were dried (K_2CO_3) and evaporated. The resulting thick oil slowly crystallized in the cold to give 13.44 g (56.5%) of crude **6**. The picrate was prepared according to Pasto and Johnson,[21] mp 149–152°.

Anal. Calcd for $C_{28}H_{30}N_4O_{11}$: C, 56.18; H, 5.05; N, 9.36. Found: C, 56.13; H, 5.24; H, 9.18.

The Et_2O solution containing the neutral products was evaporated and the residual oil was triturated with hexane (20 ml). The precipitated solid was filtered and recrystallized from ether–hexane to give 3.0 g (26%) of 3,4-dimethoxyphenyltonitrile (**9**), melting point, ir, nmr, and eims identical with those of an authentic sample. The above hexane filtrate was concentrated and the residue was vacuum distilled to give two fractions as described in the text. Compounds A, B, C and D (fraction 1) were analyzed by glpc on an SE-30 (3%) column at 100° and had retention times of 2.4, 2.8, 7.0, and 4.6 min, respectively. Redistillation of fraction 2 gave pure 1-(2,5-dimethoxy-4-methylphenyl)-2-chloropropane: bp 90° (0.06 mm); nmr ($CDCl_3$) δ 1.47 (d, 3, $CHCH_3$), 2.22 (s, 3, $ArCH_3$), 3.18 (d, 2, $CHCH_2$), 3.74 (s, 3, OCH_3), 3.75 (s, 3, OCH_3), 4.35 (sextet, 1, CH_3CH), 6.68 (s, 2, aromatic H's); mass spectrum (50 eV) *m/3* (rel intensity) 230 (15), 228 (44), 165 (100), 135 (34), 119 (24).

Anal. Calcd for $C_{12}H_{17}ClO_2$: C, 62.99; H, 7.50. Found: C, 63.24; H, 7.52.

***cis*-1-(3,4-Dimethoxybenzyl)-3,7-dimethyl-5,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline (7) Hydrochloride.** Following a published procedure[22] the dihydroisoquinoline (**6**, 1.0 g, 2.7 mmol) was dissolved in EtOH (125 ml), and concentrated HCl (0.22 ml) was added, followed by 0.10 g of PtO_2. The mixture was shaken with hydrogen gas at 27 psi for 17 hr. The catalyst was filtered off and the solvent was removed at reduced pressure. The solid residue was recrystallized from EtOH–Et_2O to give a first crop, 0.76 g, and a second crop, 0.07 g. A sample from the first crop had mp 233° dec; nmr (DMSO-d_6) δ 1.48 (d, 3, $CHCH_3$), 2.30 (s, 3, $ArCH_3$), *ca.* 2.67–3.85 (m, 5, CH_3CHCH_2, $CH_3CHNCHCH_2$), 3.78 [s, 6 $(OCH_3)_2$], 3.80 [s, 6, $(OCH_3)_2$], *ca.* 4.3–4.9 (br, 1, ArCHN), 6.8–7.3 (m, 4, aromatic H's).

Anal. Calcd for $C_{22}H_{30}NO_4Cl$: C, 64.77; H, 7.41; N, 3.44. Found: C, 64.85; H, 7.37; N, 3.62.

Reduction of 6 with Sodium Borohydride. The dihydroisoquinoline **6** (1.0 g, 2.7 mmol) was dissolved in anhydrous MeOH (15 ml) and the solution was stirred under nitrogen. $NaBH_4$ (0.35 g, 7.8 mmol) dissolved in anhydrous MeOH (10 ml) was added in small portions over *ca.* 5 min to the solution of the dihydroisoquinoline. The resulting solution was stirred under a nitrogen atmosphere overnight. The solvent was then removed at water-aspirator pressure and the residual solid was treated with water (20 ml) and heated on a steam bath for 15 min. After cooling, the reaction mixture was extracted with Et_2O (4 × 10 ml) and the combined, dried (K_2CO_3) extracts were evaporated to give a yellow-brown oil. Gc–eims analysis was performed on this product as described in the text.

Acknowledgment. These studies were supported by Public Health Service Grant MH 21219.

Registry No. **1**, 15588-95-1; **4**, 93-40-3; **5**, 49558-61-4; **6**, 49558-62-5; **6** picrate, 49613-56-1; **7**, 49558-63-6; **7** hydrochloride, 49558-64-7; **8**, 49558-65-8; **10**, 49558-66-9; **11**, 49558-67-0; **12**, 49558-68-1.

References and Notes

(1) M. A. Collins, *Ann. N. Y. Acad. Sci.*, **215**, 93 (1973); M. J. Walsh, *ibid.*, **215**, 98 (1973); V. E. Davis, *ibid.*, **215**, 111 (1973); G. Cohen, *ibid.*, **215**, 116 (1973).
(2) S. B. Matin, P. S. Callery, J. S. Zweig, A. O'Brien, and N. Castagnoli, Jr., *J. Med. Chem.*, submitted; P. S. Callery and N. Castagnoli, Jr., *ibid.*, submitted
(3) W. M. Whaley and T. R. Govindachari, *Org. React.*, **6**, 151 (1951).
(4) A. Klutch and M. Bordum, *J. Med. Chem.*, **10**, 860 (1967); J. Daly, J. Axelrod, and B. Witkop, *Ann. N. Y. Acad. Sci.*, **96**, 37 (1962); J.-M. Frère, *Biochem. Pharmacol.*, **20**, 3353 (1971); C. Elison and H. W. Elliott, *Ibid.*, **12**, 1363 (1963).
(5) J. S. Zweig and N. Castagnoli, Jr., unpublished results.
(6) C. Reby and J. Gardent, *Bull. Soc. Chim, Fr.*, 1574 (1972).
(7) W. M. Whaley and T. R. Govindachari, *Org. React.*, **6**, 74 (1951).
(8) T. R. Govindachari and M. V. Lakshmikantham, *Proc. Indian Acad. Sci., Sect. A*, **46**, 406 (1957).
(9) B. Munson, *Anal. Chem.*, **43**, 28A (1971).
(10) G. Fodor, J. Gal, and B. A. Phillips, *Agnew. Chem., Int. Ed. Engl.*, **11**, 919 (1972).
(11) J. F. Bieron and F. J. Dinan, in "The Chemistry of Amides," J. Zabicky, Ed., Wiley-Interscience, New York, N. Y., 1970, p 277.
(12) A. McCoubrey and D. W. Mathieson, *J. Chem. Soc.*, 696 (1949); A. J. Hill and W. M. Holliday, Abstracts of Papers, 118th National Meeting of the American Chemical Society, Sept 1950, p 58N.
(13) W. R. Vaughan and R. D. Carlson, *J. Amer. Chem. Soc.*, **84**, 769 (1962).
(14) J. von Braun, F. Jostes, and W. Munch, *Justus Liebigs Ann. Chem.*, **453**, 113 (1927).
(15) Q. N. Porter and J. Baldas, "Mass Spectrometry of Heterocyclic Compounds," Wiley-Interscience, New York, N. Y., 1971, p 414.
(16) H. O. House, "Modern Synthetic Reactions," 2nd ed, W. A. Benjamin, Menlo Park, Calif., 1972, p 19.
(17) G. R. Clemo and J. H. Turnbull, *J. Chem. Soc.*, 701 (1946).
(18) S. F. Dyke, R. G. Kinsman, J. Knabe, and H. D. Holtje, *Tetrahedron*, **27**, 6181 (1971).
(19) D. M. Bailey and C. G. DeGrazia, *J. Med. Chem.*, **16**, 151 (1973).
(20) A. T. Shulgin, U. S. Patent 3,547,999 (Dec 15, 1970).
(21) D. J. Pasto and C. R. Johnson, "Organic Structure Determination," Prentice-Hall, Englewood Cliffs, N. J., 1969, p 424.
(22) T. R. Govindachari and K. Nagarajan, *Proc. Indian Acad. Sci., Sect. A*, **42**, 136 (1955).

The Claisen Rearrangement of *N*-Allylketene *O,N*-Acetals[1a]

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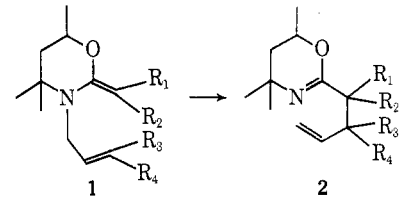
The early development of the vinyl ether–Claisen rearrangement and later modifications of this transformation in the form of the amide–Claisen of Eshenmoser and coworkers[2] and the ortho ester–Claisen of Johnson and coworkers[3] have made this rearrangement a valuable tool for the synthetic chemist. All of the above examples use one of the two required precursors to the 1,5-diene system in large excess. We wish to report a procedure which allows for the economical utilization of both precursors.

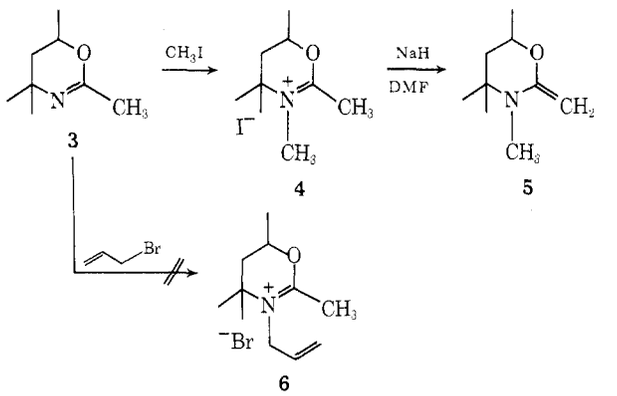
Earlier from these laboratories the ester enolate–Claisen was reported.[4] This transformation consisted of the efficient connection of an allylic alcohol and a carboxylic acid *via* ester formation. Subsequent generation and rearrangement of the derived enolate provides a useful route to γ,δ-unsaturated acids.

As a complementary procedure, we have investigated the generation of the ketene *O,N*-acetals **1** and their Claisen-type rearrangement to the dihydro-1,3-oxazines **2**.

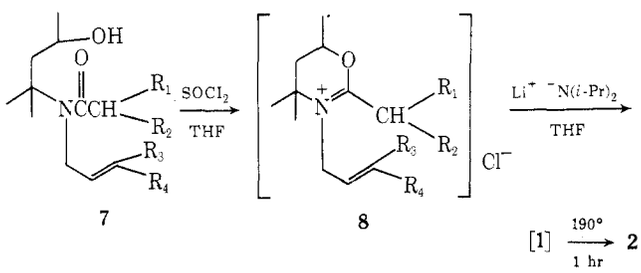


Meyers[5] has reported the preparation of a similar ketone *O,N*-acetal **5** from the dihydrooxazine **3** through alkylation with methyl iodide and then treatment with sodium hydride. Our attempts to alkylate these dihydrooxazines in excess allyl bromide or chloride, either at room temperature or reflux, were unsuccessful. The presence of hexamethylphosphoramide (HMPA), dimethylsulfoxide (DMSO), or dimethylformamide (DMF) did not improve these results. It is possible that in a less sterically congested dihydrooxazine direct alkylation would be possible.

A more circuitous route to the ketene *O,N*-acetal **1** was required. This led to the discovery that the oxazinium salts **8** were readily formed from the γ-hydroxy amides **7** by treatment with thionyl chloride in tetrahydrofuran (THF). Neutralization by lithium diisopropylamide in THF led to the ketene *O,N*-acetals **1**. The desired dihydrooxazines **2** were then obtained by heating these ketene *O,N*-acetals **1** in refluxing decalin (190°) for 1 hr.



This entire procedure could be carried out without isolation of either of the reactive intermediates, *i.e.*, the oxazinium salt 8 or the ketene *O,N*-acetal 1. The isolated yields for this transformation are shown in Table I.



The conversion of the γ-hydroxy amides 7 to the dihydroxazines 2 in a series of three steps may be performed in one flask and affords good yields of the rearranged products in the simpler cases. When there are two alkyl groups on either terminus of the 1,5-diene system, the yield is considerably diminished. For reactions leading to the dihydrooxazines **2d** and **2e** the other products were numerous and unidentified.

The required γ-hydroxy amides 7 were available from the corresponding γ-hydroxy amines 9. The yields, however, were quite low for direct acylation with acid chlorides. A procedure that incorporated the selective protection of the hydroxyl group was much more successful. Treatment of the γ-hydroxy amines 9 with chlorotrimethylsilane in methylene chloride gave the γ-trimethylsiloxy amine hydrochlorides **10.** These intermediate amines were not isolated but were treated directly in the cold with triethylamine and then the required acid chloride. Acid-catalyzed hydrolysis of the crude γ-siloxy amides 11 quickly liberated the desired γ-hydroxy amides 7. The isolated yields for these conversions are shown in Table II.

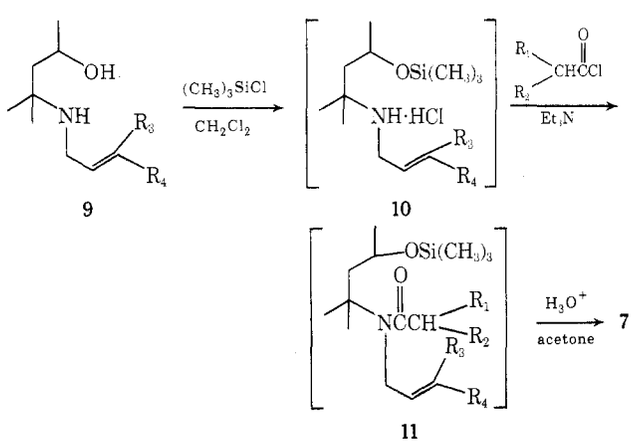
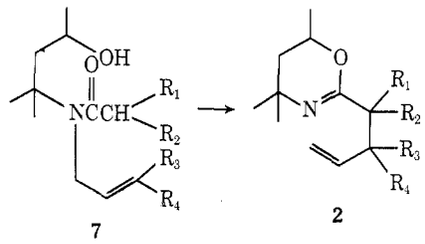
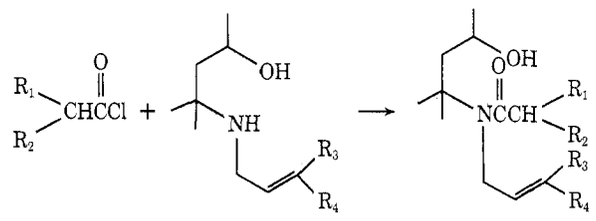


Table I
Conversion of γ-Hydroxy Amides 7 to Substituted Dihydrooxazines 2



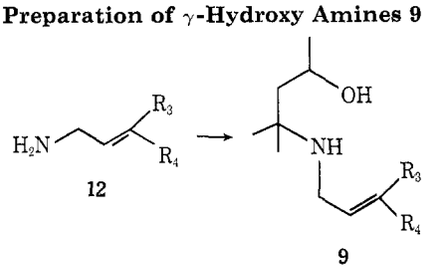
Hydroxy amide	R_1	R_2	R_3	R_4	Yield, %
7a	Ph	H	H	H	63
7b	*n*-C_4H_9	H	H	H	66
7c	*n*-C_4H_9	H	CH_3	H	60
7d	*n*-C_6H_{13}	CH_3	H	H	17
7e	*n*-C_4H_9	H	CH_3	CH_3	13

Table II
Synthesis of γ-Hydroxy Amides 7



R_1	R_2		R_3	R_4	Yield, %
Ph	H	**9a**	H	H	23
n-C_4H_9	H	**9a**	H	H	74
n-C_4H_9	H	**9b**	CH_3	H	50
n-C_6H_{13}	CH_3	**9a**	H	H	47
n-C_4H_9	H	**9c**	CH_3	CH_3	70

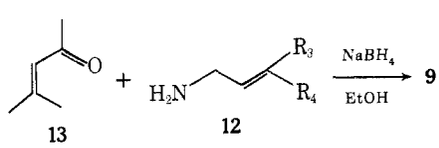
Table III
Preparation of γ-Hydroxy Amines 9



Allylamine	R_3	R_4	Yield, %[a]
12a	H	H	64
12b	CH_3	H	78
12c	CH_3	CH_3	69

[a] Yields after distillation. Distilled products contained 3–7% impurities.

The γ-hydroxy amines 9 were available by modification of a procedure due to Kohn.[6] Simple mixing of the required primary allylic amine 12 with mesityl oxide (13) in



ethanol followed, after 1 hr, by the addition of sodium borohydride gave the γ-hydroxy amines in moderate yields (Table III).

Methods are available from the work of Meyers[7] for reduction and hydrolysis of dihydro-1,3-oxazines to liberate the corresponding aldehydes. The methods presented here should be useful for the construction of dihydrooxazines (and thereby the aldehydes) such as **2** within the limitations described.

Experimental Section[8]

2-(1′-Butyl-3′-butenyl)-4,4,6-trimethyl-5,6-dihydro-1,3-oxazine (2b). To an ice-cooled solution of 169 mg (0.662 mmol) of the amide **7b** in 5 ml of THF under a static atmosphere of argon was added 52 μl (86.8 mg, 0.728 mmol) of thionyl chloride in one batch. After stirring at 0° for 10 min and at room temperature for 20 min, this mixture was cooled to −70° and treated with 4.95 ml (1.99 mmol) of a similarly cooled solution of lithium diisopropylamide in THF.[12] After 10 min the reaction mixture was allowed to warm to room temperature and 5 ml of decalin was added. After the THF and diisopropylamine were removed by distillation, the reaction mixture was heated at reflux (190°) under argon for 1 hr. After cooling to room temperature, the reaction mixture was taken up in 100 ml of ether and filtered through a Celite pad. The ether was removed under reduced pressure, and the residue was chromatographed on 20 g of silica gel. Elution with 100 ml of petroleum ether removed the decalin; the product was then eluted with 100 ml of ether. Careful rechromatography of this material on 20 g of silica gel with 100 ml of 20% ether-petroleum ether gave 97 mg (66%) of a colorless oil. An analytical sample was prepared by evaporative distillation (90°, 10 mm): ir ($CHCl_3$) 1660 (C=N), 1385, 1370, 1265, 1190, 1055, 923 cm^{-1}; nmr ($CDCl_3$) δ 1.17 (s, 6, C-4 CH_3's), 1.26 (d, 3, J = 6 Hz, C-6 CH_3), 2.23 (m, 2, allylic CH_2), 4.1 (m, 1, C-6 H), 5.0 (m, 2, $=CH_2$), 5.7 (m, 1, vinylic H).

Anal. Calcd for $C_{15}H_{27}NO$: C, 75.90; H, 11.46; N, 5.90. Found: C, 75.79; H, 11.41; N, 5.92.

2-(1′-Phenyl-3′-butenyl)-4,4,6-trimethyl-5,6-dihydro-1,3-oxazine (2a). In a manner analogous to that described for dihydrooxazine **2b,** 1.0 g (3.64 mmol) of the amide **7a** in 20 ml of THF was treated with 285 μl (475 mg, 4.00 mmol) of thionyl chloride and then 5.1 ml (10.92 mmol) of a solution of lithium diisopropylamide in THF. Reflux was maintained for 1 hr in 15 ml of decalin. Isolation of the product was carried out by chromatography on 100 g of silica gel. Elution with 200 ml of petroleum ether removed the decalin; the product was then eluted with 250 ml of ether and amounted to 586 mg (63%) of a colorless oil. An analytical sample was prepared by evaporative distillation (60°, 1 mm): ir ($CHCl_3$) 1660 (C=N), 1601 (aromatic C=C), 1265, 1185, 920 cm^{-1}; nmr ($CDCl_3$) δ 1.18 (s, 6, C-4 CH_3's), 2.6 (m, 2, allylic CH_2), 3.45 (t, 1, J = 7 Hz, benzylic H), 3.89 (m, 1, C-6 H), 5.0 (m, 2, $=CH_2$), 5.7 (m, 1, vinylic H), 7.32 (br s, 5, Ph).

Anal. Calcd for $C_{17}H_{23}NO$: C, 79.33; H, 9.01; N, 5.44. Found: C, 79.24; H, 9.03; N, 5.44.

2-(1′-Butyl-2′-methyl-3′-butenyl)-4,4,6-trimethyl-5,6-dihydro-1,3-oxazine (2c). In a manner analogous to that described for dihydrooxazine **2b,** 100 mg (0.372 mmol) of the amide **7c** in 5 ml of THF was treated with 29.2 μl (48.7 mg, 0.409 mmol) of thionyl chloride and then 3.5 ml (1.12 mmol) of a solution of lithium diisopropylamide in THF. Reflux was maintained for 1 hr in 5 ml of decalin. The product was isolated by chromatography on 10 g of silica gel. Elution with 20 ml of petroleum ether removed the decalin; the product was then eluted with 50 ml of ether. Further purification by preparative thick layer chromatography on a silica gel plate (0.2 × 20 × 20 cm), developed in 50% ether-petroleum ether, gave 56 mg (60%, R_f 0.37–0.59) of the dihydrooxazine **2c** as a colorless oil. An analytical sample was prepared by evaporative distillation (45°, 0.25 mm): ir ($CHCl_3$) 1660 (C=N), 1265, 1190, 1000, 920 cm^{-1}; nmr ($CDCl_3$) δ 0.98 (d of d, 3, J = 6 Hz, $\Delta\nu$ = 2, C-2′ CH_3), 1.18 (br s, 6, C-4 CH_3's), 4.15 (m, 1, C-6 H), 4.9 (m, 2, $=CH_2$), 5.6 (m, 1, vinylic H).

Anal. Calcd for $C_{16}H_{29}NO$: C, 76.44; H, 11.63; N, 5.57. Found: C, 76.26; H, 11.62; N, 5.51.

2-(1′-Hexyl-1′-methyl-3′-butenyl)-4,4,6-trimethyl-5,6-dihydro-1,3-oxazine (2d). In a manner analogous to that described for dihydrooxazine **2b,** 187 mg (0.630 mmol) of the amide **7d** in 5 ml of THF was treated with 59.3 μl (82.5 mg, 0.693 mmol) of thionyl chloride and then 5.0 ml (1.890 mmol) of a solution of lithium diisopropylamide in THF. Reflux was maintained for 1 hr in 5 ml of decalin. The product was isolated by chromatography on 20 g of silica gel. Elution with 150 ml of petroleum ether removed the decalin. The product was then eluted with 150 ml of ether. Further purification by preparative thick layer chromatography on a silica gel plate (0.2 × 20 × 20 cm), developed in 20% ether-petroleum ether, gave 30 mg (17%, R_f 0.37–0.59) of the dihydrooxazine **2d** as a colorless oil. An analytical sample was prepared by evaporative distillation (50°, 0.075 mm): ir ($CHCl_3$) 1650 (C=N), 1180, 1125, 920 cm^{-1}; nmr ($CDCl_3$) δ 2.24 (t, 2, J = 7 Hz, allylic CH_2), 4.1 (m, 1, C-6 H), 4.95 (m, 2, $=CH_2$), 5.7 (m, 1, vinylic H).

Anal. Calcd for $C_{18}H_{33}NO$: C, 77.36; H, 11.90; N, 5.01. Found: C, 77.46; H, 11.78; N, 4.94.

2-(1′-Butyl-2′,2′-dimethyl-3′-butenyl)-4,4,6-trimethyl-5,6-dihydro-1,3-oxazine (2e). In a manner analogous to that described for dihydrooxazine **2b,** 300 mg (1.06 mmol) of the amide **7e** in 6 ml of THF was treated with 75.5 μl (126 mg, 1.17 mmol) of thionyl chloride and then 6.0 ml (3.18 mmol) of a solution of lithium diisopropylamide in THF. Reflux was maintained for 1 hr in 5 ml of decalin. The product was isolated by chromatography on 30 g of silica gel. Elution with 200 ml of petroleum ether removed the decalin; the product was then eluted with 200 ml of ether. Further purification by rechromatography on 20 g of silica gel with 100 ml of 20% ether-petroleum ether gave 37 mg (13%) of the dihydrooxazine **2e** as a colorless oil. An analytical sample was prepared by evaporative distillation (70°, 0.08 mm): ir ($CHCl_3$) 1650 (C=N), 1275, 1185, 1055, 920 cm^{-1}; nmr ($CDCl_3$) δ 1.03 (s, 6, C-2′ CH_3's), 1.18 (br s, C-4 CH_3's), 4.1 (m, 1, C-6 H), 4.9 (m, 2, $=CH_2$), 5.9 (m, 1, vinylic H).

Anal. Calcd for $C_{17}H_{31}NO$: C, 76.92; H, 11.77; N, 5.28. Found: C, 76.77; H, 11.77; N, 5.15.

***N*-Allyl-*N*-(1,1-dimethyl-3-hydroxybutyl)hexanamide (7b).** An ice-cooled solution of 2.0 g (12.7 mmol) of the γ-hydroxy amine **9a** in 100 ml of dichloromethane (reagent grade) under a static atmosphere of argon was treated with 1.16 ml (1.38 g, 12.7 mmol) of chlorotrimethylsilane over *ca.* 2 min. After the ice bath was removed, the reaction mixture was stirred at room temperature for 15 min and then cooled to −10°. To the cooled reaction mixture was added 3.94 ml (2.85 g, 28 mmol) of triethylamine in one batch, followed by 1.76 ml (1.72 g, 12.7 mmol) of hexanoyl chloride over a 5-min period. After stirring for 10 min at −10° and for 1 hr at room temperature, the reaction mixture was poured into 1 l. of 5% ether-petroleum ether and filtered to remove triethylamine hydrochloride. The solvent was removed at reduced pressure and the residual oil was taken up in 150 ml of 10% aqueous acetone. Concentrated HCl was added dropwise until the solution just tested acidic to litmus. After stirring for 0.5 hr, this mixture was treated with 15 ml of saturated $NaHCO_3$ solution and the acetone was removed at reduced pressure. The residue was taken up in 400 ml of ether, washed with two 50-ml portions of saturated $NaHCO_3$ solution, and dried ($MgSO_4$). After removal of the drying agent, evaporation of the solvent from the filtrate at reduced pressure gave 3.3 g of an oil. Chromatography of this material on 250 g of silica gel with 1 l. of 80% ether-petroleum ether and then 600 ml of ether gave 2.4 g (74%) of the γ-hydroxy amide **7b** as a colorless oil. An analytical sample was prepared by evaporative distillation (85°, 0.01 mm): ir ($CHCl_3$) 3680, 3620, and 3550–3250 (OH), 1625 (C=O), 1410, 930 cm^{-1}; nmr ($CDCl_3$) δ 1.15 (d, 3, J = 6 Hz, CH_3CO), 1.41 (s, 3, CH_3CN), 1.47 (s, 3, CH_3CN), 2.2 (m, 4, α CH_2 and C-2 H's), 3.85 (m, 1, HCO), 3.98 (m, 2, allylic CH_2), 5.2 (m, 2, $=CH_2$), 5.8 (m, 1, vinylic H).

Anal. Calcd for $C_{15}H_{29}NO_2$: C, 70.54; H, 11.45; N, 5.48. Found: C, 70.54; H, 11.50; N, 5.39.

***N*-Allyl-*N*-(1,1,-dimethyl-3-hydroxybutyl)phenylacetamide (7a).** In a manner analogous to that described for amide **7b,** a solution of 1.0 g (6.37 mmol) of the γ-hydroxy amine **9a** in 50 ml of dichloromethane was treated successively with 804 μl (688 mg, 6.37 mmol) of chlorotrimethylsilane, 1.98 ml (1.43 g, 14 mmol) of triethylamine, and 840 μl (983 mg, 6.37 mmol) of phenylacetyl chloride. Hydrolysis of the crude γ-siloxy amide was carried out in 50 ml of acidic (HCl) 20% aqueous acetone. After isolation the product was adsorbed on 140 g of silica gel and the column was then eluted successively with 200-ml portions of 60, 70, and 80% ether-petroleum ether, ether, and 5% acetone-ether. The last solvent mixture gave 412 mg (23%) of the γ-hydroxy amide **7a** as a colorless oil. An analytical sample was prepared by evaporative distillation (130°, 0.002 mm): ir ($CHCl_3$) 3670, 3620, and 3550–3250 (OH), 1635 (C=O), 1400, 930 cm^{-1}; nmr ($CDCl_3$) δ 1.13 (d, 3, J = 6 Hz, CH_3CO), 1.43 (s, 3, CH_3CN), 1.48 (s, 3, CH_3CN), 3.65 (s, 2, benzylic H), 3.98 (m, 2, allylic CH_2), 5.1 (m, 2, $=CH_2$), 5.9 (m, 1, vinylic H), 7.40 (s, 5, Ph).

Anal. Calcd for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15; N, 5.09. Found: C, 74.01; H, 8.90; N, 4.90.

***N*-(2-Butenyl)-*N*-(1,1-dimethyl-3-hydroxybutyl)hexanamide (7c).** In a manner analogous to that described for amide **7b**, a solution of 2.0 g (11.7 mmol) of the γ-hydroxy amine **9b** in 100 ml of dichloromethane was treated successively with 1.48 ml (1.26 g, 11.7 mmol) of chlorotrimethylsilane, 3.63 ml (2.62 g, 25.7 mmol) of triethylamine, and 1.62 ml (1.58 g, 11.7 mmol) of hexanoyl chloride. Hydrolysis of the crude γ-siloxy amide was carried out in 100 ml of acidic (HCl) 10% aqueous acetone. After isolation, the product was chromatographed on 250 g of silica gel. After elution with 1 l. of 80% ether–petroleum ether, continued elution with 1 l. of ether gave 1.56 g (49.5%) of the γ-hydroxy amide **7c** as a colorless oil. An analytical sample was prepared by evaporative distillation (85°, 0.005 mm): ir ($CHCl_3$) 3600–3400 (OH), 1625 (C=O), 1410, 1185, 970 cm^{-1}; nmr ($CDCl_3$) δ 1.17 (d, 3, J = 6 Hz, CH_3CO), 1.42 (s, 3, CH_3CN), 1.48 (s, 3, CH_3CN), 1.72 (d, 3, J = 5 Hz, vinyl CH_3), 3.9 (m, 2, allylic CH_2), 5.51 (m, 2, vinylic H).

Anal. Calcd for $C_{16}H_{31}NO_2$: C, 71.33; H, 11.60; N, 5.20. Found: C, 71.26; H, 11.60; N, 5.29.

***N*-Allyl-*N*-(1′,1′-dimethyl-3′-hydroxybutyl)-2-methyloctanamide (7d).** In a manner analogous to that described for amide **7b**, a solution of 894 mg (5.69 mmol) of the γ-hydroxy amine **9a** in 50 ml of dichloromethane was treated successively with 716 μl (615 mg, 5.69 mmol) of chlorotrimethylsilane, 1.77 ml (1.28 g, 12.5 mmol) of triethylamine, and 1.0 g (5.69 mmol) of 2-methyloctanoyl chloride. Hydrolysis of the crude γ-siloxy amide was carried out in 50 ml of acidic (HCl) 10% aqueous acetone. After isolation, the product was chromatographed on 150 g of silica gel. After elution with 600 ml of 80% ether–petroleum ether, continued elution with 300 ml of ether gave 798 mg (47%) of the γ-hydroxy amide **7d** as a colorless oil. An analytical sample was prepared by evaporative distillation (140°, 0.008 mm): ir ($CHCl_3$) 3670, 3620, and 3550–3250 (OH), 1625 (C=O), 1410, 1180, 990, 927 cm^{-1}; nmr ($CDCl_3$) δ 4.00 (m, 2, allylic CH_2), 5.2 (m, 2, $=CH_2$), 5.8 (m, 1, vinylic H).

Anal. Calcd for $C_{18}H_{35}NO_2$: C, 72.68; H, 11.86; N, 4.71. Found: C, 72.60; H, 11.87; N, 4.66.

***N*-(1,1-Dimethyl-3-hydroxybutyl)-*N*-(3-methyl-2-butenyl)hexanamide (7e).** In a manner analogous to that described for amide **7b**, a solution of 814 mg (4.4 mmol) of the γ-hydroxy amine **9c** in 25 ml of dichloromethane was treated successively with 554 μl (475 mg, 4.4 mmol) of chlorotrimethylsilane, 1.36 ml (986 mg, 9.68 mmol) of triethylamine, and 610 μ (594 mg, 4.4 mmol) of hexanoyl chloride. Hydrolysis of the γ-siloxy amide was carried out in 25 ml of acidic (HCl) 20% aqueous acetone. After isolation, the product was purified by high-pressure liquid chromatography on a 2.5 × 50 cm column of silica gel (mesh 10–40 μ). Elution with 600 ml of 80% ether–petroleum ether (2 ml/min) gave 878 mg (70%) of the γ-hydroxy amide **7e** as a colorless oil. An analytical sample was prepared by evaporative distillation (140°, 0.008 mm): ir ($CHCl_3$) 3670, 3620, and 3550–3250 (OH), 1625 (C=O), 1410, 1100, 1045, 915 cm^{-1}; nmr ($CDCl_3$) δ 1.15 (d, 3, J = 6 Hz, CH_3CO), 1.40 (s, 3, CH_3CN), 1.43 (s, 3, CH_3CN), 1.68 (d, 6, J = 6 Hz, vinyl CH_3's), 3.9 (m, 2, allylic CH_2), 5.1 (br t, 1, J = 5 Hz, vinylic H).

Anal. Calcd for $C_{17}H_{33}NO_2$: C, 72.04; H, 11.73; N, 4.94. Found: C, 72.21; H, 11.79; N, 5.04.

***N*-Allyl-1,1-dimethyl-3-hydroxybutylamine (9a).** A mixture of 7.25 ml (5.7 g, 0.1 mol) of allylamine and 23 ml (19.6 g, 0.2 mol) of mesityl oxide in 50 ml of ethanol was stirred at room temperature for 1.5 hr. The reaction mixture was cooled in an ice bath and 3.8 g (0.1 mol) of sodium borohydride was added over *ca.* 15 min. This mixture was stirred for 1 hr at room temperature in a water bath and then poured into 200 ml of 10% hydrochloric acid. This acidic solution was washed with three 50-ml portions of ether, which were discarded. The acidic solution was made basic by the addition of 40% aqueous sodium hydroxide solution with cooling and extracted with two 100-ml portions of ether. The combined ethereal extracts were washed with 50-ml portions of water and with saturated brine, and dried ($MgSO_4$). After filtration to remove the drying agent and then evaporation of the filtrate at reduced pressure, the crude product was purified by vacuum distillation. In this manner there was obtained 10.1 g (64%) of the amine **9a** as a colorless liquid, bp 95–99° (20 mm), which consisted of 94% of a single volatile component by glpc[8] (4% SE-30, 180°). The analytical sample was obtained from a center fraction that boiled at 98° (20 mm): nmr ($CDCl_3$) δ 1.14 (d, 3, J = 6 Hz, CH_3CO), 1.15 (s, 3, CH_3CN), 1.22 (s, 3, CH_3CN), 3.24 (d, 2, J = 5 Hz, allylic CH_2), 4.13 (m, 1, HCO), 5.2 (m, 2, $=CH_2$), 5.9 (m, 1, vinylic H).

Anal. Calcd for $C_9H_{19}NO$: C, 68.74; H, 12.18; N, 8.91. Found: C, 68.99; H, 12.52; N, 9.11.

***N*-(2-Butenyl)-1,1-dimethyl-3-hydroxybutylamine (9b).** In a manner analogous to that described above for the γ-hydroxy amine **9a**, a solution of 2.17 g (30.6 mmol) of crotylamine and 7.0 ml (6.09 g, 61.2 mmol) of mesityl oxide in 25 ml of ethanol was treated with 1.16 g (30.6 mmol) of sodium borohydride. Work-up as before gave 4.08 g (78%) of the γ-hydroxy amine **9b** as a colorless liquid, bp 110–114° (20 mm), which consisted of 95–98% of a single volatile component by glpc[8] (4% SE-30, 180°). The analytical sample was obtained from a center fraction that boiled at 114° (20 mm): nmr ($CDCl_3$) δ 1.08 (d, 3, J = 6 Hz, CH_3CO), 1.10 (s, 3, CH_3CN), 1.18 (s, 3, CH_3CN), 1.63 (d, 3, J = 4 Hz, vinyl CH_3), 3.13 (m, 2, allylic CH_2), 4.10 (m, 1, HCO), 5.54 (m, 2, vinylic H's).

Anal. Calcd for $C_{10}H_{21}NO$: C, 70.12; H, 12.36; N, 8.18. Found: C, 69.89; H, 12.35; N, 8.15.

***N*-(3-Methyl-2-butenyl)-1,1-dimethyl-3-hydroxybutylamine (9c).** In a manner analogous to that described for the γ-hydroxy amine **9a**, a solution of 700 mg (8.26 mmol) of 3-methyl-2-butenylamine and 2.07 ml (1.76 g, 18 mmol) of mesityl oxide in 10 ml of ethanol was treated with 340 mg (9.0 mmol) of sodium borohydride. Work-up as before and bulb-to-bulb distillation of the crude product (85°, 2.5 mm) gave 1.047 g (69%) of the γ-hydroxy amine **9c** which contained no more than 7% volatile impurities by glpc[8] (4% SE-30, 180°). An analytical sample was obtained by preparative gas chromatography[8] (10% Carbowax 20M, 180°) followed by evaporative distillation (100–110°, 8 mm): nmr ($CDCl_3$) δ 1.15 (s, 3, CH_3CO), 1.20 (s, 3, CH_3CO), 1.66 (d, 6, J = 3 Hz, vinyl (CH_3's), 3.14 (d, 2, allylic CH_2), 4.06 (m, 1, HCO), 5.19 (br t, 1, J = 6 Hz, vinylic H).

Anal. Calcd for $C_{11}H_{23}NO$: C, 71.30; H, 12.51; N, 7.56. Found: C, 71.26; H, 12.63; N, 7.54.

Registry No. 2a, 43152-76-7; **2b,** 43152-77-8; **2c,** 43152-78-9; **2d,** 43207-70-1; **2e,** 43152-79-0; **7a,** 43152-80-3; **7b,** 43152-81-4; **7c,** 43152-82-5; **7d,** 43152-83-6; **7e,** 43152-84-7; **9a,** 43152-85-8; **9b,** 43152-86-9; **9c,** 43152-87-0; **12a,** 107-11-9; **12b,** 21035-54-1; **12c,** 13822-06-5; hexanoyl chloride, 142-61-0; phenylacetyl chloride, 103-80-0; 2-methyloctanoyl chloride, 43152-88-1.

References and Notes

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(2) A. E. Wick, D. Felix, K. Steen, and A. Eshenmoser, *Helv. Chim. Acta*, **47**, 2425 (1964).

(3) W. S. Johnson, L.Werthemann, W. R. Bartlett, T. J. Brocksom, T.-t. Li, D. J. Faulkner, and M.R. Peterson, *J. Amer. Chem. Soc.*, **92**, 741 (1970).

(4) R. E. Ireland and R. H. Mueller, *J. Amer. Chem. Soc.*, **94**, 5897 (1972).

(5) A. I. Meyers and N. Nazarenko, *J. Amer. Chem. Soc.*, **94**, 3243 (1972).

(6) M. Kohn, *Monatsh. Chem.*, **25**, 135 (1904).

(7) A. I. Meyers, A. Nabeya, H. W. Adickes, I. R. Politzer, G. R. Malone, A. C. Kovelesky, R. L. Nolen, and R. C. Portnoy, *J. Org. Chem.*, **38**, 36 (1973).

(8) Boiling points are uncorrected. Infrared spectra (ir) were obtained using a Perkin-Elmer infrared spectrometer, Model 237B. Nuclear magnetic resonance (nmr) spectra were taken on a Varian T-60 nmr spectrometer. Gas chromatographic analyses were carried out on a Varian Aerograph, Model 912, equipped with 0.25 in. × 10 ft columns packed with the indicated liquid phase on Chromosorb Q (NAW), 60–80 mesh. The carrier gas (helium) was maintained at 60 ml/min. Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich., and Chemalytics, Inc., Tempe, Ariz. Thionyl chloride was distilled sequentially from quinoline and tri-*n*-butyl phosphite and stored up to 1 month in a desiccator. Tetrahydrofuran (THF) was distilled from lithium aluminum hydride immediately prior to use. Diisopropylamine, decalin, triethylamine, and chlorotrimethylsilane were distilled from calcium hydride prior to use. Petroleum ether refers to that hydrocarbon fraction boiling in the range 30–60°, labelled as reagent grade. Crotylamine[9] and 3-methyl-2-butenylamine[10] were prepared by the method of Roberts and Mazur.[9] 2-Methyloctanoyl chloride was prepared from the acid,[11] which was synthesized using procedures reported by Pfeffer, Silbert, and Chirinko.[12] Other starting materials were commercial products and were used without further purification.

(9) J. D. Roberts and R. H. Mazur, *J. Amer. Chem. Soc.*, **73**, 2509 (1951).

(10) M. Olomucki and D. Hébrard, *Tetrahedron Lett.*, 13 (1969).

(11) W. Reppe and H. Kröper, *Justus Liebigs Ann. Chem.*, **582**, 38 (1953).

(12) P. E. Pfeffer, L. S. Silbert, and J. M. Chirinko, Jr., *J. Org. Chem.*, **37**, 451 (1972).