Characterization of 40 and 41. Compounds 40 and 41 were isolated from pyrolysate by preparative GC and are characterized. ^{1}H NMR of **40**: 7.16–7.06 (m, 4 H), 5.87–5.76 (m, 1 H), 4.98–4.91 (m, 2 H), 2.72–2.64 (m, 1 H), 2.56–2.48 (m, 1 H), 2.48–2.37 (m, 1 H), 2.31 (s, 3 H), 1.02 (d, 3 H). HRMS for $C_{12}H_{16}$: calcd 160.1251, found 160.1251. ^{1}H NMR of **41**: 7.15–7.06 (m, 4 H), 5.14–5.06 (m, 1 H), 3.27 (s, 2 H), 2.26 (s, 3 H), 1.60 (s), 1.585 (d overlapped, total 6 H). HRMS for $C_{12}H_{16}$: calcd for 160.1251, found 160.1255.

Acknowledgment. We thank the Department of Energy for support of this work.

Supplementary Material Available: ^{1}H NMR spectra of selected compounds (11 pages). Ordering information is given on any current masthead page.

Structural Elucidation and Independent Synthesis of the Radical–Radical Coupling Products of 3-Hydroxyanthranilic Acid with Tyrosine and Phenols

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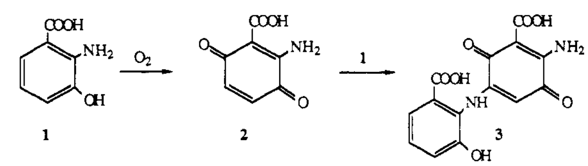
The autoxidation of 3-hydroxyanthranilic acid (3OHA) in the presence of tyrosine, *p*-cresol, or *p*-ethylphenol gives dibenzo[*b,d*]pyran-6-one products that arise from the coupling of the radical of 3OHA with that derived from the substituted phenol. As a proof of the structure of these adducts, they have been independently synthesized by employing a palladium(0)-catalyzed coupling of appropriately functionalized aryl boronic acids with methyl 6-bromo-3-methoxy-2-nitrobenzoate.

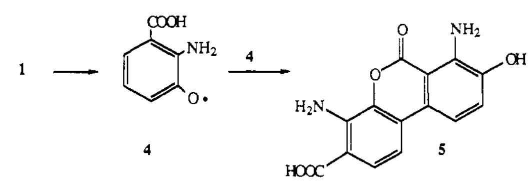
3-Hydroxyanthranilic acid (3OHA, **1**) is a normal metabolite of the amino acid tryptophan and readily undergoes autoxidation. In a number of diseases, elevated levels of urinary tryptophan metabolites have been reported.[1,2] Patients with cancer of the bladder, for example, have been found to excrete increased amounts of 3OHA and 3-hydroxykynurenine.[2,3] Evidence that oxidation of 3OHA may be intimately associated with its carcinogenicity has come from studies which have shown a marked protective effect of simultaneously administered vitamin C.[4]

The autoxidation of 3OHA may result in the production of hydrogen peroxide,[5] superoxide radicals,[5] and, in the presence of trace amounts of iron, hydroxyl radicals.[6] Oxidized 3OHA intermediates are also very reactive and have been demonstrated to bind covalently to proteins.[7] 3OHA is thought to be responsible for the tanning of cocoon protein in some species of moths.[8]

Recent reports from our laboratories have described the products from the autoxidation of 3OHA in the presence and absence of amine nucleophiles.[9] Three dimeric products have been identified from the autoxidation of **1**, cinnabarinic acid,[9a] the *p*-quinone dimer **3**, formed via conjugate addition of **1** to **2** (eq 1), and the dibenzo[*b,d*]pyran-6-one **5**,[9c] which presumably arises via an ortho,para radical–radical coupling reaction of phenoxy radical **4** (eq 2).

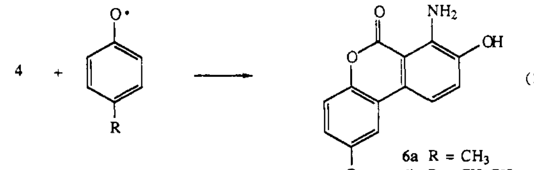


(1)



(2)

The extensively documented participation of tyrosine radicals in biochemical electron-transfer reactions[10] and the isolation of numerous fungal and bacterial metabolites which have arisen from radical dimerization of tyrosine[11] suggested that radical coupling products from tyrosine and 3OHA would be likely. In the event, autoxidation of 3OHA at pH 7 in the presence of tyrosine (4 molar equiv) or *p*-cresol or *p*-ethylphenol gave predominately cinnabarinic acid and the *p*-quinone dimer **3** along with a small quantity (0.5–1%) of the dibenzo[*b,d*]pyran-6-one products **6a**, **6b**, and **6c**, respectively (eq 3). These products were difficult



(3)

6a R = CH_3
6b R = CH_2CH_3
6c R = $CH_2CH(NH_2)COOH$

(1) Costa, C.; Angi, M. R.; De Cavli, M.; Vanzan, S.; Allegri, G. *Bull. Soc. It. Biol. Sper.* **1982**, *58*, 333–339.
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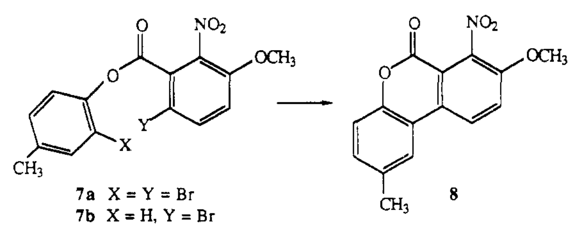
0022-3263/90/1955-4581$02.50/0

to isolate, and **6c** in particular could not be obtained in sufficient quantity for a complete spectroscopic analysis and characterization. *We report here the independent synthesis of* **6a–c** which serves as a structural proof for these adducts and demonstrates the usefulness of the palladium(0)-catalyzed aryl boronic acid–aryl bromide coupling reaction to the synthesis of highly functionalized biphenyls.

Results and Discussion

Our initial synthetic strategy involved construction of the key biphenyl bond of the target compounds via an intramolecular aryl–aryl coupling reaction of the esters **7a–c**. The nitro esters **7** were readily prepared from coupling of the appropriate carboxylic acids **9** and **10** with *p*-cresol or 2-bromo-4-methylphenol using DCC and DMAP as coupling reagents. Bromination of the known 3-methoxy-2-nitrobenzoic acid **9**[12] was not straightforward. However, when **9** was treated with Br_2 and Ag_2SO_4 in H_2SO_4 at room temperature and in the dark, a single monobrominated isomeric product **10** was obtained in 61% yield (Scheme I). That bromination had occurred para to the methoxy group of **9** was evident from ^1H NMR analysis and NOE difference spectroscopy.[13]

Attempts to convert **7a–c** to **8** via a photochemical aryl–aryl coupling procedure[14] in the presence or absence of iodine were unsuccessful, and only unreacted starting **7a–c** could be detected. Attempted reductive coupling of **7a–c** with tetrakis(triphenylphosphine)nickel(0)[15] or bis(1,5-cyclooctadiene)nickel(0)[15] led to the formation of extensive decomposition products. Semmelhack[15] has noted difficulties in these type of coupling reactions that involve nitrobenzene compounds. Treatment of **7a** under Ullmann coupling conditions[16] resulted in selective reduction to **7c**. The palladium(II) acetate[17] catalyzed coupling reaction of **7b** gave the desired lactone **8** in only 4% yield while treatment of **7c** under analogous reaction conditions failed to produce any of the required lactone.



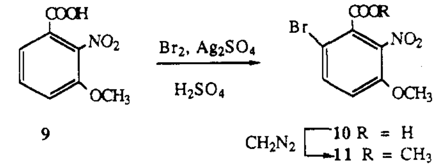
7a X = Y = Br
7b X = H, Y = Br
7c X = Br, Y = H

A successful synthesis of the desired dibenzo[*b*,*d*]pyran-6-ones **6a,b** was achieved via a Pd(0)-catalyzed cross-coupling reaction of the aryl boronic acids **12a,b** and methyl 6-bromo-3-methoxy-2-nitrobenzoate (**11**). The requisite boronic acids were prepared from their corresponding aryl bromides using standard procedures (Scheme II).[18]

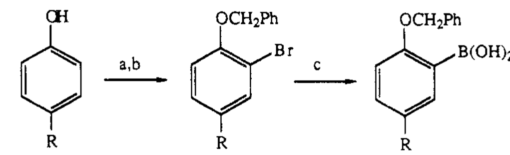
The coupling of **11** with either aryl boronic acid **12a** or **12b** in the presence of 2–3 mol % of $Pd(OAc)_2$, PPh_3, and Et_3N in dry deoxygenated dimethylformamide (DMF) at 100 °C for 3 h[19] gave the biphenyls **13a** and **13b** consistently in yields of 50–60% after purification by column chromatography (Scheme III). Hydrogenation of **13a,b** over PtO_2 gave directly the dibenzo[*b*,*d*]pyran-6-ones **14a,b** resulting from both reduction of the nitro group of **13a,b** and hydrogenolysis of the benzyl ether group and then lactonization. Compound **14a** was identical with the compound obtained from treatment of **6a** with an excess of diazomethane. Finally, demethylation of **14b** with aqueous 48% HBr at reflux gave the desired fully deprotected dibenzo[*b*,*d*]pyran-6-ones **6b**. This compound was identical by TLC, UV, ^1H NMR, and MS analyses to the product arising from the autoxidation of 3OHA in the presence of *p*-ethylphenol.

With the above methodology in hand a synthesis of the more highly functionalized derivative **6c** was then attempted. An initial study focused on coupling the arylboronic acid **18** with **11**. Benzylic bromination of **15** with bromine gave the benzyl bromide derivative **16** (Scheme IV). Alkylation of **16** with the sodium salt of ethyl nitroacetoacetate in DMF gave a mixture (1:6) of the desired α-nitro ester **18** along with the aldehyde **17**. The formation of aldehydes in these type of alkylation reactions have been previously noted.[20] All attempts at the Pd(0)-catalyzed coupling of **18** and **11**, however, were unsuccessful.

Scheme I



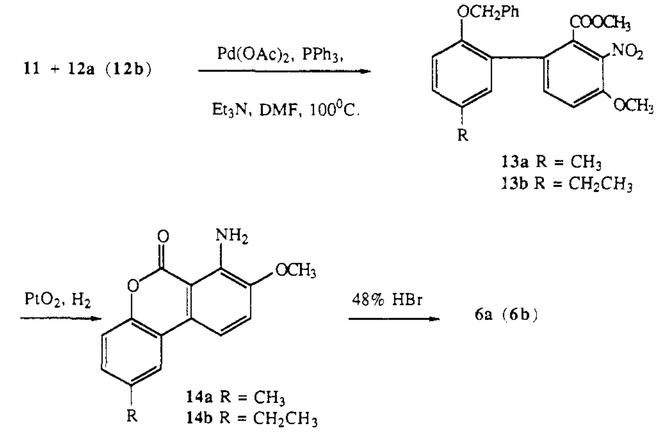
Scheme II[a]



12a R = CH_3
12b R = CH_2CH_3

[a] (a) Br_2, CH_2Cl_2; (b) $PhCH_2Br$, K_2CO_3; (c) Mg, THF; $B(On\text{-}Bu)_3$; H_3O^+.

Scheme III



(12) Albert, A.; Hampton, A. *J. Chem. Soc.* **1952**, 4985–4993.
(13) Selective irradiation of the *O*-methyl of **10** caused a NOE enhancement at H-4 by 3.1%. Selective irradiation at H-4 of **9** caused a NOE enhancement of the OMe resonance by 10.0%.
(14) Sainsbury, M. *Tetrahedron* **1980**, *36*, 3327–3359.
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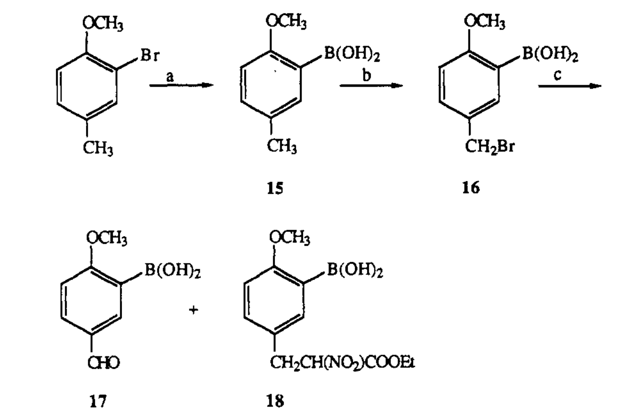
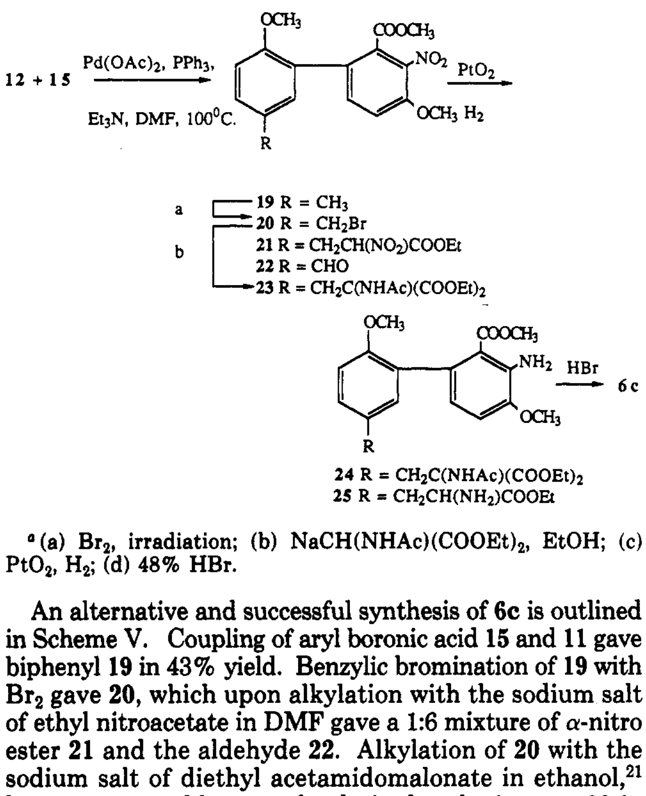
Scheme IV[a]



[a] (a) Mg, THF; $B(On\text{-}Bu)_3$; H_3O^+; (b) Br_2, irradiation; (c) $NaCH(NO_2)COOEt$.

Scheme V[a]



[a] (a) Br_2, irradiation; (b) $NaCH(NHAc)(COOEt)_2$, EtOH; (c) PtO_2, H_2; (d) 48% HBr.

An alternative and successful synthesis of **6c** is outlined in Scheme V. Coupling of aryl boronic acid **15** and **11** gave biphenyl **19** in 43% yield. Benzylic bromination of **19** with Br_2 gave **20**, which upon alkylation with the sodium salt of ethyl nitroacetate in DMF gave a 1:6 mixture of α-nitro ester **21** and the aldehyde **22**. Alkylation of **20** with the sodium salt of diethyl acetamidomalonate in ethanol,[21] however, smoothly gave the desired malonic ester **23** in 64% yield after recrystallization. Hydrogenation of **23** or **21** over PtO_2 gave the amino compounds **24** and **25**, respectively, which were converted to **6c** in 66% yield upon exposure to aqueous 48% HBr at reflux and then recrystallization from water. Pure **6c** (mp >300 °C) was identical by UV, MS, and HPLC analyses with the product isolated from the autoxidation of 3OHA in the presence of tyrosine.

In summary, a successful synthesis of the products arising from radical–radical coupling of 3OHA and tyrosine, *p*-cresol, and *p*-ethylphenol has been achieved. This synthesis serves as a structural proof of these adducts. Preliminary studies from our laboratories suggest that **6c** is present in the acid hydrolysates of bovine serum albumin (BSA) that has been first incubated with 3OHA at pH 7 in an oxygen atmosphere. These results will be the subject of a forthcoming paper. Whether cross-linked proteins found in nature involve cross-linking via a dimer of 3OHA and tyrosine residues is under active investigation.

Experimental Section

General procedures were as previously described.[9]

General Procedure for the Preparation of 6a–c from 3-Hydroxyanthranilic Acid (1). Oxygen was bubbled through a solution of **1** (200 mg, 1.31 mmol) and the 4-substituted phenol (4 equiv) in pH 7 phosphate buffer (100 mL) at room temperature for 24 h. The water was then removed by freeze-drying, and the compounds **6a–c** were isolated pure after column chromatography and then PTLC. The solvents employed for the chromatographic separations were identical with those described below for their synthesis.

6-Bromo-3-methoxy-2-nitrobenzoic Acid (10). To a stirred solution of 3-methoxy-2-nitrobenzoic acid (1 g, 5.08 mmol) and Ag_2SO_4 (0.8 g) in H_2SO_4 (20 mL) was added bromine (0.284 mL, 1 equiv), and the solution was stirred in the dark for 2 h. Water was then added, and the resulting precipitate was collected. The precipitate was dissolved in acetone, and then the solution was dried ($MgSO_4$) and evaporated to give a pale red solid (0.85 g, 61%, mp 155–158 °C). Recrystallization from ether/hexane with slow evaporation of the ether gave a white solid: mp 157–158.5 °C; ^1H NMR (DMSO-d_6) δ 3.94 (s, 3 H) 7.43 (d, J = 9.03 Hz, 1 H), 7.93 (d, J = 9.03 Hz, 1 H); ^{13}C NMR (DMSO-d_6) δ 57.25 (q), 108.59 (s), 116.84 (d), 130.60 (s), 136.56 (d), 138.70 (s), 150.24 (s), 164.2 (s). Anal. Calcd for $C_8H_6BrNO_5$: C, 34.78; H, 2.17; N, 5.0. Found: C, 34.87; H, 1.93; N, 5.13.

Methyl 6-Bromo-3-methoxy-2-nitrobenzoate (11). A solution of **10** (1 g) in ether was treated with an excess of diazomethane in ether. After 1 h the solvent was evaporated to give the pure product (**10**) as a white solid (1.0 g, 95% yield). Recrystallization from methanol/water gave white crystals: mp 126–127 °C; ^1H NMR (DMSO-d_6) δ 3.84 (3 H, s), 3.93 (3 H, s), 7.47 (1 H, d, J = 9.5 Hz), 7.96 (1 H, d, J = 9.5 Hz), 7.96 (1 H, d, J = 9.5 Hz). Anal. Calcd for $C_9H_8BrNO_5$: C, 37.27; H, 2.78; N, 4.83. Found: C, 37.58; H, 2.90; N, 4.94.

Preparation of the Aryl Boronic Acids 12a, 12b, and 15. A General Procedure. 2-(Benzyloxy)-5-methylbenzeneboronic Acid (12a). To a stirred suspension of magnesium shavings (2.81 g, 117 mmol) in dry tetrahydrofuran (THF, 75 mL) under a nitrogen atmosphere was added a crystal of iodine and then dropwise a solution of 1-bromo-2-(phenylmethoxy)-5-methylbenzene (32.5 g, 117 mmol) in THF (150 mL). The solution was heated at reflux for 1 h, cooled to room temperature, and finally added dropwise over a period of 1 h to a stirred solution of tri-*n*-butylborate (26.8 g, 117 mmol) in THF/Et_2O (100 mL, 1:1) at −78 °C. After 1 h at −78 °C, the solution was warmed to room temperature and stirred for a further 2 h. The reaction was quenched by the addition of 10% aqueous HCl (150 mL), and after 10 min the solution was extracted with ether (3 × 150 mL). The combined ether extracts were then extracted with 1 M NaOH (400 mL). A white precipitate was formed which was removed by filtration; this was found to be a sodium salt of **7a**. The precipitate was added to the aqueous extract, which was then acidified with dilute HCl to give further white precipitate which was collected by vacuum filtration and washed with a little cold water and dried (yield 14.4 g, 51%, mp 90–92 °C): ^1H NMR ($CDCl_3$) δ 2.30 (3 H, s), 5.10 (2 H, s), 6.24 (2 H, s), 6.86 (1 H, d, J = 8.6 Hz), 7.21 (1 H, dd, J = 8.6, 2.2 Hz), 7.40 (5 H, s), 7.67 (1 H, d, J = 2.2 Hz). Anal. Calcd for $C_{14}H_{15}BO_3$: C, 69.48; H, 6.20. Found: C, 69.35; H, 6.38.

2-(Benzyloxy)-5-ethylbenzeneboronic Acid (12b). Prepared from 1-bromo-2-(phenylmethoxy)-4-ethylbenzene (21 g, 72.2 mmol) as described above to give **12b** (11.4 g, 62%) as a white solid. Recrystallization hexane gave white crystals: mp 92.5–94 °C; ^1H NMR ($CDCl_3$) δ 1.21 (3 H, t, J = 7.6 Hz), 2.61 (2 H, q, J = 7.6 Hz), 5.11 (2 H, s), 6.20 (1 H, s), 6.89 (1 H, d, J = 8.6 Hz), 7.24 (1 H, dd, J = 2.2 Hz, 8.6 z), 7.39 (5 H, s), 7.70 (1 H, d, J = 2.2 Hz). Anal. Calcd for $C_{15}H_{17}BO_3$: C, 70.37; H, 6.65. Found: C, 70.35; H, 6.93.

2-Methoxy-5-methylbenzeneboronic Acid (15). Prepared from 1-bromo-2-methoxy-4-methylbenzene (63.82 g, 317.5 mmol) as described above using THF as solvent to give **15** (25.32 g, 48%)

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as a white solid. Recrystallization from hexane gave white needles: mp 90–91 °C; ^1H NMR ($CDCl_3$) δ 2.31 (3 H, s), 3.87 (3 H, s), 6.35 (2 H, s), 6.80 (1 H, d, J = 8.4 Hz), 7.23 (1 H, dd, J = 8.4, 2.2 Hz), 7.66 (1 H, d, J = 2.2 Hz). Anal. Calcd for $C_8H_{11}BO_3$: C, 61.94; H, 7.10. Found: C, 61.82; H, 6.95.

Preparation of the Biphenyl Compounds 13a, 13b, and 19. A General Procedure. Methyl 2′-(Benzyloxy)-4-methoxy-5′-methyl-3-nitrobiphenyl-2-carboxylate (13a). A solution of **12a** (8.00 g, 33 mmol), **11** (8.00 g, 27.58 mmol), Pd $(OAc)_2$ (200 mg, 0.89 mmol), triphenylphosphine (500 mg, 1.90 mmol), and triethylamine (7.2 g, 71.3 mmol) in dry dimethylformamide (DMF, 100 mL, deoxygenated by bubbling with dry nitrogen) was heated at 100 °C for 3 h under an atmosphere of nitrogen. Most of the DMF was then removed under vacuum, and the brown oily residue was dissolved in $CHCl_3$ (500 mL) and extracted with 10% aqueous NaOH (2 × 200 mL). The chloroform solution was dried ($MgSO_4$), filtered, and then evaporated. The crude product was purified by column chromatography on silica gel using ethyl acetate/hexane (1:2) as eluent. The title compound was obtained as a white solid (11.2 g, 56%). Recrystallization from methanol gave white crystals: mp 119–121 °C; ^1H NMR ($CDCl_3$) δ 2.30 (3 H, s), 3.52 (3 H, s), 3.95 (3 H, s), 4.97 (2 H, s), 6.83 (1 H, d, J = 8.2 Hz), 7.008 (1 H, d, J = 2.1 Hz), 7.08 (1 H, dd, J = 2.1, 8.2 Hz), 7.16 (1 H, d, J = 8.7 Hz), 7.2–7.3 (5 H, m), 7.44 (1 H, d, J = 8.7 Hz). Anal. Calcd for $C_{23}H_{21}NO_6$: C, 67.81; H, 5.16; N, 3.44. Found: C, 67.76; H, 5.01; N, 3.18.

Methyl 2′-(Benzyloxy)-5′-ethyl-4-methoxy-3-nitrobiphenyl-2-carboxylate (13b). Prepared from **12b** (1.24 g, 4.86 mmol) and **11** (1.24 g, 4.28 mmol) as described above. Purification on silica gel gave **13b** (0.88 g, 49%) as a white solid. Recrystallization from methanol gave white crystals: mp 103–104 °C; ^1H NMR ($CDCl_3$) δ 1.21 (3 H, t, J = 7.7 Hz), 2.61 (2 H, q, J = 7.7 Hz), 3.51 (3 H, s), 3.92 (3 H, s), 4.98 (2 H, s), 6.86 (1 H, d, J = 8.4 Hz), 7.03 (1 H, d, J = 2.1 Hz), 7.11 (dd, 1 H, J = 8.4, 2.1 Hz), 7.16 (1 H, d, J = 8.7 Hz), 7.2–7.3 (5 H, m), 7.48 (1 H, d, J = 8.7 Hz). Anal. Calcd for $C_{24}H_{23}NO_6$: C, 68.41; H, 5.46; N, 3.33. Found: C, 68.38; H, 5.2; N, 3.07.

Methyl 2′,4-Dimethoxy-5′-methyl-3-nitrobiphenyl-2-carboxylate (19). Prepared from **15** (3.48 g, 21.1 mmol) and **11** (5.51 g, 19 mmol) as described above. Purification on silica gel gave **19** (2.70 g, 43%) as a white solid. Recrystallization from methanol gave white crystals: mp 166–168 °C; ^1H NMR ($CDCl_3$) δ 2.32 (3 H, s), 3.64 (3 H, s), 3.69 (3 H, s), 3.95 (3 H, s), 7.78 (1 H, d, J = 8.4 Hz), 7.02 (1 H, d, J = 2.1 Hz), 7.14 (1 H, dd, J = 8.4, 2.1 Hz), 7.18 (1 H, d, J = 8.7 Hz), 7.44 (1 H, d, J = 8.7 Hz). Anal. Calcd for $C_{17}H_{17}NO_6$: C, 61.63; H, 5.14; N, 4.23. Found: C, 61.42; H, 5.23; N, 4.36.

7-Amino-8-methoxy-2-methyldibenzo[*b*,*d*]pyran-6-one (14a). To a solution of **13a** (0.43 g, 1.06 mmol) in ethanol (40 mL) was added PtO_2 (20 mg), and the system was evacuated and filled with H_2. The mixture was stirred overnight. The catalyst was filtered off, and the solvent was removed to leave **14a** (0.25 g, 92%) as a bright yellow solid. Recrystallization from acetone gave yellow crystals: mp 175–165 °C; ^1H NMR ($CDCl_3$) δ 2.40 (d, long range coupling, J = 0.66 Hz, 3 H), 3.93 (s, 3 H), 6.57 (br s, 2 H), 7.05 (d, 1 H, J = 8.6 Hz), 7.13, 7.14 (2 H), 7.23 (d, 1 H, J = 8.6 Hz), 7.68 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 21.11, 55.92, 103.22, 107.51, 114.77, 116.97, 118.67, 122.48, 127.60, 129.74, 133.64, 142.71, 145.98, 148.51, 163.34. Anal. Calcd for $C_{15}H_{13}NO_3$: C, 70.59; H, 5.10; N, 5.49. Found: C, 70.65; H, 5.39; N, 5.68.

7-Amino-2-ethyl-8-methoxydibenzo[*b*,*d*]pyran-6-one (14b). Prepared from **13b** (0.7 g, 1.66 mmol) as described above for the preparation of **14a**. The title compound was obtained as a yellow solid (0.41 g, 92%). Recrystallization from hexane gave an amorphous pale yellow solid: mp 98–99 °C; ^1H NMR ($CDCl_3$) δ 1.29 (3 H, t, J = 7.6 Hz), 2.71 (2 H, q, J = 7.6 Hz), 3.95 (3 H, s), 6.60 (2 H, br s), 7.08 (1 H, d (slightly broadened), J = 8.4 Hz), 7.18 and 7.19 (2 H, s), 7.28 (1 H, d, J = 8.4 Hz), 7.72 (1 H, br s); UV (EtOH) 215.8 (log ε 4.34), 240.6 (4.20), 275.0 (3.60), 305.2 (3.50), 315.6 (3.57), 376.6 (3.74). Anal. Calcd for $C_{16}H_{15}NO_3$: C, 71.38; H, 5.58; N, 5.20. Found: C, 71.12; H, 5.69; N, 4.89.

7-Amino-2-ethyl-8-hydroxydibenzo[*b*,*d*]pyran-6-one (6b). Compound **14b** (119 mg, 0.44 mmol) was suspended in 7 mL of 48% HBr and refluxed for 24 h. After 2 min all **14b** had dissolved, and much material had precipitated after 24 h. The solution was cooled, diluted with water (50 mL), basified to pH 5, and then extracted with ethyl acetate. The extracts were dried ($MgSO_4$) to give a light yellow solid. Purification by column chromatography using ethyl acetate/hexane initially as a 1:2 mixture and finally as a 1:1 mixture gave **6b** (85.5 mg, 76%) as a yellow solid: mp 209–210 °C; ^1H NMR (acetone-d_6) δ 1.25 (3 H, t, J = 7.6 Hz), 2.707 (2 H, q, J = 7.6 Hz), 6.73 (2 H, br s), 7.12 (1 H, d, J = 8.3 Hz), 7.20 (2 H, slightly broadened singlet), 7.338 (1 H, d, J = 8.3 Hz), 7.88 (1 H, br s), 8.96 (1 H, v br s). Anal. Calcd for $C_{15}H_{13}NO_3$: C, 70.59; H, 5.10; N, 5.49. Found: C, 70.63; H, 5.16; N, 5.70.

Methyl 2′,4-Dimethoxy-5′-(bromomethyl)-3-nitrobiphenyl-2-carboxylate (20). A solution of **19** (100 mg, 0.39 mmol) in dry CCl_4 (25 mL) was heated to reflux, and bromine (0.41 mmol) was added over a few minutes. The solution was heated and irradiated for 2 h. The solvent was then evaporated, and the resulting white solid was recrystallized from CCl_4/hexane to give **20** (98 mg, 61%) as white crystals: mp 153–154 °C; ^1H NMR ($CDCl_3$) δ 3.58 (3 H, s), 3.65 (3 H, s), 3.89 (3 H, s), 4.44 (2 H, s), 6.79 (1 H, d, J = 8.4 Hz), 7.12 (1 H, d, J = 8.7 Hz), 7.17 (1 H, d, J = 2.3 Hz), 7.31 (1 H, dd, J = 2.3, 8.4 Hz), 7.38 (1 H, d, J = 8.7 Hz). Anal. Calcd for $C_{17}H_{16}BrNO_6$: C, 49.76; H, 3.90; N, 3.41. Found: C, 49.72; H, 3.97; N, 3.35.

Alkylation of 20 with the Sodium Salt of Ethyl Nitroacetate. To a solution of **20** (70 mg, 0.17 mmol) in DMF (1 mL) was added a solution of the sodium salt of ethyl nitroacetate (1.1 equiv, prepared from ethyl nitroacetate and sodium hydride in DMF (3 mL)), and the mixture was stirred for 12 h. The solution was then diluted with ether (50 mL) and extracted with 1% aqueous HCl (3 × 20 mL). The ether was dried ($MgSO_4$) and evaporated. Preparative TLC (ethyl acetate/hexane, 2:1) gave **21** (higher band, 9 mg, 11%) and **22** (lower band, 38 mg, 66%) as white solids.

21: ^1H NMR ($CDCl_3$) δ 1.26 (3 H, t, J = 7.17 Hz), 3.39 (1 H, dd, J = 13.40, 5.50 Hz), 3.43 (1 H, dd, J = 13.40, 7.17 Hz), 3.56 (3 H, s), 3.62 (3 H, s), 3.88 (3 H, s), 4.22 (2 H, q, J = 7.17 Hz), 5.25 (1 H, dd, J = 9.70, 5.50 Hz), 6.76 (1 H, d, J = 8.40 Hz), 6.97 (1 H, d, J = 2.14 Hz), 7.11 (2 H, broadened doublet), 7.31 (1 H, d, J = 8.7 Hz); CIMS 462 (M + H^+).

22: mp 188–189 °C (from acetone/hexane); ^1H NMR ($CDCl_3$) δ 3.56 (3 H, s), 3.74 (3 H, s), 3.89 (3 H, s), 6.95 (1 H, d, J = 8.56 Hz), 7.16 (1 H, d, J = 8.73 Hz), 7.37 (1 H, d, J = 8.73 Hz), 7.70 (1 H, d, J = 2.06 Hz), 7.83 (1 H, dd, J = 2.06, 8.56 Hz), 9.85 (1 H, s). Anal. Calcd for $C_{17}H_{15}NO_7$: C, 59.13; H, 4.35; N, 4.06. Found: C, 59.18; H, 4.37; N, 4.13.

Methyl 5′-(2,2-Bis(ethoxycarbonyl)-2-acetamidoethyl)-2′,4-dimethoxy-3-nitrobiphenyl-2-carboxylate (23). To a solution of diethyl acetamidomalonate (630 mg, 2.90 mmol) in 20 mL of ethanol was added sodium (56 mg, 2.43 mmol). The solution was stirred for 5 min, and then **20** (1 g, 2.44 mmol) was added. After 2 h a light yellow solution was obtained, and stirring was continued for 18 h. The solvent was then evaporated, and the resulting white solid was dissolved in $CHCl_3$ (100 mL) and extracted with 5% K_2CO_3 (2 × 75 mL). The $CHCl_3$ layer was dried ($MgSO_4$) and evaporated to give a yellow viscous oil. Adding boiling CCl_4 followed by hexane gave white crystals: 850 mg (64%); mp 159–161 °C; ^1H NMR ($CDCl_3$) δ 1.26 (t, J = 7.2 Hz, 6 H), 2.02 (s, 3 H), 3.60 (s, 2 H), 3.62 (s, 3 H), 3.67 (s, 3 H), 3.95 (s, 3 H), 4.23 (q, J = 7.2 Hz, 4 H), 6.63 (br s, 1 H), 6.77 (d, J = 8.4 Hz, 1 H), 6.83 (d, J = 2.1 Hz, 1 H), 6.97 (dd, J = 8.4, 2.1 Hz, 1 H), 7.16 (d, J = 8.7 Hz, 1 H), 7.33 (d, J = 8.7 Hz, 1 H). Anal. Calcd for $C_{26}H_{30}N_2O_{11}$: C, 57.14; H, 5.49; N, 5.13. Found: C, 57.06; H, 5.56; N, 4.92.

Methyl 3-Amino-5′-(2-amino-2,2-bis(ethoxycarbonyl)-ethyl)-2′,4-dimethoxybiphenyl-2-carboxylate (25). The title compound was prepared from **23** (4.0 g, 7.33 mmol) as described above for the preparation of **14a**. Recrystallization from ethyl acetate/hexane gave white crystals (2.08 g, 55%); mp 74–75 °C; ^1H NMR ($CDCl_3$) δ 1.26 (3 H, t, J = 6.8 Hz), 2.01 (3 H, s), 3.43 (3 H, s), 3.60 (2 H, s), 3.66 (3 H, s), 3.87 (3 H, s), 4.24 (4 H, q, J = 6.8 Hz), 5.42 (2 H, br s), 6.44 (1 H, d, J = 8.1 Hz), 6.56 (slightly br s, 1 H), 6.71 (1 H, d, J = 8.4 Hz), 6.8 (2 H, m), 8.88 (d, 1 H, J = 8.24, 2.3 Hz). Anal. Calcd for $C_{26}H_{32}N_2O_9$: C, 60.47; H, 6.20; N, 5.43. Found: C, 60.87; H, 6.34; N, 5.08.

7-Amino-2-(2-amino-2,2-dicarboxyethyl)-8-hydroxydibenzo[*b*,*d*]pyran-6-one (6c). A solution of **25** (150 mg, 0.29 mmol) in 48% aqueous HBr (5 mL) was refluxed for 14 h. After this time the HBr was removed under vacuum. The residue was dissolved in H_2O, Na_2HPO_4 was added, and the pH was adjusted to 7. The flocculant was centrifuged, and the precipitate was collected and recrystallized from water to give dark green/black shiny crystals (60 mg, 66%), mp >300 °C. This compound was identical by TLC (SiO_2, eluent, butanol/acetic/H_2O, 4:2:1) and UV to that obtained from the autoxidation of 1 in the presence of tyrosine: UV (pH 5, sodium acetate buffer 0.02 M) 377.6 (log ε 3.73), 309.8 (log ε 3.53), 300.0 (log ε 3.53), 238.2 (log ε 4.22), 214 (log ε 4.38) + 1 drop NaOH to pH >10 changes UV to 402.2 (log ε 3.71), 330.4 (log ε 3.73), 242.6 (log ε 4.22), 214 (log e 4.44); ^{1}H NMR (D_2O/NaOD (1 M), TSP as internal reference) δ 2.55 (1 H, dd, J = 13.74, 8.55 Hz), 2.89 (1 H, dd, J = 13.74, 4.28 Hz), 3.38 (1 H, dd, J = 8.55, 4.27 Hz), 6.54 (1 H, d, J = 8.09 Hz), 6.626 (1 H, d, J = 8.09 Hz), 6.63 (1 H, d, J = 8.09 Hz), 6.84 (1 H, d, J = 2.29 Hz), 6.89 (1 H, dd, J = 8.09, 2.29 Hz); ^{13}C NMR (D_2O/NaOD) 39.40 (t), 56.85 (d), 114.53 (d), 118.53 (d), 122.04 (d with underlying s), 123.11 (s), 127.69 (d with underlying s), 131.01 (d with underlying s), 131.40 (s), 152.90 (s), 161.77 (s), 177.04 (s), 182.06 (s). Anal. Calcd for $C_{16}H_{14}N_2O_5$: C, 61.15; H, 4.46; N, 8.92. Found: C, 60.75; H, 4.56; N, 8.66.

On the Scope of Asymmetric Nitrile Oxide Cycloadditions with Oppolzer's Chiral Sultam. Total Syntheses of (+)-Hepialone, (−)-(1*R*,3*R*,5*S*)-1,3-Dimethyl-2,9-dioxabicyclo[3.3.1]nonane, and (−)-(1*S*)-7,7-Dimethyl-6,8-dioxabicyclo[3.2.1]octane

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Cycloadditions of nitrile oxides with acryloyl derivatives of Oppolzer's chiral sultam produce stereoisomeric Δ^2-isoxazolines in ratios of about 90/10 at 25 °C. The major diastereomers can be isolated in pure form in 70–88% yield. Syntheses of the three title natural products are used to illustrate that optically pure isoxazolines can be transformed into a wide variety of functional groups including β,γ-dihydroxy ketones, alcohols, 1,2- and 1,3-diols, 1,3,4-triols, 1,3-amino alcohols, and 1,3,4-amino diols. It is suggested that this cycloadditive strategy complements existing asymmetric aldol routes to such functionality. A novel radical ring opening was discovered when it was found racemic 5-methyl-Δ^2-isoxazolines are formed upon reduction of optically pure 5-(iodomethyl)-Δ^2-isoxazolines with tributyltin hydride at low concentration. The scope of the asymmetric cycloaddition was studied by using methacryloyl sultam **33** and crotonoyl sultam **36**. The methacryloyl sultam exhibits very low levels of asymmetric induction, and is much less reactive than a methacrylate ester model. An X-ray crystal structure of **33** suggests a reason for this behavior: the methacryloyl group deviates significantly from planarity. The crotonoyl sultam **36** provides good levels of diastereoselectivity (90/10) in the nitrile oxide cycloaddition, but regioselectivity is lacking.

Introduction

Δ^2-Isoxazolines are central intermediates in a strategy to prepare heteroatom-substituted carbon chains that is based on cycloaddition.[1] Most Δ^2-isoxazolines are easily prepared by olefin/nitrile oxide cycloadditions,[2] are stable to many common synthetic transformations, and can be converted to a wide variety of functional groups under mild conditions. In addition, the relative stereochemistry of functional groups adorning the Δ^2-isoxazoline nucleus can often be strictly controlled.[3] These assets have generated a need for practical methods to prepare optically pure Δ^2-isoxazolines.[4]

We recently reported that the acrylamide **2** derived from Opplozer's chiral sultam **1**[5] gives good levels of asymmetric induction in nitrile oxide cycloadditions (eq 1).[6] Although the degree of selectivity observed (85/15 to 95/5) is not outstanding when judged against transformations like enolate alkylations and Lewis acid catalyzed Diels–Alder reactions (which often occur at low temperature), it is quite high when compared to existing asymmetric nitrile oxide cycloadditions in particular,[4] and to other types of thermal additions in general.[3] This work also resulted in the development of a new model for the thermal addition and cycloaddition reactions of **2** (Figure 1).[6,7] In this model, the reagent (in this case, a nitrile oxide) attacks the β-face of the low-energy conformer of **2**. We also demonstrated that adducts **3** could be separated without difficulty and that the major diastereomers could be reductively cleaved with L-Selectride (Aldrich) to give optically pure isoxazolines **4**, along with recovered sultam **1**.

This paper describes the results of a study that we undertook to determine usefulness of this asymmetric nitrile oxide cycloaddition. Three natural products, (+)-hepial-

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