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Iodine-Promoted Oxidative Conversion of *o*-Vinyl Diaryl Ketones into *o*-Acetyl Diaryl Ketones, Synthesis of 1-Methyl-4-arylphthalazines as Analogues of Podophyllotoxin

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A new method is described for the metal-free oxidation of *o*-vinyl diaryl ketones in the presence of molecular iodine or *N*-iodosuccinimide to give *o*-acetyl diaryl ketones. This transformation involves the initial formation of an iodohydrin, and the *o*-carbonyl group of the iodohydrin participates in a subsequent rearrangement to give the *o*-acetyl diaryl ketone. The presence and participation of *ortho*-carbonyl group is necessary for successful conversion. The envisaged 1-methyl-4-arylphthalazines were synthesized from these *o*-acetyl diaryl ketones, and their antiproliferative activity on mammalian cell lines was studied.

Introduction

1,2-Diacylbenzenes **1** (see Figure 1) have been valuable precursors for variety of heterocyclic scaffolds such as isoindoles, isoquinolines, *N*-arylphthalimidines, and phthalazines, which are known for their significance in the areas of biology and pharmaceuticals.[1] Although a general method to synthesize this class of compounds is lacking, Kotali's protocol, which involves $Pb(OAc)_4$ promoted rearrangements of monoacylhydrazones of 2-hydroxyarylaldehydes and -ketones, constitutes a good route for the synthesis of **1**.[2] The limited availability of prefunctionalized starting materials and the toxicity of lead reagents restrict the employment of this method. In this regard, Yu's method, which has been recently reported,[3] involves a palladium-catalyzed direct C–H bond acylation through a cross-coupling reaction between aryl ketone oximes and aldehydes under oxidative conditions, and this is a significant achievement.

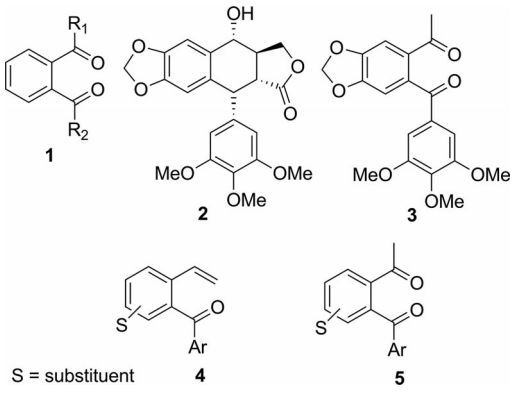

Figure 1. Podophyllotoxin and reaction intermediates discussed in text.

In our quest to arrive at a new analogue of podophyllotoxin (**2**), a natural product known for decades in cancer chemotherapy,[4] there arose a need for a convenient and efficient method to access the specifically substituted 1,2-diacylbenzene **3** (see Figure 1). Given the fact that the oxidative conversion of terminal olefins into methyl ketones under Wacker's procedure has been thoroughly investigated and industrially used,[5,6] we were tempted to explore the possibility of using *o*-vinyl diaryl ketones **4** as simple starting materials to develop a new and general method for the synthesis of *o*-acetyl diaryl ketones **5**. Although initially attracted by the promise of the Wacker oxidation and its modifications, our explorative studies culminated, to our delight, immediately at the onset in the achievement of the same conversion of **4**→**5** in high yields by using iodine or *N*-iodosuccinimide in an aqueous environment. This facile conversion enabled convenient access to compound **3** and paved the way for the envisaged analogue of podophyllotoxin based on a phthalazine scaffold. The results of this achievement along with the first biological studies are disclosed herein.

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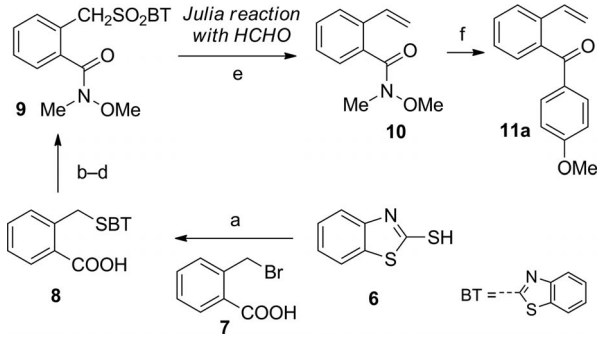
Results and Discussion

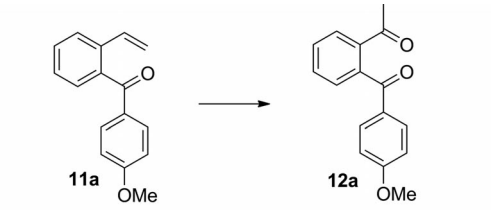
The synthesis of the requisite *o*-vinyl diaryl ketones **4** was envisaged to occur through the use of *o*-vinyl-substituted Weinreb amide (WA) **10** as the starting material, and towards this end, sulfone **9** was conceived as the basic building block (see Scheme 1). Alkylation of cheap and commercially available 2-mercaptobenzothiazole (**6**) with 2-(bromomethyl)benzoic acid (**7**)[7] was achieved by using NaH as a base and tetrahydrofuran (THF) as a solvent at –30 °C to yield **8** in 68% yield. Facile conversions that involved the carboxyl group of alkylated adduct **8** to give a WA along with the oxidation of the sulfide functionality by treatment with 30% H_2O_2 afforded the desired building block **9** in quantitative yield. A Julia olefination[8] of the in situ liberated formaldehyde from paraformaldehyde with sulfone **9** by using NaH as the base ensured ready access to multigram quantities of *o*-vinyl-substituted WA **10** in high yields. As a representative example of the preparation of *o*-vinyl diaryl ketones **4**, 4-methoxyphenylmagnesium bromide was added to WA **10** to obtain **11a** in 67% yield. To functionalize the vinyl residue along with the subsequent conversion into the acetyl unit, substrate **11a** was treated with iodine (2.0 equiv.) in a THF/H_2O (2:1) mixture as the reaction medium for a period of 24 h at 50 °C. To our surprise and delight, the reaction directly afforded diacylbenzene **12a** in 54% yield (see Table 1, Entry 1).



Scheme 1. Synthesis of *o*-vinyl diaryl ketone. Reagents and conditions: (a) NaH (1.2 equiv.), **7** (1.0 equiv.), THF, –30 °C, 6 h, 68%; (b) $SOCl_2$ (1.2 equiv.), dichloromethane (DCM), 40 °C, 6 h; (c) NH(OMe)Me·HCl (1.2 equiv.), Et_3N (3.0 equiv.), 0 °C – room temp., 3 h, 92%; (d) 30% H_2O_2 (10.0 equiv.), $Na_2WO_4{\cdot}2H_2O$ (0.5 equiv.), MeOH, 5 h, 98%; (e) NaH (1.2 equiv.), *N*,*N*-dimethylformamide (DMF), $(CH_2O)_n$ (1.5 equiv.), 0 °C – room temp., 3 h, 92%. (f) 4-$MeOC_6H_4MgBr$ (3.0 equiv.), 0 °C – room temp., 3 h, 67%.

This iodine-mediated direct conversion of the vinyl unit in **11a** into an acetyl group, which has been hitherto unreported, needed closer scrutiny and optimization. Although the iodine-mediated conversion of styrene into acetophenone in the presence of UV light and under an oxygen atmosphere has been reported,[9] the conversion **11a** into **12a** by treatment with iodine proceeded well, even in the dark and under an inert nitrogen atmosphere. The optimization studies revealed several interesting features. Among them and the most important was the necessity of water for the successful conversion. An increase in the reaction temperature

Table 1. Optimization of the reaction conditions for the synthesis of *o*-acetyl diaryl ketone.



Entry	Reagent	Solvent	*T* (°C)	Time (h)	Yield (%)
1	I_2	THF/H_2O, (2:1)	50	24	54
2	I_2	dioxane/H_2O, (2:1)	90	24	93
3	NIS	dioxane/H_2O, (2:1)	30	24	86
4	NIS	dioxane/H_2O, (2:1)	90	12	63
5	NIS	dry dioxane	30	24	–
6	I_2	dioxane/H_2O, (2:1)	90	24	76[a]

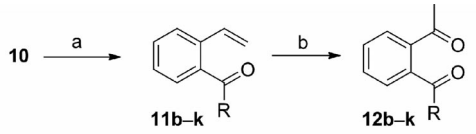
[a] The reaction was carried out in the dark and under nitrogen.

by using a mixture of dioxane/H_2O as reaction medium afforded product **12a** in an excellent isolated yield (93%), whereas the use of *N*-iodosuccinimide (NIS) as a more electrophilic iodinating agent enabled the same transformation to occur at ambient temperature and in high yields (see Table 1, Entries 2 and 3). However, increasing the reaction temperature to 90 °C (dioxane/H_2O mixture) in an effort to abate the long reaction time (24 h) under these conditions was not fruitful (see Table 1, Entry 4).

To generalize this conversion, convenient access to varied *o*-vinyl diaryl ketones became an essential requisite. The addition of various arylmagnesium bromides to **10** has now paved the way for the convenient synthesis of *ortho*-vinyl diaryl ketones **11b**–**11j** in good yields (see Table 2). As observed earlier for vinyl ketone **11a**, by using condition A [I_2 (2.0 equiv.), dioxane/H_2O (2:1), 90 °C], ketones **11b**–**11g** were transformed successfully into the anticipated 2-acetyl diaryl ketones **12b**–**12g** in very good yields. In contrast, substrates **11h**–**11j** failed to furnish the corresponding *o*-acetyl diaryl ketone **12h**–**12j** under the same conditions, and only starting materials were recovered. Presumably, under these conditions, the transformation appears restricted to substrates with electron-rich aryl moieties. However, under condition B [NIS (2.0 equiv.), dioxane/H_2O (2:1), room temperature], all the vinyl ketone **11b**–**11j** furnished the corresponding *o*-acetyl diaryl ketones **12b**–**12j** in good yields. In contrast to *ortho*-vinyl diaryl ketones **11b**–**11j**, *ortho*-vinyl valerophenone (**11k**) presented a complicated reaction mixture without obtaining the corresponding *ortho*-acetyl-valerophenone (**12k**).

Mechanistically, the facile conversion of the *ortho*-vinyl diaryl ketones into the *o*-acetyl diaryl ketones probably involves the initial formation of iodohydrin **13** followed by an internal attack from the proximate carbonyl group to lead to the formation of adduct **14**. Adduct **14** then rearranges to give product **12** through a proton loss by either of the two possible pathways as delineated in Scheme 2.

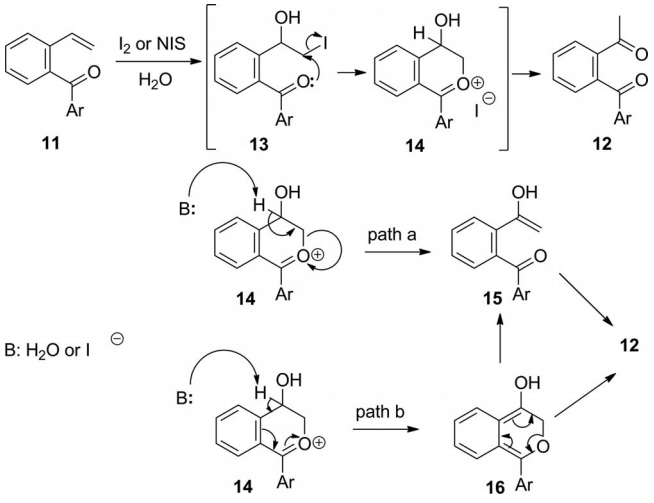
Table 2. Substrate scope for the synthesis of 1,2-diacylbenzenes.



a) 3.0 equiv. RMgBr, THF, 0 °C to r.t., 3 h; b) Condition A: 2.0 equiv. I_2, dioxane/H_2O (2:1), 90 °C or condition B: 2.0 equiv. NIS, dioxane/H_2O (2:1), r.t.

o-Vinyl ketones, **11b–k** R, yield (%)	1,2-Diacylbenzenes, **12b–k** Condition A yield (%), (time, h)	Condition B Yield (%), (time, h)
3,4-Dimethoxyphenyl, **11b**, 62	**12b**, 80 (12)	69 (24)
3,4,5-Trimethoxyphenyl, **11c**, 72	**12c**, 75 (16)	78 (24)
4-Methylphenyl, **11d**, 83	**12d**, 09 (36)	80 (36)
4-Thioanisyl, **11e**, 78	**12e**, 78 (16)	72 (24)
Thiophen-2-yl, **11f**, 82	**12f**, 90 (24)	85 (24)
4-Fluorophenyl, **11g**, 72	**12g**, 65 (24)	65 (24)
Phenyl, **11h**, 85	**12h**, - (24)	76 (36)
4-Chlorophenyl, **11i**, 67	**12i**, - (36)	72 (36)
3,4-Chlorophenyl, **11j**, 60	**12j**, - (24)	55 (24)[a]
n-Butyl, **11k**, 15	**12k** - (36)	- (36)

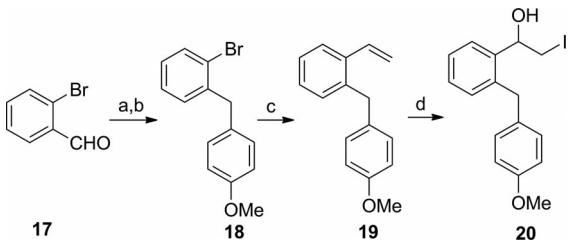
[a] Yield based on recovered starting material.



Scheme 2. Plausible mechanism.

The enhanced nucleophilicity of the carbonyl oxygen in substrates **11a**–**11g**, as a result of the electron-donating substituents, probably promoted the formation of adduct **14**, which, hence explains their successful conversion into the corresponding products **12a**–**12g**. The increased electrophilicity of the iodinating source, that is, *N*-iodosuccinimide versus iodine, enabled the rapid formation of iodohydrin **13**, which hence explains the mild reaction conditions when using *N*-iodosuccinimide as the iodinating reagent.

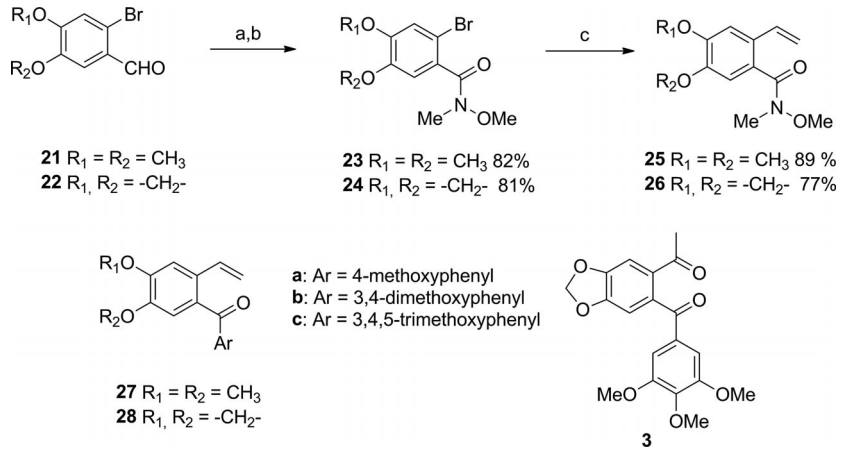
The reactivity of substrate **19**, without a carbonyl group, should offer some validity to the proposed two steps of the mechanism. Substrate **19** was quickly assembled in three simple steps (see Scheme 3), which involved the Grignard addition of 4-methoxyphenylmagnesium bromide to *o*-bromobenzaldehyde (**17**) followed by a deoxygenation of the benzylic alcohol and Suzuki vinylation of **18** by treatment with a 2,4,6-trivinylcyclotriboroxane–pyridine complex ($C_6H_9B_3O_3$·Py).[10] Subjecting substrate **19** to reaction condition B indeed furnished iodo-substituted alcohol **20** as the sole product in 79% yield, thereby substantiating the proposed iodohydrin intermediate in the mechanism. In the absence of the carbonyl group, any further sequence of events was obviated. From this experiment, it was evident that the proximate carbonyl group at the *ortho* position was the key component and was responsible for the apparent oxidation of the vinyl unit into an acetyl group.



Scheme 3. Investigation of the mechanism. Reagents and conditions: (a) 4-$MeOC_6H_4MgBr$ (2.0 equiv.), THF, room temp., 2.5 h, 67%; (b) Et_3SiH (5.0 equiv.), trifluoroacetic acid (TFA, 2.0 equiv.), room temp., 0.5 h, 89%; (c) $C_6H_9B_3O_3$·Py (0.5 equiv.), $Pd(PPh_3)_4$ (2.0 mol-%), K_2CO_3 (2.0 equiv.), DMF, 115 °C, 24 h, 75%; (d) NIS (2.0 equiv.), dioxane/H_2O (2:1), room temp., 24 h, 79%.

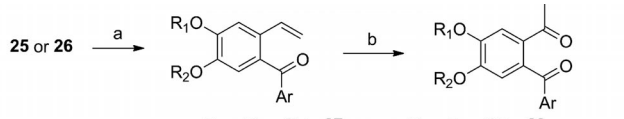
The developed protocol to convert *o*-vinyl diaryl ketones into *o*-acetyl diaryl ketones was now applied to the preparation of the synthetic target 1,2-diacylbenzene **3**, which is needed for the development of new analogues of the biologically important anticancer lead molecule, podophyllotoxin (**2**). The requisite *ortho*-vinyl-substituted Weinreb amides **25** and **26** were synthesized by starting from the corresponding 2-bromobenzaldehydes **21**[11] and **22**,[12] respectively. The oxidation of the aldehydes **21** and **22** by treatment with $KMnO_4$ followed by the activation of the carboxyl group and reaction with NH(OMe)Me afforded Weinreb amides **23** and **24** in 82 and 81% yield, respectively. The Suzuki coupling of **23** and **24** with the 2,4,6-trivinylcyclotriboroxane–pyridine complex furnished the desired *ortho*-vinyl-substituted amides **25** and **26** in good yields (see Scheme 4). These amides underwent clean reactions with 4-methoxy-, 3,4-dimethoxy-, and 3,4,5-trimethoxyphenylmagnesium bromides to give the *ortho*-vinyl-substituted ketones **27a**–**27c** and **28a**–**28c** in moderate to good yields. These ketones were subjected to the developed protocol to convert *o*-vinyl diaryl ketones into *o*-acetyl diaryl ketones by using either iodine or NIS to furnish the *o*-acetyl diaryl ketones **29a**–**29c**, **30a**, and **30b** in good yields (see Table 3). The successful preparation of the *o*-acetyl diaryl ketones not only validates the generality of the developed procedure but also allows for the convenient preparation of the synthetic target 1,2-diacylbenzene **3** and the fulfillment of the objective that was set forth.

After their successful synthesis, the 1,2-diacylbenzenes were converted into the corresponding phthalazines **31a**–**31j** in good yields by using hydrazine hydrate (see Table 4).



Scheme 4. Synthesis of 4,5-dimethoxy- and 4,5-methylenedioxy-*N*-methoxy-*N*-methyl-2-vinylbenzamides. Reagents and conditions: (a) $KMnO_4$ (1.5 equiv.), H_2O, room temp., 12 h; (b) $SOCl_2$ (1.2 equiv.) CH_2Cl_2, 45 °C, 4 h; $NH(OMe)Me{\cdot}HCl$ (1.1 equiv.), Et_3N (3.0 equiv.), 0 °C – room temp., 3 h; (c) $C_6H_9B_3O_3{\cdot}Py$ (0.5 equiv.), K_2CO_3 (2.0 equiv.), $Pd(PPh_3)_4$ (5 mol-%), dimethoxyethane (DME)/H_2O, reflux, 18 h.

Table 3. Synthesis of 4,5-dimethoxy and 4,5-methylenedioxy-2-acetyl diaryl ketones.

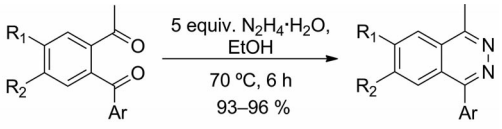


a) 3.0 equiv. ArMgBr, THF, 0°C to r.t., 3 h; b) Condition A: 2.0 equiv. I_2, dioxane/H_2O (2:1), 90 °C or condition B: 2.0 equiv. NIS, dioxane/H_2O (2:1), r.t.

o-Vinyl Weinreb amide	*o*-Vinyl ketones, Ar, yield (%)	*o*-Acetyl diaryl ketone	
		Condition A yield (%), (time, h)	Condition B yield (%), (time, h)
25	4-Methoxyphenyl, **27a**, 67	**29a**, 82 (24)	78 (24)
	3,4-Dimethoxyphenyl, **27b**, 65	**29b**, 66 (12)	58 (24)
	3,4,5-Trimethoxyphenyl, **27c**, 52	**29c**, 74 (12)	63 (24)
26	4-Methoxyphenyl, **28a**, 72	**30a**, 72 (12)	68 (24)
	3,4-Dimethoxyphenyl, **28b**, 56	**30b**, 65 (12)	66 (24)
	3,4,5-Trimethoxyphenyl, **28c**, 67	**3**, 74 (12)	62 (24)

The biological activities of the phthalazines on mammalian cell lines were studied. The compounds were first evaluated for their antiproliferative effects in the mouse fibroblast cell line L-929 (see Table 5). The IC_{50} (half maximal inhibitory concentration) values were measured by an MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] assay that ranged from >40 to 6.8 μg/mL. Compounds **31d**, **31f**, and **31j**, which had the highest inhibitory activities, were also tested with the human cancer cell line KB-3–1, in which they showed a slightly higher sensitivity. To discriminate between a cytostatic and a cytotoxic effect, compounds **31d**, **31f**, and **31j** were incubated with L-929 cells that had already been grown to confluency. As the cells did not propagate any further, a reduction in the MTT activity was a result of the acute toxic effects on the cells. In this assay, we observed a reduction in metabolic activity only with **31d** at the highest concentration of 40 μg/mL, and compounds **31f** and **31j** showed no toxic effect up to this concentration. As colchicine also did not affect the MTT reducing potency of the cells up to this concentration, it is assumed that compound **31d** has an additional effect on the cells that cannot be explained by the binding at the colchicine site alone.

Table 4. Synthesis of 1-methyl-4-arylphthalazines.



1-Methyl-4-aryl-phthalazines/Ar		R_1, R_2	Yield [%]
Ar = 4-Methoxyphenyl-	**31a**	H	95
= 3,4-Dimethoxyphenyl-	**31b**	H	96
= 3,4,5-Trimethoxyphenyl-	**31c**	H	94
= 4-Methylphenyl-	**31d**	H	94
= 4-Chlorophenyl-	**31e**	H	96
= 4-Methoxyphenyl-	**31f**	OMe	93
= 3,4-Dimethoxyphenyl-	**31g**	OMe	94
= 3,4,5-Trimethoxyphenyl-	**31h**	OMe	95
= 3,4-Dimethoxyphenyl-	**31i**	$-OCH_2O-$	96
= 3,4,5-Trimethoxyphenyl-	**31j**	$-OCH_2O-$	95

Table 5. Antiproliferative and cytotoxic activities in mammalian cell cultures. Values show the IC_{50} [μg/mL] measured by an MTT assay after 5 or 1 d of incubation.

Compound	L-929[a] [5 d]	KB-3–1[b] [5 d]	L-929 [1 d]
31a	37		
31b	>40		
31c	>40		
31d	6.8	6.0	35
31e	37		
31f	15	2.8	>40
31g	40		
31h	>40		
31i	>40		
31j	22	18	>40
Colchicine	0.015		>40

[a] Murine cell line originated from connective tissue. [b] Clone of the human HeLa cell line derived from cervix carcinoma.

The possible influence of compounds **31d**, **31f**, and **31j** on the cytoskeleton, microtubules and microfilaments, and the endoplasmic reticulum (ER) of the cells was also investigated by immunofluorescence staining with rat kangaroo cells (PtK2) that were incubated with **31d** (10, 50 μg/mL), **31f** (50 μg/mL), and **31j** (50 μg/mL) overnight. Visual inspections of the stained cells showed no specific effects to the actin cytoskeleton or on the ER system. The microtubular cytoskeleton was affected only when incubated with **31d** and **31j** at concentrations of 50 μg/mL (see Figure 2). However, at this concentration many cells had detached from the glass surface indicating that there is an effect in addition to the interference with the microtubules.

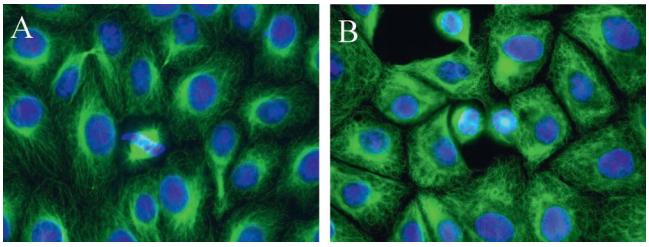


Figure 2. Influence of compound **31j** (50 μg/mL) on microtubules of PtK2 rat kangaroo cells (incubation time 16 h). The cells treated with the vehicle showed a normal microtubular network (green) in the interphase cells and the bipolar mitotic spindle (A). The network of cells treated with **31j** was less dense, and the mitotic cells often showed monopolar spindles (B).

Conclusions

In summary, we have developed a new method to convert *ortho*-vinyl diaryl ketones into *ortho*-acetyl diaryl ketones by using iodine or *N*-iodosuccinimide in an aqueous environment. The apparent oxidation of the vinyl residue into an acetyl group is a result of the proximity of the carbonyl group. The achieved formal oxidative conversion is metal-free, nontoxic, inexpensive, and high yielding as well as employs environmentally benign reagents. The developed procedure has paved the way for the convenient synthesis of an important building block in the search towards new analogues of podophyllotoxin. The biological studies of the phthalazine derivatives that were prepared from these *ortho*-acetyl diaryl ketones have shown interesting results with regard to the irrelevance of the substituents in the A and E rings of podophyllotoxin.

Experimental Section

General Methods: High-resolution NMR spectroscopic data were recorded using tetramethylsilane (TMS) as the internal standard with 400 and 500 MHz spectrometers. Infrared spectra are reported in cm^{-1}. High resolution mass spectra (HRMS) were recorded by the electrospray ionization (ESI) method with a Q-Tof Micro mass spectrometer with a lock spray source. Dry tetrahydrofuran was obtained by heating the solvent at reflux with sodium and benzophenone for several hours. *N*,*N*-Dimethylformamide and dichloromethane were dried with CaH_2 followed by distillation and then stored under N_2 over molecular sieves (4 Å). Distilled solvents were used for the reactions and column chromatography. Unless otherwise specified, mixtures of ethyl acetate/hexanes were employed throughout as the solvent system, and various polarities of the mixture were used depending on the nature of the substrate.

2-[(Benzo[*d*]thiazol-2-ylthio)methyl]benzoic Acid (8): To a stirred solution of 2-mercaptobenzothiazole (3.0 g, 14.0 mmol) in dry THF (30 mL) was added 60% NaH (1.1 g, 27.9 mmol) at –30 °C, and the resulting mixture was stirred for 5 min. To this was added 2-(bromomethyl)benzoic acid (2.33 g, 8.37 mmol) in portions over a period of 1 min, and the stirring was continued at –30 °C for 6 h. Upon completion, the reaction was quenched with a saturated aqueous NH_4Cl solution, and the resulting mixture was warmed to room temperature. The solvents were removed under vacuum, and the resulting residue was dissolved in ethyl acetate. The solution was washed with water, and the organic layer was dried with Na_2SO_4. Removal of the solvents under vacuum furnished a cream colored solid, which was washed of with diethyl ether (3 × 15 mL) to afford the desired product **8** (2.87 g, 68%) as a white solid; m.p. 121–123 °C. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 1046, 1374, 1732, 3276 cm^{-1}. ^1H NMR {400 MHz, deuterated dimethyl sulfoxide D_6[DMSO]}: δ = 5.01 (s, 2 H, SCH_2), 7.39 (td, J = 0.4 Hz, J = 7.6 Hz, 1 H, Ar), 7.45 (td, J = 0.8 Hz, J = 7.6 Hz, 1 H, Ar), 7.51 (td, J = 0.8 Hz, J = 8.0 Hz, 1 H, Ar), 7.56 (td, J = 0.8 Hz, J = 7.6 Hz, 1 H, Ar), 7.71 (d, J = 7.6 Hz, 1 H, Ar), 7.95 (t, J = 8.4 Hz, 2 H, Ar), 8.03 (d, J = 8.0 Hz, 1 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 36.0, 120.9, 121.3, 124.2, 126.0, 127.8, 129.8, 131.4, 131.5, 132.1, 135.3, 139.0, 152.9, 167.5, 169.1 ppm. HRMS (ESI): calcd. for $C_{15}H_{12}NO_2S_2[M + H]^+$ 302.0309; found 302.0320.

2-[(Benzo[*d*]thiazol-2-ylsulfonyl)methyl]-*N*-methoxy-*N*-methylbenzamide (9): To a stirred solution of acid **8** (2.5 g, 8.3 mmol) in dry CH_2Cl_2 (40 mL) was added $SOCl_2$ (0.66 mL, 9.1 mmol) at 0 °C under N_2. The reaction mixture was heated at reflux for 4 h. *N*,*O*-dimethylhydroxylamine hydrochloride (996 mg, 9.96 mmol) followed by triethylamine (3.18 mL, 24.9 mmol) was added at 0 °C, and the reaction mixture was stirred at room temperature for 3 h. The mixture was diluted with CH_2Cl_2, and the resulting solution was washed with water (2 × 10 mL), aqueous $NaHCO_3$ solution, and then brine. The organic layer was dried with Na_2SO_4, and the solvent was evaporated under vacuum to give the Weinreb amide (2.62 g, 92%) as a white solid. To a stirred solution of the Weinreb amide (3.5 g, 10.1 mmol) in MeOH (50 mL) was added 30% H_2O_2 (11.5 mL, 0.1 mol) and $Na_2WO_4{\cdot}2H_2O$ (1.66 g, 5.05 mmol), and the resulting mixture was stirred at room temperature for 12 h. The solvent was evaporated under vacuum to give a residue, which was dissolved in ethyl acetate. The solution was washed with water, and the organic layer was dried with Na_2SO_4. The solvent was removed under vacuum to give the *ortho*-substitued sulfone (i.e., Weinreb amide **9**, 3.74 g, 98%) as a white solid; m.p. 117–119 °C, IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 1014, 1330, 1466, 1644, 2998, 3291 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.15–4.00 (br. s, 6 H, NCH_3, OCH_3), 5.04 (s, 2 H, SCH_2), 7.13–7.29 (m, 3 H, Ar), 7.43 (t, J = 7.2 Hz, 1 H, Ar), 7.31–7.57 (m, 3 H, Ar), 7.81 (d, J = 8.0 Hz, 1 H, Ar), 8.10 (d, J = 8.0 Hz, 1 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 32.7, 57.2, 122.1, 124.6, 127.5, 127.9, 128.5, 129.9, 132.9, 136.7, 152.4, 165.1, 168.2 ppm. HRMS (ESI): calcd. for $C_{17}H_{17}N_2O_4S_2$ [M + H]$^+$ 377.0630; found 377.0640.

***N*-Methoxy-*N*-methyl-2-vinylbenzamide (10):** To a suspension of NaH (345 mg, 11.1 mmol) in dry DMF (5 mL) was added a solution of sulfone **9** (2.5 g, 6.6 mmol) in dry DMF (20 mL) at 0 °C. After 5 min, paraformaldehyde (220 mg, 7.3 mmol) in dry DMF (1 mL) was added, and the reaction mixture was warmed to room

temperature and then stirred for 1.5 h. The reaction mixture was quenched with a saturated NH_4Cl solution, and the resulting solution was extracted with ethyl acetate. The organic layer was dried with anhydrous Na_2SO_4. Evaporation of solvent and then purification of residue on neutral alumina by column chromatography gave *ortho*-vinyl-substituted Weinreb amide **10** (1.16 g, 92%) as a colorless liquid. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 1076, 1446, 1645, 2938 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.00–3.60 (br. s, 6 H, NCH_3, OCH_3), 5.26 (d, J = 11.2 Hz, 1 H, ArCHCH_2), 5.68 (d, J = 17.2 Hz, 1 H, ArCHCH_2), 6.71 (dd, J = 11.2 Hz, J = 17.6 Hz, 1 H), 7.32–7.19 (m, 3 H), 7.52 (d, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 32.1, 60.8, 111.7, 116.3, 122.0, 123.7, 125.0, 126.4, 129.2, 133.4, 134.4, 135.7, 172.1 ppm. HRMS (ESI): calcd. for $C_{11}H_{14}NO_2$ [M + H]$^+$ 192.1025; found 192.1034.

General Procedure for the Addition of the Grignard Reagents to the Weinreb Amide: To a solution of the aryl-, heteroaryl-, or alkylmagnesium bromide (3.0 mmol) in dry THF (4 mL) was added a solution of *o*-vinyl-substituted WA **10**, **25**, or **26** (1.0 mmol) in dry THF (4 mL) at 0 °C under an inert atmosphere, and the resulting mixture was stirred at room temperature for 3 h. Upon completion of the reaction, the mixture was quenched by the cautious addition of a saturated aqueous ammonium chloride solution. The aqueous layer was extracted with ethyl acetate, and the organic layer was washed with water and dried with Na_2SO_4. Evaporation of solvent and then purification of residue on silica gel by column chromatography (hexane/ethyl acetate) furnished the corresponding ketones. The analytical and spectroscopic data for the products 4-tolyl(2-vinylphenyl)methanone (**11d**) and phenyl(2-vinylphenyl)methanone (**11h**) matched those from the literature.[13]

(4-Methoxyphenyl)(2-vinylphenyl)methanone (11a): Brown liquid (67% yield). IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 1082, 1460, 1682, 2994 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.86 (s, 3 H, OMe), 5.21 (d, J = 10.8 Hz, 1 H, ArCHCH_2), 5.70 (d, J = 17.2 Hz, 1 H, ArCHCH_2), 6.73 (dd, J = 11.2 Hz, J = 17.6 Hz, 1 H, -CH), 6.91 (d, J = 8.8 Hz, 2 H, Ar), 7.30–7.38 (m, 2 H, Ar), 7.42–7.50 (m, 1 H, Ar), 7.66 (d, J = 8.0 Hz, 1 H, Ar), 7.78 (d, J = 8.8 Hz, 2 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.6, 113.8, 116.4, 125.8, 127.2, 128.1, 130.0, 130.5, 132.8, 134.2, 136.2, 138.5, 163.9, 197.0 ppm. HRMS (ESI): calcd. for $C_{16}H_{15}O_2$[M + H]$^+$ 239.1072; found 239.1078.

(3,4-Dimethoxyphenyl)(2-vinylphenyl)methanone (11b): Brown color gum (62% yield). IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 1080, 1284, 1454, 1668, 2986 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 3.91, 3.94 (2 s, 6 H, 2 OCH_3), 5.20 (dd, J = 1.0 Hz, J = 11.0 Hz, 1 H, ArCHCH_2), 5.68 (dd, J = 1.0 Hz, J = 17.5 Hz, 1 H, ArCHCH_2), 6.72 (dd, J = 11.0 Hz, J = 17.5 Hz, 1 H, -CH), 6.78 (d, J = 8.5 Hz, 1 H, Ar), 7.06 (dd, J = 1.0 Hz, J = 7.5 Hz, 1 H, Ar), 7.40 (d, J = 7.0 Hz, 1 H, Ar), 7.53–7.63 (m, 3 H, Ar), 7.82 (d, J = 7.5 Hz, 1 H, Ar) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 56.1, 56.2, 108.3, 112.1, 128.0, 128.5, 130.3, 130.4, 130.5, 131.1, 133.1, 134.4, 138.3, 148.2, 151.0, 197.5 ppm. HRMS (ESI): calcd. for $C_{17}H_{17}O_3$ [M + H]$^+$ 269.1178; found 269.1166.

(3,4,5-Trimethoxyphenyl)(2-vinylphenyl)methanone (11c): Light brown crystalline solid (72% yield); m.p. 120–122 °C, IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 1129, 1333, 1463, 1504, 1658, 2940 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 3.81 (s, 6 H, 2 OCH_3), 3.92 (s, 3 H, OCH_3), 5.23 (d, J = 11.5 Hz, 1 H, ArCHCH_2), 5.71 (d, J = 17.5 Hz, 1 H, ArCHCH_2), 6.75 (dd, J = 11.0 Hz, J = 17.0 Hz, 1 H, -CH), 7.05 (s, 2 H, Ar), 7.32–7.36 (m, 2 H, Ar), 7.44–7.49 (m, 1 H, Ar), 7.67 (d, J = 8.0 Hz, 1 H, Ar) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 56.3, 61.0, 108.0, 116.5, 125.9, 127.2, 128.4, 130.4, 132.6, 134.3, 136.6, 137.9, 143.0, 153.0, 197.1 ppm. HRMS (ESI): calcd. for $C_{18}H_{18}O_4Na$ [M + Na]$^+$ 321.1103; found 321.1091.

[4-(Methylthio)phenyl](2-vinylphenyl)methanone (11e): Light yellow gum (78% yield). IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 1092, 1435, 1590, 1654, 2255, 2925, 2985, 3057 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.50 (s, 3 H, -SMe), 5.21 (dd, J = 1.0 Hz, J = 1.0 Hz, 1 H, ArCHCH_2), 5.69 (dd, J = 11.2 Hz, J = 17.6 Hz, 1 H, ArCHCH_2), 6.73 (dd, J = 11.2 Hz, J = 17.6 Hz, 1 H, -CH), 7.21–7.25 (m, 2 H, Ar), 7.30–7.33 (m, 2 H, Ar), 7.43–7.50 (m, 1 H, Ar), 7.66 (d, J = 7.6 Hz, 1 H, Ar), 7.69–7.33 (m, 2 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.8, 116.6, 124.9, 125.9, 127.3, 128.3, 130.3, 130.7, 133.8, 134.2, 136.5, 138.5, 138.2, 146.6, 197.3 ppm. HRMS (ESI): calcd. for $C_{16}H_{15}OS$ [M + H]$^+$ 255.0844; found 255.0847.

Thiophen-2-yl(2-vinylphenyl)methanone (11f): Colorless gum (82% yield). IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 1086, 1287, 1446, 1668, 2996 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.27 (d, J = 11.2 Hz, 1 H, ArCHCH_2), 5.73 (d, J = 17.6 Hz, 1 H, ArCHCH_2), 6.86 (dd, J = 11.2 Hz, J = 17.6 Hz, 1 H, -CH), 7.10 (t, J = 4.8 Hz, 1 H, Ar), 7.34 (m, J = 7.2 Hz, 1 H, Ar), 7.41 (dd, J = 0.8 Hz, J = 4.0 Hz, 1 H, Ar), 7.43–7.51 (m, 2 H, Ar), 7.68 (d, J = 8.0 Hz, 1 H, Ar), 7.73 (d, J = 4.8 Hz, 1 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 116.7, 126.1, 127.2, 128.2, 128.3, 130.6, 134.1, 135.3, 136.0, 136.4, 137.8, 145.0, 190.1 ppm. HRMS (ESI): calcd. for $C_{13}H_{10}OSNa$ [M + Na]$^+$ 237.0350; found 237.0350.

(4-Fluorophenyl)(2-vinylphenyl)methanone (11g): Cream color gum (72% yield). IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 1150, 1262, 1422, 1597, 1663, 2986, 3054 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.23 (d, J = 10.8 Hz, 1 H, ArCHCH_2), 5.70 (d, J = 17.6 Hz, 1 H, ArCHCH_2), 6.73 (dd, J = 10.8 Hz, J = 17.6 Hz, 1 H, -CH), 7.10 (t, J = 8.4 Hz, 2 H, Ar), 7.30–7.37 (m, 2 H, Ar), 7.45–7.51 (m, 1 H, Ar), 7.67 (d, J = 8.0 Hz, 1 H, Ar), 7.81 (dd, J = 5.6, J = 8.4 Hz, 2 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 115.6, 115.8, 116.9, 126.1, 127.3, 128.4, 130.6, 133.0, 133.1, 134.2, 136.7, 137.8, 166.0 (d, $J_{C,F}$ = 255 Hz), 196.7 ppm. HRMS (ESI): calcd. for $C_{15}H_{12}OF$ [M + H]$^+$ 227.0872; found 227.0870.

(4-Chlorophenyl)(2-vinylphenyl)methanone (11i): Colorless gum (67% yield). IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 1030, 1151, 1421, 1509, 1663, 1686, 2936 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.35 (d, J = 11.2 Hz, 1 H, ArCHCH_2), 4.81 (d, J = 17.6 Hz, 1 H, ArCHCH_2), 5.85 (dd, J = 11.2 Hz, J = 17.6 Hz, 1 H, -CH), 6.40–6.47 (m, 2 H, Ar), 6.52–6.55 (m, 2 H, Ar), 6.58–6.64 (m, 1 H), 6.61 (td, J = 2.0 Hz, J = 8.0 Hz, 1 H, Ar), 6.85 (d, J = 8.4 Hz, 2 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 117.0, 126.2, 127.4, 128.5, 128.9, 130.7, 131.7, 134.2, 136.0, 136.8, 137.5, 140.0, 197.0 ppm. HRMS (ESI): calcd. for $C_{15}H_{12}OCl$ [M + H]$^+$ 243.0577; found 243.0581.

(3,4-Dichlorophenyl)(2-vinylphenyl)methanone (11j): Cream color gum (60% yield). IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 1031, 1266, 1462, 1668, 2927, 3054 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.26 (dd, J = 0.8 Hz, J = 11.2 Hz, 1 H, ArCHCH_2), 5.69 (dd, J = 0.8 Hz, J = 17.2 Hz, 1 H, ArCHCH_2), 6.73 (dd, J = 11.2 Hz, J = 17.6 Hz, 1 H, -CH), 7.31–7.39 (m, 2 H, Ar), 7.50–7.55 (m, 2 H, Ar), 7.60 (dd, J = 2.0 Hz, J = 8.4 Hz, 1 H, Ar), 7.67 (d, J = 8.0 Hz, 1 H, Ar), 7.88 (d, J = 2.0 Hz, 1 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 115.6, 115.8, 116.9, 126.1, 127.3, 128.4, 130.6, 133.0, 133.1, 134.2, 136.7, 137.8, 164.7, 167.3, 196.7 ppm.

2-Vinylvalerophenone (11k): Yellow gum (15% yield). IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 1265, 1422, 1445, 1684, 2931, 2961, 3054 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.93 (t, 3 H, CH_3), 1.35–1.43 (m, 2 H, -CH_2), 1.64–1.72 (m, 2 H, -CH_2), 2.87 (t, J = 7.5 Hz, 2 H, -CH_2), 5.32 (dd, J = 1.0 Hz, J = 11.0 Hz, 1 H, ArCHCH_2), 5.64 (dd, J = 1.0 Hz, J = 17.5 Hz, 1 H, ArCHCH_2), 7.08 (dd, J = 11.0 Hz, J = 17.5 Hz, 1 H, -CH), 7.33 (dt, J = 1.0 Hz, J = 8.0 Hz, 1 H, Ar), 7.43 (dt, J = 1.0 Hz, J = 7.5 Hz, 1 H, Ar), 7.53–7.59 (m, 2 H, Ar) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.0, 22.5, 26.6, 42.0,

116.7, 127.4, 127.5, 127.9, 131.1, 135.6, 137.2, 138.3, 205.6 ppm. HRMS (ESI): calcd. for $C_{13}H_{17}O$ [M + H]$^+$ 189.1279; found 189.1276.

General Procedure for the Synthesis of *o*-Acetyl Diaryl Ketones: A stirred solution of *o*-vinyl diaryl ketones (0.5 mmol) in dioxane/water (2:1, 8 mL) was added to a round-bottomed flask covered with aluminium foil. To this mixture was added either iodine (1.0 mmol) followed by heating the reaction mixture at 90 °C (condition A) or *N*-iodosuccinimide (1.0 mmol) followed by maintaining the reaction at 30 °C (condition B). The resulting reaction mixture was stirred for several hours until there was complete consumption of the starting material (as monitored by TLC). Upon completion, the solvents were removed under vacuum at 50 °C to obtain the product as a brown residue. The product was dissolved in ethyl acetate followed by washing with a sodium thiosulfate solution and water. The crude diketo compound was subjected to silica gel chromatography (ethyl acetate/hexanes) to furnish the pure *o*-acetyl diaryl ketones. The ^{1}H and ^{13}C NMR spectroscopic data of compounds 1-[2-(4-methoxybenzoyl)phenyl]ethanone (**12a**),[14] 2-(4-methylbenzoyl)phenylethanone (**12d**),[14] 1-[2-(thiophene-2-carbonyl)phenyl]ethanone (**12f**),[14] 1-(2-benzoylphenyl)ethanone (**12h**),[14] and 1-[2-(4-chlorobenzoyl)phenyl]ethanone (**12i**)[3] matched with the corresponding data in the literature.

1-[2-(3,4-Dimethoxybenzoyl)phenyl]ethanone (12b): Brown solid (80% yield); m.p. 95–97 °C. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 1054, 1236, 1454, 1740, 2986 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.51 (s, 3 H, $COCH_3$), 3.81, 3.93 (2 s, 6 H, 2 OCH_3), 6.76 (d, J = 8.5 Hz, 1 H, Ar), 7.03 (d, J = 8.5 Hz, 1 H, Ar), 7.38 (d, J = 8.0 Hz, 1 H, Ar), 7.53–7.62 (m, 3 H, Ar), 7.86 (d, J = 8.0 Hz, 1 H, Ar) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 27.7, 56.0, 56.1, 109.9, 110.6, 125.0, 128.3, 129.3, 129.6, 130.5, 132.1, 137.6, 141.0, 149.2, 153.4, 196.6, 198.7 ppm. HRMS (ESI): calcd. for $C_{17}H_{17}O_4$[M + H]$^+$ 285.1127; found 285.1137.

1-[2-(3,4,5-Trimethoxybenzoyl)phenyl]ethanone (12c): Light brown crystals (75% yield); m.p. 46–48 °C. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 1258, 1600, 1655 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.52 (s, 3 H, $COCH_3$), 3.79 (s, 6 H, 2 OCH_3), 3.87 (s, 3 H, OCH_3), 6.98 (s, 2 H, Ar), 7.39 (dd, J = 1.2 Hz, J = 7.2 Hz, 1 H), 7.59 (m, 2 H, Ar), 7.87 (dd, J = 1.6 Hz, J = 7.2 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.1, 56.3, 60.9, 107.0, 128.2, 129.3, 132.1, 137.7, 140.7, 142.6, 153.1, 196.6, 198.7 ppm. HRMS (ESI): calcd. for $C_{18}H_{18}O_5Na$ [M + Na]$^+$ 337.1052; found 337.1038.

1-{2-[4-(Methylthio)benzoyl]phenyl}ethanone (12e): Brown gummy liquid (78% yield). IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 1092, 1268, 1444, 1682, 1725, 3056 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.47 (s, 3 H, -COMe), 2.49 (s, 3 H, -SMe), 7.19–7.22 (m, 2 H, Ar), 7.36 (dd, J = 1.6 Hz, J = 7.2 Hz, 1 H, Ar), 7.53–7.61 (m, 2 H, Ar), 7.61–7.65 (m, 2 H, Ar), 7.86 (dd, J = 1.2 Hz, J = 8.0 Hz, 1 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.8, 27.5, 124.9, 124.9, 125.0, 128.2, 129.3, 129.7, 132.2, 133.6, 137.5, 140.8, 145.9, 196.9, 198.5 ppm. HRMS (ESI): calcd. for $C_{16}H_{15}O_2S$[M + H]$^+$ 271.0793; found 271.0784.

1-[2-(4-Fluorobenzoyl)phenyl]ethanone (12g): Brown color gum (58% yield). IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 1151, 1265, 1360, 1414, 1505, 1597, 1683, 2927, 3055 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.52 (s, 3 H, -CH_3), 7.07 (t, J = 8.4 Hz, 2 H, Ar), 7.37 (dd, J = 0.8 Hz, J = 7.2 Hz, 1 H, Ar), 7.57–7.77 (m, 2 H, Ar), 7.75 (dd, J = 5.2 Hz, J = 8.1 Hz, 2 H, Ar), 7.89 (m, 1 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.4, 115.6, 115.8, 129.2, 129.5, 129.9, 131.8, 131.9, 132.4, 140.8, 165.7 (d, J = 254 Hz), 196.3, 196.4 ppm. HRMS (ESI): calcd. for $C_{15}H_{12}O_2F$[M + H]$^+$ 243.0821; found 243.0817.

1-[2-(3,4-Dichlorobenzoyl)phenyl]ethanone (12j): Brown color gum (55% yield). IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 1252, 1347, 1444, 1682, 2927, 3027 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.55 (s, 3 H, -CH_3), 7.37 (d, J = 7.2 Hz, 1 H, Ar), 7.47–7.57 (m, 2 H, Ar), 7.61–7.70 (m, 2 H, Ar), 7.77 (s, 1 H, Ar), 7.93 (d, J = 8.0 Hz, 1 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.1, 128.0, 128.1, 129.8, 130.2, 130.7, 130.9, 132.9, 133.2, 137.0, 137.1, 137.5, 140.2, 195.6, 198.1 ppm. HRMS (ESI): calcd. for $C_{15}H_{11}O_2Cl_2$ [M + H]$^+$ 293.0136; found 293.0126.

1-(4-Methoxybenzyl)-2-vinylbenzene (19): Colorless gummy liquid (75% yield). IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 1038, 1510, 1611, 2932 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.76 (s, 3 H, OCH_3), 4.00 (s, 2 H, CH_2), 5.23 (dd, J = 1.5 Hz, J = 11.0 Hz, 1 H), 5.62 (dd, J = 1.5 Hz, J = 17.5 Hz, 1 H), 6.80 (d, J = 9.0 Hz, 2 H, Ar), 6.93 (dd, J = 11.0 Hz, J = 17.5 Hz, 1 H), 7.02 (d, J = 17.5 Hz, 2 H, Ar), 7.08–7.12 (m, 1 H, Ar), 7.18–7.24 (m, 2 H, Ar), 7.50–7.52 (m, 1 H, Ar) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 38.2, 55.4, 114.0, 115.8, 126.0, 126.7, 128.0, 128.9, 129.7, 130.4, 132.8, 134.8, 137.1, 138.3, 158.0 ppm. HRMS (ESI): calcd. for $C_{16}H_{17}O$ [M + H]$^+$ 225.1279; found 225.1283.

2-Iodo-1-[2-(4-methoxybenzyl)phenyl]ethanol (20): Colorless gummy liquid (79% yield). IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 1086, 1285, 1445, 1542, 2986, 3450 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.00 (dd, J = 3.0 Hz, J = 10.0 Hz, 1 H, CH_2I), 3.17 (dd, J = 9.5 Hz, J = 10.0 Hz, 1 H, CH_2I), 3.76 (s, 3 H, OCH_3), 3.91–4.10 (ABq, J = 15.5 Hz, 2 H, $ArCH_2$), 5.07 (dd, J = 3.0 Hz, J = 9.5 Hz, 1 H, C*H*OH), 6.81 (d, J = 9.0 Hz, 2 H, Ar), 7.01 (d, J = 8.5 Hz, 2 H, Ar), 7.15–7.18 (m, 1 H, Ar), 7.25–7.31 (m, 2 H, Ar), 7.51–7.54 (m, 1 H, Ar) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 14.3, 38.2, 55.4, 70.8, 114.2, 125.8, 127.3, 128.4, 129.5, 130.9, 132.4, 137.8, 139.4, 158.2 ppm. HRMS (ESI): calcd. for $C_{16}H_{17}O_2INa$ [M + Na]$^+$ 391.0171; found 391.0167.

General Procedure for Synthesis of 2-Bromo-*N*,*O*-dimethylbenzamides 23 and 24: To a stirred solution of the corresponding 2-bromobenzoic acids[15,16] (12 mmol) in dry CH_2Cl_2 (50 mL) was added $SOCl_2$ (14.4 mmol) at 0 °C, under N_2. The reaction mixture was heated at reflux for 4 h and then cooled to 0 °C. To this mixture was added *N*,*O*-dimethylhydroxylamine hydrochloride (14.4 mmol) followed by triethylamine (36 mmol). The reaction mixture was stirred at room temperature for 3 h and then diluted with CH_2Cl_2. The resulting solution was washed with water, an aqueous $NaHCO_3$ solution, and then brine. Drying the CH_2Cl_2 solution with Na_2SO_4 and concentration under vacuum afforded the Weinreb amides.

2-Bromo-4,5-dimethoxy-*N*-methoxy-*N*-methylbenzamide (23): White crystalline solid (82% yield); m.p. 80–82 °C. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 1430, 1512, 1652, 2941, 2980, 3052 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.01–3.52 (br. s, 6 H, NCH_3, OCH_3), 3.78, 3.80 (2 s, 6 H, $ArOCH_3$), 6.75 (s, 1 H, Ar), 6.94 (s, 1 H, Ar) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 32.4, 56.1, 61.1, 110.6, 115.2, 128.4, 128.5, 131.9, 132.0, 148.2, 150.0 ppm. HRMS (ESI): calcd. for $C_{11}H_{15}NO_4Br$ [M + H]$^+$ 304.0184; found 304.0193.

6-Bromo-*N*-methoxy-*N*-methylbenzo[*d*][1,3]dioxole-5-carboxamide (24): Brown gummy liquid (81% yield). IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 1425, 1643, 3022 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.01–3.09 (br. s, 6 H, NCH_3, OCH_3), 5.99 (s, 2 H, CH_2), 6.75 (s, 1 H, Ar), 6.98 (s, 1 H, Ar) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 32.5, 61.4, 102.2, 107.9, 110.7, 112.9, 130.2, 147.1, 149.1 ppm. HRMS (ESI): calcd. for $C_{10}H_{11}NO_4Br$ [M + H]$^+$ 287.9871; found 287.9872.

General Procedure for Vinylation through a Suzuki Coupling Reaction: A stirred solution of 2-bromo-*N*,*O*-dimethylbenzamides **23** or

24 (3.28 mmol) in DME (15 mL) was purged with N_2 for 15 min. To this were added a saturated aqueous K_2CO_3 solution (4.92 mmol, 1 mL), $Pd(PPh_3)_4$ (5 mol-%), and the 2,4,6-trivinylcyclotriboroxane–pyridine complex (1.64 mmol), and the reaction mixture was heated at reflux for 18 h. The mixture was cooled and filtered through a bed of Celite, which was washed with ethyl acetate. Evaporation of filtrate and purification of residue on neutral alumina by column chromatography furnished the *ortho*-vinyl-substituted Weinreb amides.

4,5-Dimethoxy-*N*-methoxy-*N*-methyl-2-vinylbenzamide (25): Yellow gummy liquid (89% yield). IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 1034, 1463, 1646, 2844 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 3.20–3.60 (br. s, 6 H, NCH_3, OCH_3), 3.86 (s, 3 H, OCH_3), 3.91 (s, 3 H, OCH_3), 5.23 (d, J = 11.0 Hz, 1 H), 5.62 (d, J = 17.0 Hz, 1 H), 6.73 (dd, J = 11.0 Hz, J = 17.0 Hz, 1 H), 6.79 (s, 1 H, Ar), 7.04 (s, 1 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 33.6, 56.0, 56.1, 61.2, 107.6, 109.8, 114.4, 126.7, 128.5, 132.0, 133.5, 148.6, 149.2, 162.6 ppm. HRMS (ESI): calcd. for $C_{13}H_{18}NO_4[M + H]^+$ 252.1236; found 252.1236.

***N*-Methoxy-*N*-methyl-6-vinylbenzo[*d*][1,3]dioxole-5-carboxamide (26):** Yellow gummy liquid (77% yield). IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 1255, 1484, 1642, 2254, 2977 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 3.10–3.55 (br. s, 6 H, NCH_3, OCH_3), 5.20 (d, J = 11.0 Hz, 1 H), 5.59 (d, J = 11.0 Hz, 1 H), 5.97 (s, 2 H, OCH_2), 6.69 (dd, J = 11.0 Hz, J = 18.0 Hz, 1 H), 6.73 (s, 1 H, Ar), 7.04 (s, 1 H, Ar) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 33.6, 61.2, 101.6, 104.9, 106.9, 114.7, 123.6, 129.8, 133.2, 147.1, 148.9, 169.0 ppm. HRMS (ESI): calcd. for $C_{12}H_{13}NO_4Na$ $[M + Na]^+$ 258.0742; found 258.0753.

(4,5-Dimethoxy-2-vinylphenyl)(4-methoxyphenyl)methanone (27a): Yellow gummy liquid (67% yield). IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 1261, 1509, 1601, 1730 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.75, 3.77, 3.88 (3 s, 9 H, 3 OCH_3), 5.04 (d, J = 10.8 Hz, 1 H), 5.50 (d, J = 17.6 Hz, 1 H), 6.61 (dd, J = 10.8 Hz, J = 17.6 Hz, 1 H), 6.76 (s, 1 H), 6.83 (d, J = 10.8 Hz, 2 H), 7.06 (s, 1 H), 7.69 (d, J = 8.0 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.5, 56.0, 108.0, 111.5, 113.5, 114.3, 124.8, 130.2, 131.0, 131.1, 132.2, 132.6, 134.2, 148.2, 150.5, 163.7, 196.2 ppm. HRMS (ESI): calcd. for $C_{18}H_{19}O_4[M + H]^+$ 299.1283; found 299.1291.

(4,5-Dimethoxy-2-vinylphenyl)(3,4-dimethoxyphenyl)methanone (27b): Brown gummy compound (65% yield). IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 1047, 1374, 1476, 1738, 2986, 3059 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.86, 3.93, 3.94, 3.98 (4 s, 12 H, $ArOCH_3$), 5.14 (d, J = 11.2 Hz, 1 H, $ArCHCH_2$), 5.60 (d, J = 17.2 Hz, 1 H, $ArCHCH_2$), 6.71 (d, J = 11.2 Hz, J = 17.2 Hz, 1 H, $ArCHCH_2$), 6.85 (d, J = 8.4 Hz, 1 H, Ar), 6.88 (s, 1 H, Ar), 7.15 (s, 1 H, Ar), 7.20 (dd, J = 2.0 Hz, J = 8.4 Hz, 1 H, Ar), 7.52 (d, J = 2.0 Hz, 1 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.92, 55.95, 56.00, 56.02, 107.8, 109.8, 111.4, 114.2, 126.0. 130.1, 130.90, 130.92, 134.1, 148.0, 148.9, 150.4, 153.4, 196.2 ppm. HRMS (ESI): calcd. for $C_{19}H_{21}O_5$ $[M + H]^+$ 329.1389; found 329.1380.

(4,5-Dimethoxy-2-vinylphenyl)(3,4,5-trimethoxyphenyl)methanone (27c): Yellow solid (52% yield); m.p. 88–90 °C. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 1048, 1376, 1452, 1740, 2954 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.84, 3.86, 3.94, 4.00 (4 s, 15 H, $ArOCH_3$), 5.17 (d, J = 11.2 Hz, 1 H, $ArCHCH_2$), 5.61 (d, J = 17.2 Hz, 1 H, $ArCHCH_2$), 6.73 (d, J = 10.8 Hz, J = 17.2 Hz, 1 H, $ArCHCH_2$), 6.90 (s, 1 H, Ar), 7.0 (s, 2 H, Ar), 7.10 (s, 1 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 56.0, 56.2, 56.3, 61.0, 104.7, 107.9, 108.1, 111.8, 114.5, 128.4, 130.7, 133.1, 134.3, 137.6, 142.7, 148.1, 150.8, 153.0, 153.5, 196.3 ppm. HRMS (ESI): calcd. for $C_{20}H_{23}O_6[M + H]^+$ 359.1495; found 359.1502.

(4-Methoxyphenyl)(6-vinylbenzo[*d*][1,3]dioxol-5-yl)methanone (28a): Light yellow liquid (72% yield). IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 1119, 1265, 1362, 1458, 1601, 2862, 2954 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.79 (s, 3 H, OCH_3), 5.04 (d, J = 10.8 Hz, 1 H, CH), 5.49 (d, J = 17.2 Hz, 1 H, $ArCHCH_2$), 5.95 (s, 2 H, OCH_2), 6.60 (dd, J = 10.8 Hz, J = 17.2 Hz, 1 H, $ArCHCH_2$), 6.64 (s, 1 H, Ar), 6.71 (d, J = 8.8 Hz, 2 H, Ar), 7.05 (s, 1 H, Ar), 7.71 (d, J = 8.4 Hz, 2 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.5, 101.7, 105.5, 108.6, 113.8, 114.7, 130.7, 132.0, 132.4, 132.8, 134.0, 146.9, 149.5, 163.8, 196.0 ppm. HRMS (ESI): calcd. for $C_{17}H_{15}O_4[M + H]^+$ 283.0970; found 283.0961.

(3,4-Dimethoxyphenyl)(6-vinylbenzo[*d*][1,3]dioxol-5-yl)methanone (28b): Light brown solid (56% yield); m.p. 75–77 °C. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 1226, 1268, 1648, 1671 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.93, 3.94 (2 s, 6 H, 2 OCH_3), 5.13 (d, J = 11.6 Hz, 1 H), 5.57 (d, J = 17.2 Hz, 1 H), 6.05 (s, 2 H, OCH_2), 6.67 (dd, J = 10.8 Hz, J = 17.2 Hz, 1 H), 6.81 (s, 1 H, Ar), 6.83 (d, J = 8.4 Hz, 1 H, Ar), 7.10 (dd, J = 2.0 Hz, J = 8.4 Hz, 1 H, Ar), 7.13 (s, 1 H, Ar), 7.52 (d, J = 2.0 Hz, 1 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 56.1, 56.2, 101.7, 105.4, 108.6, 110.5, 111.6, 114.6, 119.2, 126.3, 132.0, 134.0, 146.8, 148.4, 149.2, 153.6, 196.0 ppm. HRMS (ESI): calcd. for $C_{18}H_{17}O_5$ $[M + H]^+$ 313.1076; found 313.1081.

(3,4,5-Trimethoxyphenyl)(6-vinylbenzo[*d*][1,3]dioxol-5-yl)methanone (28c): Yellow solid (67% yield); m.p. 101–102 °C. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 1130, 1476, 1585, 1655, 3021 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 3.83 (s, 6 H, 2 OCH_3), 3.92 (s, 3 H, OCH_3), 5.13 (d, J = 10.5 Hz, 1 H, $ArCHCH_2$), 5.57 (d, J = 17.0 Hz, 1 H, $ArCHCH_2$), 6.03 (s, 2 H, OCH_2), 6.68 (dd, J = 10.5 Hz, J = 17.0 Hz, 1 H, $ArCHCH_2$), 6.82 (s, 1 H, Ar), 7.04 (s, 2 H, Ar), 7.13 (s, 1 H, Ar) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 56.4, 61.0, 101.8, 105.5, 107.9, 108.8, 114.0, 132.0, 132.5, 132.9, 134.1, 142.8, 146.9, 149.8, 153.0, 196.0 ppm. HRMS (ESI): calcd. for $C_{19}H_{18}O_6Na$ $[M + Na]^+$ 365.1001; found 365.1004.

1-[4,5-Dimethoxy-2-(4-methoxybenzoyl)phenyl]ethanone (29a): Yellow gummy liquid (82% yield). IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 1047, 1247, 1375, 1731, 3018 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 2.43 (s, 3 H, $COCH_3$), 3.85, 3.91, 4.00 (3 s, 9 H, 3 OCH_3), 6.86 (s, 1 H), 6.89 (d, J = 8.0 Hz, 2 H), 7.31 (s, 1 H), 7.73 (d, J = 8.0 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 27.9, 55.6, 56.40, 56.42, 110.9, 111.9, 113.9, 130.5, 131.7, 135.3, 149.2, 152.0, 163.6, 196.3, 197.4 ppm. HRMS (ESI): calcd. for $C_{18}H_{19}O_5$ $[M + H]^+$ 315.1232; found 315.1231.

1-[2-(3,4-Dimethoxybenzoyl)-4,5-dimethoxyphenyl]ethanone (29b): Brown solid (66% yield); m.p. 78–80 °C. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 1213, 1517, 1718, 3018 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 2.42 (s, 3 H, $COCH_3$), 3.89, 3.90 (2 s, 6 H, 2 OCH_3), 3.92, 3.98 (2 s, 6 H, 2 OCH_3), 6.75 (d, J = 8.5 Hz, 1 H), 6.76 (s, 1 H), 7.05 (dd, J = 1.5 Hz, J = 8.0 Hz, 1 H, Ar), 7.30 (s, 1 H, Ar), 7.57 (d, J = 1.5 Hz, 1 H, Ar) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 27.8, 56.0, 56.1, 56.3, 109.9, 110.6, 110.0, 111.9, 124.8, 130.4, 130.6, 135.0, 149.2, 149.3, 152.0, 153.4, 196.4, 197.4 ppm. HRMS (ESI): calcd. for $C_{19}H_{21}O_6$ $[M + H]^+$ 345.1338; found 345.1351.

1-[4,5-Dimethoxy-2-(3,4,5-trimethoxybenzoyl)phenyl]ethanone (29c): Brown solid (74% yield); m.p. 82–85 °C, IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 1265, 2257, 2360, 2985, 3055 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.45 (s, 3 H, $COCH_3$), 3.81 (s, 6 H, 2 OCH_3), 3.89, 3.92, 4.01 (3 s, 9 H, 3 OCH_3), 6.87 (s, 1 H, Ar), 6.99 (d, 2 H, Ar), 7.31 (s, 1 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.7, 55.4, 56.4, 61.0, 106.9, 111.0, 111.8, 126.8, 130.7, 132.6, 134.7, 149.4, 152.1, 153.1, 196.3, 197.4 ppm. HRMS (ESI): calcd. for $C_{20}H_{22}O_7Na$ $[M + Na]^+$ 397.1263; found 397.1276.

1-[6-(4-Methoxybenzoyl)benzo[*d*][1,3]dioxol-5-yl]ethanone (30a): Light yellow liquid (72% yield). IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 1121, 1361,

1610, 2865, 2961 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.35 (s, 3 H, $COCH_3$), 3.77 (s, 3 H, OCH_3), 6.04 (s, 2 H, CH_2), 6.74 (s, 1 H, Ar), 6.82 (d, J = 8.8 Hz, 2 H, Ar), 7.20 (s, 1 H, Ar), 7.64 (d, J = 8.8 Hz, 2 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.7, 55.6, 102.6, 108.7, 109.2, 113.8, 126.3, 130.3, 131.6, 132.2, 137.4, 148.5, 150.8, 160.6, 195.7, 196.9 ppm. HRMS (ESI): calcd. for $C_{17}H_{15}O_5$ $[M + H]^+$ 299.0919; found 299.0909.

1-[6-(3,4-Dimethoxybenzoyl)benzo[*d*][1,3]dioxol-5-yl]ethanone (30b): Brown solid (65% yield); m.p. 82–84 °C. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 1025, 1286, 1476, 1674, 2862, 2954 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.41 (s, 3 H, $COCH_3$), 3.89, 3.93 (s, 6 H, 2 OCH_3), 6.11 (s, 2 H, OCH_2), 6.75 (d, J = 8.4 Hz, 1 H, Ar), 6.81 (s, 1 H, Ar), 7.06 (dd, J = 1.6 Hz, J = 8.0 Hz, 1 H, Ar), 7.27 (s, 1 H, Ar), 7.56 (d, J = 2.0 Hz, 1 H, Ar) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 27.6, 56.0, 56.1, 102.6, 108.7, 109.2, 109.8, 110.6, 124.7, 130.4, 132.0, 137.2, 148.4, 149.2, 150.7, 153.3, 195.7, 196.8 ppm. HRMS (ESI): calcd. for $C_{18}H_{16}O_6Na$ $[M + Na]^+$ 351.0845; found 351.0830.

1-[6-(3,4,5-Trimethoxybenzoyl)benzo[*d*][1,3]dioxol-5-yl]ethanone (3): Brown solid (74% yield); m.p. 89–92 °C. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 1036, 1094, 1270, 1471, 1581, 1654, 2853, 2930 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.45 (s, 3 H, $COCH_3$), 3.83 (s, 6 H, 2 OCH_3), 3.90 (s, 3 H, OCH_3), 6.14 (s, 2 H, OCH_2), 6.83 (s, 1 H, Ar), 7.00 (s, 2 H, Ar), 7.30 (s, 1 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.5, 56.3. 60.9, 102.7, 106.8, 108.6, 109.2, 132.1, 132.3, 136.8, 142.5, 148.6, 150.8, 153.0, 195.8, 196.8 ppm. HRMS (ESI): calcd. for $C_{19}H_{19}O_7$ $[M + H]^+$ 359.1131; found 359.1144.

General Procedure for the Synthesis of the Phthalazines: To the solution of the 1,2-diacylbenzenes (0.5 mmol) in ethanol (4 mL) was added hydrazine hydrate (2.5 mmol), and the resulting mixture was heated at reflux for 6 h under nitrogen. After cooling to room temperature, ethanol was removed under vacuum to give the crude product, which was purified by silica gel column chromatography (ethyl acetate, hexane, and methanol) to give the phthalazines.

1-(4-Methoxyphenyl)-4-methylphthalazine (31a): Brown solid (95% yield); m.p. 48–50 °C. ^1H NMR (500 MHz, $CDCl_3$): δ = 3.05 (s, 3 H, CH_3), 3.83 (s, 3 H, OCH_3), 7.07 (d, J = 7.6 Hz, 2 H, Ar), 7.68 (d, J = 7.6 Hz, 2 H, Ar), 7.86–8.00 (m, 2 H, Ar), 8.11–8.26 (m, 2 H, Ar) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.7, 55.5, 114.1, 124.9, 125.4, 126.9, 127.1, 128.3, 131.5, 132.3, 132.4, 156.3, 159.0, 160.7 ppm. HRMS (ESI): calcd. for $C_{16}H_{15}N_2O$ $[M + H]^+$ 251.1184; found 251.1182.

1-(3,4-Dimethoxyphenyl)-4-methylphthalazine (31b): Brown solid (96% yield); m.p. 138–140 °C. ^1H NMR (500 MHz, $CDCl_3$): δ = 3.05 (s, 3 H, CH_3), 3.88, 3.91 (2 s, 6 H, 2 OCH_3), 6.97 (d, J = 8.0 Hz, 1 H, Ar), 7.19–7.22 (m, 1 H, Ar), 7.28 (s, 1 H, Ar), 7.86–7.90 (m, 2 H, Ar), 8.13 (d, J = 8.0 Hz, 2 H, Ar) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.4, 56.20, 56.25, 111.0, 113.4, 123.3, 125.2, 125.6, 127.2, 127.3, 132.6, 132.8, 149.4, 150.5, 156.6, 159.3 ppm. HRMS (ESI): calcd. for $C_{17}H_{17}N_2O_2$ $[M + H]^+$ 281.1290; found 281.1128.

1-Methyl-4-(3,4,5-trimethoxyphenyl)phthalazines (31c): Light yellow solid (94% yield); m.p. 124–126 °C. ^1H NMR (500 MHz, $CDCl_3$): δ = 3.04 (s, 3 H, CH_3), 3.89, 3.92 (2 s, 9 H, 3 OCH_3), 6.93 (s, 2 H, Ar), 7.84–7.93 (m, 2 H, Ar), 8.13 (t, 2 H, Ar) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.0 (CH_3), 56.4 (OCH_3), 61.0 (OCH_3), 107.6 (CH), 124.7 (CH), 125.2 (C), 126.7 (C), 126.8 (CH), 131.9 (C), 132.0 (CH), 132.1 (CH), 139.0 (C), 153.4 (C), 156.6 (C), 159.1 (C) ppm. HRMS (ESI): calcd. for $C_{18}H_{19}N_2O_3$ $[M + H]^+$ 311.1396; found 311.1411.

1-Methyl-4-(*p*-tolyl)phthalazines (31d): Light brown solid (94% yield); m.p. 110–112 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.46 (s, 3 H, CH_3), 3.05 (s, 3 H, CH_3), 7.36 (d, J = 8.0 Hz, 2 H, Ar), 7.62 (d, J = 8.0 Hz, 2 H, Ar), 7.81 (t, J = 7.6 Hz, 1 H, Ar), 7.89 (t, J = 8.0 Hz, 1 H, Ar), 8.07 (d, J = 8.4 Hz, 1 H, Ar), 8.13 (d, J = 8.0 Hz, 1 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.9, 21.5, 124.7, 125.3, 126.8, 127.6, 129.3, 130.1, 131.8, 131.9, 133.7, 133.2, 156.4, 159.3 ppm. HRMS (ESI): calcd. for $C_{16}H_{15}N_2$ $[M + H]^+$ 235.1235; found 235.1238.

1-(4-Chlorophenyl)-4-methylphthalazine (31e): Light yellow solid (96% yield); m.p. 116–118 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.06 (s, 3 H, CH_3), 7.54 (d, 2 H, Ar), 7.68 (d, J = 7.2 Hz, 2 H, Ar), 7.86 (d, J = 6.8 Hz, 1 H, Ar), 7.93 (d, J = 6.8 Hz, 1 H, Ar), 8.01 (d, J = 6.8 Hz, 1 H, Ar), 8.16 (d, J = 7.6 Hz, 1 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.1, 124.9, 126.5, 128.9, 131.5, 132.2, 132.3, 135.0, 135.6 ppm. HRMS (ESI): calcd. for $C_{15}H_{12}N_2Cl$ $[M + H]^+$ 255.0689; found 255.0693.

6,7-Dimethoxy-1-(4-methoxyphenyl)-4-methylphthalazine (31f): Light green solid (93% yield); m.p. 118–120 °C. ^1H NMR (500 MHz, $CDCl_3$): δ = 2.99 (s, 3 H, CH_3), 3.90 (s, 3 H, OCH_3), 3.92 (s, 3 H, OCH_3), 4.10 (s, 3 H, OCH_3), 7.08 (d, J = 8.5 Hz, 2 H, Ar), 7.28 (d, J = 9.5 Hz, 1 H, Ar), 7.35 (d, J = 6.0 Hz, 1 H, Ar), 7.68 (d, J = 9.0 Hz, 2 H, Ar) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.0, 55.3, 56.3, 56.4, 103.2, 105.3, 114.2, 121.9, 128.4, 129.3, 131.2, 153.4, 154.5, 157.5, 160.5 ppm. HRMS (ESI): calcd. for $C_{18}H_{19}N_2O_3$ $[M + H]^+$ 311.1382; found 311.1396.

1-(3,4-Dimethoxyphenyl)-6,7-dimethoxy-4-methylphthalazine (31g): Light yellow solid (94% yield); m.p. 220–222 °C. ^1H NMR: (400 MHz, $CDCl_3$): δ = 2.97 (s, 3 H, CH_3), 3.91, 3.93, 3.97, 4.09 (4 s, 12 H, 4 OCH_3), 7.02 (d, 1 H, Ar), 7.26–7.29 (m, 2 H, Ar), 7.32 (d, J = 1.6 Hz, 1 H, Ar), 7.38 (s, 1 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.1, 56.1, 56.3, 56.4, 103.1, 105.2, 111.0, 113.1, 121.7, 122.5, 123.4, 129.7, 149.2, 149.8, 153.2, 153.3, 154.6, 157.4 ppm. HRMS (ESI): calcd. for $C_{19}H_{21}N_2O_4$ $[M + H]^+$ 341.1501; found 341.1505.

6,7-Dimethoxy-1-methyl-4-(3,4,5-trimethoxyphenyl)phthalazines (31h): Light brown crystalline solid (95% yield); m.p. 115–118 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.03 (s, 3 H, CH_3), 3.94 (s, 6 H, 2 OCH_3), 3.97, 3.99, 4.15 (3 s, 9 H, 3 OCH_3), 6.99 (s, 2 H, Ar), 7.32 (d, J = 9.2 Hz, 2 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.0, 56.40, 56.44, 56.5, 61.1, 101.4, 103.1, 105.1, 107.2, 121.7, 123.4, 132.4, 138.8, 153.44, 153.48, 154.9, 157.6 ppm. HRMS (ESI): calcd. for $C_{20}H_{23}N_2O_5$ $[M + H]^+$ 371.1607; found 371.1625.

5-(3,4-Dimethoxyphenyl)-8-methyl-[1,3]dioxolo[4,5-*g*]phthalazines (31i): Brown solid (96% yield); m.p. 195–197 °C. ^1H NMR: (400 MHz, $CDCl_3$): δ = 2.94 (s, 3 H, CH_3), 3.94, 3.97 (2 s, 6 H, OCH_3), 6.17 (s, 2 H, OCH_2), 7.02 (s, 1 H, Ar), 7.15–7.50 (m, 4 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.3, 56.1, 101.4, 102.4, 103.4, 110.9, 113.2, 122.7, 123.2, 125.1, 129.6, 149.2, 149.9, 151.5, 155.1 ppm. HRMS (ESI): calcd. for $C_{18}H_{17}N_2O_4$ $[M + H]^+$ 325.1190; found 325.1190.

5-Methyl-8-(3,4,5-trimethoxyphenyl)-[1,3]dioxolo[4,5-*g*]phthalazines (31j): Brown solid (95% yield); m.p. 181–183 °C. ^1H NMR: (400 MHz, $CDCl_3$): δ = 2.93 (s, 3 H, CH_3), 3.88 (s, 6 H, 2 OCH_3), 3.92 (s, 3 H, OCH_3), 6.17 (s, 2 H, OCH_2), 6.87 (s, 2 H, Ar), 7.34 (d, J = 6.4 Hz, 2 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.3, 56.4, 61.1, 101.4, 102.4, 103.2, 107.3, 123.4, 124.9, 132.4, 151.1, 151.6, 153.4, 155.4, 158.2 ppm. HRMS (ESI): calcd. for $C_{19}H_{19}N_2O_5$ $[M + H]^+$ 355.1294; found 355.1288.

Biological Assays

MTT Assays with Mammalian Cells: MTT assays were used to measure the influence of the compounds on the propagation and

viability of [L]-929 mouse fibroblasts (DSMZ ACC2) and KB-3–1 (DSMZ ACC 158) in 96-well plates. Cells are able to reduce MTT (Sigma) to a violet formazan product, and the resulting purple color gives a measure of the metabolic activity in each well. Cells were kept in a DME medium that was supplemented with 10% FBS. For the five-day experiments, serial dilutions (60 μL) of the test compounds were added to a cell suspension of (50,000/mL, 120 μL). In a short time (1 d), the experiments with the serial dilutions (60 μL) of the test compounds were added to the cell culture (120 μL) after the cells had already formed a confluent layer. Blank and solvent controls were incubated under identical conditions. After 1 or 5 d, MTT (20 μL) in phosphate-buffered saline (PBS) was added to give a final concentration of 0.5 mg/mL. After 2 h, the precipitate of formazan crystals was centrifuged, and the supernatant was discarded. The precipitate was washed with PBS (100 μL) and then dissolved in 2-propanol that contained 0.4% hydrochloric acid (100 μL). The microplates were gently shaken for 20 min to ensure a complete dissolution of the formazan and finally measured at 590 nm using a plate reader. All experiments were carried out in two parallel experiments, and the percentage of viable cells was calculated as the mean with respect to the controls set to 100%. An IC_{50} value was determined from the resulting dose-response curves.

Fluorescence Staining: PtK2 cells (ATCC CCL-56) were grown on glass coverslips (13 mm diameter) in four-well plates. Exponentially growing cells were incubated with the compounds for 16 h. Cells were fixed with cold (–20 °C) acetone/methanol (1:1) for 10 min (in the case of microtubule and ER staining) or with 3.7% formaldehyde followed by an incubation in 0.1% Triton-X (in the case of F-actin staining). For labeling the microtubules, cells were first incubated with a mouse antibody against α-tubulin (1:500, Sigma), and for ER staining, cells were first incubated with a rat GRP-94 antibody (1:1000; Pierce) and then with a secondary goat anti-mouse or anti-rat IgG antibody conjugated with Alexa Fluor 488 (1:200, Molecular Probes) at 37 °C for 45 min. F-actin was labelled using Alexa Fluor 488 conjugated phalloidin (1 μg/mL, Molecular Probes). The nuclei and chromosomes were stained with DAPI (1 μg/mL). The cells were washed with PBS between different incubations. The coverslips were mounted using Prolong Antifade (Molecular Probes) and then viewed with a Zeiss Axiophot fluorescence microscope using the appropriate filter sets.

Supporting Information (see footnote on the first page of this article): Copies of the ^1H and ^{13}C NMR spectra and HRMS spectra of all compounds are available

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