18; H, 4.58. Found: C, 68.11; H, 4.52.

This straightforward acquisition of **20**, an enantiopure key building block, is contrasted by the comparatively humble yield (19%) by which **20** is obtained on benzoylation of 1,5-anhydro-D-fructose.[30]

4.17.2. From oxime 10 by deoximation and subsequent $NaHCO_3$-promoted elimination of benzoic acid. To a solution of 24.5 g (50 mmol) of oxime **10** in acetonitrile (150 mL) was added acetaldehyde (11.2 mL, 0.2 mol) and 2 M HCl (30 mL) followed by stirring at ambient temperature overnight (14 h), to give a mixture devoid of **10** (TLC in 2:1 CCl_4/EtOAc). Solid $NaHCO_3$ (60 g) was then added in small portions with vigorous stirring for 6 h. After filtration of the salts, the solution was poured into water (500 mL) followed by extraction with CH_2Cl_2 (2 × 100 mL), washing of the organic phase with water (2 × 100 mL), drying over Na_2SO_4 and removal of the solvent in vacuo. The yellowish syrup was dissolved in hot methanol (80 mL) to give well-formed needles on returning to ambient temperature: 15.3 g (87%) of **20**, identical to the product described under (a).

4.17.3. From ulose 17 by benzoic acid elimination. To a solution of **17** (3.8 g, 7.7 mmol) in dry acetone (50 mL) was added 1.0 g of freshly fused sodium acetate and the mixture was stirred for 30 min at ambient temperature, whereupon TLC ether/*n*-pentane, 2:1 indicated an absence of educt. Stirring into water (50 mL), chloroform extraction (3 × 30 mL), washing of the combined extracts with water, drying over Na_2SO_4, evaporation of the solvent and recrystallization of the residue from methanol afforded 2.5 g (92%) of **20** as colorless needles, identical in all respects with the product described under (a).

4.18. (6*S*)-4-Benzyloxy-6-benzyloxymethyl-2*H*-pyran-3(6*H*)-one 21

4.18.1. From 2-acetoxy-tri-*O*-benzylglucal 6. To a cooled (0 °C) solution of 2-acetoxyglucal **6** (500 mg, 1.05 mmol) in dry MeOH (30 mL) was added 300 mg of K_2CO_3 and the mixture was stirred for 2 h at ambient temperature followed by dilution with CH_2Cl_2 (70 mL), washings with water (3 × 40 mL), drying of the organic phase over Na_2SO_4, and removal of the solvents in vacuo. Purification of the syrupy residue by fast elution from a silica column (2 × 20 cm) with 14:1 toluene/EtOAc gave 253 mg (75%) of **21** as a colorless syrup of $[\alpha]_D^{20} = -32.1$ (*c* 1.1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 3.52 and 3.62 (2dd, 1H each, CH_2OBn), 4.13 (dd, 1H, 2-H_a), 4.38 (d, 1H, 2-H_b),

4.56 (s, 2H, PhCH_2), 4.61 (m, 1H, 6-H), 4.84 (2d, 1H each, PhCH_2), 5.87 (d, 1H, 5-H), 7.26–7.38 (m, 10H, 2Ph); $J_{2,2} = 16.5$, $J_{2a,6} = 2$, $J_{5,6} = 2.2$, $J_{6,CH_2} = 5.0$ and 6.1 Hz. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 69.7 and 73.5 (2BnCH_2), 71.4 (BnOCH_2), 71.9 (C-2), 78.8 (C-6), 116.5 (C-5), 148.7 (C-4), 190.1 (C-3). Anal. Calcd for $C_{20}H_{20}O_4$ (324.37): C, 74.05; H, 6.21. Found: C, 73.93; H, 6.23.

4.18.2. From tri-*O*-benzyl-1,5-anhydro-D-fructose 18 by benzoic acid elimination. Exposure of **18** to K_2CO_3 in methanol (2 h, 25 °C) and workup as above similarly gave enolone **21** (79% isol. yield).

4.19. 3,4,6-Tri-*O*-benzoyl-1,5-anhydro-D-fructose diethyldithioacetal 22

Ethanethiol (2.25 mL, 30 mmol) and BF_3–etherate solution (3.7 mL) was added to a solution of anhydrofructose tribenzoate **17** (1.50 g, 3.1 mmol) in chloroform (15 mL), and the mixture was kept at ambient temperature for 45 min. Subsequent dilution with CH_2Cl_2 (30 mL), washings with 2 M NaOH (10 mL) and water (3 × 10 mL), drying over Na_2SO_4 and evaporation to dryness gave a syrup which was purified by elution from a silica gel column (3 × 40 cm) with 20:1 CH_2Cl_2/EtOAc. Evaporation of the fractions containing **22** ($R_f = 0.5$ in CH_2Cl_2/EtOAc, 10:1) afforded 1.5 g (85%) of a colorless syrup of $[\alpha]_D^{23} = -51$ (*c* 1.1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.16 and 1.26 (two 7 Hz-t, 3H each, 2EtS-CH_3), 2.76 and 2.80 (two 7 Hz-q, 2H each, 2EtS-CH_2), 3.92 and 4.20 (2d, 1H each, 1-H_2), 4.05 (m, 1H, 5-H), 4.42 and 4.61 (two 1H-dd, 6-H_2), 5.82 (d, 1H, 3-H). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 14.1 and 14.2 (2q, 2EtS-*C*H_3), 22.3 and 22.5 (2EtS-*C*H_2), 62.0 (62.0 (C-2), 62.7 (c-6), 68.7 (C-4), 71.3 (C-1), 75.8 (C-5), 76.4 (C-3), 128.6–129.5, 133.3–133.6 (arom. C_6H_5), 164.9, 164.95, 165.3 (3Bz*C*O). Anal. Calcd for $C_{31}H_{32}O_7S_2$ (580.72): C, 64.12; H, 5.55; S, 11.04. Found: C, 64.06; H, 5.53; S, 10.90.

4.20. 1,5-Anhydro-D-fructose diethyldithioacetal 23

A solution of 580 mg (1 mmol) of tribenzoate **22** in 25 mL of 0.04 M methanolic sodium methoxide was kept at 0 °C for 6 h and subsequently neutralized by stirring with Dowex 50 WX 8 resin. Filtration and evaporation of the filtrate in vacuo afforded a syrup which gradually crystallized. Recrystallization from ether gave 230 mg (87%) of **23** as fine needles; mp 93–94 °C, $[\alpha]_D^{24} = -49.8$ (*c* 1, methanol). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.13 and 1.15 (two 3H-t, 2SEt-CH_3), 2.6–2.8 (4H-m, 2Set-CH_2), 3.10 (m, 1H, X-portion of an ABX system, 5-H), 3.36 and 3.66 (two 1H-ddd, A and B portion, 6-H_2), 3.47 (2H-m, 3-H and 4-H), 3.52 and 3.79 (two 1H-d, 1-H_2), 4.52 (t, 1H, 6-OH), 4.98 and 5.34 (two 1H-d, 3-OH and 4-OH); $J_{1,1} = 12.8$, $J_{5,6} = 1.8$ and 7.2, $J_{6,6} = 11.9$, $J_{3,3\text{-OH}} = J_{4,4\text{-OH}} = 4.4$ and 5.4, $J_{6,6\text{-OH}} = 6.0$ Hz; all OH protons are exchanged on treatment with D_2O. ^{13}C NMR (75.57 MHz, DMSO-d_6): δ 14.2 and 14.4 (2SEt-*C*H_3), 21.7 and 22.7 (2SEt-*C*H_2), 61.66 (C-6), 64.13 (C-2), 68.85 (C-4), 72.47 (C-1), 79.8 (C-3), 82.7 (C-5). MS (FD): $m/z = 268$ (M^+), 270 (M^+ 2). Anal. Calcd for $C_{10}H_{20}S_2O_4$ (268.40): C, 44.75; H, 7.51; S, 23.89. Found: C, 44.72; H, 7.47; S, 23.79.

4.21. 1,5-Anhydro-D-fructose 1[24]

4.21.1. De-O-acetylation of 2-acetoxy-glucal triacetate 4. To a cooled solution (0 °C) of **4** (6.60 g, 20 mmol) in dry methanol (200 mL) was added 20 mL of freshly prepared 1 M NaOMe/MeOH solution with vigorous stirring. De-O-acetylation being complete within a few minutes (TLC monitoring in 7:3 *n*-PrOH/water or 4:1 MeCN/water) the reaction mixture was quenched after 8–10 min by stirring methanol-washed Amberlite IR 120 (H^+ form) into the still cold solution. After 15 min, the mixture was filtered and the filtrate was taken to dryness in vacuo followed by reevaporation from water (10 mL) in vacuo at ambient temperature, finally at 0.1 Torr: 2.95 g (90%) of a colorless, fluffy solid, chromatographically homogeneous (somewhat elongated spot of $R_f \sim 0.5$ in 7:3 *n*-PrOH/water), comprising a mixture of **1**, its monohydrate **2**, and dimers (^{1}H and ^{13}C NMR) was obtained.

The analytical sample was obtained by elution of a 2.0 g portion from a Sephadex LH 20 column (3 × 40 cm) with water, collecting the product-carrying eluates, and removal of the solvent in vacuo, finally at 0.05 Torr: 1.70 g (85%) of **1**; $[\alpha]_D^{20} = -18.9$ (4 min) → −15.1 (20 min) → −10.5 (30 min) → −9.3 (50 min, constant value) (*c* 1, water), the final value corresponding to the monohydrate form **2**; lit.: $[\alpha]_D^{20} = -13$ (*c* 0.5, H_2O).[29] $[\alpha]_D^{25} = -16.8$ (*c* 1, H_2O);[8e] considerably higher rotational values, such as $[\alpha]_D^{20} = -32.9$ (*c* 0.86, H_2O)[8d] and $[\alpha]_D^{23} = -40$ (*c* 0.5, H_2O)[2] are likely to be incorrect.

^{1}H NMR (500 MHz, D_2O, 2 h after solution to allow for elaboration of the monohydrate **2**): δ 3.39 (ddd, 1H, H-5), 3.44 (dd, 1H, H-4), 3.46 (d, 1H, H-1a), 3.56 (d, 1H, H-3), 3.68 (dd, 1H, H-6a), 3.76 (d, 1H, H-1b), 3.90 (dd, 1H, H-6b), $J_{1,1} = 12.1$, $J_{3,4} = 8.9$, $J_{4,5} = 10.1$, $J_{5,6} = 2.2$ and 6.3, $J_{6,6} = 12.3$ Hz. ^{13}C NMR (125.7 MHz, D_2O): δ 62.6 (C-6), 70.4 (C-4), 73.3 (C-1), 78.4 (C-3), 82.2 (C-5), 93.9 (C-2). The ^{1}H NMR data corresponded reasonably well with those obtained at 300[5] and 400 MHz,[8c] the ^{13}C NMR signals to those observed at 25.2–125.7 MHz.[5,7a,30] Anal. Calcd for $C_6H_{10}O_5$ (162.14): C, 44.44; H, 6.22. Found: C, 44.38; H, 6.19.

When neutralizing a methanolic deacetylation solution as obtained above (from 660 mg of **4**) with thoroughly methanol-prewashed Amberlite IR 120 (H^+ form), the amorphous residue resulting after filtration and evaporation of the filtrate in vacuo, finally 0.1 Torr, contained substantial amounts of the monomethanolate **26** aside **1** as evidenced by the absence of a carbonyl resonance around 195 ppm (^{13}C NMR in CD_3OD), yet the presence of distinct OCH_3 signals at 3.27 (^{1}H NMR in D_2O) and 49.9 ppm (^{13}C NMR) due to MeOH released on equilibration of **26** with water (D_2O).

4.21.2. Desulfurization of dithioacetal 23. To a solution of 1.0 g (3.7 mmol) of **23** in 20 mL of water was added $CdCO_3$ (2.8 g, 16 mmol) and $HgCl_2$ (2.2 g, 8 mmol), and the mixture was stirred for 30 min at ambient temperature. The insoluble materials are subsequently removed by filtration through a layer of silica gel. The filtrate was then saturated

with H_2S, and after another filtration with suction through silica gel was neutralized with a weakly basic ion exchange resin (Lewatit MP 7080). Removal of the resin and concentration to dryness in vacuo left a viscous syrup, which was purified by elution from a Sephadex LH 20 column (2 × 30 cm) with water. Removal of the solvent in vacuo from the product-carrying eluates and the drying of the residue at 0.1 Torr gave 0.51 g (85%) of a colorless foam, identical (TLC, NMR) with the product described under (a).

4.21.3. Deoximation of oxime 12. Acetaldehyde (0.56 mL, 10 mmol) and 1 M HCl (5 mL) was added to a suspension of oxime **12** (440 mg, 2.5 mmol) in acetonitrile (15 mL) and the mixture was stirred for 5 h at ambient temperature. The resulting clear solution was diluted with water (5 mL) and neutralized by stirring with an acidic resin (Amberlite IR 120 H^+ form) and the filtrate was evaporated to dryness in vacuo. The syrupy residue was then eluted from a silica gel column (2 × 15 cm) with *n*-propanol/water (7:3), to give upon evaporation of the product-carrying eluates in vacuo, finally at 0.01 mm, 240 mg (60%) of **1** as a fluffy solid, identical with the product obtained under (a).

4.21.4. Hydrogenolysis of tri-*O*-benzyl derivative 18. A suspension of **18** (320 mg, 0.74 mmol) and 150 mg 10% Pd/C in EtOAc (40 mL) was hydrogenated for 2 days at ambient temperature, followed by removal of the catalyst and concentration of the filtrate in vacuo: 110 mg (91%) of **1** as a colorless syrup of $R_f = 0.5$ (CH_3CN/H_2O, 4:1), identical with the product described under (a).

4.22. (6*S*)-6-Benzoyloxymethyl-3,3-dimethoxy-tetrahydropyran-4-one 27

A 1 M sodium methoxide/MeOH solution (10 mL) was added to a suspension of 3.50 g (10 mmol) of enolone **20** in MeOH (50 mL) and the mixture was stirred for 5 min at ambient temperature, followed by neutralization with 5 mL of 2 M HCl and the addition of 100 mL of water. Extraction with CH_2Cl_2 (2 × 50 mL), washing with $NaHCO_3$ solution and water, drying (Na_2SO_4) and evaporation to dryness in vacuo left a syrupy residue which crystallized from ether/*n*-hexane: 2.40 g (81%) of **27**; mp 54–55 °C; $[\alpha]_D^{20} = -85.6$ (*c* 1.2, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.55 (dd, 1H, $J_{5,5} = 13.3$, $J_{5,6e} = 2.7$ Hz, 5-He), 2.92 (dd, 1H, $J_{5,5} = 13.3$, $J_{5,6a} = 11.5$ Hz, 5-H_{ax}), 3.31 and 3.41 (two 3H-s, 2OMe), 4.04 (m, 1H, H-6), 3.45 and 4.32 (two 1H-d, $J_{2,2} = 12.9$ Hz, 2-H_2), 4.43 (m, 2H, CH_2OBz), 7.4–8.1 (5H-m, C_6H_5). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 43.2 (C-5), 49.8 and 50.2 (2O*C*H_3), 66.0 (CH_2OBz), 70.8 (C-2), 76.6 (C-6), 98.5 (C-5), 128–133 (C_6H_5), 166.1 (Bz*C*O), 201.6 (C-4). Anal. Calcd for $C_{15}H_{18}O_6$ (294.30): C, 61.22; H, 6.17. Found: C, 61.27; H, 6.18.

Stirring an enolone solution in MeOH containing 1 M equiv of NaOMe (as Section 4.22) for longer than 5 min, for example, 30 min, the 6-de-O-benzoylated compound was the exclusive product: syrup of $[\alpha]_D^{20} = -122.6$ (*c* 1.1, $CHCl_3$) upon analogous workup and purification by elution from silica gel (2.5 × 20 cm column) with acetone/*n*-hexane.

4.23. (6*S*)-6-Benzoyloxymethyl-3,3-di(benzyloxy)-tetrahydropyran-4-one 28

Stirring a mixture of enolone **20** (1.76 g, 5 mmol), K_2CO_3 (0.7 g, 5 mmol) and benzylalcohol (20 mL) for 4 h at ambient temperature. Filtration, pouring into water (100 mL) and extraction with CH_2Cl_2 (2 × 50 mL), washing with bicarbonate solution and water left a syrup after evaporation in vacuo, which was purified by elution from silica gel (3 × 25 cm column) with 10:1 CCl_4/EtOAc: 1.92 g (86%) of **28** as well-formed, long needles of mp 96–97 °C and $[\alpha]_D^{20} = -94.8$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.59 (dd, 1H, $J_{5,5} = J_{5,6a} = 11.5$ Hz, 5-Ha), 3.58 and 4.50 (two 1H-d, $J_{2,2} = 12.9$ Hz, 2-H_2), 4.12 (1H-m, 6-H), 4.72 and 5.08 (two 1H-d, $J = 11.7$ Hz, BnCH_2), 4.83 and 4.54 (two 1H-d, $J = 10.9$ Hz, BnCH_2), 4.47 (dddd, 2H, $J_{5,CH_2} = 5.3, J_{CH_2,gem} = 11.9$ Hz, BzCH_2). ^{13}C NMR (125.75 MHz, $CDCl_3$): δ 43.6 (C-5), 65.8 (*C*H_2OBz), 71.5 (C-2), 77.3 (C-6), 77.5 and 77.8 (2BnCH_2), 99.8 (C-3), 128–138 (3C_6H_5), 166.6 (Bz*C*O), 202.1 (C-4). Anal. Calcd for $C_{27}H_{26}O_6$ (446.48): C, 72.63; H, 5.87. Found: C, 72.55; H, 5.77.

4.24. (6*S*)-4-Benzoyloxy-6-benzoyloxymethyl-2*H*-pyran-3(6*H*)-one oxime 29

A mixture of enolone **20** (3.5 g, 10 mmol) $NH_2OH{\cdot}HCl$ (0.72 g, 10 mmol), pyridine (10 mL) and 35 mL of chloroform/ethanol (5:3) was stirred at ambient temperature for 15 h, and subsequently stirred into water (150 mL). Extraction with chloroform (3 × 100 mL), washing of the combined extracts with cold 1 M HCl and water, drying over Na_2SO_4 and removal of the solvent in vacuo yields a colorless residue, which is recrystallized by dissolution in a little warm ethanol and the addition of *n*-pentane until turbidity: 3.40 g (96%), mp 133–134 °C, $[\alpha]_D^{21} = -22$ (*c* 0.6, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.39 (d, 1H, $J_{2,2} = 16.0$ Hz, H-2a), 4.46 and 4.55 (two 1H-dd, $J_{6,CH_2} = 4.3$ and 6.3 Hz, $J_{CH_2,gem} = 11.7$ Hz, CH_2OBz), 4.77 (1H-m, H-6). 5.04 (1H-d, $J_{2,2} = 16.0$ Hz, H-2b), 6.11 (1H-d, $J_{5,6} = 2.4$ Hz, H-5), 7.47, 7.60 and 8.10 (6H-, 3H- and 6H-m, 2C_6H_5), 8.96 (br s, 1H, NO*H*). ^{13}C NMR (125.75 MHz, $CDCl_3$): δ 61.9 (C-2), 65.7 (CH_2OBz), 72.3 (C-6), 130.6 (C-5), 141.7 (C-4), 147.9 (C-3), 164.6 and 166.8 (2Bz*C*O). Anal. Calcd for $C_{20}H_{17}NO_6$ (367.34): C, 65.39; H, 4.66; N, 3.81. Found: C, 65.29; H, 4.60; N, 3.77.

4.25. (6*S*)-4-Benzoyloxy-6-benzoyloxymethyl-2*H*-pyran-3(6*H*)-one phenylhydrazone 30

Phenylhydrazine (3.5 mL, 35 mmol) and acetic acid (3.5 mL) was added to a suspension of enolone **20** (3.52 g, 10 mmol) in 100 mL of EtOH. The initially clear solution started separating yellowish crystals after a few min. Filtration and recrystallization from EtOH afforded 4.02 g (91%) of **30** in the form of yellowish needles; mp 157 °C; $[\alpha]_D^{20} = -14$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.51 and 4.59 (two 1H-dd, CH_2OBz), 4.93 (1H-m, 6-H), 4.57 and 5.02 (two 1H-d, 2-H_2), 6.16 (1H-d, 5-H), 7.4–8.1 (15H-m, 3C_6H_5), 9.59 (1H-s, NH); $J_{2,2} = 15.6$, $J_{5,6} = 2.6$, $J_{6,CH_2} = 3.5$ and 6.6, $J_{CH_2,gem} =$

11.8 Hz. Anal. Calcd for $C_{26}H_{22}N_2O_5$ (442.45): C, 70.58; H, 5.01; N, 6.33. Found: C, 70.43; H, 4.95; N, 6.30.

4.26. (6*S*)-6-Benzyloxymethyl-tetrahydropyran-3,4-dione dioxime 31

A stirred mixture of enolone **20** (705 mg, 2 mmol), hydroxylamine hydrochloride (0.7 g, 10 mmol) and pyridine (10 mL) was heated at 70 °C (bath temperature) for 3 h, whereafter TLC (CH_2Cl_2/EtOAc, 5:1) indicated the absence of the educt in favor of **31**. The mixture was then poured into ice-water (100 mL), resulting in a precipitate which was collected and recrystallized from EtOH or methanol/water: 440 mg (79%); mp 187–189 °C; $[\alpha]_D^{21} = -111$ (*c* 0.5, pyridine). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.53 and 2.81 (2dd, 1H each, 5-H_2), 3.95 (m, 1H, H-6), 4.37 (2H-m, CH_2OBz), 4.40 and 4.80 (2d, 1H each, 2-H_2), 7.5–8.1 (5H-m, C_6H_5); $J_{2,2} = 17.0$, $J_{5,5} = 18.1$, $J_{5,6} = 3.8$ and 11.6 Hz. MS (EI): $m/z = 278$ (M^+). Anal. Calcd for $C_{13}H_{14}N_2O_5$ (278.26): C, 56.11; H, 5.07; N, 10.07. Found: C, 56.05; H, 4.95; N, 9.98.

Dioxime **31** was similarly obtained from enolone oxime **29** by stirring in ethanol solution with $NH_2OH{\cdot}HCl$ and NaOAc at room temperature overnight, yield: 84%.

4.27. (6*S*)-6-Benzoyloxymethyl-tetrahydropyran-3,4-dione bis(phenylhydrazone) 32

To a stirred suspension of enolone **20** (705 mg, 2 mmol) in methanol (30 mL) was added 4 mL of 1 M NaOMe/MeOH, followed after 1 min by 8 mL 50% acetic acid and phenylhydrazine (1.5 mL, 15 mmol). The product started crystallizing within minutes: 640 mg (75%) of **32** as yellow needles of mp 182 °C (dec); $[\alpha]_D^{20} = -114.3$ (*c* 1.0, $CHCl_3$), −64.3 (*c* 1.0, pyridine). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.63 and 2.93 (two 1H-dd, 5-H_2), 4.19 (m, 1H, 6-H), 4.6–4.4 (4H-m, 2-H_2 and CH_2OBz), 6.9–8.1 (15H-m, 3C_6H_6), 9.78 and 12.78 (two 1H-s, 2 N*H*); $J_{5,5} = 17.3$, $J_{5,6} = 4.0$ and 11.1 Hz. MS (FD): $m/z = 428$ (M^+). Anal. Calcd for $C_{25}H_{24}N_4O_3$ (428.49): C, 70.08; H, 5.65; N, 13.08. Found: C, 69.97; H, 5.53; N, 12.96.

4.28. (3*S*)-3-Benzoyloxymethyl-3,4-dihydro-1*H*-pyrano[3,4-*b*]quinoxaline 33

A mixture of 705 mg (2 mmol) of enolone **20**, K_2CO_3 (280 mg, 2 mmol), *o*-phenylenediamine (330 mg, 3 mmol) and MeOH (20 mL) was stirred at ambient temperature for 20 min, then poured into water (70 mL) and extracted with CH_2Cl_2 (3 × 25 mL). Washing of the combined extracts with water (10 mL), drying over Na_2SO_4 and evaporation to dryness in vacuo left a residue which crystallized from aqueous EtOH: 430 mg (67%) of **33** as colorless needles; mp 144 °C; $[\alpha]_D^{21} = -81.3$ (*c* 1.1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.31 (2H-m, 4-H_2), 4.40 (1H-m, 3-H), 4.62 (2H-m, CH_2OBz), 5.03 and 5.21 (two 1H-d, 1-H_2), 7.4–8.1 (9H-m, C_6H_5, C_6H_4). MS (FD, 5 mA): $m/z = 300$ (M^+). Anal. Calcd for $C_{19}H_{16}N_2O_3$ (320.33): C, 71.24; H, 5.03; N, 8.75. Found: C, 71.17; H, 4.95; N, 8.70.

4.29. (2*S*,4*S*,5*R*)-4-Benzoyloxy-2-benzoyloxymethyl-5-hydroxy-tetrahydropyran 34 (3,6-di-*O*-benzoyl-4-deoxy-1,5-anhydro-D-*xylo*-hexitol)

A 0.15 M solution of $Zn(BH_4)_2$ in ether (16 mL, 2.5 mmol) was added to a cooled (0 °C) suspension of enolone **20** (700 mg, 2 mmol) in ether (20 mL) and the mixture was stirred for 1 h at 0 °C and for another at ambient temperature. Evaporation to dryness in vacuo was followed by dissolution of the residue in CH_2Cl_2 (25 mL), washing with 2 M HCl and saturated. $NaHCO_3$ solution (15 mL each), drying over Na_2SO_4 and removal of the solvent. The residue was eluted from a silica gel column (2 × 20 cm) with 2:1 CCl_4/EtOAc to give 445 mg (72%) of **34**; mp 118–119 °C; $[\alpha]_D^{25} = +18.6$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.71 and 2.25 (two 1H-ddd, 3-H_2), 2.72 (br s, 1H, OH), 3.38 (1H-dd, 6-H_a), 3.84 (1H-dddd, 2-H), 4.01 (1H-ddd, 4-H), 4.25 (dd, 1H, 6-H_e), 4.41 (m, 2H, 7-H_2), 4.98 (ddd, 1H, 5-H), 7.4–8.1 (10H-m, 2C_6H_5); $J_{2,3} = 2.0$ and 11.6, $J_{3,3} = 13.0$, $J_{3,4} = 5.3$ and 11.3, $J_{4,5} = 9.2$, $J_{5,6} = 5.4$ and 10.4, $J_{6,6} = 11.1$ Hz. Anal. Calcd for $C_{20}H_{20}O_6$ (322.34): C, 65.05; H, 6.07. Found: C, 64.90; H, 6.00.

4.30. 3,6-Di-*O*-benzoyl-4-deoxy-4-*C*-methyl-1,5-anhydro-D-fructose 35

A cuprate solution consisting of 3.24 g (17.2 mmol) of CuI, 17.9 mL (28 mmol) of 5% ethereal MeLi and 100 mL of ether was cooled to −78 °C and a solution of enolone **20** (2.0 g, 5.7 mmol) in 300 mL of ether was added dropwise with stirring. After about 30 min, HCl gas was bubbled into the mixture, followed by filtration, washing of the filtrate with 2 M NaOH, 2 N HCl and NH_4Cl solution (100 mL each), dried over Na_2SO_4 and removal of the solvent. The resulting syrup crystallized from ether/*n*-hexane: 1.10 g (53%) of ulose **35**; mp 118–120 °C; $[\alpha]_D^{20} = -6.3$ (*c* 0.5, $CHCl_3$), −11.7 (*c* 0.9, acetone). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.20 (3H-d, CH_3), 2.59 (dddd, 1H, 4-H), 4.00 (1H-ddd, 5-H), 4.22 (1H-dd, 1-Ha), 4.31 (1H-d, 1-He), 4.55 and 4.65 (two 1H-dd, 6-H_2), 5.44 (1H-d, 3-H), 7.4–8.1 (10H-m, 2C_6H_5); $J_{1,1} = 15.1$, $J_{1,5} = 0.6$, $J_{3,4} = 11.8$, $J_{4,5} = 10.0$, $J_{4,Me} = 6.5$, $J_{5,6} = 2.5$ and 5.2, $J_{6,6} = 12.3$ Hz. ^{13}C NMR (75.75 MHz, $CDCl_3$): δ 13.7 (*C*H$_3$), 39.2 (C-4), 64.2 (C-6), 72.3 (C-1), 77.9 and 78.4 (C-3, C-5), 129–133 (2C_6H_5), 165.0 and 165.5 (2*C*=O), 200.3 (C-2). MS (FD, 2 mA): m/z 368 (M^+). Anal. Calcd for $C_{21}H_{20}O_6$ (368.39): C, 68.47; H, 5.47. Found: C, 68.36; H, 5.39.

As different workup procedures provided **35** as the monohydrate, that is, the 2,2-dihydroxy form, this was generated intentionally by standing **35** in aqueous acetone overnight and removal of the solvents in vacuo: crystals of **35**. H_2O on trituration with ether/*n*-hexane; mp 117–119 °C; $[\alpha]_D^{20} = -38$ (*c* 0.4, $CHCl_3$), −5.7 (*c* 0.7, acetone). ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.83 (3H-d, CH_3), 2.18 (1H-m, 4-H), 3.38 and 3.66 (two 1H-d, 1-H_2), 3.64 (1H-m, 5-H), 4.39 and 4.49 (two 1H-dd, 6-H_2), 5.81 and 5.85 (two 1H-s, 2O*H*); $J_{1,1} = 11.6$, $J_{3,4} = 10.9$, $J_{4,Me} = 6.7$, $J_{5,6} = 2.0$ and 5.2, $J_{6,6} = 12.1$ Hz. ^{13}C NMR (75.75 MHz, $CDCl_3$): the signal for C-2 appears at 90.5 ppm; no carbonyl resonance around 200 ppm. MS (FD, 5 mA): m/z 386 (MH^+)

and 368 (M^+-H_2O). Anal. Calcd for $C_{21}H_{22}O_7$ (386.41): C, 65.28; H, 5.74. Found: C, 65.37; H, 5.75.

4.31. (2*S*,5*S*)-5-Benzoyloxy-2-benzoyloxymethyl-5-methyl-tetrahydropyran-4-one 36

A 2 M ether solution of methylmagnesium iodide (2.7 mL) was stirred into a precooled (−78 °C) solution of enolone **20** (500 mg, 1.4 mmol) in ether (100 mL). After 15 min, the reaction was quenched by pouring into a half saturated NH_4Cl solution (100 mL), followed by separation of the organic phase, washing with water (100 mL), drying (Na_2SO_4) and removal of the solvent. The resulting syrup crystallized on trituration with ether/hexane: 110 mg (21%) of **36** as colorless prisms of mp 125–127 °C; $[\alpha]_D^{20} = -89$ (*c* 1, $CHCl_3$). Purification of the mother liquor on silica gel (2.5 × 25 cm column) by elution with 19:1 CH_2Cl_2/EtOAc afforded another 250 mg; total yield: 69%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.71 (3H-s, CH_3), 2.66 and 2.82 (two 1H-dd, 3-H_2), 4.02 (1H-d, 6-He), 4.36 (1H-dd, 6-Ha), 4.44 (3H-m, 2-H, CH_2OBz), 7.4 and 8.1 (10H-m, 2C$_6H_5$); $J_{2,3} = 3.2$ and 10.8 Hz, $J_{2,6} = 0.8$, $J_{3,3} = 16.9$, $J_{6,6} = 10.9$ Hz. MS (FD, 7 mA): $m/z = 368$ (M^+). Anal. Calcd for $C_{21}H_{20}O_6$ (368.37): C, 68.47; H, 5.47. Found: C, 68.35; H, 5.40.

4.32. (2*S*,5*S*)-5-Allyl-5-benzoyloxy-2-benzoyloxymethyl-tetrahydropyran-4-one 37

A 1 M solution of allylmagnesium bromide in ether (17 mL) and titan-IV-isopropoxide (6.0 mL, 20.1 mmol) was added with stirring to a cooled (−78 °C) solution of enolone **20** (2.0 g, 5.7 mmol) in CH_2Cl_2 (40 mL). After 15 min, the mixture was allowed to warm to room temperature. Dilution with CH_2Cl_2 (200 mL), washing with 2 M HCl, 2 M NaOH and NH_4Cl solution (100 mL each), drying over Na_2SO_4 and evaporation to dryness in vacuo gave a crystalline residue which was recrystallized from ether: 1.90 g (85%) of **37**; mp 105–106 °C; $[\alpha]_D^{20} = -65$ (*c* 0.7, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.60 and 2.83 (two 1H-dd, 3-H_2), 2.79 (2H-m, CH_2CH=CH_2), 4.19 and 4.34 (two 1H-d, 6-H_2), 4.55 (3H-m, 2-H, CH_2OBz), 5.27 (2H-m, CH=CH_2), 5.94 (1H-dddd, CH=CH_2), 7.4–8.1 (10H-m, 2C$_6H_5$); $J_{2,3} = 2.6$ and 11.0, $J_{3,3} = 16.7$, $J_{6,6} = 11.1$ Hz. MS (FD, 2 mA): $m/z = 394$ (M^+). Anal. Calcd for $C_{23}H_{22}O_6$ (394.43): C, 70.04; H, 5.62. Found: C, 70.05; H, 5.53.

4.33. (2*S*)-2-Benzoyloxymethyl-5,5-bis(nitromethyl)-tetrahydropyran-4-one 38

A mixture of enolone **20** (705 mg, 2 mmol), K_2CO_3 (700 mg, 5 mmol) and nitromethane (10 mL) was stirred at ambient temperature for 5 h, then filtered, and poured into water (50 mL) and extracted with CH_2Cl_2 (2 × 50 mL), washing of the combined extracts with water, drying over Na_2SO_4 and removal of the solvent in vacuo left a syrup. Purification by elution from a silica gel column (3 × 20 cm) with 2:1 CCl_4/EtOAc gave 526 mg (75%) of **38** as a colorless syrup of $[\alpha]_D^{20} = -32.4$ (*c* 1.2, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.76 and 2.96 (two 1H-dd, 3-H_2), 4.22 (1H-dddd, 2-H), 3.93 and 4.25 (two 1H-d, 6-H_2), 4.46 and 4.53 (two 1H-dd, CH_2OBz), 4.83 (2H-m, CH_2NO$_2$), 4.91 and 5.12 (two 1H-dd, CH_2NO$_2$), 7.4–8.1 (5H-m, C$_6H_5$); $J_{2,3} = 3.3$ and 11.5, $J_{2,CH_2OBz} = 3.8$ and 5.4, $J_{6,6} = 12.4$ Hz. ^{13}C NMR (75.75 MHz, $CDCl_3$): δ 41.1 (C-3), 52.2 (C-5), 65.5 (*C*OBz), 70.4 (C-6), 74.0 and 75.9 (C-8, C-9), 76.9 (C-2), 128–133 (Phenyl-C), 166.1 (PhC=O), 201.0 (C-4). Anal. Calcd for $C_{15}H_{16}N_2O_8$ (352.29): C, 51.14; H, 4.58; N, 7.95. Found: C, 51.09; H, 4.48; N, 7.84.

4.34. (2*S*,5*S*)-2-Benzoyloxymethyl-5-hydroxy-5-acetonyl-tetrahydropyran-4-one 41 and (5*R*)-epimer

A 1.6 M solution of *n*-butyl lithium in *n*-hexane (9.4 mL) was added to a cooled (−78 °C) solution of 1.67 g (16.5 mmol) of di-isopropylamine in THF (20 mL) under an N_2 atmosphere and then kept at 0 °C for 30 min. Upon cooling down to −78 °C, a solution of acetone (870 mg, 15 mmol) in THF (10 mL) was added dropwise and this mixture was gradually added (10 min) into a precooled (−78 °C) solution of enolone **20** (3.52 g, 10 mmol) in THF (20 mL). After stirring for another 10 min 2 mL of THF/water (1:1) was added, the mixture was allowed to warm to −20 °C, at which temperature it was kept for 2 h and then poured into 50 mL of 1 M acetic acid. After separation of the THF layer the aqueous phase was extracted with ether (50 mL), and the combined organic phases were washed with aqueous $NaHCO_3$ (2 × 30 mL) and water, dried and taken to dryness in vacuo. The syrupy residue crystallized on trituration with ether: 1.29 g (42%) of **41** as needles of mp 103–105 °C; $[\alpha]_D^{20} = -31.6$ (*c* 1.2, $CHCl_3$). Removal of the solvent from the mother liquor, elution of the residue from a silica gel column (2.5 × 20 cm) with 2:1 CCl_4/EtOAc and workup of the first product-containing eluate gave another 0.55 g (12%, total yield: 64%) of **41** [for the (5*R*)-isomer eluted next cf. below]. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.26 (3H-s, CH_3), 2.72 and 2.84 (two 1H-dd, 3-H_2), 3.13 and 3.34 (two 1H-d, CH_2Ac), 3.26 and 4.04 (two 1H-d, 6-H_2), 4.00 (1H-m, 2-H), 4.20 (br s, 1H, OH), 4.41 and 4.48 (two 1H-dd, CH_2OBz), 7.4–8.1 (m, 5H, C$_6H_5$); $J_{2,3} = 3.1$ and 11.5, $J_{2,CH_2} = 4.0$ and 5.5, $J_{3,3} = 13.3$, $J_{6,6} = 11.4$, $J_{BzOCH_2,gem} = 11.9$, $J_{AcCH_2,gem} = 16.6$ Hz. ^{13}C NMR (75.75 MHz, $CDCl_3$): δ 31.6 (*C*H$_3$), 41.9, 49.7, 66.1 and 75.0 (C-3, C-6, *C*H$_2$OBz, *C*H$_2$Ac), 77.0 (C-2), 122.7–129.0 (Phenyl-C), 165.6 (PhC=O), 206.6 and 207.0 (C-4 and AcC=O). Anal. Calcd for $C_{16}H_{18}O_6$ (306.31): C, 62.74; H, 5.92. Found: C, 62.77; H, 6.04.

X-ray structure, solved by direct methods using SHELXS-97.[31] Space group $P2_1$, monoclinic, unit cell dimensions $a = 14.593$, $b = 8.671$, $c = 6.135$ Å, $\alpha = 90°$, $\beta = 100.50°$, $\gamma = 90°$, $V = 763.31$ Å^3, $D_c = 1.333$ g/cm^3, μ(Mo Kα) = 0.49 cm^{-1}, crystal size 0.62 × 0.50 × 0.19 mm, 3490 reflections collected/ 2618 unique ($R_{int} = 0.0635$) data parameters = 2107/ 247, Goof = 1.078, $R_{indices}$ ($I > 2\sigma\pm$): $R_1 = 0.0342$, $\omega R_2 = 0.0916$, $R_{indices}$ (all data: ($R_1 = 0.0416$, $\omega R_2 = 0.0935$; Refinement by full matrix least-squares on F^2 for all data using SHELX-97XL.[32] Stereostructure and selected torsional angles: Figure 1.

Full crystallographic details have been deposited (No. CCDC 663502) with the Cambridge Crystallographic

Data Centre. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or from CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) +44 1223/336-033; e-mail: deposit@ccdc.cam.ac.uk.

(5R)-Epimer of **41**: On elution of **41** from the silica gel column with CCl_4/EtOAc (2:1), a further fraction appeared. On evaporation to dryness in vacuo 285 mg (9%) of a chromatographically uniform, colorless syrup of $[\alpha]_D^{20} = -24.3$ (*c* 1, $CHCl_3$) was obtained. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.12 (3H-s, CH_3), 2.76 (2H-s, AcCH_2), 2.42 and 2.90 (two 1H-dd, 3-H_2), 3.81 and 3.91 (two 1H-d, 6-H_2), 4.11 (1H-m, 2-H), 4.37 (2H-m, CH_2OBz), 5.86 (1H-s, OH), 7.5–8.1 (5H-m, C_6H_5); $J_{2,3} = 3.0$ and 10.9, $J_{3,3} = 14.6$, $J_{6,6} = 12.2$ Hz. Anal. Calcd for $C_{16}H_{18}O_6$ (306.31): C, 62.74; H, 5.62. Found: C, 67.21; H, 5.47.

4.35. (−)-Bissetone [(2*S*,5*S*)-5-acetonyl-5-hydroxy-2-hydroxymethyl-tetrahydropyran-4-one] 42

To a cooled solution of **41** (918 mg, 3 mmol) in MeOH (30 mL) was added 0.6 mL of 1 M NaOMe/MeOH and the mixture was kept for 2 h at 0 °C, then for 6 h at ambient temperature. Neutralization by stirring with Amberlite IR-120 (H^+ form), concentration in vacuo and elution of the residue from a silica gel column (2 × 25 cm) with 10:1 EtOAc/MeOH afforded 557 mg (92%) of **42** as a colorless syrup of $[\alpha]_D^{20} = -69.4$ (*c* 1.0, EtOH); lit.: −43.6 (*c* 4.25, EtOH) for the obviously impure, *B. polyanthes*-derived[25] product. ^{1}H NMR and ^{13}C NMR data correlated well: ^{1}H NMR (300 MHz, D_2O): δ 2.24 (3H-s, CH_3), 2.49 (1H-dd, $J_{2,3e} = 2.6$, $J_{3,3} = 13.6$ Hz, 3-He), 2.83 (1H-dd, $J_{2,3a} = 11.8$, $J_{3,3} = 13.6$ Hz, 3-Ha), 3.22 and 3.54 (two 1H-d, $J_{CH_2,gem} = 17.5$ Hz, AcCH_2), 3.65 and 3.75 (two 1H-dd, $J_{2,CH_2} = 2.9$ and 5.9, $J_{CH_2,gem} = 12.3$, CH_2OBz), 3.85 (1H-dddd, $J_{2,3} = 2.6$ and 11.8, $J_{2,CH_2} = 2.9$ and 5.9 Hz, 2-H), 3.40 and 4.04 (two 1H-d, $J_{6,6} = 11.2$ Hz, 6-H_2). ^{13}C NMR (75.75 MHz, $CDCl_3$): δ 33.5 (CH_3), 44.3 (C-3), 52.2 (AcCH_2), 66.2 (CH_2OBz), 77.6 (C-6), 79.9 (C-5), 83.2 (C-2), 213.2 and 214.2 (C-4 and AcC=O). Anal. Calcd for $C_9H_{14}O_5$ (202.20): C, 53.46; H, 6.98. Found: C, 53.29; H, 6.88.

4.36. *S,S*-Palythazine [(3*S*,8*S*)-1,3,4,6,8,9-hexahydro-dipyrano[3,4-*b*:3′,4′-*e*]pyrazine-3,8-dimethanol] 45

Enolone oxime **29** (3.67 g, 10 mmol) was dissolved in precooled (−20 °C) methanolic sodium methoxide (0.236 g Na in 120 mL of methanol) and kept overnight in a refrigerator (0 °C). Neutralization by stirring with Amberlite IRA 120 (H^+-form), filtration, and evaporation to dryness left the 3-monoxime of 6-hydroxymethyl-tetrahydropyran-3,4-dione **43** as a chromatographically uniform solid (1.1 g, 89%), which was directly subjected to hydrogenation with 10% Pd/C (1.0 g) in ethanol (10 mL) and ethanolic HCl (2 mL, containing 2.5 M equiv HCl). After consumption of 2 M equiv of H_2 (ca. 7–8 h) the catalyst was removed, followed by the addition of water (0.3 mL), neutralization with a strongly basic ion exchange resin (Merck III) and evaporation to dryness. The resulting residue was dissolved in EtOAc/EtOH (3:1) and stirred in the open air for 3 days (monitoring by TLC in 3:1 EtOAc/MeOH; **45** gave a yellow-brown spot on charring with H_2SO_4; several faster moving minor spots). Partial crystallization occurred on standing (0.39 g); purification of the mother liquor on a silica gel column by elution with EtOAc/MeOH (3:1) gave the major crop (0.97 g; total yield: 57%). Recrystallization from EtOH/EtOAc gave **45** as colorless prisms (or needles) of mp 223–225 °C (upon sublimation from 190 °C on), $[\alpha]_D^{23} = -198.8$ (*c* 0.35, methanol). UV (CH_3OH): $\lambda_{max} = 287$ nm ($\lg\varepsilon = 4.03$), 305 (3.58). ^{1}H NMR (100 MHz, DMSO-d_6): δ 2.80 (7 Hz-d, 4H, 4-H_2), 9-H_2), 3.56 (5 Hz-t, 4H, 2 CH_2OH), 3.86 (oct, 2H, H-3 and H-8), 4.74 (s, 4H, 1-H_2, 6-H_2), 4.87 (6 Hz-t, 2H, 2OH); addition of D_2O eliminates the triplet at 4.86 ppm and reduces that at 3.56 to a doublet. ^{13}C NMR (25.6 MHz, DMSO-d_6: δ 148.0 and 146.2 (pyridine-*C*), 75.5 (d, C-3/C-8), 67.7 (hydroxymethyl-*C*), 63.6 (C-1/C-6), 32.3 (C-4/C-9). MS (FD): $m/z = 252$ (M^+), 234 (m−H_2O). Anal. Calcd for $C_{12}H_{16}O_4$ (252.26): C, 57.13; H, 6.39; N, 11.11. Found: C, 57.06; H, 6.22; N, 11.13.

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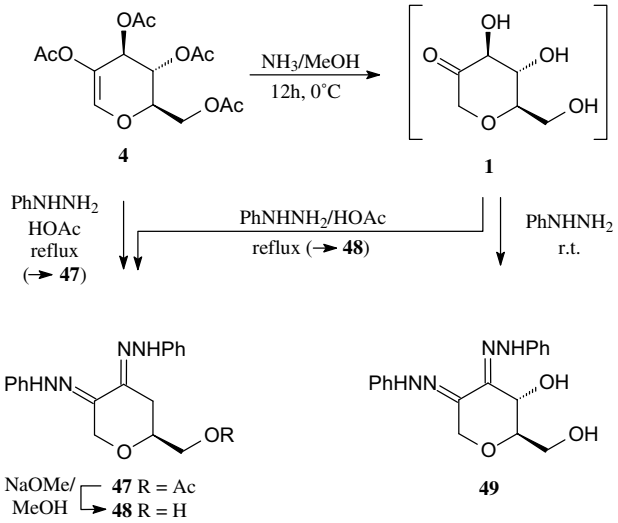
24. (a) 1,5-Anhydro-D-fructose **1**, albeit in impure form, was already obtained 80 years ago by Maurer and Mahn[15a] upon exposure of acetoxyglucal **4** to methanolic ammonia (16 h, 0 °C): the 'amorphous precipitate' reduced Fehling solution, yet had poor microanalytical data. Repetition of this experiment showed the product to contain **1** (∼80%) and several side components (TLC).The formation of **1** upon treatment with NH_3/MeOH has also been documented by the osazones generated on reaction with phenylhydrazine: in dilute acid and at ambient temperature **49** was obtained, whilst brief heating in 50% acetic acid elaborated osazone **48** due to concomitant 3,4-elimination of water.[24b,c] The same product was also obtained on heating **4** with phenylhydrazine in 50% acetic acid (→**47**) and subsequent de-O-acetylation:[24b].



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