A New Synthetic Approach Toward (+)-Ambruticin Analogs: Preparation of a C10–C11 *cis*-Isomer Fragment

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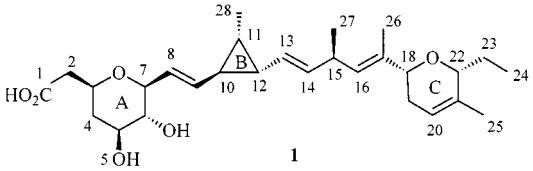
A new methodology has been applied to synthesize an isomer of the west part of (+)-ambruticin based on an efficient asymmetric de novo access to the A unit and sequential stereospecific reactions catalyzed by Pd^0 for the construction of the B unit.

Introduction

Ambruticin (**1**), an antifungal antibiotic discovered[1] in the late 1970s, has been isolated from fermentation extracts of the Myxobacteria species *Polyangium cellulosum var. fulvum*. Its complete structure was determined through elegant spectroscopic analyses,[2] degradative studies and chemical transformation, and by single-crystal X-ray analysis of a derivative.[3] Interest in the synthesis of this compound stems not only from its particular structure, but is also due to its unique oral in vivo activity against histoplasmosis and coccidiomycosis.[4] More recently,[5] Höfle's group has isolated analogs of (+)-ambruticin bearing an amino group at the C5 position from the Myxobacteria *Sorangium cellulosum So ce10*. The mode of action of (+)-ambruticin is still unknown, which makes the synthesis of analogs for further study and modification of its biological activity even more important.



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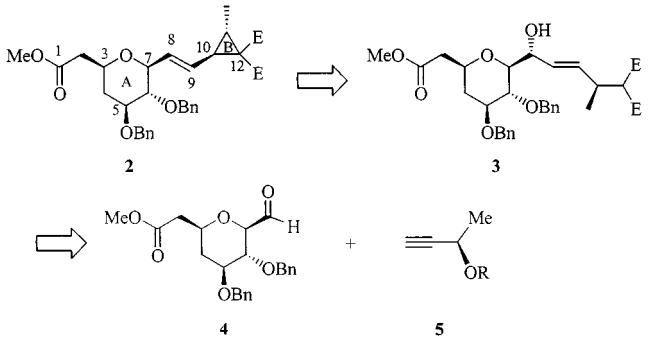
Despite widespread interest among chemists, only one total synthesis of ambruticin has been published to date, that by Kende's group.[6] Several fragments[7] of the molecule have, however, been described in the literature. A common strategy for the construction of the whole framework involves C7−C8 and C13−C14 disconnections. As part of our ongoing program on the synthesis of optically active vinylcyclopropanes,[8] we have long been interested in the synthesis of (+)-ambruticin (**1**). We wish to report herein our recent results concerning a new strategy for the preparation of an isomeric fragment of **1**. We envisaged the C13−C14 disconnection leading to the west part **2** (Scheme 1). The west part **2**, previously reported as a derivative of enantiomerically pure A and B units, was seen as an entire building block resulting from the cyclopropanation of **3**, as catalyzed by Pd^0 complexes. Disconnection of **3** leads to two fragments, the β-C-glycosyl aldehyde **4**[9] and the propargylic alcohol **5**.[10] We have already validated the methodology on the basis of a regio-, stereo- and enantiospecific alkylation and cyclopropanation starting from benzaldehyde as a simple model of **4**, and proved that (*R*)-but-1-yn-3-ol was the appropriate enantiomer for the B unit.[8]



2 **3** **4** **5**

Scheme 1. Retrosynthesis

Results and Discussion

We have shown that β-C-glycosyl aldehydes of type **4** can be synthesized starting from the corresponding gluconolactone.[9] As the lactone precursor of the A unit required a long synthetic scheme,[7c] a more straightforward access to **4** was needed.

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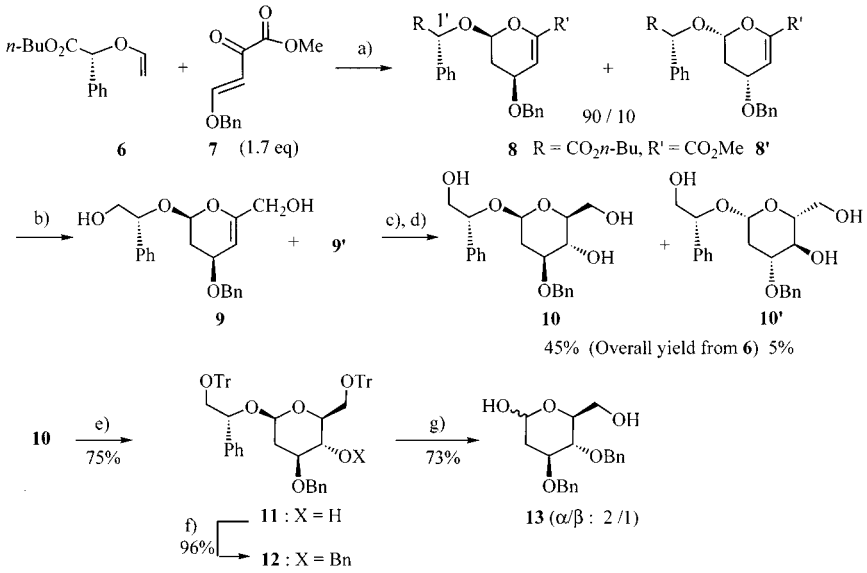


Scheme 2. a) 2.5% $Eu(fod)_3$, petroleum ether/toluene, ΔT; b) $LiAlH_4$; c) $BH_3 \cdot Me_2S$, THF; d) NaOH, H_2O_2; e) TrCl, Pyr; f) BnBr, NaH, DMF; g) 6 N HCl, THF

Synthesis of the A Unit of (+)-Ambruticin

For this purpose, we anticipated that the L-2-deoxy sugar **13**,[11] de novo synthesized from the key heteroadduct **8** (Scheme 2), would serve as an efficient precursor of **4**. Thus, the seven-step synthesis of **13** was successfully scaled up with some improvements relating to the required diastereomeric purification step, which was efficiently carried out at the stage of the triol **10** on a ten-gram scale.

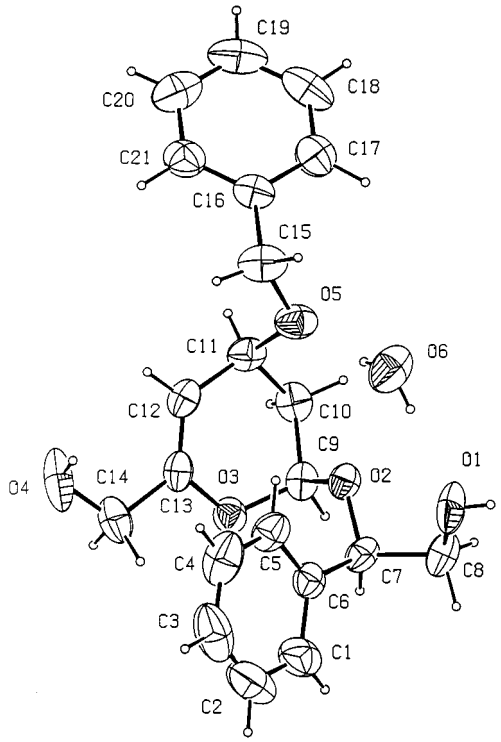
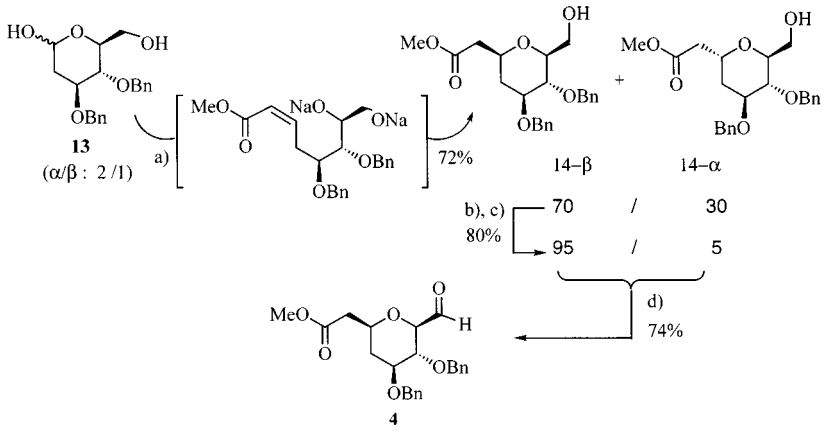


Figure 1. ORTEP drawing of the crystal structure of the allylic diol $9 \cdot H_2O$

The absolute configurations at the four stereogenic centers created have previously been assigned following a three-step conversion of **10** into L-3,4,6-tribenzyl-2-deoxygluconolactone.[11a,12] The relationship between the inducing and induced stereogenic centers was definitively established by X-ray structure analysis of the crystalline diol **9** (Figure 1). Moreover, the permanent (*R*) character of the inducing center was evidenced by the specific rotation of the phenylethanediol[13] obtained together with lactol **13**. Both these factors were fully supportive of the structural assignments.

In 1996, Liu and Donaldson[7e] described an access to the hydroxy ester **14-β** involving a five-step procedure. At the same time, we investigated a more straightforward route to the ester **14-β** from the lactol **13** by direct introduction of the methoxycarbonylmethyl moiety (Scheme 3). To the best of our knowledge, such stereocontrolled *C*-glycosylations on a substrate bearing a free hydroxy group at C-6 had not previously been reported.[14] As mentioned previously in the case of fully protected glucose,[15] Horner's reagent was found to give the best results, leading in this case to the expected hydroxy ester **14** in 72% yield. In accordance with the findings of Monti et al.,[15] the use of THF as solvent ensured completion of the presumed second step, i.e. Michael cyclization of the transient methyl octenoate, but led to a moderate β selectivity (β:α = 70:30). Base-catalyzed epimerization (conditions: NaOMe/NaOH/60°C) of the mixture of *C*-deoxyglycosides **14** was found to proceed smoothly (β:α = 95:5)[16] and subsequent refluxing in an excess of anhydrous methanolic HCl resulted in efficient in situ reesterification (80% overall yield from the 70:30 mixture of **14**). The aldehyde **4** was finally



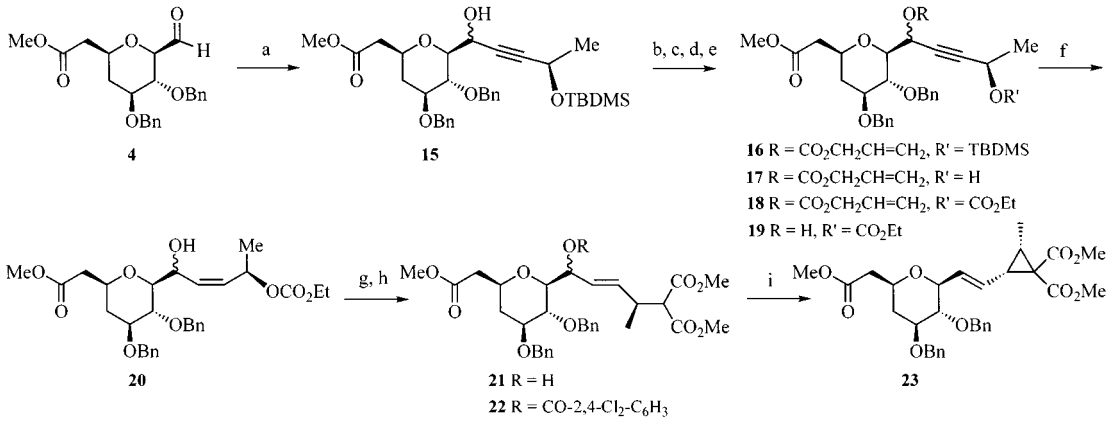
Scheme 3. a) NaH, THF, $(MeO)_2POCH_2CO_2Me$; b) MeONa, MeOH, ΔT; c) MeOH, HCl, ΔT; d) DMSO, $(COCl)_2$, NEt_3, CH_2Cl_2

obtained in 74% yield by employing Swern conditions at low temperature.

Synthesis of a C10 Isomer of the West Part of (+)-Ambruticin

With fragment A in hand, and anticipating that we needed the (*R*,*R*) configuration for the alkenyl side chain of the required intermediate, we chose to condense the aldehyde **4** with a protected derivative **5** of (*R*)-but-1-yn-3-ol under chelating Grignard conditions.[17] After numerous unsuccessful attempts using (*R*)-*O*-ethyloxycarbonylbut-1-yn-3-ol, we were pleased to find that (*R*)-*O*-*tert*-butyldimethylsilylbut-1-yn-3-ol reacted with the aldehyde **4** to give the alcohols **15** in 49% yield and with a diastereoselectivity of 85:15 (29% of aldehyde **4** was recovered). Protection of the free OH group of the major epimer **15** using allyl chloroformate led to **16** in quantitative yield. Selective removal of the trialkylsilyl group from **16** using nBu$_4$NF gave the alcohol **17** (93% yield), which upon treatment with ethyl chloroformate afforded **18** (94% yield). Selective removal of allyloxycarbonyl group then gave the propargylic alcohol **19**. Partial hydrogenation was achieved in the presence of Pd/C, poisoned[18] with pyridine, leading to **20** (Scheme 4).

The allylic alcohol **20** was then subjected to palladium(0)-catalyzed alkylation, which was readily carried out at room temperature in THF using in situ preformed $Pd(dppe)_2$ with subsequent addition of sodium dimethyl malonate. We were delighted to find that the alkylation occurred exclusively on the carbon atom bearing the carbonate group to give a single isomer **21** with purely (*E*) stereochemistry at the double bond. Compound **21** was then converted into the corresponding benzoate **22** using 2,4-dichlorobenzoyl chloride. The final cyclopropanation step was carried out in THF at room temperature using in situ preformed $Pd(dppe)_2$ as catalyst and DBU as base. The reaction was very clean and led exclusively to the *cis*-disubstituted cyclopropane **23**, which was accompanied only by a small amount of starting material. The *cis* relationship of the methyl group and the vinylic chain, the β configuration at the anomeric center (J = 9 Hz), the (*E*) stereochemistry of the double bond (J = 15.5 Hz), and the *cis* stereochemistry of the cyclopropane ring (J = 9.6 Hz) were confirmed



Scheme 4. a) (*R*)-BrMgC≡C−CH(Me)(OTBDMS), $MgBr_2$, Et_2O, −60°C to room temp., 49%; b) $ClCO_2CH{=}CH_2$, pyridine, CH_2Cl_2, 0°C to room temp., 99%; c) Bu_4NF, THF, 0°C to room temp., 93%; $ClCO_2Et$, pyridine, CH_2Cl_2, 0°C to room temp., 94%; e) $Pd(OAc)_2$/TPPTS, CH_3CN/H_2O 6:1, Et_2NH, room temp., 91%; f) Pd/C, pyridine, MeOH, H_2, room temp., 56%; g) 10% $Pd(OAc)_2$/dppe, then $NaCH(CO_2Me)_2$, THF, room temp., 60%; h) 2,4-Cl_2-C_6H_3−COCl, pyridine, CH_2Cl_2, 0°C to room temp., 89%; i) 10% $Pd(OAc)_2$/dppe, then DBU, THF, room temp., 60%

at this stage by ^{1}H- and ^{13}C-NMR spectroscopy and by NOE experiments. We have previously shown that the configuration of the cyclopropane[8] is dictated by the absolute configuration at the carbon atom bearing the free OH group in **15**. Thus, the configuration of the major alcohol **15** is (*S*), which does not conform to Cram′s chelating rule for the addition of a Grignard to a C-glycosyl aldehyde.[17]

This unprecedented diastereoselectivity is currently under investigation in our laboratory and will be applied to the total synthesis of (+)-ambruticin and analogs. Further results will be reported in due course.

Conclusion

We have described a new synthetic approach to the (+)-ambruticin skeleton. A new method for preparing the A ring has been described and has proved to be highly efficient. Our methodology has led to the synthesis of an epimer of the west part of (+)-ambruticin, which broadens the access to analogs.

Experimental Section

General: ^{1}H-NMR spectra: Bruker AC 200, AM 250 or AC 400 spectrometers; 200, 250 or 400 MHz, respectively; chemical shifts (δ) are reported in ppm units by reference to Me_4Si; coupling constants (*J*) are reported in Hertz and refer to apparent peak multiplicities. − ^{13}C-NMR spectra: Bruker AC 200, AM 250 or AC 400; 50, 63 or 100 MHz, respectively. − High-resolution mass spectra: Varian MAT311 at the C.R.M.P.O. (Rennes). Low-resolution mass measurements: Fisons Hewlett Packard 5989 instrument. − Optical rotations: Perkin−Elmer 241 polarimeter at 589 nm. − IR spectra: Bruker FT-IR 45 or Mattson Genesis spectrophotometer. − Elemental analyses were performed at the "Service Regional de Microanalyse" (Université Pierre et Marie Curie) and at CNRS-ICSN (Gif-sur-Yvette). − Thin-layer chromatography: Silica-gel plates (Merck F_{254}); spots were detected by exposure to UV and/or vanillin. − Anhydrous THF and diethyl ether were distilled from sodium/benzophenone; CH_2Cl_2 was distilled from calcium hydride.

(1′*R*,4*S*,6*S*)-4-Benzyloxy-2,3-dihydro-2-hydroxymethyl-6-(2-hydroxy-1-phenylethoxy)-4*H*-pyran (9): Diastereomerically pure adduct **8**[11] (4.8 mmol, 2.2 g) was dissolved in anhydrous Et_2O (10 mL) under argon and treated at 0°C with lithium aluminum hydride (0.36 g, 9.6 mmol) in anhydrous Et_2O (40 mL). After 15 h at 20°C, satd. aqueous Na_2SO_4 (16 mL) was added at 0°C, and, after 1 h at 20°C, the organic layer was filtered and concentrated under reduced pressure. The diol **9** crystallized from the cold Et_2O solution in the form of white needles (1.45 g, 85%), m.p. 60°C, $[\alpha]_D^{20} = -0.8$ (*c* = 1, CH_2Cl_2). − R_f = 0.44 (cyclohexane/EtOAc, 3:7). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.98 (ddd, *J* = 2.8, 5.9, 14.5 Hz, 1 H, 5-H_{ax}), 2.38 (dt, 1 H, 5-H_{eq}), 3.28 (m, OH), 3.52−3.70 (m, 4 H, 2 CH_2OH), 4.06 (m, 1 H, 4-H), 4.54 (d, *J* = 12.0 Hz, 1 H, CH_2Ph), 4.62 (dd, *J* = 3.6, 8.7 Hz, 1 H, C*H*Ph), 4.64 (d, *J* = 12.0 Hz, 1 H, CH_2Ph), 5.11 (d, *J* = 4.3 Hz, 1 H, 2-H), 5.28 (t, *J* = 3.1 Hz, 1 H, 5-H), 7.15−7.40 (m, 10 H, H_{arom}). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 32.1 (C-4), 62.3, 65.7, 67.2, 70.5 (*C*H_2Ph), 82.5 (*C*HPh), 97.2, 97.3, 126.0−129.0, 138.3, 139.3, 152.2 (C-2). − IR (neat): $\tilde{\nu}$ = 3380 cm^{-1} (OH), 1685 (C=C).

X-ray Crystal Structure Determination of 9: $C_{21}H_{24}O_5 \cdot H_2O$; M_r = 374.42, orthorhombic, $P2_12_12_1$, *a* = 8.883(1), *b* = 9.854(2), *c* = 22.521(2) A, *V* = 1971.3(5) Å^{-3}, *Z* = 4, D_x = 1.262 Mg.m^{-3}, λ (Mo-K_α) = 0.71073 Å, μ = 0.90 cm^{-1}, *F*(000) = 800, *T* = 253 K. Crystal dimensions: 0.35 × 0.24 × 0.12 mm. The intensity data were collected with a Nonius CAD-4 automatic diffractometer using graphite-monochromated Mo-K_α radiation.[19] The cell parameters were obtained by fitting a set of 25 high-θ reflections. The data collection [$2\theta_{max}$ = 54°, scan ω/2θ = 1, t_{max} = 60 s, *hkl* ranges: *h* = 0.11, *k* = 0.12, *l* = 0.28, intensity controls without appreciable decay (0.25%)] gave 2454 reflections, of which 1641 were independent with $I > 2\,\sigma(I)$. After Lorentz and polarization corrections,[20] the structure was solved with SIR-97,[21] which revealed the nonhydrogen atoms of the structure and the water molecule. After anisotropic refinement, all the hydrogen atoms of the structure were located on a Fourier difference map. The whole structure was refined with SHELXL-97[22] using full-matrix least-squares techniques {use of F^2 magnitude: *x*, *y*, *z*, β_{ij} for C and O atoms, *x*, *y*, *z* for H atoms; 323 variables and 2454 observations [1641 with $I > 2\,\sigma(I)$]; calcd. $w = 1/[\sigma^2(F_o^2) + (0.0528\,P)^2 + 0.0755\,P]$, where $P = (F_o^2 + 2\,F_c^2)/3$ with the resulting *R* = 0.042 and S_W = 1.001 (residual Δρ = 0.166eÅ^{-3})}. Atomic scattering factors were taken from the International Tables for X-ray Crystallography (**1992**). The ORTEP view was created with the program PLATON-98.[23] All calculations were performed with a Silicon Graphics Indy computer. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC-112890. Copies of the data can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. [Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

(*R*)-2-Hydroxy-1-phenylethyl-3-*O*-Benzyl-2-deoxy-L-glucoside (10, Large-Scale Procedure): A mixture of adducts **8** and **8′** [48 mmol, 21.9 g, diastereomeric ratio **8** (2*S*,4*S*,1′*R*)/**8′** (2*R*,4*R*,1′*R*) = 90:10] was dissolved in anhydrous Et_2O (100 mL) under argon and treated at 0°C with lithium aluminum hydride (3.6 g, 96 mmol) in anhydrous Et_2O (400 mL). After 15 h at 20°C, satd. aqueous Na_2SO_4 (16 mL) was added at 0°C. After 1 h, AcOEt (100 mL) was added and the organic layer was filtered, dried with $MgSO_4$, and filtered once more. Removal of the solvent left a colorless oil, which was used for the next step without further purification. The minor diastereomer (2*R*,4*R*,1′*R*) of **9** was detected in the ^{1}H-NMR spectrum of the crude product (400 MHz, $CDCl_3$) by the signals at δ = 5.20 (d, 1 H, 5-H) and 5.13 (t, 1 H, 2-H). − To a solution of the aforementioned crude allylic diol **9** (16 g) in anhydrous THF (400 mL), $BH_3 \cdot Me_2S$ (2.25 equiv., 49 mL of a 2 M solution in THF) was added dropwise at 0°C. After stirring for 1 h at 0°C and for 40 h at room temp., the reaction mixture was treated with 25% aq. sodium hydroxide (20 mL), followed by 30% aqueous H_2O_2 (20 mL) and then refluxed for 2 h. After cooling, satd. aqueous NaCl (240 mL) was added and the THF was removed in vacuo. The remaining aqueous phase was extracted with Et_2O (3 × 60 mL) and EtOAc (3 × 60 mL), the combined organic layers were dried with $MgSO_4$, and the solvents were evaporated. Flash chromatography of the crude product (eluent: cyclohexane/EtOAc, 1:1 to 3:7) afforded first the diastereomerically pure triol **10** (11.2−11.8 g, 62−66% over the two steps) as a colorless oil, R_f = 0.23 (cyclohexane/EtOAc, 3:7), $[\alpha]_D^{26} = +1.2$ (*c* = 1.7, CH_2Cl_2). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.50 (m, OH), 1.65 (q, *J* = 11.4 Hz, 1 H, 2-H_{ax}), 1.80 (m, OH), 2.42 (ddd, *J* = 1.9, 4.5, 12.3 Hz, 1 H, 2-H_{eq}), 3.18 (m, 1 H, 5-H), 3.35−3.50 (m, 3 H, 3,4,6-H), 3.68 (m, 2 H, 2′,6-H), 3.80 (m, 1 H, 2′-H), 4.49 (d, *J* = 11.6 Hz, 1 H, H_{benz}), 4.67 (dd, *J* = 3.7, 8.5 Hz, 1 H, 1′-H), 4.70 (d, *J* = 11.6 Hz, 1 H, H_{benz}), 4.73 (dd, *J* = 1.9, 9.8 Hz, 1 H, 1-H), 7.30−7.40 (m, 10 H). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 35.8, 62.6, 65.8, 70.9, 70.9, 75.5, 78.8, 82.9, 100.3,

125.3−129.0, 137.9, 139.4. − IR (neat): $\tilde{\nu}$ = 3400 cm^{-1} (OH), 3031, 2929, 2873 cm^{-1}. − $C_{21}H_{26}O_6$ (374.42): calcd. C 67.36, H 7.00; found. C 67.03, H 7.31. − The minor isomer **10′** (1.2 g, 7%) was next eluted and isolated, R_f = 0.16 (cyclohexane/EtOAc, 3:7) as a colorless oil, $[\alpha]_D^{26}$ = −75.5 (*c* = 0.95, CH_2Cl_2). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.71 (q, *J* = 12 Hz, 1 H, 2-H_{ax}), 2.00 (m, OH), 2.32 (m, 1 H, 2-H_{eq}), 3.1−3.9 (m, 7 H), 4.46 (d, *J* = 12 Hz, 1 H, H_{benz}), 4.48 (m, 1 H, 1′-H), 4.67 (d, *J* = 12 Hz, 1 H, H_{benz}), 4.88 (dd, 1 H, 1-H), 7.30−7.40 (m, 10 H).

(*R*)-1-Phenyl-2-(α,α-diphenylbenzyloxy)ethyl-3-*O*-Benzyl-2-deoxy-6-*O*-(α,α-diphenylbenzyl)-L-glucoside (11): To a solution of triol **10** (27 mmol, 10.1 g) in freshly distilled pyridine (50 mL) was added trityl chloride (18.8 g, 2.5 equiv.). After stirring for 4 d at room temp. under argon, the solvent was evaporated in vacuo and the residue was taken up in AcOEt (50 mL). The resulting solution was washed with satd. aqueous NaCl (3 × 50 mL), dried with $MgSO_4$, and concentrated to dryness. The crude product was purified by column chromatography (cyclohexane/EtOAc, 95:5) furnishing **9** (19.8 g, 85%) as a powder, m.p. 82°C, $[\alpha]_D^{20}$ = +31.8 (*c* = 0.67, CH_2Cl_2). − R_f = 0.10 (cyclohexane/EtOAc, 9:1). − IR (neat): $\tilde{\nu}$ = 3455 cm^{-1} (OH). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.67 (q, *J* = 11.5 Hz, 1 H, 2-H_{ax}), 2.45 (dd, *J* = 4.2, 11.6 Hz, 1 H, 2-H_{eq}), 3.25−3.40 (m, 4 H), 3.50 (m, 3 H), 4.55 (d, *J* = 11.7 Hz, 1 H, H_{benz}), 4.68 (d, *J* = 11.7 Hz, 1 H, H_{benz}), 4.82 (dd, *J* = 3.6, 7.8 Hz, 1 H, 2′-H), 4.94 (dd, *J* = 8.2 Hz, 1 H, 1-H), 7.10−7.50 (m, 40 H, H_{arom}). − $C_{59}H_{54}O_6$ (859.022): calcd. C 82.49, H 6.34; found C 82.46, H 6.51.

(*R*)-1-Phenyl-2-(α,α-diphenylbenzyloxy)ethyl-3,4-Di-*O*-benzyl-2-deoxy-6-*O*-(α,α-diphenylbenzyl)-L-glucoside (12): To a suspension of NaH (previously rinsed with hexane to remove mineral oil, 0.82 g, 34 mmol) in DMF (30 mL) at 0°C were successively added dropwise a solution of tris(ether) **11** (19.5 g, 22.7 mmol) in DMF (50 mL) and benzyl bromide (4.1 mL, 34 mmol). After stirring for 24−48 h at room temp. (during which gas evolution ceased and an almost clear yellow solution was obtained), the reaction was quenched with H_2O (50 mL) at 0°C. The resulting mixture was extracted with Et_2O (4 × 100 mL), the combined extracts were dried ($MgSO_4$), and the solvent was evaporated. Chromatography (cyclohexane/EtOAc, 95:5) of the residue gave benzyl ether **12** (20.7 g, 96%) as a powder, m.p. 76°C, $[\alpha]_D^{26}$ = +4.1 (*c* = 0.61, CH_2Cl_2). − R_f = 0.25 (cyclohexane/EtOAc, 9:1). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.83 (q, *J* = 11 Hz, 1 H, 2-H_{ax}), 2.53 (m, 1 H, 2-H_{eq}), 3.32 (dd, *J* = 10.4, 3.6 Hz, 1 H, 6-H), 3.35 (m, 2 H, 2′,5-H), 3.50 (m, 2 H, 2′,6-H), 3.64 (m, 2 H, 3,4-H), 4.32 (d, *J* = 10.3 Hz, 1 H, H_{benz}), 4.62 (d, *J* = 11.7 Hz, 1 H, H_{benz}), 4.69 (d, *J* = 11.7 Hz, 1 H, H_{benz}), 4.73 (d, *J* = 10.3 Hz, 1 H, H_{benz}), 4.90 (m, 2 H, 1,1′-H), 6.90 (m, 2 H, H_{arom}), 7.10−7.40 (m, 43 H, H_{arom}). − $C_{66}H_{60}O_6$ (949.19): calcd. C 83.52, H 6.37; found C 83.33, H 6.71.

3,4-Di-*O*-benzyl-2-deoxy-L-glucopyranose (13): To a solution of tetrakis(ether) **12** (20.2 g, 21.5 mmol) in THF (300 mL) at room temperature was added 3 N aqueous HCl (200 mL). After stirring for 48−96 h (during which a clear solution was maintained by dilution with THF as necessary), the mixture was poured into satd. aqueous $NaHCO_3$ (400 mL) and exhaustively extracted with hot EtOAc (10 × 100 mL). The combined organic layers were washed with satd. aqueous NaCl (20 mL), dried ($MgSO_4$), and concentrated. The residue was chromatographed (cyclohexane/EtOAc, 9:1 to 3:7), giving first (−)-1-phenyl-1,2-ethanediol (2.37 g), R_f = 0.36 (cyclohexane/EtOAc, 3:7), $[\alpha]_D^{20}$ = −68 (*c* = 1, $CHCl_3$), and then lactol L-**13** (5.78 g, 78%, 90−95% based on **12** consumed), R_f = 0.30 (cyclohexane/EtOAc, 3:7), as a clear oily mixture of anomers (α.β = 2:1), $[\alpha]_D^{26}$ = −18.6 (*c* = 1.29, EtOH), which slowly crystallized; m.p. 92−95°C. − IR (neat): $\tilde{\nu}$ = 3400 cm^{-1} (OH). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.51 (ddd, 11 Hz < *J* < 12.2 Hz, 1 β-H, 2-H_{ax}), 1.58 (ddd, *J* = 3.3, 11.5, 12.5 Hz, 1 $H_α$, 2-H_{ax}), 2.23 (dd, *J* = 4.9, 12.5 Hz, 1 $H_α$, 2-H_{eq}), 2.32 (ddd, *J* = 1.7, 4.9, 12.5 Hz, 1 $H_β$, 2-H_{eq}), 3.32−3.55 (m, 2 $H_β$ and 1 $H_α$), 3.58 (m, 2 $H_β$ and 1 $H_α$), 3.75 (dd, *J* = 11.6 Hz, 1 $H_{α,β}$, 6-H), 3.94 (m, 1 $H_α$, 5-H), 4.05 (m, 1 $H_α$, 3-H), 4.59−4.70 (m, 3 $H_{αβ}$, H_{benz}), 4.78 (m, 1 $H_β$, 1-H), 4.87 (d, *J* = 11.0 Hz, 1 $H_β$, H_{benz}), 4.88 (d, *J* = 10.8 Hz, 1 $H_α$, H_{benz}), 5.34 (s, 1 $H_α$, 1-H), 7.20−7.40 (m, 10 H, H_{arom}). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 35.5, 37.9, 62.1, 62.4, 71.5, 71.7, 71.7, 74.9, 75.5, 77.0, 78.4, 78.9, 92.0, 94.1, 127.6−128.4, 138.1−138.5. − HR MS (LSI): calcd. for [M − H^+] 343.1545 ($C_{20}H_{23}O_5$); found 343.1563.

[2,3-Di-*O*-benzyl-4,6-dideoxy-6-(methoxycarbonyl)-D-*gluco*-β-*C*-pyranosyl]methanol (14): To a suspension of NaH (previously rinsed with hexane to remove mineral oil, 0.99 g, 41.25 mmol, 2.5 equiv.) in dry THF (130 mL) at 0°C, a solution of trimethyl phosphonoacetate (6.00 g, 33 mmol, 2 equiv.) in dry THF (10 mL) was added dropwise. After stirring for 3 h at 0−20°C and for 5 h at room temp., a solution of the lactol L-**13** (5.68 g, 16.5 mmol) in dry THF (100 mL) was slowly added to the white suspension. After stirring for 40 h at room temp., the yellow mixture was refluxed for 6 h. The cooled reaction mixture was then treated with 0.01 N aq. HCl (to pH = 2) and extracted with EtOAc (3 × 60 mL). The combined extracts were washed with aqueous NaCl (10 mL), dried with $MgSO_4$, and the solvent was evaporated. Flash chromatography of the crude product (cyclohexane/EtOAc, 5:1 to 3:7) afforded hydroxy ester **14** (4.76 g, 72%), R_f = 0.60 (cyclohexane/EtOAc, 3:7) as a clear oily mixture of isomers (β.α = 70:30). This product was then added to a methanolic solution of sodium methoxide obtained from sodium (0.51 g) and dry methanol (250 mL). After refluxing for 40 h, the cooled mixture was treated with excess dry HCl in methanol and was then refluxed for a further 1 h. After cooling once more, dry $NaHCO_3$ was added until neutrality was reached and the solvent was removed. The crude residue was chromatographed (cyclohexane/EtOAc, 7:3), giving the hydroxy ester **14**[7e] (3.81 g, 80%, 58% overall yield based on **13**), R_f = 0.60 (cyclohexane/EtOAc, 3:7), contaminated with 5% of the α isomer. − IR (neat): $\tilde{\nu}$ = 3490 cm^{-1} (OH), 1739 (C=O) cm^{-1}. − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.41 (q, *J* = 11.3 Hz, 1 H, 2-H_{ax}), 2.00 (m, 1 H, OH), 2.22 (ddd, *J* = 2.0, 4.9, 12.8 Hz, 1 H, 2-H_{eq}), 2.45 (dd, *J* = 5.7, 15.4 Hz, 1 H, 1′-H), 2.62 (dd, *J* = 7.4, 15.4 Hz, 1 H, 1′-H), 3.29−3.37 (m, 1 H), 3.43 (t, *J* = 9.8 Hz, 1 H), 3.62−3.74 (m, 2 H), 3.68 (s, 3 H), 3.80−3.90 (m, 2 H), 4.63 (d, *J* = 11.3 Hz, 1 H), 4.70 (d, *J* = 10.7 Hz, 1 H), 4.78 (d, *J* = 11.3 Hz, 1 H), 4.94 (d, *J* = 10.7 Hz, 1 H), 7.30−7.40 (m, 10 H, H_{arom}). The α isomer was detected by the following proton signals:[7e] δ = 1.76 (ddd, 1 H), 1.95 (ddd, 1 H), 2.43 (dd, 1 H), 2.68 (dd, 1 H), 4.55 (ABq, 1 H). − ^{13}C NMR (100 MHz, $CDCl_3$): β isomer: δ = 36.6, 40.4, 51.8, 62.4, 71.5, 71.9, 75.1, 78.1, 79.0, 80.5, 127.6−128.4, 138.3, 138.4, 171.2; α isomer: δ = 32.2, 38.2, 51.9, 60.6, 64.9, 71.4, 73.2, 74.8, 75.0, 77.3, 127.6−128.4, 138.0, 138.1, 171.8.

[2,3-Di-*O*-benzyl-4,6-dideoxy-6-(methoxycarbonyl)-D-*gluco*-β-C-pyranosyl]aldehyde (4): To a solution of DMSO (2.88 mL, 4 equiv.) in anhydrous CH_2Cl_2 (12 mL) at −75°C, a solution of oxalyl chloride (1.68 mL, 2.2 equiv.) in CH_2Cl_2 (12 mL) was added dropwise, followed, after 15 min, by a solution of hydroxy ester **14** (3.6 g, 9 mmol) in CH_2Cl_2 (70 mL). After stirring for 1 h at −75°C, the reaction mixture was allowed to warm slowly and at −45°C NEt_3 (6 mL, 5 equiv.) was slowly added. After stirring at −45°C for 8 h, the reaction was quenched with H_2O at −25°C and the resulting mixture was extracted with CH_2Cl_2 (4 × 100 mL). The combined

extracts were dried ($MgSO_4$), the solvent was evaporated, and the residue was purified by chromatography (Et_2O/petroleum ether, 1:1) to give the β-aldehyde **4** (2.7 g, 74%) as an oil; $[\alpha]_D^{26} = -8.5$ ($c = 1$, $CHCl_3$). – $R_f = 0.6$ (cyclohexane/EtOAc, 3:7). – ^1H NMR (400 MHz, $CDCl_3$): δ = 1.43 (ddd, 11 Hz < *J* < 12.2 Hz, 1 H, 2-H_{ax}), 2.22 (ddd, *J* = 2.0, 4.4, 14 Hz, 1 H, 2-H_{eq}), 2.49 (dd, *J* = 6.0, 15.9 Hz, 1 H, 1′-H), 2.72 (dd, *J* = 7.0, 15.9 Hz, 1 H, 1′-H), 3.53 (dd, *J* = 8.7, 9.9 Hz, 1 H, 4-H), 3.70 (s, 3 H), 3.77 (m, 1 H, 1-H or 3-H), 3.82 (dd, *J* = 0.9, 9.9 Hz, 1 H, 5-H), 3.90 (m, 1 H, 3-H or 1-H), 4.64 (d, *J* = 11.4 Hz, 1 H, H_{benz}), 4.66 (d, *J* = 10.8 Hz, 1 H, H_{benz}), 4.71 (d, *J* = 11.4 Hz, 1 H, H_{benz}), 4.90 (d, *J* = 10.8 Hz, 1 H, H_{benz}), 7.30–7.40 (m, 10 H, H_{arom}), 9.63 (d, *J* = 0.9 Hz, 1 H, 6-H). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 36.0, 36.3, 51.9, 71.6, 72.1, 75.0, 77.6, 80.3, 81.8, 127.5–128.5, 137.6, 138.0, 170.9, 197.5. – HR MS (LSI): calcd. for [M + H^+] 399.1808 ($C_{23}H_{27}O_6$); found. 399.1807.

(4*R*)-4-(*O*-*tert*-Butyldimethylsilyl)-1-[2,3-di-*O*-benzyl-4,6-dideoxy-6-(methoxycarbonyl)-D-*gluco*-β-C-pyranosyl]pent-2-yne-1,4-diol (15): Two solutions of $MgBr_2$ in diethyl ether (5 mL) were prepared by adding 1,2-dibromoethane (0.59 mL, 8 equiv.) to magnesium (166 mg, 8 equiv.). To a solution of methyllithium (2.2 mL, 4 equiv.) in diethyl ether (3.3 mL) at −5°C was added (*R*)-3-(*tert*-butyldimethylsilyloxy)but-1-yne (703 mg, 4.4 equiv.). After 30 min, the first $MgBr_2$ solution (8 equiv.) was added. The resulting mixture was cooled to −60°C, whereupon a precipitate appeared. The second $MgBr_2$ solution was added to a solution of the aldehyde **4** (345 mg, 1 equiv.) in diethyl ether (3.5 mL) and then this mixture was added to the acetylenic Grignard reagent. The resulting mixture was stirred at −60°C for 1 h, allowed to warm to room temperature, and then slowly quenched with cold aqueous NH_4Cl. The aqueous phase was extracted with diethyl ether. The combined organic extracts were washed with water, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography (SiO_2, cyclohexane/EtOAc, 8:2 then 7:3) of the residue afforded two diastereomers **15** (37 mg, 108 mg, diastereomer ratio: 15:85, 49%), $R_f = 0.73$, 0.61 (cyclohexane/EtOAc, 6:4), along with 101 mg of recovered starting material **4**. – **Major Diastereomer 15a:** $[\alpha]_D^{20} = -20$ ($c = 1$, $CHCl_3$). – ^1H NMR (200 MHz, $CDCl_3$): δ = 0.12, 0.13 (2 s, 6 H, $SiMe_2$), 0.89 (s, 9 H, *t*Bu), 1.41 (d, *J* = 6.5 Hz, 3 H, CH*Me*), 1.42 (m, 1 H, 4′-H_{ax}), 2.24 (m, 1 H, 4′-H_{eq}), 2.45, 2.67 (2 dd, *J* = 15.8, 5.8, 7.2 Hz, 2 H, 6′-H), 2.5 (br. s, 1 H, OH), 3.44 (dd, *J* = 9.4, 3 Hz, 1 H, 1′-H), 3.54 (pseudo t, *J* = 9.4 Hz, 1 H, 2′-H), 3.68 (s, 3 H, CO_2Me), 3.70–3.90 (m, 2 H, 3′,5′-H), 4.53 (qd, *J* = 6.5, 1.3 Hz, 1 H, 4-H), 4.58–4.96 (m, 5 H, CH_2Ph), 7.25–7.36 (m, 10 H, H_{arom}). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = −4.9, −4.5 ($SiMe_2$), 18.1 [*C*(Me)$_3$], 25.3 (CH*Me*), 25.7 (C*Me*$_3$), 36.3, 40.0 (C-4′,6′), 51.7 (OMe), 58.9, 62.6 (C-1,4), 71.4 (*C*H_2Ph), 72.0 (CH_{pyran}), 75.1 (*C*H_2Ph), 79.6 (CH_{pyran}), 80.4 (C-1′), 88.8 (C≡C), 127.5, 127.9, 128.3, 138.1, 138.2 (C_{arom}), 170.9 (CO). – MS (CI, NH_3): *m*/*z* = 583 [M + 1], 600 [M + 18]. – **Minor Diastereomer 15b:** ^1H NMR (200 MHz, $CDCl_3$): δ = 0.14, 0.15 (2 s, 6 H, $SiMe_2$), 0.92 (s, 9 H, *t*Bu), 1.43 (d, *J* = 6.5 Hz, 3 H, CH*Me*), 1.45 (m, 1 H, 4′-H_{ax}), 2.31 (m, 1 H, 4′-H_{eq}), 2.48, 2.71 (2 dd, *J* = 15.7, 6.5, 6.7 Hz, 2 H, 6′-H), 2.6 (br. s, 1 H, OH), 3.36 (dd, *J* = 9.1, 1.5 Hz, 1 H, 1′-H), 3.72 (s, 3 H, CO_2Me), 3.64–3.90 (m, 3 H, 2′,3′,5′-H), 4.56–5.06 (m, 6 H, CH_2Ph, $H_{1,4}$), 7.29–7.36 (m, 10 H, H_{arom}). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = −5.0, −4.6 ($SiMe_2$), 18.1 [*C*(Me)$_3$], 25.3 (CH*Me*), 25.7 (CMe_3), 36.3, 40.2 (C-4′,6′), 51.7 (OMe), 58.9, 61.8 (C-1,4), 71.3 (*C*H_2Ph), 72.1 (CH_{pyran}), 75.2 (*C*H_2Ph), 78.4 (CH_{pyran}), 80.0 (CH_{pyran}), 80.4 (C-1′), 82.0, 88.8 (C≡C), 127.5, 127.8, 128.0, 128.3, 138.1, 138.2 (C_{arom}), 170.9 (CO). – MS (CI, NH_3): *m*/*z* = 583 [M + 1], 600 [M + 18].

(1*S*,4*R*)-1-*O*-Allyloxycarbonyl-4-*O*-*tert*-butyldimethylsilyl-1-[2,3-di-*O*-benzyl-4,6-dideoxy-6-(methoxycarbonyl)-D-*gluco*-β-C-pyranosyl]pent-2-yne-1,4-diol (16): To a solution of alcohol **15a** (218 mg, 1 equiv.) and pyridine (48 μL, 2 equiv.) in anhydrous CH_2Cl_2 (2 mL), allyloxycarbonyl chloride (60 μL, 1.2 equiv.) was slowly added at 0°C. The resulting mixture was stirred for 1 h at 0°C and then for 1 h at room temp. After completion of the reaction, the 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) of the residue afforded the diprotected derivative **16** as a colorless oil (256 mg, 99%), $R_f = 0.5$ (cyclohexane/EtOAc, 8:2), $[\alpha]_D^{20} = 15$ ($c = 1.1$, $CHCl_3$). – ^1H NMR (200 MHz, $CDCl_3$): δ = 0.12, 0.13 (2 s, 6 H, $SiMe_2$), 0.89 (s, 9 H, *t*Bu), 1.39 (d, *J* = 6.5 Hz, 3 H, CH*Me*), 1.38 (m, 1 H, 4′-H_{ax}), 2.3 (m, 1 H, 4′-H_{eq}), 2.45, 2.79 (2 dd, *J* = 15.8, 7.6, 5.6 Hz, 2 H, 6′-H), 3.69 (s, 3 H, CO_2Me), 3.43–3.90 (m, 4 H, 1′,2′,3′,5′-H), 4.51 (qd, *J* = 6.5, 1.4 Hz, 1 H, 4-H), 4.65 (m, 2 H, CH_2CH=CH_2), 4.60, 4.65/4.71, 4.96 (2 AB system, *J* = 10.8, 11.5 Hz, 4 H, CH_2Ph), 5.27 (dq, *J* = 10.4, 1.4 Hz, 1 H, CH=CH_2), 5.36 (dq, *J* = 16.1, 1.4 Hz, 1 H, CH=CH_2), 5.69 (pseudo t, *J* = 1.7 Hz, 1 H, 1-H), 5.92 (ddt, *J* = 16.1, 10.4, 5.7 Hz, 1 H, C*H*=CH$_2$), 7.28–7.37 (m, 10 H, H_{arom}). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = −4.9, −4.5 ($SiMe_2$), 18.1 [*C*(Me)$_3$], 25.0 (CH*Me*), 25.7 (C*Me*$_3$), 36.1, 40.0 (C-4′,6′), 51.6 (OMe), 58.8 (C-4), 67.9 (C-1), 68.6 (O*C*H_2CH=CH$_2$), 71.3 (*C*H_2Ph), 71.7 (CH_{pyran}), 75.1 (*C*H_2Ph), 78.5 (CH_{pyran}), 79.1 (CH_{pyran}), 80.3 (CH_{pyran}), 90.5 (C≡C), 118.8 (CH=*C*H_2), 127.5, 127.9, 128.3 (C_{arom}), 131.3 (*C*H=CH$_2$), 138.0, 138.2 (C_{arom}), 153.9 (O*C*O$_2$), 171.0 (*C*O$_2$Me). – MS (CI, NH_3): *m*/*z* = 684 [M + 18].

(1*S*,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 (17): To a solution of the *O*-silyl compound **16** (246 mg, 1 equiv.) in anhydrous THF (4 mL) at 0°C was slowly added tetrabutylammonium fluoride (440 μL, 1 M in THF, 1.2 equiv.). The resulting mixture was stirred for 1 h at 0°C and then for 1 h at room temp. After completion of the reaction, water was added and the aqueous phase was extracted with diethyl ether. The organic phase was washed with aqueous NaCl, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography (SiO_2, cyclohexane/EtOAc, 7:3) of the residue afforded the alcohol **17** as a colorless oil (189 mg, 93%), $R_f = 0.17$ (cyclohexane/EtOAc, 7:3), $[\alpha]_D^{20} = 1$ ($c = 1.2$, $CHCl_3$). – ^1H NMR (200 MHz, $CDCl_3$): δ = 1.39 (d, *J* = 6.6 Hz, 3 H, CH*Me*), 1.45 (m, 1 H, 4′-H_{ax}), 1.94 (br. s, 1 H, OH), 2.29 (m, 1 H, 4′-H_{eq}), 2.49, 2.75 (2 dd, *J* = 15.8, 7.1, 5.8 Hz, 2 H, 6′-H), 3.69 (s, 3 H, CO_2Me), 3.89–3.47 (m, 4 H, 1′,2′,3′,5′-H), 4.45 (qd, *J* = 6.6, 1.5 Hz, 1 H, C*H*OH), 4.65 (dt, *J* = 5.7, 1.4 Hz, 2 H, CH_2CH=CH$_2$), 4.61, 4.74/4.71, 4.98 (2 AB system, *J* = 11.0, 11.4 Hz, 4 H, CH_2Ph), 5.28 (dq, *J* = 10.4, 1.4 Hz, 1 H, CH=CH_2), 5.37 (dq, *J* = 16.1, 1.4 Hz, 1 H, CH=CH_2), 5.66 (pseudo t, *J* = 1.8 Hz, 1 H, 1-H), 5.94 (ddt, *J* = 16.1, 10.4, 5.7 Hz, 1 H, C*H*=CH$_2$), 7.27–7.38 (m, 10 H, H_{arom}). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 25.8 (CH*Me*), 35.9, 39.9 (C-4′,6′), 51.7 (OMe), 58.0 (C-4), 67.9 (C-1), 68.7 (O*C*H_2CH=CH$_2$), 71.4 (*C*H_2Ph), 71.7 (CH_{pyran}), 74.8 (*C*H_2Ph), 78.1, 79.0, 80.4 (CH_{pyran}), 89.9 (C≡C), 118.9 (CH=*C*H_2), 127.5, 127.6, 128.0, 128.4 (C_{arom}), 131.2 (*C*H=CH$_2$), 138.1 (C_{arom}), 153.9 (O*C*O$_2$), 171.0 (*C*O$_2$Me). – MS (CI, NH_3): *m*/*z* = 570 [M + 18].

(1*S*,4*R*)-1-*O*-Allyloxycarbonyl-1-[2,3-di-*O*-benzyl-4,6-dideoxy-6-(methoxycarbonyl)-D-*gluco*-β-C-pyranosyl]-4-*O*-ethoxycarbonylpent-2-yne-1,4-diol (18): To a solution of alcohol **17** (189 mg, 1 equiv.) and pyridine (55 μL, 2 equiv.) in anhydrous CH_2Cl_2 (3 mL) at 0°C was slowly added ethyl chloroformate (39 μL, 1.2 equiv.). The resulting mixture was stirred for 1 h at 0°C and then for 1 h at room

temp. After completion of the reaction, the 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) of the residue afforded the diprotected derivative **18** as a colorless oil (202 mg, 94%), R_f = 0.31 (cyclohexane/EtOAc, 8:2), $[\alpha]_D^{20}$ = 30 (c = 1, $CHCl_3$). − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.30 (t, J = 7.1 Hz, 3 H, OCH_2Me), 1.50 (d, J = 6.6 Hz, 3 H, $CHMe$), 1.43 (m, 1 H, 4′-H_{ax}), 2.31 (m, 1 H, 4′-H_{eq}), 2.49, 2.79 (2 dd, J = 15.8, 7.3, 5.8 Hz, 2 H, 6′-H), 3.71 (s, 3 H, CO_2Me), 3.49−3.85 (m, 4 H, 1′,2′,3′,5′-H), 4.20 (q, J = 7.1 Hz, 2 H, OCH_2Me), 4.59−5.02 (m, 6 H, $CH_2CH{=}CH_2$, CH_2Ph), 5.33 (m, 3 H, 4-H, $CH{=}CH_2$), 5.69 (m, 1 H, 1-H), 5.96 (ddt, J = 16.1, 10.4, 5.7 Hz, 1 H, $CH{=}CH_2$), 7.38−7.28 (m, 10 H, H_{arom}). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.2 (OCH_2Me), 21.0 ($CHMe$), 36.0, 40.0 (C-4′,6′), 51.7 (OMe), 63.8 (OCH_2Me), 64.2 (C-4), 67.7 (C-1), 68.8 ($OCH_2CH{=}CH_2$), 71.4 (CH_2Ph), 71.7 (CH_{pyran}), 75.1 (CH_2Ph), 78.4 (CH_{pyran}), 78.8 (C≡C), 78.9, 80.3 (CH_{pyran}), 85.7 (C≡C), 119.0 ($CH{=}CH_2$), 127.6, 128.0, 128.4 (C_{arom}), 131.3 ($CH{=}CH_2$), 138.0, 138.2 (C_{arom}), 153.9 (OCO_2), 171.0 (CO_2Me). − MS (CI, NH_3): m/z = 642 [M + 18].

(1*S*,4*R*)-1-[2,3-Di-*O*-benzyl-4,6-dideoxy-6-(methoxycarbonyl)-D-*gluco*-β-C-pyranosyl]-4-*O*-ethoxycarbonylpent-2-yne-1,4-diol (19): To a solution of the allyloxycarbonyl compound **18** (202 mg, 1 equiv.) and diethylamine (73 μL, 2.2 equiv.) in acetonitrile (4.3 mL) was added a mixture of $Pd(OAc)_2$ (7 mg, 10 mol.%) and TPPTS (110 mg, 20 mol.%) in water (0.7 mL). The resulting mixture was vigorously stirred at room temperature until completion of the reaction and then concentrated under reduced pressure. The resulting aqueous phase was extracted with ethyl acetate, and the combined extracts were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography (SiO_2, cyclohexane/EtOAc, 7:3) of the residue afforded **19** as a colorless oil (160 mg, 91%), R_f = 0.28 (cyclohexane/EtOAc, 7:3), $[\alpha]_D^{20}$ = 5 (c = 0.8, $CHCl_3$). − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.29 (t, J = 7.1 Hz, 3 H, OCH_2Me), 1.40 (m, 1 H, 4′-H_{ax}), 1.54 (d, J = 6.7 Hz, 3 H, $CHMe$), 1.71 (br. s, 1 H, OH), 2.24 (m, 1 H, 4′-H_{eq}), 2.48, 2.69 (2 dd, J = 15.8, 7.2, 5.7 Hz, 2 H, 6′-H), 3.71 (s, 3 H, CO_2Me), 3.42−3.91 (m, 4 H, 1′,2′,3′,5′-H), 4.19 (q, J = 7.1 Hz, 2 H, OCH_2Me), 4.72 (m, 1 H, 1-H), 4.62, 4.71/4.67, 4.97 (2 AB system, J = 10.8, 11.5 Hz, 4 H, CH_2Ph), 5.34 (qd, J = 6.7, 1.6 Hz, 1 H, 4-H), 7.37−7.27 (m, 10 H, H_{arom}). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.2 (OCH_2Me), 21.3 ($CHMe$), 36.4, 40.1 (C-4′,6′), 51.9 (OMe), 62.7 (C-1), 64.0 (C-4), 64.4 (OCH_2Me), 71.6 (CH_2Ph), 72.2 (CH_{pyran}), 76.4 (CH_2Ph), 79.7, 80.1 (CH_{pyran}), 80.5 (C-1′), 83.1, 84.1 (C≡C), 127.7, 128.0, 128.5, 138.0 (C_{arom}), 154.1 (OCO_2), 171.0 (CO_2Me). − MS (CI, NH_3): m/z = 541 [M + 1], 558 [M + 18].

(1*S*,4*R*)-1-[2,3-Di-*O*-benzyl-4,6-dideoxy-6-(methoxycarbonyl)-D-*gluco*-β-C-pyranosyl]-4-*O*-ethoxycarbonylpent-2-ene-1,4-diol (20): To a solution of **19** (160 mg, 1 equiv.), containing suspended Pd/C (16 mg, 10% w/w) in methanol (1.5 mL), was added pyridine (15 μL, 5% w/w) and the reaction mixture was stirred under hydrogen at room temp. for 1 h. After filtering through a short plug of silica gel using diethyl ether as eluent, the solvent was evaporated under reduced pressure. Column chromatography (SiO_2, cyclohexane/EtOAc, 8:2 then 7:3) afforded **20** as a colorless oil (90 mg, 56%), R_f = 0.28 (cyclohexane/EtOAc, 7:3), $[\alpha]^{20}{}_D$ = −21 (c = 0.7, $CHCl_3$). − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.23 (t, J = 7.1 Hz, 3 H, OCH_2Me), 1.38 (d, J = 5.8 Hz, 3 H, $CHMe$), 1.39 (m, 1 H, 4′-H_{ax}), 2.25 (ddd, J = 12.7, 4.9, 1.6 Hz, 1 H, 4′-H_{eq}), 2.44, 2.62 (2 dd, J = 15.6, 7.1, 5.9 Hz, 2 H, 6′-H), 2.85 (d, J = 6.7 Hz, 1 H, OH), 3.78 (t, J = 9.7 Hz, 1 H, 2′-H), 3.44 (dd, J = 9.7, 3.3 Hz, 1 H, 1′-H), 3.68 (s, 3 H, CO_2Me), 3.74 (m, 1 H, 3′-H), 3.84 (m, 1 H, 5′-H), 4.08 (q, J = 7.1 Hz, 2 H, OCH_2Me), 4.55−4.95 (m, 5 H, CH_2Ph, $CHOH$), 5.67 (m, 3 H, $CH{=}CH$, $CHMe$), 7.32−7.26 (m, 10 H, H_{arom}). − ^{13}C NMR (63 MHz, $CDCl_3$): δ = 14.3 (OCH_2Me), 21.1 ($CHMe$), 36.5, 40.4 (C-4′,6′), 51.8 (OMe), 63.8 (OCH_2Me), 68.2 (C-1), 71.5 (CH_2Ph), 71.6 (C-4), 74.7 (CH_2Ph), 71.9, 79.2, 80.6 (CH_{pyran}), 81.0 (C-1′), 127.7, 128.0, 128.4, 128.5 (C_{arom}), 129.2, 133.9 ($CH{=}CH$), 138.3 (C_{arom}), 154.5 (OCO_2), 171.1 (CO_2Me). − MS (CI, NH_3): m/z = 560 [M + 18].

Methyl (3*S*,4*E*,6*S*)-6-[2,3-Di-*O*-benzyl-4,6-dideoxy-6-(methoxycarbonyl)-D-*gluco*-β-C-pyranosyl]-6-hydroxy-2-methoxycarbonyl-3-methylhex-4-enoate (21): $Pd(OAc)_2$ (3.7 mg, 10 mol-%) and bis(diphenylphosphanyl)ethane (9.9 mg, 1.5 equiv./Pd) were stirred in anhydrous THF (0.8 mL) at 30°C under argon for 30 min. To this orange mixture, a solution of **20** (90 mg, 1 equiv.) in THF (0.4 mL) was added at room temp. Dimethyl malonate (27 μL, 1.4 equiv.) was added to a suspension of NaH (9 mg, 1.4 equiv., 60% in oil) in THF (1.6 mL). After 15 min at room temp., the catalyst mixture was added to the anion of the dimethyl malonate. After 1 h, the mixture was treated with aqueous NH_4Cl and the aqueous phase was extracted with diethyl ether. The combined organic extracts were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography (SiO_2, cyclohexane/EtOAc, 7:3) afforded **21** as a colorless oil (58 mg, 60%), R_f = 0.15 (cyclohexane/EtOAc, 7:3). 29 mg (32%) of starting material **20** was recovered. − $[\alpha]_D^{20}$ = −11 (c = 0.8, $CHCl_3$). − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.05 (d, J = 6.8 Hz, 3 H, $CHMe$), 1.36 (m, 1 H, 4′-H_{ax}), 2.23 (m, 1 H, 4′-H_{eq}), 2.45, 2.64 (2 dd, J = 15.7, 7.2, 5.7 Hz, 2 H, 6′-H), 2.96 (m, 1 H, 3-H), 3.23 (t, J = 9.7 Hz, 1 H, 2′-H), 3.29 (d, J = 8.6 Hz, 1 H, 2-H), 3.43 (dd, J = 9.7, 3 Hz, 1 H, 1′-H), 3.66 (s, 3 H, CO_2Me), 3.70 [s, 6 H, $CH(CO_2Me)_2$], 3.71−3.84 (m, 2 H, 3′,5′-H), 4.30 (dd, J = 7.1, 3.0 Hz, 1 H, 6-H), 4.54−4.98 (m, 4 H, CH_2Ph), 5.55 (dd, J = 15.5, 7.1 Hz, 1 H, 5-H), 5.67 (dd, J = 15.5, 7.5 Hz, 1 H, 4-H), 7.26−7.31 (m, 10 H, H_{arom}). − ^{13}C NMR (63 MHz, $CDCl_3$): δ = 18.1 ($CHMe$), 37.0 (C-3), 36.4, 40.4 (C-4′,6′), 51.9 (CO_2Me), 52.5 [$CH(CO_2Me)_2$], 57.6 (C-2), 71.2 (C-6), 71.3 (CH_2Ph), 72.6 (CH_{pyran}), 74.6 (CH_2Ph), 79.1, 81.0 (CH_{pyran}), 81.1 (C-1′), 127.7, 127.8, 128.5 (C_{arom}), 129.5, 135.3 (C-4,5), 138.4, 138.6 (C_{arom}), 168.5, 168.7 [$CH(CO_2Me)_2$], 171.1 (CO_2Me). − MS (CI, NH_3): m/z = 602 [M + 18].

Methyl (3*S*,4*E*,6*S*)-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 (22): To a solution of alcohol **21** (57 mg, 1 equiv.) and pyridine (16 μL, 2 equiv.) in anhydrous CH_2Cl_2 (1 mL) at 0°C was slowly added 2,4-dichlorobenzoyl chloride (22 μL, 1.2 equiv.). The resulting mixture was stirred for 1 h at 0°C and then for 1 h at room temp. After completion of the reaction, the 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) of the residue afforded the benzoyl derivative **22** as a colorless oil (66 mg, 89%), R_f = 0.45 (cyclohexane/EtOAc, 7:3), $[\alpha]_D^{20}$ = −10 (c = 0.9, $CHCl_3$). − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.05 (d, J = 6.8 Hz, 3 H, $CHMe$), 1.38 (m, 1 H, 4′-H_{ax}), 2.23 (m, 1 H, 4′-H_{eq}), 2.45, 2.65 (2 dd, J = 15.5, 7.3, 5.6 Hz, 2 H, 6′-H), 2.97 (m, 1 H, 3-H), 3.23 (dd, J = 9.8, 8.6 Hz, 1 H, 2′-H), 3.29 (d, J = 8.6 Hz, 1 H, 2-H), 3.60 (dd, J = 9.8, 1.4 Hz, 1 H, 1′-H), 3.66 (s, 3 H, CO_2Me), 3.67, 3.70 [2 s, 6 H, $CH(CO_2Me)_2$], 3.71−3.87 (m, 2 H, 3′,5′-H), 4.55−4.99 (m, 4 H, CH_2Ph), 5.74 (m, 3 H, 4,5,6-H), 7.26−7.37 (m, 11 H, H_{arom}), 7.44 (d, J = 1.9 Hz, 1 H, $CH_{benzoyl}$), 7.78 (d, J = 8.4 Hz, 1 H, $CH_{benzoyl}$). − ^{13}C NMR (63 MHz, $CDCl_3$): δ = 18.0 ($CHMe$), 36.3 (CH_{2pyran}), 37.1 (C-3), 40.5 (CH_{2pyran}), 51.8 (CO_2Me), 52.5, 52.6 [$CH(CO_2Me)_2$], 57.4 (C-2), 71.3 (CH_2Ph), 71.8 (CH_{pyran}), 74.6

(CH_2Ph), 75.6, 78.0 (CH_{pyran}), 79.9 (C-6), 80.9 (C-1′), 124.5 (*C*H=CH), 125.1, 127.0, 127.7, 127.8, 127.9, 128.5, 130.9, 132.8, 138.2, 138.4, 138.5 (C_{arom}), 139.6 (*C*H=CH), 163.6 (*C*OAr), 168.3, 168.6 [CH(*C*O_2M*e*)$_2$], 171.2 (*C*O_2Me). − MS (CI, NH_3): *m*/*z* = 774 [M + 18].

Methyl (2*S*,3*R*)-3-[(*E*)-2-(2,3-Di-*O*-benzyl-4,6-dideoxy-6-(methoxycarbonyl)-D-*gluco*-β-C-pyranosyl)ethenyl]-2-methylcyclopropane-1,1-dicarboxylate (23): $Pd(OAc)_2$ (1.9 mg, 10 mol-%) and bis(diphenylphosphanyl)ethane (5.1 mg, 1.5 equiv./Pd) were stirred in anhydrous THF (0.4 mL) at 30°C for 30 min under argon. To this orange mixture containing the catalyst, a solution of the benzoyl compound **22** (65 mg, 1 equiv.) in THF (0.2 mL) was added at room temp., followed by DBU (18 µL, 1.4 equiv.). After 1 h at room temp., the reaction mixture was treated with aqueous NH_4Cl and the aqueous phase was extracted with diethyl ether. The combined organic extracts were washed with brine, dried with Na_2SO_4, and concentrated under reduced pressure. Column chromatography (SiO_2, cyclohexane/EtOAc, 8:2) of the residue afforded **23** as a colorless oil (28 mg, 60%), R_f = 0.4 (cyclohexane/EtOAc, 7:3). − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.19 (d, *J* = 6.7 Hz, 3 H, CH*Me*), 1.43 (q, *J* = 11.5 Hz, 1 H, 4′-H_{ax}), 1.95 (m, 1 H, 2-H), 2.23 (ddd, *J* = 12.6, 4.9, 1.7 Hz, 1 H, 4′-H_{eq}), 2.37 (t, *J* = 9.6 Hz, 1 H, 3-H), 2.44, 2.65 (2 dd, *J* = 15.4, 6.9, 6.2 Hz, 2 H, 6′-H), 3.18 (t, *J* = 9 Hz, 1 H, 2′-H), 3.69 (s, 3 H, CO_2Me), 3.72, 3.75 [2 s, 6 H, C(CO_2Me)$_2$], 3.62−3.78 (m, 2 H, 1′,3′-H), 3.85 (m, 1 H, 5′-H), 4.63, 4.70/4.70, 4.85 (2 AB system, *J* = 11.0, 11.6 Hz, 4 H, CH_2Ph), 5.59 (dd, *J* = 15.5, 9.6 Hz, 1 H, CH=C*H*), 5.79 (dd, *J* = 15.5, 6 Hz, 1 H, C*H*=CH), 7.29−7.37 (m, 20 H, H_{arom}). − ^{13}C NMR (63 MHz, $CDCl_3$): δ = 10.0 (CH*Me*), 26.9 (C-2), 34.5 (C-3), 36.8 (CH_{2pyran}), 38.8 (C-1), 40.6 (CH_{2pyran}), 51.8 (CO_2Me), 52.3, 52.8 [C(CO_2Me)$_2$], 71.7 (CH_{pyran}), 71.8, 75.1 (CH_2Ph), 79.2, 80.3 (CH_{pyran}), 82.3 (C-1′), 127.6, 127.7, 128.3, 128.4, 128.5 (C_{arom}), 126.5, 132.2 (CH=CH), 138.5, 138.6 (C_{arom}), 167.0, 170.9 [C(*C*O_2Me)$_2$], 171.3 (*C*O_2Me). − MS (CI, NH_3): *m*/*z* = 584 [M + 18].

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