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Synthesis of tryptophan derivatives via a palladium-catalyzed N-heteroannulation

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ABSTRACT

Tryptophan derivatives were prepared from 2-(2-nitrophenyl)-2-propen-1-yl substituted pyrazines, derived from Schöllkopf's chiral auxiliary, using a palladium-catalyzed, carbon monoxide-mediated reductive N-heteroannulation reaction. A diastereomeric ratio of products ranging from 4:1 to >30:1 was observed.

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1. Introduction

Tryptophan derivatives are important building blocks for the synthesis of more complex indole alkaloids. Among several other methods, tryptophan and a variety of functionalized tryptophan derivatives can be prepared using two general strategies employing Schöllkopf's chiral auxiliary. Based on Larock's¹ palladium-catalyzed heteroannulation of alkynes and 2-halo-1-benzeneamines to afford indoles, Cook et al. developed a methodology using 1^2 for the preparation of both D- and L- tryptophan derivatives (Scheme 1).³ Very high enantioselectivities (>99:1) have been observed. Cook et al. have extensively used this reaction in the total synthesis of mitragynine, 9-methoxygeissoschizol, 9-methoxy-Nb-methylgeissoschizol,⁴ (+)-12-methoxy-Na-methylvellosimine, (+)-12-methoxyaffinisine, and (-)-fuchsiaefoline.⁵ The chiral auxiliary is readily removed by treatment with HCl to give the corre-

sponding tryptophan ester (Scheme 1). A drawback to this methodology is the formation of regioisomers in some cases.

The second use of Schöllkopf's chiral auxiliary in tryptophan synthesis is the alkylation of the chiral 2,5-dihydro-3,6-dialkoxy-5-(1-methylethyl)pyrazines with either 3-bromomethyl⁶- or 3-N,N-dimethylaminomethyl⁷-indoles (Scheme 2). These reactions afford tryptophan derivatives in high yields and diastereomeric ratios (\geq 30:1). Potential drawbacks to this route are the availability of substituted indole electrophiles and the need to protect the indole nitrogen.

We and others have developed a facile palladium-catalyzed, carbon monoxide-mediated reductive N-heteroannulation of 1-(2-nitrophenyl)-1-alkenes affording indole derivatives.⁸ Based on this methodology, a novel and expedient route to optically active tryptophan derivatives was envisioned using a building block also derived from Schöllkopf's chiral auxiliary. The goal was to develop



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Scheme 1.







a short reaction sequence that would be useful for the preparation of novel amino acids related to tryptophan having either a D- or L- configuration. Herein we report the results of this study.

2. Results and discussion

Kosugi-Migita-Stille cross-coupling of 2-nitrophenyltributyltin **2** with (2S,5R)-2,5-dihydro-3,6-dimethoxy-2-(2-bromo-2-propenyl)-5-(1-methylethyl)pyrazine **3**⁹ was initially examined. The reaction of **3** using bis(acetonitrile)palladium dichloride (5 mol %), triphenylarsine (10 mol %), and copper iodide (10 mol %) in *N*-methylpyrrolidone at 80 °C gave the expected product **4** (Scheme 3). However, an unacceptable amount of isomerization (4:1–10:1) of one of the chiral centers was observed. The mechanism for the isomerization is unclear. However, the isomerization appears to be thermally induced since heating a sample of pure **4** in DMF at 120 °C for 12 h resulted in a 5:1 diastereomeric mixture. Although poor selectivity was obtained in some coupling reactions of **2** and **3**, the isomeric mixture was subjected to the previously reported reductive N-heteroannulation conditions in order to establish if the sequence was viable. Thus, compound **4** was treated with bis(dibenzylidenacetone)palladium, 1,10-phenanthroline, and 1,3-bis(diphenylphosphino)propane under 6 atm of carbon monoxide in DMF at 120 °C. The expected tryptophan derivative **5** was isolated without any additional deterioration of the isomer ratio (Scheme 3). It should be noted that the reaction of **4** using our original, simpler, palladium diacetatetriphenylphosphine catalyst system did not affect cyclization.¹⁰

In order to improve the isomer ratio of **4**, we next turned our attention to a catalyst system consisting of bis(dibenzylidene)palladium (5 mol %), triphenylphosphine (20 mol %), and copper iodide (75 mol %) in DMF at *ambient temperature*.¹¹ These conditions gave a higher yield of **4** (64%) and only one diastereomer was observed in the crude ¹H NMR spectrum.

Reversing the polarity of the Kosugi–Migita–Stille cross-coupling partners was next examined. The goal was to develop a more flexible coupling partner to be used with an array of aromatic halides. The bromine of the chiral auxiliary *ent*- 3^{12} was transformed into a trimethyltin group using hexamethylditin in the presence of a palladium catalyst (Scheme 4). Note that the enantio-



mer of **3** (compared to Scheme 3) was used in all the reactions discussed below. Coupling of **6** with 2-nitro-1-iodobenzene gave *ent*-**4** in a 15:1 diastereomeric ratio.

A number of annulation precursors were prepared via coupling of **6** with halonitroarenes using the $Pd(dba)_2$ -PPh₃-CuI conditions. The results of these reactions are summarized in Table 1. In contrast to the reaction described in Scheme 3, no epimerization was apparent in any of the coupling reactions (entries 2-11). Thus, methoxy-, fluoro-, carbomethoxy-, and nitro-functionalized substrates, in addition to a pyridine derivative, were obtained in 58-82% yield (entries 1-7). We were unable to couple either 3-methoxy-2-nitro-1-iodobenzene or 6-methoxy-2-nitro-1-iodobenzene with 6. Only the homo-coupling product 7 and recovered aryl iodide were isolated from the reaction mixtures (Scheme 5).¹³ The iodides were transformed instead into the corresponding tin compounds **14**¹⁴ and **15** using a related procedure as for the preparation of 6 (Scheme 4). Kosugi–Migita–Stille cross-coupling of 14 and 15 with alkenylbromide ent-3 gave the expected products 16 and 17 (entries 8 and 9).

In addition to the tryptophan precursors, homotryptophan and isotryptophan precursors **20** and **21** were prepared by the stereoselective alkylation of Schöllkof's chiral auxilliary with 2-bromo-4-iodo-1-butene and 1,3-dibromo-1-propene to give **18** and **19**, respectively (Scheme 6). The alkylation products were subsequently coupled with **2** to give **20** and **21** (Table 1, entries 10 and 11).

With a selection of substrates having both electron-withdrawing and electron-donating substituents on the aromatic ring in hand 8-13, 16-17, 20-21 (Table 1), the palladium-catalyzed Nheteroannulation was next examined. The starting material was completely consumed in all cases. Depending on the functional group on the aromatic ring, a varying degree of isomerization was observed for most substrates. The isopropyl groups of the major and minor isomers were readily distinguished by ¹H NMR. A characteristic of the minor cis-isomers is the significant upfield shift of the isopropyl methyl group resonances. One methyl group resonates between 0.02 and 0.38 ppm while the other between 0.81 and 0.94 ppm in the ¹H NMR spectra. The corresponding methyl resonances for the major trans-isomers were observed at 0.61–0.66 and 0.91–1.00 ppm, respectively. This upfield shift can be explained by a conformation wherein the isopropyl group is shielded by the aromatic ring of the indole nucleus.^{15,16}

(78-88%) and diastereomeric Good vields ratios $(dr = 12:1 \rightarrow 30:1)$ were observed for three of the four possible methoxy-substituted substrates (entries 2, 3 and 8). In contrast, the more hindered compound 17 gave 29 with both a lower yield (47%) and lower diastereomeric ratio (dr = 6:1, entry 9). The isomerization may occur before cyclization to give the indole. However, isomerization was also observed by simply heating a sample of 23 (dr = 22:1) in DMF at 120 °C for 16 h resulting in a 7:1 diastereomeric mixture. Electron-withdrawing groups (-F, -CO₂Me, and -NO₂) were also tolerated and gave the expected products (entries 4-6). However, the fluoro-substituted compound 10 gave 24 with a significant amount of isomerization (dr = 4.5:1) although the reaction proceeded in excellent yield. A very low yield of product was obtained from cyclization of the nitro-substituted compound 12. The starting material was completely consumed in the reaction; however, no additional product was isolated.

Pyridine-derived substrate **13** smoothly gave aza-tryptophan derivative **27** (entry 7). The homotryptophan derivative **30**, the one-carbon homolog of ent-**5**, was obtained from **20** in good yield with a 15:1 diastereomeric ratio (entry 10). Finally, annulation of **21** gave the isotryptophan derivative **31** in low yield with almost complete isomerization (entry 11). In addition, an incomplete reduction forming an *N*-hydroxyindole **32** was also observed as a minor product.¹⁷ Considering the high degree of isomerization

for the indole product, the diastereoselectivity for hydroxyindole **32** was surprisingly high >30:1.

3. Conclusion

In summary, we have developed a novel route to tryptophan derivatives using two sequential palladium-catalyzed reactions, a Kosugi–Migita–Stille cross-coupling and a carbon monoxide-mediated reductive N-heteroannulation. This reaction sequence may be useful for the preparation of novel amino acids related to tryptophan having either D- or L-configuration.

4. Experimental

4.1. General procedures

NMR spectra were determined in CDCl₃ at 600 MHz (¹H NMR) or 150 MHz (¹³C NMR). The chemical shifts are expressed in δ values relative to Me₄Si (0.0 ppm, ¹H and ¹³C) or CDCl₃ (77.0 ppm, ¹³C) internal standards.

Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl prior to use. Hexanes and ethyl acetate were distilled from calcium hydride. Chemicals prepared according to the literature procedures have been footnoted as first time used; anhydrous benzene, DMF, NMP, and toluene and all other reagents were obtained from commercial sources and used as received. All reactions were performed under a nitrogen atmosphere in oven-dried glassware unless stated otherwise. Solvents were removed from reaction mixtures and products extracted on a rotary evaporator at water aspirator pressure. Chromatography was performed on Silica Gel 60 (40–63 μ m, EMD).

4.1.1. (2*R*,5*S*)-2,5-Dihydro-3,6-dimethoxy-5-(1-methylethyl)-2-(2-trimethylstannyl-2-propen-1-yl)pyrazine 6

To a solution of (2R,5S)-2-(2-bromo-2-propen-1-yl)-2,5-dihydro-5-(1-methylethyl)-3,6-dimethoxypyrazine ent-**3**^{12b} (1.00 g, 3.30 mmol) in benzene (25 mL) at ambient temperature and under an atmosphere of nitrogen were added diisopropylethylamine (85 mg, 0.66 mmol) and hexamethylditin (2.16 g, 6.60 mmol), followed by bis(dibenzylideneacetone)palladium (Pd(dba)₂) (95 mg, 0.16 mmol) and triphenylphosphine (PPh₃) (173 mg, 0.66 mmol). The solution was heated for 24 h at 80 °C. The reaction mixture was quenched by the addition of CuSO₄ (satd-aqueous, 150 mL). The reaction mixture was extracted with hexane $(3 \times 100 \text{ mL})$ and the combined organic layers were washed with brine (100 mL). The combined organic phases were dried over MgSO₄, filtered through Celite, and the solvents were removed under reduced pressure. The resulting residue was purified by chromatography (hexanes/EtOAc, 99:1) to afford 6 (1.01 g, 2.61 mmol, 80%) as a colorless oil. ¹H NMR δ 0.13 (s, 9H), 0.67 (d, J = 6.6 Hz, 3H), 1.03 (d, J = 6.6 Hz, 3H), 2.26 (dsept, J = 7.2, 3.6 Hz, 1H), 2.59 (dd, J = 13.2, 7.2 Hz, 1H), 2.83 (dd, J = 13.2, 7.2 Hz, 1H), 3.66 (s, 3H), 3.68 (s, 3H), 3.89 (t, J = 3.6 Hz, 1H), 4.05 (pent, J = 3.6 Hz, 1H), 5.25 (d, J = 3.0 Hz, 1H), 5.72 (d, J = 3.0 Hz, 1H); ^{13}C NMR δ -8.8, 16.6, 19.1, 31.7, 44.3, 52.2, 52.4, 56.4, 60.7, 128.4, 151.7, 163.5, 163.7; IR (neat) 1220, 1692 cm $^{-1}; \ [\alpha]_D^{25} = -12.0$ (c 1.2, CH₂Cl₂); HRMS (ESI) calcd for C₁₅H₂₉N₂O₂Sn (M+H⁺) 389.1251, found 389.1246.

4.1.2. (2*R*,5*S*)-2,5-Dihydro-3,6-dimethoxy-5-(1-methylethyl)-2-(2-(2-nitrophenyl)-2-propen-1-yl)pyrazine *ent*-4

To a solution of **6** (400 mg, 1.03 mmol) in DMF (10 mL) were added 2-nitro-1-iodobenzene (214 mg, 0.861 mmol), $Pd(dba)_2$ (25 mg, 0.043 mmol), and PPh_3 (45 mg, 0.17 mmol). Next Cul (123 mg, 0.646 mmol) was added in one portion and the reaction

Table 1

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^a Yield of isolated product and diastereomeric ratio in parentheses.

^b The corresponding bromide was used.

^c Prepared from the corresponding 1-iodo-compound and Me₆Sn₂.

mixture was stirred at ambient temperature for 26 h. The mixture was diluted with Et_2O (50 mL), washed with 10% aqueous NH_4OH

 $(3\times 50$ mL), H_2O (50 mL), and brine (50 mL). The organic phase was dried over MgSO_4, filtered, and the solvents were removed



under reduced pressure. The resulting oil was purified by chromatography (hexanes/EtOAc, 97:3) to afford *ent-4* [(2*R*,5*S*)/(2*S*,5*S*) = 15:1, 173 mg, 0.500 mmol, 58%] as a yellow oil. ¹H NMR δ 0.61 (d, *J* = 6.6 Hz, 3H), 0.97 (d, *J* = 6.6 Hz, 3H), 2.15 (dsept, *J* = 6.6, 3.6 Hz, 1H), 2.84 (dd, *J* = 13.8, 6.0 Hz, 1H), 2.92 (dd, *J* = 13.8, 6.0 Hz, 1H), 3.39 (s, 3H), 3.50 (s, 3H), 3.77 (t, *J* = 3.6 Hz, 1H), 4.06 (q, *J* = 6.0 Hz, 1H), 5.11 (s, 1H), 5.26 (s, 1H), 7.22 (d, *J* = 7.2 Hz, 1H), 7.36 (t, *J* = 7.8 Hz, 1H), 7.48 (t, *J* = 7.2 Hz, 1H), 7.90 (d, *J* = 8.4 Hz, 1H); ¹³C NMR δ 16.6, 18.9, 31.9, 40.4, 51.9, 52.1, 55.1, 60.9, 118.6, 124.0, 127.8, 131.9, 132.6, 138.7, 144.2, 147.9, 162.5, 163.2; IR (neat) 1233, 1242, 1350, 1515, 1693 cm⁻¹; $[\alpha]_{25}^{25} = -21.8$ (*c* 1.2, CH₂Cl₂); HRMS (ESI) calcd for C₁₈H₂₄N₃O₄ (M+H⁺) 346.1767, found 346.1761.

4.1.3. Alternative method. (2*S*,5*R*)-2,5-Dihydro-3,6-dimethoxy-5-(1-methylethyl)-2-(2-(2-nitrophenyl)-2-propen-1-yl)pyrazine 4

To a solution of (2S,5R)-2-(2-bromo-2-propen-1-yl))-2,5-dihydro-5-(1-methylethyl)-3,6-dimethoxypyrazine **3** (310 mg, 1.02 mmol) in N-methylpyrrolidone (3 mL) were added tributyl-(2-nitrophenyl)stannane (506 mg, 1.23 mmol), PdCl₂(PhCN)₂ (20 mg, 0.051 mmol), and AsPh₃ (31 mg, 0.10 mmol). Next CuI (19 mg, 0.10 mmol) was added and the reaction mixture was stirred at 80 °C for 3 days. The mixture was diluted with EtOAc (20 mL), washed with 10% aqueous NH₄OH (3 \times 20 mL), H₂O (20 mL), and brine (20 mL). The organic phase was dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. The resulting oil was purified by chromatography (hexanes/EtOAc, 95:5) to afford **4** [(2*S*,5*R*/2*R*,5*R*) = 10:1, 162 mg, 0.469 mmol, 46%] as a yellow oil. ¹H NMR (partial data minor isomer) δ 0.72 (d, I = 6.9 Hz, 3H), 1.04 (d, I = 6.9 Hz, 3H), 3.10 (dd, *I* = 14.4, 4.9 Hz, 2H), 3.50 (s, 3H), 3.62 (s, 3H), 5.10 (s, 1H), 5.30 (s, 1H).

4.1.4. (2R,5S)-2,5-Dihydro-2-(2-(4-methoxy-2-nitrophenyl)-2-propen-1-yl)-5-(1-methylethyl)-3,6-dimethoxy-pyrazine 8

Reaction of 1-iodo-4-methoxy-2-nitrobenzene (240 mg, 0.861 mmol) with **6** (400 mg, 1.03 mmol) in the presence of Pd(dba)₂ (25 mg, 0.043 mmol), PPh₃ (45 mg, 0.17 mmol), and CuI (123 mg, 0.646 mmol) in DMF (10 mL), as described for *ent*-**4**

(51 h), gave after extraction and chromatography (hexanes/EtOAc, 95:5) **8** (221 mg, 0.589 mmol, 68%) as a yellow oil. ¹H NMR δ 0.62 (d, *J* = 7.2 Hz, 3H), 0.97 (d, *J* = 7.2 Hz, 3H), 2.16 (dsept, *J* = 7.2, 3.6 Hz, 1H), 2.80 (dd, *J* = 13.8, 6.0 Hz, 1H), 3.45 (s, 3H), 3.52 (s, 3H), 3.78 (t, *J* = 3.6 Hz, 1H), 3.85 (s, 3H), 4.04 (dt, *J* = 4.2, 2.4 Hz, 1H), 5.06 (d, *J* = 1.2 Hz, 1H), 5.21 (s, 1H), 7.03 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.13 (d, *J* = 8.4 Hz, 1H), 7.42 (d, *J* = 3.0 Hz, 1H); ¹³C NMR δ 16.6, 18.9, 31.9, 40.5, 52.0, 52.1, 55.0, 55.8, 60.8, 108.7, 118.1, 119.1, 131.0, 132.8, 143.9, 148.2, 158.9, 162.6, 163.1; IR (neat) 1220, 1528, 1692 cm⁻¹; $[\alpha]_D^{25} = -20.2$ (*c* 1.0, CH₂Cl₂); HRMS (ESI) calcd for C₁₉H₂₆N₃O₅ (M+H⁺) 376.1873, found 376.1867.

4.1.5. (2*R*,5*S*)-2,5-Dihydro-3,6-dimethoxy-2-(2-(5-methoxy-2nitrophenyl)-2-propen-1-yl)-5-(1-methylethyl)pyrazine 9

Reaction of 3-iodo-4-nitro-1-methoxybenzene (240 mg 0.861 mmol) with 6 (400 mg, 1.03 mmol) in the presence of Pd(dba)₂ (25 mg, 0.043 mmol), PPh₃ (45 mg, 0.17 mmol), and CuI (123 mg, 0.646 mmol) in DMF (10 mL), as described for ent-4 (43 h), gave after extraction and chromatography (hexanes/EtOAc, 95:5) **9** (224 mg, 0.597 mmol, 69%) as a yellow oil. ¹H NMR δ 0.63 (d, J = 6.6 Hz, 3H), 0.98 (d, J = 6.6 Hz, 3H), 2.18 (dsept, J = 6.6, 3.0 Hz, 1H), 2.86 (dd, J = 14.4, 6.0 Hz, 1H), 2.94 (dd, J = 14.4, 6.0 Hz, 1H), 3.45 (s, 3H), 3.52 (s, 3H), 3.79 (t, J = 3.6 Hz, 1H), 3.86 (s, 3H), 4.06 (dt, J = 4.2, 1.8 Hz, 1H), 5.09 (d, J = 1.8 Hz, 1H), 5.23 (d, J = 1.8 Hz, 1H), 6.65 (d, J = 3.0 Hz, 1H), 6.84 (dd, J = 9.6, 3.0 Hz, 1H), 8.02 (d, J = 9.6 Hz, 1H); ¹³C NMR δ 16.5, 18.8, 31.7, 40.3, 51.9, 52.0, 55.0, 55.7, 60.8, 112.9, 116.7, 117.5, 126.8, 140.6, 141.6, 145.2, 162.5, 162.7, 163.0; IR (neat) 1230, 1336, 1513, 1693 cm⁻¹; $[\alpha]_{D}^{25} = -17.5$ (c 1.2, CH₂Cl₂); HRMS (ESI) calcd for C₁₉H₂₆N₃O₅ (M+H⁺) 376.1873, found 376.1867.

4.1.6. (2R,5S)-2,5-Dihydro-3,6-dimethoxy-2-(2-(4-fluoro-2nitrophenyl)-2-propen-1-yl)-5-(1-methylethyl)pyrazine 10

Reaction of 4-fluoro-1-iodo-2-nitrobenzene (230 mg, 0.861 mmol) with **6** (400 mg, 1.03 mmol) in the presence of Pd(PPh₃)₂Cl₂ (30 mg, 0.043 mmol), PPh₃ (23 mg, 0.86 mmol), and Cul (123 mg, 0.646 mmol) in DMF (10 mL), as described for *ent*-**4** (72 h), gave after extraction and chromatography (hexanes: EtOAc, 95:5) **10** (191 mg, 0.526 mmol, 61%) as a yellow oil. ¹H NMR δ 0.62

(d, *J* = 6.6 Hz, 3H), 0.98 (d, *J* = 6.6 Hz, 3H), 2.17 (dsept, *J* = 6.6, 3.0 Hz, 1H), 2.81 (dd, *J* = 14.4, 6.0 Hz, 1H), 2.91 (dd, *J* = 14.4, 6.0 Hz, 1H), 3.44 (s, 3H), 3.52 (s, 3H), 3.79 (t, *J* = 4.2 Hz, 1H), 4.04 (dt, *J* = 4.2, 2.4 Hz, 1H), 5.09 (d, *J* = 1.8 Hz, 1H), 5.27 (d, *J* = 1.8 Hz, 1H), 7.21 (d, *J* = 2.4 Hz, 1H), 7.23 (d, *J* = 1.8 Hz, 1H), 7.64 (ddd, *J* = 8.4, 1.8, 0.6 Hz, 1H); ¹³C NMR δ 16.6, 18.9, 31.9, 40.4, 52.0, 52.1, 55.0, 60.9, 111.6 (d, *J* = 26.3 Hz), 119.0, 119.8 (d, *J* = 20.7 Hz), 133.5 (d, *J* = 7.1 Hz), 134.8 (d, *J* = 3.9 Hz), 143.3, 148.0 (d, *J* = 7.8 Hz), 161.0 (d, *J* = 249.3 Hz), 162.5, 163.3; IR (neat) 808, 1219, 1234, 1245, 1347, 1550, 1692 cm⁻¹; $[\alpha]_D^{25} = -26.5$ (*c* 1.4, CH₂Cl₂); HRMS (ESI) calcd for C₁₈H₂₃FN₃O₄ (M+H⁺) 364.1673, found 364.1667.

4.1.7. Methyl 4-(1-((2R,5S)-2,5-dihydro-5-(1-methylethyl)-3,6dimethoxypyrazin-2-yl)prop-2-en-1-yl)-3-nitrobenzoate 11

Reaction of methyl 4-iodo-3-nitrobenzoate (263 mg, 0.861 mmol) with 6 (400 mg, 1.03 mmol) in the presence of Pd(dba)₂ (25 mg, 0.043 mmol), PPh₃ (45 mg, 0.17 mmol), and CuI (123 mg, 0.646 mmol) in DMF (10 mL), as described for ent-4 (72 h), gave after extraction and chromatography (hexanes/EtOAc, 97:3) **11** (215 mg, 0.533 mmol, 62%) as a yellow oil. ¹H NMR δ 0.62 (d, J = 6.6 Hz, 3H), 0.97 (d, J = 6.6 Hz, 3H), 2.16 (dsept, J = 6.6, 3.0 Hz, 1H), 2.85 (dd, / = 13.8, 6.0 Hz, 1H), 2.95 (dd, / = 13.8, 6.0 Hz, 1H), 3.38 (s, 3H), 3.51 (s, 3H), 3.79 (t, J = 3.6 Hz, 1H), 3.96 (s, 3H), 4.06 (dt, J = 4.2, 2.4 Hz, 1H), 5.17 (s, 1H), 5.34 (s, 1H), 7.33 (d, J = 7.8 Hz, 1H), 8.13 (d, J = 7.8 Hz, 1H), 8.54 (s, 1H); ¹³C NMR δ 16.6, 18.9, 31.9, 40.2, 52.0, 52.1, 52.6, 55.0, 60.9, 119.6, 125.2, 130.0, 132.2, 133.0, 142.9, 143.5, 147.9, 162.4, 163.4, 164.9; IR (neat) 1113, 1240, 1283, 1532, 1692, 1729 cm $^{-1}; \ [\alpha]_D^{25} = -8.1$ (c 1.0, CH₂Cl₂); HRMS (ESI) calcd for C₂₀H₂₆N₃O₆ (M+H⁺) 404.1822, found 404.1816.

4.1.8. (2*R*,5*S*)-2,5-Dihydro-3,6-dimethoxy-2-(2-(2,4-dinitrophenyl)-2-propen-1-yl)-5-(1-methylethyl)pyrazine 12

Reaction of 1-bromo-2,4-dinitrobenzene (213 mg, 0.861 mmol) with **6** (400 mg, 1.03 mmol) in the presence of Pd(dba)₂ (25 mg, 0.043 mmol), PPh₃ (45 mg, 0.17 mmol), and CuI (123 mg, 0.646 mmol) in DMF (10 mL), as described for *ent*-**4** (72 h), gave after extraction and chromatography (hexanes/EtOAc, 95:5) **12** (276 mg, 0.707 mmol, 82%) as a yellow oil. ¹H NMR δ 0.62 (d, *J* = 7.2 Hz, 3H), 0.98 (d, *J* = 7.2 Hz, 3H), 2.16 (dsept, *J* = 6.6, 3.0 Hz, 1H), 2.84 (dd, *J* = 14.4, 6.0 Hz, 1H), 2.98 (dd, *J* = 14.4, 6.0 Hz, 1H), 3.9 (s, 3H), 3.54 (s, 3H), 3.80 (t, *J* = 4.2 Hz, 1H), 4.05 (dt, *J* = 4.2, 2.4 Hz, 1H), 5.21 (s, 1H), 5.41 (s, 1H), 7.48 (d, *J* = 8.4 Hz, 1H), 8.34 (dd, *J* = 8.4 Hz, 2.4, 1H), 8.75 (d, *J* = 2.4 Hz, 1H); ¹³C NMR δ 16.6, 18.9, 32.0, 40.3, 52.1, 52.2, 55.0, 61.0, 119.6, 120.6, 126.5, 133.2, 142.7, 144.9, 146.7, 147.8, 162.3, 163.7; IR (neat) 1237, 1350, 1529, 1691 cm⁻¹; $[\alpha]_D^{25} = -4.3$ (*c* 1.1, CH₂Cl₂); HRMS (ESI) calcd for C₁₈H₂₃N₄O₆ (M+H⁺) 391.1618, found 391.1612.

4.1.9. (2*R*,5*S*)-2,5-Dihydro-3,6-dimethoxy-2-(2-(3-nitropyridin-2-yl)prop-2-en-1-yl)-5-(1-methylethyl)pyrazine 13

Reaction of 2-chloro-3-nitropyridine (136 mg, 0.861 mmol) with **6** (400 mg, 1.03 mmol) in the presence of Pd(dba)₂ (25 mg, 0.043 mmol), PPh₃ (45 mg, 0.17 mmol), and CuI (123 mg, 0.646 mmol) in DMF (10 mL), as described for *ent*-**4** (24 h), gave after extraction and chromatography (EtOAc) **13** (180 mg, 0.520 mmol, 60%) as an orange oil. ¹H NMR δ 0.63(d, *J* = 7.2 Hz, 3H), 0.99 (d, *J* = 7.2 Hz, 3H), 2.16 (dsept, *J* = 6.6, 3.0 Hz, 1H), 2.97 (dd, *J* = 13.8, 6.0 Hz, 1H), 3.17 (dd, *J* = 13.8, 6.0 Hz, 1H), 3.23 (s, 3H), 3.58 (s, 3H), 3.92 (t, *J* = 3.6 Hz, 1H), 4.19 (dt, *J* = 4.2, 2.4 Hz, 1H), 5.37 (s, 1H), 5.45 (s, 1H), 7.32 (dd, *J* = 8.4, 4.8 Hz, 1H), 8.06 (d, *J* = 8.4 Hz, 1H), 8.73 (dd, *J* = 4.8, 1.2 Hz, 1H); ¹³C NMR δ 16.7, 18.9, 31.8, 39.3, 51.6, 52.1, 55.5, 60.9, 121.3, 121.9, 131.7, 142.7, 145.3, 151.6, 155.0, 162.2, 163.7; IR (neat) 732, 785, 1225, 1354, 1527, 1683 cm⁻¹; $[\alpha]_D^{25} = +4.8$ (*c* 1.0, CH₂Cl₂); HRMS (ESI) calcd for C₁₇H₂₃N₄O₄ (M+H⁺) 347.1719, found 347.1714.

4.1.10. Bis-2,3-((2*R*,5*S*)-2,5-dihydro-3,6-dimethoxy-5-methylethyl-2-pyrazinylmethyl)-1,4-butadiene 7^{12b}

To a solution of 6 (370 mg, 0.956 mmol) in DMF (10 mL) was added 1-iodo-3-methoxy-2-nitrobenzene (133 mg, 0.478 mmol), Pd(dba)₂ (14 mg, 0.024 mmol), PPh₃ (25 mg, 0.096 mmol) and CuI (68 mg, 0.36 mmol). The reaction was stirred at ambient temperature for 48 h. Next Et₂O (30 mL) was added and the organic phase was washed with NH₄OH (10%, aq, 3×30 mL), H₂O (30 mL), and brine (30 mL). The organic phase was dried over MgSO₄, filtered, and the solvent was removed under reduced pressure. The resulting oil was purified by chromatography (hexanes/EtOAc, 95:5) to afford **7** (47 mg, 0.10 mmol, 22%) as a yellow oil. ¹H NMR δ 0.65 (d, *J* = 6.6 Hz, 6H), 1.02 (d, *J* = 6.6 Hz, 6H), 2.23 (dsept, *J* = 7.2, 3.6 Hz, 2H), 2.46 (dd, J = 13.8, 7.2 Hz, 2H), 2.93 (dd, J = 13.8, 4.2 Hz, 2H), 3.62 (s, 6H), 3.66 (s, 6H), 3.83 (t, J = 3.6 Hz, 2H), 4.15 (pent, J = 3.6 Hz, 2H), 4.85 (s, 2H), 5.13 (d, J = 1.8 Hz, 2H); ¹³C NMR & 16.5, 19.1, 31.4, 39.0, 52.0, 52.2, 55.3, 60.6, 115.1, 145.1, 163.0, 163.2; IR (neat) 1011, 1194, 1232, 1693 cm⁻¹; $[\alpha]_{D}^{25} = -50.8$ (c 1.2, CH₂Cl₂); HRMS (ESI) calcd for C₂₄H₃₉N₄O₄ (M+H⁺) 447.2971, found 447.2966.

4.1.11. (3-Methoxy-2-nitrophenyl)trimethylstannane 15

To a solution of 1-iodo-3-methoxy-2-nitrobenzene (1.57 g, 5.63 mmol) in toluene (25 mL) were added hexamethylditin (2.03 g, 6.19 mmol), Pd(PPh₃)₂Cl₂ (39 mg, 0.056 mmol), and PPh₃ (30 mg, 0.11 mmol). The reaction mixture was heated at 80 °C and stirred for 4 days. It was then diluted with EtOAc (50 mL) and washed with 10% aqueous NH₄OH (3 × 50 mL), H₂O (50 mL), and brine (50 mL). The organic phase was dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. The resulting oil was purified by chromatography (hexanes) to afford **15** (1.02 g, 3.23 mmol, 57%) as a yellow oil.¹⁸ ¹H NMR δ 0.33 (s, 9H), 3.92 (s, 3H), 7.03 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.11 (dd, *J* = 7.2, 1.2 Hz, 1H), 7.43-7.47 (m, 1H); ¹³C NMR δ –8.3, 56.3, 113.4, 127.8, 132.4, 139.9, 146.2, 152.4; IR (neat) 775, 1269, 1519 cm⁻¹.

4.1.12. (2R,5S)-2,5-Dihydro-3,6-dimethoxy-2-(2-(2-methoxy-6-nitrophenyl)prop-2-en-1-yl)-5-(1-methylethyl)pyrazine 16

Reaction of (6-methoxy-2-nitrophenyl)trimethylstannane 14^{8c} (470 mg, 1.49 mmol) with ent-3 (225 mg, 0.744 mmol) in the presence of Pd(dba)₂ (21 mg, 0.037 mmol), PPh₃ (39 mg, 0.15 mmol), and CuI (106 mg, 0.558 mmol) in DMF (10 mL), as described for ent-4 (36 h), gave after extraction and chromatography (hexanes/ EtOAc, 95:5) **16** (151 mg, 0.402 mmol, 54%) as a yellow oil. ¹H NMR δ 0.68 (d, J = 6.6 Hz, 3H), 0.99 (d, J = 6.6 Hz, 3H), 2.17 (dsept, J = 6.6, 3.0 Hz, 1H), 2.81 (br s, 1H), 2.97 (d, J = 12.0 Hz, 1H), 3.38 (s, 3H), 3.57 (s, 3H), 3.82 (s, 3H), 3.90 (t, J = 3.6 Hz, 1H), 4.17 (t, J = 3.6 Hz, 1H), 5.05 (s, 1H), 5.43 (d, J = 1.2, 1H), 7.02 (dd, J = 7.8, 0.6 Hz, 1H), 7.28 (t, *J* = 7.8 Hz, 1H), 7.33 (dd, *J* = 7.8, 0.6 Hz, 1H); ^{13}C NMR δ 16.9, 18.9, 32.1, 40.6, 52.1, 52.2, 55.0, 56.2, 61.0, 114.0, 115.5, 119.2, 127.2, 127.9, 138.2, 150.1, 157.4, 163.1, 163.2; IR (neat) 799, 1055, 1230, 1527, 1693 cm⁻¹; $[\alpha]_{D}^{25} = -27.2$ (c 1.0, CH_2Cl_2); HRMS (ESI) calcd for $C_{19}H_{26}N_3O_5$ (M+H⁺) 376.1873, found 376.1867.

4.1.13. (2*R*,5*S*)-2,5-Dihydro-3,6-dimethoxy-2-(2-(3-methoxy-2nitrophenyl)prop-2-en-1-yl)-5-(1-methylethyl)pyrazine 17

Reaction of **15** (142 mg, 0.449 mmol) with *ent*-**3** (113 mg, 0.374 mmol) in the presence of Pd(dba)₂ (11 mg, 0.019 mmol), PPh₃ (20 mg, 0.075 mmol), and CuI (53 mg, 0.28 mmol) in DMF (10 mL), as described for *ent*-**4** (72 h), gave after extraction and chromatography (hexanes/EtOAc, 95:5) **17** (99 mg, 0.26 mmol, 70%) as a yellow oil. ¹H NMR δ 0.65 (d, *J* = 7.2 Hz, 3H), 1.00 (d, *J* = 6.6 Hz, 3H), 2.19 (dsept, *J* = 7.2, 3.6 Hz, 1H), 2.71 (dd, *J* = 14.4, 7.2 Hz, 1H), 2.94 (dd, *J* = 13.2, 3.6 Hz, 1H), 3.46 (s, 3H), 3.58 (s, 3H), 3.87 (s, 3H), 3.92 (t, *J* = 3.6 Hz, 1H), 4.08 (dt, *J* = 4.2, 3.6 Hz,

1H), 5.17 (d, J = 1.2 Hz, 1H), 5.24 (d, J = 0.6 Hz, 1H), 6.90 (t, J = 7.8 Hz, 2H), 7.32 (t, J = 7.8 Hz, 1H); ¹³C NMR δ 16.7, 18.9, 31.9, 40.7, 52.0, 52.1, 54.8, 56.4, 60.9, 110.9, 119.9, 121.5, 130.2, 136.8, 140.3, 141.0, 150.6, 162.7, 163.3; IR (neat) 1055, 1250, 1532, 1693 cm⁻¹; $[\alpha]_{D}^{25} = +3.7$ (*c* 1.0, CH₂Cl₂); HRMS (ESI) calcd for C₁₉H₂₆N₃O₅ (M+H⁺) 376.1873, found 376.1867.

4.1.14. (2*R*,5*S*)-2-(3-Bromo-3-buten-1-yl)-2,5-dihydro-3,6-dimethoxy-5-methylethylpyrazine 18

BuLi (1.91 mL, 4.77 mmol, 2.5 M in hexane) was added to a -78 °C cold solution of (S)-2,5-dihydro-3,6-dimethoxy-2-methylethylpyrazine (800 mg, 4.34 mmol) and N,N'-dimethylethylene urea (0.99 g, 8.7 mmol) in dry THF (40 mL) under a nitrogen atmosphere. After 1 h, a solution of 2-bromo-4-iodo-1-butene (1.36 g, 5.21 mmol) in dry THF (10 mL) was added over 30 min. The reaction mixture was allowed to warm to ambient temperature overnight. The reaction was guenched with a 0.1 M phosphate buffer (30 mL) and extracted with Et₂O (3×30 mL). The combined organic phases were dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. The resulting oil was purified by chromatography (hexane/EtOAc 9:1) to afford 18 (419 mg, 1.32 mmol, 31%) as a pale yellow oil. ¹H NMR δ 0.70 (d, J = 7.2 Hz, 3H), 1.04 (d, J = 6.6 Hz, 3H), 1.86–1.92 (m, 1H), 2.19–2.17 (m, 1H), 2.25 (dsept, J = 7.2, 3.6 Hz, 1H), 2.42-2.52 (m, 2H), 3.69 (s, 3H), 3.71 (s, 3H), 3.94 (t, J = 3.0 Hz, 1H), 4.02 (dt, J = 7.2, 4.2 Hz, 1H), 5.39 (d, J = 1.8 Hz, 1H), 5.57 (d, J = 1.8 Hz, 1H); ¹³C NMR δ 16.7, 19.0, 31.9, 32.6, 37.1, 52.4, 52.5, 54.3, 60.9, 116.5, 134.3, 163.4, 163.8; IR (neat) 1194, 1234, 1690 cm⁻¹; $[\alpha]_D^{25} = -2.3$ (*c* 1.2, CH₂Cl₂); HRMS (ESI) calcd for C₁₃H₂₂BrN₂O₂ (M+H⁺) 317.0865, found 317.0859.

4.1.15. (2*R*,5*S*)-2-(3-Bromo-2-propen-1-yl)-2,5-dihydro-3,6-dimethoxy-5-methylethylpyrazine 19

At first BuLi (2.71 mL, 5.97 mmol, 2.2 M in cyclohexane) was added dropwise to a -78 °C cold solution of (S)-2,5-dihydro-3,6dimethoxy-2-methylethylpyrazine (1.00 g, 5.43 mmol) in dry THF (15 mL) under a nitrogen atmosphere. After stirring for 30 min, a solution of 1,3-dibromo-1-propene (1.41 g, 7.06 mmol, 1:1 E/Zmixture) in THF (5 mL) was slowly added. After stirring for 90 min, the reaction was quenched with water (30 mL) and the mixture was extracted with Et_2O (3 × 30 mL). The combined organic phases were dried (MgSO₄), filtered, and the solvents were removed under reduced pressure. The resulting oil was purified by chromatography (hexane/EtOAc 95:5) to afford **19** (1.25 g, 4.12 mmol, 76%) as a yellow oil. Spectroscopic data from a 1:1 mixture of Z:E-19: ¹H NMR δ 0.68 (d, I = 6.6 Hz, 3H), 0.69 (d, I = 6.6 Hz, 3H), 1.04 (d, J = 7.2 Hz, 6H), 2.25 (dsept, J = 6.6, 3.0 Hz, 2H), 2.46-2.50 (m, 1H), 2.53–2.57 (m, 1H), 2.62 (dpent, J = 6.6, 1.2 Hz, 1H), 2.75-2.79 (m, 1H), 3.68 (s, 3H), 3.67 (s, 3H), 3.70 (s, 3H), 3.71 (s, 3H), 3.93-3.95 (m, 2H), 4.04-4.07 (m, 1H), 4.12-4.14 (m, 1H), 6.05–6.09 (m, 3H), 6.22–6.24 (m, 1H); 13 C NMR δ 16.6, 19.0, 31.8, 34.8, 37.4, 52.4, 52.5, 54.5, 54.8, 60.9, 106.7, 109.7, 130.7, 133.4, 162.5, 163.0, 164.1, 164.3 (6 peaks overlap); IR (neat) 1010, 1235, 1691 cm⁻¹; $[\alpha]_{D}^{25} = -14.4$ (*c* 1.4, CH₂Cl₂); HRMS (ESI) calcd for C₁₂H₂₀BrN₂O₂ (M+H⁺) 303.0708, found 303.0703.

4.1.16. (2*R*,5*S*)-2,5-Dihydro-3,6-dimethoxy-2-(3-(2-nitrophenyl)-3-buten-1-yl)-5-(1-methylethyl)pyrazine 20

Reaction of tributyl(2-nitrophenyl)stannane **2** (721 mg, 1.75 mmol) with **18** (370 mg, 1.17 mmol) in the presence of Pd(dba)₂ (34 mg, 0.058 mmol), PPh₃ (61 mg, 0.23 mmol), and Cul (167 mg, 0.877 mmol) in DMF (10 mL), as described for *ent*-**4** (18 h), gave after extraction and chromatography (hexanes/EtOAc, 95:5) **20** (308 mg, 0.857 mmol, 73%) as a yellow oil. ¹H NMR δ 0.68 (d, *J* = 6.6 Hz, 3H), 1.03 (d, *J* = 7.2 Hz, 3H), 1.78–1.84 (m, 1H), 1.96–2.02 (m, 1H), 2.24 (dsept, *J* = 6.6, 3.6 Hz, 1H), 2.30–2.39 (m, 2H),

3.65 (s, 3H), 3.67 (s, 3H), 3.92 (t, *J* = 3.6 Hz, 1H), 4.02 (dt, *J* = 4.2, 3.6 Hz, 1H), 4.99 (s, 1H), 5.19 (d, *J* = 1.2 Hz, 1H), 7.30 (d, *J* = 7.8 Hz, 1H), 7.40 (t, *J* = 8.4Hz, 1H), 7.53 (t, *J* = 7.2 Hz, 1H), 7.85 (d, *J* = 7.8 Hz, 1H); ¹³C NMR δ 16.6, 19.0, 31.8, 31.9, 32.6, 52.3, 52.4, 54.8, 60.8, 114.4, 124.0, 127.9, 131.0, 132.4, 138.5, 146.9, 148.4, 163.5, 163.7; IR (neat) 1194, 1235, 1525, 1690 cm⁻¹; $[\alpha]_{D}^{25} = +4.8$ (*c* 1.0, CH₂Cl₂); HRMS (ESI) calcd for C₁₉H₂₆N₃O₄ (M+H⁺) 360.1923, found 360.1918.

4.1.17. (2*R*,5*S*)-2,5-Dihydro-3,6-dimethoxy-2-((2-nitrophenyl)-2-propen-1-yl))-5-(1-methylethyl)pyrazine (*E*/*Z*) 21

Reaction of 2 (1.02 g, 2.47 mmol) with 19 (500 mg, 1.65 mmol) in the presence of Pd(dba)₂ (47 mg, 0.083 mmol), PPh₃ (86 mg, 0.33 mmol), and CuI (236 mg, 1.24 mmol) in DMF (10 mL), as described for ent-4 (48 h), gave after extraction and chromatography (hexanes/EtOAc, 9:1) 21 (444 mg, 1.29 mmol, 78%) as a yellow oil. Spectroscopic data from the E/Z-mixture: ¹H NMR (Zisomer) δ 0.68 (d, J = 7.2 Hz, 3H), 1.03 (d, J = 7.2 Hz, 3H), 2.25 (dsept, J = 7.2, 3.6 Hz, 1H), 2.56 (dddd, J = 15.0, 7.2, 6.0, 1.8 Hz, 1H,), 2.66-2.79 (m, 1H, overlapped by 2H of E-isomer), 3.63 (s, 3H), 3.65 (s, 3H), 3.97 (t, J = 3.6 Hz, 1H), 4.08 (dt, J = 4.2, 1.8 Hz, 1H), 5.74 (dt, J = 7.8, 4.2 Hz, 1H), 6.80 (d, J = 12.0 Hz, 1H), 7.40 (dt, J = 8.4, 1.8, 1H), 7.49–7.52 (m, 1H, overlapped by 2H of E-isomer), 7.56 (dt, *J* = 7.8, 1.2 Hz, 1H), 8.01 (dd, *J* = 6.6, 1.2 Hz, 1H). ¹H NMR (*E*-isomer) δ 0.69 (d, *J* = 7.2 Hz, 3H), 1.03 (d, *J* = 6.6 Hz, 3H), 2.25 (dsept, J = 7.2, 3.6 Hz, 1H), 2.66–2.79 (m, 2H, overlapped by 1H of Z-isomer), 3.71 (s, 3H), 3.73 (s, 3H), 3.91 (t, J = 3.6 Hz, 1H), 4.18 (dt, J = 3.6, 1.8 Hz, 1H), 6.08 (dt, J = 7.8, 7.2 Hz, 1H), 6.89 (d, *J* = 15.6 Hz, 1H), 7.33 (ddd, *J* = 8.4, 6.0, 3.0 Hz, 1H), 7.49–7.52 (m, 2H, overlapped by 1H of 1H of Z-isomer), 7.86 (d, J = 8.4 Hz, 1H); ¹³C NMR (both isomers) δ 16.5, 16.6, 19.0, 31.8, 32.8, 37.9, 52.3, 52.4, 52.4, 52.5, 55.0, 55.3, 60.8, 60.9, 124.3, 124.4, 127.6, 127.6, 127.7, 128.1, 128.6, 129.6, 131.6, 132.0, 132.6, 132.8, 132.8, 133.1, 147.7, 148.1, 162.8, 162.9, 164.0, 164.2;¹⁹ IR (neat) 738, 1236, 1522, 1691 cm⁻¹; $[\alpha]_D^{25} = -7.7$ (*c* 1.0, CH₂Cl₂); HRMS (ESI) calcd for C₁₈H₂₄N₃O₄ (M+H⁺) 346.1767, found 346.1761.

4.1.18. 3-(((2*R*,5*S*)-2,5-Dihydro-3,6-dimethoxy-5-(1methylethyl)pyrazin-2-yl)methyl)-1*H*-indole *ent*-5²⁰

At first, ent-4 (140 mg, 0.405 mmol), Pd(dba)₂ (14 mg, 0.024 mmol), 1,3-bis-(diphenylphosphino)propane (dppp) (10 mg, 0.024 mmol), and 1,10-phenanthroline (phen) (10 mg, 0.048 mmol) were dissolved in anhydrous DMF (3 mL) in a threaded ACE glass pressure tube. The tube was fitted with a pressure head, and the solution was saturated with carbon monoxide (four cycles of 6 atm of CO). The reaction mixture was heated at 120 °C (oil bath temperature) under CO (6 atm) for 18 h. Water (10 mL) was added and the orange solution was extracted with EtOAc (3×30 mL). The combined organic phases were dried over MgSO₄, filtered, and the solvent was removed under reduced pressure. The resulting crude product was purified by chromatography (hexanes/EtOAc, 8:2 then 1:1) to afford ent-5 [(2R,5S)/ (25,55) = 15:1, 108 mg, 0.345 mmol, 85%) as a yellow solid. mp 99–102 °C; ¹H NMR δ 0.62 (d, J = 7.2 Hz, 3H), 0.93 (d, J = 7.2 Hz, 3H), 2.14 (dsept, J = 7.2, 3.6 Hz, 1H), 3.29 (t, J = 3.6 Hz 2H), 3.37 (t, J = 3.6 Hz, 1 H), 3.66 (s, 3 H), 3.68 (s, 3 H), 4.36 (q, J = 3.6 Hz, 1 H)1H), 6.89 (d, J = 1.8 Hz, 1H), 7.07 (t, J = 7.2 Hz, 1H), 7.13 (t, J = 7.2 Hz, 1H), 7.26 (d, J = 7.2, 1H), 7.64 (d, J = 7.2 Hz, 1H), 8.03 (br s, 1H); 13 C NMR δ 16.5, 19.0, 29.5, 31.3, 52.1, 52.2, 56.7, 60.4, 110.7, 111.6, 118.9, 119.4, 121.6, 122.7, 128.4, 135.8, 163.0, 163.7; IR (neat) 725, 1010, 1222, 1236, 1660, 1697 cm⁻¹; $[\alpha]_{D}^{25} = -54.8$ (c 1.3, CH₂Cl₂); HRMS (ESI) calcd for C₁₈H₂₄N₃O₂ (M+H⁺) 314.1869, found 314.1863. Partial data for the minor isomer: ¹H NMR δ 0.12 (d, J = 6.7 Hz, 3H), 0.84 (d, J = 6.7 Hz, 3H), 3.71 (s, 3H).

4.1.19. 3-(((2*R*,5*S*)-2,5-Dihydro-3,6-dimethoxy-5-(1methylethyl)-pyrazin-2-yl)methyl)-6-methoxy-1*H*-indole 22

Reaction of 8 (112 mg, 0.298 mmol) in the presence of $Pd(dba)_2$ (10 mg, 0.018 mmol), dppp (7.0 mg, 0.018 mmol), phen (7.0 mg, 0.036 mmol), and CO (6 atm) in DMF (3 mL), as described for ent-5 (26 h), gave after chromatography (hexanes/EtOAc, 8:2 then 6:4) 22 [(2R,5S)/(2S,5S) = 12:1, 71 mg, 0.21 mmol, 70%] as a yellow solid. Mp 111–114 °C; ¹H NMR δ 0.61 (d, J = 6.6 Hz, 3H), 0.92 (d, *J* = 7.2 Hz, 3H), 2.13 (dsept, *J* = 6.6, 3.0 Hz, 1H), 3.24 (d, *J* = 4.8 Hz, 2H), 3.36 (t, J = 3.0 Hz, 1H), 3.65 (s, 3H), 3.67 (s, 3H), 3.82 (s, 3H), 4.33 (q, J = 4.2 Hz, 1H), 6.74 (dd, J = 8.4, 1.8 Hz, 1H), 6.76 (d, J = 1.8 Hz, 1H), 6.78 (d, J = 1.8 Hz, 1H), 7.49 (d, J = 9.0 Hz, 1H), 7.88 (br s, 1H); ¹³C NMR δ 16.5, 19.0, 29.6, 31.3, 52.1, 52.2, 55.6, 56.8, 60.4, 94.2, 109.0, 111.6, 120.0, 121.4, 122.9, 136.4, 156.2, 163.0, 163.7; IR (neat) 780, 1027, 1157, 1224, 1693 cm⁻¹; $[\alpha]_{D}^{25} = -44.6$ (c 1.2, CH₂Cl₂); HRMS (ESI) calcd for C₁₉H₂₆N₃O₃ (M+H⁺) 344.1974, found 344.1969. Partial data of minor isomer: ¹H NMR δ 0.15 (d, I = 7.2 Hz, 3H), 0.85 (d, I = 7.2 Hz, 3H), 3.65 (s, 3H), 3.70 (s, 3H); ¹³C NMR δ 30.0, 30.9, 52.0, 52.1, 57.2, 60.7, 108.9, 120.2, 121.6, 122.9.

4.1.20. 3-(((2*R*,5*S*)-2,5-Dihydro-3,6-dimethoxy-5-(1methylethyl)-pyrazin-2-yl)methyl)-5-methoxy-1*H*-indole 23

Reaction of 9 (145 mg, 0.386 mmol) in the presence of Pd(dba)₂ (13 mg, 0.023 mmol), dppp (10 mg, 0.023 mmol), phen (9.0 mg, 0.046 mmol), and CO (6 atm) in DMF (3 mL), as described for ent-5 (22 h), gave after chromatography (hexanes/EtOAc, 8:2 then 6:4) 23 [(2R,5S)/(2S,5S) = 22:1, 112 mg, 0.326 mmol, 85%] as a yellow oil. ¹H NMR δ 0.63 (d, I = 6.6 Hz, 3H), 0.94 (d, I = 6.6 Hz, 3H), 2.15 (dsept, J = 6.6, 3.6 Hz, 1H), 3.26 (d, J = 4.8 Hz, 2H), 3.40 (t, J = 3.6 Hz, 1H), 3.67 (s, 3H), 3.70 (s, 3H), 3.86 (s, 3H), 4.36 (q, *I* = 4.2 Hz, 1H), 6.80 (dd, *I* = 8.4, 1.8 Hz, 1H), 6.88 (d, *I* = 2.4 Hz, 1H), 7.10 (d, *J* = 2.4 Hz, 1H), 7.15 (d, *J* = 9.0 Hz, 1H), 7.95 (br s, 1H); ¹³C NMR δ 16.4, 19.0, 29.5, 31.2, 52.2, 52.3, 55.9, 56.7, 60.4, 101.3, 111.3, 111.4, 111.9, 123.6, 128.8, 131.0, 153.7, 163.0, 163.8; IR (neat) 794, 1012, 1232, 1435, 1692 cm⁻¹; $[\alpha]_D^{25} = -49.5$ (c 1.2, CH_2Cl_2); HRMS (ESI) calcd for $C_{19}H_{26}N_3O_3$ (M+H⁺) 344.1974, found 344.1969. Partial data for the minor isomer: ¹H NMR δ 0.15 (d, J = 6.9 Hz, 3H), 0.85 (d, J = 6.7 Hz, 3H), 3.72 (s, 3H).

4.1.21. 6-Fluoro-3-(((2R,5S)-2,5-dihydro-3,6-dimethoxy-5-(1-methylethyl)-pyrazin-2-yl)methyl)-1*H*-indole 24

Reaction of 10 (118 mg, 0.325 mmol) in the presence of Pd(dba)₂ (11 mg, 0.019 mmol), dppp (8.0 mg, 0.019 mmol), phen (8.0 mg, 0.039 mmol), and CO (6 atm) in DMF (3 mL), as described for ent-5 (21 h), gave after chromatography (hexanes/EtOAc, 8:2 then 6:4) **24** [(2R,5S)/(2S,5S) = 4.5:1, 90 mg, 0.27 mmol, 84%] as a vellow oil. Spectroscopic data of (2R,5S)-24 from the mixture: ¹H NMR δ 0.62 (d, I = 6.6 Hz, 3H), 0.93 (d, I = 6.6 Hz, 3H), 2.13 (dsept, *J* = 6.6, 3.6 Hz, 1H), 3.25 (d, *J* = 4.2 Hz, 2H), 3.37 (t, *J* = 3.6 Hz, 1H), 3.65 (s, 3H), 3.67 (s, 3H), 4.34 (q, J = 4.2 Hz, 1H), 6.83 (dt, J = 9.6, 1.8 Hz, 1H), 6.86 (d, J = 1.8 Hz, 1H), 6.93 (dd, J = 9.0, 1.8 Hz, 1H), 7.53 (dd, J = 8.4, 5.4 Hz, 1H), 8.03 (br s, 1H); ^{13}C NMR δ 16.5, 19.0, 29.5, 31.3, 52.1, 52.2, 56.7, 60.4, 97.0 (d, J = 25.6 Hz), 107.7 (d, J = 24.6 Hz), 111.8, 120.1 (d, J = 6.3 Hz), 122.9 (d, J = 3.9 Hz), 125.0, 135.6 (d, J = 12.0 Hz), 159.8 (d, J = 235.6 Hz), 162.9, 163.8; IR (neat) 799, 1012, 1140, 1194, 1220, 1692 cm⁻¹; $[\alpha]_D^{25} = -41.8$ (c 0.9, CH_2Cl_2); HRMS (ESI) calcd for $C_{18}H_{23}FN_3O_2$ (M+H⁺) 332.1774, found 332.1769. Partial data for the minor (25,55)-24 isomer: ¹H NMR δ 0.10 (d, J = 6.6 Hz, 3H), 0.84 (d, J = 6.6 Hz, 3H), 1.82 (dsept, J = 7.2, 3.6 Hz, 1H), 3.64 (s, 3H), 3.70 (s, 3H); ¹³C NMR δ 16.2, 19.4, 29.8, 31.1, 52.0, 52.2, 57.0, 60.7, 96.9 (d, J = 25.6 Hz), 107.7 (d, J = 24.6 Hz), 112.6, 120.3 (d, J = 6.3 Hz), 123.1 (d, J = 4.0 Hz), 125.1, 135.7 (d, J = 12.0 Hz), 159.9 (d, I = 235.6 Hz), 162.4, 163.2.

4.1.22. Methyl 3-(((2R,5S)-2,5-dihydro-3,6-dimethoxy-5-(1methylethyl)-pyrazin-2-yl)methyl)-1*H*-indole-6-carboxylate 25

Reaction of **11** (87 mg, 0.22 mmol) in the presence of Pd(dba)₂ (7.0 mg, 0.013 mmol), dppp (5.0 mg, 0.013 mmol), phen (5.0 mg, 0.026 mmol), and CO (6 atm) in DMF (3 mL), as described for *ent*-**5** (23 h), gave after chromatography (hexanes/EtOAc, 8:2 then 6:4) **25** [(2*R*,5*S*)/(2*S*,5*S*) = 10:1, 60 mg, 0.16 mmol, 73%] as a tan solid. Mp 119–121 °C; ¹H NMR δ 0.61 (d, *J* = 6.6 Hz, 3H), 0.91 (d, *J* = 7.2 Hz, 3H), 2.12 (dsept, *J* = 7.2, 3.0 Hz Hz, 1H), 3.29 (d, *J* = 4.2 Hz, 2H), 3.34 (t, *J* = 3.6 Hz, 1H), 3.64 (s, 3H), 3.67 (s, 3H), 3.92 (s, 3H), 4.35 (q, *J* = 4.8 Hz, 1H), 7.08 (d, *J* = 2.4 Hz, 1H), 7.66 (d, *J* = 8.4 Hz, 1H), 7.76 (dd, *J* = 8.4, 1.2 Hz, 1H), 8.05 (s, 1H), 8.57 (br s, 1H); ¹³C NMR δ 16.4, 18.9, 29.4, 31.4, 51.8, 52.2, 52.3, 56.6, 60.4, 112.1, 113.3, 119.0, 120.0, 123.3, 126.3, 132.0, 135.1, 162.8, 163.8, 168.3; IR (neat) 769, 1086, 1196, 1237, 1276, 1697, 1710 cm⁻¹; [α]_D²⁵ = -43.1 (c 1.2, CH₂Cl₂); HRMS (ESI) calcd for C₂₀H₂₆N₃O₄ (M+H⁺) 372.1923, found 372.1918.

4.1.23. 3-(((2*R*,5*S*)-2,5-Dihydro-3,6-dimethoxy-5-(1methylethyl)-pyrazin-2-yl)methyl)-6-nitro-1*H*-indole 26

Reaction of 12 (165 mg, 0.423 mmol) in the presence of Pd(dba)₂ (15 mg, 0.025 mmol), dppp (11 mg, 0.025 mmol), phen (10 mg, 0.051 mmol), and CO (6 atm) in DMF (3 mL), as described for ent-5 (18 h), gave after chromatography (hexanes/EtOAc, 8:2 then 6:4) **26** (18 mg, 0.050 mmol, 12%) as a yellow oil. ¹H NMR δ 0.62 (d, *J* = 7.2 Hz, 3H), 0.92 (d, *J* = 6.6 Hz, 3H), 2.13 (dsept, *J* = 6.6, 3.6 Hz, 1H), 3.30 (d, J = 4.8 Hz, 2H), 3.39 (t, J = 3.6 Hz, 1H), 3.65 (s, 3H), 3.68 (s, 3H), 4.35 (q, J = 4.2 Hz, 1H), 7.23 (d, J = 1.8 Hz, 1H), 7.70 (d, J = 9.0 Hz, 1H), 7.98 (dd, J = 8.4, 1.8 Hz, 1H), 8.28 (d, J = 1.8 Hz, 1H), 8.50 (br s, 1H); ¹³C NMR δ 16.5, 18.9, 29.2, 31.5, 52.2, 52.3, 56.4, 60.6, 107.9, 113.2, 114.7, 119.5, 128.7, 133.1, 134.1, 143.2, 162.6, 164.0; IR (neat) 735, 1011, 1220, 1309, 1504, 1692 cm⁻¹; $[\alpha]_D^{25} = -36.6$ (c 1.3, CH₂Cl₂); HRMS (ESI) calcd for $C_{18}H_{23}N_4O_4$ (M+H⁺) 359.1719, found 359.1714. Partial data for minor isomer: ¹H NMR δ 0.02 (d, J = 6.6 Hz, 3H), 0.81 (d, J = 7.2 Hz, 3H), 3.66 (s, 3H), 3.70 (s, 3H), 3.93 (s, 3H), 7.14 (d, *I* = 1.8 Hz, 1H), 8.03 (s, 1H), 8.50 (br s, 1H).

4.1.24. 3-(((2*R*,5*S*)-2,5-Dihydro-3,6-dimethoxy-5-(1-methyl-ethyl)-pyrazin-2-yl)methyl)-1*H*-pyrrolo[3,2-b]pyridine 27

Reaction of 13 (140 mg, 0.404 mmol) in the presence of Pd(dba)₂ (14 mg, 0.024 mmol), dppp (10 mg, 0.024 mmol), phen (10 mg, 0.049 mmol), and CO (6 atm) in DMF (3 mL), as described for ent-5 (18 h), gave after chromatography (hexanes/EtOAc, 8:2 then EtOAc) **27** [(2*R*,5*S*)/(2*S*,5*S*) = 11:1, 100 mg, 0.318 mmol, 79%] as a tan solid. Mp 148–151 °C; ¹H NMR δ 0.64 (d, J = 7.2 Hz, 3H), 0.96 (d, J = 6.6 Hz, 3H), 2.18 (dsept, J = 6.6, 3.0 Hz, 1H), 3.27 (dd, J = 14.4, 6.6 Hz, 1H), 3.53 (m, 2H), 3.63 (s, 3H), 3.66 (s, 3H), 4.40 (dt, J = 3.6, 3.0 Hz, 1H), 7.05 (dd, J = 8.4, 4.8 Hz, 1H), 7.28 (d, J = 1.8 Hz, 1H), 7.60 (dd, J = 8.4, 1.2 Hz, 1H), 8.46 (dd, J = 4.2, 1.2 Hz, 1H), 8.84 (br s, 1H); 13 C NMR δ 16.6, 19.0, 28.4, 31.5, 52.2, 52.3, 56.4, 60.6, 112.7, 116.5, 118.0, 126.4, 128.6, 142.6, 145.9, 163.5, 163.6; IR (neat) 765, 1012, 1220, 1695 cm⁻¹; $[\alpha]_D^{25} = -23.2$ (c 1.1, CH₂Cl₂); HRMS (ESI) calcd for $C_{17}H_{23}N_4O_2$ (M+H⁺) 315.1821, found 315.1816. Partial data for the minor isomer: ¹H NMR δ 0.38 (d, J = 7.2 Hz, 3H), 0.94 (d, J = 7.2 Hz, 3H), 3.64 (s, 3H), 3.69 (s, 3H).

4.1.25. 3-(((2R,5S)-2,5-Dihydro-3,6-dimethoxy-5-(1methylethyl)-pyrazin-2-yl)methyl)-4-methoxy-1*H*-indole 28

Reaction of **16** (123 mg, 0.327 mmol) in the presence of Pd(dba)₂ (11 mg, 0.020 mmol), dppp (8 mg, 0.02 mmol), phen (8 mg, 0.04 mmol), and CO (6 atm) in DMF (3 mL), as described for *ent*-**5** (23 h), gave after chromatography (hexanes/EtOAc, 8:2 then 1:1) **28** (99 mg, 0.29 mmol, 88%) as a yellow oil. ¹H NMR δ 0.66 (d, *J* = 7.2 Hz, 3H), 1.00 (d, *J* = 6.6 Hz, 3H), 2.21 (dsept, *J* = 7.2, 2.2 mmol) (dsept, 2.2 mmol) (dsept, 3.2 mmol)

3.6 Hz, 1H), 3.18 (ddd, J = 14.4, 7.2, 0.6 Hz, 1H), 3.59 (s, 3H), 3.61 (dd, J = 4.2, 0.6 Hz, 1H), 3.63 (t, J = 3.6 Hz, 1H), 3.69 (s, 3H), 3.91 (s, 3H), 4.36 (pent, *J* = 3.6 Hz, 1H), 6.45 (d, *J* = 7.8 Hz, 1H), 6.83 (d, *J* = 1.8 Hz, 1H), 6.91 (dd, *J* = 7.8, 0.6 Hz, 1H), 7.04 (t, *J* = 8.4 Hz, 1H), 7.98 (br s, 1H); 13 C NMR δ 16.5, 19.1, 31.3, 31.4, 52.2, 52.3, 55.0, 57.1, 60.4, 99.3, 104.3, 112.6, 118.0, 121.4, 122.4, 137.6, 155.0, 163.5, 164.2; IR (neat) 701, 1086, 1236, 1690 cm⁻¹; $[\alpha]_{D}^{25} = -22.3$ (c 1.0, CH₂Cl₂); HRMS (ESI) calcd for C₁₉H₂₆N₃O₃ (M+H⁺) 344.1974, found 344.1969.

4.1.26. 3-(((2R,5S)-2,5-Dihydro-3,6-dimethoxv-5-(1methylethyl)-pyrazin-2-yl)methyl)-7-methoxy-1H-indole 29

Reaction of 17 (107 mg, 0.285 mmol) in the presence of Pd(dba)₂ (10 mg, 0.017 mmol), dppp (7 mg, 0.02 mmol), phen (7 mg, 0.03 mmol), and CO (6 atm) in DMF (3 mL), as described for ent-5 (22 h), gave after chromatography (hexanes/EtOAc, 8:2) 29 [(2R,5S)/(2S,5S) = 6:1, 46.0 mg, 0.134 mmol, 47%] as a yellow oil. ¹H NMR δ 0.62 (d, I = 6.6 Hz, 3H), 0.93 (d, I = 7.2 Hz, 3H), 2.13 (dsept, J = 6.6, 3.0 Hz, 1H), 3.26 (d, J = 4.8 Hz, 2H), 3.37 (t, J = 3.6 Hz, 1H), 3.66 (s, 3H), 3.68 (s, 3H), 3.93 (s, 3H), 4.35 (g, J = 4.2 Hz, 1H), 6.59 (d, J = 7.2 Hz, 1H), 6.88 (d, J = 2.4 Hz, 1H), 6.98 (t, J = 7.8 Hz, 1H), 7.24 (d, J = 8.4 Hz, 1H), 8.18 (br s, 1H); ¹³C NMR δ 16.7, 19.2, 29.9, 31.5, 52.3, 52.5, 55.4, 55.5, 56.9, 60.6, 101.7, 112.5, 119.5, 122.5, 126.5, 130.0, 146.1, 163.2, 163.9; IR (neat) 729, 1013, 1048, 1225, 1259, 1693 cm⁻¹; $[\alpha]_D^{25} = -25.2$ (*c* 1.1, CH₂Cl₂); HRMS (ESI) calcd for C₁₉H₂₆N₃O₃ (M+H⁺) 344.1974, found 344.1969.

4.1.27. 3-(2-((2R,5S)-2,5-Dihydro-3,6-dimethoxy-5-(1methylethyl)-pyrazin-2-yl)ethyl)-1H-indole 30

Reaction of 20 (138 mg, 0.384 mmol) in the presence of Pd(dba)₂ (13 mg, 0.023 mmol), dppp (9.0 mg, 0.02 mmol), phen (9.0 mg, 0.05 mmol), and CO (6 atm) in DMF (3 mL), as described for ent-5 (19 h), gave after chromatography (hexanes/EtOAc, 9:1) **30** [(2*R*,5*S*)/(2*S*,5*S*) = 16:1, 90.0 mg, 0.275 mmol, 72%) as a yellow oil. ¹H NMR δ 0.74 (d, J = 6.6 Hz, 3H), 1.08 (d, J = 7.2 Hz, 3H), 2.10-2.16 (m, 1H), 2.24-2.33 (m, 2H), 2.72-2.84 (m, 2H), 3.70 (s, 3H), 3.75 (s, 3H), 4.01 (t, *J* = 3.6 Hz, 1H), 4.14 (dt, *J* = 4.8, 3.6 Hz, 1H), 6.98 (d, J = 1.8 Hz, 1H), 7.12 (dt, J = 7.8, 0.6 Hz, 1H), 7.19 (dt, *J* = 7.2, 1.2 Hz, 1H), 7.34 (d, *J* = 7.8 Hz, 1H), 7.64 (d, *J* = 7.8 Hz, 1H), 7.95 (br s, 1H); ¹³C NMR δ 16.7, 19.0, 20.2, 31.8, 34.5, 52.3, 52.4, 55.1, 60.9, 111.0, 116.3, 119.0, 119.1, 121.1, 121.8, 127.6, 136.4, 163.6, 163.9; IR (neat) 701, 1086, 1236, 1690 cm⁻¹; $[\alpha]_D^{25} = -2.7$ (c 0.8, CH_2Cl_2); HRMS (ESI) calcd for $C_{19}H_{26}N_3O_2$ (M+H⁺) 328.2025, found 328.2020. Partial data for minor isomer: ¹H NMR δ 0.79 (d, J = 6.6 Hz, 3H), 1.10 (d, J = 7.2 Hz, 3H), 3.71 (s, 3H), 3.76 (s, 3H), 7.02 (d, J = 1.8 Hz, 1H).

4.1.28. 2-((2,5-Dihydro-3,6-dimethoxy-5-(1-methylethyl)pyrazin-2-yl)methyl)-1H-indole 31 and 2-(((2R,5S)-2,5-dihydro-3,6-dimethoxy-5-(1-methylethyl)-pyrazin-2-yl)methyl)-1hydroxyindole 32

The reaction of 21 (217 mg, 0.628 mmol) in the presence of Pd(dba)₂ (22 mg, 0.038 mmol), dppp (16 mg, 0.038 mmol), phen (15 mg, 0.075 mmol), and CO (6 atm) in DMF (3 mL), as described for ent-5 (22 h), gave after chromatography (hexanes/EtOAc, 95:5 then 9:1) **31** [(2*R*,5*S*)/(2*S*,5*S*) = 1.2:1, 68 mg, 0.22 mmol, 35%] and 32 (22 mg, 0.067 mmol, 11%) both as a yellow oil. Spectroscopic data of **31** from the isomer mixture: ¹H NMR (minor) δ 0.58 (d, *I* = 7.2 Hz, 3H), 1.05 (d, *I* = 6.6 Hz, 3H), 2.23 (dsept, *I* = 6.6, 3.0 Hz, 1H), 2.91 (ddd, *J* = 14.4, 9.6, 0.6 Hz, 1H), 3.49 (dd, *J* = 14.4, 3.0 Hz, 1H), 3.76 (s, 3H), 3.83 (s, 3H), 4.00 (dd, J = 4.8, 3.6, 1H), 4.30 (ddd, J = 9.6, 4.8, 1.8 Hz, 1H), 6.28 (d, J = 9.6 Hz, 1H), 7.06 (t, J = 7.8 Hz, 1H), 7.12 (d, J = 7.2 Hz, 1H), 7.29 (d, J = 7.8 Hz, 1H), 7.55 (s, 1H); ¹H NMR (major) δ 0.73 (d, I = 7.2 Hz, 3H), 1.03 (d, *I* = 6.6 Hz, 3H), 2.23 (dsept, *I* = 6.6, 3.0 Hz, 1H), 3.03 (ddd, *I* = 14.4, 9.6, 0.6 Hz, 1H), 3.44 (dd, J = 14.4, 3.0 Hz, 1H), 3.77 (s, 3H), 3.82 (s, 3H), 3.91 (t, *J* = 3.6 Hz, 1H), 4.24 (dt, *J* = 3.0, 1.8 Hz, 1H), 6.28 (d, J = 9.6 Hz, 1H), 7.06 (t, J = 7.8 Hz, 1H), 7.12 (d, J = 7.2 Hz, 1H), 7.29 (d, I = 7.8 Hz, 1H), 7.54 (s, 1H); ¹³C NMR δ 16.7, 16.9, 19.0, 19.4, 31.0, 32.1, 32.8, 33.6, 52.4, 52.5, 52.6, 52.7, 55.9, 56.1, 60.7, 61.1, 100.7, 100.9, 110.4, 110.5, 119.3, 119.4, 119.8, 119.9, 120.9, 121.0, 128.3, 128.4, 135.9, 137.0, 137.1, 161.9, 162.5, 164.1, 164.7; IR (neat) 732, 1229, 1243, 1688 cm⁻¹; $[\alpha]_{D}^{25} = +0.35$ (*c* 1.0, CH₂Cl₂); HRMS (ESI) calcd for C₁₈H₂₄N₃O₂ (M+H⁺) 314.1869, found 314.1863. Spectroscopic data for **32**: ¹H NMR δ 0.77 (d, *J* = 7.2 Hz, 3H), 0.99 (d, J = 6.6 Hz, 3H), 2.14 (dsept, J = 6.6, 3.0 Hz, 1H), 3.24 (dd, J = 14.4, 8.4 Hz, 1H), 3.65 (dd, J = 15.0, 3.6 Hz, 1H), 3.81 (s, 3H), 3.82 (s, 3H), 4.01 (t, J = 3.6 Hz, 1H), 4.15 (dt, J = 3.0, 1.8 Hz, 1H), 6.18 (s, 1H), 7.03 (t, J = 7.8 Hz, 1H), 7.17 (t, J = 7.2 Hz, 1H), 7.45 (d, J = 8.4 Hz, 1H), 7.52 (d, J = 7.8 Hz, 1H), 11.71 (br s, 1H); ¹³C NMR δ 17.6, 19.0, 29.5, 32.9, 53.3, 53.6, 57.8, 62.4, 94.9, 108.1, 118.8, 120.0, 121.0, 123.1, 132.4, 133.8, 162.2, 168.5; IR (neat) 1008, 1227, 1250, 1670 cm $^{-1}; \; [\alpha]_D^{25} = -8.5 \; (c \; 1.2, \; CH_2Cl_2);$ HRMS (ESI) calcd for C₁₈H₂₄N₃O₃ (M+H⁺) 330.1818, found 330.1812.

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