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Epoxides Derived from Pyranosyl Dienes: Unusually Stable Glycosyl Donors

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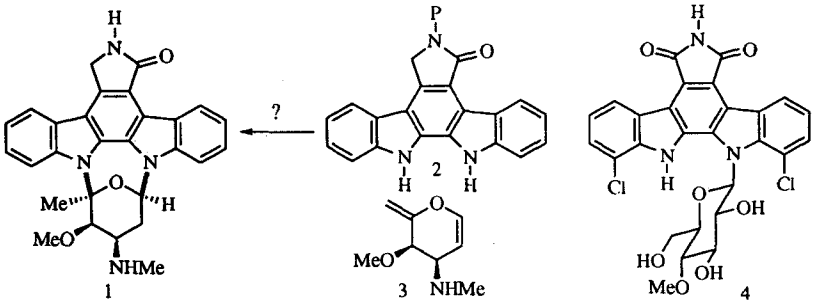
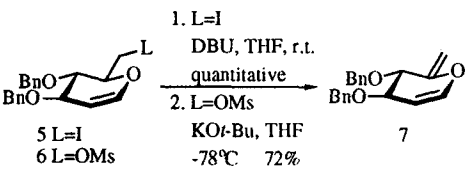
Abstract: A pyranosyl diene appropriately substituted for use in a total synthesis of staurosporine has been synthesized. The mono-epoxides and bis-epoxides obtained from treatment of this diene with dimethyldioxirane are unusually stable.

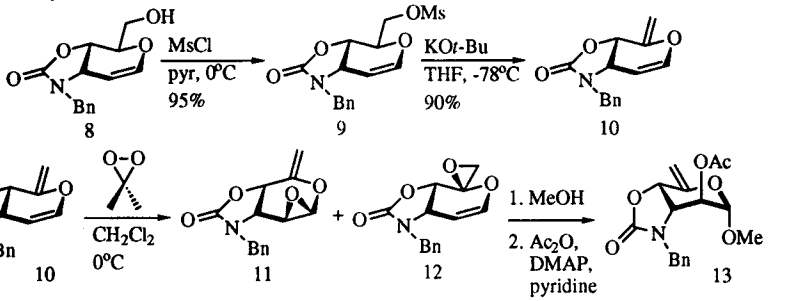
Indolocarbazole alkaloids, in which one of the indolic nitrogens is N-glycosidically linked to a sugar domain, include the clinically promising rebeccamycin **4** and its congeners.[4] We recently reported a synthesis of rebeccamycin **4** using a glycal derived 1,2 anhydrosugar for indole glycosylation.[5] More complicated members of this growing family of bioactive natural products possess a carbohydrate sector that is wedged between two indolic nitrogens of an indolocarbazole through two unusual glycosidic linkages. Staurosporine **1** is such a natural product. It is one of the most potent inhibitors of protein kinase C and has thus far eluded chemical synthesis.[6] Recently, we disclosed an approach that we expect will lead to staurosporine **1** and related natural products.[7] The route we described exploited, at distinct stages, an endo-



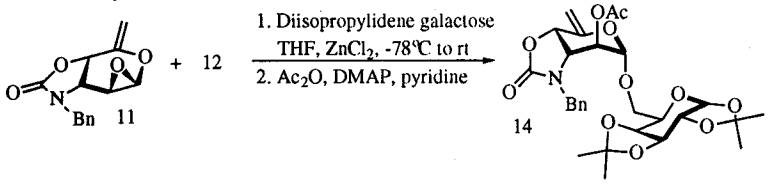
and an exo-glycal. The endo-glycal was activated for glycosylation via its derived mono-epoxide while the exo-glycal served as a target for intramolecular iodoglycosylation. The possibility of utilizing a bis-glycal equivalent of **3**, either directly or in derived activated form, of course, presented itself.



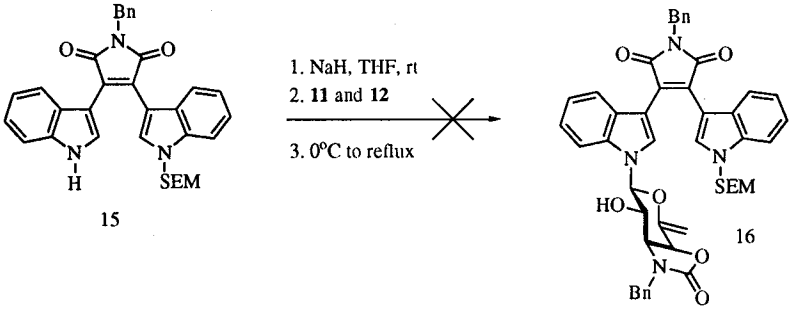
We first determined that bis-glycal **7** could be readily prepared by elimination of an iodide or mesylate with DBU or with potassium *tert*-butoxide respectively in high yield.[8] We then applied this capability to the synthesis of a diene that might be of relevance to the staurosporine undertaking.[9] Accordingly, mesylate **9**, obtained from **8**, yielded **10** upon treatment with potassium *tert*-butoxide.[7] Contrary to our fears, this diene proved to be remarkably stable.



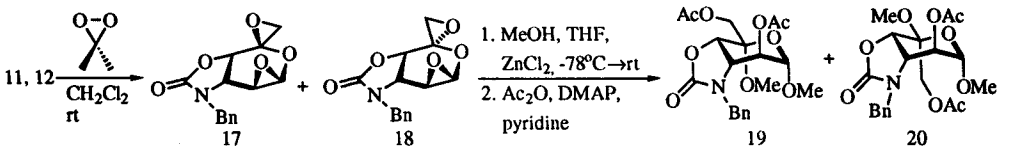
The direct epoxidation of **10** with dimethydioxirane was examined. We obtained a 2.3:1 mixture of regioisomeric mono-epoxides **11** and **12** at 0°C in methylene chloride. Apparently, each of the epoxidations was quite stereoselective. When these epoxides were submitted to methanolysis, only **11** yielded a methyl glycoside and then quite slowly compared to typical 1,2-anhydrosugars.[10] The structure of the resultant product was best revealed via its derived acetate **13**. A further testimony of the stability of **11** and **12** is that they survive flash chromatography on silica gel with minimal decomposition. None of the many endocyclic epoxides we have previously prepared survived such treatment. Mono-epoxide **11** did react with 1,2:3,4 di-O-isopropylidenegalactopyranose under the conditions shown.[11] After acetylation, the novel disaccharide **14** was obtained in 65% yield from **10** (91% based on **11**).



Unfortunately, however, our standard conditions for indole glycosylation using **15** failed to result in reaction with **11** or **12**. Remarkably, attempted use of **11** as the donor led to its substantial recovery.

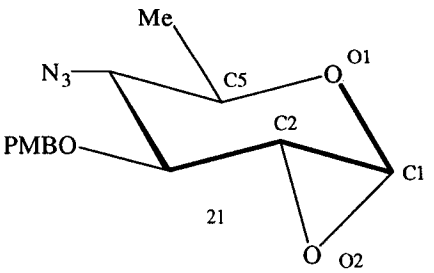


We also studied the installation of a second epoxide on both **11** and **12**. In the case of **12** an apparently stereospecific reaction led to **17**. Epoxidation of substrate **11** with the same reagent was less selective leading to **17** and **18**. The structure of compound **17** was verified crystallographically (vide infra).



The bis-epoxides exhibited remarkable stability toward methanolysis. Unlike typical 1,2 anhydrosugars which react with methanol in the absence of promoter, **17** and **18** require mediation by zinc chloride for solvolysis. Acetylation of the resulting products led to diacetates **19** and **20**. In each case, clean inversion of configuration had occurred. However, the reaction occurred more slowly than previously noted with endo-1,2-oxiranes.

The attenuated glycosyl donating powers of epoxides **11**, **12**, **17** and **18** probably arise from decreased "onium" character at the O1-C1 linkage. For the sake of comparison, the corresponding relevant bond lengths from a crystallographic determination of structure **17** and the previously prepared **21** are shown.[12] We note that the O1-C1 bond distance of **17** is slightly longer. This increased bond length might suggest that onium ion involvement of the pyranosidal oxygen with the anomeric carbon is suppressed relative to the corresponding situation in **21**.



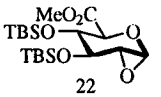
17

Bond	Bond length[13]
O1-C1	1.395(9)
O1-C5	1.383(9)
C1-C2	1.44(1)
C1-O2	1.40(1)
C2-O2	1.458(8)
C5-O3	1.421((8)
C6-O3	1.46(1)
C5-C6	1.44((1)

21

Bond	Bond length
O1-C1	1.378(8)
O1-C5	1.437(8)
C1-C2	1.452(9)
C1-O2	1.408(8)
C2-O2	1.462(8)

Several reasons can be advanced for the diminished glycosyl donating capacity of 1,2-epoxides of hexoses bearing a 5,6-methylene (cf **11**) or 5,6-spiroepoxide linkage (cf **17** and **18**). Obviously, in each of these systems C5 is more electron withdrawing relative to the usual 1,2-oxiranes. Diminished participation of the ring oxygen would suppress the tendency toward heterolysis thereby enhancing the stability of these compounds. One example of this principle is glucaronic ester epoxide **22** which also exhibits unusual stability.[14]



22

To pin down this effect in detail would require the synthesis and evaluation of many more substrates. At present, the increased stability and reduced glycosyl donor properties of the novel oxiranes described here is striking, although it undercuts their utility in the staurosporine project.

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References and Notes

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4. Gribble, G. W.; Berthel, S. J. *Studies in Natural Products Chemistry, Volume 12*; Elsevier Science Publishers: New York 1993; pp 365-409.
5. Gallant, M.; Link, J. T.; Danishefsky, S. J. *J. Org.Chem.* **1993**, *58*, 343-349.
6. Recent synthetic activity: (a) Shankar, B. B.; McCombie, S. W. *Tetrahedron Lett.* **1994**, *35*, 3005-3008. (b) McCombie, S. W.; Bishop, R. W.; Carr, D.; Dobek, E.; Kirkup, M. P.; Kirschmeier, P.; Lin, S. I.; Petrin, J.; Rosinski, K.; Shankar, B.; Wilson, O. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1537-1542.
7. Link, J. T.; Gallant, M.; Danishefsky, S.; Huber, S. J. *J. Am. Chem. Soc.* **1993**, *115*, 3782-3783.
8. Previous studies of pyranosyl dienes: (a) Descotes, G.; Martin, J. C.; Dung, T. *Carbohydrate Res.* **1978**, *62*, 61-71. (b) Blackburne, I. D.; Fredericks, P. M.; Guthrie, R. D. *Aust. J. Chem.* **1976**, *29*, 381-391. (c) Kiss, J. *Carbohydrate Res.* **1969**, *11*, 579-581.
9. We utilized the D-sugar for our investigations rather than the more expensive L-sugar necessary to reach staurosporine.
10. Epoxide **12** slowly decomposed during the reaction and no methyl glycoside was isolated.
11. Halcomb, R. L.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 6661-6666.
12. Halcomb, R. L. *Chapter One: A Method for the Synthesis of β-linked Oligosaccharides Based on the Direct Epoxidation of Glycals Chapter Two: Synthesis and Glycosylation Studies of the Oligosaccharide Domains of Esperamicin and Calicheamicin*, Yale University 1992.
13. Bond lengths are given in angstroms with estimated standard deviations in the least significant figure in parenthesis.
14. Dr. Serge Boyer, unpublished results.

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