Toward the Development of Radiolabeled Fluorophenyl Azide-Based Photolabeling Reagents: Synthesis and Photolysis of Iodinated 4-Azidoperfluorobenzoates and 4-Azido-3,5,6-trifluorobenzoates

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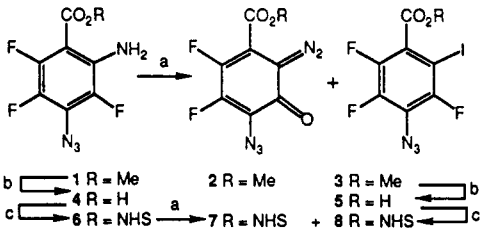
Two approaches for the incorporation of iodine into functionalized perfluorophenyl azides (PFPAs) were demonstrated by the synthesis of **3**, **5**, and **8**, with the azido and iodo groups in the same aryl ring, and **14** and **15**, with the azido and iodo groups in different aryl rings. These compounds opened the way for the incorporation of radioactive iodine into PFPAs and for their attachment to other molecules as photolabels. The syntheses of trifluorophenyl azides (TFPAs) **21–23** and iodide **20** provide two possible approaches for the incorporation of a tritium atom into fluorinated photolabels. Photolysis of azide **3** in cyclohexane gave 20% of CH insertion product and in Et_2NH/cyclohexane gave 24% of NH insertion product. The relatively low yield of CH and NH insertion from **3** compared with the corresponding noniodinated PFPA **24** was probably due to the heavy atom effect. Photolysis of azide **15** in Et_2NH/cyclohexane gave 41% of NH insertion product. Some photodeiodination was observed both with **3** and **15**. Our results demonstrate that the iodinated PFPAs studied are much better at undergoing CH and NH insertion than their nonfluorinated analogues, thus constituting an improved series of iodinated photolabeling reagents. Photolysis of TFPA **22** in cyclohexane gave 37% of CH insertion product and in Et_2NH/cyclohexane gave 63% of NH insertion product, results comparable to those of PFPA **24**. Thus, the desirable photochemical characteristics of the PFPAs are largely preserved in the TFPAs.

Introduction

Photoaffinity labeling (PAL) is a widely used technique for studying the proximity of components within biological systems.[1,2] PAL experiments frequently utilize an aryl azide as the photoreactive group.[3] Photolysis leads to a highly reactive nitrene intermediate which can establish a covalent bond to a nearby molecule by way of a CH or NH insertion reaction or by trapping of the ring-expanded dehydroazepine intermediate by a nucleophilic group.[4]

For many PAL applications the aryl azide moiety must also carry a radioactive atom to aid in the subsequent identification and isolation of the photolabeled target molecules.[5] Radioiodinated aryl azides are useful PAL reagents.[6] The low labeling levels sometimes observed[7] with these azides have been attributed to photodeiodination,[8] ring expansion of the nitrene intermediate to the much less reactive dehydroazepine intermediate,[9] and/or a heavy atom facilitated intersystem crossing to the triplet manifold.[10]

Scheme I[a]



[a] Key: (a) $NaNO_2/H_2SO_4/CH_3CO_2H$, then solid NaI; (b) $NaOH/H_2O$/MeOH, then HCl; (c) DCC/NHS.

We[11,12] and others[13–16] have been developing a series of functionalized perfluorophenyl azides (PFPAs) as a new class of PAL reagents with improved CH insertion efficiency over nonfluorinated analogues. It is important to work out methods for the incorporation of a radioactive iodine atom or tritium atom somewhere within the PFPA photolabel. Herein we report the synthesis and photochemical properties[17] of several new iodinated PFPAs. We also report the synthesis of the first members of a new series of trifluorinated photolabels, namely 4-azido-3,5,6-trifluorobenzoic acid and its methyl and *N*-hydroxysuccinimidyl esters. These trifluorophenyl azide (TFPA) photolabels bear a proton in the 2-position potentially exchangeable with tritium under basic conditions.

Results and Discussion

Synthesis of the Iodinated PFPA and TFPA Photolabels. Our first approach was to incorporate the iodine atom into the aromatic ring together with the azido group.

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(6) For examples, see: (a) Imai, N.; Kometani, T.; Crocker, P. J.; Bowdan, J. B.; Demir, A.; Dwyer, L. D.; Mann, D. M.; Vanaman, T. C.; Watt, D. S. *Bioconjugate Chem.* **1990**, *1*, 138. (b) Imai, N.; Dwyer, L. D.; Kometani, T.; Ji, T.; Vanaman, T. C.; Watt, D. S. *Bioconjugate Chem.* **1990**, *1*, 144.

(7) (a) Ho, L. T.; Nie, Z. M.; Mende, T. J.; Richarson, S.; Chavan, A.; Kolaczkowska, E.; Watt, D. S.; Haley, B. E.; Ho, R. J. *Second Messengers Phosphoproteins* **1989**, *12*, 209. (b) Chavan, A. J.; Kim, H.; Haley, B. E.; Watt, D. S. *Bioconjugate Chem.* **1990**, *1*, 337.

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(15) Pinney, K. G.; Katzenellenbogen, J. A. *J. Org. Chem.* **1991**, *56*, 3125.

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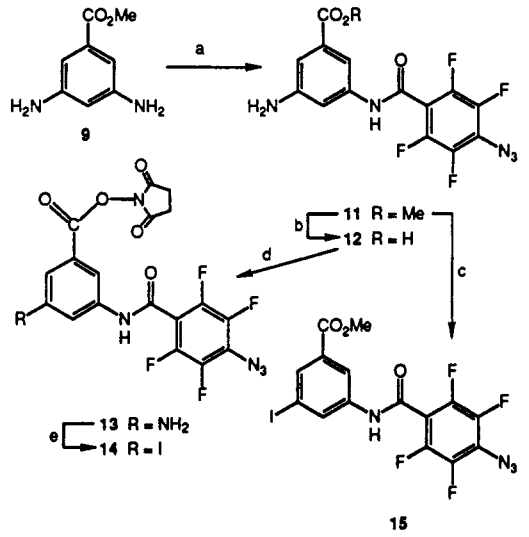
Scheme II[a]



[a] Key: (a) acid 10/DCC; (b) NaOH/MeOH/H_2O, then HCl; (c) $NaNO_2$/HCl, then NaI; (d) NHS/DCC; (e) $NaNO_2/H_2SO_4$/CH_3CO_2H, then KI.

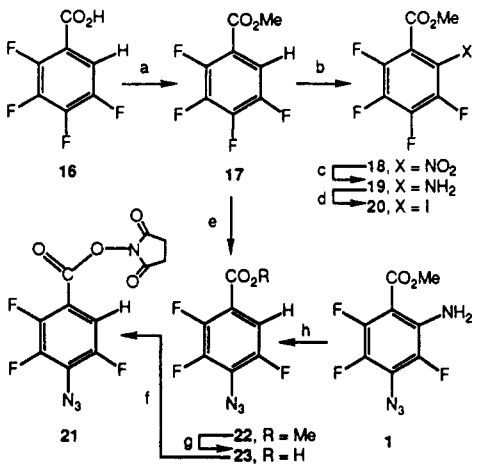
Diazotization of amino ester 1[12] under anhydrous conditions followed by treatment with NaI led to iodo ester 3 and a byproduct shown by MS, Ir and ^{19}F NMR spectra to be azido diazo oxide 2 (Scheme I).[17] The mass spectrum of 2 showed intense peaks corresponding to $M^+ - N_2$ and $M^+ - 2N_2$. The IR spectrum of 2 showed two strong absorptions at 2150 and 2121 cm^{-1} for the diazo and azido groups. The ortho diazo-keto structure of 2 was supported by the ^{19}F NMR spectrum which showed two fluorines with a coupling constant (19.20 Hz) characteristic for aromatic ortho fluorines.[18] Compound 2 appears to be the first azide-substituted benzoquinonediazide described and results from a well precedented[19,20] competitive reaction involving nucleophilic substitution of an ortho fluorine atom in the diazonium salt intermediate by a water molecule. The ^{19}F NMR spectrum of iodide 3 exhibited the expected deshielding of the fluorine atom next to the bulky iodine atom.[21]

The *N*-hydroxysuccinimide (NHS) active ester 8 was prepared from ester 3 via acid 5. Alternatively, ester 1 was hydrolyzed to acid 4[12] which was then converted into NHS ester 6. Anhydrous diazotization of 6 followed by treatment with NaI gave NHS ester 8. NHS ester 7 was an expected byproduct of this iodination reaction (cf. 2). The MS, IR, and ^{19}F NMR spectra of 7 were closely related with those of 2.

A second approach was designed to overcome some of the limitations of iodinated PFPAs (see photolysis of 3 below) through placement of the iodine atom on an aromatic ring other than that of the PFPA. One of the possible disadvantages of this strategy is that the photolabeling reagent is quite bulky and may therefore interfere with substrate recognition in PAL studies.

In the event, acylation of diamine 9[22] with 0.5 equiv of 4-azido-2,3,5,6-tetrafluorobenzoic acid (10)[12] in the presence of dicyclohexylcarbodiimide (DCC) gave monoamide 11 in 58% yield (Scheme II). Diazotization of 11 followed by treatment with sodium iodide produced the iodide 15 in 51% yield. In order to facilitate attachment of this series of photolabels to other molecules, ester 11 was hydrolyzed to give the free acid 12, which in turn was converted into the *N*-hydroxysuccinimide active ester 13. Anhydrous diazotization followed by treatment with KI gave iodo NHS ester 14. This last reaction sequence should allow synthesis of 14 bearing a radioactive iodine atom and has the advantage that the radioactivity can be introduced immediately prior to the coupling step.

Scheme III[a]



[a] Key: (a) $MeOH/CCl_4/H_2SO_4$; (b) HNO_3/H_2SO_4; (c) H_2/Pd; (d) $CH_3CO_2H/H_2SO_4/NaNO_2$, then NaI; (e) NaN_3/acetone/H_2O; (f) NHS/DCC; (g) NaOH/MeOH/H_2O, then HCl; (h) CF_3CO_2H/$NaNO_2$, then ether/KI.

We next describe a new series of *trifluorophenyl* azide (TFPA) photolabels in which the azide group is flanked on either side by a fluorine atom. This series was developed with an eye toward the eventual introduction of a tritium atom into the TFPA. Since an aryl C–H bond is essentially inert in the photochemical step, a tritium-labeled TFPA is expected to overcome the disadvantage of photodeiodination as well as heavy atom effects associated with iodinated PFPAs (see photolysis of 3 and 13 below). Streitwieser et al.[23] have reported the successful hydrogen isotope exchange of pentafluorobenzene with sodium methoxide in MeO[^{3}H]. Thus, the single hydrogen atom on the ring of a TFPA might be expected to undergo hydrogen isotope exchange under similar conditions. The TFPAs are expected to show desirable photochemical properties given that the presence of two fluorine atoms ortho to an azido group in a related series of aryl azides effectively enhances the ability of the corresponding nitrene to undergo CH insertion.[13,14]

Esterification of the commercially available tetrafluorobenzoic acid 16 gave ester 17[24] (Scheme III). Azide 22 was readily prepared via nucleophilic substitution of the para fluorine atom of ester 17 with azide ion. The ^1H NMR spectrum of azide 22 showed that the ring proton was coupled to three fluorines and the coupling constants were in agreement with the known values for ortho, meta, and para F–H coupling.[18] The structure of azide 22 also was confirmed by comparison with a sample of 22 obtained as an unexpected byproduct from an attempted diazotization and iodination of amine 1.[12] Azide 22 apparently was obtained via reduction of the diazonium group, possibly by an impurity[25] in the ether added after diazotiza-

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(21) Reference 18, p 347.
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(23) Streitwieser, A., Jr.; Hudson, J. A.; Mares, F. *J. Am. Chem. Soc.* **1968**, *90*, 648.
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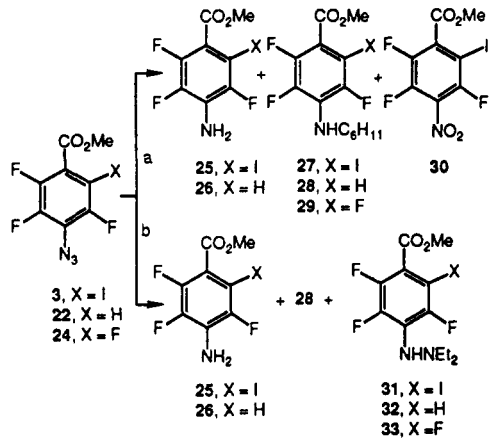
Scheme IV[a]



[a] Key: (a) $h\nu$ 350 nm, cyclohexane; (b) $h\nu$ 350 nm, Et_2NH/cyclohexane.

tion. Basic hydrolysis of **22** gave azido acid **23**. In order to facilitate the attachment of **23** and eventually the corresponding tritiated derivative to other molecules, NHS active ester **21** was prepared.

In order to provide an alternative means of introducing a tritium atom into this series of photolabels by way of a catalytic tritiation reaction, iodide **20** was synthesized. Due to the presence of the four fluorine atoms in the phenyl ring, the hydrogen in the ring of **17** was rather unreactive toward electrophilic substitution. However, we were able to accomplish the nitration of **17** with a mixture of fuming nitric acid and fuming sulfuric acid at 50 °C. Nitro derivative **18** was reduced to amine **19**[20] via catalytic hydrogenation. Anhydrous diazotization followed by treatment with excess NaI gave iodide **20** in 60% yield.

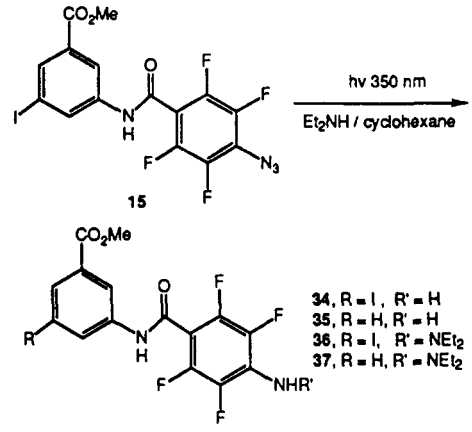
Photolysis of Iodinated PFPAs 3 and 15 and TFPA 22. Iodinated azide **3** was selected as a representative substrate for photolysis studies of ring-iodinated PFPAs. A solution of azide **3** in cyclohexane was photolyzed at 350 nm to give aniline **25** (18%), amine **27** (12%), deiodinated amine **28** (8%, also isolated from the photolysis of azide **22** in cyclohexane, see below), and nitrobenzene **30** (11%) (Scheme IV). The ^1H NMR spectrum of amine **28** showed that there was one proton in the aromatic region which was coupled to three fluorine atoms. The coupling constants were in agreement with the known values for F–H coupling of aromatic compounds.[18] The formation of **28** indicates that the fluorine substituents in the ring were only able to partially suppress photolytic homolysis of the C–I bond in **3**.

The isolation of nitrobenzene **30** was unexpected since no compound corresponding to **30** was isolated when noniodinated PFPA **24** was photolyzed under similar conditions.[12] Possibly the iodine atom is facilitating the formation of **30** through singlet to triplet nitrene conversion and reaction of the latter with dissolved oxygen. We note that photolysis of *p*-nitrophenyl azide in the presence of oxygen is known to give small amounts of the corresponding nitrobenzene.[26]

A photolysis of azide **3** was also carried out in diethylamine/cyclohexane. Aniline **25** (57%) and substituted hydrazine **31** (24%) derived from NH insertion were obtained but no ring expansion product was observed. The relatively low yield of CH and NH insertion products from azide **3** upon photolysis compared to the noniodinated PFPA **24** (57% of CH insertion product **29** when photolyzed in cyclohexane and 60% of NH insertion product **33** when photolyzed in diethylamine/cyclohexane)[12] was possibly due to the heavy atom effect[10] which promoted the formation of triplet derived products. Nevertheless, these observed yields of NH and CH insertion products from azide **3** demonstrate that iodinated PFPAs still partially retain the favorable photochemical properties of PFPAs and are much better at undergoing CH and NH insertion than their nonfluorinated analogues.[8]

Photolysis of trifluorinated azide **22** under conditions similar to those for azide **3** gave aniline **26** (19%) and CH insertion product **28** (37%) in cyclohexane. In diethylamine/cyclohexane, photolysis of **22** gave aniline **26** (20%), CH insertion product **28** (8%), and NH insertion product **32** (63%). The yields of CH and NH insertion products from **22** are comparable to those of tetrafluoro analogue **24**, indicating a promising prognosis for the tritiated analogue of azide **22**.

We also investigated whether placement of the iodine atom in an aromatic ring different from the PFPA ring system as embodied in PFPA **15** might lead to an improvement in photochemical performance over that of **3**. Due to the low solubility of **15** in cyclohexane, photolysis was carried out in diethylamine/cyclohexane under conditions similar to those used for photolysis of **3**. Four products, aniline **34** (22%), aniline **35** (20%), hydrazine **36** (21%), and hydrazine **37** (20%), were isolated. The deiodinated products **35** and **37** were characterized by ^1H NMR spectra which showed the presence of four aromatic protons with three of them in the 4, 5, and 6 positions as determined from the coupling patterns. The MS of **35** and **37** confirmed that the iodine had been replaced by a hydrogen. The structure of **35** was further established by an independent synthesis via coupling of 4-amino-2,3,5,6-tetrafluorobenzoic acid with methyl 3-aminobenzoate in the presence of DCC. The relatively high yield of NH insertion (**36** + **37**) from azide **15** compared to that of azide **3** showed that separation of the iodine atom and the PFPA in two different rings reduced the heavy atom effect thereby resulting in a more efficient photolabel. The formation of deiodinated products (**35** + **37**) showed that photodeiodination could not be prevented by separation of the iodine atom from the PFPA ring system.



In conclusion, iodinated and functionalized PFPA **3**, **5**, and **8** with azido and iodo groups in the same aryl ring and **14** and **15** with the two groups in different aryl rings have been developed such that incorporation of a radioactive iodine atom into these efficient photolabeling reagents is now possible. TFPAs **21**–**23** represent a new series of fluorinated arylazide photolabels designed to allow incorporation of a tritium atom in the ring while preserving

(25) Diazonium ions can be reduced by alcohols. See: Lewis, E. S.; Chambers, D. J. *J. Am. Chem. Soc.* **1971**, *93*, 3267.
(26) Liang, T.-Y.; Schuster, G. B. *J. Am. Chem. Soc.* **1987**, *109*, 7803.

the desirable photochemical characteristics of the PFPAs, as confirmed by photolysis studies with **22**. Photolysis results with **3** and **15** suggest that iodinated PFPAs are superior at undergoing CH and NH insertion compared to their nonfluorinated analogues. Some photodeiodination was observed with **3** and **15** as had been reported with nonfluorinated iodinated azides.

Experimental Section

^{1}H NMR spectra were measured at 300 MHz in $CDCl_3$ unless otherwise specified. ^{19}F NMR spectra were referenced to C_6F_6, −162.9 ppm, as internal standard. IR spectra were recorded in $CDCl_3$. The relative intensity is reported in the parentheses after the m/z value. All reactions involving azides were run under subdued light by wrapping the flasks with aluminum foil. Reagent-grade solvents were used without further purification unless otherwise specified. $MgSO_4$ was used as the drying agent for organic solutions. Photolysis were carried out in a Rayonet photochemical reactor with 350-nm lamps at ambient temperature. Solutions were purged with Ar for 1 min before photolysis.

Diazotization and Iodination of 1. Preparation of Methyl 4-Azido-2-diazo-5,6-difluoro-3-oxo-4,6-cyclohexadiene-1-carboxylate (2) and Methyl 4-Azido-2-iodo-3,5,6-trifluorobenzoate (3). A solution of 32.0 mg (0.130 mmol) of **1**[12] in acetic acid (0.5 mL) was added to a stirred solution of 26.0 mg (0.377 mmol) of $NaNO_2$ in concentrated H_2SO_4 (0.1 mL) at 0 °C, the solution was stirred for 10 min, then 60 mg (0.40 mmol) of NaI was added and followed by 0.5 mL of acetic acid, and the mixture was stirred for 30 min. The precipitate was filtered, washed with water, and dried to leave a yellow solid which was separated by preparative TLC (1:1:0.2 CH_2Cl_2–hexane–acetone) to give 10.8 mg (32%) of benzoquinonediazide **2** (R_f = 0.73–0.65) as a yellow solid, mp 127–128 °C, and 14.1 mg (30%) of iodide **3** (R_f = 0.82–0.77) as a colorless solid, mp 73–74 °C. Diazide **2**: ^{1}H NMR δ 3.978 (s); ^{19}F NMR δ −131.82, −134.31 (J = 19.20 Hz); IR 2150, 2121, 1712, 1591, 1470 cm^{-1}; MS 255 (12, M$^+$), 227 (7, M$^+$ − N_2), 199 (8, M$^+$ − 2N_2), 140 (26), 59 (100). Anal. Calcd for $C_8H_3F_2N_5O_3$: C, 37.66; H, 1.18; N, 27.45. Found: C, 37.73; H, 1.05; N, 27.32. Iodide **3**: ^{1}H NMR δ 3.989 (s); ^{19}F NMR δ −103.46 (F_3), −139.16 (F_6), −143.90 (F_5) ($J_{3,5}$ = 5.75 Hz, $J_{3,6}$ = 11.36 Hz, $J_{5,6}$ = 20.03 Hz); IR 2127, 1740, 1617, 1478, 1457 cm^{-1}; MS 357 (36, M$^+$), 329 (78), 314 (10), 298 (5), 286 (8), 270 (62), 202 (100), 187 (5), 174 (41), 159 (12), 143 (51), 124 (65). Anal. Calcd for $C_8H_3F_3IN_3O_2$: C, 26.91; H, 0.85; N, 11.77. Found: C, 26.99; H, 0.76; N, 11.93.

4-Azido-2-iodo-3,5,6-trifluorobenzoic Acid (5). To a solution of 31 mg of **3** in MeOH (3 mL) was added 20% aqueous NaOH (0.2 mL) and H_2O (1 mL). The solution was stirred at 25 °C for 2 h. It was acidified with 2 N HCl to pH < 1 and extracted with $CHCl_3$ (3 × 3 mL). The extract was dried and evaporated to leave 29 mg (97%) of **5** as a white crystalline solid, mp 104–105 °C. Recrystallization (CH_2Cl_2/hexane) raised the mp to 111–112 °C: IR 3000, 2137, 1753, 1717, 1615, 1478, 1455 cm^{-1}; MS 343 (99, M$^+$), 326 (5), 315 (82), 287 (3), 270 (27), 188 (100), 160 (14), 144 (25), 143 (19), 124 (35); HRMS calcd for $C_7HF_3IN_3O_2$ 342.9070, found 342.9070.

***N*-Succinimidyl 2-Amino-4-azido-3,5,6-trifluorobenzoate (6).** A mixture of 102 mg (0.439 mmol) of acid **4**,[12] 51.2 mg (0.445 mmol) of *N*-hydroxysuccinimide (NHS), and 91.7 mg (0.445 mmol) of dicyclohexylcarbodiimide (DCC) in 4 mL of dry THF was stirred overnight. It was filtered, and the filtrate was evaporated to leave 152.6 mg of white solid which was recrystallized (CH_2Cl_2/petroleum ether), giving 121 mg (84%) of **6** as colorless crystals, mp 184–185 °C: ^{1}H NMR δ 2.914 (s, 4), 5.75 (b, 2); IR 3694, 3609, 3519, 3398, 2934, 2129, 1745, 1651, 1599, 1493, 1482 cm^{-1}. Anal. Calcd for $C_{11}H_6F_3N_5O_4$: C, 40.13; H, 1.84; N, 21.27. Found: C, 39.93; H, 1.61; N, 21.25.

***N*-Succinimidyl 4-Azido-2-iodo-3,5,6-trifluorobenzoate (8).** NHS ester **8** was prepared from acid **5** in a manner similar to ester **6** and was isolated as a colorless solid (88%), mp 136–137 °C: ^{1}H NMR δ 2.928 (s); IR 2137, 1814, 1788, 1748, 1611, 1480, 1455 cm^{-1}; MS 440 (18, M$^+$), 326 (60), 314 (4), 298 (7), 270 (96), 171 (6), 143 (40), 124 (36), 56 (100); HRMS calcd for $C_{11}H_4F_3IN_4O_4$ 439.9224, found 439.9229.

Diazotization and Iodination of 6. Preparation of *N*-Succinimidyl 4-Azido-2-diazo-5,6-difluoro-3-oxo-4,6-cyclohexadiene-1-carboxylate (7) and 8. Diazotization and iodination of **6** was carried out in a same manner as that of **1** to produce a mixture of **7** and **8**. The mixture was separated by fractional crystallization ($CHCl_3$/petroleum ether) to give **7** (56%) as a yellow crystalline solid, mp 125–126 °C: ^{1}H NMR δ 2.925 (s); ^{19}F NMR δ −131.79, −125.03 (J = 19.05 Hz); IR 2960, 2144, 2110, 1751, 1599, 1524, 1470 cm^{-1}; MS 338 (6, M$^+$), 310 (4, M$^+$ − N_2), 282 (2, M$^+$ − 2N_2), 224 (7), 156 (4), 140 (96), 44 (100); HRMS (ZAB-HF) calcd for $C_{11}H_4F_2N_6O_5$ + H 339.0287, found 339.0290. Alternatively, the mixture was separated by preparative TLC (5:5:2 hexane–$CHCl_3$–acetone, **7**: R_f = 0.0–0.3, **8**: R_f = 0.5) to give **8** (20%). Pure **8** also can be obtained via simply passing the mixture through a short silica gel column with the same solvents. The ^{1}H NMR and IR spectra are identical with those for **8** obtained from acid **5**.

Methyl 3-(4-Azido-2,3,5,6-tetrafluorobenzamido)-5-aminobenzoate (11). A mixture of 148 mg (0.891 mmol) of diamine **9**,[22] 125 mg (0.607 mmol) of DCC, and 105 mg (0.447 mmol) of 4-azidotetrafluorobenzoic acid (**10**)[12] in $CHCl_3$ (10 mL) was stirred for 15 h. The mixture was filtered, and the solid was dried to leave a white solid (170 mg). The solid was stirred with $CHCl_3$ (30 mL) for 2 h and filtered, and the solid was dried to leave 100 mg (58%) of **11** as white powder, mp 177–178 °C: ^{1}H NMR ($CDCl_3$ + DMSO-d_6) δ 3.828 (s, 3), 7.080 (s, 1), 7.354 (s, 1), 7.590 (s, 1), 9.799 (s, 1); MS 383 (100, M$^+$), 355 (20), 296 (40), 162 (80); HRMS calcd for $C_{15}H_9F_4N_5O_3$ 383.0640, found 383.0643.

3-(4-Azido-2,3,5,6-tetrafluorobenzamido)-5-aminobenzoic Acid (12). Ester **11** was hydrolyzed in a manner similar to ester **3** to give acid **12** (97%) as a white solid, mp 160 °C (dec): ^{1}H NMR ($CDCl_3$ + DMSO-d_6) δ 6.859 (s, 1), 7.141 (d, J = 1.2 Hz, 1); 7.293 (d, J = 1.2 hz, 1), 10.114 (s, 1). Anal. Calcd for $C_{14}H_7F_4N_5O_3$: C, 45.54; H, 1.91; N, 18.96. Found: C, 45.69; H, 1.76; N, 18.83.

Methyl 3-(4-Azido-2,3,5,6-tetrafluorobenzamido)-5-iodobenzoate (15). To a stirred solution of 27.3 mg (0.0713 mmol) of **11** in acetone (1 mL) and 6 N HCl (0.4 mL) at 0 °C was added 25.2 mg (0.365 mmol) of $NaNO_2$. The resulting yellow solution was stirred at 5 °C for 1 h, and then a solution of 19.6 mg (0.130 mmol) of NaI in water (0.4 mL) was added. The yellow solution was stirred at 5 °C for 30 min, and then it was diluted with $CHCl_3$ (2 mL) and washed with water (3 × 2 mL). The organic phase was dried and evaporated to leave a pale yellow oily solid. It was dissolved in CH_2Cl_2 (0.5 mL), and the solution was added dropwise into hexane (4 mL) producing a precipitate. The precipitate was centrifuged, and the solid was precipitated one more time to give 18 mg (51%) of **15** as an almost colorless solid, mp 140–141 °C: ^{1}H NMR δ 3.929 (s, 3), 7.741 (b, 1), 8.055 (s, 1), 8.203 (s, 1), 8.400 (s, 1); IR 3000, 2130, 1730, 1719, 1700, 1650, 1538, 1524, 1489 cm^{-1}; MS 494 (100, M$^+$), 466 (2), 463 (7), 339 (7), 218 (15), 162 (40); HRMS calcd for $C_{15}H_7F_4IN_4O_3$ 492.9493, found 493.9480.

***N*-Succinimidyl 3-(4-Azido-2,3,5,6-tetrafluorobenzamido)-5-aminobenzoate (13).** NHS ester **13** was prepared from acid **12** in a manner similar to ester **6** and was isolated as a colorless solid (87%) after crystallization (THF/petroleum ether), mp 115–116 °C: ^{1}H NMR δ 2.902 (s, 4), 4.000 (b, 2), 7.208 (s, 1), 7.340 (s, 1), 7.677 (s, 1), 7.716 (s, 1); IR 3747, 3694, 2127, 1775, 1742, 1699, 1649, 1542, 1488, 1251 cm^{-1}; HRMS (FAB) calcd for $C_{18}H_{10}F_4N_6O_5$ + H 467.0719, found 467.0731.

***N*-Succinimidyl 3-(4-Azido-2,3,5,6-tetrafluorobenzamido)-5-iodobenzoate (14).** A solution of 13 mg (0.028 mmol) in **13** in acetic acid (0.6 mL) was added to a stirred solution of 23 mg (0.33 mmol) of $NaNO_2$ in concentrated H_2SO_4 (0.2 mL) at 5 °C and the resulting yellow mixture was stirred at 5 °C for 20 min, and then 60 mg (0.36 mmol) of KI was added and the mixture was stirred for 40 min. The mixture was diluted with water (3 mL) and extracted with $CHCl_3$ (2 × 3 mL). The extract was dried and evaporated to leave a brown solid which was dissolved in THF (0.4 mL), and the solution was added dropwise into petroleum ether (8 mL) producing a precipitate. The precipitate was centrifuged, and the solid was precipitated one more time to give 6.7 mg (41%) of colorless solid, mp 105–106 °C: ^{1}H NMR δ 2.923 (s, 4), 7.780 (s, 1), 8.170 (sb, 1), 8.276 (s, 1), 8.515 (s, 1); IR 2128, 1780, 1740, 1700, 1529, 1489, 1247, 1205 cm^{-1}; HRMS (FAB) calcd for $C_{18}H_8F_4IN_5O_5$ + H 577.9577, found 577.9560.

Methyl 3,4,5,6-tetrafluorobenzoate (17).[24] To a solution of 0.96 g of 2,3,4,5-tetrafluorobenzoic acid (**16**) in MeOH (1 mL) and

CCl_4 (10 mL) was added concentrated H_2SO_4 (0.3 mL). The mixture was refluxed for 5 h. The cooled mixture was washed with 5% Na_2CO_3 (1 × 10 mL) and water (2 × 10 mL) and then dried and evaporated to leave 1.03 g (100%) of **17** as a colorless liquid: ^1H NMR δ 3.958 (s, 3), 7.614 (m, 1).

Methyl 4-Azido-3,5,6-trifluorobenzoate (22). (a) A mixture of 1.457 g (7.00 mmol) of **17** and 0.679 g (10.4 mmol) of NaN_3 in acetone (12 mL) and water (5 mL) was refluxed for 25 h. The mixture was cooled and diluted with water (30 mL), and the precipitate was filtered, washed with water, and dried to leave 1.352 g (84%) of colorless powder: ^1H NMR δ 3.944 (s, 3), 7.513 (ddd, J = 11.0, 5.6, 2.3 Hz, 1); ^{19}F NMR δ −128.02 (F_3), −137.03 (F_6), −144.36 (F_5); IR 2956, 2136, 1725, 1633, 1500, 1477, 1438, 1366, 1249 cm^{-1}. Sublimation (42 °C (0.05 mm)) gave the analytical sample of **22** as a colorless solid, mp 55–56 °C. Anal. Calcd for $C_8H_4F_3N_3O_2$: C, 41.57, H, 1.74, N, 18.18. Found: C, 41.52, H, 1.51, N, 18.06.

(b) To a stirred solution of 22 mg (0.091 mmol) of **1**[12] in CF_3CO_2H (0.5 mL) at 0 °C was added in one portion 23 mg (0.33 mmol) of $NaNO_2$. The resulting yellow solution was stirred at 0 °C for 1 h and then was diluted by ether (5 mL) and centrifuged. The clear yellow supernatant was treated with 40 mg (0.24 mmol) of KI and stirred for 1 h at 0 °C. The solution was washed with water (2 × 5 mL), dried, and evaporated to leave a mixture of liquid and solid. It was separated by preparative TLC (1:1 $CHCl_3$–hexane) to give 13.7 mg (59%) of **22** as a crystalline colorless solid, mp 52–53 °C. The ^1H NMR and IR spectra are identical with those for **22** obtained by method a: MS 231 (M^+, 20), 203 (75), 188 (65), 172 (15), 160 (20), 144 (34), 143 (100); HRMS calcd for $C_8H_4F_3N_3O_2$ 231.0255, found 231.0261.

4-Azido-3,5,6-trifluorobenzoic Acid (23). Ester **22** was hydrolyzed in a manner similar to ester **3** to give acid **23** (67%) as a white powder: ^1H NMR δ 7.564 (ddd, J = 10.9, 5.7, 2.3 Hz); ^{19}F NMR δ −127.49 (F_3), −135.51 (F_6), −143.94 (F_5); IR 2139, 1708, 1480, 1281 cm^{-1}. The analytical sample of **23** was obtained by crystallization ($CHCl_3$–pentane) as a colorless solid, mp 140–142 °C. Anal. Calcd for $C_7H_2F_3N_3O_2$: C, 38.73; H, 0.93; N, 19.37. Found: C, 38.76; H, 0.77; N, 19.40.

***N*-Succinimidyl 4-Azido-3,5,6-trifluorobenzoate (21).** NHS ester **21** was prepared from acid **23** in a manner similar to ester **6** and was isolated as a colorless solid (87%), mp 143–144 °C: ^1H NMR δ 2.918 (s, 4), 7.628 (ddd, J = 10.6, 5.3, 2.2 Hz, 1); IR 2136, 1746, 1489, 1478, 1392, 1389 cm^{-1}; MS 314 (3, M^+), 300 (1), 286 (1), 258 (1), 200 (85), 172 (20), 144 (100); HRMS calcd for $C_{11}H_5F_3O_4N_4$ 314.0263, found 314.0283.

Methyl 2-Amino-3,4,5,6-tetrafluorobenzoate (19).[20] A solution of 318 mg of **17** in fuming H_2SO_4 (1 mL) and fuming HNO_3 (1 mL) was stirred in an ice bath for 5 min and then heated at 50 °C for 2.5 h. The solution was diluted with ice (20 mL) and extracted with $CHCl_3$ (2 × 5 mL). The extract was washed with H_2O (2 × 10 mL), dried, and evaporated to leave 228 mg (59%) of nitro **18** as an almost colorless liquid: ^1H NMR δ 3.970 (s). A mixture of 228 mg of **18** and 28 mg of 30% Pd/C in methanol (25 mL) was hydrogenated at 60 psi for 2 h. It was filtered, and the filtrate was evaporated to leave 186 mg (93%) of **19** as a pale yellow solid, mp 100–101 °C (lit.[20] mp 104–105 °C): ^1H NMR 3.929 (s, 3), 5.8 (mb, 2).

Methyl 2-Iodo-3,4,5,6-tetrafluorobenzoate (20). To a stirred mixture of concentrated H_2SO_4 (1 mL) and 200 mg (2.89 mmol) of $NaNO_2$ at 0 °C was added CH_3CO_2H (3 mL) and $(CH_3CO)_2O$ (0.3 mL), the solution was stirred for 20 min, and then 210 mg (0.941 mmol) of amine **19** was added, and the resulting yellow solution was stirred at 0 °C for 1 h. It was diluted with $(CH_3CO)_2O$ (2 mL) and stirred for 5 min, and then 400 mg (2.66 mmol) of NaI and $(CH_3CO)_2O$ (2 mL) was added, and the mixture was stirred for 30 min. To the mixture was added 400 mg of NaI, and it was stirred for 2 h and diluted with water (10 mL) and ether (30 mL). The mixture was washed with 5% aqueous NaS_2O_3 (2 × 10 mL) and water (2 × 10 mL), dried, and evaporated to leave a mixture of liquid and solid. It was separated by preparative TLC (2:1 hexane–ether) to give 190 mg (60%) of **20** (R_f = 0.70) as a crystalline white solid which was sublimed (30 °C (0.01 mm)) to give a white solid, mp 61–62 °C: ^1H NMR δ 4.001 (s); ^{19}F NMR δ −113.18 (F_3), −137.29 (F_6), −150.12 (F_4 or F_5), −152.83 (F_5 or F_4); IR 2957, 1744, 1624, 1611, 1506, 1467, 1437, 1370, 1288, 1236, 1049 cm^{-1}; MS 334 (M^+, 70), 303 (100), 275 (20), 192 (22), 176 (12), 148 (55). Anal. Calcd for $C_8H_3IF_4O_2$: C, 28.77; H, 0.91. Found: C, 29.01, H, 0.75.

Photolysis of Iodo PFPA 3 in Cyclohexane. A 2.0 × 10^{-3} M solution of iodo PFPA **3** in cyclohexane was photolyzed for 2 h. The crude reaction mixture after evaporation of the solvent was separated by preparative TLC (7:6 $CHCl_3$–hexane) to give aniline **25** (18%), amine **27** (12%), amine **28** (8%), and nitrobenzene **30** (11%). Aniline **25**: ^1H NMR δ 3.948 (s, 3), 4.168 (s, 2); ^{19}F NMR δ −113.65 (F_3), −140.70 (F_6), −155.54 (F_5) ($J_{3,5}$ = 12.67 Hz, $J_{3,6}$ = 9.99 Hz, $J_{5,6}$ = 20.38 Hz); IR 3509, 3413, 1732, 1637, 1507, 1464 cm^{-1}; MS 331 (100, M^+), 300 (95), 288 (4), 272 (8), 145 (46); HRMS calcd for $C_8H_5H_3INO_2$ 330.9316, found 330.9322. Amine **27**: ^1H NMR δ 1.0–1.4 (m, 5), 1.6 (m, 1), 1.78 (m, 2), 2.0 (m, 2), 3.60 (b, 1), 3.82 (b, 1), 3.938 (s, 3); ^{19}F NMR δ −110.35 (F_3), −140.16 (F_6), −154.04 (F_5) ($J_{3,5}$ = 13.12 Hz, $J_{3,6}$ = 8.95 Hz, $J_{5,6}$ = 19.64 Hz); MS 413 (92, M^+), 382 (9), 370 (100); HRMS calcd for $C_{14}H_{15}F_3INO_2$ 413.0095, found 413.0100. Amine **28**: ^1H NMR δ 1.18 (m, 3), 1.35 (m, 2), 1.64 (m, 1), 1.75 (m, 2), 2.03 (m, 2), 3.65 (m, 1), 3.882 (s, 3), 3.96 (m, 1), 7.370 (ddd, J = 12.6, 6.1, 2.0 Hz, 1). ^{19}F NMR δ −136.67 (F_3), −139.58 (F_6), −156.06 (F_5) ($J_{3,5}$ = 10.81, $J_{3,6}$ = 11.98, $J_{5,6}$ = 18.67); MS 287 (50, M^+), 256 (10), 244 (100); HRMS calcd for $C_{14}H_{16}F_3NO_2$ 287.1129, found 287.1130. Nitrobenzene **30**: ^1H NMR δ 4.045 (s); ^{19}F NMR δ −99.48 (F_3), −136.43 (F_6), −139.88 (F_5) ($J_{3,5}$ = 2.13 Hz, $J_{3,6}$ = 13.40 Hz, $J_{5,6}$ = 21.40 Hz); IR 1748, 1619, 1555, 1469, 1434 cm^{-1}; MS 361 (100, M^+), 330 (60), 315 (8), 300 (10), 284 (18), 272 (8), 256 (10), 188 (6), 173 (6), 157 (46), 145 (10), 129 (48); HRMS calcd for $C_8H_3F_3INO_4$ 360.9056, found 360.9080.

Photolysis of Iodo PFPA 3 in Diethylamine/Cyclohexane. A 2.0 × 10^{-3} M solution of iodo azide **3** in cyclohexane containing 5.0 × 10^{-2} M diethylamine was photolyzed for 1 h. The residue after evaporation of the solvents was separated by preparative TLC (5:5:1 hexane–$CHCl_3$–acetone) to give aniline **25** (57%) and substituted hydrazine **31** (24%). Hydrazine **31**: ^1H NMR δ 1.099 (t, J = 7.90 Hz, 6), 2.742 (q, J = 7.90 Hz, 4), 3.951 (s, 3), 4.437 (s, 1); ^{19}F NMR δ −108.86 (F_3), −140.00 (F_6), −149.14 (F_5) ($J_{3,5}$ = 10.26 Hz, $J_{3,6}$ = 9.37 Hz, $J_{5,6}$ = 19.88 Hz); IR 3324, 2980, 2819, 1731, 1619, 1479, 1467 cm^{-1}; MS 402 (100, M^+), 387 (55), 371 (15), 359 (16), 330 (42), 302 (46), 216 (8); HRMS calcd for $C_{12}H_{14}F_3IN_2O_2$ 402.0049, found 402.0052.

Photolysis of Azide 22 in Cyclohexane. A 3.0 × 10^{-3} M solution of azide **22** in cyclohexane was photolyzed for 1 h. The crude photolysis mixture was separated by preparative TLC (1:1 CH_2Cl_2–hexane) to give aniline **26** (19%, R_f = 0.10) and amine **28** (37%, R_f = 0.22). Aniline **26**: ^1H NMR δ 3.896 (s, 3), 4.268 (s, 2), 7.429 (ddd, J = 11.1, 5.8, 2.1 Hz, 1); ^{19}F NMR δ −138.53 (F_3), −139.40 (F_6), −156.74 (F_5); MS 205 (M^+, 66), 174 (100), 146 (22); HRMS calcd for $C_8H_6F_3NO_2$ 205.0350, found 205.0356. Amine **28**: colorless solid, mp 60–61 °C. The ^1H NMR, ^{19}F NMR and MS spectra are identical with those for **28** obtained from photolysis of **3** in cyclohexane.

Photolysis of Azide 22 in Cyclohexane in the Presence of Diethylamine as Trapping Reagent. A 4.0 × 10^{-3} M solution of azide **22** in cyclohexane containing 5.0 × 10^{-2} M of diethylamine was photolyzed for 2 h. The crude photolysis mixture was separated by preparative TLC (1:1.5 ether–hexane) to give aniline **26** (20%, R_f = 0.41), amine **28** (8%, R_f = 0.68), and hydrazine **32** (63%, R_f = 0.57). Hydrazine **32**, colorless solid, mp 70–71 °C: ^1H NMR δ 1.103 (t, J = 7.1 Hz, 6), 2.748 (q, J = 7.1 Hz, 4), 3.890 (s, 3), 4.540 (s, 1), 7.376 (ddd, J = 12.1, 5.9, 2.0, 1); ^{19}F NMR δ −133.84 (F_3), −138.58 (F_6), −150.94 (F_5); MS 276 (M^+, 100), 261 (70), 245 (20), 233 (32), 204 (60), 145 (10); HRMS calcd for $C_{12}H_{15}F_3N_2O_2$ 276.1085, found 276.1075.

Photolysis of Iodo Azide 15 in Diethylamine/Cyclohexane. A 1.0 × 10^{-3} M solution of iodo azide **15** in ethylamine/cyclohexane (1:40 v/v) was photolyzed for 2 h. The residue after evaporation of the solvents was separated by preparative TLC (15:15:4 hexane–CH_2Cl_2–acetone) to give aniline **34** (22%) and **35** (20%) and substituted hydrazine **36** (21%) and **37** (20%). Aniline **34**: ^1H NMR (acetone-d_6) δ 3.897 (s, 3), 5.909 (s, 2), 8.074 (s, 1), 8.353 (s, 1), 8.503 (s, 1), 9.930 (s, 1); MS 468 (100, M^+), 437 (10), 192 (78), 164 (8); HRMS calcd for $C_{15}H_9F_4IN_2O_3$ 467.9591, found 467.9614. Aniline **35**: ^1H NMR δ 3.929 (s, 3), 4.341 (s, 2), 7.463 (t, J = 8.0 Hz, 1), 7.706 (s, 1), 7.851 (d, J = 7.7 Hz, 1), 8.001 (d, J = 8.4 Hz, 1), 8.113 (s, 1); MS 342 (40, M^+), 311 (9), 192 (100), 164 (10); HRMS calcd for $C_{15}H_{10}F_4N_2O_3$ 342.0624, found 342.0625.

Hydrazine **36**: ^{1}H NMR δ 1.123 (t, J = 7.1 Hz, 6), 2.771 (q, J = 7.1 Hz, 4), 3.923 (s, 3), 4.620 (m, 1), 7.705 (m, 1), 8.032 (s, 1), 8.167 (s, 1), 8.432 (s, 1); MS 539 (100, M^+), 480 (4); HRMS calcd for $C_{19}H_{18}F_4IN_3O_3$ 539.0323, found 539.0302. Hydrazine **37**: ^{1}H NMR δ 1.125 (t, J = 7.1 Hz, 6), 2.771 (q, J = 7.1 Hz, 4), 3.927 (s, 3), 4.588 (s, 1), 7.461 (t, J = 8.0 Hz, 1), 7.706 (s, 1), 7.849 (d, J = 7.8 Hz, 1), 7.998 (d, J = 8.0 Hz, 1), 8.112 (s, 1); MS, 413 (100, M^+), 398 (25), 382 (6), 296 (20), 263 (12), 163 (3); HRMS calcd for $C_{19}H_{19}F_4N_3O_3$ 413.1357, found 413.1329.

Synthesis of Methyl 3-(4-Amino-2,3,5,6-tetrafluorobenzamido)benzoate (35). A mixture of 452 mg (2.16 mmol) of 4-aminotetrafluorobenzoic acid with 324 mg (2.14 mmol) of methyl 3-aminobenzoate and 447 mg (2.16 mmol) of DCC in $CHCl_3$ (10 mL) was stirred overnight. The mixture was filtered, and the solid was washed by $CHCl_3$ (30 mL). The filtrate was evaporated to leave a solid which was stirred with $CHCl_3$ (10 mL) and filtered, and the solid was dried to leave 267 mg (36%) of **35** as a colorless solid. The ^{1}H NMR spectrum is identical with that for **35** obtained above. The analytical sample of **35** was obtained via recrystallization (THF/hexane) as colorless needles, mp 185–186 °C. Anal. Calcd for $C_{15}H_{10}F_4N_2O_3$: C, 52.64, H, 2.94, N, 8.18. Found: C, 52.95, H, 2.89, N, 8.08.

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Supplementary Material Available: ^{1}H NMR (300-MHz) spectra of compounds **7**, **8**, **11**, **13–15**, **21**, **25–28**, **30–32**, **34**, **36**, and **37** (17 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Notes

Synthesis of *C*-Disaccharides through Dimerization of *exo*-Glycals

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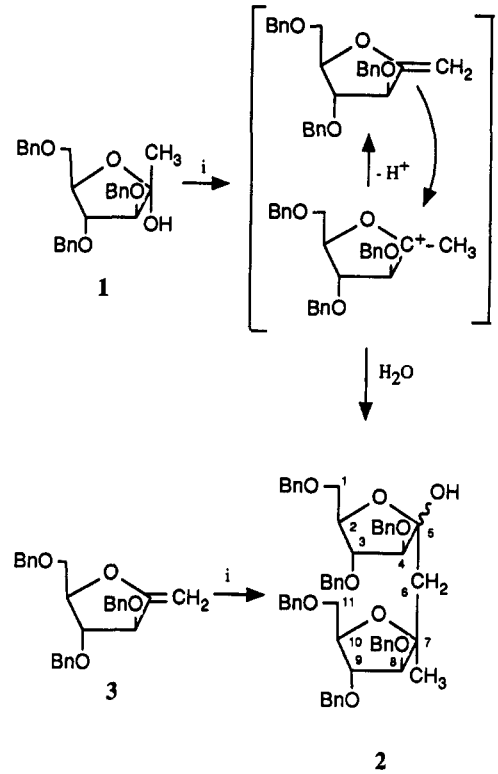
In our studies directed toward the synthesis of potential antimetabolites of natural carbohydrates, we were interested into a convenient method to synthesize *C*-disaccharides, sugars in which two monosaccharides are linked through a carbon atom rather than an oxygen.

The interest in these compounds, documented in the recent literature,[1,2] is supported inter alia by the fact that they can act as inhibitors of glycosidases. Compounds which exhibit this property have shown antiviral,[3] antitumoral,[4] antihyperglycemic,[5] and antiobesity[6] properties.

Scheme I[a]



[a] (i) BF_3·OEt_2, MeCN, 0 °C.

In particular, analogues of sucrose, the sugar of greater commercial relevance, are of interest for the studies of the relation between structure and sweetness and in the search of regulation or modification of enzymatic processes in which sucrose is involved.

Although many examples of synthesis of *C*-disaccharides have been described, to our knowledge only four examples[2] of the synthesis of *C*-disaccharides of nonreducing sugars

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