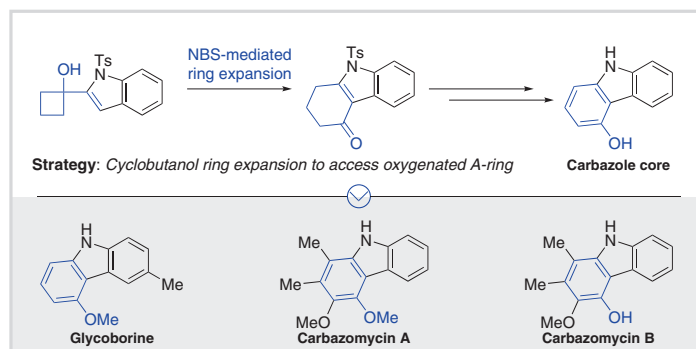


# A Cyclobutanol Ring-Expansion Approach to Oxygenated Carbazoles: Total Synthesis of Glycoborine, Carbazomycin A and Carbazomycin B

Philipp Natho   
 Lewis A. T. Allen   
 Philip J. Parsons\*

Department of Chemistry, Imperial College London, London, W12 0BZ, U.K.  
 p.parsons@imperial.ac.uk



Received: 27.11.2022

Accepted after revision: 28.12.2022

Published online: 24.01.2023 (Version of Record)

DOI: 10.1055/s-0042-1751411; Art ID: ST-2022-11-0510-L



License terms:

© 2023. The Author(s). This is an open access article published by Thieme under the terms of the Creative Commons Attribution License, permitting unrestricted use, distribution and reproduction, so long as the original work is properly cited. (<https://creativecommons.org/licenses/by/4.0/>)

**Abstract** The transition-metal-free total syntheses of the oxygenated carbazole natural products glycoborine, carbazomycin A and carbazomycin B are reported. The key step involves an NBS-mediated cyclobutanol ring expansion to 4-tetralones for the preparation of the tricyclic carbazole core.

**Key words** total synthesis, ring expansion, cyclization, antifungal agents, rearrangement

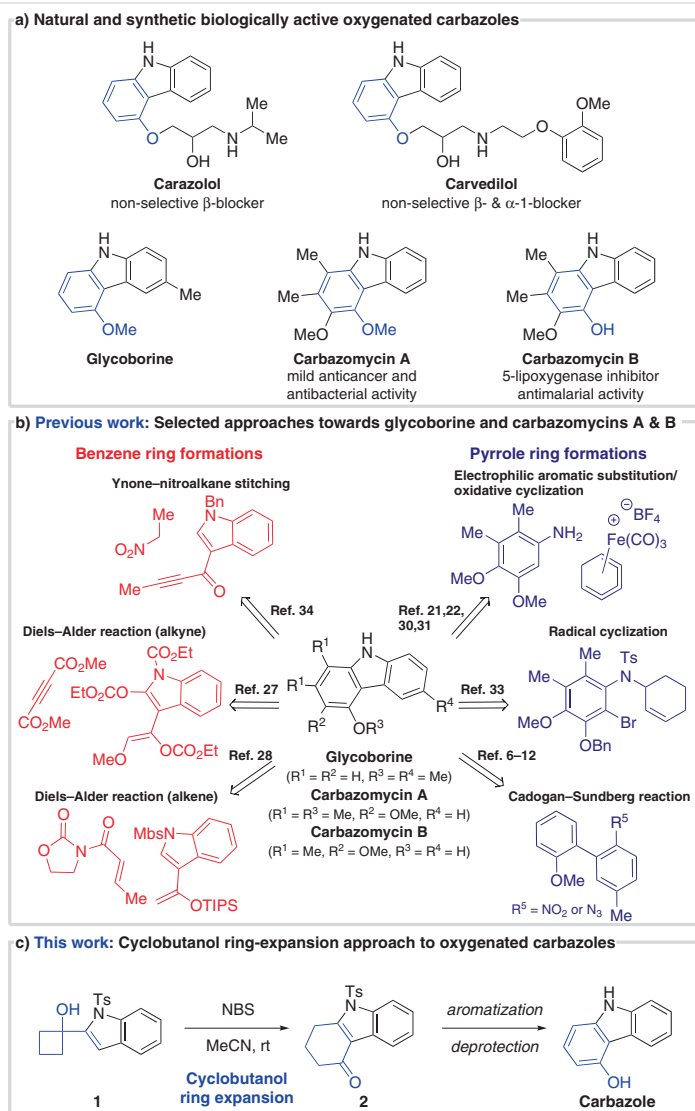
In the last few decades, the carbazole core has attracted the interest of synthetic organic chemists due to its versatile application in various fields of chemistry, such as the design of efficient photochemical materials or active pharmaceutical ingredients (APIs). The development of APIs, such as carazolol or carvedilol, is often inspired by initial hits from naturally occurring biologically active carbazoles (Scheme 1, a). Interestingly, these marketed drugs contain oxygenated functionality at the 5-position, which is rarely found in naturally occurring carbazoles.

The first natural 5-oxygenated carbazole alkaloid, glycoborine, was reported by Chakravarty only two decades ago. It was isolated as a constituent in trace amounts (0.0001% w/w) of the petroleum ether extract of the roots of *Glycosmis arborea* (Scheme 1, a),<sup>1</sup> and extracts of this plant have been used in traditional treatments of fever or liver diseases.<sup>2</sup> Given the low structural complexity of glycoborine, it has been a suitable target for synthetic chemists to test the applicability of their newly developed methodologies towards the carbazole core. In fact, the majority of these pro-

ocols focus on the assembly of the pyrrole core as the strategic step by using the Fischer indole synthesis,<sup>1,3</sup> nickel-catalyzed reductive cyclization,<sup>4</sup> palladium-catalyzed cyclization of diarylamines,<sup>5</sup> or a variant of the Cadogan-Sundberg reaction (Scheme 1, b).<sup>6–12</sup>

The carbazomycins are a family of naturally occurring carbazoles that also contain oxygenation on the same position (Scheme 1, a). These compounds were isolated by Nakamura from the extract of cultured mycelia of *Streptovorticillium ehimensis* strain H1051-MY10,<sup>13–15</sup> and they are characterized by their unusual asymmetric substitution pattern, in which only one aromatic ring is fully substituted with electron-donating substituents. Several carbazomycins exhibit antifungal,<sup>16</sup> antibacterial<sup>13</sup> and anticancer activity;<sup>17,18</sup> in addition, carbazomycin B displays inhibitory activity against 5-lipoxygenase ( $IC_{50} = 1.5 \mu\text{g/mL}$ )<sup>19</sup> and is active against malaria ( $IC_{50} = 2.37 \mu\text{g/mL}$  against *Plasmodium falciparum*, K1 multi-drug resistant strain).<sup>20</sup> Given these interesting biological effects, their total synthesis has received considerable attention (Scheme 1, b).<sup>21–34</sup> Elegant examples include an iron-mediated one-pot oxidative coupling by Knölker,<sup>21,22,30,31</sup> a radical cyclization by Crich and Rumthao,<sup>32</sup> and most recently, a one-pot domino benzanulation between indole-3-ynones and nitroalkanes by Mehta.<sup>34</sup>

To complement these previously reported approaches to carbazole natural products, and encouraged by a recent total synthesis report utilizing a cyclobutanol ring expansion,<sup>35</sup> we were inspired to develop a strategy based on our previously developed cyclobutanol ring expansion methodology (Scheme 1, c). In 2018, we reported that heteroaromatic-substituted cyclobutanols undergo regioselective ring expansion to 4-tetralones by treatment with *N*-bromosuccinimide in acetonitrile.<sup>36–40</sup> Following our group's longstanding interest in the synthesis of biologically active nat-



**Scheme 1** (a) Biologically active carbazoles, (b) previous routes to oxygenated carbazoles, and (c) the present approach via a cyclobutanol ring expansion

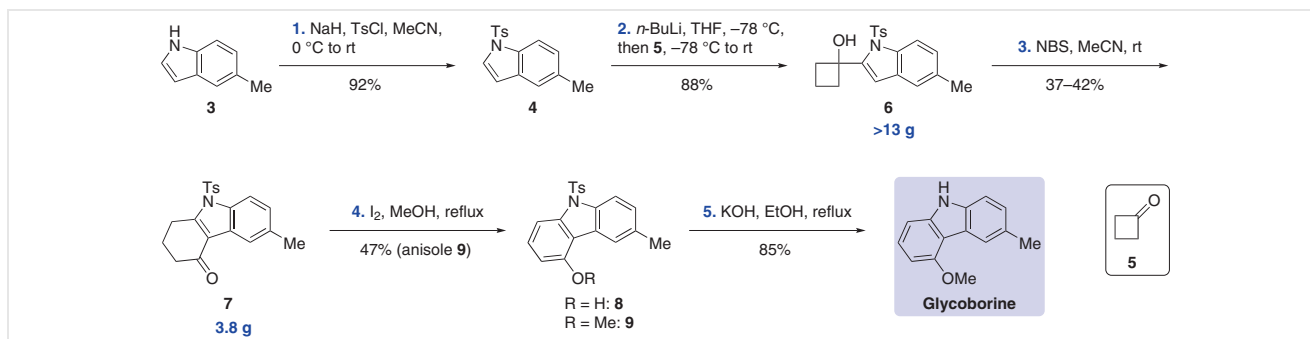
ural products,<sup>41–44</sup> we now report the successful total syntheses of glycoborine, carbazomycin A and carbazomycin B.<sup>45</sup>

Our synthetic plan was guided by the oxygenation pattern of the carbazoles of interest (Scheme 1, c). Thus, we hypothesized that the respective carbazole cores could be accessed by aromatization of a suitably substituted 4-tetralone intermediate **2**. The key feature of our synthetic plan is the disconnection of the tricyclic intermediate to cyclobutanol **1**, provided by the addition of protected indole to an appropriately substituted cyclobutanone.

With our synthetic plan laid out, we initiated our studies towards the total synthesis of glycoborine (Scheme 2).<sup>45</sup> Synthesis of the core began with tosyl-protection of com-

mercially available 5-methylindole (**3**) in 92% yield. Subsequent C2-lithiation with *n*-butyllithium, followed by addition to commercially available cyclobutanone (**5**) provided the cyclobutanol **6** in 88% yield on a decagram scale. This key intermediate was then converted into the 4-tetralone **7** by our previously reported cyclobutanol ring expansion in the presence of *N*-bromosuccinimide in acetonitrile. Notably, the 4-tetralone **7** was afforded on a multigram scale within 30 minutes.

To complete the total synthesis of glycoborine in short order, we next aimed to convert 4-tetralone **7** into the phenol **8** (see the Supporting Information). To our surprise, this proved to be a non-trivial quest: several aromatization conditions were examined, including bromination–elimination



**Scheme 2** Total synthesis of glycoborine; NBS = *N*-bromosuccinimide

sequences, DDQ in toluene, or dichloromethane, and 10% Pd/C in boiling diphenyl ether. Yet, these conditions furnished the desired phenol in trace quantities only. Finally, we turned our attention to an iodine-mediated procedure reported by Teclé.<sup>46</sup> To our delight, treatment of 4-tetralone **7** with a superstoichiometric quantity of iodine in boiling methanol not only affected the desired aromatization but also afforded anisole **9** in 47% yield. Finally, removal of the *N*-tosyl protecting group with potassium hydroxide in boiling degassed ethanol delivered glycoborine in 85% yield.<sup>47</sup> Our synthetic sample exhibited identical spectroscopic properties to those of the natural isolate.<sup>1</sup>

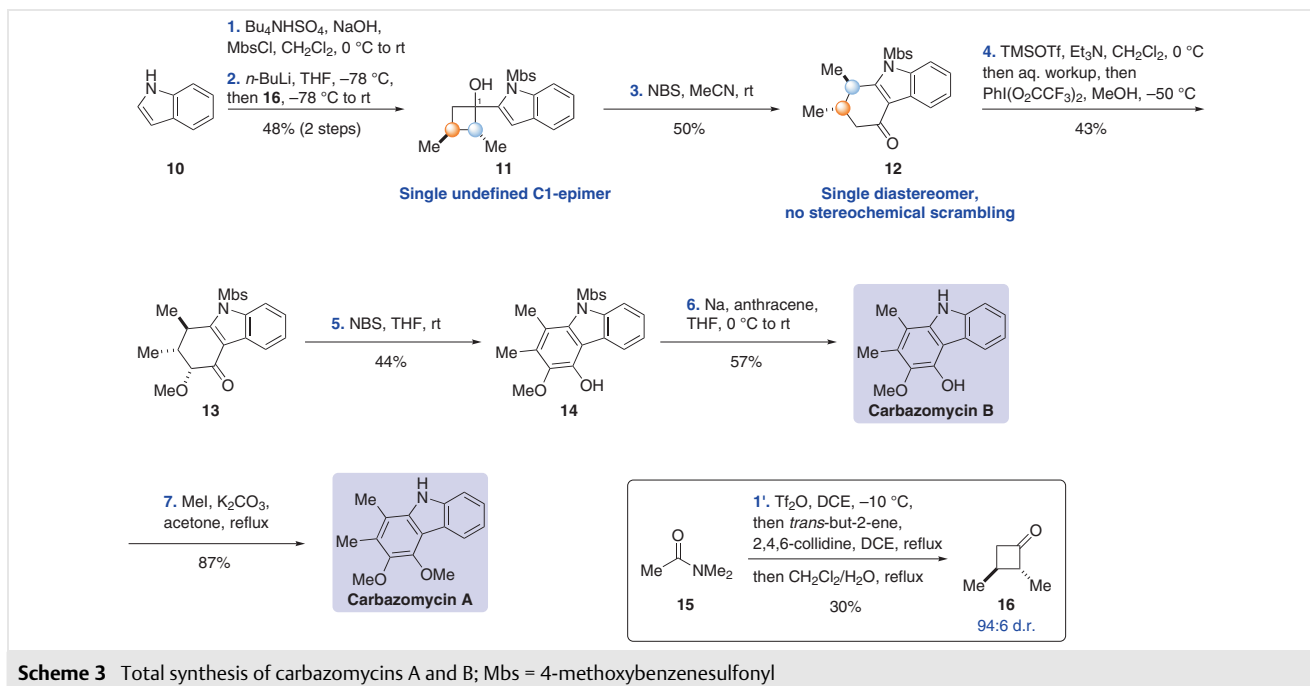
We then turned our attention to the structurally more challenging carbazomycins A and B.<sup>45</sup> The synthetic sequence began with the preparation of *trans*-2,3-dimethylcyclobutanone (**16**) in 30% yield by a stereospecific thermal [2+2]-cycloaddition between *trans*-but-2-ene gas and the keteniminium salt of dimethylacetamide (**15**), followed by mild hydrolysis in boiling dichloromethane according to an adapted procedure by Ghosez.<sup>48,49</sup> Although the isolated yield of the cyclobutanone was reduced by its volatility and that of *trans*-but-2-ene, we found the reaction to be scalable to gram-quantities nonetheless; producing sufficient quantities for the total synthesis (Scheme 3). Next, addition of C2-lithiated Mbs-protected indole<sup>50</sup> to cyclobutanone **16** afforded key cyclobutanol **11** in 55% yield as a single undefined C1-epimer on a multi-gram scale. Treatment of cyclobutanol **11** with *N*-bromosuccinimide under our standard ring-expansion conditions afforded the *trans*-1,2-dimethylated 4-tetralone **12** as a single diastereomer in 50% yield within only five minutes.

In line with our previous studies, full stereochemical retention, as well as exclusive formation of the  $\beta,\gamma$ -substituted 4-tetralone (vs the  $\alpha,\beta$ -substituted 4-tetralone) was observed (Scheme 3). This regioselectivity is attributed to exclusive initial migration of the most-substituted carbon as the partial carbocation character in the transition state is stabilized by inductive effects and hyperconjugation.<sup>51,52</sup> The migratory ability of carbon moieties in such migratory shifts has been well-studied and not only explains the observed regioselectivity, but also the retention of stereo-

chemistry at the migrating center. A further 1,2-sigmatropic rearrangement—supported by the acylium-like character of the carbonyl group—affords the *trans*-1,2-dimethylated 4-tetralone after aromatization, intercepting Nishida's route towards carbazomycins A and B in very short order (three vs eight synthetic steps in the longest linear sequence from indole).<sup>28,53</sup>

With the tricyclic backbone in hand, we turned our attention to installing the  $\alpha$ -methoxy group. We initially followed Nishida's described two-step protocol consisting of silyl enol ether formation by treatment of ketone **12** with Hünig's base and trimethylsilyl trifluoromethylsulfonate in dichloromethane, followed by removal of volatiles and subjection to [bis(trifluoroacetoxy)iodo]benzene in methanol.<sup>28</sup> In our hands, this protocol returned starting material exclusively, which we reasoned to be a consequence of the conjugate acid of Hünig's base removing the labile TMS group before the nucleophilic substitution with the hypervalent iodine species. To our delight, substitution of Hünig's base with lower boiling triethylamine, and inclusion of a mild aqueous work-up after silyl enol ether formation rendered the subsequent  $\alpha$ -methoxylation successful to afford ketone **13** in 43% yield. Notably, the  $\alpha$ -methoxylation proceeded stereospecifically to afford the *cis-trans*-substituted 4-tetralone exclusively (Scheme 3).

Conversion into the natural products was then achieved following Nishida's report (Scheme 3).<sup>28</sup> Aromatization of ketone **13** with four equivalents of *N*-bromosuccinimide in THF afforded carbazole **14** in 44% yield. The importance of the Mbs-protecting group and the stereochemical relationship between the substituents on the tetralone ring for the success of the aromatization is key to note at this stage. Earlier studies within our group revealed that the *N*-tosyl-protected derivative failed to deliver the desired phenol under NBS-mediated conditions or alternative protocols, including Saegusa–Ito and iodine-mediated conditions. We attribute the aromatization of the Mbs-protected analogue to the greater electron-density induced by the alkoxy-resonance donor. Equally, we observed that, unlike the *cis-trans*-isomer, the *cis-cis*-isomer does not undergo aromatization under NBS-mediated conditions, confirming the ne-



necessity for control of the stereochemical relationship between the methyl groups from the outset of the synthetic sequence.

Finally, reduction of the sulfonyl protecting group using sodium anthracenide provided carbazomycin B in 57% yield, and this was converted, using Moody's methylation conditions, into carbazomycin A in 87% yield (Scheme 3).<sup>26,54</sup> Our synthetic samples of carbazomycins A and B were spectroscopically identical to those of the natural isolates.<sup>14</sup>

In conclusion, we have reported a complementary strategy to oxygenated carbazoles. The total synthesis of glyco-borine was achieved in a scalable, five-step and transition-metal-free sequence in 10% overall yield. Carbazomycin B was synthesized in six steps and converted into carbazomycin A in one further synthetic step. The reported syntheses are enabled by an NBS-mediated cyclobutanol ring expansion developed by our group, demonstrating its immediate applicability for medicinal chemistry or total synthesis applications. Extension to other classes of natural products, as well as biological evaluations are currently ongoing.

### Conflict of Interest

The authors declare no conflict of interest.

### Funding Information

The authors gratefully acknowledge the receipt of an EPSRC Imperial College London President's Scholarship (to P.N.). Additional generous

funding from the late Dr. Isabel Bader and Dr. Alfred Bader (to P.J.P.) is gratefully recognized.

### Acknowledgment

We thank Pete Haycock (Imperial College London) and Dr. Lisa Haigh (Imperial College London) for NMR and mass spectrometric analysis, respectively.

### Supporting Information

Supporting information for this article is available online at <https://doi.org/10.1055/s-0042-1751411>.

### References

- Chakravarty, A. K.; Sarkar, T.; Masuda, K.; Takey, T.; Doi, H.; Kotani, E.; Shiojima, K. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **2001**, *40*, 484.
- Chakravarty, A. K.; Sarkar, T.; Masuda, K.; Shiojima, K. *Phytochemistry* **1999**, *50*, 1263.
- Chakraborty, A.; Chowdhury, B. K.; Jash, S. S.; Biswas, G. K.; Bhattacharyya, S. K.; Bhattacharyya, P. *Phytochemistry* **1992**, *31*, 2503.
- Yan, Q.; Gin, E.; Wasinska-Kalwa, M.; Banwell, M. G.; Carr, P. D. *J. Org. Chem.* **2017**, *82*, 4148.
- Brütting, C.; Hesse, R.; Jäger, A.; Kataeva, O.; Schmidt, A. W.; Knölker, H.-J. *Chem. Eur. J.* **2016**, *22*, 16897.
- Gao, H.; Xu, Q.-L.; Yousufuddin, M.; Ess, D. H.; Kürti, L. *Angew. Chem. Int. Ed.* **2014**, *53*, 2701.
- Bhatthula, B. K. G.; Kanchani, J. R.; Arava, V. R.; Subha, M. C. S. *Tetrahedron* **2019**, *75*, 874.
- Kuethe, J. T.; Childers, K. G. *Adv. Synth. Catal.* **2008**, *350*, 1577.

- (9) Nykaza, T. V.; Ramirez, A.; Harrison, T. S.; Luzung, M. R.; Radosevich, A. T. *J. Am. Chem. Soc.* **2018**, *140*, 3103.
- (10) Yang, L.; Zhang, Y.; Zou, X.; Lu, H.; Li, G. *Green Chem.* **2018**, *20*, 1362.
- (11) Yang, L.; Li, H.; Zhang, H.; Lu, H. *Eur. J. Org. Chem.* **2016**, 5611.
- (12) Akiyama, T.; Wada, Y.; Yamada, M.; Shio, Y.; Honma, T.; Shimoda, S.; Tsuruta, K.; Tamenori, Y.; Haneoka, H.; Suzuki, T.; Harada, K.; Tsurugi, H.; Mashima, K.; Hasegawa, J.; Sato, Y.; Arisawa, M. *Org. Lett.* **2020**, *22*, 7244.
- (13) Sakano, K.-I.; Ishimaru, K.; Nakamura, S. *J. Antibiot.* **1980**, *33*, 683.
- (14) Sakano, K.-I.; Nakamura, S. *J. Antibiot.* **1980**, *33*, 961.
- (15) Nakamura, S.; Kaneda, M.; Sakano, K.; Kushi, Y.; Iitaka, Y. *Heterocycles* **1981**, *15*, 993.
- (16) Kaneda, M.; Naid, T.; Kitahara, T.; Nakamura, S.; Hirata, T.; Suga, T. *J. Antibiot.* **1988**, *41*, 602.
- (17) Nishiyama, T.; Hatae, N.; Yoshimura, T.; Takaki, S.; Abe, T.; Ishikura, M.; Hibino, S.; Choshi, T. *Eur. J. Med. Chem.* **2016**, *121*, 561.
- (18) Karwehl, S.; Jansen, R.; Huch, V.; Stadler, M. *J. Nat. Prod.* **2016**, *79*, 369.
- (19) Hook, D. J.; Yacobucci, J. J.; O'Connor, S.; Lee, M.; Kerns, E.; Krishnan, B.; Matson, J.; Hesler, G. *J. Antibiot.* **1990**, *43*, 1347.
- (20) Intaraudom, C.; Rachtawee, P.; Suvannakad, R.; Pittayakhajonwut, P. *Tetrahedron* **2011**, *67*, 7593.
- (21) Knölker, H.-J.; Bauermeister, M. *J. Chem. Soc., Chem. Commun.* **1989**, 1468.
- (22) Knölker, H.-J.; Fröhner, W. *Tetrahedron Lett.* **1999**, *40*, 6915.
- (23) Markad, S. B.; Argade, N. P. *Org. Lett.* **2014**, *16*, 5470.
- (24) Schmidt, A. W.; Reddy, K. R.; Knölker, H.-J. *Chem. Rev.* **2012**, *112*, 3193; and references cited therein.
- (25) Knölker, H.-J.; Reddy, K. R. *Chem. Rev.* **2002**, *102*, 4303; and references cited therein.
- (26) Moody, C. J.; Shah, P. *J. Chem. Soc., Perkin Trans. 1* **1989**, 376.
- (27) Beccalli, E. M.; Marchesini, A.; Pilati, T. *Tetrahedron* **1996**, *52*, 3029.
- (28) Wu, S.; Harada, S.; Morikawa, T.; Nishida, A. *Chem. Pharm. Bull.* **2018**, *66*, 178.
- (29) Hibino, S.; Tonari, A.; Choshi, T.; Sugino, E. *Heterocycles* **1993**, *35*, 441.
- (30) Knölker, H.-J.; Bauermeister, M.; Bläser, D.; Boese, R.; Pannek, J.-B. *Angew. Chem.* **1989**, *101*, 225.
- (31) Knölker, H.-J.; Bauermeister, M. *Helv. Chim. Acta* **1993**, *76*, 2500.
- (32) Crich, D.; Rumthao, S. *Tetrahedron* **2004**, *60*, 1513.
- (33) Clive, D. L. J.; Etkin, N.; Joseph, T.; Lown, J. W. *J. Org. Chem.* **1993**, *58*, 2442.
- (34) Singh, S.; Samineni, R.; Pabbaraja, S.; Mehta, G. *Org. Lett.* **2019**, *21*, 3372.
- (35) Leclair, A.; Wang, Q.; Zhu, J. *ACS Catal.* **2022**, *12*, 1209.
- (36) Natho, P.; Kapun, M.; Allen, L. A. T.; Parsons, P. J. *Org. Lett.* **2018**, *20*, 8030.
- (37) Natho, P.; Allen, L. A. T.; White, A. J. P.; Parsons, P. J. *J. Org. Chem.* **2019**, *84*, 9611.
- (38) Natho, P.; Rouse, A. B.; Greenfield, J. L.; Allen, L. A. T.; White, A. J. P.; Yang, Z.; Parsons, P. J. *Tetrahedron* **2020**, *76*, 131636.
- (39) Natho, P.; Allen, L. A. T.; Parsons, P. J. *Tetrahedron Lett.* **2020**, *61*, 151695.
- (40) Petti, A.; Natho, P.; Lam, K.; Parsons, P. J. *Eur. J. Org. Chem.* **2021**, 854.
- (41) Parsons, P. J.; Jones, D. R.; Walsh, L. J.; Allen, L. A. T.; Onwubiko, A.; Preece, L.; Board, J.; White, A. J. P. *Org. Lett.* **2017**, *19*, 2533.
- (42) Chandler, M.; Parsons, P. J. *J. Chem. Soc., Chem. Commun.* **1984**, 322.
- (43) Parsons, P. J.; Pennicott, L.; Eshelby, J.; Goessman, M.; Highton, A.; Hitchcock, P. *J. Org. Chem.* **2007**, *72*, 9387.
- (44) Greenwood, E.; Hitchcock, P.; Parsons, P. *Tetrahedron* **2003**, *59*, 3307.
- (45) Natho, P. The Discovery and Application of Metal-Free Cyclobutanol Ring Expansion Reactions, *Ph.D. Thesis*; Imperial College London, UK, **2021**.
- (46) Tecle, H.; Bergmeier, S. C.; Wise, L. D.; Hershenson, F. M.; Coughenour, L. L.; Heffner, T. G. *J. Heterocycl. Chem.* **1989**, *26*, 1125.
- (47) **5-Methoxy-3-methyl-9H-carbazole (Glycoborine)**  
To a solution of 5-methoxy-3-methyl-9-tosyl-9H-carbazole (**9**) (20 mg, 0.055 mmol) in degassed ethanol (5 mL) was added finely ground potassium hydroxide (15 mg, 0.27 mmol) in one portion. The resulting solution was heated at reflux for 20 hours, before cooling to room temperature and removal of the volatiles under reduced pressure. The concentrate was dissolved in ethyl acetate (10 mL), and the organic layer was washed with deionized water (2 × 10 mL) and saturated aqueous sodium chloride solution (15 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford the title compound (10 mg, 0.047 mmol, 85%) as a white solid (mp 135.1–136.8 °C [Lit.<sup>1</sup> 155–156 °C; PE–CHCl<sub>3</sub>]). IR (neat): 3405, 3042, 3004, 2948, 2915, 2837, 1606, 1586, 1506, 1459, 1260, 1100 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 8.14 (br s, 1 H), 7.91 (br s, 1 H), 7.33 (t, J = 8.0 Hz, 1 H), 7.28 (dd, J = 8.2, 0.7 Hz, 1 H), 7.22 (ddd, J = 8.2, 1.7, 0.7 Hz, 1 H), 7.01 (dd, J = 8.2, 0.7 Hz, 1 H), 6.67 (dd, J = 8.0, 0.7 Hz, 1 H), 4.09 (s, 3 H), 2.55 (d, J = 0.8 Hz, 3 H). <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>): δ = 156.2, 141.2, 136.9, 128.9, 126.5, 126.2, 123.0, 122.8, 112.5, 109.6, 103.5, 100.2, 55.4, 21.5. HRMS (APCI): m/z [M + H]<sup>+</sup> calcd for C<sub>14</sub>H<sub>14</sub>ON: 212.1070; found: 212.1067. The spectroscopic data (<sup>1</sup>H NMR, <sup>13</sup>C{<sup>1</sup>H} NMR and IR) are consistent with the literature.<sup>1</sup>
- (48) Falmagne, J.-B.; Escudero, J.; Taleb-Sahraoui, S.; Ghosez, L. *Angew. Chem.* **1981**, *93*, 926.
- (49) Houge, C.; Frisque-Hesbain, A. M.; Mockel, A.; Ghosez, L.; Declercq, J. P.; Germain, G.; Van Meerssche, M. *J. Am. Chem. Soc.* **1982**, *104*, 2920.
- (50) Ramalingan, C.; Lee, I.-S.; Kwak, Y.-W. *Chem. Pharm. Bull.* **2009**, *57*, 591.
- (51) Nagakura, I.; Savary, D. N.-H.; Schlosser, M. *Helv. Chim. Acta* **1980**, *63*, 1257.
- (52) ten Brink, G.-J.; Arends, I. W. C. E.; Sheldon, R. A. *Chem. Rev.* **2004**, *104*, 4105.
- (53) Wu, S.; Harada, S.; Morikawa, T.; Nishida, A. *Tetrahedron: Asymmetry* **2017**, *28*, 1083.
- (54) **Carbazomycin B**  
Carbazomycin B was synthesized according to a procedure by Nishida and co-workers.<sup>28</sup> A solution of anthracene (65 mg, 0.36 mmol) in THF (1.5 mL) was purged with nitrogen for 10 minutes, before sodium metal (13 mg, 0.57 mmol) was added. The suspension was stirred at room temperature for 30 minutes, before being sonicated for a further 20 minutes. The dark blue solution was removed from the sonication bath, and a solution of 3-methoxy-9-((4-methoxyphenyl)sulfonyl)-1,2-dimethyl-9H-carbazol-4-ol (**14**) (30 mg, 0.073 mmol) in THF (1 mL) was added in one portion. The resulting green solution was stirred at room temperature for 1 hour, before it was diluted with dichloromethane (10 mL), and deionized water (10 mL) was added. The aqueous layer was separated and extracted with dichloromethane (3 × 10 mL). The combined organic extracts were washed with deionized water (20 mL), dried over sodium

sulfate, filtered, and concentrated under reduced pressure. The crude material was purified by flash column chromatography (10–30% EtOAc/pentane) to afford the title compound (10 mg, 0.041 mmol, 57%) as a white solid.

IR (neat): 3425, 3053, 2988, 2923, 2854, 1638, 1612, 1500, 1453, 1411, 1321, 1300, 1144, 1083, 1003  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 8.25 (m, 1 H), 7.78 (br s, 1 H), 7.43–7.32 (m, 2 H), 7.22 (ddd,  $J$  = 8.1, 6.8, 1.4 Hz, 1 H), 6.06 (s, 1 H), 3.83 (s, 3 H), 2.40 (s, 3 H), 2.37 (s, 3 H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 142.0, 139.2, 138.4, 136.7, 127.0, 124.8, 123.3, 122.6, 119.5, 110.0, 109.3, 109.3, 61.5, 13.2, 12.8. HRMS (APCI):  $m/z$  [ $M + H$ ] $^+$  calcd for  $\text{C}_{15}\text{H}_{16}\text{NO}_2$ : 242.1176; found: 242.1182. The spectroscopic data ( $^1\text{H}$  NMR,  $^{13}\text{C}\{^1\text{H}\}$  NMR and IR) are consistent with the literature.<sup>28</sup>

#### Carbazomycin A

Carbazomycin A was synthesized according to a procedure by Moody and Shah.<sup>26</sup> To a solution of carbazomycin B (8.0 mg, 0.033 mmol) in acetone (2 mL) was added dried potassium carbonate (50 mg, 0.36 mmol) and iodomethane (0.3 mL, 4.8 mmol) sequentially. The resulting reaction mixture was then

heated at reflux for 3 hours, before it was allowed to cool to room temperature, and diluted with dichloromethane (5 mL). The organic phase was separated and washed with deionized water ( $3 \times 5$  mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude material was purified by flash column chromatography (10% EtOAc/pentane) to afford the title compound (7.3 mg, 0.029 mmol, 87%) as a yellow oil.

IR (neat): 3436, 3351, 2998, 2989, 2930, 1610, 1498, 1455, 1395, 1293, 1088, 1051  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 8.23 (m, 1 H), 7.83 (s, 1 H), 7.45–7.33 (m, 1 H), 7.22 (ddd,  $J$  = 8.0, 6.8, 1.5 Hz, 1 H), 4.11 (s, 1 H), 3.90 (s, 1 H), 2.41 (s, 1 H), 2.39 (s, 1 H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 146.0, 144.5, 139.4, 136.4, 128.8, 125.1, 122.9, 122.5, 119.5, 114.4, 113.5, 110.3, 61.1, 60.6, 13.7, 12.6. IR (neat): 3436, 3351, 2998, 2989, 2930, 1610, 1498, 1455, 1395, 1293, 1088, 1051  $\text{cm}^{-1}$ . HRMS (APCI):  $m/z$  [ $M + H$ ] $^+$  calcd for  $\text{C}_{16}\text{H}_{18}\text{NO}_2$ : 256.1332; found: 256.1329. The spectroscopic data ( $^1\text{H}$  NMR,  $^{13}\text{C}\{^1\text{H}\}$  NMR and IR) are consistent with the literature.<sup>28</sup>