Synthetic Study of Selective Benzylic Oxidation

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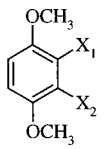
Oxidation of bisbenzyl ethers was studied using 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ). Compared to other benzylic oxidations such as Kornblum type reaction of benzyl bromides or MnO_2 oxidation of benzyl alcohols, DDQ oxidation offered advantages of being mild and highly selective to provide monoaldehyde products. We have explored factors which influence the course of the reaction and exemplified the synthetic value of the approach by preparing a number of aromatic intermediates (**7**−**8**, **15**−**25**).

Introduction

In organic synthesis, differentiation of identical functional groups is of great desire but often challenging to achieve. We have recently carried out Kornblum type reactions[1a−c] on dibromoxylene (**1**), to achieve α-bromomethylbenzaldehyde[2] in a selective manner. The reaction instead gave an array of oxidized products in which the desired aldehyde was obtained in only a minor quantity. A search in the literature for related benzyl bromide oxidative conversion to the aldehydes[3] revealed that such poor selectivity was not uncommon.[4]



1, $X_1=X_2=CH_2Br$
2, $X_1=X_2=CH_2OCH_3$
3, $X_1=X_2=CH_2O$-*i*-Pr
4, $X_1=CH_2OCH_3$, $X_2=H$
5, $X_1=CH_2O$-*i*-Pr, $X_2=H$
6, $X_1=CH_2O$-*t*-Bu, $X_2=H$
7, $X_1=CHO$, $X_2=CH_2OCH_3$
8, $X_1=CHO$, $X_2=CH_2O$-*i*-Pr
9, $X_1=CHO$, $X_2=H$

The low selectivity was presumably caused by the lack of differentiation between the first and subsequent S_N2 bromide substitution step by DMSO (or trialkylamine *N*-oxide), a key step in these oxidation processes. On the other hand, oxidations operating on electron-rich benzylic systems (such as benzyl ethers **2** and **3**) would appear much more promising in achieving selectivity since aldehyde product would discourage further such oxidation due to its electron-deficient nature (Scheme 1).

Benzyl ethers have been oxidized by hydride-transfer agents such as trityl tetrafluoroborate and 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) to the corresponding aldehydes. The reaction involves hydride transfer from an electron-rich system to form an electron-deficient charge-transfer complex.[5] As it is quite evident that such a process may have great value in selective benzylic oxidation, we were not aware of any study dealing with this subject. It is therefore the purpose of this report to discuss some of our findings with regard to the mechanistic features of selective oxidation of bisbenzyl ethers using DDQ.[6] The evaluation of oxidation conditions and preparation of some useful aromatic precursors will also be described.

Results and Discussion

The benzyl ethers (**2**−**5**, **10**−**14**) for this study have been prepared in a straightforward manner from the corresponding benzyl bromides via alkoxide replacement. Oxidation of bisbenzyl ethers **2** and **3** were first examined using conditions similar to those described in the literature.[5] We found that these ethers could be indeed oxidized selectively to give clean formation of α-alkoxytolualdehydes **7** (77.5%) and **8** (90%). The selectivity was not compromised when excessive DDQ (2 equiv) was used on **8**, as ether **3** was the only product obtained. These results seemed to confirm our hypothesis that the intrinsic inertness of the aldehyde product was the key for selective oxidation.

We next examined oxidation of diethers **11**−**13** representing *o*-, *m*-, and *p*-bisbenzyl ethers in order to look at how aromatic substitution could affect reactivity and selectivity. All oxidations took place cleanly and yielded only monoaldehydes **16**−**18** (Table 1). We found however that the rate of oxidation followed the order of para > meta ≫ ortho which was different from para > ortho > meta as normally seen with electrophilic arene substitutions. As shown in Figure 1, conversions of *p*- and *m*-diethers (**13** and **12**) to the corresponding aldehydes were rapid, whereas oxidation of *o*-diether (**11**) was sluggish. As to be further demonstrated in the following section, these results largely reflected the effect of steric hindrance.

Introduction of an electron-donating group greatly enhanced the rate of product formation without compro-

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(1) (a) Nace, H. R.; Monagle, J. J. *J. Org. Chem.* **1959**, *24*, 1792−1793. (b) Kornblum, N.; Jones, W. J.; Anderson, G. J. *J. Am. Chem. Soc.* **1959**, *81*, 4113−4114. (c) Godfrey, A. G.; Ganem, B. *Tetrahedron Lett.* **1990**, *23*, 4825−4826. (d) Mukaiyama, S.; Inanaga, J.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 2221−2222. (e) Franzen, V.; Otto, S. *Chem. Ber.* **1961**, *94*, 1360.

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(4) Under various conditions α,α'-dibromo xylenes or trisbenzyl bromides are oxidized to the corresponding benzene di- or tricarbaldehydes: (a) Feely, W.; Lehn, W. L.; Boekellheide, V. *J. Org. Chem.* **1957**, *22*, 1135. (b) Klandermann, B. H. *J. Org. Chem.* **1966**, *31*, 2618. (c) Reid, W.; Komgstein, F.-J. *Chem. Ber.* **1956**, *92*, 2532.

(5) (a) Piva, O.; Amougay, A.; Pete, J.-P. *Tetrahedron Lett.* **1991**, *32* , 3993−3996. (b) Lee-Ruff, E.; Ablenas, F. J. *Can. J. Chem.* **1989**, *67*, 699−702. (c) Horita, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O. Tetrahedron 1986, 42, 3061. (d) Nakajima, R. Abe, Yonemitsu, O. *Chem. Pharm. Bull.* **1988**, *36* (10), 4244−4247. (e) Xu, Y.-C.; Lebeau, E.; Attardo, G.; Myers, P. L.; Gillard, J. *J. Org. Chem.* **1994**, *59*, 4868−4874.

(6) Triphenylcarbenium tetrafluoroborate, a hydride transfer agent, was briefly examined and found to be less satisfactory.

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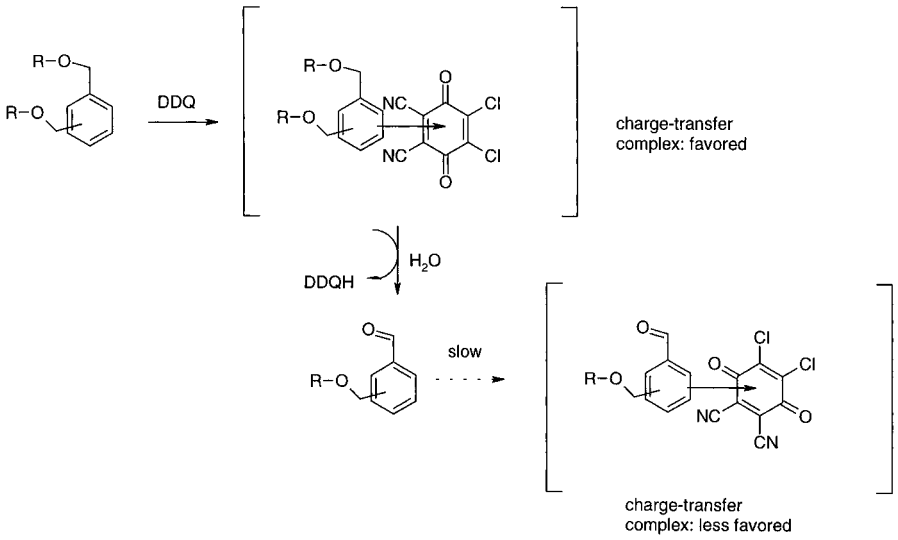
Scheme 1. Mono-Oxidation of Bisbenzyl Ethers



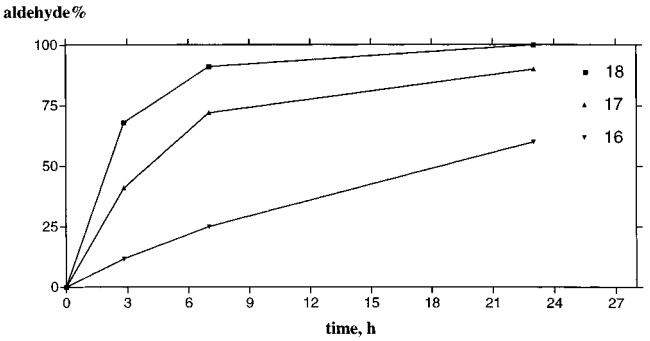


Figure 1.

mising the selectivity. As shown in Table 1, compound **14**, being an *o*-diether (as compared with **11**), underwent rapid oxidation to give monoaldehyde **19** in quantitative yield. The benzyl ether para to the activating methoxy group was specifically oxidized and the assignment of the product was established on the basis of the deshielding effect of the proton signal (at C-5) adjacent to the aldehyde group.[7] Reaction with **14a** also proceeded smoothly to give para-oxidized product **19a** as the only product.[8] Oxidations of **14b** and **14c** were studied to compare the competition between meta and ortho oxidations. In the case of **14b**, *o*-ether was electronically favored, but it was as well more hindered by the two flanking groups. As a result, both **19b** and **19c** were obtained in essentially equal amounts. On the other hand, **14c** gave predominantly **19d** from ortho oxidation. These results indicated that the electronic nature played a major role in determining the regioselectivity of the reaction. But the reaction course could be altered, as we saw with **14b** and **14c**, by the steric hindrance of the system.

We have made further observations as we explored other factors affecting the oxidation process. Comparing *o*-ethers **2** and **3**, the latter carrying the bulkier isopropyl group reacted faster than **2**. Similarly, isopropyl ether **10** reacted faster than methyl ether **11**. These results suggested that the reaction was also influenced by the electronic nature (but not the size) of the alkyl group of the ethers. To establish this point systematically, benzyl ethers (**4**−**6**) carrying groups of different size (therefore different electronic density) were oxidized. The oxidation experiments confirmed that the rate of the reaction was greatly accelerated by electron-donating groups (*t*-Bu > *i*-Pr > Me). It was remarkable that the reaction of *tert*-butyl ether **6** was almost instantaneous. The rapid collapse of the charge-transfer complex was evident as the isobutene signals (1.73 ppm and 4.66 ppm) as well as the aldehyde signals for **9** were detected shortly by ^{1}H NMR (carried out in anhydrous CD_2Cl_2 at room temperature).

Finally, oxidation of **20** represented an interesting case where Boc-protected benzyl amine was competing with benzyl ether. As a result, benzyl carbamate was preferentially oxidized to give aldehyde **8** as the only product.

In an attempt to optimize the oxidation protocol for synthetic applications, we examined two sets of conditions (damp conditions, A, and anhydrous conditions, B, see the Experimental Section for details). Under condition A, water was present during the entire course of the reaction such that aldehyde would form as soon as the hydride transfer was complete. Whereas under condition B, the aldehyde would form after quenching with water. We found that both conditions were effective for selective oxidation of activated ethers. However, condition A gave generally higher yields and was also effective for relative inert ethers such as **2** and **11**, where condition B worked poorly; A became the standard condition for our selective oxidation study (Table 1).

Having explored the scope of the oxidation process and established effective reaction conditions, we carried out conversions based on initial oxidation products to various useful intermediates including α-halotolualdehydes mentioned earlier in this report. These aldehydes were used recently to generate 1-hydroxy quinodimethane[9] thereby serving as useful synthons for podophyllotoxin type of molecules.[10] Thus starting from aldehyde **8**, aldehyde **21** (similarly, iodo analog **21a**) was obtained in one step

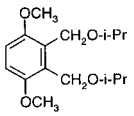
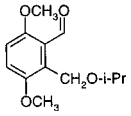
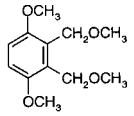
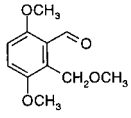
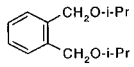
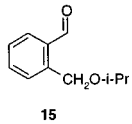
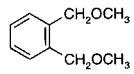
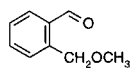
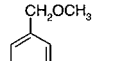
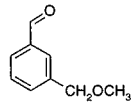
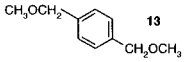
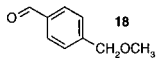
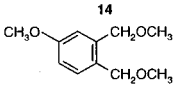
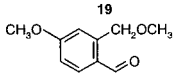
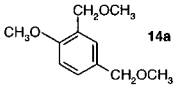
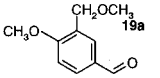
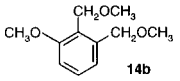
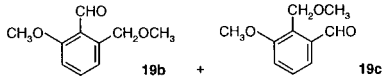
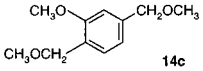
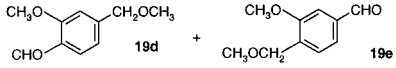
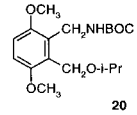
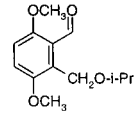
(7) The assignment was further supported by the ^{1}H−^{13}C correlation that the aldehyde carbon correlated with the C-5 proton but not with the C-2 proton.

(8) Compounds **14**, **14a**, and **14c** were highly reactive. Prolonged exposure to DDQ resulted in formation of a considerable amount of dialdehydes.

(9) Attardo, G.; Wang, W.; Kraus, J.-L.; and Belleau, B. *Tetrahedron Lett.* **1994**, *27*, 4743−4746.

(10) Choy, W. *Tetrahedron* **1990**, 46, 2281−2286.

Table 1

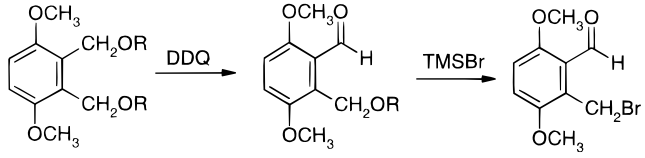
Starting ether	Product	Condition	Time	Yield
 **3**	 **8**	A B	overnight overnight	90% 85%
 **2**	 **7**	A B	3 days 4 days	77.5% <50%
 **10**	 **15**	A B	overnight overnight	90% 88%
 **11**	 **16**	A	one day	53%
 **12**	 **17**	A	one day	80%
 **13**	 **18**	A	overnight	96%
14 	**19** 	A	3 h	98%
 **14a**	 **19a**	A	3 h	95%
 **14b**	 **19b** + **19c** 1:1	A	overnight	98%
 **14c**	 **19d** + **19e** 5:1	A	3 h	96%
 **20**	 **8**	A	overnight	80%

using a trimethylsilyl halide-mediated halogenation reaction[11] (Scheme 2).

The sequence of **1** → **3** → **8** represented a novel approach for differentiating identical functional groups, thereby providing useful means to obtain multifunctional aromatic intermediates. As an example, **23** (difficult to obtain otherwise) was cleanly derived from **8** and then oxidized to **21** in high yield. In addition, **23** was also used to prepare α-azidotolualdehyde **25** in 95% yield (Scheme 3).

The selective oxidation approach has also been used for synthesis of other systems. We have prepared benzopyran molecules such as isochromans starting with bromide **23**.[12] We are currently investigating synthesis of other useful aromatic templates.

Scheme 2



2, R=Me
3, R=*i*-Pr

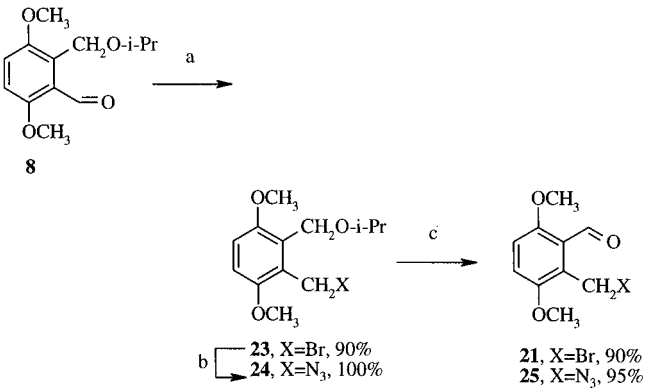
7, R=Me, 77%
8, R=*i*-Pr, 90%

21, 65%

(11) For halogenation of ethers, see: Jung, M. E.; Lyster, M. A. *J. Org. Chem.* **1977**, *42*, 3761−3765.

(12) Unpublished results.

Scheme 3



(a) $NaBH_4$/MeOH, 0 °C to rt to give alcohol **22**, 93%; then, CBr_4/Ph_3P or $Ph_3P{\cdot}Br_2$, 90%; (b) NaN_3/DMSO; (c) DDQ, condition A.

As discussed, the classical Kornblum reaction, as a method for aldehyde synthesis, largely failed to afford single oxidation amid multiple benzyl bromides. A recent study on MnO_2 oxidation of bisbenzyl alcohols[13] also suggests that it is challenging to achieve selective benzylic oxidation. As demonstrated, the free radical process, while achieving marginal single oxidation of *m*- and *o*-bisbenzyl alcohols, failed to selectively oxidize the *p*-counterpart. In the light of these results, the level of selectivity in DDQ-effected oxidation is truly remarkable. Despite wide use of DDQ as a mild oxidizing agent, it has not been studied in the systems where reaction selectivity is an issue. Our results have demonstrated that the benzylic oxidation could be modulated by factors of both electronic and steric origins, allowing excellent selectivity and chemical yields, and DDQ is perhaps the most suitable reagent[6] for these transformations.

To conclude, we have studied selective oxidation using DDQ and shown that chemically equivalent benzyl ethers can be effectively differentiated. We have explored factors affecting the course of the reaction and found that both electronic and steric factors are important for the outcome of the reactions. Our finding that oxidation is encouraged by an electron-releasing ether alkyl group is of synthetic value for effective oxidation of relative inert *o,o′*-bisbenzyl ether. The fact that the reaction rate is reduced by aromatic but not side chain steric hindrance is also revealing. It suggests that an initial aromatic stacking is perhaps required, which seems to depend on the steric environment of the ring as well as the electronic density of the entire system.[14] The knowledge we acquired during this investigation on the reactivity of benzyl carbamate versus benzyl ether could be used for selective chemical manipulations. Finally, the preparation of intermediates **7**, **8**, and **15**−**25** has demonstrated that DDQ-based selective benzylic oxidation is a viable approach that should find wide synthetic applications.

Experimental Section

Chemicals described in the study, such as 2,3-dichloro-5,6-dicyanobenzoquinone, chlorotrimethylsilane, triphenyl phosphine dibromide, sodium methoxide, isobutene, were all purchased from Aldrich Chemical Co. Reagent grade solvents such as dichoromethane, chloroform, methanol, and tetrahydrofuran were used as received without further purification. In the cases where anhydrous conditions were required, anhydrous solvents purchased from Aldrich Chemical Company were used under the protection of nitrogen. The products were purified by flash chromatography (silica gel 60, 0.040−0.065 mm/230−400 mesh).

General Procedure for Preparation of *iso*propyl Benzyl Ethers.[15] A solution of 2-propanol (2.62 mL, 34.2 mmole) in 30 mL of THF was slowly added to a prestirred mixture of sodium hydride (60%, 1.60 g, 39.0 mmol) and dibromide **1** (5.00 g, 15.0 mmol) in 30 mL of THF. The mixture was stirred at rt for 4 h then quenched with water. The ethyl acetate extract (500 mL) was washed with water (150 mL) and brine (150 mL) and dried over magnesium sulfate. The desired ether **3** was obtained as a white solid (3.46g, 79%) after chromatography (eluent, hexane:ether = 10:3): mp 44−45 °C; ^{1}H NMR (δ) 1.20 (12 H, d, J = 7.5 Hz), 3.69 (2H, sept., J = 7.5 Hz), 3.77 (6H, s) 4.63 (4H, s), 6.77 (2H, s); ^{13}C NMR (δ) 22.21, 55.60, 60.67, 71.16, 112.12, 128.07, 152.68; MS 282 (M^+, 12), 222 (80), 180 (100), 149 (20); HRMS calcd 282.1831, found 282.1833.

Ether 5: oil, 80%; ^{1}H NMR (δ) 1.26 (6H, d, J = 7.7 Hz), 3.79 (6H, s), 3.82 (1H, m), 4.56 (2H, s), 6.76 (1H, d, J = 2.2 Hz), 6.77 (1H, s), 7.07 (1H, d, J = 2.2 Hz); ^{13}C NMR (δ) 21.28, 54.69, 54.96, 63.71, 70.34, 110.22, 111.49, 128.00, 150.06, 152.79; MS 210 (M^+, 90), 167 (17), 151 (100), 137 (90), 121 (80); HRMS calcd 210.1256, found 210.1265.

Ether 10: oil, 75%; ^{1}H NMR (δ) 1.25 (12H, d, J = 6.3 Hz), 3.72 (2H, m), 4.61 (4H, s), 7.28 (2H, dd, J = 3.5 Hz, 5.5 Hz), 7.42 (2H, dd, J = 3.5 Hz, 5.5 Hz); ^{13}C NMR (δ) 21.2, 66.8, 70.1, 126.6, 127.7, 136.0; MS (CI) 223 (M + H^+, 100), 163 (60), 120 (17); HRMS (CI) calcd 223.1698, found 223.1702.

General Procedure for the Preparation of Methyl Benzyl Ethers. A solution of bis- or monobenzyl bromide was treated with excessive commercially available sodium methoxide (1−2 equiv of the bromide) and stirred at room temperature for a few hours until the reaction was complete. The crude product was purified by flash chromatography using ether/hexane as a eluent system.

Ether 2: oil, 100%; ^{1}H NMR (δ) 3.43 (6H, s), 3.82 (6H, s), 4.61 (4H, s), 6.85 (2H, s); ^{13}C NMR (δ) 55.5, 57.4, 64.0, 110.9, 126.4, 151.6; MS 226 (M^+, 28), 194 (95), 179 (100); HRMS calcd 226.1205, found 226.1202.

Ether 4: oil, 84%; ^{1}H NMR (δ) 3.34 (3H, s), 3.78 (3H, s), 3.79 (3H, s), 4.49 (2H, s), 6.80 (2H, s), 6.98 (1H, s); ^{13}C NMR (δ) 54.76, 55.02, 57.44, 68.47, 110.39, 112.20, 113.66, 126.75, 150.32, 152.69; MS 182 (M^+, 100), 151 (73), 121 (34); HRMS calcd 182.0943, found 182.0948.

Preparation of Ether 6 (Similar to Livinghouse's Conditions[16]). To a solution of benzyl alcohol (1g, 6.06 mmol) in 5 mL of dichloromethane cooled to −78 °C was condensed 5 mL of isobutene. To this well-stirred bilayer mixture was added catalytic amount of triflic acid (70 μL, 0.79 mmole). The dark-green mixture was stirred at −5 °C for 2 h to become a solution with lightened color. Triethylamine (253 μL, 1.81 mmole) was added and the resulting product mixture was washed with sodium bicarbonate solution. The organic layer was dried and then evaporated. The desired product was obtained from chromatographic purification (hexane:ether) (oil, 44%): ^{1}H NMR (δ) 1.33 (9H, s), 3.80 (6H, s), 4.52 (2H, s), 6.77 (2H, m), 7.13 (1H, d, J = 2.2 Hz); ^{13}C NMR (δ) 27.00, 54.97, 55.05, 57.98, 72.61, 110.04, 111.02, 113.04, 129.00, 150.01, 152.09; MS 224 (M^+, 90), 151 (100), 121 (30); HRMS calcd 224.1412, found 224.1408.

Preparation of Ether 14. To a solution of 3,4-dimethylanisole (4.30 g, 31.6 mmole) in anhydrous carbon tetrachloride (100 mL) was added *N*-bromosuccinimide (11.4 g, 63.8 mmole) and a catalytic amount of AIBN (0.100 g). The mixture was refluxed for 4 h. It was cooled to 50 °C and filtered. The filtrate was evaporated and the product was purified by

(13) Constantinides, I.; Macomber, R. S. *J. Org. Chem.* **1992**, *57*, 6063−6067.

(14) The 5-bromo analog of ether **3** underwent only slow oxidation (5% of product) using method A.

(15) For general benzyl ether synthesis, see: (a) Ortiz, B; Walls, F.; Yuste, F.; Barrios, H.; Sanchez-Obregon, R.; Pinelo, L. *Synth. Commun.*, **1993**, 23 (6), 749−756. (b) Blagg, J.; Davies, G. S.; Holman, N. J.; Laughton, C. A.; Mobbs, B. *J. Chem. Soc. Perkin Trans. 1* 1986, 1581−1589. (c) Mann, S. *J. Chem. Soc.* **1954**, 2819−2825.

(16) Holcombe, J. L.; Livinghouse, T. *J. Org. Chem.* **1986**, 111−113.

chromatography using hexane to give the desired product as a liquid (8.83 g, 94%): ^{1}H NMR (δ) 3.83 (3H, s), 4.64 (2H, s), 4.67 (2H, s), 6.84 (1H, dd, J = 8.5 and 2.7 Hz,), 6.92 (1H, d, J = 2.7 Hz), 7.30 (1H, d, J = 8.5 Hz); ^{13}C NMR (δ) 29.1, 29.7, 54.5, 113.7, 115.6, 127.6, 131.6, 137.1, 159.2; 4 g of the above-obtained product (13.6 mmole) was converted to the ether product **14** according to the general procedure for preparation of methyl benzyl ethers as mentioned above (2.27 g, 85%, as an oil): ^{1}H NMR (δ) 3.36 (3H, s), 3.42 (3H, s,), 3.82 (3H, s), 4.44 (2H, s), 4.53 (2H, s), 6.80 (1H, dd, J = 8.3 and 2.7 Hz), 6.92 (1H, d, J = 2.7 Hz), 7.26 (1H, d, J = 8.3 Hz); ^{13}C NMR (δ) 54.3, 56.9, 57.4, 70.9, 71.0, 11.65, 113.0, 127.1, 129.7, 137.5, 158.5; MS 196 (M^+, 2), 164 (95), 149 (100); HRMS calcd 196.1099, found 196.1106.

General Procedures for Selective Oxidation. Method A.[5c] To diether in 10:1 dichloromethane:water (0.02−0.07 M) was added DDQ and the reaction mixture was vigorously stirred at room temperature. The mixture was then washed with sodium bicarbonate (saturated) and brine and dried over magnesium sulfate. After solvent was evaporated, the crude product was further purified by chromatography.

Aldehyde 16: oil, 53%, ^{1}H NMR (δ) 3.47 (3H, s), 4.85 (2H, s), 7.45 (1H, m), 7.59 (1H, m), 7.84 (1H, d, J = 7.6 Hz), 10.20 (1H, s); ^{13}C NMR (δ) 57.67, 70.91, 126.81, 127.14, 131.50, 132.45, 132.89, 139.87, 191.81; MS 150 (M, 40), 135 (100), 118 (56), 105 (8), 90 (5); HRMS calcd, 150.0681, found 150.0684.

Method B. To a solution of benzyl ether (0.02−0.07 M in dichloromethane) was added DDQ (1.5 equiv). The reaction mixture was stirred at room temperature (or reflux for inert ethers) overnight or longer. Then the mixture was washed with sodium bicarbonate solution (saturated) and brine. After evaporation of the solvent and rapid chromatographic purification (eluent, ethyl acetate:hexane), the desired aldehyde was obtained.

Aldehyde 7: oil, four days, excess DDQ, ∼50% (Method A, three days, 77.5%); ^{1}H NMR (δ) 3.40 (3H, s), 3.81 (3H, s), 3.83 (3H, s), 4.77 (2H, s), 6.93 (1H, d, J = 9.2 Hz), 7.07 (1H, d, J = 9.2 Hz), 10.54 (1H, s); ^{13}C NMR (δ) 55.4, 55.8, 57.6, 62.6, 111.5, 116.4, 124.3, 126.6, 151.6, 151.3, 155.2, 191.5; HRMS calcd 210.0896, found 210.0890.

Conversion of 8 to α-Halotolualdehydes 21 and 21a. A solution of compound **8** in dichloromethane (0.05 M) was treated with 3 equiv of trimethylsilyl bromide (or TMSI). The reaction mixture was stirred overnight at rt and then washed with sodium bicarbonate (saturated). Solvent was evaporated to give desired product **21** (65%): mp 72−73 °C; ^{1}H NMR (δ) 3.86 (3H, s), 3.87 (3H, s), 5.05 (2H, s), 6.94 (1H, d, J = 10.6 Hz), 7.08 (1H, d, J = 10.6 Hz), 10.60 (1H, s); ^{13}C NMR (δ) 42.92, 55.36, 55.56, 111.69, 116.64, 123.12, 123.93, 151.28, 155.59, 191.19; MS 260 (M^+ + 2, 31), 258 (M^+, 32), 179 (100), 164 (20), 149 (18); HRMS calcd, 257.9891, found 257.9886.

Iodide 21a (60%): mp 110−112 °C ^{1}H NMR (δ) 3.85 (3H, s), 3.90 (3H, s), 5.01 (2H, s), 6.90 (1H, d, J = 10 Hz), 7.03 (1H, d, J = 10 Hz), 10.62 (1H, s); ^{13}C NMR (δ) −3.94, 55.33, 55.47, 110.90, 116.65, 120.71, 129.43, 150.42, 156.40, 191.27; MS (M^+, 7), 179 (100), 149 (10), 121 (15), 91 (23); HRMS calcd 305.9753, found 305.9756.

Conversion of 8 to 23. Aldehyde **8** (1.04 g, 4.37 mmole) in THF:MeOH (36 mL:8 mL, 0.09M) was reduced by sodium borohydride (165.32 mg, 4.37 mmole) for 15 min as it warmed from 0 °C to rt, to give, after acidic workup, the corresponding alcohol **22** (1.04g, 99%): ^{1}H NMR (δ) 1.20 (6H, d, J = 6.1 Hz), 3.50 (1H, br s), 3.74 (1H, sept. J = 6.1 Hz), 3.76 (3H, s), 3.78 (3H, s), 4.68 (2H, s) 4.72 (2H, s), 6.78 (1H, d, J = 11 Hz), 6.81 (1H, d, J = 11 Hz); ^{13}C NMR (δ) 21.14, 55.35, 55.47, 59.94, 70.63, 110.29, 110.73, 126.06, 130.36, 150.87, 151.06. A solution of this compound (**22**, 0.99 g, 4.14 mmole) in 80 mL of THF was treated with triphenylphosphine (2.28g, 8.69 mmol) and carbon tetrabromide (2.88g, 8.69 mmole) and stirred for 30 min at rt then filtered. The filtrate was evaporated and the crude product was chromatographed to give 1.17 g (94%) of desired bromide **23**: mp 34−35 °C; ^{1}H NMR (δ) 1.23 (6H, d, J = 6.3 Hz), 3.72 (1H, sept., J = 6.3 Hz), 3.77 (3H, s), 3.84 (3H, s), 4.67 (2H, s), 4.77 (2H, s), 6.78 (1H, d, J = 8 Hz), 6.82 (1H, d, J = 8 Hz); ^{13}C NMR (δ) 21.18, 24.56, 55.40, 55.61, 59.31, 70.60, 110.84, 111.72, 126.31, 126.90, 151.08, 151.10; MS 304 (M^+ + 2, 35), 302 (M^+, 35), 181 (100); HRMS calcd 302.0517, found 302.0526.

Preparation of α-Azidotolualdehyde 25. Compound **23** (200 mg, 0.66 mmol) was stirred at rt in DMF (10 mL) with sodium azide (64 mg, 0.99 mmole) for 2 h. The reaction mixture was poured into water and extracted with ethyl acetate to give azido product **24** (183 mg, 100%): ^{1}H NMR (δ) 1.24 (6H, d, J = 4.5 Hz), 3.73 (1H, m), 3.80 (3H, s), 3.86 (3H, s), 4.70 (2H, s), 4.80 (2H, s), 6.80 (1H, d, J = 6.8 Hz), 6.86 (1H, d, J = 6.8 Hz); ^{13}C NMR (δ) 21.20, 44.40, 55.06, 59.48, 70.42, 110.18, 111.30, 124.21, 126.49, 151.16, 151.62; MS 265 (M^+, 30), 179 (30), 164 (100); HRMS calcd 265.1426, found 265.1431; IR, NaCl film, cm^{-1}, 2975.4, 2091.9, 1488.1, 1259.3, 1097.2, 1052.7, 804.8, 719.9. A sample of this product (31 mg, 0.118 mmol) in 5 mL of dichloromethane and 0.5 mL of water was treated with DDQ (80.6 mg, 0.355 mmol) and the reaction mixture was vigorously stirred at room temperature for 36 h. The mixture was washed with sodium bicarbonate (saturated) and brine and dried over magnesium sulfate. Desired product **25** (28 mg) was obtained (95%): mp; 112−113 °C; ^{1}H NMR (δ) 4.89 (3H, s), 4.90 (3H, s), 5.08 (2H, s), 6.98 (1H, d, J = 6.1 Hz), 7.12 (1H, d, J = 6.1 Hz), 10.63 (1H, s); ^{13}C NMR (δ) 22.83, 55.38, 55.72, 75.76, 76.08, 76.40, 111.29, 116.90, 121.61, 127.21, 150.78, 156.24, 191.09; IR, NaCl film, cm^{-1}, 2971.1, 2104.5, 1729.5, 1680.0, 1489.0, 1435.9, 1276.7, 1092.6, 1073.6, 817.3, 718.2; MS 221 (M, 7), 193 (8), 178 (100), 164 (95), 148 (52), 135 (53); HRMS calcd 221.0800, found 221.0804.

Preparation of 20. A methanolic solution of **24** (100 mg, 0.38 mmole, 15 mL) containing di-*tert*-butyl dicarbonate (123 mg, 0.566 mmole) was catalytically hydrogenated (Pd/C/10%, H_2, 1 atm, 40 mg, 0.038 mmole) for 2 h at rt. The catalyst was filtered and the filtrate was evaporated to give a product which was further purified to give the desired product (112 mg, oil, 87%): ^{1}H NMR (δ) 1.24, (6H, d, J = 7.5 Hz), 1.44 (9H, s), 3.77 (1H, m), 3.79 (6H, s), 4.45 (2H, d, J = 5Hz), 4.66 (2H, s), 5.45 (1H, s), 6.80 (2H, m); ^{13}C NMR (δ) 21.20, 27.53, 35.19, 55.30, 55.60, 59.85, 70.51, 77.68, 110.17, 110.49, 126.12, 127.89, 151.28, 154.73; MS 339 (M^+, 8), 209 (100), 167 (50); HRMS calcd 339.2046, found 339.2051.

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Supporting Information Available: Spectral data for compounds **8**, **11**−**13**, **14a**−**c**, **15**, **17**−**19**, and **19a-e**, including copies of ^{1}H NMR, ^{13}C NMR, low-resolution mass, and high-resolution mass spectra (126 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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