2-Methyl-6-hydroxy-6-cyclopentyl-2-heptene (11). To a mixture of 2.0 g (288 mmol) of Li sand (5% Na) and 100 mL of dry hexane in a three-necked, 250-mL flask fitted with a mechanical stirrer and maintained under a He atmosphere was added 13.9 mL (19.4 g, 130 mmol) of cyclopentyl bromide (Aldrich). After 10% of the bromide had been added, the mixture was brought to reflux. The mixture became cloudly, developed a purple color, and was refluxed 1 h after the addition was complete. The mixture was cooled to −70 °C, 19.4 mL (16.4g, 130 mmol) of 2-methyl-2-hepten-6-one added, and the solution stirred an additional 2 h. The reaction mixture was acidified with 80 mL of saturated NH_4Cl and extracted three times with 50-mL portions of ether, the combined organic phases were dried ($MgSO_4$), and the solvent was removed in vacuo. The resulting oil was distilled to give 6.0 g (6.2 mL, 30%) of 11: bp 108–111 °C (6 mmHg); IR (neat) 3480 cm^{-1}; ^1H NMR (CCl_4) δ 1.17 (s, 3 H), 1.4–2.4 (m, 13 H), 1.6 (brs, 6 H), 2.75 (s, 1 H), 5.48 (brt, 1 H, J = 7 Hz). Anal. Calcd for $C_{13}H_{24}O$: C, 79.51; H, 12.24. Found: C, 79.79; H, 12.06.

1-Isopropyl-7-methylbicyclo[4.3.0]non-6-ene (4) from 11. By use of a procedure similar to the previous preparation of 4, 6.8 g (3.8 mmol) of 11 was converted into 4.5 g (73%) of distilled 4, bp 105–107 °C (20 mmHg).

Registry No. 1, 80447-64-9; 2, 1569-60-4; 3, 80325-37-7; 4, 80447-65-0; 5, 80461-60-5; 6, 88-69-7; 7, 1004-77-9; 8, 80447-66-1; 8 ketal, 80447-67-2; 9, 80447-68-3; 10, 80447-69-4; 11, 80447-70-7.

Addition of Lithio-α-thiophenyl Nitriles to Aldehydes and Ketones[†]

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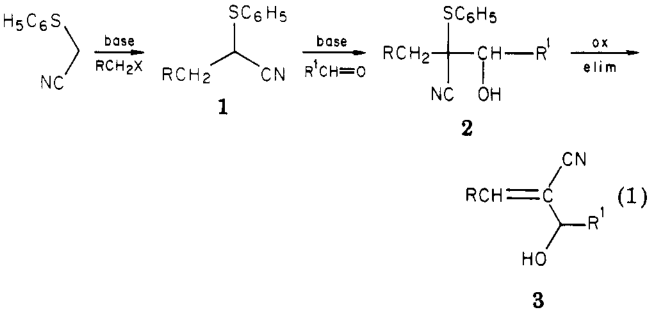
Department of Chemistry, University of California, Santa Cruz, California 95064

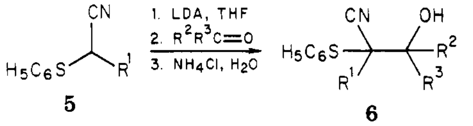
Received August 21, 1981

In connection with a natural product synthesis currently under investigation in our laboratories, we required a method for the construction of α′-hydroxy-α,β-unsaturated nitriles based on the scheme shown in eq 1.



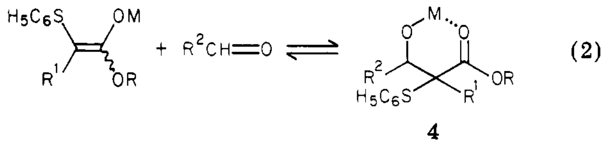
Literature precedent[2] indicated that the initial alkylation would proceed without problem; however, the outcome of the second carbon–carbon bond-forming step was not secure. Our cause for concern was based on the lack of precedent for such reactions (1 → 2) and reinforced by recent reports[3] concerning reactions of this type with α-thiophenyl esters and lactones. In particular, one report[3a] mentioned problems in obtaining good yields from lithio-α-thiophenyl esters and aldehydes. These workers conveniently solved this problem by using a $ZnCl_2$ additive, which presumably perturbs the equilibrium (unfavorable for M = Li) shown in eq 2 to the product side by chelation[4] of the 1,2-adduct 4. Given the apparent geometrical constraints in such a chelated intermediate, the utility of this device for the case at hand was not clear should the addition equilibrium (eq 3) be found unfavorable.

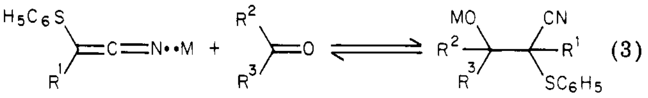
Table I. 1,2-Addition Reactions with Aldehydes and Ketones[a]



entry	R^1	R^2	R^3	product yield, %
1	CH_3 (5a)	H	$CH(CH_3)_2$	(6a) 89
2	CH_3 (5a)	H	C_6H_5	(6b) 90
3	CH_3 (5a)		$-(CH_2)_5-$	(6c) 90[b]
4	n-C_4H_9 (5b)	H	$CH(CH_3)_2$	(6d) 90
5	n-C_4H_9 (5b)	H	C_6H_5	(6e) 80
6	n-C_4H_9 (5b)		$-(CH_2)_5-$	(6f) 62[c]
7	n-C_4H_9 (5b)		$-(CH_2)_4-$	(6g) 67[d]
8	i-C_4H_9 (5c)	H	$CH(CH_3)_2$	(6h) 53
9	i-C_4H_9 (5c)	H	C_6H_5	(6i) 54
10	i-C_4H_9 (5c)		$-(CH_2)_5-$	(6j) 0
11	$CH_2=CHCH_2$ (5d)	H	$CH(CH_3)_2$	(6k) 72
12	n-C_4H_9 (5b)	H	$CH_2=C(CH_3)$	(6l) 44

[a] All yields refer to chromatographically purified products. Satisfactory combustion analysis was obtained for representative samples from experiments 3, 6, and 8. All substances were obtained as colorless oils unless otherwise noted. Routine characterization included TLC, ^1H NMR, IR, and EI MS. [b] Mp 72–74 °C. [c] Mp 90–91 °C. [d] Mp 53–56 °C.





In practice, the anticipated problems were encountered in initial experiments. Reaction of the anion of α-(phenylthio)propionitrile (**5a**) from lithium diisopropylamide in THF) with isobutyraldehyde at −70 °C for 30 min afforded only a 30% yield of the desired product. Longer reaction times or elevated temperatures offered no improvement. Eventually, it was found that immediate quenching of the reaction mixture (within 15 s of addition of the carbonyl electrophile) dramatically increased the yield for the case above.[5] This procedure was found to be generally applicable to a variety of 1,2 adducts (Table I). Furthermore, reaction of these lithionitriles with α,β-unsaturated carbonyl electrophiles revealed a curious and potentially useful propensity for the exclusive formation of 1,4 adducts (Table II) in almost all of the cases studied.

In general, the 1,2-addition products are formed in good yields with aldehydes and ketones. The representative

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[†] Dedicated to Professor Gilbert Stork on the occasion of his 60th birthday.

[1] Undergraduate Research Associate (1980–1981).

[2] (a) P. Brownbridge, L. Fleming, A. Pearce, and S. Warren, *J. Chem. Soc., Chem. Commun.*, 751 (1976); (b) P. Brownbridge and S. Warren, *J. Chem. Soc., Perkin Trans.* 1, 2272 (1977); (c) M. Makoza, E. Bislecka, and M. Ludwikow, *Tetrahedron Lett.*, 2391 (1972); (d) Y. Masuyama, Y. Ueno, and M. Okawara, *Chem. Lett.*, 835 (1977).

[3] (a) T. R. Hoye and M. J. Kurth, *J. Org. Chem.*, **45**, 3549 (1980; (b) B. M. Trost and H. C. Arndt, *Ibid.*, **38**, 3140 (1973); (c) N. Kumeda, J. Nobami, and M. Kinoshita, *Tetrahedron Lett.*, 3523 (1980).

[4] The utility of this modification was first described by House and co-workers: H. O. House: D. S. Cummrine: A. Y. Teranishi, H. D. Olmstead, *J. Am. Chem. Soc.*, **95**, 3310 (1973).

[5] The advantage of short reaction times in aldol reactions with aldehydes and ketone enolates was described in early studies by House and co-workers. See ref 4.

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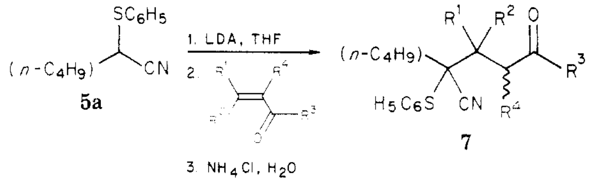
Table II. 1,4-Addition Reactions with Aldehydes and Ketones[a]



entry	R^1	R^2	R^3	R^4	product yield, %
1	H	$-(CH_2)_3-$		H	(**7a**) 80
2	CH_3	$-(CH_2)_3-$		H	(**7b**) 53
3	H	H	CH_3	H	(**7c**) 50
4	H	H	H	CH_3	(**7d**) 89
5	CH_3	H	CH_3	H	(**7e**) 70
6	CH_3	CH_3	CH_3	H	(**7f**) 48

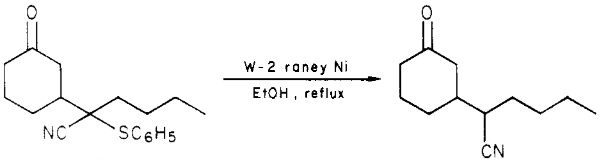
[a] All yields refer to chromatographically purified products. These substances were diastereomeric mixtures of undetermined composition which were obtained as colorless oils. Satisfactory combustion analysis was obtained for representative samples from experiments 1, 4, and 6. Routine characterization included TLC, ^1H NMR, IR, and EI MS.

examples included in Table I indicate the fairly wide tolerance of steric hinderance about the reacting centers. Only one case (entry 10) failed to give any product under the standard conditions (immediate quench) and led only to slow degradation of the starting material under more vigorous conditions. The poor yield for case 12 is due to competitive formation of the 1,4 adduct (vide infra). In all cases, the adducts were mixtures of diastereomers of varied composition ranging from 55:45 to 80:20[6] (based on ^1H NMR integration of **HCOH**). The highest selectivity was observed with benzaldehyde as the electrophile.

Reaction of the lithio nitrile from **5b** with α,β-unsaturated aldehydes and ketones led almost exclusively to the 1,4-addition products[7] (Table II). Products derived from 1,2 addition were not observed in the reaction mixture and quenching after short reaction times gave only poor yields of the 1,4 adducts. The best preparative procedure in our hands required a 1-h reaction at 0 °C. Only methacrolein afforded resonable amounts of the 1,2 adduct after a short (<15 s) reaction time at -78 °C (entry 12, Table I). This 1,2 adduct, **61**, was cleanly transformed to the 1,4 adduct, **7d**, upon treatment with 1 equiv of lithium diisopropylamide at -78 °C followed by warming to 0 °C for 1 h.

The lack of 1,2-addition products in these cases is particularly interesting considering the previously reported[7,8] behavior of other α-heteroatom-substituted nitrile anions. Although we were able to verify a kinetic 1,2-addition/thermodynamic 1,4-addition pathway for only one case, it is unlikely that the 1,4 addition becomes the kinetically preferred mode of addition for the other cases studied. Differences in steric congestion between these adducts could account for a more rapidly reversible 1,2 addition with the ketone electrophiles as compared with methacrolein, making detection of such intermediates more difficult in the former case. The ready reversibility of these 1,2 additions as compared to other α-heteroatom-substituted additions is understandable in terms of the acidifying effect[9] of the α-sulfur substituent.

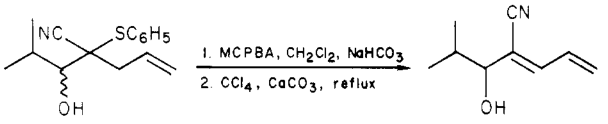
Finally, we mention examples of two further transformations of these adducts which indicate the potential synthetic utility of this methodology. Desulfurization proceeds in good yield for the cyclohexenone adduct **7a** (eq 4). This observation thus enables the overall conjugate addition of RCH_2CN to α,β-unsaturated carbonyl substrates. Oxidation (*m*-chloroperbenzoic acid, $NaHCO_3$, CH_2Cl_2, -78 → 0 °C) and elimination of the crude sulfoxide[10] (CCl_4, $CaCO_3$, reflux) derived from **6k** affords the hydroxy nitrile **9** in 79% overall yield. Spectroscopic evidence, especially ^{13}C NMR (see supplementry material), indicated that a single isomer was formed. We have not unambiguously proven the stereochemistry, but we favor the geometry shown on the basis of steric interactions apparent in the transition state for the elimination.



7a

8

(4)



9

(5)

Experimental Section

General Procedures. NMR spectra were recorded on a JEOL FX-60 spectrometer at 60 MHz in $CDCl_3$ relative to a tetramethylsilane internal standard. Infrared spectra were obtained on a Perkin-Elmer 237B spectrophotometer as films (liquid samples) or $CHCl_3$ solutions (solid samples). Mass spectra were determined on a Finnegan 4000 instrument at 70 eV. Melting points were determined on a Thomas-Hoover Unimelt apparatus in open capillary tubes and are uncorrected. TLC data were obtained on Analtech silica gel 250-μm Uniplates visualized by treatment with 10% ethanolic phosphomolybdic acid and charring. Column chromatography was performed by the technique described by Still et al.[11] Analytical samples were obtained by crystallization or bulb-to-bulb distillation of chromatographically purified products. Microanalyses were performed by Micro-Tech Laboratories, Inc. The thiophenylnitriles were prepared by the method of Makoza et al.[2c]

Representative Procedure for 1,2-Addition Reactions. 1-[1-Cyano-1-(phenylthio)ethyl]cyclohexanol (6c). A solution of 2-(phenylthio)valeronitrile (0.250 g, 1.72 mmol in 0.5 mL THF) was added dropwise to a solution of lithium diisopropylamide (1.84 mmol in 5 mL THF) at -78 °C under N_2. After 30 min at -78 °C, cyclohexanone (0.168 g, 1.72 mmol) was added neat. Within 15 s the reaction was quenched at -78 °C with ca. 10 mL of 10% aqueous NH_4Cl. The mixture was allowed to warm to room temperature and the organic layer was separated. The organic layer was washed with water and brine. The combined aqueous layers were extracted twice with Et_2O and the total combined organics were dried with $MgSO_4$ and concentrated. Chromatography (silica gel, 5:1 petroleum ether/EtOAc) of the residue yielded 0.376 g (90%) of a colorless oil, which solidified on standing. An analytical sample was obtained by crystallization from hexane/Et_2O: mp 72–74 °C; R_f (5:1 petroleum ether/EtOAc) -0.46; ^1H NMR ($CDCl_3$) δ 1.45 (s, 3 H), 1.60–2.25 (m, 11 H),

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[6] The stereochemistry of these adducts has not been determined.

[7] Such behavior has been reported in a few instances for α-thiophenyl esters (A. Schultz and Y. K. Yee, *J. Org. Chem.*, **41**, 4045 (1976) and the addition of an α-selenophenyl nitrile to cyclohexenone (P. A. Grieco and Y. Yokoyama, *J. Am. Chem. Soc.*, **99**, 5210 (1977)).

[8] (a) G. Stork and L. Maldonado, *J. Am. Chem. Soc.*, **96**, 2572 (1974); (b) G. Stork, A. M. Touzin, and A. Y. W. Leong, *J. Org. Chem.*, **41**, 3491 (1976); (c) E. Leete, *J. Org. Chem.*, **41**, 3438 (1976); (d) A. Casares and L. Maldonado, *Synth. Commun.*, **6**, 11 (1976); (f) G. Stork, A. A. Orzorio, and A. Y. W. Leong, *Tetrahedron Lett.*, 5175 (1978); (g) N. Seuron, L. Wartski, and J. Seyden-Penne, *Tetrahedron Lett.*, 2175 (1981).

[9] F. G. Bordwell, M. Van der Puy, and N. R. Vanier, *J. Org. Chem.*, **41**, 1885 (1976).

[10] B. M. Trost, T. N. Saltzman and K. Hirosi, *J. Am. Chem. Soc.*, **98**, 4887 (1976). See also ref 2d.

[11] W. C. Still, M. Kahn, and A. Mitra, *J. Org. Chem.*, **43**, 2923 (1978).

7.32–7.86 (m, 5 H); IR ($CHCl_3$) 3601, 2965, 2875, 2245, 675 cm^{-1}; mass spectrum, *m/e* (relative intensity) 262 (10, M^+), 261 (40), 244 (25), 205 (33), 163 (100), 104 (68), 99 (82), 81 (66), 60 (36).

Anal. Calcd for $C_{15}H_{19}NOS$: C, 68.75; H, 7.27; N, 5.33. Found: C, 68.93; H, 7.32; N, 5.36.

Representative Procedure for 1,4-Addition Reactions. 3-[1-(Phenylthio)-1-cyanopentyl]cyclohexanone (7a). Cyclohexenone (0.056 g, 0.589 mmol) was added neat to a solution of the anion prepared from 1-(phenylthio)valeronitrile (0.120 g, 0.589 mmol) and lithium diisopropylamide (0.704 mmol) in 3 mL of THF prepared as described above at −78 °C. The mixture was allowed to warm to 0 °C and, after 1 h at that temperature, quenched and worked up as described above to yield 0.141 g (80%) of a colorless oil after chromatographic purification. Bulb-to-bulb distillation (0.05 torr, oven temperature 70–100 °C) afforded an analytical sample: R_f (5:1 petroleum ether/EtOAc) −0.25; ^1H NMR ($CDCl_3$) δ 0.63–2.88 (m, 18 H), 7.26–7.81 (m, 5 H); IR (neat) 2975, 2250, 1725, 750, 687 cm^{-1}; mass spectrum, *m/e* (relative intensity) 303 (13, M^+), 302 (34), 301 (34), 275 (25), 205 (33), 109 (53), 97 (96), 69 (88), 55 (88).

Anal. Calcd for $C_{18}H_{23}NOS$: C, 71.24; H, 7.57; N, 4.59. Found: C, 71.73; H, 7.69; N, 4.64.

Acknowledgment. We thank the Research Corporation and the Faculty Research Committee of the University of California for support of our work.

Registry No. 5a, 33695-43-1; **5b**, 36638-50-3; **5c**, 80485-14-9; **5d**, 80485-15-0; **6a** (isomer 1), 80501-97-9; **6a** (isomer 2), 80501-98-0; **6b** (isomer 1), 80485-16-1; **6b** (isomer 2), 80485-17-2; **6c**, 80485-18-3; **6d** (isomer 1), 80501-99-1; **6d** (isomer 2), 80485-19-4; **6e** (isomer 1), 80485-20-7; **6e** (isomer 2), 80485-21-8; **6f**, 80485-22-9; **6g**, 80485-23-0; **6h** (isomer 1), 80502-00-7; **6h** (isomer 2), 80485-24-1; **6i** (isomer 1), 80485-25-2; **6i** (isomer 2), 80485-26-3; **6k** (isomer 1), 80485-27-4; **6k** (isomer 2), 80485-28-5; **6l** (isomer 1), 80485-29-6; **6l** (isomer 2), 80485-30-9; **7a**, 80485-31-0; **7b**, 80485-32-1; **7c**, 80485-33-2; **7d**, 80485-34-3; **7e**, 80485-35-4; **7f**, 80485-36-5; **8**, 80485-37-6; **9**, 80485-38-7; 2-methylpropanal, 78-84-2; benzaldehyde, 100-52-7; cyclohexanone, 108-94-1; cyclopentanone, 120-92-3; 2-cyclohexen-1-one, 930-68-7; 3-methyl-2-cyclohexen-1-one, 1193-18-6; 3-buten-2-one, 78-94-4; 2-methylpropenal, 78-85-3; 3-penten-2-one, 625-33-2; 4-methyl-3-penten-2-one, 141-79-7.

Supplementary Material Available: Spectral and chromatographic characterization data for compounds **6a–l**, **7a–f**, **8**, and **9** (5 pages). Ordering information is given on any current masthead page.

Synthesis of *tert*-Butylarenes from Acetylarenes

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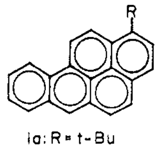
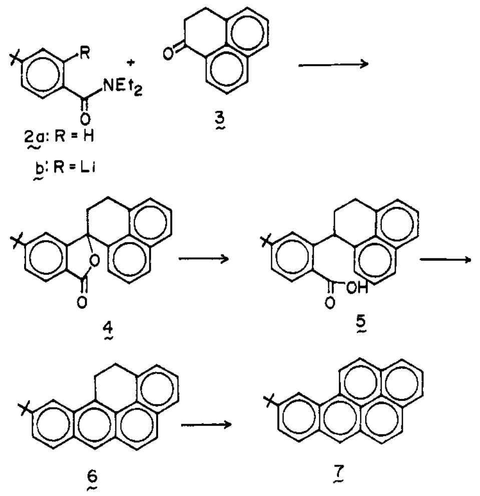
Received August 28, 1981

In connection with studies to determine the role of steric factors on the biological activities of benzo[*a*]pyrene and its oxidized metabolites,[1] we required 1-*tert*-butylbenzo[*a*]pyrene (**1a**). While electrophilic substitution of benzo[*a*]pyrene is known to occur predominantly in the 6-position, Friedel–Crafts acylation affords mainly the thermodynamically favored 1-acetylbenzo[*a*]pyrene (**1b**) isomer.[2] Therefore, we undertook initially the determination of whether synthesis of **1a** might be accomplished through direct *tert*-butylation of benzo[*a*]pyrene under acidic conditions.



1a: R = t-Bu
b: R = CH_3CO

Scheme I



Treatment of benzo[*a*]pyrene with *tert*-butyl alcohol in refluxing trifluoroacetic acid[3] afforded smoothly a single isomeric *tert*-butylbenzo[*a*]pyrene which melted sharply at 193–194 °C. It was accompanied by a minor amount of a di-*tert*-butylated benzo[*a*]pyrene derivative. Analysis of the high-resolution 500-MHz NMR spectrum of the monosubstituted product in comparison with benzo[*a*]pyrene, the proton chemical shifts of which were previously assigned,[4] failed to support the presumptive assignment as the 1-*tert*-butylbenzo[*a*]pyrene isomer. Particularly revealing was the exceptional low-field shift of one of the sterically crowded bay-region protons (i.e., H_{10} or H_{11}) which appeared as a singlet at δ 9.00. This strongly suggested that the *tert*-butyl group was located in the adjacent C-9 or C-12 positions. In other spectral regions the most significant differences were the absence of the H_9 triplet at δ 7.82 and the appearance of H_{10} as a singlet rather than a doublet. These features in addition to the small upfield shift ($\Delta\delta = -0.11$ ppm) of the H_8 proton strongly support tentative assignment of the unknown as 9-*tert*-butylbenzo[*a*]pyrene (**7**).

This assignment was confirmed by an unequivocal synthesis (Scheme I) based on that recently reported for the synthesis of 3-methylcholanthrene.[5] Metalation of *N*,*N*-diethyl-4-*tert*-butylbenzamide (**2a**) with *sec*-butyllithium and *N*,*N*,*N′*,*N′*-tetramethylethylenediamine in tetrahydrofuran afforded *N*,*N*-diethyl-2-lithio-4-*tert*-butylbenzamide (**2b**).[6] Reaction of **2b** with perinaphthanone[7] (**3**) followed by treatment of the product with *p*-toluenesulfonic acid in refluxing benzene gave the lactone **4**. The latter was reduced with zinc and alkali to the carboxylic

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[1] Harvey, R. G. *Acc. Chem. Res.* **1981**, *14*, 218.

[2] Windaus, A.; Raichle, K. *Justus Leibigs Ann. Chem.* **1939**, *537*, 160. Clar, E. "Polycyclic Hydrocarbons"; Academic Press: New York, 1964: Vol. 2, p 130.

[3] Fu, P. P.; Harvey, R. G. *J. Org. Chem.* **1977**, *42*, 2407. Svanholm, V.; Parker, V. *J. Chem. Soc., Perkin Trans. 1* **1973**, 562.

[4] Bartle, K. D.; Jones, D. W.; Matthews, R. S. *Spectrochim. Acta, Part A* **1969**, *25A*, 1603. Haigh, C. W.; Mallion, R. B. *J. Mol. Spectrosc.* **1969**, *29*, 478.

[5] Jacobs, S. A.; Harvey, R. G. *Tetrahedron Lett.* **1981**, *22*, 1093. Jacobs, S. A.; Cortez, C.; Harvey, R. G. *J. Chem. Soc., Chem. Commun.* **1981**, 1215. Harvey, R. G.; Cortez, C.; Jacobs, S. A. *J. Org. Chem.*, in press.

[6] Beak, P.; Brown, R. A. *J. Org. Chem.* **1977**, *42*, 1823; **1979**, *44*, 4463.

[7] Fieser, L. F.; Gates, M. D. *J. Am. Chem. Soc.* **1940**, *62*, 2336.

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