

# Total Synthesis of Eustifolines A–D and Glycomaurrol via a Divergent Diels–Alder Strategy

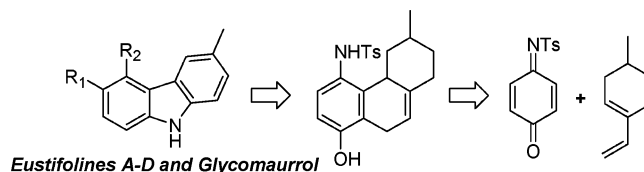
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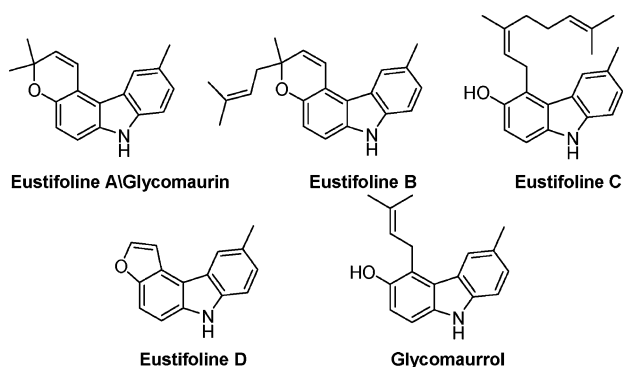
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## ABSTRACT



The Diels–Alder reaction between a quinone monoimine and cyclic diene allows for the construction of substituted carbazoles in a regiospecific manner. This methodology has successfully been employed in a divergent strategy, culminating in the synthesis of eustifolines A–D and glycomaurrol.

The naturally occurring carbazoles glycomaurrol and glycomaurin (Figure 1) were isolated in 1989 from the stem



**Figure 1.** Eustifolines A–D, glycomaurin, and glycomaurrol.

bark of *Glycosmis mauritiana*, a small tree growing in the dry zone of Sri Lanka.<sup>1</sup> The following year, eustifolines A–D

were isolated from the root bark of *Murraya euchrestifolia*, a shrub growing in the central and southern parts of Taiwan;<sup>2</sup> eustifoline A is in fact the same compound as glycomaurin. Until this year, the only synthetic effort toward these compounds has been the semisynthesis of glycomaurin by Wickramasinghe and co-workers in 1989 in their efforts to verify its structure.<sup>1</sup> Very recently, the syntheses of two of the members of this class (eustifoline D and glycomaurrol) were reported by Knölker and co-workers using an elegant cross-coupling strategy to assemble the carbazole core of the targets.<sup>3</sup>

The wide variety and important biological activity of naturally occurring carbazoles have made them attractive targets for organic synthesis.<sup>4</sup> Although there are many useful synthetic routes to some carbazoles, the regiocontrolled preparation of these compounds with specific substitution patterns remains a significant challenge to the synthetic organic chemist.

The substitution pattern represented by the title compounds, namely, 5-alkyl-6-alkoxy (or hydroxyl), is particu-

(1) Kumar, V.; Reisch, J.; Wickramasinghe, A. *Aust. J. Chem.* **1989**, *42*, 1375.

(2) Ito, C.; Furukawa, H. *Chem. Pharm. Bull.* **1990**, *38*, 1548.

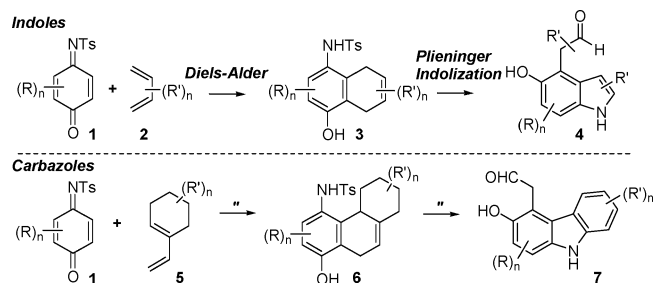
(3) Forke, R.; Krah, M. P.; Krause, T.; Schlechtingen, G.; Knölker, H.-J. *Synlett* **2007**, 268.

(4) Knölker, H.-J.; Reddy, K. R. *Chem. Rev.* **2002**, *102*, 4303.

larly elusive. Usually such compounds are prepared via a Fischer indole synthesis with a cyclohexanone-derived hydrazone (and subsequent dehydrogenation),<sup>5</sup> alkylation<sup>6</sup> or Claisen rearrangement<sup>1</sup> beginning with a 6-hydroxycarbazole, or annulation of an existing indole moiety.<sup>7</sup> Drawbacks to these methods include the lack of regiocontrol in functionalizing an existing carbazole or the necessity to prepare precursors with preexisting and extensive substitution.

We have recently reported a general synthesis of indoles<sup>8</sup> which uses as its key transformation a Diels–Alder reaction of a quinoid monoimine and subsequent Plieninger indolization<sup>9</sup> of the adducts (Scheme 1), as well as applications to

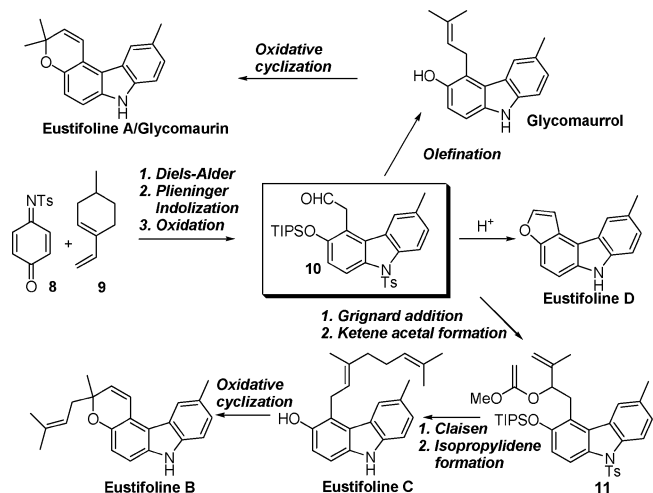
**Scheme 1.** Synthesis of Indoles and Carbazoles



target oriented synthesis.<sup>10</sup> During our work, it occurred to us that the use of a diene bearing a cyclohexyl ring fused at the 1,2-positions would allow extension of this methodology to the formation of carbazoles in a regiospecific manner. In this communication, we illustrate the implementation of this strategy in the first total synthesis of eustifolines A–C and alternative syntheses of glycomaurrol and eustifoline D.

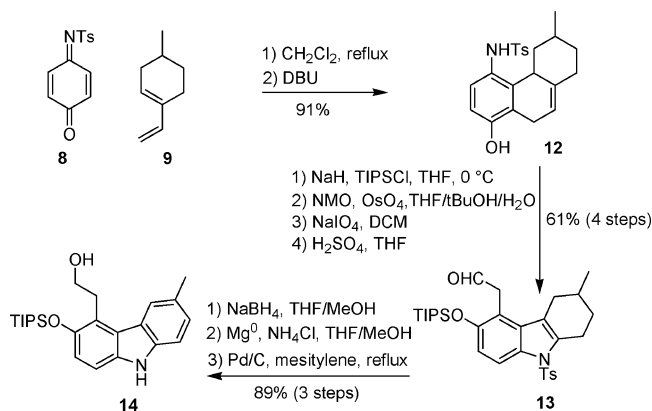
Our divergent synthetic strategy has as its cornerstone the synthesis of carbazole **10** or a closely related compound (Scheme 2). The aldehyde group in **10** would be elaborated

**Scheme 2.** Synthetic Strategy



in a number of ways to access the target molecules. Acid-catalyzed ring closure of **10**, for instance, yields eustifoline D, whereas olefination of the aldehyde gives glycomaurrol. Oxidative cyclization of glycomaurrol provides access to eustifoline A (glycomaurin). Isopropenyl Grignard addition to **10** and ketene acetal formation yield **11**, which is a suitable substrate for a Claisen rearrangement en route to eustifoline C. Again, oxidative cyclization of eustifoline C can be utilized to access eustifoline B.

**Scheme 3.** Synthesis of Key Intermediates **13** and **14**

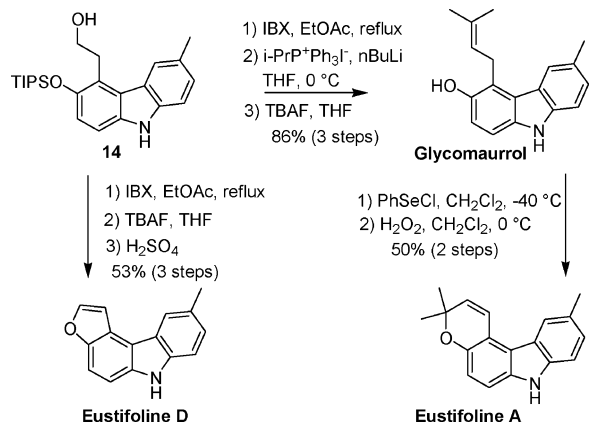


Our synthetic efforts commenced (Scheme 3) with the readily available quinone imine **8** and diene **9** which underwent a facile Diels–Alder cycloaddition in refluxing  $\text{CH}_2\text{Cl}_2$ . Treatment of the resulting adducts with catalytic DBU then afforded the desired aromatized species **12** as a 1:1 mixture of diastereomers in 91% overall yield.

The lack of diastereoselectivity in the formation of **12** was of no concern because both stereocenters would later become  $\text{sp}^2$  hybridized. The phenolic moiety was protected via treatment with NaH and TIPSCl. Conversion of the dihydronaphthalene to the tetrahydrocarbazole **13** was accomplished via oxidative cleavage of the double bond (via the diol) followed by treatment of the resulting dicarbonyl with acid to afford the desired tetrahydrocarbazole in 61% yield over the four steps. Aldehyde reduction, tosyl removal, and dehydrogenation yielded carbazole **14** in 89% yield over the three steps. Tosyl removal was required to effect the dehydrogenation. Reduction of the aldehyde was found necessary to effect clean tosyl removal and dehydrogenation.

- (5) Mulwad, V. V.; Dalvi, M. B.; Mahaddalkar, B. S. *Indian J. Chem., Sect. B.: Org. Chem. Incl. Med. Chem.* **2002**, *41*, 1477.
- (6) Hall, T. J.; Jackson, A. H.; Oliviera-Campos, A. M. F.; Queiroz, M. J. R. P.; Shannon, P. V. R. *Heterocycles* **1990**, *31*, 401.
- (7) Duval, E.; Cuny, G. D. *Tetrahedron Lett.* **2004**, 5411.
- (8) (a) Banfield, S. C.; England, D. B.; Kerr, M. A. *Org. Lett.* **2001**, *3*, 3325. (b) Zawada, P. V.; Banfield, S. C.; Kerr, M. A. *Synlett* **2003**, 971.
- (c) England, D. B.; Kerr, M. A. *J. Org. Chem.* **2005**, *70*, 6519.
- (9) (a) Plieninger, H.; Suhr, K. *Chem. Ber.* **1956**, *89*, 270. (b) Plieninger, H.; Volkl, A. *Chem. Ber.* **1976**, *109*, 2121.
- (10) (a) Jackson, S. K.; Banfield, S. C.; Kerr, M. A. *Org. Lett.* **2005**, *7*, 1215. (b) England, D. B.; Magolan, J.; Kerr, M. A. *Org. Lett.* **2006**, *8*, 2209. (c) Leduc, A. B.; Kerr, M. A. *Eur. J. Org. Chem.* **2007**, 237. (d) Ganton, M. D.; Kerr, M. A. *J. Org. Chem.* **2007**, *72*, 574. (e) Jackson, S. K.; Kerr, M. A. *J. Org. Chem.* **2007**, *72*, 1405–1411.

**Scheme 4.** Synthesis of Glycomaurrol and Eustifolines A and D

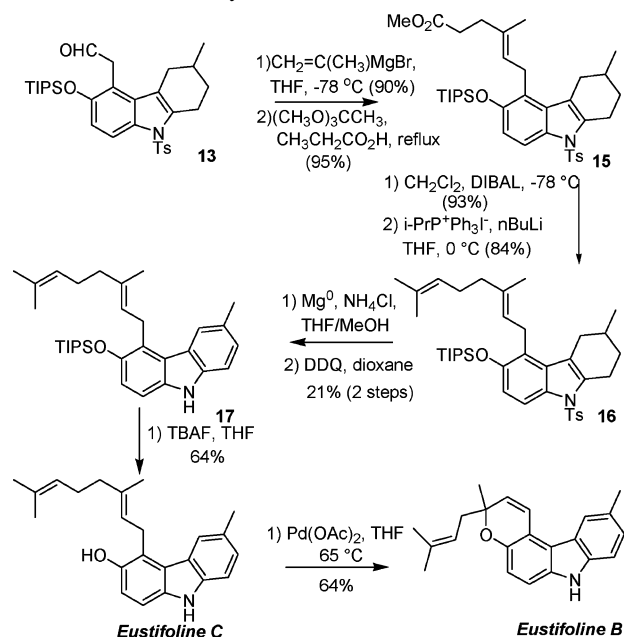


The preparation of glycomaurrol, as well as eustifolines D and A, required reoxidation of **14** to the corresponding aldehyde (Scheme 4). This, however, proved more challenging than expected with a variety of common methods (Swern, Dess–Martin, Ley, and PDC oxidations) giving undesired side products and unsatisfactory yields. Although treatment with IBX in DMSO appeared to provide clean oxidation (by TLC), it suffered from low isolated yields and longer reaction times. Finally, it was found that treatment with IBX in refluxing EtOAc afforded the desired aldehyde in excellent yield.<sup>11</sup> Olefination of the crude aldehyde with a triphenylphosphonium isopropyl ylide followed by desilylation with TBAF yielded glycomaurrol in 86% yield over the three steps. Cyclization of glycomaurrol with PhSeCl followed by oxidation with H<sub>2</sub>O<sub>2</sub> afforded eustifoline A in 50% yield over the two steps. Eustifoline D was prepared by oxidizing carbazole **14** and subjecting the resulting aldehyde to desilylation with TBAF followed by treatment with acid to effect benzofuran formation in 53% yield over the three steps.

Upon the successful syntheses of eustifolines A and D and glycomaurrol, we turned our attention to the more elaborate eustifolines B and C (Scheme 5). It should be noted that, at the outset, we initially sought to advance carbazole **14** (via oxidation to its corresponding aldehyde) to these target molecules. However, upon oxidation of **14** with IBX to the aldehyde, many of the transformations in Scheme 5 resulted in low yields, undesired side products, and difficult purifications. The reasons for this are unclear. We, therefore, turned our attention to tetrahydrocarbazole **13** as our step-off point for the formation of eustifolines B and C.

Treatment of **13** with isopropenyl magnesium bromide followed by in situ generation of a ketene acetal en route to a Johnson–Claisen rearrangement led to the formation of ester **15** with the desired *E* geometry about the double bond in 86% overall yield. Reduction to the aldehyde using DIBAL and olefination with triphenylphosphonium isopropyl ylide gave **16** bearing the requisite isopropylidene moiety in

**Scheme 5.** Synthesis of Eustifolines B and C



78% overall yield. With the geranyl side chain installed, attention was turned to the dehydrogenative conversion of the tetrahydrocarbazole to the desired carbazole. *N*-Tosyl removal was effected with magnesium metal in methanolic aqueous ammonium chloride. Use of the previously proven Pd/C in mesitylene to promote dehydrogenation to **17** failed to produce the desired product, possibly due to transfer hydrogenation to the terpenoid side chain. Success was realized by using DDQ in dioxane albeit in less than optimal yields (however not atypical to literature precedent<sup>4</sup>). A substantial effort was put forth to improve the efficiency of dehydrogenation; however, the geranyl side chain proved incompatible with most methods. A strategy which would allow the use of the higher-yielding palladium-catalyzed oxidation would have required a severe sacrifice of step economy. In the end, we settled on the DDQ-mediated process which gave **17** in 21% yield over the two steps. Desilylation gave eustifoline C in 64% yield. Oxidative cyclization, this time using Pd(OAc)<sub>2</sub>, generated eustifoline B in 64% yield.<sup>12</sup>

In conclusion, we have presented a general, regioselective synthesis of carbazoles resulting in the syntheses of five natural products, three of which represent the inaugural syntheses. The yields are excellent providing glycomaurrol in 42% overall yield and eustifolines A, B, C, and D in 21%, 3%, 4%, and 26% overall yields, respectively. The methods described here are applicable to the preparation of a wide variety of substituted carbazoles of both academic and medicinal interest.

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(11) More, J. D.; Finney, N. S. *Org. Lett.* **2002**, *4*, 3001.

(12) Koh, J. H.; Mascarenhas, C.; Gagne, M. R. *Tetrahedron* **2004**, *60*, 7405.

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**Supporting Information Available:** Full experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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