Investigation of the Tert-Butyl Benzyl Moiety as a Protecting Group for Alcohols

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by

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Abstract

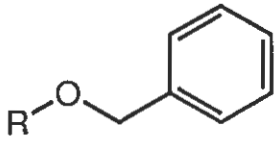
The molecule 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (**2**) has been investigated as a possible reagent to regenerate alcohols from their benzylated derivatives. A linear free energy study undertaken to investigate the effects which different benzyl substituents have on the DDQ deprotection reaction has shown that a para-tert-butylbenzyl (TBPM, which denotes tert-butylphenylmethylene) moiety is intermediate in reactivity and may increase the synthetic selectivity possible in molecules with more than one alcohol group. Investigation into the chemical environments compatible with the oxidative removal of TBPM by DDQ afforded positive results in simple to moderately complex compounds.

Introduction

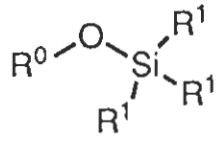
Often in the synthesis of complex molecules one functional group will interfere in a reaction intended for a different functional group. This problem can be overcome through the use of protecting groups. Protecting groups mask the interfering functionality by temporarily changing its chemical nature, allowing the reaction of interest to be carried out. Successful protection of a functional group involves the formation of an inert derivative and the eventual removal of the protecting group under mild conditions to regenerate the original functionality.[1] The alcohol functional group is found in natural and synthetic compounds and is often protected as an ether derivative (via a nucleophilic substitution reaction of the corresponding alkoxide). Two of the most widely used ether derivatives include benzyl (Bn) and trialkylsilyl ethers (**1**). Both of these entities are inert to most commonly used reagents and serve as excellent protecting groups in many situations.

1

Common Alcoholic Protecting Groups



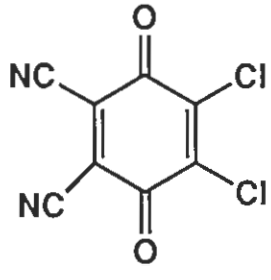
Alcohol Protected as Benzyl Ether
R= rest of the molecule



Alcohol Protected as Silyl Ether
R^0 = rest of the molecule
R^1= various alkyl chains

The acidic and reductive environments often used to remove these ether moieties (acidic conditions for trialkyl sily ethers and catalytic hydrogenation for benzyl ethers) can be a source of problems, however, when other sensitive functional groups are also present in the molecule.[2] The ability to deprotect alcohols in a manner that would avoid these acidic or reductive conditions would be a valuable tool for the synthetic chemist. Previous research efforts have shown that 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (2) has the ability to deprotect alcohols under neutral conditions in excellent yields without also causing the aformentioned side reactions.[5,6]

2
DDQ

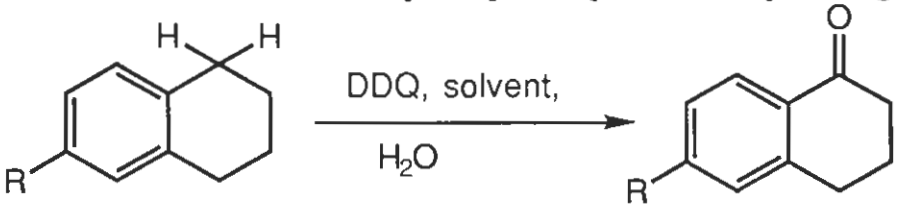


Literature Review

Findlay and Turner described how the benzylic position para to an electron donating group was readily oxidized by DDQ to the corresponding carbonyl group (Scheme 1).[3]

Scheme 1

Oxidation of the benzylic para position by DDQ

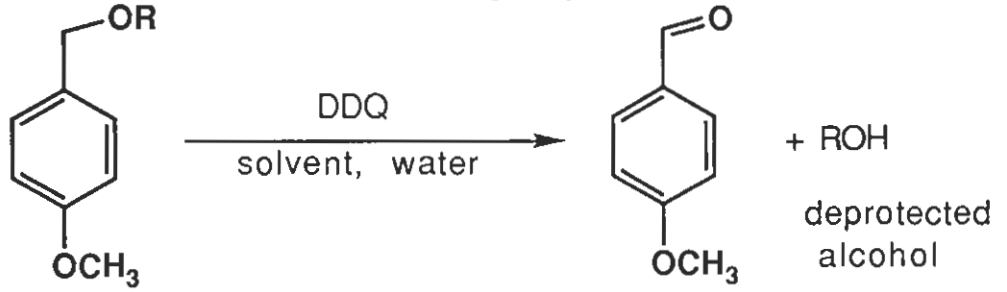


R = electron-donating group

Oikawa, et. al., utilized the extra reactivity afforded by the electron-donating moiety to successfully remove a para-methoxybenzyl (MPM, which denotes methoxyphenylmethyl) protecting group from an alcohol with DDQ (Scheme 2).[5]

Scheme 2

Removal of MPM group with DDQ



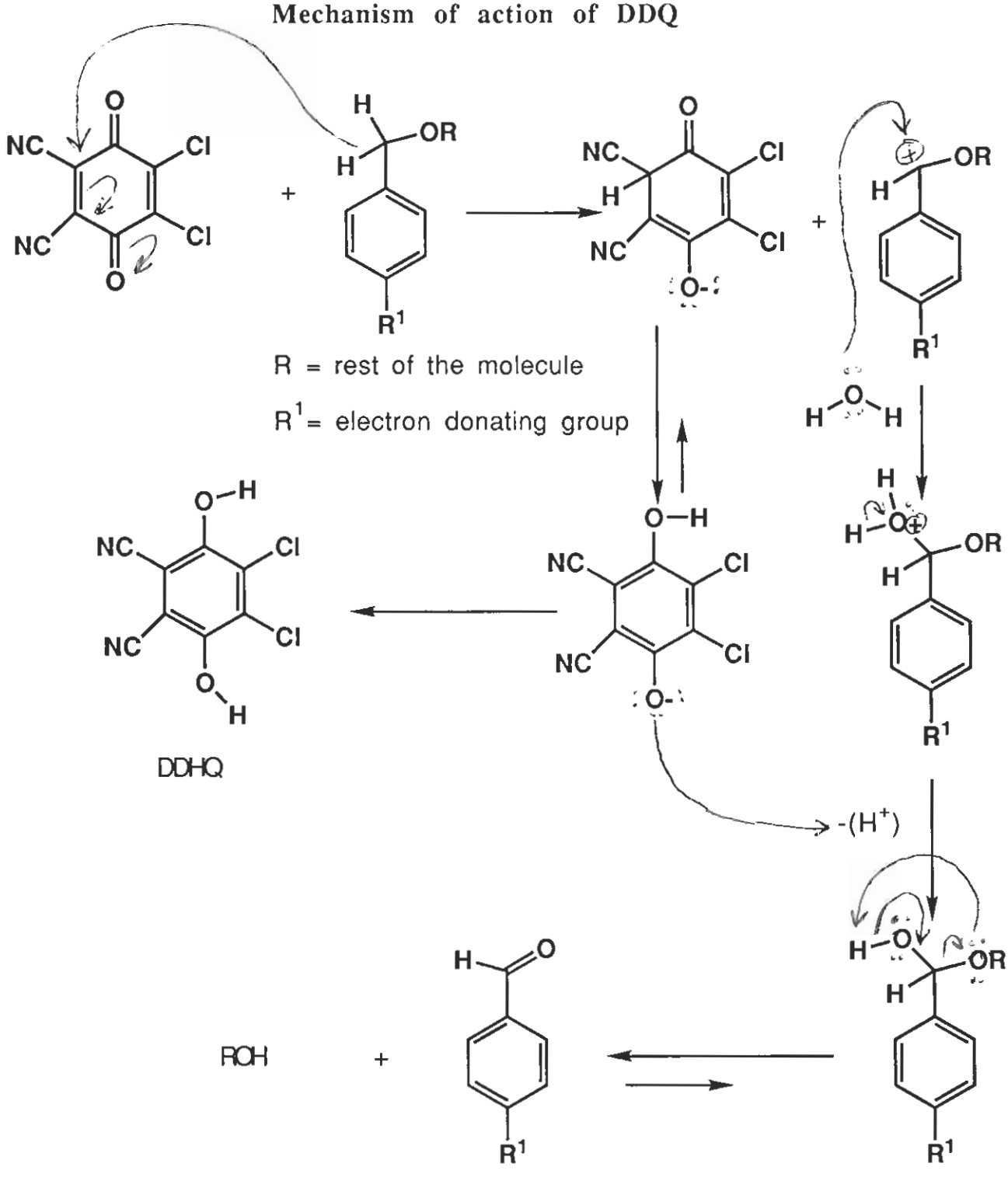
(R = rest of the molecule)

MPM protected alcohol

A mechanism of action for DDQ involving an initial rate-determining hydride ion transfer from the para-benzylic position to the DDQ molecule (the aromatization of DDQ is the driving force of the reaction) followed by addition of water and decompostion of the resultant hemiacetal has been postulated by Ohki and coworkers (Scheme 3).[4] This proposed mechanism accounts for the substituent effects seen by Findlay and Turner in that the carbocation formed from the hydride transfer would be stabilized through the resonance and inductive modes of the electron-donating entity.

Scheme 3

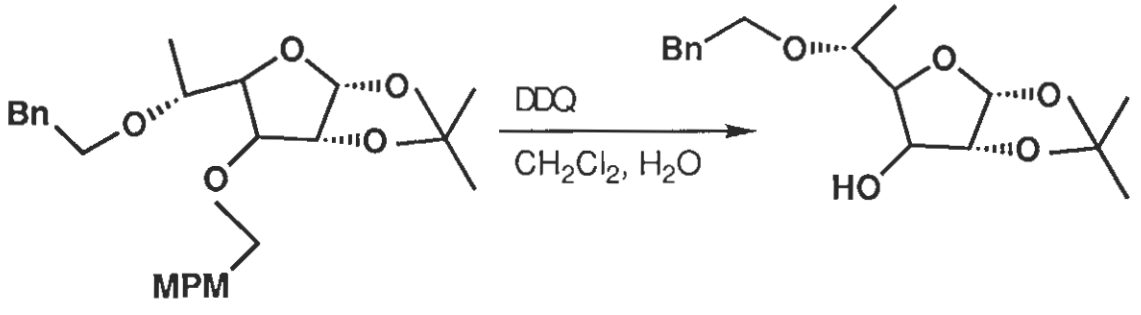
Mechanism of action of DDQ



Oikawa found that the best results were achieved using a methylene chloride solvent sytem. This procedure has additional merit in that the slightly acidic byproduct, 2,3-dichloro-5,6-dicyanohydroquinone (DDHQ), is insoluble in both methylene chloride and water and is therefore removed from the reaction mixture, keeping the system close to neutrality. Using the MPM group, Oikawa's research team was able to deprotect primary alcohols without any interference in the presence of other functional groups, such as the acid-sensitive isopropylidene moiety and an allylic double bond. A molecule that contained two isopropylidene groups, however, reacted unusually slowly. Compounds of secondary alcohols containing benzoyl, tosyl, epoxide, alkene, and keto functionalities also gave good results. Not surprisingly, an unsubstituted benzyl group (Bn), lacking the extra stabilization induced by an electron-donating group, was almost unreactive towards DDQ oxidation, allowing Oikawa to selectively remove a MPM protecting group in the presence of benzylated alcohols (Scheme 4).[5] Other commonly used alcoholic

Scheme 4

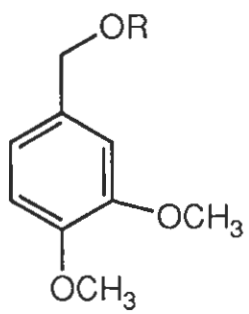
Selective Deprotection of MPM with DDQ



protecting groups, including tetrahydropyranyl, methoxymethyl (MOM), acetyl, and tert-butyldimethylsiliyl (TBDMS), were also unaffected by DDQ. Yonemitsu further examined the possiblity of selectively removing one protecting group in the presence of others with DDQ.[6] In addition to corroborating the results of earlier work with MPM ethers,[5] he found that a 3,4-dimethoxybenzyl (DMPM) protecting group (**3**) was sufficiently more

3

DMPM



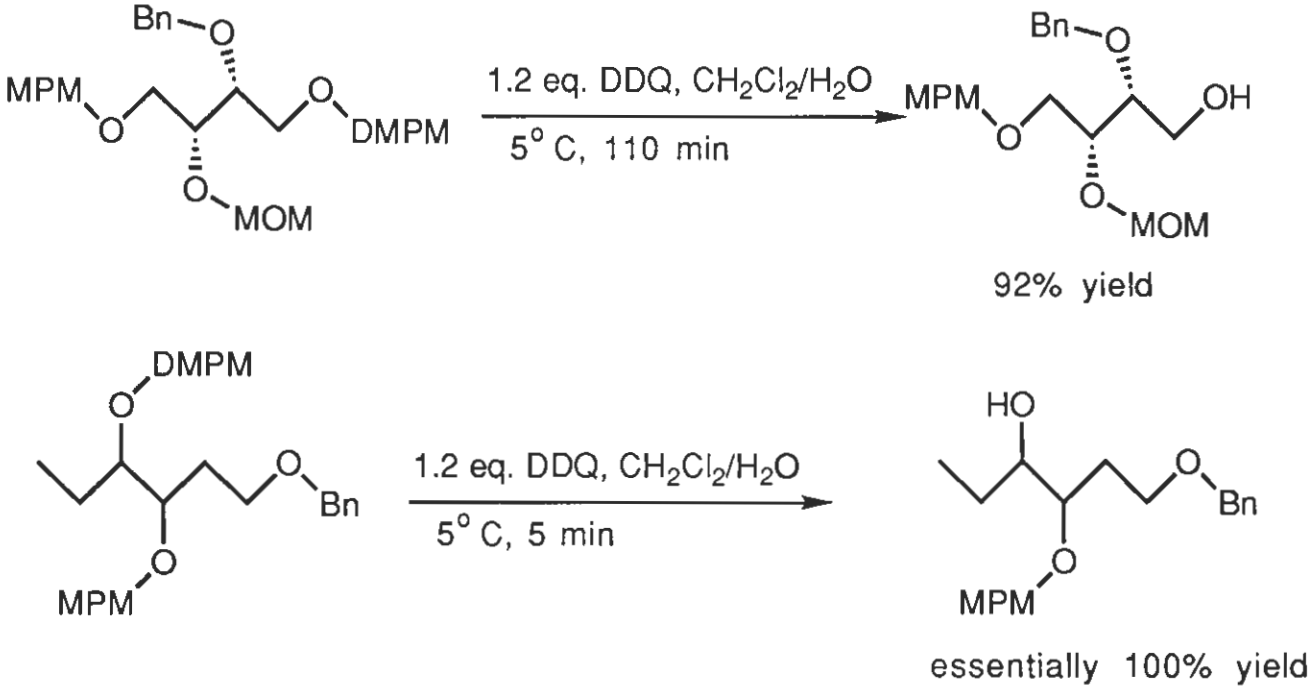
R = rest of the molecule

3,4- dimethoxybenzyl protected alcohol

reactive towards DDQ than the MPM ethers that the DMPM group could be selectively removed in the presence of the MPM moiety (Scheme 5).[6]

Scheme 5

Selective Removal of DMPM with DDQ



Theory

The purpose of this research is to investigate the synthetic flexibility of the DDQ deprotection sequence. Oikawa has shown that MPM ethers may be oxidatively cleaved in the presence of Bn protecting groups,[5] and Yonemitsu has shown that DMPM ethers may be oxidatively cleaved in the presence of MPM ethers.[6] We wish to further increase this flexibility by finding a less reactive, substituted benzyl protecting group as an intermediate between the unreactive Bn group and the strongly stabilized (and thus very reactive) MPM and DMPM groups. To this end we investigated the effects of substituents in general on the DDQ deprotection

reaction via a linear free energy study.

Linear free energy relationships describe the effects different substituents have on reaction rates (as compared to a standard reaction). The change in reaction rate a substituent causes in the studied reaction often varies linearly between many different reactions that contain the same substituent. For example, the change in the free energy of activation for the hydrolysis of ethyl benzoate upon introduction of a substituent is directly proportional to the change in the free energy of ionization that is caused by the introduction of the same substituent into the dissociation of benzoic acid. This linear change is due to the effects of the substituent on the reaction (a combination of resonance, field, and inductive effects) and may cause the reaction to either speed up or slow down. When a standard reaction is defined, the dissociation of benzoic acid, sigma (σ) values for different substituents may be determined. These sigma values (or substituent constants) can then be used in the correlation of other reaction series. Furthermore, upon studying the effects of different substituents on a certain reaction, a rho (ρ) value that denotes the reaction constant (for benzoic acid dissociation rho equals one) can be determined. This reaction constant is a measure of a particular reaction's sensitivity to substituent effects. The relationship in Equation 1 (where k_X is the reaction rate of the substituted reaction

$$\log (k_X/k_H) = \text{sigma}*\text{rho} \qquad \textbf{(Eqn. 1)}$$

and k_H is the reaction rate of the unsubstituted (H) reaction) can then be set up. By experimentally determining reaction rates and knowing sigma values for the various substituents tested (found in physical organic

texts),[7,10] a value for rho can be found (Figure 1). This experimentally gives an indication of the studied reaction's sensitivity to substituent effects.[7]

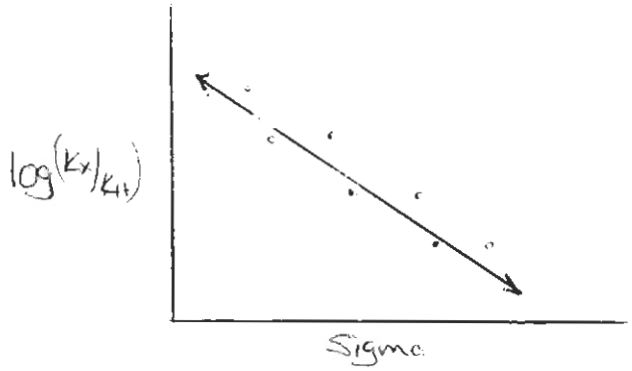
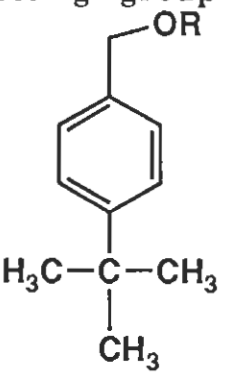


Figure 1. General Plot of experimentally determined reaction rates (log k_X/k_H) versus sigma (substituent constant) values. The slope of the line, rho, gives an indication of the studied reaction's sensitivity to substituent effects.

We theorized that a para-tert-butylbenzyl (TBPM) protecting group (**4**) (having a substituent, para-tert-butyl, which is less electron-donating in nature than the MPM group) will be intermediate in reactivity towards DDQ and can occupy the synthetic niche we are trying to fill. Therefore, the purpose of this study was to determine the effectiveness of the TBPM protecting group in various synthetic environments.

4

TBPM protecting group for alcohols



(R = rest of the molecule)

p-t-butylbenzyl (TBPM) protected alcohol

Results and Discussions

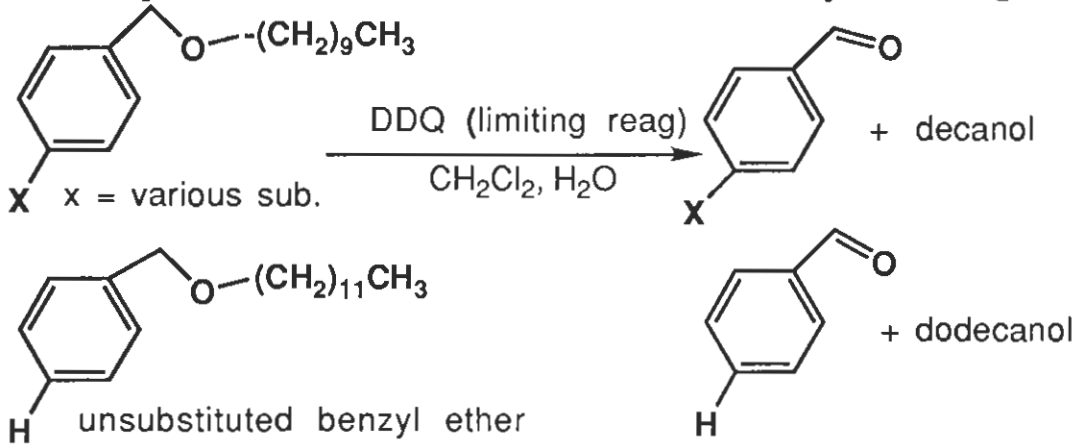
Kinetics Study of the DDQ Reaction

The initial work performed on this project was a linear free energy investigation of the DDQ reaction sequence.[8] Various meta- and para-substituents were examined for their effects upon the DDQ-induced deprotection of benzyl alkyl ethers relative to an unsubstituted benzyl ether. All of the ethers investigated were synthesized from commercially available meta- and para- substituted benzyl alcohols (or benzaldehydes, which were reduced to benzyl alcohols). The formation of the corresponding alkoxides and subsequent reaction with an alkyl bromide yielded the protected substrates. Due to the heterogeneous nature of the DDQ system (making exact duplication of reaction conditions nearly impossible), experimental kinetic data was gathered from a series of

competition reactions (Scheme 6).[9] Relative initial reaction rates were obtained using

Scheme 6

Competition reaction used in kinetic study of DDQ



small, limiting amounts of DDQ. The molar amounts of the alcohols generated were determined by gas chromatographic analysis referenced to an internal standard (tetradecane). The molar ratios of the deprotected alcohols could then be used as a measure of log (k_X/k_H). The amounts of the other reaction products, the benzaldehydes, were not quantified. In analyzing the experimental data, a distinction between the meta- and para- substituents was necessary. Unlike the para-substituents, the meta-substituents cannot stabilize the initially formed (and rate-determining) carbocation intermediate (see Scheme 3, Mechanism of action of DDQ) by resonance, thus making an unequivocal examination of the two types impossible. This distinction has been adjusted for by the determination of sigma$^+$ (σ^+) values for para substituents.[10] These sigma$^+$ values take into account the extra stability afforded a benzylic cation by direct resonance with the para substituent and make kinetic predictions more closely

resemble experimental findings. Figures 2 and 3 show the results of our kinetic investigation. The large negative rho value found for both types of substituents, indicating that all of these substituents have a large effect upon the DDQ deprotection reaction, is acceptable based upon Ohki's proposed mechanism (with rate limiting carbocation formation)[4] and upon experimental results with Bn, MPM, and DMPM type ethers.[5,6]

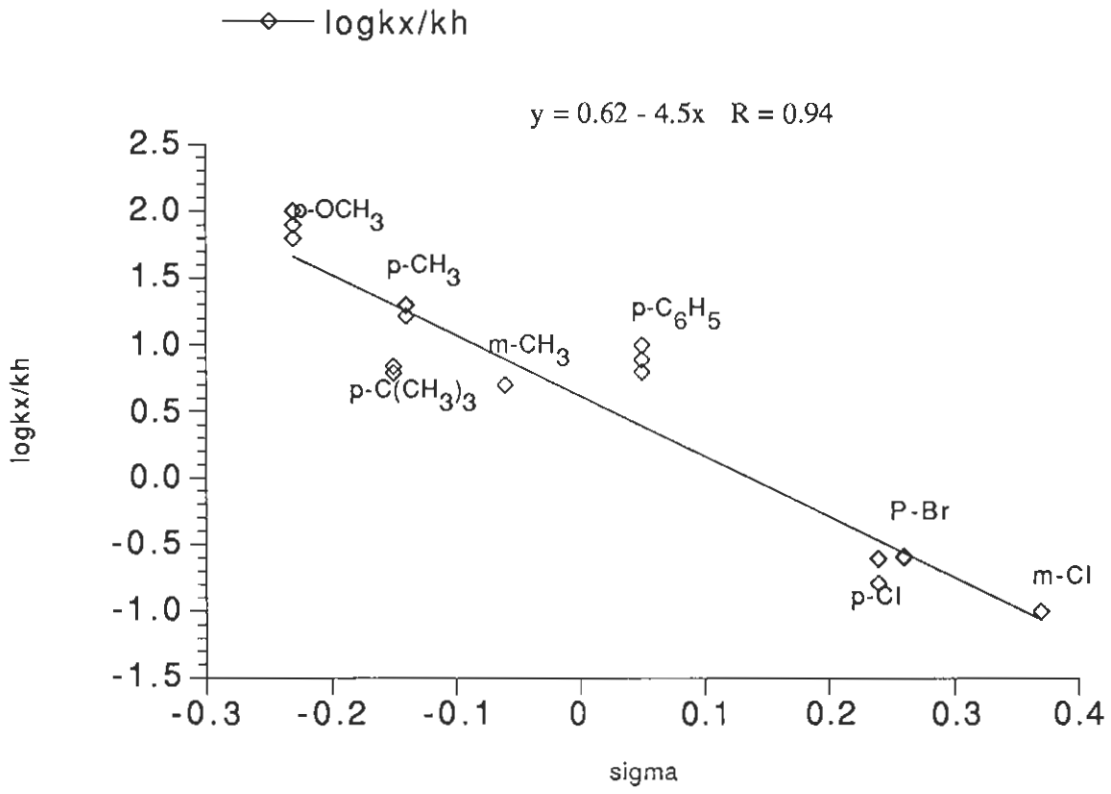


Figure 2. Graph of sigma vs. log (k/k_0). Both meta and para substituents are shown.

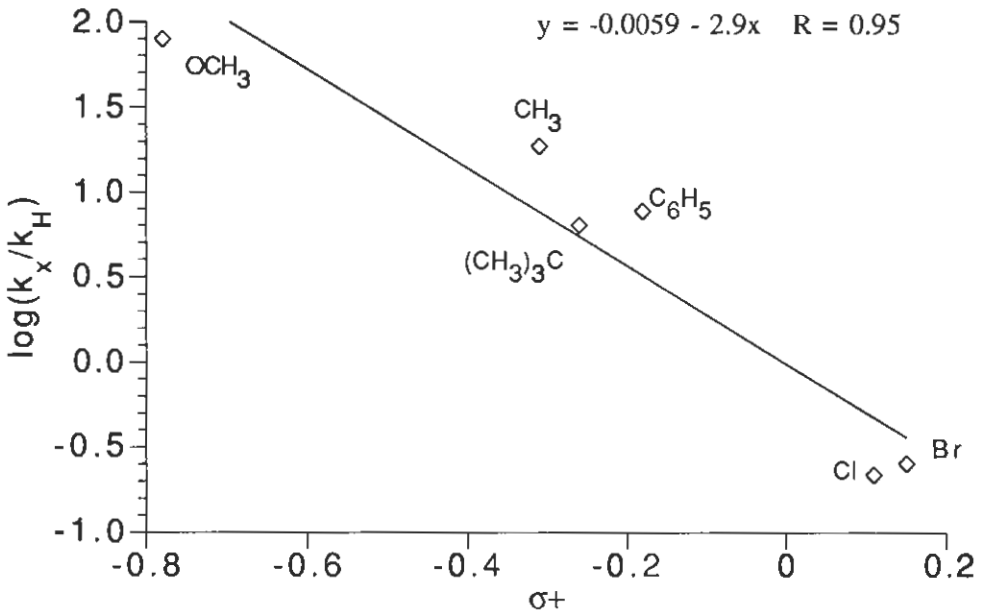


Figure 3. Graph of sigma+ vs. log (k/k_0). Only para substituents are shown. All data points are averages of two or three trials per substituent.

In theory the correlation coefficients for both sigma and sigma+ values should equal one (the linear free energy study should yield a straight line). Both figures lack this absolute linearity (but are close with correlation coefficients of approximately 0.95), presumably due to experimental error. On both plots it can be seen that the substituent with the greatest effect upon reaction rate is the para-methoxy entity. This finding corresponds to Oikawa's finding that the MPM group reacts quickly with DDQ and is in agreement with chemical theory that predicts that a para-methoxy group will be very electron-donating in nature, stabilizing the initial carbocation.[1] It can also be seen that the para-tert-butylbenzyl (TBPM) substituent is

less reactive than the para-methoxy (MPM) moiety, confirming our initial hypothesis and allowing synthetic investigation of the TBPM ether as a protecting group for alcohols to proceed.

TBPM as a Protecting Group

The results of our investigation into the synthetic applications of the TBPM protecting group are summarized in Table 1. All of the TBPM ethers were constructed from the readily available alcohols. The corresponding alkoxides, generated via deprotonation with sodium hydride, were reacted with tert-butylbenzyl bromide to yield the protected entities. After reaction with DDQ, the yields of the deprotected alcohols were determined by either isolation or gas chromatographic analysis with an internal standard (Scheme 7).

Scheme 7

Formation and deprotection of TBPM ethers with DDQ

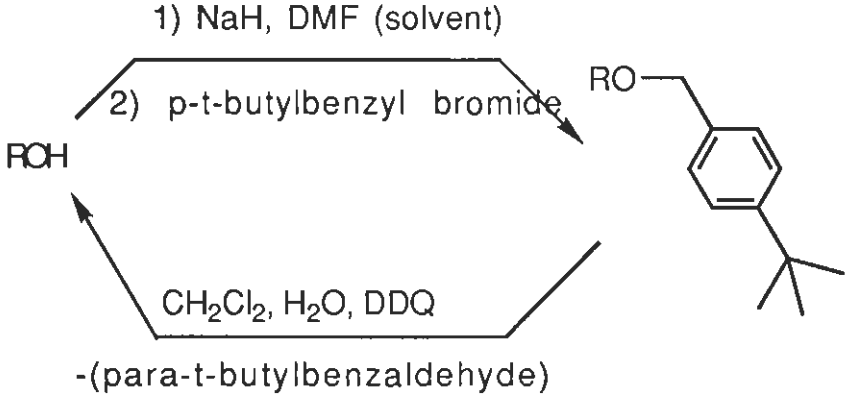
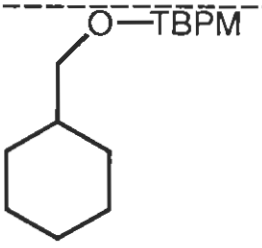
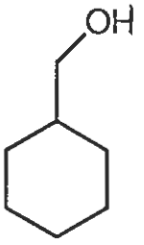
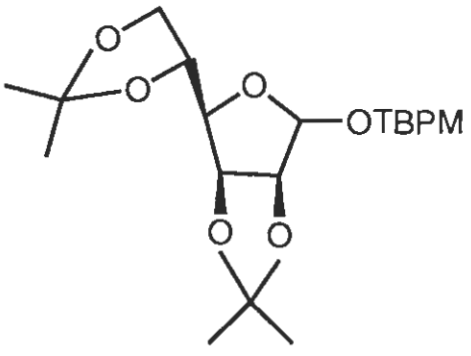
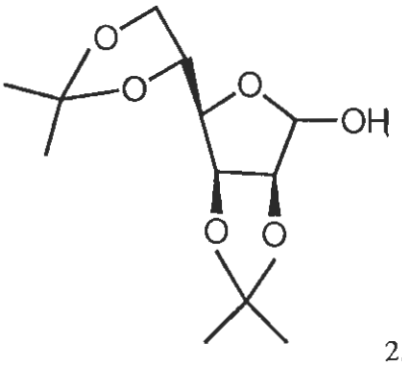
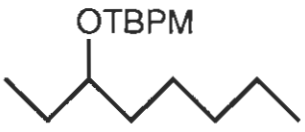
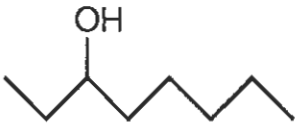
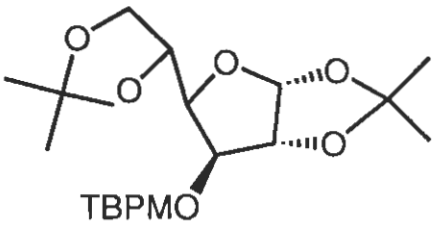


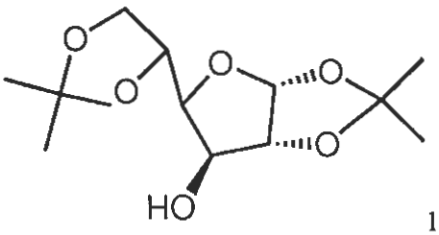
Table 1

Molecules protected with TBPM ethers[a]

Protected Molecule	Deprotected Alcohol	Amt. DDQ	Yield
 (5)	 (6)	2.0 eq.	65% (60%)[b]
 (7)	 (8)	2.0 eq.	???[c]
 (9)	 (10)	2.0 eq.	(100%)[b]
		1.3 eq.	95% (100%)[b]

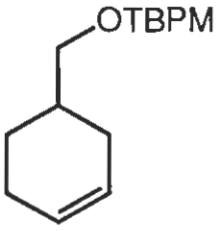


(11)

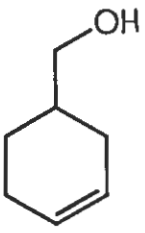


(12)

1.1 eq. ???[c]



(13)



(14)

1.1 eq. 88%(100%)[b]

Yields shown in parantheses are from the gas chromatographic quantification of the liberated p-tert-butylbenzaldehyde rather than from the deprotected alcohol itself (with tetradecane as the internal standard).

a. Reaction Conditions: CH_2Cl_2/H_2O (10:1) (0.5 M), Room Temp., DDQ

b. Yield determined (or determination attempted) by gas chromatographic analysis and an internal standard (tetradecane).

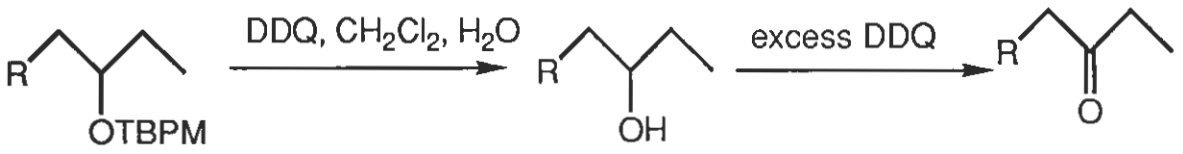
c. Yield determined (or determination attempted) by isolation of the product (column chromatography).

Initial work was done with simple, primary alcohols. The protected molecule **5** was reacted with two equivalents of DDQ to yield **6** in 60% yield. Upon observing that the DDQ deprotection worked well with simpler molecules, a more complex synthetic environment was examined. The protected mannose derivative (**7**) was reacted with two equivalents of DDQ. The starting product was consumed (as observed by thin layer

chromatography of the reaction mixture), but the alcohol product could not be isolated. Further attempts to deprotect **7** with another oxidizing agent, ammonium cerium (IV) nitrate (CAN), also failed to yield the starting alcohol. We noted that the first molecule we deprotected was a primary alcohol, while **7** was a secondary alcohol. Previous research in this lab had shown that a sugar molecule with a primary alcohol could be deprotected with DDQ.[13] In order to see if the substitution pattern of the alcohol or the particular chemical environment of **7** was causing the difficulties isolating the product **8**, a simple secondary alcohol (**10**) was protected as the TBPM ether (**9**) and reacted with two equivalents of DDQ. Gas chromatographic analysis showed that the reaction went essentially to completion (the yield from liberated benzaldehyde was approximately one hundred percent, indicating that all of the TBPM ether had been deprotected) and that the primary product was **10**. It was also seen that another product was being formed. Investigation with known samples revealed that the corresponding ketone, 3-octanone, was also being formed. Becker, et. al.,[11] noted that benzylic alcohols could be oxidized to the corresponding carbonyls with treatment of DDQ. Although the benzylic position is better able to stabilize the intermediate carbocation, we theorized that perhaps the secondary alcohols we were trying to deprotect, especially the acetal **7** with its several neighboring electronegative oxygens, could also be further oxidized to ketones by the large excess of DDQ present in the reaction mixture (and thus explain why we couldn't isolate **8**) (Scheme 8). To test this hypothesis, several

Scheme 8

Oxidation of deprotected alcohol to carbonyl

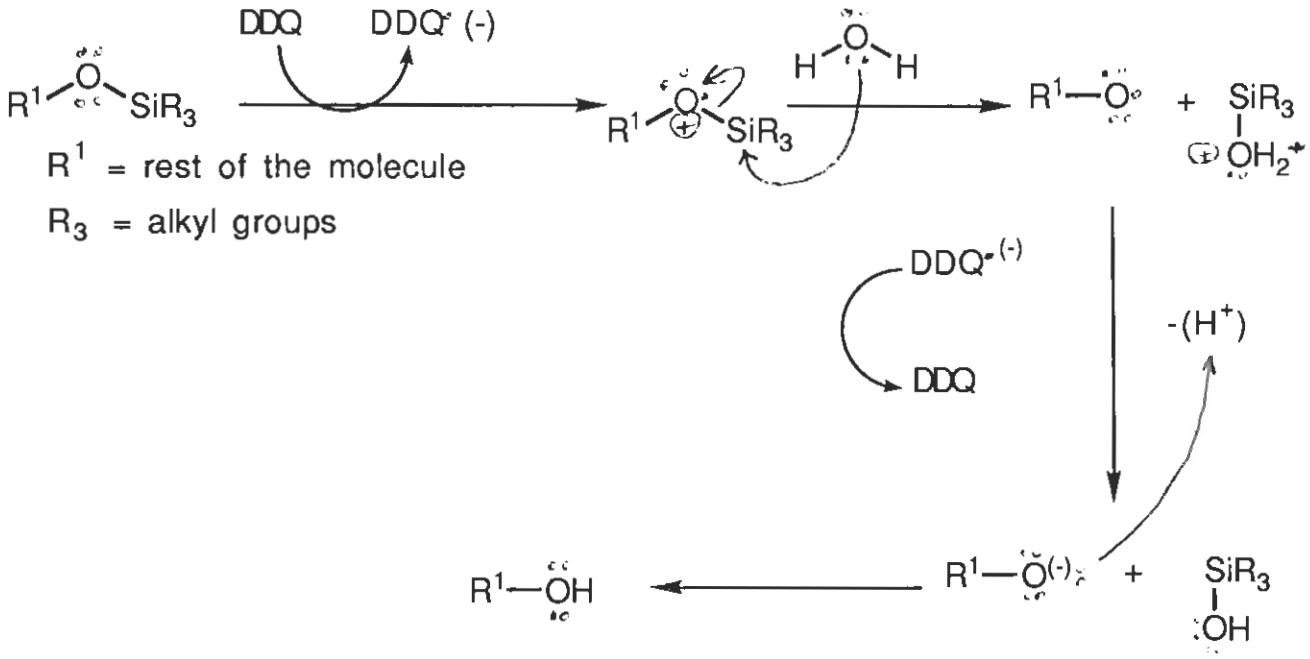


R = rest of the molecule

reactions were carried out. Molecule 9 was again subjected to DDQ oxidation, but the amount of DDQ used was cut to 1.3 equivalents (eliminating most of the excess DDQ should limit the amount of oxidation to the carbonyl that could take place). This resulted in a much smaller amount of 3-octanone being produced. Believing an explanation for the missing product had been found, we attempted to deprotect molecule **11**, a glucose derivative that has a secondary alcohol but lacks the acetal functionality (adjacent to the alcohol) found in 7 that could presumably be more easily oxidized. The deprotection of **11** was carried out with 1.1 equivalents of DDQ, but again no product could be isolated. With the amount of DDQ used being just sufficient to remove the TBPM ether, we are not as sure that the reason the deprotected alcohol **12** cannot be isolated is due to its further oxidation to a carbonyl. Tanemura, et. al., have reported that DDQ can be used in catalytic amounts to remove trialkyl silyl ethers[12]. This is thought to proceed via a radical mechanism (Scheme 9) that removes the silyl protecting group, generating

Scheme 9

Catalytic Deprotection of silyl ethers with DDQ



the deprotected alcohol. While only preliminary work into this possibility has been carried out in this lab, it has been proven that unprotected alcohols subjected to DDQ can generate the same type of alkoxy radicals that Tanemura's group reports with its trialkyl silyl ethers. Our inability to recover the DDQ reaction products might, therefore, be due to the deprotected alcohols we are generating undergoing a similar process with a miniscule (catalytic) amount of excess DDQ. Ceasing work with the troublesome complex molecules, we next began to investigate which types of functional groups were compatible with the DDQ reaction sequence. Molecule **13**, containing an alkene functionality, was subjected to oxidative deprotection with 1.1 equivalents of DDQ (we had observed that even in simple molecules some further oxidation to the corresponding ketone took place, thus the excessive amount of DDQ was reduced). The alcohol **14** was

successfully deprotected in eighty-eight percent yield, showing that the alkene functionality is stable in the DDQ environment.

Conclusion

In conclusion, the oxidative removal of the tert-butylbenzyl (TBPM) protecting group with DDQ is currently feasible only with simple molecules. It is not possible to isolate more complex alcohols after the deprotection reaction. Several theories have been put forth to explain this product disappearance, but none of them are conclusive and more work needs to be done in this area. Research into the compatibility of other functional groups with the TBPM deprotection by DDQ has just recently been started and future investigation should be continued in this regard to explore the synthetic possibilities of this particular alcoholic protecting group.

Experimental

General

Infra-red (IR) spectra were taken with a Mattson Polaris spectrometer. Nuclear magnetic resonance (NMR) spectra were taken with an EM-360L spectrometer using tetramethylsilane (TMS) as an internal standard. Thin layer chromatography was performed with silica gel glass plates and mixutures of ethyl acetate and hexane, with visualization being performed with either ultraviolet (UV) absorption or charring with 10% sulfuric acid (aq). Gas chromatography (GC) was done on a Hewlett Packard 5890 with a HP-5 column. Column chromatography was conducted using 70-270 mesh, 60A silica gel as supplied by Aldrich and various mixtures of ethyl acetate and hexane as the eluent.

Dimethyl formamide (DMF) was distilled from calcium hydride under reduced pressure. Ethyl acetate and hexane for chromatography were distilled at atmospheric pressure. Sodium hydride was washed with distilled hexane prior to use to remove the mineral oil stabilizer. All other reagents were used without purification as supplied by Aldrich. Anhydrous reactions were carried out under a nitrogen atmosphere with oven dried glassware (120°C for at least three hours).

Preparation and Deprotection of Benzyl Alkyl Ethers for Kinetic Study

The following is the general procedure used for the preparation and subsequent deprotection by DDQ of all of the alkyl ethers utilized in the linear free energy investigation. The different substituents studied were generated from the corresponding substituted benzaldehydes or benzyl alcohols.

Meta-chlorobenzyl alcohol

Meta-chlorobenzaldehyde (1.41 g, 10.0 mmoles) and 95% ethanol (25 mL, 0.4 M) were added to a round bottomed flask equipped with a stir bar. The vessel was cooled in an ice-water bath, and sodium borohydride (0.27g, 7.1 mmoles) was added. The mixture was allowed to stir for thirty minutes. The reaction was monitored by thin layer chromatography (TLC) using 5% ethyl acetate (EthOAc) in hexane as the mobile phase and visualized by UV. The reaction was worked up by the addition of water (10mL), removal of most of the solvent under reduced pressure (RotoVap), and partition by ether (3X10 mL). The combined organic layers were washed with aqueous sodium hydroxide (2X5 mL), saturated aqueous ammonium chloride (5 mL), water (10 mL), and then dried over sodium

sulfate. The solution was gravity filtered and the solvent removed by reduced pressure and purified by Kugelrohr apparatus. The product (m-chloro-benzyl alcohol, 0.69 g, 48% yield) was isolated as a clear, colorless oil. 1 H-NMR $CDCl_3$ delta 3.7 (1 H, s), 4.5 (2 H, s), 7.2 (4 H, s); IR 3367, 2952, 2879, 1600, 1577, 1475, 1433, 1206 cm^{-1}

Meta-chlorobenzyl decyl ether

Sodium hydride (0.151g, 6.29 mmoles), m-chlorobenzyl alcohol (0.69g, 4.8 mmoles), and DMF (8.1 mL, 0.6 M) were added to a round bottomed flask equipped with a stir bar, condenser, and N_2 adapter. The mixture was heated on low for a half hour and then cooled in an ice bath. Decyl bromide (1.02g, 4.60mmoles) was added and refluxed on low overnight. The reaction was monitored by TLC versus starting material in 1% EthOAc/hexane as mobile phase and visualized by UV. The reaction was quenched with saturated aqueous ammonium chloride and extracted with ether (3X25 mL). The solvent was removed under reduced pressure, and column chromatography (in 2% EthOAc/hexane on a 19/22 column) was used to isolate the product (fractions 6-10, 0.69g, 53% yield) as a clear, colorless oil. Mass Spectra m/z 125 (base peak), 91 (EI); 1 H-NMR delta $CDCl_3$ 0.7-1.4 (b), 3.2-3.5 (t), 4.4 (s), 7.1-7.4 (m); IR 2927, 2856, 1577, 1467, 1357, 1247, 1104 cm-1

Oxidative Competition Reaction

Meta-chlorobenzyl decyl ether (0.113g, 0.401 mmoles) and benzyl dodecyl ether (0.110g, 0.399 mmoles) were placed in a 20 mL screw cap vial equipped with a stir bar. Dichloromethane (8 mL, 0.05M), water (0.8 mL), tetradecane (0.040g, 0.20 mmoles, internal standard), and DDQ (0.025g, 0.11 mmoles) were then placed in the screw cap vial. The mixture was allowed to stir for 24 hours. Gas chromatographic analysis revealed

yields for the decanol and dodecanol to be 0.0029 mmoles and 0.029 mmoles, respectivley, for a log (k/k_{o}) value of -1.0.

Cyclohexylmethyl Tert-butylbenzyl Ether

Sodium hydride (0.800g, 20.0 mmoles), cyclohexylmethyl alcohol (1.14g, 9.98 mmoles), and DMF (17 mL, 0.6 M) were charged to a round bottomed flask equipped with a stir bar, condenser, and N_2 adapter. The mixture was refluxed on low for a half an hour and then cooled in an ice bath. Tert-butylbenzyl bromide (3.41g, 15.0 mmoles) was added and refluxed on low overnight. The reaction was monitored by TLC using 1% EthOAc/hexane as a mobile phase and visualized by UV. The excess t-butylbenzyl bromide was destroyed by addition of 15% sodium hydroxide (5 mL) and allowed to stir for several hours. The reaction was quenched with saturated aqueous ammonium chloride and extracted with diethyl ether (3X25 mL). The solvent was removed under reduced pressure and column chromatography (24/40 column, 1% EthOAc/hexane as eluent) used to isolate the product. Fractions 16-19 were collected to yield the pure product as a clear, slightly white oil (0.93g, 36% yield). 1 H-NMR $CDCl_3$ delta 1.0-1.8 (b) 3.3-3.6 (d), 4.6 (s), 7.4-7.5 (s). IR 2929, 1514, 1450,1362, 1247, 1087 cm-1

Deprotection of Cyclohexylmethyl T-butylbenzyl Ether with DDQ

The protected alcohol (0.650g, 2.50 mmoles) and DDQ (1.15g, 5.07 mmoles) were charged to a round bottomed flask equipped with a stir bar. Dichloromethane (5.0 mL, 0.5 M), water (0.5 mL), and tetradecane (0.033g, 0.17 mmoles, internal standard) were added and the mixture allowed to stir overnight. Gas chromatographic analysis showed a yield of 65% of the

deprotected alcohol.

2,3,5,6-O-Diisopropylidene Mannofuranose Tert-butylbenzyl Ether

The mannose derivative (2.07g, 7.96 mmoles), sodium hydride (0.596g, 14.9 mmoles), and DMF (12.4 mL, 0.6M) were added to a round bottomed flask equipped with a stir bar, condenser, and N_2 adapter and allowed to reflux on low for a half an hour and then cooled in an ice bath. Tert-butylbenzyl bromide (2.54g, 11.2 mmoles) was added and the mixture refluxed on low overnight. The reaction was monitored by TLC versus starting material in 5% EthOAc/hexane and visualized by UV. The excess t-butylbenzyl bromide was destroyed by the addition of 15% sodium hydroxide (3 mL) and allowed to stir for several hours. The reaction was quenched with saturated aqueous ammonium chloride and extracted with ether (5X15 mL). The solvent was removed under reduced pressure and column chromatography (24/40 column, 6% EthOAc/hexane as eluent) used to isolate the product in fractions 11-18 (1.0 g, 31%) as a clear, colorless, syrupy oil. (Further analysis reveals product to be the less polar anomer). 1 H-NMR $CDCl_3$ delta 1.1-1.6 (m), 3.8-4.1 (b), 4.4-4.8 (b), 5.0-5.3 (m), 7.3-7.4 (s). IR 2961, 1515, 1458, 1381, 1265, 1211, 1067 cm-1

Deprotection of 2,3,5,6-O-Diisopropylidene Mannofuranose Tert-butylbenzyl Ether with DDQ

The protected alcohol (0.176g, 0.433 mmoles) and DDQ (0.197g, 0.866 mmoles) were charged to a round bottomed flask equipped with a stir bar. Dichloromethane (0.90 mL, 0.5 M) and water (0.1 mL) were added and the mixture allowed to stir overnight. The reaction was monitored versus

starting material by TLC in 15% EthOAc/hexane. After determining by TLC that after one day there was still starting material remaining, more DDQ (0.15g, 0.65 mmoles), dichloromethane (1.0 mL) and water (0.10 mL) were added. At T+3 days reaction was worked up. Water (5 mL) was added and the mixture extracted with ether (6X5 mL). The solvent was removed under reduced pressure and column chromatography (14/20 column, 10%-100% EthOAc/hexane as eluent) used to isolate the product. The deprotected alcohol was never found.

Deprotection of 2,3,5,6-O-Diisopropylidene Mannofuranose Tert-butylbenzyl Ether with CAN

The protected alcohol (0.195g, 0.480 mmoles) and ammonium cerium (IV) nitrate (CAN, 0.263g, 0.480 mmoles) were added to a round bottomed flask equipped with a stir bar. Acetonitrile and water (9:1 ratio, 2.4 mL, 0.2 M) were added to the mixture and allowed to stir overnight. The reaction was monitored versus starting material by TLC with 25% EthOAc/hexane as the mobile phase and visualized by UV and charring. The reaction was extracted with ether (6X5 mL) and the solvent removed under reduced pressure. Column chromatography was used (14/20 column, 10%-50% EthOAc/hexane as eluent) to isolate the product. Fractions 18-24 were collected to yield a clear, colorless, viscous oil. NMR analysis revealed it to not be the deprotected alcohol (which itself was never found).

3-Octyl Tert-butylbenzyl Ether

3-Octanol (1.30g, 9.98 mmoles), sodium hydride (0.800g, 20.0 mmoles), and DMF (17 mL, 0.6 M) were charged to a round bottomed flask equipped

with a stir bar, condenser, and N_2 adapter. The mixture was allowed to reflux on low for a half an hour and then cooled in an ice-bath. Tert-butylbenzyl bromide (3.41g, 15.0 mmoles) was added and allowed to reflux on low overnight. The reaction was monitored versus starting material by TLC using 15% EthOAc/hexane as the mobile phase and visualized by UV. The excess t-butylbenzyl bromide was destroyed by 15% sodium hydroxide (4 mL) and allowed to stir for several hours. The reaction was quenched with saturated aqueous saturated ammonium chloride and extracted with ether (4X10 mL). The solvent was removed under reduced pressure and column chromatography (24/40 column, 3%EthOAc/hexane as eluent) used to isolate a clear, colorless oil as product (2.1g, 76% yield) in fractions 6-8. 1 H-NMR $CDCl_3$ delta 0.8-1.4 (b), 3.3-3.6 (b), 4.5 (s), 7.3-7.4 (s). IR 2982, 2971, 1515, 1462, 1363, 1269, 1067 cm-1

Deprotection of 3-Octyl Tert-butylbenzyl Ether with DDQ

The protected alcohol (0.266g, 0.969mmoles), DDQ (0.438g, 1.93 mmoles), dichloromethane (1.9 mL, 0.5 M), water (0.2 mL), and tetradecane (0.080g, 0.40 mmoles, internal standard) were added to a round bottomed flask equipped with a stir bar. The reaction was allowed to stir overnight. Gas chromatographic analysis revealed that the deprotected alcohol was the predominant product but that 3-octanone was also being formed in approximately 10% yield (based on relative peak areas).

Deprotection of 3-Octyl Tert-butylbenzyl Ether with DDQ (2nd attempt)

The protected alcohol (0.269g, 0.975 mmoles), DDQ (0.288g, 1.27

mmoles), dichloromethane (2.0 mL, 0.5 M), water (0.2 mL), and tetradecane (0.099g, 0.50 mmoles, internal standard) were charged to a round bottomed flask equipped with a stir bar. The reaction was allowed to stir overnight. Gas chromatographic analysis revealed that the deprotected alcohol was formed in 95% yield and that very little 3-octanone was present.

alpha-1,2,5,6-Diisopropylidene Glucofuranoside Tert-butylbenzyl Ether

The glucose derivative (1.56g, 6.00 mmoles), sodium hydride (0.480g, 12.0 mmoles), and DMF (10 mL, 0.6 M) were added to a round bottomed flask equipped with a stir bar, condenser, and an N_2 adapter. The mixture was allowed to reflux on low for a half an hour and then cooled in an ice bath. Tert-butylbenzyl bromide (2.04g, 8.99 mmoles) was added and the mixture allowed to reflux on low overnight. The reaction was monitored versus starting material by TLC in 15% EthOAc/hexane as the mobile phase and visualized by UV and charring. The excess t-butylbenzyl bromide was destroyed by the addition of 15% sodium hydroxide (3 mL) and allowed to stir for several hours. The reaction was quenched with saturated aqueous ammonium chloride (2 mL) and extracted with ether (5X15 mL). The solvent was removed under reduced pressure and the product isolated by column chromatography (24/40 column, 7% EthOAc/hexane as eluent) as a clear, slightly yellow, viscous oil (1.5g, 60% yield) in fractions 12-25. 1 H-NMR $CDCl_3$ delta 1.1-1.6 (m), 3.9-4.3 (b), 4.5-4.7 (m), 5.9-6.0 (d), 7.3-7.5 (s).

Deprotection of the alpha-1,2,5,6-Diisopropylidene

Glucofuranoside Tert-butylbenzyl Ether with DDQ

The protected alcohol (0.299g, 0.736 mmoles), DDQ (0.184g, 0.810 mmoles), dichloromethane (1.5 mL, 0.5 M) ,water (0.15 mL), and tetradecane (0.070g, 0.35 mmoles) were added to a round bottomed flask equipped with a stir bar. The mixture was allowed to stir for two days. The reaction was monitored versus starting material by TLC with 20% EthOAc/hexane as mobile phase and visualized by UV and charring, and by gas chromatographic analysis. The reaction mixture was vacuum filtered and the solvent removed under reduced pressure. Column chromatography (14/20 column, 15%-50% EthOAc/hexane as eluent) was used to isolate the product. The deprotected alcohol was never recovered.

3-Cyclohexene Methanol

3-Cyclohexene-1-carboxaldehyde (1.11g 10.1 mmoles) and 95% ethanol (25 mL, 0.4 M) were added to a round bottomed flask equipped with a stir bar and cooled in an ice bath. Sodium borohydride (0.267g, 7.06 mmoles) was added and the mixture allowed to warm to room temperature while stirring. The reaction was monitored versus starting material by TLC in 10% EthOAc/hexane as the mobile phase and visualized by UV and charring. The starting material was not visible by either UV or charring and was monitored by GC. The reaction was worked up by the addition of water (10mL) and removal of most of the solvent under reduced pressure. The remaining mixture was extracted with ether (3X10 mL). The combined organic layers were washed with 10% sodium hydroxide (2X5 mL), saturated aqueous ammonium chloride (1X5 mL), and water (1X5 mL) and then dried over sodium sulfate. The product was purified by Kugelrohr apparatus to yield a clear, colorless oil (0.53g, 47% yield). 1 H-

NMR $CDCl_3$ delta 1.0-2.2 (6H, b), 3.1-3.3 (1H,s), 3.4-3.6 (2H,dd), 5.5-5.7 (2H,s).

3-Cyclohexene Methyl Tert-butylbenzyl Ether

3-Cyclohexene methanol (approx. 0.450g, approx. 4 mmoles), sodium hydride (0.320g, 8.00 mmoles), and DMF (6.5 mL, 0.6M) were added to a round bottomed flask equipped with a stir bar, condenser, and an N_2 adapter and allowed to reflux on low for a half an hour and then cooled in an ice bath. Tert-butylbenzyl bromide (1.36g, 5.99 mmoles) was added and the mixture allowed to reflux on low overnight. The reaction was monitored by TLC in 5% EthOAc/hexane as the mobile phase and visualized by UV and charring. The reaction was also monitored by GC to check the disappearance of the starting material. The reaction was quenched with saturated aqueous ammonium chloride (4 mL) and extracted with ether (4X10 mL). The solvent was removed under reduced pressure and column chromatography (14/20 column, 3% EthOAc/haxane as the eluent) used to isolate a clear, colorless oil (0.54g, approx. 50% yield) in fractions 3-5. 1 H-NMR $CDCl_3$ delta 1.3-1.5 (s), 1.7-2.2 (b), 3.3-3.5 (dd), 4.5 (s), 5.6-5.8 (s), 7.3-7.4 (s).

Deprotection of 3-cyclohexene Methyl Tert-butylbenzyl Ether with DDQ

The protected alcohol (0.313g, 1.21 mmoles), DDQ (0.302g, 1.33 mmoles), dichloromethane (2.2 mL, 0.5M), water (0.25 mL) and tetradecane (0.099g, 0.50 mmoles, internal standard) were added to a round bottomed flask equipped with a stir bar. The reaction was allowed to stir overnight. Gas chromatographic analysis revealed that the

deprotected alcohol was formed in 88% yield.

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