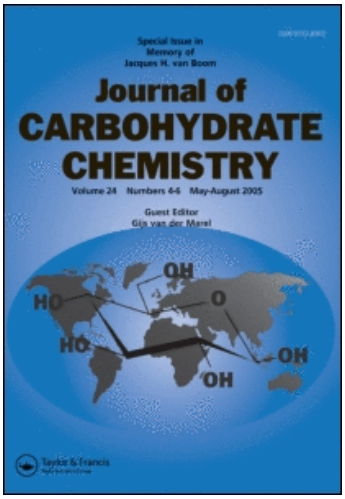

Journal of Carbohydrate Chemistry

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

Reaction of Glycosyl Halides with Benzyl Grignard Reagents: Unexpected *o*-Tolyl Alkylation of Tetra-*O*-acetylglucopyranosyl Bromide and Direct Synthesis of (B-Glycosyl)phenylmethanes

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To cite this Article Panigot, J. and Curley Jr., W.(1994) 'Reaction of Glycosyl Halides with Benzyl Grignard Reagents: Unexpected *o*-Tolyl Alkylation of Tetra-*O*-acetylglucopyranosyl Bromide and Direct Synthesis of (B-Glycosyl)phenylmethanes', Journal of Carbohydrate Chemistry, 13: 2, 293 — 302
To link to this Article: DOI: 10.1080/07328309408009194
URL: http://dx.doi.org/10.1080/07328309408009194

J. CARBOHYDRATE CHEMISTRY, 13(2), 293-302 (1994)

REACTION OF GLYCOSYL HALIDES WITH BENZYL GRIGNARD REAGENTS: UNEXPECTED *o*-TOLYL ALKYLATION OF TETRA-*O*-ACETYLGLUCOPYRANOSYL BROMIDE AND DIRECT SYNTHESIS OF (ß-GLYCOSYL)PHENYLMETHANES

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Received March 5, 1993 - Final Form October 21, 1993

ABSTRACT

The synthesis of (ß-glycosyl)phenylmethanes by Grignard alkylation of glycosyl halides is investigated. Reaction of tetra-*O*-acetylglucopyranosyl bromide with benzylmagnesium chloride gave a good yield of a 3:1 mixture of 2-(ß-D-glucopyranosyl)toluene and (ß-glucosyl)phenylmethane. The requirement for an equatorial 2-acetoxy group and 6-acetoxymethyl group for the formation of the unexpected *o*-tolyl rearrangement product is explored by using xylosyl, mannosyl, and 2-deoxyglucosyl halides as substrates for the alkylation. Synthesis of (ß-glucosyl)phenylmethane by alkylation of 2,3,4,6-tetra-*O*-benzylglucosyl bromide with benzylmagnesium chloride is also presented.

INTRODUCTION

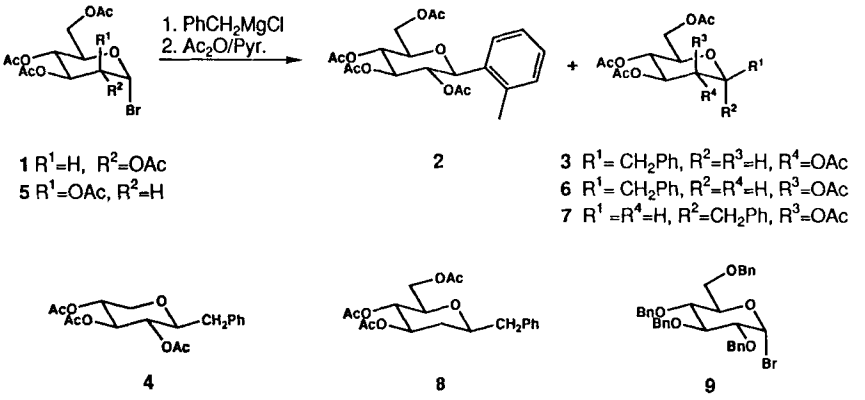
C-glycosyl compounds have become of interest because a number of natural products of this type show promising antitumor and antiviral activity.[1] Thus, recent efforts have been described to develop efficient strategies for the preparation of these compounds.[2] We became interested in these types of compounds in efforts to prepare stable *C*-glycosyl and *C*-

glucuronosyl benzene and phenylmethane analogues of cancer chemopreventive vitamin A conjugates.[3]

Many years ago, Hurd and Bonner demonstrated smooth conversion of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide[4] (1) to the ß-D-glucopyranosyl benzene via alkylation with phenylmagnesium bromide.[5] However, reaction of 1 with a benzyl Grignard reagent was claimed to yield no isolable, crystalline alkylated glucose.[5] In recent years, (ß-glycosyl)phenylmethanes have been prepared by multistep syntheses involving palladium-catalyzed coupling of 1-tributylstannyl glucal with benzyl bromide[2d,e] and treatment of *C*-1 lithiated 2-phenylsulfonyl glucal with benzaldehyde followed by hydrogenolysis.[2f] We have reexamined the reaction of 1 with benzylmagnesium chloride and find it proceeds smoothly to give primarily the unexpected rearrangement product 2-(ß-D-glucopyranosyl)toluene which was isolated as its acetate (2). Observations on this unusual rearrangement and the factors that appear to control it are described herein.

RESULTS AND DISCUSSION

Reaction of benzylmagnesium chloride with 1 followed by acetylation of the crude *C*-glycosyl compound (Scheme 1) produced a white solid. Analysis of the ^{1}H NMR spectrum of this solid showed, unexpectedly, a singlet at 2.4 ppm as well as a broadened multiplet at 2.8 ppm integrating for a ratio of 4.5:1. After independent synthesis of the (2,3,4,6-tetra-*O*-acetyl-ß-D-glucopyranosyl)phenylmethane (3) and 2-(2,3,4,6-tetra-*O*-acetyl-ß-D-glucopyranosyl)toluene (see below), these results were found to correspond to formation of a 3:1 mixture of 2 to 3 in good yield. Further evidence for the formation of 2 came from elaboration of the glucuronide obtained after oxidation of the 6-hydroxymethyl group[6] and analysis of the ^{1}H–^{13}C shift correlation spectrum.[7] Nitration of the *C*-glucuronosyl compound also gave a compound whose ^{1}H NMR pattern was consistent with a 1,2,4-trisubstituted arene. Compound 2 has also recently been synthesized directly from 1 and *o*-tolylmagnesium bromide.[8] We have repeated this synthesis and have found, after acetylation, 2 to be the sole product of this reaction. Additionally, the NMR spectrum of 2 agrees with the pattern observed for the major component of the rearrangement mixture. While reaction of benzyl Grignard reagents with other electrophiles has



Scheme 1. Glycosyl halides and their alkylation products when reacted with benzylmagnesium chloride

been shown to give ortho alkylation as a very minor by-product,[9] the predominance of the *o*-tolyl alkylation product in this instance was surprising and deserved investigation.

Benzyl alkylation of a xylopyranosyl halide with benzylmagnesium chloride has recently been reported in the patent literature,[10] although the nature of the *C*-glycosyl compound thus prepared was incompletely characterized. In our hands, preparation of 2,3,4-tri-*O*-acetyl-ß-D-xylopyranosyl chloride by reaction of xylose tetraacetate with aluminum chloride by the method of Korytnyk and Mills,[11] followed by reaction with benzylmagnesium chloride and acetylation, produced a waxy white material. The ^{1}H NMR spectrum of this material exhibited an eight-line multiplet centered at about 2.8 ppm. Additionally, the NMR pattern observed for the proton at *C*-1 of the *C*-glycoside was a complex multiplet which was shifted upfield from the corresponding proton in **2**. Both spectral characteristics are consistent with structure **4**.

To determine whether the change from the α-bromo glycosyl halide to the ß-chloro glycosyl halide affected the course of the above reaction, 2,3,4,6-tetra-*O*-acetyl-ß-D-glucopyranosyl chloride was prepared and reacted with benzylmagnesium chloride. After acetylation, analysis of the ^{1}H NMR spectrum showed no difference between this product and that obtained from **1**. Further confirmation of the influence of the 6-acetoxymethyl group on the site of alkylation was obtained by treatment of 2,3,4-tri-*O*-acetyl-α-D-

xylopyranosyl bromide with benzyl Grignard reagent. Although a 2.4:1 α/ß mixture was obtained, alkylation produced exclusively the *C*-xylosyl phenylmethanes.

It has been shown that halogen displacement from acetylated glycopyranosyl halides is affected by the participation of an equatorial 2-acetoxy group.[11,13,14] Given this, the course of the reaction of benzyl Grignard reagent with 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl bromide[15] (**5**) was investigated. After acetylation, a 5:3 α/ß mixture of solely 2,3,4,6-tetra-*O*-acetyl-ß-D-mannopyranosyl phenylmethanes (**6** and **7**) was observed. The α/ß alkylation ratio was as expected based on the work of Hurd and Holysz on the reaction of **5** with phenylmagnesium bromide.[16]

To further confirm the participatory nature of the equatorial 2-acetoxy group not only in halide displacement but, apparently, in influencing the benzyl to *o*-tolyl rearrangement, 3,4,6-tri-*O*-acetyl-α-D-2-deoxyglucosyl bromide[17] was prepared, treated with benzyl Grignard reagent and reacetylated. The benzyl alkylation product **8** was obtained exclusively.

Since it appeared that participating acetoxy groups were needed for rearrangement to occur, the known 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl bromide[18] (**9**) was prepared and reacted with benzyl Grignard reagent. While the structure of the product could not be clearly assigned, hydrogenolysis followed by acetylation established the compound to be the desired product **3** by comparison of the ^{1}H NMR signals to the tetraacetate prepared by another method[2f] and by comparison with the minor product in the reaction with **1**. The reaction of benzylmagnesium chloride with **9** to give solely the (ß-glycosyl)phenylmethane is interesting in light of the mixture of epimers obtained by Bihovsky *et al.* from the reaction of **9** with other organomagnesium halides.[19] It has been shown that anion stability plays a role in reactivity in halide displacement from glycosyl halides and may account for these observed differences.[13]

The results above suggest that the unexpected preponderance of the *o*-tolyl alkylation product requires participation of both the equatorially disposed 2-acetoxy group as well as the 6-acetoxymethyl group present in **1**. A possible intermediate emphasizing chelation controlled alkylation, which would account for the observed formation of the *o*-tolyl product only from the reaction of carbohydrate substrate **1**, is shown in Figure 1.

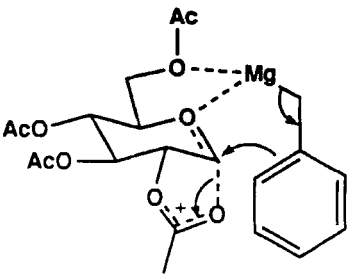


Fig. 1. Proposed mechanism of o-tolyl alkylation of **1** by benzylmagnesium chloride.

While the acetate groups are cleaved by the Grignard reagent during this reaction, reactions of this type performed with limiting Grignard reagent indicate that alkylation is competitive with deacetylation.[5] One possibility is that the "normal" alkylation product arises from deacetylated bromosugar while the rearrangement product appears to require the acetate groups based on the results from the tetra-*O*-benzyl sugar.

Finally, alkylation of **9** with benzyl Grignard reagent provides a direct access to the widely sought (*C*-glucosyl)phenylmethanes more efficiently than either of the current literature methods.[2e,f] These compounds could find use as enzyme inhibitors,[2f] precursors for *C*-glycosyl natural products, or as isosteres for aryl-*O*-glucosides.[2d,e]

EXPERIMENTAL

General Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. ^{1}H NMR spectra were recorded on an IBM AC250 spectrometer operating at 250 MHz in $CDCl_3$ solutions unless otherwise noted and referenced to residual $CHCl_3$ at δ 7.24 ppm. ^{13}C NMR and ^{1}H-^{13}C shift correlation spectra were obtained on the same instrument. UV spectra were recorded with a Beckman DU-40 spectrophotometer. Infrared spectra were determined using an Analect RFX-40 FT-IR. Electron impact high resolution mass spectra were obtained with a Kratos MS-30 spectrometer. TLC was performed on 0.25 mm silica gel 60 F_{254} precoated aluminum plates from EM Science and visualized either with fluorescence quenching of 254 nm light or spraying with 10% H_2SO_4/ethanol and charring. Column chromatography was performed on silica gel (70-230 mesh, EM Sciences). Glycosyl halides were

prepared according to published procedures.[4,11,12,15,17] Benzyl chloride, magnesium turnings, acetic anhydride, pyridine, carbohydrate substrates, and anhydrous ether were used as obtained. Alkylation isomer ratios were determined by comparison of the integration of appropriate regions of the ^1H NMR spectra.

Reaction of 1 with Benzylmagnesium Chloride 5.0 g of Mg turnings (0.205 g-atoms) were suspended in 50 mL of ether and 20 mL (0.174 mol) of benzyl chloride in 100 mL of ether was added over 30 min and heated at reflux another 1 h. Bromosugar **1** (5 g, 0.012 mol) was dissolved in 100 mL of ether and added to the refluxing Grignard reagent solution. The mixture was heated at reflux for 3 h and poured into 250 mL of H_2O. 10 mL of glacial HOAc was added. The mixture was shaken and separated. The aqueous layer was concentrated and the residue reacted with 75 mL acetic anhydride and 75 mL pyridine for 18 h. The reaction was poured into 250 mL of H_2O and extracted with 2 x 100 mL of ether. The ether extracts were washed with 2 x 100 mL of H_2O, dried ($MgSO_4$), and solvent removed. The crude material was chromatographed with 1:1 EtOAc/hexane as eluent and produced 1.6 g of solid which subsequently was found to be a 3:1 mixture of **2** to **3** but which showed only one molecular formula by mass spectrometry: HRMS calcd for $C_{21}H_{26}O_9$ 422.1577, found 422.1578.

Reaction of 2,3,4-tri-*O*-Acetyl-β-D-xylopyranosyl Chloride with Benzylmagnesium Chloride[10] 1,2,3,4-tetra-*O*-acetylxylopyranose (2.07 g, 6.5 mmol) and aluminum chloride (3.3 g, 24.8 mmol) were combined in 125 mL of dry $CHCl_3$ for 1.5 h. The reaction was then washed consecutively with 2 x 50 mL of saturated $NaHCO_3$, 50 mL of H_2O, 50 mL of saturated $NaHCO_3$, 50 mL of brine, dried ($MgSO_4$), filtered and concentrated. The crude xylosyl chloride was dissolved in 100 mL of ether and added to benzylmagnesium chloride prepared from 2.43 g of Mg turnings (0.10 g-atom) and 11.5 mL (0.1 mol) of benzyl chloride in 250 mL of ether. The reaction mixture was kept at reflux for 4 h and poured into 400 mL of H_2O. The mixture was shaken and the separated aqueous layer was concentrated and the residue was reacted with 75 mL each of Ac_2O and pyridine for 8 h. Work-up and chromatography as for the synthesis of **2/3** yielded 989 mg (43% yield) of **4**: mp 105-107 °C; IR (neat) 3027, 2962, 2942, 2931, 2886, 2871, 1745, 1494, 1456, 1432, 1369, 1249, 1224, 1132, 1037, 993, 937, 750, 701; UV (MeOH) λ 258 nm (log ε 2.53), 220 nm (log ε 2.83); ^1H NMR δ 1.96 (s,3H, OAc), 2.02 (s, 6H, overlapping OAc), 2.65-2.85 (m, 2H, benzyl CH_2), 3.18

(t, 1H, J=10 Hz), 3.55-3.65 (m, 1H), 4.05 (dd, 1H, J=5.6 Hz, 10 Hz), 4.90 (t, 1H, J=9.2 Hz), 4.96 (m, 1H), 5.16 (t, 1H, J=9.2 Hz), 7.15-7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 20.48, 20.52 (-OAc), 38.21, 66.71, 69.35, 72.45, 74.11, 78.94, 126.46, 128.23, 129.27, 137.20, 169.58, 170.19; HRMS calcd for $C_{18}H_{22}O_7$ 350.1365, found 350.1383.

Reaction of 3,4,6-tri-*O*-Acetyl-α-D-2-deoxyglucosyl Bromide with Benzylmagnesium Chloride 1.0 g (3.6 mmol) of 1,5-anhydro-3,4,6-tri-*O*-acetyl-2-deoxy-D-*arabino*-hex-1-enitol was dissolved in 20 mL of benzene and saturated with HBr (g). The reaction mixture was allowed to stand at room temperature for 1 h, concentrated, and the residue redissolved and reconcentrated with 2 x 20 mL of benzene. The residue was dissolved in 125 mL of ether and added to benzylmagnesium chloride prepared from 1 g (0.041 g-atom) of Mg turnings and 5 mL (43 mmol) of $PhCH_2Cl$ in 300 mL of ether. The mixture was heated at reflux for 4 h, poured into 100 mL of H_2O, and 5 mL of glacial HOAc added. The aqueous layer was concentrated, reacted with 50 mL of Ac_2O and 50 mL of pyridine at 0 °C and allowed to warm to room temperature over 18 h. Work-up and chromatography as for the synthesis of **2/3** gave 371 mg (28% yield) of the benzyl alkylation product **8** as a clear oil which was not fully purified but characterized with regard to its mode of alkylation by ^1H NMR: δ 1.98 (s, 3H), 1.99 (s, 3H), 2.01 (s, 3H), 2.2-2.3 (m, 1H), 2.6-3.0 (m, 3H), 3.5-3.6 (m, 1H), 4.0-4.4 (m, 3H), 4.75-4.9 (m, 1H), 5.1-5.2 (m, 1H), 7.0-7.2 (m, 5H).

Reaction of 9 with Benzylmagnesium Chloride 479 mg (0.695 mmol) of 1-*p*-nitrobenzoyl-2,3,4,6-tetra-*O*-benzylglucose[18b] was dissolved in 10 mL of dry CH_2Cl_2 and HBr (g) was bubbled in for 5 min. The precipitated 4-nitrobenzoic acid was removed by filtration and the CH_2Cl_2 solution was concentrated. The residue was dissolved in 50 mL of ether and added to benzylmagnesium chloride prepared from 0.5 g Mg (0.020 g-atom) and 1.7 mL of $PhCH_2Cl$ (0.0147 mol) in 50 mL of ether. The mixture was heated at reflux for 5 h, and poured into 100 mL of H_2O containing 5 mL of glacial HOAc. The mixture was shaken and separated. The ether layer was dried ($MgSO_4$), filtered, concentrated, and the residue chromatographed with 15:85 EtOAc/hexane to yield 255 mg (60% yield) of the benzyl alkylation product as a clear oil which was used as obtained and characterized by ^1H NMR: δ 2.73 (dd, 1H, J=8.6 Hz, 14.0 Hz), 3.18 (dd, 1H, J=2.7 Hz, 14.0 Hz), 3.3-3.4 (m, 2H), 3.45-3.55 (m, 1H), 3.6-4.8 (m, 4H), 4.4-5.0 (m, 8H), 7.1-7.4 (m, 25H).

Conversion of (2,3,4,6-tetra-*O*-Benzyl-ß-D-glucopyranosyl)phenylmethane to 3[2f] After catalytic hydrogenation for 19 h under 40 psi of H_2 of 1.09 g (1.77 mmol) of (2,3,4,6-tetra-*O*-benzyl-ß-D-glucopyranosyl) phenylmethane in 50 mL of glacial HOAc containing 100 mg of 10% Pd-C, the reaction mixture was filtered, concentrated under reduced pressure, and the residue reacted with 30 mL each of Ac_2O and pyridine at 0 °C and allowed to warm to room temperature over 18 h. Work-up as for the synthesis of **2/3** and crystallization from 2-propanol yielded 194 mg (26% yield) of **3**: mp 118-119 °C; IR (KBr) 3089, 3060, 3039, 2962, 2948, 2937, 2888, 1733, 1602, 1498, 1454, 1442, 1367, 1224, 1105, 1085, 1029, 975, 908, 754, 698; UV (MeOH) λ 258 nm (log ε 2.33), 218 nm (log ε 2.88); ^{1}H NMR (acetone-d_6) 1.92 (s, 3H), 1.94 (s, 3H), 1.96 (s, 3H), 1.97 (s, 3H), 2.72 (dd, 1H, J=14.5 Hz, 8.4 Hz), 2.88 (dd, 1H, J=14.5 Hz, 3.2 Hz), 3.72-3.90 (m, 1H), 4.00 (dd, 1H, J=12.1 Hz, 2.4 Hz), 4.21 (dd, 1H, J=12.1 Hz, 5.8 Hz), 4.86 (t, 1H, J=9.6 Hz), 4.96 (t, 1H, J=9.8 Hz), 5.22 (t, 1H, J=9.5 Hz), 7.1-7.4 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 20.52 (4x, -OAc), 38.01 (benzyl-CH_2), 62.36, 68.97, 72.20, 74.54, 75.65, 78.37 (pyranose-C1), 126.49, 128.20, 129.42, 137.17, 169.37, 169.55, 170.25; HRMS calcd for $C_{21}H_{26}O_9$ 422.1577, found (M+1) 423.1679.

Reaction of 5 with Benzylmagnesium Chloride 2.5 g (6 mmol) of **5** was dissolved in 100 mL of ether and added to benzylmagnesium chloride prepared from 3 g (0.123 g-atoms) of Mg turnings and 8.5 mL (74 mmol) of $PhCH_2Cl$ in 200 mL of ether. The reaction was kept at reflux for 4 h, poured into 200 mL of H_2O and 20 mL of glacial HOAc was added. The mixture was shaken and separated, the aqueous layer was concentrated under reduced pressure, and the residue was reacted with 50 mL of Ac_2O and 50 mL of pyridine at 4 °C for 18 h. Work-up as for the synthesis of **2/3** gave 1.53 g (60% yield) of an oil which was not further purified but characterized with regard to its mode of alkylation by ^{1}H NMR: δ 1.97 (s, 3H), 2.00 (s, 3H), 2.04 (s, 3H), 2.20 (s, 3H), 2.65 (dd, 1H, J=5.4 Hz, 13.5 Hz), 2.85-3.1 (m, 2H), 3.55 (m, 1H), 3.74 (t, 1H, J=6.5 Hz), 3.95-4.2 (m, 2H), 4.9-5.4 (m, 2H), 7.1-7.35 (m, 5H).

Synthesis of 2[8] A solution of 4.00 g (9.73 mmol) of **1** in 125 ml of ether was added to 250 mL of a refluxing solution of *o*-tolylmagnesium bromide prepared from 25 g (146 mmol) of *o*-bromotoluene and 3.55 g (0.146 g-atom) of magnesium turnings. The mixture was heated at reflux for 5 h, cooled, and poured into 150 mL of H_2O. Glacial HOAc was added until the

magnesium salts were dissolved (*ca.* 15 mL). The mixture was shaken and the layers were separated. The aqueous layer was concentrated to dryness. The residue was acetylated with 100 ml of Ac_2O and 100 ml of pyridine at 0 °C. The acetylation was allowed to stir and warm to room temperature overnight. The mixture was poured into 500 ml of water and the product isolated by filtration to give 0.97 g (24%) of **3**, mp 117-119 °C (lit[8] mp 116-118 °C), ^{1}H NMR δ 1.76 (s, 3H, CH_3), 1.99 (s, 3H, CH_3), 2.04 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 3.8 (ddd, 1H, H-5, $J_{5,6a}$=2.2 Hz, $J_{5,6b}$=4.7 Hz, $J_{5,4}$=9.8 Hz), 4.14 (dd, 1H, $J_{6a,6b}$=12.3 Hz, $J_{6a,5}$=2.2 Hz), 4.23 (dd, 1H, $J_{6a,6b}$=12.3 Hz, $J_{6b,5}$=4.7 Hz), 4.66 (d, 1H, H-1, $J_{1,2}$=9.4 Hz), 5.2-5.4 (m, 3H, H-2, H-3, H-4), 7.1-7.4 (m, 4H, aromatic).

ACKNOWLEDGMENTS

Partial financial support of this work by a grant from the National Cancer Institute (CA49837) and a Training Grant Postdoctoral Fellowship to M.J.P. (T 32 CA09498-07) is gratefully acknowledged. Helpful discussions with Dr. Duane D. Miller are also well appreciated. The assistance of The Ohio State University Campus Chemical Instrument Center in obtaining mass spectra is acknowledged. We thank Ms. Kimberly Risch for the preparation of this manuscript.

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