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Cycloaddition Across the Benzofuran Ring as an Approach to the Morphine Alkaloids

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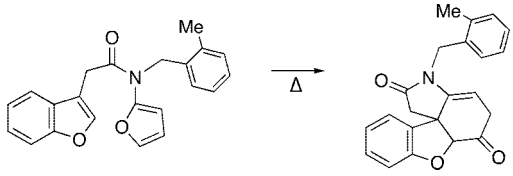
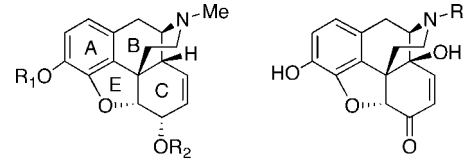


The intramolecular Diels−Alder reaction of several amidofurans tethered onto a benzofuran ring was examined as a strategy for the synthesis of morphine. Bromo substitution on the furan ring did not provide sufficient activation to allow the cycloaddition to take place across the aromatic benzofuran. However, the presence of a large *o*-methylbenzyl group on the amido nitrogen atom causes the reactive *s-trans* conformation of the amidofuran to be highly populated, thereby facilitating its Diels−Alder cycloaddition across a tethered benzofuran.

Morphinan alkaloids, of which morphine (**1**) is representative, are particularly important to the medical community given their longstanding prescription as analgesics in the management of severe pain and as anesthetics.[1] The downside of employing opiads as analgesics is the potential for physical and psychological dependence associated with long-term use. Small variations of the substituents in the core pentacycle (i.e., **2**−**6**), particularly in the C-ring, have profound effects on the biological response. For example, 14-hydroxymorphinans such as naloxone (**4**) and naltrexone (**5**) behave as potent analgesics and narcotic antagonists.[2] Most synthetic derivatives have been prepared by functional group manipulation around the C-ring. Unfortunately, the preparation of these semisynthetic derivatives usually requires transformation of the natural alkaloid into a common intermediate such as noroxymorphone (**6**).[2] In view of the relative scarcity of natural sources, many synthetic approaches and several total syntheses of morphine (**1**) have been reported,[3−6] often including the synthesis of other morphinans.[7] The challenging framework of morphine and its potent derivatives insures that any novel method that can rapidly construct polyfunctionalized analogues, particularly C-ring derivatives, would be attractive for both synthetic and medicinal chemistry.



1; $R_1 = R_2 = H$
2; $R_1 = Me$, $R_2 = H$
3; $R_1 = R_2 = Me$

4; R = allyl
5; R = CH_2c-Pr
6; R = H

Our synthetic approach toward the morphinan alkaloids was guided by a longstanding interest in developing new applications of the intramolecular [4 + 2]-cycloaddition of furans (IMDAF) toward the synthesis of complex natural products.[8] The yields of intramolecular Diels−Alder reactions involving furan are known to be highly sensitive to both diene and dienophile substitution, as well as to the nature and length of the tether.[9] In particular, substitution on the furan ring greatly affects the chemical reactivity of these reactions.[10] Several years ago we began a synthetic program to provide general access to a variety of alkaloids by [4 + 2]-cycloaddition of substituted 2-amidofurans.[8] Our recently completed synthesis of (±)-erysotramidine[11] and (±)-lycoricidine[12] nicely demonstrates the utility of this process for the construction of various alkaloids. Most noteworthy is that the key reaction employed in our synthesis of (±)-strychnine involved a novel cycloaddition of the furan ring across the 2,3-double bond of the indole ring (**7**−**9**).[13] The reaction was remarkably efficient given that two heteroaromatic systems are compromised in the cycloaddition (Scheme 1).

In the context of extending the IMDAF cycloaddition toward a synthesis of morphine, we wondered whether the furan ring might also undergo cycloaddition across a tethered benzofuran.

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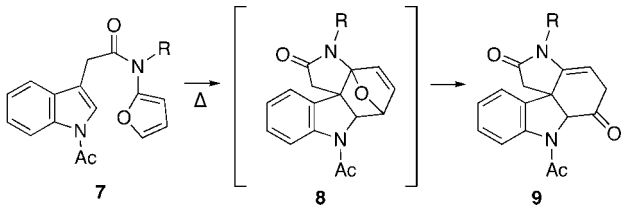
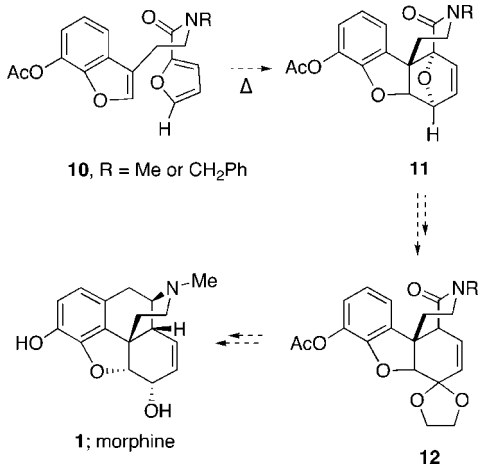
SCHEME 1



SCHEME 2

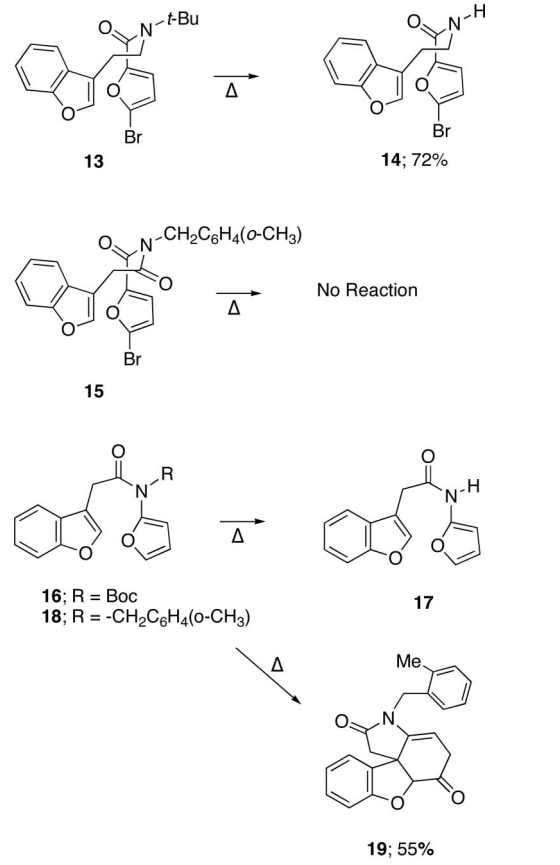


Five-membered heteroaromatics such as benzothiophene or benzofuran have, despite their aromaticity, frontier orbital energies and shapes similar to those of cyclopentadiene.[14] The reactivity of the heteroaromatic dienophile is, however, sharply decreased because of the loss of aromaticity in the cycloaddition transition state. Nevertheless, the remarkable rate enhancement observed by incorporating an sp^2 center in the furanyl tether[15] combined with our recent success with cycloadditions across indolyl-substituted π-systems[16] prompted us to examine possible synthetic applications of this reaction.

Our projected approach toward morphine features an IMDAF reaction of 2-amidofuran **10** across a substituted benzofuran ring (Scheme 2). The close proximity of both heteroaromatic systems and the high reactivity associated with the internal cycloaddition should facilitate the proposed reaction. Although benzofurans are rarely employed as 2π-partners in Diels−Alder chemistry, there is a report published by Ciganek in 1981 describing an intramolecular Diels−Alder reaction of a tethered diene derivative across the benzofuran ring.[17] If successful, our intention was to convert the oxabicyclic ring system found in the resulting cycloadduct **11** to the corresponding ketal **12** and then close the final B-ring of morphine from **12** making use of a procedure reported by Rapoport[18] and Evans.[19] Accordingly, we decided to study the facility of this process using some model substrates prior to commencing with the synthesis of morphine.

The rate enhancement in the Diels−Alder reaction of furans by incorporating a bromine or another halogen group at the 5-position of the heteroaromatic ring appears to be a general phenomenon.[20] The origin of the increased bimolecular cy-

SCHEME 3



cloaddition rate for 5-bromo-substituted furans was recently investigated by Houk and Pieniazek using quantum mechanical calculations.[21] The increased rate of cycloaddition for 5-bromo-substituted furans when compared to the unsubstituted examples was attributed to an increase in reaction exothermicity.[21] This both decreased the activation enthalpy and increased the barrier to retrocycloaddition. Bromine substitution on furan also increased reactant energy and stabilized the product due to the preference of the electronegative halogen atom to be attached to a more highly alkylated and therefore more electropositive framework. With this in mind, we decided to investigate the IMDAF reaction of bromofuranyl amide **13**. Unfortunately, all of our attempts to effect the cycloaddition of **13** only resulted in the removal of the labile *t*-butyl group to give **14**. Thermal conditions (heating at 180 °C in xylene), microwave assistance, and the addition of several Lewis acids failed to promote the desired cycloaddition. Similarly, our attempts to cycloadd across the benzofuran ring using the related *N*-(2-methylbenzyl)imide **15** also failed to produce a cycloadduct (Scheme 3).

We also studied the thermolysis of the simpler benzofuranyl amides **16** and **18**, which are devoid of the bromo group, but now have the nitrogen atom attached directly to the furan ring. The only product isolated from heating a sample of the Boc amidofuran **16** to 120 °C corresponded to the NH-amide **17**. However, the thermolysis of **18** in toluene at 120 °C gave the rearranged cycloadduct **19** in 55% yield. It would seem as

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though the presence of the large *o*-methylbenzyl group on the amido nitrogen causes the reactive *s-trans* conformer to be highly populated, thereby promoting the intramolecular cycloaddition. Apparently, bromo substitution on the furan ring is not important enough a factor to allow the [4 + 2]-cycloaddition to occur with aromatic benzofurans of type **13** or **15**.

In summary, the intramolecular [4 + 2]-cycloaddition reaction of several amidofurans tethered onto a benzofuran ring was examined as a strategy for the synthesis of morphine. Although the cycloaddition failed using furanyl amides of type **13** and **15**, the presence of a large *o*-methylbenzyl group on the amido nitrogen atom of the related carboxamide **18** facilitates the cycloaddition across the tethered benzofuran ring. Further application and extension of the methodology is currently ongoing in our laboratory and will be reported in due course.

Experimental Section

5-Bromofuran-2-carboxylic acid (2-Benzofuran-3-yl-ethyl)-*tert*-butylamide (13). To a solution of 2-benzofuran-3-yl-ethanol[22] (6.2 g, 38 mmol) in CH_2Cl_2 (200 mL) at 0 °C were added Et_3N (8.0 mL, 57 mmol) and TsCl (8.4 g, 44 mmol). The resulting solution was allowed to slowly warm to rt and was then stirred for 12 h. At the end of this time, the reaction mixture was washed with H_2O, dried over Na_2SO_4, and concentrated under reduced pressure to give 10.1 g (84%) of the crude tosylate that was immediately used in the next step. The crude tosylate was dissolved in 160 mL of MeCN and was treated sequentially with $NaHCO_3$ (8.1 g, 96 mmol) and *tert*-butylamine (8.4 mL, 80 mmol). The resulting suspension was warmed to 55 °C for 2 h. The mixture was then cooled to rt and was treated with additional $NaHCO_3$ (8.1 g, 96 mmol) and *tert*-butylamine (8.4 mL, 80 mmol). After heating for an additional 8 h at 55 °C, the suspension was cooled to rt, filtered through a pad of Celite, and concentrated under reduced pressure to leave behind a tan oil. The crude (2-benzofuran-3-yl-ethyl) *tert*-butylamine solidified upon standing in the freezer (5.0 g, 72%) and was used directly in the next step without further purification.

To a solution of the above amine (0.44 g, 2.0 mmol) and Et_3N (0.5 mL, 3.6 mmol) in 15 mL of CH_2Cl_2 at 0 °C was added a cooled solution of 5-bromo-2-furoyl chloride (0.4 g, 2.0 mmol) in CH_2Cl_2 (5 mL) dropwise. After warming to rt over 1 h, the reaction mixture was subjected to normal aqueous workup. The crude product was purified by silica gel flash chromatography to give **13** (0.84 g, 73%) as a pale yellow oil: IR (neat) 1639, 1476, 1452, 1012 and 744 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.61 (s, 9H), 3.07 (t, 2H, J = 8.1 Hz), 3.83 (t, 2H, J = 8.1 Hz), 6.32 (d, 1H, J = 3.4 Hz), 6.86 (d, 1H, J = 3.4 Hz), 7.17−7.34 (m, 2H), 7.40 (d, 1H, J = 8.1 Hz), 7.46 (d, 1H, J = 7.5 Hz), and 7.51 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.8, 28.7, 45.7, 58.2, 111.5, 113.2, 116.8, 118.0, 119.2, 122.4, 123.0, 124.3, 127.6, 141.8, 151.7, 155.2, and 160.7; HRMS calcd for $C_{19}H_{20}BrNO_3$ 389.0627, found 389.0625.

3-Bromofuran-2-carboxylic acid (2-Benzofuran-3-ylethyl) amide (14). Heating a sample of the above amide **13** at 180 °C in xylene for 12 h afforded the secondary amide **14** in 72% isolated yield as a pale yellow oil: IR (film) 3298 (br), 1649, 1597, 1530, 1472, 1453, 1305, 1094, 1010, and 747 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 3.00 (t, 2H, J = 6.6 Hz), 3.75 (q, 2H, J = 6.6 Hz), 6.42 (d, 1H, J = 3.6 Hz), 6.48 (br s, 1H), 7.06 (d, 1H, J = 3.6 Hz), 7.26 (t, 1H, J = 7.2 Hz), 7.32 (t, 1H, J = 7.2 Hz), 7.49 (d, 1H, J = 7.8 Hz), 7.50 (s, 1H), and 7.60 (d, 1H, J = 7.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 24.0, 38.7, 111.6, 114.1, 116.5, 117.1, 119.4, 122.6, 124.3, 124.5, 127.7, 141.8, 149.8, 155.4, and 157.3; HRMS calcd for $C_{15}H_{12}BrNO_3$ 333.0001, found 333.0003.

***N*-(2-(Benzofuran-3-yl)acetyl)-5-bromo-*N*-(2-methylbenzyl)furan-2-carboxamide (15).** To a stirred suspension containing 0.29 g (1.5 mmol) of 5-bromo-2-furoic acid and 4 Å molecular sieves in 7 mL of CH_2Cl_2 were added 0.26 mL (3.0 mmol) of oxalyl chloride and 2 drops of DMF. The reaction mixture was stirred at rt for 1.5 h, filtered over Celite, and concentrated under reduced pressure. The residue was dissolved in 3 mL of THF, and the solution was added to a stirred suspension containing 0.2 g (1.65 mmol) of 2-methylbenzylamine and 4 Å molecular sieves in 7 mL of THF. The reaction mixture was stirred at rt for 1.5 h, filtered over Celite, diluted with H_2O, and extracted with EtOAc. The organic layer was washed with a saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$, filtered, and concentrated to provide 0.4 g (91%) of 5-bromo-*N*-(2-methylbenzyl)furan-2-carboxamide as a yellow solid: mp 86−88 °C; IR (thin film) 3287, 3125, 3064, 2925, 1646, 1597, 1530, 1471, 1306, 1125, 1012, 927, 798, and 740 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.37 (s, 3H), 4.61 (d, 2H, J = 5.2 Hz), 6.39 (br s, 1H), 6.44 (dd, 1H, J = 3.6 and 0.8 Hz), 7.10 (d, 1H, J = 3.6 Hz), and 7.21−7.31 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.3, 41.6, 114.4, 117.0, 124.6, 126.5, 128.3, 129.1, 130.9, 135.5, 136.9, 150.0, and 157.1.

To a stirred solution containing 0.5 g (1.7 mmol) of the above amide and 0.33 mL (2.3 mmol) of Et_3N in 15 mL of THF was added 0.45 g (2.3 mmol) of 2-(benzofuran-3-yl)acetyl chloride dropwise. The mixture was heated at reflux for 18 h, cooled to rt, concentrated under reduced pressure, and purified by silica gel chromatography to give 0.13 g (20%) of carboxamide **15**: ^1H NMR ($CDCl_3$, 400 MHz) δ 2.26 (s, 3H), 4.08 (s, 2H), 5.05 (s, 2H), 6.39 (d, 1H, J = 3.9 Hz), 6.95 (d, J = 3.6 Hz, 1H), 6.98−7.04 (m, 2H), 7.11 (d, J = 3.6 Hz, 2H), 7.21 (t, J = 7.4 Hz, 1H), 7.28 (dt, J = 7.8 and 1.4 Hz, 1H), 7.44 (d, J = 8.0 Hz, 1H), 7.49 (d, J = 7.6 Hz, 1H), and 7.58 (s, 1H); HRMS calcd for $C_{23}H_{18}NO_4Br$ 451.0419, found 451.0438.

***tert*-Butyl 2-(benzofuran-3-yl)acetyl(furan-2-yl)carbamate (16).** To a solution containing 0.4 g (2.2 mmol) of furan-2-yl carbamic acid *tert*-butyl ester in 10 mL of THF at 0 °C was added dropwise 0.96 mL (2.4 mmol) of *n*-BuLi (2.5 M in hexane). The reaction mixture was stirred at 0 °C for 20 min. In a separate flask, 0.38 g (2.2 mmol) of benzofuran-3-acetic acid was dissolved in 15 mL of THF and 0.24 mL (2.2 mmol) of 4-methylmorpholine at 0 °C, and then 0.29 mL (2.2 mmol) of isobutyl chloroformate was added dropwise. After stirring for 5 min, the white precipitate that formed was removed by filtration and was washed with 10 mL of THF. The filtrate was cooled to 0 °C, and the preformed lithiate obtained from the above Boc carbamate was added dropwise via syringe. After stirring at 0 °C for 20 min, the reaction mixture was quenched with H_2O and extracted with EtOAc. The organic layer was washed with saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to afford 0.45 g (60%) of **16** as a white solid: mp 72−74 °C; IR (film) 3125, 2980, 1787, 1747, 1257, 1152, 1094, and 744 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.42 (s, 9H), 4.25 (d, 2H, J = 0.8 Hz), 6.13 (dd, 1H, J = 3.2 and 0.8 Hz), 6.41 (dd, 1H, J = 3.2 and 2.0 Hz), 7.22−7.33 (m, 3H), 7.46 (d, 1H, J = 8.0 Hz), 7.57 (d, 1H, J = 8.0 Hz), and 7.66 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.7, 32.6, 84.2, 106.0, 111.3, 111.4, 112.9, 119.8, 122.5, 124.3, 127.8, 140.6, 143.3, 143.5, 151.4, 155.6, and 171.9; HRMS calcd for $C_{19}H_{19}NO_5$ 341.1263, found 341.1257.

2-(Benzofuran-3-yl)-*N*-furan-2-ylacetamide (17). To a solution containing 0.44 g (1.3 mmol) of benzofuran **16** in 10 mL of CH_3CN was added 0.46 g (2.1 mmol) of magnesium perchlorate. The solution was heated to 45 °C for 1.5 h, then cooled to room temperature, and the solvent was removed under reduced pressure. The residue was subjected to flash silica gel chromatography to afford 0.11 g (34%) of **17** as a white solid: mp 104−106 °C; IR (film) 3242, 3208, 3061, 1668, 1557, 1452, 1097, and 746 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.78 (s, 2H), 6.31 (m, 2H), 6.97 (s,

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1H), 7.26 (t, 1H, $J = 7.6$ Hz), 7.33 (t, 1H, $J = 7.6$ Hz), 7.50 (d, 1H, $J = 7.6$ Hz), 7.55 (d, 1H, $J = 7.6$ Hz), 7.64 (s, 1H), and 7.86 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.7, 95.8, 111.5, 111.8, 113.1, 119.5, 123.2, 125.1, 127.0, 135.5, 143.5, 144.7, 155.4, and 166.2; HRMS calcd for $C_{14}H_{11}NO_3$ 241.0739, found 241.0750.

2-(Benzofuran-3-yl)-*N*-furan-2-yl-*N*-(2-methylbenzyl)acetamide (18). To a solution containing 0.1 g (0.42 mmol) of the above primary amide **17** in 10 mL of DMF at 0 °C was added 0.017 g (0.42 mmol) of NaH. The mixture was stirred for 2 h at 0 °C, and then a solution of 0.12 g (0.5 mmol) of α-iodo *o*-xylene in 5 mL of DMF at 0 °C was added by cannula. The reaction mixture was stirred at 0 °C for 3 h, then quenched with water and extracted with EtOAc. The combined organic layer was dried over Na_2SO_4, and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography to provide 0.073 g (51%) of the titled compound as a pale yellow oil: IR (film) 3122, 3061, 2925, 1683, 1608, 1501, 1453, 1180, 1156, 1097, and 744 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.19 (s, 3H), 3.63 (s, 2H), 4.88 (s, 2H), 5.85 (d, 1H, $J = 3.2$ Hz), 6.30 (dd, 1H, $J = 3.2$ and 1.6 Hz), 7.05−7.36 (m, 7H), 7.42−7.45 (m, 2H), and 7.52 (d, 1H, $J = 8.0$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.9, 29.6, 49.4, 105.6, 111.2, 111.3, 113.6, 119.8, 122.5, 124.3, 125.8, 127.5, 127.6, 129.1, 130.2, 134.4, 136.5, 140.2, 142.7, 147.6, 155.1, and 170.8; HRMS calcd for $C_{22}H_{19}NO_3$ 345.1365, found 345.1361.

1-(2-Methylbenzyl)-8*a*,10-dihydrobenzofuro[3,2-*d*]indole-2,9(1*H*,3*H*)-dione (19). A solution containing 0.073 g (0.21 mmol) of furanyl amide **18** in 5 mL of toluene was heated at reflux for 18 h. After cooling to rt, the solution was concentrated under reduced pressure. The resulting residue was purified by flash silica gel chromatography to provide 0.04 g (55%) of the titled compound **19** as a yellow solid: mp 174−175 °C; IR (thin film) 3046, 2926, 1727, 1673, 1475, 1465, 1397, 1212, and 748 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.40 (s, 3H), 2.77 (ddd, 1H, $J = 18.0$, 7.2, and 1.6 Hz), 2.89 (d, 1H, $J = 17.2$ Hz), 2.94 (dd, 1H, $J = 18.0$ and 2.8 Hz), 3.08 (d, 1H, $J = 17.2$ Hz), 4.68 (d, 1H, $J = 16.0$ Hz), 4.71 (d, 1H, $J = 1.6$ Hz), 4.90 (d, 1H, $J = 16.0$ Hz), 4.92 (dd, 1H, $J = 7.2$ and 2.8 Hz), 6.90 (t, 1H, $J = 8.0$ Hz), 6.96 (t, 1H, $J = 7.2$ Hz), 7.09 (d, 2H, $J = 7.2$ Hz), 7.15−7.26 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.5, 35.2, 42.2, 45.8, 51.8, 86.3, 94.9, 110.7, 122.0, 123.0, 126.4, 126.7, 127.9, 130.3, 130.5, 130.9, 132.9, 135.7, 142.3, 158.2, 172.5, and 201.0; HRMS calcd for $C_{22}H_{19}NO_3$ 345.1365, found 345.1368.

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Supporting Information Available: ^{1}H and ^{13}C NMR data of various key compounds lacking CHN analyses. This material is available free of charge via the Internet at http://pubs.acs.org.

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