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Synthesis of Stachybotrin C and All of Its Stereoisomers: Structure Revision

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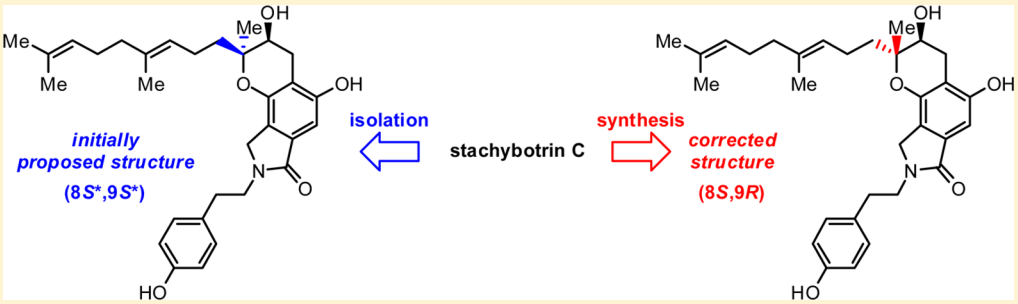
Supporting Information



ABSTRACT: We disclose the first total synthesis of stachybotrin C, a potent neuroprotective natural compound. All of the four stereoisomers have been prepared and fully characterized with the aim to attribute the absolute configuration of the two adjacent stereocenters of the stachybotrin C.

INTRODUCTION

As recently discussed by R. W. Hoffmann,[1] the goal of the natural product synthesis has deeply changed during the past two centuries. However, among the aims of the total synthesis, the confirmation of the structure of new isolated compounds remains a strong object of motivation and particularly the unambiguous attribution of the relative and absolute configurations of stereogenic centers.

In 1997, Hanada et al.[2] reported the isolation of stachybotrin C **1** (Figure 1) from the culture broths of *Stachybotrys parvispora* F4708. These authors also stated some interesting biological properties for this natural compound since it has exhibited significant neurite outgrowth in PC12 cells and has shown protecting effects against neuronal damage. Because of its potent neuritogenic properties, stachybotrin C **1** has been sought for the treatment of neurodegenerative diseases.[3] The structure of **1** has been deduced by classical spectroscopic analyses, and while the relative configuration of the two adjacent stereocenters has been established by NOESY analyses,[4] the absolute configurations of the two chiral centers were not determined. Despite efforts described by Inoue and co-workers in 2006 and more recently by us,[5] to our knowledge, no total synthesis has been reported. In this article, we described the first total synthesis of **1** and its other stereoisomers in order to confirm the structure and to establish the absolute configurations of the two chiral centers.

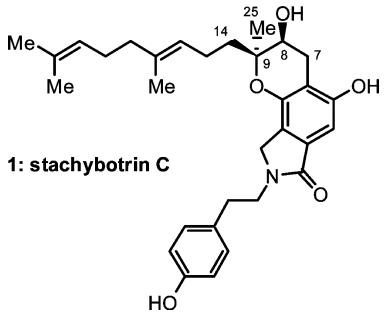


Figure 1. Proposed structure of stachybotrin C.

Our strategy to prepare **1** in its racemic form has been based upon the retrosynthetic analysis outlined in Scheme 1, which consists in two key steps: a thermal Claisen transposition[6] and a regioselective epoxidation to form the 3-chromanol moiety.[7]

RESULTS AND DISCUSSION

Our first task was to prepare the 2,3-dihydro-1*H*-isoindolone derivative **3** from commercially available 3,5-dihydroxybenzoic acid **2** as previously reported (Scheme 2).[5b] A copper-catalyzed

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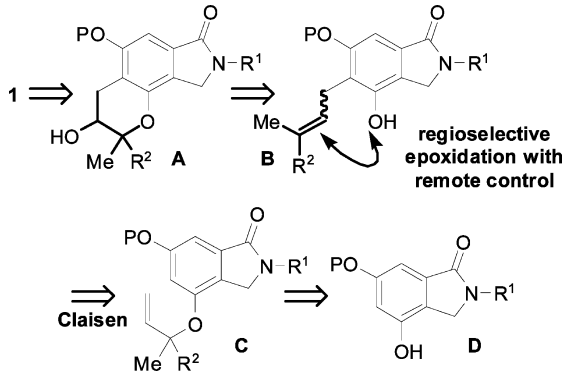
Scheme 1. Stachybotrin C Retroanalysis

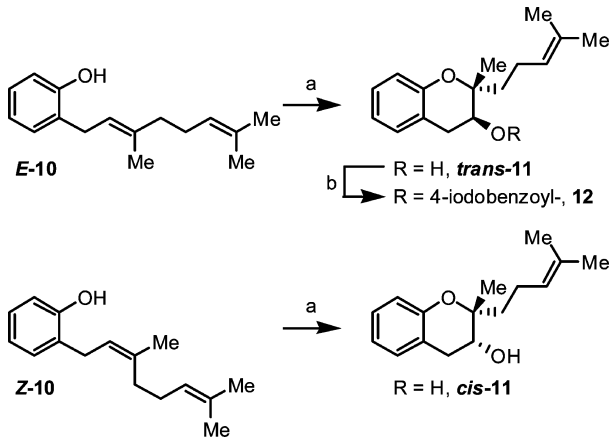


coupling reaction between the phenol **3** and the carbonate **4**[5b] afforded the propargylic ether intermediate easily converted into the corresponding alkene **5** by hydrogenation in the presence of Lindlar catalyst. A Claisen-transposition (1,3-shift) mediated under thermal condition in the presence of a catalytic amount of 3,5-di-*tert*-butyl-4-hydroxytoluene (BHT) gave the prenylated derivative **6** as a mixture of two unseparable *E*/*Z* olefins (in 2:1 ratio) isolated in good yield (80%). The BHT seems to catalyze the reaction as a Brönsted acid, since in its absence no rearrangement occurred and only the starting material has been recovered.

Next we examined the direct formation of the 3-chromanol using a methodology reported by Lattanzi and co-workers.[7] For this purpose the alkene **6** has been submitted to oxidative reaction conditions by the use of a catalytic amount of $VO(acac)_2$ in the presence of *tert*-butylhydroperoxide (TBHP) and 20 mol % of trifluoroacetic acid (TFA) in methylene chloride under reflux. We were delighted to observe the formation of the expected 3-chromanol obtained as a mixture of two racemic diastereoisomers **7** and **8** along with a small amount of the 5-exocyclization product **9**. The mass balance of the products formed confirms the regioselective oxidation of the alkene closer to the aromatic moiety indicating that the epoxidation occurs via the coordination of the phenol function to the vanadium.[8] We also paid particular attention to an asymmetric epoxidation version of this key step, different reaction conditions have been evaluated but none of these allowed a regioselective oxidation of the desired olefin.

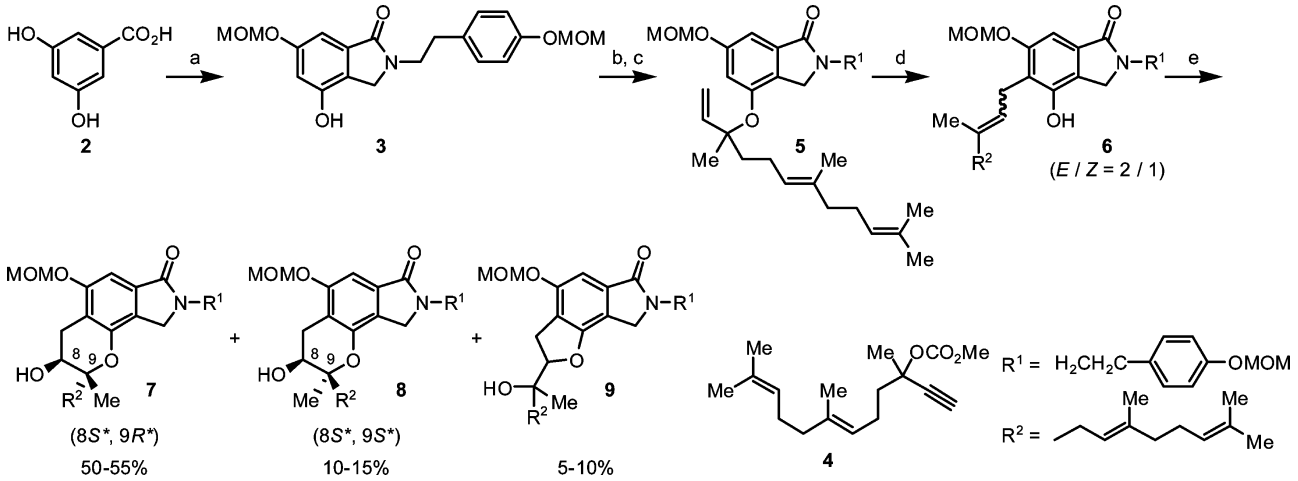
Initially, we tried to characterize the relative configuration of C-8 and C-9 for both diastereoisomers **7** and **8** with the help of NOESY analyses and other NMR sequences. Although we had in hand the two stereoisomers, it was not possible to conclude toward the stereochemical relationship between the two chiral centers for the major and minor 3-chromanols. In the same time, we focused our efforts to convert **7** and **8** as benzoic ester derivatives with the aim to obtain crystals suitable for X-ray diffraction analysis. Because no crystal has been obtained, simplified 3-chromanols have been prepared from the phenol ***E*-10**[9] and ***Z*-10**[10] as depicted in Scheme 3. After derivatization of ***trans*-11** into the ester **12**, crystals were grown by slow evaporation of methanol at room temperature. The crystal

Scheme 3. Preparation of Simplified 3-Chromanols[a]



[a]Reagents and conditions: (a) $VO(acac)_2$ (1.5 mol %), TBHP (1.3 equiv), TFA (20 mol %), CH_2Cl_2, 40 °C, 3 h, ***trans*-11** 60% yield and ***cis*-11** 43% yield. (b) 4-Iodobenzoic acid, DCC, DMAP, CH_2Cl_2, rt, 12 h, 68% yield. DCC = dicyclohexylcarbodiimide, DMAP = 4-(dimethylamino)pyridine.

Scheme 2. Synthesis of Racemic Diastereoisomers of Stachybotrin C[a]



[a]Reagents and conditions: (a) see ref 5b. (b) **4**, K_2CO_3 (2 equiv), KI (2 equiv), CuI (20 mol %), acetone, reflux, 2 d, 75−80%. (c) H_2 (1 atm), Pd Lindlar, EtOAc, rt, 8 h, 90%. (d) BHT (10 mol %), xylene, reflux, 6 h, 80%. (e) $VO(acac)_2$ (1.5 mol %), TBHP (1.3 equiv), TFA (20 mol %), CH_2Cl_2, 40 °C, 3 h.

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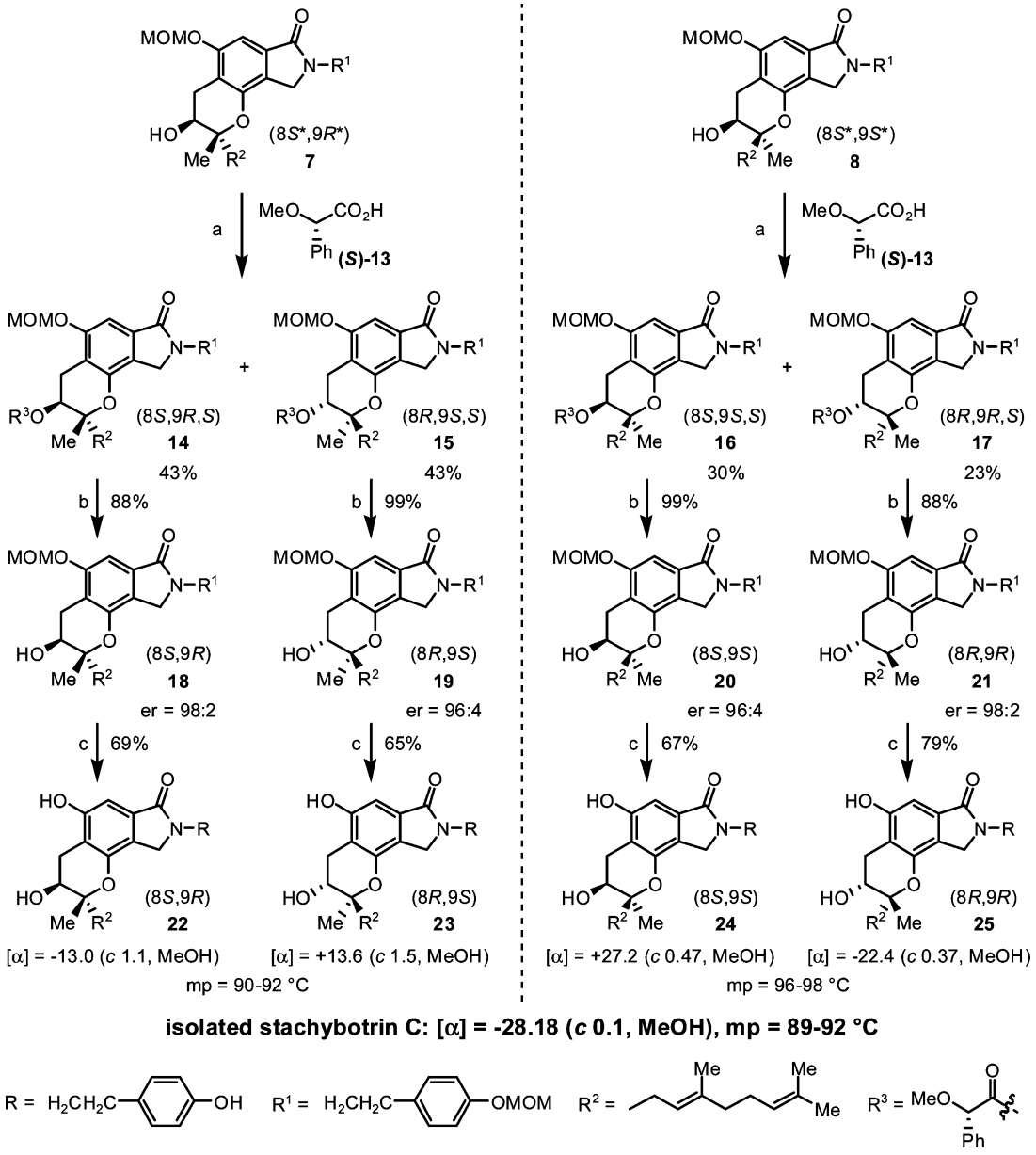
Scheme 4. Synthesis of the Stachybotrin C and Its Stereoisomers[a]



[a]Reagents and conditions: (a) DCC, DMAP, CH_2Cl_2, rt, 14 h. (b) MeONa, MeOH, rt, 2 h. (c) AcCl, MeOH, rt, 6 h.

structure[11] confirms the *trans* relative configuration in **12** between the unsaturated side chain and the alcohol function and therefore that **11** has been isolated as the *trans*-isomer as reported by Lattanzi and co-workers.[7,11] By comparison of the ^{1}H and ^{13}C NMR spectra of **7** and **8** with ***trans*-11** and ***cis*-11**, the *trans* relative configuration has been assigned to the compound **7**, while the *cis* relative configuration was assigned to **8**.[11]

Being sure of the relative configuration in each diastereoisomer **7** and **8**, we then tackled isolation of each stereoisomer. To do so, enantiomerically pure (*S*)-*O*-methyl mandelic acid **13** was reacted with **7** to provide the pair of diastereomeric esters **14** and **15** as a 1:1 mixture. In a similar way, the compound **8** has been converted into diastereomeric esters **16** and **17** (Scheme 4). Choice of the installation of this group served the dual purpose of creating a pair of separable diastereoisomers in order to obtain after cleavage of this function enantiopure stachybotrin C (or stereoisomers), as well as a diagnostic for assigning the absolute configuration of the stereogenic centers.[12]

After separation, each diastereoisomer has been then subjected to NMR analyses. The assignment of the absolute configuration was based on the shielding effects of the phenyl ring on identifiable protons on the 3-chromanol derivatives. According to the model, the hydrogen of the alcohol, the ester carbonyl and the methoxy group of the *O*-methyl mandelate all lie in a plane. For example, when viewed in this manner for the isomer **14**, the C-25 methyl group observes shielding of protons proximal to the phenyl group of the ester relative to the chemical shifts of the corresponding protons of racemic alcohol **7**. On the contrary, for the isomer **15**, the C-7 methylene group were shielded while the chemical shift of the protons of the C-25 methyl group remain unchanged (Figure 2). These data

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indicate that the absolute configuration of the C-8 is *S* for **14** and *R* for **15**.

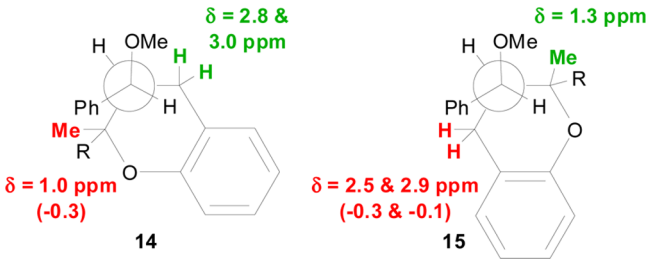

Figure 2. Assignment of the absolute configurations on esters **14** and **15**.

For the purpose of establishing which synthesized isomer corresponds to the natural stachybotrin C, the ester moiety was cleaved using sodium methoxide to afford alcohols **18**–**21**. After isolation of these products, their enantiomeric purity has been determined by chiral HPLC. The methoxymethylether have been then cleaved by in situ formation of HCl affording after purification all the four stereoisomers of stachybotrin C.

Careful NMR analysis of all isomers and comparison with the ^{1}H and ^{13}C NMR of the natural stachybotrin C[2] has been carried out.[11] The compound **22** possesses all the NMR data and also the melting point consistent with the natural product. Only the optical rotation differs substantially from ours. Thus, as indicated in the literature,[2] the compound **1** having the reported relative configuration (8*S**,9*S**) has an optical rotation of −28.18 (*c* 0.1, MeOH), whereas the synthesized product **22** has $[\alpha]$ = −13.0 (*c* 1.1, MeOH). The compound **22** has a high enantiomeric purity, as demonstrated above by chiral HPLC analyses of its precursor **18** (e.r. = 98:2). We believe therefore that the aforementioned literature value is probably affected by an inedaquate purity of the sample of natural stachybotrin C.

CONCLUSION

In summary, we have demonstrated the validity of the sequence thermal Claisen transposition followed by a regioselective epoxidation to prepare the stachybotrin C and all of its stereoisomers. Because 3-chromanol pattern is frequently encountered in the large family of natural products, application of this methodology is in progress and will be reported in due course. The present work further shows that the initially reported relative configuration of the two stereogenic centers has been misassigned indicating that NMR spectroscopy is not a definitive technique for structure determination. This proves that total synthesis still has a crucial role to solve structural elucidation of natural products.

EXPERIMENTAL SECTION

General Information. All reagents and solvents were used as purchased from commercial suppliers or were purified/dried according to Armarego W. L. F. and Chai C. L. L. (Purification of Laboratory Chemicals, sixth edition, Elsevier). NMR analyzes were done on a 300 or 500 MHz spectrometer. δ values are given in parts per million (ppm), coupling constants (*J* values) are given in Hertz (Hz), and multiplicity of signals are reported as usual. HRMS analyzes were obtained using a Q-TOF or a TOF-Q instrument for ESI. Melting points were taken on a hot bench. Chiral HPLC analyzes were performed using Daicel Chiralpak IA and IC columns. TLC analyzes were carried out using precoated silica gel 60 F_{254} plates and purifications for columns chromatography using silica gel 60 (70–200 mesh and 40–60 mesh) or using silica gel 60 PF_{254} for preparative thin layer chromatography. Petroleum ether (PE) used for purifications was the low boiling point fraction (40–60 °C). Experimental procedures for compounds prior to **5** have been given in ref 5b.

6-Methoxymethoxy-2-[2-(4-methoxymethoxyphenyl)ethyl]-4-((*E*)-1,5,9-trimethyl-1-vinyldeca-4,8-dienyloxy)-2,3-dihydroisoindol-1-one 5. To a solution of (*E*)-4-(1-ethynyl-1,5,9-trimethyldeca-4,8-dienyloxy)-6-methoxymethoxy-2-[2-(4-methoxymethoxyphenyl)ethyl]-2,3-dihydro-isoindol-1-one (2.29 g, mmol, 1.0 equiv) in EtOAc (100 mL) was added Lindlar Pd (15% w/w, 340 mg) and the suspension was stirred for 6 h under an atmosphere of H_2. Then, the reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduce pressure. The residue was purified by column chromatography on silica gel using CH_2Cl_2/EtOAc 4/1 as eluent affording **5** as a pale yellow oil (2.07 g, 90%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.48 (s, 3H), 1.57 (s, 3H), 1.61 (s, 3H), 1.69 (s, 3H), 1.82–1.48 (m, 2H), 2.17–1.95 (m, 6H), 2.62 (t, *J* = 7.6, 2H), 3.46 (s, 3H), 3.48 (s, 3H), 3.80 (t, *J* = 7.8, 2H), 4.15 (d, *J* = 3.1, 2H), 5.13–5.08 (m, 2H), 5.14 (s, 2H), 5.30–5.18 (m, 2H), 6.07 (dd, *J* = 11.0 and 17.6, 1H), 6.89 (d, *J* = 1.9, 1H), 6.96 (d, *J* = 8.4, 2H), 7.11 (d, *J* = 1.8, 1H), 7.16 (d, *J* = 8.4, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 60.8, 61.3, 62.5, 62.6, 63.4, 63.4, 63.7, 63.7, 65.6, 67.1, 67.7, 68.4, 69.4, 71.4, 71.5, 78.4, 81.6, 81.7, 83.9, 85.8, 87.0, 87.4, 89.3, 89.5, 90.0, 90.9, 90.9, 91.4, 91.6, 92.3, 92.5, 94.4, 96.8, 97.9, 98.4, 101.2; HRMS (ESI) $[M + Na]^+$ calcd for $C_{35}H_{47}NO_6Na$ 600.3301, found 600.3300.

4-Hydroxy-6-methoxymethoxy-2-[2-(4-methoxymethoxyphenyl)ethyl]-5-((2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trienyl)-2,3-dihydroisoindol-1-one (*E*)-6 and 4-Hydroxy-6-methoxymethoxy-2-[2-(4-methoxymethoxyphenyl)ethyl]-5-((2*Z*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trienyl)-2,3-dihydroisoindol-1-one (*Z*)-6. To a solution of **5** (2.53 g, 4.38 mmol, 1.0 equiv) in dry xylene (75 mL), a catalytic amount of BHT was added, and the mixture was allowed to stir under reflux for 6 h. The solvent was then removed under reduced pressure, and the residue was purified by column chromatography on silica gel using Et_2O/PE 7/3 as eluent affording a mixture of unseparable diastereoisomers **6** in ratio *E*/*Z* 2/1 (2.0 g, 80%). (***E*)-6**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.58 (s, 6H), 1.66 (s, 3H), 1.82 (s, 3H), 1.94–2.29 (m, 8H), 2.90 (t, *J* = 7.3, 2H), 3.45 (s, 3H), 3.46 (s, 3H), 3.53 (d, *J* = 7.0, 2H), 3.80 (t, *J* = 7.7, 2H), 4.20 (s, 2H), 5.05–5.10 (m, 2H), 5.12 (s, 2H), 5.20 (s, 2H), 5.23–5.29 (m, 1H), 6.46 (bs, 1H), 6.93 (d, *J* = 8.6, 2H), 7.13 (d, *J* = 8.6, 2H), 7.14 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.0, 16.2, 17.7, 23.0, 23.5, 25.7, 26.3, 26.6, 33.9, 39.6, 39.7, 44.4, 48.0, 55.9, 56.2, 94.5, 94.9, 101.2, 101.3, 116.4, 119.8, 121.2, 121.8, 123.5, 124.3, 129.6, 131.3, 132.0, 132.2, 165.6, 139.0, 150.5, 155.8, 155.8, 168.7. (***Z*)-6**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.60 (s, 3H), 1.36 (s, 3H), 1.68 (s, 3H), 1.74 (s, 3H), 1.94–2.13 (m, 4H), 2.18 (m, 2H), 2.29 (m, 2H), 2.90 (t, *J* = 7.3, 2H), 3.45 (s, 3H), 3.46 (s, 3H), 3.53 (d, *J* = 7.0, 2H), 3.80 (t, J = 7.7, 2H), 4.20 (s, 2H), 4.96–5.10 (m, 2H), 5.12 (s, 2H), 5.20 (s, 2H), 5.31–5.25 (m, 1H), 6.46 (bs, 1H), 6.93 (d, *J* = 8.6, 2H), 7.12 (d, *J* = 8.6, 2H), 7.14 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.0, 17.6, 22.8, 23.5, 25.7, 26.2, 26.6, 32.0, 33.9, 39.7, 44.4, 48.1, 55.9, 56.1, 94.5, 94.9, 101.2, 116.4, 119.8, 121.7, 121.9, 123.5, 124.2, 129.6, 131.3, 132.0, 132.2, 135.9, 139.1, 150.4, 155.8, 155.8, 168.7; HRMS (ESI) [M + Na]+ calcd for $C_{35}H_{47}NO_6Na$ 600.3301, found 600.3303.

Compounds 7, 8, and 9. To a solution of **6** (577 mg, 0.87 mmol, 1.0 equiv) in dry dichloromethane was added $VO(acac)_2$ (4 mg, 0.013 mmol, 1.5 mol %). After 5 min, TBHP (5.5 M in decane, 200 μL, 1.1 mmol, 1.3 equiv) and TFA (13 μL, 0.17 mmol, 0.2 equiv) were added, and the mixture was stirred at 40 °C for 4 h. Then, the solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel using CH_2Cl_2/EtOAc 4/1 as eluent affording **7** as a major product (279 mg, 54%), **8** (80 mg, 15%) and **9** (40 mg, mixture of diastereoisomers, 8%). **7**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.34 (s, $3H_{25}$), 1.57 (s, $3H_{24}$), 1.58 (s, $3H_{23}$), 1.59–1.65 (m, $2H_{14}$), 1.67 (s, $3H_{22}$), 1.96 (m, $2H_{18}$), 2.04 (m, $2H_{19}$), 2.12 (m, $2H_{15}$), 2.79 (dd, *J* = 5.7 and 17.8, $1H_7$), 2.91 (t, *J* = 7.5, $2H_{2'}$), 3.00

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(dd, J = 5.1 and 17.8, 1H$_7$), 3.46 (s, 3H-MOM), 3.47 (s, 3H-MOM), 3.75−3.85 (m, 2H$_{1'}$), 3.93 (m, 1H$_8$), 4.17 (m, 2H$_{13}$), 5.05−5.11 (m, 2H$_{16,20}$), 5.14 (s, 2H-MOM), 5.22 (s, 2H-MOM), 6.96 (d, J = 8.5, 2H$_{3'}$), 7.09 (s, 1H$_4$), 7.16 (d, J = 8.5, 2H$_{4'}$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.9 (C_{24}), 17.6 (C_{23}), 19.1 (C_{25}), 21.6 (C_{15}), 25.6 (C_{22}), 26.6 (C_{19}), 26.9 (C_7), 34.0 ($C_{2'}$), 37.0 (C_{14}), 39.6 (C_{18}), 44.3 ($C_{1'}$), 47.9 (C_{13}), 55.9 (CH_3-MOM), 56.3 (CH_3-MOM), 67.6 (C_8), 79.0 (C_9), 94.6 (CH_2-MOM), 94.7 (CH_2-MOM), 100.0 (C_4), 112.3 (C_6), 116.5 ($C_{5'}$ and $C_{7'}$), 122.5 (C_{12}), 123.6 (C_{16}), 124.2 (C_{20}), 129.7 ($C_{4'}$ and $C_{8'}$), 131.5 ($C_{3'}$), 132.0 (C_3), 132.7 (C_{21}), 135.8 (C_{17}), 148.2 (C_{11}), 155.9 ($C_{6'}$), 156.2 (C_5), 168.6 (C_2); HRMS (ESI) [M + Na]+ calcd for $C_{35}H_{47}NO_7Na$ 616.3250, found 616.3253; HPLC (Daicel Chiralpak IA, i-PrOH/n-heptan 4/1, 1 mL/min, 254 nm) $t_{8R,9S}$ = 8.52 min (49.9%), $t_{8S,9R}$ = 13.92 min (50.1%). **8**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.29 (s, 3H$_{25}$), 1.59 (s, 6H$_{24,23}$), 1.67 (s, 3H$_{22}$), 1.71−1.81 (m, 2H$_{14}$), 1.96−1.99 (m, 2H$_{18}$), 2.04−2.11 (m, 2H$_{19}$), 2.12−2.16 (m, 2H$_{15}$), 2.83 (dd, J = 4.8 and 18.0, 1H$_7$), 2.91 (t, J = 7.5, 2H$_{2'}$), 2.96 (dd, J = 4.9 and 18.0, 1H$_7$), 3.46 (s, 3H-MOM), 3.47 (s, 3H-MOM), 3.79 (t, J = 7.4, 2H$_{1'}$), 3.93 (t, J = 4.7, 1H$_8$), 4.16 (s, 2H$_{13}$), 5.07−5.10 (m, 1H$_{20}$), 5.14 (s, 2H-MOM), 5.14−5.17 (m, 1H$_{16}$), 5.22 (s, 2H-MOM), 6.96 (d, J = 8.4, 2H$_{3'}$), 7.08 (s, 1H$_4$), 7.16 (d, J = 8.4, 2H$_{4'}$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.9 (C_{24}), 17.7 (C_{23}), 21.4 (C_{25}), 21.8 (C_{15}), 25.7 (C_{22}), 26.7 (C_{19}), 26.9 (C_7), 34.0 ($C_{2'}$), 34.5 (C_{14}), 39.7 (C_{18}), 44.2 ($C_{1'}$), 47.8 (C_{13}), 55.9 (CH_3-MOM), 56.3 (CH_3-MOM), 68.1 (C_8), 78.9 (C_9), 94.5 (CH_2-MOM), 94.6 (CH_2-MOM), 100.0 (C_4), 112.4 (C_6), 116.4 ($C_{5'}$ and $C_{7'}$), 122.4 (C_{12}), 123.8 (C_{16}), 124.2 (C_{20}), 129.7 ($C_{4'}$ and $C_{8'}$), 131.4 ($C_{3'}$), 132.1 (C_3), 132.7 (C_{21}), 135.6 (C_{17}), 148.0 (C_{11}), 155.9 ($C_{6'}$), 156.2 (C_5), 168.5 (C_2); HRMS (ESI) [M + Na]+ calcd for $C_{35}H_{47}NO_7Na$ 616.3250, found 616.3253; HPLC (Daicel Chiralpak IC, i-PrOH/n-heptan 3/1, 1 mL/min, 254 nm) $t_{8S,9S}$ = 23.25 min (51.3%), $t_{8R,9R}$ = 31.72 min (48.7%). **9**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19 (s, 3H), 1.32 (s, 3H), 1.59 (s, 3H), 1.61 (s, 3H), 1.62 (s, 3H), 1.64 (s, 3H), 1.67 (s, 3H), 1.68 (s, 3H), 1.95−2.20 (m, 2 × 6H), 2.91 (t, J = 2.91, 2 × 2H), 3.19 (m, 2 × 2H), 3.47 (s, 2 × 6H), 3.80 (m, 2 × 2H), 4.14 (s, 2 × 2H), 4.78 (q, J = 4.8, 2 × 1H), 5.08−5.16 (m, 2 × 2H), 5.14 (s, 2 × 1H), 5.22 (s, 2 × 1H), 6.96 (d, J = 7.0, 2 × 2H), 7.10 (s, 2 × 1H), 7.15 (d, J = 7.2, 2 × 2H); ^{1}H NMR (75 MHz, $CDCl_3$) δ 16.0, 17.7, 21.1, 21.9, 22.1, 22.9, 25.6, 26.6, 26.6, 28.1, 28.4, 33.9, 36.9, 38.8, 39.6, 44.3, 47.6, 55.9, 56.2, 73.5, 73.6, 90.3, 90.8, 101.6, 115.4, 116.5, 119.0, 119.1, 123.8, 123.9, 124.1, 124.2, 129.6, 131.5, 131.5, 132.1, 132.1, 135.0, 135.7, 135.8, 154, 1, 154.5, 155.9, 168.2; HRMS (ESI) [M + Na]+ calcd for $C_{35}H_{47}NO_7Na$ 616.3250, found 616.3254.

Compounds 14 and 15. To a solution of **7** (93 mg, 0.16 mmol, 1.0 equiv) in dry dichloromethane (5 mL) were added (*S*)-methoxyphenylacetic acid (29 mg, 0.17 mmol, 1.1 equiv), dicyclohexylcarbodiimide (42 mg, 0.20 mmol, 1.3 equiv) and 4-(dimethylamino)-pyridine (2 mg, 0.016 mmol, 0.1 equiv), and the solution was stirred at room temperature for 20 h. Then, the reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified on preparative TLC using Et_2O/PE 7/3 as eluent affording **14** (50 mg, 43%) and **15** (50 mg, 43%) as colorless oils. **14**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.97 (s, 3H), 1.24−1.34 (m, 2H), 1.48 (s, 3H), 1.58 (s, 3H), 1.66 (s, 3H), 1.64−2.05 (m, 6H), 2.77 (dd, J = 6.0 and 18.0, 1H), 2.92 (t, J = 7.2, 2H), 3.09 (dd, J = 5.4 and 18.1, 1H), 3.40 (s, 3H), 3.46 (s, 6H), 3.80 (t, J = 8.0, 2H), 4.15 (d, J = 3.1, 2H), 4.76 (s, 1H), 4.89 (t, J = 6.9, 1H), 4.76−5.12 (m, 2H), 5.14 (s, 2H), 5.22 (s, 2H), 6.97 (d, J = 8.6, 2H), 7.10 (s, 1H), 7.17 (d, J = 8.6), 7.32−7.36 (m, 3H), 7.38−7.42 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.8, 17.6, 19.2, 21.2, 24.1, 25.7, 26.6, 34.0, 36.7, 39.6, 44.3, 47.8, 55.9, 56.3, 57.2, 69.8, 82.3, 94.5, 94.6, 99.9, 111.5, 116.4, 122.3, 123.1, 124.1, 127.3, 128.6, 128.9, 129.6, 131.4, 132.0, 132.9, 135.6, 136.0, 148.0, 155.9, 155.9, 168.4, 169.9; $[\alpha]_D$ = +29.9 (c 1.075, $CHCl_3$), $[\alpha]_D$ = +24.4 (c 1.0, MeOH). **15**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.31 (s, 3H), 1.47−1.57 (m, 2H), 1.51 (s, 3H), 1.60 (s, 3H), 1.66 (s, 3H), 1.91−1.95 (m, 2H), 1.99−2.10 (m, 4H), 2.49 (dd, J = 5.1 and 18.1, 1H), 2.88 (dd, J = 5.2 and 18.2, 1H), 2.94 (t, J = 7.6, 2H), 3.36 (s, 3H), 3.40 (s, 3H), 3.46 (s, 3H), 3.80−3.83 (m, 2H), 4.17 (d, J = 3.1, 2H), 4.78 (s, 1H), 5.00 (t, J = 6.3, 1H), 5.05 (t, J = 6.8, 1H), 5.09 (dd, J = 6.5 and 8.2, 2H), 5.14 (s, 2H), 6.97 (d, J = 8.5, 2H), 7.04 (s, 1H), 7.18 (d, J = 8.3, 2H), 7.19 (d, J = 7.2, 2H), 7.22 (d, J = 7.0, 1H), 7.26−7.29 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.9, 17.7, 20.1, 21.5, 23.5, 25.7, 26.6, 30.3, 32.2, 34.0, 36.8, 39.6, 44.3, 47.8, 55.9, 56.2, 57.3, 70.0, 82.3, 94.5, 94.6, 99.9, 111.2, 116.4, 122.1, 123.0, 124.1, 126.6, 128.4, 128.5, 129.7, 131.5, 132.1, 132.8, 135.7, 136.0, 147.9, 155.9, 168.5, 170.1; $[\alpha]_D$ = +8.2 (c 1.0, $CHCl_3$); HRMS (ESI) [M + Na]$^+$ calcd for $C_{44}H_{55}NO_9Na$ 764.3769, found 764.3770.

Compound 18. To a solution of **14** (85 mg, 0.114 mmol, 1.0 equiv) in MeOH was added a solution of MeONa in MeOH (25% w/w, 40 μL, 0.17 mmol, 1.5 equiv) at 0 °C, and the mixture was stirred at room temperature for 2 h. The reaction mixture was quenched with HCl 2 N, and the product was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and the filtrate was concentrated under reduced pressure. Then, the crude material was purified on preparative TLC using Et_2O/PE 4/1 affording **18** (60 mg, 88%) as a colorless oil: $[\alpha]_D$ = −11.2 (c 1.0, MeOH); HPLC (Daicel Chiralpak IA, i-PrOH/n-heptan 4/1, 1 mL/min, 254 nm) $t_{8R,9S}$ = 8.63 min (2%), $t_{8S,9R}$ = 14.03 min (98%).

Stachybotrin C 22. To a solution of **18** (60 mg, 0.10 mmol, 1.0 equiv) in dry MeOH (3 mL) was added acetyl chloride (36 μL, 0.50 mmol, 5.0 equiv) at 0 °C. The solution was stirred at room temperature for 20 h. Water was added, and the product was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and the filtrate was concentrated under reduced pressure. The residue was purified on preparative TLC using Et_2O as eluent affording stachybotrin C **22** as a white solid (35 mg, 69%): mp = 90−92 °C; ^{1}H NMR (500 MHz, MeOD) δ 1.26 (s, 3H$_{25}$), 1.56 (s, 6H$_{24,23}$), 1.66 (s, 3H$_{22}$), 1.66−1.68 (m, 2H$_{14}$), 1.95−1.98 (m, 2H$_{18}$), 2.01−2.07 (m, 2H$_{19}$), 2.13−2.18 (m, 2H$_{15}$), 2.64 (dd, J = 6.9 and 17.6, 1H$_7$), 2.86 (t, J = 7.2, 2H$_{2'}$), 2.97 (dd, J = 5.4 and 17.6, 1H$_7$), 3.75 (t, J = 7.2, 2H$_{1'}$), 3.86 (t, J = 6.1, 1H$_8$), 4.14 (s, 2H$_{13}$), 5.06 (t, J = 6.8, 1H$_{16}$), 5.14 (t, J = 7.0, 1H$_{20}$), 6.68 (d, J = 8.3, 2H$_{5',7'}$), 6.72 (s, 1H$_4$), 7.04 (d, J = 8.3, 2H$_{4',8'}$); ^{13}C NMR (125 MHz, MeOD) δ 16.0 (C_{24}), 17.8 (C_{23}), 18.8 (C_{25}), 22.6 (C_{15}), 25.9 (C_{22}), 27.7 (C_{19} and C_7), 34.8 ($C_{2'}$), 38.5 (C_{14}), 40.8 (C_{18}), 45.6 (C_{13} and $C_{1'}$), 68.4 (C_8), 80.2 (C_9), 100.8 (C_4), 113.2 (C_6), 116.3 ($C_{5'}$), 116.4 ($C_{7'}$), 121.6 (C_{12}), 125.4 (C_{16}), 125.5 (C_{20}), 130.7 ($C_{4'}$ and $C_{5'}$), 130.8 ($C_{3'}$), 132.2 (C_3), 132.8 (C_{21}), 136.2 (C_{17}), 149.9 (C_{11}), 157.1 ($C_{6'}$), 157.9 (C_5), 171.1 (C_2); HRMS (ESI) [M + Na]$^+$ calcd for $C_{31}H_{39}NO_5Na$ 528.2726, found 528.2721; $[\alpha]_D$ = −13.0 (c 1.06, MeOH), $[\alpha]_D$ = −14.8 (c 0.23, MeOH).

Compound 19. Prepared from **15** following the procedure described for **18**: $[\alpha]_D$ = +12.0 (c 1.1, MeOH); HPLC (Daicel Chiralpak IA, i-PrOH/n-heptan 4/1, 1 mL/min, 254 nm) $t_{8R,9S}$ = 8.48 min (96%), $t_{8S,9R}$ = 13.94 min (4%).

***ent*-Stachybotrin C 23.** Prepared from **19** following the procedure described for **22**. Identical spectroscopic data to **22**: $[\alpha]_D$ = +13.6 (c 1.5, MeOH).

Compounds 16 and 17. Prepared from **8** following the procedure described for **14** and **15**. **16**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06 (s, 3H), 1.19−1.43 (m, 2H), 1.48 (s, 3H), 1.62 (s, 3H), 1.70 (s, 3H), 1.77−1.83 (m, 2H), 1.89−1.94 (m, 2H, 2.00−20.5 (m, 2H), 2.86 (dd, J = 5.0 and 18.4, 1H), 2.93 (t, J = 7.6, 2H), 3.00 (dd, J = 5.2 and 18.4, 1H), 3.37 (s, 3H), 3.46 (s, 3H), 3.46 (s, 3H), 3.80 (dd, J = 6.1 and 8.4, 2H), 4.16 (d, J = 2.6, 2H), 4.74 (s, 1H), 4.74 (t, J = 7.3, 1H), 5.07−5.11 (m, 2H), 5.14 (s, 2H), 5.22 (s, 2H), 6.97 (d, J = 8.6, 2H), 7.11 (s, 1H), 7.18 (d, J = 8.6), 7.31−7.35 (m, 3H), 7.37−7.41 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.9, 17.7, 21.2, 21.4, 24.1, 25.7, 26.7, 34.0, 34.4, 39.6, 44.2, 47.8, 56.0, 56.3, 57.1, 70.3, 82.2, 94.5, 94.7, 99.9, 111.6, 116.4, 122.4, 123.0, 124.2, 127.3, 128.7, 128.9, 129.7, 131.5, 132.1, 135.4, 136.0, 148.0, 155.9, 156.0, 168.5, 170.0; $[\alpha]_D$ = +45.4 (c 1.14, MeOH). **17**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.23 (s, 3H), 1.58 (s, 3H), 1.61 (s, 3H), 1.61−1.70 (m, 2H), 1.69 (s, 3H), 1.92−2.09 (m, 6H), 2.55 (dd, J = 4.5 and 18.4, 1H), 2.82 (dd, J = 4.7 and 18.4, 1H), 2.94 (t, J = 7.6, 2H), 3.35 (s, 3H), 3.38 (s, 3H), 3.46 (s, 3H), 3.82 (t, J = 7.0, 2H), 4.18 (s, 2H), 4.76 (s, 1H), 5.05−5.16 (m, 5H), 5.14 (s, 2H), 6.97 (d, J = 8.6, 2H), 7.03 (s, 1H), 7.11−7.40 (m, 7H), 7.19 (d, J = 7.2, 2H), 7.22 (d, J = 7.0, 1H), 7.26−7.29 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.9, 17.7, 21.3, 21.6, 23.4, 25.7, 26.6, 34.0, 35.2, 39.7, 44.2, 47.8, 55.9, 56.2, 57.3, 70.2, 82.2, 94.5, 94.5, 99.8, 111.3, 116.4,

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122.1, 123.4, 124.2, 126.5, 128.3, 128.5, 129.7, 131.5, 132.1, 132.8, 135.6, 135.8, 147.8, 155.9, 155.9, 168.5, 170.0; $[\alpha]_D$ = −8.7 (*c* 1.12, MeOH); HRMS (ESI) $[M + Na]^+$ calcd for $C_{44}H_{55}NO_9Na$ 764.3769, found 764.3770.

Compound 20. Prepared from **16** following the procedure described for **18**: $[\alpha]_D$ = +22.9 (*c* 1.2, MeOH); HPLC (Daicel Chiralpak IC, *i*-PrOH/*n*-heptan 3/1, 1 mL/min, 254 nm) $t_{8S,9S}$ = 23.55 min (97%), $t_{8R,9R}$ = 32.13 min (2%).

Compound 24. Prepared from **20** following the procedure described for **22**: mp = 96−98 °C; ^{1}H NMR (300 MHz, MeOD) δ 1.31 (s, $3H_{25}$), 1.53 (s, $3H_{24}$), 1.56 (s, $3H_{23}$), 1.64 (s, $3H_{22}$), 1.63−1.76 (m, $2H_{14}$), 1.93−2.22 (m, $6H_{18,19,15}$), 2.68 (dd, *J* = 6.6 and 17.8, $1H_7$), 2.86 (t, *J* = 7.2, $2H_{2'}$), 2.96 (dd, *J* = 5.5 and 17.8, $1H_7$), 3.76 (dt, *J* = 3.2 and 7.2, $2H_{1'}$), 3.86 (t, *J* = 5.9, $1H_8$), 4.16 (d, *J* = 1.3, $2H_{13}$), 5.06 (m, $1H_{16}$), 5.14 (dd, *J* = 5.7 and 7.4, $1H_{20}$), 6.69 (d, *J* = 8.5, $2H_{5',7'}$), 6.72 (s, $1H_4$), 7.04 (d, *J* = 8.5, $2H_{4',8'}$); ^{13}C NMR (75 MHz, MeOD) δ 15.9 (C_{24}), 17.7 (C_{23}), 22.2 (C_{25}), 22.7 (C_{15}), 25.9 (C_{22}), 27.7 (C_{19}), 27.7 (C_7), 34.2 ($C_{2'}$), 34.8 (C_{14}), 40.8 (C_{18}), 45.6 (C_{13} and $C_{1'}$), 69.6 (C_8), 80.1 (C_9), 100.9 (C_4), 113.5 (C_6), 116.3 ($C_{5'}$ and $C_{7'}$), 121.6 (C_{12}), 125.4 (C_{16}), 125.5 (C_{20}), 130.7 ($C_{4'}$ and $C_{8'}$), 130.8 ($C_{3'}$), 132.2 (C3), 132.8 (C_{21}), 136.2 ($C_{17'}$), 149.8 (C_{11}), 157.1 ($C_{6'}$), 158.0 (C_5), 171.1 (C_2); HRMS (ESI) $[M + Na]^+$ calcd for $C_{31}H_{39}NO_5Na$ 528.2726, found 528.2721; $[\alpha]_D$ = +27.2 (*c* 0.47, MeOH).

Compound 21. Prepared from **17** following the procedure described for **18**: $[\alpha]_D$ = −22.4 (*c* 1.33, MeOH); HPLC (Daicel Chiralpak IC, *i*-PrOH/*n*-heptan 3/1, 1 mL/min, 254 nm) $t_{8S,9S}$ = 23.87 min (1%), $t_{8R,9R}$ = 32.66 min (99%).

Compound 25. Prepared from **21** following the procedure described for **22**. Identical spectroscopic data to **24**: $[\alpha]_D$ = −23.7 (*c* 0.35, MeOH).

***(E)*-2-(3,7-Dimethylocta-2,6-dienyl)phenol (*E*)-10.**[9] To a solution of phenol (100 mg, 1.06 mmol, 1.0 equiv) in dry Et_2O (3 mL) was added sodium (73 mg, 3.18 mmol, 3.0 equiv), and the mixture was stirred at room temperature for 1 h. Then, (*E*)-1-bromo-3,7-dimethyl-octa-2,6-diene (230 mg, 1.06 mmol, 1.0 equiv) diluted in dry Et_2O (2 mL) was added, and the solution was heated at 30 °C overnight. Sodium was then removed by filtration, HCl 0.1 N was added, and the product was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using EP/Et_2O 4/1 as eluent affording (*E*)-**10** as a light brown oil (170 mg, 70%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.60 (s, 3H), 1.69 (s, 3H), 1.77 (s, 3H), 2.11 (m, 4H), 3.37 (d, *J* = 7.2, 2H), 4.98−5.18 (m, 1H), 5.26−5.43 (m, 1H), 6.81 (dd, *J* = 1.3 and 8.4, 1H), 6.86 (td, *J* = 1.2 and 7.5, 1H), 7.10 (d, *J* = 7.7, 1H), 7.13 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.1, 17.7, 25.7, 26.4, 29.7, 39.7, 115.7, 120.7, 121.6, 123.8, 126.8, 127.5, 129.9, 131.9, 138.4, 154.4; HRMS (ESI) $[M + H]^+$ calcd for $C_{16}H_{23}O$ 231.17489, found 231.1749.

***(2R*,3S*)*-2-Methyl-2-(4-methylpent-3-enyl)chroman-3-ol *trans*-11.**[7] Prepared from (*E*)-**10** following the procedure described for **7** and **8**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.33 (s, 3H), 1.55 (s, 3H), 1.54−1.69 (m, 2H), 1.66 (s, 3H), 2.07−2.19 (m, 2H), 2.78 (dd, *J* = 5.7 and 16.8, 1H), 3.05 (dd, *J* = 4.9 and 16.8, 1H), 3.87 (t, *J* = 5.3, 1H), 5.08 (tt, *J* = 1.2 and 7.1, 1H), 6.82 (d, *J* = 8.2, 1H), 6.86 (t, *J* = 7.4, 1H), 7.05 (d, *J* = 7.4, 1H), 7.11 (t, *J* = 7.8, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.6, 19.3, 21.7, 25.6, 31.1, 37.1, 68.2, 78.6, 117.3, 119.0, 120.5, 123.9, 127.6, 130.0, 132.0, 152.8; HRMS (ESI) $[M + Na]^+$ calcd for $C_{16}H_{22}O_2Na$ 269.15175, found 269.1516.

***(Z)*-2-(3,7-Dimethylocta-2,6-dienyl)phenol (*Z*)-10.**[10] Prepared from phenol and (*Z*)-1-bromo-3,7-dimethyl-octa-2,6-diene[13] following the procedure described for (*E*)-**10**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.63 (s, 3H), 1.70 (s, 3H), 1.77 (s, 3H), 2.06−2.28 (m, 4H), 3.37 (d, *J* = 7.1, 1H), 5.09−5.20 (m, 1H), 5.32 (t, *J* = 7.2, 1H), 6.80 (dd, *J* = 1.2 and 8.4, 1H), 6.86 (td, *J* = 1.2 and 7.6, 1H), 7.10 (d, *J* = 7.5, 1H), 7.13 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.6, 23.4, 25.7, 26.3, 29.4, 32.0, 115.6, 120.7, 122.4, 123.8, 126.9, 127.5, 129.9, 132.2, 138.5, 154.2; HRMS (ESI) $[M + H]^+$ calcd for $C_{16}H_{23}O$ 231.17489, found 231.1749.

***(2R*,3R*)*-2-Methyl-2-(4-methylpent-3-enyl)chroman-3-ol *cis*-11.** Prepared from (*Z*)-**10** following the procedure described for **7** and **8**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27 (s, 3H), 1.58 (s, 3H), 1.66 (s, 3H), 1.66−1.82 (m, 2H), 2.09−2.17 (m, 2H), 2.78 (dd, *J* = 4.8 and 17.0, 1H), 3.05 (dd, *J* = 4.8 and 17.0, 1H), 3.86 (t, *J* = 4.8, 1H), 5.14 (tt, *J* = 1.4 and 7.1, 1H), 6.83 (d, *J* = 8.1, 1H), 6.88 (dd, *J* = 1.1 and 7.4, 1H), 7.06 (d, *J* = 7.5, 1H), 7.11 (dt, *J* = 1.5 and 7.4, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.6, 21.3, 21.8, 25.6, 31.0, 34.7, 68.5, 78.4, 117.3, 119.0, 120.5, 124.1, 127.6, 130.1, 131.8, 152.6; HRMS (ESI) $[M + Na]^+$ calcd for $C_{16}H_{22}O_2Na$ 269.15175, found 269.1516.

***(2R*,3S*)*-2-Methyl-2-(4-methylpent-3-enyl)chroman-3-yl 4-iodobenzoate 12.** To a solution of *trans*-**11** (92 mg, 0.37 mmol, 1.0 equiv) in dry dichloromethane (2 mL) were added *p*-iodobenzoic acid (102 mg, 0.41 mmol, 1.1 equiv), DCC (99 mg, 0.48 mmol, 1.3 equiv) and DMAP (5 mg, 0.04 mmol, 0.1 equiv), and the solution was stirred at room temperature for 20 h. Then, the reaction mixture was filtered to remove DCU, and the filtrate was concentrated under reduce pressure. The residue was purified on preparative TLC using EP/Et_2O 9/1 as eluent affording **12** as a pale yellow solid (120 mg, 68%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38 (s, 3H), 1.55 (s, 3H), 1.68 (s, 3H), 1.67−1.75 (m, 2H), 2.16 (m, 2H), 2.91 (dd, *J* = 5.6 and 17.2, 1H), 3.25 (dd, *J* = 5.1 and 17.2, 1H), 5.05 (t, *J* = 6.9, 1H), 5.32 (t, *J* = 5.4, 2H), 6.88 (m, 2H), 7.04 (d, *J* = 7.0, 1H), 7.14 (t, *J* = 7.0, 1H), 7.70 (d, *J* = 8.5, 2H), 7.80 (d, *J* = 8.4, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.5, 20.1, 21.6, 25.6, 28.2, 37.2, 70.8, 101.0, 117.2, 118.3, 120.5, 123.6, 127.7, 129.4, 129.5, 131.1, 132.1, 137.8, 152.7, 165.4; HRMS (ESI) $[M + Na]^+$ calcd for $C_{23}H_{25}O_3INa$ 499.0746, found 499.0744.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H, ^{13}C NMR spectra of all compounds, X-ray (CIF) and HPLC analysis. 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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■ REFERENCES

(1) (a) Hoffmann, R. W. *Angew. Chem., Int. Ed.* **2013**, *52*, 123−130. (b) Nicolaou, K. C.; Snyder, S. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1012−1044.

(2) (a) Nozawa, Y.; Yamamoto, K.; Ito, M.; Sakai, N.; Mizoue, K.; Mizobe, F.; Hanada, K. *J. Antibiot.* **1997**, *50*, 635−640. (b) Nozawa, Y.; Ito, M.; Sugawara, K.; Hanada, K.; Mizoue, K. *J. Antibiot.* **1997**, *50*, 641−645.

(3) (a) Wilson, R. M.; Danishefsky, S. J. *Acc. Chem. Res.* **2006**, *39*, 539−549. (b) Joyner, P. M.; Cichewicz, R. H. *Nat. Prod. Rep.* **2011**, *28*, 26−47. (c) Williams, P.; Sorribas, A.; Howes, M.-J. R. *Nat. Prod. Rep.* **2011**, *28*, 48−77.

(4) There is a strong debate over the relative configuration of the stereogenic centers in the literature. Recently, Argade and co-workers reported the synthesis of racemic NG-121, a natural compound also isolated from *Stachybotrys parvispora* whose strucure is similar to

stachybrotrin C and for which the relative configuration is trans and not cis as claimed by Hanada et al. See: Singh, M.; Argade, N. P. *Synthesis* **2012**, *44*, 3797−3804.
(5) (a) Inoue, S.; Kim, R.; Hoshino, Y.; Honda, K. *Chem. Commun.* **2006**, 1974−1975. (b) Tumma, N.; Jacolot, M.; Jean, M.; Chandrasekhar, S.; van de Weghe, P. *Synlett* **2012**, 2919−2922.
(6) Hoarau, C.; Pettus, T. R. R. *Synlett* **2003**, 127−137.
(7) Lattanzi, A.; Scettri, A. *Synlett* **2002**, 942−946.
(8) (a) Chang, A. O.; Sharpless, K. B. *J. Org. Chem.* **1977**, *42*, 1587−1590. (b) Mihelich, E. D.; Daniels, K.; Eickhoff, D. J. *J. Am. Chem. Soc.* **1981**, *103*, 7690−7692.
(9) (a) Yamada, S.; Ono, F.; Katagiri, T.; Tanaka, J. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 750. (b) Sakakura, A.; Sakuma, M.; Ishihara, K. *Org. Lett.* **2011**, *13*, 3130−3133.
(10) (a) Bigi, F.; Casiraghi, G.; Sartori, G. *Synthesis* **1981**, 310−312. (b) Chukicheva, I. Y.; Fedoriva, I. V.; Koroleva, A. A.; Kuchin, A. V. *Chem. Nat. Prod.* **2012**, *48*, 535−540.
(11) See the Supporting Information.
(12) (a) Trost, B. M.; Belletire, J. M.; Godleski, S.; McDougal, P.; Balkovec, J. *J. Org. Chem.* **1986**, *51*, 2370−2374. (b) Trost, B. M.; Bunt, R. C.; Pullay, S. R. *J. Org. Chem.* **1994**, *59*, 4202−4205.
(13) Snyder, S. A.; Treitler, D. S.; Brucks, A. P. *J. Am. Chem. Soc.* **2010**, *132*, 14303−14314.