

SYNTHESIS OF VARIOUS SUBSTITUTED DIBENZO[*b,d*]PYRANONES
INCLUDING AMINO ACID DERIVATIVES BY $S_{RN}1$ METHODOLOGY

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Abstract - An easy preparation of the title compounds involving a $S_{RN}1$ ortho-arylation of phenolates by *o*-bromobenzonitrile followed by SiO_2 -catalysed lactonisation is described. Activated or not activated phenols are efficient. Access to benzonaphthopyranones is exemplified by the reactions with 2-naphtholate. Reactions with chiral *p*-hydroxyphenylamino acid derivatives are also reported.

A large number of synthetic routes have been reported for the preparation of dibenzopyranone or benzonaphthopyranone skeleton.¹ The research of new methodology, however, remains an active area;²⁻⁵ the biological activity of compounds such as the antibiotics of the gilvocarcin group which have promising antitumor activity⁶ or the derivatives of ellagic acid which show inhibition property of mutagenicity of aromatic hydrocarbons,⁷ has stimulated interest in this class of compounds.

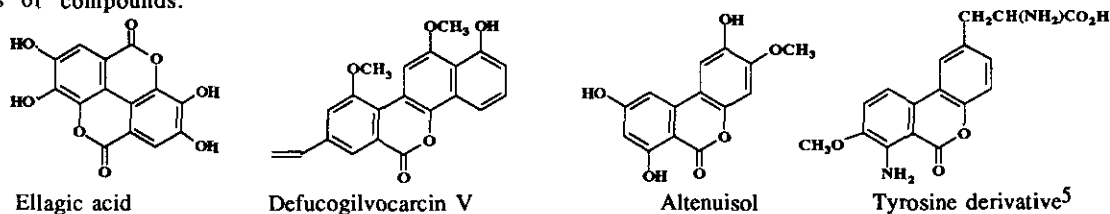
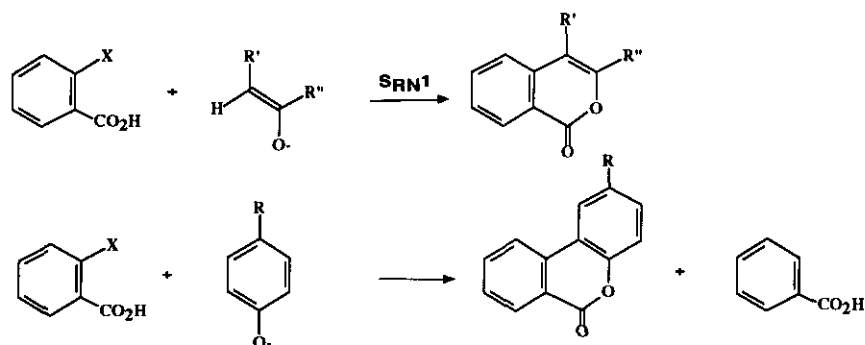


Figure 1. Examples of natural compounds with arylbenzopyranone skeleton.

In the course of our work on heterocyclic compounds synthesis, we had previously reported an efficient access to isocoumarin type compounds by photostimulated $S_{RN}1$ reactions of linear⁸ or cyclic⁹ ketone enolates with *o*-halobenzoic acid (Scheme 1).

Aryloxides have been demonstrated to act as efficient C-nucleophiles in $S_{RN}1$ reactions¹⁰⁻¹² and we have reported straightforward synthesis of various substituted hydroxybiaryl derivatives.¹¹ However, our attempts to prepare dibenzopyranones by reacting *o*-halobenzoic acid with phenolates were disappointing. For example, the photostimulated reaction of *o*-iodobenzoic acid with *p*-*tert*-butylphenolate in liquid ammonia or in DMSO (20°C) led in both cases to only small amounts (5%) of the expected dibenzo[*b,d*]pyran-6-one, while the major reaction was the dehalogenation of the substrate (Scheme 1).



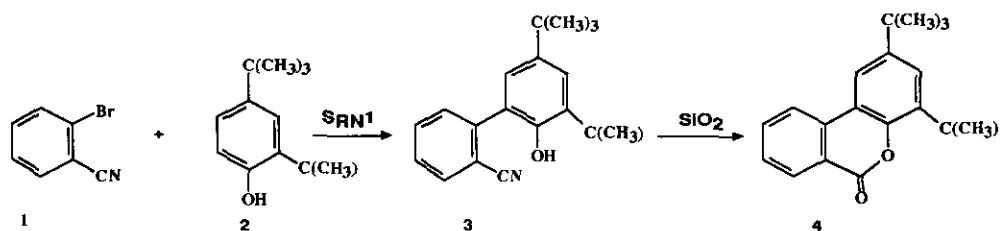
Scheme 1

We then turned our investigations to $S_{RN}1$ reactions of *o*-halobenzonitriles and formation of the lactonic ring by reaction between a cyano and a hydroxy group, as earlier described for *o*-hydroxybenzylidenearylacetonitriles¹³ or for 2-(*o*-hydroxybenzyl)benzonitriles,⁴ the latter of which were obtained *via* $S_{RN}1$ arylation of phenols by cyanobenzyl azosulfides.

We report herein a general and regiospecific preparation of the title compounds by reactions proceeding *via* the photostimulated $S_{RN}1$ mechanism¹⁴ between *o*-bromobenzonitriles and various phenolates including tyrosine and hydroxyphenylglycine derivatives.

Phenolates and naphtholate as nucleophiles

The photostimulated reaction of 2-bromobenzonitrile (1) with the phenolate of 2,4-ditert-butylphenol (2) (*tert*-BuOK in NH_3) led in 1 h to the cyanobiaryl derivative (3). This compound was quantitatively converted into the dibenzopyranone (4) through purification on silica gel or alumina column as well as on thin layer chromatography.

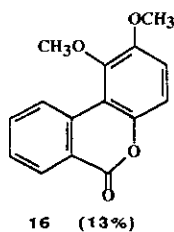
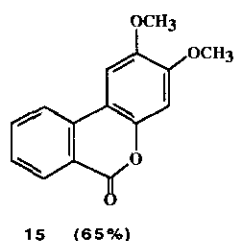


Scheme 2

To determine the scope and the limitations of this methodology, various *para*-substituted phenolates were used. The results of the preparation of the corresponding dibenzo[*b,d*]pyran-6-ones are summarized in Table 1. Moderate to good yields (50 to 86%) were observed for phenols bearing either electron-donating (C(CH₃)₃, OCH₃) or electron-withdrawing groups (OCF₃, F, CN) on *para* position.

Table 1 : Preparation of dibenzo[*b,d*]pyran-6-ones

			yield
1	2	4	78%
1	5	6	80%
1	7	8 ¹⁷	86%
1	9	10	49%
1	11	12	51%
1	13		0%
1	14	15+16	78%

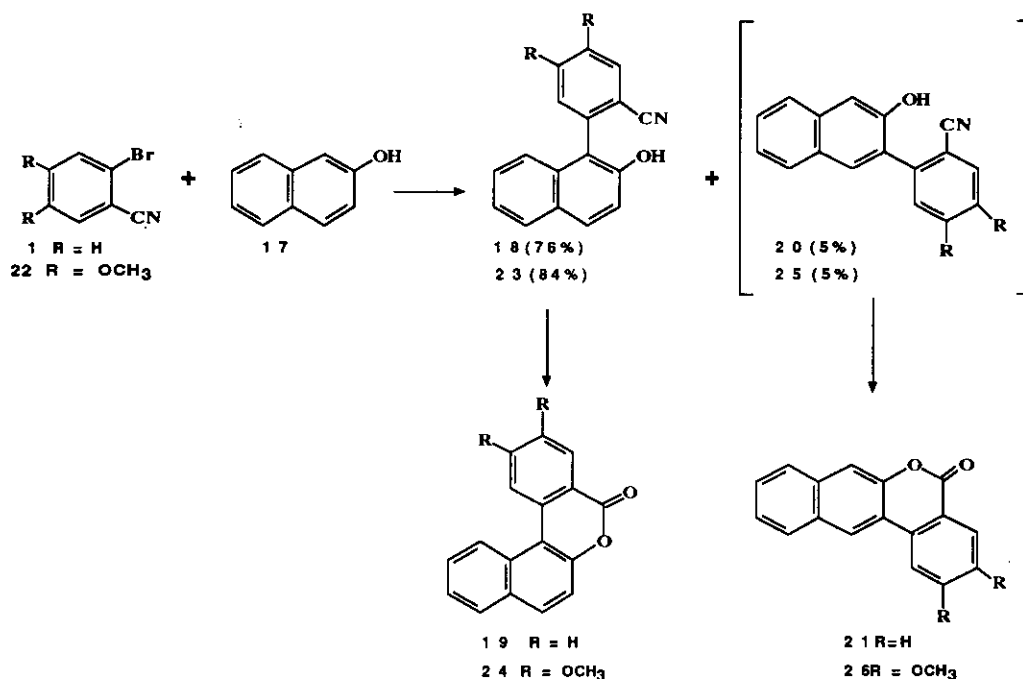


The only exception is the reaction with the phenol (13) which carries a *p*-nitro group : no coupling product was isolated after 7 h irradiation and both of the reactants were recovered quantitatively. One possible explanation is that, under the above described conditions, *p*-nitrophenol acted as an electron sink rather than as a nucleophile. Aromatic nitro compounds are indeed known to be good electron acceptors and able to quench the electron transfer in $S_{RN}1$ reaction.¹⁴

When the two *ortho* positions of the phenolate are available, the yields of disubstitution remain low. The major side reaction which in some cases lowered the yields of coupling products is the reduction of the halobenzonitrile substrate.¹⁴

As far as the regioselectivity was concerned, it is well established that *ipso* substitution occurs invariably in aromatic $S_{RN}1$ reactions.¹⁴ With respect to the aryloxy anion, while *para* versus *ortho* substitution has been addressed, no report has appeared on the relative reactivity of the two *ortho* positions. We found that coupling occurred predominantly at the less hindered *ortho* position when they were differentiated sterically: as can be seen from the Table 1, the reaction of 3,4-dimethoxyphenol (14) with *o*-bromobenzonitrile afforded the 2,3-dimethoxydibenzopyran-6-one (15) and the 1,2-dimethoxy derivative (16) in yields of 65% and 13% respectively.

As a route to benzonaphthopyranone, the reaction of 1 with the 2-naphtholate (17) was investigated (Scheme 3). Under identical conditions to those previously used for phenolates reactions, a mixture of two products (18)(76%) and (21)(5%) was obtained. The minor product was the benzonaphthopyranone resulting from the carbon-carbon coupling on the less nucleophilic site C3 of the naphtholate. The major one is the 1-(*o*-cyanophenyl)-2-hydroxynaphthalene which remains stable when treated with silica gel at room temperature and can be purified by chromatography. A similar observation was made in the reaction of 3,4-dimethoxy-6-bromobenzonitrile (22) with 17 : 23 and 26 were isolated in yields of 84% and 5% respectively. Compounds (18) and (23) can only be lactonised by refluxing the $CHCl_3$ solution in presence of SiO_2 . Under this condition, the desired benzonaphthopyranones (19) and (24) were obtained quantitatively. It may be understood on steric grounds that the compounds (20) and (25) smoothly cyclized on SiO_2 chromatography while 18 and 23 required forcing conditions; 18 and 23 might need a heat activation in order to adopt a correct conformation required for the intramolecular attack of the hydroxy group on the adjacent cyano group.



Scheme 3

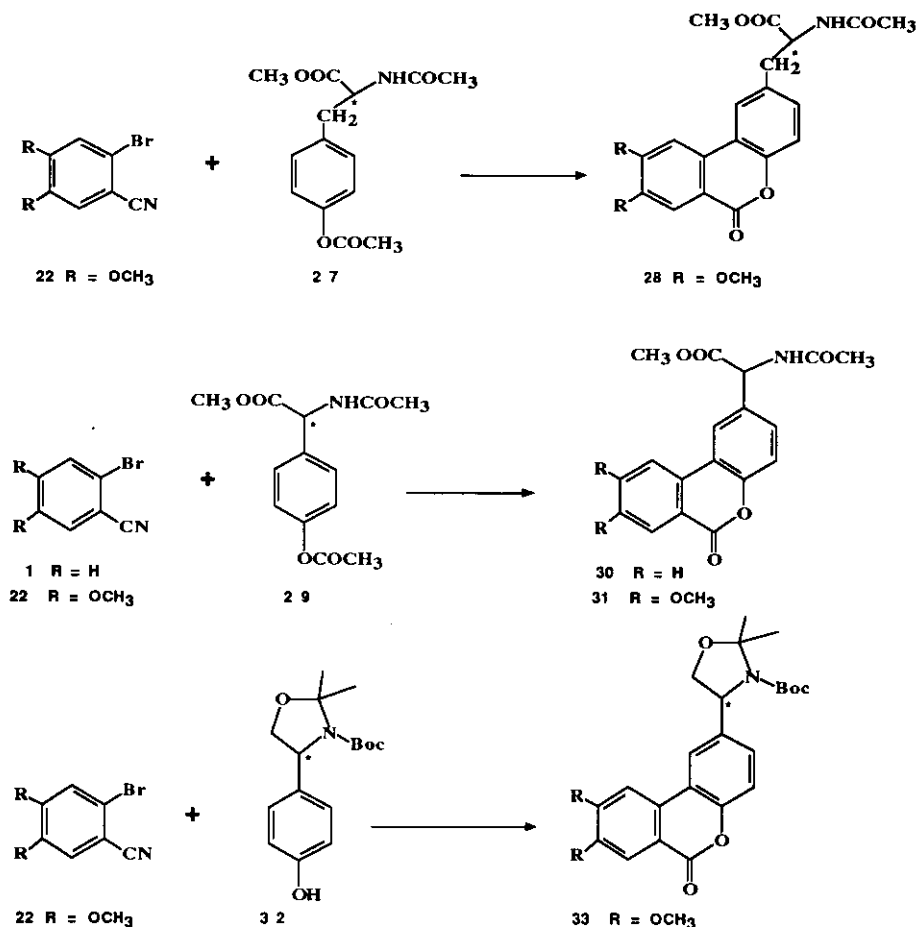
Phenolates from amino acids as nucleophiles

As a further extension, we then applied our methodology to reactions involving phenolates derived from hydroxyphenyl amino acids, namely tyrosine and *p*-hydroxyphenylglycine.

The first question which needs to be addressed is the racemization problem of amino acids. In a control experiment, we learned that (l)-tyrosine, protected as *N,O*-diacetyl methyl ester (**27**), is racemization free under the standard S_{RN}1 reaction conditions. In addition, we observed that, under the alkaline S_{RN}1 conditions (NH₃, *tert*-BuOK), the *O*-acetyl group was readily removed. Thus, **27** can be used directly as a masked nucleophile. As a result, the reaction of 3,4-dimethoxy-6-bromobenzonitrile with **27**, followed by usual work-up led to the optically active dibenzo[*b,d*]pyran-6-one (**28**) ([α]_D = +44.7°) in 52% yield.

Racemization of phenylglycine derivatives is an usual problem and it was reported¹⁵ that, even in liquid ammonia, *N*-Boc-hydroxyiodophenylglycine methyl ester is completely racemized within 1 h and expectedly, the *N*-acetyl methyl ester of (d)-hydroxyphenylglycine (**29**) ([α]_D = -144°) was observed to be racemized under the standard S_{RN}1 conditions. Thus, the dibenzopyranones (**30**) and (**31**) isolated in 65% and 79% yields respectively from reactions with the substrates (**1**) or (**22**) were racemic compounds.

To overcome this racemization problem, the oxazolidine derivative of (d)-*p*-hydroxyphenylglycine (**32**) has been prepared. In a blank experiment under $S_{RN}1$ conditions, this product remained chemically stable and its optical rotation value was unchanged. The $S_{RN}1$ reaction with 2-bromo-4,5-dimethoxybenzonitrile (**22**) gave the substituted dibenzopyranone (**33**) ($[\alpha]_D^{25} = +94^\circ$) in 77% yield after purification. The amino acid function might be easily recovered after reaction by classical methods.¹⁶



Scheme 4

A variety of dibenzo[*b,d*]pyran-6-ones, including chiral amino acid derivatives, and benzonaphthopyranones are efficiently prepared by our methodology. Advantages of this photostimulated $S_{RN}1$ arylation of phenols by *o*-halobenzonitriles include ease of operation, good chemical yields with conservation of chirality of amino acid derivatives and few restrictions concerning the choice of phenol.

EXPERIMENTAL

Melting points were measured on a Reichert melting point apparatus and are uncorrected. Low resolution mass spectra (EI) were obtained on a AEI MS 50 spectrometer. Infrared spectra were recorded in CHCl_3 on a Nicolet 205 spectrophotometer. Optical rotations were recorded at 20°C with a Perkin Elmer 241 polarimeter. ^1H Nmr spectra (in CDCl_3) were recorded on a Bruker WP 200 SY spectrometer. Chemical shifts from tetramethylsilane are given in ppm. Purifications were achieved by preparative thin layer chromatography or by column chromatography on SiO_2 .

General Procedure

In a 100 ml two-necked Pyrex flask containing freshly sublimed *tert*-BuOK (336 mg, 3 mmol), liquid ammonia (50 ml) was condensed through a dry ice condenser cooled at -78°C. Under argon atmosphere, the phenolic compound (3 mmol) and the substrate (1) or (22) (1 mmol) were successively introduced. External irradiation of the ammonia solution (-33°C) was performed by a high pressure mercury lamp (Hanovia 400 W) and the course of the reaction was monitored by analyzing aliquots (tlc). After consumption of the substrate, the solvent was evaporated in a well ventilated hood. 0.1 N HCl (100 ml) was added and the aqueous phase was extracted by ethyl acetate (2 x 50 ml). After evaporation, the residue was dissolved in CH_2Cl_2 , 1 g of SiO_2 was added and stirring was kept up overnight at room temperature. Silica gel was removed by filtration, washed by acetone and the products were separated by thin layer chromatography.

2,4-Di-*tert*-butyldibenzol**b,d**pyran-6-one (4) : Yield 78%; mp 163°C ; ms m/z 308 (M^+), 293; ir 1730 cm^{-1} (C=O); ^1H nmr δ 1.40 (s, 9H, 3 CH_3), 1.50 (s, 9H, 3 CH_3), 7.43 (m, 2H), 7.67 (t, J=8 Hz, 1H), 7.87 (s, 1H), 8.03 (d, J=8 Hz, 1H), 8.40 (d, J=8 Hz, 1H). Anal. Calcd for $\text{C}_{21}\text{H}_{24}\text{O}_2$: C, 81.82; H, 7.79. Found: C, 81.84; H, 7.83.

2-*tert*-Butyldibenzol**b,d**pyran-6-one (6) : Yield 80 %; mp 106-107°C; ms m/z 252 (M^+), 237; ir 1729 cm^{-1} ; ^1H nmr δ 1.45 (s, 9H, 3 CH_3), 7.28 (d, J=8 Hz, 1H), 7.54 (t, J=8 Hz, 1H), 7.51 (d, J=8 Hz, 1H), 7.80 (t, J=8 Hz, 1H), 8.03 (s, 1H), 8.14 (d, J=8 Hz, 1H), 8.36 (d, J=8 Hz 1H). Anal. Calcd for $\text{C}_{17}\text{H}_{16}\text{O}_2$: C, 80.93; H, 6.39. Found : C, 80.84; H, 6.38.

2-Trifluoromethoxydibenzol**b,d**pyran-6-one (8)¹⁷ : Yield 86%; mp 145°C; ms m/z 280 (M^+), 252; ir 1757 cm^{-1} ; ^1H nmr δ 7.30 (m, 1H), 7.40 (s, 1H), 7.65 (t, J=8 Hz, 1H), 7.90 (m, 2H), 8.10 (d, J=8 Hz, 1H), 8.40 (d, J=8 Hz 1H). Anal. Calcd for $\text{C}_{14}\text{H}_7\text{O}_3\text{F}_3$: C, 60.00; H, 2.50. Found C, 60.24; H, 2.63.

2-Fluorodibenzof[*b*]pyran-6-one (10): Yield 49%; mp 150-153°C; ms m/z 214 (M^+), 186; ir 1744 cm^{-1} ; ^1H nmr δ 7.17 (td, $J=6$ Hz, $J' \approx 2$ Hz, 1H), 7.30 (dd, $J=7$ Hz, $J'=3.5$ Hz, 1H), 7.63 (m, 2H), 7.80 (t, $J=6$ Hz, 1H), 7.97 (d, $J=6$ Hz, 1H), 8.37 (d, $J=6$ Hz, 1H). Anal. Calcd for $\text{C}_{13}\text{H}_7\text{O}_2\text{F}$: C, 72.92; H, 3.27. Found: C, 72.59; H, 3.64.

2-Cyanodibenzof[*b*]pyran-6-one (12): Yield 51%; mp 240-242°C; ms m/z 221 (M^+), 193; ir 2226 cm^{-1} (CN), 1735 (CO); ^1H nmr δ 7.47 (d, $J=8$ Hz, 1H), 7.69 (t, $J=8$ Hz, 1H), 7.75 (d, $J=8$ Hz, 1H), 7.91 (t, $J=8$ Hz, 1H), 8.10 (d, $J=8$ Hz, 1H), 8.38 (s, 1H), 8.42 (d, $J=8$ Hz, 1H). Anal. Calcd for $\text{C}_{14}\text{H}_7\text{NO}_2$: C, 76.03; H, 3.17; N, 6.33. Found: C, 75.79; H, 3.41; N, 6.33.

2,3-Dimethoxydibenzof[*b*]pyran-6-one (15): Yield 65 %; mp 176-178°C; ms m/z 256 (M^+), 241; ir 1722 cm^{-1} ; ^1H nmr δ 3.97 (s, 3H, OCH₃), 4.00 (s, 3H, OCH₃), 6.83 (s, 1H), 7.37 (s, 1H), 7.50 (t, $J=8$ Hz, 1H), 7.80 (t, $J=8$ Hz, 1H), 7.97 (d, $J=8$ Hz, 1H), 8.37 (d, $J=8$ Hz, 1H). Anal. Calcd for $\text{C}_{15}\text{H}_{12}\text{O}_4$: C, 70.33; H, 4.68. Found C, 70.44; H, 4.73.

1,2-Dimethoxyldibenzof[*b*]pyran-6-one (16): Yield 13%; mp 105-108°C; ms m/z 256 (M^+), 241; ir 1731 cm^{-1} (C=O); ^1H nmr δ 3.95 (s, 3H, OCH₃), 3.97 (s, 3H, OCH₃), 7.07-7.17 (AB system, $J=8$ Hz, 2H), 7.60 (t, $J=8$ Hz, 1H), 7.83 (t, $J=8$ Hz, 1H), 8.47 (d, $J=8$ Hz, 1H), 9.03 (d, $J=8$ Hz, 1H). Anal. Calcd for $\text{C}_{15}\text{H}_{12}\text{O}_4$: C, 70.33; H, 4.68. Found: C, 70.03; H, 5.10.

1-(2-Cyanophenyl)-2-hydroxynaphthalene (18): Yield 76%; mp 205-207°C; ms m/z 245 (M^+); ir 2240 (CN), 3606-3300 cm^{-1} (OH); ^1H nmr δ 7.20 (m, 2H), 7.36 (m, 2H), 7.60 (m, 2H), 7.83 (m, 4H).

Benzo[*d*]naphtho[*b*]pyran-8-one (19): Quantitatively formed by refluxing 18 (122 mg, 0.5 mmol) in CHCl_3 (20 ml) in presence of 1g of SiO_2 (1 g); mp 155°C; ms m/z 246 (M^+); ir 1731 cm^{-1} (C=O); ^1H nmr δ 7.45-7.70 (m, 4H), 7.90 (m, 3H), 8.50 (d, $J=8$ Hz, 1H), 8.65 (d, $J=8$ Hz, 1H), 8.75 (d, $J=8$ Hz, 1H). Anal. Calcd for $\text{C}_{17}\text{H}_{10}\text{O}_2$: C, 82.94; H, 4.06. Found: C, 82.77; H, 4.40.

Benzo[*d*]naphtho[*b*]pyran-7-one (21): Yield 5%; mp 196-197°C; ms m/z 246 (M^+); ir 1730 cm^{-1} (C=O); ^1H nmr δ 7.57 (m, 3H), 7.77 (s, 1H), 7.90 (m, 3H), 8.33 (d, $J=8$ Hz, 1H), 8.43 (d, $J=8$ Hz, 1H), 8.56 (s, 1H). Anal. Calcd for $\text{C}_{17}\text{H}_{10}\text{O}_2$: C, 82.94; H, 4.06. Found: C, 82.66; H, 4.34.

1-(2-Cyano-4,5-dimethoxyphenyl)-2-hydroxynaphthalene (23): Yield 84%; mp 196-203°C; ms m/z 305 (M^+); ir 2250 (CN), 3350-3600 cm^{-1} (OH); ^1H nmr δ 3.87 (s, 3H, OCH₃), 3.93 (s, 3H, OCH₃), 6.93 (s, 1H), 7.16-7.40 (m 5H), 7.80 (m, 2H).

10.11-Dimethoxybenzo[*d*]naphtho[*b*]pyran-8-one (24): Quantitatively formed by refluxing **23** (152 mg, 0.5 mmol) in CHCl_3 (20 ml) in presence of SiO_2 (1 g); mp 190°C; ms m/z 306 (M^+); ir 1732 cm^{-1} (C=O); ^1H nmr δ 4.03 (s, 3H, OCH₃), 4.10 (s, 3H, OCH₃), 7.46 (d, J=8 Hz, 1H), 7.56 (t, J=8 Hz, 1H), 7.67 (t, J=8 Hz, 1H), 7.83 (s, 1H), 7.85 (d, J=8 Hz, 1H), 7.94 (d, J=8 Hz, 1H), 8.02 (s, 1H), 8.71 (d, J=8 Hz, 1H). Anal. Calcd for $\text{C}_{19}\text{H}_{14}\text{O}_4$: C, 74.53; H, 4.57. Found: C, 74.43; H, 4.84.

10.11-Dimethoxybenzo[*d*]naphtho[*b*]pyran-8-one (26): Yield 5%; mp 290-292°C; ms m/z 306 (M^+); ir 1728 cm^{-1} (C=O); ^1H nmr δ 4.03 (s, 3H, OCH₃), 4.20 (s, 3H, OCH₃), 7.53 (m, 2H), 7.63 (s, 1H), 7.73 (s, 1H), 7.80 (s, 1H), 7.85 (d, J=8 Hz, 1H), 7.95 (d, J=8 Hz, 1H), 8.40 (s, 1H). Anal. Calcd for $\text{C}_{19}\text{H}_{14}\text{O}_4$: C, 74.53; H, 4.57. Found: C, 74.25; H, 4.63.

2-Acetylamino-3-(8,9-dimethoxy-6-oxo-dibenzo[*b,d*]pyranyl)propionic acid methyl ester (28): Yield 52%; mp 233-234°C. $[\alpha]_{\text{D}} = +44.74^\circ$ (c = 0.2, CHCl_3); ms m/z 399 (M^+), 340; ^1H nmr δ 2.02 (s, 3H, NCOCH₃), 3.25 (m, 2H, CH₂), 3.73 (s, 3H, CO₂CH₃), 3.98 (s, 3H, OCH₃), 4.08 (s, 3H, OCH₃), 4.98 (m, 1H, CH), 6.17 (d, J=7.5 Hz, 1H, NH), 7.13 and 7.20 (AB system, J=8 Hz, 2H), 7.37 (s, 1H), 7.67 (s, 1H), 7.74 (s, 1H). Anal. Calcd for $\text{C}_{21}\text{H}_{21}\text{NO}_7$: C, 63.18; H, 5.30; N, 3.51. Found: C, 63.25; H, 5.61; N, 3.61.

Acetylamino-(6-oxodibenzo[*b,d*]pyranyl)acetic acid methyl ester (30): Yield 65%; mp 209-210°C; ms m/z 325 (M^+) 294, 282, 266; ir 1750 cm^{-1} (C=O); ^1H nmr δ 2.05 (s, 3H, NCOCH₃), 3.75 (s, 3H, CO₂CH₃), 5.70 (d, J=7.5 Hz, CH), 6.75 (d, J=7.5 Hz, NH), 7.34 (d, J=8 Hz, 1H), 7.46 (d, J=8 Hz, 1H), 7.60 (t, J=8 Hz, 1H), 7.83 (t, J=8 Hz, 1H), 8.09 (s, 1H), 8.14 (d, J=8 Hz, 1H), 8.36 (d, J=8 Hz, 1H). Anal. Calcd for $\text{C}_{18}\text{H}_{15}\text{NO}_5$: C, 66.46; H, 4.65. Found: C, 66.16; H, 4.98.

Acetylamino-(8,9-dimethoxy-6-oxo-dibenzo[*b,d*]pyranyl)-acetic acid methyl ester (31): Yield 75%; mp 274-275°C; ms m/z 385; ^1H nmr δ 2.10 (s, 3H, NCOCH₃), 3.80 (s, 3H, CO₂CH₃), 4.03 (s, 3H, OCH₃), 4.13 (s, 3H, OCH₃), 5.67 (d, J=8 Hz, CH), 6.67 (d, J=8 Hz, NH), 7.36 (s, 2H), 7.44 (s, 1H), 7.74 (s, 1H), 7.98 (s, 1H). Anal. Calcd for $\text{C}_{20}\text{H}_{19}\text{O}_7\text{N}$: C, 62.36; H, 4.93. Found: C, 62.05; H, 4.75.

N-tert-Butoxycarbonyl-2,2'-dimethyl-4-(4-hydroxyphenyl)-1,3-oxazolidine (32): Prepared as described.¹⁶ Mp 185-186°C; $[\alpha]_{\text{D}} = -94.33^\circ$ (c = 0.3, MeOH); ms m/z 293 (M^+), 193; ir 3600 (OH), 1694 cm^{-1} (C=O); ^1H nmr δ 1.22 (s, 6H, 2CH₃), 1.45 (s, 3H, CH₃), 1.57 (s, 3H, CH₃), 1.75 (s, 3H, CH₃), 3.86 (m, 1H, H-CH), 4.26 (m, 1H, HC-H), 4.75 and 4.89 (bs + bs, 1H, HC-N), 6.81 (d, J=8 Hz, 2H), 7.13 (d, J=8 Hz, 2H). Anal. Calcd for $\text{C}_{16}\text{H}_{23}\text{NO}_4$: C, 65.50; H, 7.90; N, 4.77. Found: C, 65.87; H, 7.57; N, 4.48.

8,9-Dimethoxy-2-(2,2'-dimethyl-3-tert-butoxycarbonyloxazolidin-4-yl)dibenzo[b,d]pyran-6-one (33) : Yield 77 %; mp 176-180°C; $[\alpha]_D = -33.50^\circ$ (c = 0.2, CHCl₃); ms m/z 455 (M⁺), 398; ¹H nmr δ 1.23 (s, 6H, 2 CH₃), 1.47 (s, 3H, CH₃), 1.63 (s, 3H, CH₃), 1.83 (s, 3H, CH₃), 3.97 (m, 1H), 4.00 (s, 3H, OCH₃), 4.10 (s, 3H, OCH₃), 4.33 (m, 1H), 4.90 and 5.03 (bm + bm, 1H CH-N), 7.36 (d, J=8 Hz, 1H) 7.43 (m, 2H), 7.77 (s, 1H), 7.90 (s, 1H) Anal. Calcd for C₂₅H₂₉NO₇: C, 65.95; H, 6.37; N, 3.08. Found: C, 65.54; H, 6.40; N, 3.22.

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