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Communications

Synthesis of Higher Sugars via Allyltin Derivatives of Simple Monosaccharides[1]

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Summary: The addition of monosaccharide allyltin derivatives to aldehydo sugars has been examined. The efficiency, rate yield, and stereoselectivity of the reactions are strongly dependent on the Lewis acid catalyst used. The major product is syn, and in the most striking case, two monosaccharides have been coupled directly to give an assembly containing nine contiguous chiral centers.

Sir: Syntheses of higher sugars have gained considerable attention in the past few years,[2] due partly to the fact that higher sugars are (a) components of some antibiotics and (b) are chiral, highly functionalized synthons for the preparation of complex natural products such as macrolide antibiotics.[3,4] The most convenient route to higher sugars consists of the direct coupling of two appropriately chosen monosaccharide subunits containing many of the required stereogenic centers.[4] However, unless the process can be carried out with high stereoselectivity, the advantages of convergency are compromised. Reaction of allyltin derivatives with aldehydes in the presence of Lewis acids is known to give homoallylic alcohols in high yield and with high syn selectivity,[5] the application of this strategy for the synthesis of higher sugars was therefore appealing, and in this paper we report some of our results.

We chose, as the chiral allyltin derivative, compound **2c**, which was prepared from the readily available iodide **2a** according to the procedure of Baldwin and co-workers[6] (Scheme I). Compound **2c** reacted with methyl 2,3,4-tri-*O*-benzyl-α-D-*gluco*-hexadialdo-1,5-pyranoside **3**[7] to yield two diastereoisomeric higher sugars **4** and **5**. The steric course of this reaction was found to be catalyst dependent. Thus, when $TiCl_4$ was used, the reaction was very fast even at −78 °C (<5 min), and the ratio of products **4**:**5** was 3:1. However, when the more mild Lewis acid, zinc chloride, was employed, the reaction was slower, the yields were higher (90%), and the ratio of **4**:**5** was 10:1. Oxidation of **4** with Jones[8] reagent followed by reduction with zinc borohydride afforded **5**, establishing that the compounds were epimeric at C-6. The C-6 configurations of **4** and **5** were assumed to be 6*S* and 6*R*, respectively, in accordance with our previous observations, and also on the basis of the cyclic Cram model for 1,2-asymmetric induction,[10a] which was recently applied by us for assignment of higher sugars.[10b]

The sugar subunits in **4** and **5** are connected via an unfunctionalized methylene bridge, which is of limited use for further transformations. In order to obtain a more useful substrate, we chose compound **7**, which was pre-

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[3] Inch, T. D. *Tetrahedron* **1984**, *40*, 3161.

[4] Hanessian, S. *Total Synthesis of Natural Products: The Chiron Approach*; Pergamon Press: New York, 1983.

[5] (a) Yamamoto, Y. *Aldrichimica Acta* **1987**, *20*, 45. (b) Keck, G. E.; Boden, E. P. *Tetrahedron Lett.* **1984**, *25*, 1879; (c) Keck, G. E.; Abbott, D. E. *Ibid.* **1984**, *25*, 1883.

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[9] Complexation of **3** by Lewis acid involving carbonyl and α-oxygen atoms[10b] fixes the conformation of the aldehydo group, and the attack of **2c** from "behind the ring" afforded **4** as the major isomer. This conclusion was supported by the result of the condensation of **2c** with acetaldehyde and benzaldehyde, where little diastereoselection was seen, the ratio of diastereoisomeric products being ~1:1 and 2:1, respectively.

[10] (a) Cram, D. J.; Kopecky, K. R. *J. Am. Chem. Soc.* **1959**, *81*, 2748. Cram, D. J.; Wilson, D. R. *Ibid.* **1963**, *85*, 1245. (b) Jarosz, S. *Carbohydr. Res.* **1988**, *183*, 201.

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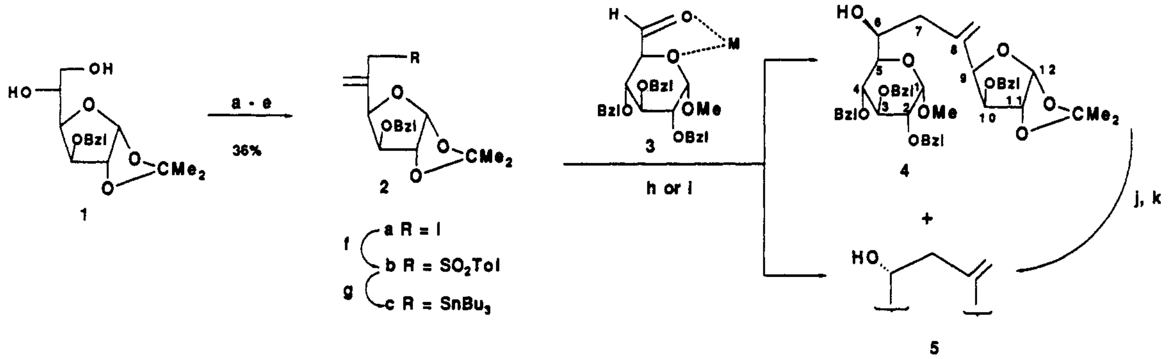
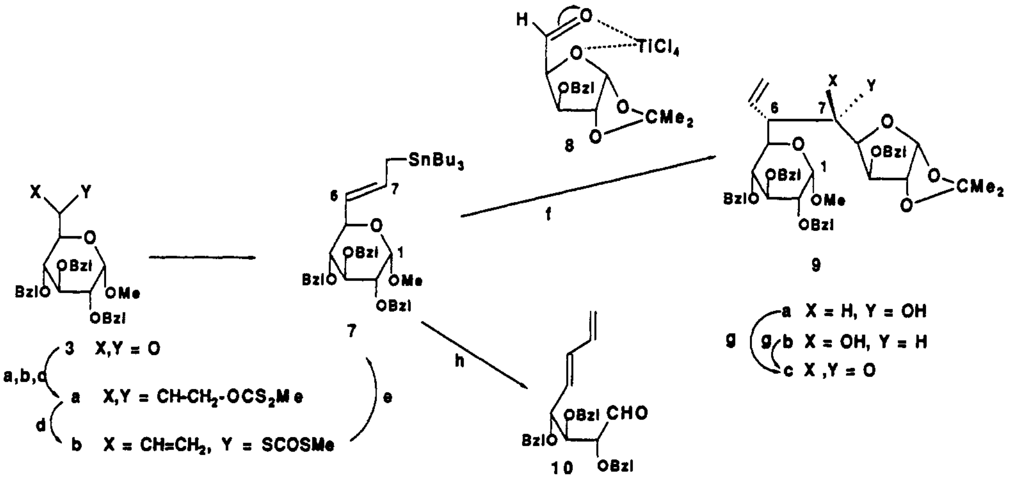
Scheme I[a]



[a] (a) TrCl/Py/DMAP; (b) $(COCl)_2$/DMSO/Et_3N; (c) $Ph_3P{=}CH_2$, benzene, room temperature; (d) H^+/acetone/water; (e) Ph_3P/I_2/imidazole; (f) $NaSO_2Tol$/MeOH, reflux (95%); (g) Bu_3SnH/AIBN, benzene (70%); (h) $TiCl_4/CH_2Cl_2$/−78 °C/5 min, 60%, ratio **4**:**5** = 3:1; (i) $ZnCl_2/CH_2Cl_2$/ 0 °C/20 min, 90%, ratio **6**:**7** > 10:1; (j) Jones oxidation; (k) $Zn(BH_4)_2$/ether/0 °C/80%, ratio **4**:**5** = 1:3.

Scheme II[a]



[a] (a) $Ph_3P{=}CHCOOEt$; (b) DIBAL-H; (c) $NaH/CS_2/MeI$; (d) toluene, reflux, 2 h; (e) Bu_3SnH/AIBN/toluene argon, reflux, 15 min, 47% overall; (f) $TiCl_4/CH_2Cl_2$/0 °C ratio **9a**:**9b** = 7:2; (g) Jones oxidation; (h) $ZnCl_2/CH_2Cl_2$/0 °C.

pared from **3** according to a known procedure[11] (Scheme II). Thus, **3** was converted into xanthate **3a**, which underwent smooth [3,3]-sigmatropic rearrangement to give **3b**. This compound, when treated with tri-*n*-butyltin hydride afforded the allyltin derivative **7** for which the trans configuration was assigned ($J_{6,7}$ = 15.0 Hz).

When **7** was reacted with 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-pentadialdo-1,4-furanose (**8**)[12] in the presence of zinc chloride, *only* decomposition was observed, the dieno aldehyde **10** being isolated in 84% yield.

Because the addition is undoubtedly directed by the overlapping of HOMO of nucleophile (**7**) and LUMO of electrophile (**8**) we reasoned that if a stronger Lewis acid were used, complexation[13] would lower the LUMO of **7** substantially, and the coupling reaction should proceed faster. Indeed, replacing zinc chloride with titanium tetrachloride as activator for **8** induced rapid coupling at 0 °C to give **9a** and **9b** in 55% yield and in the ratio 3.5:1[14] (Scheme II). Oxidation of **9a** and **9b** gave ketone **9c**, which indicated that the products differed at the C-7-OH.

To determine the configuration of **9a** (Scheme III) the free hydroxyl group was acetylated,[15] and the double bond was cleaved by ozone, the ozonide being reduced first with methyl disulfide and then with zinc borohydride. Hydrolysis of the acetate at C-7, followed by reaction of the resulting diol with acetone, afforded acetonide **11**. A small coupling constant between H-6 and H-7 ($J_{6,7}$ = 2.9 Hz) indicated at the cis arrangement of sugar substituents connected with the dioxolane ring and confirmed the expected[3] 6,7-syn configuration of the major isomer **9a**.

In order to establish that the 7,8-anti configuration was indeed as shown in **9a**, the C-10/11 isopropylidene ring was hydrolyzed and the resulting aldose acetylated. The expected[16] L-*ido* configuration of the new pyranose ring was assigned on the basis of the value $J_{7,8}$ < 1.0 Hz, which unequivocally indicated *S* configuration at C-7. It is also worth noting that the L-*ido*-pyranose ring in **12** existed in $^1C_4$ rather than $^4C_1$ conformation as could be deduced from

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[11] (a) Ueno, Y.; Sano, H.; Okawara, M. *Synthesis* **1980**, 1011. (b) Mortlock, S. V.; Thomas, E. J. *Tetrahedron Lett.* **1988**, *29*, 2479.

[12] Wolfrom, M. L.; Hanessian, S. *J. Org. Chem.* **1962**, *27*, 1800.

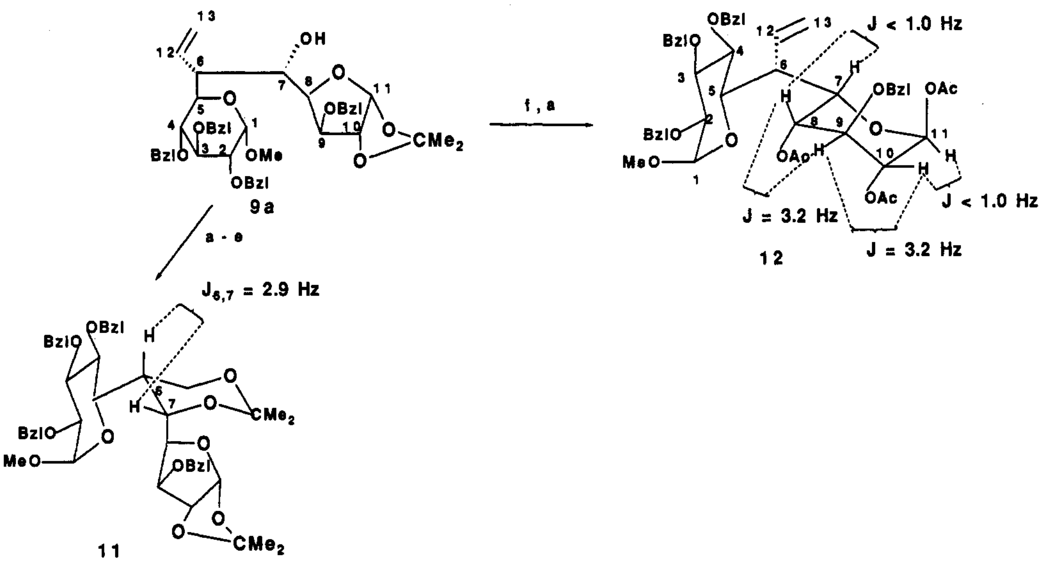
[13] Houk, K. N.; Strozier, R. W. *J. Am. Chem. Soc.* **1973**, *95*, 4094.

[14] Slow addition (2 h, by a syringe pump) of **7** to a precomplexed **8** at −78 °C resulted in very low yield (<10%) of the coupling products **9a** and **9b** together with ca. 70% of **10**. We reasoned that at these temperatures, the coupling process is slowed down. Accordingly, when the temperature was raised to 0 °C and **7** was added in one portion to the precomplexed aldehyde, the yield was as shown in Scheme II.

[15] When the double bond in **9a** was converted into the aldehyde group (O_3 then Me_2S) the resulting aldol underwent facile dehydration.[1a] However, when the free hydroxyl group was protected *prior* to ozonolysis, we were able to suppress this undesired reaction.

[16] Assuming the complexation of titanium tetrachloride to the carbonyl and α-oxygen atoms (formula **8** in Scheme II), the attack of the nucleophile should occur "from behind the ring", yielding, as the main isomer, alcohol having the *S* configuration at C-7.

Scheme III[a]



[a] (a) Ac_2O/Py/DMAP; (b) O_3, CH_2Cl_2, -78 °C; (c) Me_2S, then $Zn(BH_4)_2$; (d) MeONa/MeOH; (e) acetone, CSA, room temperature; (f) CF_3COOH/H_2O/dioxane, room temperature.

the appropriate coupling constants, $J_{8,9} = J_{9,10} = 3.2$ Hz.

In conclusion, the method presented here allows the direct connection of "the ends" of two simple monosaccharide subunits. It should be also pointed out that either the coupling products **9a** and **9b** or dieno aldehyde **10** (which will be used in the synthesis of carbocycles) *can be obtained from the same precursor*, allyltin derivative **7**, using appropriate reaction conditions.

Distannoxane as Reverse Micelle-Type Catalyst: Novel Solvent Effect on Reaction Rate of Transesterification

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Summary: Distannoxane-catalyzed transesterification has an unusual solvent effect: the reaction proceeds more than 100 times faster in hydrocarbon and halocarbon solvents than in polar solvents. The effect is attributed to the unique reverse micelle-type structure of the distannoxane.

Sir: The interactions between reactants and solvents have considerable influence on organic reactions. It is often found that polar solvents accelerate reactions, especially when the reaction goes through a polar transition state.[1] In addition, Breslow et al. found that the Diels-Alder reaction, when conducted in aqueous solution, was accelerated due to the hydrophobic interactions between the reactants.[2] Grieco et al. reported analogous reactions which were attributed to micelle formation.[3] More recently, Liotta et al. uncovered a rate increase by the use of ethylene glycol as a reaction medium.[4] Despite different methodologies, the reactions of these three groups have the something in common, namely the aggregation of reactants induced by highly self-associating solvents incompatible with hydrophobic solutes. In this paper, we

Table I. Distannoxane-Catalyzed Reaction of Butyrate Esters 2 with Benzyl Alcohol in Various Solvents at 80 °C[a,b]

2	solvent	yield of 4,[c] %	10^6k, L mol^{-1} min^{-1}
methyl butyrate	heptane	92	810 ± 50
	toluene	62	350 ± 40
	1,2-dichloroethane	71	300 ± 50
	acetonitrile	7	19 ± 2
	1,4-dioxane	8	36 ± 5
	diglyme	1	5 ± 2
ethyl butyrate	heptane	68	450 ± 40
	acetonitrile	2	9 ± 2
	1,4-dioxane	2	5 ± 3
	diglyme	1	1 ± 0.5
butyl butyrate	heptane	50	270 ± 50
	acetonitrile	3	8 ± 1
	1,4-dioxane	1	4 ± 1
	diglyme	1	3 ± 2

[a] Reaction conditions: butyrate ester-benzyl alcohol-1 = 1:2:0.005. The reaction was followed by means of GLC. [b] No reaction occurred in heptane or acetonitrile in the absence of the catalyst under the similar conditions. [c] Determined on the basis of GLC analysis after 20 h.

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(1) For recent relevant discussion on the Claisen rearrangements, see: Brandes, E.; Grieco, P. A.; Gajewski, J. J. *J. Org. Chem.* **1989**, *54*, 515 and references cited therein.

(2) Rideout, D. C.; Breslow, R. *J. Am. Chem. Soc.* **1980**, *102*, 7817. Breslow, R.; Maita, U.; Rideout, D. *Tetrahedron Lett.* **1983**, *24*, 1901. Breslow, R., Maitra, U. *Tetrahedron Lett.* **1984**, *25*, 1239.

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