Synthesis of Sugar-Derived 2′- and 3′-Substituted Furans and Their Application in Diels−Alder Reactions[‡]

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Dedicated to Professor Janusz Jurczak on the occasion of his 60th birthday

Keywords: Diels−Alder cyclization / Furyl sugars / Retro Diels−Alder reaction

A convenient synthesis of 2′- and 3′-furyl sugars in which the furan and the sugar parts are directly connected is presented. The key step comprises HF·py-induced cyclization of α,β-unsaturated carbonyl compounds (ketones or aldehydes) possessing terminal hydroxymethylene groups protected as TBDPS ethers. Treatment of such furan derivatives with *N*-phenylmaleimide under high-pressure conditions (11 kbar) produces the corresponding [4+2] adducts, with the *endo* forms predominating. At p = 1 atm and T = 20 °C, however, the *exo* isomers are formed as the main products. The [4+2] adducts undergo retro Diels–Alder reactions at elevated temperatures at atmospheric pressure.

Introduction

Furan rings are often present in natural products such as alkaloids;[2] such units may also be used as building blocks in the preparation of biologically important compounds (such as the higher carbon sugar antibiotic tunicamine,[3] prepared from **I**; Figure 1). Those containing a furan ring in the skeleton can be prepared by two general routes. The first consists of the treatment of activated simple derivatives of furan with the corresponding acceptors (such as 2- and 3-furyllithium, which − upon treatment with aldehydes − afford furyl alcohols of type **I** and **II**). The second requires construction of the five-membered heterocyclic ring from non-furyl precursors. The latter method is more difficult, but allows highly functionalized furan derivatives to be prepared in a regioselective and stereoselective manner. As far as the furan regioisomers are concerned, the 3-substituted ones are much more difficult to prepare than the corresponding 2-substituted derivatives.

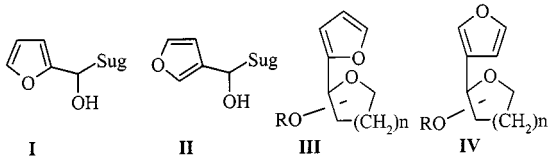

Figure 1. Different types of furyl sugar derivatives

Only a limited number of examples of the preparation of furyl sugars of type **III** is to be found in the literature. They may be prepared by means of hetero Diels−Alder reactions between furfural and alkoxydienes, producing six-membered ring derivatives,[4] or by Ferrier-type reactions between glycals and furan.[5] Even less is known about the preparation of 3-substituted furyl sugars[6] (such as **IV** in Figure 1). The synthesis of 2′- and 3′-substituted furan derivatives of type **III** and **IV** and their application in the Diels−Alder reaction is presented in this paper.

Results and Discussion

The strategy for the synthesis of compounds of type **III** and **IV** is outlined in Figure 2. The required starting materials are sugar allylic alcohols that also incorporate carbonyl functions (aldehydes or ketones); they should undergo cyclization with elimination of a molecule of water, providing 2′- and 3′-substituted furans. Such unsaturated precursors can be prepared from hydroxy aldehydes or vicinal diols (Figure 2).

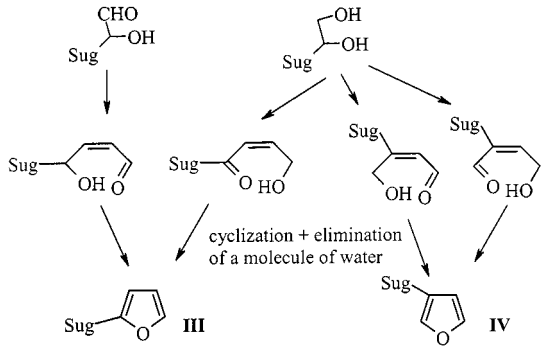

Figure 2. Strategies leading to 2- and 3-furyl sugars

[‡] Preceding communication: Ref.[1]

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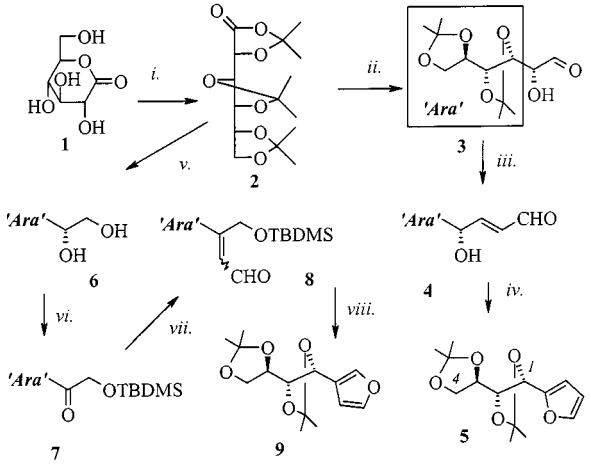
We have recently elaborated an efficient synthesis of 3,4:5,6-di-*O*-isopropylidene-D-glucose (**3**) by semireduction of the ester grouping in triacetonide **2**, easily accessible[7] from D-gluconolactone (**1**). This hydroxyaldehyde was used as a model compound for the preparation of 2′-furyl sugars. Treatment of **3** with $Ph_3P{=}CHCHO$ provided the (*E*)-α,β-unsaturated aldehyde **4**, which upon treatment with a mild acidic catalyst (PPTs) in refluxing toluene (the cyclization was not observed at lower temperatures) afforded furan **5** [(*E*) → (*Z*) isomerization had to have preceded this process], albeit in moderate yield (49%; Scheme 1). This low yield probably resulted from the instability of the furan ring even under such mild acidic conditions.



Scheme 1. *i.* $ZnCl_2$, acetone, ref.[7]; *ii.* DIBAL-H, then Et_3N, ref.[7]; *iii.* $Ph_3P{=}CH{-}CHO$ (46%); *iv.* PPTs (49%); *v.* $LiAlH_4$ (85%); *vi.* 1. TBDMSCl, Et_3N (91%), 2. Swern oxidation; *vii.* 1. $Ph_3P{=}CHCO_2Me$ (95%), 2. DIBAL-H (90%), 3. Swern oxidation; *viii.* 6.6 M HF·py in MeOH (76%)

Triacetonide **2** might also serve as precursor of 3′-substituted furans. After reduction of **2** with $LiAlH_4$, the resulting diol[8] **6** was protected at the primary position (91%) and the secondary one was oxidized to ketone **7**. Unfortunately, compound **7** did not react with $Ph_3P{=}CH{-}CHO$, which would have produced **8** directly. The conversion of **7** into unsaturated sililoxy aldehyde **8**, however, was accomplished in three simple steps involving treatment with $Ph_3P{=}CHCO_2Me$ (95%), followed by reduction of the ester function to an alcohol (with DIBAL-H, 90%), and subsequent oxidation of the latter to an aldehyde. Deprotection of the hydroxy function in **8** with fluoride should afford a free alcohol, cyclization of which under conditions similar to those producing **5** should provide the 3′-substituted furan **9**. We observed, however, that this cyclization occurred *directly* under the conditions of the deprotection step, affording compound **9** in 76% yield. This process presumably had to have been preceded by a (*E*) → (*Z*) isomerization of a double bond (Figure 3). If this observation is general, it could also open an easy route to 2′-substituted furyl sugars in which the sugar and the furan ring are joined directly to one another.

We have recently also elaborated a convenient route to higher carbon sugar alditol **14** (Scheme 2), using

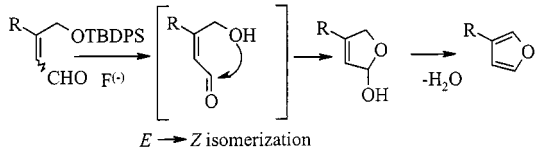
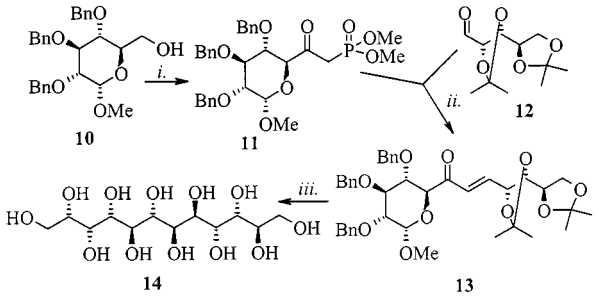


Figure 3. Conversion into furans induced by fluoride ion

Horner−Emmons methodology. The key step consisted of treatment of phosphonate **11** (prepared from glycoside **10**) with aldehyde **12**, with subsequent functionalization of resulting enone **13**.[9] This phosphonate methodology (affording α,β-unsaturated ketones), together with the fluoride ion induced cyclization process (shown in Figure 3) might open an easy route to furan derivatives substituted at the 2′-position with sugar moieties.

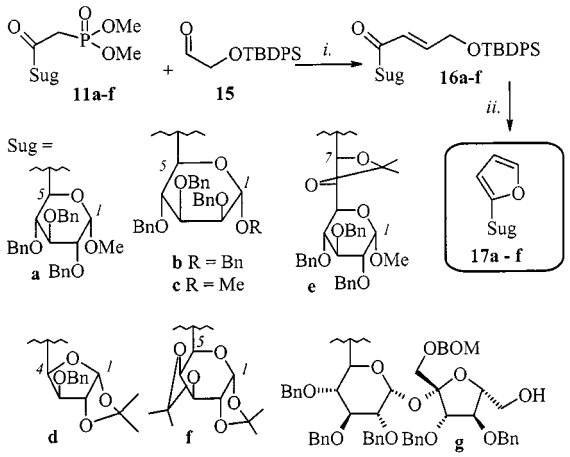


Scheme 2. *i.* 1. Jones oxidation, 2. CH_2N_2, 3. $MeP(O)(OMe)_2$, BuLi, THF; *ii.* K_2CO_3, 18-crown-6, toluene, room temp.; *iii.* ref.[9]

Synthesis of 2′-Substituted Furan-Sugar Derivatives

Sugar phosphonates **11a**,[9] **11b**,[10] **11c**, **11d**,[11] **11e**, and **11f**[12] are easily available from the corresponding monosaccharides according to the methodology shown in Scheme 2. Treatment of these phosphorus species with *O*-(*tert*-butyldiphenylsilyl)glycoladehyde[13] (**15**) afforded the enones **16a−f** in good yields (60−80%). Treatment of these compounds with an HF·py complex removed the silyl blocks from the primary hydroxy groups, and induced (*E*)/(*Z*) isomerization of the double bonds and subsequent cyclization to furans **17a−f** (ca. 80% yield, Scheme 3). This mild method was recently applied by us for the preparation of the even more complicated furan derivative **17g**, substituted at the 2′-position with a sucrose unit.[14]

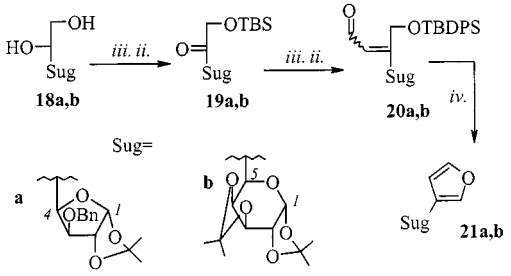
The furan structures of these derivatives were confirmed by their ^{13}C NMR spectra, which show signals at δ = 151 (quaternary C-α), 143 (C-α), 111, and 110 (both C-β atoms). This method for the preparation of 2-substituted furans **17a−f**, with the heteroaromatic moieties connected *directly* to a sugar of *different* ring size, seems to be general and is presumably more convenient than other syntheses presented in the literature.[4,5] Formation of the furan ring under the conditions for deprotection of silyl ethers (HF·py complex in methanol) is superior to the classical method, which involves treatment of appropriate precursors with acid.



Scheme 3. *i.* K_2CO_3, 18-crown-6, benzene, room temp. (60−80%); *ii.* HF·py in methanol (ca. 80%)

Synthesis of 3′-Substituted Furan-Sugar Derivatives

The synthesis of 3′-substituted furan derivatives followed the route already presented. The primary OH groups in sugar diols **18a**[15] and **18b**[16] were protected as *tert*-butyldiphenylsilyl (TBDPS) ethers (80%), the secondary ones oxidized to ketones (**19a**, **19b**), and the resulting carbonyl derivative treated with $Ph_3P{=}CH{-}CO_2Me$ (95%). The α,β-unsaturated esters thus formed were easily converted into target enones **20a** and **20b** by reduction with DIBAL-H (90%), followed by oxidation with Swern reagent[17] (Scheme 4). Deprotection of the primary hydroxy functions with an HF·py complex resulted in formation of 3′-substituted furans **21a** and **21b** (70−85%).



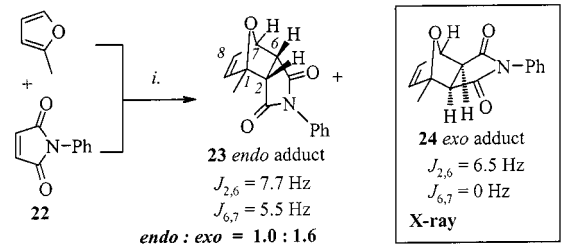
Scheme 4. *i.* TBDPSCl, Et_3N (69−84%); *ii.* Swern oxidation; *iii.* 1. $Ph_3P{=}CHCO_2Me$, xylene reflux (95%), 2. DIBAL-H (ca. 90%); *iv.* HF·py in methanol

The furan structure of these derivatives was also easily confirmed by their ^{13}C NMR spectra, which showed signals at δ = 141, 143 (both C-α), 120 (quaternary C-β), and 111 (C-β). Thus, the method presented here enables derivatives with directly interconnected furan and carbohydrate ring moieties to be obtained. Both 2′- and 3′-substituted furans with different sugar ring sizes (or even with linear sugar moieties) are available by this simple method.

Diels−Alder Reactions between the Furan Derivatives and *N*-Phenylmaleimide

With ready access now to chiral furans with sugar substituents at the 2′- and 3′-positions (**17** and **21**, respectively), we decided to examine their applicability as dienes in Diels−Alder reactions. The furan system is an activated diene and readily undergoes [4+2] cycloaddition with activated dienophiles. 2-Methylfuran, for example, reacts at room temperature with maleic anhydride to afford the corresponding Diels−Alder adduct, which slowly undergoes the retro cycloaddition.[18] Such adducts are not usually stable at elevated temperatures and the best yields are obtained when this reaction is performed under high pressure conditions.

Highly active *N*-phenylmaleimide (**22**) was chosen as the dienophile in our study. Model high-pressure treatment of **22** with 2-methylfuran afforded two products in a 1.0:1.6 ratio [19] and 85% overall yield (Scheme 5). The 6-H resonance in the ^1H NMR spectrum of **23** showed coupling not only to 2-H ($J_{2,6}$ = 7.7 Hz), but also to 7-H ($J_{6,7}$ = 5.5 Hz). No coupling with the 7-H resonance was seen in the spectrum of **24**. These data strongly suggested the *endo* structure for **23** and the *exo* form for **24**.[20] This assumption was further corroborated by X-ray analysis of product **24** (the structure is shown in Figure 4).



Scheme 5. *i.* 11 kbar, room temp., toluene/benzene, 4:1, 24 h (85%)

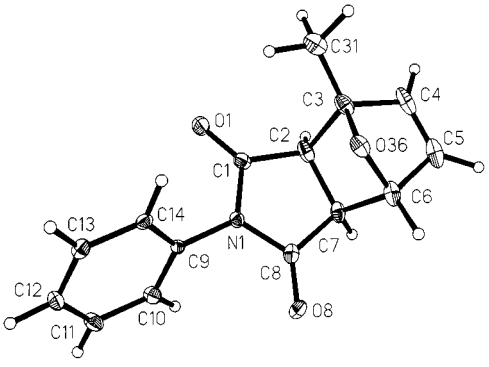
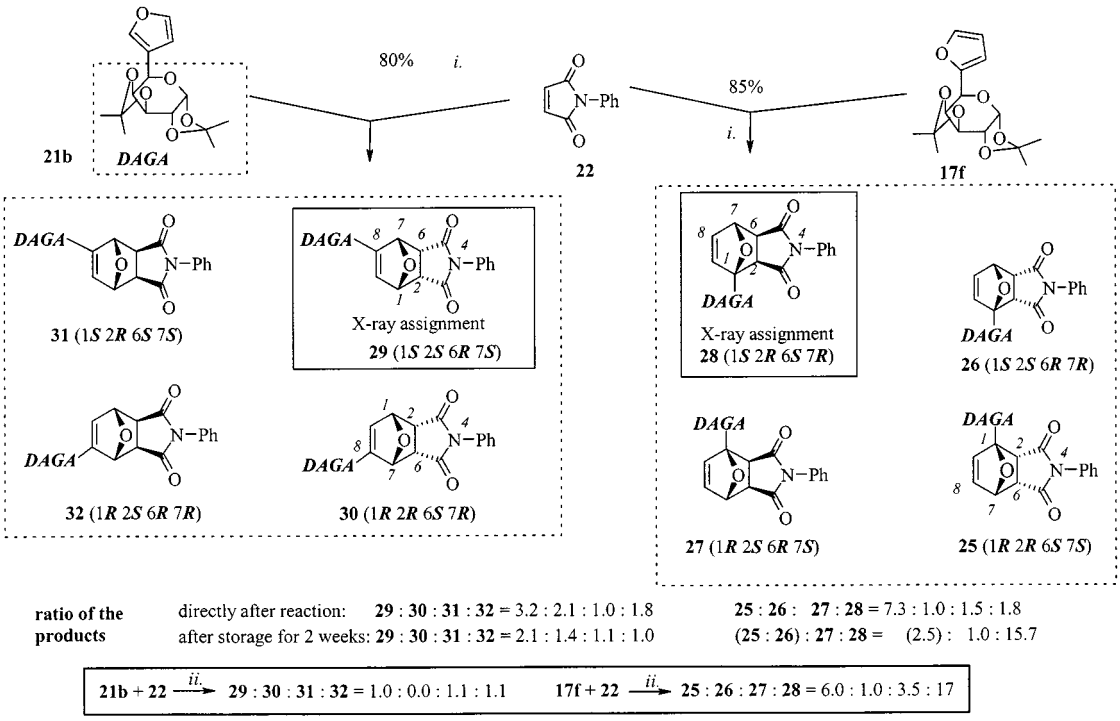


Figure 4. Structure of **24**

We next examined Diels−Alder reactions between **22** and furans **17f** (2′-substituted) and **21b** (3′-substituted), both derived from "diacetonogalactose" (Scheme 5). High-pressure cycloaddition between 2′-substituted furan **17f** and *N*-phenylmaleimide (**22**) afforded an 85% yield of four diastereoisomers, in the ratio 5.5 (**25**/**26**):1.0 (**27**):1.2 (**28**) (see ref.[1]). The *exo* structure could be assigned to compounds **27** and **28** on the basis of the ^1H NMR spectroscopic data; no coupling constants between 6-H and 7-H protons were seen. Consequently, the remaining isomers **25** and **26** had to be *endo*. This was also verified by the ^1H NMR spectro-



Scheme 6. *i.* 11 kbar, toluene/benzene, 4:1, room temp., 12 h; *ii.* p = 1 atm, toluene, room temp., four weeks

scopic data; the $J_{6,7}$ value in the spectrum of **25** amounted to 5.3 Hz (the amount of **26** was very low and this compound could not be separated from **25**. The corresponding signals of **26** overlapped with those of **25**). As expected, the kinetic *endo* products predominated.

Similar results were obtained from treatment of the 3′-substituted derivative **21b** with dienophile **22**. Four products were formed in 80% overall yield: the two *endo* compounds **29** ($J_{6,7}$ = 4.0, $J_{1,2}$ = 3.8 Hz) and **30**, and the two *exo* ones **31** and **32** ($J_{6,7}$ = $J_{1,2}$ = 0 Hz). The ratio of **25/26** was assigned as 88:12 (by ^{1}H NMR), hence **25/26/27/28** = 7.3:1.0:1.5:1.8.

The Diels−Alder adducts were not stable at atmospheric pressure at higher temperatures; in toluene solutions at 110 °C they readily underwent the retro Diels−Alder process in 0.5−2 h, affording the substrates **17f** and **22**, or **21b** and **22**, respectively. The adducts derived from **17f** and **22** (at least the *endo* ones **25** and **26**) were also not stable at room temperature. They underwent the retro reaction, but the resulting diene and dienophile would then react together to afford mostly the *exo* adducts. The original composition of the mixture [5.5 (**25/26**):1.0 (**27**):1.2 (**28**)] thus changed to 2.5 (**25/26**):1.0 (**27**):15.7 (**28**) on storage for 2 weeks at room temperature. Even below 0 °C the retro Diels−Alder process was still observed (with subsequent cycloaddition producing the *exo* products). The adducts derived from the 3′-substituted furan **21b** were more stable at room temperature and only rather small changes in the proportion of the isomers were noted (see Scheme 6).

A separate experiment examining the [4+2] cycloaddition between **17b** and **22** performed at room temperature and at p = 1 atm over 4 weeks afforded all four stereoisomers − **25**, **26**, **27**, and **28** − in a ratio of 6.0:1.0:3.5:17; thus, with the last (*exo*) in high preponderance. The same process (room temp., p = 1 atm) for **21b** + **22** provided only three stereoisomers − **29**, **31**, and **32** − in a ratio of 1.0:1.1:1.1. No detectable amounts of **30** were formed under these con-

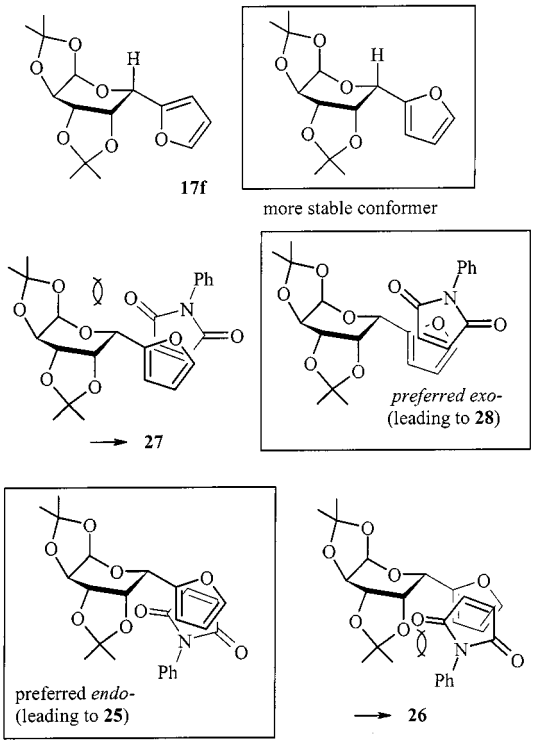


Figure 5. Transition states in the [4+2] cycloaddition between **17f** and **22**

ditions. The stereochemistry of the Diels−Alder reaction performed at $p = 1$ atm thus differed significantly from that observed under high pressure conditions.

Determination of the Configurations of the Diels−Alder Adducts

Although the *endo* and *exo* natures of the adducts could easily be deduced from ^{1}H NMR spectra, assignment of the positions of the sugar moieties on the heterotricyclic ring

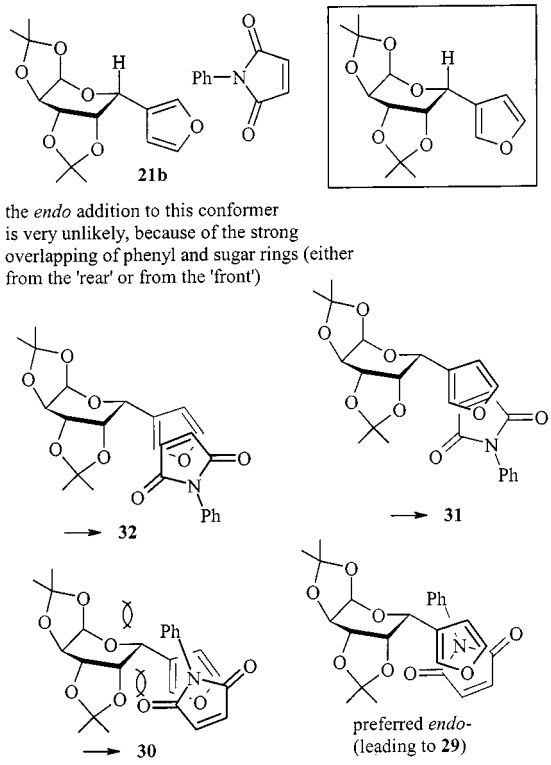


Figure 6. Transition states in the [4+2] cycloaddition between **21b** and **22**

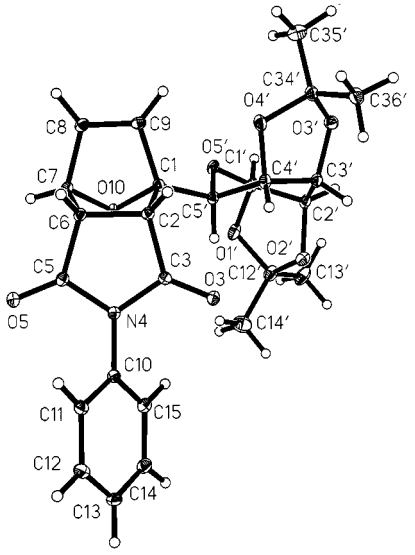


Figure 7. Structure of **28**

was not easy. Analysis of models of these cycloadditions enabled us to suggest the structure **25** for the main *endo adduct* and **28** for the main *exo adduct* obtained on treatment of **17f** with **22** (Figure 5). Analogously, compound **29** should be obtained as the main *endo* isomer in the reaction between **21b** and **22**, while the expected quantities of the *exo* adducts **31** and **32** would be comparable (Figure 6).

These predictions were supported by the X-ray analysis. Structure **28** was assigned to the main *exo* isomer produced on treatment of **17f** with **22** (Figure 7), while structure **29** was assigned to the main *endo* product produced on treatment of **21b** with **22** (Figure 8). X-ray structures of the *endo* isomers **25** and **26** could not be obtained, because of the instabilities of the adducts.

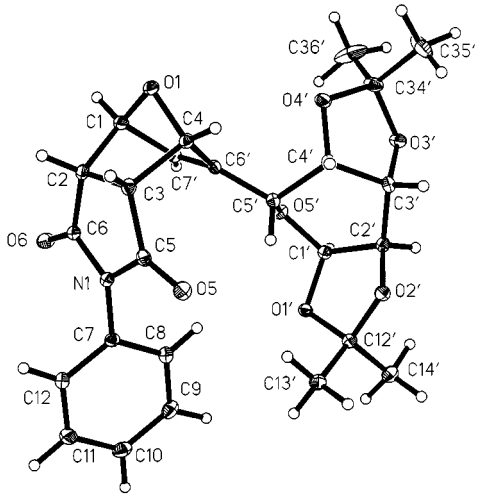


Figure 8. Structure of **29**

Conclusion

The method presented in this paper opens an easy route to 2′- and 3′-furyl sugars and has no particular limitations concerning the sugar synthon. Such substituted furyl derivatives may be used as dienes in the reaction with *N*-phenylmaleimide; this process affords the corresponding cycloadducts in good yields. Under high-pressure conditions (11 kbar), the *endo* adducts predominate, whilst at $p = 1$ atm and at room temp. the *exo* isomers are formed as the main products. At elevated temperatures (110 °C) and at $p = 1$ atm the adducts undergo clean retro Diels−Alder process in ca. 0.5−2 h.

Experimental Section

General: NMR: Varian Gemini 200 spectrometer (200 MHz and 50 MHz, for ^{1}H and ^{13}C, respectively), $CDCl_3$ as used as a solvent and Me_4Si as internal standard (this spectrometer was also used for recording DEPT 135° spectra). COSY (^{1}H-^{1}H and ^{1}H-^{13}C) spectra were recorded with a Bruker AM 500 spectrometer (500 MHz and 125 MHz, for ^{1}H and ^{13}C, respectively) in the same

solvent. − MS: AMD-604 spectrometer (LSIMS; *m*-nitrobenzyl alcohol was used as a matrix, to which sodium acetate was added). For the numbering of protons see Schemes. The protons of the furan ring are numbered as 2′, 3′. − Optical rotations: Digital Jasco DIP 360 polarimeter for solutions in $CHCl_3$ at room temperature. − Column chromatography was performed on silica gel (Merck, 70−230 or 230−400 mesh). HPLC: Shimadzu LC-8A liquid chromatograph with Shimadzu SPD-6A UV detector and Nucleosil 100-7 column from Macherey−Nagel. For flash chromatography a fraction of petroleum ether with boiling range 70−90 °C was used as "mixture of hexanes". − THF and dichloromethane were distilled prior to use from potassium or calcium hydride, respectively. Dry toluene and benzene were stored over sodium wire. All solutions were dried with anhydrous sodium sulfate.

1-(2′-Furyl)-1,2:3,4-di-*O*-isopropylidene-D-*arabino*-tetritol (5). − a) 3,4:5,6-Di-*O*-isopropylidene-D-glucose[7] (**3**; 0.85 g, 3.8 mmol) was dissolved in dry benzene (20 mL) containing $Ph_3P{=}CHCHO$ (1.5 g, 5 mmol) and the mixture was stirred at room temperature for 2 h. Chromatographic purification (hexanes/ethyl acetate, 4:1 to 2:1) afforded compound **4** [(2*E*)-2,3-Didehydro-2,3-dideoxy-5,6:7,8-di-*O*-isopropylidene-D-*gluco*-oct-2-enose] (46%, syrup). − $[\alpha]_D = -16.0$ ($c = 1.1$). − HR MS: calcd. for $C_{14}H_{22}O_6 + Na^+$ 309.1314; found 309.1295. − ^{1}H NMR (selected signals): δ = 1.35, 1.39, 1.42 (double) [3 × s, 2 × 3 H, 6 H, 2 × $C(CH_3)_2$], 6.44 (ddd, 1 H, J = 15.7, 7.9, 2.0 Hz, 2-H), 7.00 (dd, J = 15.7, 3.6 Hz, 1 H, 3-H), 9.62 (d, 1 H, J = 7.9, 1-H). − ^{13}C NMR: δ = 25.0, 26.5, 26.8, 26.9 [2 × $C(CH_3)_2$], 67.8, (C-8), 69.4, 76.6, 77.5, 81.5 (C-4, C-5, C-6, C-7), 109.9, 110.1 [2 × $C(CH_3)_2$], 132.1, 155.6 (C-2,C-3), 193.0 (C-8). − **b)** Compound **4** (0.306 g, 1.06 mmol) was dissolved in dry toluene (10 mL) to which PPTs (ca. 30 mg) was added. The mixture was boiled under reflux for 12 h, cooled to room temp., and concentrated. The title product was isolated by column chromatography (hexanes/ethyl acetate, 10:1 to 6:1) (0.14 g, 0.52 mmol, 49%). − $[\alpha]_D = +23.8$ ($c = 1.7$). − ^{1}H NMR: δ = 1.23, 1.29, 1.46, 1.49 [4 × s, 4 × 3 H, 2 × $C(CH_3)_2$], 3.91 (dd, J = 4.3, 8.6 Hz, 1 H, 4_a-H, 4.06 (dd, J = 5.9, 8.6 Hz, 1 H, 4_b-H, 4.21 (m, 1 H, 3-H), 4.30 (t, J = 7.3 Hz, 1 H, 2-H), 4.95 (d, J = 7.3 Hz, 1 H, 1-H), 6.34 (dd, J = 1.8, 3.3 Hz, 1 H, 3′-H), 6.40 (dd, J = 0.8, 3.3 Hz, 1 H, 4′-H), 7.42 (dd, J = 0.8, 1.7 Hz, 1 H, 5′-H). − ^{13}C NMR: δ = 25.1, 26.3, 26.6, 27.1 [2 × C(CH_3)$_2$], 66.7 (C-4), 74.3, 76.4, 79.1 (C-1, C-2, C-3), 109.0, 110.3 (C-3′, C-4′), 109.5, 109.9 [2 × $C(CH_3)_2$], 142.8 (C-5′), 151.3 (C-2′). − $C_{14}H_{20}O_5$ (268.31): calcd. C 62.67, H 7.51; found C: 62.65; H 7.59.

1-(3′-Furyl)-1,2:3,4-di-*O*-isopropylidene-D-*arabino*-tetritol (9): 3,4:5,6-Di-*O*-isopropylidene-D-glucitol[8] (**6**; 3.0 g, 11.5 mmol) was dissolved in dry dichloromethane (40 mL) containing *tert*-butyldimethylsilyl chloride (2.0 g, 13.0 mmol), triethylamine (2 mL), and catalytic amounts of DMAP (ca. 10 mg). The mixture was stirred at room temperature for 2 d and the product 1-*O*-*tert*-butyldimethylsilyl-3,4:5,6-di-*O*-isopropylidene-D-glucitol − was isolated by column chromatography (hexane/ethyl acetate, 7:1) (91%, syrup). − $[\alpha]_D = +11.9$ ($c = 1.6$). − HR MS (ESI): calcd. for $C_{18}H_{36}O_6Si + Na^+$ 399.2179; found 399.2189. − ^{13}C NMR: δ = −5.5, −5.4 [Si(CH_3)$_2$], 18.2 [SiC(CH_3)$_3$], 25.8 [SiC(CH_3)$_3$], 25.2, 26.6, 26.8, 27.0 [2 × C(CH_3)$_2$], 64.6, 67.2 (C-1, C-6), 70.2, 77.0, 77.2, 79.5 (C-2, C-3, C-4, C-5), 109.4, 109.5 [2 × $C(CH_3)_2$]. − This product (2.6 g, 6 mmol) was oxidized with Swern reagent[17] and the resulting ketone **7** was treated with $Ph_3P{=}CHCO_2Me$ (2.5 g, 7.8 mmol) in boiling xylene (20 mL) over 10 h. The α,β-unsaturated esters [1:3 mixture of (*E*)/(*Z*) isomers; HR MS: calcd. for $C_{21}H_{38}O_7Si + Na^+$: 453.2284; found 453.2282] thus formed (2.5 g, 5.8 mmol, 95%) were dissolved in dry CH_2Cl_2 (50 mL), cooled to −23 °C, and reduced with DIBAL-H (20 mL of a 1 M solution in hexane). Standard workup followed by column chromatography (hexanes/ethyl acetate, 4:1) afforded the desired allylic alcohol as a mixture of (*E*)/(*Z*) isomers (2.1 g, 5.2 mmol, 90%). − HR MS: calcd. for $C_{20}H_{38}O_6Si + Na^+$: 425.2335; found 425.2327. − Oxidation of these allylic alcohols (1.9 g, 4.7 mmol) with Swern reagent[17] afforded aldehyde **8**. Crude **8** was dissolved in methanol (20 mL) and treated with a 6.6 M solution of HF·py complex in methanol (10 mL) at room temperature over 2 d to afford 3′-substituted furan **9** (0.9 g, 3.4 mmol, 76%). − $[\alpha]_D = -10.0$ ($c = 0.6$). − HR MS: calcd. for $C_{14}H_{20}O_5$ 268.1310; found 268.1326. − ^{1}H NMR: δ = 1.29, 1.31, 1.44 (double) [3 × s, 2 × 3 H, 6 H, 2 × $C(CH_3)_2$], 3.87 (t, J = 7.5 Hz, 1 H, 2-H), 3.91 (dd, J = 8.5 Hz, 1 H, 4_a-H), 4.09 (dd, J = 6.2 Hz, 1 H, 4_b-H), 4.17 (m, 1 H, 3-H), 4.91 (d, J = 7.7 Hz, 1 H, 1-H), 6.45 (dd, J = 0.8, 1.8 Hz, 1 H, 4′-H), 7.38 and 7.46 (2 × m, 2 × 1 H, 2′-H, 5′-H). − ^{13}C NMR: δ = 25.0, 26.2, 26.7, 26.8 [2 × C(CH_3)$_2$], 66.9 (C-4), 74.4, 76.6, 81.7 (C-1, C-2, C-3), 108.9, (C-4′), 109.1, 109.4 [2 × $C(CH_3)_2$], 124.0 (C-3′), 140.0, 143.0 (C-2′, C-5′). − $C_{14}H_{20}O_5$: calcd. C 62.67, H 7.51; found C 62.82, H 7.61.

Dimethyl (Methyl 2,3,4-tri-*O*-benzyl-α-D-*manno*-heptopyranos-6-ulos-7-yl)phosphonate (11b): A solution of BuLi (2.5 M in hexane, 3.6 mL) was added at −78 °C to a stirred solution of dimethyl methylphosphonate (1 mL, 9.34 mmol) in dry THF (20 mL), and the mixture was stirred under argon at −78 °C for 15 min. A solution of methyl (methyl 2,3,4-tri-*O*-benzyl-α-D-*manno*-heptopyranos)uronate (1.1 g, 2.23 mmol; prepared by oxidation of the parent alcohol[21] **15** with Jones reagent[22] and subsequent esterification with CH_2N_2) in THF (5 mL) was added, stirring was continued for an additional 20 min at −78 °C, and the mixture was allowed to come to room temperature. TLC (hexanes/ethyl acetate, 2:1) showed disappearance of starting material and formation of a new, very polar product. The mixture was partitioned between ethyl acetate and brine, the organic layer was separated, washed twice with water, dried, and concentrated. The crude product was purified by column chromatography (hexanes/ethyl acetate, 1:1 to 3:7) to afford **11b** as an oil (1.04 g, 1.78 mmol, 80%). − $[\alpha]_D = +10.3$ ($c = 1.3$). − HR MS: calcd. for $C_{31}H_{37}O_9P + Na^+$ 607.2073; found 607.2073. − ^{1}H NMR: δ = 3.25 (dd, J = 14.3, 22.2 Hz, 1 H, 7_a-H), 3.42 (dd, J = 14.3, 22.1 Hz, 1 H, 7_b-H), 3.71, 3.75 [2 × d, 6 H, J = 11.2 Hz, P(OCH_3)$_2$], 3.95 (dd, J = 2.7, 8.8 Hz, 1 H, 3-H), 4.09 (dd, J = 8.9, 9.0 Hz, 1 H, 4-H), 4.24 (d, J = 9.1 Hz, 1 H, 5-H), 4.78 (d, J = 2.1 Hz, 1 H, 1-H). − ^{13}C NMR: δ = 38.8 (d, J = 129.7 Hz, C-7), 52.9, 53.2 [2 × d, J = 5.7, 6.0 Hz, P(OCH_3)$_2$], 55.3 (OMe), 72.4, 73.9, 74.7, (3 × OCH$_2$Ph), 74.3, 75.0, 75.7, 79.5 (C-2, C-3, C-4 and C-5), 99.7 (C-1), 197.8 (d, J = 7.0 Hz, C-6).

Typical Procedure for the Preparation of Sugar Enones 16: Solid anhydrous potassium carbonate (0.3 g) was added to a solution of the appropriate sugar phosphonate (**11a**−**f**, 1 mmol) and aldehyde **15** (1.1 mmol; prepared directly before use by ozonolysis of a TBDPS-protected allyl alcohol followed by treatment with Me_2S) in dry benzene (10 mL), followed by 18-crown-6 (1 mmol; catalytic amounts of 18-crown-6 or Bu_4NBr can also be used without significant decrease in reaction yield). Formation of the desired product could easily be observed by TLC (viewing under UV light). After the mixture had been stirred for 16 h at room temperature, water was added and the product was extracted with ethyl acetate. The organic phase was washed with water and brine, dried, and concentrated. The product was purified by column chromatography (hexanes/ethyl acetate, 10:1 to 5:1).

Methyl (7*E*)-2,3,4-Tri-*O*-benzyl-8-*O*-*tert*-butyldiphenylsilyl-6,7-dideoxy-6-oxo-α-D-*gluco*-oct-7-eno-1,5-pyranoside (16a): 81%, syrup.

− ^{1}H NMR (selected signals): δ = 1.07 [s, 9 H, SiC(CH$_3$)$_3$], 3.41 (s, 3 H, OCH$_3$), 3.54 (dd, *J* = 3.5, 9.7 Hz, 1 H, 2-H), 3.72 (dd, *J* = 9.0, 9.7 Hz, 1 H), 4.06 (dd, *J* = 9.2, 9.3 Hz, 1 H), 4.30−4.45 (m, 3 H), 4.60−5.10 (m, 7 H), 6.80 (broad d, *J* = 15.6 Hz, 1 H), 7.00 (m, 1 H) (7-H and 8-H). − ^{13}C NMR: δ = 19.2 [Si*C*(CH$_3$)$_3$], 26.7 [SiC(*C*H$_3$)$_3$], 55.7 (OCH$_3$), 63.0 (C-9), 73.6, 75.0, 75.9 (3 × O*C*H$_2$C$_6$H$_5$), 72.6, 79.0, 79.3, 81.7 (C-2, C-3, C-4 and C-5), 98.8 (C-1), 125.4 (C-7), 127.6−138.5 (C$_{arom}$), 147.2 (C-8), 195.0 (C-6).

Benzyl (7*E*)-2,3,4-Tri-*O*-benzyl-8-*O*-*tert*-butyldiphenylsilyl-6,7-dideoxy-6-oxo-α-D-*manno*-oct-7-eno-1,5-pyranoside (16b): 78%, syrup. − ^{1}H NMR (selected signals): δ = 1.06 [s, 9 H, SiC(CH$_3$)$_3$], 3.80 (dd, *J* = 2.6, 2.7 Hz, 1 H), 3.99 (dd, *J* = 2.9, 8.4 Hz, 1 H), 4.21−4.81 (m, 12 H), 5.01 (d, *J* = 2.2 Hz, 1 H, 1-H), 6.89 (broad d, *J* = 15.6 Hz, 1 H), 7.03 (m, 1 H) (7-H and 8-H). − ^{13}C NMR: δ = 19.2 [Si*C*(CH$_3$)$_3$], 26.7 [SiC(*C*H$_3$)$_3$], 63.1 (C-9), 69.5, 72.4, 72.6, 74.8 (4 × O*C*H$_2$C$_6$H$_5$), 74.5, 75.46, 75.53, 79.3 (C-2, C-3, C-4 and C-5), 97.8 (C-1), 124.7 (C-7), 127.6−138.5 (C$_{arom}$), 147.0 (C-8), 195.0 (C-6).

Methyl (7*E*/7*Z*)-2,3,4-Tri-*O*-benzyl-8-*O*-*tert*-butyldiphenylsilyl-6,7-dideoxy-6-oxo-α-D-*manno*-oct-7-eno-1,5-pyranoside (16c): 57%, syrup, ca. 1:1 (*E*)/(*Z*) mixture. − ^{13}C NMR (selected diagnostic signals for both isomers) δ = 19.2 [Si*C*(CH$_3$)$_3$], 26.7 [SiC(*C*H$_3$)$_3$], 63.1, 63.3 [C-9 for (*E*)and (*Z*)], 121.7, 124.3 [C-7 for (*E*)and (*Z*)], 146.7 147.0 [C-8 for (*E*) and (*Z*)], 194.8, 194.9 [C-6 for (*E*) and (*Z*)].

(6*E*)-3-*O*-Benzyl-7-*O*-*tert*-butyldiphenylsilyl-5,6-dideoxy-1,2-*O*-isopropylidene-5-oxo-α-D-*xylo*-hept-6-eno-1,4-furanose (16d): 65%, syrup. − ^{1}H NMR (selected signals): δ = 1.08 [s, 9 H, SiC(CH$_3$)$_3$], 1.34, 1.52 [2 × s, 2 × 3 H, C(CH$_3$)$_2$], 4.34 (m, 2 H), 4.53 (d, *J* = 7.2 Hz, 1 H), 4.62 (d, *J* = 3.3 Hz, 1 H), 4.84 (d, *J* = 3.5 Hz, 1 H), 6.12 (d, *J* = 3.5 Hz, 1 H, 1-H). Signals of 2-H and 3-H overlapped with H$_{arom}$ and the corresponding olefinic coupling constant not visible. − ^{13}C NMR: δ = 19.3 [Si*C*(CH$_3$)$_3$], 26.4, 27.0 [C(*C*H$_3$)$_2$], 26.8 [SiC(*C*H$_3$)$_3$], 63.3 (C-8), 72.4 (O*C*H$_2$C$_6$H$_5$), 82.2, 83.7, 85.0 (C-2, C-3, and C-4), 105.9 (C-1), 112.3 [*C*(CH$_3$)$_2$], 124.1 (C-6), 127.5−135.6 (C$_{arom}$), 145.9 (C-7), 195.6 (C-5).

Methyl (9*E*)-2,3,4-Tri-*O*-benzyl-11-*O*-*tert*-butyldiphenylsilyl-9,10-dideoxy-6,7-*O*-isopropylidene-8-oxo-L-*threo*-α-D-*gluco*-undec-9-eno-1,5-pyranoside (16e): 63%, syrup. − ^{1}H NMR (selected signals): δ = 1.09 [s, 9 H, SiC(CH$_3$)$_3$], 1.35, 1.52 [2 × s, 2 × 3 H, C(CH$_3$)$_2$], 2.25 (m, 2 H), 3.40 (s, 3 H, OCH$_3$), 3.50−3.65 (m, 2 H), 4.00 (m, 2 H), 4.36 (broad s, 1 H), 4.61−5.50 (m, 8 H), 7.08 (broad d, *J* = 15.7 Hz). − ^{13}C NMR: δ = 19.3 [Si*C*(CH$_3$)$_3$], 26.1, 27.0 [C(*C*H$_3$)$_2$], 26.7 [SiC(*C*H$_3$)$_3$], 55.1 (OCH$_3$), 63.2 (C-11), 73.3, 74.7, 75.7 (3 × O*C*H$_2$Ph), 69.7, 77.8, 78.1, 79.6, 79.8, 82.6 (C-2, C-3, C-4, C-5, C-6 and C-7), 97.8 (C-1), 110.9 [*C*(CH$_3$)$_2$], 122.3 (C-9), 127.5−138.6 (C$_{arom}$), 147.8 (C-10), 199.4 (C-8).

(6*E*)-8-*O*-*tert*-Butyldiphenylsilyl-6,7-dideoxy-1,2:3,4-di-*O*-isopropylidene-6-oxo-α-D-*galacto*-oct-6-eno-1,5-pyranose (16f): 75% yield, syrup. − ^{1}H NMR (selected signals): δ = 1.09 [s, 9 H, SiC(CH$_3$)$_3$], 1.30, 1.32, 1.43, 1.51 [4 × s, 4 × 3 H, 2 × C(CH$_3$)$_2$], 3.67 (broad d, *J* = 6.7 Hz, 1 H), 4.30−4.70 (m, 5 H), 5.68 (dd, *J* = 1.6, 4.9 Hz, 1 H), 7.00 (m, 1 H), 7.15 (d, *J* = 16.0 Hz, 1 H) (2-H and 3-H). − ^{13}C NMR: δ = 19.1 [Si*C*(CH$_3$)$_3$], 24.2, 24.7, 25.8, 26.5 [2 × C(*C*H$_3$)$_2$], 26.6 [SiC(*C*H$_3$)$_3$], 63.2 (C-9), 70.2, 70.6, 72.4, 73.3 (C-2, C-3, C-4 and C-5), 96.3 (C-1), 108.7, 109.6 [2 × *C*(CH$_3$)$_2$], 123.3 (C-7), 127.6−135.2 (C$_{arom}$), 146.2 (C-8), 196.6 (C-6).

3-*O*-Benzyl-5-(*tert*-butyldiphenylsilyloxymethylene)-5,6-dideoxy-1,2-*O*-isopropylidene-7-oxo-α-D-*xylo*-hept-5-eno-1,4-furanose (20a): *tert*-Butyldiphenylsilyl chloride (TBDPS-Cl; 0.83 g, 5.5 mmol) was added to a solution of diol **18a**[15] (1.55 g, 5 mmol) in dry dichloromethane (30 mL), followed by triethylamine (1.5 mL) and DMAP (30 mg). The mixture was stirred at room temperature for 18 h, concentrated, and the product − 3-*O*-benzyl-6-*O*-*tert*-butyldiphenylsilyl-1,2-*O*-isopropylidene-α-D-glucofuranose − (2.16 g, 3.9 mmol, 79%) was isolated by column chromatography (hexanes/ethyl acetate, 6:1 to 4:1). A solution of this product in CH$_2$Cl$_2$ (30 mL) was added to a solution of Swern reagent[17] (prepared from 1 mL of oxalyl chloride and 3 mL of DMSO in 50 mL of CH$_2$Cl$_2$ at −78 °C) and the mixture was stirred for 30 min at −78 °C. Triethylamine (3 mL) was added, and the mixture was stirred for another 30 min at −78 °C, allowed to come to room temperature, and partitioned between brine and ether. The organic phase was separated, washed with water, dried, and concentrated, and the crude ketone was dissolved in dry xylene (100 mL). Ylide Ph$_3$P=CHCO$_2$Me (2.4 g, 7 mmol) was added, and the mixture was heated to reflux for 6 h and concentrated. The product − methyl [3-*O*-benzyl-5-(*tert*-butyldiphenylsilyloxymethylene)-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hept-5-eno-1,4-furanos]uronate [mixture of (*E*)/(*Z*) isomers] − was isolated by column chromatography (hexanes/ethyl acetate, 6:1 to 4:1) (2.22 g, 3.7 mmol, 95%). Data for the main isomer. − [α]$_D$ = −93.7 (*c* = 1.1). − HR MS: calcd. for C$_{35}$H$_{42}$O$_7$Si + Na$^+$ 625.2597; found 625.2575. − ^{1}H NMR (selected signals): δ = 1.09 [s, 9 H, C(CH$_3$)$_3$], 1.26, 1.46 [2 × s, 2 × 3 H, C(CH$_3$)$_2$], 3.65 (OCH$_3$), 5.79 (d, *J* = 3.8 Hz, 1 H, 1-H), 5.86 (m, 1 H, 4-H), 6.47 (m, 1 H, 6-H). − ^{13}C NMR: δ = 19.3 [Si*C*(CH$_3$)$_3$], 26.3, 26.9, [C(*C*H$_3$)$_2$], 26.8 [SiC(*C*H$_3$)$_3$], 51.0 (OCH$_3$), 64.0 (*C*H$_2$OTBDPS), 72.3 (*C*H$_2$Ph), 76.6, 82.5, 83.4 (C-2, C-3, C-4), 104.8 (C-1), 111.6 [*C*(CH$_3$)$_2$], 112.9, (C-6), 158.1 (C-5), 166.4 (C = O). − This mixture of isomers (2.2 g, 3.65 mmol) was dissolved in dry dichloromethane (50 mL) and cooled to −23 °C under argon. DIBAL-H (14 mL of a 1 M solution in hexanes) was added dropwise and the mixture was stirred at −23 °C for 2 h. Water (50 mL) was added to decompose excess DIBAL-H, the mixture was stirred for 30 min at room temp., and ethyl acetate (100 mL) was then added. The organic layer was separated, washed with 2% sulfuric acid, then sodium bicarbonate solution to neutrality, and then brine. The product was isolated by column chromatography (hexanes/ethyl acetate, 5:1) (1.93 g, 3.36 mmol, 92%). − HR MS: calcd. for C$_{34}$H$_{42}$O$_6$Si + Na$^+$ 597.2648; found 597.2677. − This mixture of allylic alcohols was oxidized with Swern reagent[17] as previously described, to afford title product **20a** as a mixture of (*E*)/(*Z*) isomers.

6-(*tert*-Butyldiphenylsilyloxymethylene)-6,7-dideoxy-1,2:3,4-di-*O*-isopropylidene-8-oxo-α-D-*galacto*-oct-6-eno-1,5-pyranose (20b): This product was prepared analogously to **20a**, starting from 1,2:3,4-di-*O*-isopropylidene-D/L-*glycero*-α-D-*galacto*-hepto-1,5-pyranose[16] (4.73 g, 18.7 mmol).

Typical Procedure for Preparation of 2- and 3-Substituted Sugar Furans 17 and 21: Enone **16a**−**f** or **20a**/**20b** (1 mmol) was dissolved in methanol (10 mL) and treated with HF·py complex (2 mL of a 6.6 M solution in pyridine) for 16 h at ca. 40 °C. Water was added and the product was extracted with ethyl acetate. The organic phase was washed with water and brine, dried, and concentrated. The corresponding furyl sugar derivatives **17a**−**f** and **21a**/**21b** were purified by column chromatography (hexanes/ethyl acetate, 8:1 to 4:1).

Methyl 2,3,4-Tri-*O*-benzyl-5-*C*-(2′-furyl)-α-D-glucopyranoside (17a): 77%, syrup. − [α]$_D$ = +12.5. − HR MS: calcd. for C$_{31}$H$_{32}$O$_6$ + Na$^+$ 523.2097; found 523.2106. − ^{1}H NMR (selected signals): δ = 3.41 (s, 3 H, OCH$_3$), 3.61 (dd, *J* = 3.6, 9.5 Hz, 1 H, 2-H), 3.82 (dd, *J* = 9.2, 9.7 Hz, 1 H), 3.97−4.10 (m, 2 H), 4.50−4.99 (m, 7 H), 6.40 (s, 1 H), 7.01 (dd, *J* = 2.5, 5.8 Hz, 1 H). − ^{13}C NMR: δ = 55.4 (OCH$_3$), 73.5, 74.7, 75.8 (3 × O*C*H$_2$C$_6$H$_5$), 66.2, 79.5,

80.5, 81.4 (C-2, C-3, C-4 and C-5), 98.5 (C-1), 110.0, 110.5 (C-3′ and C-4′), 127.5−138.7 (C_{arom}), 142.7 (C-5′), 151.0 (C-2′).

Benzyl 2,3,4-Tri-*O*-benzyl-5-*C*-(2′-furyl)-α-D-mannopyranoside (17b): 82%, syrup. − HR MS: calcd. for $C_{37}H_{36}O_6 + Na^+$ 599.2410; found 599.2414. − ^{1}H NMR (selected signals): δ = 3.86 (dd, *J* = 1.9, 3.0 Hz, 1 H), 4.02 (dd, *J* = 3.1, 9.5 Hz, 1 H), 4.12−4.74 (m, 10 H), 4.98 (d, *J* = 1.5 Hz, 1 H, 1-H), 6.36 (dd, *J* = 1.8, 3.2 Hz, 1 H), 6.41 (broad d, *J* = 3.2 Hz, 1 H) (3′-H′ and 4′-H). − ^{13}C NMR: δ = 69.2, 72.5, 72.7, 75.0 (4 × O*C*H$_2$C$_6$H$_5$), 68.0, 74.8, 77.6, 79.6 (C-2, C-3, C-4, and C-5), 97.6 (C-1), 109.6, 110.4 (C-3′ and C-4′), 128.1−135.1 (C_{arom}), 142.6 (C-5′), 151.6 (C-2′).

Methyl 2,3,4-Tri-*O*-benzyl-5-*C*-(2′-furyl)-α-D-mannopyranoside (17c): 62%, syrup. − $[\alpha]_D$ = +39.0. − HR MS: calcd. for $C_{13}H_{20}O_6 + Na^+$ 295.1158; found 295.1152. − ^{1}H NMR: δ = 3.41 (OCH$_3$), 3.45−3.85 (m, 3 H, 2-H, 3-H and 4-H), 4.43 (d, *J* = 9.7 Hz, 1 H, 5-H), 4.83 (d, *J* = 1.5 Hz, 1 H, 1-H), 6.36−6.42 (m, 2 H), 7.44 (m, 1 H, 5′-H). − ^{13}C NMR: δ = 55.1, 58.1, 59.1, 60.2 (4 × OCH$_3$), 67.3, 77.2, 78.7, 80.7 (C-2, C-3, C-4 and C-5), 98.3 (C-1), 109.2, 110.3 (C-3′ and C-4′), 142.6 (C-5′), 151.5 (C-2′).

3-*O*-Benzyl-4-*C*-(2′-furyl)-1,2-*O*-isopropylidene-α-D-xylofuranose (17d): 60% syrup. − $[\alpha]_D$ = −38.4. − HR MS: calcd. for $C_{18}H_{20}O_5 + Na^+$ 339.1209; found 339.1205. − ^{1}H NMR (selected signals): δ = 1.34, 1.53 [2 × s, 2 × 3 H, C(CH$_3$)$_2$], 4.04 (d, *J* = 3.0 Hz, 1 H), 4.25 and 4.38 (AB of O*C*H$_2$C$_6$H$_5$, *J* = 12.0 Hz, 2 H), 4.69 (d, *J* = 3.8 Hz, 1 H), 5.26 (d, *J* = 3.1 Hz, 1 H), 6.05 (d, *J* = 3.8 Hz, 1 H, 1-H), 6.42 (dd, *J* = 1.8, 3.2 Hz, 1 H), 6.48 (d, *J* = 3.2 Hz, 1 H) (3-H and 4-H). − ^{13}C NMR: δ = 26.2, 26.8 [C(*C*H$_3$)$_2$], 72.2 (O*C*H$_2$C$_6$H$_5$), 76.2, 82.6, 83.1 (C-2, C-3, and C-4), 104.5 (C-1), 109.1, 110.6 (C-3′ and C-4′), 111.8 [*C*(CH$_3$)$_2$], 127.6, 127.7, 128.3, 134.2 (4 × C_{arom}), 142.0 (C-5′), 149.0 (C-2′).

Methyl 2,3,4-Tri-*O*-benzyl-7-*C*-(2′-furyl)-6,7-*O*-isopropylidene-D-*threo*-α-D-*gluco*-1,5-pyranoside (17e): 74%, syrup. − HR MS: calcd. for $C_{36}H_{40}O_8 + Na^+$ 623.2621; found 623.2626. − ^{1}H NMR (selected signals): δ = 1.49, 1.53 [2 × s, 2 × 3 H, C(CH$_3$)$_2$], 3.25 (dd, *J* = 8.8, 10.3 Hz, 1 H), 3.38 (s, 3 H, OCH$_3$), 3.52 (dd, *J* = 3.4, 9.6 Hz, 1 H), 3.83−4.02 (m, 3 H), 4.63−4.82 (m, 6 H), 4.96 (d, *J* = 10.6 Hz, 1 H), 5.26 (d, *J* = 8.2 Hz, 1 H), 6.30 (dd, *J* = 1.8, 3.3 Hz, 1 H), 6.37 (d, *J* = 3.3 Hz, 1 H) (3′-H and 4′-H). − ^{13}C NMR: δ = 26.0, 26.8 [C(*C*H$_3$)$_2$], 55.0 (OCH$_3$), 73.3, 74.5, 76.0 (3 × O*C*H$_2$C$_6$H$_5$), 68.3, 70.8, 78.2, 78.3, 79.9, 82.7 (C-2, C-3, C-4, C-5, C-6 and C-7), 97.6 (C-1), 109.5 [*C*(CH$_3$)$_2$], 109.8, 110.6 (C-3′ and C-4′), 127.5−138.8 (C_{arom}), 143.1 (C-5′), 151.4 (C-2′).

5-*C*-(2′-Furyl)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (17f): 79%. − M.p. 72−73 °C (after sublimation). − $[\alpha]_D$ = −127.4. − HR MS: calcd. for $C_{15}H_{20}O_6 + Na^+$ 319.1158; found 319.1154. − ^{1}H NMR: δ = 1.36 (6 H), 1.49 (3 H), 1.59 (3 H) [2 × C(CH$_3$)$_2$], 4.37 (dd, *J* = 2.4, 5.0 Hz, 1 H, 2-H), 4.48 (dd, *J* = 1.8, 7.9 Hz, 1 H, 4-H), 4.69 (dd, *J* = 2.2, 7.8 Hz, 1 H, 3-H), 4.93 (broad s, 1 H, 5-H), 5.63 (d, *J* = 4.9 Hz, 1 H, 1-H), 6.35 (dd, *J* = 1.8, 3.3 Hz, 1 H, 4′-H), 6.51 (dd, *J* = 0.8, 3.3 Hz, 1 H, 3′-H), 7.39 (dd, *J* = 0.9, 1.8 Hz, 1 H, 5′-H). − ^{13}C NMR: δ = 24.4, 24.9, 25.9, 26.9 [2 × C(*C*H$_3$)$_2$], 64.5, 70.6, 70.9, 72.0 (C-2, C-3, C-4 and C-5), 96.6 (C-1), 108.7, 109.5 [2 × *C*(CH$_3$)$_2$], 108.8, 110.3 (C-3′ and C-4′), 141.9 (C-5′), 150.7 (C-2′).

3-*O*-Benzyl-4-*C*-(3′-furyl)-1,2-*O*-isopropylidene-α-D-xylofuranose (21a): 84%, syrup. − $[\alpha]_D$ = −54.3 (*c* = 1.1). − HR MS: calcd. for $C_{18}H_{20}O_5 + Na^+$ 339.1208; found 339.1211. − ^{1}H NMR: δ = 1.33, 1.52 [2 × s, 2 × 3 H, C(CH$_3$)$_2$], 3.91 (d, *J* = 2.9 Hz, 1 H, 3-H),.4 68 (d, *J* = 3.8 Hz, 1 H, 2-H), 5.18 (d, *J* = 2.9 Hz, 1 H, 4-H), 6.01 (d, *J* = 3.8 Hz, 1 H, 1-H), 6.44 (d, 1.H, *J* = 1.1 Hz, 4′-H), 7.39, 7.48 (2 × m, 2 × 1 H, 2′-H, 3′-H). − ^{13}C NMR: δ = 26.0, 26.6 [C(*C*H$_3$)$_2$], 72.0 (*C*H$_2$Ph) 75.1, 82.8, 83.0 (C-2, C-3, C-4), 104.4 (C-1), 110.5 (C-4′), 111.3 [*C*(CH$_3$)$_2$], 119.8 (C-3′), 141.0, 142.6 (C-2′, C-5′). − $C_{18}H_{20}O_5$ (316.35): calcd. C 68.34, H 6.37; found C 68.40, H 6.39.

5-*C*-(3′-Furyl)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (21b): 69%. − M.p. 91−92 °C. − $[\alpha]_D$ = −85.8 (*c* = 1.5). − HR MS: calcd. for $C_{15}H_{20}O_6 + Na^+$ 319.1157; found 319.1165. − ^{1}H NMR: δ = 1.35, 1.36, 1.49, 1.57 [4 × s, 4 × 3 H, 2 × C(CH$_3$)$_2$], 4.35 (m, 2 H, 2-H, 4-H), 4.68 (dd, *J* = 2.3, 7.9 Hz, 1 H, 3-H), 4.82 (d, 1 H, 5-H), 5.62 (d, *J* = 5.0 Hz, 1 H, 1-H), 6.49 (dd, *J* = 0.7, 1.7 Hz, 1 H, 4′-H), 7.38 (t, *J* = 1.7 Hz, 1 H, 5′-H), 7.51 (m, 1 H, 2′-H). − ^{13}C NMR: δ = 24.3, 24.8, 25.9, 26.2 [2 × C(*C*H$_3$)$_2$], 63.4, 70.5, 70.9, 73.2(C-2, C-3, C-4, C-5), 96.6 (C-1), 108.4, 109 [2 × *C*(CH$_3$)$_2$], 110.1 (C-4′), 121.8 (C-3′), 140.6, 142.6 (C-2′, C-5′).

High-Pressure Reaction between 2-Methylfuran and *N*-Phenylmaleimide: A solution of 2-methylfuran (0.5 g, 6.1 mmol) and **22** (0.88 g, 5 mmol) in a 4:1 mixture of toluene and benzene (10 mL) was placed in a piston-cylinder-type apparatus[4,23] and kept under 1.1 GPa hydrostatic pressure for 12 h. The solvent was removed under reduced pressure, and the products were isolated by column chromatography (hexane/ethyl acetate, 4:1) to afford the following compounds.

***endo*-1-Methyl-4-phenyl-10-oxa-4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene-3,5-dione (23)**: 32%. − M.p. 115−116 °C. − ^{1}H NMR: δ = 1.88, (s, 3 H, CH$_3$), 3.27 (d, *J* = 7.7 Hz, 1 H, 2-H), 3.81 (dd, *J* = 5.5, 7.7 Hz, 1 H, 6-H), 5.43 (dd, *J* = 1.6, 5.5 Hz, 1 H, 7-H), 6.38 (d, *J* = 5.7 Hz, 1 H, 9-H), 6.54 (dd, *J* = 1.6, 5.7 Hz, 1 H, 8-H). − ^{13}C NMR: δ = 18.5 (CH$_3$), 48.6, 50.6 (C-2, C-6), 79.4 (C-7), 88.9 (C-1), 135.1, 137.7 (C-8, C-9), 173.9, 174.0 (C-3, C-5).

***exo*-1-Methyl-4-phenyl-10-oxa-4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene-3,5-dione (24):** 53%. − M.p. 144−146 °C. − ^{1}H NMR: δ = 1.19, (s, 3 H, CH$_3$), 2.88 (d, *J* = 6.5 Hz, 1 H, 2-H), 3.13 (d, 1 H, *J* = 6.5, Hz, 6-H), 5.32 (d, *J* = 1.8 Hz, 1 H, 7-H), 6.37 (d, *J* = 5.6 Hz, 1 H, 9-H), 6.56 (dd, *J* = 1.8, 5.6 Hz, 1 H, 8-H). − ^{13}C NMR: δ = 15.7 (CH$_3$), 49.5, 50.6 (C-2, C-6), 81.1 (C-7), 88.6 (C-1), 137.0, 140.7 (C-8, C-9), 174.0, 175.2 (C-3, C-5). − For the X-ray structure see Figure 4.

Procedure for the Preparation of the Diels−Alder Adducts: A solution of furyl sugars **17f** or **21b** (2.7 mmol) and *N*-phenylmaleimide **22** (0.514 g, 3.0 mmol) in a 4:1 mixture of toluene and benzene (10 mL) was placed in a piston-cylinder-type apparatus[4,23] and kept at 1.1 GPa hydrostatic pressure at room temperature for 6−12 h [100% conversion of **17f** and **21b** was noted after that time (TLC: hexanes/diethyl ether, 1:2; $R_{f\,substrate}$ = 0.8, $R_{f\,products}$ = 0.1−0.3)]. The mixture was concentrated under reduced pressure and the products were analyzed by HPLC (phase: hexanes/ethyl acetate, 2:1; constant flow: 3 mL/min), first directly after the reaction and then after having been kept at room temperature for 2 weeks under *p* = 1 atm.

Reaction between 2-Substituted Furan 17f and *N*-Phenylmaleimide (22): Directly after the reaction, four products **25**−**28** were obtained in 85% overall yield in a (**28**+**27**)/(**26**+**25**) ratio of 1.0:2.6 (determined by weight after preparative flash chromatography) or **28**/**27**/(**26**+**25**) ratio 1.2:1.0:5.5 (determined on the basis of HPLC UV detector, retention times: 3.2, 3.7, and 6.5 s, respectively; from the ^{1}H NMR spectrum of the mixture of **25**/**26** the ratio was assigned as **26**/**25** = 12:81; hence, the proportion of all four isomers was calculated as **25**/**26**/**27**/**28** = 7.3:1.0:1.5:1.8.). After two weeks the diastereoisomer ratio had changed to **28**/**27**/(**26**+**25**) =

15.7:1.0:(2.5) (HPLC), while after two months there were only traces of products **26** and **25**. The whole mixture was then subjected to preparative HPLC separation, from which were obtained fraction **I**, containing product **28** contaminated with **27**, and fraction **II**, enriched in product **27**. Fraction **I** was dissolved in chloroform in a small beaker, which was placed in a desiccator containing *n*-heptane. After 5 d, fine, colorless single crystals of pure **28**, suitable for X-ray analysis, were obtained.

(1*R*,2*R*,6*S*,7*S*)-1-*C*-(1,2:3,4-Di-*O*-isopropylidene-α-D-galactopyranos-5-yl)-4-phenyl-10-oxa-4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene-3,5-dione (25): ^{1}H NMR (*in the spectra of all Diels−Alder adducts the ''prime'' notation is used for the diacetonogalactose moiety*): δ = 1.36 (6 H), 1.50 (3 H), 1.67 [3 × s, 2 × C(CH$_3$)$_2$], 3.75 (dd, *J* = 7.7, 5.3 Hz, 1 H, 6-H), 3.86 (d, 1 H), 4.37 (dd, *J* = 1.5, 4.8 Hz, 1 H), 4.58 (broad s, 1 H), 4.66 (m, 2 H), 5.46 (d, *J* = 5.3 Hz, 1 H), 5.67 (d, *J* = 4.8 Hz, 1 H), 6.60 (broad s, 1 H), 7.10 (dd, *J* = 1.4, 7.7 Hz, 1 H), 7.32−7.46 (m, 5 H, H$_{arom}$). − ^{13}C NMR: δ = 23.9, 24.9, 25.9, 26.1 [2 × C(*C*H$_3$)$_2$], 46.6, 47.3 (C-2 and C-6), 65.8, 70.9, 71.0, 71.3, 79.8 (5 × CH), 91.6 (C-1), 96.7 (C-1′), 108.9, 109.7 [2 × *C*(CH$_3$)$_2$], 126.2−129.0 (C$_{arom}$), 134.2, 135.3 (C-8 and C-9), 173.5, 173.7 (C-3 and C-5).

(1*S*,2*S*,6*R*,7*R*)-1-*C*-(1,2:3,4-Di-*O*-isopropylidene-α-D-galactopyranos-5-yl)-4-phenyl-10-oxa-4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene-3,5-dione (26): This product, because of small quantities and lack of stability was not characterized. It could only be observed as contamination in the ^{1}H NMR spectrum of product **25**. − ^{1}H NMR (selected signals): δ = 3.52 (d, *J* = 6.8 Hz, 1 H, 2-H), 5.52 (d, *J* = 5.0 Hz, 1 H, 1′-H), 6.78 (broad s, 1 H).

(1*R*,2*S*,6*R*,7*S*)-1-*C*-(1,2:3,4-Di-*O*-isopropylidene-α-D-galactopyranos-5-yl)-4-phenyl-10-oxa-4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene-3,5-dione (27): ^{1}H NMR: δ = 1.33, 1.34, 1.47, 1.61 [4 × s, 4 × 3 H, 2 × C(CH$_3$)$_2$], 3.11, 3.17 (AB of 2-H and 6-H, *J* = 6.7 Hz, 2 H), 4.32−4.39 (m, 2 H), 4.50 (broad s, 1 H), 4.64 (dd, *J* = 2.2, 8.1 Hz, 1 H, 3′-H), 5.45 (d, *J* = 1.7 Hz, 1 H, 7-H), 5.66 (d, *J* = 5.1 Hz, 1 H, 1′-H), 6.35 (m, 1 H, 8-H), 6.70 (d, *J* = 5.7 Hz, 1 H, 9-H), 7.20−7.50 (m, 5 H, H$_{arom}$). − ^{13}C NMR: δ = 24.25, 24.72, 25.49, 25.96 [2 × C(*C*H$_3$)$_2$], 48.1, 50.4 (C-2 and C-6), 64.7, 70.5, 70.6, 71.0, 81.9 (5 × CH), 90.8 (C-1), 96.2 (C-1′), 108.9, 109.0 [2 × *C*(CH$_3$)$_2$], 126.4−129.1 (C$_{arom}$), 131.2, 140.2 (C-8 and C-9), 172.9, 175.0 (C-3 and C-5).

(1*S*,2*R*,6*S*,7*R*)-1-*C*-(1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranos-5-yl)-4-phenyl-10-oxa-4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene 3,5-dione (28): For X-ray analysis see Figure 7. − M.p. 171−172 °C. − [α]$_D$ = −91.4. − HR MS: calcd. for C$_{25}$H$_{27}$O$_8$N + H$^+$ 470.1815; found 470.1812. − ^{1}H NMR: δ = 1.30, 1.37, 1.43, 1.55 [4 × s, 4 × 3 H, 2 × C(CH$_3$)$_2$], 3.14, 3.24 (AB of 2-H and 6-H, *J* = 6.5 Hz, 2 H), 4.30 (broad s, 1 H, 5′-H), 4.35 (dd, *J* = 2.4, 5.0 Hz, 1 H, 2′-H), 4.72 (dd, *J* = 2.4, 8.1 Hz, 1 H, 3′-H), 5.24 (dd, *J* = 1.8, 8.1 Hz, 1 H, 4′-H), 5.33 (d, *J* = 1.7 Hz, 1 H, 7-H), 5.59 (d, *J* = 5.0 Hz, 1 H, 1′-H), 6.55 (ddd, 1 H, *J* = 1.0, 1.7, 5.7 Hz, 8-H), 6.87 (d, *J* = 5.7 Hz, 1 H, 9-H), 7.20−7.23 (m, 2 H, H$_{arom}$), 7.35−7.46 (m, 3 H, H$_{arom}$). − ^{13}C NMR: δ = 24.32, 25.04, 25.88, 25.92 [2 × C(*C*H$_3$)$_2$], 48.0, 51.0 (C-2 and C-6), 66.8 (C-5), 70.3 (C-2), 70.8 (C-4), 71.1 (C-3$_c$), 80.6 (C-7), 92.2 (C-1), 96.5 (C-1′), 108.8, 109.5 [2 × *C*(CH$_3$)$_2$], 126.4−129.1 (C$_{arom}$), 136.3 (C-8), 138.6 (C-9), 174.3, 174.8 (C-3 and C-5). All assignments were made on the basis of COSY homo- and heteronuclear correlation. − C$_{25}$H$_{27}$O$_8$N (469.49): calcd. C 63.96, H 5.80, N 2.98; found C 63.27, H 5.86, N 2.86.

Reaction between 3′-Substituted Furan 21b and *N*-Phenylmaleimide (22): Directly after the reaction, four products − **29**, **30**, **31**, and **32** − were obtained in 80% overall yield in 3.2:2.1:1.0:1.8 ratio. After storage at room temperature for two weeks, this ratio had changed to 2.1:1.4:1.1:1.0 (determined by weight after preparative flash chromatography).

(1*S*,2*S*,6*R*,7*S*)-8-*C*-(1,2:3,4-Di-*O*-isopropylidene-α-D-galactopyranos-5-yl)-4-phenyl-10-oxa-4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene-3,5-dione (29): For X-ray assignment see Figure 8. − M.p. 159−160 °C. − [α]$_D$ = −169.0 (*c* = 1.2). − HR MS (ESI): calcd. for C$_{25}$H$_{27}$NO$_8$ + Na$^+$ 492.1629; found 492.1644. − ^{1}H NMR: δ = 1.21, 1.28, 1.34, 1.41 (4 × s, 4 × 3 H, 4 × CH$_3$), 3.73 (m, 2 H, 2-H, 6-H),.4.34 (dd, *J* = 2.6, 5.1 Hz, 1 H, 2′-H), 4.37 (t, *J* = 2.2 Hz, 1 H, 5′-H), 4.44, (dd, *J* = 2.2, 7.7 Hz, 1 H, 4′-H), 4.66 (dd, *J* = 2.6, 7.7 Hz, 1 H, 3′-H), 5.31 (d, *J* = 4.0 Hz, 1 H, 7-H), 5.43 (m, 1 H, 1-H), 5.57 (d, *J* = 5.0 Hz, 1 H, 1′-H), 6.39 (t, *J* = 1.9 Hz, 1 H, 9-H). − ^{13}C NMR: δ = 24.7, 24.9, 25.4, 25.9 [2 × C(*C*H$_3$)$_2$], 46.3, 47.0 (C-2, C-6), 66.1, 70.3, 70.9, 71.5 (C-2′, C-3′, C-4′, C-5′), 79.6, 80.6 (C-1, C-7), 96.4 (C-1′), 108.9, 109.8 [2 × *C*(CH$_3$)$_2$], 127.9 (C-9), 146.9 (C-8), 173.8, 174.0 (C-3, C-5).

(1*R*,2*R*,6*S*,7*R*)-8-*C*-(1,2:3,4-Di-*O*-isopropylidene-α-D-galactopyranos-5-yl)-4-phenyl-10-oxa-4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene-3,5-dione (30): This compound was obtained only in very small quantities and could not be separated from the major isomer **31**. The presence of **30** could be deduced only from the ^{1}H NMR spectrum (500 MHz) of crude **31** [signals at δ = 3.03, 3.42 (2 × d, *J* = 6.7 Hz, 2-H, 6-H), 5.56 (d, *J* = 5.0 Hz, 1 H, 1′-H), 6.41 (t, *J* = 1.4 Hz, 1 H, 9-H)].

(1*S*,2*R*,6*S*,7*S*)-8-*C*-(1,2:3,4-Di-*O*-isopropylidene-α-D-galactopyranos-5-yl)-4-phenyl-10-oxa-4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene-3,5-dione (31): 24%, + ca. 4% of **30**. − ^{1}H NMR: δ = 1.34, 1.35, 1.53 (double), (3 × s, 2 × 3 H, 6 H, 4 × CH$_3$), 3.05, 3.46 (2 × d, 2 × 1 H, *J* = 6.7 Hz, 2-H, 6-H), 4.26 (dd, *J* = 2.0, 7.8 Hz, 1 H, 4′-H), 4.36 (dd, *J* = 2.5, 5.0 Hz, 1 H, 2′-H), 4.62 (broad s, 1 H, 5′-H), 4.66 (dd, *J* = 2.5, 7.8 Hz, 1 H, 3′-H), 5.35 (d, *J* = 0.9 Hz, 1 H, 1-H), 5.42 (s, 1 H, 7-H), 5.60 (d, *J* = 5.0 Hz, 1 H, 1′-H), 6.39 (t, *J* = 1.4 Hz, 1 H, 9-H). − ^{13}C NMR: δ = 24.5, 24.8, 25.8, 26.0 [2 × C(*C*H$_3$)$_2$], 47.2, 48.1 (C-2, C-6), 65.8, 70.1, 70.8, 73.0 (C-2′, C-3′, C-4′, C-5′), 81.6, 82.0 (C-1, C-7), 96.4 (C-1′), 108.6, 109.6 [2 × *C*(CH$_3$)$_2$], 132.0 (C-9), 148.9 (C-8), 175.6, 175.7 (C-3, C-5).

(1*R*,2*S*,6*R*,7*R*)-8-*C*-(1,2:3,4-Di-*O*-isopropylidene-α-D-galactopyranos-5-yl)-4-phenyl-10-oxa-4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene-3,5-dione (32): 17.5%. − M.p. 95−96 °C. − [α]$_D$ = −124.7 (*c* = 0.9). − HR MS: calcd. for C$_{25}$H$_{27}$NO$_8$ + Na$^+$ 492.1629; found 492.1623. − ^{1}H NMR: δ = 1.35 (double), 1.47, 1.54, (3 × s, 2 × 3 H, 6 H, 4 × CH$_3$), 3.06, 3.40 (2 × d, 2 × 1 H, *J* = 6.6 Hz, 2-H, 6-H), 4.32 (dd, *J* = 2.0, 7.8 Hz, 1 H, 5′-H), 4.36 (dd, *J* = 2.4, 5.0 Hz, 1 H, 2′-H), 4.67 (m, 2 H, 3′-H, 5′-H), 5.34 (d, *J* = 0.7 Hz, 1 H, 7-H), 5.46 (s, 1 H, 1-H), 5.58 (d, *J* = 5.0 Hz, 1 H, 1′-H), 6.42 (t, *J* = 1.7 Hz, 1 H, 9-H). − ^{13}C NMR: 24.4, 24.7, 25.8, 26.1 [2 × C(*C*H$_3$)$_2$], 47.5, 48.4 (C-2, C-6), 65.5, 70.2, 70.7, 72.6 (C-2′, C-3′, C-4′, C-5′), 81.9, 82.3 (C-1, C-7), 96.2 (C-1′), 108.6, 109.6 [2 × *C*(CH$_3$)$_2$], 132.1 (C-9), 148.3 (C-8), 175.5, 175.7 (C-3, C-5).

Retro Diels−Alder Reactions of Adducts 25−28 and 29−32: A mixture containing adducts **25**−**28** (0.2 g) was dissolved in toluene and boiled under reflux for 3 h. TLC indicated complete conversion of the Diels−Alder adducts into furan **17f** and *N*-phenylmaleimide (**22**). The same process performed using **29**−**32** afforded 3′-substituted furan **21b** and **22**.

Treatment of 17f and 21b with *N*-Phenylmaleimide at Room Temperature at Normal Pressure: Stoichiometric amounts of furan **17f** and dienophile *N*-phenylmaleimide (**22**) and (separately) **21b** and **22** in

toluene were kept at room temperature under normal pressure for 4 weeks. After that time, the [4+2] cycloadducts **25**, **26**, **27**, and **28** (from **17f** and **22**) had been formed in the ratio 6.0:1.0:3.5:17.0, and **29**, **31**, and **32** (from **21b** and **22** in the ratio 1.0:1.1:1.1 (by ^{1}H NMR). No detectable amounts of stereoisomer **30** was formed under these conditions.

X-ray Analysis of Cycloadducts. − Crystal Data for 24: $C_{15}H_{13}NO_3$, M_W = 255.26, T = 110(2), Mo-K_α radiation, orthorhombic, space group $P2_12_12_1$, a = 6.7685(8) Å, b = 11.9087(12), c = 15.5273(15), V = 1251.6(2) Å^3, Z = 4, D_c = 1.355 Mg·m^{-3}, μ = 0.095 mm^{-1}, F(000) = 536, crystal size 0.2 × 0.2 × 0.15 mm, diffractometer Kuma KM4CCD, 3.66° ≤ θ ≤ 23.96°, 6599 collected reflections, 1960 (R_{int} = 0.0515) independent reflections, 225 parameters. The structure was solved using the SHELXS-97 program and refined (including H atoms) using SHELXL-97 to $R_1(F)$ = 0.0481, $wR_2(F^2)$ = 0.1067 and S = 1.118. − **Crystal Data for 28:** $C_{25}H_{27}NO_8$, M_W = 469.48, T = 293, Mo-K_α radiation, orthorhombic, space group $P2_12_12_1$, a = 10.736(1) Å, b = 14.228(1), c = 15.630(1), V = 2387.5(3) Å^3, Z = 4, D_c = 1.306 Mg·m^{-3}, μ = 0.098 mm^{-1}, F(000) = 992, crystal size 0.4 × 0.3 × 0.3 mm, diffractometer Kuma KM4CCD, 2.61° ≤ θ ≤ 28.63°, 17045 collected reflections, 5786 (R_{int} = 0.0164) independent reflections, 416 parameters. The structure was solved using the SHELXS-97 program and refined (including H-atoms) using SHELXL-97 to $R_1(F)$ = 0.0306, $wR_2(F^2)$ = 0.0723 and S = 1.104. − **Crystal Data for 29:** $C_{25}H_{27}NO_8$, M_W = 469.48, T = 100, Mo-K_α radiation, monoclinic, space group $P2_1$, a = 10.058(2) Å, b = 11.058(2), c = 11.159(2), β = 111.93(3)° V = 1151.3(4) Å^3, Z = 2, D_c = 1.306 Mg·m^{-3}, μ = 0.098 mm^{-1}, F(000) = 992, crystal size 0.4 × 0.3 × 0.3 mm, diffractometer Kuma KM4CCD, 3.91° ≤ θ ≤ 28.71°, 8093 collected reflections, 5206 (R_{int} = 0.0272) independent reflections, 416 parameters. The structure was solved using the SHELXS-97 program and refined (including H atoms) using SHELXL-97 to $R_1(F)$ = 0.0352, $wR_2(F^2)$ = 0.0868 and S = 1.041. − Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-159 150 (**28**), -159 151 (**24**), and -159 152 (**29**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) + 44-1223/336-033, E-mail: deposit@ccdc.cam.ac.uk].

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Received January 18, 2001
[O01022]