Solid-Phase Synthesis

Reversible Substrate Anchoring: NC-SPOS as a Sustainable Approach to Solid-Supported Organic Synthesis**

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Dedicated to Professor George M. Whitesides

The goal of solid-phase organic synthesis (SPOS) is to accelerate and standardize synthetic operations to be compatible with parallel and automated approaches. In conventional SPOS, substrates are covalently attached to an insoluble matrix and time-consuming workup procedures are simplified to physical separation steps. Products are released after multiple reaction cycles by the chemoselective cleavage of a linker moiety.[1] A major problem with this technology is the difficulty in analytical characterization of synthetic intermediates and impossibility of purification from covalently bound side-products. Moderate loading capacities, limited mechanical stability, and unsatisfactory reagent penetration are further disadvantages of the polymeric supports common to this approach. Matrix material is usually discarded after use because regeneration of the matrix–linker construct is inconvenient and uneconomical. In the search for superior options, alternative concepts[2] have recently been investigated that attempt to amalgamate the advantages of a high-molecular-weight carrier with solution-phase chemistry, such as in soluble-polymer-supported[3] and dendrimer-supported organic synthesis.[4] In other studies distinct techniques for product isolation have been introduced, for example, special product-precipitation methods[5] and liquid/liquid phase separation, including the use of ionic liquids and fluorous phases.[2,6] Inverse approaches consist of the application of immobilized reagents, catalysts, and scavengers.[7] In contrast to reactions with solid-phase resins, reactions with soluble supports can be performed (and analyzed) under homogeneous conditions. Method validation is thus facilitated, but often the practical simplicity and efficiency gained by the use of insoluble supports are lost.[2]

Our interest in the efficacious generation of molecular diversity within biocatalytic synthesis[8] has led us to develop a novel approach to SPOS by using the *noncovalent attachment of substrates* to a solid matrix through hydrophobic interactions (noncovalent SPOS, NC-SPOS).[9] When tagged with a hydrophobic anchor unit, substrates in a highly polar, hydrophilic solvent, such as water, become immobilized on a hydrophobic matrix (Figure 1). Thus, standard SPOS operations, including washing and filtration steps, may be performed on immobilized substrates. As the anchoring affinity depends on the partition coefficient ($\lg P$) of the anchor unit between the matrix and the solution phase,[10] anchored products are released into the solution phase when switched to a nonpolar organic solvent. A typical NC-SPOS reaction procedure would thus consist of three steps: 1) adsorption of the anchor–substrate unit onto the matrix, 2) single or multiple reactions under aqueous conditions, each followed by washing, and 3) final desorption and/or cleavage of the anchor–product unit.

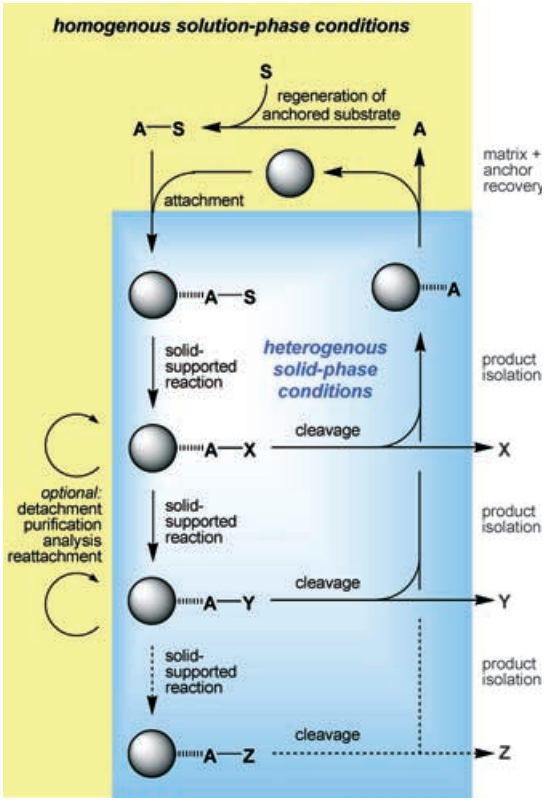

Figure 1. Basic concept of NC-SPOS. A = hydrophobic anchor unit; S = substrate; X, Y, and Z = products. Bead symbols indicate a hydrophobic solid-phase support. Dashed bonds represent noncovalent attachment. The yellow area denotes the nonpolar organic phase, while the blue box indicates the polar hydrophilic phase.

As the attachment is reversible, phase switching may be performed, in principle, at any stage of a given reaction sequence; in this way the NC-SPOS technique displays the same advantages as common solution-phase chemistry. Thus, the reaction can be monitored conveniently by conventional TLC, and reaction intermediates are amenable to spectroscopic analysis (or even optional chromatographic purification) by application of an organic solvent under homogenous conditions. As phase switching is freely reversible, compounds released into solution for analysis may be readsorbed onto the solid matrix by subsequent change to the polar

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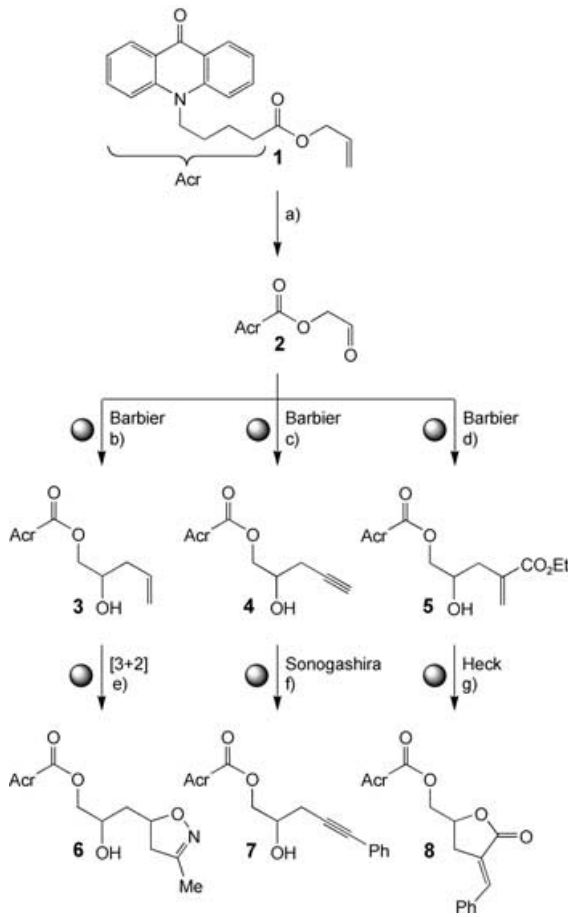
solvent. Likewise, it is immediately obvious that in a multistep synthetic sequence, for example, individual steps may also be performed under nonaqueous conditions if the type of reaction or the choice of reagent is incompatible with SPOS operations or requires a moisture-free organic solvent; thereafter, the NC-SPOS process can be continued after reattachment of the intermediates to the matrix under aqueous conditions.

The final product is released from the hydrophobic anchor unit by conventional linker cleavage and isolated from the solid matrix by washing (Figure 1). Both the collected solid phase and the hydrophobic anchor unit can be recycled. Loading capacity is broadly adjustable and limited only by the accessible hydrophobic surface area of the solid matrix. A broad variety of suitable solid-phase supports with designed properties is commercially available, because the NC-SPOS concept relies on the same phenomenon as conventional solid-phase extraction (SPE) and reversed-phase (RP) chromatography.[11] Although it is very simplistic in design, this approach of reversible substrate binding as a fully integrated strategy of SPOS has, to the best of our knowledge, not been pursued previously.[12] However, polycyclic-arene-based protecting groups with high adsorptive affinity to charcoal or graphite have been reported to facilitate the recovery of tagged products from organic solvent media[13] or for chromatographic purification.[14]

For a first realization of the NC-SPOS concept, we chose standard C_{18}-modified RP silica gel as the hydrophobic matrix and *N*-alkylated acridone derivatives as the hydrophobic anchor moieties (usually 0.5 g of RP matrix per mmol of substrate). The choice of an acridone tag, aside from its low polarity and high (photo)chemical stability, was based on its extremely efficient, bright blue fluorescence, which facilitates the effective establishment of ultrasensitive reaction screening by TLC or HPLC analysis.[15] Indeed, initial experiments with an anchored allyl ether moiety demonstrated that basic alkene functionalization (epoxidation by peracids, dihydroxylation by $KMnO_4$ or by acid epoxide hydrolysis, cleavage by O_3) and carbonyl reactions (aldehyde reduction/oxidation by $NaBH_4/H_2O_2$, hydrazone condensation) could be achieved selectively by typical SPOS procedures.[9]

To test the suitability of the NC-SPOS concept as a rapid reactivity-screening system (Scheme 1), the allyl ester **1** was initially chosen as a generic example of an anchor–substrate unit from which products could be released by simple adjustment of the pH value without further addition of contaminating reagents. The ester functionality has been applied successfully in many SPOS operations because it is easy to generate and can be cleaved selectively under mild conditions that are tolerated by a very broad variety of further functional groups. At an experimental lg *P* value of ≈ 2.5, no remaining **1** could be detected in the solution phase of a RP-matrix/water mixture by UV measurement at $\lambda = 399$ nm, and less than 2% of **1** became desorbed in the presence of 10% methanol as an organic cosolvent. However, when small aliquots of the NC-SPOS slurry were transferred to a TLC plate that was then dried and developed with an organic solvent, a sharp homogenous spot of **1**, indistinguishable from an unbound reference sample, was observed.



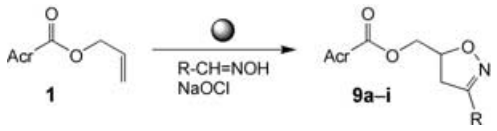
Scheme 1. Screening for NC-SPOS reactions. Reagents and conditions: a) O_3, MeOH, −78 °C, then DMS, RT, 24 h, quantitative; b) $SnCl_2$/KI, allyl bromide (6 equiv), H_2O, RT, 90%; c) $SnCl_2$/KI, ethyl 2-bromomethylacrylate (6 equiv), H_2O, RT, 85%; d) $SnCl_2$/KI, propargyl bromide (6 equiv), H_2O, RT, 70%; e) $CH_3CH{=}NOH$ (3 equiv), NaOCl, 0 °C→RT, 8 h, 79%; f) 5 mol% $Pd(OAc)_2$/TPPTS, PhI (1.1 equiv), NEt_3 (2.5 equiv), RT, 20 h, 90%; g) 5 mol% $Pd(OAc)_2$/TPPTS, PhI (1.1 equiv), NEt_3 (2.5 equiv), RT, 20 h, 40%. Bead symbols indicate reactions performed by hydrophobic attachment of the substrates to a reversed-phase silica support. DMS = dimethyl sulfide; TPPTS = tris-(*m*-sulfonatophenyl)phosphane, trisodium salt.

Subsequent to early findings of Breslow, Grieco, and their respective co-workers[16] that water can increase the rate and selectivity of Diels–Alder reactions, a large variety of reactions have been adapted to aqueous conditions.[17] As an entry to the multistep construction of larger entities, we tested metal-mediated Barbier-type allyl additions[18] as one of the best developed reactions in aqueous media by using aldehyde **2** under NC-SPOS conditions. As to be expected, in situ formation of the organometallic allyl reagents from elemental Zn or Sn was largely unsuccessful since the metal surface must be activated by acid treatment or sonication, which also led to partial cleavage of the linker cleavage and unsatisfactory yields. In contrast, in the case of In-mediated reactions good yields were obtained, but inorganic precipitates hampered filtration and matrix purification for reuse. However, the homogenous reagents generated from $SnCl_2$/KI[19] with allyl

bromide, ethyl 2-bromomethylacrylate,[20] and even propargyl bromide consistently gave high yields of isolated adducts **3**–**5**.

Further reactivity screening included 1,3-dipolar cycloaddition of nitrile oxides[21] and Pd-catalyzed C–C cross-coupling reactions[22] to carrier-adsorbed alkenes as consecutive synthesis steps. Generation of the nitrile oxide reagent could be performed advantageously in situ from the corresponding oxime by using 11% aqueous NaOCl at 0°C to furnish Δ^2-isoxazoline **6** in good yield. Also, Pd-catalyzed C–C cross-coupling reactions such as Heck and Sonogashira reactions, which have emerged as valuable tools in organic synthesis to build new C–C bonds, were performed successfully in water by using water-soluble phosphine ligands. In the latter case, air sensitivity of the catalytic Pd complex proved challenging because of the difficulty of degassing the RP-silica solid phase in a practical manner. The Heck reaction, performed without added organic cosolvent, was compromised by competing partial cleavage of the ester linker under the slightly alkaline conditions, because an equivalent of base is needed to scavenge the acid by-product. The reported yield for isolated product thus accounts only for the anchor-conjugated adduct (40%, nonoptimized; *E*/*Z* ratio 16:1) that remained adsorbed to the solid phase, an adduct that, interestingly, proved to be lactone **8** formed by an intramolecular transesterification (>95% purity). In addition, a considerable quantity of further unlabeled Heck product was detected in the aqueous phase. Therefore, the unsatisfactory yield is due to the insufficient stability of the anchoring ester under the reaction conditions, but it should be pointed out that this is not a limitation inherent to the NC-SPOS approach. The ester conjugate was chosen as a simple, uniform linker moiety in this demonstration of reaction screening, but it could be readily replaced by more appropriate functionalities for more focused studies on Heck-type conversions.[1]

In a first attempt to address the potential of the NC-SPOS technique for diversity generation in parallel syntheses, we focused on isoxazoline formation by [3+2] cycloaddition because these reactions are highly atom economical and usually give high yields, and, for comparison, they are well documented under various reaction conditions.[21] Also, isoxazolines are medicinally important pharmacophores and provide versatile building blocks for the synthesis of complex natural products.[23] A series of oximes (Scheme 2, Table 1) was subjected to NaOCl oxidation as before in the presence of RP-silica-bound allyl ester **1**, and product formation was conveniently determined by TLC monitoring. After the usual aqueous washing, all the resulting isoxazolines **9a**–**h** were obtained as single regioisomers by methanol desorption from the solid phase. The crude products from aromatic oximes



Scheme 2. Examples of 1,3-dipolar additions of nitrile oxides to alkene **1** by NC-SPOS. Reagents and conditions: R–CH=NOH (1.5 equiv), NaOCl, 0°C→RT, 16 h.

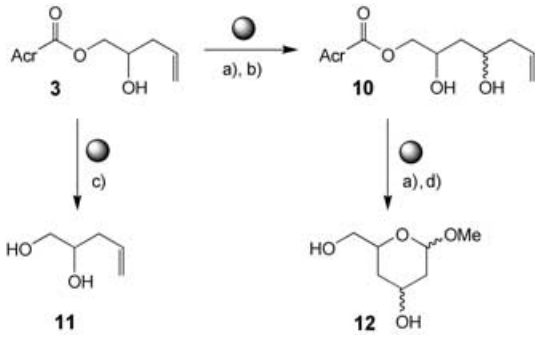
Table 1: Solid-supported 1,3-dipolar cycloaddition of different dipoles to alkene **1**.

R^1	Product	Yield [%][a]
Ph	**9a**	84
p-F-C_6H_4	**9b**	70
p-NO_2-C_6H_4	**9c**	45
p-Me_2N-C_6H_4	**9d**	65
o,*p*-$(MeO)_2$-C_6H_3	**9e**	70
o-Py[b]	**9f**	40
Me	**9g**	46[c]
Et-$(CHCH_3)_2$	**9h**	67[c]
Ph-$(CH_2)_2$	**9i**	80[c]

[a] Yield of chromatographically purified products after isolation. [b] Py = pyridyl. [c] Reaction performed with 3 equivalents of oxime.

were pure by NMR spectroscopic analysis, with only minor impurities from excess reagent and some anchor carboxylic acid arising from undesired cleavage of the anchoring ester linkage. Owing to the lower stability of alkyl oximes (**6** and **9g**–**i**) more reagent was required (up to 3 equiv), and extended exposition to strongly alkaline medium (pH ≈ 11) resulted in diminished yields. For full characterization, products were purified by conventional column chromatography. Yields were within the usual range observed for conventional solution-phase and solid-phase synthesis protocols.[21]

The effectiveness of the protocols for cleavage and matrix/anchor regeneration is illustrated in an exemplary manner by the NC-SPOS synthesis of a small stereocombinatorial[24] library of dideoxyglycosides (Scheme 3). By diverging from



Scheme 3. Examples of cleavage reactions for NC-SPOS products. Reagents and conditions: a) O_3, MeOH, −78°C, then DMS, RT, quantitative; b) $SnCl_2$/KI, allyl bromide (6 equiv), H_2O, RT, 90%; c) aqueous HCl/EtOH, reflux, 2 h, 85%; d) HCl/MeOH, reflux, 30 min, 89%.

the racemic alkene intermediate **3**, ozonolytic generation of the corresponding aldehyde electrophile followed by a second Barbier-type allyl addition gave a mixture of diastereomeric *syn*/*anti* adducts **10** in a 1:1 ratio. Ozonolysis and reductive workup furnished an anchored mixture of 2,4-dideoxysugars, consisting of four distinct α,β anomers (all pairs of enantiomers, eight different stereoisomers altogether) as evident by NMR analysis of a desorbed aliquot (later readsorbed by slurrying with fresh RP silica in water). For cleavage, the solid-phase material was treated with HCl in methanol at room temperature. Solvent exchange to water followed by

filtration provided a fraction of solid matrix containing the free anchor moiety and an aqueous solution of free methyl dideoxyglycosides **12.** The latter were isolated in 89% yield by evaporation of the water and characterized by NMR spectroscopic analysis; the expected diastereomers were obtained in a 3:3:1:1 ratio. Finally, the solids were leached with methanol to furnish the regenerated RP matrix (98% total recovery) and the detached hydrophobic anchor unit as the methyl ester ready for reuse (86% total recovery; >95% purity). Similarly, diol **11** was isolated by acidic cleavage (HCl/EtOH) in 96% total yield together with the ethyl ester of the anchor unit. Cleavage from the anchor could also be performed under aqueous alkaline conditions; this, however, required an additional ion-exchange treatment for neutralization.

In conclusion, we have proposed NC-SPOS as a novel concept for facilitated organic processes and have demonstrated that many modern synthetic reactions can be carried out under such conditions. For all the reactions screened, aided by highly sensitive fluorescent labeling, we have been able to replace an organic-substrate-solubilizing phase with a hydrophobic surface-modified solid matrix and use reagents in water as an environmentally friendly solvent. A general NC-SPOS reaction procedure often takes less time than the equivalent common SPOS process, because there are none of the diffusion limitations that are typical for polymer supports and tedious washing cycles are thus unnecessary. We have generally been able to avoid the use of a vast excess of reagent, which is otherwise typical for SPOS conditions, and thereby minimize potential product contamination from hydrophobic reagents. Clearly, limitations can arise for aqueous NC-SPOS reactions with building blocks or reagents that are poorly soluble in water because these components may stick to the support and lower the reaction rates. However, for those individual reactions investigated, but not optimized, yields so far are comparable to conventional solution-phase conversions and may be improved with further experimentation.

The main problems of conventional SPOS, that is, analysis and purification of intermediates, particularly during multistep syntheses, are overcome by our new freely reversible attachment strategy. The recovery of the RP-silica solid phase and anchor units is facile and efficient, so the technique is highly environmentally benign, in keeping with the philosophy of green chemistry.[25] The NC-SPOS strategy offers practical simplicity that is readily applicable to both automation and scaleup. The study of more sophisticated aspects, such as multiparallel and combinatorial synthesis, asymmetric catalysis, use of anchored scavengers and/or other anchor–linker combinations, further reaction types, and application to multistep syntheses, is currently underway.

Experimental Section

Example synthesis of **3**: A solution of **1** (335 mg, 1 mmol) in MeOH (10 mL) at −78 °C was treated with ozone until a blue color persisted. After the mixture had been purged with O_2 for a further 5 min, dimethyl sulfide (0.5 mL) was added, and the mixture was then allowed to warm to room temperature for 2 h. RP silica 100 (C_{18}, endcapped, 230–400 mesh; 500 mg) was added, and the solvent was removed in vacuo. Further portions of MeOH (3 × 10 mL) were added and evaporated to remove all volatile compounds. In a separate flask, an aqueous solution (10 mL) containing KI (510 mg, 3.0 mmol) and $SnCl_2$ (342 mg, 1.8 mmol) was stirred with allyl bromide (0.14 mL, 6.4 mmol) to give an orange-red reagent solution. This mixture was added to the adsorbed RP silica, and the resulting slurry was stirred at room temperature overnight, during which time the color faded away. After filtration through a thin RP-silica layer (prewashed with MeOH), the solid residue was washed with water (50 mL) and dried. For product release, the solid was washed with methanol, and the filtrates were evaporated to give **3** as a yellow oil (350 mg, 90%); $R_f = 0.4$ (40% EtOAc/cyclohexane); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.52$ (dd, 2H, $J = 8.0$, 1.7 Hz, H_{ar}), 7.68 (ddd, 2H, $J = 8.0$, 7.0, 1.7 Hz, H_{ar}), 7.41 (br d, 2H, $J = 8.7$ Hz, H_{ar}), 7.22 (ddd, 2H, $J = 8.0$, 7.0, 0.7 Hz, H_{ar}), 5.72 (m, 1H, H-4′), 5.08 (m, 2H, H-5′), 4.30 (t, 2H, $J = 7.5$ Hz, H-5), 4.11 (dd, 1H, $J = 11.4$, 3.2 Hz, H-1′a), 3.97 (dd, 1H, $J = 11.4$, 7.0 Hz, H-1′b), 3.85 (m, 1H, H-2′), 2.44 (t, 2H, $J = 6.9$ Hz, H-2), 2.23 (m, 2H, H-3′), 1.95–1.80 ppm (m, 4H, H-3, H-4); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 177.94$ (C=O), 173.09 (C-1), 141.76 (C_{ar}), 134.01 (C_{ar}), 133.41 (C-4′), 128.11 (C_{ar}), 122.54 (C_{ar}), 121.35 (C_{ar}), 118.65 (C-5′), 114.46 (C_{ar}), 69.41 (C-2′), 68.42 (C-1′), 45.77 (C-5), 38.18 (C-3′), 33.93 (C-2), 26.68 (C-4), 22.20 ppm (C-3); MS (70 eV): m/z (%): 379 (49) [M^+], 208 (100).

Cleavage of **3**: A sample of **3** (100 mg, 0.26 mmol) adsorbed to RP silica (500 mg) was heated at reflux in a mixture of EtOH (30 mL) and concentrated HCl (1 mL) for 2 h. After complete conversion (according to TLC), the solvent was removed by evaporation, and then water (15 mL) and further RP silica (1 g) were added. The resulting slurry was filtered, the solids washed with water (15 mL), and the combined filtrates were evaporated to yield **11** (26 mg, 96%) as a colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 5.82$ (m, 1H, H-4), 5.14 (m, 2H, H-5), 3.80 (m, 1H, H-2), 3.67 (dd, 1H, $J = 11.2$, 3.1 Hz, H-1a), 3.48 (dd, 1H, $J = 11.2$, 7.2 Hz, H-1b), 2.25 ppm (m, 2H, H-3); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 132.77$ (C-4), 119.84 (C-5), 71.75 (C-2), 66.54 (C-1), 37.81 ppm (C-3); MS (70 eV): 124.1 [M+Na]$^+$. The filtered solids were washed with acetone, and the filtrates were evaporated to give the ethyl ester of the anchor unit as a yellow solid (80 mg, 94%).

Synthesis of **12**: A sample of **1** (335 mg, 1 mmol) was processed as above to give adduct **3**, still anchored to the RP silica. The dried solid was taken up in MeOH (10 mL), and the mixture was treated with ozone. This was then followed by reductive workup and solvent removal as above. The resulting RP silica containing the anchored aldehyde was treated again with the aqueous allylation reagent to give the corresponding 1,3-diol adduct **10** (1:1 diastereomeric ratio verified by NMR spectroscopic analysis on a small aliquot); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 8.50$ (dd, 2H, $J = 8.0$, 1.7 Hz, H_{ar}), 7.65 (ddd, 2H, $J = 8.0$, 7.0, 1.7 Hz, H_{ar}), 7.41 (br d, 2H, $J = 8.7$ Hz, H_{ar}), 7.23 (ddd, 2H, $J = 8.0$, 7.0, 0.7 Hz, H_{ar}), 5.85–5.70 (m, 1H, H-6′), 5.15–5.05 (m, 2H, H-7′), 4.27 (t, 2H, $J = 7.5$ Hz, H-5), 4.16–4.04 (m, 4H, H-1′, H-2′, H-4′), 2.44 (t, 2H, $J = 6.9$ Hz, H-2), 2.27 (m, 2H, H-3′), 1.94–1.87 (m, 4H, H-3, H-4), 1.64–1.60 ppm (m, 2H, H-5′); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 178.03$ (C=O), 173.26 (C-1), 141.61 (C_{ar}), 134.62 (C-6′), 134.21 (C_{ar}), 127.91 (C_{ar}), 122.19 (C_{ar}), 121.46 (C_{ar}), 118.45 (C-7′), 114.62 (C_{ar}), 71.31, 70.41 (C-2′), 68.80, 68.62 (C-1′), 67.74, 67.07 (C-4′), 45.87 (C-5), 42.58, 42.13 (C-3′), 38.85, 38.57 (C-5′), 33.66 (C-2), 26.61 (C-4), 22.15 ppm (C-3); MS (70 eV) m/z (%): 423 (9) [M^+], 296 (100).

Ozonolysis of **10** under standard conditions resulted in the anchored 2,4-dideoxysugars (NMR spectroscopic analysis). For cleavage, the RP silica containing the adsorbed product was heated under reflux in HCl-saturated MeOH (30 mL) for 2 h. After complete conversion (according to TLC), the solvent was removed, and then water (15 mL) and further RP silica (500 mg) were added. After filtration, the remaining solids were washed with water (15 mL), and the solution was evaporated to yield the stereoisomeric mixture of **12** (116 mg, 79% overall) as a colorless syrup; ^{1}H NMR ($CDCl_3$,

500 MHz): $\delta = 4.81$ (d, 0.3H, $J = 3.2$ Hz), 4.74 (dd, 0.1H, $J = 9.5$, 2.2 Hz), 4.28 ppm (d, 0.3H); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 101.77$, 99.83, 99.52 ppm.

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