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# Reagent Control of [1,2]-Wagner–Meerwein Shift Chemoselectivity Following the Nazarov Cyclization: Application to the Total Synthesis of Enokipodin B

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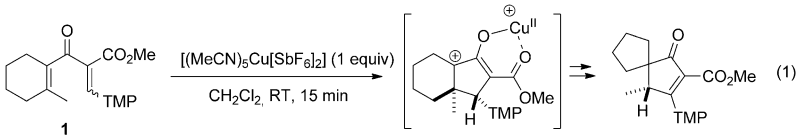
**Abstract:** An approach toward the carbon framework of various sesquiterpenes from the herbertane and cuparane families is described, including the concise total synthesis of enokipodin B. The key step is the construction of the vicinal quaternary centers of the skeleton through a tandem Nazarov cyclization/Wagner–Meerwein rearrangement mediated by a copper(II) complex. During this study, it was also found that changing the ligand architecture on the copper(II) promoter improved the chemoselectivity of the cationic rearrangement.

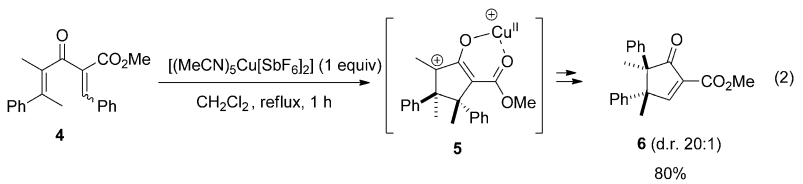
**Keywords:** copper · cyclization · rearrangement · sesquiterpenes · total synthesis

## Introduction

Efficient and stereroselective carbon–carbon bond-forming methods enable chemists to prepare biologically active molecules. Amongst them, the Nazarov reaction is a powerful tool for the construction of functionalized cyclopentenones.[1,2] Over the past decade, many innovations have led to the renaissance of this transformation. Several groups have established the versatility of the interrupted Nazarov cyclization, in which the oxyallyl cation intermediate is trapped with nucleophiles to form a new stereocenter.[3] In addition, new alternative initiation protocols, including $Au^{I}$- or $Pt^{II}$-catalyzed [3,3]-rearrangement/4π-electrocyclization,[4] electrocyclic opening of dichlorocyclopropanes,[5] or conjugate addition[6] have been also reported. These advances have not only expanded the utility of the Nazarov cyclization as a preparative method for substituted cyclopentenones, but have also galvanized research activity in 4π-electrocyclization chemistry.

Over the past few years, we have been engaged in the study of a Nazarov cyclization/Wagner–Meerwein rearrangement sequence.[7,8] By using one equivalent of copper(II) complexes, we were able to exercise control over the fate of the oxyallyl cation intermediate, allowing two sequential [1,2]-shifts to occur. This strategy allowed us to access spirocyclic compounds of type **3** from substrate **1** (see [Eq. (1)]; TMP = 2,4,6-trimethoxyphenyl), and cyclopentenones with vicinal quaternary centers (see **6**, [Eq. (2)]). In particular, we have learned that highly chemoselective Wagner–Meerwein shifts occur following the Nazarov cyclization of acyclic substrates of type **4**. The chemoselectivity was found to be dependent upon two factors: the migratory aptitude and the steric bulk of the competing migrating groups.[7]




Herein, we report the importance of a third factor: the substitution pattern of the ligand on copper(II). This finding allowed us to pursue a new strategic approach toward a family of natural products, which is demonstrated in a total synthesis of enokipodin B.

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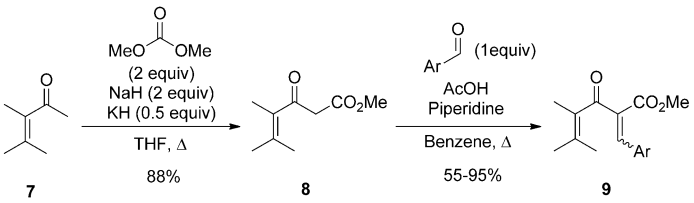
## Results and Discussion

**Controlling reaction pathways with copper(II) bisoxazoline complexes**: During our studies of acyclic substrates that exhibit chemoselective [1,2]-rearrangement (see **4**, [Eq. (2)], we found that bisoxazoline ligands on the promoter have an unexpectedly strong impact on selectivity in the cyclization/rearrangements of type **9** substrates. These were prepared through alkylation of the enone **7** with dimethylcarbonate to give β-ketoester **8** in 88% yield (Scheme 1). Knoevenagel



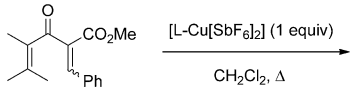

**7** **8** **9**

Scheme 1. Synthesis of substrates **9**.

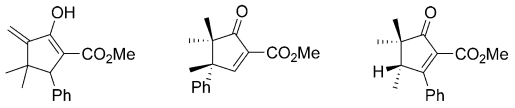
condensation with the appropriate aryl aldehyde provides substrates of type **9**. The Knoevenagel product is obtained as an *E*/*Z* mixture, but *E*/*Z* isomerization is facile under the reaction conditions, and only the *Z* isomer cyclizes.[9]

Our initial experiments focused on substrate **9a** (Table 1). The reaction was carried out under typical reaction conditions: Dichloromethane under reflux in the presence of one equivalent of $[(MeCN)_5Cu[SbF_6]_2]$. However, the only product obtained was the simple Nazarov cycloadduct **10a**, in a high yield of 92% (Table 1, entry 1). Fortunately, the elimination was completely suppressed when a bulkier copper(II) bisoxazoline complex was used as promoter. In addition, we were surprised to find that different copper(II) complexes gave different ratios of rearrangement products **11a** and **12a**. Cyclization/rearrangements conducted with ligands **L1** and **L2** led to a mixture of **11a** and **12a** (Table 1, entries 2 and 3), whereas the **L3** copper complex gave **11a** selectively in 83% yield and with an enantiomeric excess (*ee*) of 23%. Although a chiral bisoxazoline ligand is expected to influence the sense of rotation in the Nazarov electrocyclization, we and others have found that the impact on torquoselectivity is often modest.[7b,10,11] Thus, the poor enantioselectivity observed here is not a surprise.

Table 1. Effect of the ligand on the rearrangement sequence.

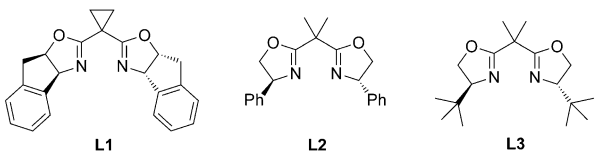



**9a**




**10a** **11a** **12a**

| Entry | Ligand | *t* [h] | Product (ratio) | Yield [%] |
|---|---|---|---|---|
| 1 | $(MeCN)_5$ | 0.2 | **10a** | 92 |
| 2 | **L1** | 0.4 | **11a/12a** (1.2:1) | 80 |
| 3 | **L2** | 0.4 | **11a/12a** (1.5:1) | 79 |
| 4 | **L3** | 0.4 | **11a/12a** (>20:1) | 83 (*ee* 23%) |



**L1** **L2** **L3**

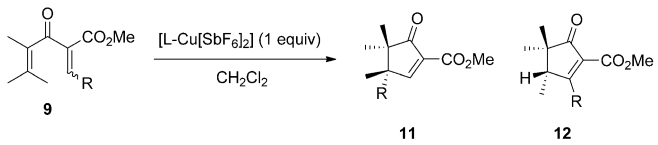
In the next set of experiments, we examined the cyclization/rearrangement of a series of substrates **9**. The sequence afforded products of type **11** as major product, with alkyl and alkoxy groups at the *meta* and *para* positions of the aromatic ring in good yields (up to 88%; Table 2, entries 1–5). In some cases, two different ligands were tested, and ligand **L3** was found to be most selective for rearrangement products of type **11** (Table 2, entries 2–6). We observed also that the steric hindrance had a strong impact on the migration. For example, substrate **9h** has electron-donating character equivalent to that of *para*-methoxyphenyl **9f**, but in **9h** the methoxy group is expected to hinder aryl migration. Indeed, a mixture of compounds **11h** and **12h** is obtained, in ratios of 1:3 and 1:6 (Table 2, entry 7). On the other hand, substrate **9i** (bearing an *ortho*-dimethoxyphenyl group) furnished only the product **12i** (Table 2, entry 8). The structure of the ligand had an impact on chemoselectivity for substrates containing both electron-donating and electron-deficient aryl rings (Table 2, entry 5 (OMe) and entry 6 (Br)). Other substituents at C5 (2-thienyl and cinammyl) were also tested (Table 2, entries 9 and 10). In each case, compound **11** was obtained as the major product in good yield. In most of cases, the products of type **11** and **12** were separable by flash chromatography.

Carrying out the cyclization of substrates **9d**, **9e**, **9h**, and **9j** with the acetonitrile copper(II) complex instead of the bisoxazoline complexes afforded elimination products of type **10** (see Table 1). Exceptions to this include **9f**, which cyclized without incident to produce **11f**,[7d] and **9l**, which decomposed (Table 3, see below). On the whole, these findings are consistent with earlier studies, in which we found that the large bisoxazoline ligand can block elimination, allowing rearrangement pathways to compete.[7b]

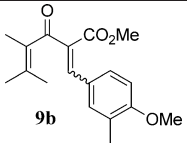
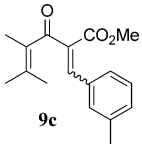
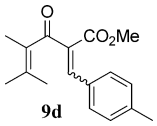
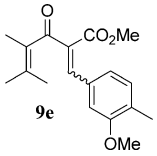
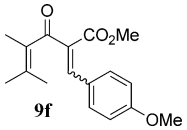
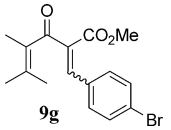
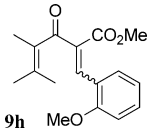
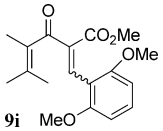
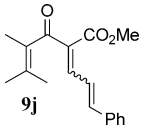
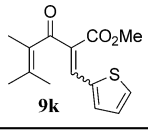
We continued our study of the impact of the ligand on the migration pattern by preparing substrate **9l**, which has an ethyl group at C2. In this case, cyclization generates the oxyallyl cation **13**, with two methyl groups in a position to migrate from C2 to C1. The [1,2]-methyl shift was selective for the methyl group opposite the bulky TMP, especially when the complex employing ligand **L3** (Table 3, 3:1 ratio of **12l** to **12′l** by using either ligand **L1** or **L2** and 10:1 ratio using ligand **L3**).

Table 2. $Cu^{II}$-promoted Nazarov cyclization/Wagner–Meerwein rearrangement.

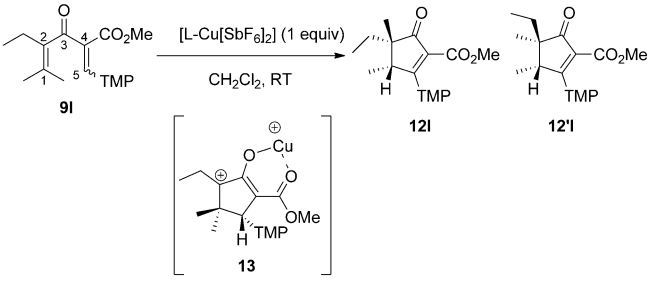



9 11 12

| Entry | Substrate | Ligand | Product (ratio) | Yield [%] |
|---|---|---|---|---|
| 1 |  | | **11b/12b** | |
| | | **L3** | 12:1 | 84 |
| 2 |  | | **11c/12c** | |
| | | **L1** | 1.5:1 | 88 |
| | | **L3** | >20:1 | 68[d] |
| 3 |  | | **11d/12d** | |
| | | **L1** | 2.2:1 | 85 |
| | | **L3** | 4.3:1 | 76 |
| 4 |  | | **11e/12e** | |
| | | **L1** | 2:1 | 92 |
| | | **L3** | 5:1 | 72[a],[12] (*ee*=20%) |
| 5 |  | | **11f/12f** | |
| | | **L1** | 6:1 | 90 |
| | | **L3** | >20:1 | 88[d] |
| 6 |  | | **11g/12g** | |
| | | **L1** | 1:1.5 | 86 |
| | | **L3** | 6:1 | 62[b,d] |
| 7 |  | | **11h/12h** | |
| | | **L1** | 1:3 | 63 |
| | | **L3** | 1:6 | 67[c,d] |
| 8 |  | | **11i/12i** | |
| | | **L1** | <1:20 | 66[d] |
| 9 |  | | **11j/12j** | |
| | | **L1** | 10:1 | 85 |
| 10 |  | | **11k/12k** | |
| | | **L1** | 10:1 | 76 |

[a] Yield of isolated **11e**. [b] Yield of isolated **11g**. [c] Yield of isolated **12h**. [d] *ee* not determined.

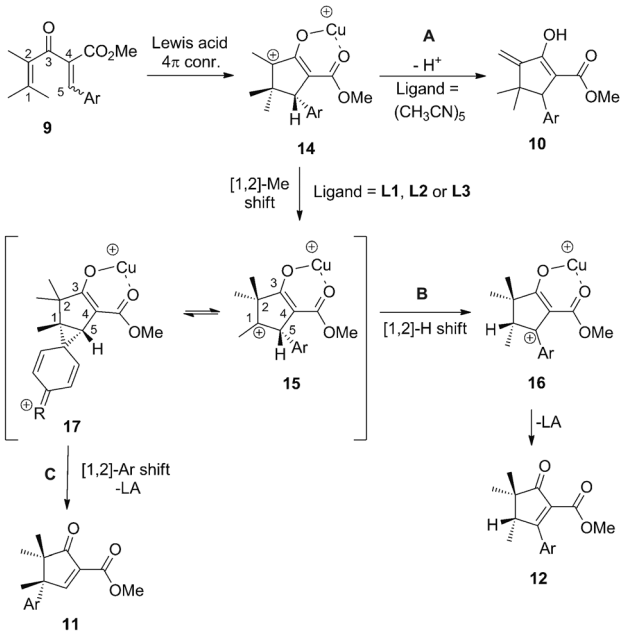
Table 3. Effect of the ligand on the rearrangement sequence.




9l 12l 12'l 13

| Entry | Ligand | *t* [h] | Product (ratio) | Yield [%] |
|---|---|---|---|---|
| 1 | $(MeCN)_5$ | 0.1 | – | decomposition |
| 2 | **L1** | 0.1 | **12l/12'l** (3:1) | 87 |
| 3 | **L2** | 0.1 | **12l/12'l** (3:1) | 75 |
| 4 | **L3** | 0.1 | **12l/12'l** (10:1) | 76 |

Thus, although chiral bisoxazolines were not effective for achieving asymmetric induction, our results suggest that bisoxazoline ligands can affect selectivities in the rearrangement sequence by virtue of their steric profile. Without the bisoxazoline ligand, elimination of a proton was favored over the first [1,2]-migration step (Table 1, entry 1; Scheme 2, path A). The use of any bisoxazoline ligand (**L1**, **L2**, or **L3**) led to suppression of this elimination. For the competing [1,2]-methyl shifts in **9l** (Table 3), the use of ligand **L3** led to high diastereoselectivity. The bisoxazoline ligand architecture of **L3** also had a strong impact on selectivity in the second [1,2]-migration (Table 2, entries 2–6 and Table 3, entries 2–4; Scheme 2, path C). A possible explana-




9 14 10 15 16 17 11 12

Scheme 2. Cyclization/rearrangement pathways of substrates **9**.

tion for the different selectivities may be that complexes with ligands **L1** and **L2** disrupt overlap of the C5 aryl ring with the C1 cation more effectively than the complex with **L3** does. This disruption would allow a hydride shift (path B, Scheme 2) to compete with formation of the phenonium ion intermediate and the subsequent aryl shift (path C, Scheme 2), compromising the selectivity (i.e., the ratio of **11** to **12**).

**Application to the synthesis of enokipodins**: The ability to install adjacent quaternary centers in cyclopentenones of type **11** encouraged us to employ this sequence toward the total synthesis of enokipodins A–D (Figure 1). They are nat-

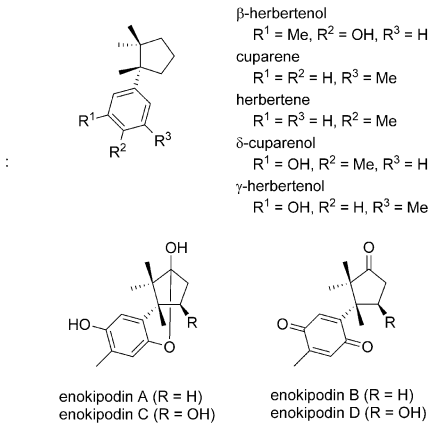
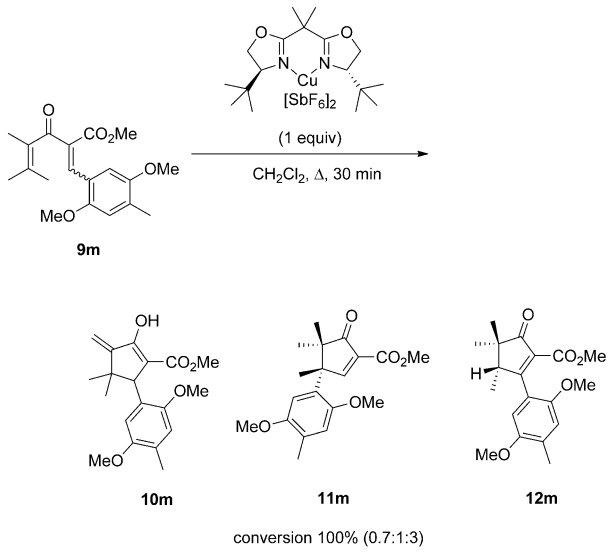



Figure 1. Enokipodins A—D.

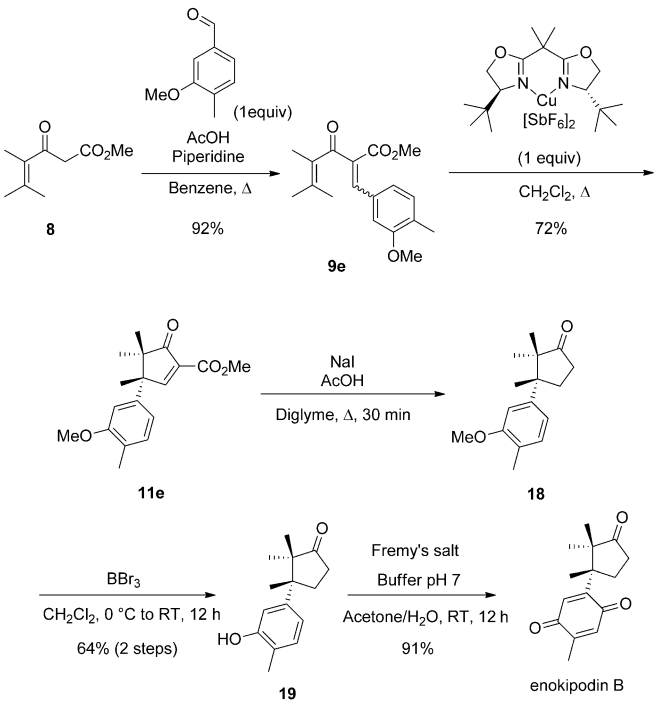
ural products isolated by Ishikawa et al. from the edible mushroom *Flammulina vellutepes* (Enokitake).[13] They possess antifungal activity against *Cladosporium herbarum* and antibiotic activity against the Gram-positive bacteria *Bacillus subtilis* and *Staphylococcus aureus*.[13] The enokipodins are highly oxidized members of a large family of sesquiterpene natural products that includes cuparene,[14] δ-cupar enol,[14a,15] herbertene,[14e,16] β-herbertenol,[16b–d,17] and γ-herbertenol (Figure 1).[18] The syntheses of many herbertane and cuparane family members, including the enokipodins,[19] have been disclosed over the years, with different strategies for the introduction of the adjacent quaternary centers of the cyclopentane ring.

Application of the cyclization/rearrangement sequence to the synthesis of the cuparane and herbertane natural products requires reactions that are highly selective for products of type **11**, favoring the [1,2]-aryl migration pathway (Scheme 2). First, we carried out cyclization of substrate **9m** by using the reaction conditions shown in Table 2, hoping to directly access the ring system corresponding to the enokipodins. Poor selectivity was observed in this reaction: both the elimination product **10m** and the hydride-shift product **12m** were obtained along with desired compound **11m**, even with ligand **L3** (Scheme 3). The steric bulk of the *ortho*-methoxy group is probably responsible for the poor efficiency of the [1,2]-aryl shift.




Scheme 3. Attempt towards a synthesis of the core of enokipodins.

Since the cyclization and rearrangement of compound **9e** had proceeded with good selectivity (Table 2, entry 4), we chose to examine **11e** as the pivotal intermediate in the synthesis.[20] By using the general approach in which the β-ketoester **8** serves as the starting point for assembly of the skeleton, compound **11e** was obtained after two synthetic operations (Scheme 4). Then, in an attempt to remove the carbomethoxy group with retention of the enone functionality, we applied the conditions developed by Agosta (NaI/AcOH in diglyme under reflux conditions).[21] We were surprised to




Scheme 4. Synthesis of enokipodin B from β-ketoester **8**.

observe that ketone **18** was the only product isolated from this reaction, a product that represents the unexpected net reduction of precursor **11e**. Demethylation with boron tribromide provides intermediate **19** (64% over two steps), which was easily converted to enokipodin B through oxidation with Fremy's salt.[22] By using this strategy, the total synthesis of enokipodin B was achieved in only six steps and in 33.9% overall yield from enone **7**. Furthermore, Kuwahara has shown that it was possible to obtain enokipodin A from reduction of the benzoquinone moiety of enokipodin B.[19b]

This strategy is both concise and general, enabling the synthesis of enokipodin B and the carbon skeleton of several other family members from a common precursor (β-ketoester **8**). The condensation of **8** with appropriate aldehydes, and subsequent cyclization/rearrangement allowed the preparation of cyclopentenones bearing the substitution patterns of β-herbertenol (**11b**), cuparene (**11c**), herbertene (**11d**), δ-cuparenol (**11e**), and infuscol A (**11f**)[23] (Table 2, entries 1–5).

## Conclusion

We have developed an efficient and convergent strategy to access the carbon framework of several natural products based on a Nazarov cyclization/rearrangement sequence mediated by the copper complex [*t*BuBox-Cu[$SbF_6$]$_2$]. By using this strategy, the total synthesis of enokipodin B was achieved in only six steps from enone **7**. Chemoselectivity of the sequence can be favored or disfavored by both substituents on the substrate and bisoxazoline ligands on the promoter. Ongoing work in our laboratory is focused on improving the enantioselective version of this reaction sequence.

## Experimental Section

**General procedure for the cyclization**: The copper complex [L-Cu[$SbF_6$]$_2$] (1 equiv) was added to a stirred solution of α-alkylidene β-keto esters in $CH_2Cl_2$ (0.03 M) under argon. The reaction mixture was stirred at room temperature or heated at reflux until completion of the reaction and then quenched with aqueous $NH_4OH$ and extracted with diethyl ether. The combined organic layers were washed with brine, dried over magnesium sulfate, and filtered. After removal of the solvents under reduced pressure, the crude product was purified by flash column chromatography by using different gradients of pentane and ethyl acetate to obtain the pure desired products.

**Compound 11a**: Pale yellow oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 8.51 (s, 1H), 7.37–7.34 (m, 2H), 7.30–7.26 (m, 1H), 7.18–7.16 (m, 2H), 3.89 (s, 3H), 1.50 (s, 3H), 1.24 (s, 3H), 0.57 ppm (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 207.3, 175.4, 162.8, 141.9, 132.2, 128.6, 127.3, 126.9, 53.8, 53.1, 52.2, 26.2, 25.3, 19.8; IR (neat): $\tilde{\nu}$ = 2970, 1755, 1720, 1624, 1435, 1339, 1319, 1284, 1250, 995 cm$^{-1}$; HRMS (EI+): *m/z* calcd for $C_{16}H_{18}O_3$: 258.1254 [$M+H^+$]; found: 258.1251.

**Compound 11b**: Pale yellow oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 8.47 (s, 1H), 6.93–6.90 (m, 2H), 6.78 (d, $J$ = 8.4 Hz, 1H), 3.89 (s, 3H), 3.82 (s, 3H), 2.22 (s, 3H), 1.46 (s, 3H), 1.22 (s, 3H), 0.58 (s, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 207.6, 176.0, 162.9, 156.8, 133.4, 132.0, 129.1, 126.7, 125.2, 109.7, 55.3, 54.0, 52.5, 52.1, 26.2, 25.4, 19.9, 16.4 ppm; IR (neat): $\tilde{\nu}$ = 2974, 1755, 1724, 1612, 1508, 1458, 1435, 1338, 1250, 1134 cm$^{-1}$; HRMS (EI+): *m/z* calcd for $C_{18}H_{22}O_4$: 302.1518 [$M+H^+$]; found: 302.1511.

**Compound 11c**: Pale yellow oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 8.51 (s, 1H), 7.26–7.22 (m, 1H), 7.09 (d, $J$ = 7.5 Hz, 1H), 6.98–6.94 (m, 2H), 3.89 (s, 3H), 2.36 (s, 3H), 1.49 (s, 3H), 1.24 (s, 3H), 0.58 ppm (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 207.4, 175.7, 162.8, 141.8, 138.2, 132.1, 128.4, 127.9, 127.5, 123.9, 53.8, 52.9, 52.1, 26.2, 25.3, 21.6, 19.8 ppm; IR (neat): $\tilde{\nu}$ = 2978, 2940, 1732, 1462, 1331, 1254, 1161, 1022, 964 cm$^{-1}$; HRMS (EI+): *m/z* calcd for $C_{17}H_{20}O_3$: 272.1413 [$M+H^+$]; found: 272.1415.

**Compound 11e**: Pale yellow oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 8.49 (s, 1H), 7.09 (d, $J$ = 7.7 Hz, 1H), 6.64 (dd, $J$ = 7.7 Hz, 1H), 6.58 (s, 1H), 3.89 (s, 3H), 3.82 (s, 3H), 2.20 (s, 3H), 1.49 (s, 3H), 1.24 (s, 3H), 0.61 ppm (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 207.4, 175.5, 162.9, 157.8, 140.6, 132.2, 130.6, 125.8, 118.9, 108.6, 55.4, 53.9, 53.1, 52.2, 26.1, 25.4, 19.9, 15.8 ppm; IR (neat): $\tilde{\nu}$ = 2924, 2855, 1755, 1724, 1612, 1582, 1508, 1250, 1203, 1134, 991 cm$^{-1}$; HRMS (EI+): *m/z* calcd for $C_{18}H_{22}O_4$: 302.1518 [$M+H^+$]; found: 302.1515.

**Compound 11f**: Pale yellow oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 8.46 (s, 1H), 7.07 (d, $J$ = 8.8 Hz, 2H), 6.88 (d, $J$ = 8.8 Hz, 2H), 3.89 (s, 3H), 3.81 (s, 3H), 1.48 (s, 3H), 1.22 (s, 3H), 0.57 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 207.5, 175.7, 162.9, 158.6, 133.9, 132.1, 127.9, 113.9, 55.3, 54.0, 52.5, 52.2, 26.1, 25.3, 19.9; IR (neat): $\tilde{\nu}$ = 2970, 2932, 1755, 1721, 1612, 1512, 1439, 1296, 1250, 1184, 1030 cm$^{-1}$; HRMS (EI+): *m/z* calcd for $C_{17}H_{20}O_4$: 288.1361 [$M+H^+$]; found: 288.1353.

**Compound 11g**: Pale yellow oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 8.43 (s, 1H), 7.48 (d, $J$ = 8.7 Hz, 2H), 7.04 (d, $J$ = 8.5 Hz, 2H), 3.89 (s, 3H), 1.48 (s, 3H), 1.23 (s, 3H), 0.58 ppm (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 205.7, 174.4, 162.6, 141.0, 132.6, 131.7, 128.5, 121.3, 53.7, 52.7, 52.2, 26.2, 25.3, 19.8 ppm; IR (neat) $\tilde{\nu}$ = 2974, 2928, 1756, 1720, 1624, 1435, 1389, 1338, 1250, 1076, 1007 cm$^{-1}$; HRMS (EI+): *m/z* calcd for $C_{16}H_{17}O_3Br$: 336.0361 [$M+H^+$]; found: 336.0365.

**Compound 12h**: Yellow oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.39 (ddd, $J$ = 8.4, 7.5, 1.7 Hz, 1H), 7.19 (dd, $J$ = 7.6, 1.7 Hz, 1H), 7.01 (dt, $J$ = 7.5, 1.0 Hz, 1H), 6.94 (d, $J$ = 8.4 Hz, 1H), 3.79 (s, 3H), 3.68 (s, 3H), 3.19 (q, $J$ = 7.4 Hz, 1H), 1.24 (s, 3H), 1.10 (s, 3H), 0.96 ppm (d, $J$ = 7.4 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 208.0, 177.4, 164.4, 156.3, 131.2, 131.0, 128.4, 123.4, 120.5, 111.0, 55.3, 51.7, 48.8, 47.7, 25.9, 20.6, 14.1 ppm; IR (neat): $\tilde{\nu}$ = 2947, 2924, 1740, 1697, 1612, 1510, 1462, 1346, 1288, 1258, 1230, 1203, 1126, 1022, 995 cm$^{-1}$; HRMS (EI+): *m/z*, calcd for $C_{17}H_{20}O_4$: 288.1368 [$M+H^+$]; found: 288.1361.

**Compound 12i**: Yellow oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.30 (t, $J$ = 8.3 Hz, 1H), 6.58 (d, $J$ = 8.4 Hz, 2H), 3.76 (s, 6H), 3.64 (s, 3H), 3.25 (q, $J$ = 7.4 Hz, 1H), 1.23 (s, 3H), 1.09 (s, 3H), 0.91 (d, $J$ = 7.4 Hz, 3H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 208.4, 178.5, 163.8, 156.7, 131.4, 130.7, 112.7, 103.8, 55.7, 51.5, 48.7, 48.2, 25.4, 20.8, 13.5 ppm; IR (neat): $\tilde{\nu}$ = 2947, 2928, 1732, 1601, 1574, 1454, 1331, 1234, 1207, 1150, 1122, 1034 cm$^{-1}$; HRMS (EI+): *m/z* calcd for $C_{18}H_{22}O_5$: 318.1467 [$M+H^+$]; found: 318.1462.

**Compound 11j**: Pale yellow oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 8.22 (s, 1H), 7.34–7.26 (m, 5H), 6.30 (d, $J$ = 16.4 Hz, 1H), 6.06 (d, $J$ = 16.3 Hz, 1H), 3.87 (s, 3H), 1.33 (s, 3H), 1.14 (s, 3H), 1.04 ppm (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 207.0, 174.4, 162.8, 140.8, 136.5, 132.4, 132.1, 128.7, 127.9, 126.3, 53.8, 52.1, 50.9, 23.5, 22.1, 21.7 ppm; IR (neat): $\tilde{\nu}$ = 2918, 1755, 1724, 1620, 1455, 1435, 1338, 1260, 1207, 991 cm$^{-1}$; HRMS (EI+): *m/z* calcd for $C_{18}H_{20}O_3$: 284.1413 [$M+H^+$]; found: 284.1419.

**Compound 11k**: Orange oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 8.33 (s, 1H), 7.24 (d, $J$ = 5.2 Hz, 1H), 6.99 (dd, $J$ = 5.1, 3.6 Hz, 1H), 6.74 (d, $J$ = 3.5 Hz, 1H), 3.88 (s, 3H), 1.56 (s, 3H), 1.21 (s, 3H), 0.72 ppm (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 206.4, 173.2, 162.7, 146.2, 132.4, 126.9, 124.7, 124.4, 54.6, 52.2, 51.4, 26.1, 24.9, 20.2 ppm; IR (neat): $\tilde{\nu}$ = 2970, 2928, 1755, 1720, 1620, 1435, 1335, 1315, 1281, 1254, 1207, 991 cm$^{-1}$; HRMS (EI+): *m/z* calcd for $C_{14}H_{16}O_3S$: 264.0820 [$M+H^+$]; found: 264.0826.

**Synthesis of enokipodin B**: Potassium nitrosodisulfonate (21.5 mg, 0.08 mmol) and disodium hydrogen phosphate buffer pH 7 (0.1 mL) were

added to a solution of **19** (7.5 mg, 0.032 mmol) in acetone (0.75 mL) and water (0.15 mL). The reaction mixture was stirred at room temperature overnight. Then, the solvent was evaporated and the mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over magnesium sulfate, and filtered. The solvent was removed by rotary evaporation. The crude product was purified by flash column chromatography (eluent pentane/ethyl acetate 8:2) to give enokipodin B (7 mg, 91%) as an orange solid.

**Enokipodin B**: Orange solid. M.p. 138–142 °C; $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 6.69$ (s, 1H), 6.56 (d, $J = 1.6$ Hz, 1H), 2.50–2.42 (m, 2H), 2.27 (ddd, $J = 12.8$, 10.1, 9.8 Hz, 1H), 2.04 (d, $J = 1.6$ Hz, 3H), 1.88 (ddd, $J = 12.8$, 8.6, 2.4 Hz, 1H), 1.32 (s, 3H), 1.22 (s, 3H), 0.76 ppm (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta = 220.9$, 188.2, 187.8, 153.5, 144.5, 135.3, 134.1, 52.4, 49.0, 33.8, 31.1, 23.1, 22.1, 20.6, 14.9 ppm; IR (neat): $\tilde{\nu} = 2966$, 2924, 1740, 1655, 1597, 1462, 1381, 1246, 1095, 1063, 935 cm$^{-1}$; HRMS (EI+): $m/z$ calcd for $C_{15}H_{18}O_3$: 246.1256 [$M+H^+$]; found: 246.1257. These data matched with the data reported previously.[14a]

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