

Synthesis of Ecteinasclidin 743 Analogues from Cyanosafraclin B: Isolation of a Kinetically Stable Quinoneimine Tautomer of a 5-Hydroxyindole

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Phthalimido derivatives of cyanosafraclin B have been synthesized as analogues of the antitumor agent ecteinasclidin 743. As part of this study, a quinoneimine has been prepared, which is a kinetically stable tautomer of a 5-hydroxyindole.

This quinoneimine tautomer is stable under acidic and mild basic conditions.

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Introduction

YondelisTM (**1**) (Ecteinasclidin 743, trabectidin) is a tetrahydroisoquinoline alkaloid of the ecteinasclidin family isolated from *Ecteinasclidia turbinata*^[1] that displays highly cytotoxic activity against a variety of tumor cells (Figure 1).^[2,3] YondelisTM is currently in advanced stages of clinical development worldwide.^[4] Therefore, the ecteinasclidins have aroused significant synthetic interest. Total syntheses of **1** have been reported by Corey,^[5] Fukuyama,^[6] and Zhu.^[7] Other groups have also described synthetic approaches towards **1** and related tetrahydroisoquinoline alkaloids.^[8–13]

Corey and Schreiber discovered an analogue of **1**, named phthalasclidin (**2**),^[14] which exhibits comparable biological activity to that of **1**. Similarly, Myers developed a synthesis of bishydroquinone-safraclins analogues, with greater activity in antiproliferative assays than the natural product.^[15] These findings have aroused considerable interest and have led to a search of other simplified tetrahydroisoquinolines with similar or more potent antitumor efficacies to those displayed by the parent naturally occurring compound **1**.

A practical synthesis of **1** from cyanosafraclin B (**3**) (Figure 1) has been accomplished by Cuevas, Manzanares and co-workers.^[16] Key for the success of this semisynthetic method was the ready availability of **3** by a fermentation process. That approach was also applied for the preparation of other natural ecteinasclidins.^[17] Considering the excellent

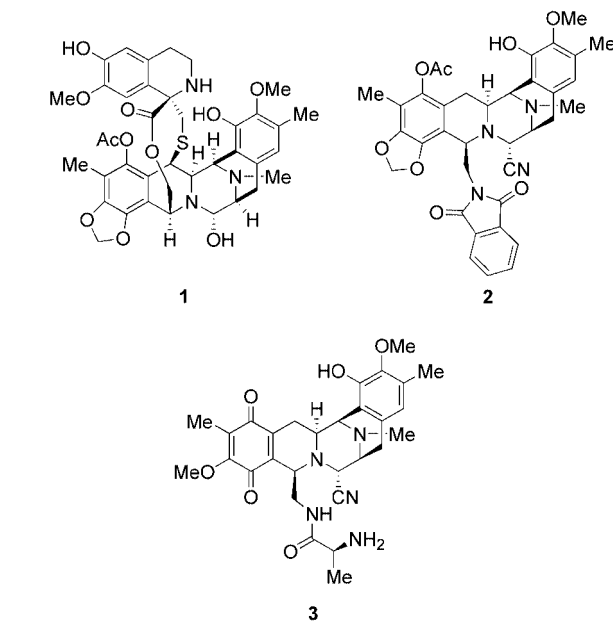


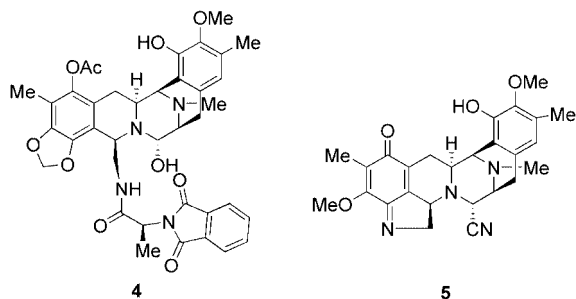
Figure 1. Ecteinasclidin 743 (**1**), phthalasclidin (**2**), and cyanosafraclin B (**3**).

activity displayed by phthalasclidin (**2**), we embarked on the synthesis of several analogues such as **4** (Figure 2) that could be defined as safraclins-phthalimide derivatives. These compounds have the same basic functionalization of **2** but with a phthalimide as the C-subunit anchored through the alanine side chain. As part of these studies, we have also prepared a quinoneimine derivative **5** that is remarkably stable and does not isomerize to the more stable 5-hydroxyindole under acidic or mild basic conditions. Here we report the synthesis of **4**, as well as the preparation and reactivity of the stable quinoneimine **5**.

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Figure 2. Phthalimido derivative **4** and quinoneimine **5**.

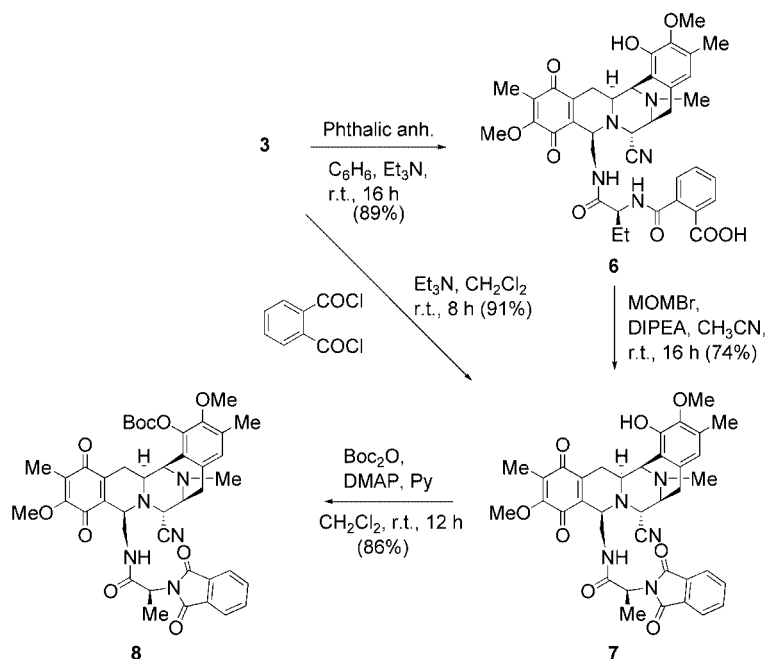
Results and Discussion

Synthesis of Phthalimide Derivative **4:** For the synthesis of target **4** we planned to form first the phthalimide from the free amino group, followed by subsequent transformation of the *p*-benzoquinone into the methylenedioxy aryl ring by the route developed by Cuevas, Manzanares and co-workers.^[16] However, reaction of **3** with phthalic anhydride failed to provide the expected phthalimide **7**, leading exclusively to the phthalimidic acid **6** under all the conditions examined. Phthalimidic acid **6** did not react with carbonyl diimidazole or triphosgene as activating agents. However, in an attempt at protecting the phenol and carboxylic acid groups as MOM derivatives, we finally succeeded in preparing **7**. Thus, reaction of **6** with MOMBr and *i*Pr₂NEt in CH₂Cl₂ gave the **7** in 60–74% yields (Scheme 1). A more direct synthesis of this phthalimide derivative was achieved by treatment of **3** with phthaloyl dichloride (1.0 equiv.) and

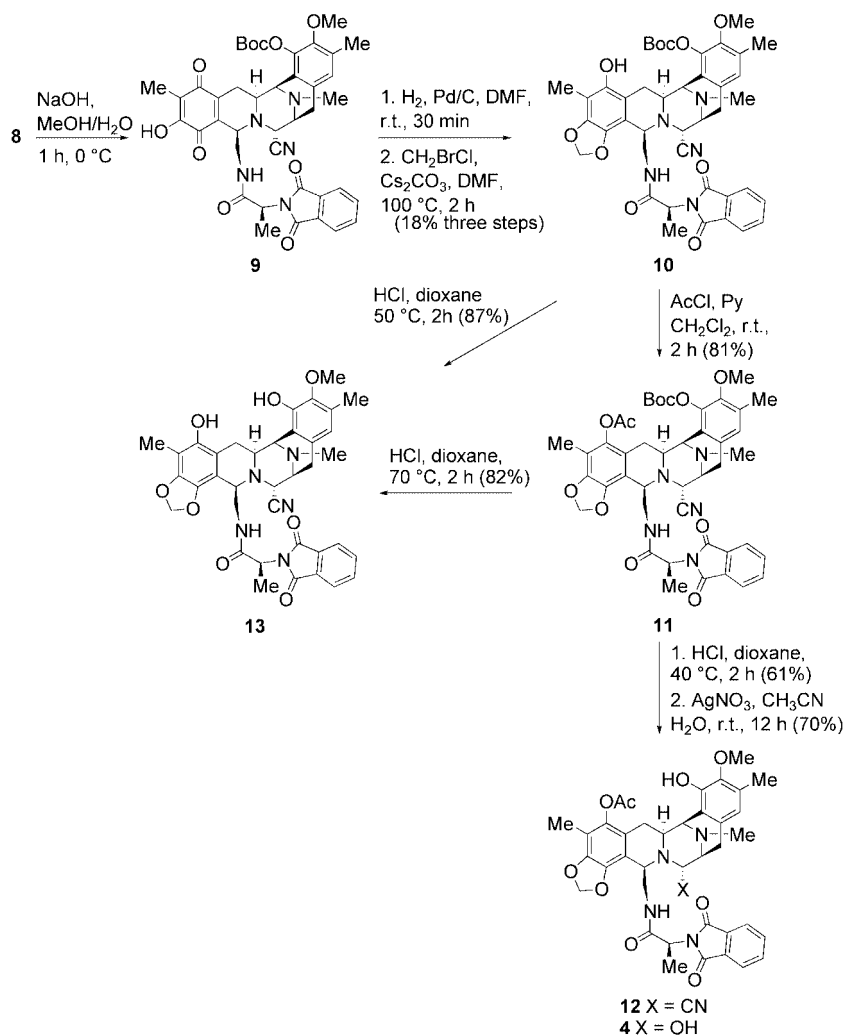
Et₃N (2.1 equiv.) in CH₂Cl₂, which provided **7** in excellent yield. Protection of the free phenol of **7** with Boc₂O (1.2 equiv.), pyridine (1.5 equiv.) and DMAP (0.01 equiv.) in CH₂Cl₂ gave carbonate **8** in good yield. This two step sequence could also be carried out in one pot in 88% overall yield.

Saponification of the vinilogenous ester **8** was performed with an excess of NaOH under high-dilution conditions to give hydroxy derivative **9** after acidification of the reaction mixture to pH 5. Immediate catalytic hydrogenation of **9** with Pd/C in DMF, followed by reaction with CH₂BrCl and Cs₂CO₃ at 100 °C gave rise to methylenedioxy derivative **10** in 18% yield for the three steps (Scheme 2). The low overall yield reflects the lability of hydroxyquinone derivative **9**. Acetylation of the phenol group of **10** with AcCl (1.2 equiv.) and pyridine (2 equiv.) in CH₂Cl₂ gave **11** in 81% yield. Deprotection of the Boc group could not be effected with TFA, which led only to unchanged starting material. However, reaction of **11** with HCl in dioxane at 40 °C gave **12** (61%), along with small amounts of diphenol **13**. At higher temperatures, diphenol **13** was exclusively obtained. Diphenol **13** was also obtained by cleavage of the Boc group of **10** under similar acidic conditions. Finally, substitution of the cyano group by a hydroxy was achieved with AgNO₃ in aqueous MeCN^[16] to give **4** in 70% yield. Thus, **4** was obtained in 8 steps from **3** in 5% overall yield.

Table 1 summarizes the results on *in vitro* activities of compounds of Scheme 1 and Scheme 2 against three human tumor cell lines. Among all the derivatives examined, only **12** and **4**, with structures more closely related to that of **2**, display significant *in vitro* antitumor activity in the order of 10^{−2} μM concentrations.



Scheme 1.



Scheme 2.

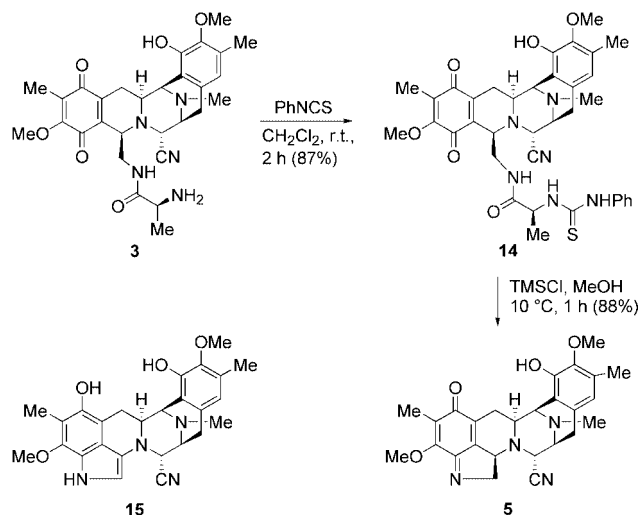
Table 1. In vitro activities (GI₅₀ = concentration causing 50% growth inhibition) of compounds **4** and **6–13** (μM concentrations) compared with those of parent **1**.

Compound	Breast (MB-231)	Lung (A549)	Colon (HT29)
1	0.003	0.003	0.003
4	0.03	0.04	0.05
6	0.34	0.80	0.80
7	0.097	0.14	0.22
8	0.31	0.37	0.69
9	3.26	4.83	4.57
10	0.94	0.73	0.81
11	1.02	0.37	0.65
12	0.02	0.02	0.03
13	1.37	1.18	1.16

Synthesis of Stable Quinoneimine 5: In the original approach developed by Cuevas, Manzanares and co-workers, the alanine residue of **3** was removed by an Edman degradation on a derivative in which the quinone ring had been refunctionalized to a methylenedioxy arene ring. However, when the Edman degradation was carried out on thiourea

14, prepared by reaction of **3** with phenylisothiocyanate, we obtained quinoneimine **5** in excellent yield by an intramolecular condensation of the initially formed primary amine with the quinone carbonyl (Scheme 3). Unexpectedly, none of the 5-hydroxyindole derivative **15** was formed in this reaction. Quinoneimine **5** was recovered unchanged in the presence of acids such as HCl or trifluoroacetic acid at room temperature for long reaction times. Furthermore, **5** does not suffer isomerization after being heated with pyridine in CH₂Cl₂ under refluxing conditions for 14 h. Quinoneimine **5** shows only moderate in vitro antitumor activity (IC₅₀ = 2.17 μM; murine P388 and melanoma MEL28) but displays a new type of structure that could be further functionalized for the synthesis of analogues of **1**.

Furthermore, **5** is interesting by itself as it represents the first quinoneimine that does not spontaneously isomerize to give the corresponding hydroxyindole. Simple quinoneimines **16a**^[18] and **16b**,^[19] which cannot suffer tautomerization because of the presence of a quaternary center at C-2, have been described (Figure 3).^[20] On the other hand, (L)-α-dopachrome (**17**) and (L)-α-methyldopachrome (**18**) are rela-



Scheme 3.

tively stable derivatives in dilute solutions,^[21] although these compounds are better represented as the *o*-quinones **17b** and **18b**, respectively. At neutral pH, derivatives **17** and **18** spontaneously rearrange via a quinone-methide to give 5,6-dihydroxyindole-2-carboxylate derivatives.^[22,23] Attempts to synthesize an unsubstituted analogue of **16a–b** by deprotection of quinones **19** with different protecting groups R failed and complex reaction mixtures were obtained.

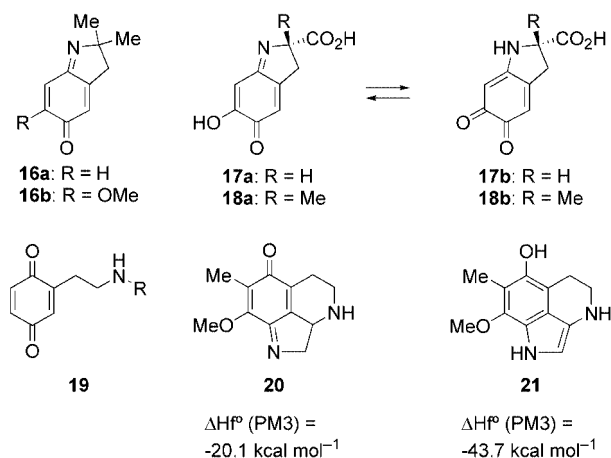
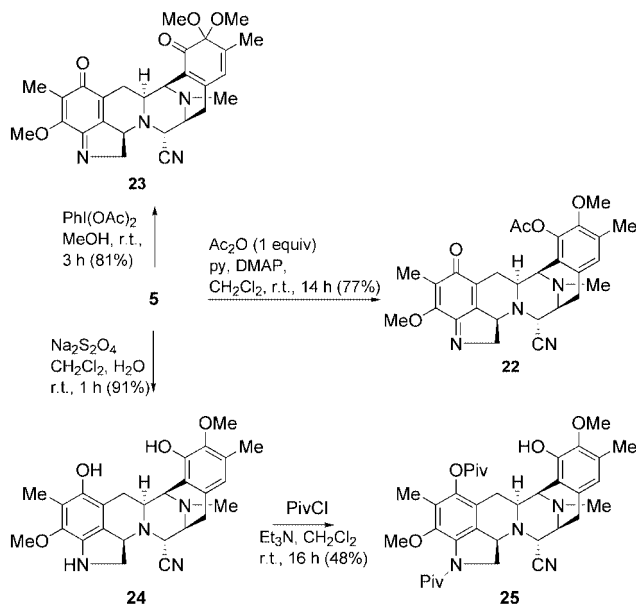


Figure 3. Stable quinoneimines and model compounds.

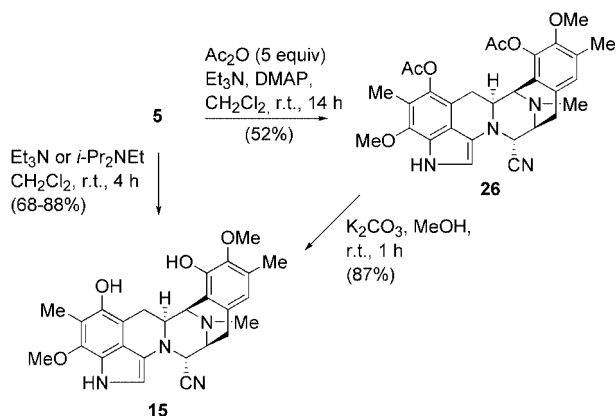
Semiempirical calculations (PM3 level) show that hydroxyindole **15** ($\Delta H^\circ_f = -60.7 \text{ kcal mol}^{-1}$) is considerably more stable than the quinoneimine tautomer **5** ($\Delta H^\circ_f = -36.7 \text{ kcal mol}^{-1}$). This energy difference ($\Delta \Delta H^\circ_f = 24 \text{ kcal mol}^{-1}$) is higher than that computed at the same level for the 2,4-cyclohexadienone/phenol equilibrium ($\Delta \Delta H^\circ_f = 11.8 \text{ kcal mol}^{-1}$). For this equilibrium, $\Delta \Delta H$ (25 °C) = $17.9 \text{ kcal mol}^{-1}$ has been determined experimentally.^[24] Simplified models **20** and **21** of quinoneimine **5** and hydroxyindole **15**, respectively, reproduce this pattern (Figure 3) and indicate that there is not any subtle steric or hydrogen bond stabilization in quinoneimine **5**.

The quinoneimine structure of **5** is preserved under a variety of reaction conditions (Scheme 4). Reaction of **5** with 1 equiv. of Ac_2O , pyridine and DMAP in CH_2Cl_2 gives rise to monoacetate **22** in 77% yield. The quinoneimine nucleus is also stable under oxidizing conditions. Thus, treatment of **5** with $\text{PhI}(\text{OAc})_2$ in MeOH leads to *o*-quinone dimethyl acetal **23** in 81% yield. On the other hand, treatment of **5** with $\text{Na}_2\text{S}_2\text{O}_4$ in $\text{H}_2\text{O}/\text{CH}_2\text{Cl}_2$ gave rise to indoline **24** in 92% yield. However, reduction of **5** with Zn in $\text{HOAc}/\text{H}_2\text{O}$ gave poor results. Derivative **24** is relatively unstable, suffering readily reoxidation to give starting quinoneimine **5**, although it can be handled in the presence of air for a few minutes. Stable bispivaloyl derivative **25** was obtained in 48% yield by reaction of freshly prepared **24** with PivCl and Et_3N .



Scheme 4.

In contrast to that found in the presence of pyridine, amines such as Et_3N or $i\text{Pr}_2\text{NEt}$ promote the isomerization of **5** to indole derivatives (Scheme 5). Thus, acetate **26** was obtained in 73% yield by reaction with 10 equiv. of Ac_2O and Et_3N . Methanolysis of **26** (MeOH , K_2CO_3 , room tem-



Scheme 5.

perature) cleanly gave hydroxyindole **15** in 87% yield. Indole **15** could also be obtained by treatment of **5** with either Et_3N or $i\text{Pr}_2\text{NEt}$ (68–88% yield).

Summary

In summary, phthalimide derivatives of cyanosafracin **B** (**2**), with the substitution at the A ring of the ecteinascidins, have been prepared from **3**. These compounds display significant antitumor activities in vitro at the μM level, although the most active derivatives **4** and **12** are only an order of magnitude less potent than parent ecteinascidin 743 (**1**). We have also isolated the first quinoneimine tautomer of a 5-hydroxyindole, which is remarkably stable under acidic and mild basic conditions, despite the large difference in energy that favors tautomerization to the indole. Quinoneimine **5** is prepared in two steps from cyanosafracin **B** (**2**), which is readily available by fermentation in large amounts. Quinoneimine **5** and derivatives such as **15**, and **24**, are new types of hexacyclic tetrahydroisoquinoline scaffolds that could be useful for the preparation of antitumor compounds.

Experimental Section

General Remarks: The NMR spectra were carried out at 23 °C, unless otherwise stated. Only the most significant MS fragmentations are given. The FAB-MS spectra were obtained by using *m*-nitrobenzyl alcohol as the matrix. R_f were determined on TLC aluminum sheets coated with 0.2 mm GF₂₅₄ silica gel. All reactions were carried out under an atmosphere of Ar. Solvents were purified and dried by standard methods. Chromatographic purifications were carried out with flash-grade silica gel. "Usual extractive workup" means pouring the crude reaction mixture onto water, partitioning between CH_2Cl_2 and water (or 10% aqueous HCl for reaction involving bases as reagents), followed by extraction, drying (MgSO_4), and evaporation of the solvent.

Phthalimide Acid 6: A solution of **2** (1.00 g, 1.78 mmol), phthalic anhydride (262 mg, 1.78 mmol), pyridine (0.16 mL, 1.95 mmol), and DMAP (10 mg, 0.08 mmol) in benzene (15 mL) was stirred at 23 °C for 16 h. After the usual extractive workup, **6** (1123 mg, 89%) was obtained as a greenish solid, which was used without further purification. R_f = 0.06 (hexane/EtOAc, 1:1). IR (cm^{-1}): $\tilde{\nu}$ = 3371, 2922, 1649, 1439, 1354, 1282, 1234, 1165. ^1H NMR (CDCl_3 , 300 MHz): δ = 1.09 (d, J = 6.9 Hz, 3 H), 1.69 (s, 3 H), 1.99–1.85 (m, 1 H), 2.13 (s, 3 H), 2.34 (s, 3 H), 2.57 (d, J = 18.6, 1 H), 3.04 (dd, J = 18.6, 3.6 Hz, 2 H), 3.19 (br. d, J = 10.9 Hz, 1 H), 3.31 (dt, J = 12.2, 4.1 Hz, 1 H), 3.38 (d, J = 6.9 Hz, 1 H), 3.58–3.47 (m, 1 H), 3.74–3.65 (m, 1 H), 3.76 (s, 3 H), 3.87 (br. s, 1 H), 3.97 (s, 3 H), 4.14 (d, J = 2.8 Hz, 1 H), 4.18 (s, 1 H), 6.04 (br. s, 1 H), 6.15 (d, J = 6.1 Hz, 1 H), 6.32 (s, 1 H), 7.32 (d, J = 7.7 Hz, 1 H), 7.52 (m, 2 H), 7.95 (d, J = 7.7 Hz, 1 H). ^{13}C NMR (CDCl_3 , 75 MHz, DEPT): δ = 8.21 (CH_3), 15.19 (CH_3), 17.64 (CH_3), 24.49 (CH_2), 24.78 (CH_2), 40.05 (CH_2), 41.65 (CH_3), 49.61 (CH), 54.12 (CH), 55.08 (CH), 55.61 (CH), 55.74 (CH), 58.81 (CH), 60.79 (CH_3), 60.91 (CH_3), 117.21 (C), 117.73 (C), 120.02 (CH), 128.54 (CH), 129.09 (C), 129.84 (CH), 131.04 (CH), 131.78 (C), 132.47 (CH), 132.92 (C), 135.92 (C), 137.69 (C), 141.52 (C), 143.08 (C), 147.38 (C), 156.15 (C), 163.68 (C), 169.44 (C), 173.45 (C), 181.22 (C), 186.11 (C). APCI-MS: m/z (%) 698 [$\text{M}^+ + 1$, 100], 550 ($\text{M}^+ - 148$,

92). The structure of **6** was confirmed by COSY, HMQC, HMBC, and NOESY correlations.

Phthalimide 7. Method a: To a solution of **6** (800 mg, 1.12 mmol) and Et_3N (0.17 mL, 0.12 mmol) in CH_2Cl_2 (15 mL) at 23 °C was added MOMBr (0.10 mL, 1.23 mmol) and the mixture was stirred at 23 °C for 16 h. After the usual extractive workup and chromatography (hexane/EtOAc, 1:1), **7** (572 mg, 74%) was obtained as a pale greenish solid.

Method b: A solution of **2** (2.50 g, 4.45 mmol), phthaloyl dichloride (899 mg, 4.45 mmol), and Et_3N (1.3 mL, 9.35 mmol) in CH_2Cl_2 (30 mL) was stirred at 23 °C for 8 h. After the usual extractive workup and chromatography (hexane/EtOAc, 1:1), **7** (2.80 g, 91%) was obtained. R_f = 0.34 (hexane/EtOAc, 1:3). ^1H NMR (CDCl_3 , 300 MHz): δ = 1.19 (d, J = 7.7 Hz, 3 H), 1.62–1.73 (ddd, J = 18.2, 8.5, 1.4 Hz, 1 H), 1.74 (s, 3 H), 2.21 (s, 3 H), 2.33 (s, 3 H), 2.49 (d, J = 18.2 Hz, 1 H), 3.01–3.21 (m, 5 H), 3.40 (br. d, J = 8.5 Hz, 1 H), 3.72 (s, 3 H), 3.82 (s, 3 H), 3.87 (m, 1 H), 4.06 (m, 1 H), 4.18 (d, J = 2.4 Hz, 1 H), 5.46 (d, J = 6.1 Hz, 1 H), 6.52 (s, 1 H), 7.65–7.73 (m, 4 H). ^{13}C NMR (CDCl_3 , 75 MHz, DEPT): δ = 8.42 (CH_3), 14.72 (CH_3), 15.73 (CH_3), 24.26 (CH_2), 25.49 (CH_2), 41.22 (CH_2), 41.73 (CH_3), 49.28 (C), 54.65 (C), 54.96 (C), 55.92 (C), 56.24 (C), 58.91 (C), 60.15 (C), 60.32 (C), 116.57 (C), 117.34 (C), 120.61 (CH), 123.32 (CH), 123.39 (CH), 127.68 (C), 129.34 (C), 130.52 (C), 131.44 (C), 134.19 (CH), 135.71 (C), 141.04 (C), 143.18 (C), 147.14 (C), 167.53 (C), 169.25 (C), 180.72 (C), 185.61 (C). API-ES-MS: m/z (%) 680 [$\text{M}^+ + 1$, 100]. FAB-HRMS: m/z calcd. for $\text{C}_{37}\text{H}_{37}\text{N}_5\text{O}_8$: 679.2642, found 679.2644. $\text{C}_{37}\text{H}_{37}\text{N}_5\text{O}_8$ (679.71): C 65.38, H 5.49, N 10.30; found C 65.33, H 5.62, N 10.72. The structure of **7** was confirmed by COSY, and HMQC correlations.

Boc-Phthalimide Derivative 8. Method a: A solution of **7** (2.71 g, 4.0 mmol), Boc_2O (1.67 g, 8 mmol), pyridine (0.65 mL, 8 mmol), and DMAP (48 mg, 0.4 mmol) in CH_2Cl_2 (10 mL) was stirred for 12 h at 23 °C. After the usual extractive workup and chromatography (hexane/EtOAc, gradient 3:1 to 1:1), **8** (2.68 g, 86%) was obtained as a pale greenish solid.

Method b (one-pot preparation from 2): A solution of **2** (3.00 g, 5.46 mmol), phthaloyl dichloride (0.780 mL, 5.47 mmol), and Et_3N (1.6 mL, 11.47 mmol) in CH_2Cl_2 (15 mL) was stirred at 23 °C for 8 h. To the reaction mixture was added a solution of DMAP (37 mg, 0.056 mmol), pyridine (0.88 mL, 10.92 mmol), and Boc_2O (2270 mg, 10.92 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred at 23 °C for 12 h. After the usual extractive workup and chromatography (hexane/EtOAc, 1:1), **8** (3.74 g, 88%) was obtained. R_f = 0.41 (hexane/EtOAc, 1:3). ^1H NMR (CDCl_3 , 300 MHz): δ = 1.13 (d, J = 7.6 Hz, 3 H), 1.58 (s, 9 H), 1.85 (s, 3 H), 2.21 (s, 3 H), 2.28 (s, 3 H), 2.57 (d, J = 23.1 Hz, 1 H), 3.02 (br. d, J = 23.1 Hz, 1 H), 3.21–3.08 (m, 3 H), 3.41 (t, J = 8.1 Hz, 1 H), 3.73 (s, 3 H), 3.83 (s, 3 H), 3.91–3.82 (m, 2 H), 4.07 (br. d, J = 2.0 Hz, 1 H), 4.31 (q, J = 7.7 Hz, 1 H), 5.66 (m, 1 H), 6.88 (s, 1 H), 7.75–7.66 (m, 4 H) (two H signals were not observed). ^{13}C NMR (CDCl_3 , 75 MHz, DEPT): δ = 8.81 (CH_3), 14.84 (CH_3), 16.03 (CH_3), 24.74 (CH_2), 25.15 (CH_2), 27.60 (3 CH_3), 41.84 (CH_2), 41.87 (CH_3), 49.27 (CH), 54.81 (CH), 54.93 (CH_2), 57.41 (CH), 57.44 (CH), 59.72 (CH_3), 61.03 (CH_3), 61.12 (CH), 84.41 (C), 110.23 (C), 117.56 (C), 123.11 (C), 123.62 (2 CH), 127.79 (CH), 128.02 (C), 130.54 (C), 132.08 (C), 132.41 (C), 134.37 (2 CH), 135.87 (C), 140.92 (C), 143.17 (C), 148.52 (C), 151.30 (C), 156.46 (C), 167.98 (C), 169.09 (C), 181.22 (C), 185.12 (C). ES-MS: m/z (%) 780 [$\text{M}^+ + 1$, 100], 753 ($\text{M}^+ - 26$, 31). $\text{C}_{42}\text{H}_{45}\text{N}_5\text{O}_{10}$ (779.83): C 64.69, H 5.82, N 8.98; found C 64.61, H 5.94, N 8.93. The structure of **8** was supported by a COSY correlation.

Phenol Derivative 10: To a solution of **8** (2000 mg, 2.56 mmol) in MeOH (300 mL) at 0 °C, was added portionwise a solution of NaOH (25 g, 625 mmol) in H₂O (400 mL). The purple solution was stirred for 1 h at ca. 0 °C. The solution was acidified to pH 5 with 4 M HCl and extracted with EtOAc. The organic layer was dried (MgSO₄), filtered and evaporated, affording the vinylogous acid **9** that was used in the next step without further purification. ¹H NMR showed the disappearance of the methoxy group. A solution of crude **9** (448 mg, 0.58 mmol) and Pd/C (40 mg, 10%, 0.058 mmol) in DMF (6 mL) was stirred under H₂ (1 atm) at 23 °C for 30 min. Then, the mixture was filtered under Ar and transferred to a sealed tube containing Cs₂CO₃ (570 mg, 1.75 mmol). CH₂BrCl was added (0.75 mL, 11.6 mmol) and the mixture was heated at 100 °C for 2 h. The reaction was cooled, filtered through celite, and after the usual extractive workup and chromatography (hexane/EtOAc, 1:1), **10** (89 mg, 18%, three steps) was obtained as a pale yellow solid. *R*_f = 0.24 (hexane/EtOAc, 2:3). ¹H NMR (CDCl₃, 300 MHz): δ = 1.25 (d, *J* = 7.2 Hz, 3 H), 1.52–1.58 (m, 1 H), 1.59 (s, 9 H), 1.97 (s, 3 H), 2.23 (s, 3 H), 2.25 (s, 3 H), 2.65 (dd, *J* = 15.3, 2.8 Hz, 1 H), 2.68 (d, *J* = 18.6 Hz, 1 H), 3.03 (dd, *J* = 17.8, 8.1 Hz, 1 H), 3.24 (dt, *J* = 11.7, 3.2 Hz, 1 H), 3.42–3.51 (m, 2 H), 3.65 (dd, *J* = 14.1, 8.0 Hz, 1 H), 3.79 (s, 3 H), 3.92 (d, *J* = 2.4 Hz, 1 H), 4.03 (br. s, 1 H), 4.13 (d, *J* = 2.4 Hz, 1 H), 4.19 (q, *J* = 7.2 Hz, 1 H), 4.77 (s, 1 H), 5.40 (br. t, *J* = 5.6 Hz, 1 H), 5.77 (d, *J* = 1.6 Hz, 1 H), 5.85 (d, *J* = 1.6 Hz, 1 H), 6.93 (s, 1 H), 7.81 (m, 4 H). ¹³C NMR (CDCl₃, 75 MHz, DEPT): δ = 8.77 (CH₃), 14.53 (CH₃), 15.93 (CH₃), 26.43 (CH₂), 27.79 (CH₂), 40.45 (CH₂), 41.75 (CH₃), 49.51 (CH), 54.99 (CH), 55.41 (CH), 56.82 (CH), 57.09 (CH), 59.03 (CH), 60.58 (CH₃), 100.92 (CH₂), 117.45 (C), 123.13 (C), 125.58 (2 CH₂), 127.75 (CH), 130.07 (C), 130.35 (C), 130.49 (C), 130.79 (C), 131.72 (C), 139.17 (C), 143.25 (C), 146.71 (C), 151.78 (C), 164.63 (C), 169.51 (C). FAB-MS: *m/z* (%) 780 [M⁺ + 1, 4], 753 (M⁺ – CN, 4). FAB-HRMS: calcd. for C₄₂H₄₅N₅O₁₀: 780.3245, found 780.3257.

Acetyl Derivative 11: To a solution of phenol **10** (13 mg, 0.017 mmol), pyridine (1.5 μL, 18.35 μmol), and DMAP (ca. 2 mg) in CH₂Cl₂ (0.5 mL) was added acetyl chloride (1.3 μL, 0.018 mmol). The mixture was stirred at 23 °C for 2 h. After the usual extractive workup and chromatography (hexane/EtOAc, 1:2), **11** (10 mg, 81%) was obtained. ¹H NMR (CDCl₃, 500 MHz): δ = 1.11 (d, *J* = 4.3 Hz, 3 H), 1.59 (s, 9 H), 1.86 (dd, *J* = 16.4, 7.1 Hz, 1 H), 2.21 (s, 3 H), 2.23 (s, 3 H), 2.34 (s, 3 H), 2.45 (s, 3 H), 2.73 (d, *J* = 10.9 Hz, 1 H), 2.74–2.81 (m, 1 H), 3.15 (dd, *J* = 10.8, 4.9 Hz, 1 H), 3.31–3.35 (m, 2 H), 3.49 (d, *J* = 4.6 Hz, 1 H), 3.82 (s, 3 H), 3.81–3.89 (m, 2 H), 4.13 (s, 1 H), 4.17 (d, *J* = 1.5 Hz, 1 H), 4.48 (q, *J* = 4.3 Hz, 1 H), 5.65 (m, 1 H), 5.89 (d, *J* = 0.8 Hz, 1 H), 5.98 (d, *J* = 0.8 Hz, 1 H), 6.93 (s, 1 H), 7.72–7.75 (m, 2 H), 7.82–7.85 (m, 2 H). ¹³C NMR (CDCl₃, 125 MHz, DEPT): δ = 9.32 (CH₃), 15.62 (CH₃), 26.87 (CH₂), 27.67 (CH₂), 41.14 (CH₂), 41.29 (CH₂), 41.65 (C), 48.49 (C), 51.32 (CH₂), 53.64 (C), 55.12 (C), 55.44 (C), 56.65 (C), 57.32 (C), 59.20 (C), 60.51 (C), 61.85 (C), 83.57 (C), 101.61 (C), 119.49 (C), 123.39 (CH), 127.77 (CH), 131.26 (C), 131.93 (C), 133.74 (C), 134.02 (CH), 140.59 (C), 142.90 (C), 167.46 (C). FAB-MS: *m/z* (%) 822 [M⁺ + 1, 12], 795 (M⁺ – 26, 18), 695 (M⁺ – 126, 24). FAB-HRMS: *m/z* for C₄₄H₄₈N₅O₁₁: calcd. 822.3350, found 822.3336. The structure of **11** was confirmed by COSY, HMQC, and HMBC correlations.

Dihydroxy Derivative 13: A solution of **11** (23 mg, 0.029 mmol) in dioxane (3 mL) and 4 M HCl (2 mL) was heated at 50 °C for 2 h. After the usual extractive workup and chromatography (hexane/EtOAc, 1:3), **13** (16 mg, 87%) was obtained. ¹H NMR (CDCl₃, 400 MHz): δ = 1.27 (d, *J* = 7.7 Hz, 1 H), 1.91 (s, 3 H), 2.24 (s, 3 H), 2.31 (s, 3 H), 2.63 (d, *J* = 18.2 Hz, 1 H), 3.01–3.09 (m, 2 H),

3.27 (dt, *J* = 11.7, 3.2 Hz, 1 H), 3.37–3.42 (m, 2 H), 3.44–3.48 (m, 1 H), 3.79 (s, 3 H), 3.95 (q, *J* = 7.7 Hz, 1 H), 4.04 (m, 2 H), 4.17 (d, *J* = 3.2 Hz, 1 H), 4.73 (s, 1 H), 5.19 (br. t, *J* = 5.3 Hz, 1 H), 5.72 (d, *J* = 1.6 Hz, 1 H), 5.82 (d, *J* = 1.6 Hz, 1 H), 6.00 (s, 1 H), 6.53 (s, 1 H), 7.65–7.78 (m, 4 H). ¹³C NMR (CDCl₃, 100 MHz, DEPT): δ = 8.68 (CH₃), 14.52 (CH₃), 15.80 (CH₃), 25.30 (CH₂), 28.71 (CH₂), 41.34 (CH₂), 41.77 (CH₃), 48.84 (CH), 55.26 (CH), 56.33 (CH), 56.51 (CH), 59.63 (CH), 60.69 (CH₃), 100.74 (C), 107.71 (C), 117.08 (C), 117.85 (C), 121.21 (CH), 123.46 (CH), 128.79 (C), 130.95 (C), 131.54 (C), 134.14 (CH), 146.97 (C), 167.59 (C), 168.55 (C). FAB-MS: *m/z* (%) 680 [M⁺ + 1, 25], 653 (M⁺ – 27, 38). FAB-HRMS: *m/z* for C₃₇H₃₈N₅O₈: calcd. 680.2720, found 680.2718. The structure of **13** was confirmed by COSY, HMQC, and HMBC correlations.

Cyano-safraclin-phthalimide 12: A solution of **11** (27 mg, 0.033 mmol) in dioxane (4 mL) and 4 M HCl (3 mL) was heated at 40 °C for 2 h. After the usual extractive workup and chromatography (hexane/EtOAc, gradient 2:1 to 1:3), **12** (16 mg, 61%) was obtained. ¹H NMR (CDCl₃, 300 MHz): δ = 1.09 (d, *J* = 7.2 Hz, 3 H), 1.97 (s, 3 H), 2.18 (s, 3 H), 2.30 (s, 3 H), 2.33 (s, 3 H), 2.64 (d, *J* = 18.3 Hz, 1 H), 3.12–2.97 (m, 2 H), 3.42–3.32 (m, 3 H), 3.77 (s, 3 H), 4.04 (m, 1 H), 4.10 (m, 2 H), 4.36 (q, *J* = 7.2 Hz, 1 H), 5.64 (m, 1 H), 5.84 (d, *J* = 1.6 Hz, 1 H), 5.93 (d, *J* = 1.6 Hz, 1 H), 6.51 (s, 1 H), 7.64–7.79 (m, 4 H). FAB-MS: *m/z* (%) 722 [M⁺ + 1, 29], 695 (M⁺ – 26, 44). HR-FAB-MS: *m/z* found for C₃₉H₄₀N₅O₉: calcd. 722.2826, found 722.2831.

Hydroxy-safraclin-phthalimide 4: A solution of **12** (8 mg, 0.021 mmol) and AgNO₃ (70 mg, 0.41 mmol) in CH₃CN (1 mL) and H₂O (1 mL) was stirred at 23 °C for 12 h. After the usual extractive workup and chromatography (gradient 100:0 to 100:2 CH₂Cl₂/MeOH), **4** (6 mg, 70%) was obtained as a white solid. *R*_f = 0.23 (CH₂Cl₂/MeOH, 40:1). ¹H NMR (CDCl₃, 500 MHz): δ = 1.04 (d, *J* = 7.1 Hz, 3 H), 2.02 (s, 3 H), 2.22 (s, 3 H), 2.34 (s, 3 H), 2.37 (s, 3 H), 2.60 (d, *J* = 18.1 Hz, 1 H), 2.81 (m, 1 H), 3.04 (dd, *J* = 18.4, 8.3 Hz, 1 H), 3.25–3.30 (m, 1 H), 3.31–3.35 (m, 1 H), 3.44 (br. d, *J* = 11.7 Hz, 1 H), 3.81 (s, 3 H), 4.08–4.21 (m, 2 H), 4.42 (q, *J* = 7.2 Hz, 1 H), 4.49 (s, 1 H), 4.59 (s, 1 H), 5.78 (d, *J* = 4.3 Hz, 1 H), 5.89 (d, *J* = 1.3 Hz, 1 H), 5.96 (d, *J* = 1.3 Hz, 1 H), 6.57 (s, 1 H), 7.70–7.73 (m, 2 H), 7.78–7.83 (m, 2 H). ¹³C NMR (CDCl₃, 125 MHz, DEPT): δ = 14.14 (CH₃), 15.62 (CH₃), 22.70 (CH₂), 29.72 (CH₂), 30.94 (CH), 35.80 (CH), 41.54 (CH₂), 101.49 (C), 106.84 (C), 123.29 (C), 133.85 (C), 141.10 (C), 145.85 (CH), 194.10 (C) (signals assigned on the basis of HMQC and HMBC experiments). MALDI-TOF-MS: *m/z* 713 [M⁺ + 1], 695 (M⁺ – 17). FAB-HRMS: calcd. for C₃₈H₃₈N₄O₃: 694.2658, found 694.2626. The structure of **4** was confirmed by COSY, HMQC, and HMBC correlations.

Cyanosafraclin N-Phenylthiourea 14: A solution of cyanosafraclin B (**3**) (1.50 g, 2.73 mmol) and phenyl isocyanate (650 μL, 738 mg, 5.46 mmol) in CH₃CN (15 mL) was stirred at 23 °C for 16 h. The reaction was evaporated and the residue was purified by flash chromatography (SiO₂, hexane/EtOAc, gradient 10:0 to 1:1) to give **14** as a yellow solid (1.63 g, 87%). m.p. 176–179 °C. *R*_f = 0.32 (hexane/EtOAc, 2:1). IR (neat film): ν̃ = 3368, 2937, 2854, 1652, 1520, 1501, 1458, 1319, 1236, 1167 cm^{–1}. ¹H NMR (CDCl₃, 300 MHz): δ = 0.87 (d, *J* = 7.3 Hz, 3 H), 1.75 (ddd, *J* = 12.5, 6.1, 2.2 Hz, 1 H), 1.84 (s, 3 H), 2.14 (s, 3 H), 2.27 (s, 3 H), 2.52 (d, *J* = 18.2 Hz, 1 H), 3.14–2.92 (m, 4 H), 3.34 (m, 2 H), 3.61 (dd, *J* = 12.5, 7.3 Hz, 1 H), 3.72 (s, 3 H), 3.84 (br. s, 3 H), 3.87 (s, 3 H), 4.10 (dd, *J* = 9.7, 2.0 Hz, 1 H), 4.19 (t, *J* = 6.9 Hz, 1 H), 5.69 (t, *J* = 5.7 Hz, 1 H), 6.03 (s, 1 H), 6.20 (s, 1 H), 6.69 (d, *J* = 7.6 Hz, 1 H), 7.16 (d, *J* = 7.3 Hz, 1 H), 7.24 (t, *J* = 7.3 Hz, 1 H), 7.38 (t, *J* = 7.3 Hz, 2

H), 7.87 (s, 1 H). ^{13}C NMR (CDCl_3 , 75 MHz, DEPT): δ = 8.74 (CH_3), 15.83 (CH_3), 18.52 (CH_3), 24.58 (CH_2), 25.14 (CH_2), 40.23 (CH_2), 41.76 (CH_3), 53.51 (CH), 54.74 (CH), 55.03 (CH), 55.82 (CH), 56.34 (CH), 58.60 (CH), 60.81 (CH_3), 60.92 (CH_3), 116.39 (C), 117.45 (C), 120.24 (CH), 124.42 (CH), 126.84 (CH), 128.69 (C), 129.49 (C), 129.91 (CH), 130.56 (C), 135.29 (C), 136.10 (C), 142.45 (C), 185.71 (C), 143.21 (C), 147.01 (C), 155.71 (C), 172.03 (C), 178.97 (C), 181.09 (C). $\text{C}_{36}\text{H}_{40}\text{N}_6\text{O}_6\text{S}$ (684.80): C 63.14, H 5.89, N 12.27, O 14.02, S 4.68; found C 63.02, H 6.04, N 12.40, O 13.59, S 4.95. The structure of **14** was confirmed by COSY, HMQC, and HMBC experiments.

Quinoneimine 5: To a solution of **14** (800 mg, 1.168 mmol) in MeOH (30 mL) was added TMSCl (740 μL , 634 mg, 5.84 mmol) at 0 °C. The reaction mixture was stirred at 23 °C during 3 h, and evaporated under reduced pressure. The resulting residue was diluted with CH_2Cl_2 , washed with 5% an aqueous solution of NaHCO_3 . After the usual extractive workup and chromatography (hexane/EtOAc, gradient 4:1 to 1:1), **5** (473 mg, 88%) was obtained as a pale brown solid. m.p. 188–190 °C; R_f = 0.14 (hexane/EtOAc, 2:1). IR (neat film): $\tilde{\nu}$ = 3428, 2935, 1614, 1442, 1242, 985 cm^{-1} . ^1H NMR (CDCl_3 , 500 MHz): δ = 1.90 (s, 3 H), 2.25 (s, 3 H), 2.30 (s, 3 H), 2.55 (d, J = 17.9, 1 H), 2.76 (br. d, J = 19.4, 1 H), 3.07 (dd, J = 18.3, 8.6 Hz, 1 H), 3.42 (m, 1 H), 3.46 (d, J = 10.1 Hz, 1 H), 3.76 (s, 3 H), 3.79 (m, 2 H), 4.16 (s, 3 H), 3.93 (d, J = 2.5 Hz, 1 H), 4.24 (d, J = 3.1 Hz, 1 H), 4.66 (m, 1 H), 5.86 (br. s, 1 H), 6.46 (s, 1 H). ^{13}C NMR (CDCl_3 , 125 MHz, DEPT): δ = 9.44 (CH_3), 16.23 (CH_3), 25.27 (CH_2), 25.99 (CH_2), 42.45 (CH_2), 43.44 (CH_3), 56.22 (CH), 59.31 (CH), 60.15 (CH), 60.89 (CH), 61.29 (CH), 61.37 (CH_3), 67.20 (CH_3), 104.34 (C), 116.82 (C), 121.79 (CH), 126.29 (C), 128.58 (C), 129.86 (C), 130.61 (C), 143.42 (C), 145.75 (C), 147.43 (C), 155.31 (C), 162.65 (C), 186.63 (C). EI-MS: m/z (%) 460 [M^+ , 21], 434 ($\text{M}^+ - \text{CN}$, 10). The structure of **5** was confirmed by COSY, NOESY, HMQC, and HMBC experiments.

Acetyl Quinoneimine 22: To a solution of quinoneimine **5** (220 mg, 0.48 mmol) and DMAP (3 mg, 0.024 mmol) in CH_2Cl_2 (15 mL) was added pyridine (70 μL , 0.50 mmol) and Ac_2O (45 μL , 0.48 mmol). The reaction mixture was stirred for 14 h at 23 °C and, after the usual extractive workup, **22** (185 mg, 77%) was obtained as a pale yellow solid. R_f = 0.22 (hexane/EtOAc, 2:1). ^1H NMR (CDCl_3 , 300 MHz): δ = 1.84 (s, 3 H), 2.14 (s, 3 H), 2.25 (s, 3 H), 2.32 (s, 3 H), 2.52 (d, J = 18.5 Hz, 1 H), 2.80 (d, J = 19.4 Hz, 1 H), 3.11 (dd, J = 18.5, 7.9 Hz, 1 H), 3.39 (m, 1 H), 3.46 (d, J = 9.6 Hz, 1 H), 3.78 (s, 3 H), 3.90 (m, 1 H), 3.81 (m, 2 H), 4.18 (s, 3 H), 4.23 (d, J = 3.0 Hz, 1 H), 4.41 (m, 1 H), 6.81 (s, 1 H). ^{13}C NMR (CDCl_3 , 75 MHz, DEPT): δ = 8.92 (CH_3), 16.14 (CH_3), 21.17 (CH_3), 25.60 (CH_2), 26.13 (CH_2), 41.99 (CH_2), 43.12 (CH_3), 56.25 (CH), 58.77 (CH), 60.52 (CH), 61.07 (CH), 61.39 (CH), 61.44 (CH_3), 65.91 (CH_3), 105.29 (C), 117.66 (C), 120.88 (C), 127.04 (C), 127.12 (C), 129.84 (C), 131.01 (C), 144.81 (C), 145.53 (C), 146.45 (C), 155.98 (C), 163.11 (C), 182.42 (C), 188.14 (C). EI-MS: m/z (%) 502 [M^+ , 24], 476 ($\text{M}^+ - \text{CN}$, 17), 434 (12). The structure of **22** was supported by a COSY experiment.

Quinoneimine *o*-Quinone Dimethyl Acetal 23: To a solution of quinoneimine **5** (140 mg, 0.30 mmol) in MeOH (5 mL) was added a solution of PIDA (193 mg, 0.60 mmol) in MeOH (5 mL). After 2 h at 23 °C celite was added, the mixture was evaporated under reduced pressure and chromatographed (hexane/EtOAc, 1:1) to afford **23** as an orange vitreous solid (119 mg, 81%). R_f = 0.19 (hexane/EtOAc, 1:1). ^1H NMR (CDCl_3 , 300 MHz): δ = 1.84 (m, 1 H), 1.86 (s, 3 H), 1.90 (d, J = 1.6 Hz, 3 H), 2.10 (d, J = 20.6 Hz, 1 H), 2.25 (s, 3 H), 2.60 (m, 1 H), 2.67 (dd, J = 20.6, 7.6 Hz, 1 H), 3.07 (s, 3 H), 3.26 (m, 1 H), 3.26 (s, 3 H), 3.35 (dt, J = 7.7, 1.6 Hz, 1

H), 3.73 (m, 1 H + 1 H), 3.85 (d, J = 2.8 Hz, 1 H), 4.12 (d, J = 8.1 Hz, 1 H), 4.14 (s, 3 H), 4.63 (dd, J = 17.8, 7.3 Hz, 1 H), 5.92 (d, J = 1.6 Hz, 1 H). ^{13}C NMR (CDCl_3 , 75 MHz, DEPT): δ = 8.97 (CH_3), 16.78 (CH_3), 24.98 (CH_2), 27.91 (CH_2), 41.41 (CH_3), 49.89 (CH_3), 51.48 (CH_3), 52.98 (CH), 54.63 (CH), 59.87 (CH), 60.41 (CH_3), 66.51 (CH_2), 94.09 (C), 115.51 (C), 124.99 (C), 125.47 (CH), 125.77 (C), 127.70 (C), 145.21 (C), 147.34 (C), 148.62 (C), 154.86 (C), 162.14 (C), 188.65 (C), 193.88 (C). EI-MS: m/z (%) 490 (100) [M^+], 464 ($\text{M}^+ - \text{CN}$, 23). EI-HRMS: calcd. for $\text{C}_{27}\text{H}_{30}\text{N}_4\text{O}_5$: 490.2216; found 490.2229. The structure of **23** was confirmed by COSY, NOESY, HMQC, and HMBC experiments.

Indoline 24: To a solution of **5** (72 mg, 0.156 mmol) in CH_2Cl_2 (3 mL) at 23 °C was added a solution of $\text{Na}_2\text{S}_2\text{O}_4$ (271 mg, 1.56 mmol) in H_2O (4 mL) and the mixture was stirred vigorously for 2 h. After the usual extractive workup, **24** (66 mg, 92%) was obtained. Indoline **24** is rather unstable and suffers oxidation by air to give **5**. ^1H NMR (CDCl_3 , 500 MHz, COSY, HMQC, HMBC): δ = 2.06 (s, 3 H), 2.23 (s, 3 H), 2.28 (s, 3 H), 2.45 (dd, J = 10.2, 6.4), 2.53 (d, J = 10.7 Hz, 1 H), 2.88 (dd, J = 10.2, 3.2 Hz, 1 H), 3.02 (dd, J = 10.8, 4.8 Hz, 1 H), 3.06 (dd, J = 6.8, 4.7 Hz, 1 H), 3.42 (d, J = 5.9 Hz, 1 H), 3.48 (m, 1 H), 3.63 (m, 1 H), 3.73 (s, 3 H), 3.74 (s, 3 H), 3.80 (d, J = 1.6 Hz, 1 H), 4.11 (dd, J = 6.6, 4.3 Hz, 1 H), 4.23 (d, J = 1.9 Hz, 1 H), 4.32 (dd, J = 13.7, 1.3 Hz, 1 H), 5.85 (br. s, 1 H), 6.42 (s, 1 H). ^{13}C NMR (CDCl_3 , 75 MHz, DEPT): δ = 9.12 (CH_3), 15.73 (CH_3), 25.34 (CH_2), 25.57 (CH_2), 30.99 (CH_2), 42.13 (CH_3), 53.41 (CH), 55.06 (CH), 55.76 (CH), 56.14 (CH), 59.72 (CH), 60.24 (CH_3), 61.47 (CH_3), 112.96 (C), 116.44 (C), 121.42 (CH), 125.85 (C), 126.23 (C), 129.13 (C), 130.50 (C), 133.58 (C), 142.17 (C), 142.83 (C), 146.97 (C), 154.96 (C), 162.23 (C). The structure of **24** was confirmed by COSY, HMQC, and HMBC experiments.

Bis(pivaloyl)indoline 25: To a solution of indoline **24** (6 mg, 0.013 mmol) in CH_2Cl_2 (0.3 mL) at 23 °C was added pyridine (3.2 μL , 0.04 mmol) and pivaloyl chloride (5 μL , 0.04 mmol). After the usual extractive workup, **25** (4 mg, 48%) was obtained. ^1H NMR (CDCl_3 , 300 MHz, COSY, NOE): δ = 1.38 (s, 9 H), 1.41 (s, 9 H), 1.98 (s, 3 H), 2.32 (s, 3 H), 2.36 (s, 3 H), 2.40 (br. dd, J = 17.2, 11.4 Hz, 1 H), 2.54 (d, J = 18.3 Hz, 1 H), 2.78 (dd, J = 18.3, 4.7 Hz, 1 H), 3.08 (dd, J = 18.3, 8.0 Hz, 1 H), 6.43 (s, 1 H), 3.51–3.44 (m, 3 H), 3.53 (m, 1 H), 3.56 (s, 3 H), 3.79 (s, 3 H), 3.84 (d, J = 2.3 Hz, 1 H), 5.68 (s, 1 H), 4.49 (d, J = 9.3, 6.7 Hz, 1 H), 4.17 (m, 2 H). ^{13}C NMR (CDCl_3 , 75 MHz): δ = 9.92 (CH_3), 15.56 (CH_3), 25.48 (CH_2), 25.72 (CH_2), 27.46 (CH_3), 28.44 (CH_3), 38.83 (C), 39.32 (C), 42.15 (CH_2), 54.94 (CH), 55.89 (CH), 58.07 (CH), 58.34 (CH), 59.07 (CH), 60.25 (CH_3), 60.72 (CH_3), 108.03 (C), 116.07 (C), 118.86 (C), 121.74 (CH), 124.06 (C), 129.01 (C), 129.22 (C), 130.49 (C), 143.13 (C), 146.96 (C), 175.72 (C), 177.12 (C). FAB-MS: m/z 630 (100) [M^+], 604 ($\text{M}^+ - \text{CN}$, 38). The structure of **25** was confirmed by COSY and NOESY experiments.

Diacetylindole 26: Ac_2O (215 μL , 2.28 mmol) was added to a solution of quinoneimine **5** (105 mg, 0.228 mmol) and Et_3N (317 μL , 2.28 mmol) in CH_2Cl_2 (10 mL), at 23 °C. The reddish solution was stirred during 6 h. After the usual extractive workup and chromatography (hexane/EtOAc, gradient 10:1 to 1:2), **26** (78 mg, 52%) was obtained as a light yellow solid. R_f = 0.78 (hexane/EtOAc, 2:1). IR (neat film): $\tilde{\nu}$ = 3591, 3415, 2138, 1671, 1452, 1248, 1085, 1008 cm^{-1} . ^1H NMR (CDCl_3 , 300 MHz, COSY): δ = 2.15 (s, 3 H), 2.22 (s, 3 H), 2.35 (s, 3 H), 2.36 (s, 3 H), 2.40 (s, 3 H), 2.55 (dd, J = 17.9, 12.3 Hz, 1 H), 2.62 (d, J = 18.2, 1 H), 2.93 (dd, J = 17.9, 7.8 Hz, 1 H), 3.15 (dd, J = 18.2, 9.4 Hz, 1 H), 3.51 (br. d, J = 9.4 Hz, 1 H), 3.62 (dt, J = 12.3, 7.8 Hz, 1 H), 3.72 (s, 3 H), 3.80 (s, 3 H), 3.82 (m, 1 H), 4.32 (d, J = 2.8 Hz, 1 H), 6.36 (d, J =

3.29 Hz, 1 H), 6.78 (s, 1 H), 7.64 (br. s, 1 H). ^{13}C NMR (CDCl_3 , 75 MHz, DEPT): δ = 9.70 (CH_3), 15.64 (CH_3), 20.30 (CH_3), 20.69 (CH_3), 25.35 (CH_2), 27.16 (CH_2), 41.94 (CH_3), 54.68 (CH), 56.97 (CH), 57.36 (CH), 58.28 (CH), 60.37 (CH_3), 60.46 (CH_3), 104.27 (CH), 113.25 (C), 117.13 (C), 117.63 (C), 119.50 (C), 122.90 (C), 123.99 (C), 127.03 (C), 127.86 (C), 129.90 (C), 131.21 (C), 137.90 (C), 141.67 (C), 147.83 (C), 166.43 (C), 168.30 (C), 168.89 (C). FAB-MS: m/z (%) 544 (100) [M^+], 518 ($\text{M}^+ - \text{CN}$, 29). The structure of **26** was supported by a COSY experiment.

Indole 15. Method a: Formation of the indole **15** by isomerization of the quinoneimine with base: to a solution of quinoneimine **5** (25 mg, 0.054 μmol) in CH_3CN (2 mL) was added $i\text{Pr}_2\text{NEt}$ (50 μL , 0.28 mmol) and the mixture was stirred at 23 °C for 24 h. After the usual extractive workup, **15** (22 mg, 88%) was obtained as a brownish solid.

Method b: Formation of **15** by saponification of the diacetylindole **26**: To a solution of the **26** (70 mg, 0.128 mmol) in MeOH (1 mL), at 23 °C, K_2CO_3 (13 mg, 0.092 mmol) was added in one portion and the green mixture was stirred for 1.5 h. After the usual extractive workup, **15** was obtained (51 mg, 87%) as a white solid: R_f = 0.23 (2:3 hexane/EtOAc). ^1H NMR (300 MHz, CDCl_3 , COSY, HMQC): δ = 2.21 (s, 3 H), 2.23 (s, 3 H), 2.33 (s, 3 H), 2.52 (dd, J = 16.6, 11.3 Hz, 1 H), 2.63 (d, J = 18.2 Hz, 1 H), 3.14 (dd, J = 18.2, 8.5 Hz, 1 H), 3.26 (dd, J = 16.6, 3.6 Hz, 1 H), 3.50 (br. d, J = 8.5 Hz, 1 H), 3.64 (dt, J = 11.3, 2.8 Hz, 1 H), 3.74 (s, 3 H), 3.83 (s, 3 H), 4.29 (d, J = 2.4 Hz, 1 H), 4.34 (d, J = 2.4 Hz, 1 H), 4.51 (br. s, 1 H), 5.92 (br. s, 1 H), 6.41 (d, J = 2.2 Hz, 1 H), 6.44 (s, 1 H), 7.34 (s, 1 H, NH). ^{13}C NMR (75 MHz, CDCl_3 , DEPT): δ = 9.23 (CH_3), 15.67 (CH_3), 25.65 (CH_2), 25.96 (CH_2), 42.08 (CH_3), 54.85 (CH), 56.02 (CH), 57.64 (CH), 59.09 (CH), 60.37 (CH_3), 60.76 (CH_3), 103.91 (CH), 105.89 (C), 113.53 (C), 116.57 (C), 117.38 (C), 119.83 (C), 121.28 (CH), 126.97 (C), 128.92 (C), 130.18 (C), 141.58 (C), 142.87 (C), 146.74 (C). EI-MS: m/z (%) 460 [M^+ , 9], 434 ($\text{M}^+ - \text{CN}$, 1).

Acknowledgments

We thank the MEC (projects PPQ2000-0114-P4 and CTQ2004-02869) and the ICIQ foundation for support and to the MEC for a predoctoral fellowship to P. A. C.

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Received: November 9, 2005

Published Online: February 9, 2006