Natural Product Synthesis

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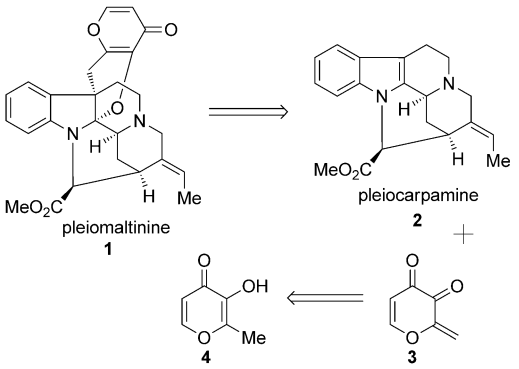
# Development of an Alkaloid–Pyrone Annulation: Synthesis of Pleiomaltinine**

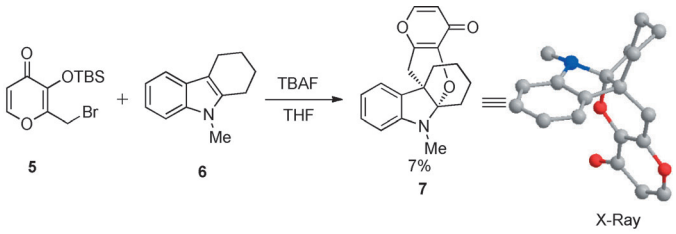
*Robert E. Ziegler, Shin-Jowl Tan, Toh-Seok Kam, and John A. Porco Jr.**

γ-Pyrone natural products are an important class of compounds that exhibit a wide range of biological activity.[1] Similarly, indole-containing compounds are found throughout nature as well as in pharmaceuticals and agrochemicals.[2] Recently, Kam and co-workers isolated pleiomaltinine[3] **1** (Scheme 1), an unusual alkaloid-pyrone natural product that is able to reverse multidrug resistance in vincristine-resistant KB (VJ300) cells ($IC_{50} = 12\ \mu g\,mL^{-1}$ in the presence of vincristine [$0.1\ \mu g\,mL^{-1}$]). They proposed that pleiomaltinine may be derived biosynthetically from the indole-alkaloid pleiocarpamine[4] **2**, co-isolated from the same plant species (*Alstonia angustofolia*) and 2-methylene-3,4-diketone[5] **3** derived from dehydrogenation of naturally occurring maltol (**4**). We were intrigued by intermediate **3** and its potential reactivity in cycloaddition chemistry, which was expected to be analogous to that of *o*-quinone methides.[6] Herein, we report the development of a method for the synthesis of alkaloid-pyrones using a novel pyrone annulation, and the application of this method to the synthesis of pleiomaltinine **1** from pleiocarpamine **2**.



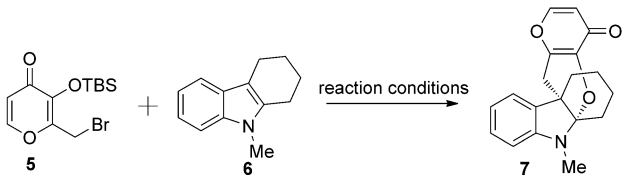

***Scheme 1.*** Pleiomaltinine **1** and its proposed biosynthesis.

After initial unsuccessful attempts to generate reactive intermediate **3** by dehydrogenation of **4** with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ),[7] we considered that **3** could alternatively be derived from a precursor such as 3-siloxy-4-pyrone **5**[8] by fluoride-induced desilylation.[9] In the event, treatment of **5** and *N*-methyl carbazole **6** with tetra-*n*-butylammonium fluoride (TBAF) led to the formation of cycloadduct **7**[10] in low yield (Scheme 2). Further optimization through a solvent screen revealed that benzene afforded **7** in 43% yield (Table 1, entry 1). Cycloadduct **7** was also produced in protic solvents such as methanol without the inclusion of additives (entry 2). With these results in hand, we hypothesized that HBr could be produced as a byproduct and




***Scheme 2.*** Initial pyrone annulation result. TBAF = tetra-*n*-butylammonium fluoride, TBS = *tert*-butyldimethylsilyl.

***Table 1:*** Optimization of the pyrone annulation.




| Entry | Conditions[a] | *t* [h] | Yield [%][b] |
|---|---|---|---|
| 1 | **6** (2.0 equiv), TBAF (1.5 equiv), benzene (0.1 M) | 0.5 | 43 |
| 2 | **6** (1.5 equiv), MeOH (0.1 M) | 0.25 | 50 |
| 3 | **6** (1.5 equiv), CSA (1.0 equiv), $CH_2Cl_2$ (0.1 M) | 30 | 82 |
| 4 | **6** (1.5 equiv), aq. HCl (50 equiv), $CH_2Cl_2$ (0.1 M) | 5 | 61 |
| 5 | **6** (1.5 equiv), $SnCl_4{\cdot}5\,H_2O$ (11 mol%), $CH_2Cl_2$ (0.1 M) | 31 | 76 |
| 6 | **6** (1.5 equiv), HCl (10 mol%) in dioxane (0.1 M) | 32 | 67 |
| 7 | **6** (1.5 equiv), HCl (1.3 equiv) in dioxane, $CH_3CN$ (0.2 M) | 0.5 | 81 |

[a] All reactions performed at 25 °C. [b] Yield of isolated product after silica gel chromatography. CSA = camphorsulfonic acid, HCl = hydrochloric acid, TBAF = tetra-*n*-butylammonium fluoride, TBS = *tert*-butyldimethylsilyl.

[*] R. E. Ziegler, Prof. Dr. J. A. Porco Jr.
Department of Chemistry, Center for Chemical Methodology and Library Development (CMLD-BU), Boston University
590 Commonwealth Avenue, Boston, MA 02215 (USA)
E-mail: porco@bu.edu
S.-J. Tan, Prof. Dr. T.-S. Kam
Department of Chemistry, University of Malaysia
Kuala Lumpur 50603 (Malaysia)

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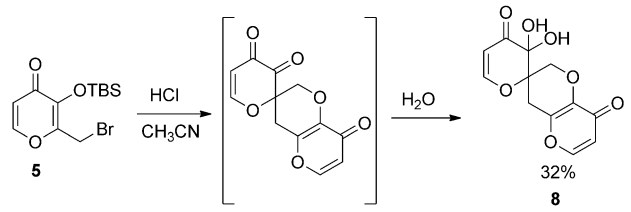
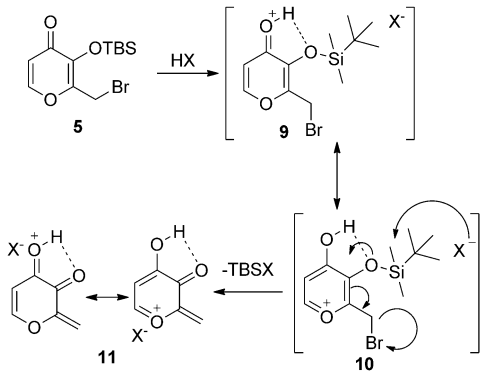
that Brønsted acids may catalyze the reaction. This was supported by the addition of $Et_3N$ in methanol, which greatly reduced the reaction rate and yield for the pyrone annulations. After evaluation of a number of Brønsted and Lewis acids, we found that the treatment of **5** and *N*-methyl carbazole **6** with a stoichiometric amount of anhydrous HCl in $CH_3CN$ provided **7** in 81% yield (entry 7). Lowering the amount of HCl to substoichiometric levels resulted in dramatically slower conversion (32 h, entry 6). During the course of our optimization studies, we observed a minor side product in varying amounts. Treatment of **5** with HCl/$CH_3CN$ in the absence of carbazole **6** produced dimer[11] **8** in 32% yield, thereby lending support to the formation of 2-methylene-3,4-diketone intermediate **3** (Scheme 3).




***Scheme 3.*** Pyrone dimerization.

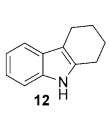
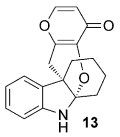
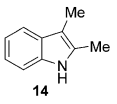
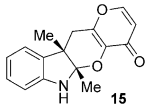
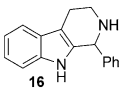
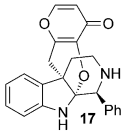
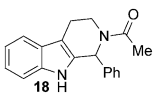
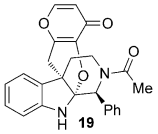
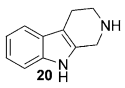
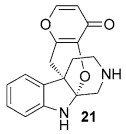
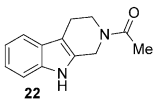
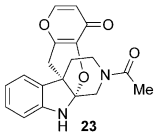
Our proposed mechanism for the formation of the 2-methylene-3,4-diketone intermediate is shown in Scheme 4. Protonation of siloxypyrone **5** at the carbonyl oxygen[12] to give **9** should weaken the O–Si bond by hydrogen bonding. Desilylation of the aromatic oxidopyrylium[13] tautomeric form **10** may be followed by bromide expulsion, thereby forming the reactive, protonated 2-methylene-3,4-diketone derivative **11**. The latter intermediate may then react with indoles and related substrates either in a concerted inverse-demand hetero-Diels–Alder cycloaddition[14] or in a stepwise Michael–Mannich sequence.[15]




***Scheme 4.*** Proposed mechanism for the formation of intermediate **11**. TBS = *tert*-butyldimethylsilyl, X = Br,Cl.

We next examined the substrate scope for the pyrone annulation (Table 2). Free indoles were well tolerated, while electron withdrawing groups on the indole nitrogen inhibited the reaction. This limitation was presumably due to the decreased nucleophilicity at the C3 position, which led to the major formation of dimer **8**. β-Carbolines were also found to be viable substrates when using an excess of siloxypyrone **5**, which furnished cycloadducts in good yield (entries 3–6). Furthermore, the cycloadducts derived from phenyl β-carboline substrates were obtained as single diastereomers with the phenyl group *trans* to the *cis*-fused pyrone moiety (entries 3 and 4).[16]

***Table 2:*** Substrate scope.

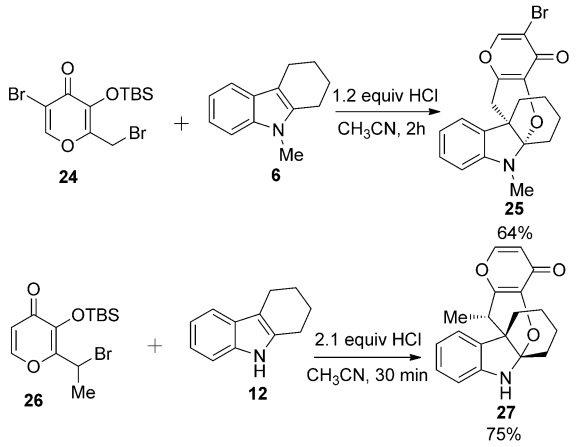
| Entry | Precursor | Cycloadduct | Method[a] | *t* [min] | Yield [%][b] |
|---|---|---|---|---|---|
| 1 |  12 |  13 | A | 10 | 80 |
| 2 |  14 |  15 | A | 15 | 84 |
| 3 |  16 |  17 | B | 60 | 71 |
| 4 |  18 |  19 | B | 45 | 77 |
| 5[c] |  20 |  21 | B | 60 | 62 |
| 6[c] |  22 |  23 | B | 60 | 51 |

[a] Method A: indole precursor (1.5 equiv), pyrone **5** (1 equiv), HCl (1.5 equiv), $CH_3CN$ (0.2 M); method B: indole precursor (1 equiv), pyrone **5** (2 equiv), HCl (3.0 equiv), $CH_3CN$ (0.2 M). [b] Yield of isolated product after silica gel chromatography. [c] Dimethyl sulfoxide used as solvent.

The annulation was also found to be applicable to other siloxypyrone reaction partners (Scheme 5). The known bromomaltol[17] was silyl-protected and brominated to afford bromosiloxypyrone **24**, which was then further reacted with *N*-methyl carbazole **6** to afford cycloadduct **25** in good yield. We also wished to evaluate a diastereoselective variant of the pyrone annulation. Accordingly, siloxypyrone **26** was prepared from commercially available ethyl maltol. Adduct **27** was obtained in good yield as a single diastereomer from the reaction of **26** with tetrahydrocarbazole **12** under our standard conditions. Product **27** may result from formal *endo* cycloaddition[18] of **12** and the lower energy (as determined by DFT calculations) reaction partner, (*Z*)-2-methylene-3,4-diketone **28** (Figure 1).[16]

As part of our optimization efforts (Table 1), we evaluated mild thermolysis for pyrone annulations, but did not observe




***Scheme 5.*** Further applications of the pyrone annulation.

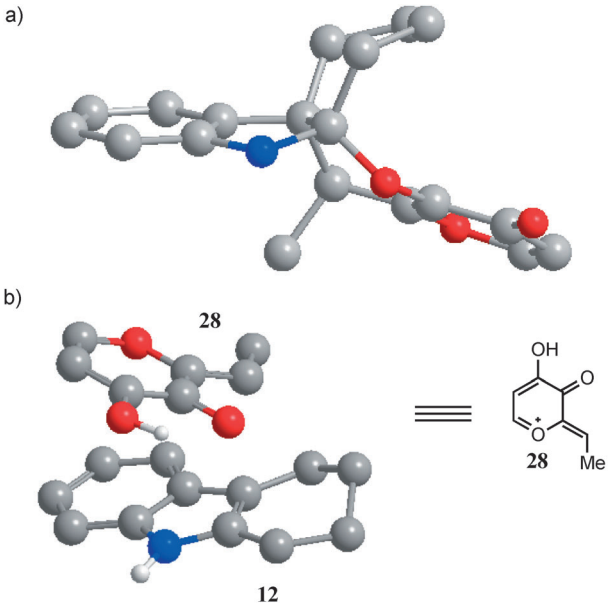
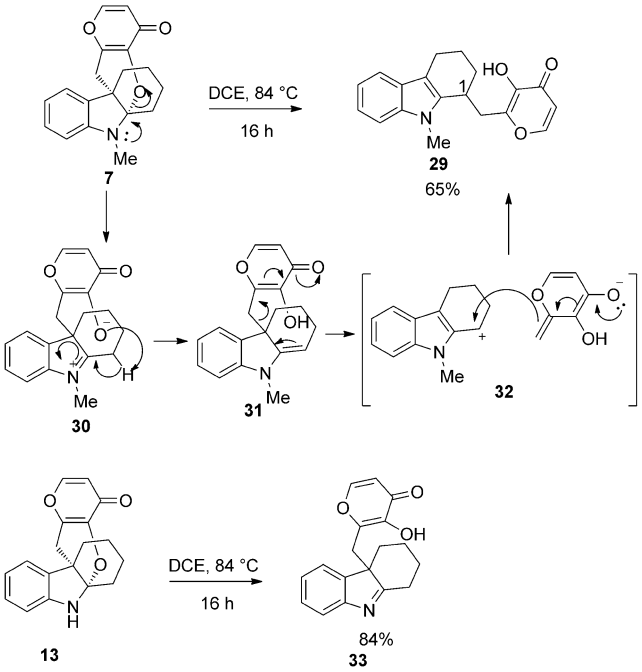



***Figure 1.*** a) Molecular model (Spartan AM1 '10) of **27**. b) Proposed [4+2] transition state.

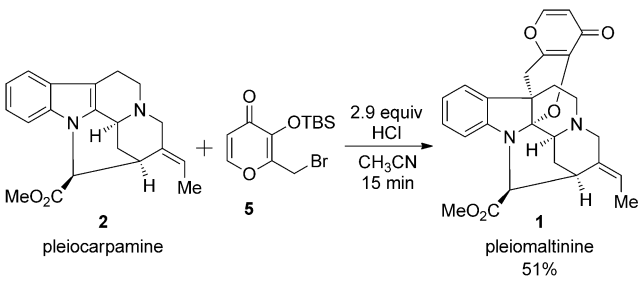
the formation of the expected cycloadduct **7**. Instead, an interesting transformation involving a [1,3] shift of the hydroxypyrone moiety to the 1 position of the carbazole occurred to afford 3-hydroxypyrone **29** (Scheme 6). The reaction could also be conducted cleanly by refluxing cycloadduct **7** in 1,2-dichloroethane (DCE). A proposed mechanism for this transformation involves an initial ring opening of the hemiaminal ether to form zwitterion **30**. Subsequent proton transfer affords the enamine **31**,[19] which can restore aromaticity to the indole by elimination of the pyrone, thereby creating ion pair **32**. Vinylogous addition of the pyrone[20] to the stabilized carbocation yields the observed product **29**. Carbazole/carboline allylic carbocations similar to **32** have been proposed in the literature.[21] In contrast, the thermolysis of N–H cycloadduct **13** provided indolenine **33** (84%). Efforts to further rearrange **33** under basic conditions




***Scheme 6.*** Thermolysis of carbazole-pyrone cycloadducts. DCE = 1,2-dichloroethane.

(for example, with NaH, $Cs_2CO_3$, or DBU) resulted either in retrocycloaddition or decomposition. Rearrangements were also attempted with cycloadducts **17** and **19** in an attempt to produce carbazole-hydroxypyrone structures bearing a fully substituted carbon. Unfortunately, the use of thermal and Lewis acid (for example, $Zn(OTf)_2$, $Yb(OTf)_3$, or $Sc(OTf)_3$) conditions with these substrates has thus far proved unsuccessful. The major reaction pathway observed in these cases was retrocycloaddition to afford the starting indole or β-carboline.

Finally, the application of the pyrone annulation method to plant-derived pleiocarpamine[22] **2** using siloxypyrone **5** with HCl in $CH_3CN$ provided pleiomaltinine **1** in 51% yield as a single diastereomer after purification by preparative HPLC (Scheme 7). The diastereoselectivity of the reaction




***Scheme 7.*** Synthesis of pleiomaltinine.

arises from pyrone annulation on the convex face of the pentacyclic alkaloid framework (Figure 2). Both synthetic and natural pleiomaltinine gave matching $^1H$ and $^{13}C$ NMR spectra as well as TLC and HPLC retention values.[16]

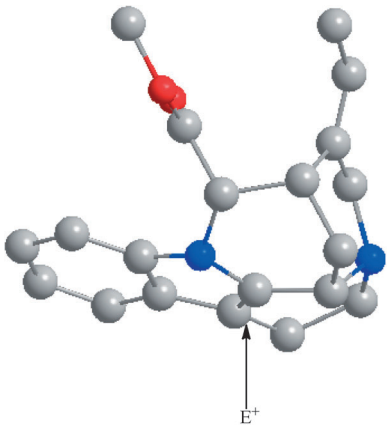



***Figure 2.*** Molecular model (Spartan AM1 '10) of pleiocarpamine **2**.

In summary, we have developed a novel pyrone annulation of carbazoles and related heterocycles with 3-siloxy-4-pyrones that provides access to unusual alkaloid-pyrone structures. Further rearrangements of the alkaloidal-pyrone structures were observed, including a formal [1,3] shift to access a 1-substituted carbazole. Application of the pyrone annulation to the plant-derived alkaloid pleiocarpamine resulted in the synthesis of the unusual alkaloid-pyrone pleiomaltinine. Further studies concerning the development of asymmetric pyrone annulations, as well as additional reactivity studies of the resulting alkaloid-pyrone structures, are currently in progress and will be reported in due course.

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