Regioselective $FeCl_3$-Promoted Biomimetic Synthesis of Dimeric Isorhapontigenin

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Abstract: An efficient approach to the preparation of natural (±)-gneafricanin F and the first synthesis of (±)-gnemonol M were developed. The regioselective, oxidative coupling of 5-*tert*-butyl-isorhapontigenin catalyzed by $FeCl_3 \cdot 6H_2O$ in different solvent systems was used as the key synthetic step.

Key words: isorhapontigenin, gneafricanin F, gnemonol M, biomimetic synthesis, oxidative coupling

Stilbenes, such as resveratrol (**1**) and isorhapontigenin (**2**), as well as their oligomers, are naturally occurring polyphenols found in several plant families.[1] Stilbenes have attracted considerable attention in chemical and biological fields over the past thirty years because of their structural complexity and diverse bioactivities.[2] Thus far, about 22 isorhapontigenin oligomers, including **3**–**7** (Figure 1), have been reported, most of which have the same basic structures as resveratrol oligomers. However, the biosynthesis of oligomeric isorhapontigenin has not received as much attention as the synthesis of resveratrol oligomers.[3] Thus, we report herein on an approach to the synthesis of (±)-gneafricanin F (**6**) and (±)-gnemonol M (**7**) using regioselective oxidative coupling promoted by $FeCl_3 \cdot 6H_2O$.

During the oxidative coupling of **2**, phenoxyl radicals are generated as intermediates. The formed radical has at least four possible free radicals related to coupling reactions: R_5, R_8, R_{10}, and R_{12} (Scheme 1).[4] Different oxidative coupling modes lead to a variety of isorhapontigenin oligomer frameworks such as a dihydrobenzofuran ring, a benzocyclopentane ring, a dibenzo[2.1]octadiene, a dibenzobicyclo[3.2.1]octadiene, and a dibenzobicyclo[3.3.0]octadiene system.[1,2] These results have been verified previously by two research groups. In particular, Lin et al. studied the oxidative coupling reactions of natural product **2** catalyzed by Ag_2O and $FeCl_3 \cdot 6H_2O$. The 8–5 coupling product **3** was obtained in 30% yield when Ag_2O was used as an oxidant,[5] and more than seven coupling products, **3**–**6**, were isolated in the presence of the $FeCl_3 \cdot 6H_2O$ as oxidant.[6] The other report from Hou et al. discussed the synthesis of **3** using oxidative dimerization of **2**, which was subjected to horseradish peroxidase and H_2O_2.[7] The lack of regioselectivity in the coupling sites largely limits the effective construction of diverse frameworks of oligomeric isorhapontigenin on the basis of the aforementioned facts. In view of our previous success in the synthesis of dimeric resveratrol,[3a,e] we decided to introduce a bulky *tert*-butyl group in **2** to impede the undesired 8–5 coupling mode in the coupling reaction. This was expected to enhance the formation of structurally diverse isorhapontigenin dimers efficiently.

The coupling precursor, 5-(*tert*-butyl)isorhapontigenin (**11**), was prepared as shown in Scheme 2. First, aldehyde

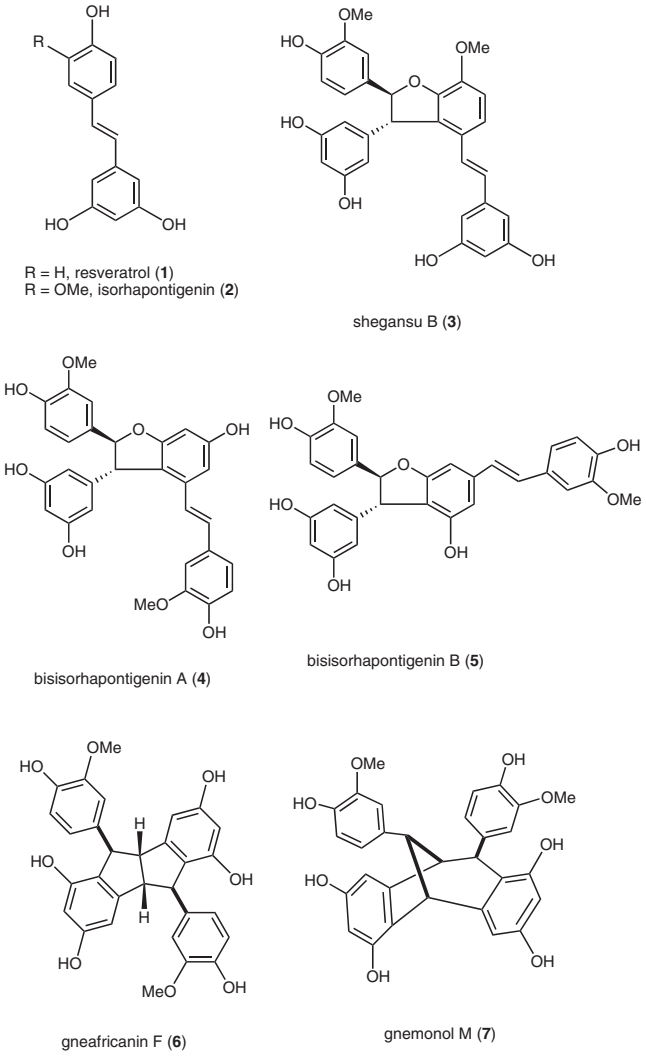

Figure 1 Selected isorhapontigenin-related natural products

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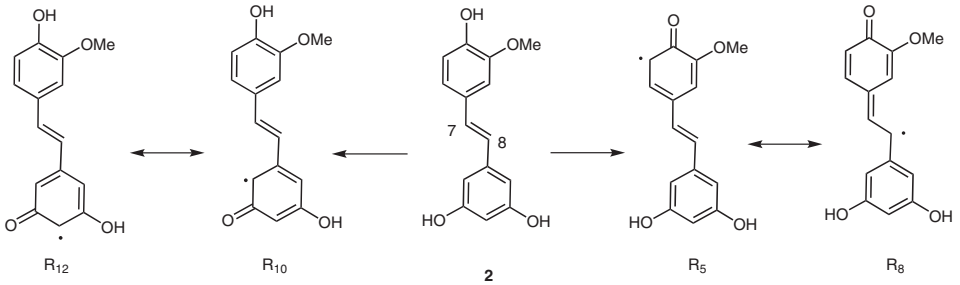
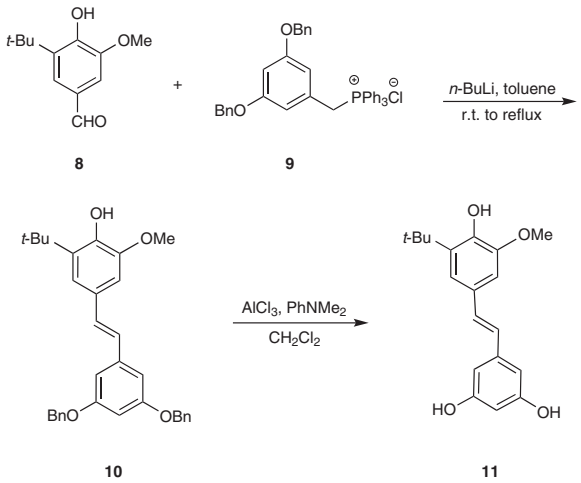


Scheme 1 Four important free radicals in the oxidative coupling of **2**



Scheme 2 Preparation of the coupling precursor **11**

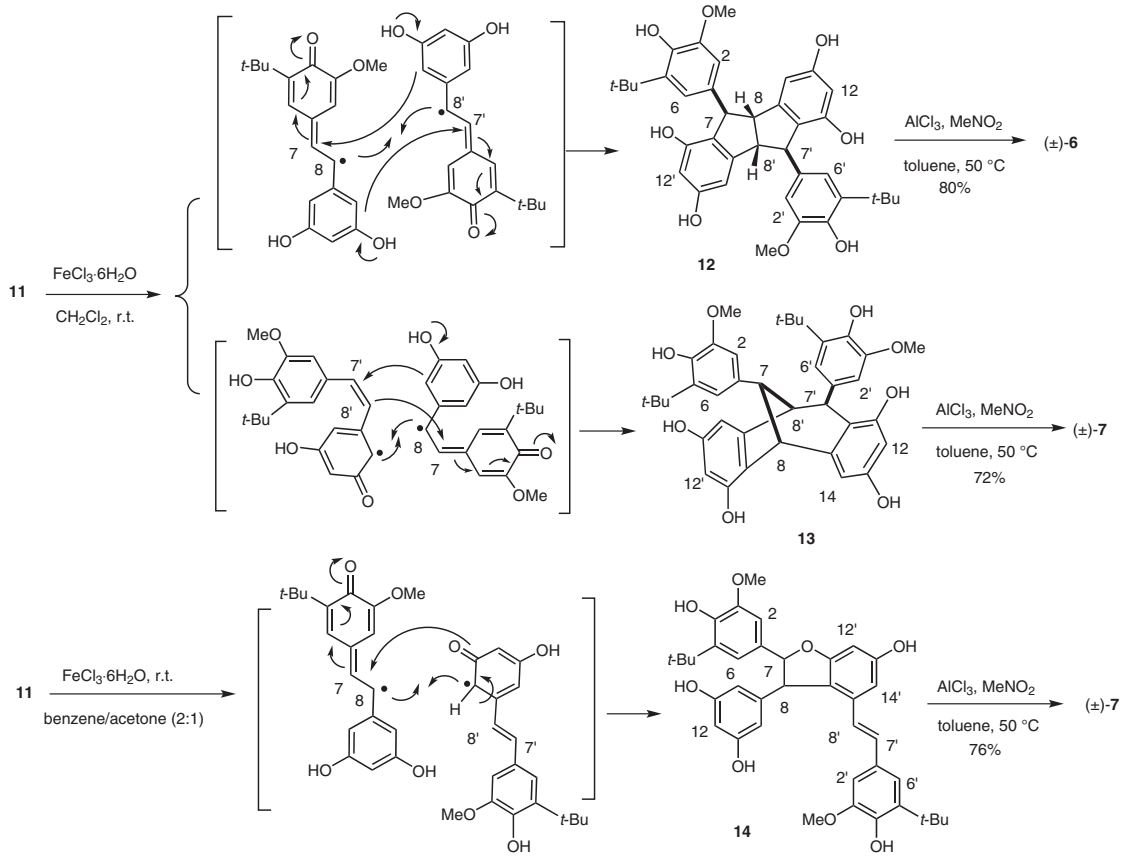
8 was synthesized from commercial creosol through a straightforward two-step sequence of alkylation and oxidation.[8] Second, phosphonium salt **9** was prepared from 3,5-dihydroxybenzoic acid in five steps, according to our previous study.[3e] A Wittig reaction between aldehyde **8** and phosphonium salt **9** by refluxing in toluene afforded the (*E*)-stilbene **10** in good yield. Finally, the desired coupling precursor **11** was obtained through a subsequent debenzylation reaction of **10** in 59% overall yield.

The oxidative dimerization of **11** was accomplished through a one-electron $FeCl_3 \cdot 6H_2O$ oxidant in several different solvent systems (Scheme 3). When compound **11** was treated with an equimolar amount of $FeCl_3 \cdot 6H_2O$ in dichloromethane under an argon atmosphere at room temperature for one hour, all the starting materials were consumed and two major dimeric intermediates, 8–8 coupling product **12** and 8–10 coupling product **13**, were isolated in 23% and 21% yield, respectively. The absence of an 8–5 coupling product in the reaction mixture confirms that the *tert*-butyl protecting group at the C-5 position of isorhapontigenin (**2**) hinders the reaction. Interestingly, this outcome is consistent with a portion of the work by Velu et al.[9] They described the oxidative dimerization of stilbene derivatives catalyzed by $FeCl_3 \cdot 6H_2O$ in dichloromethane. The result was a mixture of two dimers, which possessed the same skeletons as **12** and **13**, and had 7–16% yields.

Subsequently, the *tert*-butyl groups of dimer **12** were smoothly removed by treatment with aluminum trichloride and nitromethane in toluene at 50 °C to afford racemic **6** in 80% yield. Dimeric product **13** was also subjected to the same debutylation reaction to produce (±)-**7**, which to our knowledge, is the first report on the biosynthesis of gnemonol M (**7**). All the spectral data of (±)-**6** and (±)-**7** are in good agreement with the data reported in literature for natural products.[10]

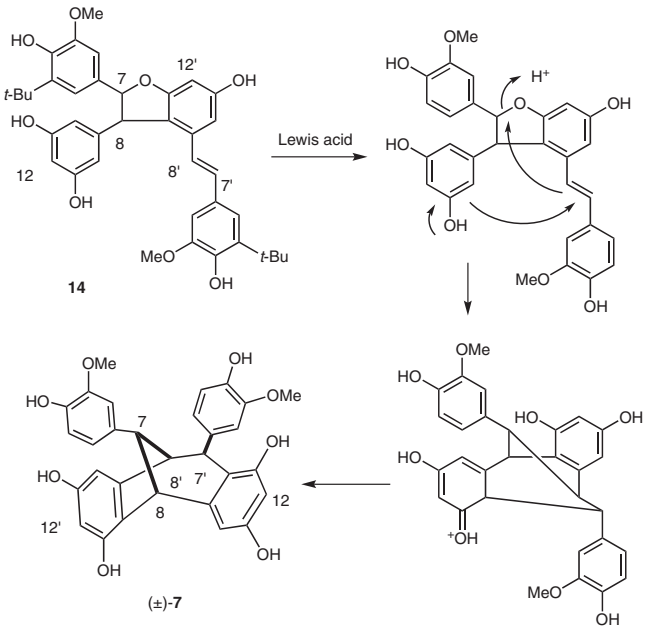
When a mixture of benzene and acetone (2:1) was used as the solvent instead of dichloromethane, with $FeCl_3 \cdot 6H_2O$ as the oxidant, the coupling reaction of **11** provided 15% of unreacted **11** and 25% of a predominant dimer, the 8–10 coupling product **14** (Scheme 3). This result, different from that in dichloromethane can be ascribed to acetone, which as a soft oxygenated solvent, solvated the starting material and formed Fe^{3+} complex by exchanging partially water ligands. Solvated stilbenes cannot arrange the same way they do in dichloromethane for steric reasons in the coupling reaction, and the resulting Fe^{3+} complex softened and induced reaction leading towards dihydrofuran ring skeleton. In addition, we compared the solvent effect of the ferric chloride dimerization reaction in pure acetone and benzene. Although the same dimeric product **14** was isolated, the coupling yield varied significantly. Using acetone, compound **14** was obtained in 28% yield, and **11** was recovered in 52% yield. In contrast, compound **14** was formed in 14% yield, and **11** was recovered in 43% yield using benzene owing to a number of unidentified compounds formed. It is worth noting that this result was different from our previous work, in which 3,5-di-*tert*-butylresveratrol was treated with $FeCl_3 \cdot 6H_2O$ in dichloromethane to give (±)-ampelopsin F and afford (±)-pallidol when using a mixture of benzene and acetone as solvent.[3a] Thus, substituent effect and steric effect in the substrates may result in the variance of coupling products under the same oxidative conditions. Further detailed investigation on these mechanisms is ongoing in our group.

A direct debutylation reaction of dimer **14** was conducted to synthesize the corresponding product (±)-**4**. The expected deprotected product (±)-**4** was not produced.[6a] Instead, the natural product (±)-**7** was obtained based on the spectral evidence. The unexpected transformation of **14** to (±)-**7** can be considered as the result of the debutylation and isomerization,[11] which is catalyzed by the strong Lewis acid, aluminum trichloride, in a one-pot reaction



Scheme 3 Oxidative coupling reaction of **11** with $FeCl_3 \cdot 6H_2O$

(Scheme 4). When the debutylation reaction occurs, an acid simultaneously protonates the oxygen atom on the dihydrofuran ring. This is followed by two successive nucleophilic attacks of electron-rich C10 and C8′ atoms on C7′ and C7, respectively, to generate the fused bicyclic ring. Finally, a standard rearomatization leads to the formation of (±)-**7**. This transformation mechanism was also supported by one of Niwa's observations that (+)-ε-viniferin, a resveratrol dimer possessing same skeleton with **14**, when treated with HCl, CF_3SO_3H, or H_2SO_4, provided three natural dimeric products including (+)-ampelopsin F, a structural analogue of **7**.[12]



Scheme 4 Proposed mechanism for the formation of (±)-**7** from **14**

In conclusion, a concise and highly efficient synthesis route for isorhapontigenin-based natural products, (±)-gneafricanin F (**6**) and (±)-gnemonol M (**7**) has been achieved by employing an oxidative coupling reaction catalyzed by $FeCl_3 \cdot 6H_2O$ in different solvent systems. The introduction of a 5-*tert*-butyl protecting group in **11** tempers the reactivity of **2**, forces the oxidative coupling to undergo several unfavorable coupling pathways, and significantly improves the yields of the desired dimers. This strategy may be used to synthesize a variety of naturally occurring oligomeric isorhapontigenin compounds and the corresponding research is currently in progress in our laboratory.

All NMR spectra were recorded on a Varian Mercury 400 MHz instrument in the solvent indicated. The FABMS data were obtained on a VG ZAB-HS mass spectrometer; HRMS spectra were measured on a Autostec-3090 mass spectrometer. IR spectra were obtained on a Nicolet NEXUS 670 FT-IR spectrometer. All solvents were freshly purified and dried by standard techniques prior to use. Purification of products was performed by column chromatography (CC) on silica gel (200–300 mush), purchased from QingDao Marine Chemical Co. (QingDao, China).

Stilbene 10

A stirred solution of phosphonium salt **9** (7.2 g, 12.0 mmol) in anhyd toluene (80 mL) was added to a solution of *n*-BuLi (2.4 mL, 12.0 mmol) in *n*-hexane under argon. After stirring for 30 min, aldehyde **8** (2.0 g, 10.0 mmol) was added and the mixture was refluxed under stirring for 2 h. After cooling to r.t., EtOH (20 mL) was added. The reaction mixture was concentrated and extracted with EtOAc (150 mL). The EtOAc layer was washed with H_2O (150 mL), brine (150 mL), and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue purified by CC on silica gel [petroleum ether (bp 60–90 °C)–EtOAc, 10:1] to give **10** (3.0 g, 91%) as a pale yellow solid; mp 132–134 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.51 (s, 9 H, *t*-C_4H_9), 3.96 (s, 3 H, OCH_3), 5.12 (s, 4 H, CH_2Ar), 6.16 (br s, 1 H, OH), 6.59 (t, *J* = 2.4 Hz, 1 H, H-12), 6.83 (d, *J* = 2.4 Hz, 2 H, H-10, 14), 6.93 (d, *J* = 16.2 Hz, 1 H, H-8), 7.01 (d, *J* = 2.1 Hz, 1 H, H-2), 7.08 (d, *J* = 2.1 Hz, 1 H, H-6), 7.09 (d, *J* = 16.2 Hz, 1 H, H-7), 7.36–7.51 (m, 10 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 29.3 (3 C), 34.6, 56.0, 69.9 (2 C), 101.0, 105.3 (2 C), 105.6, 118.8, 125.7, 127.5 (4 C), 127.9 (3 C), 128.5 (4 C), 129.3, 135.4, 136.8 (2 C), 139.8, 144.4, 146.8, 160.1 (2 C).

FABMS: *m*/*z* = 494.5 $[M]^+$.

Coupling Precursor 11

N,*N*-Dimethylaniline (15.4 mL, 0.12 mol) was added to a well-stirred solution of stilbene **10** (2.0 g, 4.0 mmol) in anhyd CH_2Cl_2 (80 mL) at 0 °C. After 5 min, anhyd $AlCl_3$ (3.2 g, 24.0 mmol) was added to the reaction mixture. After stirring for an additional 4 h at r.t., the reaction mixture was quenched with H_2O (20 mL) at 0 °C and poured into aq 1.0 M HCl (20 mL). The resulting mixture was extracted with EtOAc (3 × 40 mL). The combined EtOAc layers were washed with brine (100 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue purified by CC on silica gel (CH_2Cl_2–MeOH, 20:1) to give **11** (0.82 g, 65%) as a pale yellow solid; mp 118–120 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.39 (s, 9 H, *t*-C_4H_9), 3.81 (s, 3 H, OCH_3), 6.10 (br s, 1 H, OH), 6.30 (t, *J* = 2.1 Hz, 1 H, H-12), 6.57 (d, *J* = 2.1 Hz, 2 H, H-10, 14), 6.72 (d, *J* = 16.5 Hz, 1 H, H-8), 6.84 (d, *J* = 2.1 Hz, 1 H, H-2), 6.90 (d, *J* = 16.5 Hz, 1 H, H-7), 6.94 (d, *J* = 2.1 Hz, 1 H, H-6).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 29.2 (3 C), 34.5, 56.0, 101.9, 105.7 (2 C), 105.9, 118.7, 125.1, 127.8, 130.0, 135.2, 140.4, 144.3, 146.7, 156.7 (2 C).

HRMS (ESI): *m*/*z* calcd for $C_{19}H_{22}O_4$ $[M - H]^+$: 313.1445; found: 313.1450.

Dimerization of 11 with $FeCl_3$·6H_2O in Dichloromethane

A mixture of compound **11** (398 mg, 1.27mmol) and $FeCl_3$·6H_2O (343 mg, 1.27 mmol) in anhyd CH_2Cl_2 (14 mL) was stirred at r.t. under argon for 1 h. After removal of the solvent under reduced pressure, the resulting residue was diluted with EtOAc (30 mL), which was then washed with H_2O (30 mL) and brine (30 mL), and dried ($MgSO_4$). The solvent was evaporated in vacuo and the residue was subjected to CC on silica gel (CH_2Cl_2–MeOH, 40:1) to give two major dimers **12** (90.6 mg, 23%) and **13** (83.5 mg, 21%).

12

R_f = 0.15 (CH_2Cl_2–MeOH, 15:1); pale yellow amorphous powder.

IR (neat): 3424, 2957, 2871, 1699, 1599, 1457, 1428, 1258, 1140, 1072 cm^{-1}.

^{1}H NMR (400 MHz, acetone-d_6): δ = 1.40 (s, 18 H, *t*-C_4H_9), 3.76 (s, 6 H, OCH_3), 3.91 (br s, 2 H, H-8, 8′), 4.59 (br s, 2 H, H-7, 7′), 6.21 (d, *J* = 1.6 Hz, 2 H, H-14, 14′), 6.66 (br s, 4 H, H-2, 6, 2′, 6′), 6.78 (d, *J* = 1.6 Hz, 2 H, H-12, 12′), 7.12 (br s, 2 H, OH), 7.81 (br s, 2 H, OH), 8.09 (br s, 2 H, OH).

^{13}C NMR (100 MHz, acetone-d_6): δ = 31.3, 35.1, 54.9, 56.4, 60.5, 102.4, 103.4, 109.0, 118.2, 123.1, 133.4, 136.9, 143.6, 147.9, 150.4, 155.3, 159.2.

HRMS (ESI): *m*/*z* calcd for $C_{38}H_{42}O_8$ $[M + H]^+$: 627.2952; found: 627.2961.

13

R_f = 0.14 (CH_2Cl_2–MeOH, 15:1); pale yellow amorphous powder.

IR (neat): 3405, 2956, 2927, 2859, 1696, 1599, 1458, 1426, 1294, 1259, 1141, 1071 cm^{-1}.

^{1}H NMR (400 MHz, acetone-d_6): δ = 1.25 (s, 9 H, *t*-C_4H_9), 1.38 (s, 9 H, *t*-C_4H_9), 3.44 (br s, 1 H, H-8), 3.62 (s, 3 H, OCH_3), 3.72 (br s, 1 H, H-7′), 3.75 (s, 6 H, OCH_3), 4.15 (br s, 1 H, H-8′), 4.23 (br s, 1 H, H-7), 6.08 (d, *J* = 1.6 Hz, 1 H, H-14), 6.17 (d, *J* = 2.0 Hz, 1 H, H-14′), 6.46 (br s, 2 H, H-12, 2′), 6.52 (br s, 1 H, H-6′), 6.56 (br s, 1 H, H-12′), 6.78 (br s, 1 H, H-2), 6.89 (br s, 1 H, H-6), 7.04 (br s, 1 H, OH), 7.14 (br s, 1 H, OH), 7.39 (br s, 1 H, OH), 7.91 (br s, 1 H, OH), 7.95 (br s, 1 H, OH), 8.01 (br s, 1 H, OH).

^{13}C NMR (100 MHz, acetone-d_6): δ = 29.6 (3 C), 30.0 (3 C), 35.1, 35.2, 47.9, 50.0, 51.8, 56.2, 56.5, 58.5, 101.8, 104.2, 105.8, 106.8, 109.4, 110.3, 113.5, 118.9, 119.2, 128.0, 134.8, 137.4, 143.5 (2 C), 147.6, 147.7, 147.8, 150.8, 153.1, 155.4, 157.2, 157.9, 158.5, 159.2, 159.3.

ESI-HRMS: *m*/*z* calcd for $C_{38}H_{42}O_8$ $[M + H]^+$: 627.2952; found: 627.2948.

Dimerization of 11 with $FeCl_3$·6H_2O in Benzene–Acetone

A mixture of compound **11** (221 mg, 0.71mmol) and $FeCl_3$·6H_2O (190 mg, 0.71 mmol) was dissolved in a mixture of benzene and acetone (9.0 mL/4.5 mL) under argon. After stirring at r.t. for 1 h, the reaction mixture was quenched with H_2O (10 mL) and extracted with EtOAc (20 mL). The EtOAc layer was washed with H_2O (20 mL) and brine (20 mL), and dried ($MgSO_4$), and concentrated. The residue was subjected to CC on silica gel (CH_2Cl_2–MeOH, 50:1) to give unreacted **11** (33 mg) and dimer **14** (55.4 mg, 25%).

14

R_f = 0.15 (CH_2Cl_2–MeOH, 25:1); pale yellow amorphous powder.

IR (neat): 3396, 2957, 2870, 1690, 1600, 1454, 1428, 1297, 1258, 1154, 1068 cm^{-1}.

^{1}H NMR (400 MHz, acetone-d_6): δ = 1.31 (s, 9 H, *t*-C_4H_9), 1.32 (s, 9 H, *t*-C_4H_9), 3.82 (s, 6 H, OCH_3), 3.83 (s, 3 H, OCH_3), 4.51 (d, *J* = 6.8 Hz, 1 H, H-8), 5.43 (d, *J* = 6.8 Hz, 1 H, H-7), 6.27 (d, *J* = 2.0 Hz, 1 H, H-12), 6.29 (d, *J* = 2.0 Hz, 2 H, H-10,14), 6.33 (d, *J* = 2.0 Hz, 1 H, H-12′), 6.67 (d, *J* = 16.0 Hz, 1 H, H-8′), 6.74 (br s, 1 H, H-2′), 6.75 (d, *J* = 2.0 Hz, 1 H, H-14′), 6.83 (br s, 1 H, H-6′), 6.87 (br s, 1 H, H-6), 6.92 (br s, 1 H, H-2), 6.93 (d, *J* = 16.0 Hz, 1 H, H-7′), 7.54 (br s, 1 H, OH), 7.56 (br s, 1 H, OH), 8.37 (br s, 2 H, OH), 8.55 (br s, 1 H, OH).

^{13}C NMR (100 MHz, acetone-d_6): δ = 29.6 (3 C), 30.5 (3 C), 35.1, 35.2, 56.3, 56.5, 57.4, 94.7, 96.7, 102.1, 103.8, 106.4, 107.3 (2 C), 107.4, 117.4, 119.5, 120.0, 123.3, 128.9, 130.5, 132.2, 135.8 (2 C), 136.2, 145.4, 145.7, 147.2, 148.2, 148.4, 159.5, 159.8 (2 C), 162.4.

ESI-HRMS: *m*/*z* calcd for $C_{38}H_{42}O_8$ $[M + H]^+$: 627.2952; found: 627.2960.

(±)-Gneafricanin F (6)

A solution of $AlCl_3$ (0.5 g, 3.75 mmol) in $MeNO_2$ (1 mL) was added to a solution of compound **12** (48 mg, 0.08 mmol) in anhyd toluene (5 mL) at 50 °C. The reaction mixture was stirred for 50 min, then quenched with ice-water (4 mL), and extracted with EtOAc (2 × 20

mL). The combined organic layers were washed with brine (30 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was purified by preparative TLC (CH_2Cl_2–MeOH, 25:1) to afford (±)-**6** (32 mg, 80%) as a pale yellow amorphous powder; R_f = 0.27 (CH_2Cl_2–MeOH, 10:1).

IR (neat): 3385, 2925, 2855, 1727, 1601, 1514, 1462, 1427, 1383, 1279, 1125, 1077, 1038 cm^{-1}.

^1H NMR (400 MHz, acetone-d_6): δ = 3.78 (s, 6 H, OCH_3), 3.86 (br s, 2 H, H-8, 8′), 4.57 (br s, 2 H, H-7, 7′), 6.20 (d, *J* = 2.0 Hz, 2 H, H-12, 12′), 6.54 (dd, *J* = 2.0, 8.4 Hz, 2 H, H-6, 6′), 6.64 (d, *J* = 2.0 Hz, 2 H, H-14, 14′), 6.68 (dd, *J* = 2.0, 8.4 Hz, 2 H, H-5, 5′), 6.83 (d, *J* = 2.0 Hz, 2 H, H-2, 2′), 7.32 (br s, 2 H, OH), 7.84 (br s, 2 H, OH), 8.09 (br s, 2 H, OH).

^{13}C NMR (100 MHz, acetone-d_6): δ = 54.4, 56.2, 60.4, 102.5, 103.4, 112.0, 115.5, 123.0, 138.3, 145.6, 148.1, 150.4, 155.3, 159.3.

ESI-HRMS: *m*/*z* calcd for $C_{30}H_{26}O_8$ $[M - H]^+$: 513.1555; found: 513.1550.

(±)-Gnemonol M (7)

A solution of $AlCl_3$ (0.4 g, 3.0 mmol) in $MeNO_2$ (1 mL) was added to a solution of compound **13** (37 mg, 0.06 mmol) in anhyd toluene (3 mL) at 50 °C. The reaction mixture was stirred for 1.5 h, then quenched with ice-water (3 mL), and extracted with EtOAc (2 × 15 mL). The combined organic layers were washed with brine (20 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was purified by preparative TLC (CH_2Cl_2–MeOH, 25:1) to afford (±)-**7** (22 mg, 72%) as a pale yellow amorphous powder; R_f = 0.23 (CH_2Cl_2–MeOH, 10:1).

IR (neat): 3364, 2927, 2861, 1695, 1602, 1512, 1463, 1263, 1127, 1033 cm^{-1}.

^1H NMR (400 MHz, acetone-d_6): δ = 3.47 (br s, 1 H, H-8), 3.64 (s, 3 H, OCH_3), 3.70 (br s, 1 H, H-7′), 3.80 (s, 6 H, OCH_3), 4.14 (br s, 1H, H-8′), 4.21 (br s, 1 H, H-7), 6.07 (d, *J* = 2.0 Hz, 1 H, H-12), 6.16 (d, *J* = 2.4 Hz, 1 H, H-12′), 6.41 (d, *J* = 8.4 Hz, 1 H, H-6′), 6.44 (d, *J* = 2.4 Hz, 1 H, H-14′), 6.55 (d, *J* = 2.0 Hz, 1 H, H-14), 6.56 (d, *J* = 8.0 Hz, 1 H, H-5′), 6.62 (br s, 1 H, H-2′), 6.68 (d, *J* = 8.0 Hz, 1 H, H-6), 6.73 (d, *J* = 8.0 Hz, 1 H, H-5), 6.97 (br s, 1 H, H-2), 7.29 (br s, 1 H, OH), 7.35 (br s, 1 H, OH), 7.50 (br s, 1 H, OH), 7.87 (br s, 1 H, OH), 7.98 (br s, 1 H, OH), 8.06 (br s, 1 H, OH).

^{13}C NMR (100 MHz, acetone-d_6): δ = 47.5, 50.1, 51.1, 56.0, 56.3, 57.8, 101.8 (2 C), 105.7, 112.1, 112.3, 113.0, 113.3, 115.2 (2 C), 120.9, 121.4, 127.8, 136.2, 139.0, 145.5 (2C), 147.3, 147.6 (2 C), 148.0, 157.2, 157.8, 158.6, 159.3.

ESI-HRMS: *m*/*z* calcd for $C_{30}H_{26}O_8$ $[M + H]^+$: 515.1700; found: 515.1705.

Transformation of 14 to (±)-Gnemonol M (7)

A solution of $AlCl_3$ (0.26 g, 2.0 mmol) in $MeNO_2$ (1 mL) was added to a solution of compound **14** (27 mg, 0.04 mmol) in anhyd toluene (2 mL) at 50 °C. The reaction mixture was stirred for 40 min, then quenched with ice-water (3 mL), and extracted with EtOAc (2 × 15 mL). The combined organic layers were washed with brine (20 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was purified by preparative TLC (CH_2Cl_2–MeOH, 25:1) to afford (±)-**7** (16 mg, 76%) as a pale yellow amorphous powder.

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