Protecting Group-Directed, Diastereoselective Samarium Diiodide-Promoted Carbocyclization: Application to the Synthesis of Cyclitols†

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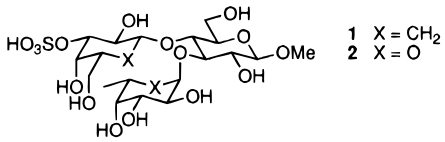
Received December 20, 1996

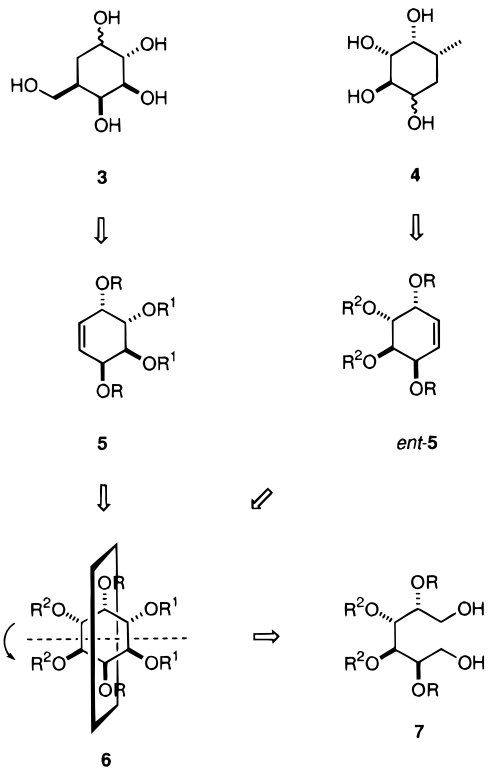
The recognition of elements of symmetry[1,2] in organic synthesis is extremely useful for the efficient preparation of complex chiral molecules. The existence of a latent plane of symmetry[1] allows the enantiodivergent synthesis of both enantiomers of a given molecule from a common precursor, while the presence of a C_2 axis of symmetry[3] greatly simplifies the number of steps of a synthetic sequence.

We would like to report our preliminary work on the application of this strategy to the synthesis of cyclitols **6** and **9** as key intermediates for the preparation of the carbasugar-containing pseudotrisaccharide **1**. This trisaccharide is a hydrolytically stable analog[4] of the previously described trisaccharide **2**, found to inhibit neural cell division,[5] and is closely related to the biologically important[6] Lewis X and sialyl Lewis X oligosaccharides. Apart from the intrinsic interest of this pseudotrisacchride,[7] its synthesis would be also valuable for structural studies, since it has been shown that the conformation of *C*-[8] or *S*-disaccharides[9] can be different from that of *O*-disaccharides.[10]



The carbasugar components of **1**, cyclitols **3** and **4**, belong to the D-galacto and L-fuco series, respectively (Scheme 1). A closer look at them shows that they could be prepared from the enantiomeric pair of conduritols **5**,

Scheme 1



which in turn, can be derived from inositol **6** due to the presence of a latent plane of symmetry.[1,11] On the other hand, the presence of a C_2 axis of symmetry in **6** would result in a significant simplification of the synthesis,[3] and D-mannitol (**7**; R = R^2 = H) could be used as starting material.

In principle, **6** could be prepared through the samarium diiodide-promoted pinacol coupling[12,13] of the dialdehyde derived from **7**, but the stereochemical outcome of such a reaction is usually opposite to that required.[14,15] However, we have found (Scheme 2) that

† Dedicated to Prof. Hans Paulsen on the occasion of his 75th birthday.

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(1) (a) Hudlicky, T. *Chem. Rev.* **1996**, *96*, 3−30. (b) Hudlicky, T.; Natchus, M. G. In *Organic Synthesis: Theory and Applications*; Hudlicky, T., Ed.; JAI Press: Greenwich, CT, 1993; Vol. 2, pp 1−25.

(2) Bertz, S. H.; Sommer, T. J. In *Organic Synthesis: Theory and Applications*; Hudlicky, T., Ed.; JAI Press: Greenwich, CT, 1993; Vol. 2, pp 67−92.

(3) The simplification of a synthesis taking advantage of elements of symmetry is based on the concept of reflexivity.[2]

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(7) For the chemistry of pseudosugars, see: (a) Suami, T.; Ogawa, S. *Adv. Carbohydr. Chem. Biochem.* **1990**, *48*, 21−90. (b) Hudlicky, T.; Entwistle, D. A.; Pitzer, K. K.; Thorpe, A. J. *Chem. Rev.* **1996**, *96*, 1195−1220.

(8) Espinosa, J.-F.; Cañada, F. J.; Asensio, J. L.; Martín-Pastor, M.; Dietrich, H.; Martín-Lomas, M.; Schmidt, R. R.; Jiménez-Barbero, J. *J. Am. Chem. Soc.* **1996**, *118*, 10862−10871.

(9) Geyer, A.; Hummel, G.; Eisele, T.; Reinhardt, S.; Schmidt, R. R. *Chem. Eur. J.* **1996**, *2*, 981−988.

(10) The conformational study of pseudodisaccharides bearing a carbasugar in the reducing end has been reported: Duus, J. Ø.; Bock, K.; Ogawa, S. *Carbohydr. Res.* **1994**, *252*, 1−18.

(11) The plane of symmetry is defined by the different protecting groups (R^1 and R^2) at both sides of the molecule. A further simplification of the synthesis could be imagined if the olefin and *trans*-diol functional groups in **5** and *ent*-**5** were interconvertible with each other, defining then a latent plane of symmetry that would make possible the use of any of these compounds as a more advanced intermediate in the synthesis. Efforts in this direction will be addressed in the near future.

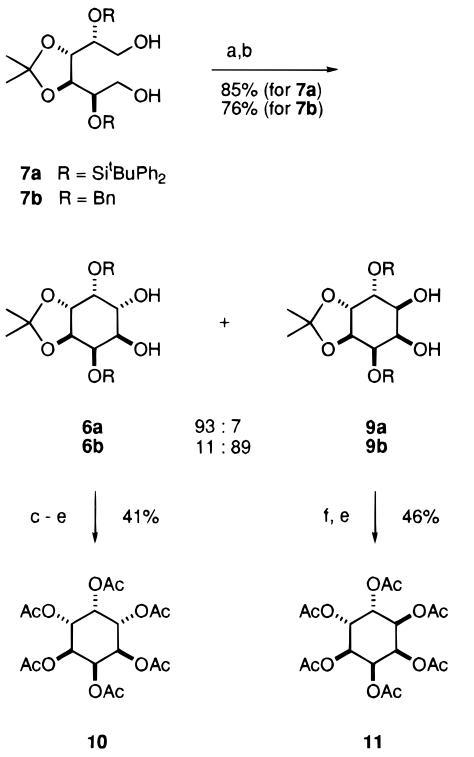
(12) For recent reviews on applications of samarium diiodide in organic synthesis, see: Molander, G. A. *Chem. Rev.* **1996**, *96*, 307−338.

(13) For samarium diiodide-promoted pinacol coupling of related carbohydrate derivatives, see: (a) Chiara, J. L.; Martín-Lomas, M. *Tetrahedron Lett.* **1994**, *35*, 2969−2972. (b) Guidot, J. P.; Le Gall, T.; Mioskowski, C. *Tetrahedron Lett.* **1994**, *35*, 6671−6672. (c) Chiara, J. L., Valle, N. *Tetrahedron: Asymmetry* **1995**, *6*, 1895−1898. (d) Sawada, T.; Shirai, R.; Iwasaki, S. *Tetrahedron Lett.* **1996**, *37*, 885−886.

(14) A *cis*-diol is usually the main stereoisomer in intramolecular pinacol coupling reactions,[13] although the opposite stereochemistry has been observed in acyclic systems: Taniguchi, N.; Kaneta, N.; Uemura, M. *J. Org. Chem.* **1996**, *61*, 6088−6089. See also: Kang, M.; Park, J.; Konradi, A. W.; Pedersen, S. F. *J. Org. Chem.* **1996**, *61*, 5528−5531.

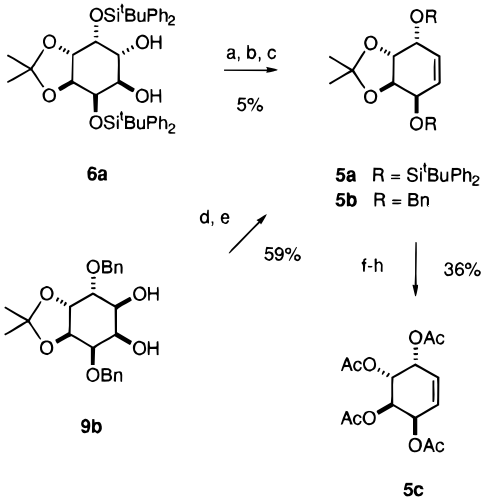
S0022-3263(96)02389-4 CCC: $14.00

Scheme 2[a]



[a] Key: (a) Swern oxidation; (b) SmI_2, *t*-BuOH, THF, −60 °C; (c) CF_3CO_2H, MeOH; (d) TBAF, THF; (e) Ac_2O, Py; (f) H_2, Pd(C), AcOH, MeOH.

Scheme 3[a]



[a] Key: (a) $SOCl_2$, Et_3N, CH_2Cl_2; (b) $NaIO_4$, $RuCl_3$, CH_2Cl_2, H_2O; (c) NaTeH, DMF, 70 °C; (d) $Im_2C(S)$, PhMe; (e) $P(OEt)_3$, 165 °C; (f) *p*-TsOH, MeOH; (g) Na, NH_3, −78 °C; (h) Ac_2O, Py.

the sequence of oxidation and samarium diiodide-promoted carbocyclization of diol **7a**[16] gives diastereoselectively *neo*-inositol **6a**.[17] On the other hand, benzyl-protected diol **7b**,[16] when submitted to the two-step procedure, gave the expected diastereoselectivity, leading to *allo*-inositol **9b**. To our knowledge, this is the first example of a pinacol coupling where stereoselectivity can be driven by the appropriate choice of the protecting groups at the adjacent positions. An additional proof of the structures of inositols **6a** and **9b** was obtained (Scheme 2) by its conversion into peracetates **10** and **11**, whose physical properties matched those previously described.[18]

Once the diastereoselective cyclitol formation was attained, we focused on the dihydroxy-elimination of **6a**, which turned out to be difficult due to both the *trans*-diequatorial configuration of the diol system and the presence of the relatively labile silyl protecting groups. All conventional methods tested[19] met with failure, but hydrogen telluride-mediated[20] elimination of a cyclic sulfate[21] derived from **6a** afforded (Scheme 3) conduritol E derivative **5a**, albeit in low yield. On the other hand, access to conduritol **5b** was easily achieved from *cis*-diol **9b** by using the Corey−Winter method.[22] Its structure was secured by transformation into conduritol E peracetate **5c**, whose physical properies matched those previously described.[23]

In summary, this paper describes a samarium diiodide-mediated carbocyclization that allows the preparation, for the first time, of a *trans*-diol by applying such methodology. The *cis*-diol, arising from the usual diastereoselectivity, can be obtained by simply changing the protecting groups of the vicinal positions. Work directed toward the synthesis of the target carbasugars, taking advantage of the C_2 axis of symmetry existent in **5**, is currently underway and will be reported in due course.

Acknowledgment. Financial support by Comunidad Autónoma de Madrid and CSIC (to M.C. and C.J., respectively), and DGICYT (Grant No. PB93-0127-C02-01), is greatly appreciated. Dr. J.-L. Chiara is gratefully acknowledged for helpful discussions.

Supporting Information Available: Experimental procedures and spectroscopic data for the reported compounds (7 pages).

JO9623898

(15) Typically, a *trans*-directing effect of adjacent alkoxy groups is observed in intramolecular pinacol coupling reactions promoted by samarium diiodide, and it has been attributed to steric and/or electrostatic interactions involving the ketyl radical anion and the alkoxy substituent.[13]

(16) **7a** and **7b** were prepared in five and four steps, respectively, from D-mannitol. See the Supporting Information.

(17) All new compounds showed correct microanalytical and spectroscopic data.

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(23) See ref 18a. For other syntheses of conduritol E, see: Angelaud, R.; Landais, Y. *J. Org. Chem.* **1996**, *61*, 5202−5203 and references cited therein.