

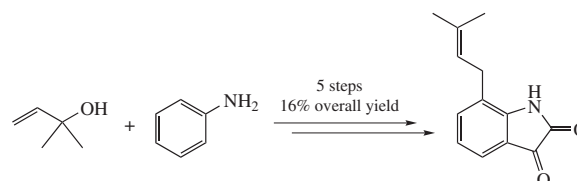
The first synthesis of 7-prenylisatin

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The first synthesis of 7-prenylisatin, an isatin-type antibiotic with prominent activity against *Bacillus subtilis*, has been accomplished in 16% overall yield from 2-methylbut-3-en-2-ol and aniline via a five-step procedure. The protocol includes the aromatic aza-Claisen rearrangement and the Sandmeyer isonitrosoacetanilide isatin synthesis as key steps.



Natural products play an important role in drug discovery in recent decades,^{1–5} and some of them serve as leads for pharmaceuticals development or as tested compounds in clinical trials.⁶ The identification of 7-prenylisatin **1** produced by the actinomycete *Streptomyces* sp. MBT28 was reported in 2015.⁷ Its structure was established via NMR-based metabolomics and multivariate data analysis. When tested against *Bacillus subtilis*, 7-prenylisatin **1** exhibited the minimal inhibitory concentration (MIC) value of *ca.* 25 µg ml^{–1}.⁷ The published data for other isatin-type compounds also demonstrate their antibacterial, antifungal, and cytotoxic properties,^{8–10} making them promising leads in drug discovery. Despite prominent bioactivity and the related biosynthetic results, the chemical synthesis of 7-prenylisatin **1** has never been reported to date. We describe herein the first synthesis of this compound, which would benefit its structure–activity relationship (SAR) investigations as well as the further design of (prenyl)isatin analogues.

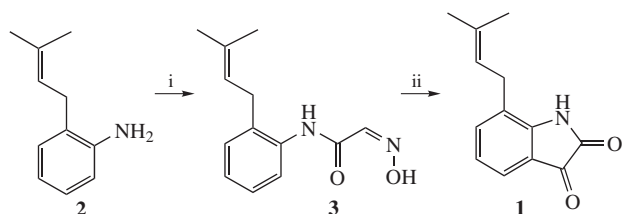
In our retrosynthetic analysis we planned to create the 2,3-pyrrolidinedione skeleton of compound **1** by the Sandmeyer isonitrosoacetanilide isatin synthesis including intramolecular cyclization of isonitrosoacetanilide **3**, which could be obtained by one-pot condensation of *ortho*-substituted aniline **2**, chloral hydrate and hydroxylamine hydrochloride. In turn, compound **2** could be synthesized via the aza-Claisen rearrangement starting from *N*-(2-methylbut-3-en-2-yl)aniline, which could be easily prepared via a direct palladium-catalyzed coupling of aniline with *tert*-butyl (2-methylbut-3-en-2-yl) carbonate.

For the synthesis of the key precursor **2** (Scheme 1), commercially available 2-methylbut-3-en-2-ol was reacted with *n*-BuLi (1.0 mol equiv.) in dry THF at 0 °C to afford lithium alcoholate, and the solution was subsequently treated with di-*tert*-butyl dicarbonate to give *tert*-butyl (2-methylbut-3-en-

2-yl) carbonate in 94% yield.¹¹ Then *N*-(2-methylbut-3-en-2-yl)aniline was obtained in 76% yield by the reaction of the latter with aniline upon treatment with Pd(PPh₃)₄ (2 mol%) in THF–DMF (20:1, v/v) at room temperature. The aza-Claisen rearrangement of *N*-(2-methylbut-3-en-2-yl)aniline was carried out with *p*-TsOH (10 mol%) in MeCN–H₂O (10:1, v/v) at 70 °C to construct the *ortho*-substituted phenyl group in the key precursor **2**, which was isolated in 57% yield.^{12–15} Compound **2** was characterized by ¹H NMR spectrum with methylene protons triplet at δ 2.63 ppm; the absence of proton signal at the *ortho*-position of aniline corresponded to the result of *N*-prenylated aniline rearrangement through migration of the prenyl group to the *ortho*-position.[†] With the key precursor **2** in hand, we turned to the construction of the pyrrolidinedione moiety. The Sandmeyer isonitrosoacetanilide isatin synthesis strategy was adopted.^{16–19} The treatment of the *ortho*-substituted phenyl aniline **2** with chloral hydrate, Na₂SO₄, hydrochloric acid and hydroxylamine hydrochloride at 80 °C for 1.5 h afforded isonitrosoacetanilide **3** in 76% yield.[‡] At the final step, the intramolecular cyclization of compound **3** occurred in concentrated sulfuric acid at less than 70 °C, and then after heating to 80 °C for *ca.* 10 min, 7-prenylisatin

[†] For experimental details and characteristics of the compounds obtained, see Online Supplementary Materials.

[‡] (E)-2-(Hydroxyimino)-N-[2-(3-methylbut-2-en-1-yl)phenyl]acetamide **3**. A solution of Na₂SO₄ (23.1 g, 162 mmol) in water (33 ml), 2-(3-methylbut-2-en-1-yl)aniline **2** (1.47 g, 9 mmol), hydrochloric acid (1.23 ml, 27 mmol), and finally a solution of hydroxylamine hydrochloride (1.89 g, 27 mmol) in water (9 ml) were added to a stirred solution of chloral hydrate (1.62 g, 10 mmol) in water (21 ml) at room temperature. The mixture was heated to 80 °C for 1.5 h and then cooled to room temperature. The residue was extracted with EtOAc (3 × 30 ml), the organic phases were washed with brine, dried over anhydrous MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified by chromatography on silica gel (EtOAc–light petroleum, 1:10) to afford compound **3** (1.5 g, 76%) as yellow oil. IR (ν/cm^{–1}): 1130, 1255, 1315, 1460, 1620, 1670, 2960, 3390, 3455. ¹H NMR (400 MHz, CDCl₃) δ: 1.76 (s, 3 H, Me), 1.83 (s, 3 H, Me), 2.85 (t, 2 H, CH₂, *J* 5.2 Hz), 4.18 (br. s, 1 H, NH), 4.91–4.83 (m, 1 H, CH), 6.61 (s, 1 H, CH), 6.91–6.83 (m, 2 H, Ar), 7.11 (t, 1 H, Ar, *J* 9.6 Hz), 7.58 (t, 1 H, Ar, *J* 8.0 Hz), 7.88 (br. s, 1 H, OH). ¹³C NMR (100 MHz, CDCl₃) δ: 18.1 (Me), 27.9 (Me), 37.9 (CH₂), 113.2 (CH), 117.7 (Ar), 121.6 (Ar), 127.2 (Ar), 128.3 (Me₂C), 131.5 (Ar), 134.9 (Ar), 140.1 (Ar), 142.9 (CH), 146.8 (C=O). HRMS (ESI), *m/z*: 233.1283 [M+H]⁺ (calc. for C₁₃H₁₇N₂O₂, *m/z*: 233.1285).



Scheme 1 Reagents and conditions: i, chloral hydrate, Na₂SO₄, aq. HCl, NH₂OH·HCl, H₂O, 80 °C; ii, H₂SO₄, 70 °C.

1 was isolated as the main product in 51% yield.[§] The ¹H, ¹³C NMR and HRMS data of the synthesized compound **1** were close to the reported ones for the natural sample.⁷ Therefore, our synthetic strategy may be considered as an efficient one from the viewpoint of simple steps, low-cost materials, mild reaction conditions and easy operations, and definitely has a potential for the synthesis of other isatin derivatives.

In conclusion, the first synthesis of 7-prenylisatin was developed from commercially available 2-methylbut-3-en-2-ol and aniline using a five-step procedure involving the aromatic aza-Claisen rearrangement of N-prenylated aniline and the Sandmeyer reaction for preparing isonitrosoacetanilide isatin as key steps. The synthetic strategy can provide rapid access to various analogues of (prenyl) isatin derivatives, which is helpful in evaluation of biological activity and search for new lead compounds.

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[§] 7-Prenylisatin **1**. Concentrated H₂SO₄ (7 ml) was warmed to 50 °C with stirring, then (*E*)-2-(hydroxyimino)-*N*-[2-(3-methylbut-2-en-1-yl)-phenyl]acetamide **3** (0.81 g, 3.5 mmol) was added in batches to keep the temperature between 60 and 70 °C. After that, the mixture was heated to 80 °C and kept at this temperature for *ca.* 10 min to complete the reaction. Then the mixture was cooled to room temperature and poured into ice water with continuous stirring for *ca.* 30 min. The orange precipitate was filtered off, washed with water and recrystallized from EtOH–H₂O (1:1, v/v) to afford compound **1** (0.38 g, 51%) as orange solid, mp 177–180 °C. IR (ν/cm^{−1}): 1120, 1240, 1310, 1475, 1610, 1655, 1690, 2970, 3410. ¹H NMR (400 MHz, CDCl₃) δ: 1.75 (s, 3H, Me), 1.77 (s, 3H, Me), 3.26 (d, 2H, CH₂, *J* 7.2 Hz), 5.25–5.20 (m, 1H, CH), 7.07–7.01 (m, 1H, Ar), 7.37 (d, 1H, Ar, *J* 7.8 Hz), 7.48 (d, 1H, Ar, *J* 7.8 Hz). ¹³C NMR (100 MHz, CDCl₃) δ: 18.5 (Me), 26.6 (Me), 30.0 (CH₂), 118.1 (CH), 120.5 (Ar), 124.2 (Ar), 124.5 (Ar), 125.5 (Me₂C), 136.4 (Ar), 139.8 (Ar), 148.2 (Ar), 159.1 (C=O), 183.2 (C=O). HRMS (ESI), *m/z*: 216.1017 [M+H]⁺ (calc. for C₁₃H₁₄NO₂, *m/z*: 216.1019).

Published data⁷ for comparison. ¹H NMR (600 MHz, CDCl₃) δ: 1.78 (br. s, 3H, Me), 1.80 (d, 3H, Me, *J* 1.2 Hz), 3.31 (br. d, 2H, CH₂, *J* 7.2 Hz), 5.24 (m, 1H, CH), 7.06 (t, 1H, Ar, *J* 7.8 Hz), 7.39 (br. d, 1H, Ar, *J* 7.8 Hz), 7.49 (br. d, 1H, Ar, *J* 7.8 Hz). ¹³C NMR (125 MHz, CDCl₃) δ: 18.3 (Me), 25.9 (Me), 29.7 (CH₂), 118.4 (CH), 120.0 (Ar), 123.7 (Ar), 124.0 (Ar), 125.1 (Me₂C), 136.1 (Ar), 139.1 (Ar), 147.9 (Ar), 159.2 (C=O), 183.1 (C=O). HRMS (ESI), *m/z*: 216.1018 [M+H]⁺.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2019.03.018.

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