Synthesis of γ-Lactam Lignans via Aza-Michael Addition

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Abstract: The synthesis of γ-lactam lignans from thuriferic acid via Michael addition of substituted anilines under basic conditions, followed by lactam ring closure, is described.

Key words: lignans, lactams, Michael additions, thuriferic acid, privileged structure

γ-Lactams are important molecules with numerous pharmacological properties such as, psychotropic agents,[1] muscarinic acid agonists,[2] antihypertensive agents,[3] peptide mimics,[4] β-turn peptidomimetics,[5] non-peptide mimics of somatostatin/sandostatin,[6] serine protease inhibitors,[7] and anti-asthma drug rolipram.[8] Unlike β-lactams, to date γ-lactams have been found as components of only a few natural products such as fischerellin B,[9] the antibiotic lactonamycin,[10] and the alkaloid gelsemine.[11] Reports regarding the construction of γ-lactam libraries have been published.[12] Within this context, and in the search for ligands for a range of biological targets, we initiated a program to synthesize γ-lactam libraries based on the concept of privileged structure.[13] The 1-aryltetralin system **1**[14] represents a privileged structure which remains to be exploited by combinatorial chemistry. Indeed, lignans of the type 1-aryltetralin are the constituents of plants or their synthetic derivatives and present a wide range of biological activities[15] including inhibition of the polymerization of tubulin, inhibition of DNA topoisomerase II, immunosuppressive activity, and anti-HIV activity. Recently, cyclolignans as inhibitors of the insulin-like growth factor-1 receptor (IGF-1R) have been reported.[16] Interestingly, the combination of **1** with γ-lactam rings was carried out by Kadow and co-workers[17] with the synthesis of antitumor lactams from the anticancer drug etoposide, a glucoside derivative of the cytotoxic 1-aryltetralin lignan podophyllotoxin. We chose thuriferic acid **2**,[18,19] a lignan isolated from *Juniperus thurifera* leaves,[20] which encompasses the 1-aryltetralin scaffold **1**, and whose chemical reactivity has been the subject of a few studies[18,19a] (Figure 1). In this paper we present the synthesis of γ-lactam lignans **3**, which were synthesized by the conjugate addition of substituted anilines to the methyl ester of thuriferic acid **5**, followed by intramolecular cyclization of the corresponding β-amino ketones. To our knowledge there is only one example[21] of a Michael addition to a related substrate of **2**, namely 3-carboxy-2-methylene-4-(3′,4′,5′-trimethoxyphenyl)-6,7-dimethoxy-1-tetralone, which was prepared from morpholine.

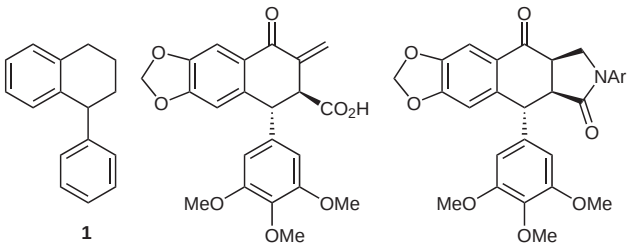
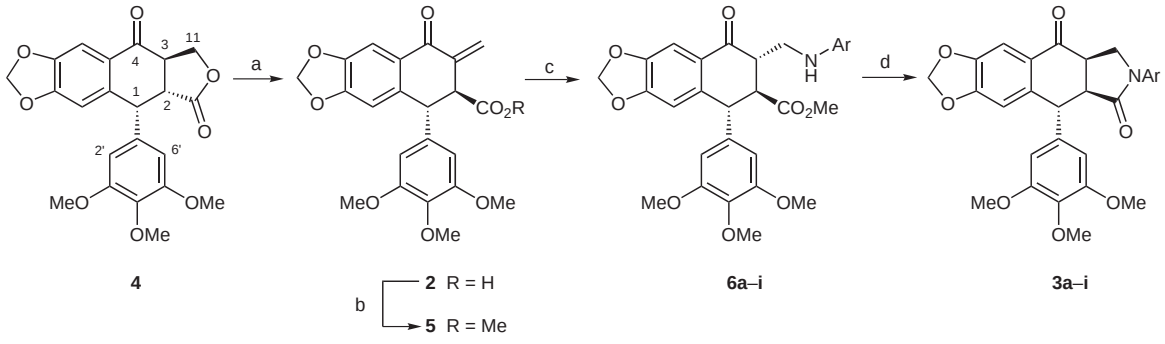


Figure 1



Scheme 1 *Reagents and conditions:* (a) *t*-BuOK, *t*-BuOH, reflux; (b) MeI, $NaHCO_3$, DMF, r.t.; (c) $ArNH_2$, Et_3N, THF, reflux; (d) *t*-BuOK (cat.), *t*-BuOH, DMF, r.t.

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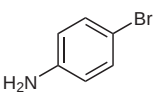
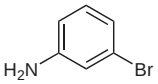
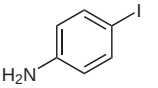
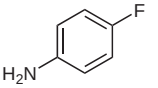
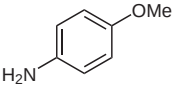
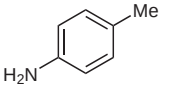
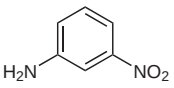
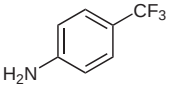
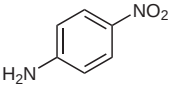
Two protocols have been described[18a,c] for the synthesis of thuriferic acid **2** from podophyllotoxone **4**. On a large scale, **2** was synthesized using the procedure of Höfert and Matusch.[18a] To facilitate the purification step the crude acid thus obtained, after evaporation of *t*-BuOH, was converted into methyl ester **5** (Scheme 1).

The Michael addition of substituted anilines to **5** in the presence of Et_3N in THF at reflux afforded β-amino ketones **6a**–**i**, which were characterized by ^1H NMR spectroscopy[22] (Table 1). For halogenoanilines (Table 1, entries 1–4) and activated anilines (Table 1, entries 5 and 6), the reaction with **5** catalyzed by Et_3N (4 equiv) provided **6a**–**f** after 24 hours at reflux in THF in 78–95% yields. Intramolecular cyclization of these β-amino ketones was never observed when an excess of reactants and/or base were used. Importantly, treatment of **5** with the more basic 4-aminopyridine instead of Et_3N led to naphthoic acid methyl ester **7**.[23] 3-Nitroaniline gave compound **6g** in 43% yield after heating for 48 hours (Table 1, entry 7). 4-Trifluoroaniline provided **6h** in 53% yield, regardless of the reaction time (Table 1, entry 8). Attempts to optimize the reaction with 4-nitroaniline were unsuccessful (Table 1, entries 9 and 10). The stereochemistry of **6a**–**i** was assigned on the basis of the $J_{1,2}$ (8–11 Hz) and $J_{2,3}$ (9–13 Hz) coupling constants which were in agreement with the 1,2 antidiaxial and 2,3 antidiaxial configurations previously reported for 11-chloro-3,11-dihydrothuriferic acid.[18b,c]

As expected, the β-amino ketone **6a** proved sensitive to retro-Michael reaction, for example, the conversion of the carbonyl group at C-4 into the corresponding methyloxime[24] was attempted under two different conditions and failed ($MeONH_2$·HCl, NaOAc in MeOH–THF, reflux[25a] or $MeONH_2$·HCl, pyridine·HCl, EtOH, reflux[25b]). Addition of arylhydrazines[26] to **6a** gave the same result. Finally, cyclization of **6a**–**i** into the desired γ-lactam lignans **3a**–**i**[27,28] occurred under base catalysis[29] (*t*-BuOK) in 45–72% yields (Table 1). Surprisingly, while picropodophyllone (C-2 epimer of **4**) reacted at C-4 with *O*-methylhydroxylamine as described,[30] the corresponding 4-oxime derivatives of **3a** failed to form under the same reaction conditions.

In summary, the synthesis of γ-lactam lignans **3** was achieved from thuriferic acid **2** via Michael addition of substituted anilines under basic conditions followed by lactam ring closure. Extension of this work to construct diversified libraries of γ-lactam lignans for biological evaluation, using resins and parallel solution methodologies, is currently under investigation.

Table 1 Synthesis of β-Amino Ketones and γ-Lactams

	Michael addition of anilines **5** → **6a–i**			γ-Lactams **6a–i** → **3a–i**	
Entry	Aniline	Product[a]	Yield (%)[b]	Product[a]	Yield (%)[b]
1[c]		**6a**	94	**3a**	63
2[c]		**6b**	95	**3b**	69
3[c]		**6c**	78	**3c**	67
4[c]		**6d**	78	**3d**	72
5[c]		**6e**	90	**3e**	65
6[c]		**6f**	93	**3f**	64
7[d]		**6g**	43	**3g**	45
8[c,d]		**6h**	53	**3h**	53
9[d,e]		**6i**	23	**3i**	65
10[f]		**6i**	31	**3i**	65

[a] All products were characterized by ^1H NMR, ^{13}C NMR, IR, and mass spectroscopy.
[b] All yields reported are isolated yields of compounds, estimated to be 95% pure by ^1H NMR spectroscopy.
[c] Et_3N (4 equiv), aniline (4 equiv), 24 h.
[d] Et_3N (4 equiv), aniline (4 equiv), 48 h.
[e] Et_3N (4 equiv), aniline (4 equiv), 5 d.
[f] Et_3N (10 equiv), aniline (10 equiv), 5 d.

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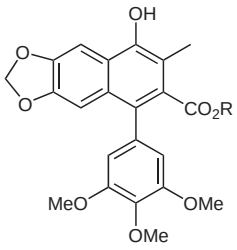

7 R = Me

Figure 2

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(27) **Synthesis of 6 and 3; General Procedure**
To a solution of the methyl ester of thuriferic acid **5** (50 mg, 0.117 mmol) in anhyd THF (2 mL) were added Et_3N and the aniline at r.t. (Table 1). The reaction mixture was then heated at 65 °C for the reaction time indicated, concentrated under reduced pressure, and the crude product was purified by chromatography on silica gel (cyclohexane–EtOAc, 5:2) to give the desired β-amino ketones **6**. This compound (0.165 mmol, 1 equiv) was diluted in DMF (2.5 mL) and a 1 M solution of *t*-BuOK in *t*-BuOH (1 M; 16.5 μL, 0.1 equiv) was added at r.t. The mixture was stirred for 20 min then the pH was adjusted to 7 by the addition of aq NH_4Cl. The mixture was extracted with EtOAc (3 × 20 mL), the combined organic phases were dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel (cyclohexane–EtOAc, 3:1) to furnish the γ-lactam lignans **3**.
Compound **6i**: Yellow powder; yield: 31%; mp 194 °C; $[\alpha]_D^{20}$ –84 (*c* 0.19, $CHCl_3$). IR: 3400–3300, 2940, 1734, 1671, 1601, 1506, 1480 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$):

δ = 8.07 (d, 2 H, *J* = 9.2 Hz, $H_{3''}$, $H_{5''}$), 7.47 (s, 1 H, H_5), 6.55 (d, 2 H, *J* = 9.2 Hz, $H_{2''}$, $H_{6''}$), 6.33 (s, 2 H, $H_{2'}$, $H_{6'}$), 6.29 (s, 1 H, H_8), 6.00 (m, 2 H, OCH_2O), 5.19 (br s, 1 H, NH), 4.36 (d, 1 H, *J* = 10.7 Hz, H_1), 3.86 (s, 3 H, $OMe_{4'}$), 3.80 (s, 6 H, $OMe_{3',5'}$), 3.63 (m, 1 H, H_{11a}), 3.49 (s, 3 H, CO_2Me), 3.48 (m, 1 H, H_{11b}), 3.24 (dd, 1 H, *J* = 12.9, 10.7 Hz, H_2), 3.19 (m, 1 H, H_3). ^{13}C NMR (75 MHz, acetone-d_6): δ = 195.8, 174.0, 155.8, 155.5, 154.4, 149.2, 143.7, 139.6, 139.1, 138.5, 128.4, 127.7, 112.9, 110.0, 108.6, 106.7, 104.1, 61.5, 57.4, 54.0, 53.1, 50.9, 50.0, 43.7. MS (DCI, NH_3): *m*/*z* = 565 $[M + H]^+$.

Compound **3i**: Yellow powder; yield: 65%; mp 235–240 °C; $[\alpha]_D^{20}$ –110 (*c* 0.34, $CHCl_3$). IR: 2940, 1716, 1670, 1597, 1521, 1481 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.22 (d, *J* = 9.3 Hz, 2 H, $H_{3''}$, $H_{5''}$), 7.79 (d, *J* = 9.3 Hz, 2 H, $H_{2''}$, $H_{6''}$), 7.48 (s, 1 H, H_5), 6.73 (s, 1 H, H_8), 6.27 (s, 2 H, $H_{2'}$, $H_{6'}$), 6.04 (m, 2 H, OCH_2O), 4.81 (d, *J* = 1.7 Hz, 1 H, H_1), 4.38 (d, *J* = 9.7 Hz, 1 H, H_{11a}), 4.01 (m, 1 H, H_{11b}), 3.81 (s, 3 H, $OMe_{4'}$), 3.76 (s, 6 H, $OMe_{3',5'}$), 3.40 (dd, *J* = 7.6, 1.7 Hz, 1 H, H_2), 3.29 (m, 1 H, H_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 193.9, 172.3, 153.7, 153.5, 144.1, 143.6, 139.6, 138.1, 137.0, 126.9, 124.5, 118.6, 109.3, 105.8, 104.6, 102.0, 60.6, 56.0, 50.5, 43.3, 42.9, 39.5. MS (DCI, NH_3): *m*/*z* = 533 $[M + H]^+$, 550 $[M + NH_4]^+$.

(28) The 2,3-*cis* stereochemistry of **3a**–**i** was deduced from the $J_{1,2}$ and $J_{2,3}$ coupling constants (1.7 and 7.6 Hz, respectively for **3i**) and was confirmed from NOESY correlations of H_2/H_3, H_2/$H_{2',6'}$, and H_3/$H_{2',6'}$. Molecular modeling [Insight II, Discover, MD simulations (300 K), cff 91, ε = 4.8 for $CDCl_3$] provided a unique global minimum conformation for **3i** which fitted the NOE data (Figure 3).

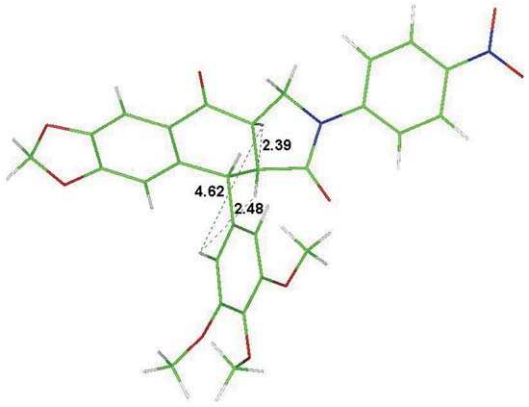

Figure 3

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