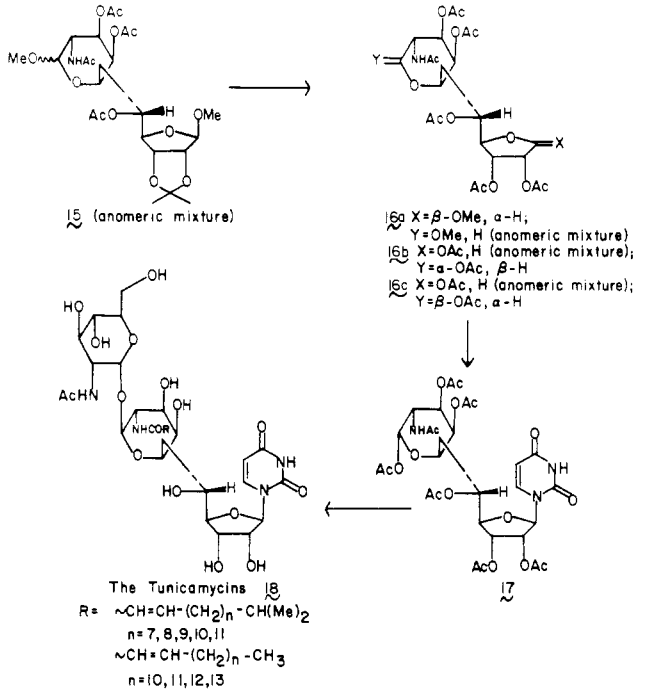
to the methyl galactoside **14** (39% overall from **11**).

A five step sequence ((i) $Ph_3P$, THF; (ii) $Ac_2O$, Py; (iii) $H_2$, $Pd(OH)_2/C$, MeOH; (iv) $K_2CO_3$, MeOH; (v) $Ac_2O$, $Et_3N$, DMAP) achieved the transformation of **14** to **15** in 77% yield. Cleavage of the acetonide was accomplished through the action of methanolic HCl. The resultant diol was acetylated to afford (76%) the tunicamine derivative **16a** as an anomeric mixture of galactosides. Acetolysis of the anomeric methoxyl functions (AcOH, $Ac_2O$, $H_2SO_4$, $CH_2Cl_2$) afforded (50%) a product that was ca. a 1:1 mixture of anomeric acetates in the hexose ring. Each of these components was also an anomeric mixture of ribosyl acetates with a strong preference for the desired $\beta$-ribosyl acetate. The galactosyl anomers were separated by preparative HPLC into components **16b,c**. Treatment of **16b**[21] with 2,4-bis[(trimethylsilyl)oxy]pyrimidine under the conditions of Vorbruggen ($Me_3SiOTf$, MeCN, room temperature)[22] afforded a 50% isolated yield of (heptaacetyltunicaminyl)uracil **17**. *The chromatographic*




*properties and infrared and high-field PMR spectra of the synthetic* ***17*** *were identical with those of the compound prepared from tunicamycin.*[23,24] We emphasize that in this fully synthetic route[8] to tunicaminyluracil, all nonanomeric stereochemistry is tightly controlled by taking advantage of biases within the reacting substrate molecules.

**Acknowledgment.** This research was supported by PHS Grant CA 28824. NMR spectra were obtained through the auspices of the Northeast Regional NSF/NMR Facility at Yale University, which was supported by NSF Chemistry Division Grant CHE 7916210. An NIH Postdoctoral Fellowship (Grant 1 F32 CA07586) to M.B. is gratefully acknowledged. In addition, we wish to acknowledge the contributions of Dr. Kuo-Hua Chao for development of the catalyst system and Ms. J. Y. Lee for providing a route to racemic **3**, thereby establishing the fully synthetic route. We also acknowledge the receipt of an authentic sample of a tunicamycin from the Eli Lilly Co. from which a reference sample of **17** was prepared.

**Supplementary Material Available:** High-field NMR spectra of synthetically and naturally derived compound **17** (2 pages). Ordering information is given on any current masthead page.

(21) The analogous Hilbert-Johnson reaction of **16c** afforded an adduct assigned as a pyranose nucleoside (incorporation of uracil in the galactosyl hexose).

(22) Vorbruggen, H.; Krolikiewicz, K.; Bennua, B. *Chem. Ber.* **1981**, *114*, 1234.

(23) An authentic sample of (heptaacetyltunicaminyl)uracil was prepared from tunicamycin by the following sequence: (i) hydrolysis (3 N HCl, reflux, 3 h), (ii) ether wash, (iii) concentration in vacuo, (iv) acetylation ($Ac_2O$, Py), (v) preparative HPLC.

(24) Optical rotations for representative structures are as follows: **4**, $[\alpha]^{25}_D$ -83.7° (*c* 1.91, $CHCl_3$); **5**, $[\alpha]^{25}_D$ -49.5° (*c* 1.10, $CHCl_3$); **6**, $[\alpha]^{25}_D$ -38.8° (*c* 1.33, $CHCl_3$); **7**, $[\alpha]^{25}_D$ -37.5° (*c* 1.27, $CHCl_3$); **9**, $[\alpha]^{25}_D$ -39.5° (*c* 1.07, $CHCl_3$); **11**, $[\alpha]^{25}_D$ -70.1° (*c* 1.01, $CHCl_3$) fully synthetic compound **17**, $[\alpha]^{25}_D$ +61.8 (*c* 0.21, $CHCl_3$); naturally derived compound **17**, $[\alpha]^{25}_D$ +60.8 (*c* 0.49, $CHCl_3$).

## A Fully Synthetic Route to Hikosamine

Samuel Danishefsky* and Clarence Maring

*Department of Chemistry, Yale University*
*New Haven, Connecticut 06511*

*Received July 12, 1985*

Hikizimycin (**1**, cf. anthelmycin) was isolated from a strain of *Streptomyces longissimus* and from the broth of Streptomyces A5.[1a,b] It has broad but weak antibacterial properties. More important are the anthelmintic properties which hikizimycin confers against a variety of common parasites.[2] A provocative feature of hikizimycin is the presence of an undecose with heterofunctions at every carbon atom. This component, called hikosamine, has been obtained in protected form by mild degradation of hikizimycin.[3]

Long chain (> six carbons) monosaccharide moieties are found in a variety of natural products of diverse function.[4] Accordingly, we have sought to develop new chemistry for the synthesis of such complex systems. An important contribution in the hikizimycin area had been provided by Secrist and Barnes.[5a,b] These workers coupled a hexodialdose related to 4-deoxy-4-azidoglucose with a phosphorane derived from L-arabinose. The ability to achieve an olefination reaction via a $\beta$-heterosubstituted phosphorane was a major feature of the Secrist-Barnes synthesis of methyl peracetyl-$\alpha$-hikosaminide (**18**). Below we relate a totally synthetic route to compound **18**.

A key feature of the synthesis is the use of the recently developed diene-aldehyde cyclocondensation reaction[6a,b] to fashion "carbohydrate matrices" in either the *galacto* or *manno* series (cf. formation of **3a** and **10**). The interior stereochemistry in these matrices is developed by drawing upon the conformational biases of the rings (cf. **3a** → **4d** and **10** → **12**).[6] Chirality is communicated from the *galacto* ring to its side chain through a recently demonstrated adaptation of the Sakurai reaction (cf. **4d** → **5**) and further communicated via the side chain to define the sense (D rather than L) of the emerging *manno* precursor **10**. Provision is made for specific disconnection of the manno ring (cf. **12** → **13**) and for introduction of the 4-amino function in the surviving pyranose (cf. **14** → **17**).

Hexodialdose **4d**, derivable[7,8] from galactose, was synthesized starting with the Eu(fod)$_3$-mediated[6b] cyclocondensation of furfural

(1) (a) Hamill, R. L.; Hoehn, M. H. *J. Antibiot. Ser. A* **1964**, *17*, 100. (b) Vuilhorgne, M.; Ennifar, S.; Das, B. C.; Paschal, J. W.; Nagarajan, R.; Hagaman, E. W.; Wenkert, E. *J. Org. Chem.* **1977**, *42*, 3289.

(2) Uchida, K.; Wolf H. *J. Antibiot.* **1974**, *27*, 783. Gonzalez, A.; Vazquez, G. D.; Jimenez, A. *Biochem. Biophys. Acta* **1979**, *561*, 403.

(3) Uchida, K. *Agric. Biol. Chem.* **1976**, *40*, 395.

(4) For examples of such long chain monosaccharides, see: Danishefsky, S. J.; Maring, C. J.; Barbachyn, M. R.; Segmuller, B. E. *J. Org. Chem.* **1984**, *49*, 4564, ref 2-6.

(5) (a) Secrist, J. A., III; Barnes, K. D. *J. Org. Chem.* **1980**, *45*, 4526. (b) Barnes, K. D. Ph.D. Thesis, The Ohio State University, 1980.

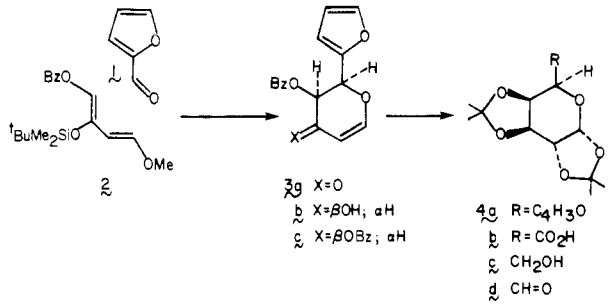
(6) (a) Danishefsky, S. J.; Maring, C. J. *J. Am. Chem. Soc.* **1985**, *107*, 1269. (b) Bednarski, M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1983**, *105*, 3716.

(7) Horton, D.; Nakadate, M.; Tronchet, J. M. J. *Carbohydr. Res.* **1968**, *7*, 56.

(8) In practice, the D isomer **4c** obtained from D-galactose[7] was used in further steps. The synthesis of racemic **4c** demonstrates in principle the feasibility of synthesizing racemic hikosamine since all subsequent steps involve internal asymmetric induction.

0002-7863/85/1507-7762$01.50/0 

with diene **2**. Subsequent treatment with trifluoroacetic acid afforded **3a** in 55–60% yield. Reduction with $NaBH_4$–$CeCl_3$[9] afforded **3b** (90%), which on benzoylation (BzCl–Py) gave **3c**. Hydroxylation of **3c**[10] followed by the sequence of (i) acetalization ($Me_2CO$, $H_2SO_4$ catalyst), (ii) debenzoylation ($K_2CO_3$/MeOH), and (iii) acetalization ($Me_2CO$, $H_2SO_4$ catalyst) provided (53% overall) the furyl bis acetonide **4a**. Oxidative cleavage of the furan ($O_3/CH_2Cl_2$, MeOH, −78 °C), followed by reduction ($BH_3$·THF) of the resultant **4b**, provided racemic **4c** (50%).[11] The D isomer was converted to the D-hexodialdose **4d**[8] thus completing the preparation of the *galacto* "matrix" sugar.

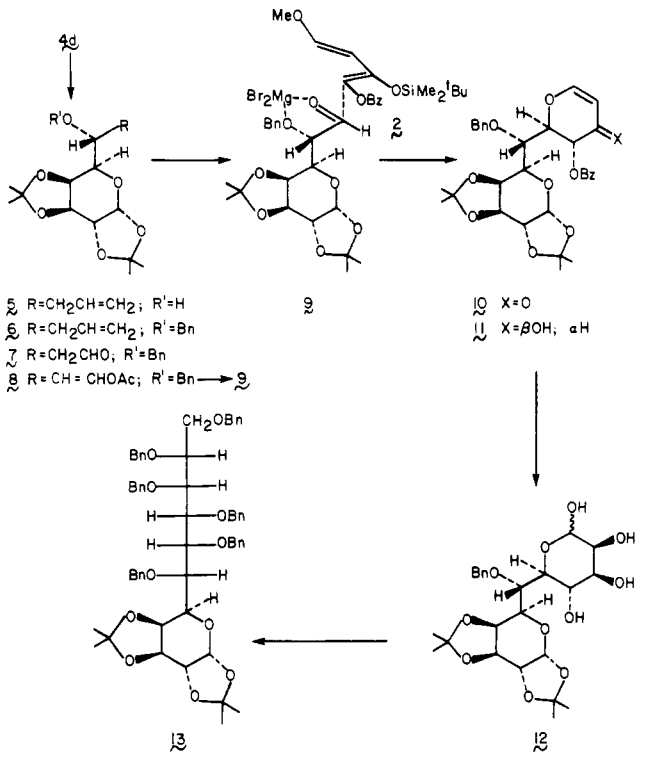


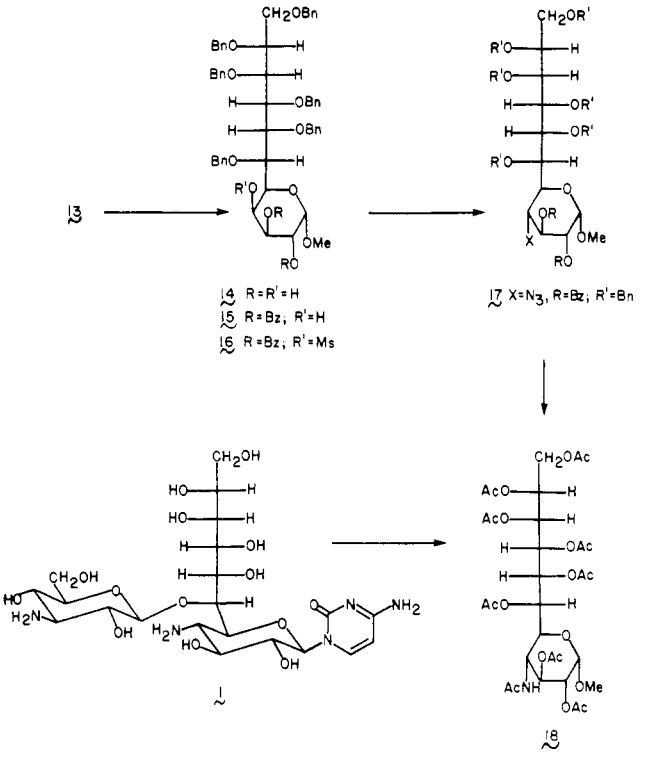

Boron trifluoride etherate mediated allylation of **4d**, as previously described,[12] afforded carbinol **5** and thence (BnBr, NaH/DMF) the benzyl ether **6** (mp 60.5–62.0 °C, 95%). Ozonolytic cleavage ((i) $O_3/CH_2Cl_2$, −78 °C; (ii) Zn, AcOH) of **6** led to the crude aldehyde **7**, which was converted ($Ac_2O$, $Et_3N$,DMAP/$CH_2Cl_2$) to enol acetate **8** and thence by ozonolytic cleavage, as above, to the heptodialdose **9** (85% from **6**).

Magnesium bromide ($CH_2Cl_2$, $PhCH_3$, 0 °C) mediated cyclocondensation[13a] of **9** with diene **2**[6a] afforded a 75% yield of the undecose **10**[13b] (m.p. 184–185 °C) as the only observed product. *This result provides an excellent illustration of the capacity of magnesium bromide to impose chelation control and exo topicity upon the course of the hetero Diels–Alder Reaction.*[13a]

Reduction of **10** ($NaBH_4$; $CeCl_3$) gave, as above (cf. **3a** → **3b**), the equatorial alcohol **11** (95%). Henbest-type epoxidation of the allylic alcohol[14] followed by debenzoylation with $K_2CO_3$ in methanol provided **12**. Reduction of the hemiacetal system ($LiBH_4$/THF, reflux) followed by perbenzylation of the resultant pentaol (BnBr, NaH/DMF) afforded the hexabenzyl derivative **13** (70% from **11**) thus completing the second phase of the synthesis.

The program directed toward the introduction of the 4-α-amino function commenced with the action of methanolic HCl on **13**. The conformational biases in the galactosyl residue of axial anomer **14** lent themselves to synthetic exploitation. Selective benzoylation of the $C_2$ and $C_3$ equatorial hydroxyl groups[16] (BzCl–Py) served to distinguish the $C_4$-axial alcohol. Mesylation (MsCl–Py) of the resultant **15**[15] provided **16** (93%). Reaction of **16** with $(n\text{-}Bu)_4NN_3$ ($PhCH_3$, 85 °C) afforded **17** (75%). The latter, upon debenzoylation ($K_2CO_3$/MeOH), diacetylation, reduction of the azide




(Ph$_3$P), acetylation of the amino group, debenzylation ($H_2$, Pd-$(OH)_2$/C), and peracetylation afforded compound **18**. The PMR spectrum at 250 MHz of the material thus obtained was identical with that of a reference sample of **18** provided by Dr. Secrist. A fully synthetic route to hikosamine based on internal asymmetric induction for the control of the 10 contiguous hetero-bearing chiral centers[15] has thus been accomplished.[17]

**Acknowledgment.** This work was supported by PHS Grant AI 16943. A Heyl Fellowship to C.M. is gratefully acknowledged.

(9) Luche, J.-L.; Gemal, A. L. *J. Am. Chem. Soc.* **1979**, *101*, 5848. At this stage the 8:1 mixture of **3b** and the respective reduction product of the trans cyclocondensation product were separable by flash chromatography.

(10) VanRheenan, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973.

(11) For use of a 2-furyl group as a latent carboxylic acid, see: Schmid, G.; Fukuyama, T.; Akaska, K.; Kishi, Y. *J. Am. Chem. Soc.* **1979**, *101*, 259.

(12) Danishefsky, S.; DeNinno, M. *Tetrahedron Lett.* **1985**, *26*, 823.

(13) (a) Danishefsky, S. J.; Pearson, W. H.; Harvey, D. F.; Maring, C. J.; Springer, J. P. *J. Am. Chem. Soc.* **1985**, *107*, 1256. (b) An X-ray crystallographic determination of compound **10** obtained via a nonstereoselective route confirms all of the configurational assignments provided here.

(14) Henbest, H. B.; Wilson, R. A. L. *J. Chem. Soc.* **1957**, 1958.

(15) At this stage a 1.5:1 mixture of **15** to its equatorial anomer was separable by flash chromatography. To attain high stereoselectivity at the anomeric center, the equatorial anomer could presumably be recycled to the axial series. This has not been done. The equatorial isomer itself has not been carried forward because of a lack of reference sample.

(16) Reist, E. J.; Spencer, R. R.; Calkins, D. F.; Baker, B. R., Goodman, L. *J. Org. Chem.* **1965**, *30*, 2312.

(17) For a route to carbohydrates via reagent based control, see: Ko, S. Y.; Lee, A. W. M.; Masamune, S.; Reed, L. A., III; Sharpless, K. B.; Walker, F. J. *Science (Washington D.C.)* **1983**, *220*, 949.

NMR spectra were obtained through the auspices of the Northeast Regional NSF/NMR Facility at Yale University, which was supported by NSF/Chemistry Division Grant CHE 7916210. We thank Dr. John Secrist for providing us with the authentic sample.

## Oxidation and Reduction Potentials of Transient Free Radicals[1]

Danial D. M. Wayner and David Griller*

*Division of Chemistry*
*National Research Council of Canada*
*Ottawa, Ontario, Canada K1A 0R6*
*Received July 8, 1985*

The oxidation and reduction potentials of free radicals are fundamental quantities of particular importance. For example, reduction potentials of alkyl radicals can be combined with other thermodynamic data to give $pK_a$ values for hydrocarbons.[2-5]

Despite their significance, only a few of these potentials have been measured. This is because most free radicals have short lifetimes and are therefore not suitable as starting materials for standard electrochemical methods.[6] As a result, they must be formed as the products of electrochemical reactions. Hence, carbonium and carbanions serve as the reagents with all the attendant experimental difficulties.

In response to these problems, we have devised a method for measuring oxidation and reduction potentials, in which the transient radicals are actually used as the starting materials for the electrochemical reaction. The apparatus (Figure 1) was built around a standard three-electrode cell, which was fitted with quartz windows and a gold mesh working electrode. Modulated photolysis was used for radical generation with phase-sensitive electrochemical detection as a device for enhancing instrumental sensitivity.[7,8]

Radicals were generated by modulated photolysis of acetonitrile solutions containing appropriate precursors (vide infra) and tetrabutylammonium perchlorate (0.1 M) as the supporting electrolyte. Samples were flowed slowly through the cell so as to avoid problems associated with sample depletion and/or product formation. The photolysis source was a 1000-W mercury-xenon lamp which was only capable of generating average radical concentrations of $10^{-7}$-$10^{-8}$ M, i.e., well below the normal level of detection for conventional electrochemical apparatus. The voltage at the working electrode was scanned slowly (20 mV/s) until the reduction or oxidation potentials of the radicals were reached, at which points small currents oscillating at the modulation frequency were obtained due to the formation of the carbanions or carbonium ions. The phase-sensitive detector gave the amplitude of the oscillating signals, which was output onto an $x$-$y$ recorder. The resulting trace was a polarogram of the free radical, Figure 2.

Two chemical systems were used for radical generation: first, the photodecomposition of ketones, eq 1 and, second, photolysis

$$\mathrm{RC(O)R} \xrightarrow{h\nu} 2\mathrm{R}\cdot + \mathrm{CO} \quad (1)$$

$$t\text{-BuO} - \mathrm{OBu}\text{-}t \xrightarrow{h\nu} 2\ t\text{-BuO}\cdot \quad (2)$$

$$t\text{-BuO}\cdot + \mathrm{RH} \rightarrow t\text{-BuOH} + \mathrm{R}\cdot \quad (3)$$

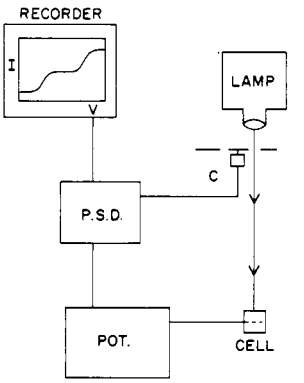



**Figure 1.** Diagram of apparatus. C, light chopper; POT, potentiostat; PSD, phase sensitive detector.

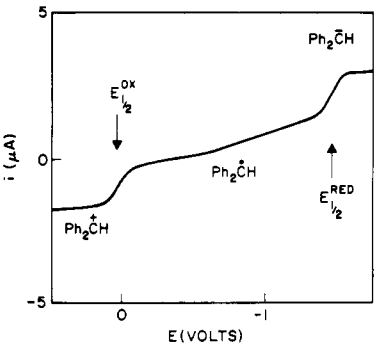



**Figure 2.** Polarogram of $(C_6H_5)_2\dot{C}H$ showing oxidation ($E_{1/2}^{ox}$) and reduction ($E_{1/2}^{red}$) potentials. Radical generation by modulated photolysis (43 Hz) of $t$-BuO-OBu-$t$ (0.5 M) in acetonitrile containing diphenylmethane (1.0 M).

**Table I.** Oxidation and Reduction Potentials of Transient Free Radicals[a]

| radical | $E_{1/2}^{ox}$, V | $E_{1/2}^{red}$, V | method[b] |
|---|---|---|---|
| $Ph\dot{C}H_2$ | 0.40 ± 0.03 | −1.78 ± 0.02 (−1.76)[c] | 1, 2, 3 |
| $Ph_2\dot{C}H$ | 0.02 ± 0.02 (0.01)[d] | −1.47 ± 0.02 (−1.49)[c] | 1, 2, 3 |
| $Ph\dot{C}(CH_3)_2$ | −0.20 ± 0.02 | −2.10[e] | 2 |

[a] In acetonitrile containing 0.1 M tetrabutylammonium perchlorate. All potentials measured with respect to $Ag/AgNO_3$ (0.1 M in acetonitrile) which has a potential of 0.334 V vs. the standard calomel electrode. [b] Method 1: see eq 1. Method 2: see eq 2, 3. Method 3: photolysis of $(C_6H_5)_2CHC(O)CH_2(C_6H_5)$. [c] Reference 2. [d] Reference 13. [e] Tentative value; limiting current of reduction wave poorly defined.

of di-*tert*-butyl peroxide (0.5 M) in the presence of hydrogen donors, eq 2, 3. Both sources led to the same oxidation and reduction potentials. The results for several radicals are reported in Table I. Clearly, radical generation by more than one well-authenticated route builds confidence in the reliability of the values reported, as does the excellent agreement with literature data in instances where they were available.

Several simple tests lend support to the measured values. No polarograms were detected by the phase-sensitive method, in the absence of photolysis or of the radical precursors. Moreover, simple dc detection of electrochemical signals due to the samples as a whole showed that little electrochemistry took place in the voltage range of interest (1.0 to −2.0 V vs. $Ag/AgNO_3$).

Analysis of the polarograms showed that the systems were, in most instances, quasi-reversible or reversible. That is, the rates of the electrochemical reactions were essentially mass transport limited. The difference between the oxidation and reduction potentials therefore represents the difference in the heats of formation, in solution, of the carbonium and carbanions derived from a given radical. For the benzyl radical in the gas phase[9-11]

(1) Issued as NRCC Publication No. 25119.
(2) Jaun, B.; Schwarz, J.; Breslow, R. *J. Am. Chem. Soc.* **1980**, *102*, 5741-5748 and references cited therein.
(3) Wasielewski, M. R.; Breslow, R. *J. Am. Chem. Soc.* **1976**, *98*, 4222-4229.
(4) Breslow, R.; Chu, W. *J. Am. Chem. Soc.* **1970**, *92*, 2165.
(5) Breslow, R.; Balusubramanian, K. *J. Am. Chem. Soc.* **1969**, *91*, 5182-5183.
(6) Pulse radiolysis and flash photolysis techniques have seen limited application in this context; see: Henglein, A. In "Electroanalytical Chemistry"; Bard, A. J., Ed.; Marcel Dekker: New York, 1976; Vol. 9, pp 163-244.
(7) For a related technique using optical detection, see: Griller, D. *Rev. Chem. Intermed.* **1984**, *5*, 21-36 and references cited therein.
(8) Direct photolysis has been used to generate long-lived ions for electrochemical investigation; see: Boyd, D. C.; Bohling, D. A.; Mann, K. R. *J. Am. Chem. Soc.* **1985**, *107*, 1641-1644 and references cited therein.
(9) Houle, F. A.; Beauchamp, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 3290-3294.

0002-7863/85/1507-7764$01.50/0 Published 1985 by the American Chemical Society