Selective Cleavage of Isopropyl Aryl Ethers by Aluminum Trichloride†

Martin G. Banwell,* Bernard L. Flynn, and Scott G. Stewart

Research School of Chemistry, Institute of Advanced Studies, The Australian National University, Canberra, ACT 0200, Australia

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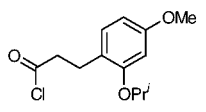
During the course of work[1,2] on the total synthesis of lamellarin-type marine natural products,[3] we sought a protecting group for phenols that would be robust enough to ensure its survival at elevated temperatures and/or under strongly basic conditions. A further requirement was that deprotection could be achieved under conditions that left methoxy-substituted arenes unaffected, viz., these latter units would not themselves be cleaved to give phenols. Among the various phenol-protecting groups currently available,[4] we were attracted to the isopropyl ethers introduced by Simpson[5] (and popularized by Sargent[6] and Stermitz[7]) because they are both robust and readily installed, generally by reacting the phenol with 2-bromopropane in the presence of potassium carbonate. We were, however, concerned that the reaction conditions often used[6,8] for deprotection (BCl_3 in CH_2Cl_2 at 0 °C or HBr−HOAc at 100 °C) might also cleave methyl aryl ethers,[9] especially when this unit was activated by an *o*- or *p*-related carbonyl.[10] In connection with another project, we recently observed[11] that reaction of the acid chloride **1** with $AlCl_3$ in CH_2Cl_2 at 18 °C gave the lactone **2** rather than the desired indanone **3**. This result, which



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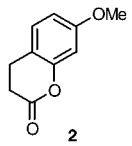

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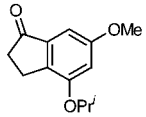

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implies that $AlCl_3$ has the capacity to cleave isopropyl aryl ethers while leaving methyl aryl ethers intact, prompted a study of the capacity of this Lewis acid to selectively cleave the title ethers in the presence of a variety of other functionalities. The results of this study are reported herein and reveal that $AlCl_3$ is a useful reagent for such purposes.

The outcomes from subjecting a series of isopropyl aryl ethers to reaction with $AlCl_3$ in CH_2Cl_2 at 18 °C are shown in Table 1 (see the Experimental Section for detailed procedures). Thus, treatment (entry 1, Table 1) of lamellarin K trisisopropyl ether (**4**) with 3.6 mol equiv of $AlCl_3$ under these conditions affords the natural product **5** in 96% yield. This compares with the 81% yield obtained when BCl_3 (3 mol equiv in CH_2Cl_2 at 0 °C) is used to effect the same conversion. Under very similar conditions, but now using 2.6 mol equiv of $AlCl_3$, lamellarin T diisopropyl ether **6** (entry 2) is cleaved to give the natural product **7**[3] in 89% yield. Twofold deprotection of the 2,3-diarylbenzo[*b*]furan **8** (to give product **9**, see entry 3) was also readily effected, although in this instance more extended reaction times (24 h vs 2 h) were required for complete reaction. In each of these cases, there was no evidence for competing demethylation. Furthermore, there were no complications arising from incomplete reaction, an unwanted situation that has recently been observed[12] by James and Snieckus during efforts to effect two-fold deprotection of a bisisopropyl aryl ether with either BCl_3 or $TiCl_4$. A variety of functional groups (aryl halides, 1,1-dihaloalkenes, aldehydes, acetates) appear to stand up to these new cleavage conditions as evidenced by the high yield conversions outlined in entries 4−6 of Table 1. Of particular significance are the outcomes of the reactions shown in entries 5 (X = CHO) and 6 where the *o*- or *p*-relationship between the OMe and aldehyde groups in compounds **16** and **20** means that there is likely to be activation of the former groups toward cleavage. Despite this, there is no evidence for such cleavage when $AlCl_3$ is used to promote the desired deisopropylation reactions. In contrast, when compound **20** was treated with BCl_3 in CH_2Cl_2 at 0 °C a ca. 5:3 mixture of 2,3-dihydroxybenzaldehyde and 3-hydroxy-2-methoxybenzaldehyde (**21**) was obtained (76% combined yield at 72% conversion). Interestingly, $AlCl_3$ also has some capacity to effect cleavage of compounds attached to solid supports via a phenolic linkage. Thus, reaction of Wang resin/phenol conjugate **22** with $AlCl_3$ under the now standard conditions used in all previous

†Aspects of the work described herein are the subject of a patent application (AIPO Patent Office Provisional Application No. PO6565, lodged May 2nd, 1997).

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(13) Very recently, Mata (Mata, E. G. *Tetrahedron Lett*. **1997**, *38*, 6335) has described cleaving penicillin derivatives from the Merrifield and Wang resins using $AlCl_3$.

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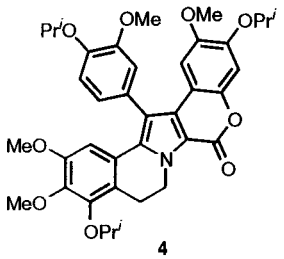
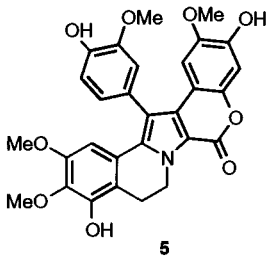
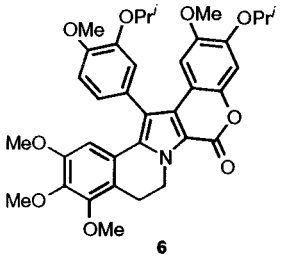
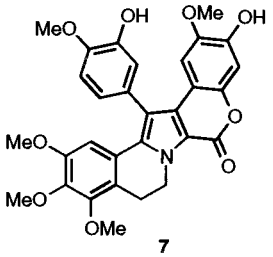
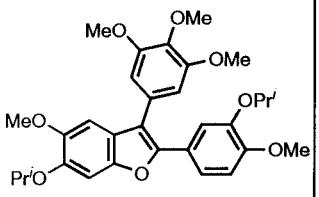
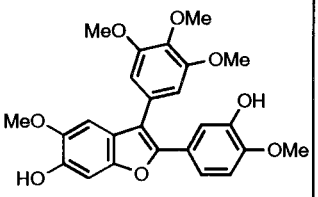
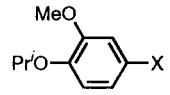
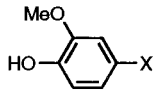
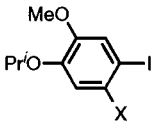
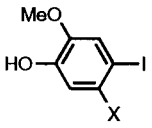
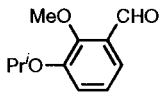
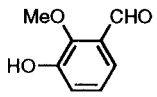
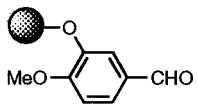
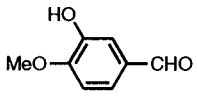
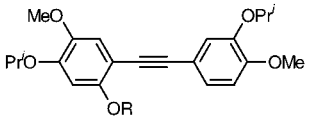
Table 1. Cleavage of Some Isopropyl Aryl Ethers with $AlCl_3$

Entry	Isopropyl Aryl Ether	Cleavage Product	Reaction Time (h)	% Yield
1	 **4**	 **5**	2 h	96 (81*)
2	 **6**	 **7**	2 h	89
3	 **8**	 **9**	24 h	92
4	 **10** X = Br **12** X = OCHO **14** X = $CH{=}CBr_2$	 **11** X = Br **13** X = OCHO **15** X = $CH{=}CBr_2$	16 h (X = Br) 6 h (X=CHO) 3 h (X = $CH{=}CBr_2$)	90 93 80
5	 **16** X = CHO **18** X = OAc	 **17** X = CHO **19** X = OAc	20 h (X=CHO) 2 h (X=OAc)	95 90
6	 **20**	 **21**	3 h	86 (20*)
7	 **22**	 **23**	16	80 (100¶)

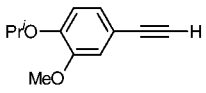
* Yields obtained using boron trichloride; ¶ Yield obtained using trifluoroacetic acid.

cases resulted in formation of the cleavage product **23** although the maximum yield that could be realized was 80% and only when extended reaction times (16 h) were used.[13] In contrast, a quantitative yield of compound **23** was obtained when the conjugate **22** was treated with a 1:1 mixture of CH_2Cl_2 and trifluoroacetic acid for 0.5 h.

There are a number of circumstances under which $AlCl_3$ does not effect smooth cleavage of the isopropyl aryl ether linkage. For example, when either tolan **24** or **25**



24 R = H
25 R = $COCH_2I$



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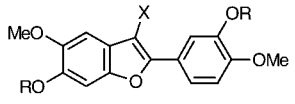
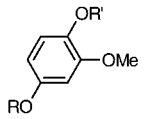


27 R = Pr^i, X = I
28 R = H, X = Pr^i



29 R = Pr^i, R' = TIPS
30 R = R' = H

is subjected to the reaction conditions employed for the conversions shown in Table 1, only complex mixtures of the reaction products are obtained. The same sort of outcome is observed with arylacetylene **26**. Such results suggest that the deprotection conditions defined here are incompatible with alkynes. In contrast to the outcome shown in entry 3 of the table, reaction of the 2-aryl-3-iodobenzo[*b*]furan **27** with $AlCl_3$ affords a complex mixture of products, one component of which is tentatively identified as the C-3 isopropylated product **28** (ca. 27% yield). When substrate **29** is subjected to the same cleavage conditions, there appears to be some preference for initial cleavage of the isopropyl group, but the triisopropylsilyl (TIPS) group is also readily removed, with the end result being that it is almost impossible to prevent the formation of significant quantities of the hydroquinone **30**.

Despite the limitations noted above, $AlCl_3$ would seem to be a useful reagent for cleaving a range of isopropyl aryl ethers. With the developments described here, we believe that the isopropyl moiety represents an especially valuable protecting group for phenols and warrants greater attention than it has been accorded to date. Indeed, with the increasing number of biologically active polyphenolic natural products being discovered,[14] isopropyl protection of phenols would seem to be a useful tool in developing serviceable syntheses of these compounds and their analogues.

Experimental Section

General experimental procedures have been described previously.[15] Unless otherwise specified, NMR spectra were recorded using deuteriochloroform as the solvent. Compounds **4**,[2] **6**,[11] **8**,[16] **10**,[17] **14**,[16] **16**,[16] **24**,[16] **25**,[11] and **27**[16] were prepared according to the cited procedures. The remaining substrates were prepared according to the methods defined below.

Preparation of the Substrates 12, 18, 20, 22, 26 and 29. a. 3-Methoxy-4-isopropoxyphenyl Formate (12). *m*-Chloroperoxybenzoic acid (958 mg, 70% peracid, 3.88 mmol) was added in portions over 0.25 h to a magnetically stirred mixture of 3-methoxy-4-isopropoxybenzaldehyde[2] (500 mg, 2.59 mmol) and potassium hydrogen carbonate (778 mg, 7.77 mmol) in CH_2Cl_2 (30 mL). The resulting slurry was stirred at room temperature for a further 3 h, at which point TLC analysis (silica, 9:1 hexane/ethyl acetate elution) showed that all of the starting material (R_f = 0.3) had been consumed. Consequently, the reaction mixture was diluted with CH_2Cl_2 (100 mL), washed with sodium metabisulfite (1 × 150 mL of a 5% w/v aqueous solution) and brine (1 × 150 mL), then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting white solid was subjected to flash chromatography (silica, 19:1 hexane/ethyl acetate elution), and concentration of the appropriate fractions produced 3-methoxy-4-isopropoxyphenyl formate (**12**) (436 mg, 80%) (R_f = 0.7 in 7:3 hexane/ethyl acetate) as a clear, colorless oil: IR (neat, NaCl, cm^{-1}) 1762, 1740, 1602; ^1H NMR (300 MHz) δ 8.26 (s, 1H), 6.86 (d, J = 8.4 Hz, 1H), 6.64 (m, 2H), 4.46 (septet, J = 6.1 Hz, 1H), 3.81 (s, 3H), 1.34 (d, J = 6.1 Hz, 6H); ^{13}C NMR (75 MHz) δ 159.5, 150.9, 145.3, 143.7, 116.0, 112.2, 105.5, 71.8, 55.8, 21.8; MS (70 eV) *m*/*z* 210 (27, $M^{+\bullet}$), 195.0 [4, $(M - CH_3^{\bullet})^+$], 168 [31, $(M - C_3H_6)^{+\bullet}$], 140 [100, $(M - CO - C_3H_6)^{+\bullet}$]; HRMS calcd for $C_{11}H_{14}O_4$ 210.0892, found 210.0893.

b. 2-Iodo-5-isopropoxy-4-methoxyphenyl Acetate (18). *m*-Chloroperoxybenzoic acid (14.52 g, 60% peracid, 50 mmol) was added to a magnetically stirred mixture of $KHCO_3$ (15.0 g, 108.3 mmol), 3-isopropoxy-4-methoxybenzaldehyde[18] (7.0 g, 36.1 mmol), and CH_2Cl_2 (180 mL) maintained at 0 °C. The reaction mixture was allowed to warm to room temperature, and after 2 h, it was filtered through Celite. The filtrate was concentrated under reduced pressure, and the residue was treated with NH_3 (150 mL of a saturated methanolic solution), allowed to stand for 1.5 h, and then concentrated under reduced pressure. The residue was treated with CH_2Cl_2 (150 mL), pyridine (29.0 mL, 361 mmol), and acetic anhydride (17 mL, 180.5 mmol). The resultant solution was stirred at room temperature for 17 h, diluted with CH_2Cl_2 (100 mL), and then washed with $NaHCO_3$ (1 × 150 mL of a saturated aqueous solution) and citric acid solution (2 × 150 mL of 10% w/v solution in water). The separated organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a light-yellow oil, which was subjected to flash chromatography (silica, 1:1 hexane/CH_2Cl_2 then CH_2Cl_2 elution). Concentration of the appropriate fractions then gave 3-isopropoxy-4-methoxyphenyl acetate (7.1 g, 88%) (R_f = 0.3, CH_2Cl_2) as a light-tan colored oil: IR (neat, KBr plates, cm^{-1}) 1762, 1604; ^1H NMR (300 MHz) δ 6.84 (d, J = 7.5 Hz, 1H), 6.65 (s, 1 H), 6.64 (d, J = 7.5 Hz, 1H), 4.64 (septet, J = 6.0 Hz, 1H), 3.84 (s, 3H), 2.28 (s, 3H), 1.37 (d, J = 6.0 Hz, 6H); ^{13}C NMR (75 MHz) δ 168.2, 147.8, 147.3, 143.6, 112.9, 111.7, 108.3, 71.1, 55.8, 21.7, 20.5; MS (70 eV) *m*/*z* 224 (11, $M^{+\bullet}$), 182 [18, $(M - C_3H_6$ or $CH_2CO)^{+\bullet}$], 140 [100, $(M - C_3H_6 - CH_2CO)^{+\bullet}$], 125 [60, $(M - C_3H_6 - CH_2CO - H_3C^{\bullet})^+$]. Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.3; H, 7.2. Found: C, 64.2; H, 7.1.

Silver trifluoroacetate (3.80 g, 17.2 mmol) and iodine (4.0 g, 15.76 mmol) were added to a solution of 3-isopropoxy-4-methoxyphenyl acetate in anhydrous $CHCl_3$ (30 mL), and the resulting suspension was stirred at 18 °C for 4 h. The reaction mixture was then filtered under reduced pressure through a sintered glass funnel. The silver iodide thus retained was rinsed with $CHCl_3$ (1 × 30 mL), and the combined filtrates were washed with $Na_2S_2O_5$ (1 × 40 mL of a 10% aqueous solution), $NaHCO_3$ (1 × 40 mL of a saturated aqueous solution), and water (1 × 40 mL) and then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a light-yellow oil. This material was subjected to flash chromatography (silica, 1:1 hexane/CH_2Cl_2 then CH_2Cl_2 elution). Concentration of the appropriate fractions then gave compound **18** (4.10 g, 87%) (R_f = 0.4, CH_2Cl_2) as a cream powder, mp 60−61 °C: IR (KBr disk, cm^{-1}) 1763, 1748, 1586; ^1H NMR (300 MHz) δ 7.18 (s, 1H), 6.66 (s, 1H), 4.47 (septet, J = 5.7 Hz, 1H), 3.83 (s, 3H), 2.34 (s, 3H), 1.36 (d, J = 5.7 Hz, 6H); ^{13}C NMR (75 MHz) δ 168.8, 148.7, 148.1, 144.8, 120.9, 109.7, 77.7, 71.6, 56.4, 21.8, 21.1; MS (70 eV) *m*/*z* 350 (30, $M^{+\bullet}$), 308 [67, $(M - C_3H_6$ or $CH_2CO)^{+\bullet}$], 266 [100, $(M - C_3H_6 - CH_2CO)^{+\bullet}$], 251 (54, $M - C_3H_6 - CH_2CO - H_3C^{\bullet})^+$]. Anal. Calcd for $C_{12}H_{15}IO_4$: C, 41.2; H, 4.3; I, 36.2. Found: C, 41.2; H, 4.3; I, 36.5.

c. 3-Isopropoxy-2-methoxybenzaldehyde (20). A magnetically stirred solution of 3-hydroxy-2-methoxybenzaldehyde (**21**)[19] (400 mg, 2.6 mmol) and potassium carbonate (1.26 g, 9.1 mmol) in DMF (6 mL) was treated in one portion with 2-bromopropane (296 μL, 3.2 mmol). The resulting mixture was heated at 100 °C for 3 h and then cooled, diluted with water (40 mL), and extracted with diethyl ether (3 × 50 mL). The combined organic fractions were washed with water (5 × 60 mL) and then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give an orange oil. This material was

(19) Akashi, T.; Kawamura, K.; Shiratsuchi, M.; Ishihama, H. *Chem. Pharm. Bull.* **1986**, *34*, 2024.

subjected to flash chromatography (silica, 19:1 hexane/ethyl acetate elution), and concentration of the appropriate fractions afforded the title compound **20** (453 mg, 89%) (R_f = 0.6) as a clear, colorless oil: IR (neat, NaCl, cm^{-1}) 1692, 1584; ^1H NMR (300 MHz) δ 10.41 (s, 1H), 7.38 (dd, J = 7.7 and 1.7 Hz, 1H), 7.12 (m, 2H), 4.57 (septet, J = 6.0 Hz, 1H), 3.98 (s, 3H), 1.39 (d, J = 6.0 Hz, 6H); ^{13}C NMR (75 MHz) δ 190.2, 153.7, 150.1, 129.9, 123.8, 121.4, 119.2, 71.3, 61.9, 21.9; MS (70 eV) m/z 194 (25, $M^{+\bullet}$), 152 [100, $(M - C_3H_6)^{+\bullet}$], 134 [68, $(M - CO - C_3H_6)^{+\bullet}$]; HRMS calcd for $C_{11}H_{14}O_3$ 194.0943, found 194.0940.

d. Wang Resin/3-Hydroxy-4-methoxybenzaldehyde Conjugate (22). The procedure described by Hamper et al.[20] for the attachment of 4-hydroxybenzaldehyde to Wang resin was followed. Thus, Wang resin (642 mg of 200−400 mesh material, 0.73 mmol/g loading, Calbiochem-Novabiochem) was washed with CH_2Cl_2 (1 × 10 mL) and THF (1 × 10 mL). The dried resin was then treated with THF (12 mL), 3-hydroxy-4-methoxybenzaldehyde (**23**, isovanillin) (500 mg, 3.8 mmol), and triphenylphosphine (447 mg, 1.7 mmol), and the resulting mixture was stirred at room temperature for 5 min. Diethyl azodicarboxylate (298 μL, 1.9 mmol) was then added dropwise, and the resulting mixture was stirred overnight at room temperature. The reaction solvents were then removed, and the resin was washed successively with THF, DMF, methanol, CH_2Cl_2, and diethyl ether (2 × 5 mL of each). The filtered resin was dried under reduced pressure to give conjugate **22** (652 mg). This material had ca. 10% w/w attached 3-hydroxy-4-methoxybenzaldehyde as determined by trifluoroacetic acid (TFA) cleavage (see below).

e. 3-Methoxy-4-isopropoxyphenylacetylene (26). *n*-Butyllithium (51 mL of a 1.6 M solution in hexane, 82 mmol) was added dropwise to a magnetically stirred solution of β,β-dibromo-4-isopropoxy-3-methoxystyrene[2] (14.4 g, 41 mmol) in THF (250 mL) maintained under a nitrogen atmosphere at −78 °C (dry ice/acetone bath). The resulting dark-red solution was stirred at −78 °C for a further 0.33 h and then allowed to warm to room temperature. After an additional 1.5 h, the reaction mixture was quenched with ammonium chloride (150 mL of a saturated aqueous solution) and the THF was removed under a stream of nitrogen. The residue was extracted with diethyl ether (1 × 150 mL), and the separated organic phase was dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a light-yellow oil. This material was subjected to flash chromatography (silica, 2:1 then 1:1 hexane/CH_2Cl_2 elution), and concentration of the appropriate fractions then gave compound **26** (6.6 g, 85%) (R_f = 0.4, 1:1 hexane/CH_2Cl_2) as a clear, amber oil: IR (neat, KBr, cm^{-1}) 3286, 2105, 1598; ^1H NMR (300 MHz) δ 7.04 (dd, J = 8.2 and 1.5 Hz, 1H), 6.98 (d, J = 1.5 Hz, 1H), 6.78 (d, J = 8.2 Hz, 1H), 4.51 (septet, J = 6.0 Hz, 1H), 3.81 (s, 3H), 3.01 (s, 1H), 1.33 (d, J = 6.0 Hz, 6H); ^{13}C NMR (75 MHz) δ 149.6, 148.1, 125.1, 115.2, 114.6, 114.1, 83.7, 75.6, 71.1, 55.7, 21.8; MS (70 eV) m/z 190 (28, $M^{+\bullet}$), 148 [100, $(M - C_3H_6)^{+\bullet}$], 133 [90, $(M - C_3H_6 - H_3C^{\bullet})^+$]; HRMS calcd for $C_{12}H_{14}O_2$ 190.0994, found 190.0990.

f. 3-Methoxy-4-(triisopropylsiloxy)phenylisopropyl Ether (29). Triisopropylsilyl chloride (90 μL, 0.52 mmol) was added to a magnetically stirred solution of 2-methoxy-1,4-benzenediol-4-formate (**13**)[21] (56 mg, 0.33 mmol) and imidazole (46 mg, 0.67 mmol) in DMF (1 mL). The resulting mixture was stirred at room temperature for 16 h then quenched with water (2 mL) and extracted with CH_2Cl_2 (1 × 20 mL). The separated organic phase was washed with water (5 × 20 mL) and then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting light-yellow oil was subjected to flash chromatography (silica, 19:1 hexane/ethyl acetate elution) and afforded, after concentration of the appropriate fractions, 3-methoxy-4-(triisopropylsiloxy)phenyl formate (79 mg, 73%) (R_f = 0.5, 4:1 hexane/ethyl acetate elution) as a clear, colorless oil: IR (neat, NaCl, cm^{-1}) 1744, 1601; ^1H NMR (300 MHz) δ 8.27 (s, 1H), 6.84 (d, J = 8.6 Hz, 1H), 6.63 (d, J = 2.7 Hz, 1H), 6.57 (dd, J = 8.6 and 2.7 Hz, 1H), 3.78 (s, 3H), 1.23 (m, 3H); 1.05 (m, 18H); MS (70 eV) m/z 324 (9, $M^{+\bullet}$), 281 [100, $(M - CO - CH_3^{\bullet})^+$]; HRMS calcd for $C_{17}H_{28}O_4Si$ 324.1757, found 324.1757.

Anhydrous potassium carbonate (41 mg, 0.30 mmol) was added to a magnetically stirred solution of 3-methoxy-4-(triisopropylsiloxy)phenyl formate (48 mg, 0.15 mmol) in methanol (1 mL). The resulting solution was left to stir at room temperature for 2 h and then treated with water (3 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a viscous, yellow oil, which was subjected to flash chromatography (silica, 9:1 hexane/ethyl acetate elution). Concentration of the appropriate fractions afforded 3-methoxy-4-(triisopropylsiloxy)phenol (40 mg, 91%) (R_f = 0.5, silica, 4:1 hexane/ethyl acetate elution) as a clear, colorless oil: IR (neat, NaCl, cm^{-1}) 3562, 1610; ^1H NMR (300 MHz) δ 6.75 (d, J = 8.6 Hz, 1H), 6.46 (d, J = 2.7 Hz, 1H), 6.38 (dd, J = 8.6 and 2.7 Hz, 1H), 5.22 (s, 1H), 3.85 (s, 3H), 1.23 (m, 3H), 1.07 (m, 18H); MS (70 eV) m/z 296 (19, $M^{+\bullet}$), 253 [73, $(M - C_3H_6)^{+\bullet}$], 238 [100, $(M - C_3H_6 - H_3C^{\bullet})^+$]; HRMS calcd for $C_{16}H_{28}O_3Si$ 296.1808, found 296.1802.

A magnetically stirred solution of 3-methoxy-4-(triisopropylsiloxy)phenol (280 mg, 0.94 mmol) and potassium carbonate (456 mg, 3.3 mmol) in DMF (6 mL) was treated in one portion with 2-bromopropane (348 μL, 2.8 mmol). The resulting mixture was heated at 100 °C for 24 h and then cooled to room temperature, diluted with water (10 mL), and extracted with diethyl ether (3 × 20 mL). The combined organic phases were washed with water (2 × 5 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give an orange oil. This material was subjected to flash chromatography (silica, 49:1 hexane/ethyl acetate elution), and two major fractions were obtained.

Concentration of the fraction containing the more mobile component afforded the title compound **29** (60 mg, 34% at 56% conversion) (R_f = 0.7, silica, 4:1 hexane/ethyl acetate elution) as a clear, colorless oil: ^1H NMR (300 MHz) δ 6.75 (d, J = 8.7 Hz, 1H), 6.47 (d, J = 2.7 Hz, 1H), 6.37 (dd, J = 8.7 and 2.7 Hz, 1H), 4.36 (septet, J = 6.2 Hz, 1H), 3.80 (s, 3H), 1.31 (d, J = 6.2 Hz, 6H), 1.25 (m, 3H), 1.10 (d, J = 6.8 Hz, 18H); ^{13}C NMR (75 MHz) δ 151.3, 150.9, 141.2, 118.0, 110.6, 105.0, 72.3, 55.7, 22.1, 17.8, 12.5; MS (70 eV) m/z 338 (76, $M^{+\bullet}$), 296 [47, $(M - C_3H_6)^{+\bullet}$], 253 [100, $(M - C_3H_6 - C_3H_7^{\bullet})^+$]; HRMS calcd for $C_{19}H_{34}O_3Si$ 338.2277, found 338.2283.

Concentration of the fraction containing the less mobile component afforded starting material (123 mg, 44% recovery) (R_f = 0.5, silica, 4:1 hexane/ethyl acetate elution), which was identical, in all respects, with an authentic sample.

Generalized Procedure for the $AlCl_3$-Promoted Cleavage of Isopropyl Aryl Ethers. A solution of the substrate (1 mmol) in CH_2Cl_2 (2.45 mL/mmol of substrate) was treated in one portion with $AlCl_3$ (1.15−1.3 mmol/isopropoxy group), and the resulting mixture was stirred at room temperature for the specified time (see below). Saturated aqueous ammonium chloride (5 mL/mmol of substrate) was added to the reaction mixture, which was then extracted with CH_2Cl_2 (3 × 25 mL/mmol of substrate). The CH_2Cl_2 extracts were washed with water (2 × 50 mL/mmol of substrate), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting crude products were purified according to the procedures described below.

a. Lamellarin K (5). Subjection of lamellarin K trisisopropyl ether (**4**) to the reaction conditions defined in the generalized procedure afforded a solid on workup. This material was subjected to flash chromatography (silica, 20:1, 10:1, then 5:1 CH_2Cl_2/methanol elution), and concentration of the appropriate fractions then gave lamellarin K (**5**) (96%) (R_f = 0.6, 10:1 CH_2Cl_2/methanol elution) as white needles, mp 230−232 °C (lit.[2] mp 230−232 °C), which was identical, in all respects, to authentic material.

b. Lamellarin T (7). Subjection of lamellarin T bisisopropyl ether (**6**) to the reaction conditions defined in the generalized procedure afforded a solid on workup. This material was subjected to flash chromatography (silica, 99:1, 95:5, then 9:1 CH_2Cl_2/methanol elution), and concentration of the appropriate fractions then gave lamellarin T (**7**) (89%) (R_f = 0.2, 20:1 CH_2Cl_2/methanol elution) as white needles, mp 283−284 °C (lit.[3] mp 214−218 °C), which was identical, in all respects, to authentic material.

c. 6-Hydroxy-2-(3′-hydroxy-4′-methoxyphenyl)-5-methoxy-3-(3′,4′,5′-trimethoxyphenyl)benzo[*b*]furan (9). Subjec-

(20) Hamper, B. C.; Dukesherer, D. R.; South, M. S. *Tetrahedron Lett.* **1996**, *37*, 3671.

(21) Guzman, J. A.; Mendoza, V.; Garcia, E.; Garibay, C. F.; Olivares, L. Z.; Maldonado, L. A. *Synth. Commun.* **1995**, *25*, 2121.

tion of the trisisopropyl ether **8** to the reaction conditions defined in the generalized procedure afforded a solid on workup. This material was recrystallized (hexane/CH_2Cl_2) to give the title compound **9**[16] (92%) as white needles, mp 186−188 °C (lit.[16] mp 186−188 °C), which was identical, in all respects, to authentic material.

d. 4-Bromo-2-methoxyphenol (11). The crude product obtained by treating ether **10** under the reaction conditions defined in the generalized procedure was subjected to flash chromatography (silica, 10:1 hexane/ethyl acetate elution). Concentration of the appropriate fractions (R_f = 0.4, silica, 4:1 hexane/ethyl acetate elution) then gave the title compound **11**[17] (90%) as a clear, colorless oil. The spectroscopic data obtained on this material were in accord with those previously reported.[17]

e. 4-Hydroxy-3-methoxyphenyl Formate (13). The crude product obtained by treating ether **12** under the reaction conditions defined in the generalized procedure was subjected to flash chromatography (silica, 4:1 hexane/ethyl acetate elution). Concentration of the appropriate fractions then gave the title compound **13**[21] (93%) (R_f = 0.3, silica, 7:3 hexane/ethyl acetate elution) as a clear, colorless oil: IR (neat, NaCl, cm^{-1}) 3551, 3298, 1737, 1621; ^1H NMR ($CDCl_3$) δ 8.30 (s, 1H), 6.93 (d, J = 8.5 Hz, 1H), 6.67 (m, 2H), 5.68 (s, 1H), 3.89 (s, 3H); ^{13}C NMR δ 159.7, 146.6, 143.7, 142.6, 114.2, 113.1, 104.5, 55.9; MS (70 eV) m/z 168 (73, $M^{+\bullet}$), 140 [99, $(M - CO)^{+\bullet}$], 125 [100, $(M - CO - H_3C^{\bullet})^+$]; HRMS calcd for $C_8H_8O_4$ 168.0423, found 168.0418.

f. β,β-Dibromo-3-hydroxy-4-methoxystyrene (15). The crude product obtained by treating compound **14** under the reaction conditions defined in the generalized procedure was subjected to flash chromatography (silica, 9:1 hexane/ethyl acetate elution). Concentration of the appropriate fractions then gave the title compound **15** (80%) (R_f = 0.6, silica, 4:1 hexane/ethyl acetate elution) as a clear, colorless oil: IR (neat, NaCl, cm^{-1}) 3517, 1599; ^1H NMR (300 MHz) δ 7.39 (s, 1H), 7.19 (d, J = 2.0 Hz, 1H), 7.04 (dd, J = 8.3 and 2.0 Hz, 1H), 6.90 (d, J = 8.3 Hz, 1H), 5.78 (s, 1H), 3.90 (s, 3H); ^{13}C NMR (75 MHz) δ 146.0, 136.4, 127.3, 122.5, 114.2, 110.3, 86.9, 55.9, 29.6; MS (70 eV) m/z 310 (60), 308 (100), 306 (61, $M^{+\bullet}$), 295 (28), 293 (50), 291 [30, $(M - CH_3^{\bullet})^+$]; HRMS calcd for $C_9H_8{}^{79}Br_2O_2$ 305.8891, found 305.8895.

g. 5-Hydroxy-2-iodo-4-methoxybenzaldehyde (17). The crude product obtained by treating compound **16** under the reaction conditions defined in the generalized procedure was subjected to flash chromatography (silica, 4:1 hexane/ethyl acetate elution). Concentration of the appropriate fractions (R_f = 0.2) then gave the title compound **17** (95%) as a white crystalline solid, mp 143−145 °C (lit.[22] mp 141−143 °C). The spectroscopic data obtained on this material were in accord with those previously reported.[22]

h. 5-Hydroxy-2-iodo-4-methoxyphenyl Acetate (19). The solid obtained by treating compound **18** (1.75 g, 5.0 mmol) under the reaction conditions defined in the generalized procedure was suspended in diethyl ether (10 mL) and then filtered and washed with additional diethyl ether (10 mL). The resulting solid was dried under reduced pressure to give compound **19** (90%) as a colorless, crystalline solid, mp 98−99 °C: IR (KBr disk, cm^{-1}) 3378, 1733; ^1H NMR (300 MHz) δ 7.10 (s, 1H), 6.67 (s, 1 H), 6.32 (s, 1H), 3.70 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (75 MHz) δ 168.9, 146.2, 145.3, 144.7, 119.6, 109.4, 76.3, 56.1, 20.8; MS (70 eV) m/z 308 (31, $M^{+\cdot}$), 266 [100, $(M - CH_2CO)^{+\bullet}$]. Anal. Calcd for $C_9H_9IO_4$: C, 35.1; H, 2.9; I, 41.2. Found: C, 35.2; H, 2.9; I, 41.3.

i. 3-Hydroxy-2-methoxybenzaldehyde (21). The crude product obtained by treating compound **20** under the reaction conditions defined in the generalized procedure was subjected to flash chromatography (silica, 9:1 hexane/ethyl acetate elution). Concentration of the appropriate fractions then gave the title compound **21**[19] (86%) (R_f = 0.1, silica, 9:1 hexane/ethyl acetate elution), which was identical, in all respects, to an authentic sample.

j. Deprotection of 3-Isopropoxy-2-methoxybenzaldehyde (20) Using BCl_3. Boron trichloride (566 μL of a 1 M solution in CH_2Cl_2, 0.57 mmol) was added to a magnetically stirred solution of 3-isopropoxy-2-methoxybenzaldehyde **20** (100 mg, 0.51 mmol) in CH_2Cl_2 (6 mL). The reaction mixture was stirred at room temperature for 1 h and then diluted with ammonium chloride (10 mL of a saturated aqueous solution). The separated aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic extracts were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting solid was subjected to flash chromatography (silica, 9:1 hexane/ethyl acetate elution).

Concentration of the fractions containing the most mobile component afforded starting material **20** (28 mg, 28% recovery) (R_f = 0.5), which was identical, in all respects, to an authentic sample.

Concentration of the fractions containing the component of intermediate mobility afforded 2,3-dihydroxybenzaldehyde (25 mg, 35%) (R_f = 0.3), which was identical, in all respects, to an authentic sample obtained from the Aldrich Chemical Co.

Concentration of the fractions containing the least mobile component afforded compound **21** (15 mg, 20%) (R_f = 0.1), which was identical, in all respects, to an authentic sample.

k. Cleavage of Wang Resin/Phenol Conjugate 22 Using $AlCl_3$. Dichloromethane (4 mL) was added to conjugate **22** (100 mg) and the resulting slurry was stirred vigorously at room temperature for 10 min. The reaction mixture was then treated with $AlCl_3$ (39 mg, 0.292 mmol), and stirring was continued overnight. After this time, the resin was filtered off and washed with CH_2Cl_2 (4 × 10 mL). The combined filtrates were washed with HCl (2 × 10 mL of a 10% v/v aqueous solution) and then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give 3-hydroxy-4-methoxybenzaldehyde **23** (8 mg, 80%), which was identical, in all respects, to an authentic sample obtained from the Aldrich Chemical Co.

l. Cleavage of Wang Resin/Phenol Conjugate 22 Using TFA. Dichloromethane (2.5 mL) was added to conjugate **22** (100 mg), and the resulting slurry was stirred vigorously at room temperature for 0.16 h. The reaction mixture was then treated with TFA (2.5 mL), and stirring was continued at room temperature for a further 0.5 h. The resin was then filtered off and washed with CH_2Cl_2 (4 × 10 mL). The combined filtrates were concentrated under reduced pressure to give 3-hydroxy-4-methoxybenzaldehyde **23** (10 mg, 100%), which was identical, in all respects, to an authentic sample obtained from the Aldrich Chemical Co.

m. 6-Hydroxy-2-(3′-hydroxy-4′-methoxyphenyl)-3-isopropyl-5-methoxybenzo[*b*]furan (28). The crude reaction mixture obtained by treating compound **27** under the reaction conditions defined in the generalized procedure was subjected to flash chromatography (silica, 4:1 hexane/ethyl acetate elution). Concentration of the appropriate fractions then gave the title compound **28** (27%) (R_f = 0.2) as white crystalline masses, mp 151−153 °C: IR (KBr, cm^{-1}) 3432, 1509; ^1H NMR (300 MHz) δ 7.21 (d, J = 2.1 Hz, 1H), 7.16 (dd, J = 8.2 and 2.1 Hz, 1H), 7.10 (s, 1H), 7.07 (s, 1H), 6.94 (d, J = 8.2 Hz, 1H), 5.76 (s, 1H), 5.68 (s, 1H), 3.97 (s, 3H), 3.95 (s, 3H), 3.42 (septet, J = 7.0 Hz, 1H), 1.45 (d, J = 7.0 Hz, 6H); ^{13}C NMR (75 MHz) δ 149.2, 148.9, 146.3, 145.4, 143.8, 143.2, 125.0, 120.7, 120.2, 119.7, 113.8, 110.5, 101.9, 97.6, 56.6, 56.0, 25.4, 22.2; MS (70 eV) m/z 328 (100, $M^{+\bullet}$), 313 [38, $(M - CH_3^{\bullet})^+$]; HRMS calcd for $C_{19}H_{20}O_5$ 328.1311, found 328.1316.

n. Deprotection of 3-Methoxy-4-triisopropylsiloxyphenylisopropyl Ether (29). Aluminum trichloride (15 mg, 0.115 mmol) was added, in one portion, to a magnetically stirred solution of 3-methoxy-4-(triisopropylsiloxy)phenylisopropyl ether **29** (30 mg, 0.087 mmol) in CH_2Cl_2 (200 μL). Stirring was continued at room temperature for 3 h, and then the reaction mixture was treated with ammonium chloride solution (2 mL of a saturated aqueous solution) and the aqueous layer was extracted with CH_2Cl_2 (3 × 3 mL). The CH_2Cl_2 extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a light-yellow oil. This material was subjected to flash chromatography (silica, 4:1 hexane/ethyl acetate elution), and two fractions were obtained.

Concentration of those fractions containing the more mobile component afforded 3-methoxy-4-(triisopropylsiloxy)phenol (4 mg, 53%) (R_f = 0.5), which was identical, in all respects, to the material obtained earlier.

Concentration of those fractions containing the less mobile component afforded methoxyhydroquinone **30** (3 mg, 24%) (R_f

(22) Kobayashi, S.; Kihara, M.; Yamahara, Y. *Chem. Pharm. Bull.* **1978**, *26*, 3113.

= 0.2), which was identical, in all respects, to an authentic sample obtained from the Aldrich Chemical Co.

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Supporting Information Available: Selected NMR spectra for compounds **12**, **13**, **15**, **20**, **26**, **28**, and **29** (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

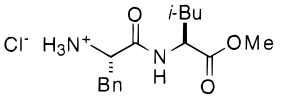
JO9808526

Additions and Corrections

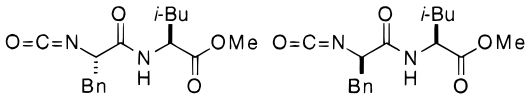
Vol. 61, 1996

James S. Nowick,* Darren, L. Holmes, Glenn Noronha, Eric M. Smith, Tram M. Nguyen, Sheng-Lin Huang, and Edward H. Wang. Synthesis of Peptide Isocyanates and Isothiocyanates.

Page 3929. Efficient stirring is essential to prevent epimerization in the synthesis of peptide isocyanates described in this paper. When L,L-phenylalanylleucine methyl ester hydrochloride (L,L-**1a**) was converted to the corresponding isocyanate (L,L-**2a**) with magnetic stirring or slow (≤300 rpm) mechanical stirring, 1.3−8.8% of the epimeric isocyanate (D,L-**2a**) formed (Table 2). When the reaction mixture was mechanically stirred rapidly (>400 rpm), little epimerization (<0.5%) occurred. These studies show that the conditions described in the paper (rapid mechanical stirring) must be used to prevent significant epimerization.



L,L-1a



L,L-2a D,L-2a

Table 2. Percentage Epimerization upon Conversion of Peptide L,L-1a to Isocyanate 2

stirring method[a]	stirring rate[b]	percentage D,L-**2a** formed[c]
magnetic, small stirbar	315	8.5
magnetic, large stirbar	315	1.3
mechanical	102	8.8
mechanical	201	2.5
mechanical	295	3.1
mechanical	402	0.0
mechanical	504	0.4
mechanical	603	0.3
mechanical	901	0.0

[a] Mechanical stirring was performed with a 35-mm Teflon paddle; magnetic stirring was performed with either a small (4 × 4 × 12 mm) or a large (6 × 6 × 25 nm) magnetic stirring bar. [b] The rates of mechanical and magnetic stirring were measured using a Fowler Digital Hand-Held Tachometer. [c] The percentage of D,L-**2a** formed was measured by trapping isocyanate with L-α-methylbenzylamine and analyzing the resulting mixture of diastereomeric ureas by ^{1}H NMR spectroscopy.

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Vol. 62, 1997

Bosco D'Sa, Dale McLeod, and John G. Verkade*. Nonionic Superbase-Catalyzed Silylation of Alcohols.

Page 5058, column 1, last sentence should read as follows: By contrast, we observed that by utilizing the most widely used conditions (i.e., the less convenient solvent DMF at 24 °C), the catalysts DBU (20 min[10b]), TMG (1 h[10a]), DMAP (12 h[10f]), and 2 equiv of imidazole (no Et_3N, 3 h[14]) led to a 91, 88, 99, and 71% yield, respectively, of the TBDMS-silylated product of (±)-**9** using TBDMSCl.

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10.1021/jo9840123
Published on Web 10/14/1998

Vol. 63, 1998

Akiya Ogawa,* Ryoichi Obayashi, Mikio Doi, Noboru Sonoda,* and Toshikazu Hirao*. A Novel Photoinduced Thioselenation of Allenes by Use of a Disulfide−Diselenide Binary System.

Page 4281. The following Supporting Information paragraph should be added.

Supporting Information Available: NMR spectra for **4b**, **4c**, **4d**, **4d′**, and **5a** (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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10.1021/jo984988f
Published on Web 10/21/1998

Josep Llacay, Jaume Veciana, José Vidal-Gancedo, José Luis Bourdelande, Rafael González-Moreno, and Concepció Rovira*. Persistent and Transient Open-Shell Species Derived from C_{60}−TTF Cyclohexene-Fused Dyads.

Page 5202. In ref 16 the following sentence should be added: Gorgues et al. have also reported a preliminary account on another synthesis of one compound of series **1**, bearing SCH_3 as substituent. Boulle, C.; Rabreau, J. M.; Hudhomme, P.; Cariou, M.; Jubault, M.; Gorgues, A.; Orduna, J.; Garin, J. *Tetrahedron Lett.* **1997**, *38*, 3909.

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Published on Web 10/29/1998