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Total synthesis of lycogarubin C utilizing the Kornfeld–Boger ring contraction

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ABSTRACT

An efficient synthesis of lycogarubin C (**3**) was completed in seven steps from the known 1-(phenylsulfonyl)indole-3-carbaldehyde in 30% overall yield, via a Diels–Alder reaction between (*Z*)-1,2-di(1*H*-indol-3-yl)ethene **9b** and dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (**7**), followed by a Kornfeld–Boger ring contraction to form the pyrrole ring.

Lycogarubins A–C (**1**–**3**) and lycogalic acid A (**4**) are marine natural products isolated from the fruit bodies of the slime mold *Lycogala epidendrum* independently by Asajawa and co-workers[1] and Steglich and co-workers[2] in 1994 (Fig. 1). Previous syntheses of lycogarubins include a one-pot reaction from methyl 3-(indol-3-yl)pyruvate,[2] a palladium-catalyzed Suzuki cross-coupling reaction,[3] the oxidative condensation of 3-arylpyruvic acid with ammonia,[4] and a one-step synthesis from indole-3-pyruvic acid catalyzed by hemoprotein StaD[5] and by the cytochrome P450 enzymes StaP, RebP,[6] RebO, and RebD.[7]

Our recent synthesis of 1,2-di(1*H*-indol-3-yl)ethyne **6**[8] prompted us to utilize this substrate in a novel synthesis of lycogarubin C (**3**). Thus, an inverse-electron demand Diels–Alder reaction between **6** and the well-known 1,2,4,5-tetrazine ester **7**[9] should give bisindole **5**, which by a subsequent Kornfeld–Boger reductive ring contraction reaction[9,10] should provide a simple route to lycogarubin C (**3**) (Scheme 1).

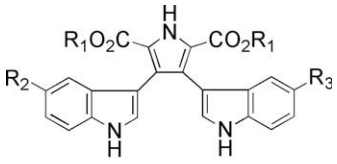
In our initial attempt, heating **6** (R = SO_2Ph) and tetrazine **7** in toluene only resulted in recovered starting alkyne **6** and the decomposition of **7**. Likewise, reactions in refluxing xylene, mesitylene, dichlorobenzene, and diphenyl ether were unsuccessful (Scheme 2).

We reasoned that the electron-withdrawing phenylsulfonyl-protecting groups might be deactivating the dienophilic alkyne. However, attempted Diels–Alder reactions between **6** (R = H) and **7** in refluxing toluene led to the recovery of ethyne **6** (Scheme 2).

Believing that steric hindrance in the ethyne **6** was the reason for the failure of the Diels–Alder reaction, we redirected our approach to the corresponding (*Z*)-1,2-di(1*H*-indol-3-yl)ethene **9** as the dienophile (Scheme 3).

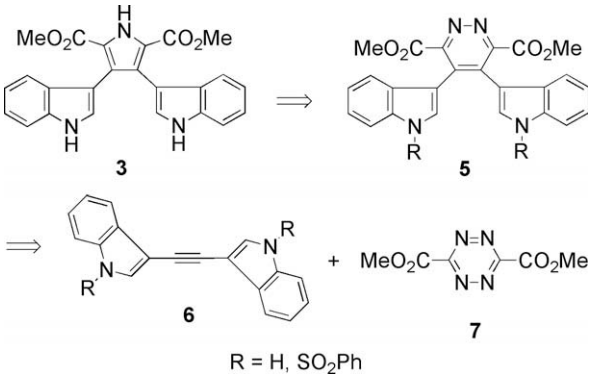
Thus, a Diels–Alder reaction of alkene **9** with tetrazine **7** should give intermediate **10** (or a tautomer), which upon treatment with zinc in acetic acid followed by N-deprotection should give lycogarubin C (**3**) (Scheme 3).

The requisite (*Z*)-1,2-di(1*H*-indol-3-yl)ethene **9a**[11] (R_1 = H, R_2 = SO_2Ph) and **9b**[12] (R_1 = R_2 = SO_2Ph) were prepared from the known indole-3-carbaldehyde **11**.[13] Reduction of **11** with $NaBH_4$ in EtOH provided alcohol **12** in 97%. Bromination of **12** with PBr_3 afforded the corresponding bromide **13**[14] in 95% yield. A Wittig



1: R_1 = Me, R_2 = R_3 = OH
2: R_1 = Me, R_2 = OH, R_3 = H
3: R_1 = Me, R_2 = R_3 = H
4: R_1 = R_2 = R_3 = H

Figure 1.



R = H, SO_2Ph

Scheme 1.

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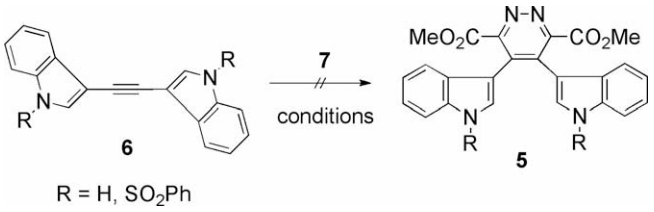
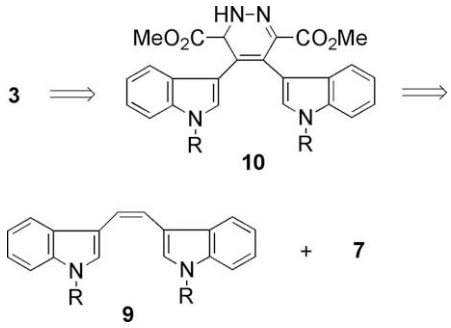


Scheme 2.



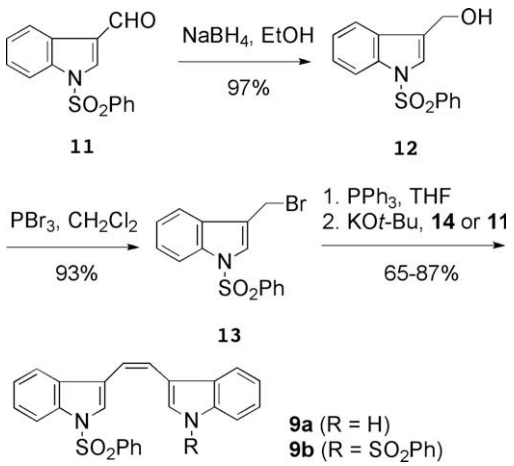
Scheme 3.

reaction protocol of **13** with indole-3-carbaldehyde (**14**)[15] gave alkene **9a** (cis:trans, 4:1) in 87% from **13**. Similarly, alkene **9b** was obtained in 65% from **13** using aldehyde **11** (Scheme 4).

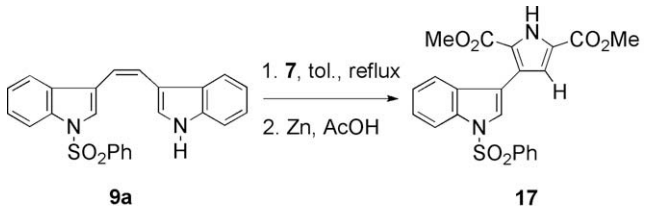
The Diels–Alder reaction between **9a** and tetrazine **7** afforded a mixture of the corresponding Diels–Alder product **15** (not shown), which upon treatment with zinc in acetic acid gave a mixture of three different products **16**,[16] **17**[17], and **18**[18] in 21%, 25%, and 29% yield, respectively (Scheme 5). We believe that **17** is formed by acid-catalyzed loss of indole from the initial Diels–Alder adduct.

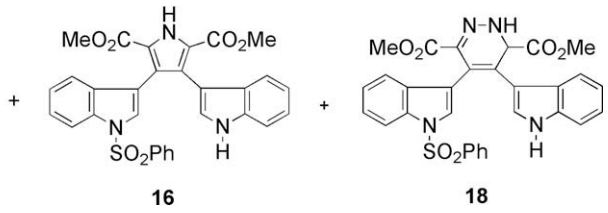
Deprotection of **16** under mild conditions using Mg and NH_4Cl in methanol provided lycogarubin C (**3**)[19] in 93% yield (Scheme 6).

Since the unprotected indole in **9a** is clearly unsatisfactory for the zinc reductive ring contraction (cf. Scheme 5), we turned to the use of fully protected bisindolealkene **9b**. To our delight, the Diels–Alder reaction between **9b** and tetrazine **7** followed by reduction with zinc and acetic acid provided the desired bisindolylpyrrole **20**[20] in 54% yield from **9b**. Cleavage of the phenylsulfonyl groups with Mg and NH_4Cl gave lycogarubin C (**3**)[19] in 91% yield (Scheme 7).

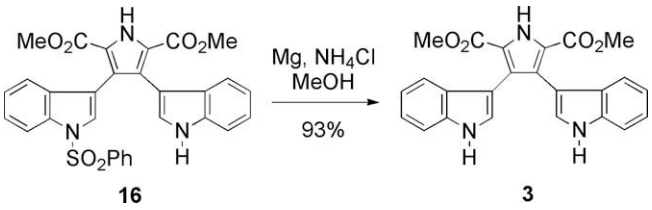


Scheme 4.

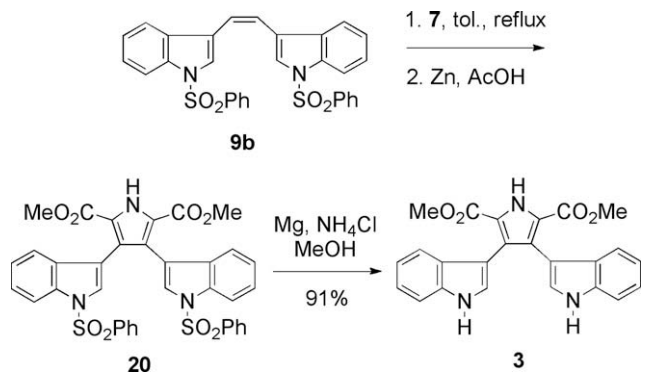




Scheme 5.



Scheme 6.



Scheme 7.

In summary, we have described a convenient synthesis of the bis(indolyl)pyrrole lycogarubin C (**3**) that features a Diels–Alder reaction between bis(indolyl)ethene **9b** and dimethyl 1,2,4,5-tetrazinedicarboxylate (**7**) followed by a Kornfeld–Boger zinc reductive ring contraction.

Acknowledgments

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11. Compound **9a**: yellow oil (cis:trans, 4:1); ^{1}H NMR (500 MHz, acetone-d_6) (*cis*-isomer) δ 8.05 (br s, 1H), 7.94 (m, 1H), 7.66 (m, 2H), 7.20–7.43 (m, 8H), 7.06–7.13 (m, 2H), 6.95–6.99 (m, 1H), 6.80–6.88 (m, 2H), 6.44 (d, 1H); ^{13}C NMR (500 MHz, acetone-d_6) δ 138.2, 135.9, 135.1, 134.1, 130.3, 129.6, 127.1, 126.6, 125.2, 124.2, 124.1, 123.6, 122.6, 121.0, 120.9, 120.3, 120.0, 116.5, 113.8, 113.5, 111.7.
12. Compound **9b**: white solid; mp 152–155 °C; ^{1}H NMR (500 MHz, acetone-d_6) δ 8.00–8.07 (m, 2H), 7.85–7.89 (m, 4H), 7.64–7.72 (m, 2H), 7.61 (s, 2H), 7.54–7.60 (m, 4H), 7.34–7.42 (m, 4H), 7.10–7.34 (m, 2H), 6.86 (s, 2H); ^{13}C NMR (500 MHz, acetone-d_6) δ 137.9, 134.8, 134.6, 130.0, 129.7, 127.0, 125.3, 124.8, 123.7, 121.4, 120.5, 119.6, 113.7.
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16. Compound **16**: ^{1}H NMR (500 MHz, acetone-d_6) δ 11.45 (br s, 1H), 10.15 (br s, 1H), 7.80 (d, J = 8.6 Hz, 1H), 7.56–7.64 (m, 4H), 7.44–7.50 (m, 2H), 7.37 (d, J = 8.2 Hz, 1H), 7.22–7.26 (m, 1H), 7.09–7.20 (m, 3H), 6.97–7.07 (m, 2H), 6.85–6.88 (m, 1H), 3.64 (s, 3H), 3.60 (s, 3H); ^{13}C NMR (500 MHz, acetone-d_6) δ 160.6, 160.4, 138.2, 136.2, 134.6, 134.1, 131.6, 129.8, 129.7, 126.8, 126.3, 125.4, 125.3, 124.3, 123.6, 123.5, 123.1, 122.0, 121.3, 121.0, 119.7, 119.1, 116.6, 113.2, 111.4, 107.9, 51.1, 51.0; HRMS (ESI): m/z calcd for $C_{30}H_{23}O_6N_3S$: 554:1386. Found: 554.1372.
17. Compound **17**: ^{1}H NMR (500 MHz, acetone-d_6) δ 11.59 (br s, 1H), 8.07–8.12 (m, 4H), 7.57–7.69 (m, 4H), 7.37–7.41 (m, 1H), 7.28–7.32 (m, 1H), 7.14 (d, J = 2.8 Hz, 1H), 3.88 (s, 3H), 3.77 (s, 3H); ^{13}C NMR (500 MHz, acetone-d_6) δ 160.4, 160.3, 138.2, 135.0, 134.5, 130.7, 129.8, 127.2, 126.4, 125.9, 124.9, 123.9, 123.1, 121.8, 120.8, 116.6, 115.9, 113.8, 51.5, 51.3; HRMS (ESI): m/z calcd for $C_{22}H_{18}O_6N_2S$: 439.0964. Found: 439.0953.
18. Compound **18**: ^{1}H NMR (500 MHz, acetone-d_6) δ 11.56 (br s, 1H), 10.40 (br s, 1H), 8.00 (d, J = 8.2 Hz, 1H), 7.85–7.88 (m, 2H), 7.82 (d, J = 8.0 Hz, 1H), 7.60–7.64 (m, 1H), 7.44–7.54 (m, 4H), 7.35–7.39 (m, 1H), 7.21–7.31 (m, 3H), 7.10–7.15 (m, 1H), 6.96–7.05 (m, 1H), 5.38 (s, 1H), 3.73 (s, 3H), 3.60 (s, 3H); ^{13}C NMR (500 MHz, acetone-d_6) δ 165.1, 163.9, 137.8, 136.5, 135.9, 134.5, 129.8, 129.4, 127.3, 127.1, 126.9, 126.5, 125.4, 125.3, 125.1, 123.9, 123.1, 122.0, 120.9, 120.1, 119.5, 113.9, 113.8, 112.2, 110.8, 51.9, 51.8, 35.2.
19. Lycogarubin C (**3**): yellowish solid; mp 123–125 °C (Lit.[3] mp 122–125 °C); ^{1}H NMR (500 MHz, acetone-d_6) δ 11.06 (br s, 1H), 10.04 (br s, 2H), 7.26–7.30 (m, 2H), 7.16–7.20 (m, 2H), 7.07 (d, J = 2.8 Hz, 2H), 6.95–6.99 (m, 2H), 6.79–6.83 (m, 2H), 3.64 (s, 6H); ^{13}C NMR (500 MHz, acetone-d_6) δ 160.8, 136.3, 128.2, 125.4, 125.3, 123.0, 120.9, 119.9, 118.7, 111.2, 108.6, 50.9.
20. Compound **20**: yellow solid; mp 205–207 °C; ^{1}H NMR (500 MHz, acetone-d_6) δ 11.79 (br s, 1H), 7.86–7.89 (m, 2H), 7.67–7.71 (m, 6H), 7.56–7.60 (m, 2H), 7.44–7.48 (m, 4H), 7.16–7.24 (m, 4H), 6.96–7.03 (m, 2H), 3.57 (s, 6H); ^{13}C NMR (500 MHz, acetone-d_6) δ 160.2, 138.1, 134.5, 134.2, 131.4, 129.7, 126.7, 126.4, 124.6, 124.0, 123.3, 121.9, 120.8, 115.7, 113.3, 51.2.