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Synthesis of Novel Angular Heterocyclic Lignans by an $InCl_3$-Catalyzed Friedel–Crafts-Type Cyclization

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Keywords: Friedel–Crafts cyclization / Heterocyclic lignans / Indium / Michael addition / Privileged structures

The synthesis of a 1-aryltetralin privileged structure-based library of novel angular heterocyclic lignans is described. Indolotetralins **3**, tetrahydroquinolinotetralins **4**, and thiochromanotetralins **5** were obtained from the methyl ester of thuriferic acid **2** according to a three-step procedure involving an $InCl_3$-catalyzed Friedel–Crafts-type cyclization as the key step.

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Introduction

The search for privileged structures is rapidly becoming a crucial component of strategy in drug discovery as they represent an ideal source of lead compounds with enhanced drug-like properties.[1] The concept of "privileged structures" was introduced in 1988 by Evans et al.[2] when focusing on the design of benzodiazepine-based CCK-A antagonists and has since received general acceptance.[1,3] A privileged structure is a "single molecular scaffold able to provide ligands for diverse receptors" through judicious modification of functional groups. Some common molecular frameworks can act on different gene families, indicating that diverse protein targets can contain structurally common ligand binding sites.[4] Thus, the privileged structures would form favorable noncovalent interactions with receptors giving rise to a broad binding pattern, the side-chains attached to the scaffold in a well-defined fashion being responsible for molecular recognition of the receptor. This was supported by the study of Fesik and co-workers,[5] an NMR-based screening of fragment binding against 11 protein targets which identified 12 recurring fragments (e.g., carboxylic acid, diphenylmethane and biphenyl above all). This result suggests that the use of these preferred molecular motifs in a combinatorial library design should qualitatively enrich a screening compound collection. It is noteworthy that natural compounds encompass privileged structures as their biosynthesis involves different proteins and they may bind to other proteins as well.[6] The evolution of this concept has been pursued for privileged structures associated with a target receptor family[1d] (e.g., 5,5-*trans*-fused lactams for serine protease, reverse turn mimic for G protein-coupled receptor). However, Schnur et al.[7] refute the so-called target family privileged structures having analyzed target family ligands in the MDDR database which contains compounds targeted and tested for potential therapeutic value that were compiled from literature data and confirm even more the definition of the original concept of privileged structures by Evans et al.[2]

The 1-aryltetralin system **1** is a privileged structure found in natural cyclolignans and synthetic derivatives which present a wide range of biological activities,[8–10] such as the inhibition of tubulin polymerization and DNA topoisomerase II, and immunosuppressive, anti-HIV, and antidepressant activities. Recently, cyclolignans have been reported as inhibitors of the insulin-like growth factor receptor (IGF-1R).[11,12] To the best of our knowledge there have been only a few reports on the synthesis of angular lignans possessing the 1-aryltetralin scaffold **1**: The synthesis of pyrazolignans[13] and isoxazolines[14] from 7-ketolignanolides with hydrazine and oxime derivatives, respectively. As an extension to our previous work,[15] we describe herein the synthesis of novel angular heterocyclic lignans **3**–**5** from methyl thuriferate **2**, a derivative of the cyclolignan thuriferic acid[16] that possesses three independently addressable functional groups, by using indium halides[17] as mild Lewis acid catalysts (Figure 1). Thus, these compounds combine the 1-aryltetralin privileged-structure **1** and heterocyclic motifs found in many biologically important derivatives, namely indole,[1b,18] tetrahydroquinoline[19] and thiochrom-

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ane[20] structures. The synthesis of **3**–**5** was accomplished by an $InCl_3$-catalyzed intramolecular Friedel–Crafts-type reaction[21,22] as the key step.

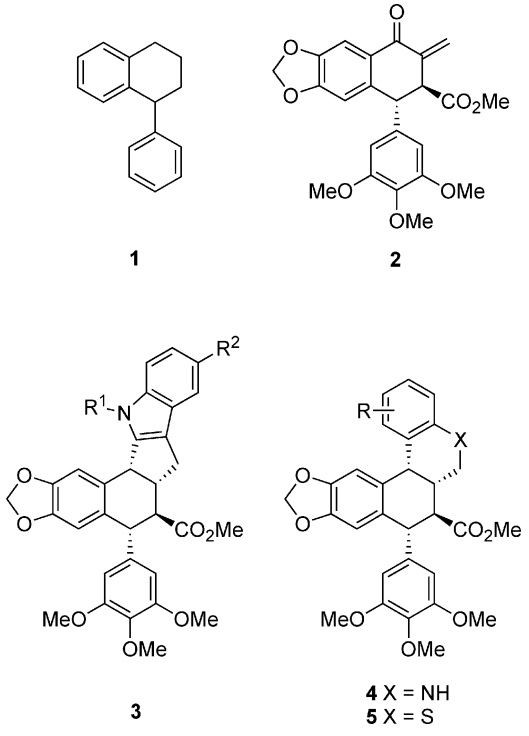


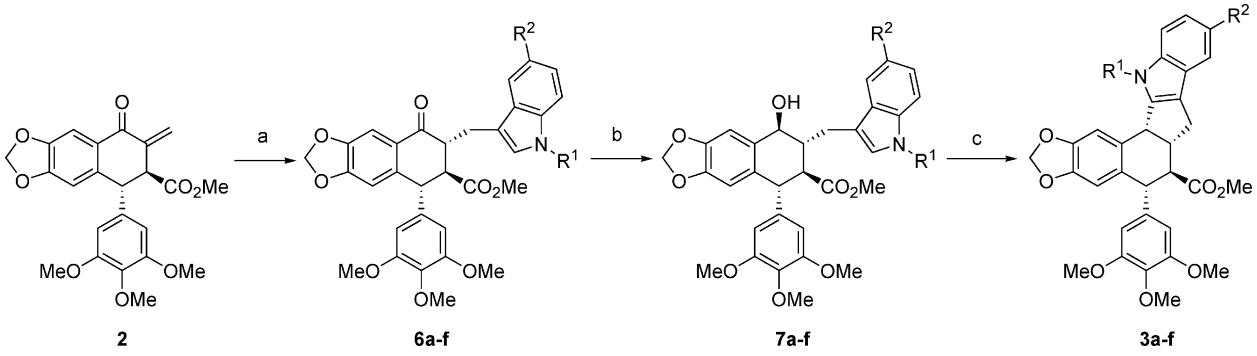
Figure 1. Structures of indolotetralins **3**, tetrahydroquinolinotetralins **4** and thiochromenotetralins **5**.

Results and Discussion

Indolotetralins **3**, tetrahydroquinolinotetralins **4**, and thiochromanotetralins **5** were obtained in three steps from the methyl ester of thuriferic acid **2**: Sequential stereoselective Michael addition of the requisite nucleophile to **2**, stereoselective reduction of the substituted tetralone derivative, and $InCl_3$-catalyzed intramolecular Friedel–Crafts-type cyclization from the resulting benzyl alcohol (Scheme 1 and Scheme 2). The Michael addition of indoles to **2** was performed[23,24] by using a catalytic amount of $InBr_3$ (10 mol-%) at room temperature in DCM (Table 1, entries 1–5) or at reflux in DCE for 5-nitroindole (Table 1, entry 6), affording the desired β-indolyl ketones **6a**–**f** in good yields (83–100%) and with *dr* > 95%, as judged by ^{1}H NMR. The 2,3-*trans* stereochemistry was assigned on the basis of the coupling constants $J_{1,2}$ and $J_{2,3}$ for compounds **6c** (10.7 and 11.5 Hz), **6d** (10.5 and 11.7 Hz), and **6f** (10.9 and 12 Hz). Stereoselective reduction of **6a**–**f** with $NaBH_4$ at 0 °C gave the corresponding benzylic alcohols **7a**–**f** in 82–96% yield and with *dr* > 95% (Table 1, entries 1–6). The 3,4-*trans* stereochemistry was deduced from the coupling constants $J_{2,3}$ and $J_{3,4}$ for compounds **7c** (10.7 and 8.6 Hz), **7d** (10.7 and 8.3 Hz), and **7f** (11 and 8 Hz).

Recently, direct carbon–carbon formation between allylic and benzylic alcohols (i.e., diphenylmethanol and 1-phenylethanol) and active methylenes (i.e., diesters, keto esters, and diketones), alkoxy ketones, and indoles catalyzed by indium trichloride was demonstrated by Baba and coworkers.[25] Two mechanisms for the activation of alcohols, probably via the generation of a benzylic cation, have been proposed for this reaction: Alkylation of indium-activated alcohol and a two-step mechanism (i.e., dimerization of the alcohol followed by alkylation), without forgetting a possible interaction between $InCl_3$ and the active methylene. Benzylic alcohols **7a**–**e** underwent an $InCl_3$-catalyzed intramolecular Friedel–Crafts-type cyclization[26] to give the indolotetralin compounds **3a**–**e** in 73–96% yields (Table 2, entries 1–5). Note that these compounds exhibit a *cis* junction (*dr* > 95%) at the fusion of the rings. This protocol was much less effective for **3f** due to the presence of the deactivating nitro group on the indole ring (Table 2, entry 6). The stereochemical assignment of **3** was established on the basis of NOESY correlations of compounds **3b** and **3c** (**3b**: NMe/5-H, 3-H/4-H, 1-H/3-H, 2-H/2′-H,6′-H; **3c**: NH/5-H, 3-H/4-H, 1-H/3-H, 2-H/2′-H,6′-H, Figure 2).[27]

The Michael additions of anilines[15a] in refluxing THF and thiophenols[28] in THF at room temperature were both catalyzed by Et_3N and gave the corresponding β-amino ketones **8a**–**e** (Table 1, entries 7–11) and β-thioketones **9a**–



Scheme 1. Synthesis of indolotetralins **3a**–**f**. Reagents and conditions: (a) $InBr_3$, indole, DCM, room temp.; (b) $NaBH_4$, THF, MeOH, 0 °C to room temp.; (c) $InCl_3$, DCE, reflux.

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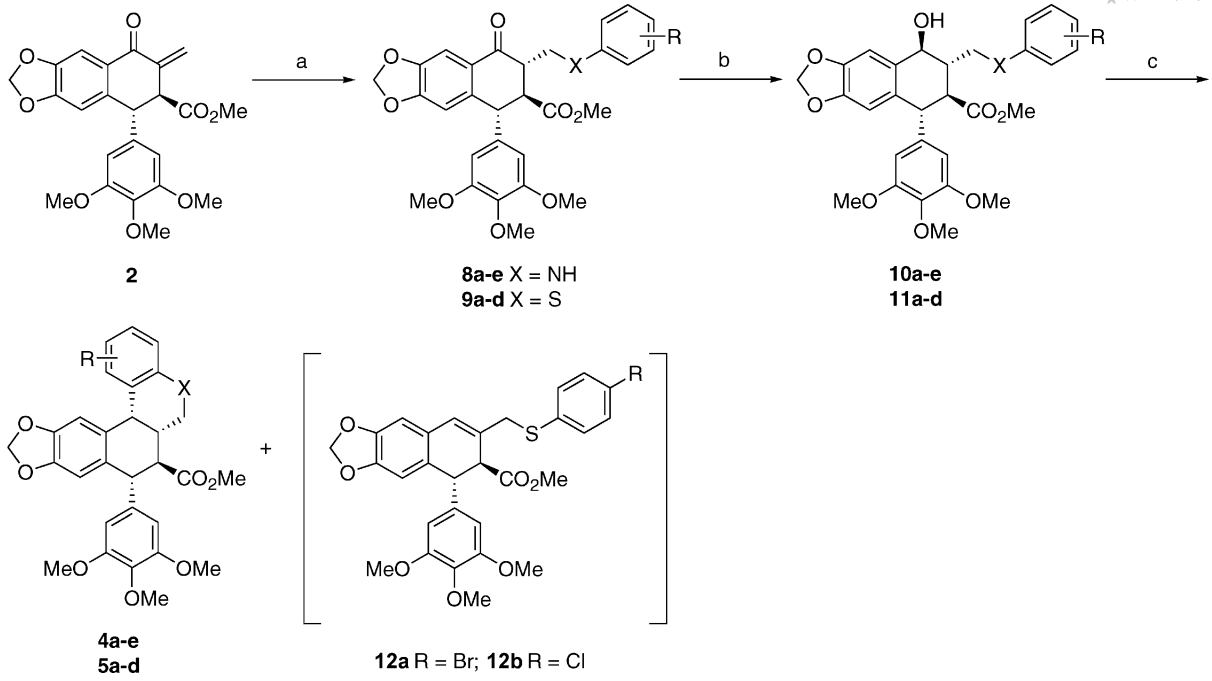

Scheme 2. Syntheses of tetrahydroquinolino-tetralins **4a**–**e** and thiochromano-tetralins **5a**–**d**. Reagents and conditions: (a) Et_3N, aniline or thiophenol, THF; (b) $NaBH_4$, THF, MeOH, 0 °C to room temp.; (c) $InCl_3$, DCE, reflux.

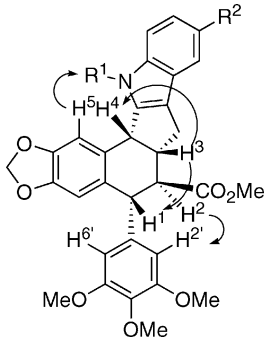

Figure 2. Relevant NOESY correlations for **3b** (R^1 = Me, R^2 = H) and **3c** (R^1 = H, R^2 = Br).

d (Table 1, entries 12–15) in good-to-excellent yields (*dr* > 95%), respectively. In the latter case, no reaction with 4-nitrothiophenol was observed even in the presence of an excess of base (Table 1, entry 16).

Reduction of the Michael adducts **8a**–**e** and **9a**–**d** with $NaBH_4$ in MeOH at 0 °C gave **10a**–**e** (83–100% yields, *dr* > 95%) and **11a**–**d** (82–95% yields, *dr* > 95%), respectively (Table 1). The 2,3- and 3,4-*trans* stereochemistry of **10** was deduced from the coupling constants $J_{2,3}$ (10.9–11.4 Hz) and $J_{3,4}$ (9.2–9.5 Hz), and was further confirmed by NOESY cross-peaks between 1-H/3-H, 2-H/4-H, and 2-H/2′-H,6′-H for **10d**. The coupling constants $J_{2,3}$ (10.8–10.9 Hz) and $J_{3,4}$ (8.0–9.5 Hz) allowed the stereochemical assignment of **11**.

It is worth noting that all attempts to hydroalkoxylate enone **2** were unsuccessful. With the aim of preparing chromanotetralins, many attempts were made but all revealed either the lack of reactivity of **2** towards oxa-Michael addition or its tendency for aromatization. All experiments were run with benzyl alcohol as a model substrate known for its reactivity. Thus, tributylphosphane-catalyzed hydroalkoxylation[29] or the use of $[Rh(cod)Cl_2]_2$ in the presence of K_2CO_3 in THF at reflux led to aromatization yielding the corresponding arylnaphthalene, whereas the $[Rh(cod)(OMe)]_2$-catalyzed reaction led to transfer hydrogenation with the *exo* methylene of the coupling partner **2**.[30] Other methodologies applied {e.g., Tf_2NH, $Cu(OTf)_2$, $InBr_3$, $InCl_3$, $PdCl_2$, $[PdCl_2(MeCN)_2]$} were also ineffective.[31–33]

Cyclization of **10a**–**e** using a catalytic amount of $InCl_3$ in refluxing DCE furnished tetrahydroquinolinotetralins **4a**–**e** in 62–93% yields and with *dr* > 95% (Table 2, entries 7–11). Interestingly, Yadav et al.[26] recently developed an $InCl_3$-catalyzed tandem Michael/Friedel–Crafts cyclization that provides novel access to optically active tetrahydroquinolines from δ-hydroxy-α,β-unsaturated aldehydes and arylamines. As for the synthesis of thiochromanotetralins **5a**–**d**, this reaction was applied with success when electron-donating groups were attached to the thioether ring, giving rise to **5c** (76%, *dr* > 95%) and **5d** (86%, *dr* > 95%) from **11c** and **11d**, respectively (Table 2, entries 14 and 15), although sulfur is generally not a good substituent for electrophilic aromatic substitutions.[20c] In the case of **11a** and **11b**, characterized by the presence of a deactivating group on the thioether ring, we observed competition between intramolecular cyclization and dehydration at position C-4, leading to **5a** and **5b**, each one as an inseparable 1:1 mixture with the resulting 1,2-dihydronaphthalene **12a** and **12b**, respectively. Use of $InBr_3$ improved the yields of **5a** and **5b** slightly, as judged by ^1H NMR (Table 2, entries 12 and 13).

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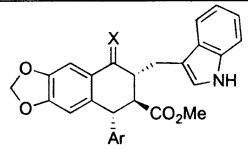
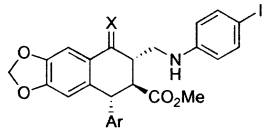
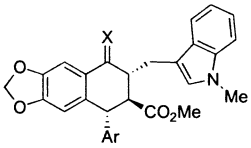
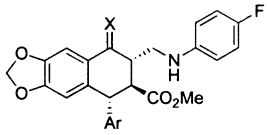
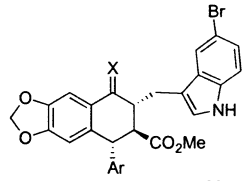
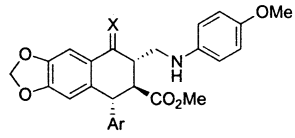
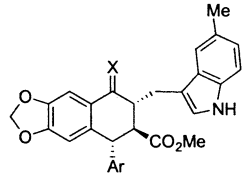
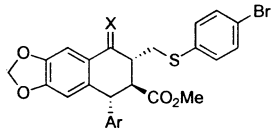
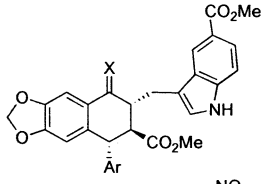
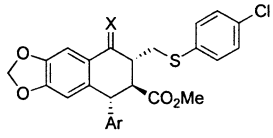
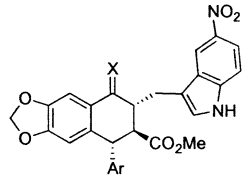
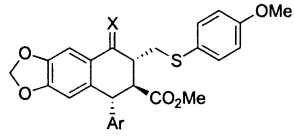
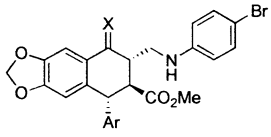
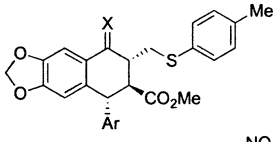
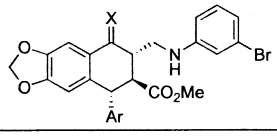
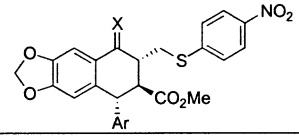
Table 1. Michael addition to methyl thuriferate **2** and reduction of the adducts (reagents and conditions are given in the footnotes).

Entry	Product	Yield (%)	Entry	Product	Yield (%)
1		**6a** (X = O)[a] 83 **7a** (X = OH, H)[b] 82	9		**8c** (X = O)[d] 84 **10c** (X = OH, H)[e] 98
2		**6b** (X = O)[a] 100 **7b** (X = OH, H)[b] 96	10		**8d** (X = O)[d] 78 **10d** (X = OH, H)[e] 83
3		**6c** (X = O)[a] 90 **7c** (X = OH, H)[b] 87	11		**8e** (X = O)[d] 90 **10e** (X = OH, H)[e] 97
4		**6d** (X = O)[a] 86 **7d** (X = OH, H)[b] 83	12		**9a** (X = O)[f] 100 **11a** (X = OH, H)[e] 90
5		**6e** (X = O)[a] 92 **7e** (X = OH, H)[b] 91	13		**9b** (X = O)[f] 87 **11b** (X = OH, H)[e] 82
6		**6f** (X = O)[c] 92 **7f** (X = OH, H)[b] 88	14		**9c** (X = O)[f] 86 **11c** (X = OH, H)[e] 85
7		**8a** (X = O)[d] 94 **10a** (X = OH, H)[e] 100	15		**9d** (X = O)[f] 86 **11d** (X = OH, H)[e] 95
8		**8b** (X = O)[d] 95 **10b** (X = OH, H)[e] 100	16		**9e** (X = O)[g] NR[h]

[a] Indole (1.3 equiv.), $InBr_3$ (10%), CH_2Cl_2, room temp., 2 h. [b] $NaBH_4$ (1.5 equiv.), THF/MeOH (1:1), 0 °C to room temp., 2 h (β-OH configuration). [c] 5-Nitroindole (1.3 equiv.), $InBr_3$ (10%), DCE, reflux, 1 h. [d] Aniline (4 equiv.), Et_3N (4 equiv.), THF, reflux, 24 h (see ref.[27]). [e] $NaBH_4$ (2 equiv.), THF/MeOH (1:1), 0 °C to room temp., 1 h (β-OH configuration). [f] Thiophenol (2 equiv.), Et_3N (0.5 equiv.), THF, room temp., 2.5 h. [g] 4-Nitrothiophenol (5 equiv.), Et_3N (5 equiv.), THF, reflux, 48 h. [h] No reaction; Ar = 3,4,5-trimethoxyphenyl.

Cyclization of **11a** was attempted with a catalytic amount of *p*-toluenesulfonic acid in refluxing toluene.[20c] This resulted in the exclusive formation of **12a**. Treatment of **11a** with $TiCl_4$ (the Angle protocol)[34] afforded a mixture of **11a** and of its epimer after 1 h at –78 °C in DCM. The same reaction at room temperature gave **12a** in quantitative yield. Cyclization of **12a** into **5a** by an intramolecular hydroarylation reaction with polyphosphoric acid[35–37] at 100 °C or with the mild catalyst[38] $RuCl_3$/AgOTf were unsuccessful.

The relative stereochemistry of **4** was determined on the basis of the *J* values ($J_{2,3}$ = 10.4–10.9 Hz, $J_{3,4}$ = 3.7–4.2 Hz) and NOESY data (**4d**: 1-H/4-H, 2-H/2′-H,6′-H, 3-H/4-H, 3′′-H/2′-H,6′-H). The coupling constants $J_{2,3}$ (**5c**: 10.5 Hz; **5d**: 10.6 Hz) and $J_{3,4}$ (**5c**: 4.6 Hz; **5d**: 4.8 Hz) allowed the stereochemical assignment of compounds **5**.

The mechanism for the $InCl_3$-catalyzed intramolecular Friedel–Crafts-type cyclization is presumably an electrophilic aromatic substitution. Indirect evidence of the in-

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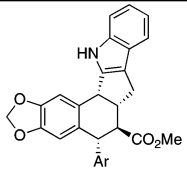
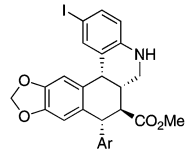
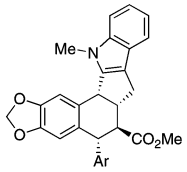
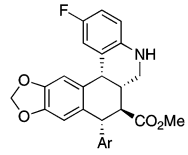
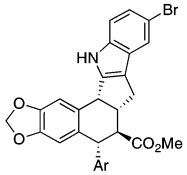
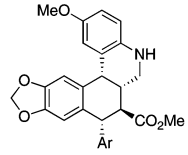
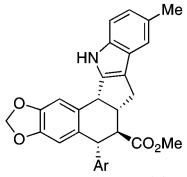
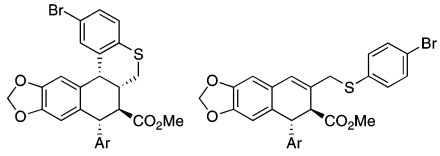
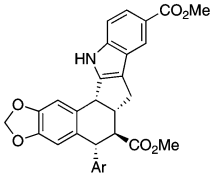
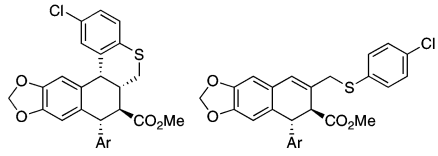
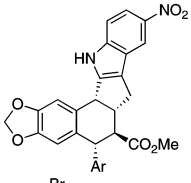
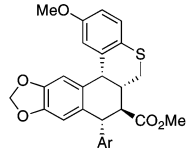
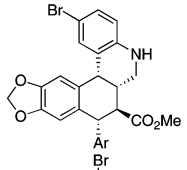
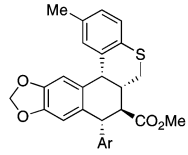
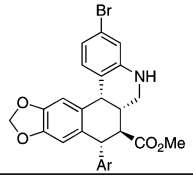
Table 2. $InCl_3$-catalyzed intramolecular Friedel–Crafts-type cyclization (reagents and conditions are given in the footnotes).

Entry	Product		Yield (%)	Entry	Product		Yield (%)
1[a]		**3a**	73	9[b]		**4c**	78
2[a]		**3b**	95	10[b]		**4d**	84
3[a]		**3c**	91	11[b]		**4e**	80
4[a]		**3d**	96	12[c]		**5a** **12a**	51[d]
5[a]		**3e**	86	13[c]		**5b** **12b**	49[d]
6[a]		**3f**	27	14[b]		**5c**	76
7[b]		**4a**	93	15[b]		**5d**	86
8[b]		**4b**	62				

[a] $InCl_3$ (10%), DCE, reflux, 30 min. [b] $InCl_3$ (10%), DCE, reflux, 20 min. [c] $InBr_3$ (10%), DCE, reflux, 15 min. [d] Inseparable mixture of **5a**,**b** and **12a**,**b** in a 1:1 ratio, as determined by ^1H NMR spectroscopy. Ar = 3,4,5-trimethoxyphenyl.

volvement of the benzyl cation at C-4 has been provided by additional experiments. It should be noted that this intermediate was stabilized by the methyleneoxy group in the *para* position. In this event, reduction of β-indolyl ketone **6e** and amino ketone **8d** with L-selectride at –78 °C gave in each case a separable mixture (1:1 ratio) of the corresponding α-OH (e.g., $J_{3,4}$ = 2.5 Hz for the reduced product from **6e**) and β-OH isomers at the C-4 position in good yields. Cyclization of these C-4 α-OH isomers catalyzed by $InCl_3$ (10 mol-%) led to the same products as those obtained from the C-4 β-OH isomers (i.e., **3e** and **4d**) and with satisfying yields, a result that apparently indicates the formation of the benzyl carbocation by activation of the benzyl alcohol under the influence of $InCl_3$. In the case of the cyclization of **7a**–**f**, it is not certain whether indolotetralins **3a**–**f** result from electrophilic substitution directly at the C-2 position

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of the indole or from electrophilic substitution at C-3 followed by rearrangement of an intermediate spiroindolenine to C-2.[39]

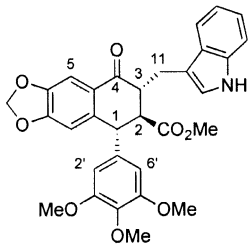
Conclusions

In conclusion, this account describes a mild and convenient strategy for the stereoselective synthesis of a 1-aryltetralin privileged structure-based library of novel angular heterocyclic lignans such as indolotetralins **3**, tetrahydroquinolinotetralins **4**, and thiochromanotetralins **5** from the methyl ester of thuriferic **2**. The key reaction is an $InCl_3$-catalyzed Friedel–Crafts-type cyclization initiated by benzylic carbocation formation. The ester group of **2** at the C-2 position provides an opportunity for the further synthetic development of these structures. A biological evaluation of these compounds is currently under investigation.

Experimental Section

General Procedure for the Synthesis of 3-(Indol-3-ylmethyl)tetralones 6a–e: Indium tribromide (8.7 mg, 10 mol-%) and the indole (1.3 equiv.) were successively added to a solution of the methyl ester of thuriferic acid **2** (105 mg, 0.246 mmol) in DCM (5 mL) at room temperature. The reaction mixture was stirred for 2 h at room temperature and subjected to evaporation under reduced pressure. Purification of the crude product by flash chromatography on a silica gel column (cyclohexane/ethyl acetate, 7:3) gave the corresponding 3-(indol-3-ylmethyl)tetralones **6a**–**e**.

Compound 6a: Off-white solid (110 mg, 83% yield); m.p. 146–149 °C. $[\alpha]_D^{20}$ = –72.6 (c = 0.14, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 8.03 (br. s, 1 H, NH), 7.66 (d, J = 7.4 Hz, 1 H, 4′′-H), 7.48 (s, 1 H, 5-H), 7.30 (dd, J = 8.0, 0.8 Hz, 1 H, 7′′-H), 7.12 (m, 2 H, 5′′-H, 6′′-H), 7.02 (d, J = 2.0 Hz, 1 H, 2′′-H), 6.29 (s, 2 H, 2′-H, 6′-H), 6.24 (s, 1 H, 8-H), 5.96 (s, 2 H, OCH_2O), 4.34 (d, J = 10.6 Hz, 1 H, 1-H), 3.84 (s, 3 H, 4′-OMe), 3.76 (s, 6 H, 3′-OMe, 5′-OMe), 3.32 (m, 3 H, 2-H, 3-H, 11a-H), 3.28 (s, 3 H, CO_2Me), 3.17 (m, 1 H, 11b-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 195.7 (C-4), 172.9 (C-13), 153.3 (C-3′, C-5′), 152.3 (C-7), 147.3 (C-6), 141.1 (C-1′), 137.2 (C-4′), 136.6 (C-9), 135.9 (C-8′′), 127.7 (C-9′′), 127.2 (C-10), 123.6 (C-2′′), 121.8 (C-6′′), 119.2 (C-4′′, C-5′′), 112.8 (C-3′′), 110.9 (C-7′′), 108.3 (C-8), 106.1 (C-5, C-2′, C-6′), 101.8 (OCH_2O), 60.9 (4′-OMe), 56.2 (3′-OMe, 5′-OMe), 54.2 (C-2), 51.5 (CO_2Me), 49.8 (C-3), 49.4 (C-1), 24.0 (C-11) ppm. MS (ES+): m/z = 566 $[M + Na]^+$. HRMS (DCI/NH_3): calcd. for $C_{31}H_{29}O_8N$ 543.1893; found 543.1874.



Compound 6f: Indium tribromide (8.3 mg, 10 mol-%) and 5-nitroindole (49.3 mg, 0.304 mM) were added successively to a solution of the methyl ester of thuriferic acid **2** (100 mg, 0.234 mmol) in DCM (5 mL) at room temperature. The reaction mixture was stirred at reflux for 1 h at room temperature and subjected to evaporation under reduced pressure. Purification of the crude product by flash chromatography on a silica gel column (cyclohexane/ethyl acetate, 7:3) gave the corresponding 3-indol-3-ylmethyltetralone **6f**. Yellow solid (126.7 mg, 92% yield); m.p. 179–181 °C. $[\alpha]_D^{20}$ = –118.2 (c = 1.02, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3469, 3019, 2975–2915, 1732, 1671, 1593, 1506, 1480 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.64 (d, J = 1.9 Hz, 1 H, 4′′-H), 8.55 (br. s, 1 H, NH), 8.05 (dd, J = 9.0, 1.9 Hz, 1 H, 6′′-H), 7.47 (s, 1 H, 5-H), 7.33 (d, J = 9.0 Hz, 1 H, 7′′-H), 7.25 (m, 1 H, 2′′-H), 6.28 (s, 2 H, 2′-H, 6′-H), 6.22 (s, 1 H, 8-H), 5.96 (s, 2 H, OCH_2O), 4.34 (d, J = 10.9 Hz, 1 H, 1-H), 3.83 (s, 3 H, 4′-OMe), 3.76 (s, 6 H, 3′-OMe, 5′-OMe), 3.40 (s, 3 H, CO_2Me), 3.35 (m, 1 H, 3-H), 3.25 (m, 2 H, 11-H), 3.20 (dd, J = 12.0, 10.9 Hz, 1 H, 2-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 195.3 (C-4), 172.8 (C-13), 153.4 (C-3′, C-5′), 152.5 (C-7), 147.4 (C-6), 141.6 (C-5′′), 141.3 (C-1′), 138.8 (C-8′′), 137.2 (C-4′), 136.3 (C-9), 127.3 (C-9′′), 127.0 (C-10), 126.9 (C-2′′), 117.5 (C-6′′), 116.6 (C-4′′), 115.6 (C-3′′), 111.0 (C-7′′), 108.4 (C-8), 106.1 (C-5, C-2′, C-6′), 101.9 (OCH_2O), 60.9 (4′-OMe), 56.2 (3′-OMe, 5′-OMe), 54.4 (C-2), 51.9 (CO_2Me), 50.0 (C-3), 49.6 (C-1), 23.5 (C-11) ppm. MS (ES+): m/z = 589 $[M + H]^+$, 611 $[M + Na]^+$. MS (ES–): m/z = 587 $[M - H]^-$. HRMS (DCI/CH_4): calcd. for $C_{31}H_{28}N_2O_{10}{\cdot}C_2H_5$ 617.2145; found 617.2135.

General Procedure for the Synthesis of 3-(Phenylaminomethyl)-tetralones 8a–e: Et_3N (132 μL, 0.938 mmol) and the aniline (0.938 mmol, 4 equiv.) were added to a solution of the methyl ester of thuriferic acid **2** (100 mg, 0.234 mmol) in THF (4 mL) at room temperature. The reaction mixture was then heated at 65 °C for 24 h, concentrated under reduced pressure, and the crude product was purified by flash chromatography on silica gel (cyclohexane/EtOAc, 5:2) to give the desired β-amino ketones **8a**–**e**.

Compound 8a: Off-white solid (131.6 mg, 94% yield); m.p. 162 °C. $[\alpha]_D^{20}$ = –4.1 (c = 0.29, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3357, 2928, 1729, 1670, 1593, 1506, 1480 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.45 (s, 1 H, 5-H), 7.25 (d, J = 8.8 Hz, 2 H, 3′′-H, 5′′-H), 6.55 (d, J = 8.8 Hz, 2 H, 2′′-H, 6′′-H), 6.33 (s, 2 H, 2′-H, 6′-H), 6.26 (s, 1 H, 8-H), 6.00 (m, 2 H, OCH_2O), 4.35 (d, J = 10.6 Hz, 1 H, 1-H), 3.86 (s, 3 H, 4′-OMe), 3.80 (s, 6 H, 3′-OMe, 5′-OMe), 3.50 (m, 1 H, 11a-H), 3.47 (s, 3 H, CO_2Me), 3.39 (dd, J = 13.8, 3.7 Hz, 1 H, 11b-H), 3.24 (dd, J = 12.6, 10.6 Hz, 1 H, 2-H), 3.21 (m, 1 H, 3-H) ppm. ^{13}C NMR [75 MHz, $(CD_3)_2CO$]: δ = 195.5 (C-4), 173.3 (C-13), 154.6 (C-3′, C-6′), 153.5 (C-7), 148.9 (C-1′′), 148.4 (C-6), 143.0 (C-1′), 138.7 (C-4′), 137.8 (C-9), 132.5 (C-3′′, C-5′′), 127.7 (C-10), 115.4 (C-2′′, C-6′′), 109.2 (C-8), 108.5 (C-4′′), 107.7 (C-2′, C-6′), 105.9 (C-5), 103.3 (OCH_2O), 60.7 (4′-OMe), 56.6 (3′-OMe, 5′-OMe), 53.4 (C-2), 52.1 (CO_2Me), 50.0 (C-1), 49.2 (C-3), 43.6 (C-11) ppm. MS (DIC/NH_3): m/z = 598, 600 $[M + H]^+$. HRMS (DCI/CH_4): calcd. for $C_{29}H_{29}NO_8Br$ 598.1077, 600.1092; found 598.1071, 600.1101.

General Procedure for the Synthesis of 3-(Phenylthiomethyl)tetralones 9a–d: Et_3N (17 μL, 0.117 mmol) and the thiophenol (0.468 mmol, 2 equiv.) were added to a solution of the methyl ester of thuriferic acid **2** (100 mg, 0.234 mmol) in THF (2 mL) at room temperature. The reaction mixture was stirred at room temperature for 2.5 h, concentrated under reduced pressure, and the crude product was purified by flash chromatography on silica gel (cyclohexane/EtOAc, 5:2) to give the desired β-thioketones **9a**–**d**.

Compound 9a: White solid (144 mg, 100% yield); m.p. 154 °C. $[\alpha]_D^{20}$ = –78.5 (c = 0.35, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3013, 2975–2900, 2943, 1730, 1673, 1593, 1505, 1480 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.48 (s, 1 H, 5-H), 7.38 (d, J = 8.5 Hz, 2 H, 3′′-H,

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5′′-H), 7.24 (d, J = 8.5 Hz, 2 H, 2′′-H, 6′′-H), 6.33 (s, 2 H, 2′-H, 6′-H), 6.26 (s, 1 H, 8-H), 6.00 (m, 2 H, OCH_2O), 4.33 (d, J = 10.9 Hz, 1 H, 1-H), 3.86 (s, 3 H, OMe), 3.80 (s, 6 H, OMe), 3.42 (m, 2 H, 2-H, 11a-H), 3.40 (s, 3 H, CO_2Me), 3.26 (m, 1 H, 11b-H), 3.21 (m, 1 H, 3-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 193.5 (C-4), 172.4 (C-13), 153.4 (C-3′, C-5′), 152.7 (C-7), 147.5 (C-6), 141.4 (C-1′), 137.3 (C-4′), 136.2 (C-9), 135.8 (C-1′′), 131.9 (C-3′′, C-5′′), 131.4 (C-2′′, C-6′′), 126.5 (C-10), 120.2 (C-4′′), 108.5 (C-8), 106.2 (C-5), 106.1 (C-2′, C-6′), 102.0 (OCH_2O), 60.9 (4′-OMe), 56.2 (3′-OMe, 5′-OMe), 53.4 (C-2), 52.0 (CO_2Me), 49.3 (C-3), 49.1 (C-1), 33.4 (C-11) ppm. MS (ES+): m/z = 615, 617 $[M + H]^+$, 637, 639 $[M + Na]^+$. HRMS (DCI/CH_4): calcd. for $C_{29}H_{27}O_8BrS{\cdot}C_2H_5$ 643.1001, 645.0986; found 643.0977, 645.0984.

General Procedure for the Synthesis of 3-(Indol-3-ylmethyl)tetralols 7a–f: $NaBH_4$ (1.5 equiv.) was added to a solution of **6a**–**f** (100 mg) in THF (3 mL) and MeOH (3 mL) cooled beforehand to 0 °C. The reaction mixture was stirred for 2 h at 0 °C and then poured into water (20 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed with brine (20 mL), dried with $MgSO_4$, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (cyclohexane/EtOAc, 3:2) afforded the desired alcohols **7a**–**f**.

Compound 7a: White solid (82.3 mg, 82% yield); m.p. 146–149 °C. $[\alpha]_D^{20}$ = +41.2 (c = 0.19, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3600–3450, 3479, 3010, 2960–2900, 1729, 1593, 1504, 1484 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.13 (s, 1 H, NH), 7.78 (d, J = 7.5 Hz, 1 H, 4′′-H), 7.35 (d, J = 7.3 Hz, 1 H, 7′′-H), 7.19 (m, 2 H, 5′′-H, 6′′-H), 7.11 (d, J = 2.2 Hz, 1 H, 2′′-H), 6.96 (s, 1 H, 5-H), 6.27 (s, 2 H, 2′-H, 6′-H), 6.17 (s, 1 H, 8-H), 5.86 (m, 2 H, OCH_2O), 4.65 (m, 1 H, 4-H), 4.27 (d, J = 10.7 Hz, 1 H, 1-H), 3.84 (s, 3 H, 4′-OMe), 3.77 (s, 6 H, 3′-OMe, 5′-OMe), 3.45 (s, 3 H, CO_2Me), 3.18 (dd, J = 15.0, 4.6 Hz, 1 H, 11a-H), 2.87 (m, 2 H, 2-H, 11b-H), 2.83 (m, 1 H, 3-H), 2.06 (br. s, 1 H, OH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.3 (C-13), 153.2 (C-3′, C-5′), 146.9 (C-7), 146.6 (C-6), 138.8 (C-1′), 136.8 (C-4′), 136.2 (C-8′′), 132.1 (C-9), 131.4 (C-10), 127.9 (C-9′′), 123.0 (C-2′′), 122.3 (C-6′′), 119.7 (C-5′′), 119.1 (C-4′′), 112.3 (C-3′′), 111.2 (C-7′′), 108.3 (C-8), 106.8 (C-5), 105.9 (C-2′, C-6′), 100.9 (OCH_2O), 72.6 (C-4), 60.9 (4′-OMe), 56.1 (3′-OMe, 5′-OMe), 53.8 (C-2), 51.5 (CO_2Me), 49.6 (C-1), 45.3 (C-3), 27.0 (C-11) ppm. MS (ES+): m/z = 568 $[M + Na]^+$. MS (ES–): m/z = 544 $[M - H]^-$. $C_{31}H_{31}NO_8$ (545.58): calcd. C 68.25, H 5.73, N 2.57; found C 68.24, H 5.94, N 2.57.

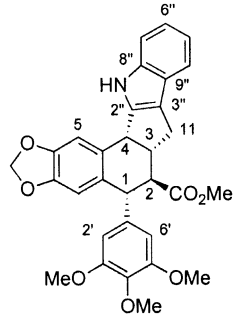
General Procedure for the Synthesis of Alcohols 10a–e and 11a–d: $NaBH_4$ (13.6 mg, 0.360 mmol) was added to a solution of **8a**–**e** (or **9a**–**d**) (0.180 mmol) in THF (3 mL) and MeOH (3 mL) cooled beforehand to 0 °C. The reaction mixture was stirred for 2 h at 0 °C and then poured into water (20 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed with brine (20 mL), dried with $MgSO_4$, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (cyclohexane/EtOAc, 3:2) furnished the desired alcohols **10a**–**e** (or **11a**–**d**).

Compound 10a: Off-white solid (108 mg, 100% yield); m.p. 178–180 °C. $[\alpha]_D^{20}$ = –1.7 (c = 0.12, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3525–3300, 3011, 2976–2900, 1732, 1594, 1505, 1484 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.25 (d, J = 8.7 Hz, 2 H, 3′′-H, 5′′-H), 7.04 (s, 1 H, 5-H), 6.57 (d, J = 8.7 Hz, 2 H, 2′′-H, 6′′-H), 6.26 (s, 2 H, 2′-H, 6′-H), 6.16 (s, 1 H, 8-H), 5.89 (m, 2 H, OCH_2O), 4.74 (d, J = 9.3 Hz, 1 H, 4-H), 4.17 (d, J = 11.2 Hz, 1 H, 1-H), 3.83 (s, 3 H, 4′-OMe), 3.78 (s, 6 H, 3′-OMe, 5′-OMe), 3.48 (s, 3 H, CO_2Me), 3.32 (m, 2 H, 11-H), 2.80 (t, J = 11.2 Hz, 1 H, 2-H), 2.29 (m, 1 H, 3-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.8 (C-13), 153.2 (C-3′, C-5′), 147.0 (C-7), 146.9 (C-1′′), 146.8 (C-6), 138.3 (C-1′), 136.9 (C-4′), 132.0 (C-2′′, C-6′′), 131.7 (C-9), 131.1 (C-10), 115.2 (C-2′′, C-6′′), 110.2 (C-4′′), 108.4 (C-8), 106.1 (C-5), 105.8 (C-2′, C-6′), 101.2 (OCH_2O), 72.3 (C-4), 60.8 (4′-OMe), 56.1 (3′-OMe, 5′-OMe), 52.2 (CO_2Me), 51.8 (C-2), 49.5 (C-11), 48.3 (C-1), 45.0 (C-3) ppm. HRMS (DCI/CH_4): calcd. for $C_{29}H_{31}O_8NBr$ 600.1233, 602.1218; found 600.1228, 602.1207.

Compound 11a: White solid (100 mg, 90% yield); m.p. 162 °C. $[\alpha]_D^{20}$ = –30.3 (c = 1.93, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3550–3300, 3012, 2974–2900, 1729, 1593, 1505, 1484 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.39 (d, J = 8.5 Hz, 2 H, 3′′-H, 5′′-H), 7.25 (d, J = 8.5 Hz, 2 H, 2′′-H, 6′′-H), 7.02 (s, 1 H, 5-H), 6.25 (s, 2 H, 2′-H, 6′-H), 6.17 (s, 1 H, 8-H), 5.88 (m, 2 H, OCH_2O), 4.81 (t, J = 8.2 Hz, 1 H, 4-H), 4.15 (d, J = 10.9 Hz, 1 H, 1-H), 3.83 (s, 3 H, OMe), 3.78 (s, 6 H, OMe), 3.47 (s, 3 H, OMe), 3.27 (dd, J = 13.6, 4.6 Hz, 1 H, 11a-H), 3.11 (dd, J = 13.6, 4.8 Hz, 1 H, 11b-H), 2.93 (t, J = 10.9 Hz, 1 H, 2-H), 2.48 (d, J = 8.2 Hz, 1 H, OH), 2.37 (m, 1 H, 3-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.5 (C-13), 153.2 (C-3′, C-5′), 147.1 (C-7), 146.8 (C-6), 138.3 (C-1′), 136.9 (C-4′), 135.3 (C-1′′), 132.1 (C-3′′, C-5′′) 131.6 (C-9), 131.2 (C-10), 131.0 (C-2′′, C-6′′), 120.3 (C-4′′), 108.5 (C-8), 106.4 (C-5), 105.9 (C-2′, C-6′), 101.1 (OCH_2O), 71.5 (C-4), 60.9 (4′-OMe), 56.2 (3′-OMe, 5′-OMe), 52.6 (C-2), 51.8 (CO_2Me), 49.5 (C-1), 44.6 (C-3), 35.6 (C-11) ppm. MS (ES+): m/z = 639, 641 $[M + Na]^+$. HRMS (DCI/CH_4): calcd. for $C_{29}H_{29}BrNO_8S{\cdot}C_2H_5$ 645.1158, 647.1142; found 645.1160, 647.1157.

General Procedure for the $InCl_3$-Catalyzed Intramolecular Friedel–Crafts Cyclization: A solution of alcohol **7a**–**f**, **10a**–**e**, or **11c**,**11d** (0.07 mmol) in DCE (2 mL) was heated at reflux, and indium trichloride (1.5 mg, 0.007 mmol) was then added. The reaction mixture was stirred for the indicated reaction time (see Table 2: 20 or 30 min), cooled to room temperature, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (cyclohexane/EtOAc, 5:1) gave the desired polycyclic compounds **3a**–**f**, **4a**–**e**, or **5c**,**5d**.

Compound 3a: Off-white solid (23 mg, 73% yield); m.p. 220–222 °C. $[\alpha]_D^{20}$ = –112.4 (c = 0.11, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3468, 3012, 2975–2900, 1729, 1592, 1504, 1482 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.96 (s, 1 H, NH), 7.46 (d, J = 6.5 Hz, 1 H, 4′′-H), 7.34 (dd, J = 8.3, 1.6 Hz, 1 H, 7′′-H), 7.13 (m, 2 H, 5′′-H, 6′′-H), 6.94 (s, 1 H, 5-H), 6.27 (s, 2 H, 2′-H, 6′-H), 6.24 (s, 1 H, 8-H), 5.94 (s, 2 H, OCH_2O), 4.61 (d, J = 6.9 Hz, 1 H, 4-H), 4.06 (d, J = 11.1 Hz, 1 H, 1-H), 3.83 (s, 3 H, 4′-OMe), 3.73 (s, 6 H, 3′-OMe, 5′-OMe), 3.54 (m, 1 H, 3-H), 3.45 (s, 3 H, CO_2Me), 3.11 (dd, J = 14.7, 6.5 Hz, 1 H, 11a-H), 2.97 (t, J = 11.1 Hz, 1 H, 2-H), 2.58 (d, J = 14.7 Hz, 1 H, 11b-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.2 (C-13), 153.1 (C-3′, C-5′), 146.7 (C-7), 146.3 (C-6), 144.0 (C-2′′), 140.6 (C-8′′), 137.3 (C-1′), 136.7 (C-4′), 132.3 (C-9), 128.0 (C-10), 125.1 (C-9′′), 121.1 (C-5′′), 120.0 (C-6′′), 118.9 (C-4′′), 116.7



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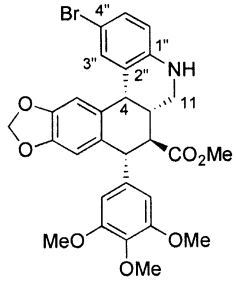
(C-3′′), 111.7 (C-7′′), 109.3 (C-8), 107.1 (C-5), 106.1 (C-2′, C-6′), 101.1 (OCH_2O), 60.9 (4′-OMe), 56.1 (3′-OMe, 5′-OMe), 51.8 (C-2), 51.6 (CO_2Me), 49.2 (C-1), 46.1 (C-3), 42.8 (C-4), 29.8 (C-11) ppm. MS (ES+): *m*/*z* = 528 $[M + H]^+$, 550 $[M + Na]^+$. HRMS (DCI/CH_4): calcd. for $C_{31}H_{30}NO_7$ 528.2022; found 528.2018.

Compound 4a: Off-white solid (37.9 mg, 93% yield); m.p. 269 °C. $[\alpha]_D^{20}$ = –61.6 (*c* = 0.50, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3011, 2975–2900, 1728, 1593, 1504, 1484 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.15 (dd, *J* = 8.4, 1.9 Hz, 1 H, 5′′-H), 7.07 (d, *J* = 1.9 Hz, 1 H, 3′′-H), 6.65 (s, 1 H, 5-H), 6.56 (d, *J* = 8.4 Hz, 1 H, 6′′-H), 6.37 (s, 1 H, 8-H), 6.05 (s, 2 H, 2′-H, 6′-H), 5.96 (m, 2 H, OCH_2O), 4.26 (d, *J* = 10.1 Hz, 1 H, 1-H), 4.08 (d, *J* = 3.8 Hz, 1 H, 4-H), 3.99 (s, 1 H, NH), 3.77 (s, 3 H, OMe), 3.64 (s, 6 H, OMe), 3.63 (m, 1 H, 11a-H), 3.62 (s, 3 H, CO_2Me), 3.17 (dd, *J* = 12.5, 3.4 Hz, 1 H, 11b-H), 2.76 (dd, *J* = 10.9, 10.1 Hz, 1 H, 2-H), 2.61 (m, 1 H, 3-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.7 (C=O), 153.1 (C-3′, C-5′), 147.0 (C-7), 145.9 (C-6), 141.7 (C-1′′), 140.6 (C-1′), 136.3 (C-4′), 131.4 (C-3′′, C-9), 130.2 (C-5′′), 129.7 (C-10), 124.1 (C-2′′), 115.4 (C-6′′), 109.7 (C-5, C-8), 108.4 (C-4′′), 105.0 (C-2′, C-6′), 101.0 (OCH_2O), 60.8 (4′-OMe), 56.0 (3′-OMe, 5′-OMe), 51.8 (CO_2Me), 49.2 (C-2), 49.0 (C-1), 44.3 (C-11), 41.1 (C-4), 33.9 (C-3) ppm. MS (ES+): *m*/*z* = 604, 606 $[M + Na]^+$. HRMS (DCI/CH_4): calcd. for $C_{29}H_{29}BrNO_7$ 582.1127, 584.1112; found 582.1124, 584.1116.



Compound 5c: Off-white solid (29.3 mg, 76% yield); m.p. 210 °C. $[\alpha]_D^{20}$ = –27.5 (*c* = 0.12, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3010, 2976–2900, 1728, 1593, 1505, 1483 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.27 (d, *J* = 8.5 Hz, 1 H, 6′′-H), 6.73 (dd, *J* = 8.5, 2.5 Hz, 1 H, 5′′-H), 6.55 (m, 2 H, 5-H, 3′′-H), 6.36 (s, 1 H, 8-H), 6.19 (s, 2 H, 2′-H, 6′-H), 5.93 (m, 2 H, OCH_2O), 4.19 (d, *J* = 10.6 Hz, 1 H, 1-H), 4.07 (d, *J* = 4.8 Hz, 1 H, 4-H), 3.80 (s, 3 H, 4′-OMe), 3.70 (s, 9 H, 3′-OMe, 5′-OMe, 4′′-OMe), 3.53 (s, 3 H, CO_2Me), 3.16 (m, 1 H, 11a-H), 3.05 (m, 1 H, 3-H), 2.52 (t, *J* = 10.6 Hz, 1 H, 2-H), 2.44 (m, 1 H, 11b-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.1 (C-13), 158.0 (C-4′′), 153.2 (C-3′, C-5′), 147.0 (C-7), 146.2 (C-6), 141.3 (C-2′′), 139.6 (C-1′), 136.7 (C-4′), 132.0 (C-9), 129.2 (C-10, C-6′′), 126.2 (C-1′′), 116.9 (C-3′′), 101.1 (C-5′′), 109.6 (C-5), 109.1 (C-8), 105.3 (C-2′, C-6′), 101.0 (OCH_2O), 60.8 (4′-OMe), 55.8 (3′-OMe, 5′-OMe), 55.1 (4′′-OMe), 52.6 (C-2), 51.7 (CO_2Me), 49.7 (C-1), 43.9 (C-4), 37.9 (C-3), 31.8 (C-11) ppm. HRMS (FAB+): calcd. for $C_{30}H_{30}NO_8S$ 550.1661; found 550.1656. HRMS (DIC/NH_3): calcd. for $C_{30}H_{31}NO_8S$ 551.1740; found 551.1732.

Supporting Information (see also the footnote on the first page of this article): General experimental procedures, ^1H and ^{13}C NMR spectra, and HRMS (or elemental analysis) for compounds **6a–f**, **8a–e**, **9a–d**, **7a–f**, **9a–d**, **10a–e**, **11a–d**, **3a–f**, **4a–e**, and **5c**,**5d**.

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