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DO UPPER LIMITS TO THE MULTIPLE SPIRO ACETALIZATION OF THE CYCLOHEXANE RING EXIST?‡

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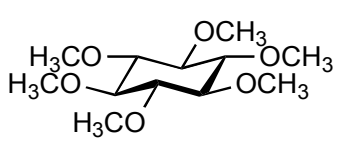
Abstract – An attempt to transform the pyranoside (**5**) into the bifacial ligand (**3**) is described. The first subtarget is acetal (**13**) whose conversion into tris acetal (**17**) is made possible by remote C-H activation. Regrettably, triol (**20**) does not lend itself to comparable triple cyclization.

The concept of bifacial chelation relates to the capacity of a singular molecular entity to coordinate to a pair of metal ions residing on apposite faces of the organic core.[1] The structural features associated with this phenomenon hold fundamental interest and could potentially serve a wide range of applications. However, the reluctance of candidate substrates to become involved in appropriate modes of geometric alignment has inhibited progress in this area. For example, the previously synthesized hexamethoxycyclohexane (**1**)[2] and its hexaspiro tetrahydrofuran homolog (**2**)[3] have proven to be markedly inert to alkali metal ion coordination.

The unalterable preference for outward projection of the C-O bonds in **1** and **2** has been attributed to the operation of six stabilizing gauche interactions in the all *O*-equatorial conformer, and to the energetic costs associated with the orientation of multiple alkoxy substituents axially on the same face of the cyclohexane scaffold.[4]



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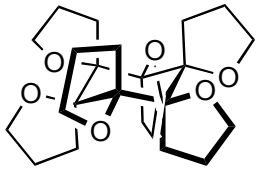

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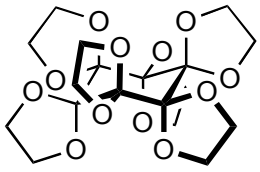

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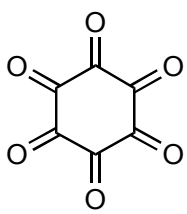

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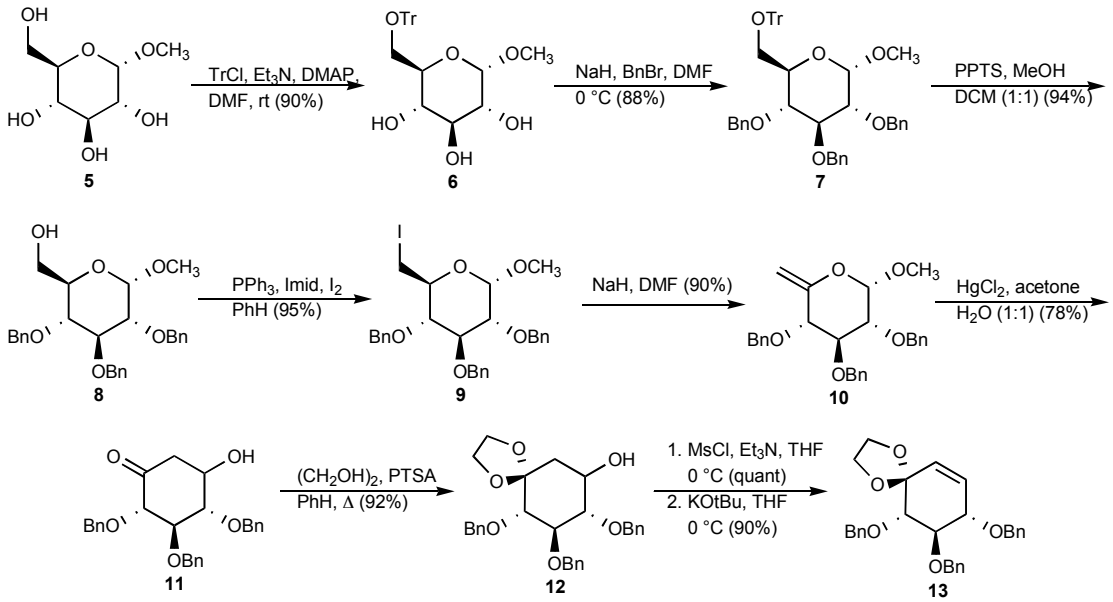
‡This paper is dedicated to the memory of Ivar Ugi, whose fundamental contributions to heterocyclic and computational chemistry have played an important role in these fields.

Multiple oxygenated centers can be projected in the desirable axial-rich manner under suitable circumstances that include the use of bulky substituents[5] or of inositol orthoformate platforms.[6] The latter tactic has made possible the elaboration of attractive linear homoditopic ligands.[7] Because of their insolubility in common solvents, the polymers derived therefrom are inadequate as ionophores. Since the introduction of additional oxygen atoms was expected to be beneficial, a more advanced target became the hexaspiro acetal (**3**). While the chelation advantages offered by **3** are obvious, its acquisition by synthesis was viewed as problematic. A notably brief route involving the multiple ketalization of readily available hexaketone (**4**) (as the octahydrate)[8] proved not to be serviceable because of its extreme insolubility under applicable conditions.[9] A more unconventional protocol was clearly warranted. A route that utilizes commercially available methyl α-D-glucopyranoside (**5**) as the starting material is outlined herein.

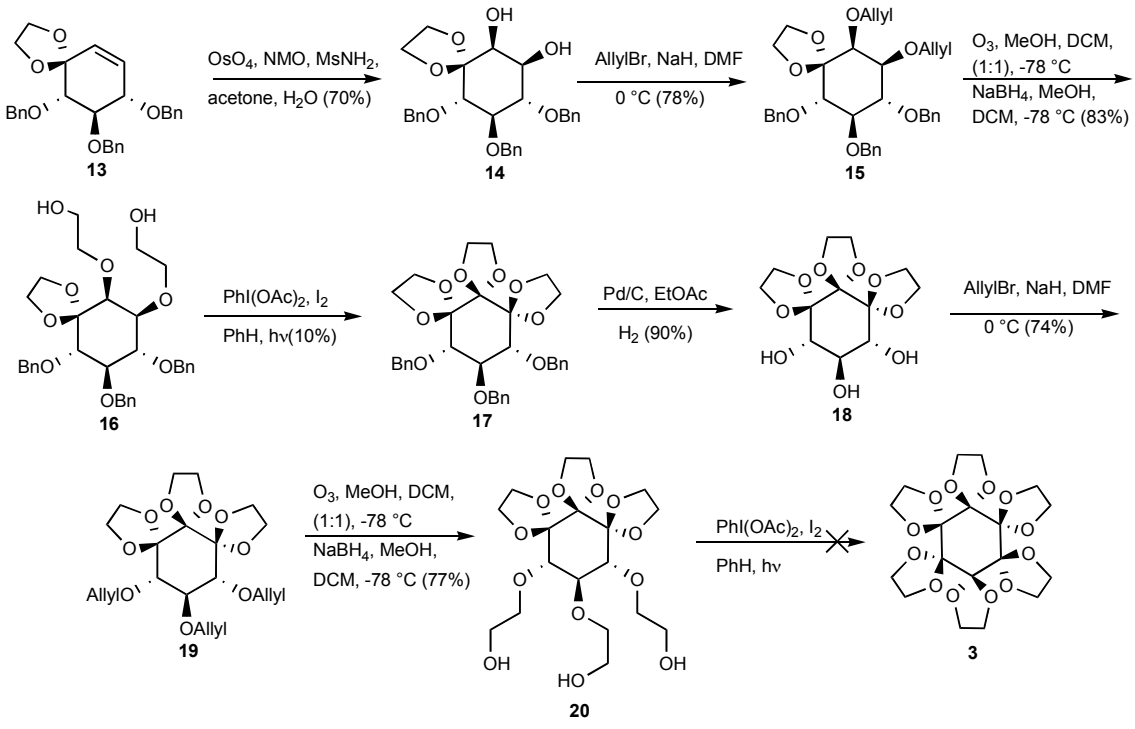
The conversion of **5** to **7** was initially accomplished in an efficient two-step maneuver (Scheme 1). Removal of the trityl group under mildly acidic conditions afforded alcohol (**8**), which was subjected to iodination according to a modification of Garegg's method[10] to yield **9**. Upon exposure to sodium hydride in dimethylformamide at room temperature, **9** underwent smooth dehydroiodination to afford the exocyclic methylene derivative (**10**), whose response to mercury(II) chloride in aqueous acetone was next examined. Ferrier's carbocyclic ring closure[11] occurred to deliver the β-hydroxy cyclohexanone (**11**) in 78% yield. The conversion of **11** to **12** by reaction with ethylene glycol in the presence of *p*-toluenesulfonic acid was then optimized to deliver **12** with minimal competing β-elimination. The spiro acetal (**13**) was subsequently generated in exclusive fashion by elimination of the corresponding mesylate under basic conditions.

Scheme 1



We next sought to functionalize the double bond contained within **13** in a manner that would ultimately permit the installation of two additional acetal fragments. For the usual reasons, recourse to acidic conditions of any type had to be avoided. The bypass of this significant restriction began with the dihydroxylation of **13** involving osmium tetraoxide in the presence of *N*-methylmorpholine *N*-oxide (Scheme 2). The resulting diol (**14**) was then converted into the diallyloxy derivative (**15**) by *O*-alkylation with allyl bromide. Ozonolysis followed by reductive workup with sodium borohydride afforded the key intermediate **16**. The availability of this diol provided the opportunity for proper exploration of its targeted photochemical ring closure upon irradiation in the presence of iodobenzene diacetate with iodine serving as initiator.[12] Since no acidic reagents are directly involved, it was expected that the acetal units would have a better chance of survival relative to sequential installation. Indeed, trispiro acetal (**17**) was obtained, but in a quite modest, although reproducible, 10% yield.[13] The inefficiency of this step can be attributed to the presence in **16** of numerous methylene groups connected to oxygen which remain prone to involvement in alternative cyclizative transformations.

Scheme 2



The route continued with hydrogenolytic removal of the benzyl groups in **17** under standard conditions to afford triol (**18**). A reliable supply of this highly oxygenated intermediate enabled us the opportunity to implement our chain-extension strategy once again. Treatment of **18** with allyl bromide and sodium hydride in DMF led to installation of all three allyloxy substituents as in **19**. Subsequent ozonolysis and borohydride reduction resulted in efficient conversion to **20**. Regrettably, remote C-H activation in the predescribed manner could not be accomplished. Rather than generating **3**, a complex, inseparable

mixture of compounds was formed, the composition of which changed with time. Thereby implicated was an appreciable sensitivity of the products being formed. Acetic acid generated in the course of this otherwise mild reaction could be inducing decomposition. Attempts were therefore made to carry out the process in the presence of reagents (e.g., calcium carbonate, sodium bicarbonate, and propylene oxide) capable of removing any acid formed. Unfortunately, these modifications did not change the outcome. Many other routes pursued in the quest for **3** have proven equally unsuccessful.[9] Thus, the statement put forth in the title is offered as a challenge awaiting resolution.

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REFERENCES AND NOTES

1. L. A. Paquette, J. T. Negri, and R. D. Rogers, *J. Org. Chem.,* 1992, **57**, 3947.
2. (a) J. E. Anderson, *J. Chem. Soc., Perkin Trans. 2*, 1993, 441. (b) J. E. Anderson, S. J. Angyal, and D. C. Craig, *Carbohydr. Res.,* 1995, **272**, 141.
3. (a) N. S. Zefirov, V. V. Samoshin, O. A. Subbotin, V. I. Baranenkov, and S. Wolfe, *Tetrahedron*, 1978, **34**, 2953. (b) N. S. Zefirov, L. G. Gurvich, A. S. Shashkov, M. Z. Krimer, and E. A. Vorob'eva, *Tetrahedron*, 1976, **32,** 1211. (c) N. S. Zefirov, V. V. Samoshin, and V. A. Palyulin, *Zh. Org. Khim.,* 1983, **19**, 1888.
4. P. R. Rablen, L. A. Paquette, and W. T. Borden, *J. Org. Chem.,* 2000, **65**, 9180.
5. (a) H. Fazldeen, M. P. Hegarty, and F. N. Lahey, *Phytochemistry,* 1978, **17**, 1609. (b) H. Fazldeen, *Aust. J. Chem.*, 1982, **35**, 2589.
6. (a) L. A. Paquette, C. S. Ra, J. C. Gallucci, H. J. Kang, N. Ohmori, M. P. Arrington, W. David, and J. S. Brodbelt, *J. Org. Chem.,* 2001, **66**, 8629. (b) J. Tae, R. D. Rogers, and L. A. Paquette, *Org. Lett.*, 2000, **2**, 139.
7. (a) L. A. Paquette and J. Tae, *J. Am. Chem. Soc.*, 2001, **123**, 4974. (b) L. A. Paquette, J. Tae, and J. C. Gallucci, *Org. Lett.*, 2000, **2**, 143.
8. K. Kanakararajan and A. W. Czarnik, *J. Org. Chem.*, 1986, **51**, 5241.
9. P. R. Selvaraj, Ph.D. Dissertation, The Ohio State University, 2006.
10. P. J. Garegg and B. Samuelsson, *J. Chem. Soc., Perkin Trans. 1*, 1980, 2866.
11. R. J. Ferrier and A. E. Stuetz, *Carbohydr. Res.*, 1990, **200**, 237.
12. (a) K. Furuta, T. Nagata, and H. Yamamoto, *Tetrahedron Lett.*, 1988, **29**, 2215. (b) J. I. Conception, C. G. Francisco, R. Hernandez, J. A. Salazar, and E. Suarez, *Tetrahedron Lett.*, 1984, **25**, 1953. (c) P. de Armas, R. Carrau, J. I. Concepcion, C. G. Francisco, R. Hernandez, and E. Suarez, *Tetrahedron Lett.*, 1985, **26**, 2493. (d) R. Freire, R. Hernandez, M. S. Rodriguez, and E. Suarez, *Tetrahedron Lett.*, 1987, **28**, 981.
13. Although two isomeric di(bis)-spiro acetals can in principle be formed from **16**, neither was found in the complex reaction mixtures.