

Cyclization of Aryl Silanes with
Unexpected Retention of Silicon

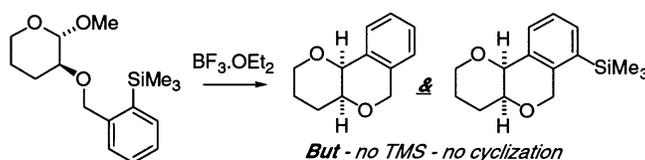
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ABSTRACT

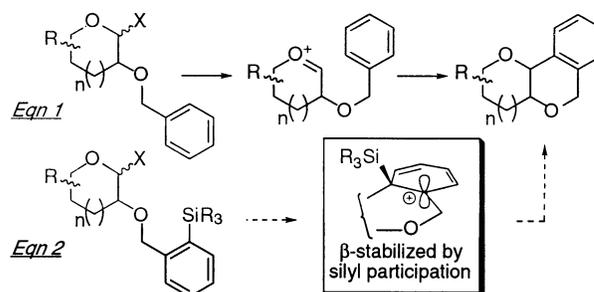


Intramolecular Friedel–Crafts cyclization of 2-*O*-benzyl ethers at a model pyranose acetal is activated by incorporation of a trimethylsilyl group, albeit via unexpected, presumably steric means.

The intramolecular Friedel–Crafts condensation of suitably tethered benzylic aryls at activated cyclic oxoniums, eq 1, offers a rapid entry to isochroman targets.¹ In fact, this process is a major competing pathway during intermolecular glycosylation.² These side reactions have been adapted, notably by Martin,³ yet remain subject to subtle and unpredictable stereoelectronic control,⁴ especially in the pyranose series.⁵ Moreover, many employ exotic anomeric activation or require electron-rich arenes.

We recently considered a directly analogous arylsilane-mediated Friedel–Crafts closure^{6,7} to promote the overall desired annulation, eq 2. We expected this *ortho*-silyl moiety

to enhance the process on electronic grounds (increased nucleophilicity and augmented stability of intermediate carbocation) as well as cater to regiocontrol in arenes with more complex substitution patterns.



We constructed a prototypical substrate via epoxidation of dihydropyran in MeOH,⁸ followed by benzylation with

(1) For example, the pyranonaphthoquinone antibiotics: Brimble, M. A.; Nairn, M. R.; Prabakaran, H. *Tetrahedron* **2000**, *56*, 1937.

(2) (a) Martin, O. R. *Tetrahedron Lett.* **1985**, *26*, 2055. (b) Suzuki, K.; Maeta, H.; Suzuki, T.; Matsumoto, T. *Tetrahedron Lett.* **1989**, *30*, 6879. Maeta, H.; Matsumoto, T.; Suzuki, K. *Carbohydr. Res.* **1993**, *249*, 49. (c) Bürlil, R.; Vasella, A. *Helv. Chim. Acta* **1996**, *79*, 1159. (d) Crich, D.; Cai, W.; Dai, Z. *J. Org. Chem.* **2000**, *65*, 1291. (e) Araki, Y.; Kobayashi, N.; Ishido, Y.; Nagasawa, J. *Carbohydr. Res.* **1987**, *171*, 125. (f) Miethchen, R.; Gabriel, T. *J. Fluorine Chem.* **1994**, *67*, 11. (g) Hosoya, T.; Takashiro, E.; Matsumoto, T.; Suzuki, K. *J. Am. Chem. Soc.* **1994**, *116*, 1004. (h) Kovensky, J.; Sinay, P. *Eur. J. Org. Chem.* **2000**, 3523.

(3) (a) Martin, O. R. *Carbohydr. Res.* **1987**, *171*, 211. (b) Martin, O. R.; Hendricks, C. A. V.; Deshpande, P. P.; Cutler, A. B.; Kane, S. A.; Rao, S. P. *Carbohydr. Res.* **1990**, *196*, 41. (c) Rousseau, C.; Martin, O. R. *Tetrahedron: Asymmetry* **2000**, *11*, 409. Other related studies: (d) Martin, O. R.; Rao, S. P.; El-Shenawy, H. A.; Kurz, K. G.; Cutler, A. B. *J. Org. Chem.* **1988**, *53*, 3287. (e) Martin, O. R.; Rao, S. P.; Kurz, K. G.; El-Shenawy, H. A. *J. Am. Chem. Soc.* **1988**, *110*, 8698.

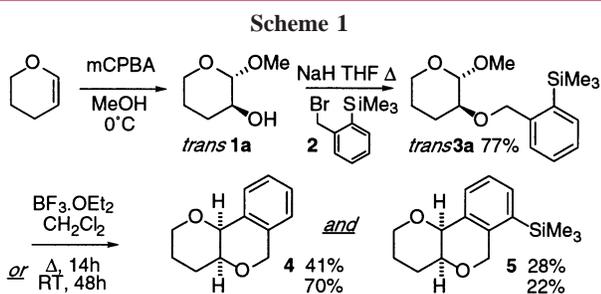
(4) For example, double C-glycosidation: Martin, O. R.; Mahnken, R. E. *J. Chem. Soc., Chem. Commun.* **1986**, 497. Martin, O. R.; Rao, S. P.; Hendricks, C. A. V.; Mahnken, R. E. *Carbohydr. Res.* **1990**, *202*, 49.

(5) A brief survey of unactivated benzyl substrates is illustrative. 1,6-Anhydro-D-glucose: no tricyclic products (ref 3b). 1-*O*-Acetyl hexapyranoses (manno- and gluco-): “complex mixtures” (refs 2a and 3a). α -Glucopyranosyl chloride: 74% yield. Verlhac, P.; Leteux, C.; Toupet, L.; Veyrières, A. *Carbohydr. Res.* **1996**, *291*, 11.

(6) For reviews of arylsilanes in regioselective electrophilic aromatic substitutions, see: Eaborn, C. *J. Organomet. Chem.* **1975**, *100*, 43; Fleming, I. In *Comprehensive Organic Chemistry*; Barton, D. H. R., Ollis, W. D., Eds.; Pergamon: Oxford, 1979; Vol. 3, Chapter 13, p 613.

(7) For specific intramolecular examples, see: (a) Miller, R. B.; Tsang, T. *Tetrahedron Lett.* **1988**, *29*, 6715. (b) Majetich, G.; Zhang, Y.; Feltmann, T. L.; Belfoure, V. *Tetrahedron Lett.* **1993**, *34*, 441. (c) Cho, I.-S.; Tu, C.-L.; Mariano, P. S. *J. Am. Chem. Soc.* **1990**, *112*, 3594.

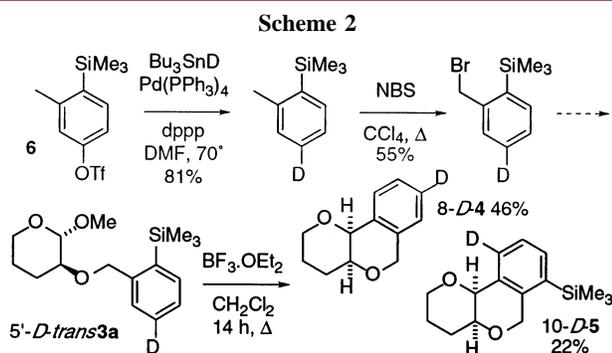
(8) Sweet, F.; Brown, R. K. *Can. J. Chem.* **1966**, *44*, 1571.



the requisite bromide **2**,⁹ Scheme 1. A survey of Lewis acids ensued. Eventually, after some optimization,¹⁰ exposure to BF₃·OEt₂ (2 equiv) in CH₂Cl₂ at high dilution effected ring closure in good overall yields, albeit in a somewhat unexpected fashion.

To our surprise, two products were obtained: the anticipated tricycle **4**, arising from ipso substitution, and the curiously meta-substituted **5**, in which the silyl group had apparently failed to participate. Cis stereochemistry was confirmed by zero Hz ³*J* interactions across each new ring junction, in agreement with previously reported values.^{2d,3b} No corresponding *trans* products were identified.

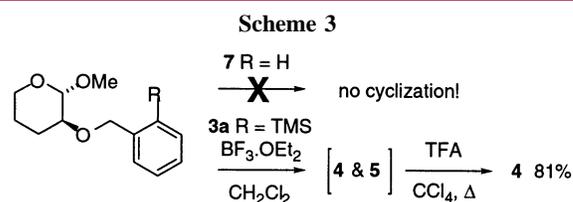
This contradictory role of TMS suggested two separate yet competing reactions. To discount other pathways (e.g., protodesilylation of **5**) we resorted to isotopic labeling, para to the silyl moiety. Regiospecific palladium-mediated stannylation¹¹ of a corresponding aryl triflate **6**¹² allowed synthesis of the labeled benzyl precursor. Annulation proceeded with complete regiospecific retention of deuterium in each product as appropriate, Scheme 2.¹³



We presumed that **5** arose from simple minimization of steric interactions, with the TMS held distal in the developing transition state. Similar observations have been made during related intermolecular Friedel–Crafts-type reactions, with non-ipso substitution competitive in hindered cases.¹⁴ However, intriguingly, *nor*-silyl analogue **7**¹⁵ proved to be

consistently resistant to ring closure despite considerable effort. We therefore believe the TMS is playing an auxiliary steric role, due to crowded ortho substitution, as evidenced by modeling.¹⁶ First, the Si–C=C–CH₂ dihedral angle is torqued (3.43°); this deviation may enhance initial electrophilic attack, reminiscent of the elusive Mills–Nixon effect.¹⁷ In addition, whereas the benzyl group of **7** aligns perpendicular to the reactive site, the steric demands of the TMS group in **3a** force the tether to present its π-system in parallel as required.

These findings have since been developed into a practical two-step protocol. Cyclization followed by desilylation of the initial crude product mixture affords the *cis*-fused tricycle **4** exclusively and in good overall yield, Scheme 3.



This direct contrast with unreactive *nor*-silyl precursor **7** highlights the effectiveness of the silicon moiety in attaining the *cis*-fused pyranoisochroman framework and thus may present a solution to this aberrant reaction.

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Supporting Information Available: Experimental procedures and full data for **3**, **4** and **5**, including ¹H and ¹³C NMR spectra; details of deuterium labeling studies. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(9) Severson, R. G.; Rosscup, R. J.; Lindberg, D. R.; Engberg, R. D. *J. Am. Chem. Soc.* **1957**, *79*, 6540.

(10) Overall yield was highly susceptible to concentration, e.g., at reflux: 0.276 M, 19%; 0.036 M, 45%; 0.004 M, 72%.

(11) Dupré, B.; Meyers, A. I. *J. Org. Chem.* **1991**, *56*, 3197.

(12) Prepared from the known phenol: Speier, J. L. *J. Am. Chem. Soc.* **1952**, *74*, 1003. See Supporting Information for details.

(13) This also discounted a 1,5-silylatropic shift in the intermediate cation and electrophilic aromatic substitutions by opportunistic TMS-X species.

(14) For example, see: Ishibashi, H.; Sakashita, H.; Ikeda, M. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1953 and references therein.

(15) Cox, P.; Lister, S.; Gallagher, T. *J. Chem. Soc., Perkin Trans. 1* **1990**, *11*, 3151.

(16) PC Spartan Pro, AM1 parametrization.

(17) Mills, W. H.; Nixon, I. G. *J. Chem. Soc.* **1930**, 2510. For a discussion correctly refuting this phenomenon, see: Siegel, J. S. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1721.