A New Method for the Deprotection of Benzyl Ethers or the Selective Protection of Alcohols

Jacob Madsen, Christel Viuf, and Mikael Bols*[a]

Abstract: A new selective method for the deprotection of benzyl ethers situated next to alcohols in the α, β, or γ position is presented which uses either NIS or DIB/I_2 as a reagent. After initial formation of a hypoiodite intermediate, the reaction is believed to follow a radical pathway to resemble the Hoffman – Löffler – Freytag reaction. The formation of the intermediate hypoiodite is suggested on the basis of NMR studies. Depending on the substrate, the corresponding benzylidene derivatives or diols are isolated.

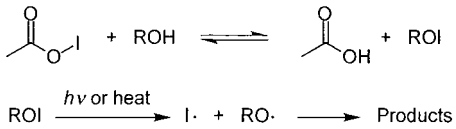
Keywords: benzylidene acetal · β-fragmentation · hypervalent compounds · radicals · selective deprotection

Introduction

In carbohydrate chemistry, and particularly in oligosaccharide synthesis, the manipulation of a protecting group is an important, although time-consuming task.[1] Therefore, reliable and efficient methods for the selective removal of a protecting group in the presence of other equivalent or identical groups are of interest.[2] In this paper we report that benzyl ethers next to unprotected alcohols are generally transformed into the corresponding benzylidene derivatives by means of *N*-iodosuccinimide (NIS) or a hypervalent iodine reagent.

Compounds that contain hypervalent iodine have previously been described as useful synthetic tools in organic chemistry.[3] The combination of diacetoxyiodobenzene (DIB) and iodine, which generates acetyl hypoiodite, has been used by Suárez et al. in reactions with alcohols[4] to give acetals or spiroketals, and with hemiacetals[5] to result in β fragmentations. Additionally, it has been suggested that alcohols react with hypoiodite intermediates[6] or NIS[7] to form alkyl hypoiodites. The O–I bond can then be homolytically cleaved by visible light or heat to form a highly reactive alkoxy radical (Scheme 1). However, to the best of our knowledge, the existence of the alkyl hypoiodite has only been proven by NMR spectroscopy in one case.[8]

It has been reported that *para*-methoxybenzyl ethers (PMB) have been used to protect neighboring hydroxy groups in the 1,2- or 1,3-position by means of benzylidene acetals.[9] In these reactions the PMB protecting group is oxidized by DDQ



Scheme 1. Acetyl hypoiodite and an alcohol in equilibrium with acetic acid and an alkyl hypoiodite. The O–I bond is homolytically cleaved by heat or light to give an alkoxy radical.

followed by a nucleophilic attack by the hydroxy group. Thus, the oxidation of PMB is the initial step. Similar chemistry to that reported in this paper is not known.

In this paper (for a preliminary report, see [10]) we report a new transformation that allows a monobenzylated diol to be converted into a benzylidene derivative in the presence of other alcohols or benzyl ethers.

Results and Discussion

It was previously found that when phenylthio 2-*O*-dimethyl-(1-*O*-methyl-2,4,6-tri-*O*-benzyl-α-D-glucopyranos-3-oxy)silyl-3,4,6-tri-*O*-acetyl-β-D-galactopyranoside (**1**) was treated with NIS in $MeNO_2$, a mixture of methyl 3-*O*-(3,4,6-tri-*O*-acetyl-α-D-galactopyranosyl)-2,4,6-tri-*O*-benzyl-α-D-glucopyranoside (**2**) and methyl 2,6-di-*O*-benzyl-3-*O*-(3,4,6-tri-*O*-acetyl-α-D-galactopyranosyl)-α-D-glucopyranoside (**3**) was formed.[10] This indicated that the reaction was intermolecular and that silicon did not participate. On the other hand, the regioselectivity of the debenzylation suggested an intramolecular reaction and, therefore, the only possibility seemed to be participation of the free OH group at C2 in the galactose unit.

The presence of an unprotected alcohol was found to be essential: when glucose derivative **4**[11] was treated with five equivalents NIS, no reaction was observed, even on addition of water or methanol (Scheme 2).

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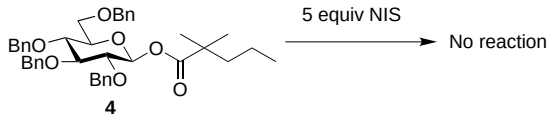
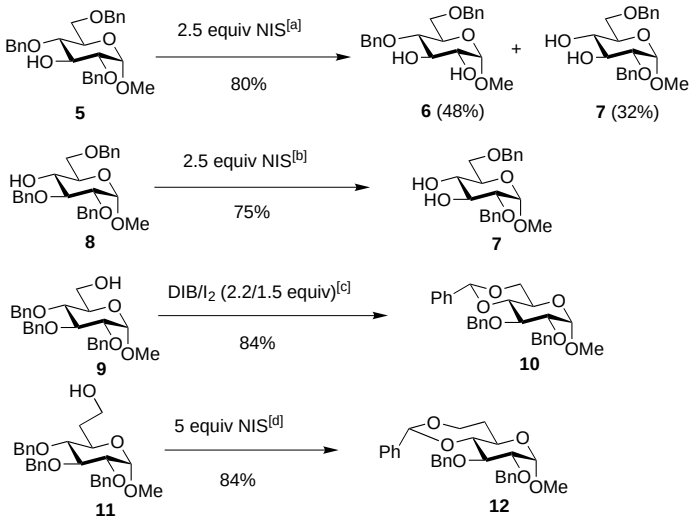


Scheme 2. Without an unprotected alcohol present in the molecule no reaction occurred. The reaction was carried out with and without MeOH or H_2O.

In contrast, when the readily available alcohol **5**[12] was treated with NIS (2.5 equiv), the quantitative conversion to less polar products was observed (by thin-layer chromatography) with simultaneous formation of iodine. These products could not be purified by chromatography on account of their instability; however, hydrolysis of the reaction mixture with TFA/H_2O (5:1) gave the two diols **6**[12] and **7**[13] in 48% and 32% yield, respectively (total yield 80%). Compound **6** and **7** were identified by conversion to the corresponding diacetates (Scheme 3).



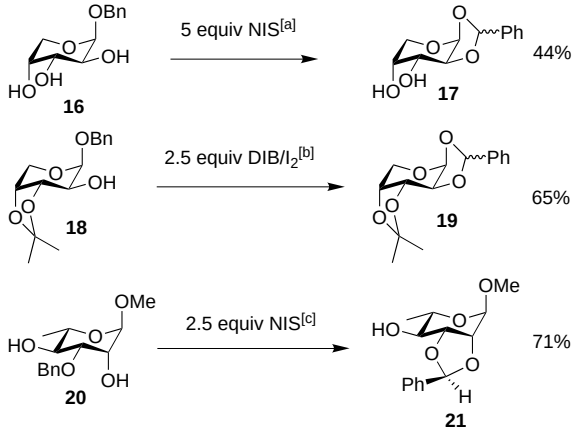
Scheme 3. Formation of five-membered rings versus six- and seven-membered rings. Reaction conditions: [a] The reaction was run at reflux in $MeNO_2$ for 2 h. The product mixture was treated with TFA/H_2O 5:1 before workup. [b] The reaction mixture was irradiated for 40 min in CH_3CN. Treatment with 2.5 equiv NIS without irradiation gave **7** in 47%. Treatment with 2.2 equiv DIB/I_2 without irradiation gave **7** in 58%. [c] The reaction mixture was irradiated for 20 min in CH_3CN. Treatment with 5 equiv NIS under reflux but without irradiation gave **10** in 74% yield. [d] The reaction was carried out under reflux in $MeNO_2$ for 4 h.

Similarly, less polar products were observed when **8**[14] was treated with NIS (2.5 equiv) in dry CH_3CN and subsequently irradiated with a 150 W lamp. However, the products hydrolyzed spontaneously to give diol **7** in 75% yield.

The less polar products which formed initially were assumed to be the 1,2-*trans*-benzylidene derivatives, which could be expected to be unstable. To confirm the formation of these benzylidene derivatives, compound **9**[15] was treated with DIB/I_2 and irradiated with a 150 W lamp and **11**[16] was treated with NIS (5 equiv) under reflux. This gave the anticipated compounds **10**[17] and **12**, respectively, both in 84% yield (Scheme 3).

Mannose derivative **13**[18] was treated with NIS (5 equiv) and refluxed for 4 h. TLC suggested almost quantitative conversion to a more unpolar product **14** (Scheme 4), but after workup and chromatography, compound **14** was isolated in only 38% yield. This indicated that the benzylidene acetal was rather unstable. On the other hand when a similar reaction mixture was treated with aqueous acid followed by acetylation, diacetate **15**[19] was isolated in 64% overall yield, which showed that the debenzylation produces fairly high yields.

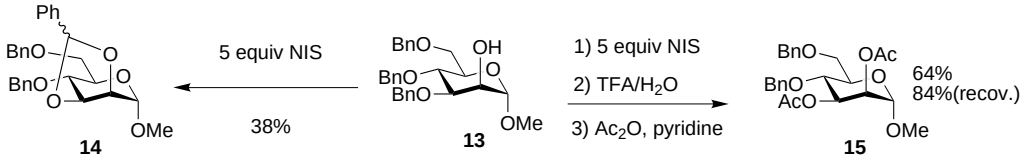
Carbohydrate derivatives with more than one unprotected hydroxyl group could also be used as substrates: treatment of arabinose derivative **16**[20] with 5 equiv NIS gave benzylidene derivative **17** in 44% yield (Scheme 5). The rather low yield



Scheme 5. Reactions with more than one unprotected hydroxy group in the substrate. [a] Reaction in refluxing $MeNO_2$ for 4 h. [b] The reaction mixture was irradiated for 20 min in CH_3CN. With 4 equiv NIS and irradiation, **19** was isolated in 47% yield, while with 5 equiv NIS and 5 h reflux, **19** was isolated in 41% yield. [c] The reaction mixture was irradiated in CH_2Cl_2 for 40 min. Without irradiation **21** was isolated in 65% yield.

can be explained by the insolubility of triol **16**, since treatment of arabinose derivative **18**[20] with DIB/I_2 (2.5 equiv) and irradiation with a 150 W lamp gave benzylidene derivative **19** in 65% yield.

Another derivative with two hydroxy groups, L-rhamnose derivative **20**,[21] was treated with NIS (2.5 equiv) in CH_2Cl_2 and irradiated with a 150 W lamp for 40 min to give only one



Scheme 4. Formation of an unstable benzylidene derivative with a D-mannose derivative. The NIS reactions were carried out in refluxing $MeNO_2$ for 3 h.

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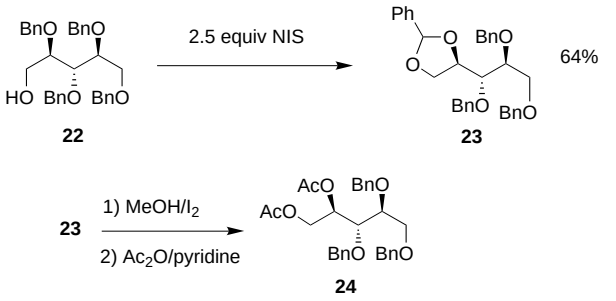
stereoisomer **21**[22] in 71% yield (Scheme 5). It should be noted that only the 2,3-*cis*-benzylidene derivative was observed and not the alternative possibility, the formation of a 3,4-*trans*-benzylidene derivative.

The reactions in Scheme 3 suggest that a 5-membered benzylidene derivative is formed in preference to a 6-membered benzylidene derivative. Furthermore, reaction **20** →**21** (Scheme 5) indicates that the formation of a 5-membered ring *cis* to the pyranoside is preferred over a 5-membered ring *trans* to the pyranoside.

In the above reactions (Schemes 3–5), we have demonstrated that the debenzylation reaction is successful with all non-anomeric hydroxy groups in different pyranosides. Interestingly, it has been shown by Suárez et al. that perbenzylated carbohydrate derivatives with an unprotected alcohol at the anomeric center reacts with DIB/I_2 to result in efficient β fragmentation, often in high yield.[5]

An acyclic carbohydrate derivative was also investigated: treatment of ribitol derivative **22**[23] with NIS (2.5 equiv) gave benzylidene derivative **23** in 64% (Scheme 6).



Scheme 6. Benzylidene formation with an acyclic ribitol derivative. The NIS reaction mixture was irradiated for 40 min in CH_3CN.

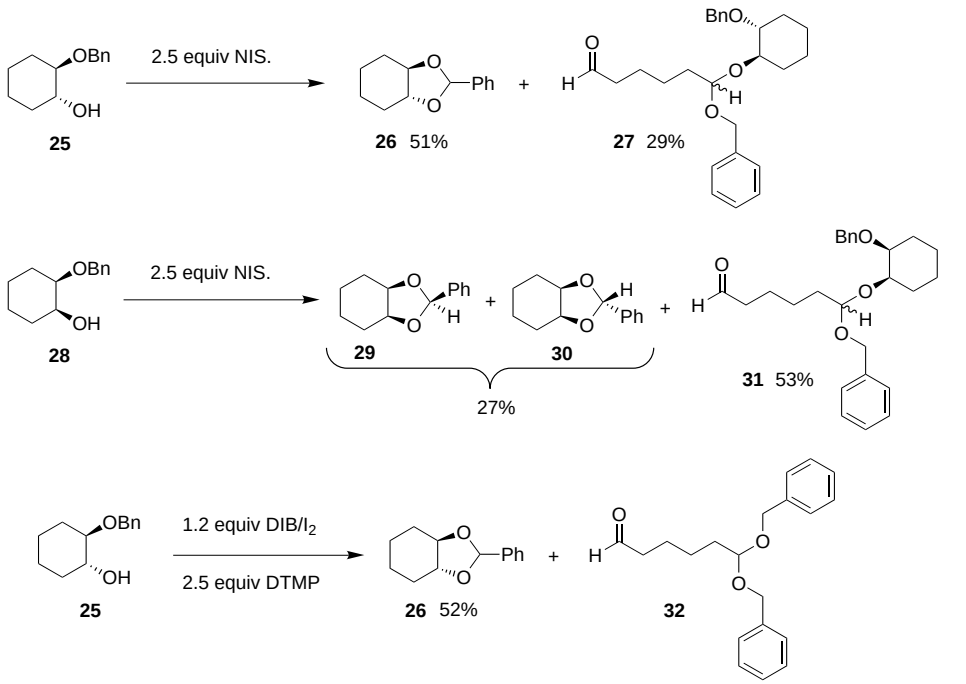
This is also an example of a five-membered benzylidene derivative being formed in preference to a six-membered derivative. The structure of **23** was confirmed by its conversion to the diacetate **24**. This was achieved by removal of the benzylidene with MeOH/I_2[24] to give the corresponding diol followed by acetylation with Ac_2O/pyridine.

Finally, we investigated compounds with a noncarbohydrate structure. Alcohol **25**[25] was treated with NIS (2.5 equiv) and irradiated for 30 min with a 150 W lamp to give the new benzylidene derivative **26** in 51% yield along with byproduct **27** in 29% yield (Scheme 7). An almost identical result was obtained without irradiation and at room temperature, although with a significantly increased reaction time. Similarly, when alcohol **28**[26] was treated with NIS (2.5 equiv) in dry CH_2Cl_2 the known benzylidene derivatives **29**[27] and **30**[27] were obtained in 27% yield along with "byproduct" **31** in 53% yield. The treatment of alcohol **25** with DIB/I_2 (2.2 equiv) and 2,6-di-*tert*-butyl-4-methyl pyridine (DTMP) gave benzylidene derivative **26** in 52% yield. However, in this case byproduct **27** was not found. Instead, a minor amount of the symmetric acetal **32** was identified (Scheme 7).

It should be noted that, unlike the *cis*-benzylidene compounds **29** and **30**, the high degree of symmetry of **26** only allows the formation of one stereoisomer at the benzylidene center. This exhibits different chemical shifts for all carbon and hydrogen atoms. Although atoms H1 and H2 of **26** have slightly different chemical shifts, they do have identical large coupling constants that are consistent with an axial position of the protons. The ^{1}H NMR spectra of **26** and its *cis* isomers are very similar except that the signals of H1 and H2 are at $\delta =$ 3.39–3.46 in **26**, while $\beta = 4.00–4.20$ in **29** and **30**. This also confirmed the axial positions of H1 and H2 in **26**.

Generally, the above reactions can be accomplished by three different methods: i) with NIS (5 equiv) at reflux temperature, ii) with NIS (2.5 equiv) and irradiation with a 150 W lamp for 20–40 min, and iii) with DIB/I_2 (2.2/2.2 equiv) and irradiation with a 150 W lamp for 20–40 min. In each case the optimized reaction conditions are described in full detail in the Experimental Section.

Evidence for hypoiodite as an intermediate in the reaction: There is little concrete evidence available in the literature for the formation of alkyl hypoiodite intermediates in the reaction between acetyl hypoiodite and alcohols.[8] Here we have investigated this possibility by means of ^{13}C NMR.



Scheme 7. Formation of noncarbohydrate benzylidene derivatives and unexpected byproducts. All reactions were irradiated for 30 min in CH_2Cl_2.

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Glucose derivative **9** was dissolved in a NMR tube with CD_3CN and a reference spectrum **A** was recorded (Figure 1). DIB/I_2 (2 equiv) was added to the NMR tube, covered with tin-foil, and spectrum **B** was recorded immediately. The tinfoil was removed and the NMR tube was irradiated under a standard lamp(60 W) for five minutes to give spectrum **C**.

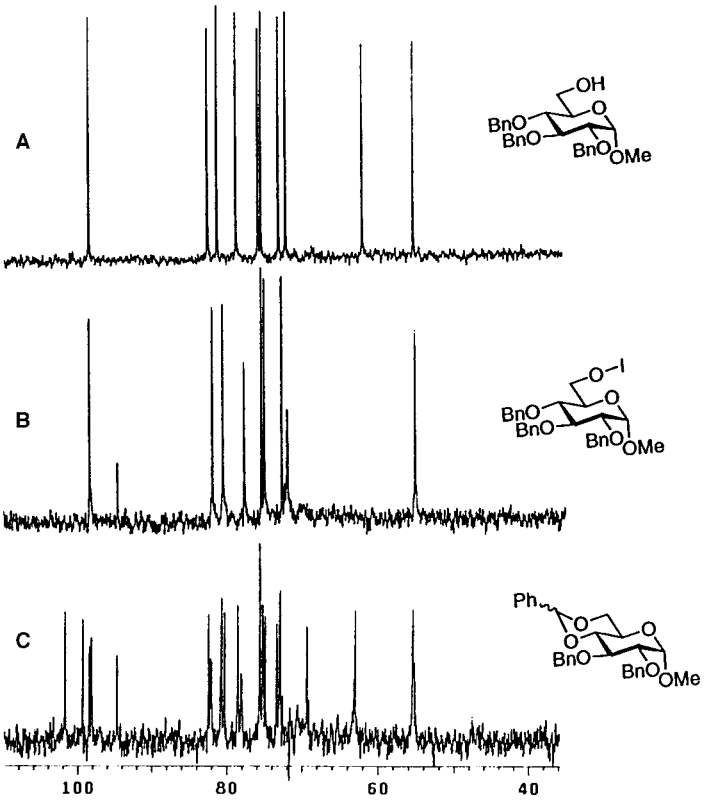


Figure 1. ^{13}C NMR spectroscopic evidence for the formation of an hypoiodite intermediate by. A) Reference spectrum of **9**. B) Compound **9** and 2 equiv DIB/I_2 in the dark. C) After 5 min of irradiation two diastereomers were formed. The peak at $\delta = 94$ is a signal from the reagent (iodobenzene).

Thus, after addition of two equivalents DIB/I_2 in the dark the peak corresponding to C6, the signal at $\delta = 62.5$, disappeared. This was interpreted as the formation of an hypoiodite. After irradiation the peak corresponding to C6 returned and three new signals in the area $\delta = 98.2 - 101.8$ appeared. The four peaks in this area correspond to the two acetals in each of the two possible stereoisomers in the products.

The same set of reaction conditions was also applied to NIS. However, in this case the peak corresponding to C6 did not disappear which indicated that the formation of hypoiodite is a slow process in this case.

Mechanistic considerations: The fact that the reaction rate significantly increased on irradiation strongly suggests that the reaction follows a radical pathway. We thus propose a mechanism which resembles that of the Hofmann–Löffler—Freytag reaction for conversion of *N*-haloamines into pyrrolidines.[28] Upon irradiation, the hypoiodite intermediate homolytically cleaves to an alkoxy radical. The newly formed alkoxy radical abstracts a hydrogen from the benzylic position to generate a stabilized benzylic radical that abstracts iodine from another hypoiodite in the solution to give an iodine derivative followed by an intramolecular substitution of iodide (Scheme 8).

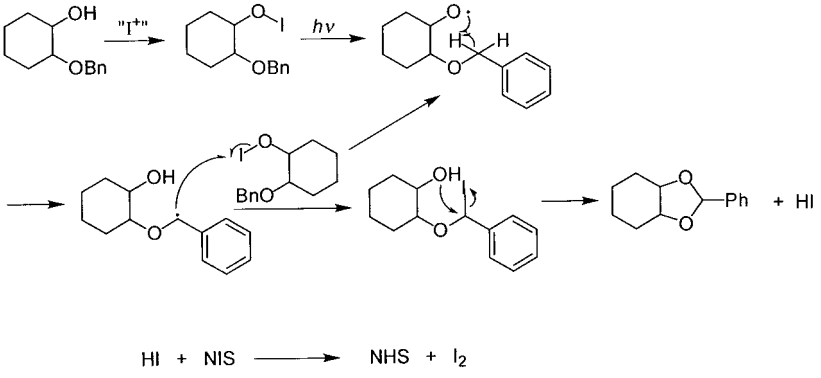
Hydrogen iodide formed in the reaction reacts with another equivalent of the reagent used. Therefore two equivalents of reagent are necessary in the reaction.

The formation of byproducts **27** and **31** is also assumed to follow a radical pathway. After generation of the alkoxy radical, β fragmentation occurs, and the bond between C1 and C2 is cleaved to give an aliphatic radical. Abstraction of iodine from another hypoiodite in the solution results in an iodine derivative followed by a intermolecular substitution of iodide by a unreacted hydroxy group from the starting material (Scheme 9).

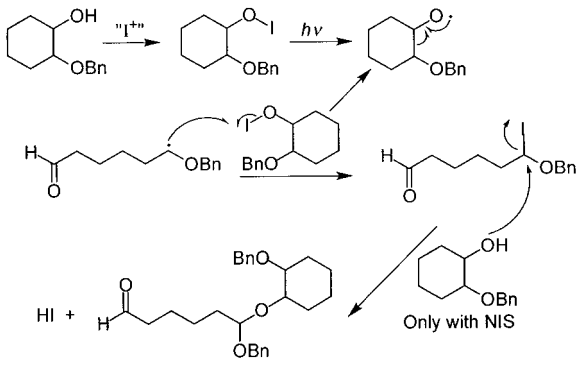
The observation that byproducts **27** and **31** only are formed when NIS is the reagent can be explained by the above NMR studies (Figure 1). When DIB/I_2 is used, all the substrate is transformed to the corresponding hypoiodite. There is, therefore, no unprotected alcohol that can react with the iodide formed. However, the generated aliphatic radical is still reactive and is assumed to be responsible for the formation of byproduct **32**.

Conclusions

In this paper we have presented a new method for the selective protection of alcohols next to benzyl ethers to form five-, six-, and seven-membered benzylidene derivatives or direct debenzylation of the benzyl ether. It is suggested that the reaction follows a radical pathway via a hypoiodite intermediate, which has been observed by ^{13}C NMR. Thus, this new reaction opens up a possibility for the selective



Scheme 8. Proposed mechanism for the formation of benzylidene derivatives.



Scheme 9. Proposed mechanism for the formation of byproducts via a β-fragmentation.

removal of one benzyl ether in a perbenzylated substrate. Furthermore, this reaction could be an explanation for the formation of sideproducts in NIS-promoted glycosidation reactions.

Experimental Section

General: All reactions were carried out under a nitrogen atmosphere in preheated glass equipment. Solvents were distilled under anhydrous conditions. Thus CH_3CN and CH_2Cl_2 was distilled from CaH_2. CH_3CN was stored in pre-dried glass equipment over 3 Å molecular sieves. All reagents were used as purchased without further purification. Columns were packed with silica gel 60 (230–400 mesh) as the stationary phase. ^{13}C NMR and ^1H NMR spectra were recorded on a Varian 200 MHz and 300 MHz Gemini instruments.

General procedure for acetylations: A sample of the compound was dissolved in pyridine (2 mL) at room temperature. Then acetic acid anhydride (1 mL) was added, and the solution was stirred for 4 h and then concentrated. The residue was taken up in toluene and reconcentrated to give the desired acetylated product in 90–100% yield.

Methyl 4,6-di-*O*-benzyl-α-D-glucopyranoside (6)[12] **and methyl 2,6-di-*O*-benzyl-α-D-glucopyranoside (7)**:[13] NIS (565 mg, 2.5 mmol, 2.5 equiv) was added to methyl 2,4,6-tri-*O*-benzyl-α-D-glucopyranoside (**5**, 464 mg, 1 mmol, 1 equiv) in $MeNO_2$ (10 mL). The mixture was refluxed for 2 h. All starting material was converted to more polar products, judged by TLC. The reaction was diluted with EtOAc (20 mL) and washed with a solution of 5% $Na_2S_2O_3$ (2×25 mL). The organic layer was dried ($MgSO_4$) and concentrated. The residue was hydrolyzed with TFA/H_2O 5:1 (1 mL). After evaporation the products were purified by column chromatography (18 cm high, 2.5 cm diameter) to give **6** (120 mg, 32%) and **7** (181 mg, 48%) as colorless oils.

Glucopyranoside ***6***: ^{13}C NMR($CDCl_3$, 50 MHz): $\delta=138.5-128.0$ (Ar), 99.3 (C1), 77.8, 75.0, 74.0, 72.6, 70.8, 68.9, 55.7 (OMe); ^1H NMR ($CDCl_3$, 200 MHz): $\delta=7.4-7.1$ (m, 10H), 4.6 (m, 5H), 3.9 (t, 1H), 3.7 (m, 4H), 3.55 (m, 1H), 3.35 (s, 3H).

Glucopyranoside ***7***: ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta=138.6$, 138.4, 129.0, 128.8, 128.7, 128.5, 128.1 (Ar), 98.3 (C1), 79.7, 74.0, 73.5, 73.48, 71.1, 70.6, 69.8, 55.7 (OMe); ^1H NMR ($CDCl_3$, 200 MHz): $\delta=7.4-7.2$ (m, 10H), 4.67 ($J_{AB}=11.5$ Hz, 2H), 4.62 ($J_{AB}=7.9$ Hz, 2H), 4.56 (d, $J=1.9$ Hz, 1H), 3.9 (m, 3H), 3.7 (3H, m), 3.4 (dd, $J=3.2$, 9.2 Hz, 1H), 3.3 (s, 3H).

Acetylation of 6: Glucopyranoside **6** was acetylated according to the general procedure. ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta=170.9$, 170.4 (Ac), 138.3, 128.9, 128.5, 128.3, 97.4 (C1), 76.5, 75.0, 74.1, 72.6, 71.9, 70.5, 68.6, 55.7 (OMe), 21.4, 21.3 (CH_3); ^1H NMR ($CDCl_3$, 200 MHz): $\delta=7.4-7.1$ (m, 10H), 5.5 (1H, H_3), 4.95 (dd, 1H), 4.85 (d, 1H), 4.6 ($J_{AB}=11.2$ Hz, 2H), 4.51 ($J_{AB}=7.5$ Hz, 2H), 3.75 (m, 4H), 3.35 (s, 3H).

Acetylation of 7: Glucopyranoside **7** was acetylated according to the general procedure. ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta=170.1$, 169.7, 137.6, 137.5, 128.4, 128.2, 127.9, 127.8, 127.6, 97.7 (C1), 76.6, 73.4, 73.1, 72.0, 69.0, 68.0, 67.8, 55.3 (OMe), 20.8, 20. 6; ^1H NMR ($CDCl_3$, 200 MHz): $\delta=7.4-7.2$ (m, 10H), 5.41 (t, $J=9.6$ Hz, 1H; H3), 5.05 (t, 9.6 Hz, 1H; H4), 4.67 (d, $J=4.1$ Hz, 1H; H1), 4.5 (m, 4H), 3.87 (m, 1H, H5), 3.57 (dd, $J=4.1$, 9.6 Hz, 1H; H2), 3.47 (m, 2H, H6a,6b), 3.38 (s, 3H, OMe), 1.99 (s, 3H, CH_3), 1.85 (s, 3H, CH_3).

Reaction of tribenzyl glucopyranoside 8 to methyl 2,6-di-*O*-benzyl-α-D-glucopyranoside (7): NIS (136 mg, 0.83 mmol, 2.5 equiv) was added to methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (**8**, 112 mg, 0.24 mmol, 1 equiv) in dry CH_3CN (5 mL). The mixture was irradiated for 4 h and allowed to cool to room temperature. The mixture was diluted with CH_2Cl_2 (50 mL) and washed sequentially with a solution of 5% $Na_2S_2O_3$ (20 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated. The residue was purified by column chromatography (18 cm high, 1 cm diameter) with EtOAc/pentane (1:2, 1:1) to give **7** (68 mg, 75%).

Methyl 4,6-*O*-benzylidene-2,3-di-*O*-benzyl-α-D-glucopyranoside (10):[17] DIB/I_2 (160 mg/85 mg, 0.51 mmol, 2.2 equiv) was added to methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**9**, 105 mg, 0.23 mmol) in dry CH_3CN (1.5 mL). The mixture was irradiated for 20 min with a 150 W lamp, CH_2Cl_2 (25 mL) was added, and the mixture was washed with a solution of 5% $Na_2S_2O_3$ (25 mL). The organic layer was dried ($MgSO_4$), filtered, and evaporated. The residue was purified by column chromatography (18 cm high, 1 cm diameter) with EtOAc/pentane (1:6) to give **10** (88 mg, 84%). ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta=139.2$, 138.7, 137.9, 129.4, 128.9, 128.8, 128.7, 128.6, 128.5, 128.1, 126.6, 101.8 (O-C-O), 99.8 (C1), 82.6, 79.7, 79.1, 75.9, 74.3, 69.6, 62.9, 55.9 (OMe); ^1H NMR ($CDCl_3$, 200 MHz): $\delta=7.6-7.25$ (m, 15H), 5.6 (s, 1H; CH-benzylidene), 4.9 ($J_{AB}=9$ Hz, 2H), 4.8 ($J_{AB}=11.4$ Hz, 2H), 4.6 (d, $J=3.8$ Hz, 1H,), 4.3 (dd, $J=3.8$, 5.7 Hz, 1H), 4.1 (m, 1H), 3.9–3.6 (m, 4H), 3.4 (s, 3H).

Methyl 4,7-*O*-benzylidene-2,3-di-*O*-benzyl-6-deoxy-α-D-*gluco*-heptopyranoside (12): NIS (265 mg, 1.17 mmol, 5 equiv) was added to methyl 2,3,4-tri-*O*-benzyl-6-deoxy-α-D-*gluco*-heptopyranoside (**11**, 112 mg, 0.23 mmol, 1 equiv) in $MeNO_2$ (2.5 mL). The mixture was refluxed for 4 h. EtOAc (25 mL) was added, and the mixture was washed with a solution of 5% $Na_2S_2O_3$ (2×25 mL). The combined aqueous layers were extracted with EtOAc (2×25 mL). The combined organic layers were dried ($MgSO_4$), filtered, and evaporated. The residue was purified by column chromatography (18 cm high, 1 cm diameter) with EtOAc/pentane (1:9) to give **12** (94 mg, 84%). ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta=139.0$, 138.7, 138.1, 128.3, 128.24, 128.2, 128.1, 128.0, 127.9, 127.8, 127.5, 127.2, 126.1, 100.1 (O-C-O), 98.1 (C1), 79.8, 79.75, 79.1,75.9, 73.4, 68.9, 57.5, 55.2, 34.7 (C7); ^1H NMR ($CDCl_3$, 200 MHz): $\delta=7.6-7.2$ (m, 15H), 5.95 (s, 1H),4.8 (m, 5H), 4.6 (d, 1H), 4.15 (m, 1H), 3.7 (m, 3H), 3.57 (dd, 1H), 3.4 (s, 3H), 1.9 (m, 2H).

Methyl 2,3-*O*-benzylidene-4,6-di-*O*-benzyl-α-D-mannopyranoside (14): NIS (252 mg, 1.1 mmol, 5 equiv) was added to methyl 2,4,6-tri-*O*-benzyl-α-D-mannopyranoside (**13**, 104 mg, 0.22 mmol, 1 equiv) in $MeNO_2$ (15 mL). The mixture was refluxed for 4 h. EtOAc (75 mL) was added and the mixture was washed with a solution of 5% $Na_2S_2O_3$ (2×50 mL). The residue was purified by column chromatography (18 cm high, 2 cm diameter) with EtOAc/pentane (1:8) to give **14** (39 mg, 38%) as a mixture of diastereomers in a 2:1 ratio. ^1H NMR ($CDCl_3$, 200 MHz): $\delta=7.5-7.1$ (m, 20H), 6.0 (s, 1H), 5.82 (s, 1H), 3.35 (s, 3H), 3.30 (s, 3H); MS: m/z: 462 [M^+].

Methyl 2,3-di-*O*-acetyl-4,6-di-*O*-benzyl-α-D-mannopyranoside (15):[18] NIS (303 mg, 1.1 mmol, 5 equiv) was added to methyl 2,4,6-tri-*O*-benzyl-α-D-mannopyranoside (**13**, 125 mg, 0.27 mmol, 1 equiv) in $MeNO_2$ (15 mL). The mixture was refluxed for 3 h. EtOAc (75 mL) was added and the mixture was washed with a solution of 5% $Na_2S_2O_3$ (2×50 mL). The organic layer was evaporated to dryness. The residue was treated with TFA/H_2O 1:1 at room temperature for 2 h, then evaporated. Pyridine (2 mL) and acetic acid anhydride (1 mL) were added to the residue and the mixture was stirred overnight at room temperature. The reaction mixture was concentrated, and the residue was taken up in toluene and reconcentrated. The residue was purified by column chromatography (18 cm high, 2 cm diameter) with EtOAc/pentane (1:6, 1:4) to afford **15** (80 mg, 64%) and the acetylated starting material (21 mg, 19%). ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta=170.0$, 169.7, 138.9, 128.3, 128.2, 127.9, 127.8, 127.6, 127.4, 98.4, 74.6, 73.4, 72.9, 71.7, 71.1, 70.0, 68.4, 54.9, 20.9, 20. 8; ^1H NMR ($CDCl_3$, 200 MHz): $\delta=7.4-7.05$ (m, 10H), 5.41 (dd, $J=3.44$, 9.5 Hz, 1H; H_3), 5.32 (dd, $J=1.72$, 3.44 Hz, 1H; H_2), 4.77 (d, $J=1.72$ Hz, 1H; H_1), 4.7 (m, 4H), 3.9 (m, 4H), 3.3 (s, 3H, OMe), 2.1 (s, 3H), 1.9 (s, 3H); MS (EI): m/z: 458 [M^+].

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1,2-*O*-Benzylidene-α-D-arabinopyranoside (17): NIS (565 mg, 2.5 mmol, 5 equiv) was added to benzyl α-D-arabinopyranoside (**16**, 120 mg, 0.5 mmol, 1 equiv) in dry CH_3CN (25 mL), and the mixture was refluxed for 5 h. The solution was diluted with EtOAc (25 mL) and washed with 5% $Na_2S_2O_3$ (7 × 10 mL). The organic layers were dried ($MgSO_4$), filtered, and concentrated. The residue was purified by column chromatography (18 cm high, 1 cm diameter) with EtOAc on silica gel to give **17** (105 mg, 44%). ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 137.5$, 129.0, 128.7, 128.5, 102.0 (O-C-O), 97.2 (C1), 93.0, 81.3, 69.6, 63. 5; ^1H NMR ($CDCl_3$, 200 MHz): $\delta = 7.5-7.3$ (m, 5H), 5.6 (s, 1H), 4.85 (d, 1H), 4.6 (m, 2H), 3.9 (d, 1H), 3.3 (dt, 1H).

1,2-*O*-Benzylidene-3,4-*O*-isopropylidene-α-D-arabinopyranoside (19): DIB/I_2 (403 mg/315 mg, 1.25 mmol, 2.5 equiv) was added to benzyl 3,4-*O*-isopropylidene-α-D-arabinopyranoside **18** (140 mg, 0.5 mmol, 1 equiv) in dry CH_3CN (5 mL). The mixture was irradiated for 20 min with a 150 W lamp. CH_2Cl_2 (40 mL) was added, and the mixture was washed with a cold solution of saturated $NaHCO_3$ (40 mL) and a 5% solution of $Na_2S_2O_3$ (20 mL). The organic layer was dried ($MgSO_4$), filtered, and evaporated. The residue was purified by column chromatography (18 cm high, 1 cm diameter) with EtOAc/pentane (1:12) to give **19** (90 mg, 65%) as a 3:5 mixture of diastereomers. ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 138.7$, 135.6, 129.5, 128.9, 128.4, 128.3, 126.1, 125.4, 109.1 (*i*-pro), 103.6, 102.0 (O-C-O), 96.1, 95.7 (C1), 72.2, 70.7, 70.1, 69.8, 69.4, 61.4, 60.2, 25.9 (CH_3), 24.1 (CH_3); ^1H NMR ($CDCl_3$, 200 MHz): $\delta = 7.6-7.3$ (m, 10H), 6.38 (s, 1H), 5.80 (s, 1H), 5.65 (d, $J = 1.73$ Hz, 2H; H1), 4.68 (dd, $J = 2.47$, 8.0 Hz, 1H), 4.66 (dd, $J = 2.47$, 8.0 Hz, 1H), 4.25 (m, 4H; H2, H4) 3.8 (m, 4H), 1.55 (2s, 6H), 1.35 (2s, 6H); HRMS (EI) calcd for $C_{15}H_{18}O_5$ [M^+]: 278.1154; found 278.1151.

Methyl *exo*-2,3-di-*O*-benzylidene-α-L-rhamnopyranoside (21):[21] NIS (281 mg, 1.25 mmol, 2.5 equiv)was added to methyl 3-*O*-benzyl-α-L-rhamnopyranoside (**16**, 134 mg, 0.5 mmol, 1 equiv) in dry CH_3CN (5 mL). The mixture was irradiated for 40 min with a 150 W lamp, diluted with CH_2Cl_2 (50 mL), and washed with a solution of 5% $Na_2S_2O_3$ (20 mL). The aqueous layer was extracted with EtOAc (2 × 25 mL). The combined organic layers were dried ($MgSO_4$), filtered, and evaporated. The residue was purified by column chromatography (18 cm high, 1 cm diameter) with EtOAc/pentane (1:10) to give **21** (93 mg, 71%). ^1H NMR ($CDCl_3$, 200 MHz): $\delta = 7.5-7.2$ (m, 5H), 6.05 (s, 1H), 4.8 (s, 1H, H1), 4.24 (dd, $J = 5.0$, 6.9 Hz, 1H; H3), 3.95 (dd, $J = 0.63$, 5 Hz, 1H; H_2), 3.55 (m, 1H), 3.38 (m, 1H), 3.2 (s, 3H), 1.2 (d, $J = 8.0$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 137.7$, 128.4, 128.2, 127.7, 102.2 (O-C-O), 97.4 (C1), 78.9, 74.6, 71.1, 64.6, 54.3, 16.7 (CH_3); MS (EI): 268 [M^+].

Acetylation of 21: Rhamnopyranoside **21** was acetylated according to the general procedure. ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 170.1$, 137.2, 129.2, 128.3, 126.1, 102.9 (O-C-O), 98.0 (C1), 77.1, 74.5, 70.4, 62.4, 55.0 (OMe), 19.9 (OAc), 16.0 (CH_3); ^1H NMR ($CDCl_3$, 200 MHz): $\delta = 7.5-7.1$ (m, 5H), 6.05 (s, 1H), 4.94 (dd, $J = 8.0$, 9.7 Hz, 1H; H4) 4.8 (s, 1H; H1), 4.4 (dd, $J = 5.3$, 8.0 Hz, 1H; H3), 4.08 (d, $J = 5.3$ Hz, 1H; H2), 3.7 (m, 1H; H5), 3.2 (s, 3H; OMe), 2.0 (s, 3H), 1.2 (d, $J = 8.0$ Hz, 3H).

3,4,5-Tri-*O*-benzyl-1,2-*O*-benzylidene-D-ribitol (23): NIS (135 mg, 0.6 mmol, 2.55 equiv) was added to 1,2,3,4-tetra-*O*-benzyl-D-ribitol (**22**, 120 mg, 0.23 mmol, 1 equiv) in dry CH_3CN (3 mL), and the mixture was irradiated with a 150 W lamp for 20 min. The solution was diluted with CH_2Cl_2 (40 mL) and washed with 5% $Na_2S_2O_3$ (2 × 25 mL). The organic layers were dried ($MgSO_4$), filtered, and concentrated. The residue was purified by column chromatography (18 cm high, 1 cm diameter) with EtOAc/pentane (1:10) to give **23** (77 mg, 64%) as a colorless oil. ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 138.3$, 138.2, 138.1, 137.4, 129.2, 128.3, 128.24, 128.22, 127.9, 127.8, 127.6, 127.5, 126.6, 103.8 (O-C-O), 79.1, 78.3, 76.3, 73.7, 73.3, 72.6, 69.7, 67.0; ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 7.4-7.1$ (m, 20H), 5.65 (s, 1H), 4.7–4.4 (m, 6H), 4.35 (q, 1H), 4.05 (m, 1H), 3.95–3.75 (m, 3H), 3.7–3.6 (m, 2H).

Acetylation of 23 to give 1,2-di-*O*-acetyl-3,4,5-tri-*O*-benzyl-D-ribitol (24): Ribitol **23** was acetylated according to the general procedure. ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 170.6$, 169.8, 138.0, 137.9, 137.6, 129.0, 128.2, 127.9, 127.6, 127.5, 77.8, 77.6, 73.4, 73.3, 72.3, 71.5, 69.0, 63.0, 20.9, 20.7.

***trans*-1,2-*O*-Benzylidene-cyclohexane (26)**

Method 1: NIS (565 mg, 2.5 mmol, 2.5 equiv) was added to *trans*-2-benzyloxycyclohexan-1-ol (**25**, 206 mg, 1 mmol, 1 equiv) in dry CH_2Cl_2 (5 mL), and the mixture was irradiated for 30 min with a 150 W lamp. The reaction mixture was diluted with CH_2Cl_2 (40 mL) and washed with a solution of 5% $Na_2S_2O_3$ (25 mL). The organic layer was dried ($MgSO_4$), filtered, and evaporated. The residue was purified by column chromatography (18 cm high, 1 cm diameter) with EtOAc/pentane (1:10) to afford **26** (105 mg, 51%) and byproduct **27** (59 mg, 29%) with a longer retention time.

Method 2: DTMP (512 mg, 2.5 mmol, 2.5 equiv) and DIB/I_2 (386 mg/302 mg, 1.2 mmol, 1.2 equiv) was added to trans-2-benzyloxycyclohexan-1-ol (**25**, 206 mg, 1 mmol, 1 equiv) in dry CH_2Cl_2 (5 mL), and the mixture was irradiated for 30 min with a 150 W lamp. The reaction mixture was diluted with CH_2Cl_2 (50 mL) and washed with a solution of 5% $Na_2S_2O_3$ (20 mL). The organic layer was dried ($MgSO_4$), filtered, and evaporated. The residue was purified by column chromatography (18 cm high, 2 cm diameter) with EtOAc/pentane (1:10) to afford **26** (106 mg, 52%) and some byproducts with longer retention times, among these **32**.

*Spectroscopic data for **26***: ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 139.3$ 128.7, 128.2, 126.1, 103.4 (C7), 82.3, 79.9 (C1, C2), 28.9, 28.5, 23.6, 23.5 (C3, C4, C5, C6); ^1H NMR ($CDCl_3$, 200 MHz): $\delta = 7.6-7.2$ (m, 5H), 6.05 (s, 1H; acetal), 3.46 (ddd, $J = 11.0$, 8.7, 3.7 Hz, 1H; H1), 3.39 (ddd, $J = 11.0$, 8.7, 3.7 Hz, 1H; H2), 2.2 (m, 2H), 1.85 (m, 2H), 1.6–1.2 (m, 4H); MS (EI): m/z: 204 [M^+], 203 [$M^+ - 1$].

*Spectroscopic data for byproduct **27***: ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta =$ 202.5, 139.1, 138.5, 138.0, 128.3, 128.2, 128.1, 127.6, 127.5, 127.4, 127.2, 103.8, 101.7, 100.7, 81.7, 79.8, 79.2, 77.2, 71.6, 71.1, 67.2, 66.6, 66.5, 43.7, 43.6, 34.3, 34.1, 31.7, 30.1, 29.8, 28.8, 24.2, 23.8, 23.4, 23.1, 21. 8; ^1H NMR ($CDCl_3$, 200 MHz): $\delta = 9.65$ (t, $J = 1.68$ Hz, 1H), 9.56 (t, $J = 1.68$ Hz, 1H), 7.3–7.1 (m, 20H), 4.76 (t, $J = 5.6$ Hz, 1H; H1), 4.65 (t, $J = 5.6$ Hz, 1H; H1), 4.52 (m, 8H), 3.48 (m, 2H), 3.26 (m, 2H), 2.32 (dt, $J = 1.68$, 7.03 Hz, 2H), 2.18 (dt, $J = 1.68$, 7.03 Hz, 2H), 2.0–1.0 (m, 28H) MS (EI): m/z: 319 [$M^+ -$ Bn]; FT-ICR MS: 433.250 [M+Na^+]; calcd 433.236.

*Spectroscopic data for **32***: ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 202.4$, 138.0, 128.3, 127.7, 127.5, 101.7, 67.2, 43.7, 33.0, 24.2, 21. 7; ^1H NMR ($CDCl_3$, 200 MHz): $\delta = 9.67$ (t, $J = 1.77$ Hz, 1H), 7.4–7.1 (m, 10H), 4.64 (t, $J =$ 5.38 Hz, 1H), 4.59 (d, $J = 10.78$ Hz, 2H), 4.47 (d, $J = 10.78$ Hz, 2H), 2.34 (dt, $J = 6.98$, 1.86 Hz, 2H), 1.8–1.05 (m, 6H).

***cis*-1,2-*O*-Benzylidene-(1*R*,2*S*)cyclohexane (29)**[27] **and *cis*-1,2-*O*-benzylidene-(1*S*,2*R*)cyclohexane (30):**[27] NIS (565 mg, 2.5 mmol, 2.5 equiv) was added to *cis*-2-benzyloxycyclohexan-1-ol (**28**, 206 mg, 1 mmol, 1 equiv) in dry CH_2Cl_2 (6 mL), and the mixture was irradiated for 55 min with a 150 W lamp. The reaction mixture was diluted with CH_2Cl_2 (50 mL) and washed with a solution of 5% $Na_2S_2O_3$ (20 mL). The organic layer was dried ($MgSO_4$), filtered, and evaporated. The residue was purified by column chromatography (18 cm high, 2 cm diameter) with EtOAc/pentane (1:10) to afford a 1:7 mixture of diastereomers **29** and **30** (55 mg, 27%) followed by "byproduct" **31** (109 mg, 53%). Diastereomers **29** and **30** were separated by additional chromatography (EtOAc/pentane 1:13).

*Spectroscopic data for **30** (minor isomer)*: ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta =$ 139.0, 128.6, 128.2, 125.9, 101.8 (C7), 74.3 (C1, C2), 27.1, 21.0; ^1H NMR ($CDCl_3$, 200 MHz): $\delta = 7.45-7.3$ (m, 5H), 6.18 (s, 1H), 4.22 (m, 2H), 1.95–1.2 (m, 8H).

*Spectroscopic data for **29** (major isomer)*: ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta =$ 138.3, 128.9, 128.2, 126.5, 103.2, 74.9, 28.2, 20. 6; ^1H NMR ($CDCl_3$, 200 MHz): $\delta = 7.6-7.3$ (m, 5H), 5.9 (s, 1H), 4.20 (m, 2H), 1.9–1.2 (m, 8H).

*Spectroscopic data for byproduct **31***: ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta =$ 202.6, 202.4, 139.1, 138.9, 138.6, 138.5, 128.3, 128.1, 128.08, 128.0, 127.6, 127.4, 127.3, 127.2, 127.1, 127.0, 126.8, 102.1, 100.4, 78.0, 74.4, 73.6, 70.4, 70.1, 70.0, 68.6, 65.9, 65.7, 43.7, 43.4, 33.7, 30.3, 29.6, 27.8, 27.5, 27.0, 26.4, 24.2, 22.3, 22.0, 21.8, 21.3, 21.1; ^1H NMR ($CDCl_3$, 200 MHz): $\delta = 9.73$ (t, $J = 1.67$ Hz, 1H), 9.67 (t, $J = 1.67$ Hz, 1H), 7.45–7.2 (m, 20H), 4.82 (t, $J = 5.4$ Hz, 1H), 4.76 (t, $J = 5.4$ Hz, 1H), 4.6 (m, 8H), 3.90 (m, 4H), 3.50 (m, 4H), 2.41 (dt, $J = 1.67$, 6.5 Hz, 2H), 2.32 (dt, $J = 1.67$, 6.5 Hz, 2H), 2.05–1.2 (m, 28H).

NMR experiment: Compound **9** (116 mg, 0.25 mmol) was dissolved in CH_3CN (0.6 mL) in a NMR tube, and spectrum **A** (Figure 1) was recorded as a reference. The NMR tube was covered with tin foil and DIB/I_2 (89 mg, 69 mg, 1.1 equiv) was added. Spectrum **B** was recorded immediately. The tin foil was removed and the NMR tube was irradiated with a 60 W lamp for 5 min and spectrum **C** was obtained.

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