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SYNTHESIS AND OXIDATIVE ACTIVATION OF AN OXABICYCLO[7.2.1] ENEDIYNE

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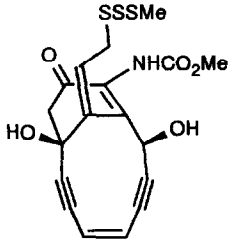
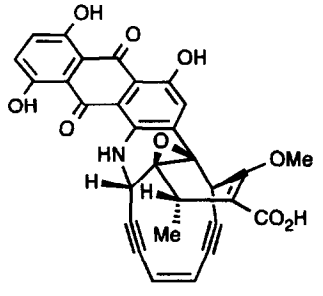
Abstract: Oxabicyclo[7.2.1] enediyne **23** which contains an *ortho*-methoxybenzyl group at the anomeric position was synthesized from methyl-2,3-anhydro-α-D-lyxofuranoside (**7**). Treatment of this stable bicyclic enediyne with ceric ammonium nitrate at room temperature in CH_3CN/H_2O gave the aromatized monocyclic compound **25**.

Modern strategies for the treatment of cancer using cytotoxic chemicals are generally based on the concept of prodrug activation. Provided that the prodrugs can be delivered selectively to the tumor cells - for example by monoclonal antibodies - toxic side effects during transport within the body would be minimized. On the other hand, if the activation of the prodrug would only be possible in tumor cells, a delivery device would be unnecessary. Still another similiar concept relies on the so-called ADEPT strategy.[1] That means the prodrug is activated by an enzyme which has been delivered selectively to tumor cells by antibodies. In order to implement such strategies, suitable prodrugs have to be available which can be furnished with various trigger devices. In this regard the recently discovered enediyne antitumor antibiotics represent ideal lead compounds. They are fascinating not only because of their unusual structures but also because of their novel mode of action.[2] Typically they are composed of three functional units: a) an enediyne which is part of a 10-membered ring, b) a trigger mechanism which through a chemical reaction leads to a reactive enediyne, and c) a part which is responsible for molecular recognition of DNA.



Calicheamicin core (1)



Dynemicin A (2)

Calicheamicin and esperamicin are activated through nucleophilic cleavage of the allylic trisulfide followed by addition of the resulting thiolate to the enone. In the case of dynemicin A (**2**) activation is initiated by reduction of the quinone system which, through shifting of electron pairs, causes the opening of the epoxide. The activation step enables the conjugated enediyne to cyclize to an aromatic diradical[3] which itself is a highly reactive species and reacts further with hydrogen donors, such as DNA, thereby inducing double strand

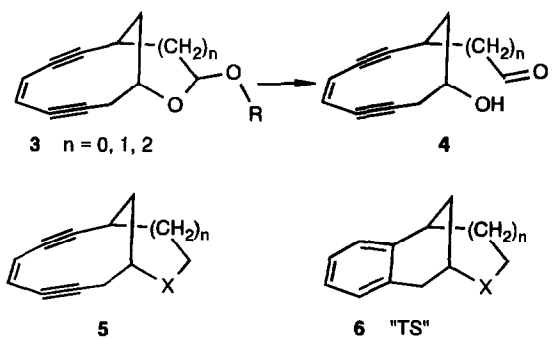
cleavage. Although the mechanisms of activation of calicheamicin and dynemicin differ markedly, a common feature is that the activation removes a blocking device which prevents the cyclization of the enediyne prodrug to the diradical. Whereas in calicheamicin the bridgehead double bond serves as a blocking device, in dynemicin A it is the epoxide which renders the Bergman cyclization impossible.

The concept of prodrug activation demands that stable enediynes or suitable precursors have to be designed which can be converted into reactive molecules by means of a chemical reaction. In general three strategies are conceivable which allow the generation of reactive enediynes. The first one, which is also implemented in the natural enediynes, is based on lowering the energy of the transition state of the Bergman cyclization by strain release. In an opposite strategy a stable enediyne would be activated by raising the energy of the ground state of the enediyne, also by strain modulation.[4] Finally, one can imagine a third principle of activation, namely the introduction of a missing π-bond into a strained enediyne precursor.[5] In all cases the aim of the activation step is to generate an enediyne with an activation barrier for the Bergman cyclization between 80 and 105 kJ mol^{-1} so that at physiological temperatures a fast cyclization to the aromatic diradical can occur.[6]

In this paper we report on the design and synthesis of an oxabicyclo[7.2.1]enediyne **22** containing an acetal functionality which could be cleaved under oxidative conditions to a reactive 10-membered enediyne.

Reactivity of Bicyclic Enediynes

The design of novel trigger mechanisms for the generation of reactive enediynes from stable ones requires that one is able to easily predict the reactivity or stability, respectively of strained enediynes. In the monocyclic series the reactivity, that is the ease of cycloaromatization, can be correlated to the distance between the ends of the conjugated enediyne.[7] According to this rule the shorter the so-called cd distance, the more reactive is the enediyne. The borderline between stable and reactive enediynes at room temperature can be drawn at about 331 pm. For example, whereas a 11-membered carbocyclic enediyne is quite stable at room temperature (cd = 366 pm) the corresponding 10-membered enediyne (cd = 325 pm) is already so strained that it cyclizes spontaneously.[7] In the bi- or polycyclic series it is not only the cd distance of the ground state that has an influence on the reactivity. As Snyder and Magnus have pointed out, strain in the transition state can increase the stability despite a short cd distance.[8] Since the transition state of the Bergman cyclization is very much product-like,[9] the additional strain in the transition state can be estimated from the strain energy (SE) of the aromatized product.



Scheme 1

Table 1. Calculated differential strain energies for some bicyclic enediynes

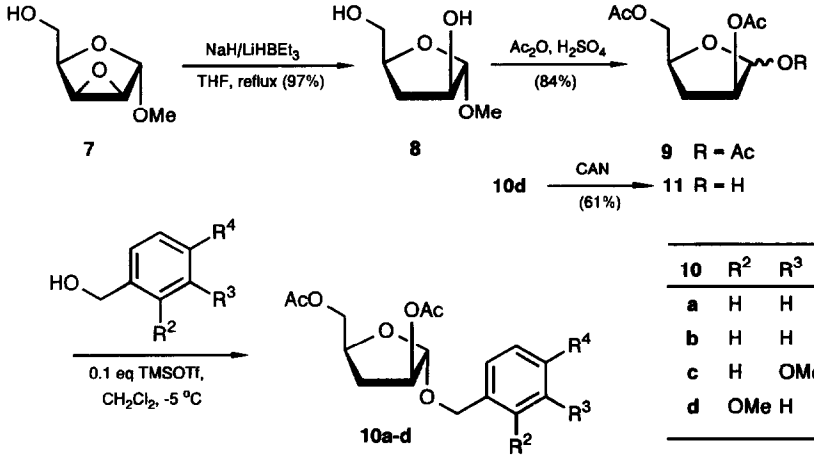
n	X	SE (GS)	SE (TS)	Δ SE [kJ mol^{-1}]
0	CH_2	51.5	82.3	30.8
1	CH_2	57.8	63.8	6.0
2	CH_2	67.5	91.5	24.0
0	O	40.8	70.5	29.7
1	O	50.2	64.6	14.4
2	O	61.6	86.1	24.5

Indeed, Magnus found for some bicyclic enediynes a correlation between the SE of the aromatized products (or parts of it) and the observed reactivity.[10] However, this model will only work if the SE in the ground states are similiar, or if one compares structurally similiar enediynes. We suggest an improved model which, in addition to the SE of the transition state (from SE of the aromatized product) takes the strain energy of the ground state into consideration. That is, we use the difference of the strain energies (ΔSE) between the transition and the ground state [ΔSE = SE (TS) - SE(GS)] as a measure for the reactivity of a strained enediyne.

For example, this model can account for structural modifications that raise the transition state as well as the ground state. In fact, it proved to be very useful in the design of oxabicyclo[7.2.1]enediynes as prodrugs for reactive enediynes. An inspection of known stable bicyclic enediynes reveals that most of them contain a 10-membered enediyne. On the other hand, it is known that 10-membered carbocyclic enediynes cyclize at physiological temperatures to the aromatic diradical.[7] In other words, cleavage of such bicyclic enediynes to 10-membered enediynes would constitute an activation by lowering the energy of the transition state. Incorporation of an acetal functionality into a bicyclic enediyne should allow cleavage of the bicyclic system as shown in Scheme 1 (**3** → **4**). Moreover, the use of different alcohols in the acetal would enable different trigger mechanisms. One of the questions to be answered was the size of oxabicyclic enediynes to use as prodrugs. Simple force-field calculations provided a clear answer. They were performed using the program PC model (V4.0). For sp^2- and sp-hybridized carbon atoms rhf-SCF π-calculations were included. This has almost no effect on the conformation of the enediynes ecept for somewhat larger (1-3 pm) cd distances. These calculations indicate that an oxabicyclo[7.3.1]enediyne would be rather unstable (small ΔSE) and might cyclize spontaneously at room temperature. On the other hand, the force-field calculations predict an oxabicyclo[7.2.1] to be quite stable. Whereas the Magnus model predicts a higher stability for the carbocyclic analogue [larger SE(TS)], our model shows that the oxygen atom lowers the energy of the transition state as well as the ground state resulting in comparable reactivity (Scheme 1). Another question to be answered was whether after cleavage of the acetal the resulting hemiacetal would open at all. Although the force-field calculations showed the 10-membered system **4** (n = 0) to be more strained than the hemiacetal **3** (n = 0, R = H), compound **4** is more stable (by 18.9 kJ mol^{-1}) as indicated by the more favorable total energy (MMX-E, without π-calculations).

Synthesis of the Oxabicyclo[7.2.1]enediyne 23

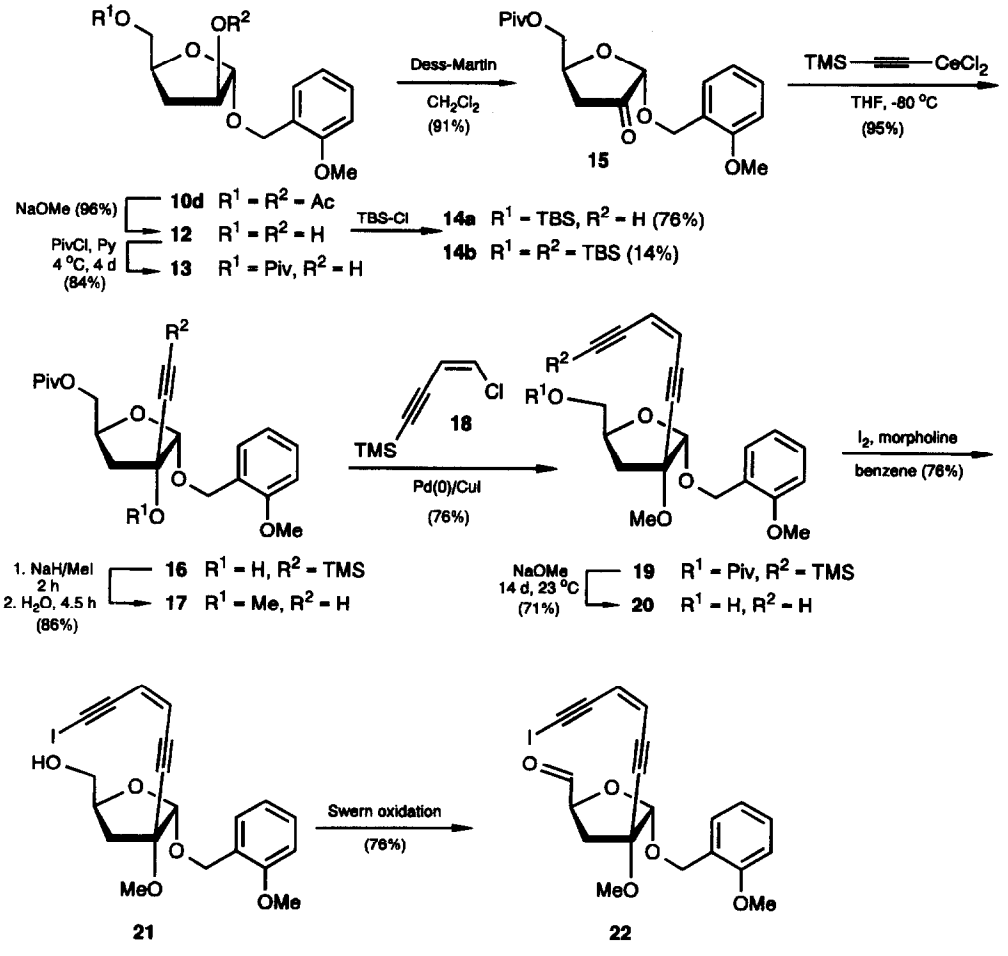
In a previous paper we described a synthetic route to an oxabicyclo[7.2.1] enediyne starting from a D-xylose derivative.[11] We then planned to modify the synthetic sequence to allow the incorporation of various alcohols at the anomeric position. For example, an electron rich benzyl alcohol might be easily cleaved via oxidation.[12] The plan for the preparation of various oxabicyclo[7.2.1] enediyne derivatives called for a stereoselective glycosylation[13] of a 2-O-acetyl-3-deoxy-furanoside. Starting with the known epoxide **7** which is available from D-xylose,[14] a regioselective epoxide opening was performed by using lithium triethylborohydride.[15] Conversion of the primary hydroxyl group to the alkoxide using sodium hydride helped to reduce the amount of the expensive reducing agent. Treatment of the crude diol **8** with acetic anhydride and sulfuric acid furnished the tri-O-acetyl-*threo*-pentofuranose **9** which served as glycosyl donor (Scheme 2).



10	R^2	R^3	R^4	yield (%)
a	H	H	OMe	30
b	H	H	H	84
c	H	OMe	H	87
d	OMe	H	H	78

Scheme 2

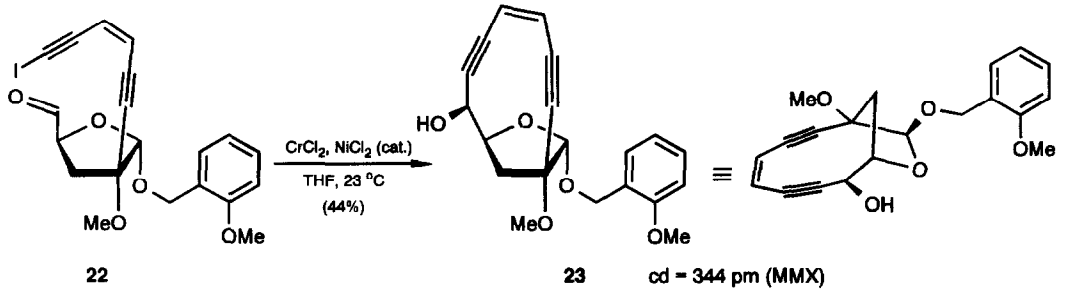
However, when **9** was reacted with 1.1 equivalents of 4-methoxybenzylalcohol and a catalytic amount of trimethylsilyl triflate in dichloromethane at -10 °C only a 30% yield of the desired glycoside **10a** could be realized. The formation of *di*-4-methoxybenzyl ether as a side product points to the Lewis acid sensitive nature of the glycoside **10a**. A similar disappointing result was obtained with boron trifluoride etherate as Lewis acid. In contrast, if other benzyl alcohols were used, high yields of the corresponding α-glycosides were obtained. Thus, benzyl alcohol gave 84% of **10b**, 3-methoxybenzylalcohol gave 87% of **10c**, and 2-methoxybenzylalcohol gave 78% of **10d**, even in a large scale reaction. The latter one was then chosen as the anomeric protecting group after a control experiment with ceric(IV) ammonium nitrate established that an oxidative removal of this group from the glycoside **10d** to give **11** (61%) was possible.[12b]



Scheme 3

After cleavage of the acetates from **10d** with NaOMe in methanol, the primary hydroxyl group of **12** was selectively protected with pivaloyl chloride to give compound **13**. Surprisingly, a highly selective protection of the primary hydroxyl group using silylating agents was not possible. For example, etherification of the primary hydroxyl group of diol **12** with *tert*-butyldimethylsilyl chloride to **14a** in dichloromethane was always accompanied by a substantial amount of the diprotected compound **14b**.[16] This ratio was even worse (48% mono plus 26% diprotected compound) with *tert*-butyldiphenylsilyl chloride. Subsequent oxidation of alcohol **13**

to the ketone **15** could be accomplished in 91% yield with the Dess-Martin periodinane reagent in dichloromethane at room temperature.[17] Addition of lithio(trimethylsilyl)acetylene to the ketone **15** gave only a low yield of the desired addition product, probably because of the relatively high acidity of the methylene protons α to the carbonyl group. However, after transmetallation of the lithium acetylide to the corresponding dichlorocerium acetylide[18] smooth addition occured, with the β-product **16** the only isomer observed. The tertiary hydroxyl group of **16** was protected as methyl ether using NaH/CH_3I in a mixture of THF and DMEU. Subsequent addition of water to the reaction mixture and stirring for several hours caused cleavage of the carbon-silicon bond affording the alkyne **17**. Through a Pd(0)/CuI-catalyzed coupling[19] of **17** with the known eneyne chloride[20] **18** the enediyne **19** was constructed. After removal of the pivaloate and the trimethylsilyl groups under basic conditions the enediyne alcohol **20** was converted to the iodoalkyne **21** with iodine in the presence of morpholine (76%).[21] Finally, oxidation of the alcohol **21** under Swern conditions provided the cyclization substrate **22**. The cyclization of **22** to the oxabicycloenediyne **23** could be achieved, as previously described,[11] by using an intramolecular Nozaki reaction (Scheme 4).[22] Thus, addition of a solution of **22** in THF to a suspension of $CrCl_2$ containing catalytic amounts of $NiCl_2$ in THF furnished the bicylic enediyne **23** in 44% isolated yield. Only one diastereomer was formed in this reaction. The configuration at the secondary hydroxyl group could be inferred through analysis of the ^1H NMR spectrum of the aromatized derivative **25** (vide infra). As expected from the force-field calculations the enediyne **23** is thermally quite stable. Although **23** decomposes in concentrated form, it can be kept in solution at 0 °C for several weeks without noticeable change.

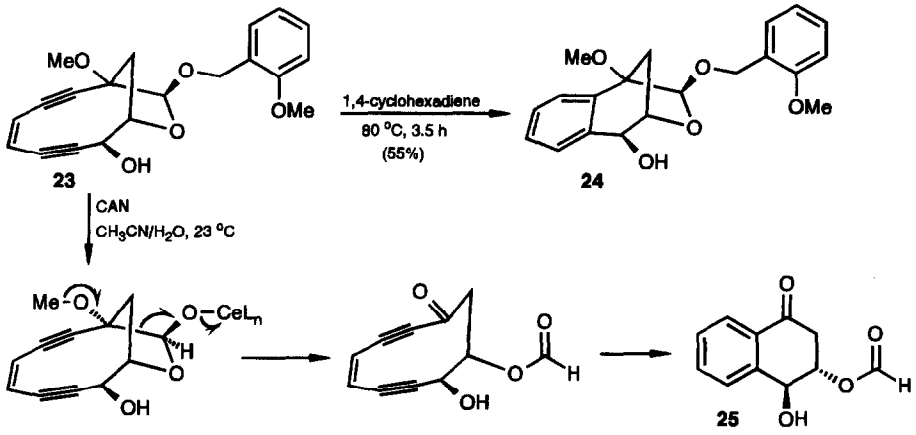


Scheme 4

Aromatization Studies

Despite the highly strained transition state for the Bergman cyclization of enediyne **23**, aromatization to **24** via the corresponding diradical could be induced by heating a solution of **23** in 1,4-cyclohexadiene for a few hours. Thus, the reactivity of compound **23** is comparable to that of the carbocyclic [7.2.1] enediyne **5** (X = CH_2, n = 0)[10] as predicted by the similiar values for Δ SE. On the other hand, cleavage of the acetal of **23** should generate a monocyclic reactive enediyne. Treatment of **23** with an excess of ceric(IV) ammonium nitrate caused disappearance of the bicyclic enediyne **23** and the formation of 2-methoxybenzaldehyde. However, instead of the expected compound resulting from acetal cleavage and opening, the naphtalenone **25** was isolated as a major fraction (18%). The structure of **25** was evident from the ^1H NMR spectrum. The methylene protons which are flanked by electron-withdrawing groups appear at δ 2.76 and 3.24, each as a doublet of doublet. A singlet at δ 8.09 points to the presence of a formyl rather than an aldehyde proton. In the IR spectrum compound **25** shows two absorptions in the carbonyl region, one at $\tilde{\nu}$ = 1727 (ketone) and the other at 1693 cm^{-1} (formyl). The structural assignment is further supported by the ^{13}C NMR data which include a C=O signal at relatively high field (160.1 ppm). In addition, the $M^+ + H$ peak is seen in the FAB-MS. From the coupling constant of $J_{3,4}$ = 7.5 Hz which indicates a 3,4-*trans* configuration,[23] one can also deduce the stereochemical course of the intramolecular Nozaki reaction. Although the structure of **25** could be proven by spectroscopic means, the exact

mode of formation of **25** remains unclear. Most probably, the initially formed hemiacetal undergoes an oxidative fragmentation under the action of excess CAN as shown in Scheme 5.



Scheme 5

To sum up, we have designed and synthesized a novel enediyne **23** embedded in a bicyclic structure that stabilizes the enediyne towards cycloaromatization. The synthetic route to the 10-oxabicyclo[7.2.1]enediyne **23** proceeds in 13 steps from the known epoxide **7**. It was also shown that oxidative activation of the enediyne **23** is indeed possible as indicated by the formation of the aromatized naphtalene derivative **25**. Based on this strategy the synthesis of other analogues with modified groups at the anomeric position should be possible that might allow selective activation in the presence of DNA. These studies are currently being pursued in our laboratories.

Acknowledgements

Financial support by the *Deutsche Forschungsgemeinschaft* is gratefully acknowledged. T. B. acknowledges a Landesgraduierten fellowship from the state Baden-Württemberg.

EXPERIMENTAL

General

^{1}H NMR: Bruker AC 250. - ^{13}C NMR: Bruker AC 250 (62.5 MHz); all spectra were recorded in $CDCl_3$ as solvent with TMS as internal standard. - IR: Mattson Polaris. - Melting points: Dr. Tottoli melting point apparatus. - EI-MS: Finnigan MAT 312. - FAB-MS spectra were recorded on a modified Finnigan MAT 312/AMD 5000 spectrometer using *para*-nitrobenzylalcohol as matrix. - Optical rotations were measured on a Perkin Elmer polarimeter 241 MC at 23 °C. - Flash chromatography: J. T. Baker silica gel 30-60 μm. - TLC: Merck Si 60 F_{254}. - Solvents were distilled prior to use; petroleum ether with a boiling range of 35-65 °C was used; THF was distilled from sodium diphenyl ketyl immediately before use. - Force-field calculations (molecular mechanics calculations) were performed by using the program PC model (V4.0) from Serena Software on a PC with a 386 processor (33 MHz). - The pH-7 buffer solution used in the workup procedures was prepared by dissolving potassium dihydrogen phosphate (85.0 g) and sodium hydroxide (14.5 g) in water (1 l).

Methyl-3-deoxy-α-D-*threo*-pentofuranoside[14] **(8):** To a solution of methyl-2,3-anhydro-α-D-lyxofuranoside[14] (40.2 g, 275 mmol) in dry THF (250 ml) was added sodium hydride (7.90 g, 330 mmol) in 10 portions. After the gas evolution had ceased the mixture was stirred for 1 h at room temperature. A solution of lithium triethylborohydride in THF (330 ml, 1 M) was added dropwise and the reaction mixture was refluxed for 1 h under argon. After cooling to 0 °C methanol (250 ml) was added carefully under nitrogen and the resulting mixture was evaporated to dryness. Caution, the filtrate might ignite due to the presence of triethyl borane. It should be destroyed oxidatively! The residue from the evaporation was dissolved in water, neutralized with 1 M

HCl, evaporated to dryness, coevaporated with methanol (2 x 100 ml), redissolved in ethyl acetate, dried with magnesium sulfate, filtered, and the filtrate was evaporated again. The resulting oil (38.0 g, 97%) was pure enough for further reactions. TLC (petroleum ether/methyl acetate = 1:1): R_f = 0.16, $[\alpha]_D$ = 132.0 (c = 1.0 in methanol) [lit.[14] $[\alpha]_D$ = 134.8 (c = 1.0 in methanol)]. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.69 (dd, ^3J = 2.8 Hz, ^2J = 13.8 Hz, 1 H, H-3), 2.34 (ddd, ^3J = 5.4 Hz, ^3J = 9.7 Hz, ^2J = 13.8 Hz, 1 H, H-3'), 3.46 (s, 3 H, OCH_3), 3.46 (dd, ^3J = 2.1 Hz, ^2J = 11.7 Hz, 1 H, H-5), 3.78 (dd, ^3J = 2.1 Hz, ^2J = 11.7 Hz, 1 H, H-5'), 4.00 (d, ^3J = 5.4 Hz, 1 H, H-2), 4.25 (m, 1 H, H-4), 4.48 (s, br., 2 H, OH), 4.76 (s, 1 H, H-1).

1,2,5-Tri-O-acetyl-3-deoxy-D-*threo*-pentofuranose (9): To a stirred solution of methyl-3-deoxy-α-D-*threo*-pentofuranoside **8** (25.3 g, 171 mmol) in acetic anhydride (180 ml) was added conc. sulfuric acid (23 drops). When the reaction was finished after stirring for 4-10 h at room temperature (monitored by TLC), the mixture was poured onto crushed ice (400 ml) and stirred for 1 h. The solution was extracted with dichloromethane (3 x 300 ml) and the combined organic layers were washed successively with a 1 M solution of sodium hydroxide, a saturated solution of sodium bicarbonate and brine, dried with magnesium sulfate, and evaporated under reduced pressure. Flash chromatography using diethyl ether/petroleum ether (7:3) for elution gave 37.4 g (84%) of **9** as an unseparable mixture of anomers (α:β = 6.6:1) as a colourless oil, TLC (diethyl ether/petroleum ether = 3:2): R_f = 0.17

α: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.69 (ddd, ^3J = 1.6 Hz, ^3J = 4.8 Hz, ^2J = 14.4 Hz, 1 H, H-3), 1.93 (s, 3 H, OAc), 1.96 (s, 6 H, OAc), 2.43 (ddd, ^3J = 6.3 Hz, ^3J = 8.6 Hz, ^2J = 14.4 Hz, 1 H, H-3'), 3.98 (dd, ^3J = 6.9 Hz, ^2J = 11.6 Hz, 1 H, H-5), 4.07 (dd, ^3J = 4.4 Hz, ^2J = 11.6 Hz, 1 H, H-5'), 4.35 - 4.45 (m, 1 H, H-4), 5.03 (dd, ^3J = 1.6 Hz, ^3J = 6.3 Hz, 1 H, H-2), 6.09 (s, 1 H, H-1).

β: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.75 - 1.85 (m, 1 H, H-3), 1.91 (s, 3 H, OAc), 1.99 (s, 6 H, OAc), 2.2 - 2.4 (m, 1 H, H-3'), 3.95 - 4.10 (m, 2 H, H-5, H-5'), 4.20 - 4.35 (m, 1 H, H-4), 5.07 (dd, ^3J = 4.2 Hz, ^3J = 8.3 Hz, 1 H, H-2), 6.18 (d, ^3J = 4.2 Hz, 1 H, H-1).

Anal. Calcd for $C_{11}H_{16}O_7$: C, 50.77; H, 6.20; Found: C, 50.91; H, 6.18.

***para*-Methoxybenzyl-2,5-di-O-acetyl-3-deoxy-α-D-*threo*-pentofuranoside (10a):** 1,2,5-Tri-O-acetyl-D-*threo*-pentofuranose **9** (140 mg, 0.54 mmol) and 4-methoxybenzylalcohol (93 mg, 0.67 mmol) in dry dichloromethane (5 ml) were stirred with mol sieves 4 Å for 17 h at room temperature under argon. After cooling to -5 °C trimethylsilyl triflate (10 µl, 0.05 mmol) was added and stirring was continued for an additional hour. Formation of di*para*methoxybenzylether consumed a part of the alcohol. Therefore, further 4-methoxybenzylalcohol (64 mg, 0.46 mmol) was added and stirring was continued for 1.5 h. The reaction was quenched by adding 10 ml of pH-7 buffer solution. The resulting mixture was extracted with dichloromethane (2 x 20 ml). The combined extracts were dried with magnesium sulfate and evaporated. Purification by repeated flash chromatography using petroleum ether/methyl acetate (4:1) for elution gave 55 mg (30%) of **10a** as a colourless oil. TLC (petroleum ether/methyl acetate = 2:1): R_f = 0.45, $[\alpha]_D$ = 88.2 (c = 1.0 in CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.66 (ddd, ^3J = 1.3 Hz, ^3J = 4.8 Hz, ^2J = 14.3 Hz, 1 H, H-3), 2.02 (s, 3 H, OAc), 2.10 (s, 3 H, OAc), 2.52 (ddd, ^3J = 6.3 Hz, ^3J = 8.6 Hz, ^2J = 14.3 Hz, 1 H, H-3'), 3.78 (s, 3 H, OCH_3), 4.09 (dd, ^3J = 7.2 Hz, ^2J = 11.5 Hz, 1 H, H-5), 4.20 (dd, ^3J = 4.0 Hz, ^2J = 11.5 Hz, 1 H, H-5'), 4.34 - 4.45 (m, 1 H, H-4), 4.43 (d, ^2J = 11.4 Hz, 1 H, CHHAr), 4.63 (d, ^2J = 11.4 Hz, 1 H, CHHAr), 5.08 (dd, ^3J = 1.3 Hz, ^3J = 6.3 Hz, 1 H, H-2), 5.12 (s, 1 H, H-1), 6.82 - 8.88 (m, 2 H, aryl H), 7.21 - 7.26 (m, 2 H, aryl H). Anal. Calcd for $C_{17}H_{22}O_7$: C, 60.35; H, 6.55; Found: C, 60.05; H, 6.64.

Benzyl-2,5-di-O-acetyl-3-deoxy-α-D-*threo*-pentofuranoside (10b): 1,2,5-Tri-O-acetyl-D-*threo*-pentofuranose **9** (130 mg, 0.50 mmol) and benzylalcohol (60 µl, 0.55 mmol) in dry dichloromethane (5 ml) were stirred with mol sieves 4 Å for 1 h at room temperature under argon. After cooling to -5 °C trimethylsilyl triflate (6 µl, 0.03 mmol) was added and stirring was continued for an additional 2 h. The reaction was quenched by adding 10 ml of pH-7 buffer solution. The resulting mixture was extracted with dichloromethane (2 x 20 ml). The combined extracts were dried with magnesium sulfate and evaporated. Purification by flash chromatography using petroleum ether/methyl acetate (4:1) for elution gave 130 mg (84%) of **10b** as a colourless oil. TLC (petroleum ether/methyl acetate = 2:1): R_f = 0.49, $[\alpha]_D$ = 76.1 (c = 1.0 in CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.67 (ddd, ^3J = 1.2 Hz, ^3J = 4.8 Hz, ^2J = 14.3 Hz, 1 H, H-3), 2.01 (s, 3 H, OAc), 2.07 (s, 3 H, OAc), 2.52

(ddd, ^3J = 6.3 Hz, ^3J = 8.6 Hz, ^2J = 14.3 Hz, 1 H, H-3'), 4.08 (dd, ^3J = 7.1 Hz, ^2J = 11.5 Hz, 1 H, H-5), 4.19 (dd, ^3J = 4.0 Hz, ^2J = 11.5 Hz, 1 H, H-5'), 4.34 - 4.44 (m, 1 H, H-4), 4.49 (d, ^2J = 11.9 Hz, 1 H, CHHAr), 4.69 (d, ^2J = 11.9 Hz, 1 H, CHHAr), 5.10 (dd, ^3J = 1.2 Hz, ^3J = 6.3 Hz, 1 H, H-2), 5.13 (s, 1 H, H-1), 7.22 - 7.31 (m, 5 H, aryl H). Anal. Calcd for $C_{16}H_{20}O_6$: C, 62.33; H, 6.54; Found: C, 62.22; H, 6.60.

***meta*-Methoxybenzyl-2,5-di-O-acetyl-3-deoxy-α-D-*threo*-pentofuranoside (10c):** 1,2,5-Tri-O-acetyl-D-*threo*-pentofuranose **9** (130 mg, 0.50 mmol) and 3-methoxybenzylalcohol (63 µl, 0.55 mmol) in dry dichloromethane (5 ml) were stirred with mol sieves 4 Å for 1 h at room temperature under argon. After cooling to -5 °C trimethylsilyl triflate (10 µl, 0.05 mmol) was added and stirring was continued for another 2 h. The reaction was quenched by adding 10 ml of pH-7 buffer solution. The resulting mixture was extracted with dichloromethane (2 x 20 ml). The combined extracts were dried with magnesium sulfate and evaporated. Purification by flash chromatography using petroleum ether/methyl acetate (4:1) for elution gave 147 mg (87%) of **10c** as a colourless oil. TLC (petroleum ether/methyl acetate = 2:1): R_f = 0.44, $[\alpha]_D$ = 88.9 (c = 1.0 in CH_2Cl_2). ^1H NMR (250 MHz, $CDCl_3$): δ = 1.67 (ddd, ^3J = 1.4 Hz, ^3J = 4.9 Hz, ^2J = 14.3 Hz, 1 H, H-3), 2.02 (s, 3 H, OAc), 2.08 (s, 3 H, OAc), 2.53 (ddd, ^3J = 6.3 Hz, ^3J = 8.6 Hz, ^2J = 14.3 Hz, 1 H, H-3'), 3.78 (s, 3 H, OCH_3), 4.09 (dd, ^3J = 7.1 Hz, ^2J = 11.6 Hz, 1 H, H-5), 4.19 (dd, ^3J = 4.0 Hz, ^2J = 11.6 Hz, 1 H, H-5'), 4.35 - 4.43 (m, 1 H, H-4), 4.47 (d, ^2J = 12.0 Hz, 1 H, CHHAr), 4.67 (d, ^2J = 12.0 Hz, 1 H, CHHAr), 5.11 (dd, ^3J = 1.4 Hz, ^3J = 6.3 Hz, 1 H, H-2), 5.13 (s, 1 H, H-1), 6.77 - 6.89 (m, 3 H, aryl H), 7.19 - 7.26 (m, 1 H, aryl H). Anal. Calcd for $C_{17}H_{22}O_7$: C, 60.35; H, 6.55; Found: C, 60.22; H, 6.60.

***ortho*-Methoxybenzyl-2,5-di-O-acetyl-3-deoxy-α-D-*threo*-pentofuranoside (10d):** 1,2,5-Tri-O-acetyl-D-*threo*-pentofuranose **9** (47.2 g, 181 mmol) and 2-methoxybenzylalcohol (24.5 ml, 199 mmol) in dry dichloromethane (600 ml) were stirred with mol sieves 4 Å for 1.5 h at room temperature under argon. After cooling to -5 °C a solution of trimethylsilyl triflate (2.4 ml, 13.5 mmol) in dry dichloromethane (10 ml) was added dropwise and stirring was continued for another 2 h. The reaction was quenched by adding saturated sodium bicarbonate solution (150 ml) and pH-7 buffer-solution (100 ml). The organic layer was separated, and the aqueous phase was extracted with dichloromethane (1 x 100 ml). The extracts were combined, dried with magnesium sulfate and evaporated. Purification by flash chromatography using petroleum ether/methyl acetate (7:2) for elution gave 47.5 g (78%) of **10d** as a colourless oil. TLC (petroleum ether/methyl acetate = 2:1): R_f = 0.40, $[\alpha]_D$ = 84.2 (c = 1.0, CH_2Cl_2). ^1H NMR (250 MHz, $CDCl_3$): δ = 1.61 (ddd, ^3J = 1.3 Hz, ^3J = 4.9 Hz, ^2J = 14.2 Hz, 1 H, H-3), 1.98 (s, 3 H, OAc), 2.04 (s, 3 H, OAc), 2.49 (ddd, ^3J = 6.3 Hz, ^3J = 8.6 Hz, ^2J = 14.2 Hz, 1 H, H-3'), 3.75 (s, 3 H, OCH_3), 4.04 (dd, ^3J = 7.1 Hz, ^2J = 11.5 Hz, 1 H, H-5), 4.15 (dd, ^3J = 4.0 Hz, ^2J = 11.5 Hz, 1 H, H-5'), 4.31 - 4.41 (m, 1 H, H-4), 4.49 (d, ^2J = 12.4 Hz, 1 H, CHHAr), 4.69 (d, ^2J = 12.4 Hz, 1 H, CHHAr), 5.07 (dd, ^3J = 1.3 Hz, ^3J = 6.3 Hz, 1 H, H-2), 5.12 (s, 1 H, H-1), 6.76 - 6.89 (m, 2 H, aryl H), 7.15 - 7.28 (m, 2 H, aryl H). Anal. Calcd for $C_{17}H_{22}O_7$: C, 60.35; H, 6.55; Found: C, 60.20; H, 6.59.

2,5-Di-O-acetyl-3-deoxy-*threo*-pentofuranose (11): To a solution of **10d** (106 mg, 0.31 mmol) in acetonitrile/water (9:1, 5 ml) was added ceric ammonium nitrate (378 mg, 0.69 mmol) and the mixture was stirred for 24 h at room temperature. Then pH-7 buffer solution (10 ml) and water (10 ml) were added and the solution was extracted with dichloromethane (2 x 30 ml). The combined organic extracts were dried with magnesium sulfate, filtered and the filtrate was evaporated in vacuo. Flash chromatography using petroleum ether/methyl acetate (1:1) for elution furnished 42 mg (61%) of **11** as a colourless oil in an α/β ratio of 4:1. TLC (petroleum ether/methyl acetate = 1:1): R_f = 0.32, $[\alpha]_D$ = 32.5 (c = 1.0 in CH_2Cl_2). ^1H NMR (250 MHz, $CDCl_3$): δ = 1.67 (ddd, ^3J = 1.5 Hz, ^3J = 4.8 Hz, ^2J = 14.3 Hz, 0.8 H, H-3α), 1.75 - 1.98 (m, 0.2 H, H-3β), 2.03 (s, 2.4 H, OAcα), 2.05 (s, 0.6 H, OAcβ), 2.06 (s, 2.4 H, OAcα), 2.08 (s, 0.6 H, OAcβ), 2.28 - 2.45 (m, 0.2 H, H-3'β), 2.54 (ddd, ^3J = 6.3 Hz, ^3J = 8.6 Hz, ^2J = 14.3 Hz, 0.8 H, H-3'α), 3.55(s, br., 0.8 H, OHα), 3.67 (s, br., 0.2 H, OHβ), 4.01 (dd, ^3J = 7.6 Hz, ^2J = 11.5 Hz, 0.8 H, H-5α), 4.16 (dd, ^3J = 3.9 Hz, ^2J = 11.5 Hz, 0.8 H, H-5'α), 4.10 - 4.30 (m, 0.6 H, H-4β, H-5β, H-5'β) 4.44 - 4.55 (m, 0.8 H, H-4α), 4.94 (ddd, ^3J = 4.2 Hz, ^3J = 8.0 Hz, ^3J = 9.3 Hz, 0.2 H, H-2β), 5.02 (dd, ^3J = 1.5 Hz, ^3J = 6.3 Hz, 0.8 H, H-2α), 5.41 (s, br., 1 H, H-1). Anal. Calcd for $C_9H_{14}O_6$: C, 49.54; H, 6.47; Found: C, 49.81; H, 6.62.

***ortho*-Methoxybenzyl-3-deoxy-α-D-*threo*-pentofuranoside (12):** To a solution of **10d** (47.5 g, 140 mmol) in dry methanol (400 ml) was added a freshly prepared solution of 1 M sodium methoxide (1 ml) in

methanol. The mixture was stirred for 14 h and quenched by adding silica gel (1 teaspoonful). After filtration and evaporation of the solvent the residue was purified by flash chromatography using petroleum ether/methyl acetate (1:1) for elution to yield 34.1 g (96%) of **12** as a colourless oil. TLC (petroleum ether/methyl acetate = 1:1): R_f = 0.25, $[\alpha]_D$ = 100.4 (c = 1.0 in CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.70 (dd, ^{3}J = 2.8 Hz, ^{2}J = 13.8 Hz, 1 H, H-3), 2.43 (ddd, ^{3}J = 5.4 Hz, ^{3}J = 9.8 Hz, ^{2}J = 13.8 Hz, 1 H, H-3'), 3.44 (dd, ^{3}J = 1.9 Hz, ^{2}J = 11.7 Hz, 1 H, H-5), 3.7 - 4.4 (s, br., 2 H, OH), 3.74 (s, 3 H, OCH_3), 3.81 (dd, ^{3}J = 2.1 Hz, ^{2}J = 11.7 Hz, 1 H, H-5'), 4.08 (d, ^{3}J = 5.4 Hz, 1 H, H-2), 4.26 - 4.32 (m, 1 H, H-4), 4.47 (d, ^{2}J = 12.4 Hz, 1 H, CHHAr), 4.66 (d, ^{2}J = 12.4 Hz, 1 H, CHHAr), 4.99 (s, 1 H, H-1), 6.75 - 6.89 (m, 2 H, aryl H), 7.14 - 7.26 (m, 2 H, aryl H). Anal. Calcd for $C_{13}H_{18}O_5$: C, 61.41; H, 7.13; Found: C, 61.43; H, 7.13.

***ortho*-Methoxybenzyl-3-deoxy-5-O-pivaloyl-α-D-*threo*-pentofuranoside (13):** Pivaloyl chloride (18.9 ml, 154 mmol) was added dropwise to a cooled (0 °C) solution of **12** (34.1 g, 134 mmol) in dry pyridine (200 ml). The reaction mixture was stirred for 4 days at 4 °C, poured onto crushed ice (200 ml) and stirred for 1 h. After evaporation to dryness, the residue was coevaporated with toluene, redissolved in diethyl ether (500 ml), and the solution was successively washed with a saturated solution of sodium bicarbonate (2 x 100 ml), and pH-7 buffer solution (50 ml), dried with magnesium sulfate, filtered and evaporated. Flash chromatography using petroleum ether/methyl acetate (3:1) for elution furnished 38.1 g (84%) of **13** as a colourless oil. TLC (petroleum ether/methyl acetate = 1:1): R_f = 0.6, $[\alpha]_D$ = 77.2 (c = 1.0 in CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.15 (s, 9 H, Piv), 1.59 (dd, ^{3}J = 3.6 Hz, ^{2}J = 13.7 Hz, 1 H, H-3), 2.3 - 2.6 (s, br., 1 H, OH), 2.40 (ddd, ^{3}J = 5.9 Hz, ^{3}J = 9.0 Hz, ^{2}J = 13.6 Hz, 1 H, H-3'), 3.74 (s, 3 H, OCH_3), 4.09 (dd, ^{3}J = 4.8 Hz, ^{2}J = 11.8 Hz, 1 H, H-5), 4.15 - 4.21 (m, 2 H, H-2, H-5'), 4.28 - 4.37 (m, 1 H, H-4), 4.46 (d, ^{2}J = 12.3 Hz, 1 H, CHHAr), 4.65 (d, ^{2}J = 12.3 Hz, 1 H, CHHAr), 5.01 (s, 1 H, H-1), 6.76 - 6.88 (m, 2 H, aryl H), 7.15 - 7.25 (m, 2 H, aryl H). Anal. Calcd for $C_{18}H_{26}O_6$: C, 63.89; H, 7.74; Found: C, 63.73; H, 7.77.

***ortho*-Methoxybenzyl-5-O-*tert*butyldimethylsilyl-3-deoxy-α-D-*threo*-pentofuranoside (14a) and *ortho*-Methoxybenzyl-2,5-di-O-*tert*butyldimethylsilyl-3-deoxy-α-D-*threo*-pentofuranoside (14b):** To a cooled solution (0 °C) of **12** (254 mg, 1.00 mmol) in dry dichloromethane (7 ml) was added imidazole (143 mg, 2.10 mmol) and *tert*butyldimethylsilyl chloride (158 mg, 1.05 mmol). The reaction mixture was stirred for 15 h at 4 °C, poured onto pH-7 buffer solution, and the resulting mixture was extracted with dichloromethane (40 ml). After drying with magnesium sulfate and evaporation of the solvent, the residue was purified by flash chromatography using petroleum ether/methyl acetate (7:1) for elution to yield 67 mg (14%) of **14b** and 280 mg (76%) of **14a**.

14a: Colourless oil, TLC (petroleum ether/methyl acetate = 6:1): R_f = 0.31, $[\alpha]_D$ = 62.2 (c = 1.0 in CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.11 (s, 6 H, SiMe), 0.91 (s, 9 H, *t*-Bu), 1.77 (dd, ^{3}J = 2.3 Hz, ^{2}J = 13.5 Hz, 1 H, H-3), 2.47 (ddd, ^{3}J = 3.9 Hz, ^{3}J = 9.9 Hz, ^{2}J = 13.5 Hz, 1 H, H-3'), 3.54 (dd, ^{3}J = 1.5 Hz, ^{2}J = 11.0 Hz, 1 H, H-5), 3.80 (s, 3 H, OCH_3), 3.89 (dd, ^{3}J = 1.8 Hz, ^{2}J = 11.0 Hz, 1 H, H-5'), 4.00 - 4.15 (m, 2 H, H-2, OH), 4.31 - 4.36 (m, 1 H, H-4), 4.54 (d, ^{2}J = 12.5 Hz, 1 H, CHHAr), 4.71 (d, ^{2}J = 12.5 Hz, 1 H, CHHAr), 5.03 (s, 1 H, H-1), 6.82 - 6.94 (m, 2 H, aryl H), 7.19 - 7.32 (m, 2 H, aryl H). Anal. Calcd for $C_{19}H_{32}O_5Si$: C, 61.92; H, 8.75; Found: C, 61.83; H, 8.77.

14b: Colourless oil, TLC (petroleum ether/methyl acetate = 6:1): R_f = 0.74, $[\alpha]_D$ = 47.6 (c = 1.0 in CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.01 (s, 3 H, SiMe), 0.02 (s, 3 H, SiMe), 0.06 (s, 6 H, SiMe), 0.85 (s, 9 H, *t*-Bu), 0.89 (s, 9 H, *t*-Bu), 1.61 (ddd, ^{3}J = 2.1 Hz, ^{3}J = 4.6 Hz, ^{2}J = 13.2 Hz, 1 H, H-3), 2.27 (ddd, ^{3}J = 5.8 Hz, ^{3}J = 8.1 Hz, ^{2}J = 13.2 Hz, 1 H, H-3'), 3.60 (dd, ^{3}J = 6.4 Hz, ^{2}J = 10.1 Hz, 1 H, H-5), 3.76 (dd, ^{3}J = 5.9 Hz, ^{2}J = 10.1 Hz, 1 H, H-5'), 3.80 (s, 3 H, OCH_3), 4.15 - 4.25 (m, 2 H, H-2, H-4), 4.52 (d, ^{2}J = 12.4 Hz, 1 H, CHHAr), 4.70 (d, ^{2}J = 12.4 Hz, 1 H, CHHAr), 4.96 (s, 1 H, H-1), 6.82 - 6.94 (m, 2 H, aryl H), 7.20 - 7.33 (m, 2 H, aryl H). Anal. Calcd for $C_{25}H_{46}O_5Si_2$: C, 62.19; H, 9.60; Found: C, 62.29; H, 9.65.

(2S-*trans*)-2-*ortho*Methoxybenzyl-5-[[(pivaloyl)oxy]methyl]dihydro-3-(2 H)-furanone (15): A solution of Dess-Martin-periodinane[17] (63.2 g, 168 mmol) in dry dichloromethane (250 ml) was added dropwise to a solution of **13** (38.0 g, 112 mmol) in dry dichloromethane (250 ml) under argon. After stirring for 1 h a 1.3 M solution of sodium hydroxide (500 ml) was added. The mixture was stirred for 10 min, the organic layer was separated, washed with a pH-7 buffer solution (80 ml), dried with magnesium sulfate, filtered, and the filtrate

was evaporated in vacuo. Flash chromatography using petroleum ether/methyl acetate (4:1) for elution gave 34.4 g (91%) of **13** as a colourless oil. TLC (petroleum ether/methyl acetate = 3:1): R_f = 0.44, $[\alpha]_D$ = 45.6 (c = 1.0 in CH_2Cl_2). ^1H NMR (250 MHz, $CDCl_3$): δ = 1.19 (s, 9 H, Piv), 2.29 (dd, ^3J = 7.9 Hz, ^2J = 18.5 Hz, 1 H, H-3), 2.64 (dd, ^3J = 6.7 Hz, ^2J = 18.5 Hz, 1 H, H-3'), 3.81 (s, 3 H, OCH_3), 4.22 (dd, ^3J = 4.6 Hz, ^2J = 12.0 Hz, 1 H, H-5), 4.36 (dd, ^3J = 3.5 Hz, ^2J = 12.0 Hz, 1 H, H-5'), 4.64 (d, ^2J = 12.1 Hz, 1 H, C<u>H</u>HAr), 4.69 -4.79 (m, 1 H, H-4), 4.82 (d, ^2J = 12.1 Hz, 1 H, CH<u>H</u>Ar), 4.91 (s, 1 H, H-1), 6.83 - 6.96 (m, 2 H, aryl H), 7.22 - 7.36 (m, 2 H, aryl H). Anal. Calcd for $C_{18}H_{24}O_6$: C, 64.27; H, 7.19; Found: C, 64.23; H, 7.27.

***ortho*-Methoxybenzyl-3-deoxy-5-O-pivaloyl-2-C-(trimethylsilyl)ethynyl-α-D-*erythro*-pentofuranoside (16):** A cooled (-40 °C) solution of lithio(trimethylsilyl)acetylene, prepared from trimethylsilylacetylene (6.8 ml, 52 mmol) and *n*-BuLi (32.6 ml 1.6 M in hexane, 52 mmol) in dry THF (70 ml) at -40 °C, was added to a cooled (-80 °C) suspension of anhydrous ceric(III) chloride in dry THF (250 ml), which had already been stirred for 2 h at 0 °C under argon. After stirring for 1.5 h at -80 °C a solution of **15** (11.7 g, 35 mmol) in dry THF (70 ml) was added and stirring was continued for 30 min. The reaction mixture was poured onto a saturated solution of ammonium chloride, filtered, and extracted with diethyl ether (2 x 100 ml). The combined organic extracts were washed with a pH-7 buffer solution (50 ml), dried with magnesium sulfate and evaporated. Flash chromatography using petroleum ether/methyl acetate (6:1) for elution afforded 14.4 g (95%) of **16** as a colourless oil. TLC (petroleum ether/methyl acetate =3:1): R_f = 0.54, $[\alpha]_D$ = 80.1 (c = 1.0 in CH_2Cl_2). ^1H NMR (250 MHz, $CDCl_3$): δ = 0.14 (s, 9 H, TMS), 1.20 (s, 9 H, Piv), 2.13 (dd, ^3J = 7.6 Hz, ^2J = 13.0 Hz, 1 H, H-3), 2.31 (dd, ^3J = 6.8 Hz, ^2J = 13.0 Hz, 1 H, H-3'), 3.57 (s, 1 H, OH), 3.82 (s, 3 H, OCH_3), 4.12 (dd, ^3J = 5.7 Hz, ^2J = 11.6 Hz, 1 H, H-5), 4.18 (dd, ^3J = 4.7 Hz, ^2J = 11.6 Hz, 1 H, H-5'), 4.42 - 4.53 (m, 1 H, H-4), 4.75 (d, ^2J = 11.8 Hz, 1 H, C<u>H</u>HAr), 4.82 (d, ^2J = 11.8 Hz, 1 H, CH<u>H</u>Ar), 5.17 (s, 1 H, H-1), 6.85 - 6.95 (m, 2 H, aryl H), 7.23 - 7.32 (m, 2 H, aryl H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 0.3, $SiMe_3$; 27.2, C(<u>C</u>H_3)$_3$; 38.8, <u>C</u>(CH_3)$_3$; 42.6, C-3; 55.3, OMe; 65.4, 66.3, C-5, benzylic C; 73.5, C-2; 75.6, C-4; 89.6, 105.7, acetylenic C; 105.8, C-1; 110.5, 120.4, 125.3, 129.4, 129.5, 157.5, aryl C; 178.1, CO. Anal. Calcd for $C_{23}H_{34}O_6Si$: C, 63.56; H, 7.89; Found: C, 63.64; H, 7.90.

***ortho*-Methoxybenzyl-3-deoxy-2-C-ethynyl-2-O-methyl-5-O-pivaloyl-α-D-*erythro*-pentofuranoside (17):** Sodium hydride (3.4 g, 140 mmol) was added portionwise to a cooled (0 °C) solution of **16** (33.3 g, 70 mmol) in dry THF (250 ml) under argon. After stirring for 30 min 1,3-dimethyl-2-imidazolidinone (DMEU) (22.5 ml, 210 mmol) and methyl iodide (29.1 ml, 420 mmol) were added and stirring was continued for 1 h at 0 °C and for 1 h at room temperature. Water (100 ml) was carefully added and the reaction mixture was stirred for another 4.5 h and then extracted with diethyl ether (2 x 200 ml). The combined organic extracts were successively washed with a saturated solution of sodium thiosulfate (2 x 100 ml) and a pH-7 buffer solution (50 ml), dried with magnesium sulfate and evaporated. Flash chromatography using petroleum ether/methyl acetate (6:1) for elution gave 22.7 g (86%) of **17** as a colourless oil. TLC (petroleum ether/methyl acetate = 3:1): R_f = 0.50, $[\alpha]_D$ = 64.3 (c = 1.0 in CH_2Cl_2). ^1H NMR (250 MHz, $CDCl_3$): δ = 1.20 (s, 9 H, Piv), 2.19 (dd, ^3J = 4.7 Hz, ^2J = 12.7 Hz, 1 H, H-3), 2.45 (dd, ^3J = 9.0 Hz, ^2J = 12.7 Hz, 1 H, H-3'), 2.57 (s, 1 H, acetylenic H), 3.38 (s, 3 H, OCH_3), 3.79 (s, 3 H, OCH_3), 4.12 - 4.25 (m, 2 H, H-5, H-5'), 4.40 - 4.51 (m, 1 H, H-4), 4.64 (d, ^2J = 12.5 Hz, 1 H, C<u>H</u>HAr), 4.81 (d, ^2J = 12.5 Hz, 1 H, CH<u>H</u>Ar), 5.09 (s, 1 H, H-1), 6.81 - 6.94 (m, 2 H, aryl H), 7.21 - 7.39 (m, 2 H, aryl H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 27.1, C(<u>C</u>H_3)$_3$; 38.7, <u>C</u>(CH_3)$_3$; 39.0, C-3; 53.8, 55.2, OMe; 64.3, 65.9, C-5, benzylic C; 74.0, C-4; 75.4, acetylenic C; 79.6, C-2; 82.9, acetylenic C; 103.4, C-1; 110.2, 120.3, 125.8, 128.9, 129.5, 157.4, aryl C; 178.2, CO. Anal. Calcd for $C_{21}H_{28}O_6$: C, 67.00; H, 7.50; Found: C, 76.09; H, 7.54.

***ortho*-Methoxybenzyl-3-deoxy-2-O-methyl-5-O-pivaloyl-2-C-[6-(trimethylsilyl)-3-hexene-1,5-diynyl]-α-D-*erythro*-pentofuranoside (19):** To a solution of **17** (22.7 g, 60 mmol) in dry benzene (200 ml) was successively added (4-chloro-3-buten-1-ynyl)-trimethylsilane[20] (15.9 g, 100 mmol), *n*-butylamine (30.0 ml, 300 mmol), CuI (1.2 g, 6 mmol), and $Pd(PPh_3)_4$ (2.3 g, 2 mmol). The resulting mixture was stirred for 17 h under argon, washed with water (7 x 100 ml), dried with magnesium sulfate and evaporated. Flash chromatography using petroleum ether/methyl acetate (8:1) for elution afforded 23.0 g (76%) of **19** as a colourless oil. TLC (petroleum ether/methyl acetate = 3:1): R_f = 0.65, $[\alpha]_D$ = 54.1 (c = 1.0 in CH_2Cl_2). ^1H NMR (250 MHz, $CDCl_3$):

δ = 0.16 (s, 9 H, TMS), 1.20 (s, 9 H, Piv), 2.22 (dd, ^3J = 4.9 Hz, ^2J = 12.7 Hz, 1 H, H-3), 2.49 (dd, ^3J = 8.9 Hz, ^2J = 12.7 Hz, 1 H, H-3'), 3.44 (s, 3 H, OCH_3), 3.79 (s, 3 H, OCH_3), 4.18 (d, ^3J = 5.7 Hz, 2 H, H-5, H-5'), 4.41 - 4.52 (m, 1 H, H-4), 4.65 (d, ^2J = 12.6 Hz, 1 H, CHHAr), 4.82 (d, ^2J = 12.6 Hz, 1 H, CHHAr), 5.12 (s, 1 H, H-1), 5.82 (d, ^3J = 11.1 Hz, 1 H, olef. H), 5.85 (d, ^3J = 11.1 Hz, 1 H, olef. H), 6.82 - 6.94 (m, 2 H, aryl H), 7.20 - 7.39 (m, 2 H, aryl H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 0.3, $SiMe_3$; 27.1, $C(CH_3)_3$; 38.8, $C(CH_3)_3$; 39.4, C-3; 54.0, 55.2, OMe; 64.3, 66.0, C-5, benzylic C; 74.1, C-4; 80.4, C-2; 84.4, 95.9, 101.7, 103.3, acetylenic C; 103.6, C-1; 110.2, 119.4, 120.4, 120.5, 125.8, 128.9, 129.5, 157.4, aryl C, olef. C; 178.2, CO. Anal. Calcd for $C_{28}H_{38}O_6Si$: C, 67.44; H, 7.68; Found: C, 67.03; H, 7.68.

***ortho*-Methoxybenzyl-3-deoxy-2-C-3-hexene-1,5-diynyl-2-O-methyl-α-D-*erythro*-pentofuranoside (20):** A freshly prepared 0.3 M solution of sodium methoxide in methanol (10 ml) was added to a solution of **19** (23.5 g, 47 mmol) in dry methanol (100 ml). After stirring for 2 weeks at room temperature the reaction was quenched by adding silica gel (2 g). After filtration and evaporation of the filtrate in vacuo, flash chromatography using petroleum ether/methyl acetate for elution gave 11.5 g (71%) of **20** as a colourless oil. TLC (petroleum ether/methyl acetate = 3:1): R_f = 0.17, $[\alpha]_D$ = 112 (c = 1.0 in CH_2Cl_2). ^1H NMR (250 MHz, $CDCl_3$): δ = 2.0 (s, br., 1 H, OH), 2.29 (dd, ^3J = 4.7 Hz, ^2J = 12.5 Hz, 1 H, H-3), 2.46 (dd, ^3J = 9.1 Hz, ^2J = 12.5 Hz, 1 H, H-3'), 3.32 (dd, ^5J = 0.7 Hz, ^4J = 2.2 Hz, 1 H, acetylenic H), 3.42 (s, 3 H, OCH_3), 3.73 (d, ^3J = 3.7 Hz, 2 H, H-5, H-5'), 3.81 (s, 3 H, OCH_3), 4.38 - 4.48 (m, 1 H, H-4), 4.67 (d, ^2J = 12.6 Hz, 1 H, CHHAr), 4.83 (d, ^2J = 12.6 Hz, 1 H, CHHAr), 5.12 (s, 1 H, H-1), 5.82 (dd, ^4J = 2.2 Hz, ^3J = 11.0 Hz, 1 H, olef. H), 5.92 (dd, ^5J = 0.7 Hz, ^3J = 11.0 Hz, 1 H, olef. H), 6.83 - 6.95 (m, 2 H, aryl H), 7.22 - 7.40 (m, 2 H, aryl H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 38.2, C-3; 54.0, 55.2, OMe; 64.3, 64.8, C-5, benzylic C; 76.5, C-4; 80.6, 80.9, 84.2, 85.1, 96.2, C-2, acetylenic C; 103.5, C-1; 110.2, 119.5, 120.4, 120.6, 125.8, 128.9, 129.5, 157.4, aryl C, olef. C. Anal. Calcd for $C_{20}H_{22}O_5$: C, 70.16; H, 6.48; Found: C, 69.77; H, 6.59.

***ortho*-Methoxybenzyl-3-deoxy-2-C-(6-iodo-3-hexene-1,5-diynyl)-2-O-methyl-α-D-*erythro*-pentofuranoside (21):** To a solution of iodine (12.7 g, 50 mmol) in dry benzene (80 ml) heated to 45 °C morpholine (13.0 ml, 150 mmol) was added under argon. After stirring for 30 min a solution of **20** (8.0 g, 23.5 mmol) in dry benzene (40 ml) was added dropwise. The reaction mixture was kept at 45 - 50 °C for 4 h, filtered, the filtrate washed with a saturated solution of sodium thiosulfate (2 x 100 ml) and a pH-7 buffer solution, dried with magnesium sulfate and evaporated. Flash chromatography using petroleum ether/methyl acetate (2:1) for elution gave 8.3 g of **21** (76%) as a colourless oil. TLC (petroleum ether/methyl acetate = 3:1): R_f = 0.17, $[\alpha]_D$ = 76.7 (c = 1.0 in CH_2Cl_2). ^1H NMR (250 MHz, $CDCl_3$): δ = 2.0 - 2.1 (s, br., 1 H, OH), 2.26 (dd, ^3J = 4.6 Hz, ^2J = 12.5 Hz, 1 H, H-3), 2.46 (dd, ^3J = 9.1 Hz, ^2J = 12.5 Hz, 1 H, H-3'), 3.43 (s, 3 H, OCH_3), 3.65 - 3.8 (s, br., 2 H, H-5, H-5'), 3.81 (s, 3 H, OCH_3), 4.38 - 4.47 (m, 1 H, H-4), 4.68 (d, ^2J = 12.6 Hz, 1 H, CHHAr), 4.84 (d, ^2J = 12.6 Hz, 1 H, CHHAr), 5.12 (s, 1 H, H-1), 5.80 (d, ^3J = 10.8 Hz, 1 H, olef. H), 5.94 (d, ^3J = 10.8 Hz, 1 H, olef. H), 6.82 - 6.96 (m, 2 H, aryl H), 7.21 - 7.41 (m, 2 H, aryl H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 15.2, CI; 38.2, C-3; 54.1, 55.2, OMe; 64.3, 64.9, C-5, benzylic C; 84.3, 91.6, 96.3, acetylenic C; 103.4, C-1; 110.2, 120.4, 120.5, 121.1, 125.8, 128.9, 129.5, 157.4, aryl C, olef. C. Anal. Calcd for $C_{20}H_{21}IO_5$: C, 51.30; H, 4.52; Found: C, 51.47; H, 4.75.

***ortho*-Methoxybenzyl-3-deoxy-2-C-(6-iodo-3-hexene-1,5-diynyl)-2-O-methyl-α-D-*erythro*-pentodialdo-1,4-furanoside (22):** To a cooled (-50 °C) solution of oxalyl chloride (3.3 ml, 38 mmol) in dry dichloromethane (50 ml) was added dimethyl sulfoxide (5.4 ml, 76 mmol) under argon. After 15 min a solution of **21** (5.9 g, 12.7 mmol) in dichloromethane (35 ml) was added and the reaction mixture was stirred for an additional hour at -50 °C. Triethylamine (23.0 ml, 165 mmol) was added and the mixture was allowed to warm to room temperature, washed with a saturated solution of sodium bicarbonate, dried with magnesium sulfate and evaporated. Flash chromatography using petroleum ether/methyl acetate (2:1) for elution afforded 4.5 g (76%) of **22** as a colourless oil. TLC (petroleum ether/methyl acetate = 1:1): R_f = 0.6, $[\alpha]_D$ = 48.2 (c = 1.0 in CH_2H_2). ^1H NMR (250 MHz, $CDCl_3$): δ = 2.56 (dd, ^3J = 2.8 Hz, ^2J = 12.3 Hz, 1 H, H-3), 2.72 (dd, ^3J = 10.1 Hz, ^2J = 12.3 Hz, 1 H, H-3'), 3.43 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3), 4.45 - 4.51 (m, 1 H, H-4), 4.72 (d, ^2J = 12.5 Hz, 1 H, CHHAr), 4.87 (d, ^2J = 12.5 Hz, 1 H, CHHAr), 5.22 (s, 1 H, H-1), 5.75 (d, ^3J = 10.8 Hz, 1 H, olef. H), 5.95 (d, ^3J = 10.8 Hz, 1 H, olef. H), 6.83 - 6.96 (m, 2 H, aryl H), 7.22 - 7.40 (m, 2 H, aryl H), 9.82 (d, ^3J = 1.3 Hz, 1

H, H-5). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 15.8, CI; 39.3, C-3; 54.3, 55.3, OMe; 64.7, benzylic C; 79.8, C-2; 80.0, C-4; 85.4, 91.4, 94.2, acetylenic C; 103.5, C-1; 110.3, 120.4, 120.5, 121.1, 125.5, 129.0, 129.5, 157.3, aryl C, olef. C; 202.4, C-5. Anal. Calcd for $C_{20}H_{19}IO_5$: C, 51.52; H, 4.11; Found: C, 51.87; H, 4.44.

(1S, 8S, 9S, 11S)-1-Methoxy-11-(2-methoxybenzyl)oxy-10-oxabicyclo[7.2.1]dodec-4-ene-2,6-diyn-8-ol (23): To a suspension of anhydrous chrome(II) chloride (3.9 g, 32 mmol), containing 2.5 % nickel(II) chloride, in dry THF (300 ml) under argon was added a solution of **22** (3.7 g, 8.0 mmol) in dry THF (120 ml) during 3 h. The reaction mixture was stirred for an additional 40 min and then poured onto a pH-7 buffer solution (150 ml). After filtration the organic layer was separated, washed with pH-7 buffer solution (50 ml), dried with magnesium sulfate and evaporated. Flash chromatography using petroleum ether/methyl acetate (2:1) for elution afforded 1.2 g (44%) of **23** as a ligth yellow foam, which decomposed even in the dark and under argon upon standing at room temperature. However, if kept in solution at 0 °C **23** was stable for several weeks. TLC (petroleum ether/methyl acetate = 1:1): R_f = 0.62, $[\alpha]_D$ = 179.4 (c = 1.0 in CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.30 - 2.45 (s, br., 1 H, OH), 2.60 (dd, ^3J = 9.4 Hz, ^2J = 13.0 Hz, 1 H, H-12), 2.80 (dd, ^3J = 3.8 Hz, ^2J = 13.0 Hz, 1 H, H-12'), 3.35 (s, 3 H, OCH_3), 3.79 (s, 3 H, OCH_3), 4.48 - 4.53 (m, 1 H, H-9), 4.65 (d, ^2J = 12.5 Hz, 1 H, CHHAr), 4.83 (d, ^2J = 12.5 Hz, 1 H, CHHAr), 4.83 (d, ^3J = 4.4 Hz, 1 H, H-8), 5.09 (s, 1 H, H-11), 5.89 (s, 2 H, olef. H), 6.81 - 6.93 (m, 2 H, aryl H), 7.20 - 7.38 (m, 2 H, aryl H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 41.4, C-12; 54.5, 55.3, OMe; 64.3, benzylic C; 64.5, C-8; 78.5, C-9; 81.6, 84.5, 91.5, 98.7, acetylenic C, C-1; 102.3, C-11; 110.3, 120.4, 123.8, 123.9, 125.7, 129.0, 129.6, 157.4, aryl C, olef. C. Correct elemental analytical data could not be obtained, because the product decomposed if it was not kept in solution.

(1S, 2S, 4S, 5S)-1,2,4,5-Tetrahydro-1-methoxy-2-(2-methoxybenzyl)oxy-1,4-methano-3-benzoxepin-5-ol (24): A solution of **23** (105 mg, 0.3 mmol) in 1,4-cyclohexadiene (5 ml) was heated to reflux for 3.5 h. After evaporation of the solvent flash chromatography using petroleum ether/methyl acetate (2:1) for elution gave 39 mg (55%) of **24** as a colourless foam. TLC (petroleum ether/methyl acetate = 1:1): R_f = 0.56, $[\alpha]_D$ = 81.5 (c = 1.0 in CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.0 - 2.1 (s, br., 1 H, OH), 2.29 (d, ^2J = 10.7 Hz, 1 H, CH_2), 2.57 (dd, ^3J = 6.4 Hz, ^2J = 10.7 Hz, 1 H, CH_2), 3.44 (s, 3 H, OCH_3), 3.77 (s, 3 H, OCH_3), 4.57 (s, 1 H, anomeric H), 4.60 (dd, ^3J = 3.8 Hz, ^3J = 6.4 Hz, 1 H, H-4), 4.61 - 4.67 (d, br., ^3J = 3.8 Hz, 1 H, H-5), 4.70 (d, ^2J = 13.5 Hz, 1 H, CHHAr), 4.82 (d, ^2J = 13.5 Hz, 1 H, CHHAr), 6.79 - 6.97 (m, 2 H, aryl H), 7.17 - 7.53 (m, 6 H, aryl H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 29.3, CH_2; 54.0, 55.3, OMe; 64.4, benzylic C; 70.4, C-4; 77.7, C-5; 84.2, C-1; 104.7, anomeric C; 110.1, 120.4, 123.6, 126.8, 128.1, 128.2, 128.4, 128.5, 130.3, 136.6, 139.4, 156.8, aryl C. Anal. Calcd for $C_{20}H_{20}O_5$: C, 70.16; H, 6.48; Found: C, 69.92; H, 6.69.

(3S, 4S)-3,4-Dihydro-3-formyloxy-4-hydroxy-1-(2H)-naphthalenone (25): To a solution of **23** (340 mg, 1.0 mmol) in acetonitrile/water (2:1, 15 ml) was added ceric ammonium nitrate (3.3 g, 6.0 mmol). The reaction mixture was stirred for 1.5 h at room temperature, poured onto a saturated solution of sodium bicarbonate, filtered and the resulting mixture was extracted with dichloromethane (2 x 50 ml). The combined organic layers were dried with magnesium sulfate and evaporated. Flash chromatography using petroleum ether/methyl acetate (2:1) for elution afforded 36 mg (18%) of **25** as a colourless foam. TLC (petroleum ether/methyl acetate = 2:1): R_f = 0.25, $[\alpha]_D$ = 9.2 (c = 0.5 in methanol). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.55 - 2.75 (s, br., 1 H, OH), 2.76 (dd, ^3J = 9.0 Hz, ^2J = 17.2 Hz, 1 H, H-2), 3.24 (dd, ^3J = 4.4 Hz, ^2J = 17.2 Hz, 1 H, H-2'), 4.97 (d, ^3J = 7.5 Hz, 1 H, H-4), 5.36 - 5.45 (m, 1 H, H-3), 7.42 - 7.47 (m, 1 H, aryl H), 7.61 - 7.70 (m, 2 H, aryl H), 8.02 (d, ^3J = 8.0 Hz, 1 H, aryl H), 8.09 (s, 1 H, formyl H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 40.8, CH_2; 70.0, 72.8, C-2, C-3; 127.0, 127.6, 128.9, 131.0, 134.8, 141.3, aryl C; 160.1, formyl C; 193.4 ketone. EI-MS: m/z = 160 (M^+ - HCOOH, 100 %), 134 (M^+ - HCOOH - HCCH, 38 %), 105 (M^+ - HCOOH - HCCH - HCO, 86 %), 77 (M^+ - HCOOH - HCCH - HCO - CO, 39%). FAB-MS (NBOH): m/z = 360 (MH^+ + NBOH, 1.3 %), 207 (MH^+, 3.7 %), 161 (MH^+ - HCOOH, 5.5 %). IR: $\tilde{\nu}$ = 3693 cm^{-1}, 3606, 2933, 2902, 2856, 1727, 1693, 1603, 1473, 1459, 1386, 1372, 1295, 1284, 1175. Due to the low amount of isolated product elemental analytical data could not be obtained.

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