Synthesis of (±)-Lotthanongine, a Novel Natural Product with a Flavan–Indole Hybrid Structure

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Abstract: First total synthesis of lotthanongine (**3**), a natural product with a flavan–indole composite structure, has been achieved via the Lewis acid-catalyzed C–C bond formation between the catechin and the indole units.

Key words: catechin, indole, polyphenol, heterocycle, hybrid

Flavan-type polyphenols are widely distributed in the plant kingdom, and show various significant biological activities.[1] Recent structural studies have identified further structural diversity of polyphenols by hybridization with other structure motifs, such as acetate[2] and terpenes.[3] Among these, lotthanongine (**3**) isolated from the roots of *Trigonostemon reidioides* Craib (Euphorbiaceae, Thai name: Lot-Tha-Nong),[4] has a structure, in which a flavan unit, afzelechin (**2**), is connected with an indole unit at its C(4) position (Figure 1).

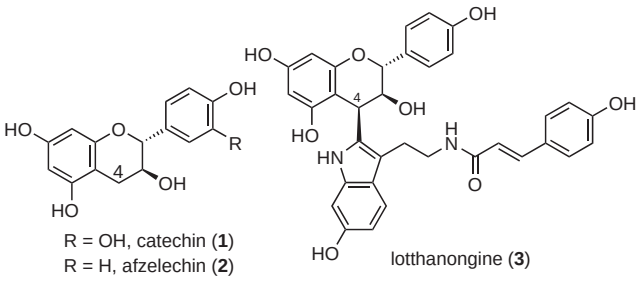


Figure 1

Attracted by the novel structure as well as the potential biological activities expectable in each component, we became interested in the total synthesis of **3**. We envisioned that the cation **A**, generated from catechin derivative (vide infra), would be susceptible of the nucleophilic attack of indole **B**, a process which is most probably involved in the biosynthesis (Figure 2).

Two questions were due to this key coupling, (1) the reactivity of the indole nucleophile, and (2) the stereoselectivity.

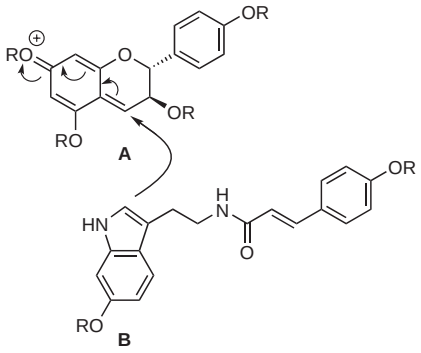
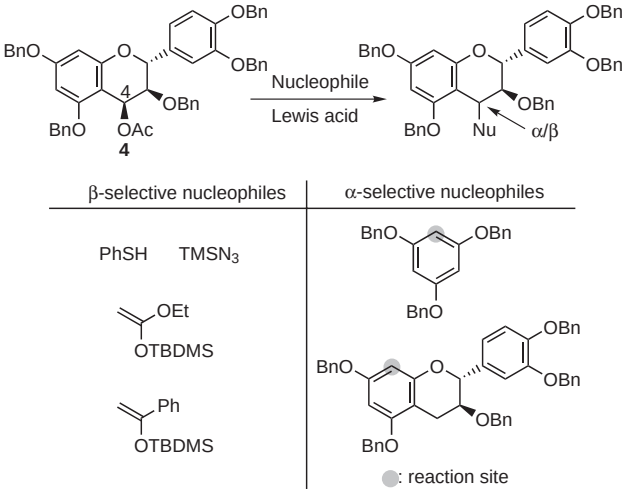


Figure 2

Concerning the latter point, we previously noted that the Lewis acid promoted S_N1-type reaction of catechin acetate **4** showed a remarkable stereochemical dichotomy depending on the nucleophilic partner (Scheme 1).[5]

Most nucleophiles showed β-selectivities including hetero-nucleophiles, such as PhSH and Me_3SiN_3, and carbon nucleophiles such as ketene silyl acetals, whereas in sharp contrast the α-selectivity prevailed for the electron-rich aromatic rings in the phloroglucinol and catechin derivatives.[5] Within the synthetic context of lotthanongine (**3**), the question was whether or not indoles are the β-selective nucleophiles for establishing the requisite stereochemistry.



Scheme 1 α-Stereoselective nucleophiles and β-stereoselective acetate **4** showed remarkable stereochemical nucleophiles

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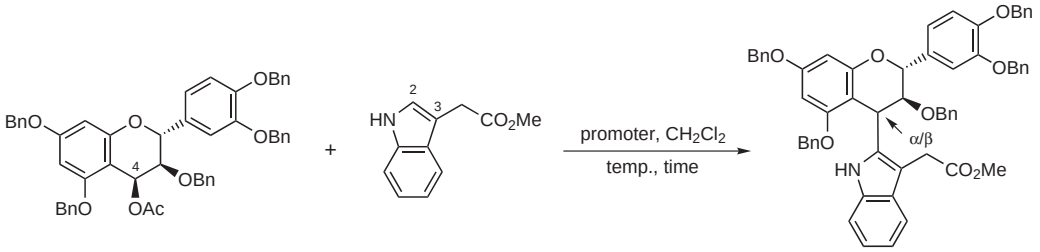
Table 1 The Reaction of Catechin Acetate **4** with 3-Substituted Indole **5**



4 **5** (3 equiv) **6**

Run	Promoter (equiv)	Temp (°C)	Time (h)	Yield (%)	α/β
1	$BF_3{\cdot}OEt_2$ (0.1)	–78 → 5	2.0	86	10:90
2	TMSOTf (0.1)	–78 → –40	2.0	94	6:94
3	Cp_2ZrCl_2 (0.1), $AgClO_4$ (0.2), MS 4Å	–78 → 25	31	84	13:87
4	$TsOH{\cdot}H_2O$ (0.1)	0	1.0	97	10:90

Table 1 shows the initial model study on the connectivity of indole and catechin derivatives. Catechin acetate **4** was allowed to react with indole-3-acetic acid methyl ester (**5**) under some sets of acidic conditions.

Representative procedure is described by the reaction catalyzed by $BF_3{\cdot}OEt_2$ (run 1). A solution of catechin acetate **4** and indole **5** (3 mol equiv) in CH_2Cl_2 was treated with 10 mol% of $BF_3{\cdot}OEt_2$ at –78 °C, and the temperature was gradually raised with monitoring of the reaction by TLC. After the complete consumption of catechin acetate **4** was assured at 5 °C, usual work up and separation by silica gel TLC gave product **6** in 86% yield. The NMR analysis showed the product was mainly composed of the β-isomer (α/β = 10:90), also that the C–C bond formation occurred at the C(2) for the indole and the C(4) position for the catechin.[6]

Further experiments showed that other Lewis acids (runs 2 and 3) or even a protic acid (run 4) were also effective to catalyze the reaction with comparable yield and selectivity, albeit the final reaction temperatures differed. TMSOTf was the most reactive and showed the highest stereoselectivity for this particular case.

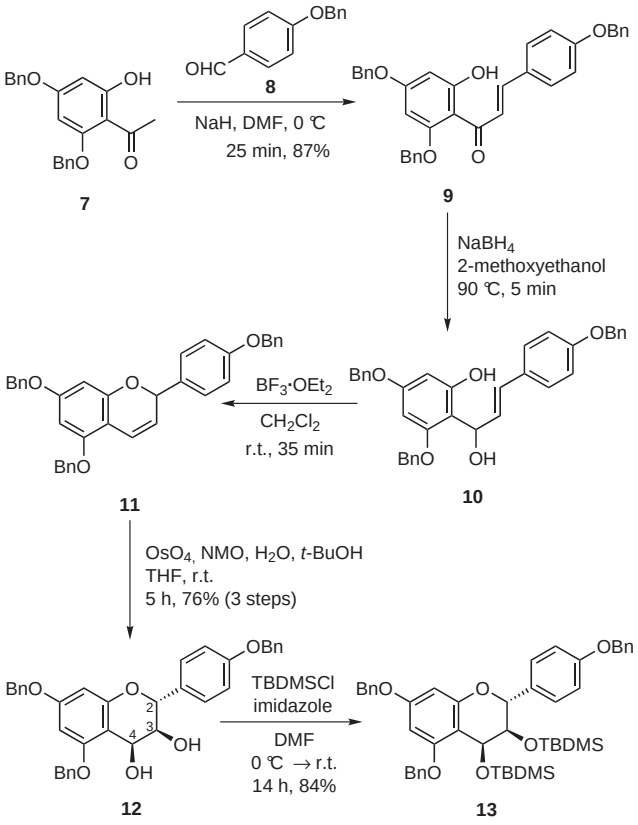
Encouraged by these results, we proceeded to the synthesis of lotthanongine (**3**). Given the poor availability of the flavan portion, afzelechin (**2**),[7] we prepared its racemic form by adopting the route of catechin synthesis by Clark-Lewis[8] and Kawamoto.[9a] Aldol condensation of acetophenone **7**[9] and aldehyde **8** was effected by using sodium hydride (DMF, 0 °C, 25 min) to give crude solid products, which were washed with Et_2O to give pure chalcone **9**[11] as yellow powders (mp 136–137 °C) in 87% yield. Reduction of **9** with $NaBH_4$ (2-methoxyethanol, 90 °C, 5 min) gave alcohol **10**, which was treated with $BF_3{\cdot}OEt_2$ (CH_2Cl_2, r.t., 35 min) to afford flavan-3-ene **11** (Scheme 2). It should be noted that alcohol **10** and alkene **11** were highly labile to silica gel chromatography, and thus, the crude materials were used without purification, respectively. Oxidation of alkene **11** by OsO_4 and *N*-methylmorpholine-*N*-oxide (*t*-BuOH, THF, H_2O, r.t., 5 h) gave crude solid diol **12**, which was washed with Et_2O to give colorless powders (single diastereomer, mp 157–159 °C, 76% yield from **9**).

Protection of diol **12** with *t*-butyldimethylsilyl (TBDMS) group [TBDMSCl (6 mol equiv), imidazole (10 mol equiv), DMF, r.t., 14 h] afforded the bis-silyl ether **13** as colorless amorphous solids. The relative stereochemistry of **13**[10] was assigned as such by ^1H NMR ($J_{2,3}$ = 10.0 Hz, $J_{3,4}$ = 2.4 Hz).

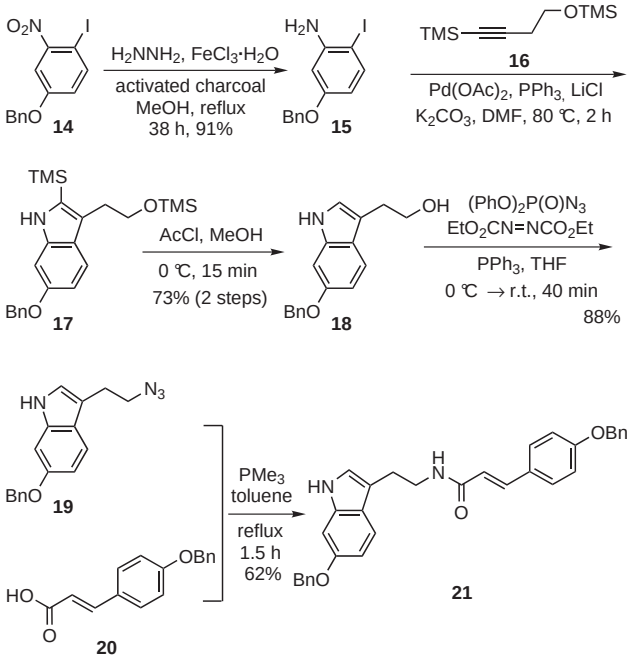
The synthesis of indole unit **21** relied on the Larock method[11] involving the Pd-catalyzed heteroannulation of an internal alkyne with an *o*-iodoaniline derivative (Scheme 3). The requisite *o*-iodoaniline **15** was prepared by the reduction of nitroarene **14**[12] with hydrazine in the presence of $FeCl_3$ and activated charcoal (MeOH, reflux, 38 h).[13] The indole skeleton was constructed via the Pd-catalyzed cyclization of *o*-iodoaniline **15** and four mole equivalents of silylacetylene **16**[14] [Pd(OAc) (0.1 equiv), DMF, 80 °C, 2 h].

The trimethylsilyl group in indole **17** was removed by acidic methanol (MeOH, AcCl, 0 °C, 15 min) to afford indole **18** in 73% overall yield from **15**. The hydroxy group in **18** was transformed into an azide group with triphenylphosphine (2 mol equiv), diphenylphosphoryl azide (2 mol equiv), and diethyl azodicarboxylate (2 mol equiv, THF, 0 °C to r.t., 40 min) in 88% yield.[15] Azide **19** was converted to indole unit **21**[16] in 62% yield via the Staudinger reaction with acid **20** using trimethylphosphine (1.2 equiv, toluene, reflux, 1.5 h).[17]

Having afzelechin **13** and indole unit **21** in hand, the stage was set for the key coupling reaction. The question at this stage was whether or not the silyl ether would be used for the key coupling reaction. To the best of our knowledge, siloxy groups had not been used as leaving groups in this context. Thus, we examined whether the promoters used



Scheme 2 Synthesis of afzelechin unit **13**



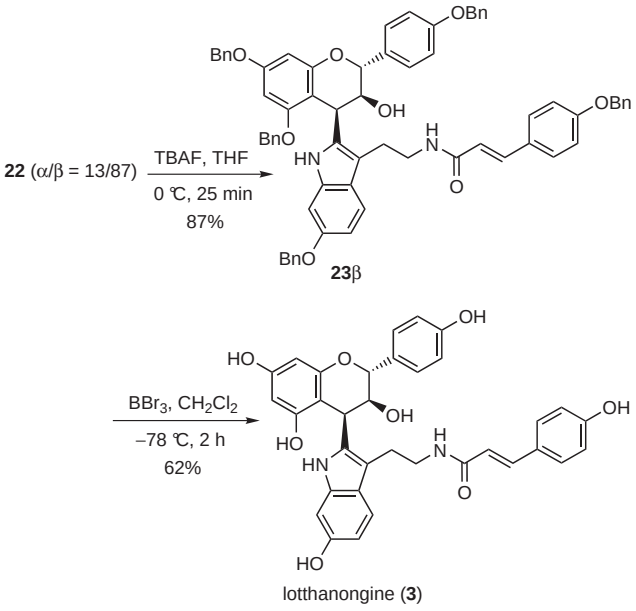
Scheme 3 Synthesis of indole unit **21**

for the activation of catechin **4** in the model studies (vide supra) were effective also for the activation of silyl ether.

Pleasingly, each acid promoter was effective for this purpose (Table 2). It turned out the difference was, however, that the catalytic conditions led to rather slow reactions with poor stereoselectivities (runs 1–4).

So we attempted the stoichiometric use of acid promoters, and Cp_2ZrCl_2–$AgClO_4$ gave best results with high β-selectivity (95%, α/β = 13:87, run 7).[5b] The other promoters gave lower stereoselectivities so long as the stoichiometric reactions were concerned (runs 5, 6, and 8).

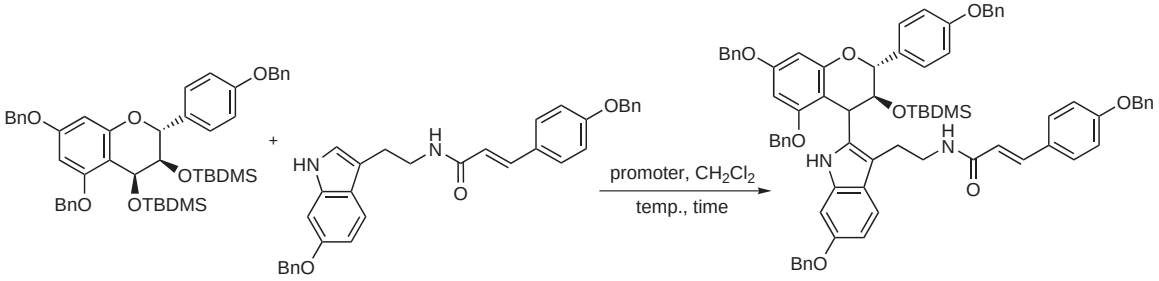
Since separation of the diastereomers of **22** was difficult by silica gel chromatography, we chose to proceed, without their separation, to the next desilylation stage. Fortunately, upon careful treatment of the α/β mixture of **22** (α/β = 13:87) with tetrabutylammonium fluoride (TBAF, 1.2 mol equiv) at 0 °C (THF, 25 min), only the β-isomer, **22**β, selectively underwent detachment of the TBDMS group, while the α-isomer, **22**α, remained intact. If the reaction was further warmed to room temperature, the α-isomer also underwent desilylation (vide infra). Finally, five benzyl groups in **23**β was removed by careful exposure to BBr_3 (10 mol equiv) at –78 °C (CH_2Cl_2, 2 h) to give lotthanongine (**3**) as amorphous solids in 62% yield (Scheme 4). The synthetic material proved to be identical with the natural product by comparison of their spectroscopic data (^{1}H NMR, ^{13}C NMR, IR) and combustion analysis.[18]



Scheme 4 Removal of protecting groups

The minor diastereomer **22**α was also converted to **24**, the α-isomer of the natural product **3** (Scheme 5). Thus, the TBDMS group in **22**α was removed by TBAF at room temperature (THF, 7 h), and removal of the benzyl protecting groups in a similar way gave the isomer **24**.[19]

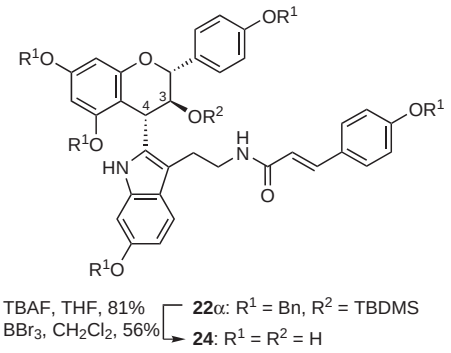
Table 2 Coupling Reaction between Afzelechin **13** and Indole **21**



13 **21** (1.2 equiv) **22**

Run	Promoter (equiv)	Temp (°C)	Time (h)	Yield (%)	α/β
1	$BF_3{\cdot}OEt_2$ (0.1)	–45 → 25	4.0	88	27:73
2	TMSOTf (0.1)	–45 → 25	4.0	89	29:71
3	Cp_2ZrCl_2 (0.1), $AgClO_4$ (0.2), MS 4Å	–45 → 25	21	77[a]	22:78
4	$TsOH{\cdot}H_2O$ (0.1)	0 → 25	21	81[b]	41:59
5	$BF_3{\cdot}OEt_2$ (1.2)	–45 → –5	1.3	90	28:72
6	TMSOTf (1.2)	–45 → –15	1.0	84	20:80
7	Cp_2ZrCl_2 (0.1), $AgClO_4$ (2.4), MS 4Å	–45 → –30	0.33	95	13:87
8	$TsOH{\cdot}H_2O$ (1.2)	–45 → 0	3.0	83	43:57

[a] Recovery: 10%.
[b] Recovery: 2%.



Scheme 5 Synthesis of the α-isomer of lotthanongine, **24**

The ^{1}H NMR data revealed the stereochemistry of **24** ($J_{2,3}$ = 9.8 Hz, $J_{3,4}$ = 8.8 Hz), confirming it diastereomeric to the natural product **3**.

In summary, the first synthesis of lotthanongine (**3**) was achieved by using the S_N1-type reaction of afzelechin **13** with indole **21**, and the structure of **3** was reconfirmed by the synthetic materials. This synthesis opened flexibility to various flavan–indole hybridized compounds.

Acknowledgment

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(6) The β-stereochemistry of the major isomer was assigned by the NOE correlations of N–H proton of the indole with H(2) and H(4) of the flavan nucleus. On the other hand, the α-stereochemistry of the minor isomer was assigned by the NOE correlations between H(2) and H(4) of the flavan

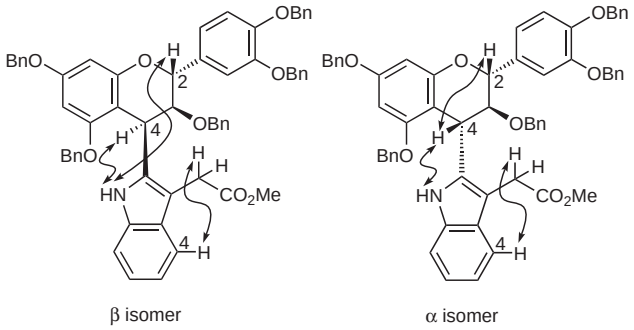

Figure 3

skeleton. The NOE correlations of the H(4) of the indole and the methylene protons of the indole side chain assured the connectivity as indicated, excluding the exchange of the C(2) and C(3) substituents (Figure 3). Compare: Jackson, A. H.; Smith, P. *J. Chem. Soc., Chem. Commun.* **1967**, 264.

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(10) Compound **13**: colorless amorphous solids. ^{1}H NMR (400 MHz, $CDCl_3$): δ = –0.52 (s, 3 H), –0.20 (s, 3 H), –0.18 (s, 3 H), –0.10 (s, 3 H), 0.69 (s, 9 H), 0.85 (s, 9 H), 3.80 (dd, 1 H, *J* = 10.0, 2.4 Hz), 4.98 (s, 2 H), 5.01 (d, 1 H, *J* = 2.4 Hz), 5.02 (s, 2 H), 5.09 (s, 2 H), 5.33 (d, 1 H, *J* = 10.0 Hz), 6.19 (d, 1 H, *J* = 2.2 Hz), 6.21 (d, 1 H, *J* = 2.2 Hz), 6.95 (d, 2 H, *J* = 8.8 Hz), 7.28–7.44 (m, 17 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.7, –5.3, –4.59, –4.58, 17.9, 18.4, 25.8, 26.0, 63.2, 70.0, 70.1, 70.2, 73.7, 76.1, 92.8, 94.1, 106.8, 114.6, 127.3, 127.6, 127.77, 127.82, 128.01, 128.04, 128.47, 128.52, 128.6, 129.2, 132.1, 136.6, 136.7, 137.1, 155.9, 157.2, 158.6, 160.5. IR (KBr): 3066, 3033, 2927, 2856, 1616, 1593, 1514, 1377, 1250, 1151, 1076, 883, 837, 775, 673 cm^{-1}. Anal. Calcd for $C_{48}H_{60}O_6Si_2$: C, 73.05; H, 7.66. Found: C, 72.87; H, 7.86.

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(16) Compound **21**: colorless powders, mp 234–236 °C. ^{1}H NMR (400 MHz, DMSO): δ = 2.81 (br t, 2 H, *J* = 7.3 Hz), 3.43 (br td, 2 H, *J* = 7.3, 5.6 Hz), 5.09 (s, 2 H), 5.13 (s, 2 H), 6.47 (d, 1 H, *J* = 16.1 Hz), 6.72 (dd, 1 H, *J* = 8.5, 2.2 Hz), 6.90 (br d, 1 H, *J* = 2.2 Hz), 7.00 (br s, 1 H), 7.03 (d, 2 H, *J* = 8.6 Hz), 7.27–7.52 (m, 14 H), 8.10 (br t, 1 H, *J* = 5.6 Hz), 10.6 (br s, 1 H). ^{13}C NMR (100 MHz, DMSO): δ = 25.4, 39.6, 69.3, 69.5, 96.0, 109.1, 111.8, 115.2, 118.9, 120.0, 121.4, 121.9, 127.5, 127.6, 127.7, 127.9, 128.4, 128.5, 129.0, 136.8, 137.7, 138.1, 154.4, 159.3, 165.1. IR (KBr): 3224, 1645, 1601, 1539, 1510, 1452, 1174, 694 cm^{-1}. Anal. Calcd for $C_{33}H_{30}N_2O_3$: C, 78.86; H, 6.02; N, 5.57. Found: C, 78.94; H, 5.91; N, 5.43.

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(18) Compound **3**: ^{1}H NMR (500 MHz, CD_3OD): δ = 2.98–3.10 (m, 2 H), 3.47–3.55 (m, 1 H), 3.69–3.77 (m, 1 H), 4.15 (dd, 1 H, *J* = 9.6, 5.7 Hz), 4.67 (d, 1 H, *J* = 5.7 Hz), 4.95 (d, 1 H, *J* = 9.6 Hz), 5.95 (d, 1 H, *J* = 2.4 Hz), 6.00 (d, 1 H, *J* = 2.4 Hz), 6.27 (d, 1 H, *J* = 15.7 Hz), 6.55 (dd, 1 H, *J* = 8.5, 2.2 Hz), 6.74 (d, 1 H, *J* = 2.2 Hz), 6.77 (d, 2 H, *J* = 8.7 Hz), 6.78 (d, 2 H, *J* = 8.7 Hz), 7.24 (d, 2 H, *J* = 8.7 Hz), 7.27 (d, 2 H, *J* = 8.7 Hz), 7.33 (d, 1 H, *J* = 8.5 Hz), 7.35 (d, 1 H, *J* = 15.7 Hz), 9.30 (br s, 1 H). ^{13}C NMR (125 MHz, CD_3OD): δ = 25.3, 36.2, 41.3, 71.8, 79.6, 95.8, 96.8, 97.8, 102.9, 109.6, 111.7, 116.1, 116.7, 118.7, 119.4, 123.9, 127.9, 130.2, 130.6, 131.7, 133.9, 138.6, 141.5, 153.6, 157.5, 158.1, 158.5, 159.1, 160.4, 169.3. IR (KBr): 3300, 1647, 1514, 1458, 1227, 1146, 829 cm^{-1}. Anal. Calcd for $C_{34}H_{30}N_2O_8$: C, 68.68; H, 5.09; N, 4.71. Found: C, 68.41; H, 5.38; N, 4.42.

(19) Compound **24**: ^{1}H NMR (400 MHz, CD_3OD): δ = 2.90–3.05 (m, 1 H), 3.05–3.20 (m, 1 H), 3.46–3.58 (m, 1 H), 3.64–3.78 (m, 1 H), 4.08 (dd, 1 H, *J* = 9.8, 8.8 Hz), 4.33 (d, 1 H, *J* = 8.8 Hz), 4.62 (d, 1 H, *J* = 9.8 Hz), 5.95 (d, 1 H, *J* = 2.4 Hz), 5.98 (d, 1 H, *J* = 2.4 Hz), 6.38 (d, 1 H, *J* = 15.9 Hz), 6.52 (dd, 1 H, *J* = 8.6, 2.4 Hz), 6.66 (d, 1 H, *J* = 2.4 Hz), 6.75 (d, 2 H, *J* = 8.6 Hz), 6.81 (d, 2 H, *J* = 8.8 Hz), 7.25 (d, 2 H, *J* = 8.6 Hz), 7.27 (d, 1 H, *J* = 8.6 Hz), 7.33 (d, 2 H, *J* = 8.8 Hz), 7.37 (d, 1 H, *J* = 15.9 Hz), 8.02 (br s, 1 H), 9.52 (br s, 1 H). ^{13}C NMR (100 MHz, CD_3OD): δ = 25.3, 41.3, 41.8, 75.1, 83.4, 96.6, 97.7, 97.9, 104.1, 109.3, 110.6, 116.1, 116.7, 118.8, 119.0, 123.6, 127.9, 130.3, 130.6, 131.0, 136.9, 138.6, 141.5, 153.5, 158.4, 158.6, 158.8, 159.0, 160.4, 169.3. IR (KBr): 3326, 1647, 1604, 1516, 1458, 1234, 1173, 1145, 1068, 831 cm^{-1}. Anal. Calcd for $C_{34}H_{30}N_2O_8$: C, 68.68; H, 5.09; N, 4.71. Found: C, 68.43; H, 5.38; N, 4.46.