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Synthesis of 7-Oxabicyclo[2.2.1]heptanes and 8-Oxabicyclo[3.2.1]octanes from C-Glycosides via an Intramolecular Cyclization

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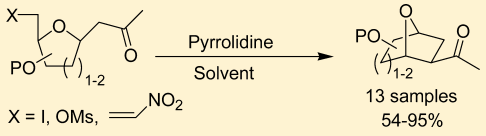
Supporting Information

ABSTRACT: A simple and effective method for the synthesis of 7-oxabicyclo[2.2.1]heptanes and 8-oxabicyclo[3.2.1]octanes from acetonyl C-glycoside substrates is described, which involves an intramolecular cyclization reaction through a nucleophilic substitution at C-5 or C-6 of C-glycosides by a 2′-enamine intermediate formed in the presence of pyrrolidine. Because anomeric epimerization occurs under these conditions, C-glycoside substrates with either anomeric configuration were converted to the same product(s) in same stereoselectivity and similar chemical yield.

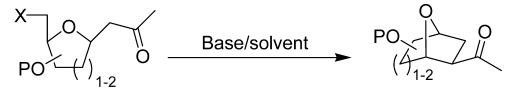


Oxabicyclic [3.2.1] and [2.2.1] skeletons are commonly found in a large number of natural products with diverse structural features and biological and medicinal importance.[1−6] Significant advancements in the oxabicyclic ring construction and thereafter ring expansion/opening have made them attractive intermediates in organic and medicinal chemistry.[7−12]

Among the synthetic methods available, the Diels−Alder reaction using furan and substituted furans has been most common for the oxabicyclo[2.2.1]heptene framework,[13−15] often in the presence of various catalysts,[16−18] whereas oxabicyclo[3.2.1]octene skeletons can also be produced by cycloadditions of furan derivatives with various oxyallyl cations.[19−22] However, the Diels−Alder reaction produces an enantiomeric mixture of *exo* and *endo* products and a chiral control group is needed to achieve enantioselectivity.[23−25] In general, the synthetic methods for 7-oxabicyclic [2.2.1] skeleton are not necessary applicable to the synthesis of oxabicyclic [3.2.1] compounds. Thus, many reactions including 1,3-dipolar cycloaddition,[26,27] various other cycloadditions,[28,29] and oxidative cyclo-etherification,[30] among others[31,32] were developed.

Through further manipulations such as dihydroxylation and epoxidation the oxabicyclic intermediates from the Diels−Alder approach can be converted to Tamiflu[33] and sugar chirons.[34] Retrospectively, oxabicyclo[3.2.1] and [2.2.1] compounds have also been derived from sugars by an intramolecular nitrone cycloaddition on substrates carrying an allyl group and an enone−nitrone by an intramolecular RCM reaction,[6] although the method takes multiple steps and requires 1,4-*cis* substitution on substrates. Because of the rich stereochemistry and easy availability, carbohydrates could be a source to oxabicyclo[2.2.1]heptane and oxabicyclo[3.2.1]octane skeletons provided a methylene (−CH_2−) tether can be placed between C1 and C5 of furanose or C1 and C6 of pyranose. Since an intramolecular displacement of a leaving group (−OTs and −OMs) at the C2-position of 1-acetonyl-1-C-mannopyranosides by the 1′-enolate led to the formation of 1,2-cyclopropaned sugars,[35,36] we reasoned if a leaving group is installed at the 6-position of C-pyranosides or the 5-position of C-furanosides a similar intramolecular SN_2 reaction may occur and provide a way to 8-oxabicyclo[3.2.1] and 7-oxabicyclo[2.2.1] compounds (see Scheme 1).

Scheme 1



X = leaving group

Two methods were employed in the preparation of 1-acetonyl-C-glycosides. One involved 1-C-allylation followed by olefin oxidation as previously reported;[37] the other provided 1-acetonyl-C-glycosides in one-step with acetylacetone in aqueous sodium bicarbonate.[38] The former was applied to the synthesis of α-C-glycosides **8**−**15**, **26**, and **27**; the latter was used to produce β-C-glycosides **3**, **6**, and **16**. In all substrates except **16**, the 6-iodides were derived by displacement of 6-OMs with iodide ion in the presence of KI in DMF at 50 °C for **6** and **14** or at 80 °C for **8**−**13**, and **15**. Iodide **16** was prepared by treatment of the 1-acetonyl-3-azido-1-C-allopyranoside with Ph_3P/I_2/imidazole.[39] The synthetic schemes are illustrated in the Supporting Information.

Because we have previously observed 1,2-cyclopropanation through an intramolecular replacement of 2-OTs (OMs) by 1′-enolate under basic conditions (K_2CO_3/MeOH),[35] similar reaction conditions were attempted on C-ribofuranoside substrates (**2a** and **2b**) with a leaving group at C-5 (OTs and OMs). The bases used included potassium carbonate, sodium methoxide, DBU, piperidine, and pyrrolidine and the solvents

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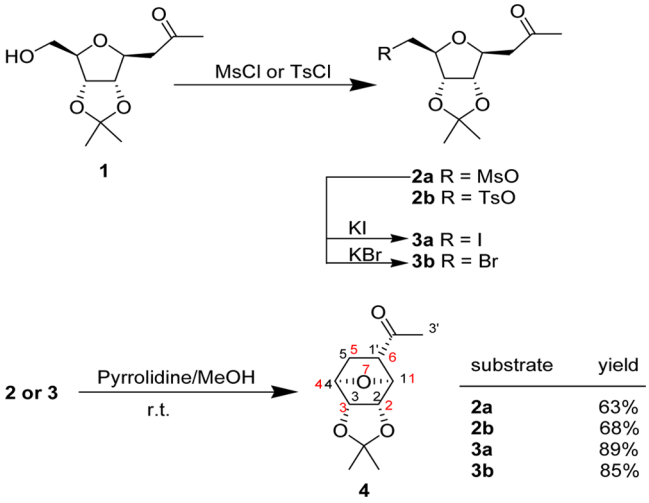
were methanol, THF, acetonitrile, and DMF. The reaction only proceeded efficiently when pyrrolidine was used as a base in methanol and THF (see Table 1). The fast conversion of **2a** to

Table 1. Formation of 4 under Various Base and Solvent Combinations[a]

entry	substrate	base	solvent	time (h)	yield (%)
1	**2a**	pyrrolidine	MeOH	20	>90
2			THF		~15−20
3		piperidine	MeOH		0
4			THF		0
5		1% NaOMe	MeOH		<10
6		DBU			0
7		K_2CO_3			<10
8	**3a**	pyrrolidine	MeOH	12	>90
9			THF	12	>90
10		piperidine	THF	8 days	40
11		DBU		4 days	70

[a]Reactions performed at room temperature; concentration of substrate at 10 mg per mL; 4 equiv of base used; and the yields estimated by ^{1}HNMR on crude.

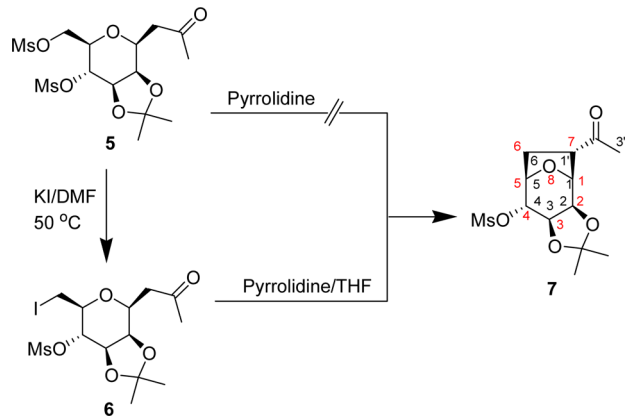
Scheme 2



4 occurred with pyrrolidine in methanol (see Scheme 2), which resulted in a C−C bond between C-5 and C-1′ as evidenced by ^{1}H and ^{13}C NMR analysis [although the products are named in the Experimental Section based on IUPAC nomenclature rules (see red numbering), the numbering based on sugar (see black) was used in the discussion and the NMR assignments]. High yields were also obtained from 5-halo (Br-, I-) substituted substrates (**3a** and **3b**) under similar conditions. In addition, we also found that the reaction of **3b** under conditions of K_2CO_3/MeOH went extremely slow at room temperature leading to less than 50% conversion after 4 days. At elevated temperature, e.g., 50 °C, the reaction produced more side products. Apparently, this intramolecular cyclization was most effective with pyrrolidine due to the superior nucleophilicity of its enamine intermediate.[40] The proper solvent for 5-OMs/OTs furanosides is methanol (entry 1) and for 5-iodofuranosides both methanol and THF are suitable solvents (entries 8 and 9).

Meanwhile, we also tested 6-O-Ms- and 6-iodo-*C*-glycopyranoside derivatives (**5** and **6**) as substrates (see Scheme 3).

Scheme 3



Surprisingly, unlike the 5-OMs-*C*-glycofuranoside there was no reaction observed when **5** was treated with pyrrolidine in methanol and THF at room temperature, and the reaction became complex at 50 °C. Consequently, **5** was converted to iodide **6** by treatment with KI in DMF at 50 °C overnight, and the subsequent cyclization to **7** from **6** was easily achieved with pyrrolidine as base in THF. It is noteworthy that the reaction was sluggish in methanol. Thus, the solvent played an important role in facilitating a conformational change particularly for C-pyranoside that requires higher free energy than C-furanoside. An aprotic solvent such as THF is more favorable to the conformation changes than MeOH due to the less extent of solvation with substrates.[41,42] Those results led us to conclude that iodides are more suitable substrates, and pyrrolidine and THF is the best combination of base and solvent.

The utility of this intramolecular cyclization was further demonstrated by effective conversion of various substrates with different functional groups into desired 7-oxabicyclic [2.2.1] (**17**, **18**) and 8-oxabicyclic [3.2.1] (**19**−**25**) products in good to excellent yield upon treatment with pyrrolidine in THF (see Table 2). As expected the benzyl and isopropylidene groups were very stable under the conditions as well as the azido group. Due to steric hindrance, the 4-OMs group in both C-glycosides (**6**, **14**) and 8-oxabicyclic products (**7**, **23**) was unreactive with nucleophiles such as iodide and azide ions, even at elevated temperature (70 °C). Consequently, 4-azido-bicyclic **24** was obtained from 4-azido-6-iodo substrate **15** instead of 4-OMs-oxabiclyclic **23**. With O-acetylated substrates, **11** and **12**, partial de-O-acetylation did occur with prolonged reaction time, leading to lower chemical yield. Since we had previously synthesized nitroalkene *C*-glycosides (**26**, **27**),[43] we expected that these molecules could undergo an intramolecular Michael addition under the same conditions. Indeed, two 7-oxabicyclic diasteromers in a ratio of ca. 1:1 were obtained from **26** and **27** in 64% and 54% overall yield, respectively.

The stereoselectivity of the reaction is controlled by the stability of the transition state, which allowed the formation of a single product (**7**, **17**−**25**) with the 1′-C-acetyl group equatorially substituted on the cyclohexane or cycloheptane ring. A pair of diastereomers (**28**/**29**, **30**/**31**) with 5,6-*trans* configuration were obtained as a result of steric effect. Additionally, because the β-elimination that leads to anomeric

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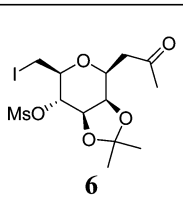
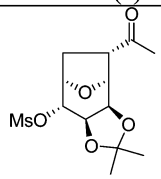
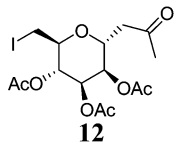
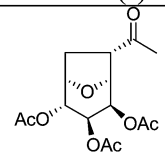
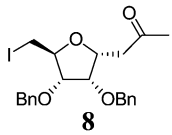
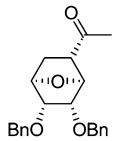
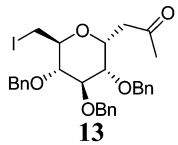
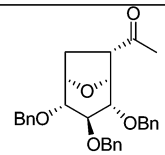
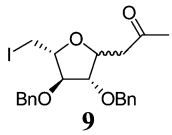
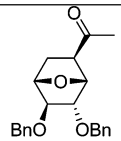
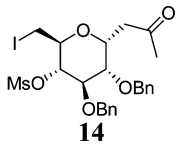
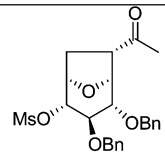
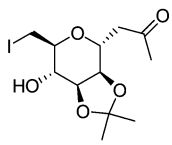
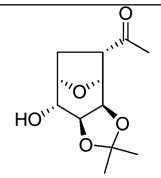
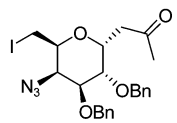
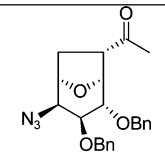
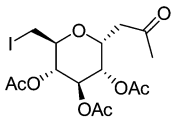
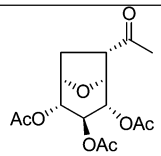
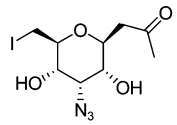
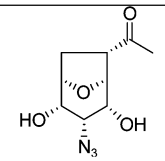
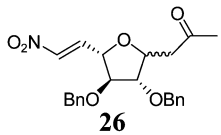
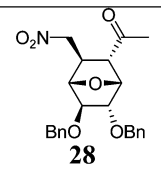
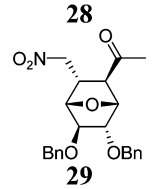
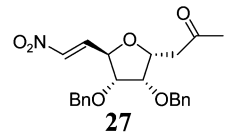
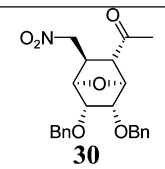
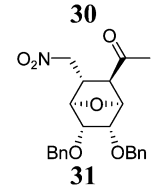
Table 2. Oxabicyles by an Intramolecular Cyclization

Substrate	Product(s)	Yield	Substrate	Product(s)	Yield
 **6**	 **7**	71%	 **12**	 **21**	60%
 **8**	 **17**	95%	 **13**	 **22**	88%
 **9**	 **18**	83%	 **14**	 **23**	94%
 **10**	 **19**	81%	 **15**	 **24**	89%
 **11**	 **20**	66%	 **16**	 **25**	65%
 **26**	 **28**  **29**	30% 34%	 **27**	 **30**  **31**	27% 27%

epimerization precedes the cyclization, the chemical yield and stereoselectivity were not affected by the anomeric configuration of the substrates.

In summary, we have developed a simple and effective method to access both the oxabicyclo[2.2.1] and oxabicyclo[3.2.1] compounds from 1-acetonyl-*C*-glycosides. The intramolecular cyclization reaction, which forms a C−C bond between C-1′ and C-6/C-5, was achieved through nucleophilic substitution at C-5 or C-6 of C-glycosides by a 2′-enamine. These bicycles can be useful intermediates for further chemical modifications.

■ EXPERIMENTAL SECTION

General Methods. The NMR spectra were recorded with a 400 MHz instrument with $CDCl_3$ as internal reference. The mass spectra were obtained using a TOF/TOF MALDI mass spectrometer in reflectron mode. The solvent and reagents were used without further purification. The bicyclic products are named based on IUPAC nomenclature rules, but the sugar numbering in the NMR assignments is maintained.

General Procedures for the Preparation of Iodides. To a solution of 5- or 6-OMs derivatives (0.2−4.0 g) in DMF (10−50 mL) was added KI (2−5 equiv) and the solution was stirred at 50 °C for **6** and **14** or at 80 °C for **3a**, **8**−**13** and **15** until the starting material disappeared (16−40 h). The reaction mixture was diluted by the addition of ethyl acetate and washed with brine three times. The organic phase was dried and concentrated to a residue. The residue was purified by flash column chromatography to give the desired products except **16**.

*2-C-(5-Iodo-2,3-di-O-isopropylidene-5-deoxy-β-D-ribofuranosyl)-acetone (**3a**).* The 5-OMs substrate **2a** (3.50 g, 11.4 mmol) was

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converted to **3a** (2.75 g, 71%) as a syrup: $[\alpha]_D$ −9.0 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.30 (s, 3H, Me), 1.50 (s, 3H, Me), 2.18 (s, 3H, Me), 2.75−2.80 (m, 2H, 1′-CH_2), 3.27 (d, 2H, 5-CH_2, *J* = 4.8 Hz), 3.84−3.89 (m, 1H, H-4), 4.28−4.35 (m, 1H, H-1), 4.42−4.47 (m, 2H, H-2, 3); ^{13}C NMR ($CDCl_3$) δ7.5 (C-5), 25.7 (Me), 27.6 (Me), 31.1 (Me), 47.1 (C-1′), 80.8 (C-1), 82.9 (C-4), 84.7 (C-3), 85.4 (C-2), 115.2, 206.1 (C-2′); HRMS calcd for $C_{11}H_{18}IO_4$ (M + H) $^+$ 341.0250, found 341.0213.

2-C-(6-Iodo-2,3-di-O-isopropylidene-4-O-mesyl-6-deoxy-β-D-mannopyranosyl)acetone (**6**). The 6-OMs substrate (4.0 g, 8.9 mmol) was converted to **6** (3.8 g, 89%) as needles (EtOAc−hexanes): mp 126−7 °C; ^1H NMR ($CDCl_3$) δ 1.38 (s, 3H, Me), 1.59 (s, 3H, Me), 2.25 (s, 3H, Me), 2.75 (dd, 1H, H-1′a, *J* = 6.4, 17.2 Hz), 2.82 (dd, 1H, H-1′b, *J* = 6.4, 17.2 Hz), 3.21 (s, 3H, OMs), 3.27 (dd, 1H, H-6a, *J* = 8.8, 11.2 Hz), 3.58 (dd, 1H, H-6b, *J* = 2.4, 11.2 Hz), 3.65 (ddd, 1H, H-1, *J* = 2.8, 10.8, 10.8 Hz), 4.17 (dd, 1H, *J* = 2.4, 11.2 Hz), 4.33 (dd, 1H, *J* = 2.4, 11.2 Hz), 4.45 (m, 1H, H-5), 4.64 (dd, 1H, H-4, *J* = 7.6, 10.0 Hz); ^{13}C NMR ($CDCl_3$) δ 4.0 (C-6), 25.7 (Me), 27.5 (Me), 30.9 (C-3′), 39.1, 45.6 (C-1′), 69.5, 72.6, 75.4, 76.2, 81.2, 110.7, 204.9 (C-2′); HRMS calcd for $C_{13}H_{21}O_7SINa$ (M + Na) $^+$ 470.9945, found 470.9987.

2-C-(5-Iodo-2,3-di-O-benzyl-5-deoxy-β-D-ribofuranosyl)acetone (**8**). The 5-OMs substrate (1.2 g, 2.68 mmol) was converted to **8** (1.04 g, 81%) as a syrup: $[\alpha]_D$ +44 (*c* 2.6, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.04 (s, 3H, Me), 2.79 (dd, 1H, H-1′a, *J* = 6.4, 17.2 Hz), 2.91 (dd, 1H, H-1′b, *J* = 8.0, 17.2 Hz), 3.22 (dd, 1H, H-5a, *J* = 4.0, 10.8 Hz), 3.36 (dd, 1H, H-5b, *J* = 4.0, 10.8 Hz), 3.76−3.90 (m, 2H, H-3, 4), 4.15 (dd, 1H, H-2, *J* = 4.0, 4.0 Hz), 4.40 (d, 1H, Bn, *J* = 11.2 Hz), 4.45−4.60 (m, 2H, H-1, Bn), 4.67 (d, 1H, Bn, *J* = 11.6 Hz), 4.74 (d, 1H, Bn, *J* = 11.2 Hz), 7.22−7.38 (m, 10H, 2 × Bn); ^{13}C NMR ($CDCl_3$) δ 9.7 (C-5), 30.6 (Me), 43.8 (C-1′), 72.9 (Bn), 73.8 (Bn), 76.6 (C-1), 77.6 (C-2), 77.8 (C-4), 83.7 (C-3), 127.8, 127.88, 127.95, 128.0, 128.06, 128.11, 128.2, 128.4, 128.46, 128.5, 128.6, 137.5, 138.1, 207.2 (C-2′); HRMS calcd for $C_{22}H_{26}IO_4$ (M + H)$^+$ 481.0876, found 481.0887.

2-C-(5-Iodo-2,3-di-O-benzyl-5-deoxy-α/β-L-arabinofuranosyl)-acetone (**9**). The 5-OMs substrate (1.1 g, 2.43 mmol) was converted to **9** (0.93 g, 80%) as a syrup: ^1H NMR ($CDCl_3$) for a mixture of α/β (c.a. 1:1) isomers: δ 2.16 and 2.17 (2s, 3H each, 2 × Me), 2.70−2.95 (m, 4H, 2 × 1′-CH_2), 3.25−3.36 (m, 4H, 2 × 5-CH_2), 3.89 (bt, 1H, H-2), 4.03 (bd, 1H, H-3), 4.03 (bd, 1H, H-3), 4.11 (bt, 1H, H-2), 4.12 (m, 1H, H-4), 4.30 (m, 1H, H-4), 4.37 (d, 1H, Bn, *J* = 11.6 Hz), 4.49−4.66 (m, 9H, 2 × H-1 and 3.5 × Bn), 7.22−7.38 (m, 20H, 4 × Bn); ^{13}C NMR ($CDCl_3$) for a mixture of α/β (c.a. 1:1) isomers: δ 6.7 (C-5, α and β), 30.6 and 30.7 (Me), 43.4 and 47.1 (C-1′), 71.5, 71.8, 71.9, 72.1, 80.2, 82.7, 83.5, 83.8, 85.0, 86.1, 86.6, 127.79, 127.82, 127.9, 128.0, 128.52, 128.53, 137.48, 137.51, 137.6, 206.7, and 206.8 (C-2′); HRMS calcd for $C_{22}H_{26}IO_4$ (M + H)$^+$ 481.0876, found 481.0877.

2-C-(6-Iodo-2,3-di-O-isopropylidene-6-deoxy-α-D-mannopyranosyl)acetone (**10**). The 6-OMs substrate (0.3 g, 0.86 mmol) was converted to **10** (0.23 g, 71%) as needles (EtOAc−hexanes): mp 115−7 °C; ^1H NMR ($CDCl_3$) δ 1.37 (s, 3H, Me), 1.52 (s, 3H, Me), 2.28 (s, 3H, Me), 2.69−2.72 (m, 2H, 1′-CH_2), 3.40−3.45 (m, 2H, H-5, 6a), 3.50−3.54 (m, 1H, H-6b), 3.90 (dd, 1H, H-4, *J* = 7.6, 7.6 Hz), 4.11 (dd, 1H, H-2, *J* = 8.0, 8.0 Hz), 4.19−4.23 (m, 2H, H-1, 3); ^{13}C NMR ($CDCl_3$) δ 7.6 (C-6), 25.2 (Me), 27.4 (Me), 30.9 (C-3′), 46.7 (C-1′), 69.7 (C-3), 72.2 (C-2), 73.7 (C-4), 75.9 (C-5), 78.0 (C-1), 110.2, 205.9 (C-2′); HRMS calcd for $C_{12}H_{20}O_5I$ (M + H)$^+$ 371.0356; found: 371.0328.

2-C-(6-Iodo-2,3,4-tri-O-acetyl-6-deoxy-α-D-glucopyranosyl)-acetone (**11**). The 6-OMs substrate (0.5 g, 1.18 mmol) was converted to **11** (0.33 g, 61%) as an oil: $[\alpha]_D$ +31 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.02 (s, 3H, Ac), 2.05 (s, 3H, Ac), 2.07 (s, 3H, Ac), 2.25 (s, 3H, Me), 2.75 (dd, 1H, H-1′a, *J* = 6.4, 16.4 Hz), 2.82 (dd, 1H, H-1′b, *J* = 7.6, 16.4 Hz), 3.16 (dd, 1H, H-6a, *J* = 7.6, 10.8 Hz), 3.32 (dd, 1H, H-6b, *J* = 4.0, 10.8 Hz), 3.65−3.72 (m, 1H, H-5), 4.77 (dd, 1H, H-1, *J* = 6.0, 6.4 Hz), 4.88 (dd, 1H, H-4, *J* = 8.0, 8.0 Hz), 5.10 (dd, 1H, H-2, *J* = 6.0, 5.6 Hz), 5.24 (dd, 1H, H-3, *J* = 5.6, 8.0 Hz); ^{13}C NMR ($CDCl_3$) δ 7.6 (C-6), 20.7 (Ac), 20.8 (Ac), 20.9 (Ac), 30.8 (Me), 42.1 (C-1′), 68.3 (C-1), 69.5 (C-2), 69.7 (C-3), 71.6 (C-4), 72.3 (C-5), 169.5 (Ac), 169.6 (Ac), 170.1 (Ac), 204.4 (C-2′); HRMS calcd for $C_{15}H_{21}O_8INa$ (M + Na)$^+$ 479.0173; found: 479.0145.

2-C-(6-Iodo-2,3,4-tri-O-acetyl-6-deoxy-α-D-mannopyranosyl)-acetone (**12**). The 6-OMs substrate (1.1 g, 2.59 mmol) was converted to **12** (0.70 g, 60%) as a syrup, an anomeric mixture (α/β c.a. 1:1) with about 5% residue solvent (EtOAc) as indicated by NMR: ^1H NMR ($CDCl_3$) δ 1.96 (s, 3H, Ac), 1.98 (s, 3H, Ac), 1.99 (s, 3H, Ac), 2.14 (s, 3H, Me), 2.55 (dd, 1H, H-1′a, *J* = 4.4, 16.0 Hz), 2.76 (dd, 1H, H-1′b, *J* = 9.2, 16.0 Hz), 3.19 (dd, 1H, H-6a, *J* = 8.4, 10.8 Hz), 3.33 (dd, 1H, H-6b, *J* = 6.0, 10.8 Hz), 3.65−3.70 (m, 1H, H-5), 4.39 (ddd, 1H, H-1, *J* = 1.0, 1.0, 5.2 Hz), 4.98 (dd, 1H, H-2, *J* = 3.2, 5.2 Hz), 5.03 (dd, 1H, H-4, *J* = 6.0, 7.2 Hz), 5.12 (dd, 1H, H-3, *J* = 3.2, 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 2.8 (C-6), 20.66 (Ac), 20.76 (Ac), 20.79 (Ac), 30.8 (Me), 43.6 (C-1′), 68.0, 68.8, 69.3, 69.5, 73.9, 169.4, 169.6, 169.8, 204.7 (C-2′); HRMS calcd for $C_{15}H_{21}O_8INa$ (M + Na)$^+$ 479.0173, found 479.0122.

2-C-(6-Iodo-2,3,4-tri-O-benzyl-6-deoxy-α-D-glucopyranosyl)-acetone (**13**). The 6-OMs substrate (0.3 g, 0.53 mmol) was converted to **13** (0.215 g, 68%) as needles (EtOAc−hexanes): mp 100−1 °C; $[\alpha]_D$ +11 (*c* 2, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.19 (s, 3H, Me), 2.53 (dd, 1H, H-1′a, *J* = 8.4, 15.2 Hz), 2.70 (dd, 1H, H-1′b, *J* = 3.6, 15.2 Hz), 3.03−3.10 (m, 1H, H-5), 3.25−3.47 (m, 4H, H-3, 4, 6a, 6b), 3.71−3.86 (m, 2H, H-1, 2), 4.55−4.79 (m, 2H, Bn), 4.86−4.95 (m, 4H, 2 × Bn), 7.24−7.37 (m, 15H, 3 × Bn); ^{13}C NMR ($CDCl_3$) δ 7.4 (C-6), 31.5 (Me), 45.8 (C-1′), 75.3 (Bn), 75.6 (C-1), 75.7 (Bn), 75.8 (Bn), 77.4 (C-5), 81.6 (C-3), 82.0 (C-4), 86.7 (C-2), 127.9, 128.0, 128.09, 128.13, 128.19, 128.22, 128.3, 128.71, 128.75, 128.8, 138.0, 138.1, 138.4, 206.8 (C-2′); HRMS calcd for $C_{30}H_{34}IO_5$ (M + H)$^+$ 601.1451, found 601.1503.

2-C-(6-Iodo-2,3-di-O-benzyl-4-O-mesyl-6-deoxy-α-D-glucopyranosyl)acetone (**14**). The 4,6-di-OMs substrate (0.278 g, 0.5 mmol) was converted to **14** (0.212 g, 72%) as needles (EtOAc−hexanes): mp 133−4 °C, $[\alpha]_D$ +42 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.16 (s, 3H, Me), 2.74−2.80 (m, 2H, 1′-CH_2), 3.20 (dd, 1H, H-6a, *J* = 7.6, 10.8 Hz), 3.60 (dd, 1H, H-6b, *J* = 4.0, 10.8 Hz), 3.66−3.75 (m, 2H, H-2, 5), 3.82 (dd, 1H, H-3, *J* = 7.2, 7.6 Hz) 4.45−4.51 (m, 2H, H-4, Bn), 4.59 (d, 1H, Bn, *J* = 11.6 Hz), 4.64−4.72 (m, 3H, H-1, Bn), 4.90 (d, 1H, Bn, *J* = 11.6 Hz), 7.19−7.37 (m, 15H, 3 × Bn); ^{13}C NMR ($CDCl_3$) δ 4.6 (C-6), 30.9 (Me), 38.7 (OMs), 41.6 (C-1′), 68.9 (C-1), 72.8 (Bn), 73.1 (C-5), 74.7 (Bn), 76.6 (C-3), 77.8 (C-2), 78.7 (C-4), 127.8, 128.1, 128.2, 128.4, 128.5, 128.6, 137.1, 137.2, 205.2 (C-2′); HRMS calcd for $C_{24}H_{30}IO_7S$ (M + H)$^+$ 589.0757, found 589.0785.

2-C-(6-Iodo-2,3-di-O-benzyl-4-azido-4,6-dideoxy-α-D-galactopyranosyl)acetone (**15**). The 6-OMs substrate (0.4 g, 0.80 mmol) was converted to **15** (0.275 g, 64%) as oil: $[\alpha]_D$ +19 (*c* 0.9, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.08 (s, 3H, Me), 2.60 (dd, 1H, H-1′a, *J* = 8.0, 16.0 Hz), 2.70 (dd, 1H, H-1′b, *J* = 6.0, 16.0 Hz), 3.23 (dd, 1H, H-6a, *J* = 6.4, 10.4 Hz), 3.31 (dd, 1H, H-6b, *J* = 7.6, 10.4 Hz), 3.70−3.77 (m, 2H, H-3, 5), 3.88 (dd, 1H, H-2, *J* = 4.8, 4.8 Hz), 4.12 (dd, 1H, H-4, *J* = 3.2, 3.2 Hz), 4.45−4.53 (m, 2H, H-1, Bn), 4.63 (d, 1H, Bn, *J* = 15.6 Hz), 4.63 (s, 2H, Bn), 7.27−7.37 (m, 10H, 2 × Bn); ^{13}C NMR ($CDCl_3$) δ 3.1 (C-6), 30.5 (Me), 41.9 (C-1′), 60.6 (C-4), 69.3 (C-1), 72.0 (C-5/3), 73.0 (Bn), 73.8 (Bn), 75.0 (C-2), 77.2 (C-3/5), 127.8, 128.07, 128.10, 128.14, 128.5, 128.6, 137.4, 137.7, 205.9 (C-2′); HRMS calcd for $C_{23}H_{27}N_3IO_4$ (M + H)$^+$ 536.1046, found 536.1029.

2-C-(6-Iodo-3-azido-3,6-dideoxy-β-D-allopyranosyl)acetone (**16**). To a mixture of 2-C-(3-azido-3,6-dideoxy-β-D-allopyranosyl)acetone (0.2 g), Ph_3P (0.4 g), and imidazole (0.3 g) in toluene (20 mL) was added iodine pellets (0.3 g). The mixture was refluxed for 1 h until all starting material was consumed. After cooling, the solution was diluted by the addition of ethyl acetate, washed with brine, 10% aqueous sodium sulfite, and water, dried, and concentrated. Purification by column chromatography (hexanes to EtOAc) gave **16** (0.15 g, 52%) as needles (EtOAc/hexanes): mp 125−6 °C; [α] −7 (*c* 0.5, EtOAc); ^1H NMR ($CDCl_3$) δ 2.24 (s, 3H, Me), 2.73 (dd, 1H, H-1′a, *J* = 6.4, 16.0 Hz), 2.81 (dd, 1H, H-1′b, *J* = 5.6, 16.0 Hz), 3.15 (m, 1H, H-5), 3.26 (dd, 1H, H-6a, *J* = 6.0, 11.2 Hz), 3.46 (dd, 1H, H-6b, *J* = 2.4, 11.2 Hz), 3.51 (dd, 1H, H-2, *J* = 3.2, 9.6 Hz), 3.54 (dd, 1H, H-4, *J* = 3.6, 9.2 Hz), 3.94 (m, 1H, H-1), 4.15 (dd, 1H, H-3, *J* = 3.2, 3.2 Hz); ^{13}C NMR

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($CDCl_3$) δ 7.5, 31.6, 46.4, 66.4, 71.4, 72.0, 72.2, 74.5, 208.8; HRMS calcd for $C_9H_{14}N_3O_4INa$ $(M + Na)^+$ 377.9927, found 377.9970.

General Procedure for Cyclization of Iodide. To a solution of iodide (0.15−0.5 g) in THF was added pyrrolidine (4−10 equiv), and the solution was stirred at room temperature for 6−12 h. After completion of the reaction the mixture was diluted by the addition of ethyl acetate and washed with 0.1 N HCl and brine. The organic phase was dried and concentrated to a residue. The residue was purified by flash column chromatography (hexanes/ethyl acetate 1:1) to give the desired products.

*(1S,2S,3R,4R,6S)-6-C-Acetyl-2,3-di-O-isopropylidene-7-oxabicyclo[2.2.1]heptane (**4**).* Iodide **3a** (0.5 g, 1.47 mmol) was converted to **4** (0.255 g, 82%) as a syrup: $[\alpha]_D$ −12 (*c* 1.3, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.25 (s, 3H, Me), 1.47 (s, 3H, Me), 1.69−1.85 (m, 2H, H-5a, 5b), 2.24 (s, 3H, Me), 3.14 (m, 1H, H-1′), 4.11 (d, 1H, H-3, *J* = 5.6 Hz), 4.22 (d, 1H, H-2, *J* = 5.6 Hz), 4.44 (d, 1H, H-4, *J* = 5.6 Hz), 4.62 (d, 1H, H-1, *J* = 5.6 Hz); ^{13}C NMR ($CDCl_3$,) δ 25.0 (Me), 25.6 (C-5), 25.9 (Me), 30.9 (C-3′), 52.4 (C-1′), 79.2 (C-1), 79.4 (C-3), 80.6 (C-4), 82.3 (C-2), 111.2 (CH), 205.7 (C-2′); HRMS calcd for $C_{11}H_{17}O_4$ $(M + H)^+$ 213.1127, found 213.1117.

*(1S,2S,3R,4R,5R,7S)-7-C-Acetyl-2,3-di-O-isopropylidene-4-O-mesyl-l-8-oxabicyclo[3.2.1]octane (**7**).* Iodide **6** (0.45 g, 1.0 mmol) was converted to **7** (0.227 g, 71%) as needles (EtOAc−hexanes): mp 174−5 °C; $[\alpha]_D$ +24 (*c* 0.65, EtOAc); ^1H NMR ($CDCl_3$) δ 1.37 (s, 3H, Me), 1.57 (s, 3H, Me), 1.94 (ddd, 1H, H-6a, *J* = 1.6, 9.6, 14.4 Hz), 2.21 (s, 3H, Me), 2.46 (ddd, 1H, H-6b, *J* = 4.8, 9.0, 14.4 Hz), 3.11 (s, 3H, Ms), 3.39 (dd, 1H, H-1′, *J* = 4.8, 9.6 Hz), 4.33 (d, 1H, H-1, *J* = 6.8 Hz), 4.47 (dd, 1H, H-2, *J* = 6.8, 6.8 Hz), 4.52 (d, 1H, H-3, *J* = 6.8 Hz), 4.60 (bd, 1H, H-5, *J* = 9.0 Hz), 4.76 (s, 1H, H-4); ^{13}C NMR ($CDCl_3$) δ 24.6, 26.2, 27.0, 28.4, 39.1, 49.3, 70.0, 74.4, 76.8, 77.2, 78.2, 109.5, 206.4; HRMS calcd for $C_{13}H_{20}O_7SNa$ $(M + Na)^+$ 343.0827, found 343.0844.

*(1S,2R,3S,4R,6S)- 6-C-Acetyl-2,3-di-O-benzyl-7-oxabicyclo[2.2.1]-heptane (**17**).* Iodide **8** (0.48 g, 1.0 mmol) was converted to **17** (0.335 g, 95%) as a solid: $[\alpha]_D$ +19 (*c* 0.4, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.42 (dd, 1H, H-6a, *J* = 9.2, 12.8 Hz), 1.94−2.02 (m, 1H, H-6b), 2.12 (s, 3H, Me), 2.37 (dd, 1H, H-1′, *J* = 4.8, 8.8 Hz), 3.68 (d, 1H, H-2, *J* = 6.0 Hz), 3.71 (d, 1H, H-3, *J* = 6.0 Hz), 4.55−4.72 (m, 6H, H-1, 4, 2 × Bn), 7.22−7.37 (m, 10H, 2 × Ph); ^{13}C NMR ($CDCl_3$) δ 28.0 (Me), 28.5 (C-5), 51.6 (C-1′), 72.8 (Bn), 73.0 (Bn), 79.4 (C-4), 80.9 (C-1), 82.1 (2C, C-2, 3), 77.8 (C-4), 83.7 (C-3), 127.8, 127.9, 128.0, 128.2, 128.3, 128.5, 128.6, 138.1, 138.2, 206.3 (C-2′); HRMS calcd for $C_{22}H_{25}O_4$ $(M + H)^+$ 353.1753, found 353.1739.

*(1R,2R,3R,4S,6S)-6-C-Acetyl-2,3-di-O-benzyl-7-oxabicyclo[2.2.1]-heptane (**18**).* Iodide **9** (0.225 g, 0.53 mmol) was converted to **18** (0.155 g, 83%) as a syrup: ^1H NMR ($CDCl_3$) δ 1.56 (dd, 1H, H-5a, *J* = 9.2, 12.4 Hz), 2.11 (s, 3H, Me), 2.15 (ddd, 1H, H-5b, *J* = 5.6, 5.6, 12.4 Hz), 3.20 (dd, 1H, H-1′, *J* = 4.2, 9.2 Hz), 3.42 (d, 1H, H-3, *J* = 1.2 Hz), 3.93 (d, 1H, H-2, *J* = 4.8 Hz), 4.44−4.54 (m, 5H, H-4, 2 × Bn), 4.66 (d, 1H, H-1, *J* = 4.8 Hz), 7.27−7.36 (m, 10H, 2 × Ph); ^{13}C NMR ($CDCl_3$) δ 28.4 (C-3′), 29.0 (C-5), 48.3 (C-1′), 71.3 (Bn), 73.1 (Bn), 78.6 (C-1), 81.0 (C-4), 86.1 (C-2), 86.2 (C-3), 128.0, 128.1, 128.2, 128.3, 128.7, 128.2, 137.6, 137.9, 207.4 (C-2′); HRMS calcd for $C_{22}H_{25}O_4$ $(M + H)^+$ 353.1753, found 353.1749.

*(1S,2R,3S,4R,5R,7S)-7-C-Acetyl-2,3-di-O-isopropyl-4-hydoxy-8-oxabicyclo[3.2.1]octane (**19**).* Iodide **10** (0.20 g, 0.54 mmol) was converted to **19** (0.106 g, 81%) as needles (EtOAc−hexanes): mp 149−150 °C; $[\alpha]_D$ +32 (*c* 0.2, EtOAc); ^1H NMR ($CDCl_3$) δ 1.36 (s, 3H, Me), 1.56 (s, 3H, Me), 1.97 (ddd, 1H, H-6a, *J* = 1.6, 9.6, 14.4 Hz), 2.21 (s, 3H, Me), 2.26 (d, 1H, 4-OH, *J* = 9.6 Hz), 2.37 (ddd, 1H, H-6b, *J* = 4.8, 9.0, 14.4 Hz), 3.41 (dd, 1H, H-1′, *J* = 4.8, 9.6 Hz), 3.80 (d, 1H, H-4, *J* = 9.6 Hz), 4.24 (d, 1H, H-1, *J* = 6.8 Hz), 4.39−4.44 (m, 2H, H-3, 5), 4.45 (dd, 1H, H-2, *J* = 6.4 Hz); ^{13}C NMR ($CDCl_3$) δ 24.5, 26.17, 26.22, 28.2, 49.6, 70.0, 70.8, 76.7, 77.3, 79.0, 109.0, 207.0; HRMS calcd for $C_{12}H_{18}O_5Na$ $(M + Na)^+$ 265.1052, found 265.1078.

*(1S,2S,3S,4R,5R,7S)-7-C-Acetyl-2,3,4-tri-O-acetyl-8-oxabicyclo-[3.2.1]octane (**20**).* Iodide **11** (0.21 g, 0.46 mmol) was converted to **20** (0.10 g, 66%) as a syrup: $[\alpha]_D$ +26 (*c* 1.7, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.09 (s, 3H, OAc), 2.10−2.17 (m, 7H, H-6a, 2 × OAc), 2.20 (s, 3H, Me), 2.31−2.40 (m, 1H, H-6b), 3.16 (dd, 1H, H-1′, *J* = 5.2, 5.2 Hz), 4.46 (d, 1H, H-5, *J* = 8.0 Hz), 4.50−4.58 (m, 3H, H-1, 3, 4), 4.84 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$) δ 21.2 (Ac), 21.3 (2C, Ac), 28.0 (C-3′), 28.4 (C-6), 52.1 (C-1′), 69.7 (C-2), 71.0 (C-3), 71.1 (C-1), 76.7 (C-5), 77.4 (C-4), 168.7 (Ac), 170.2 (Ac), 170.3 (Ac), 205.2 (C-2′); HRMS calcd for $C_{15}H_{20}O_8Na$ $(M + Na)^+$ 351.1056, found 351.1017.

*(1S,2R,3S,4R,5R,7S)-7-C-Acetyl-2,3,4-tri-O-acetyl-8-oxabicyclo-[3.2.1]octane (**21**).* Iodide **12** (0.20 g, 0.44 mmol) was converted to **21** (0.086 g, 60%) as a syrup: ^1H NMR ($CDCl_3$) δ 2.05 (s, 3H, OAc), 2.14 (s, 6H, 2 × OAc), 2.21 (s, 3H, Me), 2.25−2.32 (m, 1H, H-6a), 2.36−2.42 (m, 1H, H-6b), 3.46 (dd, 1H, H-1′, *J* = 5.2, 8.8 Hz), 4.45−4.49 (m, 2H, H-1, 5), 4.72 (d, 1H, H-2, *J* = 1.2 Hz), 5.24−5.25 (m, 2H, H-3, 4, *J* = 3.2 Hz); ^{13}C NMR ($CDCl_3$) δ 20.7 (Ac), 20.9 (Ac), 21.0 (Ac), 27.7 (C-3′), 28.2 (C-6), 50.5 (C-1′), 65.8 (C-3/4), 67.8 (C-4/3), 72.7 (C-2), 75.7 (C-5/1), 76.7 (C-1/5), 168.9 (Ac), 169.2 (Ac), 169.7 (Ac), 206.2 (C-2′); HRMS calcd for $C_{15}H_{20}O_8Na$ $(M + Na)^+$ 351.1056, found 351.1063.

*(1S,2R,3S,4S,5R,7S)-7-C-Acetyl-2,3,4-tri-O-benzyl-8-oxabicyclo-[3.2.1]octane (**22**).* Iodide **13** (0.20 g, 0.33 mmol) was converted to **22** (0.138 g, 88%) as a syrup: $[\alpha]_D$ +17 (*c* 2.1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.0−2.19 (m, 2H, H-6a, 6b), 2.10 (s, 3H, Me), 3.09 (dd, 1H, H-1′, *J* = 5.2, 8.8 Hz), 3.20 (s, 1H, H-4) 3.26 (s, 1H, H-3), 3.57 (s, 1H, H-2), 4.31 (s, 2H, Bn), 4.52 (m, 1H, H-5), 4.55 (s, 2H, Bn), 4.60 (s, 3H, H-1, Bn), 7.17−7.35 (m, 15H, 3 × Bn); ^{13}C NMR ($CDCl_3$) δ 27.8 (C-3′), 29.0 (C-6), 52.4 (C-1′), 71.1 (Bn), 71.2 (Bn), 72.1 (Bn), 75.5 (C-2), 76.0 (C-4), 76.3 (C-3), 76.8 (C-5), 77.5 (C-1), 127.7, 127.9, 127.96, 128.0, 128.1, 128.2, 128.6, 128.65, 128.7, 137.9, 138.3, 138.5, 207.2 (C-2′); HRMS calcd for $C_{30}H_{32}O_5Na$ $(M + Na)^+$ 495.2147, found 495.2144.

*(1S,2R,3R,4S,5R,7S)-7-C-Acetyl-2,3-di-O-benzyl-4-O-mesyl-8-oxabicyclo[3.2.1]octane (**23**).* Iodide **14** (0.20 g, 0.34 mmol) was converted to **23** (0.147 g, 94%) as a syrup: $[\alpha]_D$ +19 (*c* 0.9, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.11 (s, 3H, Me), 2.21−2.27 (m, 2H, H6a, 6b), 3.01 (s, 3H, OMs), 3.16 (dd, 1H, H-1′, *J* = 7.6, 10.8 Hz), 3.23 (s, 1H, H-2), 3.81 (s, 1H, H-3), 4.41 (d, 1H, Bn, *J* = 12.0 Hz), 4.48−4.65 (m, 6H, H-1, 4, 5, 1.5 × Bn), 7.21−7.37 (m, 10H, 2 × Bn); ^{13}C NMR ($CDCl_3$) δ 27.9 (C-3′),28.9 (C-6), 39.2 (OMs), 51.7 (C-1′), 71.3 (Bn), 72.7 (Bn), 74.6 (C-3), 75.1 (C-4), 75.8 (C-2), 77.0 (C-5), 77.4 (C-1), 128.1, 128.17, 128.22, 128.5, 128.7, 128.8, 137.2, 137.7, 206.3 (C-2′); HRMS calcd for $C_{24}H_{28}O_7SNa$ $(M + Na)^+$ 483.1453, found 483.1510.

*(1S,2R,3S,4R,5R,7S)-7-C-Acetyl-4-azido-2,3-di-O-benzyl-8-oxabicyclo[3.2.1]octane (**24**).* Iodide **15** (0.20 g, 0.37 mmol) was converted to **24** (0.135 g, 89%) as a syrup: $[\alpha]_D$ +50 (*c* 1.3, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.97−2.05 (m, 1H, H-6a) 2.09 (s, 3H, Me), 2.59 (dd, 1H, H-6b, *J* = 10.0, 12.8 Hz), 3.26 (dd, 1H, H-1′, *J* = 5.2, 8.2 Hz), 3.37 (s, 1H, H-3), 3.76−3.80 (m, 2H, H-2, 4), 4.35−4.62 (m, 6H, H-1, 5, 2 × Bn), 7.26−7.38 (m, 10H, 2 × Bn); ^{13}C NMR ($CDCl_3$) δ 27.7 (C-3′), 28.2 (C-6), 51.8 (C-1′), 58.5 (C-4), 71.3 (Bn), 73.8 (Bn), 75.9 (C-3), 76.1 (C-5), 76.2 (C-2), 76.3 (C-1), 127.8, 127.9, 128.11, 128.13, 128.6, 137.3, 137.5, 206.8 (C-2′); HRMS calcd for $C_{23}H_{25}N_3O_4Na$ $(M + Na)^+$ 430.1743, found 430.1744.

*(1S,2R,3R,4S,5R,7S)-7-C-Acetyl-3-azido-8-oxabicyclo[3.2.1]octane (**25**).* Iodide **16** (0.15 g, 0.42 mmol) was converted to **25** (0.063 g, 65%) as needles (EtOAc−hexanes): mp 118−9 °C; $[\alpha]_D$ −12 (*c* 0.37, EtOAc); ^1H NMR (CD_3OD) δ 1.88 (dd, 1H, H-6a, *J* = 10.8, 12.4 Hz), 2.17 (s, 3H, Me), 2.21 (dd, 1H, H-6b, *J* = 5.6 Hz), 3.03 (dd, 1H, H-1′, *J* = 5.6, 8.4 Hz), 3.22 (bs, 1H, H-3), 3.74 (bs, 1H, H-2), 3.82 (bs, 1H, H-4), 4.34 (d, 1H, H-1, *J* = 8.0 Hz), 4.30 (bs, 1H, H-5); ^{13}C NMR (CD_3OD) δ 28.3 (C-3′), 50.8 (C-1′), 54.5 (C-3), 71.2 (C-4), 71.6 (C-2), 79.5 (C-1), 80.3 (C-5); HRMS calcd for $C_9H_{13}O_4N_3Na$ $(M + Na)^+$ 250.0804, found 250.0820.

*(1R,2R,3R,4R,5S,6S)-6-C-Acetyl-2,3-di-O-benzyl-5-nitromethyl-7-oxabicyclo[2.2.1]heptane (**28**) and (1R,2R,3R,4R,5R,6R)-6-C-Acetyl-2,3-di-O-benzyl-5-nitromethyl-7-oxabicyclo[2.2.1]heptane (**29**).* A solution of **26** (0.10 g, 0.24 mmol) in THF (1 mL) was added pyrrolidine (50 μL). The mixture was kept at room temperature overnight. The mixture was diluted by the addition of EtOAc (30 mL), and the solution was washed with 0.1 N HCl and brine, dried, and concentrated. The residue was subjected to column chromotagraphy

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(hexanes to EtOAc–hexanes 1:3) to give **28** (30 mg, 30%) and **29** (34 mg, 34%).

Data for **28**: needles (EtOAc–hexanes); mp 138–9 °C; $[\alpha]_D$ +12 (*c* 1.7, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.08 (s, 3H, 3′-Me), 2.61 (dd, 1H, H-1′, *J* = 5.2, 5.2 Hz), 3.14 (m, 1H, H-5), 3.57 (d, 1H, H-3, *J* = 1.6 Hz), 4.06 (bd, 1H, H-3, *J* = 4.8 Hz), 4.31–4.35 (m, 2H, H-6a, 6b), 4.37 and 4.57 (d and d, 1H each, Bn, *J* = 12.0 Hz), 4.44 (s, 1H, H-4), 4.43 and 4.57 (d and d, 1H each, Bn, *J* = 12.0 Hz), 4.89 (dd, 1H, H-1, *J* = 5.2, 5.2 Hz), 7.22–7.41 (m, 10H, 2 × Bn); ^{13}C NMR ($CDCl_3$) δ 29.9 (C-3′), 38.3 (C-5), 58.5 (C-1′), 71.8 (Bn), 73.1 (Bn), 76.7 (C-6), 78.1 (C-1), 83.8 (C-4), 84.1 (C-3), 87.0 (C-2), 127.9, 128.2, 128.3, 128.7, 128.8, 137.0, 137.4, 201.2 (C-2′); HRMS calcd for $C_{23}H_{25}NO_6Na$ $(M + Na)^+$ 434.1580, found 434.1600.

Data for **29**: syrup; $[\alpha]_D$ +46 (*c* 3.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.12 (s, 3H, 3′-Me), 2.89 (d, 1H, H-1′, *J* = 5.6 Hz), 3.33 (m, 1H, H-5), 3.64 (s, 1H, H-3), 4.00 (d, 1H, H-2, *J* = 4.2 Hz), 4.30 (dd, 1H, H-6a, *J* = 10.4, 13.6 Hz), 4.42 and 4.54 (d and d, 1H each, Bn, *J* = 12.0 Hz), 4.46–4.53 (m, 3H, H-6b, Bn), 4.61 (d, 2H, H-1, 4, *J* = 5.6 Hz), 7.22–7.41 (m, 10H, 2 × Bn); ^{13}C NMR ($CDCl_3$) δ 28.4 (C-3′), 38.9 (C-5), 52.1 (C-1′), 71.5 (Bn), 73.4 (Bn), 74.3 (C-6), 79.8 (C-1/C-4), 81.0 (C-3), 82.5 (C-4/C-1), 85.7 (C-2), 128.2, 128.3, 128.6, 128.7, 128.8, 129.0, 137.2, 137.5, 205.1 (C-2′); HRMS calcd for $C_{23}H_{25}NO_6Na$ $(M + Na)^+$ 434.1580, found 434.1572.

*(1S,2R,3S,4R,5S,6S)-6-C-Acetyl-2,3-di-O-benzyl-5-nitromethyl-7-oxabicyclo[2.2.1]heptane (**30**) and (1S,2R,3S,4R,5R,6R)-6-C-Acetyl-2,3-di-O-benzyl-5-nitromethyl-7-oxabicyclo[2.2.1]heptane (**31**).* A solution of **27** (0.10 g, 0.24 mmol) in THF (1 mL) was added pyrrolidine (50 μL). The mixture was kept at room temperature overnight. The mixture was diluted by the addition of EtOAc (30 mL) and the solution was washed with 0.1 N HCl and brine, dried, and concentrated. The residue was subjected to column chromotagraphy (hexanes to EtOAc–hexanes 1:3) to give **30** (27 mg, 27%) and **31** (27 mg, 27%).

Data for **30**: syrup; ^1H NMR δ 2.02 (d, 1H, H-1′, *J* = 5.6 Hz), 2.15 (s, 3H, 3′-Me), 2.12 (m, 1H, H-5), 3.71 (d, 1H, H-2, *J* = 6.0 Hz), 3.88 (d, 1H, H-3, *J* = 6.0 Hz), 4.16 (dd, 1H, H-6a, *J* = 9.6, 13.2 Hz), 4.32 (dd, 1H, H-6b, *J* = 7.6, 13.2 Hz), 4.53 (s, 1H, H-1), 4.56 and 4.75 (d and d, 1H each, Bn, *J* = 11.6 Hz), 4.64 (s, 2H, Bn), 4.65 (s, 1H, H-4), 7.22–7.41 (m, 10H, 2 × Bn); ^{13}C NMR ($CDCl_3$) δ 28.2 (C-3′), 38.8 (C-5), 56.1 (C-1′), 72.9 (Bn), 73.4 (Bn), 74.7 (C-6), 77.4 (C-3), 81.3 (C-4), 82.0 (C-2), 82.4 (C-1), 128.3, 128.4, 128.7, 128.8, 137.5, 137.7, 203.9 (C-2′); HRMS calcd for $C_{23}H_{25}NO_6Na$ $(M + Na)^+$ 434.1580, found 434.1608.

Data for **31**: syrup; $[\alpha]_D$ −39 (c 1.5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.00 (s, 3H, 3′-Me), 2.77 (dd, 1H, H-1′, *J* = 5.2, 5.2 Hz), 2.82 (m, 1H, H-5), 3.58 (d, 1H, H-2, *J* = 6.0 Hz), 3.80 (d, 1H, H-3, *J* = 6.0 Hz), 4.16 (dd, 1H, H-6a, *J* = 7.6, 13.6 Hz), 4.29 (s, 1H, H-4), 4.38 (dd, 1H, H-6b, *J* = 8.0, 13.6 Hz), 4.42 and 4.71 (d and d, 1H each, Bn, *J* = 12.0 Hz), 4.57 and 4.63 (d and d, 1H each, Bn, *J* = 12.0 Hz), 4.64 (s, 1H, H-1), 7.22–7.41 (m, 10H, 2 × Bn); ^{13}C NMR ($CDCl_3$) δ 31.5 (C-3′), 39.0 (C-5), 57.4 (C-1′), 73.2 (Bn), 73.6 (Bn), 77.0 (C-6), 78.2 (C-2), 81.1 (C-1), 81.3 (C-3), 83.3 (C-5), 128.0, 128.2, 128.3, 128.4, 128.7, 137.6, 137.7, 203.6 (C-2′); HRMS calcd for $C_{23}H_{25}NO_6Na$ $(M + Na)^+$ 434.1580, found 434.1558.

■ ASSOCIATED CONTENT

Supporting Information

Synthetic schemes for substrates **8**–**16**; 1D and 2D NMR spectra of compounds (**4**–**31**). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Aoki, S.; Watanabe, Y.; Sanagawa, M.; Setiawan, A.; Kotoku, N.; Kobayashi, M. *J. Am. Chem. Soc.* **2006**, *128*, 3148–3149.
(2) Singh, S. B.; Jayasuriya, H.; Ondeyka, J. G.; Herath, K. B.; Zhang, C.; Zink, D. L.; Tsou, N. N.; Ball, R. G.; Basilio, A.; Genilloud, O.; Diez, M. T.; Vicente, F.; Pelaez, F.; Young, K.; Wang, J. *J. Am. Chem. Soc.* **2006**, *128*, 11916–11920.
(3) Ratnayake, R.; Covell, D.; Ransom, T. T.; Gustafson, K. R.; Beutler, J. A. *Org. Lett.* **2009**, *11*, 57–60.
(4) Lin, Z.; Zhu, T.; Wei, H.; Zhang, G.; Wang, H.; Gu, Q. *Eur. J. Org. Chem.* **2009**, 3045–3051.
(5) Thuong, P.-T.; Dao, T.-T.; Pham, T.-H.-M.; Nguyen, P.-H.; Le, T.-V.-T.; Lee, K.-Y.; Oh, W.-K. *J. Nat. Prod.* **2009**, *72*, 2040–2042.
(6) Ghosh, R.; Maity, J. K.; Achari, B.; Mandal, S. B. *J. Org. Chem.* **2010**, *75*, 2419–2422.
(7) Chiu, P.; Lautens, M. *Top. Curr. Chem.* **1997**, *190*, 1–85.
(8) Vogel, P.; Cossy, J.; Plumet, J.; Arjona, O. *Tetrahedron* **1999**, *55*, 13521–13642.
(9) Diethelm, S.; Schindler, C. S.; Carreira, E. M. *Org. Lett.* **2010**, *12*, 3950–3953.
(10) Padwa, A.; Brodney, M. A.; Dimitroff, M.; Liu, B.; Wu, T. *J. Org. Chem.* **2001**, *66*, 3119–3128.
(11) Rainier, J. D.; Xu, Q. *Org. Lett.* **1999**, *8*, 1161–1163.
(12) Schindler, C. S.; Carreira, E. M. *Chem. Soc. Rev.* **2009**, *38*, 3222–3241.
(13) Kappe, C. O.; Murphree, S. S.; Padwa, A. *Tetrahedron* **1997**, *53*, 14179–14231.
(14) Orugunty, R. S.; Ghiviriga, I.; Abboud, K. A.; Battiste, M. A.; Wright, D. L. *J. Org. Chem.* **2004**, *69*, 570–572.
(15) Oblak, E. Z.; Wright, D. L. *Org. Lett.* **2011**, *13*, 2263–2265.
(16) Lipshutz, B. H. *Chem. Rev.* **1986**, *86*, 795–819.
(17) Xue, Y. P.; Li, W. D. *J. Org. Chem.* **2011**, *76*, 57–64.
(18) Sáez, J. A.; Arnó, M.; Domingo, L. R. *Org. Lett.* **2003**, *5*, 4117–4120.
(19) Huang, J.; Hsung, R. P. *J. Am. Chem. Soc.* **2005**, *127*, 50–51.
(20) Fujita, M.; Oshima, M.; Okuno, S.; Sugimura, T.; Okuyama, T. *Org. Lett.* **2006**, *8*, 4113–4116.
(21) Lohse, A. G.; Hsung, R. P.; Leider, M. D.; Ghosh, S. K. *J. Org. Chem.* **2011**, *76*, 3246–3257.
(22) Chung, W. K.; Lam, S. K.; Lo, B.; Liu, L. L.; Wong, W.-T.; Chiu, P. *J. Am. Chem. Soc.* **2009**, *131*, 4556–4557.
(23) Suga, H.; Ishimoto, D.; Higuchi, S.; Ohtsuka, M.; Arikawa, T.; Tsuchida, T.; Kakehi, A.; Baba, T. *Org. Lett.* **2007**, *9*, 4359–4362.
(24) Singh, R. S.; Adachi, S.; Tanaka, F.; Yamauchi, T.; Inui, C.; Harada, T. *J. Org. Chem.* **2008**, *73*, 212–218.
(25) Benjamin, N. M.; Martin, S. F. *Org. Lett.* **2011**, *13*, 450–453.
(26) Shimada, N.; Hanari, T.; Kurosaki, Y.; Takeda, K.; Anada, M.; Nambu, H.; Shiro, M.; Hashimoto, S. *J. Org. Chem.* **2010**, *75*, 6039–6042.
(27) Xu, J.; Caro-Diaz, E. J.; Theodorakis, E. A. *Org. Lett.* **2010**, *12*, 3708–3711.
(28) Ishida, K.; Kusama, H.; Iwasawa, N. *J. Am. Chem. Soc.* **2010**, *132*, 8842–8843.
(29) Lopez, F.; Castedo, L.; Mascarenas, J. L. *Org. Lett.* **2000**, *2*, 1005–1007.
(30) Kawasumi, M.; Kanoh, N.; Iwabuchi, Y. *Org. Lett.* **2011**, *13*, 3620–3623.
(31) Davies, H. M. L.; Ahmed, G.; Churchill, M. R. *J. Am. Chem. Soc.* **1996**, *118*, 10774–10782.
(32) Garnier, E. C.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2008**, *130*, 7449–7458.

(33) Abrecht, S.; Harrington, P.; Iding, H.; Karpf, M.; Trussardi, R.; Wirz, B.; Zutter, U. *Chimia* **2004**, *58*, 621−629.
(34) Vogel, P.; Fattori, D.; Gasparini, F.; Le Drian, C. *Synlett.* **1990**, 173−185.
(35) Shao, H.; Ekthawatchai, S.; Wu, S.-H.; Zou, W. *Org. Lett.* **2004**, *6*, 3497−3499.
(36) Tian, Q.; Dong, L.; Ma, X.; Xu, L.; Hu, C.; Zou, W.; Shao, H. *J. Org. Chem.* **2011**, *76*, 1045−1053.
(37) Wang, Z.; Shao, H.; Lacroix, E.; Wu, S. H.; Jennings, H. J.; Zou, W. *J. Org. Chem.* **2003**, *68*, 8097−8105.
(38) Riemann, I.; Fessner, W.-D.; Papadopoulos, M. A.; Knorst, M. *Aust. J. Chem.* **2002**, *55*, 147−154.
(39) Bundle, D. R.; Gerken, M.; Peters, T. *Carbohydr. Res.* **1988**, *174*, 239−251.
(40) Pihko, P. M.; Majander, I.; Erkkilä, A. *Top. Curr. Chem.* **2010**, *291*, 29−75.
(41) Angyal, S. J. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 157−226.
(42) DuRetie, P. L.; Horton, D. *Carbohydr. Res.* **1971**, *18*, 57−80.
(43) Zou, W.; Vembaiyan, K.; Bhasin, M.; Williams, D. T. *Carbohydr. Res.* **2009**, *344*, 2144−2150.

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