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Regiospecific synthesis of isopestacin, a naturally occurring isobenzofuranone antioxidant

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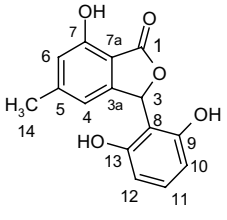
Abstract—A DBU promoted aldol cyclocondensation of hydroxyisobenzofuranone **15** with cyclohexane-1,3-dione, followed by aromatization has resulted in the first short synthesis of isopestacin (**1**).

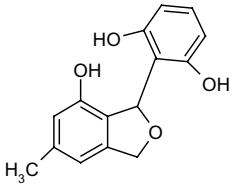
Isopestacin (**1**), an isobenzofuranone natural product was isolated in 2002 by Strobel and co-workers from culture broths of the endophytic fungus *Pestalotiopsis microspora*.[1] Its structure was determined by analysis of proton and carbon NMR data, and confirmed by X-ray crystallography. It is the first member of the isobenzofuranone family of natural products that contains a substituted benzene ring at C-3 of the benzofuranone ring. Strikingly, the resorcinol moiety is attached to the isobenzofuranone skeleton through its C-2 position. Though the structure of isopestacin contains a chiral center, the natural product isolated was composed of a racemic mixture. This compound possesses antifungal activity, and acts as an antioxidant toward both superoxide radicals and hydroxy free radicals, the activity being comparable to vitamin C.

The synthetic challenge posed by isopestacin along with its structural resemblances to pestacin (**2**),[2] recently isolated from the same fungus as a potent antioxidant, cryphonectric acid (**3**),[3] and the aromatic subunit of the PKC inhibitor balanol[4] prompted us to initiate a synthetic program on isobenzofuranone natural products. Herein, we report the first regiospecific synthesis of isopestacin (**1**), and the methodology for the generation of simple analogs thereof.

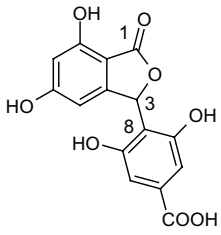
In principle, 3-aryl substituted isobenzofuranones can be prepared either by acid catalyzed condensation[5] of 3-hydroxybenzofuranones with arenes or by addition[6] of *ortho*-lithiated aromatics to aromatic aldehydes. However, the former approach is not adaptable in the present context due to regiochemical problems. For instance,



isopestacin (**1**)



pestacin (**2**)



cryphonectric acid (**3**)

Keywords: Isopestacin; Isobenzofuranone; Benzene-1,3-diol; Aromatization.
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the reaction of resorcinol with 3-hydroxybenzofuranone in the presence of an acid catalyst is reported to give the product in which the resorcinol moiety is substituted at C-4 whereas the synthesis of isopestacin (**1**) requires substitution at C-2. The possibility of using the *ortho*-lithiation methodology was avoided in view of the requirement for a protection–deprotection protocol. Alternatively, we conceived the aldol reaction of phthalaldehydic acids with cyclohexane-1,3-dione as a key-step to permit regiospecificity in the synthesis.

Phthalaldehydic acid is known to exist in the isobenzofuranone form **4**, and reacts with dimedone in refluxing ethanol containing piperidine to yield 3-(5,5-dimethylcyclohexane-1,3-dion-2-yl)benzofuranone.[7] We observed that the same reaction could be effected more efficiently in the presence of DBU at room temperature. Accordingly, the reaction was generalized for a few simple β-keto carbonyl compounds. The results are summarized in Table 1. The products **5a**,[7a] **6a**,**b**,[7b] and **7**,[7c] which existed in both keto and enol forms, were fully characterized as their acetates or enol ethers, that is **5b**, **6c**, **9b**.[8] When applied to cyclohexane-1,3-dione, isobenzofuranone **4** gave the adduct **9a** in 70% yield. This was also prepared by reacting 3-bromophthalide with cyclohexane-1,3-dione in the presence of 1 equiv of DBU in acetonitrile.

The next most important task was to aromatize the adduct **9a**. Of the many possibilities, we chose to investigate the action of I_2/CH_3OH[9] on **9a**. The reaction provided the desired dimethoxy aromatic product **11** (Scheme 1). As anticipated, attempted demethylation of **11** to the corresponding phenol **12** by $AlCl_3$ or BBr_3 proved to be difficult. For direct conversion of **9a** to phenol **12**, we turned our attention to the use of $CuCl_2$/LiCl,[10] a system that has been occasionally reported for oxidative aromatization of cyclohexenones. Treatment of **9a** with $CuCl_2$/LiCl afforded **12** in 45% yield, along with an unidentified product as a minor component. A remarkable improvement in the yield of the oxidative aromatization was noted with $Hg(OAc)_2$/NaOAc[11] as

Table 1. Reaction of phthalaldehydic acids with 1,3-dicarbonyl compounds

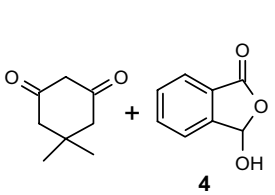
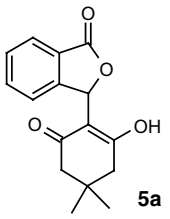
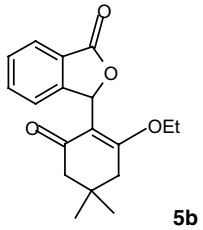
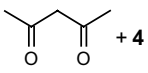
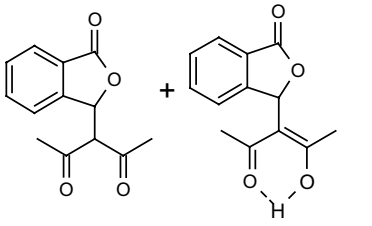
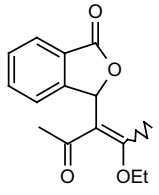
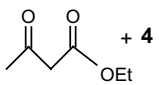
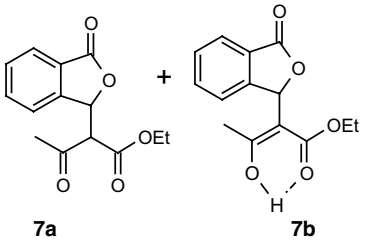
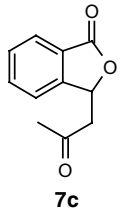
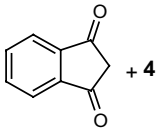
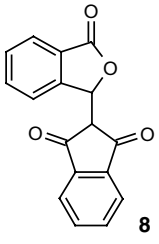
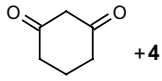
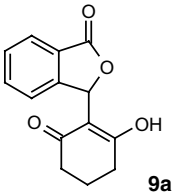
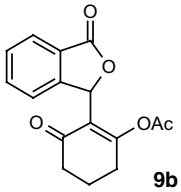
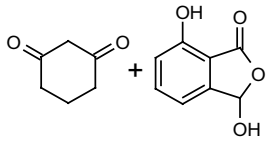
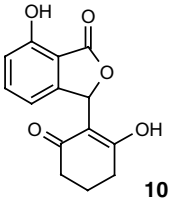
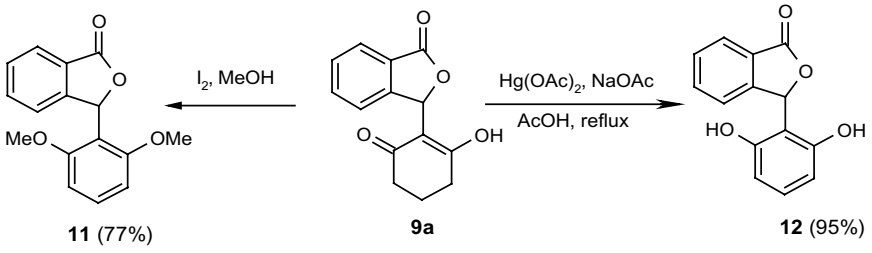
Starting materials	Product (s)	% Yield	Derivative
		95	
		81	
		55	
		86	

Table 1 (*continued*)

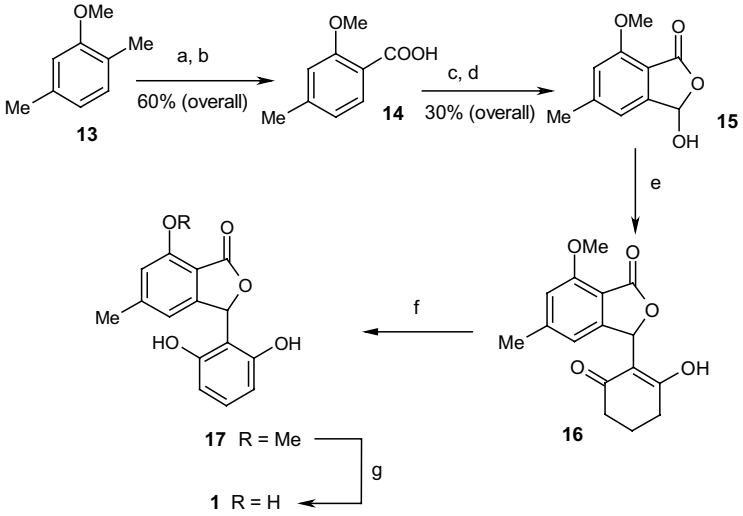
Starting materials	Product (s)	% Yield	Derivative
	 **9a**	70	 **9b**
	 **10**	74	



Scheme 1.

oxidizing agent and the desired product **12** was obtained in an excellent 95% yield.

Having standardized the model study, we proceeded to perform the synthesis of isopestacin (**1**) starting from commercially available 2,5-dimethylanisole (**13**) (Scheme 2). This was converted to the hydroxybenzofuranone **15**[12] in four steps via directed *ortho*-lithiation of the *N*,*N*-diethylamide of acid **14**, which, in turn, was prepared in two steps from anisole **13**. Condensation of **15** with cyclohexane-1,3-dione in refluxing ethanol containing 1.5 equiv of DBU furnished **16** in 60% yield. Oxidative aromatization of **16** with $Hg(OAc)_2$/NaOAc yielded **17** (93%). Room temperature demethylation of



Scheme 2. Reagents and conditions: (a) $K_2S_2O_8$, $CuSO_4{\cdot}5H_2O$, CH_3CN/H_2O; (b) NH_2SO_3H, $NaClO_2$, THF/H_2O; (c) $SOCl_2$, reflux; Et_2NH, CH_2Cl_2; (d) *sec*-BuLi, TMEDA, DMF; HCl, AcOH; (e) 1,3-cyclohexanedione, DBU, CH_3CN, reflux, 60%; (f) $Hg(OAc)_2$, NaOAc, AcOH, reflux, 93%; (g) $AlCl_3$, CH_2Cl_2, 65%.

Table 2. Comparison of the NMR data of synthetic isopestacin with those of the natural product

Position	1	3	3a	4	5	6	7	7a	8	9, 13	10	11	12	14
^{1}H data of the natural product		6.92		6.52		6.64					6.29 (d) $J = 8.2$ Hz	6.96 (t) $J = 8.2$ Hz	6.27 (d) $J = 8.2$ Hz	2.3
^{1}H data of the synthetic product		6.93		6.53		6.66					6.29 (d) $J = 8.1$ Hz	6.98 (t) $J = 8.1$ Hz	6.29 (d) $J = 8.1$ Hz	2.32
^{13}C data of the natural product	173.84	77.24	154.87	114.54	149.00	116.53	157.33	111.71	110.32	158.95	107.96	131.53	107.96	22.14
^{13}C data of the synthetic product	173.70	77.05	154.79	114.38	148.87	116.37	157.19	111.55	110.10	158.82	107.76	131.41	107.76	22.01

17[8] with anhydrous $AlCl_3$[13] in dichloromethane provided isopestacin (**1**) (mp: 269–270 °C; lit.[1] mp: 218–220 °C) in 65% yield. The spectroscopic data (Table 2) of the synthetic material were in complete agreement with those[1] of the natural product. Additionally, the TLC behavior of the synthetic compound matched that of an authentic sample of the natural product.

In conclusion, the first synthesis of isopestacin (**1**) has been completed in a regiospecific manner starting from 2,5-dimethylanisole (**13**). The methodology developed, that is cyclocondensation of phthalaldehydic acids with cyclic 1,3-diones followed by oxidative aromatization should provide an access to a wide variety of isopestacin analogs. The feasibility of introducing asymmetric induction in the cyclocondensation step by the use of enantiomerically pure amine bases is being explored.

Acknowledgements

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8. The new compounds gave satisfactory elemental analysis, EIMS and NMR data. Selected spectral data: compound **8**: Mp 215 °C; ν_{max} (KBr, cm^{-1}) 1750; ^{1}H NMR (d_6-DMSO + $CDCl_3$, 200 MHz): δ 8.05–7.77 (m, 4H), 7.72 (t, 2H, $J = 7.30$), 7.59 (t, 1H, $J = 7.30$), 7.49 (d, 1H, $J = 7.40$), 6.18 (d, 1H, $J = 2.3$), 3.67 (d, 1H, $J = 2.3$). ^{13}C NMR (d_6-DMSO, 125 MHz): δ 197.98, 196.55, 170.28, 148.79, 143.01, 142.62, 137.42, 135.39, 131.46, 130.40, 126.10, 125.81, 124.04, 123.83, 123.68, 78.36, 55.92.
Compound **9b**: Mp 125 °C; ν_{max} (KBr, cm^{-1}) 1752; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.90 (d, 1H, $J = 7.3$), 7.63 (dt, 1H, $J = 7.3$, 1.0), 7.51 (t, 1H, $J = 7.3$), 7.28 (dd, 1H, $J = 7.3$, 1.0), 6.60 (s, 1H), 2.70–2.50 (m, 4H), 2.15–1.95 (m, 2H), 1.83 (s, 3H).
Compound **10**: Mp 250 °C; IR ν_{max} (KBr, cm^{-1}) 1732; ^{1}H NMR (d_6-DMSO + $CDCl_3$, 200 MHz): δ 7.41 (s, 1H), 7.06 (t, 1H, $J = 7.8$), 6.59 (d, 1H, $J = 7.8$), 6.42 (d, 1H, $J = 7.8$), 5.08 (s, 1H), 2.63–2.40 (m, 2H), 2.30–2.15 (m, 2H), 2.0–1.75 (m, 2H). ^{13}C NMR (d_6-DMSO, 50 MHz): δ 196.50, 169.12, 169.02, 164.79, 156.18, 154.79, 153.11, 141.56, 135.37, 128.81, 122.79, 122.26, 114.79, 114.43, 113.57, 112.45, 111.47, 109.74, 72.99, 36.49, 32.93, 31.38, 26.58, 20.20, 19.56 (mixture of keto and enol forms).
Compound **17**: Mp 304 °C; IR ν_{max} (KBr, cm^{-1}) 1723; ^{1}H NMR (d_6-DMSO + $CDCl_3$, 200 MHz): δ 8.9 (br s, 1H), 6.82 (t, 1H, $J = 8.0$), 6.77 (s, 1H), 6.61 (s, 1H), 6.55 (s, 1H), 6.21 (d, 2H, $J = 8.0$), 3.87 (s, 3H), 2.28 (s, 3H). ^{13}C NMR (d_6-DMSO, 50 MHz): δ 168.94, 156.98, 153.80, 146.34, 129.56, 113.75, 111.70, 110.44, 108.47, 106.44, 73.70, 55.20, 21.72.
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