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Structural incongruities of coleophomone natural products: insights by total synthesis of a semi-synthetic derivative

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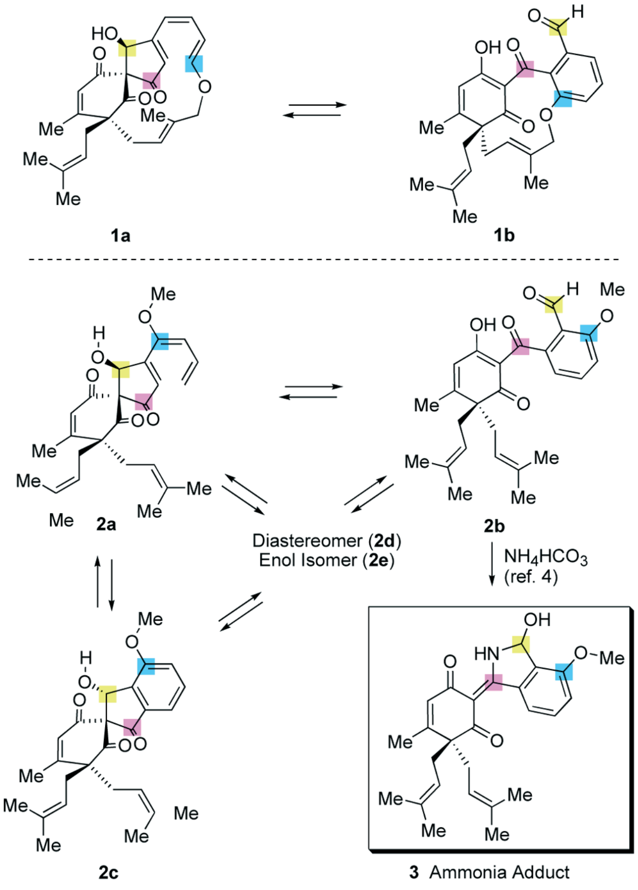
Abstract—An unexpected structural incongruity between coleophomones **1** and the reported structure of recently isolated natural product **2** was confirmed by total synthesis of key semi-synthetic derivative **3** and its positional isomer **4**. In addition, possible mechanisms for the interconversion of expected structure **22** to observed compound **2** are postulated, some of which may have an important role in the biosynthetic origin and chemistry of these structurally unique natural products. © 2003 Elsevier Science Ltd. All rights reserved.

The coleophomones (**1**) are structurally unique biologically active natural products isolated from two different fungal species by researchers at Shionogi[1] and at Merck.[2,3] The related fungal metabolite **2** was recently reported as a dynamic mixture of at least four constitutional isomers by rapid interconversion via a facile aldol–retro-aldol reaction, a feature which confounds spectral analysis.[4,5] To address this complication, the Shionogi researchers prepared the reportedly stable derivative, ammonia adduct **3**, by treatment of natural **2** with NH_4HCO_3. The structure of this compound was determined using standard methods and the identity of **2** was inferred from these findings. Intriguingly, the reported structure of **2** differs from **1** not only in the absence of cyclization between the prenyl side chain and the aromatic moiety, but also in the substitution pattern about the aromatic ring (Scheme 1). Given that this discrepancy was both surprising and inconsistent with the probable biosynthesis of these compounds



Coleophomone (**1**) Pattern (biosynthetically expected)

Compound **2** Pattern (biosynthetically abberent)

Scheme 1.

Keywords: coleophomone; natural product; structure confirmation; cyclocondensation; vinylogous amide.

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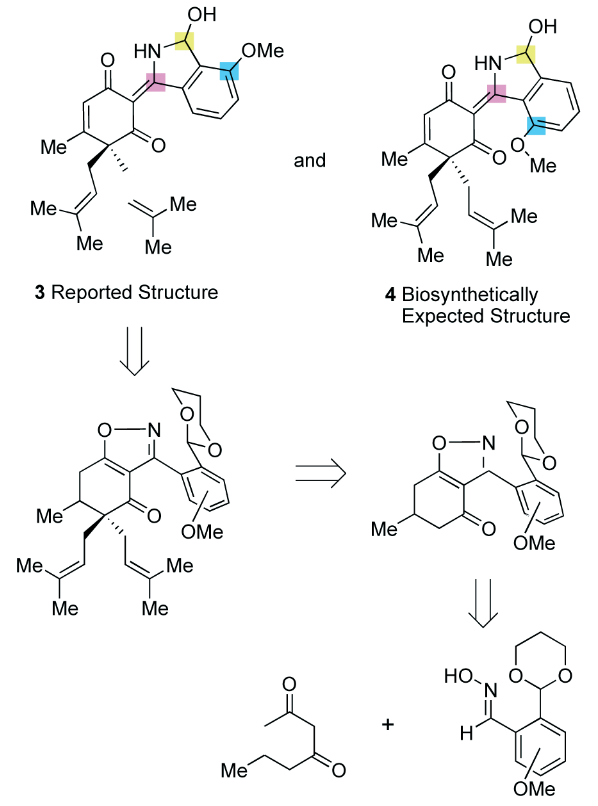


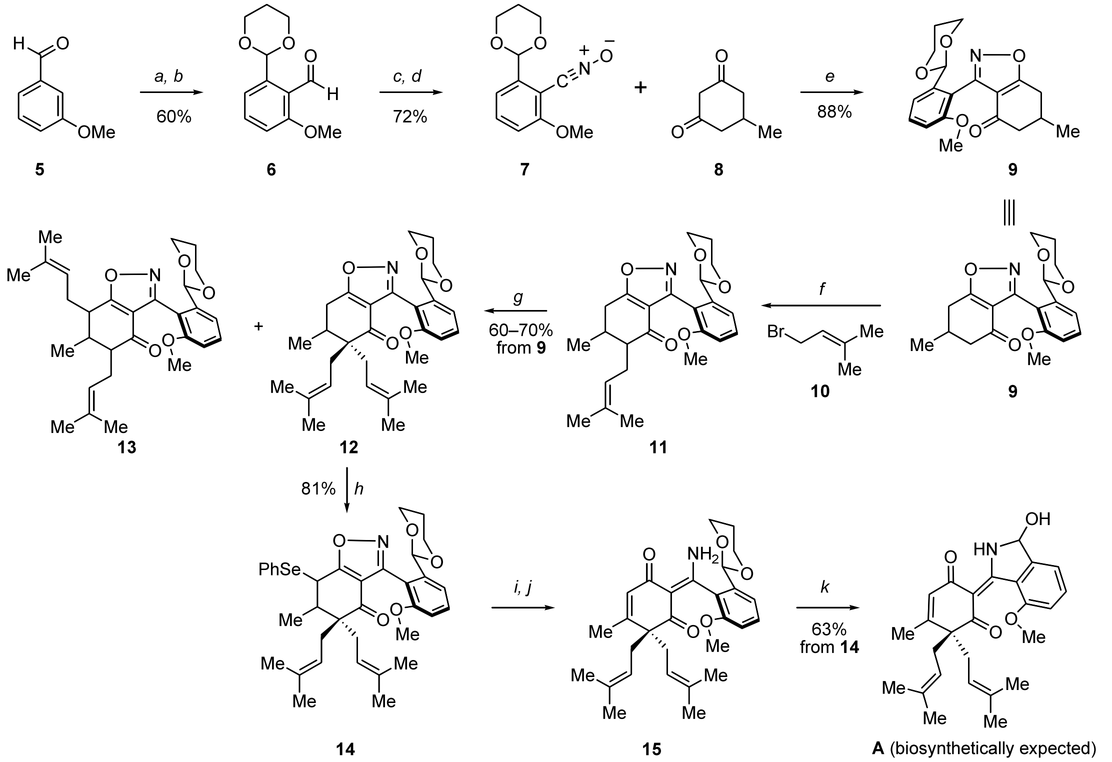
Scheme 2. Retrosynthetic analysis of reported structure **3** and biosynthetically expected isomer **4**.

(vide infra),[6] we embarked on a structure determination via total synthesis.

We now report the total synthesis of both reported structure **3** and its positional isomer **4**, the biosynthetically expected structure,[7] which serves to confirm the unusual structure of semi-synthetic **3**. As well we have postulated mechanisms for the origin of this unusual structure.

In order to avoid potential structural rearrangements during our synthetic efforts, we desired a route allowing direct access to cyclic aminals **3** and **4** without recourse to derivation of the tricarbonyl structures. In this regard, we believed our recently developed synthesis of fused isoxazoles would offer an ideal entry to the vinylogous amide functionality under mild conditions (Scheme 2).[8]

The development of a flexible, viable route to the target aminals began with a synthetic approach to **A**, the positional isomer corresponding to the expected coleophomone pattern (Scheme 3). Following precedent on related systems,[9] aldehyde **5** was converted to the corresponding dioxane acetal, which was treated with *tert*-butyllithium in Et_2O and the resulting lithium species trapped with DMF to afford aldehyde **6**. Conversion to the oxime and nitrile oxide formation (NCS, pyridine)[8] set the stage for the critical cyclocondensation reaction.



Scheme 3. *Reagents and conditions*: (a) 1,3-propanediol, CSA, C_6H_6, reflux; (b) *t*-BuLi, Et_2O, −78°C, then DMF; (c) $NH_2OH\cdot HCl$, K_2CO_3, EtOH–H_2O; (d) NCS, pyridine, CH_2Cl_2; (e) NEt_3, EtOH, 50°C; (f) LDA, THF–HMPA (6:1), **10**, −78°C; (g) Repeat *f*, 8:1 regioselectivity; (h) LDA, THF–HMPA (6:1), PhSeBr, −78°C; (i) $Mo(CO)_6$, CH_3CN–H_2O; reflux, 15 min; (j) aq. H_2O_2, CH_2Cl_2; (k) aq. HCl (1 M), rt, 2 h, THF.

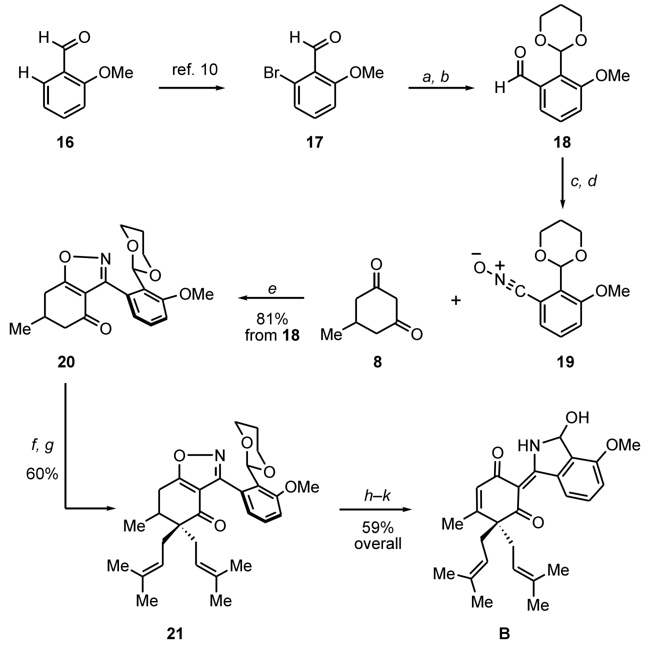
Despite the sterically encumbered and highly functionalized nature of **7**, we were pleased to find that condensation with diketone **8** proceeded exceptionally well to afford the desired fused isoxazole **9** in 88% yield.[8] Notably, this compound is obtained as a 1:1 mixture of diastereomers arising from the methyl stereogenic center and hindered rotation about the biaryl bond.

In addition to masking the latent vinylogous amide functionality, the isoxazole serves as a convenient handle for the elaboration of the cyclohexanedione ring. Although two possible alkylation modes were possible, selective functionalization was achieved simply by choice of the reaction conditions. Thus, treatment of **9** with LDA and trapping of the resulting enolate with prenyl bromide provided **11** in good yield. A second alkylation, in the presence of HMPA, provided the desired quaternary bis-prenyl compound **12** in 8:1 regioselectivity for the desired product. In contrast, the second alkylation performed in the absence of HMPA afforded positional isomer **13** almost exclusively. The ability to alkylate either position of the cyclohexane ring permitted facile introduction of the benzeneselenenyl group, affording **14**.

Selective reduction of the isoxazole to the corresponding vinylogous amide in the presence of the selenenyl functionality was achieved by brief (0.25 h) exposure of **14** to $Mo(CO)_6$ in refluxing $CH_3CN–H_2O$ (5:1), which served to reduce the N–O bond of the isoxazole without effecting C–Se bond cleavage. Further treatment of the unpurified reaction mixture with H_2O_2 afforded the unsaturated vinylogous amide **15**. Upon deprotection of the acetal with aqueous acid, targeted cyclic aminal **A** was obtained in excellent yield.

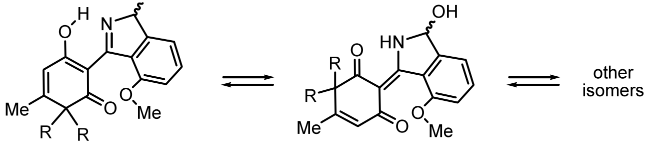
The general approach to coleophomone structures, thus established, was directly applicable to the synthesis of isomer **B** without modification or optimization of the reaction conditions (Scheme 4). Known bromide **17**[10] served as a convenient starting material for the preparation of aldehyde **18**. Following further transformation to stable nitrile oxide **19**, cyclocondensation with 5-methylcyclohexan-1,3-dione (**8**) in the presence of sodium isopropoxide provided key isoxazole **20** in good yield.[8] In contrast to **9**, this compound did not show evidence of atropisomerism.

An identical sequence of reactions employed for the preparation of **A** was utilized to convert **20** to cyclic aminal **B**, with a marginal decrease in the regioselectivity of the second alkylation with prenyl bromide as the only deviation.



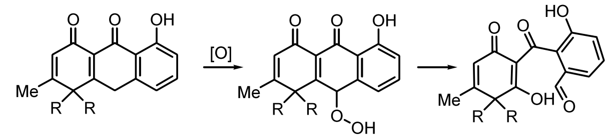
Scheme 4. *Reagents and conditions*: (a) 1,3-propanediol, CSA, C_6H_6, reflux; (b) *n*-BuLi, Et_2O, −78°C, then DMF; (c) $NH_2OH·HCl$, K_2CO_3, $EtOH–H_2O$; (d) NCS, pyridine, CH_2Cl_2; (e) 1.4 equiv. NaO^iPr, 1.5 equiv. **8**, ^{i}PrOH, 50°C; (f) LDA, THF–HMPA, **10**, −78°C; (g) Repeat *f*, 6:1 regioselectivity; (h) LDA, THF–HMPA, PhSeBr, −78°C; (i) $Mo(CO)_6$, $CH_3CN–H_2O$; reflux, 15 min; (j) aq. H_2O_2, CH_2Cl_2; (k) aq. HCl (1 M), rt, 5 min, THF.

Comparison of the ^1H and ^{13}C NMR spectra of synthetic aminals **A** and **B** with the data reported for semi-synthetic **3** confirmed that *compound **B** was identical to **3**, confirming that the reported, unusual structure is indeed correct*.[11] In fact, despite the structural similarity, the spectral properties of **A** and **B** differ significantly. The spectral data of synthetic **B** showed a single compound in numerous solvents and exactly matched the spectra of a semi-synthetic, authentic sample.[12] In contrast, **A** existed as a complex mixture of stereoisomeric amide and imine forms in aprotic solvents (Scheme 5), but as predominantly one isomer in the presence of a proton source (i.e. CD_3OH). Our initial difficulties in the characterization of **A** served as a reminder of the care which must be taken in assigning the structure of molecules interconverting between structurally distinct constitutional isomers.



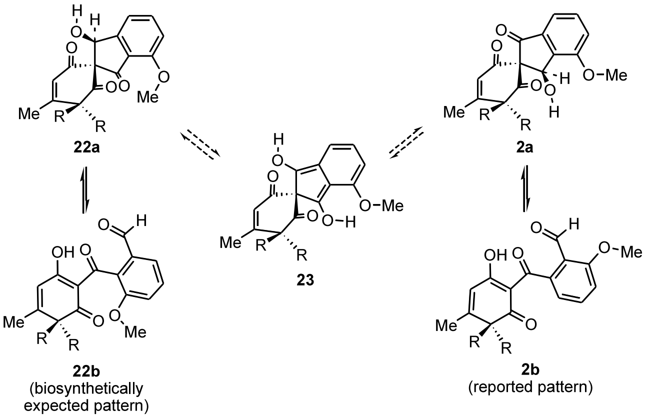
Scheme 5. Compound **A**, a mixture of imines, vinylogous amides, atropisomers, and geometrical isomers in aprotic solvents.

These results served to confirm, but not explain, the aberrant structure of compound **3** and, by association, naturally occurring **2**. The biosynthesis of **1** and **2**, which are fungal metabolites, likely proceeds via oxidative cleavage of the corresponding anthracene (Scheme 6). This analysis predicts the resulting benzophenone-like core to have the *ortho,ortho′* disubstitution pattern seen in **1**.



Scheme 6. Postulated biosynthesis of coleophomone natural products.

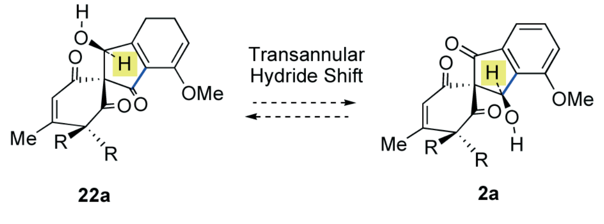
Although the incongruent structure of **2** could indeed arise from specific oxidative enzymes which introduce hydroxyl functionalities at this position, we have postulated several mechanisms for the structural interconversion of the biosynthetically expected structure **22** and the reported structure **2** (Schemes 7 and 8).



Scheme 7. Postulated origin of reported structure **2** from expected compound **22** via pseudo-symmetric enol **23**.

Scheme 7 illustrates a potential structural interconversion via pseudo-symmetrical enol **23**, which could be formed from expected isomer **22** under acidic, basic, or photochemical conditions. Indeed, precedent exists for similar isomerization under a variety of conditions.[13] Tautomerization of **23** would either regenerate isomer **22** or, alternatively, give rise to reported isomer **2**.

Likewise, a similar rearrangement via a transannular hydride shift (Scheme 8) of **22a** would also result in a structural interconversion affording reported compound **2a**.[14]



Scheme 8. Potential structural interconversion via hydride shift.

Given that these or related processes may be quite facile, the question of whether the unusual structure of **3** is biosynthetically determined, the result of a spontaneous rearrangement, or an artifact of the isolation and purification procedure remains to be established.

In conclusion, we have described a novel synthetic entry to the core structures of the coleophomone natural products, cumulating in the structure confirmation of semi-synthetic derivative **3** by total synthesis. These studies contribute to the growing interest in these structurally unusual molecules and provide a novel approach likely to be useful for continued synthetic studies and for the preparation of designed analogs. Further studies to employ this chemistry towards conclusive structure proof of compound **2** and the origin of the structural incongruity are underway.

Acknowledgements

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11. Spectral data for fully synthetic **3** and **4**: (a) **3**: ^{1}H NMR (400 MHz, CD_3OD, 50°C) δ 7.42–7.34 (m, 2H), 7.06 (dd, 1H, $J=7.5$, 1.0 Hz), 6.06 (s, 1H), 5.98 (s, 1H), 4.83–4.79 (m, 1H), 4.74–4.71 (m, 1H), 3.78 (s, 3H), 2.59–2.52 (m, 2H), 2.43–2.35 (m, 2H), 1.89 (d, 3H, $J=1.2$ Hz), 1.63 (s, 3H), 1.61 (s, 3H), 1.60 (s, 3H), 1.55 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 201.8, 189.1, 167.9, 158.7, 157.0, 136.7, 135.0, 133.7, 132.1, 130.2, 123.0, 120.1, 116.3, 108.4, 84.0, 57.8, 56.3, 38.0, 25.9, 19.4, 18.0; IR (thin film) 3198, 2920, 1653, 1610, 1523, 1424, 1269, 1227, 1051 cm^{-1}. (b) **4**: ^{1}H NMR (400 MHz, CD_3OD, 50°C) δ 8.23–8.20 (m, 1H), 7.46–7.41 (m, 1H), 7.23–7.41 (m, 1H), 7.23–7.19 (m, 1H), 6.25–6.22 (m, 1H), 6.18 (s, 1H), 4.81–4.77 (m, 2H), 3.93–3.91 (m, 3H), 2.83–2.77 (m, 2H), 2.38–2.33 (m, 2H), 1.97–1.95 (m, 3H), 1.57 (br s, 6H), 1.50 (br s, 6H); ^{13}C NMR (100 MHz, CD_3OD) δ 173.9, 159.3, 156.0, 137.0, 135.5, 134.4, 130.1, 119.7, 115.9, 114.3, 56.2, 51.1, 25.9, 19.3, 18.1 (some carbons not visible due to molecular motions).
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