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Highly stereoselective synthesis of *C*-vinyl furanosides through acid-catalyzed S_N2 inversion at the C-3 position of 1,2-dideoxy-hept-1-enitols ☆

Hitoshi Tsuchiya, Noriaki Asakura, Yasunori Ikeda, Hidetoshi Yamada *

School of Science and Technology, Kwansei Gakuin University, 2-1 Gakuen, Sanda 669-1337, Japan

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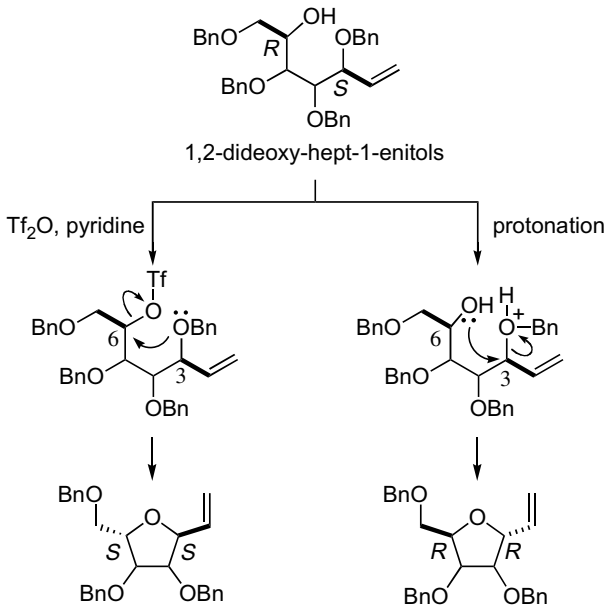
ABSTRACT

A highly stereoselective synthesis of *C*-vinyl furanosides through the S_N2 inversion at the C-3 position of the 1,2-dideoxy-hept-1-enitols is disclosed. Treatment of the 1,2-dideoxy-hept-1-enitols with diphenylammonium trifluoromethanesulfonate as the acid catalyst produced the *C*-vinyl furanosides (3,6-anhydro-1,2-dideoxy-hept-1-enitol derivatives) via a subsequent S_N2 intramolecular debenzyloxyation–cycloetherification reaction at the C-3 position.

C-Furanosides possess a wide array of applications, and some of them have remarkable biological activities as C-nucleosides.[1] Synthetically, *C*-vinyl furanosides are some of the potentially useful intermediates leading to a variety of C-furanosides,[2] and thus several stereocontrolled synthetic approaches toward the *C*-vinyl furanosides have been previously reported.[3,4] Among them, Martin et al.[3a] and Yang et al.[3b] independently developed a synthetic method for *C*-vinyl furanosides through the S_N2 inversion at the C-6 position of the 3,4,5,7-tetrabenzyloxy-6-hydroxyhept-1-enes, which are hereafter abbreviated to 1,2-dideoxy-hept-1-enitols (Scheme 1, left-hand pathway). Because of the high stereoselectivity and easy availability of the starting 1,2-dideoxy-hept-1-enitols, an inversion of the reaction site would double the available diastereomers starting from a single substrate. We herein describe the development of a highly stereoselective synthesis of *C*-vinyl furanosides through the S_N2 inversion at the C-3 position of the 1,2-dideoxy-hept-1-enitols (Scheme 1, right-hand pathway).

We stumbled across the stereoselective cycloetherification during examinations for esterification of partly protected 1,2-dideoxy-D-*gluco*-hept-1-enitol (**1**) with (1,1′-diphenyl)-2,2′-dicarboxylic acid using diphenylammonium trifluoromethanesulfonate (DPAT) with respect to the synthetic approach of corilagin (Scheme 2).[5] DPAT is an effective and practical reagent for esterification, which was developed by Tanabe and co-workers.[6] However, despite our intention to achieve first an inter- and then an intramolecular bis-macrolactonization of the diol **1**, no desired product was



Scheme 1. Left-hand pathway: Martin's or Yang's procedure; right-hand pathway: this study.

☆ Detailed general methods and NMR spectra for compounds **2** and **8** are given in the Supplementary data section.

* Corresponding author. Tel.: +81 79 565 8342; fax: +81 79 565 9077.
E-mail address: hidetosh@kwansei.ac.jp (H. Yamada).

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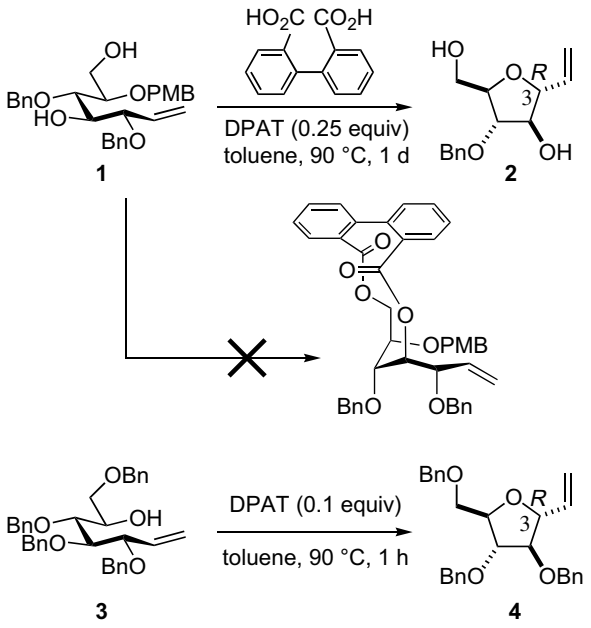


Scheme 2. Detection of the C-furanosylation. DPAT = diphenylammonium trifluoromethanesulfonate.

produced. Instead, a C-furanoside **2** was detected in 79% yield as a single diastereomer. The *R* stereochemistry at C-3 was predicted because its DPFGSE (double pulse field gradient spin echo) 1D-NOESY spectra indicated the correlation between H-2 and -4, between H-2 and -6, and between H-3 and -5. Similar intramolecular etherification proceeded using the more readily available substrate, 1,2-dideoxy-D-*gluco*-hept-1-enitol (**3**),[7] and DPAT to provide **4**[8] in 49% yield, whose C-3 stereochemistry is *R*.

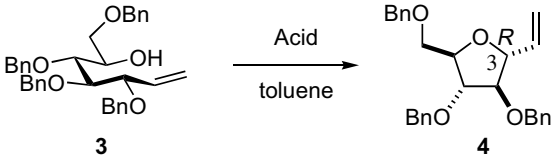
Optimization of the reaction conditions increased the yield of **4** to 60% (Table 1). Use of equimolar amounts of **3** and DPAT did not increase the yield (entry 1). The reaction was accelerated at elevated temperature with a catalytic amount of DPAT; however, the yields were not affected (entries 2–6). On the other hand, a technical elaboration in addition of reagents increased the yield. Thus, the slow addition of a toluene solution of **3** into a heated solution of DPAT in toluene using a syringe pump afforded **4** in 60% yield (entry 7). Intermolecular reactions were prevented by keeping a low concentration of substrate **3**. However, even with this slow addition method, an increase of the catalyst did not indicate further positive effects (entries 8 and 9). Attempts using several other Lewis and protic acids also provided **4** as a single diastereomer, but the yields were lower than that with the use of DPAT (entries 10–14). Although generation of unidentified side products was observed in all cases, fortunately, **4** was easily isolated from each reaction mixture by simple column chromatography on silica gel. Therefore, the conditions of entry 7 were selected for the following applications. It is not clear why diol **1** reacted more smoothly than **3**.

This reaction was applicable to 1,2-dideoxy-hept-1-enitols derived from D-mannose and D-galactose. Thus, 1,2-dideoxy- D-*manno*-hept-1-enitol (**5**)[3] and 1,2-dideoxy-D-*galacto*-hept-1-enitol (**6**)[9] were similarly treated with DPAT to provide the cyclized products **7**[8] and **8**, respectively, with inversion of C-3 stereochemistry (Scheme 3). The structure of **8** was confirmed by its conversion to the known **9**.[10]

We concluded that the reaction passed the S_N2 attack of the O-6 at the secondary allylic carbon, that is the C-3 position, following the protonation of the benzyloxy group (Scheme 1), because both D-glucose-derived **3** and its C-3 epimer, D-mannose-derived **5**, produced C-3-(*R*)-**4** and C-3-(*S*)-**7**, respectively. Recently, Cribiú and Cumpstey reported a similar inversion of the allylic stereochemistry in a trifluoroacetic acid-mediated debenzylative cycloetherification.[4a] Our results here using the 1,2-dideoxy-hept-1-enitols supported the generality of the S_N2 inversion at the allylic position. Further, this study revealed that such cycloetherification is possible using a catalytic amount of the acidic reagent in contrast to the Cribiú–Cumpstsey method, which used trifluoroacetic acid as a part of the reaction solvent. These results are in apparent contrast to method described by Martin et al.[3a] and Yang et al.[3b] which involves the S_N2 inversion at C-6. Thus, these two complementary methods provide different diastereomers stereoselectively starting from the same substrate.

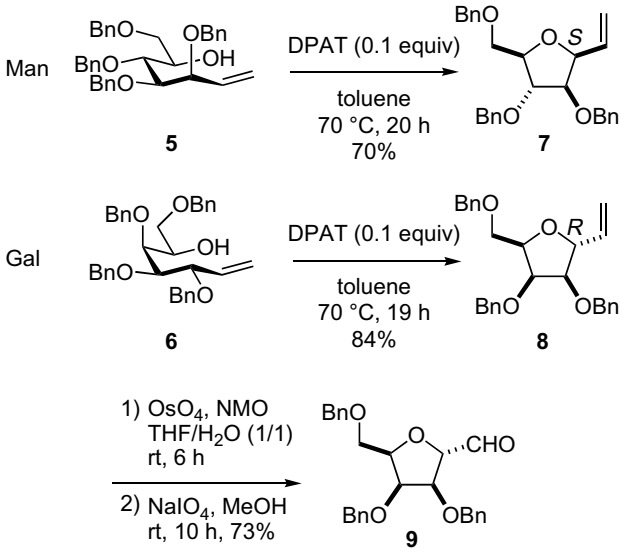
In summary, the accidentally found C-furanosylation proceeded through the S_N2 inversion at the C-3 position. This reaction could be applied to the substrates derived from D-glucose, mannose, and galactose, to produce the corresponding *C*-vinyl furanosides. Despite their moderate yields, the isolation of each product was

Table 1
Optimization of the reaction conditions



Entry	Acid (equiv)	Temperature (°C)	Time (h)	Yield (%)
1	DPAT (1.0)	90	3.5	45
2	DPAT (0.1)	rt	48	0
3	DPAT (0.1)	40	15	47
4	DPAT (0.1)	60	3	48
5	DPAT (0.1)	90	1	49
6	DPAT (0.1)	110	0.083	45
7[a]	DPAT (0.1)	80	21	60
8[a]	DPAT (0.2)	70	12	58
9[a]	DPAT (0.5)	70	12	52
10	$BF_3{\cdot}OEt_2$ (0.1)	60–100	48	31
11[a]	$Cu(OTf)_2$ (0.2)	70	21	33
12[a]	$Sn(OTf)_2$ (0.1)	70	24	37
13[a]	$Yb(OTf)_3$ (0.1)	80	24	40
14[a]	TfOH (0.2)	40	24	56

[a] A toluene solution of **3** was slowly added to a heated solution of the acid in toluene by syringe pump.



Scheme 3. C-Furanosylation using derivatives of D-mannose **5**, and D-galactose **6**. NMO = *N*-methylmorpholine-*N*-oxide.

easy. The combination of this and the previously known methods has stereoselectively doubled the available diastereomers starting from a single starting material.

1. Experimental

1.1. General methods

All commercially available reagents were used without further purification. All reactions were performed under a positive pressure of nitrogen. Column chromatography was performed on E. Merck Silica Gel 60 (0.063–0.200 mm, 70–230 mesh). The ^{1}H NMR data are indicated by a chemical shift with the multiplicity, the coupling constants, and the integration in parentheses in this order. The multiplicities are abbreviated as s, singlet; d, doublet; t, triplet; m, multiplet; and br, broadened. The ^{13}C NMR data are reported as the chemical shift with the hydrogen multiplicity obtained from the DEPT spectra.

1.2. Preparative procedures and characterization of compounds

1.2.1. 3,6-Anhydro-5-*O*-benzyl-1,2-dideoxy-D-*manno*-hept-1-enitol (2)

A mixture of (3*S*,4*R*,5*S*,6*R*)-3,5-dibenzyloxy-4,7-dihydroxy-6-(4-methoxybenzyl)oxyhept-1-ene (**1**) (31.8 mg, 66.4 μmol), (1,1′-diphenyl)-2,2′-dicarboxylic acid (16.1 mg, 66.5 μmol), and diphenylammonium trifluoromethanesulfonate (DPAT, 5.2 mg, 16.3 μmol) in toluene (7 mL) was stirred at 90 °C for 1 day. The mixture was poured into water, and it was extracted with AcOEt. The organic layer was successively washed with water and brine, dried over $MgSO_4$, filtered through a cotton pad, and evaporated. The resulting residue was purified by column chromatography on silica gel (SiO_2: 2.5 g, eluant: 2:1 to 1:1 hexane–EtOAc) to give **2** (13.1 mg, 79% yield): $[\alpha]_D^{24}$ +52.9 (*c* 0.895, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.41–7.29 (m, 5 H), 5.95 (ddd, *J* = 17.6, 10.4, 7.2 Hz, 1H), 5.30 (d, *J* = 17.6 Hz, 1H), 5.18 (d, *J* = 10.4 Hz, 1H), 4.66 (d, *J* = 11.6 Hz, 1H), 4.57 (d, *J* = 11.6 Hz, 1H), 4.39 (dd, *J* = 7.2, 3.6 Hz, 1H), 4.17 (ddd, *J* = 3.2, 3.2, 2.8 Hz, 1H), 4.11 (dd, *J* = 3.6, 3.2 Hz, 1H), 3.97 (dd, *J* = 3.2, 3.2 Hz, 1H), 3.81 (dd, *J* = 12.0, 2.8 Hz, 1H), 3.64 (dd, *J* = 12.0, 3.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 137.7 (s), 136.0 (d), 128.5 (d, 2C), 127.9 (d), 127.6 (d, 2C), 117.1 (t), 87.2 (d), 86.2 (d), 83.4 (d), 79.4 (d), 72.1 (t), 63.0 (t); HRESIMS (*m*/*z*): $[M+NH_4]^+$ calcd for $C_{14}H_{18}O_4$, 268.1549; found, 268.1547.

1.2.2. Preparation of 3,6-anhydro-4,5,7-tri-*O*-benzyl-1,2-dideoxy-D-*manno*-hept-1-enitol (4)[8] (Table 1, entry 7)

To a stirred solution of DPAT (6.0 mg, 19 μmol) in toluene (5 mL) was added a solution of (3*S*,4*R*,5*R*,6*R*)-3,4,5,7-tetrabenzyloxy-6-hydroxyhept-1-ene (**3**) (100 mg, 0.186 mmol) in toluene (4.2 mL) at 80 °C using a syringe pump at the rate of 1 mL/h. After completion of the addition, the mixture was further stirred for 17 h. The mixture was poured into water and extracted with EtOAc. The organic layer was successively washed with water, satd aq $NaHCO_3$, and brine, dried over $MgSO_4$, filtered through a cotton pad, and evaporated. The resulting residue was purified by column chromatography on silica gel (SiO_2: 3 g, eluant: 15:1 to 5:1 hexane–EtOAc) to give **4** (48 mg, 60% yield) as a pale-yellow syrup. The NMR spectra of the compound were identical to those reported.[8]

1.2.3. Preparation of 3,6-anhydro-4,5,7-tri-*O*-benzyl-1,2-dideoxy-D-*gluco*-hept-1-enitol (7)[8]

To a stirred solution of DPAT (5.9 mg, 19 μmol) in toluene (10 mL) was added a solution of (3*R*,4*R*,5*R*,6*R*)-3,4,5,7-tetrabenzyloxy-6-hydroxyhept-1-ene (**5**) (100 mg, 0.186 mmol) in toluene (10 mL) at 70 °C using a syringe pump at the rate of 0.5 mL/h during a period of 20 h. The mixture was poured into water, and it was extracted with Et_2O. The organic layer was successively washed with water, satd aq $NaHCO_3$, and brine, dried over $MgSO_4$, filtered through a cotton pad, and evaporated. The resulting residue was purified by column chromatography on silica gel (SiO_2: 3 g, eluant: 7:1 hexane–EtOAc) to give **7** (57 mg, 70% yield) as a pale-yellow syrup. The NMR spectra of the compound were identical to those reported.[8]

1.2.4. 3,6-Anhydro-4,5,7-tri-*O*-benzyl-1,2-dideoxy-D-*talo*-hept-1-enitol (8)

To a stirred solution of DPAT (13 mg, 41 μmol) in toluene (20 mL) was added a solution of (3*S*,4*R*,5*S*,6*R*)-3,4,5,7-tetrabenzyloxy-6-hydroxyhept-1-ene (**6**) (201 mg, 0.373 mmol) in toluene (12 mL) at 70 °C using a syringe pump at the rate of 2 mL/h during a period of 6 h. After completion of the addition, the mixture was further stirred for 13 h. The mixture was poured into water, and extracted with EtOAc. The organic layer was successively washed with satd aq $NaHCO_3$ and brine, dried over $MgSO_4$, filtered through a cotton pad, and evaporated. The resulting residue was purified by column chromatography on silica gel (SiO_2: 5 g, gradient elution with 15:1 to 8:1 hexane–EtOAc) to give **8** (135 mg, 84% yield) as a pale-yellow syrup: $[\alpha]_D^{23}$ −18.1 (*c* 1.2, $CHCl_3$); IR (ZnSe, thin film): 3088, 3063, 3030, 2919, 2864, 1497, 1454, 1092, 737, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.35–7.26 (m, 15 H), 5.82 (ddd, *J* = 17.2, 10.3, 6.9 Hz, 1H; H-2), 5.38 (ddd, *J* = 17.2, 1.4, 1.4 Hz, 1H; H-1), 5.19 (ddd, *J* = 10.3, 1.4, 1.4 Hz, 1H; H-1), 4.76 (d, *J* = 11.9 Hz, 1H; Bn), 4.61 (d, *J* = 11.9 Hz, 1H; Bn), 4.59 (d, *J* = 12.1 Hz, 1H; Bn), 4.59 (d, *J* = 11.9 Hz, 1H; Bn), 4.54 (d, *J* = 12.1 Hz, 1H; Bn), 4.50 (d, *J* = 11.9 Hz, 1H; Bn), 4.49 (br t, *J* = 7.1 Hz, 1H; H-3), 4.27 (ddd, *J* = 6.6, 6.2, 4.1 Hz, 1H; H-6), 4.10 (dd, *J* = 4.1, 4.1 Hz, 1H; H-5), 3.78 (dd, *J* = 9.8, 6.2 Hz, 1H; H-7), 3.75 (dd, *J* = 7.3, 4.1 Hz, 1H; H-4), 3.69 (dd, *J* = 9.8, 6.6 Hz, 1H; H-7); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.3 (s), 138.2 (s), 137.8 (s), 137.0 (d), 128.4-127.6 (many doublets, 15 C), 117.5 (t), 83.6 (d), 80.8 (d), 78.7 (d), 77.2 (d), 73.5 (t), 73.4 (t), 72.5 (t), 69.0 (t); HRESIMS (*m*/*z*): $[M+Na]^+$ calcd for $C_{28}H_{30}O_4$, 453.2042; found, 453.2022.

1.2.5. Preparation of 2,5-anhydro-3,4,6-tri-*O*-benzyl-D-talose (9)[10]

A mixture of **8** (115 mg, 0.276 mmol), OsO_4 (1.5 mg, 5.9 μmol), 4-methylmorpholine-*N*-oxide (90 mg, 0.77 mmol) in 1:1 THF–H_2O (10 mL) was stirred for 6 h at rt. Then, MeOH (10 mL) and $NaIO_4$ (171 mg, 0.798 mmol) were added to the mixture, and it was stirred at rt for 10 h. After evaporation to remove THF and MeOH, the aqueous mixture that remained was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered through a cotton pad, and evaporated. The resulting residue was purified by column chromatography on silica gel (SiO_2: 3 g, gradient elution with 3:1 to 1:1 hexane–EtOAc) to give **9** (83.2 mg, 73% yield) as a pale-yellow syrup. The NMR spectra of the compound were identical to those reported.[10]

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2008.08.017.

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