An Efficient Synthesis of Thalifoline

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Abstract: An efficient multi-step approach for the synthesis of the isoquinolin-1-one alkaloid thalifoline (**1**) is described. The key intermediate carbamate **8a** underwent a modified Bischler–Napieralski-type cyclization using Banwell's Tf_2O/DMAP conditions to form the lactam **9a** under mild conditions and in excellent yield.

Key Words: alkaloids, thalifoline, quinolines, heterocycles, isoquinoline, ring closure, cyclizations

Thalifoline (**1**),[1] first isolated from *Thalictrum minus L.* var. *adiantifolium Hort* by Doskotch et al. in 1969, is a member of a small group of naturally-occurring tetrahydroisoquinolones (Figure 1). This group of alkaloids is present in only minor amounts. Based upon the few biogenetic studies that have been conducted, they are presumed to result from the biochemical oxidation of the more prevalent alkaloid components including benzyltetrahydroisoquinoline units.[2,3] Thalifoline is structurally related to a subunit of more complex alkaoids such as baluchistanamine (**2**)[4,5] and (–)-tejedine (**3**).[5] We herein describe an efficient multi-step synthesis of thalifoline from vanillin (**4**). Using modified Bischler–Napieralski cyclization conditions developed by Banwell et al.,[6] thalifoline was obtained in 37% overall yield from vanillin. The methodology reported herein appears to be a general one which could be applicable to other 6,7-disubstituted 3,4-tetrahydroisoquinolin-1-ones.

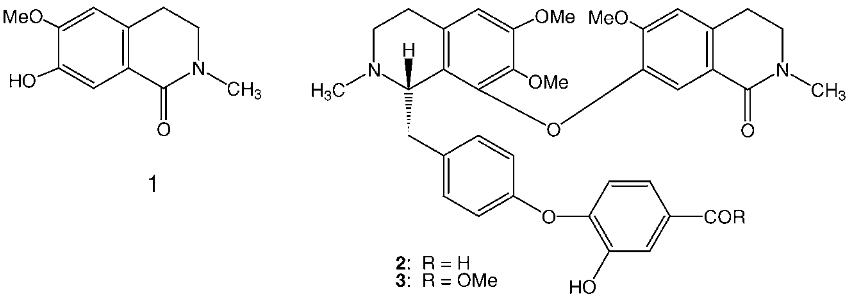
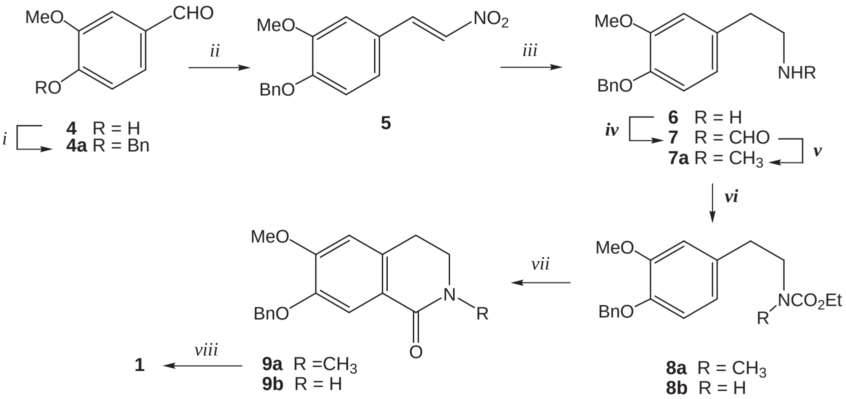


Figure 1



Scheme 1 *Reagents and conditions*: i) $BnBr/K_2CO_3$, acetone, reflux (98%); ii) $MeNO_2/NH_4Ac$, HOAc, reflux (90%); iii) $LiAlH_4$, THF, reflux (used directly in step iv); iv) HCO_2Et, reflux (78% from steps iii and iv); v) $BH_3{\cdot}THF/BF_3{\cdot}OEt_2$, THF, reflux (used directly in step vi); vi) $ClCO_2Et/NaHCO_3$, CH_2Cl_2–H_2O, 0 °C (60% from steps v and vi); vii) **8a** + Tf_2O/DMAP, CH_2Cl_2, 0 °C, (90%); viii) **9a** + H_2/Pd/C, MeOH (>98%).

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The conversion of vanillin to 4-benzyloxy-3-methoxyphenethylamine (**6**) was achieved in 84% overall yield using a standard procedure (Scheme 1). Benzylation of vanillin with benzyl bromide using K_2CO_3 in refluxing acetone afforded **4a** in 98% yield. Condensation of **4a** with nitromethane using either aqueous sodium hydroxide at 0 °C,[7] methylammonium chloride and Na_2CO_3 in ethanol,[8] or, dimethylammonium chloride and KF in toluene,[9] only afforded the β-nitrostyrene **5** in less than 50% yields and presented difficulties in purifying the product. The reaction of **4a** with nitromethane in refluxing acetic acid with ammonium acetate however, produced crystalline **5** in 90% yield. Reduction of **5** using $LiAlH_4$ in refluxing THF[10] afforded **6** in 84% overall yield from vanillin. Without further purification, **6** was converted to *N*-formyl-*N*-4-benzyloxy-3-methoxyphenethylamine (**7**) in 78% yield by reaction with ethyl formate in refluxing conditions. Reduction of **7** using $LiAlH_4$[11] afforded the desired *N*-methyl-*N*-4-benzyloxy-3-methoxyphenethylamine (**7a**) in only low yields. However with $BH_3·THF/BF_3·OEt_2$ in refluxing THF,[12] **7a** could be obtained in >90% yields and pure enough to be used directly in the subsequent step. Schotten–Baumman reaction with ethyl chloroformate[13] afforded the key intermediate *N*-ethoxycarbonyl-*N*-methyl-4-benzyloxy-3-methoxyphenethylamine (**8a**) in 60% overall yield from **7**.

Cyclization of either carbamates **8a** or **8b**, or formamide **7** under typical, or modified Bischler–Napieralski conditions proved to be difficult. These substrates were treated with $P_2O_5/POCl_3$ (2:1) as described by Wang.[14] Such conditions reportedly usually give cyclized isoquinolin-1-ones in yields as high as 98% with *o*-, *m*- or *p*-(mono)substituted phenethyl carbamates. In our cases only polar, intractable mixtures were obtained. Other conditions employed with similar results included: heating at 150 °C in polyphosphoric acid;[15] treating with $POCl_3$ in refluxing benzene;[16] or reacting with Eaton's acid ($P_2O_5/MeSO_3H$).[17] From the ^{1}H NMR spectra of the crude reaction products it was obvious that the benzyl protecting group was not inert to the relatively harsh reagents and reaction temperature conditions that were required to effect the Bischler–Napieralski cyclization.

Efficient cyclization of **8a** to afford **9a** however was achieved by using the trifluoromethanesulfonic anhydride/DMAP procedure developed by Banwell et al.[6] in their total synthesis of *Amaryllidaceae* alkaloids. Cyclization of **8a** proceeded cleanly in CH_2Cl_2 at 0 °C to form the O-benzylated thalifoline **9a** in 90% yields. On the other hand, when these same conditions were employed with **8b** or with **7**, the desired cyclization failed, affording only intractable mixtures.

Catalytic hydrogenation of **9a** near-quantitatively afforded the target molecule thalifoline whose physical properties are in agreement with those reported.[1,18,19] It should be noted that Doskotch et al. synthesized **1** using a seven-step synthesis which also commenced with vanillin, but involved a final oxidation step to form the target molecule resulting in a less than 10% overall yield. Other syntheses of **1** have been reported by Kametani et al.[18] in which **1** was produced from a minor by-product of a photo-Pschorr reaction; and by Irie et al.[19] via 3,4,5-trimethoxyphenethyl isocyanate in 16% yield.

All reactions were performed under N_2 or Ar. All compounds were purified by either flash chromatography using Scientific Adsorbents Inc. (SAI) silica gel (63–200 μm) or preparative thin layer chromatography (PLC) plates, which were made from SAI silica gel (5–15 μ) with gypsum. TLC was performed on precoated silica gel 60 F_{254} (SAI). Chemical reagents were purchased from Sigma–Aldrich. Solvents were dried using standard procedures. Mps were determined on a Fisher–Johns apparatus and are uncorrected. IRspectra were recorded on a Mattson Polaris FT instrument. MS data were presented as follows: *m*/*z*, intensity. ^{1}H NMR spectra were at 300 MHz or 500 MHz, and chemical shifts are relative to internal TMS. ^{13}C NMR spectra were recorded at 75 MHz or 125 MHz and chemical shifts are relative to the solvent (δ = 77.0 for $CDCl_3$).

O-Benzylvanillin (4a)

A solution of anhyd K_2CO_3 (31 g, 0.23 mol) in $CHCl_3$ (60 mL) and MeOH (30 mL) was refluxed for 15 min and then vanillin **4** (7.6 g, 0.05 mol) and benzyl bromide (8.9 mL, 0.08 mol) were added. After heating at reflux for 4 h, the reaction mixture was filtered, the organic phase was washed with water, dried ($MgSO_4$), filtered, and concentrated in vacuo. The product was recystallized from hexane–CH_2Cl_2 to give pure **4a**.

Yield: 12 g (96%); crystalline needles; mp 63–64 °C (lit.[20] 61–64 °C).

4-Benzyloxy-3-methoxy-β-nitrostyrene (5)

A mixture of *O*-benzylvanillin (4.0 g, 16.5 mmol), ammonium acetate (1.2 g, 15.1 mmol), nitromethane (6 mL, 87.3 mmol), and glacial HOAc was refluxed for 1.5 h. After cooling to r.t., the crystalline product was filtered and recrystallized from EtOH to afford **5**.

Yield: 3.2 g (90%); mp 121–122 °C (lit.[21] 122–123 °C).

4-Benzyloxy-3-methoxyphenethylamine (6)

A solution of 4-benzyloxy-3-methoxy-β-nitrostyrene (**5**) (1.0 g, 3.5 mmol) in anhyd THF (5 mL) was added dropwise to a stirred solution of $LiAlH_4$ (0.7 g, 17.5 mmol) in anhyd THF (15 mL). The reaction mixture was refluxed for 3 h followed by addition of aq KOH (20%) to destroy the excess $LiAlH_4$. The mixture was then extracted with EtOAc (3 × 20 mL), washed with brine (3 × 20 mL), dried (K_2CO_3), concentrated in vacuo. The oily residue was used directly in the next step.

N-Formyl-*N*-(4-benzyloxy-3-methoxy*)*phenethylamine (7)

3-Methoxy-4-benzyloxyphenethylamine (**6**) (890 mg, 3.5 mmol) was dissolved in ethyl formate (40 mL), and the reaction mixture was refluxed for 1 h. After removal of the solvent, the residue was purified by flash chromatography (silica gel; CH_2Cl_2–MeOH, 96:4) to afford **7**.

Yield: 775 mg (78%); colorless oil.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.51 (q, *J* = 7.0 Hz, 2 H), 2.75 (t, *J* = 7.0 Hz, 2 H), 3.86 (s, 3 H), 5.11 (s, 2 H), 5.72 (br s, 1 H), 6.65 (dd, *J* = 1.5, 8.0 Hz), 6.73 (d, *J* = 1.5 Hz, 1 H), 6.81 (d, *J* = 8.0 Hz, 1 H), 7.29–7.43 (m, 5 H), 8.08 (s, 1 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 35.5, 37.8, 39.7, 43.6, 53.9, 56.5, 71.6, 112.9, 113.1, 114.8, 114.9, 121.1, 121.3, 127.6, 128.3, 129.0, 131.2, 132.2, 137.6, 137.6, 147.3, 147.6, 150.3, 150.3, 161.6, 164.8.

MS: *m*/*z* (%) = 285 (M^+, 6), 240 (14), 149 (20), 91 (100).

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HRMS: *m/z* calcd for $C_{17}H_{19}NO_3$: 285.1372; found: 285.1380.

N-Ethoxycarbonyl-*N*-methyl-4-benzyloxy-3-methoxyphenethylamine (8a)

To a solution of **7** (775 mg, 2.72 mmol) in THF (20 mL) under Ar was added $BF_3\cdot OEt_2$ (0.14 mL, 1.09 mmol) via syringe. The solution was heated to a gentle reflux and then $BH_3\cdot$THF (7 mL 6.80 mmol) was added dropwise with stirring. The solution was refluxed for 2 h, cooled to 0 °C, and quenched with aq HCl (20%). The mixture was stirred at 0 °C for 1 h, then at 25 °C for 1 h. The mixture was concentrated on a rotary evaporator, then cooled to 0 °C and made basic to pH 13 using solid KOH. Water and CH_2Cl_2 were added to the resulting basic mixture to dissolve the potassium salts and the amine. The mixture was extracted with CH_2Cl_2 (4×20 mL), and the organic extracts were combined, dried ($MgSO_4$), filtered and evaporated to dryness on a rotary evaporator to afford the crude amine **7a** which was used without further purification directly in the next step.

Sat. aq $NaHCO_3$ (6 mL) was added to a solution of the crude amine **7a** in CH_2Cl_2 (4 mL). The resulting two-phase system was stirred vigorously at 0 °C, and ethyl chloroformate (0.26 mL, 2.72 mmol) in CH_2Cl_2 (1 mL) was added dropwise. The reaction mixture was allowed to warm to r.t. and stirred for a further 3 h. The CH_2Cl_2 layer was separated, and the aq phase was extracted with CH_2Cl_2 (2×10 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated in the usual manner. The resulting residue was purified by flash chromatography (hexanes–EtOAc, 9:1), to afford **8a**.

Yield: 569 mg (61%); colorless oil, which by NMR is a mixture of two rotamers.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.23 (m, 3 H), 2.13 (m, 2 H), 2.79 (br s, 2 H), 2.87 (m, 3 H), 3.47 (s, 2 H), 3.91 (s, 3 H), 5.15 (s, 2 H), 6.67–6.85 (m, 3 H), 7.30–7.47 (m, 4 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 15.2, 34.1, 34.5, 34.9, 35.2, 51.0, 51.4, 56.4, 61.6, 71.6, 113.1, 114.9, 121.2, 127.7, 128.2, 128.9, 132.8, 137.8, 147.2, 150.1, 156.8.

MS: *m/z* (%) = 343 (M$^+$, 10), 298 (3), 240 (14), 227 (4), 116 (100), 91 (98).

HRMS: *m/z* calcd for $C_{20}H_{25}NO_4$: 343.1765; found: 343.1747.

N-Methyl-4-benzyloxy-3-methoxyphenethylamine (8b)

Compound **8b** was prepared using the same procedure used for **8a**. Compound **6** (890 mg, 3.5 mmol) afforded **8b**.

Yield: 820 mg (71%); colorless oil.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.23 (t, *J* = 7.0 Hz, 3 H), 2.74 (t, *J* = 7.0 Hz, 2 H), 3.40 (m, 2 H), 3.88 (s, 3 H), 4.10 (q, *J* = 7.0 Hz, 2 H), 4.65 (br s, 1 H), 5.13 (s, 2 H), 6.56 (d, *J* = 8.5 Hz, 1 H), 6.73 (br s, 1 H), 6.8 (d, *J* = 8.5 Hz, 1 H), 7.28–7.44 (m, 5 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 15.1, 36.2, 42.6, 56.4, 61.2, 71.6, 113.0, 114.8, 121.1, 127.7, 128.2, 128.9, 132.4, 137.7, 147.3, 150.2, 157.0.

MS: *m/z* (%) = 329 (M$^+$, 8), 240 (13), 227 (4), 137 (46), 91 (100).

HRMS: *m/z* calcd for $C_{19}H_{23}NO_4$: 329.1622; found: 329.1617.

Cyclization of 8a

A solution of trifluoromethanesulfonic anhydride (Tf_2O) (1.10 M; 13 mL, 13.7 mmol) in anhyd CH_2Cl_2 (70 mL) was added over a period of 15 min to a solution, maintained at 0 °C, of **8a** (940 mg, 2.74 mmol) and DMAP (1.0 g, 8.22 mmol) in CH_2Cl_2 (50 mL). The reaction mixture was allowed to warm to r.t. and was stirred for 24 h. It was then diluted with CH_2Cl_2 (30 mL), washed with sat. aq Na_2CO_3 (3×30 mL), aq HOAc (20%; 3×30 mL), and then aq Na_2CO_3 (1×30 mL) before being dried ($MgSO_4$). The reaction mixture was filtered and the solvent was evaporated in the usual manner, to give a light brown solid. Purification by flash column chromatography (hexanes–EtOAc, 1:1) afforded **9a**.

Yield: 90%; colorless solid; mp 114–115 °C.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.91 (t, *J* = 6.0 Hz, 2 H), 3.12 (s, 3 H), 3.51 (t, *J* = 6.0 Hz, 2 H), 3.89 (s, 3 H), 5.17 (s, 2 H), 6.63 (s, 1 H), 7.27–7.47 (m, 5 H), 7.67 (s, 1 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 28.0, 35.5, 48.8, 56.5, 71.3, 110.1, 113.2, 122.4, 128.0, 128.3, 129.0, 132.3, 137.3, 147.5, 152.7, 165.2.

MS: *m/z* (%) = 297 (M$^+$, 3), 296 (19), 206 (7), 192 (4), 183 (17), 135 (9), 91 (100).

APCI HRMS: *m/z* calcd for $C_{18}H_{19}NO_3$: 297.1364; found: 297.1365.

Thalifoline (1)

To a solution of **9a** (650 mg, 2.2 mmol) in EtOH (10 mL) was added 10% Pd/C (130 mg), and the resulting mixture was stirred under H_2 at atmospheric pressure for 2 h. The reaction mixture was filtered through Celite, and the precipitate was washed with EtOH (2×10 mL). The EtOH was evaporated to afford **1**. The spectral data are in agreement with those reported in ref.[19]

Yield: 437 mg (96%); colorless solid; mp 211–212 °C (hexane–CH_2Cl_2) (lit.[1] 210–212 °C; lit.[19] 211–212 °C).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.92 (t, *J* = 7.0 Hz, 2 H), 3.12 (s, 3 H), 3.53 (t, *J* = 7.0 Hz, 2 H), 3.92 (s, 3 H), 5.71 (s, 1 H), 6.61 (s, 1 H), 7.67 (s, 1 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 28.1, 35.6, 48.9, 56.4, 109.1, 114.7, 123.2, 131.3, 145.0, 149.7, 165.1.

MS: *m/z* (%) = 207 (M$^+$, 75), 164 (99), 136 (100).

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