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Regioselective Imide Reduction : An Issue in the Total Synthesis of Staurosporine

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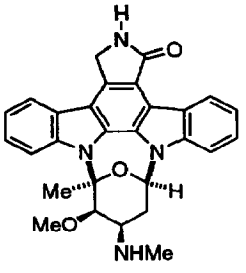
Abstract: An imide was regioselectively reduced to either of its corresponding lactams. These lactams serve as potent glycosyl acceptors and can be converted into the aglycone of staurosporine.

Staurosporine **1**, a natural product that displays a wide spectrum of bioactivity, is best known as a potent inhibitor of Protein Kinase C.[1] PKC function is operative in signal transduction and, consequently, is implicated in cell proliferation and differentiation.[2] The possibility of developing useful therapeutic agents based on modulation of protein kinases has been recognized by the pharmaceutical industry.[3]



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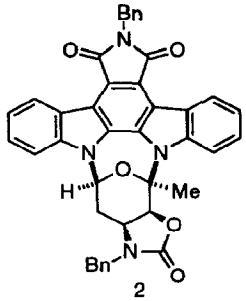

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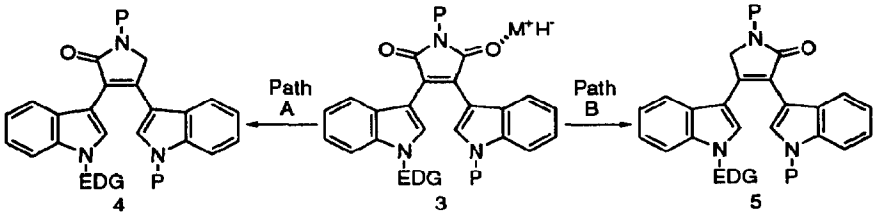
We have recently reported the first synthesis of the core structure of staurosporine (see compound **2**).[4] Significant advances remain to be accomplished for that chemistry to culminate in a total synthesis of staurosporine **1**. One fascinating issue is the matter of converting the imide (cf **2** and its precursors) to the lactam moiety present in **1**. The daunting goal of fostering communication between the widely separated "northern" and "southern" districts of staurosporine invites several interesting solutions. In this Letter we focus on the possibility of dealing with this problem by controlling the sense of imide reduction.

We began by posing the questions inherent in seco-aglycone **3**. Could the presence of substituents on

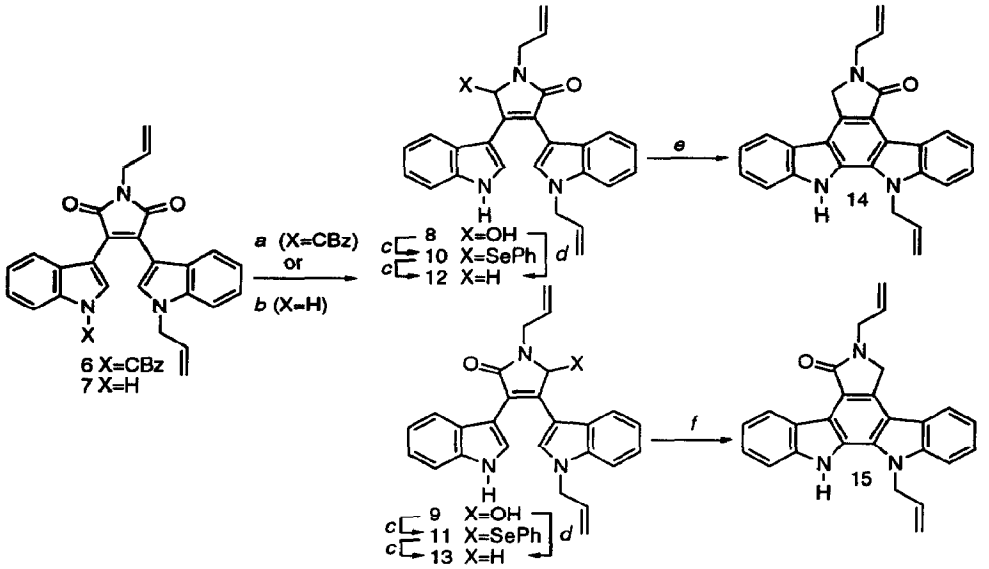


4 3 5

the indole nitrogens, which differ widely in their electronic characteristics, communicate a bias to the site of

initial reduction? If so, what would be the sense of the induction? Simple examination of resonance forms could be used to justify contrary predictions. An electron donating group (EDG) on the indolic nitrogen will render that carbonyl conjugated to it more "amide-like", thus suggesting a greater resistance to reduction (Path B). Conversely, the same carbonyl group might be more vulnerable if precoordination between reducing agent and the carbonyl oxygen is decisive (Path A). If one pathway is dominant, placement of an electron withdrawing group (EWG) on the indolic nitrogen may reverse the selectivity, potentially allowing the synthesis of both regioisomers.

To explore these questions, we synthesized seco-imides **6** and **7** according to the protocol developed in our total synthesis of rebeccamycin.[5] Treatment of **6** (EWG=CBz) with two equivalents of L-Selectride^R in THF at -78°C gave a 3 : 1 ratio of isomeric hydroxy-lactams. Allowing the reaction to warm to room temperature also removed the CBz protecting group delivering a mixture of **8** and **9**.



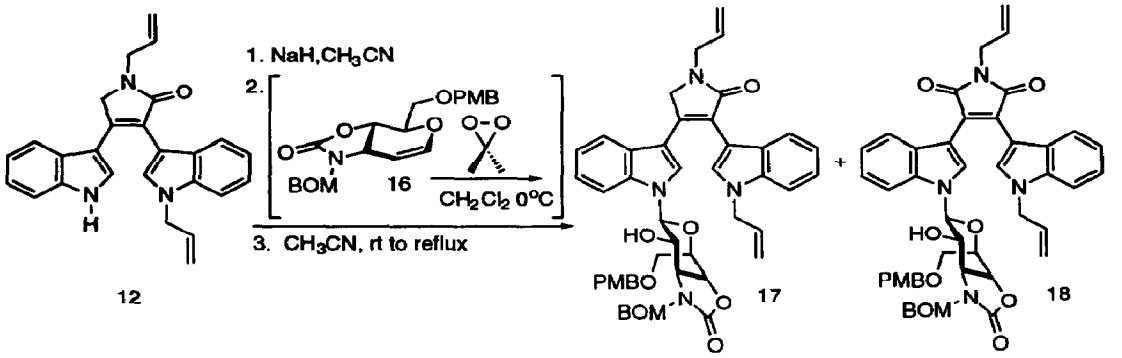
Reagents and Conditions: (*a*) L-Selectride^R (2.1 equiv), THF, -78°C→rt, 93%; (*b*) (i) NaH, THF, r.t., (ii) DIBAL, -78°C, (iii) L-Selectride^R, -78°C→r.t., 98%; (*c*) PhSeH (1.0 equiv), cat. *p*-TsOH, CH_2Cl_2, r.t.; (*d*) PhSeH (2.1 equiv), *p*-TsOH, CH_2Cl_2, r.t., 100%; (*e*) hv, I_2, air, PhH, 52% (38% of s.m. recovered); (*f*) hv, I_2, air, PhH, 63% (14% of s.m. recovered).[6]

Further reduction to **12** and **13** proved to be difficult. Success was finally achieved by treating the hydroxy-lactams with two equivalents of benzeneselenol and a catalytic amount of *p*-toluenesulfonic acid delivering lactams **12** and **13** in quantitative yield. This reaction, which proceeds via selenides **10** and **11**, is presumably driven by the formation of diphenyldiselenide. In order to determine the structure of the lactams, they were separated and then photocyclized as shown.[7,8] A combination of nOe difference spectroscopy and decoupling experiments on pentacyclic aglycones **14** and **15** revealed that the major initial reduction isomer was **8**.

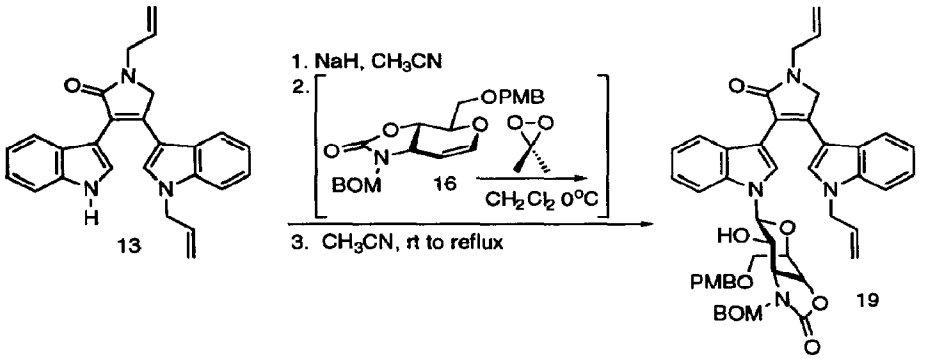
We then evaluated the consequences of donating electrons onto the indolic nitrogen. Treatment of the anion of **7**, derived with NaH, with DIBAL and L-Selectride^R yielded a 4 : 1 ratio of **9** : **8**. After further reduction **13** was obtained as the major lactam and **12** as the minor. *Apparently, in both cases, reduction*

selectivity is governed by complexation of the reducing agent to the carbonyl group which is conjugated to the EDG! Regioisomer **13**, desired for our staurosporine **1** effort was produced in nearly 80% yield from **7** over two steps. Minor regioisomer **13** was reoxidized to **7** further increasing the efficiency of this sequence.[9]

Seco-lactams **12** and **13** also proved to be potent glycosyl acceptors. Epoxidation of **16** yielded a 2.5:1 β:α ratio of epoxides.[10] Initial coupling experiments between **12** and the 1,2 anhydrosugars derived from **16** yielded the desired **17** and its oxidized counterpart imide **18**.



This reaction revealed that the benzylic aglycone position is prone to oxidation under basic conditions making early stage reduction tactically risky.[11] Efficient conversion to **17** was achieved by conducting the coupling under an argon atmosphere with rigorously degassed solvents providing a 65% yield of indole-glycoside **17**, with no formation of **18**. Surprisingly, only glycosylation of the β-epoxide was observed.



Glycosylation of lactam **13**, which could potentially lead to staurosporine **1**, was also successful. Again, only glycosylation of the β-epoxide was observed and indole-glycoside **19** was obtained in 42% yield (76% yield based on recovered **13**) when the reaction was performed with strict exclusion of oxygen. Despite our success of reaching the desired regioisomeric lactam **19** its conversion into staurosporine **1** has been hampered by our inability to remove the allyl protecting groups in acceptable yields.

Thus we have devised a practical method for regioselectively reducing imides to lactams for use in a synthetic endeavor toward staurosporine **1**. The sense of this reduction can be significantly influenced by the placement of an EWG or an EDG on the free indolic nitrogen. The selectivity with L-Selectride^{R} is rationalized by the preferred complexation of the reducing agent to the more electron rich imide carbonyl.

The potential application of this logic to a total synthesis of staurosporine **1** is being explored.

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3. See (a) McCombie, S. W.; Bishop, R. W.; Carr, D.; Dobek, E.; Kirkup, M. P.; Kirschmeier, P.; Lin, S. I.; Petrin, J.; Rosinski, K.; Shankar, B. B.; Wilson, O. *Bioorg. & Med. Chem. Lett.* **1993**, *3*, 1537-1542. (b) Vice, S. F.; Bishop, W. R.; McCombie, S. W.; Dao, H.; Frank, E.; Ganguly, A. K. *Bioorg. & Med. Chem. Lett.* **1994**, *4*, 1333-1338. and references contained therein.
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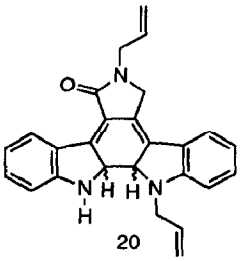
5. Gallant, M.; Link, J. T.; Danishefsky, S. J. *J. Org. Chem.* **1993**, *58*, 343-349.
6. Photocyclization of **13** also yielded **20** in 20% yield.



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7. Liu, L.; Yang, B.; Katz, T. J.; Poindexter, M. K. *J. Org. Chem.* **1991**, *56*, 3769-3775.
8. For previous regioselective syntheses of monosubstituted aglycone precursors see (a) Magnus, P. D.; Sear, N. L. *Tetrahedron* **1984**, *40*, 2795-2797. (b) Bruning, J.; Hache, T.; Winterfeldt, E. *Synthesis* **1994**, 25-27.
9. Lactam **13** was best converted to imide **7** by dissolving **13** in THF and treating with NaH while bubbling oxygen through the solution.
10. This ratio was determined by H^1-NMR analysis of the epoxides and was supported by the ratio of methyl glycosides obtained from their methanolysis followed by acetylation.
11. Other oxidants such as DDQ also promote this oxidation. Also see Caravatti, G.; Meyer, T.; Fredenhagen, A.; Trinks, V.; Metz, H.; Fabbro, O. *Biorg. & Med. Chem. Lett.* **1994**, *4*, 399-404.

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