were made basic to pH 10 with ice-cold 40% sodium hydroxide. The product was extracted with ethyl acetate (3 × 30 mL), dried (Na_2SO_4), and concentrated to a pink foam. TLC ($CHCl_3$ saturated with NH_3) indicated a single product: R_f 0.10; van Urks, immediate sky blue drying to forest green; IR (KBr) 3380, 3220, 2940, 1440, 1350, 1325, 1130, 980, 720 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 8.56 (br s, 1, indole NH), 7.65 (d, J = 16 Hz, 1, methine), 7.29–6.96 (m, 4, arom), 6.29 (d, J = 16 Hz, 1, vinyl), 3.57 (s, 2, CH_2N), 2.24 (s, 6, $N(CH_3)_2$), 1.71 (s, 1, OH), 1.44 (s, 6, $C(CH_3)_2$); mass (m/z, %) 259 (M + 1, 63), 241 (M - H_2O, 100), 214 (M - $N(CH_3)_2$, 61), 196 (M - H_2O - $N(CH_3)_2$, 21); exact mass for $C_{16}H_{22}N_2O$ calcd 258.1732, found 258.1730.

Methyl 2-Amino-2-carbomethoxy-3-[4-(1-hydroxy-3-methyl-2-butenyl)-3-indolyl]propionate (9). This compound was prepared in accordance with the procedure of Somei.[9] To 0.300 g (1.16 mmol) of dimethyl aminomalonate and 0.300 g (1.16 mmol) of gramine derivative 8 in 2 mL of acetonitrile was added, in one portion, a solution of 116 L of tri-*n*-butylphosphine (95%, 0.55 mmol) in 1 mL of acetonitrile. The reaction was heated at gentle reflux over a steam bath for 4 h. After cooling, the solution was poured into 8 mL of H_2O and extracted with hexanes (1 × 2 mL), the hexane layer was discarded, and the aqueous layer was extracted with methylene chloride (4 × 5 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated to yield 0.40 g of a golden residue. Radial chromatography (1% MeOH–$CHCl_3$) afforded 356 mg (85%) of product as a pale yellow oil: TLC ($CHCl_3$ saturated with NH_3) R_f 0.13; IR (neat, NaCl) 3360, 3210, 3010, 2930, 1725, 1290, 1200 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 8.65 (br s, 1, indole NH), 7.53, (d, J = 16 Hz, 1, methine), 7.25–6.97 (m, 4, arom), 6.18 (d, J = 16 Hz, 1, vinyl), 3.72 (s, 8, $COOCH_3$ obscuring methylene), 2.33 (br s, 2, NH_2), 1.74 (br s, 1, OH), 1.46 (s, 6, $C(CH_3)_2$); mass (m/z, %) 361 (M + 1, 8), 343 (M - H_2O, 100); exact mass for $C_{19}H_{24}N_2O_5$ calcd 360.1685, found 360.1695.

Dimethyl 3,4,5,6-Tetrahydro-6-(2-methyl-1-propenyl)-azepino[5,4,3-*cd*]indole-4,4-dicarboxylate (10). A solution of 97.9 mg (0.27 mmol) of amino alcohol **9**, 0.005 g (0.018 mmol) of *p*-toluenesulfonic acid, and 5 mL of acetonitrile was heated at gentle reflux for 2 h. After cooling, the solution was poured onto 20 mL of saturated sodium bicarbonate and extracted with ether (3 × 10 mL). The combined ethereal layers were dried (Na_2SO_4), filtered, and concentrated by rotary evaporation, and radially chromatographed (1% EtOAc–methylene chloride) to afford a golden oil: 45 mg (48%); TLC ($CHCl_3$ saturated with NH_3) R_f 0.49; van Urks slowly developing pale yellow drying to rose; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.99 (br s, 1, indole NH), 7.16 (d, 1, J = 8.2 Hz, C-14), 7.01 (m, 1, C-13), 6.94 (br s, 1, C-12), 6.77 (d, 1, J = 7.3 Hz, indole 2C-H), 5.45 (d, J = 7.8 Hz, 1, vinyl), 5.30 (d, J = 8.8 Hz, 1, methine), 3.93 (d, J = 15.6 Hz, 1, methylene), 3.77 (s, 3, $COOCH_3$), 3.71 (s, 3, $COOCH_3$), 3.50 (d, J = 15.5 Hz, 1, methylene), 2.92 (d, J = 14.1 Hz, 1, NH), 1.88 (s, 3, CH_3), 1.74 (s, 3, CH_3); mass (m/z, %) 343 (M + 1, 100), 399 (isobutane adduct, 5); exact mass for $C_{19}H_{22}N_2O_4$ calcd 342.1580, found 342.1577.

Acknowledgment. We wish to thank Eli Lilly, and Co. for their generous support of this work. Also, we thank Steven E. Klohr for obtaining the A-200 spectrum. One of us (D.B.) wishes to thank the South Dakota School of Mines and Technology for a professional development leave during which time this work was performed.

Prodrugs Based on Masked Lactones. Cyclization of γ-Hydroxy Amides

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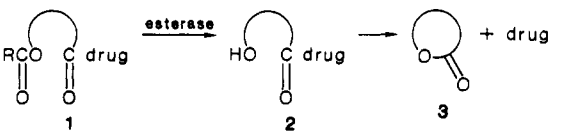
A versatile approach to prodrug design based on the lactonization of γ-hydroxy carbonyl compounds is investigated. A range of γ-hydroxy amides have been synthesized as models for amide-linked prodrugs. The rates of lactonization of these compounds have been measured, and the effects of pH, leaving group pK_a, buffer species, and ionic strength are investigated. The kinetic data are consistent with changes in the rate-determining step with the nature of the buffer and with pH over the range 6–10. Some compounds show only small changes in rate over the pH range 7–9. The best model prodrugs studied have rates of amine expulsion that would probably be adequate for therapeutic use, but precise rates of drug liberation in vivo cannot be predicted from these data due to the problems of estimating the magnitude of biological buffer catalysis and effects due to tissue binding. However, drug liberation half-lives in vivo in the region of 1 h for aromatic amides, less for aliphatic amides, may be achieved by using prodrugs that yield 4,4-dialkyl(or spiroalkyl)-(*Z*)-but-2-enoic acid lactones during drug release.

Many potentially useful drugs are not used therapeutically since an optimum concentration at the site of action cannot be achieved or cannot be maintained for an adequate period of time. These and other deficiencies may arise from poor oral absorption, inadequate permeation of cell membranes, chemical instability, rapid clearance, or toxicity to specific tissues, etc., depending on the nature of the drug.

Attempts to overcome such problems have led to the development of a number of drug delivery systems,[1] which can be mechanical or chemical in nature. The former class centers around the use of microparticulate materials and is not the subject of this paper. The chemical approach often involves the investigation of salt formation, but we

Scheme I



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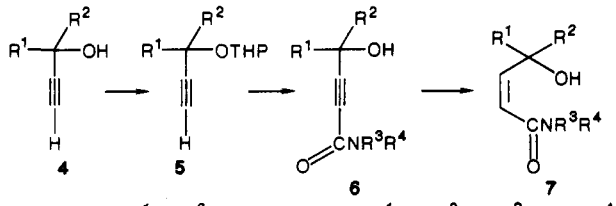
(1) Poznansky, M. J.; Juliano, R. L. *Pharm. Rev.* **1984**, *36*, 277.

0022-3263/88/1953-5130$01.50/0

Scheme II



compound	R^1	R^2
a	H	H
b	CH_3	CH_3
c	cyclohexyl	
d	2-camphyl	

compound	R^1	R^2	R^3	R^4
a	H	H	H	p-C_6H_4Br
b	CH_3	CH_3	H	p-C_6H_4Br
c	CH_3	CH_3	CH_3	C_6H_5
d	cyclohexyl		H	p-C_6H_4Br
e	2-camphyl		CH_3	C_6H_5
f	2-camphyl		H	p-C_6H_4Br

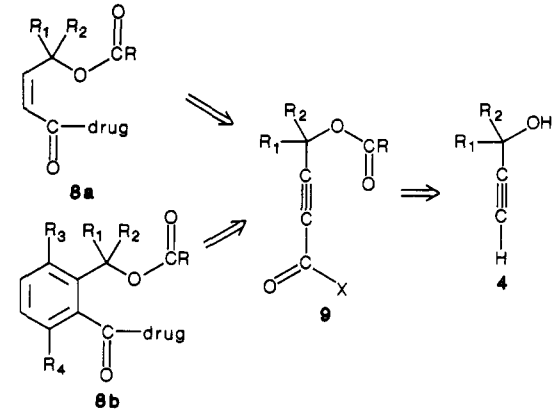
will address only the covalent modifications leading to prodrugs. These are compounds that must undergo a chemical transformation in the body, before producing the desired pharmacological effect. Although many prodrugs have been developed, they usually involve enzymatic hydrolysis of an ester functionality,[2] which necessarily precludes any drug without a suitable carboxyl or hydroxyl group.

In this paper we discuss the use of masked lactones[3] in the design of a prodrug system as shown in Scheme I. The relatively nonpolar prodrug 1 should easily be absorbed through the gut wall and then enzymatically hydrolyzed to give the corresponding alcohol 2. With sufficiently reactive carrier systems, the subsequent nonenzymatic lactonization reaction would not be rate limiting, and the rate of drug liberation could be controlled by changing the acyl group (RC=O). The choice of the acyl group will depend on the individual circumstances and is outside the scope of this paper.

It is important that the intramolecular reaction has a very high effective molarity (EM) as this allows rapid release of drug, without a corresponding increase in intermolecular reaction rates. The drug–carrier bond of 1 must have sufficient hydrolytic stability to prevent premature liberation of the drug in either the formulated product during storage or within the gut prior to absorption.

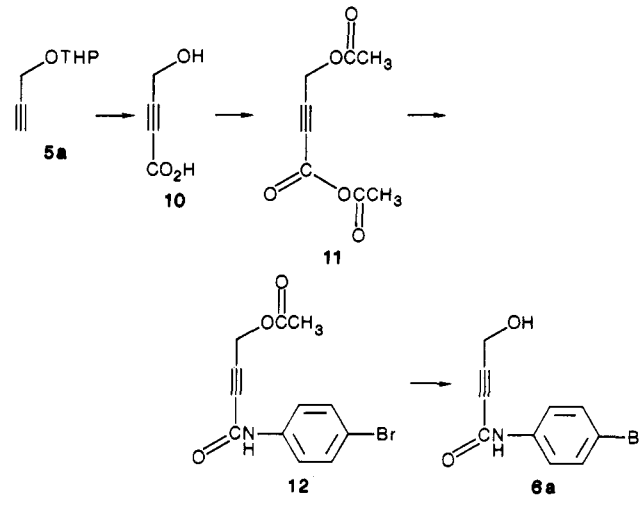
Unlike most other approaches, which are specific for one drug, the system described by 1 can be used for any drug containing an appropriate functionality, e.g. amine, amide, thiol, alcohol, phenol, heterocyclic NH. A number of intramolecular ester,[4] thioester,[5] and amide[6] alcoholysis reactions have been reported, often as model studies for enzyme reactions. However, if the method shown in Scheme I is to find widespread application, carrier systems must be found with the stability profile described above, and in addition, they should have the following characteristics: (a) easy synthesis of the prodrug system, (b) sufficient variability to allow optimization of absorption, (c) the required rate of drug liberation, (d) a nontoxic prodrug and liberate a nontoxic lactone, (e) significant improvement over existing drugs/prodrugs. There is also a strong preference for lactones that are achiral and of low molecular weight.

Scheme III[a]



[a] X = OR, Cl, etc.

Scheme IV



Although it is well-known that many intramolecular reactions exhibit very large effect molarities[7] and many theories have been proposed to explain these effects, including orbital steering,[8] proximity effects,[9] the Circe effect,[10] stereopopulation control,[11] a spatiotemporal postulate,[12] and a combination of strain plus entropy effects,[13] we believe that prediction of rates for new systems is still an uncertain exercise. Indeed, a recent compliation of EM values[4] has been referred to as "one of the largest and most variant bodies of unexplained data in physical organic chemistry".[14] In this paper we describe the synthesis and relative reactivity of some γ-hydroxy amides as models for amide-linked prodrugs and discuss the mechanism of γ-hydroxy amide cyclization reactions.

(2) Ott, A. C.; Kuizenga, M. H.; Lyster, S. C.; Johnson, B. A. *J. Clin. Endocrinol. Metab.* **1952**, *12*, 15. Von Daehne, W.; Frederiksen, E.; Gundersen, E.; Lund, F.; Moerch, P.; Petersen, H. J.; Roholt, K.; Tybring, L.; Godtfredsen, W. O. *J. Med. Chem.* **1970**, *13*, 607.

(3) During the course of this work another group published work on compound **36** and several other amides of 2-(hydroxymethyl)benzoic acid: Nielsen, N. M.; Bundgaard, H. *Int. J. Pharm.* **1986**, *29*, 9.

(4) For a comprehensive review, see: Kirby, A. J. *Adv. Phys. Org. Chem.* **1980**, *17*, 183.

(5) For example, see: Martin, R. B.; Hedrick, R. I. *J. Am. Chem. Soc.* **1962**, *84*, 106.

(6) For examples, see: Belke, C. J.; Su, S. C. K.; Shafer, J. A. *J. Am. Chem. Soc.* **1971**, *93*, 4552. Fife, T. H.; Benjamin, B. M. *J. Chem. Soc., Chem. Commun.* **1974**, 525. Tsuji, A.; Yamana, T.; Mizukami, Y. *Chem. Pharm. Bull.* **1972**, *20*, 2528 and ref 19, 23, and 24.

(7) Jencks, W. P. *Catalysis in Chemistry* and *Enzymology*; McGraw-Hill: New York, 1969.

(8) Storm, D. R.; Koshland, D. E. *J. Am. Chem. Soc.* **1972**, *94*, 5815.

(9) Bruice, T. C. *Annu. Rev. Biochem.* **1976**, *45*, 331.

(10) Jencks, W. P. *Adv. Enzymol. Relat. Areas Mol. Biol.* **1975**, *43*, 219.

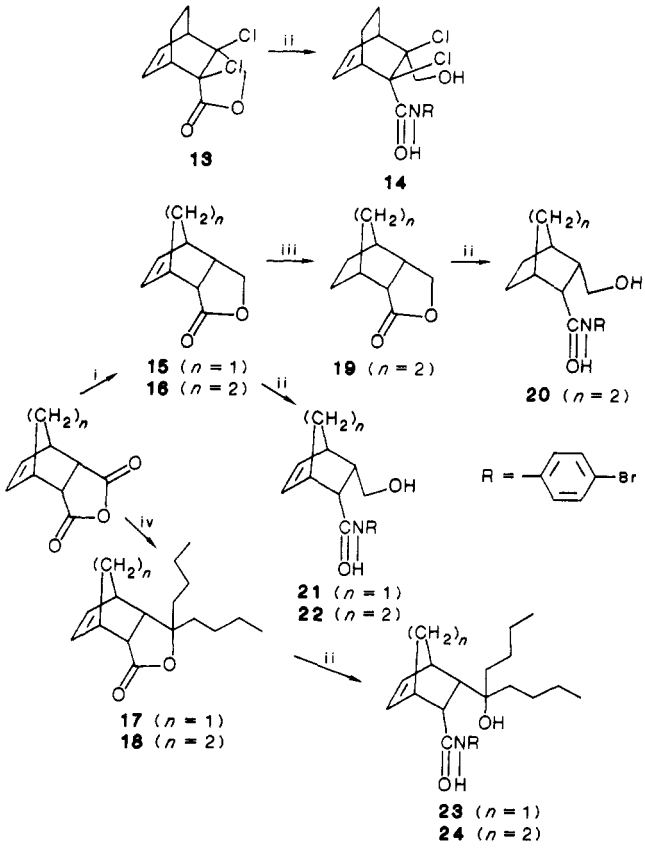
(11) Milstein, S.; Cohen, L. A. *J. Am. Chem. Soc.* **1972**, *94*, 9158. Hillery, P.; Cohen, L. A. *J. Org. Chem.* **1983**, *48*, 3465.

(12) Menger, F. M.; Venkataram, U. V. *J. Am. Chem. Soc.* **1985**, *107*, 4706.

(13) Dorigo, A. E.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 3698.

(14) Menger, F. M. *Acc. Chem. Res.* **1985**, *18*, 128.

Scheme V[a]



[a] Reagents: (i) $LiBH_4$; (ii) *p*-bromoaniline/*n*-BuLi; (iii) H_2/Pd/C; (iv) *n*-BuLi.

Synthetic Procedures

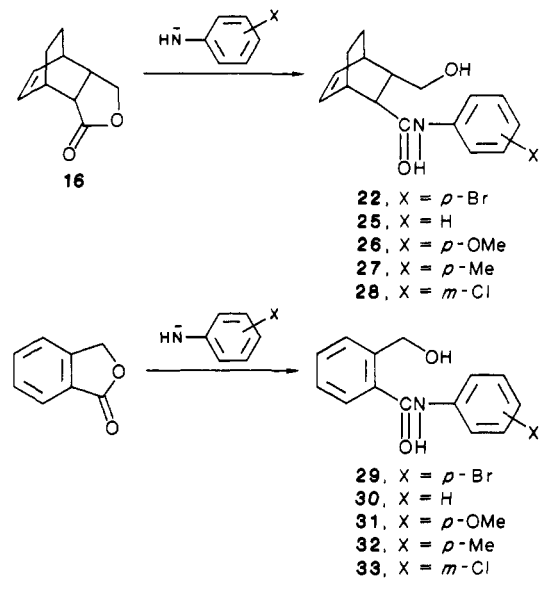
The general procedure used for the synthesis of *cis*-but-2-enamides **7** is shown in Scheme II. Compounds **4a–c** are commercially available, and **4d** was prepared by treatment of D-camphor with lithium acetylide–ethylenediamine complex. It was assumed that attack of the organolithium reagent had occurred from the less hindered exo face (single product by TLC, no pairing of peaks in the ^{13}C NMR spectrum). Conversion of the monosubstituted alkynes **5** to the hydroxy amides **6** was carried out by using the "one-pot" procedure involving sequential treatment with *n*-butyllithium, methyl chloroformate, and the amide anion formed by treatment of the amine with *n*-butyllithium,[15] followed by removal of the protecting group with Dowex 50W resin after a normal ether workup.

The retrosynthetic analysis presented in Scheme III shows that many analogues are accessible by using this type of synthetic strategy. The use of an acid halide or anhydride in place of the ester functionality used in this work would enable much milder conditions to be used for the coupling of the drug and the carried system. Indeed, it was shown that the hydroxy amide **6a** could also be synthesized via the mixed anhydride **11** as shown in Scheme IV. The ester **12** was saponified without hydrolysis of the amide, although as discussed earlier, the hydroxyl group should remain esterified or be reesterified with a new acyl group when the entire prodrug system is to be used in vivo.

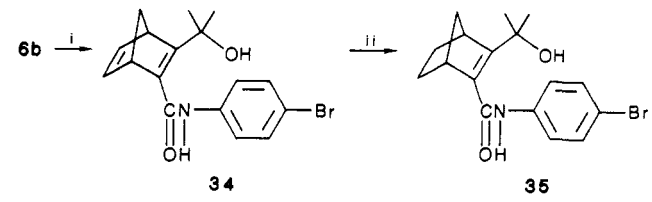
Lactones **15** and **16** were synthesized by a Diels–Alder reaction of maleic anhydride with cyclopentadiene and cyclohexadiene, respectively, followed by half-reduction

(15) Yang, K.-W.; Cannon, J. G.; Rose, J. G. *Tetrahedron Lett.* **1970**, 1791.

Scheme VI



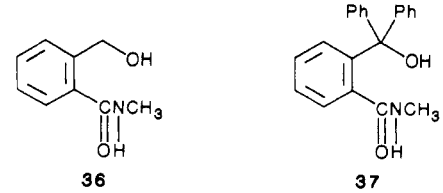
Scheme VII[a]



[a] Reagents: (i) cyclopentadiene; (ii) H_2/Lindlar.

with lithium borohydride.[16] The same procedure was used for the preparation of the dichloro lactone **13** from cyclohexadiene and dichloromaleic anhydride. The Diels–Alder adducts of maleic anhydride with the two cyclo dienes were also reacted with *n*-butyllithium to give the di-*n*-butyl-substituted lactones **17** and **18**, and **19** was prepared by catalytic hydrogenation of **16**. The lactones **15–19** were all treated with the amide anion of *p*-bromoaniline to give the corresponding amides as shown in Scheme V.

Lactone **16** and phthalide were also treated with amide anions derived from a series of substituted anilines as shown in Scheme VI. Bicycloheptadiene **35** was synthesized by a Diels–Alder reaction of **6b** with cyclopentadiene followed by catalytic hydrogenation with a Lindlar catalyst as shown in Scheme VII. *N*-Methyl-2-(hydroxymethyl)benzamide (**36**)[17] and *N*-methyl-2-(diphenylhydroxymethyl)benzamide (**37**)[18] were prepared by established procedures.



Results and Discussion

This initial study was confined to prodrug models with amide linkages, i.e. drugs attached through a primary or secondary amino group, since these are much less reactive

(16) Narasimhan, S. *Heterocycles* **1982**, *18*(special issue), 131.
(17) Katenda, H.; Theilacker, W. *Justus Liebigs Ann. Chem.* **1953**, *584*, 87.
(18) Puterbaugh, W. H.; Hauser, C. R. *J. Org. Chem.* **1964**, *29*, 853.

Table I.[a] **Rate Constants for Amide Cyclization**

compd	10^4k_o, s^{-1}	$t_{1/2}$, min	$10^2k_{cat.}$, l s^{-1} mol^{-1}
14	13.4	8.62	38.2
7d	5.12	22.6	4.15
7f	4.95	23.3	1.44
7b[b]	1.02	113	3.84
22	0.360	321	0.66
20[b]	0.318	363	0.49
24[c]	0.062	1860	0.13
7a	0.025	4620	0.11
21	0.018	6120	0.03
26	0.013	8890	0.01

[a] Reactions carried out in 10% ethanolic pH 10 borate buffer at 37 °C. [b] 1.7% ethanol. [c] 20% propan-1-ol.

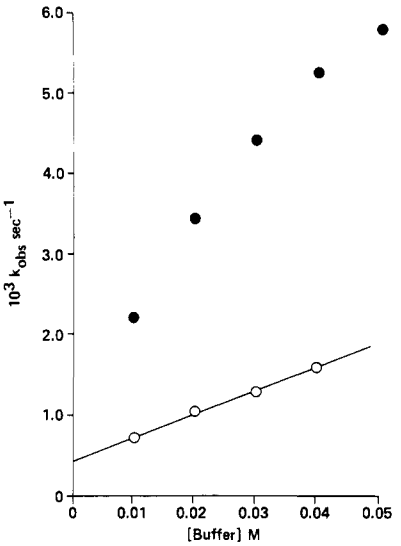


Figure 1. The dependence of k_{obsd} upon the concentration of tris (○) and phosphate (●) buffers for the cyclization of **14** at 37 °C.

than esters and thioesters, etc., and amines are poorly catered for by existing prodrug approaches. To allow direct comparisons to be made between various carrier systems, most of the amides were synthesized from the same amine, *p*-bromoaniline, which we believed would be toward the slowest end of the reactivity range.

The derived rate constants for the cyclization of these hydroxy amides are presented in Table I. Observed rate constant measurements were obtained in borax buffered solutions (buffer concentration 0.0125–0.0025 M) at pH 10.0 and ionic strength of 1.0 M (adjusted with KCl). The experimental procedures are described in more detail in the Experimental Section. In all cases the observed pseudo-first-order rate constants (k_{obsd}) increased linearly with increasing buffer concentration, and k_o represents the intercept and $k_{cat.}$ the gradient of these lines. Varying amounts of cosolvent were added to the buffer solutions to prevent precipitation.

The extrapolations of k_{obsd} to zero buffer concentration were made over a relatively narrow range of buffer concentration and although linear in this range, may not give reliable values of k_o. Indeed, we have observed distinct curvature of these plots in certain buffer systems as exemplified by Figure 1. This effect was also observed by Shafer and co-workers[19] in the cyclization of 2-(hydroxymethyl)benzamides and explained in terms of a change in the rate-determining step with buffer concentration (see later). Nevertheless, we feel that the derived rate constants

Table II.[a] **Rate Constants for Amide Cyclization**

compd	10^4k_o, s^{-1}	$t_{1/2}$, min	$10^2k_{cat.}$, l s^{-1} mol^{-1}
7c	1.60	72.2	2.56
7e	2.40	48.1	
36	0.90	128	0.54
37[b]	48.5	2.38	24.4

[a] Reactions carried out in 10% ethanolic pH 10 borate buffer at 37 °C. [b] 25% ethanol.

Table III.[a] **Rate Constants for Amide Cyclization**

compd	10^5k_o, s^{-1}	$10^3k_{cat.}$, l s^{-1} mol^{-1}
22	3.60	6.50
25	4.00	4.80
26	3.30	3.30
27	3.50	4.00
28	3.40	7.90
29	0.13	1.22
30	0.28	1.12
31	0.30	1.00
32	0.24	1.02
33	0.13	1.34

[a] Reactions carried out in pH 10 borate buffer at 37 °C; 1.7% ethanol added for **29–33** and 10% ethanol for **22** and **25–28**.

reported in Table I give a sufficiently good indication of the relative reactivity of the carrier systems for the purpose in hand.

Rate constants for the cyclization of amides derived from *N*-methylaniline and methylamine under identical conditions with those used for the *p*-bromoanilides are given in Table II. While the tertiary amides **7c** and **7e** react at a similar rate to their secondary analogues **7b** and **7f**, the *N*-methyl amide **36** is considerably more reactive than the *N*-aryl analogue **29** (Table III) (but see ref 3 for other aliphatic amides related to **36**). Unfortunately, the procedure used for the synthesis of **37** could not be modified for use with *p*-bromoaniline. Although amide **37** cyclizes much faster than any of the other hydroxy amides used in this paper, compounds of this type would be unsuitable for use as prodrugs. In addition to the high molecular weight and lipophilicity of the system, esters of the sterically hindered hydroxyl group would be extremely resistant to enzymatic hydrolysis. Thus amides of the type **7b** represent a compromise between the rate of cyclization and the accessibility of the hydroxyl group for enzymatic deprotection.

In order to achieve a sufficient rate of drug release, suitable carrier systems must be found that have EM's of many powers of 10, and it can be seen from the rate constants in Table I that only the first four carrier systems are likely to give sufficient rates of drug release in vivo. Although many enones are known to be toxic, probably through Michael addition of body nucleophiles, the lactone produced from the cyclization of amide **7b** has been identified as a trace constituent of beer,[20] so it may not cause this type of problem. The parent prodrugs are likely to be very poor Michael acceptors due to severe twisting of the conjugated systems.

The halogenated bicyclooctene **14**, although exhibiting greater reactivity, is less attractive as it is likely to have increased reactivity toward external nucleophiles, which could result in premature drug liberation. There is also no obvious synthetic route that would allow incorporation of the drug moiety under mild conditions in the latter stages of the synthesis, the water solubility is low, and

(19) Chiong, K. N. G.; Lewis, S. D.; Shafer, J. A. *J. Am. Chem. Soc.* **1975**, *97*, 418.

(20) Haley, J.; Peppard, T. L. *J. Inst. Brew.* **1983**, *89*, 87. Biot. J. M.; Verzele, M. *Bull. Soc. Chim. Belg.* **1977**, *86*, 41. Tressl, R.; Friese, L.; Fendesack, F.; Koeppler, H. *J. Agric. Food Chem.* **1978**, *26*, 1422.

Table IV.[a] Rate Constants for Amide Cyclization

compd	$10^5 k_o$, s^{-1}	$10^4 k_{cat.}$, $l\ s^{-1}\ mol^{-1}$
22	4.47	4.36
25	2.18	2.46
26	1.41	1.84
27	1.66	1.59
28	7.10	6.42

[a] Reactions carried out in 1.7% ethanolic pH 8 phosphate buffer at 37 °C.

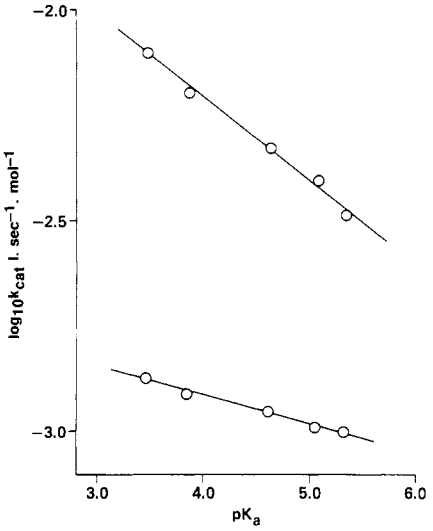


Figure 2. The dependence of $k_{cat.}$ upon the pK_a of the leaving group for the cyclization of amides **22** and **25–28** (top set) and **29–33** (bottom set) in pH 10 borate buffer at 37 °C.

certain halogenated bicyclooctanes are known to be very toxic.[21]

The nonlinearity of some of the observed rate constant extrapolations to zero buffer concentration, combined with the problems of estimating the effectiveness of buffer catalysis in body fluids[22] and the effects of tissue binding, makes it very difficult to estimate rates of drug release in vivo. It is therefore necessary to carry out biological investigations before a valid assessment of this approach to prodrug design can be made. However, the established synthetic routes could provide many analogues of **7b** and **7d** if the biological results are encouraging.

If there is a problem due to premature hydrolysis when prodrugs of the type **7** are linked through very reactive groups such as phenolic esters, it may be necessary to synthesize the prodrug by a Diels–Alder reaction as shown in Scheme III. The presence of an aromatic ring in **8b** will eliminate any tendency to Michael additon of body nucleophiles, and a substituent at R^4 will afford the carbonyl group extra protection against intermolecular hydrolysis. It might also be possible to introduce an R^3 substituent, which should give even greater EM values due to a trialkyl-locked configuration.

In a study of the cyclization of *endo*-6-hydroxybicyclo[2.2.1]heptane-*endo*-2-carboxamides, Morris and Page[23] have varied the amine leaving group and obtained β_{lg} values for the general and specific base-catalyzed reactions. We have attempted structure–reactivity correlations for analogues of **22** and **29** derived from a consistent series of 3- and 4-substituted anilines as shown in Tables III and IV.

(21) Yates, K., personal communication.

(22) An estimate of buffer catalysis in vivo may be obtained with use of the following data: extracellular HCO_3^- (25 mM); intracellular HCO_3^- (10 mM); intracellular sulfate and phosphate esters (150 mM). *The Pharmacological Basis of Therapeutics*; Goodman, L. S., Gilman, A., Eds.; MacMillan: London, 1970.

(23) Morris, J. J.; Page, M. I. *J. Chem. Soc., Perkin Trans. 2* **1980**, 679, 685.

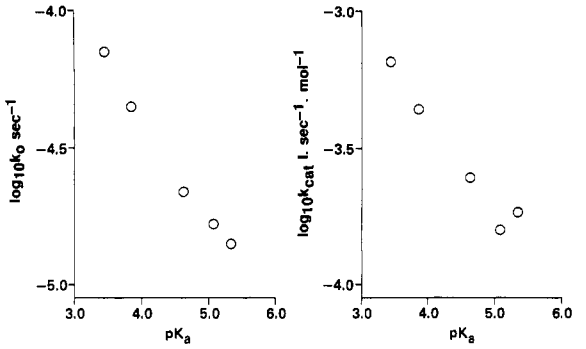


Figure 3. The dependence of k_o and $k_{cat.}$ upon the pK_a of the leaving group for the cyclization of amides **22** and **25–28** in pH 8 phosphate buffer at 37 °C.

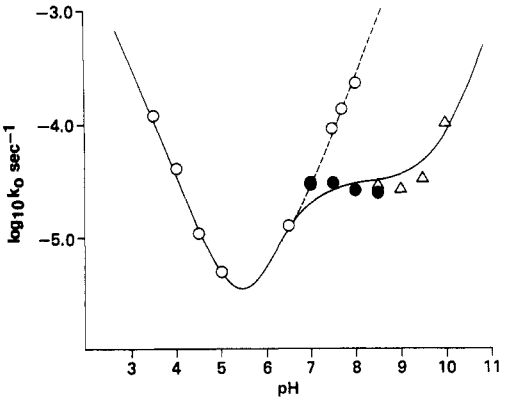


Figure 4. The dependence of k_o upon pH for the cyclization of **7b** in borate (△), tris (●), and acetate and phosphate (○) buffers at 37 °C, with 10% ethanol as cosolvent. The solid line corresponds to eq i where $a = 0.33\ s^{-1}$; $b = 1.0 \times 10^{-6}\ s^{-1}$; $c = 2.9 \times 10^{-5}$

$$k_o = a[H^+] + b + cK([H^+] + K) + dK_w/[H^+] \quad \text{(i)}$$

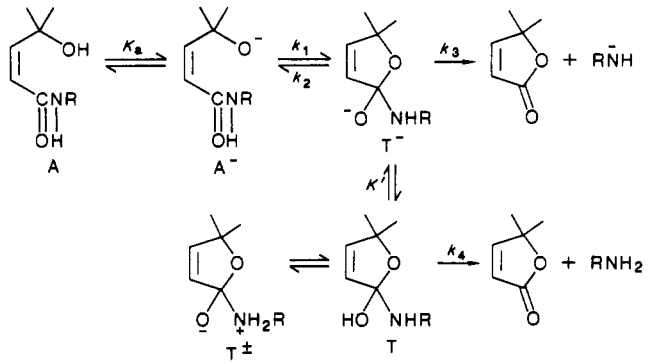
s^{-1}, $K = 1.6 \times 10^{-7}$; $dK_w = 5 \times 10^{-15}\ s^{-1}$. The dashed line corresponds to eq ii where $fK_w = 2.6 \times 10^{-12}\ s^{-1}$.

$$k_o = b + fK_w/[H^+] \quad \text{(ii)}$$

With both the bicyclooctyl and aromatic series, the k_o values obtained from experiments in borate buffer at pH 10 (Table III) show no systematic variation with leaving group pK_a, whereas $k_{cat.}$ values give good linear correlations, with β_{lg} values of -0.19 ± 0.009 and -0.068 ± 0.007, respectively (Figure 2). In phosphate buffer at pH 8, the same series of substituted bicyclooctenes exhibits different behavior. k_o and $k_{cat.}$ rate constants both give negative correlations with leaving group pK_a, with β_{lg} values of -0.37 ± 0.02 and -0.31 ± 0.04, respectively, as shown in Figure 3. Both plots appear to show a degree of curvature, and it is possible that this reflects the mechanistic change that is known to occur in this pH range (see later). Unfortunately, it is evident that these correlations are only possible for closely related compounds, since the rate constants obtained for the corresponding 2-(hydroxymethyl)benzamide derived from methylamine (**36**) in borate buffer (Table IV) are clearly inconsistent with the series of anilines. It is therefore unlikely that rates of drug liberation could be predicted on the basis of pK_a alone.

A pH profile (log k_o vs pH) for the buffer-catalyzed cyclization of enamide **7b** is shown in Figure 4. Although with this compound, the observed pseudo-first-order rate constant increases linearly with buffer concentration in all buffers used, there is an obvious anomaly in the pH range 7–8. The k_o values obtained in phosphate and tris buffers are consistent with a change in the rate-determining step with buffer species. This change in mechanism can be

Scheme VIII



explained by the fact that phosphate buffer can catalyze steps that are not rate determining in this pH range (breakdown of the tetrahedral intermediate) more efficiently than it catalyzes the slower formation of the tetrahedral intermediate (Scheme VIII). As a result, although the k_{obsd} extrapolations are linear in the range of buffer concentration used, if the buffer were diluted further, a negative deviation would occur to give a k_o value equal to that observed in tris buffer. This is the effect observed by Shafer and co-workers[19] and explained by Cunningham and Schmir.[24]

Thus for the pH range 6–10, Scheme VIII applies and we can define:

$$[T_{tot}] = [T^-] + [T] \quad (1)$$

and

$$[A_{tot}] = [A^-] + [A] \quad (2)$$

Assuming that [T] and [T⁻] interconvert rapidly enough to be treated as a single steady state intermediate, the following rate equations can be derived:

$$\frac{d[products]}{dt} = k_4[T] + k_3[T^-] \quad (3)$$

$$= [T_{tot}]\left(\frac{k_4[H^+] + k_3K'}{[H^+] + K'}\right)$$

$$\text{rate} = k_{obsd}[A_{tot}]$$

$$= k_{obsd}\left(\frac{[H^+] + K_a}{K_a}\right)\left(\frac{k_4[H^+] + (k_2 + k_3)K'}{[H^+] + K'}\right)\frac{[T_{tot}]}{k_1} \quad (4)$$

By assuming that $k_2 \gg k_3$ and that K_a is never reached (ie $K_a < [H^+]$), we can equate eq 3 and 4 and express in terms of k_{obsd}

$$k_{obsd} = \frac{k_1K_a}{[H^+]}\left(\frac{k_4[H^+] + k_3K'}{k_4[H^+] + k_2K'}\right) \quad (5)$$

At the low end of the pH 6–10 range, $k_4[H^+]$ is greater than k_3K' and k_2K' and

$$k_{obsd} = \frac{k_1K_a}{[H^+]} \quad (6)$$

The formation of [T⁻] is followed by essentially instant protonation to give [T] and rapid collapse of this intermediate via k_4. The formation of [T⁻] is therefore the rate-determining step at low pH. However, at high pH the reverse condition applies and

$$k_{obsd} = \frac{k_1k_3K_a}{k_2[H^+]} \quad (7)$$

There is virtually no protonation of [T⁻], and since k_2 is much greater than k_3, the reaction rate is attenuated to give a parallel line of lower value at any given pH.

In the pH region close to neutrality there will be a point at which k_2K' is greater than $k_4[H^+]$, but k_3K' is less than $k_4[H^+]$. Under these circumstances

$$k_{obsd} = \frac{k_1k_4K_a}{k_2K'} \quad (8)$$

The increasing concentration of [A⁻] as the pH rises is now offset by a decreasing proportion of [T] as a fraction of $[T_{tot}]$. Since [T] is in pH-independent equilibrium with [T±], whose lifetime may be little greater than that of a molecular vibration,[25] this formally neutral species is in practice intrinsically more reactive than [T⁻], the route through which does not immediately become dominant as in eq 7.

Although buffers can catalyze both formation and breakdown of the tetrahedral intermediate, they will tend to catalyze the breakdown steps k_3 and k_4 more efficiently than the formation step k_1, since the latter is intramolecular and approximation provides a sufficient driving force. Acceleration of step k_4 is particularly favored by bifunctional catalysts such as hydrogen phosphates and bicarbonate since intramolecular proton transfers without change in pK_a can transform [T] into the very reactive [T±].[24]

The buffer species also affects the dependence of rate constant on ionic strength. In tris and borate buffers (pH

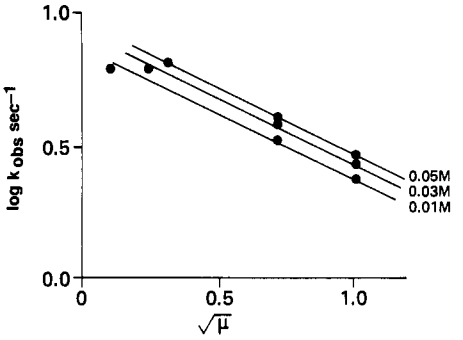


Figure 5. The dependence of k_{obsd} on the ionic strength (μ) for the cyclization of **7b** in 1.7% ethanolic phosphate buffer (pH 8.0) at 37 °C.

Table V.[a] Deuterium Isotope Effects

	buffer		
	0.01 M phosphate (pH 12.0)	0.01 M borate (pH 9.30)	0.05 M phosphate (pH 6.85)
$10^4k_{obsd}^{H_2O}$, s⁻¹	65.0	2.64	0.28[b]
$10^4k_{obsd}^{D_2O}$, s⁻¹	37.6	2.14	0.13[b]
$10^4k_{corr}^{H_2O}$, s⁻¹	11.0	3.75	0.71
$k_{corr}^{H_2O}/k_{corr}^{D_2O}$	2.90	1.75	5.55

[a] Rate constants for the cyclization of **7b** in 1.7% ethanolic buffer at 37 °C (μ uncorrected). Values of $k_{corr}^{H_2O}$ are estimated from plots of $k_{obsd} \rightarrow$ pH at the appropriate buffer concentration, using the equation pD = pH + 0.4 and the observed rate constants used to construct Figure 4 (in all three buffer systems, the k_{obsd} values lie on these plots). [b] Corrected for ionic strength.

(24) Cunningham, B. A.; Schmir, G. L. *J. Am. Chem. Soc.* **1967**, *89*, 917.

(25) Jencks, W. P. *Acc. Chem. Res.* **1980**, *13*, 161.

7–10), the observed rate constant is independent of ionic strength, while in phosphate buffer at pH 8 there is a marked decrease in k_{obsd} as ionic strength increases, as shown for the cyclization of enamide **7b** in Figure 5.

Solvent deuterium isotope effects for the same enamide in borate (pH 9.3) and phosphate buffers (pH 6.85 and 12.0) are given in Table V. The observed rate constants are corrected by using the equation pH = pD + 0.4, and an additional ionic strength correction is applied to those measured in the phosphate buffer at pH 6.85. The interpretation of deuterium isotope effects in complex, buffered reactions is not well understood[26] and depends on many factors such as the effect of solvent on the ionization of tetrahedral intermediates. We therefore offer no explanation, at present, for the data in Table V.

It is possible that the kinetic data presented in this paper could be more satisfactorily interpreted in terms of rate-limiting, diffusion-controlled proton transfer processes as proposed by Jencks and Yang in the aminolysis of methyl formate with aniline,[27] and we keep this in mind for future work.

Conclusions

We have demonstrated the principle of a novel drug delivery system based on masked lactones. The best overall model amide prodrugs studied, **7b** and **7d**, have cyclization rates that are likely to be adequate for therapeutic use. It is not possible to estimate accurately the rates of reaction in vivo, in view of the large number of buffer species in body fluids and the potentially large effects due to tissue binding; however, liberation half-lives in the region of 1 h seem possible. Prodrugs in which the drug is linked through an ester or thioester group should be much more reactive than the amide models used in this paper.

Experimental Section

Kinetic Measurements. Buffer solutions were prepared according to tables in the Rubber Handbook[28] and adjusted to μ = 1.0 M with potassium chloride. A trace of dilute hydrochloric acid or dilute sodium hydroxide solution was added, if necessary, to adjust the pH to within ±0.03 of the value reported. Dilution of the buffers and addition of alcoholic cosolvents did not result in a pH change of more than ±0.02.

pH measurements were made at 37 °C using Pye-Unicam Model 290 and Radiometer Model M26 pH meters calibrated at 37 °C with phthalate and borax standard solutions. The pH was occasionally measured at the end of kinetic runs and had never changed by more than 0.02 pH units. Solutions of substrates were prepared in 95% ethanol and stored at −10 °C. Fresh solutions of the more reactive hydroxy amides were prepared if significant reaction had occurred, as judged by UV spectroscopy. The disappearance of amide was followed spectrophotometrically with a Pye-Unicam Model PU8800 spectrometer. Constant temperature (±0.1 °C) was maintained by circulating water from a Pye-Unicam Model 3750K temperature controller through thermospacers surrounding the cell compartment.

Reactions were initiated by adding 50 μL of 5.0×10^{-3} M substrate solution to 3.0 mL of buffer solution, preincubated at the reaction temperature. The resulting solutions were normally 1.7% (v/v) ethanol and 8.3×10^{-5} M in substrate. With less soluble substrates, an appropriate amount of ethanol or propan-1-ol was added to the aqueous buffer solutions before thermal equilibration, and in all cases, the amount of aqueous buffer was reduced accordingly to give a total volume of 3.0mL before addition of the substrate.

Pseudo-first-order rate constants were calculated from linear plots of $-\ln(A - A^{\infty})$ vs t where A and A^{∞} represent the absorbance at time t and the final absorbance, respectively, or by the Guggenheim method for slower reactions. The slopes and intercepts of all linear relationships were determined by using least-squares analyses.

Overlaid wavelength scans were recorded for all reactions in order to ascertain the position of optimum absorbance change and to establish the presence of sharp isosbestic points. Under the conditions used, the hydrolysis of phthalide that resulted from cyclization of the *N*-substituted 2-(hydroxymethyl)benzamides was always much slower than the lactonization. However, the rate of reaction of these compounds was monitored at wavelengths at, or close to, the isosbestic point for the hydrolysis of phthalide (258.6 nm). All other reactions were monitored at wavelengths at which the corresponding lactone, and product of its hydrolysis, had no absorption.

Materials. ^{1}H NMR spectra were recorded on JEOL PMX 60 or JEOL FX 100 spectrometers, and ^{13}C NMR spectra were recorded on a JEOL FX 100 instrument. IR spectra were obtained on a Perkin-Elmer 297 spectrophotometer and mass spectra on a Kratos MS 25 (low resolution) instrument. Petroleum ether is the fraction bp 40–60 °C. Ether refers to diethyl ether. The latter and THF were dried by distillation from calcium hydride. Column chromatography was performed with silica gel 60 (Merck 7734). Melting points are uncorrected.

Inorganic reagents and tris(hydroxymethyl)methylamine (tris) were of AnalaR grade and were used without further purification. All buffer solutions were prepared with freshly distilled and deionized water. Deuterium oxide (99.5 atom% D) was purchased from Fluorochem.

Phthalide was obtained from Aldrich and was used without purification. *N*-Methyl-2-(hydroxymethyl)benzamide was prepared by using the method of Thielacker and Kalender: mp 123–124 °C (lit.[17] mp 122–123 °C). *N*-Methyl-2-(diphenylhydroxymethyl)benzamide was prepared by orthometalation of *N*-methylbenzamide and subsequent condensation with benzophenone according to the method of Puterbaugh and Hauser: mp 159–163 °C dec (lit.[18] mp 161–164 °C dec).

***exo*-2-Ethynyl-*endo*-2-hydroxycamphor (4d).**[29] A solution of D-camphor (8.00 g, 0.052 mol) in dry THF (25 mL) was added to a stirred suspension of lithium acetylide–ethylene diamine complex (5.52 g, 0.06 mol) in THF (30 mL). The mixture was left at room temperature overnight, refluxed for 5 h, and then partitioned between water and ethyl acetate. The aqueous layer was separated and extracted with two further portions of ethyl acetate, and the combined organic layers were washed with water and dried ($MgSO_4$). Removal of the solvent in vacuo followed by column chromatography (petroleum ether–ether, 20:1) gave the alcohol **4d** (4.20 g, 45%) as a white, waxy solid: mp 61–62 °C; IR (Nujol) 3620, 3370 (br), and 3320 cm^{-1}; NMR ($CDCl_3$) δ 2.45–1.15 (9 H, m), 1.05 (3 H, s), 0.95 (3 H, s), and 0.85 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 88.1 (s), 77.8 (s), 71.5 (d), 53.4 (s), 48.1 (t), 47.9 (s), 45.3 (d), 32.3 (t), 26.8 (t), 21.3 (q), 21.0 (q), and 10.2 (q). Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.50; H, 10.25.

***N*-(4-Bromophenyl)-4-hydroxybut-2-ynamide (6a).** A solution of *n*-butyllithium in hexane (12.90 mL, 0.02 mol) was added over a period of 5 min to a stirred solution of 3-(tetrahydropyran-2-yloxy)propyne[30] in dry THF (10 mL) at 0 °C. The mixture was warmed to room temperature over a period of 1 h and then added dropwise to a stirred solution of methyl chloroformate (1.55 mL, 0.02 mol) in THF (10 mL). After a further 45 min, the resulting mixture was added to a stirred solution of 4-bromoaniline (3.44 g, 0.02 mol) in THF (10 mL), which had previously been treated with a solution of *n*-butyllithium in hexane (12.90 mL, 0.02 mol). After a further 1 h, the mixture was partitioned between water and ethyl acetate, and the aqueous layer was removed and extracted with two more portions of ethyl acetate. The combined organic phases were washed with 5% sulfuric acid solution and water and then dried ($MgSO_4$). After

(26) Stewart, R. *The Proton: Application to Organic Chemistry*; Academic: London, 1985.
(27) Jencks, W. P.; Yang, C. C., personal communication.
(28) *Handbook of Chemistry and Physics 58th Edition*; Weast, R. C., Ed.; CRC: Boca Raton, FL, 1978.
(29) The spectroscopic data suggest that only one diastereomer was formed, and it is assumed that attack of the organolithium reagent occurred from the leass hindered *exo* face.
(30) Earl, R. A.; Townsend, L. B. *Org. Synth.* **1981**, *60*, 81.

removal of the solvent in vacuo, the residual oil was dissolved in methanol (200 mL) together with Dowex 50W resin (Fluka) (5.0 g) and then left at room temperature for 3 h. The mixture was then filtered, and the filtrate was concentrated in vacuo. Column chromatography (dichloromethane–ethyl acetate, 3:2) gave the title compound **6a** (2.08 g, 41%) as a pale yellow, crystalline solid: mp 156–157.5 °C; IR (Nujol) 1640, 1607, 1550, and 1490 cm^{-1}; NMR (CD_3OD) δ 7.45 (4 H, s), 4.75 (OH and NH), and 4.35 (2 H, s). Anal. Calcd for $C_{10}H_8NO_2Br$: C, 47.27; H, 3.17; N, 5.51. Found: C, 47.42; H, 2.98; N, 5.28.

***N*-(4-Bromophenyl)-4-hydroxy-4-methylpent-2-ynamide (6b).** By use of the procedure described above for the synthesis of amide **6a**, 3-(tetrahydropyran-2-yloxy)-3-methylbut-1-yne[31] (3.36 g, 0.02 mol) gave the title compound **6b** (2.56 g, 45%) as a pale yellow oil, which crystallized after several days: mp 125–127 °C; IR (Nujol) 2220, 1650, 1640, 1602, and 1537 cm^{-1}; NMR ($CDCl_3$) δ 8.55 (1 H, br s), 7.35 (4 H, s), 1.55 (6 H, s) and 1.50 (1 H, s); ^{13}C NMR ($CDCl_3/CD_3OD$) δ 151.4 (s), 136.9 (s), 131.9 (d), 121.8 (d), 117.4 (s), 91.5 (s), 76.3 (s), 64.5 (s), and 30.4 (q). Anal. Calcd for $C_{12}H_{12}NO_2Br$: C, 51.09; H, 4.29; N, 4.96. Found: C, 51.15; H, 4.24; N, 4.70.

***N*-Methyl-*N*-phenyl-4-hydroxy-4-methylpent-2-ynamide (6c).** By use of the procedure described above for the synthesis of amide **6a**, 3-(tetrahydropyran-2-yloxy)-3-methylbut-1-yne[31] (3.36 g, 0.02 mol) gave the title compound **6c** (1.69 g, 39%) as a pale yellow oil: IR (thin film) 2230, 1630, 1596, and 1498 cm^{-1}; NMR ($CDCl_3$) δ 7.50–7.05 (5 H, m), 3.45 (1 H, s), 3.35 (3 H, s), and 1.25 (6 H, s); ^{13}C NMR ($CDCl_3$) δ 154.1 (s), 142.9 (s), 129.0 (d), 127.8 (d), 127.1 (d), 96.8 (s), 75.1 (s), 64.2 (s), 36.2 (q), and 30.2 (q). Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.59; H, 6.92; N, 6.50.

***N*-(4-Bromophenyl)-4-cyclohexyl-4-hydroxybut-2-ynamide (6d).** Via the procedure described above for the synthesis of amide **6a**, 3-(tetrahydropyran-2-yloxy)-3-cyclohexanylprop-1-yne[31] (4.36 g, 0.02 mol) gave the title compound **6d** (2.93 g, 44%) as a white crystalline solid after recrystallization from carbon tetrachloride: mp 125–126 °C; IR (Nujol) 2240, 1645, 1605, 1597, and 1544 cm^{-1}; NMR ($CDCl_3$) δ 8.45 (1 H, br s), 7.40 (4 H, s), 3.55 (1 H, br s), and 2.20–1.15 (10 H, m). Anal. Calcd for $C_{15}H_{16}NO_2Br$: C, 55.92; H, 5.00; N, 4.35. Found: C, 55.72; H, 4.83; N, 4.20.

***N*-Methyl-*N*-phenyl-*exo*-4-camphyl-4-hydroxybut-2-ynamide (6e).** By use of the procedure described above for the synthesis of amide **6a**, *exo*-2-ethynyl-*endo*-2-(tetrahydropyran-2-yloxy)camphor[31] (1.35 g, 5.17 mmol) gave, after column chromatography (petroleum ether–ether, 10:1 → 5:1), the title compound **6e** (467 mg, 29%) as a white crystalline solid: mp 121–123 °C; IR (Nujol) 3445, 2215, 1640, and 1597 cm^{-1}; NMR ($CDCl_3$) δ 7.50–7.15 (5 H, m), 3.35 (3 H, s), and 2.25–0.55 (17 H, m). Anal. Calcd for $C_{20}H_{25}NO_2$: C, 77.40; H, 8.09; N, 4.50. Found: C, 76.81; H, 8.20; N, 4.30.

***N*-(4-Bromophenyl)-*exo*-4-camphyl-4-hydroxybut-2-ynamide (6f).** Via the procedure described above for the synthesis of amide **6a**, *exo*-2-ethynyl-*endo*-2-(tetrahydropyran-2-yloxy)-camphor[31] (0.48 g, 1.83 mmol) gave, after column chromatography (petroleum ether–ether, 10:1 → 5:1), the title compound **6f** (105 mg, 15%) as a white crystalline solid: mp 131–133 °C; IR (Nujol) 2220, 1650, and 1600 cm^{-1}; NMR ($CDCl_3$) δ 8.05 (1 H, br s), 7.40 (4 H, s), and 2.80–0.80 (17 H, m); *m/z* 375 and 377 (M^+).

Amide 6a from 12. A solution of the ester **12** (300 mg, 1.01 mol) in ethanol (10 mL) and 0.1 M sodium hydroxide solution (25 mL) was stirred at room temperature for 90 min. The bulk of the ethanol was removed in vacuo, and the residual aqueous mixture was extracted with three portions of ethyl acetate. The combined extracts were washed with water, dried ($MgSO_4$), and concentrated in vacuo to give the alkyne **12** (243 mg, 95%), which was identical in every respect with the sample obtained from **5b**.

***N*-(4-Bromophenyl)-4-hydroxybut-2(*Z*)-enamide (7a).** Lindlar catalyst (25 mg) was added to a solution of alkyne **6a** (243 mg, 0.96 mmol) in ethanol (30 mL), and the mixture was stirred vigorously under an atmosphere of hydrogen. When TLC analysis showed that no alkyne remained, the catalyst was removed by filtration through Celite, and the filtrate was concentrated in vacuo. Column chromatography (ethyl acetate–dichloromethane, 1:1) gave the alkene **7a** (176 mg, 73%) as a white crystalline solid: mp 159–160 °C; IR (Nujol) 1660, 1634, 1600, and 1547 cm^{-1}; NMR (CD_3OD) δ 7.55–7.35 (4 H, m), 6.30 (1 H, dt, *J* = 7.2 and 3.0 Hz), 6.00 (1 H, dt, *J* = 7.2 and 1.2 Hz), 5.00 (OH and NH) and 4.68 (2 H, dd, *J* = 3.0 and 1.2 Hz). Anal. Calcd for $C_{10}H_{10}NO_2Br$: C, 46.90; H, 3.94; N, 5.47. Found: C, 47.02; H, 3.79; N, 5.35.

***N*-(4-Bromophenyl)-4-hydroxy-4-methylpent-2(*Z*)-enamide (7b).** Via the procedure described above, the alkyne **6b** (100 mg, 0.36 mmol) gave, after recrystallization from ether, the alkene **7b** (88 mg, 89%) as a white crystalline solid: mp 140–141 °C; IR (Nujol) 1655, 1630, 1598, and 1540 cm^{-1}; NMR (CD_3OD) δ 7.50 (2 H, d, *J* = 9.5 Hz), 7.35 (2 H, d, *J* = 9.5 Hz), 6.35 (1 H, d, *J* = 13.0 Hz), 5.85 (1 H, d, *J* = 13.0 Hz), 4.65 (OH and NH) and 1.40 (6 H, s). Anal. Calcd for $C_{12}H_{14}NO_2Br$: C, 50.72; H, 4.97; N, 4.93. Found: C, 50.89; H, 4.85; N, 4.74.

***N*-Methyl-*N*-phenyl-4-hydroxy-4-methylpent-2(*Z*)-enamide (7c).** By use of the procedure described above, the alkyne **6c** (100 mg, 0.39 mmol) gave, after recrystallization from ether, the alkene **7c** (90 mg, 91%) as a white crystalline solid: mp 43.5–45 °C; IR (Nujol) 1645, 1620, and 1597 cm^{-1}; NMR ($CDCl_3$) δ 7.55–7.00 (5 H, m), 6.70 (1 H, br s), 6.00 (1 H, d, *J* = 13.0 Hz), 5.40 (1 H, d, *J* = 13.0 Hz), 3.35 (3 H, s), and 1.40 (6 H, s); ^{13}C NMR ($CDCl_3$) δ 167.2 (s), 153.5 (d), 143.3 (s), 129.6 (d), 127.9 (d), 126.7 (d), 118.8 (d), 69.9 (s), 37.5 (q), and 29.9 (q). Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39 Found: C, 71.22; H, 7.66; N, 6.26.

***N*-(4-Bromophenyl)-4-cyclohexyl-4-hydroxybut-2(*Z*)-enamide (7d).** By use of the procedure described above, the alkyne **6d** (500 mg, 1.55 mmol) gave, after column chromatography (ethyl acetate–dichloromethane, 1:6) and recrystallization from carbon tetrachloride, the alkene **7d** (397 mg, 79%) as a white crystalline solid: mp 146–148 °C; IR (Nujol) 1655, 1619, 1593, and 1529 cm^{-1}; NMR ($CDCl_3$) δ 8.75 (1 H, br s), 7.40 (4 H, m), 6.50 (1 H, br s), 6.35 (1 H, d, *J* = 13.5 Hz), 5.90 (1 H, d, *J* = 13.5 Hz), and 2.00–1.25 (10 H, m); ^{13}C NMR ($CDCl_3/CD_3OD$)[32] δ 166.1 (s), 154.6 (d), 137.4 (s), 132.0 (d), 122.2 (d), 117.5 (s), 71.6 (s), 37.9 (t), 25.6 (t), and 22.3 (t). Anal. Calcd for $C_{15}H_{18}NO_2Br$: C, 55.57; H, 5.60; N, 4.32. Found: C, 55.74; H, 5.46; N, 4.29.

***N*-Methyl-*N*-phenyl-*exo*-4-camphyl-4-hydroxybut-2-(*Z*)-enamide (7e).** By use of the procedure described above, the alkyne **6e** (50 mg, 0.16 mmol) gave, after column chromatography (petroleum ether–ether, 10:1 → 5:1), the alkene **7e** (36 mg, 72%) as a white semisolid: IR (thin film) 1640, 1622, and 1598 cm^{-1}; NMR ($CDCl_3$) δ 7.50–7.00 (5 H, m), 6.45 (1 H, br s), 6.05 (1 H, d, *J* = 13.0 Hz), 5.50 (1 H, d, *J* = 13.0 Hz) 3.30 (3 H, s), and 2.40–0.80 (17 H, m); ^{13}C NMR ($CDCl_3$) δ 167.6 (s), 153.6 (d), 143.6 (s), 129.6 (d), 127.7 (d), 126.9 (d), 119.9 (d), 81.2 (s), 55.0 (s), 49.1 (s), 48.0 (t), 45.6 (d), 37.6 (q), 31.2 (t), 27.1 (t), 21.2 (q), 20.7 (q), and 11.0 (q); *m/z* 313 (M^+), 298 ($M^+ - CH_3$), and 295 ($M^+ - H_2O$).

***N*-(4-Bromophenyl)-*exo*-4-camphyl-4-hydroxybut-2(*Z*)-enamide (7f).** Via the procedure described above, the alkyne **6f** (50 mg, 0.13 mmol) gave, after column chromatography (petroleum ether–ether, 10:1 → 5:1), the alkene **7f** (36 mg, 71%) as a colorless semisolid: IR (thin film) 1645, 1597, 1527, and 1488 cm^{-1}; NMR ($CDCl_3$) δ 8.00 (1 H, br s), 7.60–7.15 (4 H, m), 6.35 (1 H, d, *J* = 13.0 Hz), 5.80 (1 H, d, *J* = 13.0 Hz), and 2.50–0.80 (17 H, m); *m/z* 379 and 377 (M^+).

***N*-(4-Bromphenyl)-4-acetoxybut-2-ynamide (12).** *n*-Butyllithium (23.0 mL, 35.7 mmol) was added to a stirred solution of diisopropylamine (3.61 g, 35.7 mmol) in THF (25 mL) at 0 °C. After 15 min, a solution of alkyne **5a**[30] (5.00 g, 35.7 mmol) in THF (10 mL) was added and stirring was continued for 2 h at 0 °C. The mixture was then poured onto dry ice (100 g) and, after the carbon dioxide had vaporized, was partitioned between dichloromethane and dilute sodium hydroxide solution. The aqueous layer was removed, washed with two further portions of dichloromethane, and then carefully neutralized with dilute sulfuric acid solution. The solution was immediately extracted with three portions of dichloromethane and dried ($MgSO_4$), and the solvent was removed in vacuo to give a colorless oil. The tetrahydropyranyl protecting group was removed by treatment with a suspension of Dowex 50W resin in methanol, as described earlier, to give a white crystalline solid (2.65 g), which was dissolved

(31) Prepared by using the procedure described in ref 30. The camphor analogue was used as a diastereomeric mixture.

(32) Two of the olefinic resonances are coincident.

in acetyl chloride (25 mL). After the mixture was heated under gentle reflux for 3 h, the unreacted acetyl chloride was removed in vacuo, and the residue was then dissolved in toluene (50 mL). A solution of *p*-bromoaniline (4.56 g, 26.5 mmol) was added, and after 30 min the resulting precipitate was collected by filtration. Column chromatography (dichloromethane) gave the title compound **12** (2.91 g, 28%) as a white crystalline solid, mp 175–177 °C; IR (Nujol) 3315, 2245, 1748, 1657, 1606, and 1549 cm^{-1}; NMR ($CDCl_3$) δ 7.95 (1 H, br s) and 2.10 (3 H, s). Anal. Calcd for $C_{12}H_{10}NO_3Br$: C, 48.67; H, 3.40; N, 4.73. Found: C, 48.61; H, 3.69; N, 4.74.

***exo,exo*-2,3-Dichloro-*endo*-3-(hydroxymethyl)bicyclo[2.2.2]oct-5-ene-*endo*-2-carboxylic Acid Lactone (13).** A solution of *exo,exo*-2,3-dichlorobicyclo[2.2.2]oct-5-ene-*endo,endo*-2,3-dicarboxylic acid anhydride[33] (2.08 g, 8.42 mmol) in dry THF (25 mL) was treated with 2.0 M lithium borohydride in THF (2.5 mL, 5.0 mmol) at room temperature. The solution was stirred for 1 h and treated with 5% sulfuric acid solution (30 mL). When the effervescence had ceased, the mixture was heated on a steam bath for 30 min, cooled to room temperature, and extracted with three portions of ethyl acetate. The combined extracts were washed with water and dried ($MgSO_4$). Removal of the solvent in vacuo followed by column filtration (petroleum ether–ether, 2:1) and then recrystallization from petroleum ether/ether gave the lactone **13** (1.29 g, 66%) as a white crystalline solid: mp 228–230 °C; IR (Nujol) 1778 cm^{-1}; NMR ($CDCl_3$) δ 6.40 (1 H, dd, J = 3.5 and 8.5 Hz), 6.25 (1 H, dd, J = 3.5 and 8.5 Hz), 4.55 (1 H, d, J = 12.0 Hz), 4.25 (1 H, d, J = 12.0 Hz), 3.30–2.80 (2 H, m), 2.40–1.95 (2 H, m), and 1.55–1.15 (2 H, m). Anal. Calcd for $C_{10}H_{10}Cl_2O_2$: C, 51.53; H, 4.32; Cl, 30.42. Found: C, 51.40; H, 4.19; Cl, 30.64.

***N*-(4-Bromophenyl)-*exo,exo*-2,3-dichloro-*endo*-3-(hydroxymethyl)bicyclo[2.2.2]oct-5-ene-*endo*-2-carboxamide (14).** By use of the general procedure described for the synthesis of the unsaturated analogue **22**, the lactone **13** (700 mg, 3.0 mmol) and *p*-bromoaniline (860 mg, 5.0 mmol) gave, after recrystallization from carbon tetrachloride, the amide **14** (172 mg, 14%) as a white crystalline solid, mp 139–140 °C; IR (Nujol) 3455, 1672, 1590, 1523, and 1512 cm^{-1}; NMR ($CDCl_3$) δ 7.40 (4 H, s), 6.55 (1 H, m), 6.15 (1 H, m), 3.90 (OH and NH), 3.75 (2 H, s), 3.20–2.85 (2 H, m), 2.50–2.10 (2 H, m), and 1.45–1.10 (2 H, m). Anal. Calcd for $C_{16}H_{16}NO_2Cl_2Br$: C, 47.44; H, 3.98; N, 3.46. Found: C, 47.09; H, 3.78; N, 3.32.

***endo*-3-(Hydroxymethyl)bicyclo[2.2.2]oct-5-ene-*endo*-2-carboxylic Acid Lactone (16).** A solution of bicyclo[2.2.2]-oct-5-ene-*endo,endo*-2,3-dicarboxylic acid anhydride (0.66 g, 3.7 mmol) in dry THF (5 mL) was treated with 2.0 M lithium borohydride in THF (1.0 mL, 2.0 mmol) at room temperature. The solution was stirred for 1 h and then treated with 5% sulfuric acid solution (15 mL). When the effervescence had ceased, the mixture was heated on a steam bath for 20 min, cooled to room temperature, and extracted with three portions of ethyl acetate. The combined extracts were washed with water and dried ($MgSO_4$). Removal of the solvent in vacuo followed by column chromatography (petroleum ether–ether, 6:1) gave the lactone **16** (0.39 g, 64%) as a white crystalline solid: mp 74–77 °C; IR (Nujol) 3040 and 1760 cm^{-1}; NMR ($CDCl_3$) δ 6.40–6.05 (2 H, m), 4.45–4.10 (1 H, m), 3.90–3.65 (1 H, m), 3.20–2.50 (4 H, m), and 1.65–1.10 (4 H, m). Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37. Found: C, 73.17; H, 7.40.

***endo*-3-(Di-*n*-butylhydroxymethyl)bicyclo[2.2.1]hept-5-ene-*endo*-2-carboxylic Acid Lactone (17).** A solution of *n*-butyllithium in hexane (25.8 mL, 0.04 mol) was added dropwise to a solution of bicyclo[2.2.1]hept-5-ene-*endo,endo*-2,3-dicarboxylic acid anhydride (3.28 g, 0.02 mol) in dry THF (50 mL) at −78 °C. The mixture was allowed to warm to room temperature over a period of 1 h and was then partitioned between water and ether. The aqueous phase was separated, acidified with 5% sulfuric acid solution, and extracted with three portions of ether. The combined extracts were washed with water and dried ($MgSO_4$). Removal of the solvent in vacuo followed by column chromatography (petroleum ether–ether, 6:1) gave the lactone **17** (2.72 g, 52%) as a colorless oil: IR (thin film) 3070 and 1765 cm^{-1}; NMR ($CDCl_3$) δ 6.30–6.05 (2 H, m), 3.40 (1 H, dd, J = 9.5 and 5.0 Hz), 3.30–2.95 (2 H, m), 2.75 (1 H, dd, J = 9.5 and 5.0 Hz), and 1.80–0.95 (20 H, m). Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.82; H, 9.99. Found: C, 77.70; H, 10.18.

***endo*-3-(Di-*n*-butylhydroxymethyl)bicyclo[2.2.2]oct-5-ene-*endo*-2-carboxylic Acid Lactone (18).** Via the procedure described above for the synthesis of the bicycloheptyl analogue **17**, bicyclo[2.2.2]oct-5-ene-*endo,endo*-2,3-dicarboxylic acid anhydride (0.89 g, 5.0 mmol) and *n*-butyllithium in hexane (6.70 mL, 10.0 mmol) gave the title compound **18** (0.58 g, 42%) as a colorless oil: IR (thin film) 3045 and 1762 cm^{-1}; NMR ($CDCl_3$) δ 7.35–6.00 (2 H, m), 3.20–2.55 (3 H, m), 2.45–2.25 (1 H, dd, J = 10.5 and 2.5 Hz) and 1.90–0.75 (22 H, m). Anal. Calcd for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21. Found: C, 77.79; H, 10.15.

***endo*-3-(Hydroxymethyl)bicyclo[2.2.2]octane-*endo*-2-carboxylic Acid Lactone (19).** The unsaturated lactone **16** (0.35 g, 2.13 mmol) and 5% palladium on charcoal (10 mg) were dissolved in ethanol (10 mL). The mixture was stirred vigorously in an atmosphere of hydrogen until no starting material was detected by TLC analysis and then filtered through a Celite pade. Removal of the solvent in vacuo gave a white solid, which was recrystallized from carbon tetrachloride to give the title compound **19** (0.33 g, 96%) as a white crystalline solid: mp 139–140 °C; IR (Nujol) 1762 cm^{-1}; NMR ($CDCl_3$) δ 4.60–4.10 (2 H, m), 2.85–2.45 (2 H, m), and 2.20–1.20 (10 H, m). Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 71.98; H, 8.65.

***endo*-3-(Hydroxymethyl)bicyclo[2.2.2]octane-*endo*-2-*N*-(4-bromophenyl)carboxamide (20).** Via the general procedure described for the synthesis of the 5,6-dehydro analogue **22**, the lactone **19** (285 mg, 1.7 mmol) gave the title compound (**20**) (161 mg, 28%) as a white crystalline solid, mp 174–176 °C; IR (Nujol) 1660, 1590, and 1537 cm^{-1}; NMR ($CDCl_3/CD_3OD$) δ 7.35 (4 H, s), 4.00 (1 H, dd, J = 9.5 and 13.0 Hz), 3.65 (1 H, dd, J = 7.0 and 13.0 Hz), 2.30 (OH and NH), and 2.85–1.20 (12 H, m). Anal. Calcd for $C_{16}H_{20}NO_2Br$: C, 56.82; H, 5.96; N, 4.14. Found: C, 56.63; H, 5.84; N, 4.03.

***N*-(4-Bromophenyl)-*endo*-3-(hydroxymethyl)bicyclo[2.2.1]hept-5-ene-*endo*-2-carboxamide (21).** By use of the general procedure described for the synthesis of the bicyclooctyl analogue **22**, *endo*-3-(hydroxymethyl)bicyclo[2.2.1]hept-5-ene-*endo*-2-carboxylic acid lactone[34] (250 mg, 1.67 mmol) was reacted with the amide anion derived from *p*-bromoaniline (430 mg, 2.5 mmol) and *n*-butyllithium (1.67 mL, 2.5 mmol) to give the *N*-(4-bromophenyl) amide **21** (118 mg, 22%) as a white crystalline solid: mp 158–159 °C; IR (Nujol) 1660, 1606, 1596, and 1540 cm^{-1}; NMR ($CDCl_3$) δ 8.30 (1 H, br s), 7.32 (4 H, s), 6.40–5.95 (2 H, m), 3.90–2.45 (7 H, m), and 1.65–1.20 (2 H, m). Anal. Calcd for $C_{15}H_{16}NO_2Br$: C, 55.92; H, 4.88; N, 4.35. Found: C, 55.80; H, 4.88; N, 4.21.

***N*-(4-Bromophenyl)-*endo*-3-(di-*n*-butylhydroxymethyl)-bicyclo[2.2.1]hept-5-ene-*endo*-2-carboxamide (23).** By use of the procedure described for the synthesis of the unsubstituted analogue **21**, the lactone **17** (655 mg, 2.5 mmol) gave the title compound **23** (630 mg, 58%) as a white crystalline solid: mp 189–190 °C; IR (Nujol) 1648, 1590, and 1533 cm^{-1}; NMR ($CDCl_3/CD_3OD$) δ 7.35 (4 H, s), 6.35 (1 H, dd, J = 5.5 and 2.5 Hz), 5.85 (1 H, dd, J = 5.5 and 2.0 Hz), 3.75 (OH and NH), 3.50–2.90 (3 H, m), 2.70–2.35 (1 H, m), and 1.60–0.75 (20 H, m). Anal. Calcd for $C_{23}H_{32}NO_2Br$: C, 63.59; H, 7.42; N, 3.22. Found: C, 63.50; H, 7.19; N, 3.19.

***N*-(4-Bromophenyl)-*endo*-3-(di-*n*-butylhydroxymethyl)-bicyclo[2.2.2]oct-5-ene-*endo*-2-carboxamide (24).** Via the general procedure described for the synthesis of the analogue **21**, the lactone **18** (0.5 g, 1.81 mmol) gave the title compound **24** (388 mg, 48%) as a white crystalline solid: mp 167–169 °C; IR (Nujol) 1652, 1592, and 1530 cm^{-1}; NMR ($CDCl_3/CD_3OD$) δ 7.35 (4 H, s), 6.45 (1 H, dd, J = 9.5 and 9.0 Hz), 6.05 (1 H, dd, J = 9.5 and 8.5 Hz), 3.70 (OH and NH), 3.05–2.60 (3 H, m), 2.15–2.00 (1 H, dd, J = 10.5 and 1.0 Hz), and 1.75–0.75 (22 H, m). Anal. Calcd for $C_{24}H_{34}NO_2Br$: C, 64.28; H, 7.64; N, 3.12. Found: C, 64.10; H, 7.53; N, 2.97.

***endo*-3-(Hydroxymethyl)bicyclo[2.2.2]oct-5-ene-*endo*-2-*N*-carboxamides.** *n*-Butyllithium in hexane (1.67 mL, 2.5 mmol)

(33) Nelsen, S. F.; Travecedo, E. F.; Seppanen, E. D. *J. Am. Chem. Soc.* **1971**, *93*, 2913.

(34) Kato, M.; Kageyama, M.; Yoshikoshi, A. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1305.

was added slowly to a stirred solution of the aniline (2.5 mmol) in dry THF (5 mL) at 0 °C. The mixture was allowed to warm to room temperature, and after 30 min, a solution of the lactone **16** (250 mg, 1.52 mmol) in THF (3 mL) was added in one portion. After a further 3 h at room temperature, the mixture was partitioned between ethyl acetate and water. The organic phase was separated, washed rapidly with water, and dried ($MgSO_4$). Removal of the solvent in vacuo followed by trituration of the residue with carbon tetrachloride (5 mL) gave a solid product, which was isolated by filtration. The solid was washed with a small volume of carbon tetrachloride and then recrystallized from the same solvent.

Physical Data. *N*-(4-Bromophenyl) amide (22) (0.21 g, 25%) as a white crystalline solid: mp 154–155 °C; IR (Nujol) 1660, 1590, 1535, and 1490 cm^{-1}; NMR ($CDCl_3/CD_3OD$) δ 7.45 (2 H, d, J = 4.5 Hz), 7.35 (2 H, d, J = 4.5 Hz), 4.40 (OH and NH), 3.40 (2 H, d, J = 6.0 Hz), 2.95–2.10 (4 H, m), and 1.75–1.10 (4 H, m). Anal. Calcd for $C_{16}H_{18}NO_2Br$: C, 57.16; H, 5.40; N, 4.17. Found: C, 56.77; H, 5.45; N, 3.93.

***N*-Phenyl amide (25)** (0.15 g, 23%) as a white crystalline solid: mp 178–179 °C; IR (Nujol) 1660, 1600, and 1542 cm^{-1}; NMR ($CDCl_3/CD_3OD$) δ 7.50–6.95 (5 H, m), 6.45–6.10 (2 H, m), 3.90 (OH and NH), 3.45 (2 H, d, J = 7.0 Hz), 2.95–2.05 (4 H, m), and 1.75–1.15 (4 H, m). Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.31; H, 7.61; N, 5.36.

***N*-(4-Methoxyphenyl) amide (26)** (0.12 g, 17%) as a white crystalline solid: mp 153–154 °C; IR (Nujol) 1650, 1603, 1549, and 1515 cm^{-1}; NMR ($CDCl_3/CD_3OD$) δ 7.30 (2 H, d, J = 8.5 Hz), 6.75 (2 H, d, J = 8.5 Hz), 6.45–6.10 (2 H, m), 3.70 (3 H, s), 3.45 (2 H, d, J = 7.5 Hz) 3.15 (OH and NH), 2.95–2.10 (4 H, m), and 1.75–1.25 (4 H, m). Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.06; H, 7.37; N, 4.87. Found: C, 70.87; H, 7.55; N, 4.78.

***N*-(4-Methylphenyl) amide (27)** (0.13 g, 20%) as a white crystalline solid: mp 148–150 °C; IR (Nujol) 1658, 1606, 1545, and 1515 cm^{-1}; NMR ($CDCl_3/CD_3OD$) δ 7.35 (2 H, d, J = 9.5 Hz), 7.05 (2 H, d, J = 9.5 Hz), 6.50–6.10 (2 H, m), 4.35 (OH and NH), 3.45 (2 H, d, J = 7.0 Hz), 3.00–2.10 (4 H, m), 2.25 (3 H, s), and 1.75–1.20 (4 H, m). Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.25; H, 7.80; N, 5.16. Found: C, 75.10; H, 7.80; N, 5.09.

***N*-(3-Chlorophenyl) amide (28)** (0.22 g, 31%) as a pale yellow solid: mp 167–169 °C; IR (Nujol) 1678, 1600, and 1538 cm^{-1}; NMR ($CDCl_3/CD_3OD$) δ 7.60–6.85 (4 H, m), 6.45–6.05 (2 H, m), 4.10 (OH and NH), 3.39 (2 H, d, J = 7.0 Hz), 2.90–2.05 (4 H, m), and 1.75–1.15 (4 H, m). Anal. Calcd for $C_{16}H_{18}NO_2Cl$: C, 65.86; H, 6.22; N, 4.80. Found: C, 65.72; H, 6.18; N, 4.70.

***N*-Substituted 2-(Hydroxymethyl)benzamides.** *n*-Butyllithium in hexane (6.45 mL, 0.01 mol) was added slowly to a stirred solution of the aniline (0.01 mol) in dry THF (10 mL) at 0 °C. The mixture was allowed to warm to room temperature, and after 30 min a solution of phthalide (1.34 g, 0.01 mol) in THF (5 mL) was added in one portion. After a further 1 h at room temperature, the mixture was partitioned between ethyl acetate and water. The organic phase was separated, washed rapidly with water, and dried ($MgSO_4$). Removal of the solvent in vacuo followed by trituration of the residue with carbon tetrachloride (10 mL) gave a solid product, which was isolated by filtration. The solid was washed with a small volume of carbon tetrachloride and then recrystallized from the same solvent.

Physical Data. *N*-(4-Bromophenyl) amide (29) (0.76 g, 25%) as a white crystalline solid: mp 154–155 °C; IR (Nujol) 1655, 1600, and 1514 cm^{-1}; NMR ($CDCl_3$) δ 8.70 (1 H, br s), 7.80–7.20 (8 H, m), 4.65 (2 H, d, J = 6.0 Hz), and 3.65 (1 H, t, J = 6.0 Hz). Anal. Calcd for $C_{14}H_{12}NO_2Br$: C, 54.93; H, 3.95; N, 4.57. Found: C, 54.89; H, 3.93; N, 4.42.

***N*-Phenyl amide (30)** (0.61 g, 27%) as a white crystalline solid: mp 134–135.5 °C; IR (Nujol) 1645, 1600, and 1535 cm^{-1}; NMR ($CDCl_3$) δ 8.65 (1 H, br s), 7.75–7.00 (9 H, m), 4.65 (2 H, d, J = 6.0 Hz), and 3.95 (1 H, t, J = 6.0 Hz). Anal. Calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 73.99; H, 5.77; N, 6.03.

***N*-(4-Methoxyphenyl) amide (31)** (0.46 g, 18%) as a pale purple, crystalline solid: mp 150–151 °C; IR (Nujol) 1645, 1600, 1530, and 1515 cm^{-1}; NMR ($CDCl_3$) δ 8.35 (1 H, br s), 7.80–6.80 (8 H, m), 4.60 (2 H, d, J = 6.0 Hz), 4.00 (1 H, t, J = 6.0 Hz), and 3.80 (3 H, s). Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 69.93; H, 5.96; N, 5.40.

***N*-(4-Methylphenyl) amide (32)** (0.53 g, 22%) as a white crystalline solid: mp 155–156 °C; IR (Nujol) 1650, 1600, 1540, and 1515 cm^{-1}; NMR ($CDCl_3/CD_3OD$) δ 7.70–7.00 (8 H, m), 4.60 (2 H, s), 2.70 (OH and NH), and 2.30 (3 H, s). Anal. Calcd for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27; N, 5.80. Found: C, 74.49; H, 6.27; N, 5.78.

***N*-(3-Chlorophenyl) amide (33)** (0.57 g, 22%) as a white crystalline solid: mp 145–146 °C; IR (Nujol) 1650, 1600, and 1545 cm^{-1}; NMR ($CDCl_3/CD_3OD$) δ 7.85–6.95 (8 H, m), 4.65 (2 H, s), and 3.75 (OH and NH). Anal. Calcd for $C_{14}H_{12}NO_2Cl$: C, 64.25; H, 4.62; N, 5.35. Found: C, 63.95; H, 4.31; N, 5.25.

***N*-(4-Bromophenyl)-3-(dimethylhydroxymethyl)bicyclo-[2.2.1]hepta-2,5-diene-2-carboxamide (34).** A solution of alkene **6b** (900 mg, 3.19 mmol) and freshly distilled cyclopentadiene (2.00 g, 30 mmol) in toluene (20 mL) was heated under reflux for 8 h, cooled to room temperature, and concentrated in vacuo. Column chromatography (dichloromethane–ethyl acetate, 20:1) gave the title compound **34** (520 mg, 47%) as a colorless oil: IR (thin film) 1664, 1616, 1587, 1559, and 1522 cm^{-1}; NMR ($CDCl_3$) δ 9.70 (1 H, br s), 7.55–7.20 (4 H, m), 7.00–6.65 (2 H, m), 6.40 (1 H, s), 4.10–3.90 (1 H, m), 2.15–1.75 (2 H, m), 1.55 (3 H, s), and 1.30 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 172.7 (s), 164.6 (s), 143.1 (d), 141.2 (s), 140.9 (d), 137.1 (s), 131.6 (d), 122.0 (d), 116.7 (s), 72.4 (s), 70.0 (t), 55.9 (d), 52.8 (d), 29.7 (q), and 27.3 (q); m/z 349 + 347 (M^+), 334 + 332 ($M^+ - CH_3$), and 331 + 329 ($M^+ - H_2O$). Anal. Calcd for $C_{17}H_{18}NO_2Br$: C, 58.63; H, 5.21; N, 4.02. Found: C, 58.51; H, 5.21; N, 4.09.

***N*-(4-Bromophenyl)-3-(dimethylhydroxymethyl)bicyclo-[2.2.1]hept-2-ene-2-carboxamide (35).** Lindlar catalyst (30 mg) was added to a solution of bicycloheptadiene **34** (150 mg, 0.43 mmol) in ethanol (20 mL), and the mixture was stirred vigorously under an atmosphere of hydrogen. When TLC analysis showed that no starting material remained (ca. 2 h), the catalyst was removed by filtration through Celite, and the filtrate was concentrated in vacuo. Column chromatography (ethyl acetate–dichloromethane, 1:1) gave the title compound **35** (143 mg, 95%) as a colorless oil: IR (thin film) 1665, 1615, 1560, and 1529 cm^{-1}; NMR ($CDCl_3$) δ 9.00 (1 H, br s), 7.50–7.20 (4 H, m), 6.45 (1 H, s), 3.35–3.10 (1 H, m), 3.10–2.85 (1 H, m), and 1.95–0.95 (8 H, m); m/z 351 + 349 (M^+). Anal. Calcd for $C_{17}H_{20}NO_2Br$: C, 58.30; H, 5.75; N, 4.00. Found: C, 58.02; H, 5.80; N, 3.91.

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Registry No. 4d, 22387-58-2; **5a**, 6089-04-9; **5b**, 27943-46-0; **5c**, 42969-66-4; **5d**, 116076-34-7; **6a**, 116053-13-5; **6b**, 116053-14-6; **6c**, 116053-15-7; **6d**, 116053-16-8; **6e**, 116053-17-9; **6f**, 116053-18-0; **7a**, 116053-19-1; **7b**, 116053-20-4; **7c**, 116053-21-5; **7d**, 116053-22-6; **7e**, 116053-23-7; **7f**, 116053-24-8; **10**, 7218-52-2; **11**, 116052-95-0; **12**, 116052-96-1; **13**, 116052-97-2; **14**, 116052-98-3; **15**, 64550-47-6; **16**, 54595-30-1; **17**, 87603-93-8; **18**, 116052-99-4; **19**, 38335-07-8; **20**, 116053-00-0; **21**, 116053-01-1; **22**, 116053-02-2; **23**, 116053-03-3; **24**, 116053-04-4; **25**, 116053-05-5; **26**, 116053-06-6; **27**, 116053-07-7; **28**, 116053-08-8; **29**, 116053-09-9; **30**, 33966-11-9; **31**, 111383-24-5; **32**, 111383-18-7; **33**, 116053-10-2; **34**, 116053-11-3; **35**, 116053-12-4; **36**, 39976-03-9; **37**, 23659-57-6; $THPOCH_2C{\equiv}CCO_2H$, 116053-25-9; D-camphor, 464-49-3; lithium acetylide–ethylene diamine complex, 39990-99-3; 4-bromoaniline, 106-40-1; *exo,exo*-2,3-dichlorobicyclo[2.2.2]oct-5-ene-*endo,endo*-2,3-dicarboxylic acid anhydride, 33095-15-7; bicyclo[2.2.2]oct-5-ene-*endo,endo*-2,3-dicarboxylic acid anhydride, 24327-08-0; bicyclo[2.2.1]hept-5-ene-*endo,endo*-2,3-dicarboxylic acid anhydride, 129-64-6; phthalide, 87-41-2; cyclopentadiene, 542-92-7; aniline, 62-53-3; *p*-methoxyaniline, 104-94-9; *p*-toluidine, 106-49-0; *m*-chloroaniline, 108-42-9.