

**STEREOSELECTIVE RADICAL CYCLIZATION FOR THE SYNTHESIS OF
BICYCLIC HIGHER-CARBON SUGARS. SYNTHESIS OF THE SUGAR MOIETY OF OCTOSYL ACIDS**

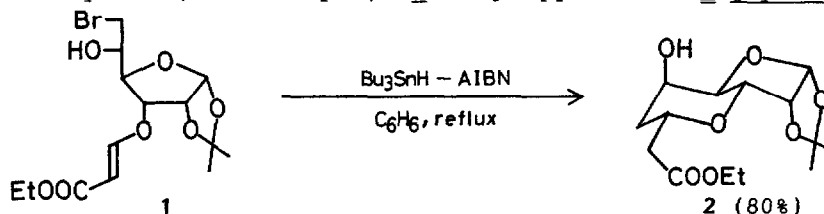
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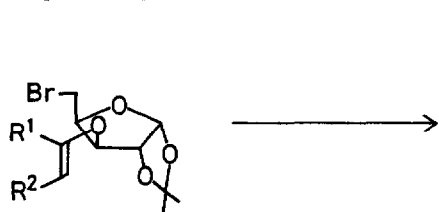
Abstract : The Bu_3SnH - AIBN induced radical cyclization of 6-bromo-6-deoxy-3- \underline{O} -[(\underline{E})-2-ethoxycarbonylethenyl]-1,2- \underline{O} -isopropylidene- α - \underline{D} -allofuranose (**1**) gave ethyl 3,7-anhydro-6,8-dideoxy-1,2- \underline{O} -isopropylidene- α - \underline{D} -glycero- \underline{D} -allo-nono-furanuronate (**2**) in 80% yield. Similar cyclizations of furanose derivatives and a synthesis of the sugar moiety of octosyl acids were described.

Tributyltin hydride (Bu_3SnH) - azobisisobutyronitrile (AIBN) induced radical additions provide versatile synthetic methods for \underline{C} -glycosyl compounds,² branched-chain sugars,³ and higher-carbon sugars.⁴ Although intramolecular radical additions are expected to proceed much more effectively,⁵ there is no report but three most recent ones concerning such intramolecular process in carbohydrate chemistry:⁶ radical cyclizations of allyl⁷ and alkynyl⁸ 2-deoxy-2-iodopyranosides (with low to medium stereoselectivity) and (2-halogenoalkyl) 2,3-dideoxy-2-enopyranosides (with medium to high stereoselectivity)⁹ affording branched-chain sugars. Recently we have shown that photo-induced radical cyclization of furanosyl derivatives proceeds effectively with high stereoselectivity affording bicyclic higher-carbon sugars.¹⁰ Therefore, Bu_3SnH - AIBN induced radical cyclization in similar furanosyl systems could afford an efficient stereoselective synthetic method for bicyclic higher-carbon sugar derivatives such as octosyl acids,¹¹ ezomycins,¹² and griseolic acids.¹³ In this communication Bu_3SnH - AIBN induced radical cyclization of terminal-halogenofuranoses bearing a \underline{O} -(2-alkoxycarbonylethenyl) group and a synthesis of the sugar moiety of octosyl acids are described.

Slow addition over 2h of a solution of Bu_3SnH (1.5 eq) in benzene to a refluxing solution of 6-bromo-6-deoxy-3- \underline{O} -[(\underline{E})-2-ethoxycarbonylethenyl]-1,2- \underline{O} -isopropylidene- α - \underline{D} -allofuranose (**1**)¹⁴ (1.0 eq) and AIBN (0.06 eq) in benzene under argon, and further refluxing of the resulting solution for 30 min gave ethyl 3,7-anhydro-6,8-dideoxy-1,2- \underline{O} -isopropylidene- α - \underline{D} -glycero- \underline{D} -allo-nono-



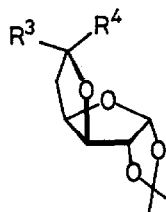
furanuronate (2)^{15,16} in 80% yield. No other diastereomer was isolated. Thus, the cyclization reaction was shown to proceed readily with almost 100% stereoselectivity. All the similar cyclization reactions of terminal-halogeno-O-(2-alkoxycarbonyl-ethenyl) derivatives¹⁴ of D-xylofuranose (3, 4, and 5), D-glucofuranose (6 and 7), and D-allofuranose (8, 9, and 10) afforded the corresponding bicyclic higher-carbon furanoses in good yields with high



3 : R¹ = H; R² = COOEt

4 : R¹ = R² = COOMe

5 : R¹ = Me; R² = COOMe

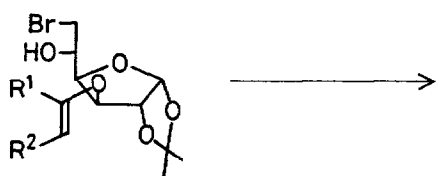


11 : R³ = CH₂COOEt; R⁴ = H (69%)

12 : R³ = COOMe; R⁴ = CH₂COOMe (67%)

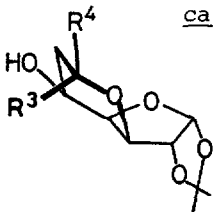
13 : R³ = CH₂COOMe; R⁴ = COOMe (15%)

14 : R³, R⁴ = Me, CH₂COOMe
(diastereomeric mixture,
ca. 4 : 1) (89%)



6 : R¹ = H; R² = COOEt

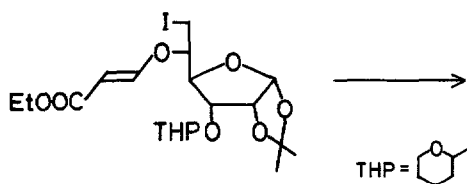
7 : R¹ = Me; R² = COOMe



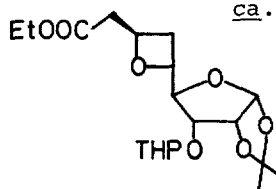
15 : R³ = H; R⁴ = CH₂COOEt

16 : R³ = CH₂COOEt; R⁴ = H
(mixture, 15 : 16 = ca. 5 : 1)
(75%)

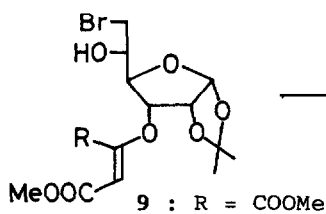
17 : R³, R⁴ = Me, CH₂COOMe
(diastereomeric mixture,
ca. 9 : 1) (77%)



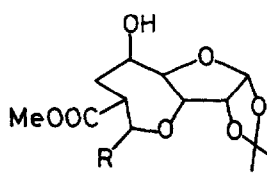
8



18 (45%) (diastereomers at C-2
19 (26%) of the THP group)

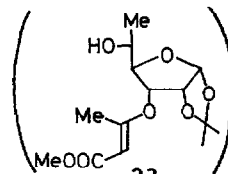


9 : R = COOMe



20 (one diastereomer) (61%)

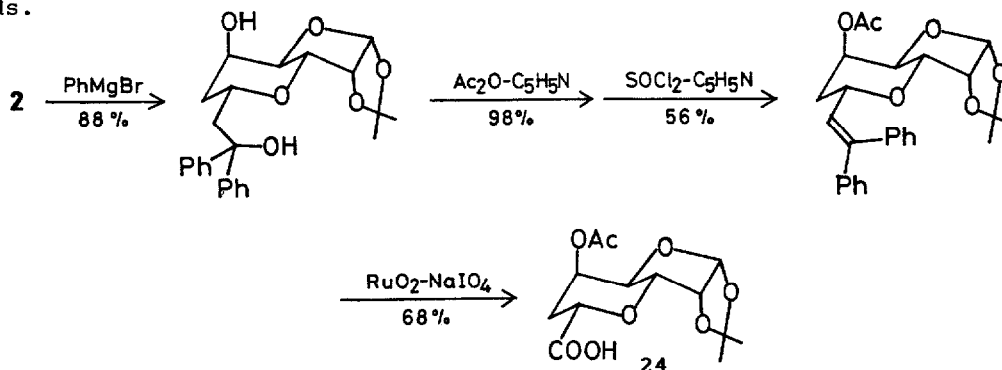
21 (diastereomeric mixture)
(21%)



22 (one diastereomer) (61%)
the reduced product (23) (13%)

stereoselectivity. Among these compounds, **3** and **8** cyclized almost 100% stereoselectively to give ethyl 3,6-anhydro-5,7-dideoxy-1,2-O-isopropylidene- α -D-glycero-D-xylo-octofuranuronate (**11**)^{15,17} (69% yield) and ethyl 5,7-anhydro-6,8-dideoxy-1,2-O-isopropylidene-3-O-tetrahydropyranyl- β -L-glycero-D-allo-nonofuranuronate (**18** and **19**)^{15,18} (45% and 26% yields), respectively. Xylo- and glucofuranose derivatives **4**, **5**, **6**, and **7** gave both the diastereomers **12**^{15,19} (67% yield) and **13**¹⁵ (15% yield); **14**²⁰ (89% yield, *ca.* 4 : 1 diastereomeric mixture); **15**²¹ and **16** (75% yield, *ca.* 5 : 1 diastereomeric mixture); and **17**²⁰ (77% yield, *ca.* 9 : 1 diastereomeric mixture), respectively. Allofuranoses **9** and **10**, different from **1**, gave seven membered anhydride compounds **20**^{15,22} (61% yield, one diastereomer) and **21**²⁰ (21% yield, diastereomeric mixture); and **22**^{15,22} (61% yield, one diastereomer) along with the reduced product **23**¹⁵ (13% yield), respectively. The formation of the seven membered anhydride rings in **20**, **21**, and **22** is possibly due to the steric hindrance of the 1'-substituents in **9** and **10** forcing the 6-C radicals to add at C-2'. And the formation of the reduced product **23** is due to the diminished reactivity of the O-[(1-methyl-2-methoxycarbonyl)ethenyl] group in **10** to carbon radicals by the effect of the electron-donating methyl group in comparison with that of the O-[1,2-bis(methoxycarbonyl)ethenyl] group in **9**.

As shown in Scheme 1, the cyclization product **2** was readily converted to the one carbon lower homolog, 5-O-acetyl-3,7-anhydro-6-deoxy-1,2-O-isopropylidene- α -D-glycero-D-allo-octofuranuronic acid (**24**)¹⁵ which is a protected derivative of the sugar moiety of octosyl acids.¹¹ Therefore, the radical cyclization can be used as a key step for the total synthesis of octosyl acids.



From the above results the Bu_3SnH - AIBN induced radical cyclization reaction of terminal-halogeno-O-(2-alkoxycarbonylethenyl)-furanoses was proved to be a very useful synthetic method for various types of bicyclic higher-carbon furanoses.

NOTES AND REFERENCES

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- 14 O-(2-Alkoxy-carbonyl-ethenyl) groups of these materials were introduced by Michael-type addition reaction of sugar OH with acetylene carboxylate derivatives; details of the reactions will be published in near future.
- 15 The structures of these compounds were confirmed by their ir and nmr spectra, and by their micro-elemental analyses.
- 16 The configuration at C-7 of this compound was determined by the H - H coupling pattern of its nmr spectrum ($J_{5,6}$ 3.5, $J_{5,6'}$ 2.3, $J_{6,7}$ 2.0, and $J_{6',7}$ 11.9 Hz).
- 17 The configuration at C-6 of this compound was determined by the H - H coupling pattern of its nmr spectrum ($J_{4,5}$ 5.0, $J_{4,5'}$ 0, $J_{5,6}$ 8.7, and $J_{5',6}$ 4.4 Hz), and by the observation of no NOE at H-1 on the irradiation at H-7,7' (cf. the NOE observation of 12; see ref. 19).
- 18 The configurations at C-7 of both the compounds were determined by their NOEs: on the irradiations at H-3,4, similar NOEs were observed at H-7 (18 : 5.6%, and 19 : 5.9%), but different NOEs were at one of THP protons (18 : 0%, and 19 : 3.8%).
- 19 The configuration at C-6 of this compound was determined by the NOE observed at H-1 (3.3%) on the irradiation at H-7,7'.
- 20 The configurations of these compounds were not determined.
- 21 The configuration at C-7 of the major product 15 was determined by the nmr spectrum of the mixture of 15 and 16.
- 22 The configurations at C-7 and C-8 of these compounds were not determined.

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