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Synthesis of bioactive indolocarbazoles: synthesis, nucleophilic ring-opening and chiral base desymmetrisation of a cyclic sulfate intermediate

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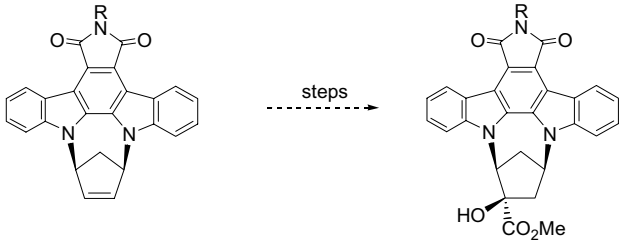
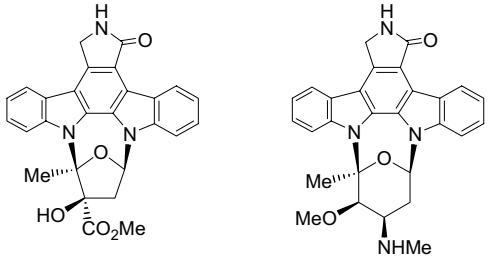
Abstract—A number of new functionalised bridged indolocarbazole systems have been prepared by ring-opening reactions of a key cyclic sulfate intermediate, prepared from the corresponding diol by the action of sulfuryl diimidazole and DBU. The same cyclic sulfate also undergoes an unprecedented asymmetric rearrangement to a chiral ketone, on treatment with a chiral lithium amide base.

In a previous report we described the synthesis of a small group of bridged indolocarbazoles, including alkene **1** and α-hydroxyester **2** (Eq. 1),[1] which are related to the natural product K252a **3**,[2] but which incorporate unnatural replacements to both the single atom bridge (i.e., they are carbocyclic analogues) and the fused lactam function.



1 R = H, Bn, PMB　　**2** R = H, Bn　　(1)

The *meso*-alkene **1** was available in quantity from very simple starting materials and provided ready access to the K252a analogue **2**, the N–H imide variant of which (**2** R = H) was found to show very promising kinase inhibitory activity.[3] In planning further exploration of



3　　**4**

such analogues we decided that compounds derived from alkene **1**, but incorporating vicinal heteroatom functions, as found in staurosporine **4**,[2] would be interesting hybrid systems. An additional aim was to generate some of the key analogues, such as **2**, in non-racemic form through a desymmetrisation of alkene **1** or some derivative. Here we describe progress in both of these areas, which has uncovered some new and novel transformations, including a new chiral base-mediated rearrangement.

The rather poor solubility characteristics of indolocarbazoles makes them challenging substrates for many types of reactions, especially if low temperatures are usually employed. Our initial efforts to effect new transformations of alkene **1** focused on epoxide generation, with the imide nitrogen protected as N–Bn or N–PMB. Epoxide generation using peracids proved very

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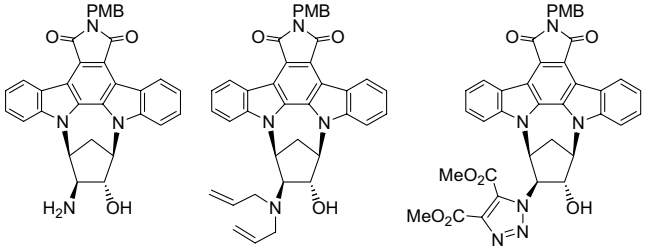
problematic (ca. 17–19% typical yield), DMDO gave a maximum yield of 47% with **1** R = PMB, but the reaction proved capricious, and complementary approaches via bromohydrin formation also proved ineffective. Experiments involving epoxide opening, using the modest supplies available from the DMDO reaction, were also discouraging, with azide (normally an excellent nucleophile for epoxide opening) giving azidoalcohol products in only very modest yields.

These problems led us to develop a complementary approach, which relies on the sequence of alkene dihydroxylation, cyclic sulfate formation and nucleophilic ring opening (Scheme 1).

In contrast to the problematic epoxidation reactions, dihydroxylation of alkene **1** at room temperature in THF was very efficient.[4] Cyclic sulfate synthesis by the usual approach of forming the corresponding cyclic sulfite with $SOCl_2$ and then oxidation with the Sharpless in situ RuO_4 acetonitrile–water system proved low-yielding due to problems with the second step.[5] Instead, and after considerable experimentation, we found that reaction of the diol **5** with sulfuryl diimidazole with DBU as base gave the desired sulfate directly and in excellent yield. This combination proved uniquely effective in our system, and may be useful in a more general sense.[6]

Ring opening of the cyclic sulfate **6** was then carried out under various conditions to give a range of products **7a**–**e** in which interesting vicinal functionality had been installed.[7] The reaction of **6** with azide attested to the excellent activating properties of the cyclic sulfate, since the ring opening occurred in high yield under conditions which left the corresponding epoxide unreacted. The direct installation of amine groups still proved difficult, the modest yield obtained by reaction of **6** in neat morpholine at reflux being one of the best results.[8] In contrast, reaction with oxygen or sulfur centred nucleophiles was relatively straightforward.

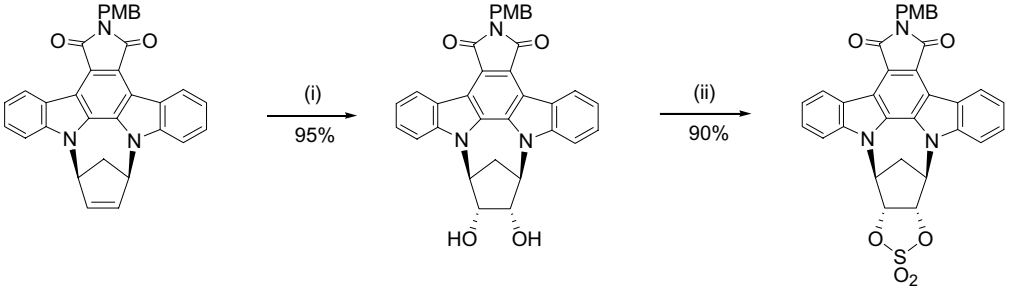
Given the apparent importance of the nitrogen functionality in bioactive systems such as staurosporine, we were pleased to demonstrate that the azide function present in **7a** could enable access to diverse nitrogen containing products, such as **8**–**10** in straightforward fashion.



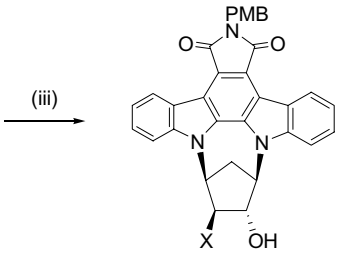
8 71% **9** 60% **10** 95%

Reagents:
(**7** to **8**) Pd(C), H_2, DMF; (**7** to **9**) Indium, NaI, allylbromide, DMF 50 °C; (**7** to **10**) $MeO_2CC{\equiv}CCO_2Me$, DMF 70 °C

Thus, azide reduction, to give the potentially versatile primary amine **8**, was possible under several types of typical hydrogenation conditions, the imide N–PMB



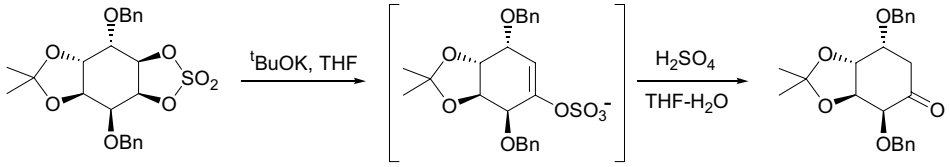
1 **5** **6**



7a-e

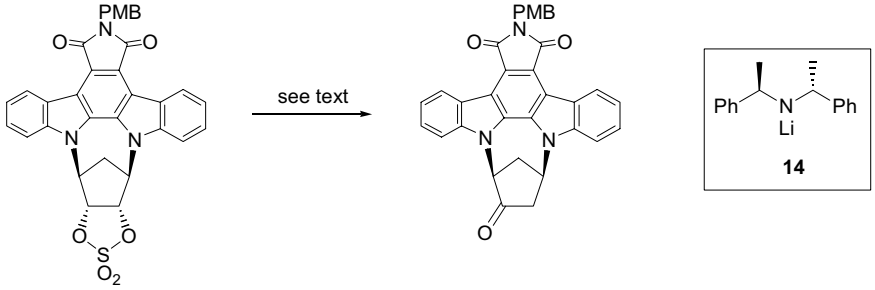
reagent (iii)	X	yield (%)
NaN_3, DMF, 80 °C	N_3	**7a** (91%)
morpholine, reflux		**7b** (36%)
$PhCO_2NH_4$, DMF, 70 °C	OCOPh	**7c** (88%)
PhSH, NaH, THF, RT	SPh	**7d** (91%)
NH_4SCN, DMF, 70 °C	SCN	**7e** (64%)

Scheme 1. Reagents and conditions: (i) OsO_4, NMO, THF; (ii) Im_2SO_2, DBU, THF; (iii) see table; then 20% H_2SO_4, THF.



11 **12** 86%

Scheme 2.



6 **13** **14**

Scheme 3.

being unaffected. Although amine **8** may prove useful in reductive alkylation sequences, we also gained access to diallyl amine **9** by means of the indium mediated Barbier type process described by Yadav et al.[9] Azide cycloaddition using dimethyl acetylenedicarboxylate as reaction partner, one of the processes highlighted by Sharpless in his 'click chemistry' approach,[10] was also effective, leading to triazole **10** in very high yield.

Whilst exploring the ring opening chemistry of cyclic sulfate **6** we were attracted to a little-known transformation involving base-mediated rearrangement of a cyclic sulfate to a ketonic product. This is exemplified by the reaction of the cyclitol derived cyclic sulfate **11** to give the ketone **12**, described by Fernández-Mayoralas and co-workers[11] (Scheme 2).

These authors proposed a β-elimination process to give an intermediate vinyl bisulfate, which on acidification gave the ketone product.[12] Unfortunately, application of these conditions to our cyclic sulfate **6** gave only very modest yields (8%) of the desired ketone **13** (which was an important intermediate in the formation of hydroxyester **2**) (Scheme 3).

Similarly, the use of LDA at low temperature also gave very modest (ca. 5%) yields of the desired ketone, and recovery of starting sulfate or the corresponding diol **5** predominated. Our main motivation for persisting with this transformation was the hope that an asymmetric variant might enable access to ketone **13** in non-racemic form. Therefore chiral alkoxides, such as metal salts of ephedrine derivatives were explored briefly, but to no effect.[13] Finally, we found that chiral lithium amide base **14** provided some more encouraging preliminary results.[14] Thus, addition of cyclic sulfate **6** to a solution of lithium amide **14** and LiCl (4 equiv) at −78 °C provided a 39% yield of ketone **13**, following acidification.[15] The enantiomeric excess of the ketone was established by HPLC to be 87%, and the absolute configuration was tentatively assigned as shown in Scheme 3 by correlation with material obtained via asymmetric hydroboration of alkene **1**.[16] Unfortunately, preliminary reaction screening has failed to uncover conditions under which higher yields of ketone **13** can be obtained, and we have not yet been able to test additional cyclic sulfate substrates.

The chiral base transformation of **6** to give ketone **13** is the first example of its type for cyclic sulfates, although the chemistry is clearly related to the analogous transformation of certain epoxides.[17] Further study is required to delineate the scope, limitations and likely mechanism of the process.

We are in the process of further modifying the indolocarbazoles described here, and initial screening results show the corresponding deprotected imides (i.e., imide N–H series) to be potent kinase inhibitors. Full details of this work will be reported in due course.

Acknowledgements

We gratefully acknowledge support for this work from The University of Nottingham, Eli Lilly and Company, Indianapolis, and NADAG, Munich.

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3. In the form of their imide N–H derivatives many of these systems display nanomolar inhibition of enzymes such as protein kinase C (PKC).
4. This dihydroxylation appears in a patent, see: Roder, H.; Lowinger, T. B.; Brittelli, D. R.; VanZandt, M. C. U.S. Patent 6,013,646, Jan. 11, 2000.
5. For an excellent review of cyclic sulfate chemistry, see: (a) Byun, H.-S.; He, L.; Bittman, R. *Tetrahedron* **2000**, *56*, 7051; For the seminal contribution, see: (b) Gao, Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 7538.
6. The use of NaH as base seems more usual, but was ineffective in our system, see, for examples, (a) Tewson, T. J.; Soderlind, M. *J. Carbohydr. Chem.* **1985**, *4*, 529; (b) Hanessian, S.; Vatele, J.-M. *Tetrahedron Lett.* **1981**, *22*, 3579.
7. *Synthesis of azide* **7a**: Cyclic sulfate **6** (0.48 g, 0.79 mmol) was dissolved in dry DMF (50 mL) with stirring under N_2. NaN_3 (0.52 g, 7.92 mmol) was added and the reaction mixture heated to 80 °C. After 5 h TLC showed complete consumption of starting material and the reaction mixture was allowed to cool to rt and concentrated in vacuo to give a brown solid. The brown solid was redissolved in THF (20 mL), 20% H_2SO_4 (5 mL) was added and the resulting mixture stirred vigorously for 18 h. The reaction mixture was partitioned between EtOAc (200 mL) and H_2O (100 mL) and the organic layer was washed with H_2O (200 mL), saturated aqueous $NaHCO_3$ solution (150 mL), brine (2 × 200 mL), dried ($MgSO_4$) and concentrated in vacuo to give crude azido alcohol. Purification by flash column chromatography using 5% MeOH–CH_2Cl_2 as the solvent system yielded **7a** as an orange solid (0.41 g, 91%); mp 267–269 °C; (Found: *m/z* (FAB$^+$) M^+ 568.1836 $C_{33}H_{24}N_6O_4$ requires 568.1859); ν_{max} ($CHCl_3$)/cm^{-1} 3449, 2930, 2108, 1750, 1695, 1385, 1350; δ_H (DMSO-d_6, 500 MHz) 2.76 (1H, d, *J* 14.8, 1′-H_α), 3.28 (1H, ddd, *J* 14.8, 7.5, 6.5, 1′-H_β), 3.74 (3H, s, OMe), 3.87 (1H, dd, *J* 5.3, 4.8, 3′-H), 4.45 (1H, dd, *J* 5.9, 5.3, 4′-H) 4.84 (2H, s, CH_2Ar), 5.40 (1H, d, *J* 7.5, 2′-H), 5.93 (1H, dd, *J* 6.5, 5.9, 5′-H), 6.35 (1H, d, *J* 4.8, OH), 6.94 (2H, d, *J* 8.8, PMB), 7.39 (2H, d *J* 8.8, PMB), 7.45 (2H, dd, *J* 8.4, 7.2, 3-H, 9-H), 7.70 (2H, dd, *J* 8.2, 7.2, 2-H, 10-H), 7.94 (1H, d, *J* 8.2, 11-H), 7.95 (1H, d, *J* 8.2, 1-H), 9.07 (1H, d, *J* 8.4, 8-H), 9.09 (1H, d, *J* 8.4, 4-H); δ_C (DMSO-d_6, 125 MHz) 36.3 (1′-CH_2), 41.0 (CH_2Ar), 56.0 (OMe), 59.6 (5′-CH) 63.1 (2′-CH), 72.2 (4′-CH), 83.6 (3′-CH), 111.1 (CH) 111.2 (CH), 114.9 (PMB-CH), 116.6 (C), 116.8 (C), 119.5 (C), 119.6 (C), 121.6 (2CH), 122.0 (2C), 125.4 (CH), 125.5 (CH), 128.0 (CH), 128.2 (CH), 129.3 (C), 129.6 (C), 129.9 (PMB-CH), 130.4 (C), 141.0 (C), 142.6 (C), 159.5 (C), 170.1 (CO), 170.2 (CO); *m/z* (FAB$^+$) 569 (M^++H, 8%), 568 (M^+, 12), 419 (5), 329 (5), 289 (15), 137 (52), 108 (5), 77 (13).
8. Cyclic sulfate ring opening by heating in neat amine has been used previously, see, for example, Hirsenkorn, R. *Tetrahedron Lett.* **1990**, *31*, 7591.
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12. The regiochemistry observed in the series of examples described in Ref. 11b suggests to us that an α-lithiation-carbenoid C–H insertion mechanism might operate, as established for a somewhat analogous reaction involving epoxides (see Ref. 17).
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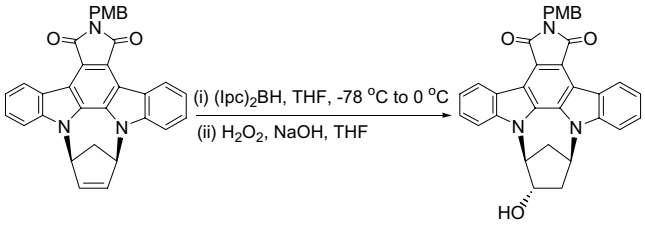
15. A mixture of chiral lithium amide **14** and LiCl was prepared by treatment of a solution of the appropriate secondary amine–HCl salt (88.0 mg, 0.34 mmol) in THF (1 mL) at −78 °C under N_2 with ^{n}BuLi (1.27 M in hexanes, 0.52, 0.66 mL). The mixture was allowed to warm to room temperature for 0.5 h before being recooled to −78 °C and then a solution of cyclic sulfate **6** (50.0 mg, 0.08 mmol) in THF (15 mL) pre-cooled to −78 °C was added dropwise. After 4 h the reaction mixture was quenched with H_2O (1 mL) and 20% H_2SO_4 (3.3 mL) added. The reaction mixture was allowed to warm to room temperature with stirring for 18 h and was then partitioned between EtOAc (75 mL) and H_2O (75 mL). The organic layer was washed with H_2O (75 mL), saturated aqueous $NaHCO_3$ solution (75 mL), brine (75 mL), dried ($MgSO_4$), and concentrated in vacuo to give a yellow solid, which was purified by flash column chromatography using a 2–10% MeOH–CH_2Cl_2 solvent system to give firstly ketone **13** (17.0 mg, 39%), $[\alpha]_D^{26}$ − 62.9 (*c* 0.60, $CHCl_3$); mp >280 °C; (Found: *m/z* (FAB$^+$) M^+ 525.1663. $C_{33}H_{23}N_3O_4$ requires 525.1689); ν_{max} ($CHCl_3$)/cm^{-1} 1753, 1697, 1384, 1349; δ_H (DMSO-d_6, 500 MHz) 2.49 (1H, dd, *J* 3.1, 19.4, 4′-H_α), 3.07 (1H, dd, *J* 7.0, 19.7, 4′-H_β), 3.26 (1H, dd, *J* 6.8, 19.4, 4′-H_α), 3.53 (1H, m, 1′-H_β), 3.74 (3H, s, OMe), 4.76 (2H, s, CH_2PMB), 5.59 (1H, d, *J* 8.1, 2′-H), 6.14 (1H, dd, *J* 6.8, 6.4, 2′-H), 6.92 (2H, d, *J* 8.8, PMB), 7.35 (2H, d *J* 8.8, PMB), 7.45 (2H, dd, *J* 7.3, 7.9, 3-H, 9-H), 7.67 (2H, dd, *J* 6.7, 8.1, 2-H, 10-H), 7.89 (1H, d, *J* 8.4, 11-H), 7.97 (1H, d, *J* 8.4, 1-H), 9.04 (1H, d, *J* 7.9, 8-H), 9.05 (1H, d, *J* 7.9, 4-H); δ_C (DMSO-d_6, 100 MHz) 37.3 (1′-CH_2), 40.9 (CH_2PMB), 45.0 (4′-CH_2), 54.1 (5′-CH), 56.0 (OMe), 58.3 (2′-CH), 110.8 (CH), 111.0 (CH), 114.9 (PMB-CH and C), 116.6 (C), 116.9 (C) 119.3 (C), 119.9 (C), 121.6 (CH), 121.8 (CH), 121.9 (C), 125.4 (CH), 125.5 (CH), 128.1 (CH), 128.2 (CH), 128.9 (C), 129.2 (C), 129.9 (PMB-CH), 130.3 (C), 141.0 (C), 141.2 (C), 159.4 (C), 169.9 (2CO), 215.1 (CO).
    Diol **5** was also recovered (5.0 mg, 11%).
16. Our lack of success in obtaining a high yield and enantiomeric excess in the asymmetric hydroboration (or hydrosilylation) of alkene **1** was another reason that the new cyclic sulfate rearrangement was pursued. Hydroboration of **1** with excess (−)-$(Ipc)_2BH$, followed by the

usual oxidative work-up, gave alcohol (−)-**14** in 33% ee maximum.



1 **14** 83% (33% ee)

By analogy to norbornene and norbornadiene systems the secondary alcohol would be expected to have the configuration shown, and when this alcohol was oxidised using Dess–Martin periodinane ketone (−)-**13** was obtained, matching the sample from the cyclic sulfate rearrangement. For background, see: Brown, H. C.; Jadhav, P. K.; Mandal, A. K. *Tetrahedron* **1981**, *37*, 3547.

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