Synthesis of β,γ-Unsaturated Aromatic Hydrocarbons by Tandem Phenylation–Reduction of α,β-Unsaturated Aldehydes and Ketones. Product Prediction and Synthetic Utility[1]

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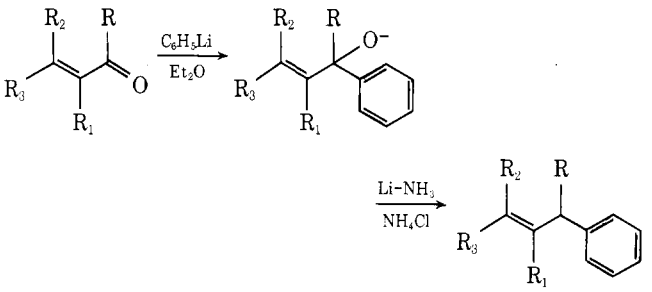
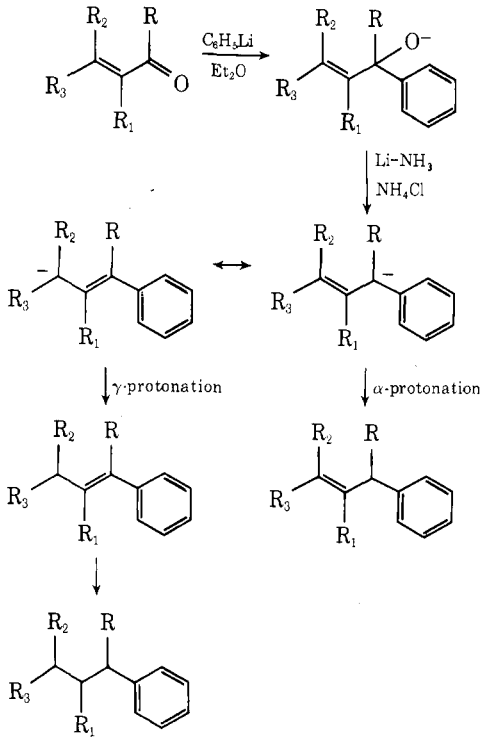
Based on 15 α,β-unsaturated aldehydes and ketones surveyed, product prediction in the tandem phenylation–reduction of such carbonyl compounds seems to be possible. If there are only hydrogens at the β position of the α,β-unsaturated system the product is the corresponding aromatic hydrocarbon. All other alkyl-substituted α,β-unsaturated aldehydes yield the corresponding β,γ-unsaturated aromatic hydrocarbons. Alkyl-substituted α,β-unsaturated ketones are less predictable and sometimes result in mixtures. Consequently, on appropriate α,β-unsaturated aldehydes and ketones, this phenylation–reduction procedure is a unique method for the rapid synthesis of β,γ-unsaturated aromatic hydrocarbons and serves as a convenient alternative to tthe Wittig reaction.

This laboratory recently introduced a convenient tandem phenylation–reduction procedure for the rapid synthesis of aromatic hydrocarbons from aldehydes and ketones.[3] The sequence involves the lithium–ammonia–ammonium chloride reduction of a benzyl alkoxide that is generated in situ by phenylation of the carbonyl system. Included in this study



were a few α,β-unsaturated aldehydes and ketones that generally yielded the corresponding β,γ-unsaturated aromatic hydrocarbon. Such a product indicates that in the reduction of the benzyl alkoxide[4] (see Scheme I) the intermediate anion

Scheme I



protonates exclusively at the benzylic position (α-protonation) forming the β,γ-unsaturated aromatic hydrocarbon that survives in statu quo. However, in a few cases, the corresponding saturated aromatic hydrocarbon was also formed indicating that some protonation occurred at the allylic position (γ-protonation) yielding the styrene system that would be rapidly reduced[5] to the aromatic hydrocarbon. The purpose of our present study was to survey a reasonable sampling of α,β-unsaturated aldehydes and ketones to establish the structural or substituent requirements that might enable product prediction and at the same time explore the synthetic utility of the method.

The general procedure is to genneerate a benzyl alkoxide in a metal–ammonia reaction vessel by the addition of the α,β-unsaturated aldehyde or ketone to phenyllithium in ether. Ammonia is subsequently distilled into the vessel, and then the resultant dark blue mixture is cautiously quenched with ammonium chloride. Table I is a listing of the α,β-unsaturated carbonyl compounds that were subjected to these phenylation–reduction conditions with the results. Eight of the α,β-unsaturated aldehydes (**3, 4, 5, 6,** and **7**) and ketones (**9, 10,** and **14**) yielded only the corresponding β,γ-unsaturated aromatic hydrocarbon indicating exclusive protonation at the benzylic position (α-protonation). In contrast, three of the α,β-unsaturated carbonyl compounds (**1, 2,** and **8**) yielded the corresponding aromatic hydrocarbon as the sole product. The aromatic hydrocarbon product is the result of protonation at *the primary allylic anion position (γ-protonation)* followed by the rapid metal–ammonia reduction of the styrene system.

Only with three α,β-unsaturated ketones (**11, 12,** and **13**) studied did mixtures result. The presence of an alkyl group (R = alkyl) at the benzylic position, after phenylation of the α,β-unsaturated ketones, introducedd the possibility of steric hindrance to protonation[6] of the intermediate anion at this carbon (α-protonation) and consequently some protonation at the allylic position (γ-protonation) is observed. This effect, however, can be very subtle. Compare, for example, (+)-pulegone (**10**) with piperitone (**11**) and (−)-carvone (**12**). Steric effects can also play an important role in protonation at the allylic position. The intermediate anion from the phenylation–reduction of ketone **13** protonates at both positions while with α-ionone (**14**) the introduction of the three neighboring methyll groups in the ring protects the γ position and only α-protonation is detected. With β-ionone (**15**) it is impossible to determine whether the protonation occurred at the α site or at both the α and γ site since the resultant olefin from either would reduce to **30**.[7] Protonation at the allylic anion position leaves a vulnerable styrene system and protonation at the benzylic position, which seems reasonable by analogy to α-

Table I. Phenylation–Reduction of α,β-Unsaturated Aldehydes and Ketones

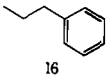
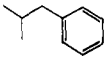
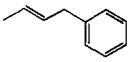
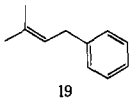
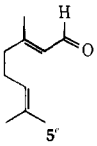
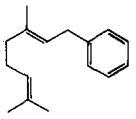
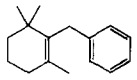
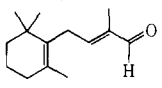
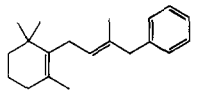
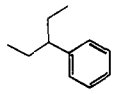
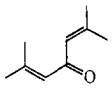
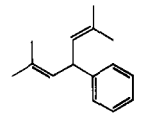
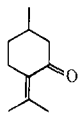
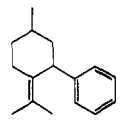
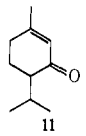
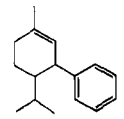
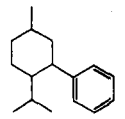
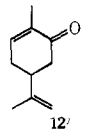
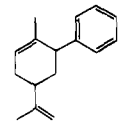
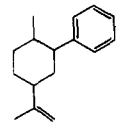
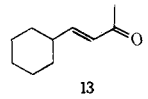
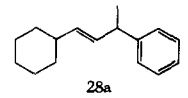
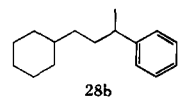
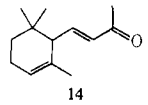
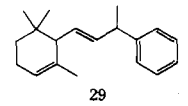
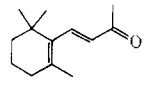
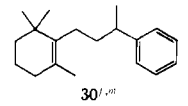
α,β-Unsaturated carbonyl compd	Product(s)		Yield	
	α-Protonation	γ-Protonation	Small scale[a] anal[c]/isol[d]	Large scale[b] anal[c]/isol[d]
 1		 16	100/94	
 2		 17	95/86	
 3	 18		92/86	96/94
 4	 19		98/95	98/94
 5[e]	 20[f]		100/90	99/94
 6	 21[f]		100/99	95/90
 7	 22[f]		99/93	99[g]/97
 8		 23	99/97	
 9	 24[f]		93/93	
 10[h]	 25[f]		98/85	
 11	 26a	 26b	83[i]/80	
 12[f]	 27a	 27b	100[k]/98	
 13	 28a	 28b	99[l]/94	
 14	 29		99/95	
 15		 30[f,m]	100/98	

Table I (*Footnotes*)

[a] Small scale reaction using 2.5 mmol of carbonyl compound. See the Experimental Section for details. [b] In this and previous studies, the reactions were performed on a small scale and for mechanistic reasons with a large excess of lithium. Included in this work are the optimal conditions for a scaled-up synthesis (25 mmol) using the minimal amount of lithium. See Experimental Section for details. [c] Analyzed by GLC (% of volatiles). [d] Isolated by column chromatography. [e] The aldehyde was a commercial sample of citral. [f] See ref 3 for the spectral data, composition analysis, and any special experimental comments or instructions. [g] The large scale reaction required 1.58 g (230 mg-atoms) of lithium. [h] Sample was (+)-pulegone. [i] Mixture (60:40) of **26a** and **26b**. [j] Sample was (−)-carvone. [k] Mixture (65:35) of **27a** and **27b**. [l] Mixture (65:35) of **28a** and **28b**. [m] May have been formed by either α-protonation or α- and γ-protonation. See discussion.

ionone (**14**), would leave a 1,3-diene system that would reduce to the olefin **30** by 1,2 addition to the less substituted double bond.

In summary, product prediction in the tandem phenylation–reduction of α,β-unsaturated aldehydes and ketones seems to be possible. If there are only hydrogens at the β position of the α,β-unsaturated system the product will be the corresponding aromatic hydrocarbon. All other alkyl substituted α,β-unsaturated aldehydes should yield the correesponding β,γ-unsaturated aromatic hydrocarbons. Only the alkyl substituted α,β-unsaturated ketones are less predictable and can result in mixtures that are difficult to separate.[8] Consequently this phenylation–reduction procedure, when used on appropriate α,β-unsaturated aldehydes and ketones, is a uniquely simple method for the rapid synthesis of β,γ-unsaturated aromatic hydrocarbons and serves as a convenient alternative to the Wittig reaction.[9]

Experimental Section[10]

General Comments. See ref 3 for general experimental comments. Gas chromatography (GLC) analyses were performed on 100 × 0.4 cm (i.d.) glass columns packed either with 4% silicon gum rubber UCC-W-982 (methylvinyl) supported on 80–100 mesh HP Chromosorb W (AW, DMCS) or with 3% silicon gum rubber OV-17 (methylphenyl) supported on 80–100 mesh HP Chromosorb W. Purification of the product by column chromatography was accomplished on chromatographic grade activated alumina (80–325 mesh, Matheson Coleman and Bell) by elution with petroleum ether. Evaporative distillations, sometimes necessary for microanalyses, were performed in a Kügelrohr oven. The assigned structure of each product (or mixture) was consistent with the spectral data and composition analysis. Significant spectral data on all new compounds are included in the Experimental Section. The phenylation–reduction of 3-methyl-2-butenal (**4**) is described, in detail, to illustrate the small-scale reaction; and (*E*)-2-butenal (**3**) to illustrate the large-scale reaction.

Phenylation–Reduction of 3-Methyl-2-butenal (4). 3-Methyl-1-phenyl-2-butene (19, Small Scale). To a metal–ammonia reaction vessel containing a stirred mixture of 280 mg (40.0 mg-atoms, ca. 25 pieces) of lithium foil in 10 ml of anhydrous ether was slowly added a solution of 790 mg (5.00 mmol) of bromobenzene in 7 ml of ether. After 1 h a solution of 210 mg (2.500 mmol) of 3-methyl-2-butenal (**4**) in 8 ml of ether was slowly added and the mixture was stirred for an additional 1 h. Ammonia (ca. 25 ml) was carefully distilled[11] into the mixture and, once the dark blue color of the mixture was established,[12] ca. 3 g of ammonium chloride was cautiously added[13] (ca. 5 min) to discharge the blue color and then the ammonia was allowed to evaporate. After the residue had been partitioned between brine and ether, the organic phase was dried ($MgSO_4$), filtered, concentrated at water aspirator pressure, and then analyzed (GLC). Following column chromatography 323 mg (95%) of 3-methyl-1-phenyl-2-butene (**19**) was obtained as a colorless oil: ir (film) 3080, 3060, 3025, 2965, 2910, 1600, 1490, 1450, 1370, 730, 690 cm^{-1}; NMR (60 MHz, CCl_4) δ 7.20 (5 H, apparent s), 5.40 (1 H, t with fine splitting, J = 7.5 and 1.5 Hz), 3.31 (2 H, d, J = 7.5 Hz), and two overlapping doublets at 1.74 (3 H, d, J = 1.5 Hz) and 1.69 (3 H, d, J = 1.5 Hz); mass spectrum m/e (rel intensity) 146 (M^+, 52), 131 (100), 91 (68), 77 (11).

Anal. Calcd for $C_{11}H_{14}$: C, 90.35; H, 9.65. Found: C, 90.37; H, 9.53.

Phenylation–Reduction of (*E*)-2-Butenal (3). (*E*)-1-Phenyl-2-butene (18, Large Scale). To a metal–ammonia reaction vessel containing a stirred mixture of 1.05 g (150 mg-atoms, ca. 50 pieces) of lithium foil in 25 ml of anhydrous ether was slowly added (ca. 10 min)[14] a solution of 5.84 g (37.0 mmol) of bromobenzene in 25 ml of ether. After 50 min, the reaction mixture was diluted with 50 ml of ether and then cooled[15] to ca. −70 °C (dry ice–acetone bath). A solution of 1.75 g (25.0 mmol) of (*E*)-2-butenal[16] in 25 ml of ether was slowly added (ca. 15 min) and after 10 min the cooling bath was removed and the mixture stirred for 50 min. After a further dilution with 75 ml of ether, ca. 200 ml of ammonia was carefully distilled[11] (30–40 min) into the mixture and after 10 min the dark blue color of the reaction mixture was discharged by the addition[13] (ca. 20 min) of excess ammonium chloride (ca. 7 g). After the ammonia had evaporated the residue was partitioned betwween ether and brine. The organic phase was dried ($MgSO_4$), filtered, concentrated at water aspirator pressure, and then analyzed (GLC). Following column chromatography 3.10 g (94%) of (*E*)-1-phenyl-2-butene (**18**) was obtained as a colorless oil: bp 110–121 °C (760 Torr); $n^{24}D$ 1.5120; ir (film) 3090, 3070, 3035, 2965, 2925, 1605, 1495, 1450, 965, 740, 690 cm^{-1}; NMR (100 MHz, $CDCl_3$) δ 7.14 (5 H, apparent s), 5.72–5.26 (2 H, m), 3.26 (2 H, d, J = 4.9 Hz), 1.64 (3 H, d, J = 4.6 Hz); mass spectrum m/e (rel intensity) 132 (M^+, 55), 117 (100), 91 (65).

Anal. Calcd for $C_{10}H_{12}$: C, 90.85; H, 9.15. Found: C, 90.68; H, 9.21.

(*E*)-1-(2,6,6-Trimethyl-2-cyclohexen-1-yl)-3-phenyl-1-butene (29). Ir (film) 3080, 3055, 3020, 2955, 2915, 2860, 1600, 1490, 1445, 1375, 1370, 1360, 965, 750, 690 cm^{-1}; NMR (60 MHz, CCl_4) δ 7.22 (5 H, s), two quartets centered at 5.67 (1 H, q, J = 16 and 6 Hz), and 5.25 (1 H, q, J = 16 and 8 Hz) on which is superimposed a multiplet at 5.53–5.26 (1 H, m), 3.45 (1 H, broad quintet, J = ca. 7 Hz), 2.25–1.69 (3 H, broad m), 1.69–1.50 (3 H, m), 1.34 (3 H, sharp d, J = 7.2 Hz) superimposed on a multiplet at 1.50–1.09 (2 H, m), and four singlets at 0.90, 0.88, 0.86, and 0.82 (6 H, two conformers); mass spectrum m/e (rel intensity) 254 (M^+, 15), 239 (4), 197 (96), 183 (40), 105 (85), 93 (100), 91 (94), 77 (83), 69 (32).

Anal. Calcd for $C_{19}H_{26}$: C, 89.70; H, 10.30. Found: C, 89.84; H, 10.15.

Acknowledgments. The authors wish to thank Dr. F. Scheidl, Hoffmann-La Roche Inc., Nutley, N.J., for the microanalyses.

Registry No.—**1**, 107-02-8; **2**, 78-85-3; **3**, 123-73-9; **4**, 107-86-8; **5**, 141-27-5; **6**, 432-25-7; **7**, 14398-40-4; **8**, 1629-58-9; **9**, 504-20-1; **10**, 89-82-7; **11**, 89-81-6; **12**, 6585-40-1; **13**, 41437-84-7; **14**, 127-41-3; **15**, 14901-07-6; **18**, 935-00-2; **19**, 4489-84-3; **29**, 59939-06-9.

References and Notes

(1) Part 8 in the series "Alkylation–Reduction of Carbonyl Systems". For part 7 see S. S. Hall, C.-K. Sha, and F. Jordan, *J. Org. Chem.*, **41**, 1494 (1976).
(2) Taken in part from the Ph.D. Thesis of F. J. M. and the M.S. Thesis of C.-K.S., Rutgers University, 1975.
(3) S. S. Hall and F. J. McEnroe, *J. Org. Chem.*, **40**, 271 (1975).
(4) For a discussion of the proposed mechanism of the reduction of benzyl alkoxides to aromatic hydrocarbons see (a) S. S. Hall, S. D. Lipsky, and G. H. Small, *Tetrahedron Lett.*, 1853 (1971); (b) S. S. Hall, S. D. Lipsky, F. J. McEnroe, and A. P. Bartels, *J. Org. Chem.*, **36**, 2588 (1971).
(5) W. Hückel and H. Bretschneider, *Justus Liebigs Ann. Chem.*, **540**, 157 (1939).
(6) A contributing factor, of course, could be that the benzylic position is a tertiary carbanion with the ketones and secondary with the aldehydes, but we feel that this is not dominating. Compare, for example, the results of ketone **13** with **14**.
(7) The phenylation–reduction of this ketone has been previously discussed in ref 3 and includes the results of some mechanistically informative experiments.
(8) These considerations do not apply to aromatic substituents on the α,β-unsaturated aldehydes and ketones. See S. S. Hall, *J. Org. Chem.*, **38**, 1738 (1973).
(9) A. Maercker, *Org. React.*, **14**, 270 (1965).
(10) GLC analyses were determined on a Hewlett-Packard Model 7610A (flame detector) chromatograph. The ir spectra were determined with a Beckman Model IR-10 or Model AccuLab 6 infrared recording spectrophotometer. The ^1H NMR spectra were determined at 60 MHz with a Varian Associates Model A-60 NMR spectrometer and at 100 MHz with a JEOL Model JNM-PS-FT-100 fast Fourier transform NMR spectrometer. The chemical shifts are expressed in δ values (parts per million) relative to a Me_4Si internal standard. The mass spectra were determined with an AEI Model MS-30

mass spectrometer (70 eV) to which was interfaced a Pye Unicam Model 104 gas chromotograph. The refractive indexes were determined with a Bausch and Lomb refractometer.

(11) To increase the efficiency of the condensation process, the reaction vessel was cooled (dry ice–acetone bath); and to prevent splattering, the apparatus was tilted slightly to allow the condensing ammonia to run down the walls of the flask.

(12) Normally ca. 10 min elapsed before proceeding with the quenching step, although the time interval does not seem critical.

(13) The NH_4Cl is most conveniently introduced by attaching a glass bulb filled with the salt to a side arm by means of tygon tubing. When the NH_4Cl is to be added, the bulb is raised and tapped gently to smoothly introduce the quenching agent. Should this step start to become violent, the addition and sometimes even the vigorous stirring should be momentarily stopped to avoid an eruption.

(14) During the addition the exothermic reaction was moderated (25–30 °C, internal thermometer) with a water bath.

(15) The temperature was lowered as a precaution to minimize the possibility of competing side reactions. See J. D. Buhler, *J. Org. Chem.*, **38**, 904 (1973).

(16) (*E*)-2-Butenal (crotonaldehyde), which is stabilized with 10% water, was distilled, bp 95–100 °C (760 Torr), just prior to use.

Diels–Alder Reactions of *o*-Benzoquinones. A Route to Derivatives of Δ^2-1-Octalone

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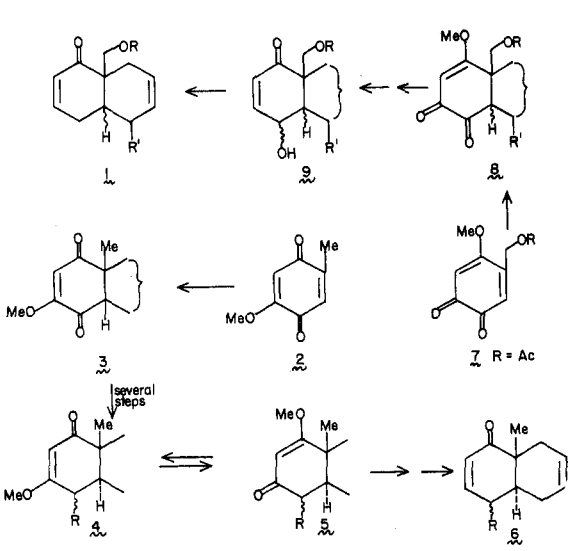
Diels–Alder reactions of 4-methoxy-5-acetoxymethyl-1,2-benzoquinone (**7**) and 4-methoxy-5-methoxymethyl-1,2-benzoquinone (**40**) have been shown to occur smoothly with acyclic dienes. In all cases, cycloaddition occurs at the 5,6 rather than 3,4 double bond. With 1-methoxybutadiene as the diene, regiospecific formation of the 8- rather than 5-methoxy isomer is observed. The applicability of stereospecific "endo" addition has been demonstrated. The adducts produced can be converted in five steps to angularly (**8a**) substituted derivatives of 4a,5,8,8a-tetrahydronaphthalen-1(4*H*)-one.

As part of a synthetic study directed at various elemanolide sesquiterpenoids, we had need to develop a simplified route to angularly functionalized hexalones of the type **1**. The known route to such systems, in the angular methyl series, involved equilibration of β-methoxyenones such as **4** with their vinylogous isomers, **5**.[1,2] Reduction affords a β-methoxyallylic alcohol which is unravelled with acid to give **6**.[3,4] System **4** is obtained by the Woodward route,[5] which starts with a Diels–Alder cycloaddition of methoxytoluoquinone **2** with 1,3-butadiene. The cis adduct **3** is epimerized to the trans series, and the C_4 ketone is selectively reduced to give an alcohol.[1] Interconversion of **4** with **5** has been achieved either on the derived tosylate, **4** (R = OTs),[2] or on the reduction product thereof, **4** (R = H). Alternatively the β-diketone, derived from hydrolysis of **4** (R = H), has been converted to a mixture of **4** and **5** (R = H).[1]



Since the stability of **4** vs. **5** is apparently a sensitive and unpredictable function of the nature of the substituents, we preferred to develop an entry to **1** in which such a process is not necessary. If, instead of a *p*-quinone, an *o*-quinone such as **7** is used as the dienophile, an adduct of the type **8** would be produced. Reduction of both carbonyl groups followed by the same type of acidic transformation which is involved in the conversion of **5** → **6** would provide **9** from **8**. Reductive transformation of **9** → **1** could easily be envisaged.

Prior to this investigation, the use of *o*-quinones as dienophiles had received relatively little attention. Of course, Gates and co-workers had utilized a 1,2-napthoquinone as a dienophile in their well-known synthesis of morphine.[6] Ansell had shown[7] that activated *o*-benzoquinones, bearing a 4-cyano or 4-carbomethoxy substituent, were sufficiently activated to react as dienophiles with reactive acyclic dienes such as 2,3-dimethylbutadiene. Subsequent work demonstrated that with simple, nonactivated *o*-quinones,[8] only with massive excesses of 2,3-dimethylbutadiene could Diels–Alder adducts be obtained. Horspool had concluded[9] that the propensity for dimerization and decomposition of simple *o*-quinones is such that Diels–Alder reaction with unactivated dienes was apparently not possible.

We expected that the enophilic powers of a 4-methoxy-*o*-quinone should be sharply reduced since cycloaddition would necessitate dissipation of the vinylogous ester resonance of the starting material. That such an effect is likely to be important is suggested by the specific dienophilicity of the 5,6 rather than 2,3 double bond of *p*-quinone **2**.[5] Furthermore, Ansell had shown that 4-methoxy-1,2-benzoquinone reacts with 2,3-dimethylbutadiene exclusively at the 5,6 rather than the 3,4 double bond,[8] presumably for the same reason. If the *enophilicity* of a system such as **7** is diminished in line with the curtailment of its *dienophilicity* at the 3,4 double bond, the possibilities of realizing cycloaddition reactions of the 5,6 double bond with a wide variety of dienes becomes more promising. This expectation has been realized in practice.

Results

The synthesis of specific compound **7** (R = OAc) started with the commercially available *p*-nitroanisole. This was