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Biomimetic Synthesis of Isoindolinones Related to the Marilines

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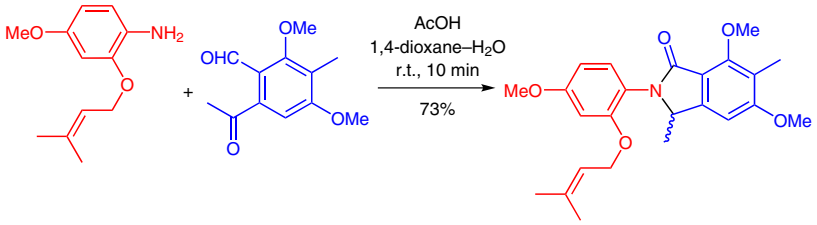

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Abstract The non-enzymatic formation of the racemic isoindolinone core structure during the biosynthesis of the marine natural products mariline A and B was mimicked by employing structurally closely related model substrates. Thus, condensation of 2-formyl-3,5-dimethoxy-4-methyl-acetophenone with different primary amines in the presence of AcOH afforded the isoindolinone products in up to 73% yield.

Key words natural products, biomimetic synthesis, heterocycles, isoindolinones, aromatic compounds.

In 2012, G. König et al. reported the discovery of the marilines, a group of natural isoindolinones produced by a sponge-derived marine fungus (*Stachylidium* sp.). Mariline A (*rac*-**1**) was shown to inhibit the human leucocyte elastase (IC_{50} = 0.86 µM), which constitutes an important cellular switch in relevant inflammatory processes.[1] All marilines share a characteristically functionalized isoindolinone core structure with a methyl substituent at C3 (Figure 1).

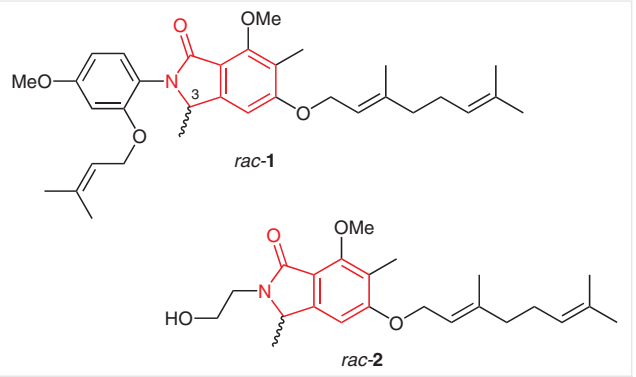
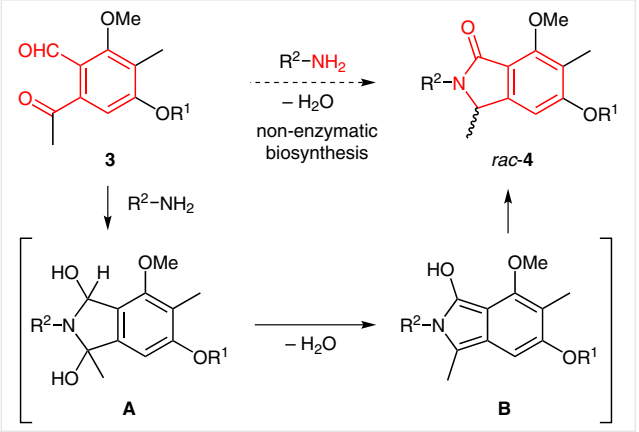


Figure 1 Structure of marilines A (*rac*-**1**) and B (*rac*-**2**); the isoindolinone unit is highlighted in red

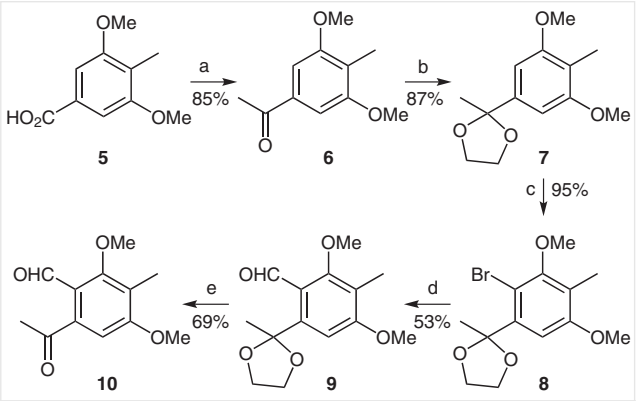
Remarkably, the marilines occur in nature as racemic mixtures. Having proven (for mariline A) that the stereocenter possesses a high degree of configurative stability, König et al. suggested a non-enzymatic transformation as the chirogenic (i.e., racemogenic) step of mariline biosynthesis.[1] More specifically, they proposed that these natural products are formed in nature by condensation of an *ortho*-formyl-acetophenone of type **3** with a primary amine, according to the isoindolinone synthesis recently discovered[2] and applied[3] in our laboratory. As briefly shown in Scheme 1, this transformation would involve the reaction of an amine component R^2-NH_2 with an *ortho*-formyl-arylketone **3** to generate (via **A**) a hydroxyisoindole intermediate (**B**), which finally tautomerizes in a stereo-uncontrolled fashion to the more stable (chiral) isoindolinone (*rac*-**4**).



Scheme 1 Proposed non-enzymatic step in the biosynthesis of the isoindolinone core of the marilines (*rac*-**4**) through condensation of an *ortho*-formyl-acetophenone (**3**) with a primary amine

The goal of the study disclosed herein was to probe the proposed biosynthetic pathway in vitro, by employing substrates that exhibit substitution patterns that are typical of the marilines. As a model substrate of type **3**, we selected the *ortho*-formyl-arylketone **10**, which carries a simplified OR^1 substituent (methoxy instead of geranyloxy). This compound was synthesized starting from the commercially available acid **5** as outlined in Scheme 2. At first, treatment of **5** with an excess (3 equiv) of MeLi in Et_2O gave methyl

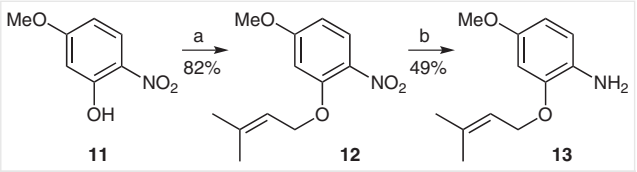
ketone **6**, which was further converted into the protected derivative **7** with ethylene glycol under standard conditions. As several attempts to directly introduce a formyl group into **7** failed, we first introduced a bromine substituent by reacting **7** with *N*-bromosuccinimide (NBS) in acetonitrile.



Scheme 2 Synthesis of the model substrate **10**. *Reagents and conditions*: (a) MeLi, Et_2O, –78 °C to r.t.; (b) $HO(CH_2)_2OH$, cat. *p*-TsOH, benzene, reflux; (c) NBS, MeCN, 0 °C to r.t.; (d) *n*-BuLi, THF, –78 °C, then EtO_2CH, –78 °C to r.t.; (e) CAN, borate/HCl buffer (pH 8), MeCN–H_2O (1:1), 60 °C.

Treatment of the resulting bromide **8** with *n*-BuLi (bromine–lithium exchange) and addition of ethyl formate[2] to the solution of lithiated intermediate then generated the formylated product **9**. The cleavage of the acetal function also turned out to be quite difficult. Whereas complex mixtures were formed under acidic aqueous conditions (due to aldol-type side reactions), the deprotection was achieved by treatment of **9** with cerium ammonium nitrate (CAN) at pH 8 (according to the protocol of Marko[4]) to afford the keto-aldehyde **10** in satisfactory yield (Scheme 2).

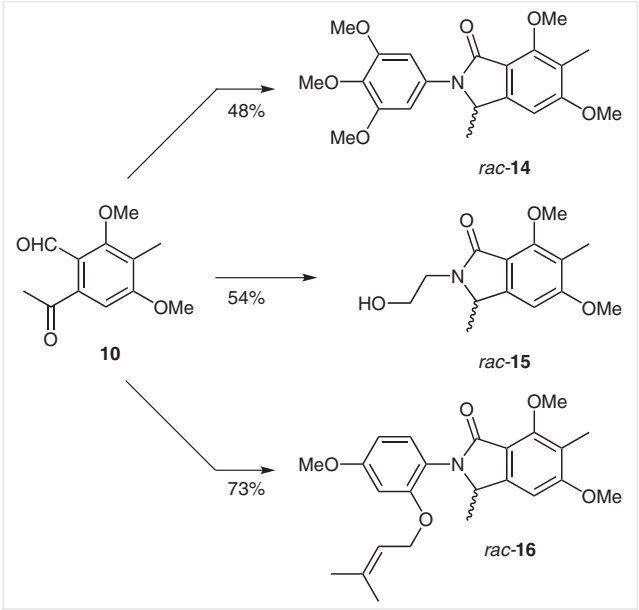
Aniline derivate **13**, corresponding to the amine component of mariline A (*rac*-**1**), was prepared from the known[5] nitrophenol **11** by O-prenylation and reduction of the nitro function of **12** through hydrogenation in the presence of Raney-Ni (Scheme 3).



Scheme 3 Synthesis of the mariline A-related aniline derivative **13**. *Reagents and conditions*: (a) NaH, prenyl bromide, DMF, 0 °C to r.t., 3.5 h; (b) H_2, cat. Raney-Ni, MeOH, r.t., 2.5 h.

Having successfully synthesized the model substrate **10** and the mariline A-related amino building block **13**, the stage was set to investigate the key question of the present study; that is, whether isoindolinones of type *rac*-**4** would readily form by condensation of **10** with different amines under mild conditions (cf. Scheme 1).

Under the mild and only slightly acidic conditions developed before in the course of our initial study,[3a] the reaction of the keto-aldehyde **10** with either trimethoxyaniline, ethanolamine or amine **13**, smoothly afforded the desired isoindolinones *rac*-**14**, *rac*-**15**, and *rac*-**16**, respectively, within 10 minutes at room temperature.[6] Notably, the highest yield (73%) was observed in the case of mariline A-related product *rac*-**16**, whereas aniline itself (as the parent aromatic amine) only gave rise to a complex mixture that did not contain significant amounts of the expected isoindolinone product. Thus, the success of the transformations shown in Scheme 4 may reflect the existence of privileged combinations (of 2-acylbenzaldehydes and amines) that nature seems to exploit in the non-enzymatic biosynthesis of certain isoindolinones.



Scheme 4 Synthesis of mariline-related isoindolinones under mild standard conditions. *Reagents and conditions*: (a) amine (2 equiv), AcOH (2.3 equiv), 1,4-dioxane–H_2O, r.t., 10 min.

In conclusion, we have elaborated reliable schemes for the synthesis of the mariline-related building blocks **10** and **13** and demonstrated their tendency to smoothly condense to the corresponding racemic isoindolinones under mild conditions. We have thereby also paved the way for the (biomimetic) synthesis of other mariline-related compounds, which are of potential pharmacological interest.[7]

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1380700.

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(6) **Synthesis of Isoindolinones; General Procedure (Scheme 4):** To a stirred solution of *o*-formyl-acetophenone **10** (111 mg, 1 mmol) in 1,4-dioxane (2 mL) were added aq AcOH (H_2O–AcOH = 9:1; 1.59 M, 0.8 mL, 2.3 mmol) and the respective amine (1 mmol). After 10 min, the reaction mixture was diluted with sat. aq NH_4Cl and extracted three times with MTBE. The organic layers were dried with $MgSO_4$. After removal of all volatiles under reduced pressure, the residue was purified by flash column chromatography to give the pure isoindolinones.

Characteristic Data for *rac*-14: R_f = 0.18 (SiO_2; cyclohexane–EtOAc, 2:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.79 (s, 2 H), 6.66 (s, 1 H), 5.02 (q, *J* = 6.6 Hz, 1 H,), 4.02 (s, 3 H), 3.92 (s, 3 H), 3.88 (s, 6 H), 3.84 (s, 3 H), 2.17 (s, 3 H), 1.44 (d, *J* = 6.6 Hz, 3 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 165.6 (s), 162.6 (s), 157.0 (s), 153.5 (s, 2C), 147.5 (s), 135.8 (s), 133.4 (s), 120.4 (s), 115.9 (s), 101.7 (d, 2C), 99.2 (d), 62.4 (q), 61.06 (q), 56.9 (d), 56.4 (q, 2C), 56.1 (q), 19.4 (q), 8.6 (q). FTIR (ATR): 1682 (s), 1590 (s), 1506 (s) cm^{-1}. HRMS (ESI): *m*/*z* [M+H]$^+$ calcd: 388.1755; found: 388.1753.

Characteristic Data for *rac*-15: R_f = 0.07 (SiO_2; cyclohexane–EtOAc, 1:3). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.35 (1 H), 6.58 (s, 1 H), 4.48 (q, *J* = 6.7 Hz, 1 H), 3.98 (s, 3 H), 3.88 (s, 3 H), 3.84 (t, *J* = 5.0 Hz, 2 H), 3.80–3.76 (m, 1 H), 3.53–3.50 (m, 1 H), 2.13 (s, 3), 1.44 (d, *J* = 6.7 Hz, 3 H). ^{13}C NMR (151 MHz, $CDCl_3$): δ = 168.7 (s), 162.2 (s), 156.4 (s), 148.5 (s), 119.9 (s), 115.5 (s), 99.3 (d), 62.7 (t), 62.3 (q), 57.1 (d), 56.0 (q), 44.6 (t), 18.9 (q), 8.6 (q). FTIR (ATR): 3405 (br), 1659 (s), 1605 (s), 1130 (s) cm^{-1}. HRMS (ESI): *m*/*z* [M+H]$^+$ calcd: 266.1387; found: 266.1387.

Characteristic Data for *rac*-16: R_f = 0.32 (SiO_2; cyclohexane–EtOAc, 2:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.24 (d, *J* = 8.2 Hz, 1 H), 6.65 (s, 1 H), 6.55–6.53 (m, 2 H), 5.34 (t, *J* = 6.5 Hz, 1 H), 5.02 (q, *J* = 6.7 Hz, 1 H), 4.53–4.45 (m, 2 H), 4.06 (s, 3 H), 3.92 (s, 3 H), 3.82 (s, 3 H), 2.18 (s, 3 H), 1.71 (s, 3 H), 1.66 (s, 3 H), 1.30 (d, *J* = 6.8 Hz, 3 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 166.3 (s), 161.9 (s), 159.8 (s), 156.7 (s), 155.7 (s), 148.9 (s), 137.3 (s), 130.9 (d), 119.8 (d), 119.4 (s), 118.9 (s), 115.9 (s), 104.7 (d), 101.0 (d), 99.2 (d), 65.8 (t), 62.4 (q), 57.1 (d), 56.0 (q), 55.7 (q), 25.8 (q), 19.2 (q), 18.4 (q), 8.6 (q). FTIR (ATR): 1686 (s), 1605 (s), 1510 (s), 1233 (s) cm^{-1}. HRMS (ESI): *m*/*z* [M+H]$^+$ calcd: 412.2118; found: 412.2117.

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