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Remarkable Switch of Regioselectivity in Diels–Alder Reaction: Divergent Total Synthesis of Borreverine, Caulindoles, and Flinderoles

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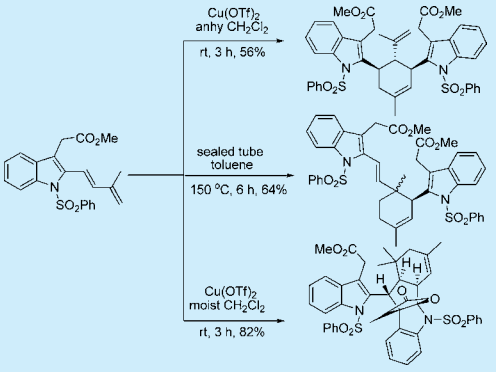
Supporting Information

ABSTRACT: Switchable reaction patterns of dimerization of indole substituted butadienes via a Lewis acid and thermal activation are reported. While under acidic conditions dimerization occurred around the internal double bond of the dienophile, a complete switch of regioselectivity was observed under thermal conditions, where dimerization occurred around the terminal double bond of the dienophile. This switch of regioselectivity was further exploited for the divergent total synthesis of structurally diverse indole alkaloid natural products.



Mono- and bis-prenylated isomers, as well as dimeric bis-prenylated indoles, form the largest group of natural products found in genus *Isolona*.[1] In 2004, Nkunya et al.[2] isolated the four dimeric prenyl indoles that occurred as diastereomeric pairs, namely caulindoles A–D (**1**–**4**), from *I. cauliflora* (Figure 1). Recently in 2010, Skaltsounis et al.[3] reported the isolation of another group of dimeric prenyl indole natural products, namely raputindole A (**5**), and its regioisomers. Biosynthetically, caulindoles might have been formed by the Diels–Alder reaction of two monoprenyl indoles, one acting as the diene and the other as a dienophile. Caulindoles and raputindoles showed optical activity, thus implying an enzymatic cyclization of the isoprene units. Caulindole A and D showed antifungal and mild antimalarial activity. **1**–**4** and their natural isomers[4] are yet to succumb to total synthesis. Interestingly, in 2009 Avery et al.[5] isolated another group of unprecedented natural products, flinderoles A–C (**6**–**8**), along with previously known compounds, borrerine (**9**), borreverine (**10**), isoborreverine (**11**), and dimethylisoborreverine (**12**). **10**–**12** were isolated in 1977 by Riche et al.[6] The structures of **10** and **11** were established by single crystal X-ray diffraction analysis. Another natural product possessing the borreverine skeleton, spermacoceine (**13**), was isolated by the research group of Balde et al.[7] in 1991 from *Borreria verticillata*. Biosynthetically flinderoles and borreverines could be derived by closure of isoprene units in the cyclopentyl ring and cyclohexene ring by [3 + 2] and [4 + 2] cycloaddition reactions respectively.

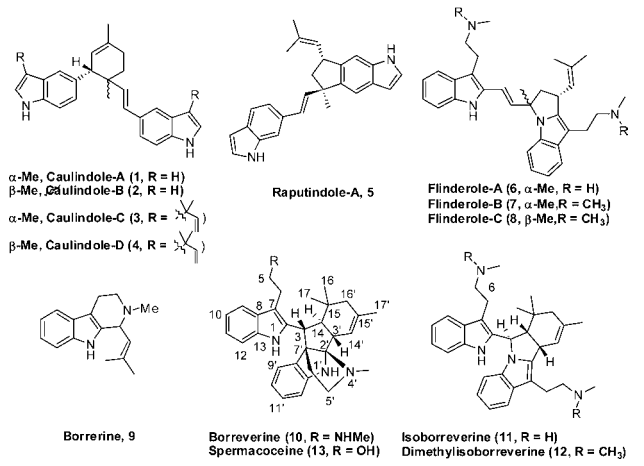


Figure 1. Structures of borreverine, caulindole, raputindole, and flinderole natural products.

Encouraged by our recent synthesis of flinderoles[8] and isoborreverines,[9] we became interested in the synthesis of caulindoles A–D (**1**–**4**), raputindole A (**5**), and borreverine (**10**). In 1979, Koch et al.[10] reported the biomimetic synthesis of **10** and isoborreverine (**11**) by the acid mediated dimerization of borrerine **9**. Treatment of **9** with TFA in benzene at 65 °C afforded **10** and **11** in a 1:1 ratio and 80% yield; when the reaction was further continued for 12 h, they isolated only **11**. Recently during their synthesis of flinderoles, May et al.[11] repeated the same reaction. In an effort to reproduce the original report of formation of **10**, a range of TFA equivalents, reaction times, and reaction temperatures were screened, but contrary to the previous report, they observed the formation of **11** only.

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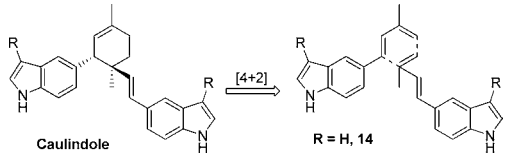
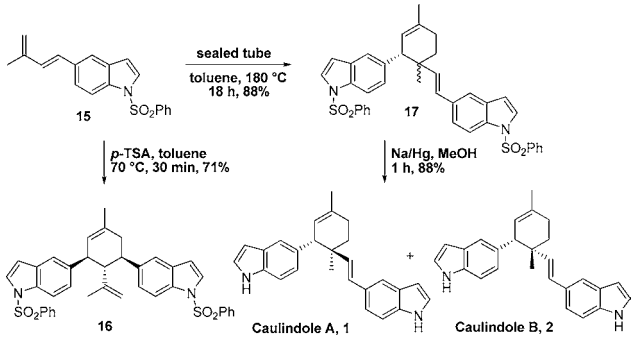
Scheme 1. Biomimetically Inspired Retrosynthesis of Caulindoles



Scheme 2. Total Synthesis of Caulindoles A (1) and B (2)

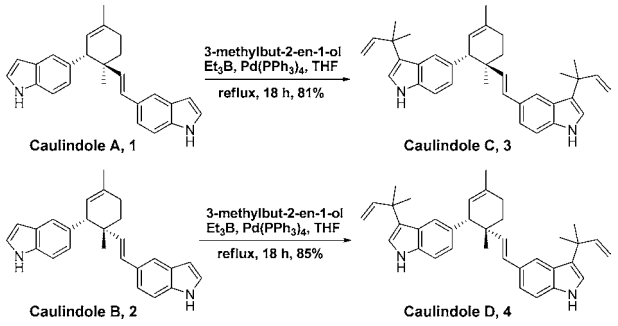


During our efforts toward the synthesis of flinderoles and isoborreverines,[9] we also tried to reproduce the results obtained by Koch et al., but in our hands, when we treated **9** with 5 equiv of TFA at rt, **11** was isolated in 95% yield; we could not observe any isolable amount of **10**. Here, we report the divergent total synthesis of structurally diverse indole alkaloid natural products: caulindoles A–D (**1**–**4**), borreverine (**10**), flinderoles A–C (**6**–**8**), and their analogues.

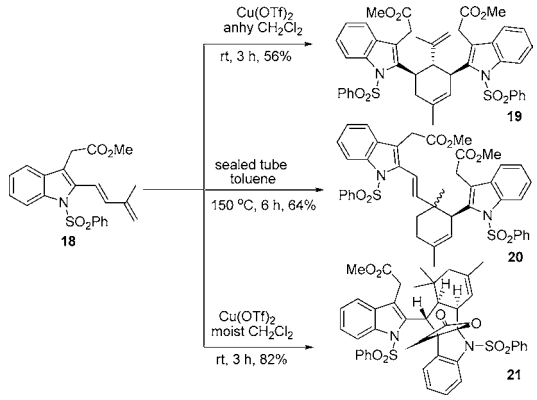
It was envisaged that, with fine-tuning of the reaction conditions, it might be possible to dimerize indole diene **14** to caulindoles by a [4 + 2] cycloaddition reaction (Scheme 1). Diels–Alder dimerization can be carried out thermally or catalyzed by a Lewis or Bronsted acid. But to our disappointment under all such reaction conditions **14** (see Supporting Information (SI) for preparation) decomposed, and we did not observe even a trace amount of [4 + 2] or [3 + 2] cycloaddition adduct. It was found that the phenyl sulfonyl protected indole diene **15** was more stable and can be stored in a round-bottom flask for many days at rt. Interestingly treatment of indole diene **15** with *p*-TSA afforded the Diels–Alder product **16**, where dimerization occurred around the internal double bond of the dienophile. The structure and relative stereochemistry of **16** was established by 2D NMR analysis (Scheme 2).

Surprisingly when diene **15** was heated in a sealed tube using toluene as a solvent at 180 °C, it afforded 1:1 diastereomeric mixture of [4 + 2] cycloaddition product **17**, with a complete switch of regioselectivity, as dimerization occurred around the terminal double bond of the dienophile. The structure and relative stereochemistry of **17** was determined by spectroscopic analysis (^{1}H, ^{13}C NMR; IR; and HRMS) and by correlation with the caulindole spectral data. Although the mechanism, reactivity, and selectivity of the Diels–Alder reaction have been greatly studied,[12] this is one rare example where two different products were obtained by changing reaction conditions in a highly regioselective manner, and to the best of our knowledge, to date no report exists in literature of the formation of different products with such a switch of regioselectivity in the Diels–Alder reaction as observed in this case. Deprotection of the phenyl sulfonyl group followed by diastereomer separation by careful silica gel column chromatography afforded the natural products **1**

Scheme 3. Total Synthesis of Caulindole C (3) and D (4)



Scheme 4. Remarkable Switch of Regioselectivity in Diels–Alder Reaction



and **2**, whose spectral data were in good agreement with the literature report.[2] After having synthesized **1** and **2**, we next turned our attention toward functionalization of C-3 and C-3′ of the indole rings of caulindole A (**1**) and B (**2**), to generate caulindole C (**3**) and D (**4**). In 2005, Tamaru et al. reported the Pd-catalyzed C-3 selective allylation of indoles.[13] We exploited this reaction for diallylation of **1** and **2**. Thus, independent treatment of **1** and **2** with the prenyl alcohol in the presence of a catalytic amount of $Pd(Ph_3P)_4$ generated **3** and **4** (Scheme 3), whose spectral data were in complete agreement with the literature report.[2] After the biomimetic synthesis of **1**–**4** and encouraged by the switch of regioselectivity in the Diels–Alder dimerization of indole diene **15**, we became interested in the dimerization of another indole diene, **18**. Based on our experience in flinderole, isoborreverine, and caulindole synthesis, it was contemplated that, unlike in the case of the Diels–Alder reaction of the indole diene **15**, there are three different Diels–Alder products that would be possible in the Diels–Alder dimerization of indole diene **18**. As in the case of diene **15** we expected diene **18** to generate a limonene derivative and caulindole isomers upon dimerization under different conditions. Based on our experience in the synthesis of flinderoles by the formal [3 + 2] cycloaddition reaction of diene and *tert*-alcohol, we also expected that the Diels–Alder reaction of diene **18** (see SI for preparation) could generate the borreverine **10**. As expected, the Diels–Alder dimerization reaction of diene **18** with catalytic $Cu(OTf)_2$ in anhydrous CH_2Cl_2 afforded the limonene derivative **19** in a highly regioselective manner (Scheme 4). The structure and relative stereochemistry of **19** was established by single crystal X-ray diffraction analysis.[14] Yet, dimerization of diene **18** in toluene at 150 °C in a sealed tube afforded the isocaulindole derivative **20** in a 1:1 endo/exo ratio. More

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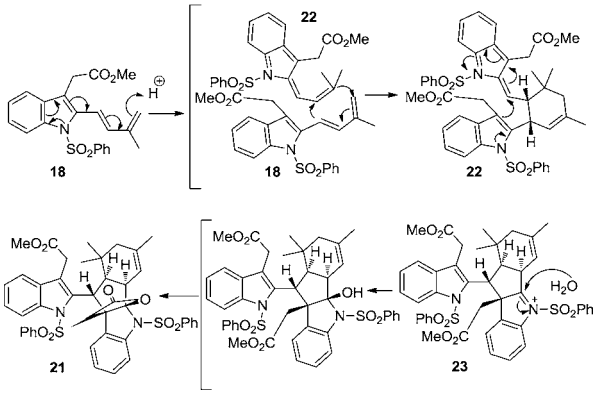
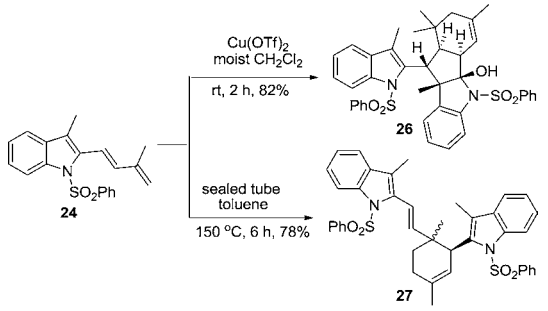
Scheme 5. Proposed Mechanism for the Formation of Lactone 21

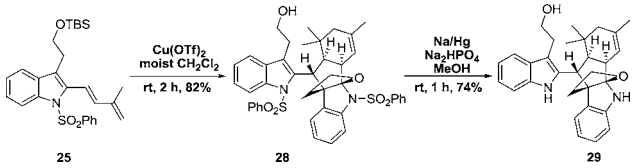


Scheme 6. Diels–Alder Dimerization of Indole Diene 24

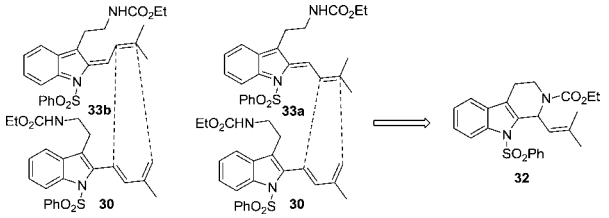


interestingly and surprisingly diene **18** on treatment with a catalytic amount of $Cu(OTf)_2$ in moist CH_2Cl_2 generated the lactone **21** in 82% yield in a highly regio- and diastereoselective manner. In this reaction five contiguous stereocenters were generated in one pot. The structure and relative stereochemistry of the lactone **21** was established by single crystal X-ray diffraction analysis.[14] In the presence of $Cu(OTf)_2$, diene **18** generates diene intermediate **22**, which, after an intermolecular Diels–Alder reaction with diene **18**, leads to intermediate **23**. Attack of H_2O present in the solvent on the imine carbon followed by the loss of a proton followed by subsequent lactonization generates **21** (Scheme 5). To further check the generality of this reaction and to prove the participation of H_2O in this reaction, we treated dienes **24**[8] and **25**[8] with $Cu(OTf)_2$ in moist CH_2Cl_2. Interestingly and as expected, diene **24** on treatment with $Cu(OTf)_2$ in moist CH_2Cl_2 generated the compound **26**, and by heating **24** in a sealed tube at 150 °C in toluene, the caulindole derivative **27** resulted as a 3:1 diastereomeric mixture (Scheme 6). Similarly diene **25** gave the Diels–Alder adduct **28** having a tetrahydrofuran ring, and deprotection of the phenyl sulfonyl group generated the 3′-epi-oxadesmethylspermacoceine **29** (Scheme 7). The structure and relative stereochemistry of **26**–**28** were established by single crystal X-ray diffraction analysis.[14] It was thought that water present in the reaction medium might be forming triflic acid from $Cu(OTf)_2$, and that it is a proton catalyzed process which is responsible for the formation of **26**. For this purpose we screened different Bronsted acids, and indeed, the reaction on treatment with triflic acid in moist CH_2Cl_2 afforded **26** in 80% yield. It was observed that a small amount of water present in commercial grade CH_2Cl_2 is optimum for this reaction and any external addition of water hampers the reaction, probably due to catalyst decomposition. Also, we attempted the reaction by adding di-

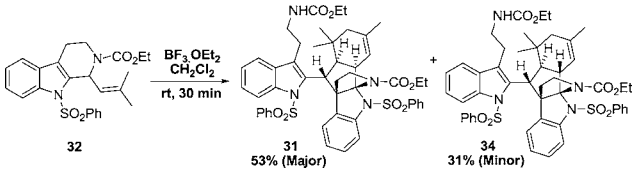
Scheme 7. Synthesis of Spermacoceine Analogue 29



Scheme 8. Retrosynthesis of Borreverine 10



Scheme 9. Diels–Alder Dimerization of 32



tert-butylpyridine, to check the possibility that a different concentration of the Bronsted acid is leading to the observed change in reaction outcome, but unfortunately the reaction did not occur in this case even after several attempts, with just the starting material recovered. We next focused on the total synthesis of borreverine **10**. Based on the above-mentioned reactions, it was contemplated that diene **30** on treatment with Lewis acid would generate the borreverine derivative, which on further functional group transformation would lead to **10**. Altough diene **30** failed to dimerize on treatment with $Cu(OTf)_2$, it smoothly underwent dimerization in the presence of $BF_3{\cdot}OEt_2$, affording the borreverine derivative **31**. Although we were delighted by these results, unfortunately we could not carry forward the Diels–Alder adduct for the completion of the total synthesis of **10**, since in all these reactions only the endo isomer resulted and for the synthesis of **10** the exo isomer was required. It was contemplated that although diene **30** afforded endo isomer **31** exclusively, masked diene **32** on treatment with a Lewis acid would generate both cisoid and transoid dienes **33a** and **33b** respectively, which will lead to the formation of a mixture of exo/endo isomers (Scheme 8). To our delight **32** resulted in two steps from tryptamine, 3-methylbut-2-enal, and $ClCO_2Et$ followed by protection of the indole nitrogen by the phenyl sulfonyl group on treatment with $BF_3{\cdot}OEt_2$ in CH_2Cl_2, generating the Diels–Alder adducts **34** and **31** as a 3:5 mixture of exo/endo isomers (Scheme 9). The structure and relative stereochemistry of both isomers were established by single crystal X-ray diffraction analysis of the major isomer **31**.[14] The mixture of endo and exo isomers was separated by careful column chromatography. Deprotection of the indole nitrogens by reduction of the sulphonamides of **34** using Na/Hg followed by LAH reduction of the resultant indole derivative **35** afforded the natural product **10** in 85% yield, whose spectral data (^1H, ^{13}C NMR; IR; and HRMS) were in complete agreement with the literature report (Scheme 10).[6] Similarly endo isomer **31** generated the epi-borreverine **37**.

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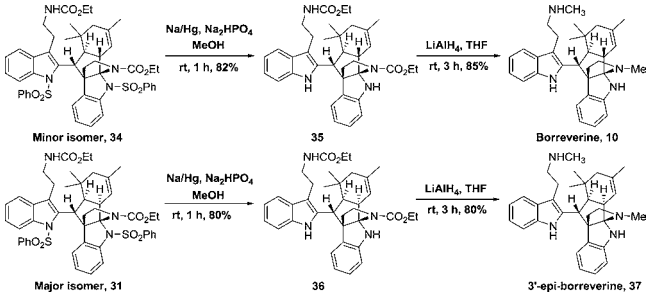
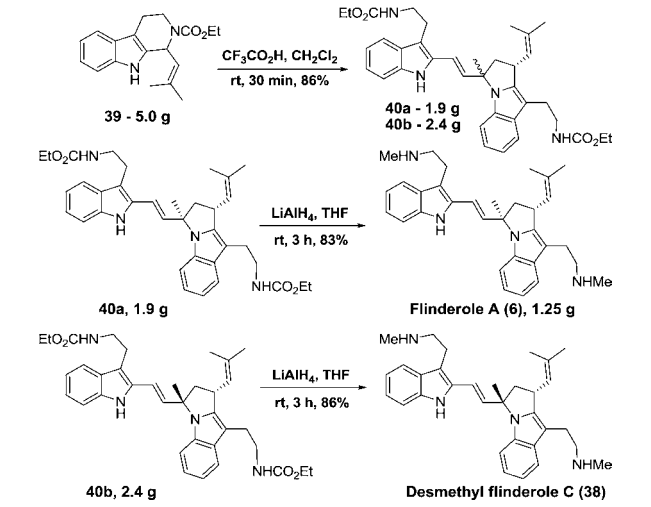
Scheme 10. Total Synthesis of Borreverine 10 and 3′-epi-Borreverine 37



Scheme 11. Total Synthesis of Flinderole A (6)



We also completed the three-step total synthesis of flinderole A (**6**) and desmethyl flinderole C (**38**) (Scheme 11). Known compound **39** synthesized in a one-pot sequence[11] from tryptamine on treatment with TFA exclusively afforded flinderole derivatives **40a,b** in a 4:5 diastereomeric ratio and in 86% yield. The mixture of **40a** and **40b** was easily separated using silica gel column chromatography. In this case not even a trace amount of [4 + 2] cycloaddition product was observed. Results were the same for other Lewis and Bronsted acids, except for a minor change in the yield of the flinderole derivatives formed. So the removal of the phenyl sulfonyl group from **32** completely changed its reactivity and pattern of reaction from a [4 + 2] to a formal [3 + 2] cycloaddition reaction. **40a** and **40b** on LAH reduction afforded **6** and **38** in 83% and 86% yield, respectively. This synthesis has an advantage over May's synthesis[11] since no HPLC purification was required, as **40a** and **40b** were easily separated in gram quantities by silica gel column chromatography.

In conclusion the biomimetic divergent total syntheses of structurally diverse indole alkaloid natural products (caulindoles A−D, borreverine, flinderole A−C, and their analogues) have been achieved. We also discovered a switch of regioselectivity in the Diels−Alder reaction by fine-tuning the reaction conditions.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data for all the compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(14) CCDC 957450 (**19**), CCDC 957454 (**21**), CCDC 957452 (**26**), CCDC 957453 (**27**), CCDC 957451 (**28**), CCDC 957448 (**31**), CCDC 957455 (**35**), and CCDC 957449 (**36**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.