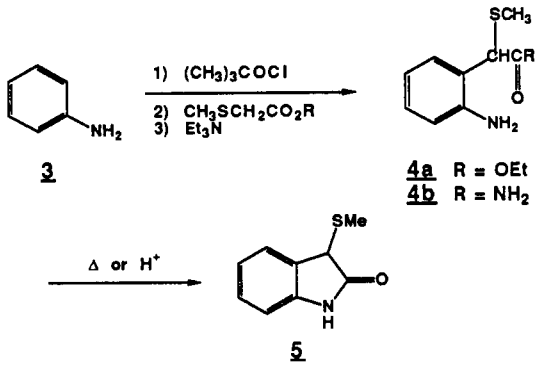
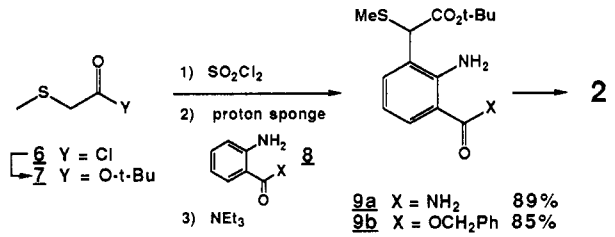
Scheme I



Scheme II



raphy in contrast to the methyl and ethyl esters which spontaneously form the oxindole. The resulting sulfides **9** can be treated with Raney nickel to remove the methylthio group and give the desired compounds **2** in 82–96% yield.

We propose that this modification of the Gassman reaction is a simple, efficient, and versatile route to *tert*-butyl *o*-aminophenylacetates and should expand the usefulness of this methodology.

Experimental Section

Boiling points and melting points are uncorrected. Nuclear magnetic resonance spectra were determined on a Varian Model EM-390 spectrometer operating at 90 MHz. Chemical shifts are reported in ppm (parts per million) relative to tetramethylsilane in chloroform-*d* solutions. Thin-layer chromatography (TLC) was performed on Analtech plates precoated with silica gel GF. Combustion analyses, mass spectra, and infrared spectra (either as neat samples or as Nujol mulls) were obtained by the Physical and Analytical Chemistry Unit of the Upjohn Co. Flash chromatography refers to the method as developed by Still[8] and utilized neutral silica gel (E. Merck, 40–63 mm). *tert*-Butyl alcohol was freshly distilled from calcium hydride under nitrogen. All other solvents were reagent grade distilled from glass (Burdick and Jackson). Reagents were used as purchased. All reactions were degassed and conducted under an inert atmosphere.

***tert*-Butyl (Methylthio)acetate (7).** *tert*-Butyl alcohol (110 mL) in 400 mL of anhydrous diethyl ether at 0 °C was treated dropwise with 1.6 M *n*-butyllithium in hexane (150 mL), stirred for 30 min at ambient temperature, and then treated dropwise with (methylthio)acetyl chloride[5] **6** (30 g, 240 mmol) in 100 mL of anhydrous diethyl ether. After 1 h at room temperature the suspension was washed with 2 × 100 mL of 1:1 brine/water, dried over anhydrous sodium sulfate, and distilled at 90–100 °C at house vacuum to give 20 g (51%) of *tert*-butyl (methylthio)acetate, **7** as a colorless oil: ^{1}H NMR δ 3.10 (s, 2 H), 2.20 (s, 3 H), 1.50 (s, 9 H); IR (neat) 2980, 1725, 1370, 1290, 1170, 1130, 950 cm^{-1}; HRMS calcd for $C_7H_{14}O_2S$ 162.0714, found 162.0700.

General Procedure for 9. *tert*-Butyl (methylthio)acetate (**7**, 12.0 g, 74 mmol) in methylene chloride (800 mL) at −70 °C was treated dropwise with sulfuryl chloride (5.9 mL, 73 mmol), stirred 30 min, then treated dropwise with a solution of Proton Sponge (16 g, 75 mmol) and anthranilamide (**8a**, 10.0 g, 73 mmol) in methylene chloride (1000 mL) over 1 h. The resulting pink slurry was then treated with triethylamine (12 mL, 86 mmol) and allowed to warm to room temperature. The mixture was washed with 3 × 250 mL water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated by rotary evaporation. Flash chromatography on 200 g silica gel, eluting with 1:1 ethyl acetate–hexane, gave **9a** (19.5 g, 89%) as a pale yellow oil: ^{1}H NMR δ 7.5 (m, 2 H), 6.75 (m, 1 H), 6.4 (br s, 2 H), 6.0 (br s, 2 H), 4.5 (s, 1 H), 2.05 (s, 3 H), 1.5 (s, 9 H); IR (neat) 3350, 3345, 1725, 1660, 1560, 1370, 1260 cm^{-1}; HRMS calcd for $C_{14}H_{20}N_2O_3S$ 296.1194, found 296.1202; TLC R_f = 0.40 in 1:1 ethyl acetate–hexane. Anal. Calcd for $C_{14}H_{20}N_2O_3S$: C, 56.73; H, 6.80; N, 9.45. Found: C, 56.73; H, 6.84; N, 9.31.

The synthesis of **9b** was carried out in a similar manner beginning with **8b**[9] (6.5 g, 28 mmol). Flash chromatography with 10% ethyl acetate in hexane as eluent gave **9b** (9.38 g, 85%) as a pale yellow oil which solidified in the refrigerator: ^{1}H NMR δ 8.0 (m, 1 H), 7.2–7.6 (m, 5 H), 6.6 (m, 2 H), 6.5 (br s, 2 H), 5.3 (s, 2 H), 4.6 (s, 1 H), 2.1 (s, 3 H), 1.5 (s, 9 H); IR (Nujol mull) 3460, 1690, 1615, 1455, 1290, 1090, 755 cm^{-1}; HRMS calcd for $C_{21}H_{25}NO_4S$ 387.1504, found 387.1486; TLC R_f = 0.52 in 20% ethyl acetate in hexane. Anal. Calcd for $C_{21}H_{25}NO_4S$: C, 65.09; H, 6.50; N, 3.61. Found: C, 65.05; H, 6.38; N, 3.74.

Raney Nickel Desulfurization. A solution of **9a** (14.5 g, 49 mmol) in absolute ethanol (400 mL) was stirred with Raney nickel (50 mL, washed to neutrality with water then with ethanol) at room temperature for 30 min, filtered through Celite, washing the filter cake with two 50-mL portions of tetrahydrofuran. The combined filtrates were concentrated in vacuo, and the resulting solid was triturated with 1:1 ethyl acetate–hexane to give **2a** (10.0 g, 82%): ^{1}H NMR δ 7.5 (m, 1 H), 7.15 (m, 1 H), 6.5 (m, 1 H), 6.1 (br s, 2 H), 5.8 (br s, 2 H), 3.5 (s, 2 H), 1.4 (s, 9 H); IR (Nujol mull) 3468, 3420, 1711, 1660, 1560, 1310, 1110 cm^{-1}; HRMS calcd for $C_{13}H_{18}N_2O_3$ 250.1317, found 250.1327; TLC R_f = 0.25 in 10% acetone in methylene chloride. Anal. Calcd for $C_{13}H_{18}N_2O_3$: C, 62.38; H, 7.25; N, 11.19. Found: C, 62.09; H, 7.29; N, 10.95.

The synthesis of **2b** was carried out in a similar manner beginning with **9b** (8.4 g, 22 mmol) to give **2b** (7.2 g, 96%) as a yellow oil: ^{1}H NMR δ 7.9 (m, 1 H), 7.1–7.6 (m, 5 H), 6.6 (m, 2 H), 6.2 (br s, 2 H), 5.3 (s, 2 H), 3.3 (s, 2 H), 1.4 (s, 9 H); IR (neat) 3480, 3370, 1710, 1690, 1620, 1575, 1285, 1155, 1140 cm^{-1}; HRMS calcd for $C_{20}H_{23}NO_4$ 341.1627, found 341.1634; TLC R_f = 0.55 in 20% ethyl acetate in hexane. Anal. Calcd for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.04; H, 6.92; N, 4.16.

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A Directed Metalation of *N*-*tert*-Butyl-*N*-methyl-2-methoxybenzamide. Short Syntheses of 2-Methoxy-6-methylbenzoic Acid and Lunularic Acid

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Introduction

Directed metalation of tertiary benzamides has been an area of considerable interest to synthetic chemists in recent years.[2] Tertiary benzamides and particularly *N*,*N*-diethylbenzamides, first reported by Beak[3] in 1977, are ex-

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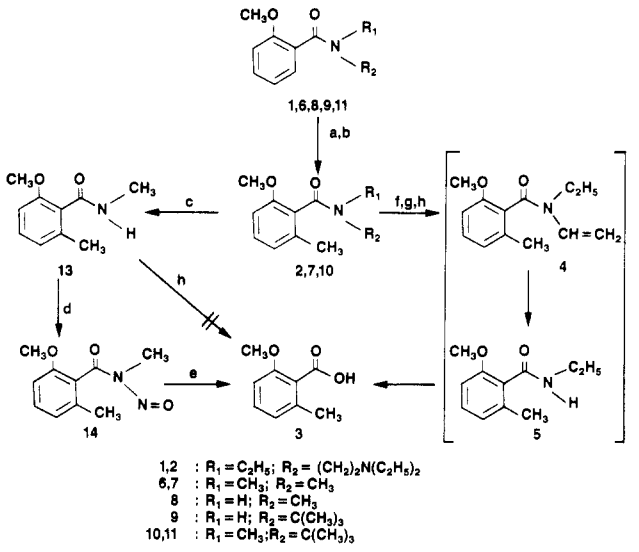
(2) (a) Beak, P.; Snieckus, V. *Acc. Chem. Res.* **1982**, *15*, 306–312 and references cited therein. (b) Snieckus, V. *Heterocycles* **1980**, *14*, 1649–1676 and references cited therein.

(3) Beak, P.; Brown, R. A. *J. Org. Chem.* **1977**, *42*, 1823.

0022-3263/90/1955-1375$02.50/0

Scheme I[a]

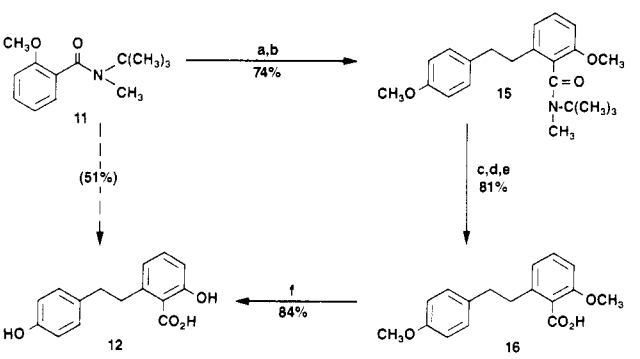


[a] (a) *sec*-BuLi·TMEDA, THF, −78 °C, 1 h; (b) CH_3I; (c) CF_3CO_2H, Δ; (d) $NaNO_2$, HOAc, $(Ac)_2O$, 0 °C; (e) KOH, C_2H_5OH, Δ; (f) CH_3I, Δ; (g) $NaOC_2H_5$, Δ; (h) 6 N HCl, Δ, 7 days.

cellent ortho directors which are usually very stable to metalation conditions. However, one problem which has always plagued tertiary benzamide systems is their resistance to hydrolysis after functionalization. This problem is especially acute for 2-substituted benzamide systems; directed metalation and subsequent reaction with electrophiles in these systems produces 2,6-disubstituted benzamides which are essentially inert to hydrolysis except in the cases where intramolecular lactone formation is possible.[2] Secondary benzamides, although useful in directed metalation syntheses,[4] usually suffer from problems which arise from the lack of solubility of the dianion generated. Many times these reactions require the use of a cosolvent (e.g., HMPA) and/or higher reaction temperatures which sometimes cause unwanted side reactions.[5] Moreover, while secondary benzamides are generally thought to be more susceptible to hydrolysis,[6] acid hydrolysis of 2,6-disubstituted secondary benzamides to the corresponding 2,6-disubstituted benzoic acids still presents quite a challenge.

Recently, Comins[6] has reported that the tertiary β-amino-2-methoxybenzamide **1** undergoes directed metalation and subsequent reaction with methyl iodide in 82% yield. Hydrolysis of the 2,6-disubstituted tertiary β-aminobenzamide **2** to the corresponding benzoic acid **3** in 77% yield was accomplished by a one-pot procedure which employed methyl iodide, sodium ethoxide, and 6 N hydrochloric acid at reflux for 7 days. Presumably, the hydrolysis proceeded by the formation of the corresponding enamine **4** and secondary benzamide **5** as shown in Scheme I, although neither **4** nor **5** was isolated. Snieckus[7] has reported that *N,N*-dimethyl-2-methoxybenzamide (**6**) undergoes directed metalation at temperatures below −90 °C and subsequent reaction with methyl iodide to give useful yields of *N,N*-dimethyl-2-methoxy-6-methylbenzamide (**7**). In fact, hydrangenol, the biochemical precursor of lunularic acid, was synthesized using this methodology. The success of the hydrangenol synthesis, once again, relied upon an intramolecular hydrolysis of the 2,6-disubstituted benzamide via lactone formation.

Scheme II[a]



[a] (a) *sec*-BuLi·TMEDA, THF, −78 °C, 1 h, CH_3I; (b) *sec*-BuLi (1.0 equiv), LDA (0.15 equiv), THF, −78 °C, 1 h, 4-$(CH_3O)C_6H_4CH_2Cl$; (c) CF_3CO_2H, Δ; (d) $NaNO_2$, HOAc, $(Ac)_2O$, 0 °C; (e) KOH, C_2H_5OH, Δ; (f) BBr_3, CH_2Cl_2, −78 °C.

The dianion generated from *N*-methyl-2-methoxybenzamide (**8**) has been reported[7] to react with methyl iodide to give **7** in 80% yield; however, Narasimhan[5] has reported that demethylation can also occur during this metalation reaction, and *N*-methylsalicylamide was isolated as an unwanted side product. Moreover, Giles[8] has reported that the dianion generated from *N-tert*-butyl-2-methoxybenzamide (**9**) gave variable yields of 2-methoxyvalerophenone in addition to *N-tert*-butyl-*N*-methyl-2-methoxy-6-methylbenzamide (**10**).

We have found that *N-tert*-butyl-*N*-methyl-2-methoxybenzamide (**11**) undergoes ortholithiation and subsequent reaction with methyl iodide to give **10** in 98% yield. We believe that **11** offers several distinct advantages for directed metalation syntheses because it is a tertiary directed metalation system which can be easily converted to a secondary system by the procedure outlined in Scheme I (**c**, **d**, **e**), subsequent to metalation, for hydrolysis to the corresponding 2,6-disubstituted benzoic acid. Therefore, we believe that **11** represents a preferable alternative to the two tertiary and two secondary benzamide systems previously discussed.

The potential usefulness of *N-tert*-butyl-*N*-methylbenzamides in the preparation of 2,6-disubstituted benzoic acids by directed metalation has been demonstrated by the syntheses of 2-methoxy-5-methylbenzoic acid (**3**) and lunularic acid (**12**), a growth inhibitor found in *Lunularia cruciata*,[9] in overall yields of 89% and 51%, respectively, from **11**. We believe that these syntheses (Scheme I and Scheme II, respectively) compare favorably to the syntheses of **3** and **12** previously reported.[6,10,11]

Results and Discussion

Metalation. *N-tert*-Butyl-*N*-methyl-2-methoxybenzamide (**11**) undergoes ortholithiation very cleanly. Treatment of a THF solution of **11** at −78 °C with 1.1 equiv of *sec*-BuLi·TMEDA produced an anion solution which was stable for at least 4 h at −78 °C and reacted with methyl iodide to give **10** in 98% yield after sublimation. The addition of the *N-tert*-butyl moiety to the *N*-methyl-2-methoxybenzamide system seems to impart a

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(9) Valio, I. F. M.; Burdon, R. S.; Schwabe, W. W. *Nature* **1969**, *223*, 1176–1178.
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(11) Hauser, F. M.; Pogany, S. A. *Synthesis* **1980**, 814–815.

greal deal of statibility to the orthoanion generated relative to the other *N*-methyl-2-methoxybenzamide systems which have been previously investigated. For example, *N*-[2-(dimethylamino)ethyl]-*N*-methylbenzamides have been reported[6] to suffer self-condensation and other side reactions at −78 °C as does **6**.[12] Although useful yields have been reported[7] for the direct metalation of **6** at −90 °C, we have found that even at −100 °C, some self-condensation product is formed;[12] as one might suspect, the amount of self-condensation product formed is dependent upon both reaction time and reaction temperature. The fact that the orthoanion generated from **11** is very resistant to self-condensation and other side reactions at −78 °C is a distinct advantage when orthofunctionalization is attempted with less reactive electrophiles which require prolonged reaction times.

2-Methoxy-6-methylbenzoic Acid (3). Treatment of **10** with trifluoroacetic acid at reflux for 2 h produced the secondary benzamide **13** quantitatively by ^{1}H NMR spectroscopy. From Comins' work, we had anticipated that **13** could be hydrolyzed in 6 N HCl at reflux. However, 6 N HCl provided only recovered **13** and minor amounts of the corresponding demethylated phenol.[13] As with **13**, the *N*,*N*-dimethylbenzamide **7** could not be hydrolyzed in 6 N HCl at reflux.

Treatment of the secondary benzamide **13** with sodium nitrite in acetic acid/acetic anhydride provided the corresponding *N*-nitrosobenzamide **14** in very high yield;[14] this material could be purified but it proved not to be necessary. On a small scale (<50 mmol), **14** could be hydrolyzed to the corresponding 2,6-disubstituted benzoic acid **3** by treatment with ethanolic KOH at reflux; however, on larger scale hydrolyses (>50 mmol), it was necessary to modify the procedure to safely accommodate the diazomethane generated. Accordingly, an ethereal solution of **14** was slowly added to ethanolic KOH solution which was maintained in a 90 °C oil bath using an Aldrich Diazald apparatus. The diazomethane thus generated was safely codistilled with the ether into acetic acid. To demonstrate that this procedure could be performed on a scale suitable for preparative synthetic work, 33.8 g (0.153 mol) of **11** was converted to 22.6 g of **3** in 89% overall yield. Two sublimations were the only purification steps required for this conversion.

Lunularic Acid (12). The natural product **12** was synthesized in 51% overall yield from **11** to demonstrate that the metalation–hydrolysis sequence is not limited to **3**. The benzyl anion of **10** was generated by the procedure previously developed by Snieckus.[7] The anion reacted slowly with 4-methoxybenzyl chloride at −78 °C; however, on warming to ambient temperature, the color dissipated and the 2-methoxy-6-[2-(4-methoxyphenyl)ethyl]benzamide **15** was isolated in 76% yield after chromatography (Scheme II). The tertiary benzamide **15** was converted to the dimethyl ether of lunularic acid **16** in 81% overall yield via the secondary benzamide **17** (95%) and the corresponding *N*-nitrosobenzamide **18** (93%). Treatment of **16** with boron tribromide provided pure **12** in 84% yield after chromatography.

Conclusion

N-*tert*-Butyl-*N*-methyl-2-methoxybenzamide (**11**) undergoes directed metalation and reaction with methyl iodide to provide *N*-*tert*-butyl-*N*-methyl-2-methoxy-6-methylbenzamide (**10**) in 98% yield. The anion generated from **11** is stable for at least 4 h at −78 °C. Treatment of **10** with trifluoroacetic acid at reflux provided the secondary benzamide **13** quantitatively which could not be hydrolyzed by 6 N HCl at reflux. Basic hydrolysis of the corresponding *N*-nitrosobenzamide **14**, prepared from **13** and sodium nitrite in acetic acid/acetic anhydride, provided 2-methoxy-6-methylbenzoic acid (**3**) in 89% overall yield from **11**. The potential synthetic usefulness of *N*-*tert*-butyl-*N*-methylbenzamides in directed metalation syntheses was further demonstrated by the synthesis of lunularic acid (**12**) in 51% overall yield from **11**.

Experimental Section

General. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Boiling points, taken from distillations, are likewise uncorrected. Infrared spectra were obtained on a Nicolet 170 SK FTIR spectrometer. Nuclear magnetic resonance (NMR) spectra for both ^{1}H and ^{13}C were obtained on a Varian XL-300 (300 MHz) spectrometer, and chemical shifts are reported in δ (ppm) relative to an internal standard of tetramethylsilane (TMS). Mass spectra were obtained on a Finnigan TXQ46 spectrometer. Elemental analyses were obtained from Galbraith Laboratories, Inc. of Knoxville, TN.

Materials. All solvents and starting materials from commercial sources were used without further purification except for tetrahydrofuran (THF), which was dried by distillation from sodium benzophenone ketyl. Triethylamine, diisopropylanine, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA), and *N*-*tert*-butylmethylamine (Fluka) were all dried by distillation from calcium hydride under nitrogen. High pressure liquid chromatography (HPLC) separations were performed on a Waters Associates Prep 500A instrument using silica gel columns. All organometallic reactions were performed under a nitrogen atmosphere using equipment that was oven-dried (120 °C) overnight and allowed to cool in a nitrogen atmosphere prior to use. The titer of the *sec*-butyllithium used was determined by titration with *sec*-butyl alcohol in xylene using 1,10-phenanthroline as indicator.[15]

***N*-*tert*-Butyl-*N*-methyl-2-methoxybenzamide (11).** A solution of 85 mL (61.7 g, 0.61 mol) of triethylamine, 73 mL (53.3 g, 0.61 mol) of *N*-*tert*-butylmethylamine, and 500 mL of dry THF was cooled to 0 °C prior to the dropwise addition of 100.0 g (0.59 mol) of *o*-anisoyl chloride in 150 mL of dry THF. After the addition was complete, the reaction was allowed to warm to ambient temperature and stir overnight. The reaction was filtered, the filter cake was washed with THF, and concentrated in vacuo. The residue was dissolved in methylene chloride and washed with 5% HCl (followed by water) and dried ($MgSO_4$). Concentration in vacuo gave 134 g of crude product, which was purified by vacuum distillation to give 125.6 g (97%) of colorless **11**: bp 122–124 °C (0.3 mm); NMR ($CDCl_3$) δ 1.53 (s, 9 H, $NC(CH_3)_3$), 2.78 (s, 3 H, NCH_3), 3.82 (s, 3 H, OCH_3), 6.87 (d, J = 8 Hz, 1 H, ArH), 6.95 (t, J = 8 Hz, 1 H, ArH), 7.20 (dd, J = 8 Hz and 2 Hz, ArH), 7.29 (td, J = 8 Hz and 2 Hz, 1 H, ArH); IR (neat) 2960, 2925, 1600, 1582, 1493, 1469, 1439, 1283, 1247, 1218, 1180, 1161, 1117, 1061, 1040, 1025, 755 cm^{-1}; MS (70 eV) *m*/*e* (rel intensity) 221 (25) 206 (10), 135 (100), 92 (9), 77 (19), 56 (8). Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65; N, 6.33. Found: C, 70.50; H, 8.66; N, 6.29.

***N*-*tert*-Butyl-*N*-methyl-2-methoxy-6-methylbenzamide (10).** A solution of 35.0 g (158 mmol) of **11**, 26.2 mL (20.2 g, 174 mmol) of TMEDA, and 2000 mL of dry THF was cooled to −78 °C (dry ice/acetone bath) prior to the dropwise addition of 129 mL (174 mmol, 1.1 equiv) of 1.35 M *sec*-butyllithium in cyclohexane. After the addition was complete, the yellow solution was allowed to stir at −78 °C for 1 h prior to the rapid addition of 27 mL (61.6 g, 433 mmol) of iodomethane. The reaction was stirred for an additional 1 h at −78 °C and then allowed to slowly warm to ambient temperature overnight. The THF was removed in vacuo, and the residue was dissolved in methylene chloride. The solution was washed with water, dried ($MgSO_4$), and concentrated

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(13) It is conceivable that for 2,6-disubstituted cases, **2** is hydrolyzed directly and **5** is not an intermediate.
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(15) Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165–168.

in vacuo to give 37.19 g of cream-colored crude product (mp 73–75 °C). Sublimation at 60 °C (0.05 mm) gave 36.4 g (98%) of colorless **10**: mp 75–76 °C (lit.[8] mp 73.5–74.5 °C); NMR ($CDCl_3$) δ 1.54 (s, 9 H, $NC(CH_3)_3$), 2.23 (s, 3 H, $ArCH_3$), 2.74 (s, 3 H, NCH_3), 3.78 (s, 3 H, OCH_3), 6.70 (d, J = 8 Hz, 1 H, ArH), 6.77 (d, J = 8 Hz, 1 H, ArH), 7.24 (t, J = 8 Hz, 1 H, ArH); IR (KBr) 2991, 2963, 2932, 1598, 1583, 1471, 1377, 1363, 1263, 1216, 1178, 1160, 1084, 1045 cm^{-1}; MS (70 eV) m/e (rel intensity) 236 (33), 220 (7), 149 (100), 91 (10), 56 (7). Anal. Calcd for $C_{14}H_{21}NO_2$: C, 71.46; H, 9.00; N, 5.95. Found: C, 71.57; H, 8.90; N, 5.91.

2-Methoxy-6-methylbenzoic Acid (3). A 35.2-g (0.15-mol) sample of **10** was carefully treated with 300 mL of trifluoroacetic acid under nitrogen. *Note*: Care must be taken to use an efficient condenser because the evolution of isobutylene can be very impressive. After the evolution of isobutylene had slowed (~15 min), the reaction was stirred at reflux for an additional 2 h. The trifluoroacetic acid was removed in vacuo, producing the crude secondary benzamide **13** as a glass: NMR ($CDCl_3$) δ 2.32 (s, 3 H, $ArCH_3$), 2.99 (d, J = 9 Hz, 3 H, NCH_3), 3.80 (s, 3 H, OCH_3), 5.70–5.85 (br s, 1 H, NH), 6.73 (d, J = 9 Hz, 1 H, ArH), 6.80 (d, J = 9 Hz, 1 H, ArH), 7.21 (t, J = 9 Hz, 1 H, ArH). *Caution*: The following reaction must be done in a properly operating fume hood. The crude product was dissolved in 160 mL of acetic acid and 1000 mL of acetic anhydride. The vessel was cooled to 0 °C, and 240 g of sodium nitrite was added in 10 equal portions over a 5-h period.[14] The reaction was maintained at 0 °C and stirred overnight. The reaction was filtered, and the filtercake was washed twice with acetic anhydride. The filtrate and washings were combined and concentratred in vacuo (bath temperature <45 °C). The residue was dissolved in 800 mL of methylene chloride and washed with 5% Na_2CO_3 until the pH of the aqueous layer was <9. The solution was dried ($MgSO_4$) and concentrated in vacuo (bath temperature <45 °C) to give 29.9 g (96%) of crude *N*-nitrosobenzamide **14**: NMR ($CDCl_3$) δ 2.26 (s, 3 H, $ArCH_3$), 3.27 (s, 3 H, NCH_3), 3.74 (s, 3 H, OCH_3), 6.76 (d, J = 9 Hz, 1 H, ArH), 6.86 (d, J = 9 Hz, 1 H, ArH), 7.30 (t, J = 9 Hz, 1 H, ArH). Using an Aldrich Diazald apparatus, the crude *N*-nitrosoamide **14** was dissolved in 500 mL of ether and added dropwise to a stirring solution of 30 g of KOH in 300 mL of ethanol which was maintained in a 90 °C oil bath. The diazomethane generated was continuously distilled off with the ether into a vessel containing acetic acid. After the addition was complete, an additional 150 mL of ether was added to ensure that all of the diazomethane had been removed. The reaction was then stirred at reflux for 30 min and concentrated in vacuo. The residue was dissolved in 600 mL of water and extracted three times with methylene chloride. The solution was made acidic (pH 3) with HCl and extracted three times with methylene chloride. The extracts were combined, dried ($MgSO_4$), and concentrated in vacuo to give 23.6 g of crude material that was light yellow in color: mp 134–138 °C. Sublimation at 80 °C (0.02 mm) produced 22.6 g (89% based on **11**) of colorless **3**: mp 137–138 °C (lit.[6] mp 138–140 °C); ^1H NMR ($CDCl_3$) δ 2.47 (s, 3 H, $ArCH_3$), 3.88 (s, 3 H, OCH_3), 6.81 (d, J = 9 Hz, 1 H, ArH), 6.85 (d, J = 9 Hz, 1 H, ArH), 7.28 (t, J = 9 Hz, 1 H, ArH); ^{13}C NMR ($CDCl_3$) 20.2, 56.2, 108.8, 121.6, 123.3, 131.2, 138.5, 157.0, 172.1; IR (KBr) 3700–3260, 3260–2740, 1700, 1587, 1475, 1441, 1402, 1297, 1271, 1091, 1074, 784 cm^{-1}; MS (70 eV) m/e (rel intensity) 166 (38), 148 (100), 119 (18), 105 (28), 90 (60), 77 (20), 65 (12), 51 (14), 39 (13). Anal. Calcd for $C_9H_{10}O_3$: C, 65.05; H, 6.06. Found: C, 65.31; H, 6.14.

***N*-*tert*-Butyl-*N*-methyl-2-methoxy-6-[2-(4-methoxyphenyl)ethyl]benzamide (15).** A solution of 5.0 g (21.3 mmol) of **10**, 0.45 mL (0.32 g, 3.2 mmol, 0.15 equiv) of diisopropylamine, and 300 mL of dry THF was cooled to −78 °C prior to the slow addition of 18.1 mL (24.5 mmol, 1.15 equiv) of 1.35 M *sec*-butyllithium in cyclohexane. The blood-red solution produced was allowed to stir at −78 °C for 1 h prior to the addition of 8 mL (9.24 g, 59.0 mmol, 2.8 equiv) of 4-methoxybenzyl chloride. The reaction was stirred at −78 °C for an additional 2 h and then allowed to slowly warm to ambient temperature overnight. The THF was removed in vacuo, and the residue was dissolved in methylene chloride. The solution was washed with 5% HCl (followed by water), dried ($MgSO_4$), and concentrated in vacuo to give 14.3 g of crude material. Purification by preparative HPLC using 10% ethyl acetate in hexane as the eluant produced 5.76 g (76%) of colorless **15** as a viscous oil: NMR ($CDCl_3$) δ 1.54 (s, 9 H, $NC(CH_3)_3$), 2.67 (s, 3 H, NCH_3), 2.73–2.97 (m, 4 H, CH_2CH_2), 3.77 (s, 3 H, OCH_3), 3.79 (s, 3 H, OCH_3), 6.72 (d, J = 8 Hz, 1 H, ArH), 6.78–6.84 (m, 3 H, ArH), 7.08–7.14 (m, 2 H, ArH), 7.19 (t, J = 8 Hz, 1 H, ArH); IR (neat) 2957, 2930, 2864, 2836, 1598, 1582, 1468, 1438, 1378, 1301, 1218, 1177, 1159, 1107, 1077, 1044 cm^{-1}; MS (70 eV) m/e (rel intensity) 356 (10), 298 (38), 269 (70), 160 (28) 121 (100), 72 (30). Anal. Calcd for $C_{22}H_{29}NO_3$: C, 74.33; H, 8.22; N, 3.94. Found: C, 74.27; H, 8.00; N, 3.99.

***N*-Methyl-2-methoxy-6-[2-(4-methoxyphenyl)ethyl]benzamide (17).** A solution of 5.50 g (15.5 mmol) of **15** in 100 mL of trifluoroacetic acid was stirred at reflux for 48 h. The solvent was removed in vacuo, and the crude product was triturated with water. Filtration, followed by drying over P_2O_5 overnight in a vacuum desiccator, gave 4.40 g (95%) of crude **17**: mp 154–157 °C. Recrystallization from ethanol provided a colorless analytical sample: mp 159–160 °C; NMR ($CDCl_3$) δ 2.81–2.90 (m, 7 H, NCH_3 and CH_2CH_2), 3.77 (s, 3 H, OCH_3), 3.78 (s, 3 H, OCH_3), 6.72–6.82 (m, 3 H, ArH), 6.85 (d, J = 8 Hz, 1 H, ArH), 6.95–7.02 (m, 2 H, ArH), 7.25 (t, J = 8 Hz, 1 H, ArH); IR (KBr) 3265, 2947, 1604, 1583, 1510, 1471, 1263, 1240, 1174, 1084, 1038 cm^{-1}; MS (70 eV) m/e (rel intensity) 299 (12), 268 (27), 134 (8), 121 (100), 77 (7). Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.22; H, 7.07; N, 4.68. Found: C, 72.15; H, 7.10; N, 4.70.

***N*-Methyl-*N*-nitroso-2-methoxy-6-[2-(4-methoxyphenyl)ethyl]benzamide (18).** A solution of 4.40 g (14.7 mmol) of crude **17**, 20 mL of acetic acid, and 100 mL of acetic anhydride was cooled to 0 °C and treated with 1.5 g (22 mmol) of sodium nitrite every 30 min until 15 g (0.22 mol) was added.[14] The temperature was maintained at 0 °C while the reaction was stirred overnight. The reaction was filtered, and the filter cake washed twice with acetic anhydride. The acetic acid/acetic anhydride was removed in vacuo (bath temperature <45 °C). The residue was dissolved in methylene chloride and washed with 5% Na_2CO_3 until the pH of the aqueous layer was <9. The solution was dried ($MgSO_4$) and concentrated in vacuo to give 4.49 g (93%) of crude product. Flash chromatography[16] using 25% ethyl acetate/hexane as eluant provided an analytical sample of **18**, which was a yellow viscous oil: NMR ($CDCl_3$) δ 2.66–2.95 (br s, 4 H, CH_2CH_2), 3.26 (s, 3 H, NCH_3), 3.73 (s, 3 H, OCH_3), 3.78 (s, 3 H, OCH_3), 6.75–6.82 (m, 3 H, ArH), 6.86 (d, J = 8 Hz, 1 H, ArH), 6.98–7.05 (m, 2 H, ArH), 7.33 (t, J = 8 Hz, 1 H, ArH); IR (neat) 2944, 1718, 1584, 1472, 1345, 1265, 1248, 1175, 1079, 1034, 808 cm^{-1}; MS (70 eV) m/e (rel intensity) 328 (1), 298 (92), 269 (58), 252, (15), 161 (51), 121 (100). Anal. Calcd for $C_{18}H_{20}N_2O_4$: C, 65.84; H, 6.14; N, 8.53. Found: C, 65.43; H, 6.03; N, 8.45.

2-Methoxy-6-[2-(4-methoxyphenyl)ethyl]benzoic Acid (16). In a reaction vessel equipped with a gas scrubber to remove the diazomethane generated, a solution of 4.49 g (13.7 mmol) of crude **18**, 10.0 g of KOH, and 150 mL of absolute ethanol was stirred at reflux overnight. The ethanol was removed in vacuo; the residue was dissolved in water and extracted twice with methylene chloride. The pH of the aqueous layer was then adjusted to pH 2 with HCl and extracted three times with methylene chloride. The extracts were combined, dried ($MgSO_4$), and concentrated in vacuo to give 3.60 g (92%) of crude **16** as a viscous oil. Crystalization from toluene/hexane provided a colorless analytical sample: mp 102–103 °C; NMR ($CDCl_3$) δ 2.76–2.85 (m, 2 H, CH_2CH_2), 2.90–2.98 (m, 2 H, CH_2CH_2), 3.69 (s, 3 H, OCH_3), 3.72 (s, 3 H, OCH_3), 6.69–6.80 (m, 4 H, ArH), 7.01–7.08 (m, 2 H, ArH), 7.18–7.27 (m, 1 H, ArH); IR (KBr) 3650–2800, 1664, 1612, 1588, 1514, 1473, 1274, 1250, 1179, 1081, 1034, 816 cm^{-1}; MS (70 eV) m/e (rel intensity) 286 (20), 121 (100), 77 (8). Anal. Calcd for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.28; H, 6.32.

2-Hydroxy-6-[2-(4-hydroxyphenyl)ethyl]benzoic (Lunularic) Acid (12). A solution of 3.60 g (12.6 mmol) of crude **16** in 125 mL of methylene chloride under static nitrogen was cooled to −78 °C and treated with 10.8 mL (28.6 g, 114 mmol) of boron tribromide. After 1 h at −78 °C, the reaction was allowed to slowly warm to ambient temperature and stir overnight. The reaction was slowly treated with 50 mL of water and stirred vigorously for 1 h. The water was separated, and the methylene chloride was dried ($MgSO_4$); concentration in vacuo gave 2.88 g (89%) of the yellowish crude material. Flash chromatography using 35%

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ethyl acetate/5% acetic acid/60% hexane as eluant provided 2.39 g (84%) of colorless lunularic acid: mp 194–195 °C dec (lit.[9] mp 195–196 °C); ^{1}H NMR (DMSO-d_6) δ 2.64–2.73 (m, 2 H, CH_2CH_2), 2.79–3.08 (m, 2 H, CH_2CH_2) 6.62–6.77 (m, 4 H, ArH), 6.98 (t, J = 8 Hz, 2 H, ArH), 7.16 (t, J = 8 Hz, 1 H, ArH); ^{13}C NMR (CD_3OD) δ 38.7, 39.7, 113.7, 115.1, 116.1 (2 C), 120.9, 123.3, 130.3 (2 C) 134.4, 146.0 156.4, 162.7 174.3; IR (KBr) 3461, 3012, 2939, 2850, 1606, 1514, 1466, 1293, 1246, 1170, 1147, 902, 825, 773 cm^{-1}; MS (70 eV) m/e (rel intensity) 258 (12), 107 (100), 105 (5), 77 (12). Anal. Calcd for $C_{15}H_{14}O_2$: C, 69.76; H, 5.46. Found: C, 69.59; H, 5.50.

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Regiocontrolled Nucleophilic Addition to Selectively Activated *p*-Quinone Diimines: Alternative Preparation of a Key Intermediate Employed in the Preparation of the CC-1065 Left-Hand Subunit

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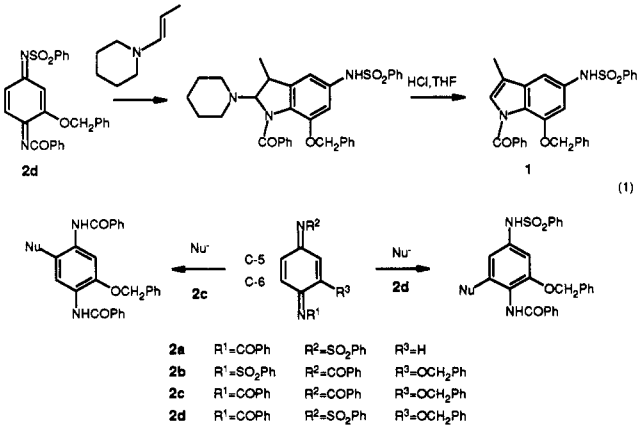
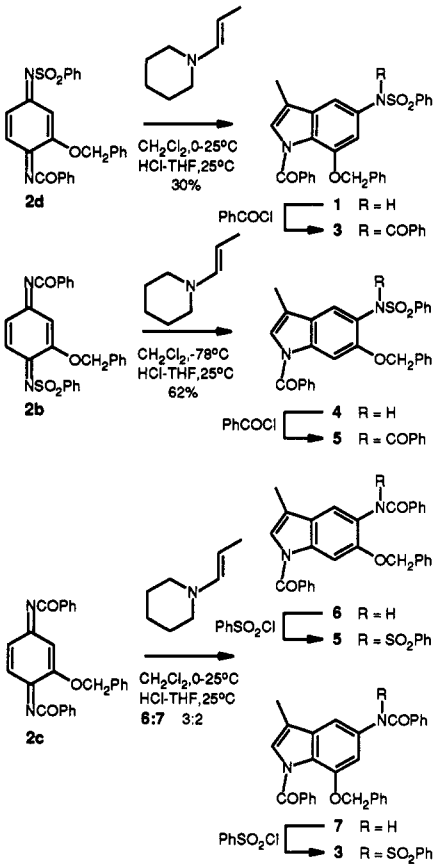
In the course of studies on the total synthesis of (+)-CC-1065 and structurally related agents[2] we have detailed the use of a regiospecific nucleophilic addition to a selectively activated *p*-quinone diimine in the preparation of indole **1**. In these studies, base-catalyzed nucleophilic addition to N^1,N^4-dibenzoyl-*p*-benzoquinone diimine **2c** proceeded predictably with selective C-5 substitution, *and* the inherent regioselectivity of this nucleophilic addition was reversed by the introduction of the N^4-phenylsulfonyl imide of *p*-quinone diimine **2d**. Thus, the selective electrophilic activation of C-6 by the N^4-phenylsulfonyl imide of **2d** proved sufficient to override the inherent preference for C-5 nucleophilic addition observed with the *p*-quinone diimine **2c**, eq 1. Herein we detail a full study of the



regiocontrol available to base-catalyzed, acid-catalyzed, and

Scheme I



Lewis acid-catalyzed nucleophilic additions to selectively activated *p*-quinone diimines and describe its application to the preparation of substituted indoles.[3,4] The reversal of the regioselectivity of nucleophilic addition to *p*-quinone diimine **2c** for reactions under control of Lewis acid activation permitted an alternative and improved preparation of N^1,N^5-dibenzoyl-5-amino-7-(benzyloxy)-3-methylindole, a key intermediate employed in the synthesis of the left-hand subunit of CC-1065.[2]

Enamine Additions to 2b–d. The nucleophilic addition of 1-piperidino-1-propene to **2c** followed by acid-catalyzed aromatization proceeded to provide a mixture of **6** and **7** in which the predominant product **6** (**6**:**7**, 3:2) was derived from nucleophilic addition to C-5 albiet in modest conversion, Scheme I. This preference for C-5 nucleophilic addition was enhanced in **2b** with the N^1-phenylsulfonyl selective activation of C-5 addition and its treatment with 1-piperidino-1-propene followed by acid-catalyzed aromatization provided **4** exclusively in good yield (62–71%). Thus, the complementary N^1-phenylsulfonyl activation in **2b** was found to further enhance the *p*-quinone diimine rate and regioselectivity of C-5 nucleophilic addition. In addition, as previously detailed,[2] the inherent preference for C-5 nucleophilic addition was reversed in **2d** with the overriding N^4-phenylsulfonyl activation of C-6 addition. Treatment of **2d** with 1-piperidino-1-propene followed by acid-catalyzed aromatization provided **1**. Thus, the noncomplementary N^4-

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