Synthesis of Diphenyl Ether Models of Thyroid Hormones. Diphenyl Ethers Linked to the 3-Oxo-2-azabicyclo[2.2.1]heptane Ring System as Substrates for Conformational Analysis

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A series of diphenyl ethers linked to 2-azabicyclo[2.2.2]octan-3-ones and 2-azabicyclo[2.2.1]heptan-3-ones were synthesized as substrates for conformational analysis using the lanthanide shift reagent NMR technique. The materials were prepared by displacement of the *exo*-6-tosyloxy bicyclic lactam with the corresponding phenoxide which results in formation of the phenyl ether with retention of stereochemistry. This double-inversion process presumably involves anchimeric assistance by the lactam nitrogen. The synthesis and properties of a number of these systems are described. Complete ^{13}C assignments for the series are presented.

The conformation of thyroid hormones (Figure 1) and conformation–activity relationships have been a subject of continued interest.[1] Although many investigations have been carried out on the solid-state conformations of these materials,[2] there is relatively little information available on the solution conformations.[3,4]

We have been involved in a program in which we are applying lanthanide shift reagent (LSR) techniques to the solution of this problem and, concurrently, developing reliable techniques for the application of LSR's to conformational problems.

Our approach centers on a series of model compounds which have a conformationally mobile substituent, on which the conformational analysis is to be carried out, attached to a rigid bicyclic structure. Complexation of the LSR to a functional group in the bicyclic system occurs and NMR LSR data on the system are collected.

Atomic coordinates obtained from X-ray crystallographic studies on the bicyclic substrate are used in conjunction with the McConnell–Robertson pseudocontact shift equation[5] to determine the "best position" for the lanthanide atom in the LSR–substrate complex. In effect, this procedure results in the determination of the resultant magnetic vector in the LSR–substrate complex.

Once this vector is known, lanthanide induced shift data can be used in conjunction with the McConnell–Robertson equation to determine the conformation of the mobile substituent. This procedure and the numerous precautions taken to ensure that the results obtained are reliable, will be described in detail elsewhere.[6] In this paper we describe the synthesis and properties of a series of bicyclic

lactams 1–3 with appended diphenyl ether substituents, which are the substrates in the aforementioned LSR studies.
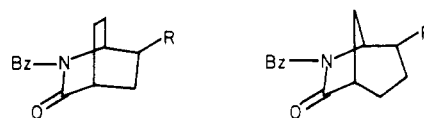
1a, R = OH
 b, R = OTs
 c, R = OCOCH₃
 d, R = OC₆H₅
 e, R = OCH₂C₆H₅
 f, R = OCH₂C₆H₄OC₆H₄CH₃
 g, R = OC₆H₄OC₆H₄CH₃

2
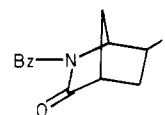
3a, R = OH
 b, R = OTs
 c, R = OC₆H₅
 d, R = OC₆H₃ICH₃
 e, R = OC₆H₂I₂CH₃
 f, R = OC₆H₃(CH(CH₃)₂)CH₃
 g, R = OC₆H₄OC₆H₄CH₃
 h, R = OC₆H₄OC₆H₂I₂CH₃
 i, R = OC₆H₃IOC₆H₂I₂CH₃
 j, R = OC₆H₃(CH₃)OC₆H₂I₂CH₃
 k, R = OC₆H₃(CH(CH₃)₂)OC₆H₂I₂CH₃
 l, R = OC₆H₃(CH₂CH(CH₃)₂)OC₆H₂I₂CH₃
 m, R = OC₆H₃(C(CH₃)₃)OC₆H₂I₂CH₃
 n, R = OC₆H₃(C₆H₅)OC₆H₂I₂CH₃
 o, R = OC₆H₃ClOC₆H₂I₂CH₃
 p, R = OC₆H₄CH₂C₆H₂I₂CH₃
 q, R = OC₆H₃ICH₂C₆H₂I₂CH₃

Since it was clear at the outset of our LSR conformational analysis program that much effort would have to be expended on the nature of the various factors affecting the complexation of the substrate with the LSR,[7] we decided that it would be appropriate to develop a system in which the complexing moiety was common to a series of molecules with different conformationally mobile portions. The bicyclic lactams 1 and 3 were good candidates since our experience indicated that the lactam was a powerful complexing moiety and that the bicyclic structures chosen were rigid, ensuring that the atomic coordinates would be invarient with different R groups. In addition, there appeared to be a reasonable route to the desired molecules

(1) (a) Jorgenson, E. C.; Lehman, P. A.; Greenberg, C.; Zenker, N. *J. Biol. Chem.* **1962**, *237*, 3832. (b) Schussler, G. C. *Science* **1972**, *178*, 172. (c) Jorgensen, E. C.; Reid, J. A. W. *Endocrinology (Baltimore)* **1965**, *76*, 312. (d) Jorgensen, E. C.; Zenker, N.; Greenberg, C. *J. Biol. Chem.* **1960**, *235*, 1732.

(2) The results are ambiguous in that half of the X-ray crystallographic determinations on triiodothyronine derivatives and its analogues show the material to be in the distal conformation, with the other half showing it to be in the proximal conformation. (a) Cody, V. *J. Am. Chem. Soc.* **1974**, *96*, 6720. (b) Cody, V. *J. Med. Chem.* **1975**, *18*, 126. (c) Cody, V.; Duax, W. L. *Biochem. Biophys. Res. Commun.* **1973**, *52*, 430. (d) Cody, V. *Science* **1978**, *201*, 1131. (e) Camerman, N.; Camerman, A. *Ibid.* **1972**, *175*, 764. (f) Camerman, N.; Camerman, A. *Can. J. Chem.* **1974**, *52*, 3048. (g) Fawcett, J. K.; Camerman, N.; Camerman, A. *J. Am. Chem. Soc.* **1976**, *98*, 587. (h) Cody, V.; Hazel, J.; Osawa, Y. *Acta Crystallogr., Sect. B* **1978**, *B34*, 3407.

(3) Emmett, J. C.; Pepper, E. S. *Nature (London)* **1975**, *257*, 334.

(4) Mazzocchi, P. H.; Ammon, H. L.; Colicelli, E.; Hohokabe, Y.; Cody, V. *Experientia* **1976**, *32*, 419.

(5) McConnell, H. M.; Robertson, R. E. *J. Chem. Phys.* **1958**, *29*, 1361.

(6) For our first results on conformational analysis of 3e see: Ammon, H. L.; Mazzocchi, P. H.; Liu, L. *Chem. Lett.* **1980**, 897. See also: Ammon, H. L.; Mazzocchi, P. H.; Colicelli, E.; Jameson, C. W.; Liu, L. *Tetrahedron Lett.* **1976**, 1745.

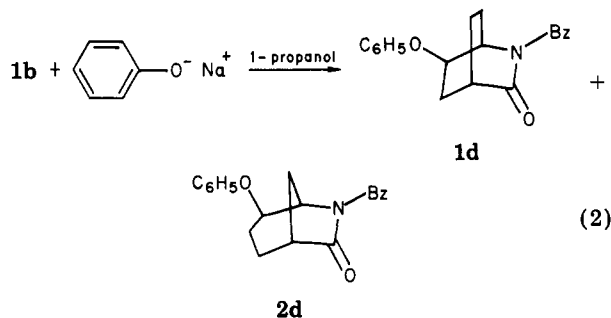(7) Raber, D. J.; Johnston, M. D., Jr.; Campbell, C. M.; Janks, C. M.; Sutton, P. *Org. Magn. Reson.* **1978**, *11*, 323.
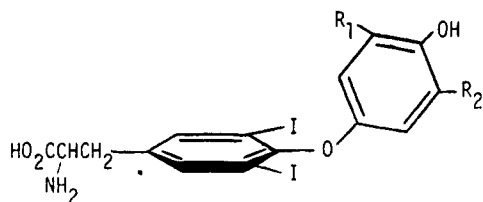
Figure 1. Distal (R_1 = H, R_2 = I) and proximal (R_1 = I, R_2 = H) conformers of triiodothyronine.

via displacement of the corresponding tosylates (**1b**, **3b**) with phenoxides.

The parent 2-benzyl-3-oxo-6-*exo*-(tosyloxy)-2-azabicyclo[2.2.2]octane was prepared according to the method of Huffman, Kamiya, and Rao[8] from the parent alcohol (eq 1). Preparation of the corresponding aryl ethers was
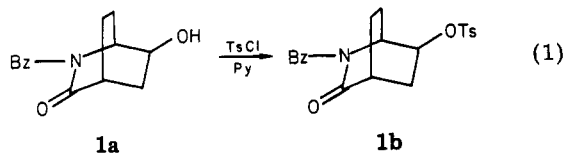
accomplished by refluxing **1b** with the sodium salt of the appropriate phenol in 1-propanol. Thus, on treatment of **1b** with sodium phenoxide (eq 2), a single product crystallized from ether which was subsequently characterized as **1d**, but a second product was subsequently isolated from the mother liquor by column chromatography. This second product was characterized as the [3.2.1] lactam **2d**. The carbonyl stretching frequencies for **1d** and **2d** at 1658 and 1690 cm^{-1} are consistent with the bicyclic [2.2.2] and bicyclo[3.2.1] lactam structures, respectively.[8] The overall yield of these two products was 45%, and the **2d**/**1d** ratio was 1.25. The exo stereochemistry of the phenoxy group in **1d** was unequivocally established by an X-ray crystallographic study,[9,10] whereas the stereochemistry of **2d** is implied from the following.
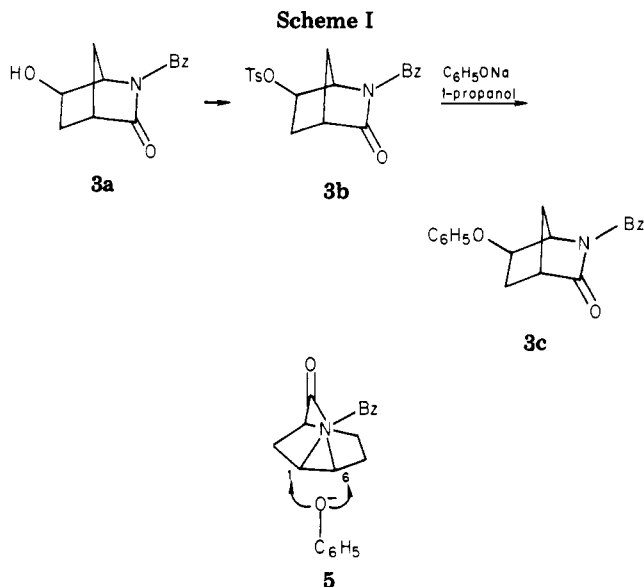
Our initial expectation was that the displacement reaction on **1a** would occur with net inversion of stereochemistry at C-6. The observed retention of stereochemistry implies that a double inversion has taken place through the aziridinium intermediate **4** (eq 3). Anchimeric
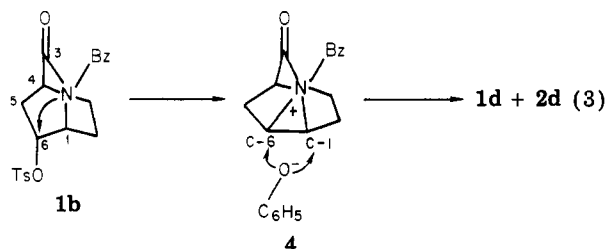
Scheme I

assistance by nitrogen has precedence in the solvolysis of this lactam system[8] and nicely explains the formation of **2d** through phenoxide attack at C-1 in **4**. The fact that this reaction resulted in the formation of two products, with the desired rigid bicyclo[2.2.2] product (**1d**) being the minor one, made this system of limited utility for subsequent NMR LSR studies. Subsequent NMR investigations (vide infra) indicated that spectral coincidences limited the number of proton data available from the LSR studies, again suggesting that this was probably not the best system available.[10] With these limitations in mind, we examined the related 2-benzyl-3-oxo-6-*exo*-hydroxy-2-azabicyclo[2.2.1]heptane system.[11]

This approach has the advantage that the proposed aziridinium ion intermediate **5** is symmetrical, and only a single product **3b** should be formed with the now expected exo stereochemistry (see Scheme I). Indeed, tosylation of **3a** followed by treatment with sodium phenoxide in 1-propanol gave a single product characterized as **3c**. The exo stereochemistry of the phenoxy group of **3c** was conclusively established by a subsequent X-ray crystallographic determination.[9,10] Furthermore, the LSR NMR spectrum of this system is such that all of the bicyclic ring proton resonances are unique and can be used as input data in subsequent NMR LSR calculations.

^{13}C Assignments for Bicyclo[2.2.2] and Bicyclo[2.2.1] Ring Systems. The ^{13}C spectra of all of the derivatives of **1** and **3** (Table I) show a resonance in the region of 174–178.5 ppm for the carbonyl carbon C-3. The C-1 and C-4 resonances in **1** are obvious from their intensities compared to those for the C-6, C-7 and the C-5, C-8 equivalent pairs. Since nitrogen is more electronegative than the carbonyl group C-1 and the C-6, C-7 pair are assigned to the downfield resonances at 37.7 and 27.6 ppm.

Tentative assignments for C-4 and C-3 can be made since these carbons show essentially no change on substitution at C-6. C-1 and C-5 experience β shifts of 10.3 and 10.1 ppm, respectively, on hydroxyl substitution (**1a**) whereas C-7 experiences a 8.1-ppm upfield γ shift.

Further assignments are made on analysis of the ^{13}C shifts on going from the alcohol **1a** to the corresponding acetate (**1c**) based on α, β, and γ shifts determined by Reich[12] in steroidal alcohol–acetate systems. Thus, on

(8) (a) Huffman, J. W.; Rao, C. B. S.; Kamiya, T. *J. Org. Chem.* **1967**, *32*, 697. (b) Huffman, J. W.; Kamiya, T.; Rao, C. B. S. *Ibid.* **1967**, *32*, 700.

(9) Ammon, H. L.; Mazzocchi, P. H.; Liu, L.; Colicelli, E. *Acta Crystallogr.*, in press.

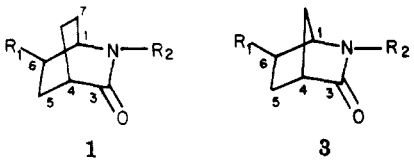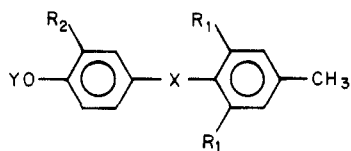(10) Colicelli, E. Ph.D. Thesis, University of Maryland, 1977.

(11) (a) Murdock, K. C.; Angier, R. B. *J. Org. Chem.* **1962**, *27*, 2395. (b) Schmid, G. H.; Walkoff, A. W. *Ibid.* **1967**, *32*, 254. (c) Schultz, R. J.; Staas, W. H.; Spurlock, L. A. *Ibid.* **1973**, *38*, 3091.

Table I.[a,b] [13]C Assignments for Bicyclic Ring Carbons of Selected Examples 1 and 3

1   3

no.	R$_1$	R$_2$	chemical shift, δ						
			C-1	C-3	C-4	C-5	C-6	C-7	C-8
1	H	H	47.2	178.5	37.7	24.1	27.6	27.6	24.1
1a	OH	benzyl	57.5	175.3	38.7	34.2	67.4	19.5	24.3
1b	OTs	benzyl	54.4	173.7	37.8	31.5	75.7	19.8	23.4
1c	OCOCH$_3$	benzyl	54.1	174.3	38.3	31.8	69.7	20.6	23.9
1d	OC$_6$H$_5$	benzyl	53.9	174.5	38.7	32.2	72.5	20.1	24.2
1e	OCH$_2$C$_6$H$_5$	benzyl	54.2	175.1	38.2	31.8	74.5	19.8	24.1
1f	OCH$_2$C$_6$H$_4$OC$_6$H$_4$CH$_3$	benzyl	54.2	174.4	38.5	31.9	74.5	20.1	24.0
1g	OC$_6$H$_4$OC$_6$H$_4$CH$_3$	benzyl	53.5	174.4	38.5	31.9	72.8	19.8	24.0
3a	OH	benzyl	63.5	178.3	44.0	35.8	70.4	36.9	
3c	OC$_6$H$_5$	benzyl	61.1	177.2	44.1	33.9	75.7	37.5	
3d	OC$_6$H$_3$ICH$_3$	benzyl	61.1	177.2	44.1	33.7	77.1	37.6	
3e	OC$_6$H$_3$I$_2$CH$_3$	benzyl	61.7	177.3	44.0	34.1	84.1	37.7	
3f	OC$_6$H$_3$(CH(CH$_3$)$_2$)CH$_3$	benzyl	61.5	177.2	44.2	34.2	76.1	37.7	
3g	OC$_6$H$_4$OC$_6$H$_4$CH$_3$	benzyl	61.0	177.3	44.1	33.8	76.2	37.5	
3i	OC$_6$H$_3$IOC$_6$H$_2$I$_2$CH$_3$	benzyl	61.1	177.2	44.1	33.7	77.7	37.6	
3k	OC$_6$H$_3$(CH(CH$_3$)$_2$)OC$_6$H$_2$I$_2$CH$_3$	benzyl	61.2	177.5	44.1	34.1	76.1	37.7	

[a] The shifts for the benzyl group carbons were invariant for each system. Thus, the methylene, ipso, ortho, meta, and para carbons appeared at 47.4, 137.3, 128.5 or 128.5 (interchangeable), and 127.6 ppm, respectively, for derivatives of 1 and at 44.9, 136.8, 128.1 or 128.7 (interchangeable), and 127.7 ppm for derivatives of 3. [b] [13]C shifts for the R$_2$ substituents are essentially identical with those observed in the corresponding methyl ethers (see ref 13 and Table II).

Table II. Diphenyl Ethers Prepared

y = CH$_3$	y = H	X	R$_1$	R$_1$	R$_2$
	13d	O	H	H	I
10h	13h	O	I	I	H
10i	13i	O	I	I	I
10j	13j	O	I	I	CH$_3$
10k	13k	O	I	I	CH(CH$_3$)$_2$
10l	13l	O	I	I	CH$_2$CH(CH$_3$)$_2$
10m	13m	O	I	I	C(CH$_3$)$_3$
10n	13n	O	I	I	C$_6$H$_5$
10o	13o	O	I	I	Cl
12	13p	CH$_2$	I	I	H
	13q	CH$_2$	I	I	I

conversion of the alcohol to the acetate, C-6 experiences a 2.3-ppm downfield shift apparently due to the elctron-withdrawing effect of the acetoxy group. The carbons β to the substituent C-1 and C-5 experience upfield shifts (3.4 and 2.4 ppm, respectively) as a result of increased steric interactions. The magnitude of these shifts is within the expected ranges.[12] For the carbons (C-7 and C-4) C-7 experiences the expected 1.1-ppm steric upfield shift, whereas C-4 is unperturbed due to its anti orientation with respect to the acetoxy group, and no shift is seen.

The ^{13}C assignments in the [2.2.1] (3) system were based on chemical shifts and multiplicities in the off-resonance decoupled spectrum for C-1, C-3, C-4, and C-6. C-5 and C-7 were assigned on the basis of a proton decoupling experiment. Although the H-5 and H-7 protons are coincident in the proton spectrum, the Yb(fod)$_3$-doped spec-

trum of 3g shows that H-5A, H-5B, H-7A, and H-7B resonances cleanly separated at an LSR/substrate ratio of 0.199. Under these conditions, irradiation at the H-5B proton frequency caused the C-5 triplet (originally at 33.8 ppm) to collapse to a doublet, and irradiation at the H-7B proton frequency caused the C-7 triplet (originally at 37.5 ppm) to collapse to a doublet.

Diphenyl Ether Synthesis. The diphenyl ethers were prepared by two routes. The first of these involved an oxidative coupling reaction[13] between the potassium salt of the appropriate bromo compound which afforded the 4-(4-methylphenoxy)-2-deuterioanisole and 4-(4-methyl-phenoxy)-2-nitroanisole (eq 4).

$$CH_3-\bigcirc-O-\bigcirc-OCH_3 \quad (4)$$
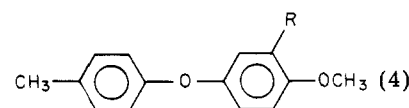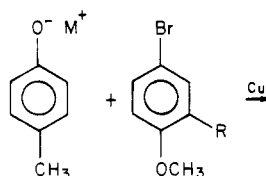
6a, R = H
b, R = D
c, R = NO$_2$

The second procedure involved the condensation of the appropriate phenol with the tosylate of 2,5-dinitro-4-methylphenol generated in situ by following the method of Blank et al.[14] The nitro compound was then catalytically hydrogenated and the resulting amine converted to the iodo compound via a Sandmeyer reaction (eq 5). The methylene-bridged analogue was prepared by reduction of the corresponding chloro compound[15] with so-

(12) (a) Reich, H. J.; Tautelat, M.; Messe, M. T.; Weigert, F. J.; Roberts, J. D. *J. Am. Chem. Soc.* 1969, *91*, 7445. (b) Christl, M.; Reich, H. J.; Roberts, J. D. *Ibid*, 1971, *93*, 3463.

(13) Bolon, D. *J. Org. Chem.* 1967, *32*, 1584.
(14) Blank, B.; Pfeiffer, R. R.; Greenberg, C. M.; Kerwin, J. F. *J. Med. Chem.* 1963, *6*, 554.

7

8a, R = H
b, R = NO_2
c, R = CH_3
d, R = $CH(CH_3)_2$
e, R = $C(CH_3)_3$
f, R = $CH_2CH(CH_3)_2$
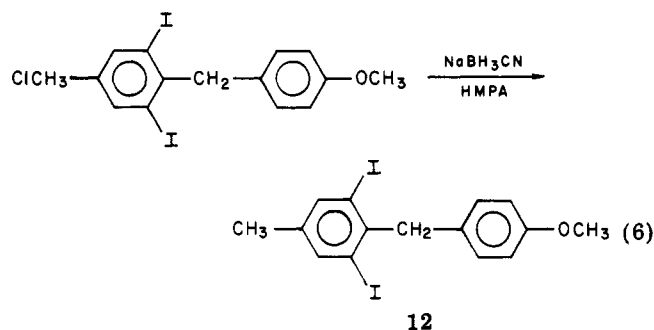**g**, R = C_6H_5

9a, R = H
b, R = NO_2
c, R = CH_3
d, R = $CH(CH_3)_2$
e, R = $C(CH_3)_3$
f, R = $CH_2CH(CH_3)_2$
g, R = C_6H_5

10h, R = H
i, R = I
j, R = CH_3
k, R = $CH(CH_3)_2$
l, R = $CH_2CH(CH_3)_2$
m, R = $C(CH_3)_3$
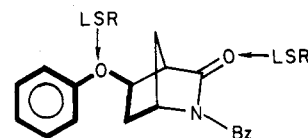**n**, R = C_6H_5
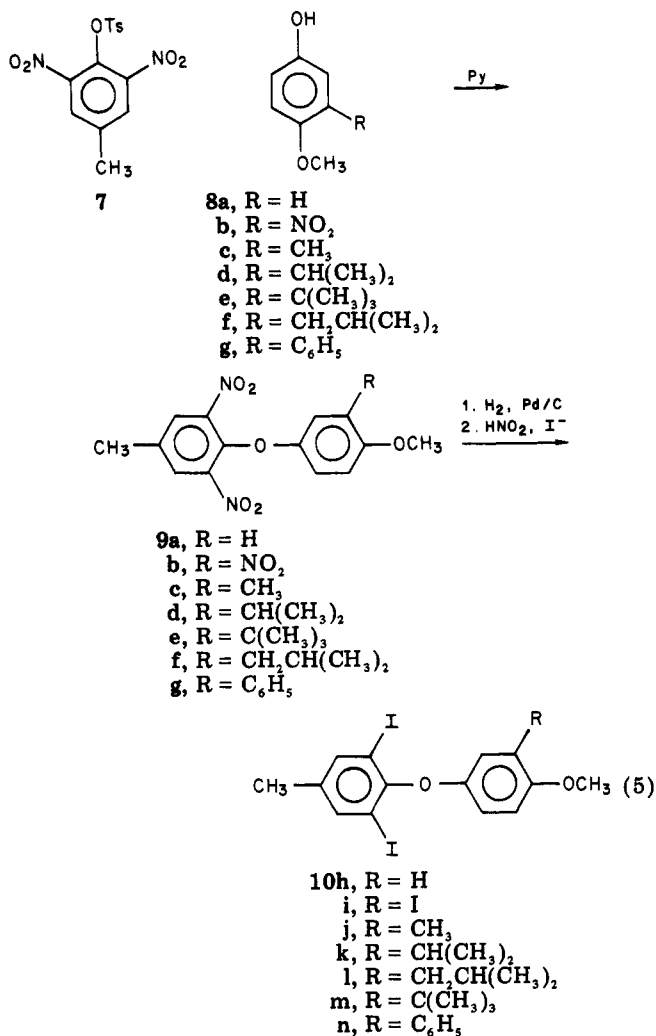
dium cyanoborohydride[16] (eq 6).

12

Ether cleavage to the phenols **13** was accomplished in most cases with hydoiodic acid although the sodium salt of propanethiol in DMF was used in some instances.[17] Attempts to prepare **13i** by cleavage of **10i** were unsuccessful, resulting in deiodination. Accordingly, the triiodo compound **13i** was prepared by iodination of **13h** with I_2 and KI[18] in methylamine and the chloro analogue by treatment of **13h** with sulfuryl chloride.[19] A listing of the diphenyl ethers prepared appears in Table II, and ^{13}C

(15) Spencer, L.; Tripp, F.; Block, B.; Barile, G. *J. Med. Chem.* **1973**, *16*, 60.

(16) Hutchins, R. O.; Marayanoff, B. E.; Milewski, C. A. *Chem. Commun.* **1971**, 1097.

(17) Feutrill, G. I.; Merrington, R. N. *Tetrahedron Lett.* **1970**, 1327.

(18) Emmett, J. C.; Pepper, E. S., personal communication.

(19) Tarbell, D. S.; Wilson, J. W.; Fanta, P. E. "Organic Syntheses"; Wiley: New York, 1963; *Collect. Vol.* III, p 267.

assignments of selected diphenyl ethers appear in Table III. We have previously reported on ^{13}C studies of a number of diphenyl ethers.[20]

Discussion

At an early stage in our investigations it was clear that a number of factors would have to be considered before we could employ any ring system in a conformational analysis program using LSR's. One important consideration was that the atomic coordinates for atoms 1–8 in derivatives of **3** should be essentially identical; i.e., there should be no large molecular structure changes for the bicyclic portion of any of these molecules as the nature of the substituent changed. It is known that coordinate changes can dramatically effect the results of LSR–substrate geometry calculations.[21] Although we were quite confident that this would be the case, we tested this propostion by comparing atomic coordinates obtained from X-ray crystallographic studies for three of the molecules, **3b,c,e**, by using a program developed by Nyburg.[22] The output of this program is in terms of a DELTA value where DELTA = $(\Delta X_i^2 + \Delta Y_i^2 + \Delta Z_i^2)^{1/2}$. In the comparison of three compounds, the largest DELTA was 0.045 Å and the SUM(DELTA^2) [where SUM(DELTA^2) = $\sum_{i=1}[(DELTA-(i^2))1^{1/2}]$] was 0.0010 Å for the **3b–3c** comparison and 0.0055 for the **3c–3e** comparison. Clearly the changes in the atomic coordinates are within the experimental error of the other procedures to be used.

Perhaps the major question to be answered concerned the relative efficiency of complexation of the LSR at the lactam carbonyl vis-a-vis the ether oxygens on the sub-

stitutent groups. For subsequent analysis it is necessary to know how much complexation occurs at each potential binding site. In fact, subsequent calculations would be extremely difficult if binding at the ether oxygen was at all competitive with carbonyl binding. To determine these relative bindings, we ran a study on the model system **15** + **16** to approximate the two portions of **3c** having potential competitive binding sites. Compound **15** was prepared from the tosylate by the elimination–hydrogenation procedure shown (eq 7). When a 1:1 mixture of **15**

16
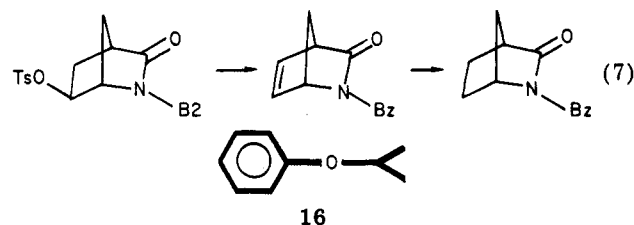
and **16** was treated with $Yb(fod)_3$ to a $Yb(fod)_3$/substrate ratio of 0.806, no shifts were observed in the proton spectrum of **16** whereas the C-8 protons in **15** were shifted by over 16 ppm.

Clearly the system as designed has only one effective binding site and a common set of nuclei in the ring system

(20) Mazzocchi, P. H.; Ammon, H. L.; Colicelli, E. *Org. Magn. Reson.* **1978**, *11*, 143.

(21) Hinckley, C. C.; Brumley, W. C. *J. Am. Chem. Soc.* **1976**, *98*, 1331.

(22) Nyburg, S. C. *Acta Crystallogr., Sect. B* **1974**, *B30*, 251.

Table III. ¹³C Assignments (ppm) for Selected Diphenyl Ethers and Diphenyl Methanes[a]

	x	y	R₂[e]	chemical shift					
				C-1'	C-2'	C-3'	C-4'	C-5'	C-6'
13h	O	H	H	150.4[b]	116.3[b]	116.1[b]	150.2[b]	116.1[b]	116.3[b]
10i	O	CH₃	I	150.3	126.2	86.0	153.3	110.9	115.7
13i	O	H	I	149.8	125.3	84.0	151.5	115.1	116.5
10j	O	CH₃	CH₃	149.8	118.1	127.9	152.8	110.4	112.3
13j	O	H	CH₃	150.1	117.9	125.1	148.6	113.2	115.5
10k	O	CH₃	CH(CH₃)₂	150.2	114.4	138.4	151.8	110.6	111.8
13k	O	H	CH(CH₃)₂	150.6	114.4	135.9	147.5	115.7	112.4
10l	O	CH₃	CH₂CH(CH₃)₂	149.6	118.1	131.2	152.6	112.7	110.8
13l	O	H	CH₂CH(CH₃)₂	150.0	118.0	128.7	148.4	115.9	113.6
10m	O	CH₃	C(CH₃)₃	149.8	111.9[b]	139.7	153.5	111.7[b]	115.5
13m	O	H	C(CH₃)₃	150.1	112.4	137.7	149.0	115.6	116.7
10n	O	CH₃	C₆H₅	150.2	117.9	137.9	151.5	112.2	114.8
13n	O	H	C₆H₅	150.1	116.7	136.7	147.2	116.0	116.7
13o	O	H	Cl	150.0	115.9[b]	120.3	146.5	116.6[b]	115.6[b]
12	CH₂[c]	CH₃	H	129.6	129.3	113.7	157.8	113.7	129.3
13p	CH₂[d]	H	H	129.8	129.5	115.2	153.4	115.2	129.5
13q	CH₂[d]	H	I	131.7	137.7	85.8	152.9	114.7	130.0

[a] The aromatic methyl carbon (C-7) appears at ~19.7 ppm and the methoxy methyl at 55.5–56.6 ppm. Chemical shifts of ring A carbons are not shown since they change little with substitution. They appear in the following ranges [C, shift range (ppm)]: 1, 138.1–138.9; 2 (6), 140.2–140.7; 3 (5), 90.5–90.9; 4, 150.3–152.2. In 12, 13p, and 13q, C-3(5) appears at 100.1 ppm, and C-4 appears at 141.6, 141.5, and 140.7 ppm in 12, 13p, and 13q, respectively. [b] May be interchanged with carbon of essentially equal chemical shift noted. [c] The CH₂ carbon appears at 50.4 ppm. [d] The CH₂ carbon appears at 49.8 ppm. [e] R₁ was I in all cases.

to use in the determination of the geometry of the sub-strate–LSR complex. The complete results of the conformational analysis studies on the mobile substituents will be published shortly.

Experimental Section

Microanalysis were performed by Dr. Franz Kasler of the Department of Chemistry, University of Maryland, and are within acceptable limits for the elements indicated. Infrared spectra were obtained on either a Beckman IR8 or a Perkin-Elmer 281 infrared spectrophotometer. Gas chromatography was accomplished on a Varian Aerograph Series 1200 instrument using a SE-30 column. The proton NMR spectra were recorded on Varian EM-360, Varian A-60D, or Varian XL-100 spectrometers in deuteriochloroform solutions (unless otherwise noted) with 1% tetramethylsilane as an internal standard. All ¹³C spectra were recorded on a Varian XL-100 spectrometer at 25.2 MHz in deuteriochloroform with 5% tetramethylsilane as an internal standard and with an internal ²H lock. A high-power pulse amplifier provided for a 90° pulse of 12-15 μs. The sweep width was routinely 5000 Hz. The carbon spectra were normally taken with broad-band decoupling. Off-resonance carbon spectra were recorded as described above with the exception that maximum heteroatom decoupling power was applied at a single frequency, 300 Hz upfield from the tetramethylsilane signal. Completely coupled carbon spectra were obtained with no proton decoupling applied, with a low-field lock (to observe the aromatic carbons of interest), and with a filter if appropriate. Single-frequency off-resonance spectra were recorded with heteroatom decoupling power applied at a single frequency corresponding to the appropriate proton resonance.

2-Benzyl-3-oxo-6-*exo*-(tosyloxy)-2-azabicyclo[2.2.1]heptane (3b). To a solution of p-toluenesulfonyl chloride (0.351 g, 0.00184 mol) in 3 mL of dry pyridine was added 2-benzyl-3-oxo-6-*exo*-hydroxy-2-azabicyclo[2.2.1]heptane (3a; 0.200 g, 0.00092 mol). The reaction mixture was allowed to stand at room temperature for 24 h and poured into 20 g of ice–water, and the precipitated solid was collected. Recrystallization from hot methanol gave a white solid: 0.246 g (72%); mp 128.5–129.5 °C; NMR (CDCl₃) δ 1.60–2.25 (m, 4 H), 2.40 (s, 3 H), 2.70 (m, 1 H), 3.72 (m, 1 H),

4.15–4.40 (m, 1 H), 4.20 (d, 2 H, J = 4 Hz), 7.05–7.75 (m, 9 H); IR (CCl₄) 3100–2940, 1710 cm⁻¹. Anal. C, H, N.

General Procedure for the Preparation of the Sodium Salts of Phenols and 4-Phenoxyphenols. A solution of 0.025 mol of phenol or 4-phenoxyphenol in 80 mL of benzene was added dropwise to an equimolar amounts of sodium hydroxide dissolved in 2 mL of water. The solvent was removed under reduced pressure. This procedure was repeated three times with fresh benzene to codistill the azeotropic water. The residue was dried in a vacuum desiccator over P₂O₅ for 2 days to leave a fine white powder.

2-Benzyl-3-oxo-6-*exo*-phenoxy-2-azabicyclo[2.2.2]octane (1d). Compound 1b (5 g, 0.0135 mol) and 3.51 g (0.0270 mol) of sodium phenoxide were added to 75 mL of 1-propanol, and the reaction mixture was heated at reflux for 12 h. p-Toluenesulfonic acid was filtered off, the reaction mixture poured into water, and the product extracted with ether. The ether was washed with 10% aqueous potassium hydroxide and water, dried (MgSO₄), and concentrated. The residue was taken up in ether to give 1d as white crystals: 0.827 g (20%); mp 122–124 °C; NMR (CDCl₃) δ 1.4–2.6 (m, 6 H), 3.75 (m, 1 H), 4.35 (m, 1 H), 4.35 and 5.02 (dd, 2 H), 6.6–7.7 (m, 10 H); IR (CHCl₃) 3050–2900, 1658, 1210, 1250 cm⁻¹. Anal. C, H, N.

2-Benzyl-3-oxo-7-*exo*-phenoxy-2-azabicyclo[3.2.1]octane (2d). Evaporation of the mother liquor from the previous recrystallization and preparative TLC (silica gel, hexane–ether) gave 2d as white crystals from hexane–ether: 1.03 g (25%); mp 68–69 °C; NMR (CDCl₃) δ 1.7–2.5 (m, 6 H), 2.6 (m, 1 H), 3.7 (m, 1 H), 4.35 (m, 1 H), 4.35 and 4.80 (dd, 2 H), 6.6–7.7 (m, 10 H); IR (CHCl₃) 3050–2900, 1680, 1210–1240 cm⁻¹. Anal. C, H, N.

2-Benzyl-3-oxo-6-*exo*-[4-(4-methylphenoxy)phenoxy]-2-azabicyclo[2.2.2]octane (1g). This material was prepared as described above from the appropriate phenol in 13% yield: mp 101–102 °C; NMR (CDCl₃) δ 1.4–2.5 (m, 6 H), 2.4 (s, 3 H), 2.7 (m, 1 H), 3.75 (m, 1 H), 4.3 (m, 1 H), 4.35 and 5.02 (dd, 2 H), 6.5–7.5 (m, 13 H); IR (CHCl₃) 3050–2900, 1650, 1200–1250 cm⁻¹. Anal. C, H, N. No effort was made to isolate rearranged product from the mother liquor.

2-Benzyl-3-oxo-6-*exo*-(benzyloxy)-2-azabicyclo[2.2.2]octane (1e). To 4.0 g (0.017 mol) of 1a in 10 mL of dry DMF was added an equimolar amount of sodium hydride in 30 mL of DMF.

The mixture was stirred for 30 min, and 2.9 g (0.017 mol) of benzyl bromide in 10 mL of DMF was added. The mixture was stirred overnight at room temperature, poured into 250 mL of water, and extracted with ether. The extract was dried and concentrated, and the residue was distilled to afford a 40% yield of **1e**: bp 184 °C (0.2 mm); NMR (CDCl₃) δ 1.2–2.3 (m, 6 H), 2.6 (m, 1 H), 3.5 (m, 2 H), 4.3 (s, 2 H), 4.6 (dd, 2 H), 7.3 (s, 10 H); IR (CHCl₃) 3050–2900, 1658, 1220, 1270 cm⁻¹. Anal. C, H, N.

2-Benzyl-3-oxo-6-*exo*-[[4-(4-methylphenoxy)benzyl]-oxy]-2-azabicyclo[2.2.2]octane (1f). Compound **1f** was obtained, by the procedure described for **1e**, from **1a** and 4-(4-methyl-phenoxy)benzyl bromide in 44% yield: mp 54–56 °C; NMR (CDCl₃) δ 1.2–2.3 (m, 6 H), 2.4 (s, 3 H), 2.6 (m, 1 H), 3.5 (m, 2 H), 4.3 (s, 2 H), 4.6 (dd, 2 H), 6.7–7.4 (m, 13 H); IR (CHCl₃) 2800–3150, 1658, 1220–1250 cm⁻¹. Anal. C, H, N.

4-(4-Methylphenoxy)-2-nitroanisole (6c). To the potassium salt of *p*-cresol (from 54 g of *p*-cresol) were added 100 mL of DMF, 116 g of 4-bromo-2-nitroanisole, 0.5 g of copper powder, and 0.5 g of cupric acetate. DMF (20 mL) was distilled off, the remaining mixture was heated at reflux for 4 h and cooled, and 300 mL of methanol and 125 mL of concentrated HCl were added sequentially. The mixture was poured onto 100 g of ice and extracted with four 250-mL portions of benzene. The combined extracts were washed with 15% NaOH and water and dried, and the solvent was removed in vacuo. Distillation of the residue gave **6c** in 18% yield: bp 154 °C (0.4 mm); mp 56–57 °C; NMR (CDCl₃) δ 2.3 (s, 3 H), 4.0 (s, 3 H), 6.7–7.5 (m, 7 H); IR (CHCl₃) 3100–2840, 1530, 1350, 1220, 1020 cm⁻¹. Anal. C, H, N.

4-(4-Methylphenoxy)-2-iodoanisole (6d). Compound **6d** was prepared from **6c** in 50% yield by the procedure described for **10k** (vide infra): bp 155 °C (0.15 mm); mp 56–58 °C; NMR (CDCl₃) δ 2.3 (s, 3 H), 3.8 (s, 3 H), 6.7–7.5 (m, 7 H); IR (CHCl₃) 3050–2860, 1270, 1230, 1050 cm⁻¹. Anal. C, H, I.

2-Isopropyl-4-(2,6-dinitro-4-methylphenoxy)anisole (9d). Compound **9d** was prepared according to the general method of Blank et al.[14] A solution of 1.18 g (0.006 mol) of 2,6-dinitro-4-methylphenol and 1.235 g (0.0065 mol) of *p*-toluenesulfonyl chloride in 10 mL of dry pyridine was heated with stirring in an oil bath (95 °C) for 30 min. 2-Isopropyl-4-hydroxyanisole (8d;[23,24] 2.10 8 g, 0.013 mol) was added and the solution stirred under reflux for 2 h. The pyridine was carefully removed by vacuum distillation, and the residue was dissolved in 50 mL of chloroform. The chloroform solution was washed successively with 2 N HCl, water, and 10% NaOH and dried (MgSO₄), and the solvent was removed in vacuo. The crude solid was treated with charcoal and recrystallized from hot absolute ethanol, giving 1.54 g (74%) of **9d** as a yellow solid, mp 141–142 °C.

2-Isopropyl-4-(2,6-diiodo-4-methylphenoxy)anisole (10k). A procedure similar to that of Blank et al.[14] was employed. A solution of (**9d**; 3.460 g, 0.01 mol) in 120 mL of hot acetic acid and ethanol (50:50 v/v) was reduced in the presence of 1.0 g of 10% Pd/C in a Parr apparatus at a 75-psi initial pressure. When the reduction was complete, the catalyst was removed by filtration, and the filtrate was added to a stirred, cooled solution which had been previously prepared by slowly adding 3.93 g of sodium nitrite to a mixture of 80 mL of concentrated sulfuric acid and 35 mL of acetic acid at 60–70 °C. The temperature was maintained at 0–5 °C during the addition. After the solution was stirred and cooled for 1 h, it was added rapidly to a mixture of 8.8 g of sodium iodide, 11.0 g of iodine, and 2.0 g of urea in 180 mL of water and 180 mL of chloroform. Stirring was continued for 2 h at room temperature, and the layers were then separated. The aqueous layer was extracted several times with chlroform, and the combined chloroform extracts were washed in turn with water, 10% sodium bisulfate, water, 5% sodium bicarbonate, and water. After the mixture was dried (MgSO₄), the solvent was removed in vacuo and the crude solid purified by recrystallization (carbon) from hot absolute ethanol to give **10k** as a light orange solid: 3.70 g (73%); mp 125.5–126.5 °C.

2,6-Diiodo-4-methyl-4′-methoxydiphenylmethane (12). To a stirred solution of 3,5-diiodo-4-(4-methoxybenzyl)benzyl chloride[15] (390 mg, 0.66 mmol) in HMPA (4.5 mL) was added sodium

cyanoborohydride (250 mg, 4.0 mmol). The mixture was stirred 16 h at 70 °C, cooled, added to half-saturated sodium chloride (20 mL), and extracted with benzene. The benzene solution was dried and evaporated, and the residue was flash chromatographed[25] in 9:1 pentane/ether, yielding 175 mg (48%) of **12** in the first fraction: NMR (CDCl₃) δ 2.21 (s, 3 H), 3.72 (s, 3 H), 4.40 (s, 2 H), 6.87 (m, 4 H), 7.67 (s, 2 H).

4-(4-Methylphenoxy)-2-iodophenol (13d). 1-Propanethiol in 20 mL of dry DMF was added to 1.0 g of NaH (50% oil dispersion) in 10 mL of DMF under nitrogen. After 5 min 1.0 g of **6d** was added, and the reaction mixture was heated at 100 °C for 3 h and stirred at room temperature for an additional 3 h. The solution was cooled, acidified with diluted HCl, and extracted with ether. The ether extract was back-extracted with 5% sodium hydroxide, the aqueous extract acidified and again extracted with ether, and the residue from evaporation of the solvent recrystallized to give 0.611 g (63%) of **13d**, mp 41–42 °C.

4-(2,6-Diiodo-4-methylphenoxy)phenol (13h). A mixture of **10h** (5.00 g, 0.0107 mol) in a solution of 30 mL of 47% HI and 20 mL of acetic acid was heated under reflux for 4 h and poured over 150 g of ice, and the resultant aqueous solution was extracted with four 20-mL portions of benzene. The benzene fraction was washed with 10% ammonium carbonate and water, dried over MgSO₄, and filtered, and the solvent was removed in vacuo. Recrystallization from a mixture of benzene and hexane gave **13h** as a white solid: 4.6 g (95%); mp 151–152 °C.

2-Iodo-4-(2,6-diiodo-4-methylphenoxy)phenol (13i). According to the method of Emmett and Pepper,[18] a solution of 2.56 g (0.01 mol) of iodine and 6 g of potassium iodide in 36 mL of water was added dropwise over 30 min to a stirred solution of 4.56 g (0.01 mol) of **13h** ethanol and 200 mL of 25% aqueous methylamine at 5 °C. The reaction mixture was stirred for 1 h at 5 °C, acidified cautiously to pH 1 with 11 N HCl, and left at 0 °C overnight. The crude product was separated by filtration and purified by chromatography on neutral alumina. The product was obtained as white crystals: 81% yield; mp 143–145 °C.

2-Chloro-4-(2,6-diiodo-4-methylphenoxy)phenol (13o). A mixture of 1.808 g (0.004 mol) of **13h** and 0.594 g (0.004 mol) of sulfuryl chloride in 6 mL of carbon tetrachloride was heated at 75 °C for 6 h, the reaction mixture taken up in ether and the ether extract washed with water. The organic phase was dried (MgSO₄) and the solvent was removed in vacuo. The residue was chromatographed on a silica gel column (CHCl₃ eluant) to afford 1.1 g (52%) of **13o**; mp 151–152 °C.

2,6-Diiodo-4-methyl-4′-hydroxydiphenylmethane (13p). A mixture of **12** (175 mg, 0.38 mmol), 47% HI (2 mL), and HOAc (2 mL) was heated to reflux 4 h, cooled, and diluted with H₂O (5 mL). The resulting crystalline **13p** was collected, washed with H₂O, and dried: 150 mg (88%); NMR (CDCl₃) δ 2.20 (s, 3 H), 3.71 (s, 1 H), 4.36 (s, 2 H), 6.78 (m, 4 H), 7.64 (s, 2 H). The analytical sample (mp 143–144 °C) was recrystallized from CCl₄. Anal. C, H.

2,3′,6-Triiodo-4′-hydroxy-4-methyldiphenylmethane (13q). To a stirred, ice-cooled solution of diiodophenol **13p** (178 mg, 0.40 mmol) in ethanol (7 mL) and 40% aqueous methylamine (5 mL) was added dropwise a solution of iodine (102 mg, 0.40 mmol) and potassium iodide (240 mg) in water (1.5 mL). After 1 h at 0 °C the mixture was brought to pH 1 by dropwise addition of concentrated HCl and refrigerated overnight. The precipitated solid was filtered and the filtrate extracted with CH₂Cl₂. The resulting brown solid was separated by flash chromatography to give **13q**: 126 mg (55%); mp 119–120 °C.

2-Benzyl-3-oxo-2-azabicyclo[2.2.1]hept-5-ene (14). To a solution of potassium *tert*-butoxide made from 0.234 g (0.006 mol) of potassium metal in 10 mL of *tert*-butyl alcohol was added 0.742 g (0.002 mol) of **3b**, and the mixture was heated at reflux for 45 h under nitrogen. The reaction mixture was poured into 20 mL of water and extracted with 150 mL of ether, and the extracts were dried over MgSO₄. The solvent was evaporated under reduced pressure, and the residue was purified by bulb-to-bulb distillation at 60–70 °C (4 mm) to yield a clear oil: 0.350 g (90% yield); NMR (CDCl₃) δ 1.85–2.50 (m, 2 H), 3.27 (m, 1 H), 3.98 (m, 1 H), 8.83 (d, 1 H, *J* = 15 Hz), 4.35 (d, 1 H, *J* = 15 Hz), 6.50 (t,

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2 H, *J* = 1.5 Hz), 7.23 (s, 5 H); IR (CCl₄) 3100–2780, 1720, 1555, 1230, 1070 cm⁻¹.

2-Benzyl-3-oxo-2-azabicyclo[2.2.1]heptane (15). A solution of 0.337 g (0.0017 mol) of cured **14** in 150 mL of ethyl acetate was reduced in a Parr apparatus at 2 atm in the presence of 200 mg of 10% Pd/C for 3 h. After removal of the catalyst and the solvent, the oily residue was purified by bulb-to-bulb distillation at 130 °C (4 mm) to give a light yellowish oil (0.340 g, 99% yield). This oil was further purified by preparative TLC (silica gel GF, ethyl acetate) and then by preparative gas chromatography on an 6 ft × ¹/₄ in. column packed with 3% SE-30 on 60/80 Chromosorb W at 190 °C: NMR (CDCl₃) δ 1.33–2.10 (m, 6 H), 2.83 (m, 1 H), 3.64 (m, 1 H), 3.89 (d, 1 H, *J* = 15 Hz), 4.66 (d, 1 H, *J* = 15 Hz), 7.25 (s, 5 H); IR (CCl₄) 3100–2820, 1720, 1240, 1070 cm⁻¹. Anal. C, H, N.

β-Amino Ester Enolate as an Acrylate Anion Equivalent for the Synthesis of α-Methylene Esters, Acids, and Lactones[1,2]

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The lithium enolate (**18**) of methyl 3-(dimethylamino)propionate (**17**) has been developed as a synthetic equivalent of the α-anion (**15**) of acrylic acid. The enolate, obtained by treatment of the free ester (**17**) with lithium diisopropylamide, may be alkylated with a variety of alkyl halides to give products which may be considered to be protected acrylate esters. Unmasking is accomplished by quaternization with methyl iodide followed by DBN-induced elimination to give the free acrylates. The products derived from allylic halides may conveniently be converted into α-methylene lactones.

The acrylate unit and related groups (**1**, Chart I) are found as structural features of a very large number of naturally occurring compounds, many of which possess useful biological activity. Included among these compounds are several classes of unsaturated carboxylic acids, esters, and lactones. Some specific examples of the acids are ambrosic acid (**2**),[3] the eremophildienoic acid (**3**),[4] the fatty acid derivatives (**4**) of β-alanine,[5] conocandin (**5**),[6] and several other closely related compounds.[7] Simple ester derivatives of some of these and similar acids are also known.[8] In addition, unsaturated ester groups such as angelates and tiglates occur as appendages of several physiologically active compounds.[9] Furthermore, acrylates are observed in reduced forms as unsaturated aldehydes (e.g., **6–8**)[10] and alcohols (e.g., **9** and **10**).[10c,e,11] However,

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