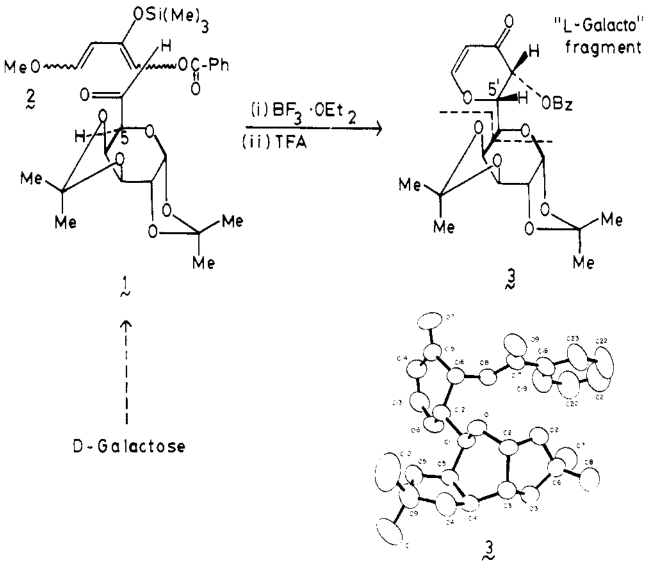
An Approach to the Synthesis of Carbon–Carbon Linked Disaccharides

Summary: Cyclocondensation of two aldose aldehydes with activated dienes was shown to occur with high diastereofacial selectivity.

Sir: The central role which polysaccharides play in all biological systems has been well-recognized.[1] The individual saccharides in the naturally occurring materials are linked through oxygen atoms via glycosidic bonds. In rare instances, there are encountered long chain monosaccharides with arrangements of 8,[2] 9,[3] 10,[4] and 11[5] contiguous carbon atoms in the form of an aldose ring bearing a row of functionalized carbons projecting from C_4 or C_5. The contiguous 11-carbon ensemble of the antiviral agent tunicamycin[6] is arranged by joining a furanose to a pyranose via a two carbon "spacer".

We have been exploring the Lewis acid catalyzed reactions of aldehydes with dienes.[7] Particular emphasis has been placed on the topological[8] and the stereochemical characteristics[9] of the process. The lack of strong diastereofacial stereoselectivity in the addition of the usual organometallic reagents to aldehydes of the type **1** has been noted by many workers.[10] In contrast, we had observed that Lewis acid catalyzed cyclocondensation of D-glyceraldehyde acetonide with the parent *trans*-1-methoxy-3-[(trimethylsilyl)oxy]butadiene had occurred with very high facial selectivity.[11] It was therefore of interest to study the stereochemical consequences of Lewis acid catalyzed cyclocondensations of aldehyde **1**.[12] If such a reaction would exhibit favorable selectivity, it could provide a route to a new class of compounds, i.e., disaccharides wherein the two aldose rings are directly joined.[13] Below we report the feasibility of such reactions and describe the remarkable stereoselectivity which it manifests.

Scheme I



To facilitate rapid construction of the newly emerging aldose, we used diene **2**.[14] If successful, a cyclocondensation reaction with this diene would produce a functionalized dihydropyrone suitable for elaboration into the second aldose. Reaction of aldehyde **1** with diene mixture **2** (2.5 equiv) in the presence of 1 equiv of $BF_3{\cdot}OEt_2$ occurred at −78 °C in ether. After 3 h, the reaction was quenched with aqueous sodium bicarbonate. Workup afforded a crude product which was treated with trifluoroacetic acid (TFA) in carbon tetrachloride at room temperature.[15] Chromatography of this reaction mixture afforded a 62% yield of a single cyclocondensation product.

The gross structure and stereochemistry of this compound, mp 221–222.5 °C; $[\alpha]_D$ +10.0° (*c* 1.20, $CHCl_3$), need not be debated. These issues were resolved through crystallographic analysis which revealed the product to be that shown as structure **3**. An ORTEP drawing of structure **3** is provided in Scheme I.[16]

It is thus seen that the topology of the cyclocondensation reaction is endo and that its diastereofacial sense is in the Cram–Felkin mode.[17,18] The latter result is in accord with that encountered with D-glyceraldehyde acetonide.[11] As in that case, there is no indication of chelation control.[9] A possible rationale to account for the observed sense of facial induction is implied in structure **1** wherein the carbon–oxygen bond of the formyl group is anti to the C_5–oxygen bond. Attack by the "nucleophilic" diene opposite to the plane of the hexose would lead to the observed diastereofacial outcome.

We note that in the product **3**, at least in the crystalline state, the C_5–O and the $C_{5'}$–O bonds are disposed in an anti-coplanar sense. This conformation is the one which minimizes dipole–dipole repulsions of the two carbon–oxygen bonds. The tendency for such an anti conformation should be even more dominant in the case of compound **1** as it undergoes bonding to an electrophilic catalyst. Thus, the superior facial selectivity of aldehyde **1** in these Lewis acid promoted cyclocondensations, relative to those observed in the course of its reactions with the usual or-

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[1] Kennedy, J. F.; White, C. A. "Bioactive Carbohydrates in Chemistry, Biochemistry, and Biology"; Wiley: New York, 1983.

[2] For example: (a) lincosamine, Magerlein, B. J. In "Structure–Activity Relationships Among the Semisynthetic Antibiotics"; Pearlman, D., Ed.; Academic Press: New York, 1977; pp 601–650. (b) 3-Deoxy-D-manno-2-octulosonic acid (KDO), Unger, F. M. *Adv. Carbohydr. Chem. Biochem.* 1981, *38*, 323.

[3] For example: acylneuraminic acids, Schauer, R. *Adv. Carbohydr. Chem. Biochem.* **1982**, *48*, 132.

[4] For example: sinefungin, Hamill, R. L.; Hoehn, M. M. "Abstracts of Papers", 11th Interscience Conference on *Antimicrobial Agents and Chemotherapy*, 1971, p 21.

[5] For example: hikosamine, Vuilhorgne, M.; Ennifar, S.; Das, B. C.; Paschal, J. W.; Nagarajan, R.; Wenkert, E. *J. Org. Chem.* **1977**, *42*, 3289.

[6] Takatsuki, A.; Kawamura, K.; Okina, M.; Kodama, Y.; Ito, T.; Tamura G. *Agric. Biol. Chem.* **1977**, *41*, 2307.

[7] Danishefsky, S.; Kerwin, J. F., Jr. *J. Am. Chem. Soc.* **1982**, *104*, 358.

[8] Danishefsky, S.; Larson, E. R.; Askin, D. *J. Am. Chem. Soc.* **1982**, *104*, 6457 and references therein.

[9] Danishefsky, S.; Pearson, W. H.; Harvey, D. F. *J. Am. Chem. Soc.* **1984**, *106*, 2456 and references therein.

[10] Howarth, G. B.; Lance, D. G.; Szarek, W. A.; Jones, J. K. N. *Can. J. Chem.* **1969**, *47*, 75. Hems, R.; Horton, D.; Nakadate, M. *Carbohydr. Res.* **1972**, *25*, 205. Hoppe, I.; Schöllkopf, U. *Liebigs Ann. Chem.* **1983**, *372*. Berg, N.; Kjolberg, O. *Carbohydr. Res.* **1977**, *57*, 65.

[11] Danishefsky, S.; Kobayashi, S.; Kerwin, J. F., Jr. *J. Org. Chem.* **1982**, *47*, 1981.

[12] Horton, D.; Nakadate, M.; Tronchet, J. M. J. *Carbohydr. Res.* **1968**, *7*, 56.

[13] For related examples of *C*-disaccharides in which the aldose rings are joined by a carbon fragment, see: Secrist, J. A., III; Wu, S.-R. *J. Org. Chem.* **1979**, *44*, 1434. Rouzand, D.; Sinay, P. *J. Chem. Soc., Chem. Commun.* **1983**, 1353. Suami, T.; Sasai, H.; Matsuno, K. *Chem. Lett.* **1983**, 819. Professor Sinay has informed us that his group has synthesized a carbon–carbon linked bis saccharide using chemistry recently developed in his laboratory (cf. Lancelin, J. M.; Morin-Allory, L.; Sinay, P. *J. Chem. Soc., Chem. Commun.* **1984**, 355).

[14] Larson, E. R.; Danishefsky, S. *J. Am. Chem. Soc.* **1983**, *105*, 6715.

[15] Catalytic TFA treatment was necessary to achieve conversion of the intermediate aldol material to cyclized product **3**.

[16] See supplementary material for the fractional coordinates, temperature parameters, bond distances, and bond angles for compounds **3** and **6**.

[17] Cram, D. J.; Elhafez, F. A. A. *J. Am. Chem. Soc.* **1952**, *74*, 5828. Cram, D. J.; Kopecky, K. R. *Ibid.* **1959**, *81*, 2748.

[18] Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199. Chérest, M.; Felkin, H. *Ibid.* **1968**, 2205.

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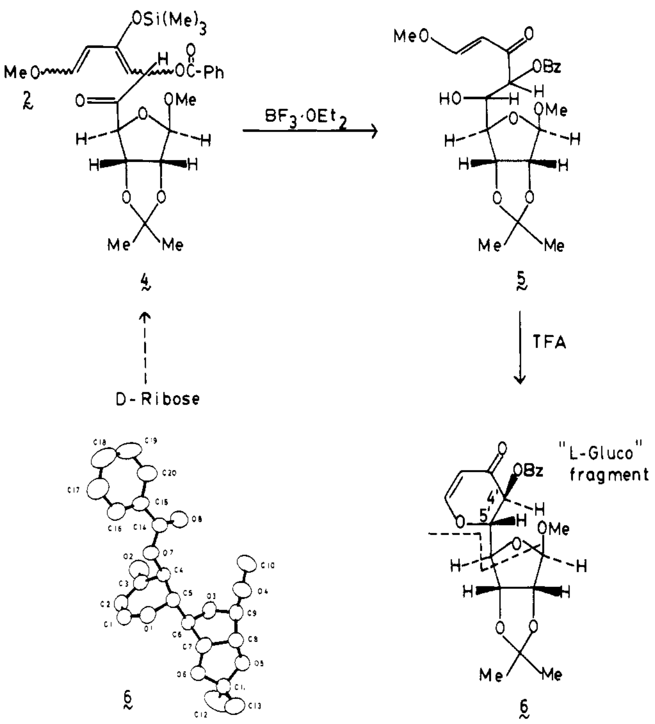
Scheme II



ganometallic reagents,[10] can be readily encompassed in this formulation.

While the reason for the facial induction is a matter for conjecture, an interesting stereochemical outcome has been achieved. The D-galactose derived aldehyde 1 has given rise to a potential L-galacto residue (see structure 3 and dotted lines) in the product. The convertibility of this type of residue to a fully substituted galactose derivative has been amply demonstrated in our previously described synthesis of lincosamine.[14]

The generality of this strict Cram–Felkin control was explored. Toward this end, the known aldehyde 4[19] derived from D-ribose was treated with diene 2 under essentially identical conditions to those employed with aldehyde 1. In this case, it was experimentally convenient to purify the major product at the stage of the β-aldol 5 by flash chromatography.[20] Subsequent cyclization with TFA afforded a cyclocondensation product, mp 184–185 °C; $[\alpha]_D$ −194.9° (*c* 1.22, $CHCl_3$), in 54% overall yield. The gross structure and stereochemistry of this compound were defined to be that shown in 6 by X-ray crystallographic analysis. A computer-drawn three-dimensional representation of structure 6 is provided[16] in Scheme II.

Again, the sense of the facial induction was that predicted by the Cram–Felkin rules.[17,18] It is also seen that, at least in the crystalline state, the carbon–oxygen bonds of the "pyranose" and "furanose" rings are arranged in the anti-periplanar conformation. This too is similar to the situation with compound 3. However, a *trans*-4′,5′-relationship is present in the derived dihydropyrone in product 6. *Thus, the aldehyde 1, derived from* D-*galactose, gives rise to an* L-*galacto fragment* (*vide supra*), *but the* D-*ribose derived aldehyde 4 produces a potential* L-*gluco precursor* (*see dotted lines in structure 6*).

While the facial sense of the cyclocondensation reactions is in the Cram–Felkin mode[17,18] in both cases, leading in each case to an L-sugar derivative, a seemingly subtle variation in the structure of the aldehyde has brought about a profound difference in the topological outcome. The effects of catalyst modifications as well as changes in the alkyl groups of the silyl enol ether are currently being evaluated.[21,22] Already this technology carries within it the potential for the construction of extended chiral networks.[23] The exploitation of this capability in the synthesis of several complex saccharides will be described shortly.

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Registry No. 1, 4933-77-1; 2, 87461-94-7; 3, 92524-95-3; 4, 33985-40-9; 5, 92524-96-4; 6, 92524-97-5.

Supplementary Material Available: Table containing the fractional coordinates, temperature parameters, bond distances, and bond angles for compounds 3 and 6 (10 pages). Ordering information is given on any current masthead page.

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(19) Arrick, R. E.; Baker, D. C.; Horton, D. *Carbohydr. Res.* **1973**, *26*, 441.

(20) In a control experiment, the crude aldol product 5 was treated with TFA and the resultant crude cyclocondensation product was carefully examined by 250-MHz ^1H NMR spectroscopy. The presence of major (6) and a minor cyclocondensation product in ca. a 15:1 ratio was revealed. The minor product (cf. ref 21) clearly has the cis-4′,5′ configuration, but the "absolute" stereochemistry of the newly fashioned ring is not known.

(21) For example, the $Eu(hfc)_3$-catalyzed[22] reaction of diene mixture 2 (*tert*-butyldimethylsilyl version) with aldehyde 4 ($CDCl_3$, room temperature) followed by catalytic TFA treatment afforded a ca. 12:1 mixture of two cyclocondensation products in 84% isolated yield. Examination of the 250-MHz ^1H NMR spectrum indicated a cis-4′,5′ relationship in both products, although the sense of facial induction was undefined. The major product obtained via lanthanide catalysis,[22] is identical with the minor cyclocondensation product[20] obtained when $BF_3·OEt_2$ was employed.

(22) For the use of such catalysts in cyclocondensation reactions, see: Bednarski, M.; Danishefsky, S. *J. Am. Chem. Soc.* **1983**, *105*, 3716.

(23) For an alternate approach to extending the chirality of carbohydrate templates, see: Fraser-Reid, B.; Magdzinski, L.; Molino, B. *J. Am. Chem. Soc.* **1984**, *106*, 731 and references therein.

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Allenic Zinc Reagents. A Remarkably Regio- and Diastereoselective Synthesis of 2-Substituted Homopropargylic Alcohols

Summary: Allenic zinc reagents react with aldehydes in a highly regio- and diastereoselective manner to furnish *threo*-homopropargylic alcohols having 96–99% diastereomeric purities.

Sir: Recently we reported that homopropargylic alcohols are readily prepared by condensation of aldehydes with allenic alanates.[1] Although this reaction is highly regioselective, it exhibits only modest diastereoselectivity. In the course of a search of a metal which would provide greater stereocontrol, we have now found that the readily

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(1) Hahn, G.; Zweifel, G. *Synthesis* **1983**, 883.

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