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Concerning directed oxidation and transacylation during a general approach to hydroxylated lactams

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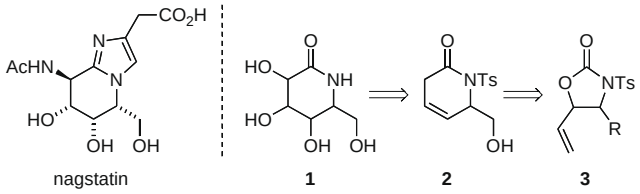
ABSTRACT

A variant of Knight's route to D-mannolactam, exploring the stereoselectivity of directed oxidation conditions, reveals a tendency for hydroxylated *N*-tosyl lactams to rearrange to γ-lactones. An attempted directed dihydroxylation in this series is shown to result in unexpectedly high *anti*-selectivity.

In studies directed towards the total synthesis of naturally occurring iminosugars, including nagstatin[1] (Scheme 1), and their analogues we have assessed a variety of synthetic routes to sugar lactam intermediates of general structure **1**.[2] Of the 16 stereoisomers of lactam **1**, 11 are described in the literature,[3] the vast majority of their syntheses originating with naturally occurring hexoses.[4] Our efforts have focused on de novo approaches that could give access to all stereoisomers including those not readily available from carbohydrate sources. One variant employed Knight's decarboxylative carbonylation of *N*-sulfonyl vinyl oxazolidinones **3**[5] and elaboration of the derived δ-lactam **2** by sequential epoxidation and dihydroxylation. This general route is very similar to Knight's synthesis of D-mannolactam.[6]

Our work differs from the published route in two key respects. First, bearing in mind application to nagstatin, our interest was in effecting hydroxy-directed epoxidation and dihydroxylation to generate the 2*S*,3*S*,4*S*,5*R*-isomer[4] (i.e., all *syn*) of lactam **1**. Second, our work was carried out on the *N*-tosyl derivative **2** rather than on the free *N*–H compound. As will become evident, these two variations led to interesting outcomes that are reported here.

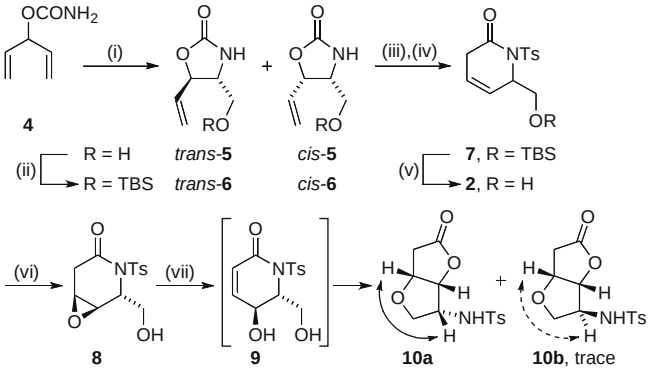
Enantiomerically enriched oxazolidinones of general structure **3** (R = CH_2OH, CH_2OR' and *N*-H/acyl variants) have been prepared from carbohydrate precursors,[7] vinyl epoxyalcohols generated by Sharpless asymmetric epoxidation of dienyl alcohols[8] and, most frequently, from N,O-diprotected serine methyl ester.[9] Since the key aspect for us was to assess *relative* stereocontrol in elaborating lactam **2**, we were content to have access to (±)-*trans*-**3** (R = CH_2OH) provided that the route was significantly shorter than the existing enantioselective routes and had the potential to be rendered asymmetric with suitable reagent development. Our solution was to effect tethered aminohydroxylation[10] (TA) of pentadienylcarbamate **4** (Scheme 2) which is a new substrate for this reaction.[11] Although the TA reaction has not yet been achieved



Scheme 1.

asymmetrically, in principle the same overall result could be achieved from **4** using tandem aziridination and hydrolysis with a chiral Rh(II)-catalyst.[12]

Carbamate **4** (Scheme 2) was prepared from divinyl alcohol using the standard procedure[13] and subsequent TA gave oxazolidinone **5** (3.8:1 trans/cis ratio) in 65% unoptimised yield.[14] The production of diastereomers in this reaction is of no consequence for



Scheme 2. Reagents and conditions: (i) $K_2OsO_2(OH)_4$, *t*-BuOCl, NaOH, *i*-Pr_2NEt, aq. *i*-PrOH (65%); (ii) TBSCl, imidazole, DMF (86%); (iii) NaH, TsCl, THF (81%); (iv) Pd_2dba_3, PPh_3, CO, THF (62%); (v) H_2SiF_6, aq. CH_3CN; (vi) MCPBA, CH_2Cl_2 (99%, used crude); (vii) DBU, CH_2Cl_2 (26%). [Full and dashed arrows in **10a**,**b** indicate, respectively, an NOE correlation or a lack thereof.]

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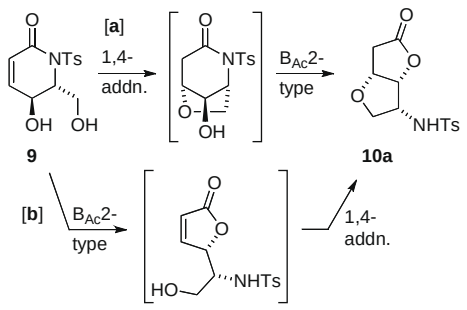
the subsequent chemistry but, in preparation for a potentially asymmetric variant, it is worth noting that this ratio is enhanced to roughly 8:1 by Pd(0)-mediated equilibration of the O-silylated diastereomers **6**.[15] Alternatively, *trans*-**5** was obtained in pure form by recrystallisation from ethyl acetate. Following N-tosylation, application of Knight's published protocol afforded lactam **7** in 62% yield on a 1.5 g scale.

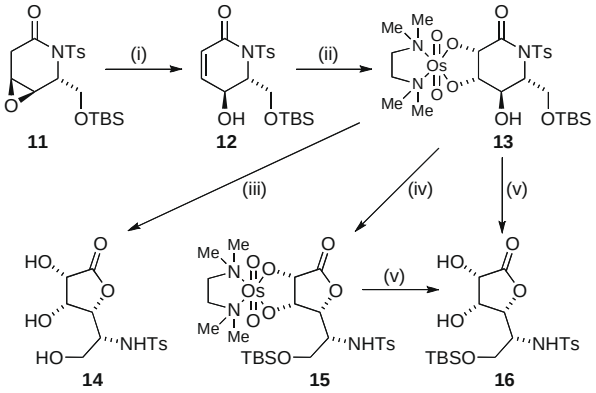
Epoxidation of this β,γ-unsaturated lactam is known to follow steric control to give the *anti*-product[6] (**11**, Scheme 4) but the viability of effecting a hydroxy-directed epoxidation was examined. In comparison with allylic alcohols, the directing effect of homoallylic hydroxy groups is not as reliable[16] although related precedent exists in the synthesis of cyclophellitol.[17] In the event, epoxidation of lactam **2** (obtained after silyl deprotection of **7**) with the usual hydroxy-directable reagents[18] gave little or none of the *syn*-epoxide; for example, with MCPBA in dichloromethane an almost quantitative yield of the *anti*-epoxide **8** resulted, the stereochemistry being secured on the basis of subsequent products. For example, treatment of this epoxide with DBU resulted in the production of bicyclic lactone **10a** along with a small quantity of diastereomer **10b** (presumably originating from *syn*-**8** impurity in the sample of epoxide **8** in a proportion probably magnified by the low mass recovery in this reaction). The structure of these products was deduced from the lack of alkene proton resonances in the ^{1}H NMR spectrum and by a strong IR absorption (1785 cm^{-1}) characteristic of a γ-lactone. The stereochemistry was supported by the NOE correlations indicated.

Clearly, after epoxide-opening (→**9**) intramolecular transacylation and 1,4-O-addition followed but the timing of these two events (pathway **a** or **b**, Scheme 3) is open to question, at least in the formation of major isomer **10a**. Some insight into this process came from examination of molecular models[19] that showed the CH_2OH group to prefer a pseudoaxial orientation, minimising 1,2-interaction with the *N*-Ts substituent.[20] This, in turn, places the 2°-OH in a pseudoaxial environment and many low-lying conformations were found (e.g., Fig. 1) in which the hydroxy lone pairs are well disposed to initiate interaction with the lactam carbonyl [∠(O···C=O) ca. 140° and an O···C distance ca. 3.5 Å]. In support of this, in the ^{1}H NMR spectrum of silyl derivative **12** (Scheme 4) the *CH*(OH)–*CH*(CH_2OTBS) coupling constant is ca. 1.5 Hz consistent with an average di-pseudoequatorial relative disposition of these protons. These observations support the possibility that pathway **b** operates in the production of lactone **10a**; isomer **10b** *must* be formed by this pathway. Although conjugate O-cyclisation has been observed in related systems, in those examples the lactams were N-unsubstituted (or merely alkylated) and therefore resistant towards attack by oxygen nucleophiles.[21]

Under the same conditions, silyl ether **11** (Scheme 4) behaved as expected and α,β-unsaturated lactam **12** was obtained, as reported.[6] Application of Donohoe's conditions for directed dihydroxylation[22] to lactam **12** produced osmate ester **13**, isolated as a



Scheme 3. Plausible pathways for the formation of bicyclic lactone **10a** in the DBU-mediated epoxide opening of lactam **8**.



Scheme 4. Reagents and conditions: (i) DBU, CH_2Cl_2 (68%); (ii) OsO_4, TMEDA, CH_2Cl_2 (93%); (iii) concd HCl, MeOH (71% from **12**); (iv) Na_2SO_3, aq acetone (40%); (v) H_2S (g), THF (63% from **15**, 82% from **13**).

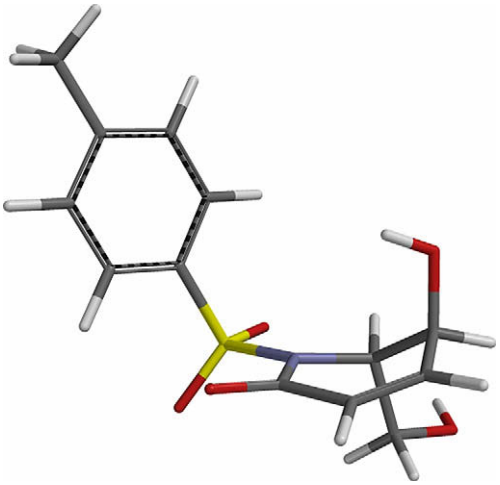


Figure 1. Representative low-lying conformation of intermediate **9**.[19]

single diastereomer in 93% yield. Although this osmate was a solid we were unable to obtain a crystal of suitable quality for X-ray diffraction and the stereochemistry was secured retrospectively from subsequent products (see below). Various products were generated from osmate **13** depending on the conditions employed to release the diol functionality. For example, stirring this intermediate with concd. HCl in methanol gave lactone **14** but less strongly acidic conditions (aq Na_2SO_3) merely effected ring interchange to give lactone **15**. Treatment of this lactone with H_2S, which is successful in cleaving osmate esters in fragile systems,[23] gave the free diol **16** in reasonable yield. Application of these mild conditions to the cleavage of the osmate in lactam **13** also resulted in lactone formation. This sulfonamido lactone **16** was highly crystalline and the structure, along with those of the preceding intermediates, was secured by X-ray crystallography (Fig. 2).[24]

This 'failure' of the directed dihydroxylation of substrate **12** is, presumably, a consequence of the preferred conformations of this lactam (cf. **9**, Fig. 1) which are dominated by those bearing a di-pseudoaxial disposition of CH_2OTBS and OH. In the context of epoxidation in cyclohexenols, Whitham demonstrated that increased rate and stereoselectivity were associated largely with the presence of a pseudoequatorial hydroxy group.[25] Furthermore, Donohoe has shown that, of the diastereomers of 5-*tert*-butylcyclohex-2-enol, only the *cis*-isomer provides good selectivity.[26] The very high *anti*-selectivity observed for the dihydroxylation of lac-

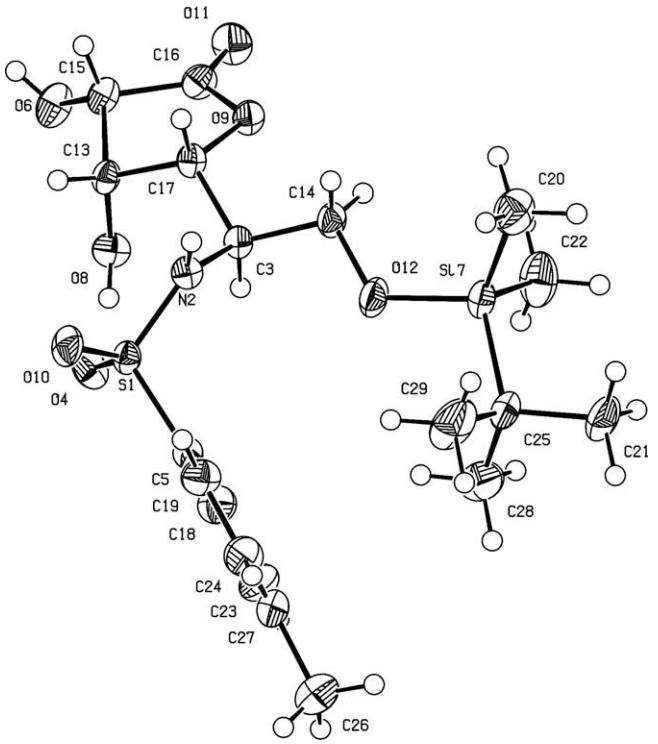


Figure 2. ORTEP representation of lactone **16**.[24]

tam **12** mirrors our recent results with butenolide spiroacetals[27] and forms part of a broader trend.[28]

The pronounced tendency for δ-lactams in this series to rearrange to γ-lactones by transacylation warrants comment because this is not generally a favourable process. Indeed, the reverse transformation is a well-known method for the production of sugar lactams from carbohydrate lactones (of various ring sizes).[29] There is, however, limited precedent for this reaction when the lactam is destabilised by further N-acylation (e.g., by Boc)[30] and there is a single example of this ring contraction in an *N*-sulfonyl substrate where it occurs as a side reaction within a study on the total synthesis of xestocyclamine A.[31] Further work would be necessary to establish the generality of this reaction and its utility in the synthesis of naturally occurring lactones from, for example, pyridine derivatives.

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References and notes

1. (a) Aoyagi, T.; Suda, H.; Uotani, K.; Kojima, F.; Aoyama, T.; Horiguchi, K.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1992**, *45*, 1404–1408; (b) Aoyama, T.; Naganawa, H.; Suda, H.; Uotani, K.; Aoyagi, T.; Takeuchi, T. *J. Antibiot.* **1992**, *45*, 1557–1558.
2. (a) Tchabanenko, K. DPhil Thesis, Oxford, **1998**.; (b) Abdulmalek, E. DPhil Thesis, Oxford, **2007**.
3. According to an exact structure search of the Chemical Abstracts database (SciFinder, Jan 2009). The (carbohydrate numbering) 2,3,4,5-*R*,*R*,*R*,*S*-, *R*,*S*,*S*,*S*-, *S*,*R*,*R*,*S*-, *S*,*R*,*S*,*S*-, and *S*,*S*,*S*,*S*- diastereomers do not appear in the hitset.
4. For example: Nishimura, Y.; Adachi, H.; Satoh, T.; Shitara, E.; Nakamura, H.; Kojima, F.; Takeuchi, T. *J. Org. Chem.* **2000**, *65*, 4871–4882.
5. (a) Knight, J. G.; Ainge, S. W.; Harm, A. M.; Harwood, S. J.; Maughan, H. I.; Armour, D. R.; Hollinshead, D. M.; Jaxa-Chamiec, A. A. *J. Am. Chem. Soc.* **2000**, *122*, 2944–2945; (b) Knight, J. G.; Tchabanenko, K. *Tetrahedron* **2002**, *58*, 6659–6664; (c) Anderson, T. F.; Knight, J. G.; Tchabanenko, K. *Tetrahedron Lett.* **2003**, *44*, 757–760; (d) Knight, J. G.; Lawson, I. M.; Johnson, C. N. *Synthesis* **2006**, 227–230.
6. Knight, J. G.; Tchabanenko, K. *Tetrahedron* **2003**, *59*, 281–286.
7. Wee, A. G. H.; McLeod, D. D.; Rankin, T. J. *Heterocycles* **1998**, *48*, 2263–2278.
8. Olofsson, B.; Somfai, P. *J. Org. Chem.* **2002**, *67*, 8574–8583.
9. For example: Ibuka, T.; Suzuki, K.; Habashita, H.; Otaka, A.; Tamamura, H.; Mimura, N.; Miwa, Y.; Taga, T.; Fujii, N. *J. Chem. Soc., Chem. Commun.* **1994**, 2151–2152. see also Refs. 5 and 6.
10. (a) Donohoe, T. J.; Helliwell, M.; Johnson, P. D.; Keenan, M. *Chem. Commun.* **2001**, 2078–2079; (b) Donohoe, T. J.; Cowley, A.; Johnson, P. D.; Keenan, M. *J. Am. Chem. Soc.* **2002**, *124*, 12934–12935; (c) Donohoe, T. J.; Johnson, P. D.; Pye, R. *J. Org. Biomol. Chem.* **2003**, *1*, 2025–2028; (d) Donohoe, T. J.; Johnson, P. D.; Keenan, M.; Pye, R. *J. Org. Lett.* **2004**, *6*, 2583–2585; (e) Donohoe, T. J.; Chughtai, M. J.; Klauber, D. J.; Griffin, D.; Campbell, A. D. *J. Am. Chem. Soc.* **2006**, *128*, 2514–2515; (f) Donohoe, T. J.; Bataille, C. J. R.; Gattrell, W.; Kloesges, J.; Rossignol, E. *Org. Lett.* **2007**, *9*, 1725–1728.
11. Kostiuk, S.L. Part II Thesis, Oxford, **2006**.
12. Application of the Du Bois conditions (Espino, C.G.; Du Bois, J. *Angew. Chem. Int. Ed.* **2001**,*40*, 598–600) to carbamate **4** resulted in a 46% yield of the *O*-Ac derivative of oxazolidinone **5** as a 1:1 mixture of diastereomers (Robertson, J.; Unsworth, W. P., unpublished results).
13. Kocovsky, P. *Tetrahedron Lett.* **1986**, *27*, 5521–5524.
14. Relative stereochemistry was assigned on the basis of NOE experiments conducted on the derived acetate esters.
15. Cook, G. R.; Sun, L. *Org. Lett.* **2004**, *6*, 2481–2484. We also found this isomerisation procedure to be applicable to the unprotected alcohol **5** and, following chromatography, a 96:4 ratio of *trans*-**5**:*cis*-**5** was obtained in essentially quantitative yield.[11]
16. Henbest, H. B.; Nicholls, B. *J. Chem. Soc.* **1957**, 4608–4612.
17. (a) Aceña, J. L.; De Alba, E.; Arjona, O.; Plumet, J. *Tetrahedron Lett.* **1996**, *37*, 3043–3044; (b) Aceña, J. L.; Arjona, O.; Plumet, J. *J. Org. Chem.* **1997**, *62*, 3360–3364.
18. E.g. $VO(acac)_2$, *t*-BuOOH Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136–6137.
19. A semi-empirical (PM3) conformational search was performed in *Spartan* using the *findboats* keyword. SPARTAN'06; Wavefunction. Irvine, CA: Shao, Y.; Molnar, L. F.; Jung, Y.; Kussmann, J.; Ochsenfeld, C.; Brown, S. T.; Gilbert, A. T. B.; Slipchenko, L. V.; Levchenko, S. V.; O'Neill, D. P.; DiStasio Jr., R. A.; Lochan, R. C.; Wang, T.; Beran, G. J. O.; Besley, N. A.; Herbert, J. M.; Lin, C. Y.; Van Voorhis, T.; Chien, S. H.; Sodt, A.; Steele, R. P.; Rassolov, V. A.; Maslen, P. E.; Korambath, P. P.; Adamson, R. D.; Austin, B.; Baker, J.; Byrd, E. F. C.; Dachsel, H.; Doerksen, R. J.; Dreuw, A.; Dunietz, B. D.; Dutoi, A. D.; Furlani, T. R.; Gwaltney, S. R.; Heyden, A.; Hirata, S.; Hsu, C.-P.; Kedziora, G.; Khalliulin, R. Z.; Klunzinger, P.; Lee, A. M.; Lee, M. S.; Liang, W. Z.; Lotan, I.; Nair, N.; Peters, B.; Proynov, E.I.; Pieniazek, P. A.; Rhee, Y. M.; Ritchie, J.; Rosta, E.; Sherrill, C. D.; Simmonett, A. C.; Subotnik, J. E.; Woodcock III, H. L.; Zhang, W.; Bell, A. T.; Chakraborty, A. K.; Chipman, D. M.; Keil, F. J.; Warshel, A.; Hehre, W. J.; Schaefer, H. F.; Kong, J.; Krylov, A. I.; Gill, P. M. W.; Head-Gordon, M. *Phys. Chem. Chem. Phys.* **2006**, *8*, 3172–3191.
20. A similar conformational search performed on the *N*–H analogue revealed no significant preference for a pseudoaxial CH_2OH.
21. Altenbach, H.-J.; Himmeldirk, K. *Tetrahedron: Asymmetry* **1995**, *6*, 1077–1080. see also Ref. 6.
22. (a) Donohoe, T. J.; Moore, P. R.; Waring, M. J.; Newcombe, N. J. *Tetrahedron Lett.* **1997**, *38*, 5027–5030; (b) Donohoe, T. J. *Synlett* **2002**, 1223–1232.
23. For example: Tius, M. A.; Drake, D. J. *Tetrahedron* **1996**, *52*, 14651–14660.
24. Crystal data for **16**: $C_{19}H_{31}NO_7SSi$, $M = 445.61$, colourless thin straw, monoclinic, $a = 6.3423(1)$, $b = 18.3958(3)$, $c = 20.0446(3)$ Å, $V = 2308.69(6)$ Å^3, $T = 150$ K, space group $P2_1/c$, $Z = 4$, 8457 reflections measured, 4997 independent all of which were used for refinement ($R_{int} = 0.072$), final $wR = 0.1699$. CCDC 721043 contains the full crystallographic data for this compound; this can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
25. Chamberlain, P.; Roberts, M. L.; Whitham, G. H. *J. Chem. Soc. (B)* **1970**, 1374–1381.
26. Donohoe, T. J.; Blades, K.; Moore, P. R.; Waring, M. J.; Winter, J. J. G.; Helliwell, M.; Newcombe, N. J.; Stemp, G. *J. Org. Chem.* **2002**, *67*, 7946–7956.
27. Robertson, J.; Naud, S. *Org. Lett.* **2008**, *10*, 5445–5448.
28. Cha, J. K.; Kim, N.-S. *Chem. Rev.* **1995**, *95*, 1761–1795.
29. (a) Hanessian, S.; Haskell, T. H. *J. Heterocycl. Chem.* **1964**, *1*, 55–56; (b) Hanessian, S.; Haskell, T. H. *J. Heterocycl. Chem.* **1964**, *1*, 57–58; (c) Weidmann, H.; Fauland, E. *Liebigs Ann. Chem.* **1964**, *679*, 192–194.
30. (a) Yamauchi, C.; Kuriyama, M.; Shimazawa, R.; Morimoto, T.; Kakiuchi, K.; Shirai, R. *Tetrahedron* **2008**, *64*, 3133–3140; (b) Dinsmore, A.; Doyle, P. M.; Steger, M.; Young, D. W. *J. Chem. Soc., Perkin Trans. 1* **2002**, 613–621; (c) Coe, D.; Drsydale, M.; Philps, O.; West, R.; Young, D. W. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2459–2472.
31. Yun, H.; Gagnon, A.; Danishefsky, S. J. *Tetrahedron Lett.* **2006**, *47*, 5311–5315.