New Aspects in the Stereoselective Ethynylation of β-C-Glycoside Aldehydes. Application to the Synthesis of an Ambruticin Fragment

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Stereoselective ethynylation of functionalized β-C-glycosyl aldehydes has been achieved with various organometallic alkynes. The diastereoselectivity is highly dependent on the organometallic alkyne and on the functionalization on the C-6 position of the glycoside. The stereoselective reaction conducted with ester-functionalized aldehyde, followed by Mitsunobu reaction and two Pd-catalyzed regio- stereo- and enantioselective alkylations afforded the "western" part of ambruticin.

Introduction

During the last two decades, the synthesis of C-glycosides has become an area of intense study among carbohydrate chemists and biochemists.[1] The discovery of naturally occurring C-nucleosides with important pharmacological properties, such as palytoxin,[2] spongistatin,[3] or ambruticin,[4] has stimulated the development of new synthetic methodologies.[5] Ambruticin (**1**), an antifungal antibiotic discovered in the late 1970s, has been isolated from fermentation extracts of Myxobacteria species *Polyangium cellulosum var. fulvum*.[6] It exhibits a unique oral in vivo activity against pathogens such as *Coccidiodes immitis*, *Histoplasma capsulatum*, and *Blastomyces dermatitidis*.[6,7] Höfle's group showed that it displays potent inhibitory activity against the yeast strain *Hansenula anomala*, and these workers have also isolated analogues of (+)-ambruticin carrying an amino group on the C5 position from Myxobacteria *Sorangium cellulosum So ce10*.[8] The mode of action of (+)-ambruticin has been shown to be related to osmoregulation in the same manner as that of pyrrolnitrin.[9] Its complete structure was determined by elegant spectroscopic analyses,[10] degradative studies and chemical transformation, and by a single X-ray of a derivative.[11]

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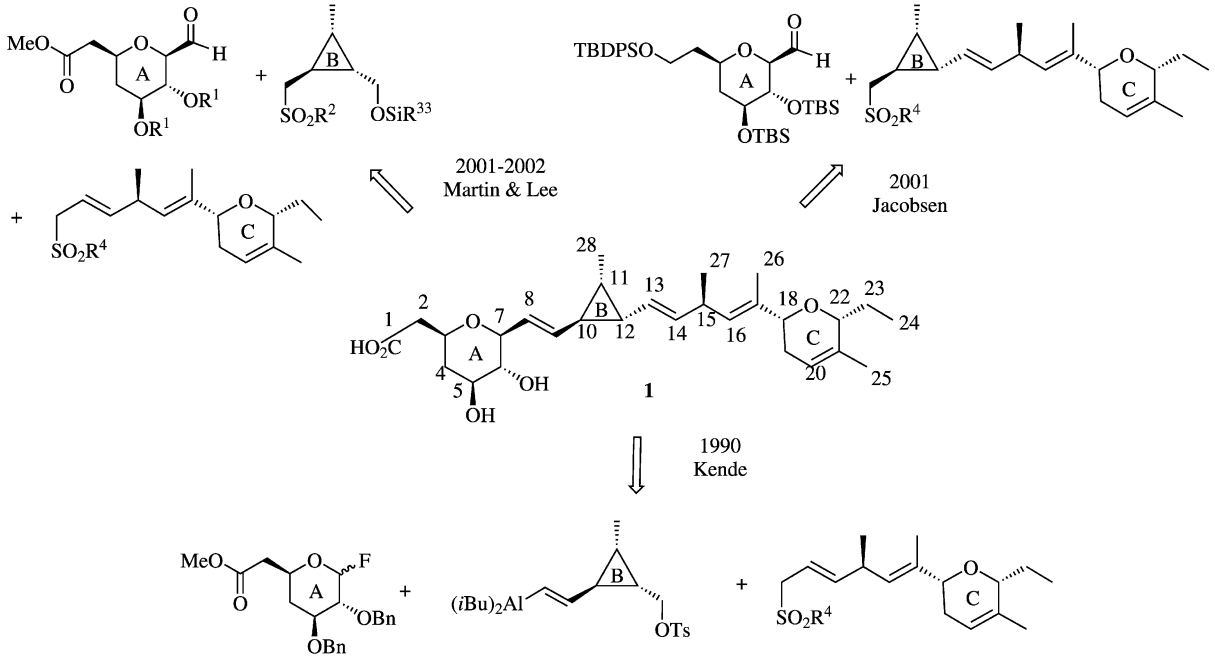
Despite widespread interest among chemists, resulting in the preparation of several fragments,[12] up to 2001, only one total synthesis − by a Sinaÿ strategy[12c] − had been published, by Kende's group.[13] Kende's condensation between a vinylalanecyclopropane and a fluoroglycoside with a subsequent Julia olefination efficiently produced ambruticin.

More recently, three groups have succeeded in the challenging total synthesis of ambruticin (Scheme 1). Martin[14] and Lee[15] employed a common strategy based on C8−C9 and C13−C14 disconnections through the functionalization of the A-ring aldehyde, a strategy that had previously been reported by our group.[16] The B-ring was prepared either by Doyle-Martin's methodology or by Kende's strategy, respectively. The key step in the synthesis of the C-ring was a ring-closing metathesis starting from a homoallylic chiral epoxide[14] or (*R*)-3-hydroxy-2-methylpent-1-ene.[15] Joining of parts A and B, and then C, was achieved by a Kocienski−Julia olefination with moderate to good selectivity. Jacobsen[17] described a highly stereocontrolled total synthesis based on the cleavage of the C8−C9 olefin, which revealed two fragments, joining of which was again achieved by a Kocienski−Julia olefination. The elegant functionalization of the B−C ring precursor was originally performed by asymmetric cyclopropanation and hydroformylation (C15). The synthesis of the A and C rings were both achieved through an asymmetric hetero-Diels−Alder reaction.

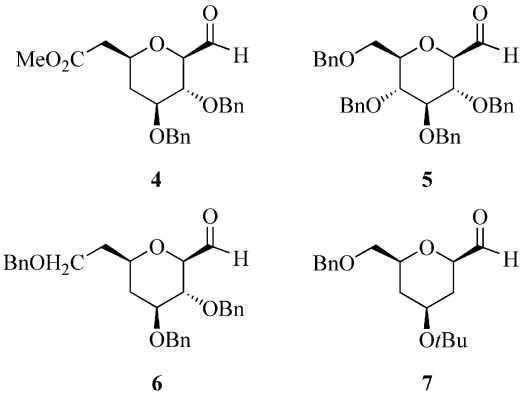
As part of a program devoted towards the synthesis of C-glycosides and vinylcyclopropanes, we have also for a long time been interested in the unique oral antifungal ambruticin. In 1994 we had envisaged a totally different approach, based on long work on the synthesis of vinylcyclopropanes.[18] In collaboration with Dujardin's group, in



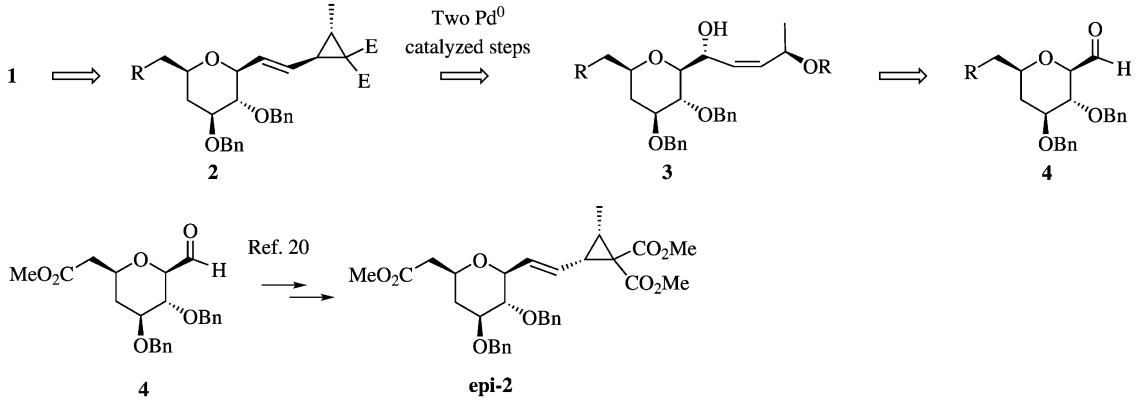
Scheme 1. Total syntheses of ambruticin

which highly efficient hetero-Diels–Alder reactions have been developed,[19] we slightly modified our approach to the A ring by changing the functionalization and the preparation (Scheme 2).[20] We had therefore envisaged a C13–C14 disconnection to provide the "western" part, which was seen as an entire building block **2** resulting from the sequential alkylation/cyclopropanation of (1*R*,4*R*)-allylic hydroxycarbonate **3**, catalyzed by Pd^0 complexes. We had previously developed a methodology for cyclopropane formation akin to an intramolecular Tsuji–Trost reaction. Unfortunately, our efforts produced a C10–C11 *cis* isomer fragment *epi*-**2** instead of the *trans* counterpart: as we knew that the configuration of the cyclopropane is dictated by the absolute configuration of the carbon atom bearing the free OH group,[18] we deduced that an unusual and unexpected stereoselectivity had occurred in the addition of the ethynyl Grignard to the β-C-glycosyl aldehyde **4**.[20]

We therefore decided to investigate this unprecedented diastereoselectivity with different C-glycoside aldehydes. As well as **4**, we also selected the totally benzylated aldehyde **5** and aldehydes **6** and **7** for our study (Scheme 3). Here we wish to report our results concerning the chain-elongation



Scheme 3. Functionalized β-C-glycosyl aldehydes



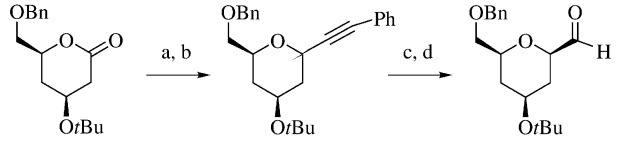
Scheme 2. Retrosynthesis of ambruticin

of C-glycoside aldehydes, and their application to the preparation of the western part of ambruticin with the correct absolute configuration on the cyclopropane at C10.

Results and Discussion

Synthesis of Aldehydes

The preparations of aldehydes **4**, **5**, and **6** were described previously.[16,20] We synthesized aldehyde **7** starting from lactone **8**.[19b] Addition of the anion of phenylacetylene to the lactone, followed by Kishi deoxygenation, stereoselectively afforded the C-glycoside **9** in 72% isolated yield (Scheme 4). Semi-hydrogenation followed by the ozonolysis of the resulting alkene gave the β-C-glycosyl aldehyde **7**.



8 **9** **7**

Scheme 4. Synthesis of aldehyde **7**; a) *n*BuLi, PhC≡CH, THF, −78 °C − room temp., 95%; b) $BF_3{\cdot}Et_2O$, Et_3SiH, CH_3CN/CH_2Cl_2, −40 °C, 79%; c) Pd/Lindlar, H_2 (1 atm), quinoline, EtOAc, room temp., 100%; d) O_3, CH_2Cl_2, −78 °C then Me_2S, 58%

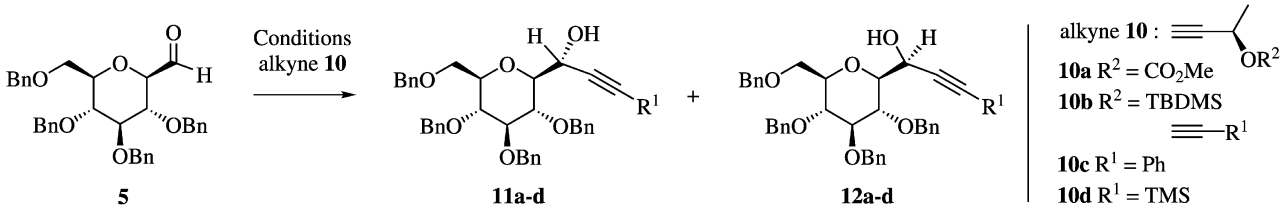
Chain-Elongation of Aldehydes

We first investigated the chain-elongating hydroxy alkylation of the aldehyde **5** with several alkynyl derivatives **10** (Scheme 5).

As shown in Table 1, the addition of the lithiated (*R*)-*O*-ethoxycarbonylbut-1-yn-3-ol (**10a**),[21] prepared by use of LDA or *t*BuLi either in the presence or in the absence of 12-crown-4 in diethyl ether or THF gave no desired products (Table 1, Entry 1). Only starting material, epimerized aldehyde, or de-*O*-benzylated aldehyde could be detected by ^1H NMR spectroscopy. We then turned our attention to less basic organometallic derivatives. The Mg, Cu,[22] Ce,[23] or Zn[24] derivatives (Table 1, Entry 2) gave no better results. We next decided to test commercially available acetylenic compounds such as phenylacetylene (**10c**) and trimethylsilylacetylene (**10d**) and were pleased to see that the addition of the Grignard reagents derived from phenylacetylene and trimethylacetylene gave the desired alcohols **11c/12c** and **11d/12d**, respectively, in 60 and 73% yields (Table 1, Entries 3, 4).[25] The diastereoselectivity could not be determined by ^1H NMR spectroscopy but was assumed to follow Cram's chelation model.[25,26] The diastereomers **11** and **12** were isolated by chromatography on silica gel, the major product **11** being less polar than **12**. Having prepared an optically pure silylated protected alcohol **10b**, we studied the reactivity of the aldehyde **5**. Grignard derivatives gave better results than Zn or Ce reagents (Table 1, Entries 5, 7). Addition of an excess of $MgBr_2$ (Table 1, Entry 4) gave better diastereoselectivity and a better yield than the use of $ZnBr_2$ (Table 1, Entry 8) or CuI (Table 1, Entry 9). Moreover, when a powerful complexing cation agent such as HMPT was used, the diastereoselectivity was reversed, as expected (Table 1, Entry 10).[27]

The optimized conditions were then tested on the functionalized aldehydes **4**, **6**, and **7** (Scheme 6).

The MeLi/$MgBr_2$ conditions, conducted at lower temperature in order to avoid addition at the ester group, ef-



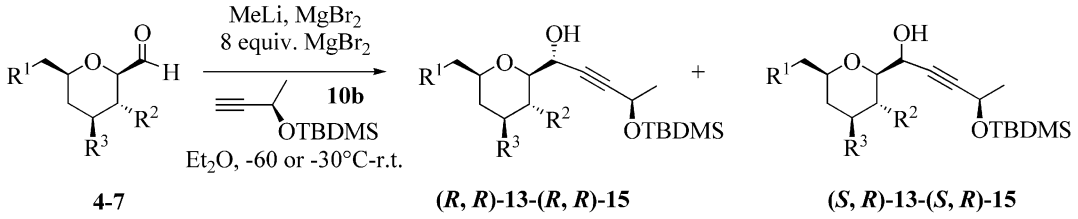
5 **11a-d** **12a-d**

Scheme 5. Hydroxy alkylation of aldehyde **5** with various alkynyl derivatives

Table 1. Hydroxy alkylation of aldehyde **5** with various alkynyl derivatives

Entry	Alkyne	Conditions	Dia **11**[a]	Dia **12**[a]	Yield[b]
1	**10a**	LDA, LDA/12-crown4, *t*BuLi, THF or Et_2O, −78 °C − room temp.	−	−	n.r.
2	**10a**	LDA/$MgBr_2$, *t*BuLi/ CuI, LDA/$CeCl_3$, LDA/$ZnBr_2$, THF or Et_2O, −78 °C − room temp.	−	−	n.r.
3	**10c**	MeLi, $MgBr_2$, 8 equiv. $MgBr_2$, Et_2O, −30 °C − room temp.	87	13	60%
4	**10d**	MeLi, $MgBr_2$, 8 equiv. $MgBr_2$, Et_2O, −30 °C − room temp.	70	30	73%
5	**10b**	MeLi, $MgBr_2$, 8 equiv. $MgBr_2$, Et_2O, −30 °C − room temp.	75	25	75%
6	**10b**	MeLi, $ZnBr_2$, 8 equiv. $ZnBr_2$, Et_2O, 0 °C. − room temp.	−	−	n.r.
7	**10b**	MeLi, $CeCl_3$, 8 equiv. $CeCl_3$, THF, −78 °C − room temp.	58	42	20%
8	**10b**	MeLi, $MgBr_2$, 8 equiv. $ZnBr_2$, Et_2O, −78 °C − room temp.	53	47	47%
9	**10b**	MeLi, $MgBr_2$, 8 equiv. CuI, THF/Me_2S, −78 °C − room temp.	70	30	50%
10	**10b**	MeLi, HMPT, −78 °C − room temp.	40	60	50%

[a] Diastereomeric ratio. [b] Global isolated yield; n.r. no reaction.



Scheme 6. Hydroxy alkylation of aldehydes **4**, **6**, and **7** with **10b**

Table 2. Hydroxy alkylation of aldehydes **4**, **6**, and **7** with **10b**

Entry	Aldehyde	(*R*,*R*) Isomer, (%)[a]	(*S*,*R*) Isomer, (%)[a]	Yield (%)[b]
1	**4**, $R^1 = CO_2Me$, $R^2 = R^3 = OBn$	(*R*,*R*)-**13**, 12	(*S*,*R*)-**13**, 88	52[c]
2	**6**, $R^1 = CH_2OBn$, $R^2 = R^3 = OBn$	(*R*,*R*)-**14**, 65	(*S*,*R*)-**14**, 35	73
3	**7**, $R^1 = OBn$, $R^2 = H$, $R^3 = O$*t*Bu	(*R*,*R*)-**15**, 80	(*S*,*R*)-**15**, 20	50[d]

[a] Diastereomeric ratio, isolated yield. [b] Global yield. [c] 28% SM recovered. [d] 12% SM recovered.

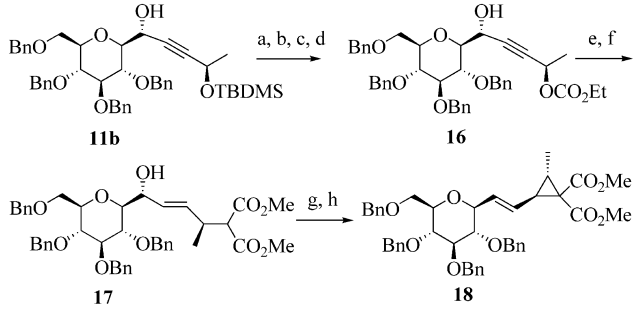
ficiently afforded the two desired alcohols **13** in a 12:88 diastereomeric ratio and 52% isolated yield, accompanied by 28% of starting material (Table 2, Entry 1). The 12:88 ratio was this time in favor of the diastereomer (*S*,*R*)-**13**, which was converted into an isomer of the C1−C13 part of ambruticin.[20] The aldehyde **6** was highly reactive at −30 °C and correspondingly afforded (*R*,*R*)-**14** and (*S*,*R*)-**14** in 73% yield. The 65:35 diastereoselectivity was in favor of the less polar alcohol (*R*,*R*)-**14**, as in the case of aldehyde **5**. Under the same conditions, the alkylation of aldehyde **7** gave the alcohols **15** in a moderate yield of 50% and a diastereomeric ratio of 80:20, with 12% of starting material being recovered.

Determination of Absolute Structures

Absolute Configuration of the Tetra-*O*-benzylated Derivative

With the major alcohol **11b** now to hand, we carried out protection and deprotection and isolated alcohol **16** in 67% overall yield. All attempts to obtain crystalline structures were unsuccessful. Considering that the preparation of a vinylcyclopropane would give us the answer concerning the configuration of the major alcohol, we decided to carry out the overall complete sequence to prepare the cyclopropane (Scheme 7).

The alkyne **16** was semi-hydrogenated and then alkylated under mild conditions by use of 10 mol % of [Pd(dppe)$_2$] and the sodium salt of dimethyl malonate. The alcohol **17** was isolated as a single diastereomer. The alkylation was totally regio-, stereo-, and enantioselective, based on the *anti* addition of Pd^0 catalyst, *anti-syn* isomerization, and *anti* addition of nucleophile.[28] This alcohol was then activated with 2,4-dichlorobenzoyl chloride and cyclized to give the cyclopropane **18**. The reaction proceeds with a clean chirality transfer from the C−O bond to the newly formed C−C bond.[29] The stereochemistry and the structure were confirmed by ^{1}H and ^{13}C NMR and NOE experiments (J_{a-b} = 7.5 Hz in **18** and 9.6 Hz in *epi*-**2**) (Figure 1).



Scheme 7. Synthesis of the tetra-*O*-benzylated western part of ambruticin; a) $ClCO_2CH_2CH{=}CH_2$, pyridine, CH_2Cl_2, 0 °C − room temp., 95%; b) Bu_4NF, THF, 0 °C − room temp., 92%; c) $ClCO_2Et$, pyridine, CH_2Cl_2, 0 °C − room temp., 92%; d) $Pd(OAc)_2$ (20 mol %)/TPPTS, CH_3CN/H_2O (6:1), Et_2NH, room temp., 83%; e) Pd/C (10 mol %), pyridine (5 mol %), H_2, room temp., MeOH, 70%; f) $Pd(OAc)_2$ (10 mol %), dppe (15 mol %), $NaCH(CO_2Me)_2$, THF, room temp., 43% (50% of SM recovered); g) 2,4-Cl_2-C_6H_3COCl, pyridine, CH_2Cl_2, 0 °C − room temp., 71%; h) $Pd(OAc)_2$ (10 mol %), dppe (15 mol %), DBU, THF, room temp., 68%

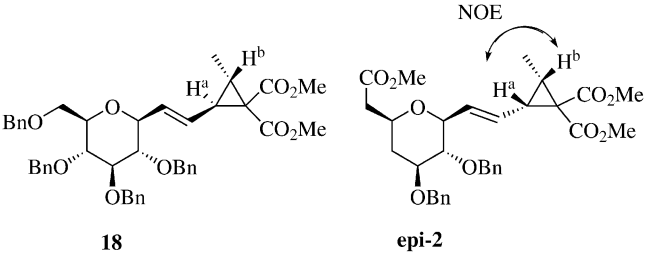
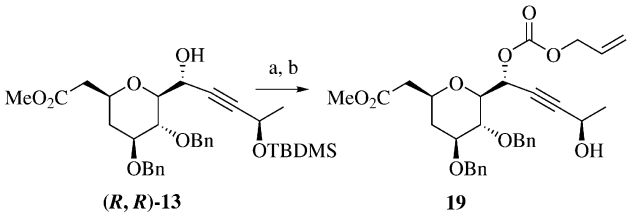


Figure 1. Comparison of cyclopropanes **18** and *epi*-**2**

Absolute Configuration of the Functionalized Substrate

We had previously shown that the same sequence as described on Scheme 7, starting with the major alcohol (*S*,*R*)-**13**, had produced an isomer of the "western" part of ambruticin, and so were able to deduce the (*S*) configuration of the stereogenic center bearing the alcohol. We took the minor isomer (*R*,*R*)-**13** and were gratified to isolate crystal-

line compound **19** after protection with the allyloxycarbonyl chloride and removal of the silyl group (Scheme 8).



Scheme 8. Protection of alcohol (*R*,*R*)-**13**; a) $ClCO_2CH_2CH=CH_2$, pyridine, CH_2Cl_2, 0 °C − room temp., 95%; b) Bu_4NF, THF, O ° − room temp., 90%

The ORTEP drawing of the crystal of compound **19** corroborated the absolute stereochemistry of the minor alcohol (Figure 2). It also confirmed that the major diastereomer obtained upon hydroxyalkylation of the aldehyde **4** was (*S*), which does not follow the commonly accepted Cram chelation model.

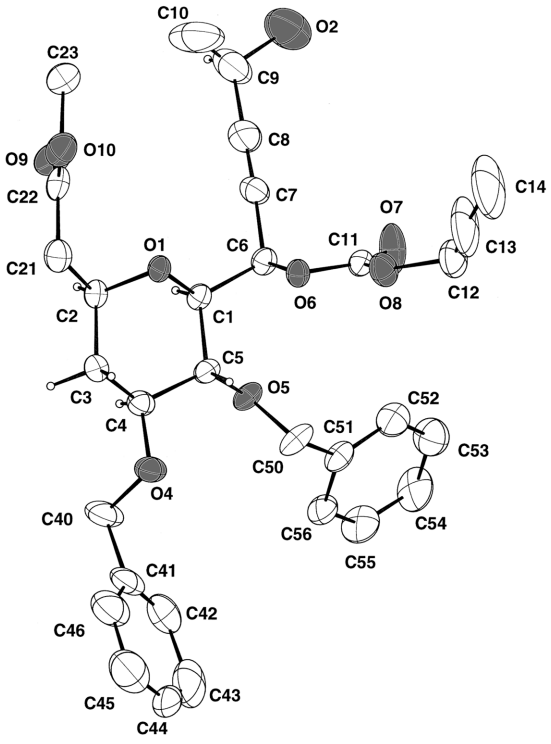
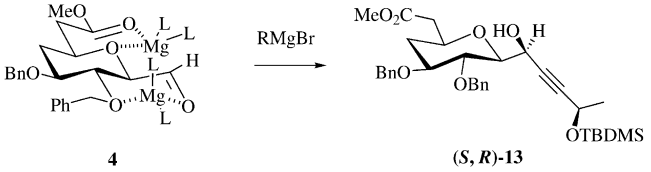


Figure 2. ORTEP drawing of the crystal structure of the alcohol **19**

Interpretation

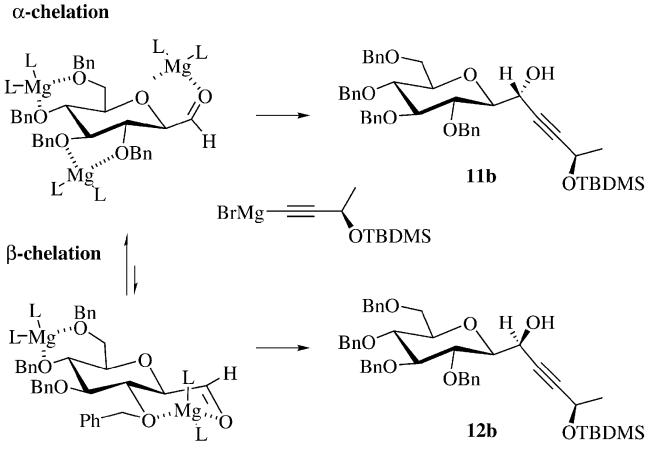
The diastereoselectivity of the hydroxyalkylation reaction on substrates **4** and **5** may be explained through α- or β-chelation.[25] The excess of $MgBr_2$ activates the aldehyde and provides a cyclic stable intermediate.

Taking the presence of the ester function on compound **4** into account, β-chelation should be favored with MgL_2 (L = Br or alkynyl derivative). The rigid intermediate consists of three six-membered ring chelates, on which a *si*-face attack affords the (*S*) isomer as the major product (Scheme 9).



Scheme 9. Cram chelation model on aldehyde **4**

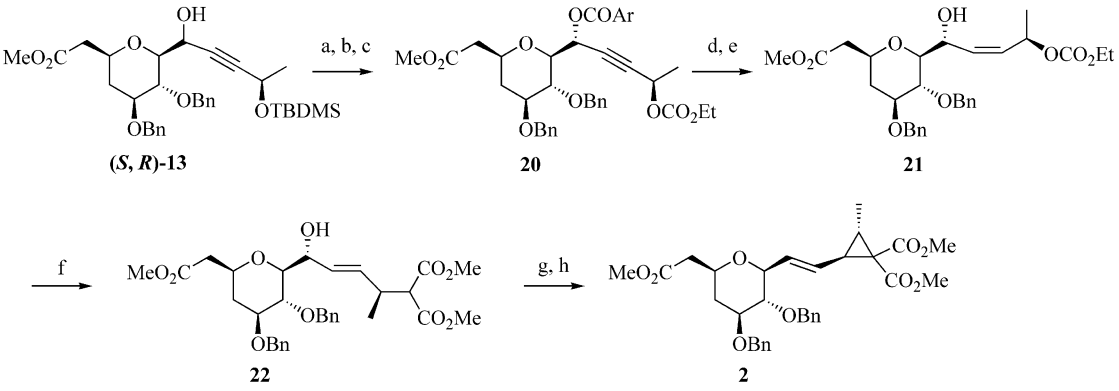
In the case of the tetra-*O*-benzylated aldehyde **5**, chelation of MgL_2 may give two intermediates, resulting from α- or β-chelation. The major chelate with the oxygen of the aldehyde and the oxygen of the pyran (α-chelation[25,30]) resulted in a *re*-face attack of the ethynyl organometallic (Scheme 10).



Scheme 10. Cram chelation model on aldehyde **5**

Synthesis of the Western Part of Ambruticin

The stereochemistry of the alcohol (*S*,*R*)-**13** was efficiently inverted through a Mistunobu reaction[31] with use of 4-nitrobenzoic acid, giving a 90% yield (Scheme 11). Removal of the silyl group, followed by protection as an ethylcarbonate, provided the ester **20**. Saponification was carefully performed with a catalytic amount of K_2CO_3 at room temperature, avoiding cleavage of the carbonate moiety. Semi-hydrogenation was then performed with deactivated Pd/C, with careful control of the hydrogen volume. The minor isomer (*R*,*R*)-**13** was also converted into the same intermediate **21** by a protection−deprotection sequence and semi-hydrogenation. Similar spectral analyses were obtained from both ((*S*,*R*)-**13** and (*R*,*R*)-**13**) transformations. The Pd-catalyzed step was smoothly conducted with $Pd(dppe)_2$ and methyl malonate sodium salt. Alcohol **22** was isolated in 80% yield as a unique diastereomer. Activation of the resulting alcohol, followed by final Pd-cyclization, gave the "western" part of ambruticin **2**.



Scheme 11. Synthesis of the western part of ambruticin; a) DEAD, PPh_3, 4-NO_2-C_6H_4-CO_2H, 90%; b) Bu_4NF, THF, 0 °C − room temp., 80%; c) $ClCO_2Et$, pyridine, CH_2Cl_2, 0 °C − room temp., 92% Ar = 4-NO_2-C_6H_4; d) K_2CO_3 2 mol % MeOH, room temp., 70%; e) Pd/C (10 mol %), H_2, room temp., EtOAc, 70%; f) $Pd(OAc)_2$ (10 mol %), dppe (15 mol %), $NaCH(CO_2Me)_2$, THF, room temp., 80%; g) 2,4-Cl_2-C_6H_3COCl, pyridine, CH_2Cl_2, 0 °C − room temp., 80%; h) $Pd(OAc)_2$ (10 mol %), dppe (15 mol %), DBU, THF, room temp., 60%

Conclusion

In conclusion, we have shown that the ethynylation of β-C-glycosyl aldehydes can be performed stereoselectively and is highly dependent on the substrate functionality at carbon 6 of the pyranoside and on the alkynyl metal (Ce, Li, Mg). We have determined the stereochemistry of the major alcohols in the case of a C-6-benzylated aldehyde and an C-6 ester aldehyde. Ethynylation of the functionalized A ring of ambruticin, followed by Mistunobu inversion and a two-step Pd-catalyzed strategy, has created a unique method for the preparation of the C1−C13 part of ambruticin. Further studies are under investigation in our laboratory for the synthesis of the C ring[32] and the completion of the total synthesis and ambruticin analogues.

Experimental Section

General: ^1H NMR spectra were recorded with a Bruker AC-200, AM-250, or AC-400 spectrometers at 200, 250, or 400 MHz, respectively; chemical shifts (δ) are reported in ppm units, with reference to Me_4Si, and coupling constants (*J*) are reported in Hertz and refer to apparent peak multiplicities. ^{13}C NMR spectra were recorded with a Bruker AC-200, AM-250, or AC-400 instruments at 50, 63, or 100 MHz, respectively. High-resolution mass spectra were performed on a Varian MAT311 instrument at the Université Pierre et Marie Curie (Paris). Low-resolution mass measurements were run with a Fisons Hewlett Packard 5989 instrument. Optical rotations were recorded with a Perkin−Elmer 241 polarimeter at 589 nm. IR spectra were recorded with a IRFT-45 Bruker spectrophotometer. Elemental analyses were carried out at the "Service Regional de Microanalyse" (Université Pierre et Marie Curie). Thin-layer chromatography was carried out on silica gel plates (Merck F_{254}) and spots were detected by UV and/or use of vanillin.

Anhydrous THF and diethyl ether were distilled from over sodium/benzophenone, and CH_2Cl_2 was distilled from over calcium hydride.

6-*O*-Benzyl-3-*O*-*tert*-butyl-2,4-dideoxy-1-(2-phenylethynyl)-α and -β-D-Glucopyranose: *n*BuLi (5.2 mL, 2.5 M solution in hexane) was added at −78 °C to a THF solution (60 mL) of phenylacetylene (1.43 mL, 13 mmol). The mixture was stirred for 15 min and then transferred by cannula to a THF solution (45 mL) of lactone **8** (3.47 g, 11.9 mmol), also at −78 °C. The reaction mixture was warmed to −40 °C over 1.5 h, and aqueous NH_4Cl (10 mL) and diethyl ether (40 mL) were added. After the mixture had been warmed to room temp., the aqueous phase was separated and extracted with diethyl ether, and the combined organic phase was washed with water and brine, dried (Na_2SO_4), and concentrated to afford crude lactol, which was purified by chromatography (SiO_2, cyclohexane/ethyl acetate, 8:2) to give the lactol as a colorless oil (4.43 g, 95%).^1H NMR (250 MHz, $CDCl_3$): δ = 7.59−7.26 (m, 10 H), 4.6, 4.55 (2s, 2 H), 4.46 (m, 1 H), 4.10 (m, 1 H), 3.4 (m, 3 H), 2.96 (m, 2 H), 1.68 (m, 2 H), 1.25 (s, 9 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 137.8, 131.2, 132.8, 130.5, 128.4, 128.1, 127.4, 127.3, 91.1, 88.1, 74.6, 74.5, 73.1, 67.0, 65.8, 60.1, 52.3, 38.7, 28.1 ppm. IR (neat): $\tilde{\nu}$ = 3345, 2220, 1380, 1365, 1260, 1210 cm^{-1}. MS (CI, NH_3): *m/z* = 412 [M + 18].

6-*O*-Benzyl-3-*O*-*tert*-butyl-2,4-dideoxy-1-(2-phenylethynyl)-D-*gluco*-β-C-pyranose (9): A solution of lactol (1.7 g, 4.31 mmol) in a CH_3CN/CH_2Cl_2 solvent mixture (85:15, 65 mL) was cooled to −40 °C, and Et_3SiH (3.44 mL, 21.6 mmol) was added. After 5 min, $BF_3{\cdot}Et_2O$ (1.59 mL, 12.9 mmol) was added very slowly, and the mixture was stirred at −40 °C for 2 h. After addition of Et_3N (3 mL, 21.6 mmol), the solution was warmed to room temp. and was concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2, washed with water and brine, dried with Na_2SO_4, and concentrated to give crude C-glycoside, which was purified by chromatography (SiO_2, cyclohexane/ethyl acetate, 9:1) to afford **9** as a pale yellow solid (1.28 g, 79%). $[\alpha]_D^{20}$ = +4 (*c* = 1.1, $CHCl_3$); m.p. 100−102 °C. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.45−7.24 (m, 10 H), 4.62, 4.54 (AB system, *J* = 12 Hz, 2 H), 4.38 (dd, *J* = 11.8, 2.1 Hz, 1 H), 3.69, 3.42 (m, 4 H), 2.12 (m, 1 H), 1.80 (m, 2 H), 1.27 (m, 1 H), 1.21 (s, 9 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 137.8, 122.3, 131.6, 128.1, 127.9, 127.8, 127.6, 127.5, 127.3, 87.2, 84.3, 75.5, 73.7, 73.2, 72.8, 66.7, 66.5, 41.3, 37.0, 28.2 ppm. IR (neat): $\tilde{\nu}$ = 2230 cm^{-1}. MS (CI, NH_3): *m/z* = 379 [M + 1], 396 [M + 18]. HRMS-DCI/NH_3: $[M + NH_4]^+$ calculated for $C_{25}H_{34}NO_3$: 396.2539; found 396.2540.

6-*O*-Benzyl-3-*O*-*tert*-butyl-2,4-dideoxy-1-[(*Z*)-2-phenylethenyl]-D-*gluco*-β-C-pyranose: Pd Lindlar (0.11 g, 10% in weight), and quinoline (100 μL, 10% in weight) were added to a solution of **9** (1.11 g, 2.9 mmol) in ethyl acetate (25 mL), and the mixture was stirred under hydrogen at room temp. for 16 h. After filtration through a short plug of silica with diethyl ether as eluent, the solvent was evaporated under reduced pressure. The crude product was purified

by chromatography (SiO_2, cyclohexane/ethyl acetate, 9:1) to give the alkene as a pale yellow oil (1.11 g, 100%). $[\alpha]_D^{20} = -37.3$ (c = 1, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 7.36−7.22 (m, 10 H), 6.61 (d, J = 11.6 Hz, 1 H), 5.70 (dd, J = 11.6, 8.6 Hz, 1 H), 4.58 (m, 2 H), 4.2 (m, 1 H), 3.6 (m, 4 H), 1.85−1.40 (m, 4 H), 1.19 (s, 9 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 138.3, 136.6, 132.3, 131.5, 128.8, 128.5, 128.2, 127.6, 127.4, 127.2, 75.0, 73.7, 73.4, 73.3, 72.3, 67.0, 41.0, 37.3, 28.3 ppm. IR (neat): $\tilde{\nu}$ = 1650 cm^{-1}. MS (CI, NH_3): m/z = 381 [M + 1], 398 [M + 18]. HRMS-DCI/CH_4: $[M + H]^+$ calculated for $C_{25}H_{33}O_3$: 381.2430; found 381.2424.

[6-*O*-Benzyl-3-*O*-*tert*-butyl-2,4-dideoxy-D-*gluco*-β-C-pyranosyl]-carbaldehyde (7): Ozone was bubbled at −78 °C through a CH_2Cl_2 solution (160 mL) of the alkene (1.03 g, 2.71 mmol) until saturation (blue color in 10 min). Argon was then passed through to eliminate the excess ozone, and Me_2S (0.6 mL, 8.1 mmol) was added. The reaction mixture was warmed to room temp. and concentrated under reduced pressure. Column chromatography (SiO_2, cyclohexane/ethyl acetate, 8:2) afforded **7** as a white solid (484 mg, 58%). $[\alpha]_D^{20}$ = +19 (c = 1, $CHCl_3$); m.p. 105 °C. ^1H NMR (200 MHz, $CDCl_3$): δ = 9.66 (d, J = 0.8 Hz, 1 H), 7.36−7.27 (m, 5 H), 4.63, 4.56 (AB system, J = 12.2 Hz, 2 H), 3.85 (ddd, J = 12.2, 2.3, 0.8 Hz, 1 H), 3.73−3.45 (m, 4 H), 2.01, 1.79 (2m, 2 H), 1.33 (m, 2 H), 1.20 (s, 9 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 201.1, 137.7, 128.1, 127.5, 127.4, 80.0, 75.5, 73.8, 73.3, 72.6, 66.6, 36.9, 35.0, 28.1 ppm. IR (KBr): $\tilde{\nu}$ = 1735 cm^{-1}. MS (EI): m/z = 249 [M − tBu]$^+$. HRMS-EI calculated for $C_{14}H_{17}O_4$: [M − tBu] 249.112681; found 249.112745.

General Procedure for the Hydroxy Alkylation of Aldehydes: Two solutions of $MgBr_2$ in diethyl ether (0.7 mL/mmol) were prepared, by addition of 1,2-dibromoethane (8 equiv.) to magnesium (8 equiv.). The alkyne (4.4 equiv.) was added at −5 °C to a solution of methyllithium (4 equiv.) in diethyl ether. After 30 minutes, the first solution of $MgBr_2$ was added and the resulted mixture was cooled to −30 °C or −60 °C. The second solution of $MgBr_2$ was added to a solution of the aldehyde (1 equiv.) in diethyl ether (3.5 mL/mmol). This mixture was then added to the Grignard acetylenic reagent. The solution was stirred at −60 °C or −78 °C, was warmed to room temperature, and was then slowly quenched with cold aqueous NH_4Cl. The aqueous phase was extracted with diethyl ether. The organic phase was washed with water, dried (Na_2SO_4), and concentrated under reduced pressure. Column chromatography (SiO_2, cyclohexane/EtOAc, 8:2 then 7:3) afforded two diastereomers.

The hydroxy alkylation of aldehyde **5** (310 mg, 0.56 mmol) in the presence of (*R*)-3-(*tert*-butyldimethylsilyloxy)but-1-yne (**10b**, 469 mg, 2.46 mmol) afforded the diastereomers **11b** (226 mg, colorless oil) and **12b** (75 mg, colorless oil). *dr* 75:25, Yield 75%.

(1*R*,4*R*)-1-(2,3,4,6-Tetra-*O*-benzyl-D-*gluco*-β-C-pyranosyl)-4-*O*-*tert*-(butyldimethylsilyl)pent-2-yne-1,4-diol (11b): $[\alpha]_D^{20}$ = +41 (c = 1.5, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ = 7.35−7.17 (m, 20 H), 4.94−4.51 (m, 10 H), 3.76−3.33 (m, 7 H), 2.59 (d, J = 11 Hz, 1 H), 1.40 (d, J = 6.5 Hz, 3 H), 0.88 (s, 9 H), 0.1, 0.09 (2s, 6 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 138.2, 137.9, 137.8, 137.6, 128.2, 128.1, 128.0, 127.7, 127.6, 127.5, 127.4, 127.3, 87.2, 86.6, 81.8, 80.0, 78.9, 77.9, 76.9, 75.2, 75.0, 74.8, 73.2, 68.5, 61.2, 58.7, 25.5, 25.0, 17.9, −4.8, −5.2 ppm. IR (neat): $\tilde{\nu}$ = 3450, 2100 cm^{-1}. MS (CI, NH_3): m/z = 754 [M + 18]. HRMS-DCI/NH_3: $[M + NH_4]^+$ calculated for $C_{45}H_{60}O_7NSi$: 754.4139; found 754.4147.

(1*S*,4*R*)-1-(2,3,4,6-Tetra-*O*-benzyl-D-*gluco*-β-C-pyranosyl)-4-*O*-*tert*-(butyldimethylsilyl)pent-2-yne-1,4-diol (12b): $[\alpha]_D^{20}$ = +28 (c = 0.9, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ = 7.35−7.18 (m, 20 H), 4.90−4.52 (m, 10 H), 3.79−3.46 (m, 7 H), 2.73 (d, J = 10.7 Hz, 1 H), 1.39 (d, J = 6.5 Hz, 3 H), 0.88 (s, 9 H), 0.10, 0.09 (2s, 6 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 138.2, 138.0, 137.8, 137.7, 128.2, 128.1, 127.7, 127.6, 127.5, 127.4, 127.3, 89.0, 86.6, 80.3, 80.0, 79.6, 78.9, 78.1, 75.3, 75.0, 74.8, 73.0, 68.6, 62.5, 58.7, 25.5, 25.2, 17.9, −4.7, −5.1 ppm. IR (neat): $\tilde{\nu}$ = 3450, 2100 cm^{-1}. MS (CI, NH_3): m/z = 754 [M + 18]. HRMS-DCI/NH_3: $[M + NH_4]^+$ calculated for $C_{45}H_{60}NO_7Si$: 754.4139; found 754.4133.

The hydroxy alkylation of aldehyde **5** (165 mg, 0.3 mmol) in the presence of phenylacetylene (**10c**, 144 μL, 1.31 mmol) afforded the diastereomers **11c** (102 mg, colorless oil) and **12c** (14 mg, colorless oil). *dr* 87:13, Yield 60%.

(1*R*)-1-(2,3,4,6-Tetra-*O*-benzyl-D-*gluco*-β-C-pyranosyl)-3-phenyl-prop-2-yne (11c): $[\alpha]_D^{20}$ = +10 (c = 1, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 7.48−7.20 (m, 25 H), 5.03−4.56 (m, 9 H), 3.95−3.52 (m, 7 H), 3.09 (d, J = 10.5 Hz, 1 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 138.1, 137.9, 137.8, 137.6, 131.5, 128.3, 128.1, 128.0, 127.9, 127.7, 127.6, 127.5, 127.4, 127.3, 122.4, 87.9, 86.6, 84.9, 80.1, 79.0, 78.3, 78.0, 75.2, 75.1, 74.8, 73.1, 68.6, 62.1 ppm. IR (neat): $\tilde{\nu}$ = 3390, 2233 cm^{-1}. MS (CI, NH_3): m/z = 672 [M + 18]. HRMS-DCI/NH_3: $[M + NH_4]^+$ calculated for $C_{43}H_{46}NO_6$: 672.3325; found 672.3317.

(1*S*)-1-(2,3,4,6-Tetra-*O*-benzyl-D-*gluco*-β-C-pyranosyl)-3-phenyl-prop-2-yne (12c): $[\alpha]_D^{20}$ = +8 (c = 0.7, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ = 7.40−7.22 (m, 25 H), 4.93−4.56 (m, 8 H), 4.92 (m, 1 H), 3.87−3.51 (m, 7 H), 3.00 (d, J = 10 Hz, 1 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 138.5, 138.4, 138.2, 138.0, 131.9, 128.6, 128.5, 128.4, 128.3, 128.0, 127.9, 127.8, 127.6, 127.3, 122.5, 87.0, 86.7, 86.4, 80.8, 79.9, 79.4, 78.4, 75.8, 75.5, 75.2, 73.4, 68.6, 63.4 ppm. IR (neat): $\tilde{\nu}$ = 3390, 2223 cm^{-1}. MS (CI, NH_3): m/z = 672 [M + 18]. HRMS-DCI/NH_3: $[M + NH_4]^+$ calculated for $C_{43}H_{46}NO_6$: 672.3325; found 672.3315.

The hydroxy alkylation of aldehyde **5** (800 mg, 1.45 mmol) in the presence of trimethylsilylacetylene (**10d**, 900 μL, 6.38 mmol) afforded the diastereomers **11d** (483 mg, colorless oil) and **12d** (206 mg, colorless oil). *dr* 70:30, Yield 73%.

(1*R*)-1-(2,3,4,6-Tetra-*O*-benzyl-D-*gluco*-β-C-pyranosyl)-3-trimethylsilylprop-2-yne (11d): $[\alpha]_D^{20}$ = +16 (c = 1.1, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ = 7.36−7.19 (m, 20 H), 4.96−4.54 (m, 8 H), 4.58 (dd, J = 10.9, 1.8 Hz, 1 H), 3.83−3.38 (m, 7 H), 2.65 (d, J = 10.9 Hz, 1 H), 0.16 (s, 9 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 138.5, 138.4, 138.2, 137.9, 128.6, 128.5, 128.4, 128.1, 128.0, 127.9, 127.8, 127.6, 104.6, 90.3, 87.0, 80.1, 79.6, 78.7, 78.4, 75.6, 75.4, 75.1, 73.4, 68.8, 62.5, −0.06 ppm. IR (neat): $\tilde{\nu}$ = 3400, 2205 cm^{-1}. MS (CI, NH_3): m/z = 668 [M + 18]. $C_{40}H_{46}O_6Si$: calcd. C 73.8, H 7.12, found C 74.3, H 7.10.

(1*S*)-1-(2,3,4,6-Tetra-*O*-benzyl-D-*gluco*-β-C-pyranosyl)-3-trimethylsilylprop-2-yne (12d): $[\alpha]_D^{20}$ = +12 (c = 1, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ = 7.36−7.24 (m, 20 H), 4.92−4.55 (m, 8 H), 4.72 (dd, J = 10.6, 3.2 Hz, 1 H), 3.84−3.65 and 3.51−3.46 (m, 7 H), 2.72 (d, J = 10.6 Hz, 1 H), 0.16 (s, 9 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 138.4, 138.2, 138.1, 128.6, 128.5, 128.4, 128.1, 128.0, 127.9, 127.8, 127.6, 127.7, 103.0, 91.8, 86.9, 80.4, 80.1, 79.5, 78.4, 75.9, 75.5, 75.2, 73.3, 68.5, 63.2, −0.05 ppm. IR (neat): $\tilde{\nu}$ = 3385, 2200 cm^{-1}. MS (CI, NH_3): m/z = 668 [M + 18]. HRMS-DCI/NH_3: $[M + NH_4]^+$ calculated for $C_{40}H_{50}NO_6Si$: 668.3407; found 668.3400.

The hydroxy alkylation of aldehyde **4** (525 mg, 1.3 mmol) in the presence of (*R*)-3-(*tert*-butyldimethylsilyloxy)but-1-yne **10b** (1.07 g,

5.72 mmol) afforded the diastereomers (*R*,*R*)-**13** (80 mg, colorless oil) and (*S*,*R*)-**13** (343 mg, colorless oil), together with unchanged aldehyde **4** (150 mg, 28%). *dr* 88:12, Yield 52%.

(1*R*,4*R*)-1-[2,3-Di-*O*-benzyl-4,6-dideoxy-6-(methoxycarbonyl)-D-*gluco*-β-C-pyranosyl]-4-*O*-(*tert*-butyldimethylsilyl)pent-2-yne-1,4-diol [(*R*,*R*)-13]: $[\alpha]_D^{20}$ = +5 (*c* = 1.1, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ = 7.39−7.28 (m, 10 H), 5.03, 4.62:4.70, 4.65 (2 AB system, *J* = 10.7, 11.6 Hz, 4 H), 4.56−4.53 (m, 2 H), 3.90−3.70 (m, 2 H), 3.68 (s, 3 H), 3.56 (app. t, *J* = 9.3 Hz, 1 H), 3.20 (dd, *J* = 2.8, 9.3 Hz, 1 H), 2.66, 2.46 (2dd, *J* = 15.8, 7.3 Hz and 15.8, 5.8 Hz, 2 H), 2.26 (dd, *J* = 12.7, 5.1 Hz, 1 H), 1.75 (broad s, 1 H), 1.45−1.39 (m, 1 H), 1.40 (d, *J* = 6.5 Hz, 3 H), 0.90 (s, 9 H), 0.15, 0.14 (2s, 6 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 171.9, 138.2, 138.1, 128.3, 128.1, 127.9, 127.5, 88.8, 82.0, 80.5, 80.0, 78.4, 72.1, 75.2, 71.3, 61.8, 58.9, 51.7, 40.2, 36.3, 25.7, 25.3, 18.1, −4.6, −5.0 ppm. MS (CI, NH_3): *m*/*z* = 583 [M + 1], 600 [M + 18]. HRMS-DCI/NH_3: $[M + NH_4]^+$ calculated for $C_{33}H_{50}NO_7Si$: 600.3357; found 600.3361.

(1*S*,4*R*)-1-[2,3-Di-*O*-benzyl-4,6-dideoxy-6-(methoxycarbonyl)-D-*gluco*-β-C-pyranosyl]-4-*O*-(*tert*-butyldimethylsilyl)pent-2-yne-1,4-diol [(*S*,*R*)-13]: $[\alpha]_D^{20}$ = −20 (*c* = 1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.38−7.26 (m, 10 H), 4.88, 4.59/4.71, 4.62 (2 AB system, *J* = 10.8, 11.5 Hz, 4 H), 4.60−4.53 (m, 2 H), 3.90−3.80 (m, 2 H), 3.68 (s, 3 H), 3.51 (app. t, *J* = 9.5 Hz, 1 H), 3.41 (dd, *J.* = 9.5, 3.2 Hz, 1 H), 2.63, 2.41 (2dd, *J* = 15.8, 7.0 Hz and 15.8, 5.9 Hz, 2 H), 2.28 (dd, *J* = 11.8, 4.8 Hz, 1 H), 1.65−1.63 (m, 1 H), 1.44 (d, *J* = 6.4 Hz, 3 H), 0.92 (s, 9 H), 0.14, 0.13 (2s, 6 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 170.9, 138.2, 138.1, 128.3, 128.1, 127.9, 127.5, 88.9, 88.8, 80.4, 80.2, 79.8, 75.1, 72.1, 71.4, 62.6, 58.9, 51.7, 40.0, 36.3, 25.7, 25.3, 18.1, −4.5; −4.9 ppm. MS (CI, NH_3): *m*/*z* = 600 [M + 18].

The hydroxy alkylation of aldehyde **6** (259 mg, 0.56 mmol) in the presence of (*R*)-3-(*tert*-butyldimethylsilyloxy)but-1-yne (**10b**) (469 mg, 2.46 mmol) afforded the diastereomers (*R*,*R*)-**14** (171 mg, colorless oil) and (*S*,*R*)-**14** (96 mg, colorless oil). *dr* 65:35, Yield 73%.

(1*R*,4*R*)-1-[2,3-Di-*O*-benzyl-6-(benzyloxymethyl)-4,6-dideoxy-D-*gluco*-β-C-pyranosyl]-4-*O*-(*tert*-butyldimethylsilyl)pent-2-yne-1,4-diol [(*R*,*R*)-14]: $[\alpha]_D^{20}$ = +25 (*c* = 1, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ = 7.34−7.36 (m, 15 H), 5.03−4.49 (m, 8 H), 3.72−3.27 (m, 6 H), 2.60 (d, *J* = 10.7 Hz, 1 H), 2.2−2.1 (m, 1 H), 1.95−1.75 (m, 2 H), 1.38 (d, *J* = 6.5 Hz, 3 H), 1.25−1.35 (m, 1 H), 0.88 (s, 9 H), 0.11, 0.10 (2s, 6 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 138.2, 138.1, 137.9, 128.2, 128.1, 127.6, 127.5, 127.3, 87.1, 82.1, 80.6, 79.7, 78.6, 72.5, 75.0, 72.8, 71.0, 66.4, 61.8, 58.7, 36.5, 35.4, 25.5, 17.9, −4.7, −5.2 ppm. IR (neat): $\tilde{\nu}$ = 3450, 2100 cm^{-1}. MS (CI, NH_3): *m*/*z* = 645 [M + 1], 662 [M + 18]. HRMS-DCI/NH_3: $[M + H]^+$ calculated for $C_{39}H_{53}O_6Si$: 645.3611; found 645.3609, $[M + NH_4]^+$ calculated for $C_{39}H_{56}O_6NSi$: 662.3877; found 662.3871.

(1*S*,4*R*)-1-[2,3-Di-*O*-benzyl-6-(benzyloxymethyl)-4,6-dideoxy-D-*gluco*-β-C-pyranosyl]-4-*O*-(*tert*-butyldimethylsilyl)pent-2-yne-1,4-diol [(*S*,*R*)-14]: $[\alpha]_D^{20}$ = +10 (*c* = 1, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 7.33−7.27 (m, 15 H), 4.98−4.50 (m, 8 H), 3.58−3.43 (m, 6 H), 2.60 (d, *J* = 10.8 Hz, 1 H), 2.2−2.1 (m, 1 H), 1.95−1.8 (m, 2 H), 1.40 (d, *J* = 6.5 Hz, 3 H), 1.20−1.30 (m, 1 H), 0.9 (s, 9 H), 0.13, 0.12 (2s, 6 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 138.1, 137.9, 128.5, 128.1, 127.5, 127.3, 87.3, 82.0, 80.6, 79.5, 78.9, 75.0, 72.8, 72.7, 71.3, 66.7, 61.4, 58.7, 36.5, 35.4, 25.3, 25.3, 17.8, −4.6, −5.2 ppm. IR (neat): $\tilde{\nu}$ = 3445, 2100 cm^{-1}. MS (CI, NH_3): *m*/*z* = 645 [M + 1], 662 [M + 18].

The hydroxy alkylation of aldehyde **7** (318 mg, 1.04 mmol) in the presence of (*R*)-3-(*tert*-butyldimethylsilyloxy)but-1-yne (**10b**) (843 mg, 4.57 mmol) afforded the diastereomers (*R*,*R*)-**15** (188 mg, colorless oil) and (*S*,*R*)-**15** (49 mg, colorless oil), together with unchanged aldehyde **7** (37 mg). *dr* 80:20, Yield 50%.

(1*R*,4*R*)-1-[6-*O*-Benzyl-3-*O*-*tert*-butyl-2,4-dideoxy-D-*gluco*-β-C-pyranosyl]-4-*O*-(*tert*-butyldimethylsilyl)pent-2-yne-1,4-diol [(*R*,*R*)-15]: $[\alpha]_D^{20}$ = +31 (*c* = 1, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ = 7.34−7.27 (m, 5 H), 4.56 (AB system, *J* = 12.1 Hz, 2 H), 4.53−4.47 (m, 2 H), 3.67−3.46 (m, 4 H), 3.42 (dd, *J* = 10, 4.3 Hz, 1 H), 2.37 (d, *J* = 5.9 Hz, 1 H), 1.90−1.76 (m, 2 H), 1.60−1.25 (m, 2 H), 1.39 (d, *J* = 6.5 Hz, 3 H), 1.23 (s, 9 H), 0.89 (s, 9 H), 0.11, 0.10 (2s, 6 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 138.2, 128.5, 127.8, 127.7, 88.7, 80.6, 78.1, 75.7, 73.8, 73.5, 73.3, 67.3, 64.9, 59.0, 37.6, 34.8, 28.6, 25.9, 25.4, 18.3, −4.39, −4.83 ppm. IR (neat): $\tilde{\nu}$ = 3450, 2100 cm^{-1}. MS (CI, NH_3): *m*/*z* = 508 [M + 18]. HRMS-DCI/NH_3: $[M + NH_4]^+$ calculated for $C_{28}H_{50}NO_5Si$: 508.3458; found 508.3447.

(1*S*,4*R*)-1-[6-*O*-Benzyl-3-*O*-*tert*-butyl-2,4-dideoxy-D-*gluco*-β-C-pyranosyl]-4-*O*-(*tert*-butyldimethylsilyl)pent-2-yne-1,4-diol [(*S*,*R*)-15]: $[\alpha]_D^{20}$ = +12 (*c* = 1, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ = 7.35−7.26 (m, 5 H), 4.55 (s, 2 H), 4.54 (dq, *J* = 6.5, 1.4 Hz, 1 H), 4.28 (dd, *J* = 7.7 Hz, 1.4 Hz, 1 H), 3.71−3.40 (m, 4 H), 3.37 (ddd, *J* = 11.6, 7.7, 1.8 Hz), 2.8 (broad s, 1 H), 2.01 (m, 1 H), 1.81 (m, 1 H), 1.40 (d, *J* = 6.5 Hz, 3 H), 1.33−1.15 (m, 2 H), 1.20 (s, 9 H), 0.89 (s, 9 H), 0.11, 0.10 (2s, 6 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 138.2, 128.5, 127.7, 88.9, 80.3, 78.9, 75.5, 73.9, 73.5, 73.1, 65.9, 59.0, 37.5, 36.7, 28.6, 25.9, 25.3, 18.3, −4.43, −4.86 ppm. IR (neat): $\tilde{\nu}$ = 3470, 2110 cm^{-1}. MS (CI, NH_3): *m*/*z* = 508 [M + 18]. HRMS-DCI/NH_3: $[M + NH_4]^+$ calculated for $C_{28}H_{50}NO_5Si$: 508.3458; found 508.3448.

(1*R*,4*R*)-1-*O*-Allyloxycarbonyl-1-(2,3,4,6-tetra-*O*-benzyl-D-*gluco*-β−C-pyranosyl)-4-*O*-(*tert*-butyldimethylsilyl)pent-2-yne-1,4-diol: Allyloxycarbonyl chloride (52 μL, 0.49 mmol) was slowly added at 0 °C to a CH_2Cl_2 (4.5 mL) solution of alcohol **11b** (300 mg, 0.41 mmol) and pyridine (66 μL, 0.81 mmol). The solution was stirred at 0 °C for 1 h and for 1 h at room temp. After completion, the reaction mixture was washed with 5% aqueous HCl and brine to pH = 7. The organic phase was dried with $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography (SiO_2, cyclohexane/EtOAc, 9:1) afforded the diprotected derivative as a colorless oil (318 mg, 95%).$[\alpha]_D^{20}$ = +3 (*c* = 1, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ = 7.33−7.19 (m, 20 H), 5.92 (ddt, *J* = 16.2, 10.5, 5.7 Hz, 1 H), 5.68 (t, *J* = 1.8 Hz, 1 H), 5.38 (dq, *J* = 16.2, 1.3 Hz, 1 H), 5.27 (dq, *J* = 10.5, 1.3 Hz, 1 H), 4.93−4.54 (m, 10 H), 4.51 (qd, *J* = 6.5, 1.6 Hz, 1 H), 3.77−3.45 (m, 7 H), 1.36 (d, *J* = 6.5 Hz, 3 H), 0.86 (s, 9 H), 0.08−0.07 (2s, 6 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 153.9, 138.2, 138.1, 137.8, 137.4, 131.1, 128.2, 128.0, 127.7, 127.6, 127.5, 127.3, 127.2, 127.1, 118.8, 89.2, 77.4, 86.8, 79.6, 78.8, 77.9, 77.2, 75.2, 74.9, 74.7, 73.2, 68.5, 68.4, 66.1, 58.7, 25.5, 24.8, 17.9, −4.82, −5.27 ppm. IR (neat): $\tilde{\nu}$ = 2225, 1750 cm^{-1}. MS (CI, NH_3): *m*/*z* = 838 [M + 18]. HRMS-DCI/NH_3: $[M + NH_4]^+$ calculated for $C_{49}H_{64}NO_9Si$: 838.4350; found 838.4338.

(1*R*,4*R*)-1-*O*-Allyloxycarbonyl-1-(2,3,4,6-tetra-*O*-benzyl-D-*gluco*-β-C-pyranosyl)pent-2-yne-1,4-diol: Tetrabutylammonium fluoride (215 μL, 1 mol·L^{-1} in THF) was slowly added at 0 °C to a solution of the *O*-silyl compound (192 mg, 0.19 mmol) in THF (2 mL). The solution was stirred at 0 °C for 1 h and at room temp. for 1 h, and was then treated with water after completion. The aqueous phase was extracted with diethyl ether. The organic phase was washed

with aqueous NaCl, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography (SiO_2, cyclohexane/EtOAc, 7:3) afforded the alcohol as a colorless oil (132 mg, 92%).$[\alpha]_D^{20}$ = +6 (*c* = 1, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ = 7.38−7.15 (m, 20 H), 5.92 (ddt, *J* = 16.1, 10.3, 5.8 Hz, 1 H), 5.62 (dd, *J* = 2.3, 1.4 Hz, 1 H), 5.37 (dq, *J* = 16.1, 1.3 Hz, 1 H), 5.26 (dq, *J* = 10.3, 1.3 Hz, 1 H), 4.93−4.45 (m, 11 H), 3.74−3.49 (m, 7 H), 1.86 (d, *J* = 5.2 Hz, 1 H), 1.38 (d, *J* = 6.5 Hz, 3 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 153.9, 138.2, 138.0, 137.7, 137.4, 131.0, 128.2, 128.1, 128.0, 127.7, 127.6, 127.4, 127.3, 119.0, 89.2, 86.8, 79.6, 78.8, 78.3, 78.1, 77.3, 75.3, 74.9, 74.8, 73.1, 68.6, 68.5, 66.1, 57.9, 23.5 ppm. IR (neat): $\tilde{\nu}$ = 3400, 2200, 1750 cm^{-1}. MS (CI, NH_3): *m*/*z* = 724 [M + 18]. HRMS-DCI/NH_3: $[M + NH_4]^+$ calculated for $C_{43}H_{50}NO_9$: 724.3486; found 724.3490.

(1*R*,4*R*)-1-*O*-Allyloxycarbonyl-1-(2,3,4,6-tetra-*O*-benzyl-D-*gluco*-β-C-pyranosyl)-4-*O*-(ethoxycarbonyl)pent-2-yne-1,4-diol: Ethyl chloroformate (20 μL, 0.21 mmol) was slowly added at 0 °C to a CH_2Cl_2 (2 mL) solution of alcohol (123 mg, 0.17 mmol) and pyridine (28 μL, 0.34 mmol). The solution was stirred at 0 °C for 1 h and at room temp. for 1 h. After completion, the reaction mixture was washed with 5% aqueous HCl and brine to pH = 7. The organic phase was dried with $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography (SiO_2, cyclohexane/EtOAc, 8:2) afforded the diprotected derivative as a colorless oil (125 mg, 92%). $[\alpha]_D^{20}$ = +25 (*c* = 1, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ = 7.35−7.17 (m, 20 H), 5.92 (ddt, *J* = 16.1, 10.3, 5.8 Hz, 1 H), 5.67 (dd, *J* = 2, 1.3 Hz, 1 H), 5.41−5.24 (m, 3 H), 4.96−4.53 (m, 10 H), 4.14 (q, *J* = 7.3 Hz, 2 H), 3.75−3.47 (m, 7 H), 1.48 (d, *J* = 6.5 Hz, 3 H), 1.26 (t, *J* = 7.3 Hz, 3 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 153.8, 138.2, 138.1, 137.7, 137.4, 131.0, 128.2, 128.0, 127.7, 127.6, 127.5, 127.4, 127.3, 127.2, 118.9, 86.8, 84.6, 80.0, 79.7, 78.6, 78.0, 77.3, 75.3, 74.9, 74.8, 73.2, 68.6, 68.4, 66.0, 63.9, 63.6, 20.8, 13.9 ppm. IR (neat): $\tilde{\nu}$ = 2219, 1735 cm^{-1}. MS (CI, NH_3): *m*/*z* = 796 [M + 18].

(1*R*,4*R*)-1-(2,3,4,6-Tetra-*O*-benzyl-D-*gluco*-β-C-pyranosyl)-4-*O*-(ethoxycarbonyl)pent-2-yne-1,4-diol (16): A mixture of $Pd(OAc)_2$ (6 mg) and TPPTS (112 mg) in water (0.4 mL) was added to a solution of the allyloxycarbonyl compound (125 mg, 0.16 mmol) and diethylamine (36 μL, 0.35 mmol) in acetonitrile (2.4 mL). The resulting mixture was vigorously stirred at room temperature until completion of the reaction and was then evaporated under reduced pressure. The resulting aqueous phase was extracted with ethyl acetate, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography (SiO_2, cyclohexane/EtOAc, 7:3) afforded the alcohol **16** as a colorless oil (92 mg, 83%). $[\alpha]_D^{20}$ = +36 (*c* = 1, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ = 7.35−7.16 (m, 20 H), 5.35 (qd, *J* = 6.7, 1.3 Hz, 1 H), 4.95−4.51 (m, 9 H), 4.21−4.13 (2q, *J* = 7.3 Hz, 2 H), 3.76−3.37 (m, 7 H), 2.73 (d, *J* = 10.9 Hz, 1 H), 1.51 (d, *J* = 6.7 Hz, 3 H), 1.28 (t, *J* = 7.3 Hz, 3 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 153.9, 138.2, 137.9, 137.8, 137.5, 128.3, 128.2, 128.1, 127.7, 127.6, 127.5, 127.4, 127.3, 86.6, 84.3, 82.6, 79.7, 79.0, 78.0, 77.9, 75.2, 75.0, 74. 8, 73.1, 68.5, 63.9, 63.8, 61.5, 21.1, 13.9 ppm. IR (neat): $\tilde{\nu}$ = 3450, 2200, 1735 cm^{-1}. MS (CI, NH_3): *m*/*z* = 712 [M + 18]. HRMS-DCI/NH_3: $[M + NH_4]^+$ Calculated for $C_{42}H_{50}NO_9$: 712.3486; found 712.3481.

(1*R*,2*Z*,4*R*)-1-(2,3,4,6-Tetra-*O*-benzyl-D-*gluco*-β-C-pyranosyl)-4-*O*-(ethoxycarbonyl)pent-2-ene-1,4-diol: Pyridine (3 μL, 5% weight) was added to a solution of **16** (65 mg, 0.093 mmol) and Pd/C (7 mg, 10% weight) in methanol (1.5 mL) and the reaction mixture was stirred under hydrogen at room temp. After filtration through a short plug of silica gel, with diethyl ether as eluent, the solvent was evaporated under reduced pressure. Column chromatography (SiO_2, cyclohexane/EtOAc, 8:2) afforded the alkene as a colorless oil (55 mg, 70%). $[\alpha]_D^{20}$ = +5 (*c* = 0.7, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ = 7.35−7.16 (m, 20 H), 5.95 (app. dd, *J* = 10, 8.7 Hz, 1 H), 5.51−5.46 (m, 2 H), 4.95−4.46 (m, 9 H), 4.17 (2q, *J* = 7.1 Hz, 2 H), 3.86 (app. t, *J* = 9.3 Hz, 1 H), 3.77−3.66 (m, 3 H), 3.63−3.43 (m, 2 H), 3.18 (dd, *J* = 9.3, 16 Hz, 1 H), 3.05 (broad s, 1 H), 1.29 (t, *J* = 7.1 Hz, 3 H), 1.27 (d, *J* = 6.2 Hz, 3 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 154.8, 138.7, 138.3, 138.2, 138.1, 132.5, 130.8, 128.6, 128.5, 128.4, 128.3, 128.1, 128.0, 127.8, 127.7, 127.6, 87.3, 81.0, 79.5, 78.5, 78.3, 75.6, 75.5, 75.1, 73.5, 70.6, 69.7, 64.8, 64.1, 20.6, 14.3 ppm. IR (neat): $\tilde{\nu}$ = 3450, 1735, 1641 cm^{-1}. MS (CI, NH_3): *m*/*z* = 714 [M + 18].

Methyl (3*S*,4*E*,6*R*)-6-(2,3,4,6-Tetra-*O*-benzyl-D-*gluco*-β-C-pyranosyl)-6-hydroxy-2-(methoxycarbonyl)-3-methylhex-4-enoate (17): $Pd(OAc)_2$ (0.6 mg, 10% molar) and bis(diphenylphosphanyl)ethane (1.7 mg, 1.5 equiv./Pd) were stirred in THF (0.1 mL) at 30 °C for 30 min. A THF (0.4 mL) solution of the alcohol (20 mg, 0.03 mmol) was added at room temp to this orange mixture. Dimethyl malonate (5 μL, 0.04 mmol) was added to a THF (0.4 mL) suspension of NaH (2 mg, 0.04 mmol, 60% in oil). After 15 min at room temp., the catalyst mixture was added to the anion of the dimethyl malonate. After one hour the solution was treated with aqueous NH_4Cl. The aqueous phase was extracted with diethyl ether. The organic phase was dried with Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography (SiO_2, cyclohexane/EtOAc, 7:3) afforded **17** as a colorless oil (9 mg, 43%), while 10 mg (50%) of starting material were recovered. $[\alpha]_D^{20}$ = +19 (*c* = 0.8, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ = 7.36−7.19 (m, 20 H), 5.75−5.65 (m, 2 H), 4.94−4.49 (m, 8 H), 4.27 (d, *J* = 3.7 Hz, 2 H), 3.73, 3.68 (2s, 6 H), 3.73−3.20 (m, 7 H), 3.31 (d, *J* = 8.9 Hz, 1 H), 3.0 (m, 1 H), 2.0 (broad s, 1 H), 1.29 (d, *J* = 6.7 Hz, 3 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 168.7, 168.6, 138.6, 138.3, 138.2 (2C), 133.4, 131.3, 128.6, 128.5, 127.9, 127.8, 127.7, 87.1, 80.7, 79.1, 78.3 (2C), 75.6, 75.2, 75.1, 73.5, 70.1, 69.1, 57.7, 52.4, 52.3, 36.9, 18.1 ppm. IR (neat): $\tilde{\nu}$ = 3450, 1735, 1670 cm^{-1}. MS (CI, NH_3): *m*/*z* = 756 [M + 18]. HRMS-DCI/NH_3: $[M + NH_4]^+$ calculated for $C_{44}H_{54}NO_{10}$: 756.3748; found 756.3746.

Methyl (3*S*,4*E*,6*R*)-6-(2,3,4,6-Tetra-*O*-benzyl-D-*gluco*-β-C-pyranosyl)-6-(2,4-dichlorobenzoyloxy)-2-(methoxycarbonyl)-3-methylhex-4-enoate: 2,4-Dichlorobenzoyl chloride (6 μL, 0.032 mmol) was slowly added at 0 °C to a CH_2Cl_2 (2 mL) solution of alcohol **17** (20 mg, 0.027 mmol) and pyridine (4 μL, 0.054 mmol). The solution was stirred at 0 °C for 1 h and at room temp. for 1 h After completion, the reaction mixture was washed with 5% aqueous HCl and brine to pH = 7. The organic phase was dried with $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography (SiO_2, cyclohexane/EtOAc, 8:2) afforded the benzoyl derivative as a colorless oil (17 mg, 71%). $[\alpha]_D^{20}$ = −9.5 (*c* = 0.9, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ = 7.79−7.13 (m, 23 H), 5.90−5.80 (m, 3 H), 4.94−4.47 (m, 8 H), 3.82−3.38 (m, 7 H), 3.70, 3.55 (2s, 6 H), 3.30 (d, *J* = 9.2 Hz, 1 H), 3.05 (m, 1 H), 1.06 (d, *J* = 6.7 Hz, 3 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 168.6, 168.4, 163.6, 138.6, 138.5, 138.4, 138.2, 137.8, 137.7, 135.1, 132.7, 131.1, 128.6, 128.5, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 127.6, 127.2, 126.1, 87.3, 80.0, 79.7, 78.4, 77.6, 75.8, 75.4, 75.2, 73.6, 73.0, 68.8, 57.5, 52.5, 52.3, 37.1, 18.0 ppm. IR (neat): $\tilde{\nu}$ = 1735, 1670 cm^{-1}. MS (CI, NH_3): *m*/*z* = 928 [M + 18].

Dimethyl (2*S*,3*S*)-2-Methyl-3-[(*E*)-2-(2,3,4,6-tetra-*O*-benzyl-D-*gluco*-β-C-pyranosyl)ethenyl]cyclopropane-1,1-dicarboxylate (18): $Pd(OAc)_2$ (0.4 mg, 10% molar) and bis(diphenylphosphanyl)-ethane, (1.1 mg, 1.5 equiv. Pd) were stirred in THF (0.1 mL) at 30

°C for 30 min. To this orange mixture, containing the catalyst, was added a THF (0.1 mL) solution of the benzoyl compound (15 mg, 0.016 mmol) at room temp. DBU (4 μL, 0.023 mmol) was then slowly added. After 1 h at room temp., the reaction mixture was treated with aqueous NH_4Cl. The aqueous phase was extracted with diethyl ether. The organic phase was washed with brine, dried with Na_2SO_4, and concentrated under reduced pressure. Column chromatography (SiO_2, cyclohexane/EtOAc, 8:2) afforded **18** as a colorless oil (11.5 mg, 68%). $[\alpha]_D^{20} = -42$ ($c = 1.1$, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ = 7.36−7.15 (m, 20 H), 5.80 (dd, J = 15.6, 7.1 Hz, 1 H), 5.51 (dd, J = 15.6, 9.1 Hz, 1 H), 4.94−4.87 (m, 8 H), 3.75, 3.67 (2s, 6 H), 3.76−3.26 (m, 7 H), 2.40 (dd, J = 9.1, 7.4 Hz, 1 H), 2.02 (m, 1 H), 1.10 (d, J = 6.3 Hz, 3 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 168.1, 138.7, 138.4, 138.3, 138.2, 130.9, 129.7, 128.6, 128.5, 128.4, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 86.8, 82.5, 79.8, 78.8, 78.3, 75.7, 75.1, 75.0, 73.6, 69.1, 52.6, 41.8, 36.4, 27.6, 14.2 ppm. IR (neat): $\tilde{\nu}$ = 1740, 1672 cm^{-1}. MS (CI, NH_3): m/z = 738 [M + 18]. HRMS-DCI/NH_3: $[M + NH_4]^+$ calculated for $C_{44}H_{52}NO_9$: 738.3642; found 738.3634.

(1*R*,4*R*)-1-*O*-Allyloxycarbonyl-1-[2,3-di-*O*-benzyl-4,6-dideoxy-6-(methoxycarbonyl)-D-*gluco*-β-C-pyranosyl]pent-2-yne-1,4-diol (19): The protection of (*R*,*R*)-**13** under the same conditions as used for **11b** with allyloxycarbonyl chloride followed by the silyl deprotection afforded the alcohol **19** in 85% overall yield. $[\alpha]_D^{20} = +1.8$ (c = 1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.34−7.26 (m, 10 H), 5.97−5.85 (m, 1 H), 5.61 (app. t, J = 1.7 Hz, 1 H), 5.36 (dq, J = 1.3, 17.2 Hz, 1 H), 5.25 (dq, J = 1.3, 9.2 Hz, 1 H), 4.90, 4.49/4.69, 4.60 (2 AB system, J = 10.2, 11.5 Hz, 4 H), 4.63−4.61 (m, 2 H), 4.50 (q, J = 6.6 Hz, 1 H), 3.90−3.80 (m, 1 H), 3.76−3.73 (m, 1 H), 3.68(s, 3 H), 3.51 (app. t, J = 9.6 Hz, 1 H), 3.45 (dd, J = 9.6, 2.0 Hz, 1 H), 2.69, 2.43 (2dd, J = 7.5, 5.9, 16.2 Hz, 2 H), 2.21 (ddd, J = 1.8, 5.0, 12.7 Hz, 1 H), 1.46 (m, 1 H), 1.41 (d, J = 6.6 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.6, 154.2, 138.3, 138.0, 131.3, 128.5, 128.4, 127.9, 127.8, 127.7, 119.3, 89.1, 81.3, 80.2, 78.8, 77.4, 75.5, 72.8, 71.8, 69.3, 66.4, 58.4, 51.9, 39.8, 36.3, 23.8 ppm. IR (neat): $\tilde{\nu}$ = 3448, 2200, 1740 cm^{-1}. MS (CI, NH_3): m/z = 570 [M + 18]. HRMS-DCI/NH_3: $[M + NH_4]^+$ calculated for $C_{31}H_{40}NO_9$: 570.2703; found 570.2694.

X-ray Crystal Structure Determination of 19: $C_{31}H_{36}O_9$; M_r = 552.6, orthorhombic, $P2_12_12_1$, a = 10.408(5), b = 11.796(10), c = 24.554(9) A, V = 3015(3) A^{-3}, Z = 4, D_x = 1.22 $Mg{\cdot}m^{-3}$, λ(Mo-K_α) = 0.71069Å, μ = 0.83 cm^{-1}, F(000) = 800, T = 223 K. The intensity data were collected with a Nonius CAD-4 automatic diffractometer with use of graphite-monochromated Mo-K_α radiation.[33] The cell parameters were obtained by fitting a set of 25-high theta reflections. The data collection ($2\theta_{max}$ = 54°, scan ω/2θ = 1, t_{max} = 60s, range *hkl*: *h* 0.12 *k* 0.14 *l* 0.29, intensity controls without appreciable decay (0.25%)] gave 2454 reflections, of which 1641 were independent with $I > 2\sigma(I)$. After Lorenz and polarization corrections,[34] the structure was solved with SIR-97,[35] which revealed the non-hydrogen atoms in the structure and the water molecule. After anisotropic refinement, all the hydrogen atoms of the structure were found by Fourier difference. The whole structure was refined with the aid of SHELXL-97[36] by full-matrix, least-square techniques (use of F-square magnitude: x, y, z, β_{ij} for C and O atoms, x, y, z for H atoms; 363 variables and 3019 observations [1641 with $I > 2\sigma(I)$]; calcd. $w = 1/(\sigma^2(F_o^2) + (0.0528P)^2 + 0.0755P)$ where $P = (F_o^2 - 2F_c^2)/3$ with the resulting R = 0.042 and S_W = 1.001 (residual $\Delta\rho \leq 0.166$ eA^{-3}). Atomic scattering factors from International tables for X-ray Crystallography (1992). ORTEP view produced with PLATON-98.[37] All the calculations were performed with a Silicon Graphic Indy computer. CCDC-112890 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) +44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

(1*R*,4*R*)-1-[2,3-Di-*O*-benzyl-4,6-dideoxy-6-(methoxycarbonyl)-D-*gluco*-β-C-pyranosyl]-4-*O*-*tert*-butyldimethylsilyl-1-*O*-(4-nitrobenzoyl)pent-2-yne-1,4-diol: A THF solution of DEAD (0.3 mL, 0.5 mmol) and 4-nitrobenzoic acid (300 mg, 2.5 mmol) was slowly added at 0 °C to a THF solution of triphenylphosphane (452 mg, 2.5 mmol) and alcohol (*S*,*R*)-**13** (315 mg, 0.5 mmol). The resulting mixture was stirred at 0 °C for 1 hand and was then warmed to room temp. The solution was hydrolyzed with aqueous HCl (1 M). The organic phase was washed with saturated aqueous Na_2CO_3 and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography (SiO_2, cyclohexane/EtOAc, 9:1) afforded the ester as a colorless oil (317 mg, 90%). $[\alpha]_D^{20} = +33$ (c = 1, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 8.20, 8.08 (2d, J = 8.8 Hz, 4 H), 7.37−7.22 (m, 10 H), 5.09 (app. t, J = 1.7 Hz, 1 H), 4.92, 4.54/4.73, 4.56 (2 AB system, J = 10.4, 11.3 Hz, 4 H), 4.20 (qd, J = 6.4, 1.7 Hz, 1 H), 3.95−3.76 (m, 2 H), 3.69 (s, 3 H),3.57−3.52 (m, 2 H), 2.73, 2.49 (2 dd, J = 6.1, 7.0, 15.7 Hz, 2 H), 2.34 (dd, J = 12.7, 1.7 Hz, 1 H), 1.65−1.50 (m, 1 H), 1.39 (d, J = 6.5 Hz, 3 H), 0.88 (s, 9 H), 0.12, 0.11 (2s, 6 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 171.0, 163.3, 150.6, 138.1, 138.0, 135.1, 131.1, 128.3, 128.0, 127.8, 127.5, 123.5, 89.1, 80.7, 79.1, 78.2, 77.5, 75.0, 72.4, 71.6, 64.3, 60.0, 51.8, 40.2, 36.3, 26.9, 26.8, 24.9, 19.2, −4.6, −5.0 ppm. IR (neat): $\tilde{\nu}$ = 2200, 1740 cm^{-1}. MS (CI, NH_3): m/z = 749 [M + 18].

(1*R*,4*R*)-1-[2,3-Di-*O*-benzyl-4,6-dideoxy-6-(methoxycarbonyl)-D-*gluco*-β-C-pyranosyl]-1-*O*-(4-nitrobenzoyl)pent-2-yne-1,4-diol: The alcohol derivative (227 mg, 85%) was obtained from the diester (317 mg, 0.18 mmol) by the classic procedure for the removal of silyl groups with tetrabutylammonium fluoride (80 μL, 1 $mol{\cdot}L^{-1}$ in THF). $[\alpha]_D^{20} = +1.5$ (c = 1, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 8.30, 8.14 (2d, J = 8.8 Hz, 4 H),7.36−7.16 (m, 10 H), 5.92 (app. t, J = 1.7 Hz, 1 H), 4.9, 4.51/4.74, 4.64 (2 AB system, J = 10.5, 11.3 Hz, 4 H), 4.52 (qd, J = 6.5, 1.6 Hz, 1 H), 3.96−3.76 (m, 2 H), 3.69 (s, 3 H), 3.64−3.47 (m, 2 H), 2.76, 2.55 (2dd, J = 6.1, 7.0, 15.8 Hz, 2 H), 2.33 (dd, J = 12.6, 1.7 Hz, 1 H), 1.60−1.55 (m, 1 H), 1.44 (d, J = 6.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.5, 163.4, 150.7, 137.9, 137.7, 134.8, 131.1, 128.6, 128.5, 128.3, 128.1, 127.9, 123.5, 88.9, 81.5, 80.1, 78.7, 77.2, 75.3, 72.8, 72.0, 64.3, 58.4, 52.3, 40.3, 36.7, 24.2 ppm. IR (neat): $\tilde{\nu}$ = 3400, 2200, 1740 cm^{-1}. MS (CI, NH_3): m/z = 635 [M + 18].

(1*R*,4*R*)-1-[2,3-Di-*O*-benzyl-4,6-dideoxy-6-(methoxycarbonyl)-D-*gluco*-β-C-pyranosyl]-4-*O*-(ethoxycarbonyl)-1-*O*-(4-nitrobenzoyl)-pent-2-yne-1,4-diol (20): Compound **20** (229 mg, 90%) was obtained by the classic procedure for the protection of the alcohol (228 mg, 0.36 mmol) with ethyl chloroformate (0.1 mL) and pyridine (93 μL, 0.72 mmol). $[\alpha]_D^{20} = +29.7$ (c = 1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.14, 8.04 (2d, J = 8.9 Hz, 4 H), 7.27−7.17 (m, 10 H), 5.90 (app. t, J = 1.6 Hz, 1 H), 5.39 (q, J = 6.6 Hz, 1 H), 4.83, 4.44 (2 AB system, J = 10.5, 11.3 Hz, 4 H), 4.09 (q, J = 7.1 Hz, 2 H),3.99−3.94 (m, 1 H), 3.78−3.75 (m, 2 H), 3.63 (s, 3 H), 3.58 (dd, J = 1.8, 9.5 Hz, 1 H), 2.68, 2.47 (2dd, J = 6.7, 6.1, 15.5 Hz, 2 H), 2.27 (dd, J = 3.3, 12.8 Hz, 1 H), 1.65−1.55 (m, 1 H), 1.39 (d, J = 6.7 Hz, 3 H), 1.2 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.9, 163.3, 154.1, 150.7, 138.1, 137.9, 134.8, 131.1, 128.9, 128.8, 128.7, 128.2, 123.8, 88.9, 81.3, 79.6, 78.7, 77.6, 75.3, 72.9, 71.9, 64.6, 64.4, 64.2, 52.2, 40.6, 36.6, 21.5, 14.5 ppm. IR (neat): $\tilde{\nu}$ = 2220, 1735 cm^{-1}. MS (CI, NH_3): m/z = 707 [M +

18]. HRMS-DCI/NH_3: $[M + NH_4]^+$ calculated for $C_{37}H_{43}N_2O_{12}$: 707.2816; found 707.2829.

(1*R*,4*R*)-1-[2,3-Di-*O*-benzyl-4,6-dideoxy-6-(methoxycarbonyl)-D-*gluco*-β-C-pyranosyl]-4-*O*-(ethoxycarbonyl)pent-2-yne-1,4-diol: K_2CO_3 (2 mol %) was added at room temp. to a methanol solution (1.5 mL) of alkyne **20** (220 mg, 0.3 mmol). The resulting mixture was stirred for 15 min, filtered, and then evaporated under reduced pressure. Column chromatography (SiO_2, cyclohexane/EtOAc, 8:2) afforded the alcohol as a colorless oil (153 mg, 70%). $[\alpha]_D^{20} = +39$ ($c = 1$, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34−7.26 (m, 10 H), 5.36 (qd, $J = 1.9$, 6.5 Hz, 1 H), 5.01, 4.61/4.70, 4.61 (2 AB system, $J = 10.7$, 11.5 Hz, 4 H), 4.21−4.15 (m, 3 H), 3.94−3.88 (m, 1 H), 3.76−3.64 (m, 2 H), 3.70 (s, 3 H), 3.34 (dd, $J = 1.7$, 9.2 Hz, 1 H), 2.77 (broad s, 1 H), 2.66, 2.46 (2 dd, $J = 7.4$, 5.8, 15.5 Hz, 2 H), 2.26 (ddd, $J = 1.6$, 4.9, 12.8 Hz, 1 H), 1.53 (d, $J = 6.5$ Hz, 3 H), 1.42−1.36 (m, 1 H), 1.24 (t, $J = 7.1$ Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.0, 154.2, 138.3, 138.2, 128.6, 128.5, 128.2, 127.9, 127.8, 127.7, 84.7, 82.8, 80.5, 80.1, 78.6, 78.5, 72.4, 71.4, 64.3, 64.1, 62.0, 51.8, 43.5, 40.4, 21.5, 14.3 ppm. IR (neat): $\tilde{\nu}$ = 3450, 2220, 1735 cm^{-1}. MS (CI, NH_3): *m*/*z* = 558 [M + 18]. HRMS-DCI/NH_3: $[M + NH_4]^+$ calculated for $C_{30}H_{40}NO_9$: 558.2703; found 558.2697.

(1*R*,4*R*)-1-[2,3-Di-*O*-benzyl-4,6-dideoxy-6-(methoxycarbonyl)-D-*gluco*-β-C-pyranosyl]-4-*O*-(ethoxycarbonyl)pent-2-ene-1,4-diol (21): Alkene **21** (105 mg) was obtained from the alkyne (150 mg, 0.27 mmol) and Pd/C (15 mg, 10% weight) by the same procedure as used for the semi-hydrogenation of **16**. $[\alpha]_D^{20} = +11$ ($c = 1$, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.38−7.26 (m, 10 H), 5.89−544 (m, 3 H), 5.03−4.59 (m, 5 H), 4.18 (q, $J = 7.1$ Hz, 2 H), 3.85−3.62 (m, 6 H), 3.13 (dd, $J = 1.7$, 9.2 Hz, 1 H), 2.66, 2.46 (2 dd, $J = 7.4$, 5.8, 15.5 Hz, 2 H), 2.26 (ddd, $J = 1.6$, 4.9, 12.6 Hz, 1 H), 1.53(d, $J = 6.5$ Hz, 3 H), 1.42−1.36 (m, 1 H), 1.24 (t, $J = 7.1$ Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 171.2, 154.6, 138.4, 132.4, 130.5, 128.3, 128.1, 127.5, 127.4, 80.6, 80.5, 79.9, 72.4, 78.1, 72.2, 72.0, 66.0, 63.9, 51.6, 43.3, 40.2, 20.7, 14.1 ppm. IR (neat): $\tilde{\nu}$ = 3450, 1735, 1670 cm^{-1}. MS (CI, NH_3): *m*/*z* = 560 [M + 18]. HRMS-DCI/NH_3: $[M + NH_4]^+$ calculated for $C_{30}H_{42}NO_9$: 560.2860; found 560.2853.

Methyl (3*S*,4*E*,6*R*)-6-[2,3-Di-*O*-benzyl-4,6-dideoxy-6-(methoxycarbonyl)-D-*gluco*-β-C-pyranosyl]-6-hydroxy-2-(methoxycarbonyl)-3-methylhex-4-enoate (22): Compound **22** (93 mg, 80%) was obtained from the carbonate derivative (105 mg, *0.2 mmol*), with $Pd(OAc)_2$ (4.5 mg, 10% molar), bis(diphenylphosphanyl)-ethane (12 mg, 1.5 equiv./Pd), dimethyl malonate (46 μL, 0.4 mmol), and NaH (17 mg, 0.44 mmol, 60% in oil) by the same procedure as used for the synthesis of **17**. $[\alpha]_D^{20} = +5$ ($c = 0.5$, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36−7.26 (m, 10 H, 5.66−564 (m, 2 H), 4.97, 4.61/4.69, 4.61 (2 AB system, $J = 10.8$, 11.7 Hz, 4 H), 4.32−4.27 (m, 1 H), 3.83−3.79 (m, 2 H), 3.82 (S, 3 H), 3.67, 3.68 (2s, 6 H), 3.59 (app. t, $J = 9$ Hz, 1 H), 3.29 (d, $J = 8.8$ Hz, 1 H), 3.19 (dd, $J = 1.7$, 9.2 Hz, 1 H), 2.96−2.94 (m, 1 H), 2.58 (d, $J = 7.4$ Hz, 1 H), 2.64, 2.44 (2 dd, $J = 7.4$, 5.8, 15.5 Hz, 2 H), 2.22 (ddd, $J = 1.6$, 4.9, 12.8 Hz, 1 H), 1.43−1.33 (m, 1 H), 1.07 (d, $J = 6.5$ Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.2, 168.7, 138.4, 133.2, 131.3, 128.9, 128.5, 128.0, 127.8, 127.7, 80.6, 78.5, 72.5, 70.4, 75.5, 71.8, 70.3, 58.0, 52.7, 52.1, 40.7, 36.8, 37.1, 18.3 ppm. IR (neat): $\tilde{\nu}$ = 3445, 1730, 1665 cm^{-1}. MS (CI, NH_3): *m*/*z* = 602 [M + 18].

Methyl (3*S*,4*E*,6*R*)-6-[2,3-Di-*O*-benzyl-4,6-dideoxy-6-(methoxycarbonyl)-D-*gluco*-β-C-pyranosyl]-6-(2,4-dichlorobenzoyloxy)-2-(methoxycarbonyl)-3-methylhex-4-enoate: The protected derivative (86 mg, 80%) was obtained from the alcohol **22** (93 mg, 0.16 mmol), by treatment with pyridine (26 μL, 0.3 mmol) and 2,4-dichlorobenzoyl chloride (55 μL, 0.03 mmol) by the same procedure as used for the activation of **17**. $[\alpha]_D^{20} = +3.8$ ($c = 0.5$, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80 (d, $J = 8.4$ Hz, 1 H), 7.46 (d, $J = 1.9$ Hz, 1 H), 7.36−7.26 (m, 11 H), 5.87−5.69 (m, 3 H), 4.88, 4.49/4.79, 4.61 (2 AB system, $J = 10.1$, 11.6 Hz, 4 H), 3.83−3.73 (m, 2 H), 3.70 (s, 3 H), 3.67, 3.68 (2s, 6 H), 3.47 (app. t, $J = 9.3$ Hz, 1 H), 3.35 (dd, $J = 1.6$, 9.3 Hz, 1 H), 3.29 (d, $J = 9.1$ Hz, 1 H), 3.01−2.90 (m, 1 H), 2.68, 2.47 (2 dd, $J = 6.7$, 6.1, 15.4 Hz, 2 H), 2.26 (dd, $J = 1.7$, 12.3 Hz, 1 H), 1.43 (m, 1 H), 1.07 (d, $J = 6.7$ Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.2, 168.6, 168.3, 163.6, 138.5, 138.4, 138.2, 138.0, 136.2, 131.6, 129.9, 127.5, 127.4, 126.8, 126.7, 126.1, 126.0, 125.0, 79.6, 79.0, 76.4, 74.2, 72.0, 71.3, 70.4, 56.3, 51.3, 51.2, 50.7, 39.3, 35.9, 35.3, 16.3 ppm. IR (neat): $\tilde{\nu}$ = 1735, 1665 cm^{-1}. MS (CI, NH_3): *m*/*z* = 774 [M + 18].

Dimethyl (2*S*,3*S*)-2-Methyl-3-[(*E*)-2-(2,3-di-*O*-benzyl-4,6-dideoxy-6-(methoxycarbonyl)-D-*gluco*-β-C-pyranosyl)ethenyl]cyclopropane-1,1-dicarboxylate (2): Cyclopropane **2** (46 mg, 81%) was obtained from the benzoyl derivative (86 mg, 0.1 mmol), by treatment with $Pd(OAc)_2$ (2.2 mg, 10% molar), bis(diphenylphosphanyl)ethane (5.9 mg, 1.5 equiv. Pd), and DBU (30 μL, 0.2 mmol) by the same procedure as used for the synthesis of **18**. $[\alpha]_D^{20} = -9.6$ ($c = 1$, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35−7.26 (m, 10 H), 5.76 (dd, $J = 6.5$, 15.4 Hz, 1 H), 5.42 (ddd, $J = 0.7$, 7.6, 15.4 Hz, 1 H), 4.84, 4.61/4.68, 4.63 (2 AB system, $J = 10.8$, 11.5 Hz, 4 H), 3.80 (m, 1 H), 3.74 (S, 3 H), 3.66 (s, 6 H), 3.64−3.57 (m, 2 H), 3.14 (app. t, $J = 9.1$ Hz, 1 H), 2.62, 2.42 (2 dd, $J = 6.1$, 6.8, 15.5 Hz, 2 H), 2.44 (t, $J = 7.6$ Hz, 1 H), 2.20 (ddd, $J = 1.7$, 4.9, 12.7 Hz, 1 H), 2.02 (dq, $J = 7.6$, 6.4 Hz, 1 H), 1.43−1.33 (m, 1 H), 1.11 (d, $J = 6.4$ Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.3, 168.4, 138.5, 138.4, 131.2, 129.0, 128.5, 128.3, 128.1, 127.7, 82.4, 80.2, 79.2, 75.1, 71.8, 71.6, 52.6, 51.8, 40.5, 36.8, 36.3, 30.2, 26.9, 12.5 ppm. IR (neat): $\tilde{\nu}$ = 1735, 1675 cm^{-1}. MS (CI, NH_3): *m*/*z* = 584 [M + 18]. HRMS-DCI/NH_3: $[M + H]^+$ Calculated for $C_{32}H_{39}O_9$: 567.2600; found 567.2596, $[M + NH_4]^+$ calculated for $C_{32}H_{42}NO_9$: 584.2860; found 584.2856.

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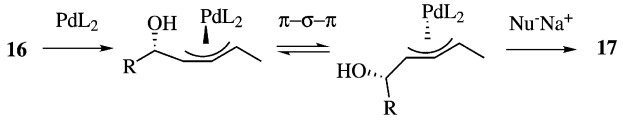

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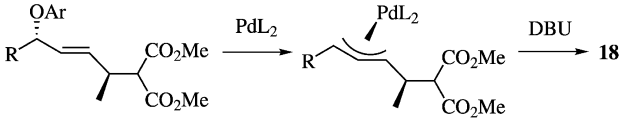

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