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Construction of 3,6-Anhydrohexosides via Intramolecular Cyclization of Triflates and Its Application to the Synthesis of Natural Product Isolated from Leaves of *Sauropus rostratus*

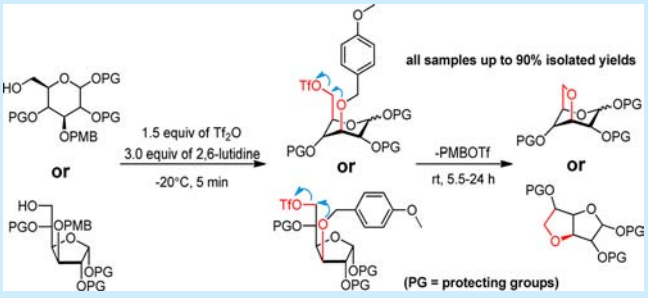
Long Liu,[†] Cheng-Qian Wang,[†] Dan Liu,[†] Wei-Gang He,[†] Jin-Yi Xu,[†] Ai-Jun Lin,[†] He-Quan Yao,[†] Genzoh Tanabe,[‡] Osamu Muraoka,[‡] Wei-Jia Xie,*[,†] and Xiao-Ming Wu*[,†]

[†]State Key Laboratory of Natural Medicines and Department of Medicinal Chemistry, China Pharmaceutical University, Nanjing 210009, P. R. China

[‡]School of Pharmacy, Kinki University, 3-4-1 Kowakae, Higashi-osaka, Osaka 577-8502, Japan

Supporting Information

ABSTRACT: A novel synthetic approach to construct various 3,6-anhydrohexosides via an intramolecular cyclization of corresponding triflates is described. The nucleophilic attack from C3 *p*-methoxybenzylated hydroxyl to C6 trifluoromethanesulfonate on triflate structures triggered the cyclization reaction to provide 3,6-anhydrohexosides in excellent yields, making the strategy more efficient with respect to the reported protocols. By applying this methodology, a concise first total synthesis of natural product isolated from leaves of *Sauropus rostratus* was accomplished.



3,6-Anhydrohexoside moieties occur in a number of bioactive natural products and synthetic molecules such as agar oligosaccharides (AOS),[1] iota (*ι*)- and kappa (*κ*)-carrageenan **1** and **2**,[2] furanodictines A (**3**) and B (**4**),[3] and staurosporine analogue **5**.[4] Most recently, a group of 3,6-anhydro-2-deoxy hexosides **6**−**8** were isolated from the leaves of *Sauropus rostratus* (Figure 1).[5] These molecules exhibit a variety of biological properties including antioxidative, antitumor, antihyperlipidemic, antiviral, and antiinflammatory activities.

In the past few decades, several synthetic protocols to construct 3,6-anhydrohexoside structures have been reported, among which the most general and reliable method is the intramolecular cyclization of a corresponding tosylate under alkaline conditions.[6] However, the tosylation reaction is time-consuming, and the product tosylates are usually obtained in low yields. The following cyclization reaction should be conducted in strong basic conditions, which are not suitable for protecting groups sensitive to alkali. Other functional groups such as mesylate,[7] fluorine,[4] triphenylphosphinium,[8] and cyclic sulfite[9] were also used as leaving groups to initiate the intramolecular cyclization reaction (Scheme 1). Unfortunately, defects such as harsh reaction conditions, low yield of

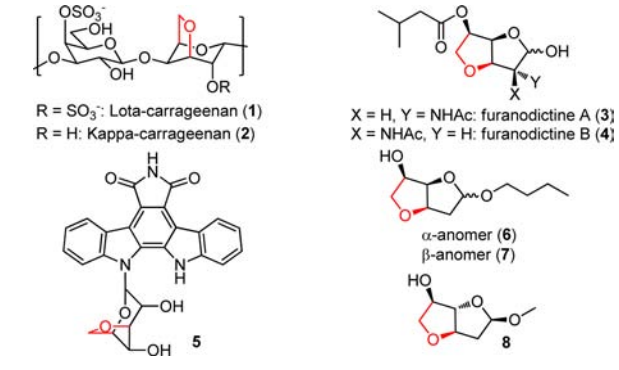
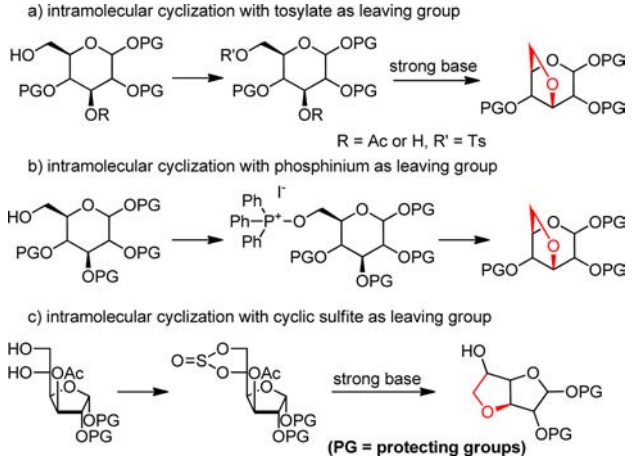


Figure 1. Bioactive molecules containing 3,6-anhydrohexoside structures.

Scheme 1. Reported Protocols To Construct 3,6-Anhydrohexoside Structures



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product, or toxic reagent restricted their further application in organic synthesis. Herein, we are pleased to develop a convenient and effective protocol to afford different 3,6-anhydrohexosides with mild organic base.

In 2011, we reported the total syntheses of neoponkoranol **9** and its epimer **5′-*epi*-9** as potent α-glucosidase inhibitors.[10a] An interesting intramolecular cyclization reaction was encountered in the course of coupling reaction between thiosugar **10** and triflate **11**, which were protected by neutral substituent benzyl. The desired sulfonium salt **12** was obtained in 37% yield together with a 3,6-anhydromannoside derivative **13** and **14** as side products (Figure 2). Triflate **11** was assumed to exist in

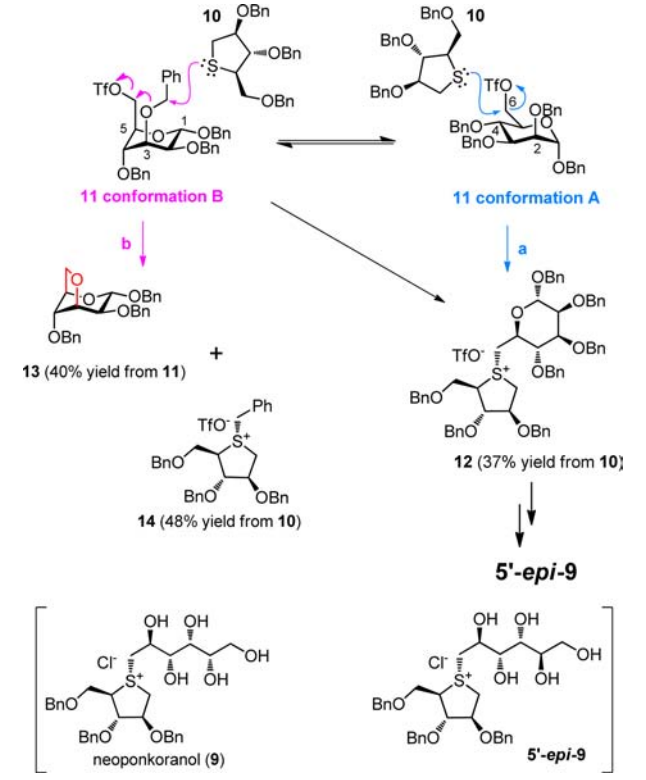

Figure 2. Plausible mechanism of the reported coupling reaction between thiosugar **10** and triflate **11**.

two formations (A and B in Figure 2) in the reacting system, and the nucleophilic attack from thiosugar might take place at either the C6 methylene (route a) or the C3 benzyloxy moiety (route b) of **11**, providing different products. When triflates were protected with electron-withdrawing groups such as esters, the coupling reaction only proceeded through route a, with the desired sulfonium salt obtained in 84% yield.[10b] Based on these facts, we speculated that with much stronger electron-donating substitution, the intramolecular cyclization might be generated more easily even without the nucleophilic attack from thiosugar to give 3,6-anhydrohexosides.

In order to prove our assumption, we initiated the investigation by using a model substrate **15**,[11] which was protected by a stronger electron-donating group (PMB). In the preliminary trial, the primary alcohol **15** was treated with 1 equiv of Tf_2O and 2.0 equiv of 2,6-lutidine in CH_2Cl_2 at −20 °C. TLC monitoring showed that a spot corresponding to triflate **16** emerged immediately after the administration of Tf_2O, although a certain amount of reactant still remained. To our delight, after being stirred at rt for 48 h, **16** was totally converted to a new compound which was isolated with the yield of 63%. The FAB mass spectrum of this compound showed a peak at m/z 515 corresponding to the sodium adduct ion to molecule **17**. In NMR spectrascopic studies, the ^{13}C chemical shift of C6 methylene from 61.9 ppm (typical signal of primary alcohol) of **15** to 69.4 ppm (typical resonance of C6 carbon of 3,6-anhydrohexosides) of **17** suggested the formation of the tricyclic structure. A NOE correlation between H-6a and H-1 as well as HMBC correlations between positions H-3 and C-6, C-3 and H-6, and H-5 and C-1 also supported the depicted structure of **17**.[12] Finally, X-ray structural analysis of **17** clearly demonstrated a key ether bridge connecting C3 and C6 on the sugar structure (Figure 3).[13] The formation of **17**,

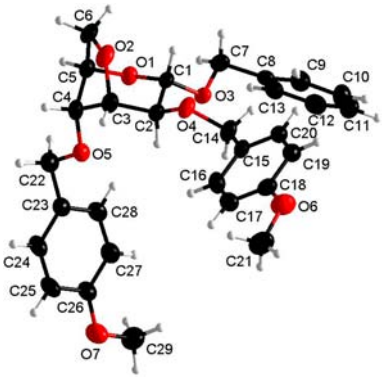

Figure 3. X-ray crystal structure of tricyclic compound **17**.

albeit in moderate yield, proved our former speculation that when substituted with appropriate groups, the intramolecular cyclization of triflate could be generated without any exogenous substrate as nucleophiles. Encouraged by this result, we then gradually increased the amount of the reacting reagents. It was found that increasing the loading of Tf_2O and 2,6-lutidine could both accelerate the reaction speed and improve the yield of **17** (Table 1, entries 2−4). When **15** was treated with 1.5 equiv of Tf_2O and 3.0 equiv of 2,6-lutidine, compound **17** was obtained with the highest yield of 95% and the reaction was finished within 24 h. The subsequent screening on various bases indicated that changing base cannot further improve the reaction yield (Table 1, entries 5−7). We then explored the reaction in different solvent. As shown from entries 8−12, none of these solvents could further increase the reaction yield, comparing to CH_2Cl_2. When conducted in DMF or DCE (1,2-dichloroethane), no formation of the desired product could be detected. Finally, our investigation was focused on the reacting temperature. Surprisingly, only a trace amount of **17** was detected when the temperature was maintained at −20 °C, indicating that **16** may exit as a thermodynamically stable conformation **16a** (−2997.7376786 hartree)[14] at low temperature while only at higher temperature could a kinetically advantageous intramolecular cyclization of **16** take place through conformation **16b** (−2997.7310263 hartree).[14] When the reacting temperature was raised to 40 °C, **17** was isolated in a yield of 85%. Thus, the reactions in entry 3 were selected for investigation of the reaction scope.

Several primary alcohols (**18**−**23**) bearing different pyranosidic structures were first synthesized according to the reported protocols[11] (Table 2, entries 1−6). All reactants were converted to corresponding triflates immediately after the introduction of Tf_2O, and the subsequent intramolecular

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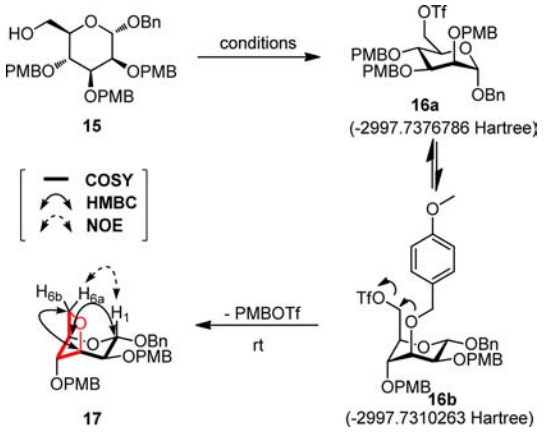
Table 1. Optimization of the Reaction Conditions[a]

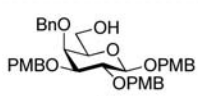
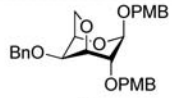
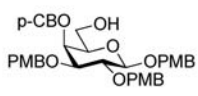
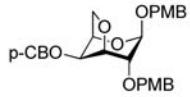
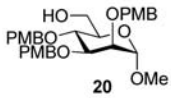
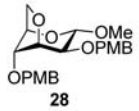
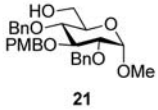
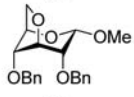
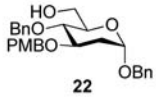
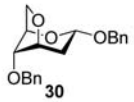
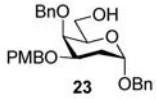
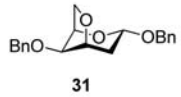
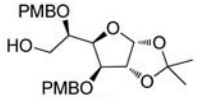
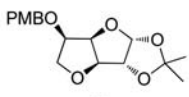
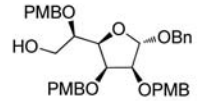
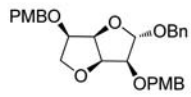


entry	Tf_2O (equiv)	base (equiv)	solvent	temp (°C)	time (h)	yield[b] (%)
1	1.0	2,6-lutidine (2.0)	CH_2C1_2	−20 to rt	48	63
2	1.2	2,6-lutidine (2.4)	CH_2C1_2	−20 to rt	48	78
3	1.5	2,6-lutidine (3.0)	CH_2C1_2	−20 to rt	24	95
4	2.0	2,6-lutidine (4.0)	CH_2C1_2	−20 to rt	24	91
5	1.5	pyridine (3.0)	CH_2C1_2	−20 to rt	24	93
6	1.5	DMAP (3.0)	CH_2C1_2	−20 to rt	24	78
7	1.5	DTBMP (3.0)	CH_2C1_2	−20 to rt	24	89
8	1.5	2,6-lutidine (3.0)	acetone	−20 to rt	24	82
9	1.5	2,6-lutidine (3.0)	MeCN	−20 to rt	24	79
10	1.5	2,6-lutidine (3.0)	THF	−20 to rt	24	35
11	1.5	2,6-lutidine (3.0)	DMF	−20 to rt	24	0
12	1.5	2,6-lutidine (3.0)	DCE	−20 to rt	24	0
13	1.5	2,6-lutidine (3.0)	CH_2C1_2	−20	24	trace
14	1.5	2,6-lutidine (3.0)	CH_2C1_2	−20 to +40	24	85

[a]All reactions were performed on a 0.5 mmol scale in anhydrous solvents. [b]Isolated yield.

cyclization occurred smoothly to afford the corresponding 3,6-anhydrohexosides in excellent yields. Changing the protecting group on other positions of the pyranoside structure had no significant effect on the reaction yields. Comparatively, compound **29** was obtained in relatively low yield with respect to **17**, **26**, **27**, and **28**. We attributed this result to steric effects that four axial-oriented bonds on **29** made occurrence of ring flip from $^4C_1$ to $^1C_4$ conformation more difficult. In order to prove our assumption, two primary alcohols **22**[11] and **23**[11] bearing 2-deoxyhexoside structures were synthesized. Cyclization reaction of **22** and **23** were finished in a shorter time, and the corresponding tricyclic products **30** and **31** were obtained in higher yields, compared to those of **29** (Table 2, entries 5 and 6). Our next examination was performed to extend the scope from hexopyranoside to hexofuranoside. Under the same reaction conditions, primary alcohols **24**[11] and **25**[11] were derived from their corresponding bicyclic products with yields

Table 2. Reaction Scope[a]

entry	reactant	product	time	yield (%)[b]
1	 **18**	 **26**	5 h	95
2[c]	 **19**	 **27**	4 h	93
3	 **20**	 **28**	24 h	97
4[d]	 **21**	 **29**	8 h	90
5[d]	 **22**	 **30**	5.5 h	98
6	 **23**	 **31**	5.5 h	92
7	 **24**	 **32**	5.5 h	95
8	 **25**	 **33**	5.5 h	91

[a]Reaction conditions: primary alcohol (0.5 mmol), Tf_2O (1.5 equiv), 2,6-lutidine (3 equiv), in CH_2C1_2 (4 mL), at −20 °C and then rt for 24 h. [b]isolated yield. [c]p-CB = *p*-chlorobenzyl. [d]1.5 equiv of NaH was added in the reacting sysntem.

up to 90% (Table 2, entries 7 and 8), clearly demonstrating that our method is effective for hexosides bearing different sugar structures.

Finally, the first total synthesis of natural product **7**, a potential anti-inflammatory agent isolated from the leaves of *Sauropus rostratus*, was attempted. The bicyclic structure of **7** was constructed by applying our newly developed strategy. Thus, commercially available 2-deoxy-D-*arabino*-hexopyranose **34** was treated with butyl alcohol in the presence of trifluoroacetic acid in dry DMF to give an inseparable mixture of butyl glucofuranosides and pyranosides,[15] which was taken on to the next step without further purification. The primary alcohol of the resulted mixture was selectively protected by the TBS group. After separation by column chromatography, compound **36** was obtained in 33% yield by two steps, which was then subjected to *p*-methoxybenzylation to afford intermediate **37** in 85% yield. Selective deprotection of the TBS group in **37** was accomplished by using TBAF to give primary alcohol **38** as the precursor of the key intramolecular cyclization reaction in 92% yield. Triflation of **38** was conducted under the same conditions outlined in Table 1, entry 3. Intramolecular cyclization of **39** was accomplished in 5

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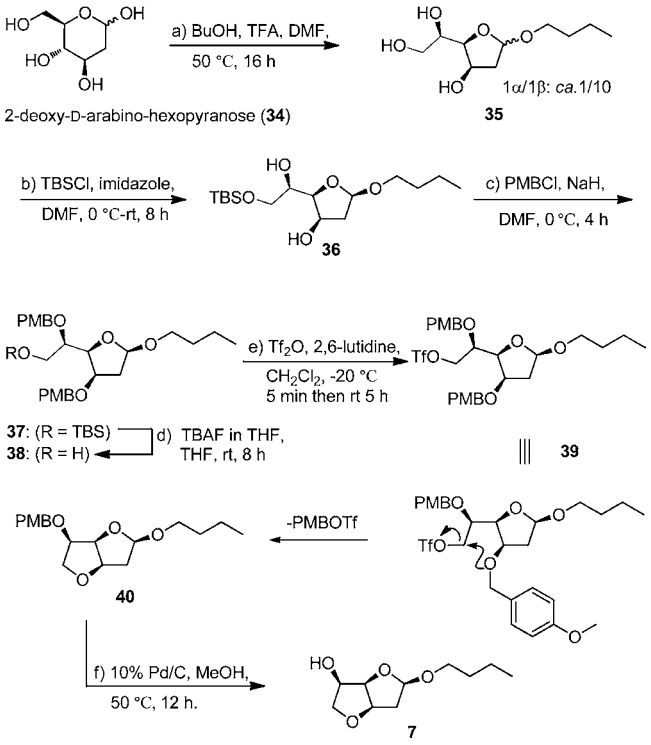
h to give the desired bicyclic product **40** with a yield of 96%, indicating that our strategy is also effective for 2-deoxyhexofuranosides. Hydrogenolysis of **40** with 10% Pd/C in methanol was performed at 50 °C to afford the natural product **7** in 86% yield (Scheme 2). The spectral properties of **7** synthesized in the present study are in exact accord with those reported.[5a]

Scheme 2. First Total Synthesis of Natural Product 7



In conclusion, we have demonstrated a highly effective approach to construct a 3,6-anhydrohexoside motif via an intramolecular cyclization reaction of C6 trifluoromethanesulfonated hexoside. This method is effective for hexosides bearing different sugar skeletons, and the 3,6-anhydro products were obtained in excellent yields under mild basic reacting conditions. The first total synthesis of natural product **7** was accomplished in six steps from a commercial source in 21% overall yield. The application of our methodology to the total synthesis of **7** highlights the potential utility of this strategy in the synthesis of other complex bioactive molecules, which is underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

General information, synthetic procedures, ^{1}H and ^{13}C NMR spectra, structures of conformers **16a** and **16b**, and X-ray data for **17** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: weijiaxie@cpu.edu.cn.
*E-mail: xmwu@cpu.edu.cn.

Notes

The authors declare no competing financial interest.

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