Aprosamine from Methyl Aprosaminides. Aqueous acid hydrolysis of either the α or β anomer under conditions identical with those used for apramycin yielded aprosamine in almost quantitative yield.

Methyl Aprosaminides from Aprosamine. Absorption of aprosamine from a neutralized aqueous solution onto Dowex 50W × 4 (H^+) resin, washing the resin with methanol, and extraction of the resin with refluxing methanol for 72 h led to a 7% yield of methyl aprosaminides.

Apramycin Hydriodide. Apramycin monohydrate (5.6 g) was dissolved in water (100 ml) and titrated to pH 8.3 with aqueous hydriodic acid. The solution was lyophilized and the residue added to refluxing 90% ethanol (250 ml). After 10 min the solution was filtered, the small amount of solids being discarded. On cooling, the filtrate deposited crystals, 3.5 g, of apramycin hydriodide monoethanolate monohydrate.

Anal. Calcd for $C_{23}H_{50}N_5O_{13}I$: C, 37.75; H, 6.88; N, 9.57; O, 29.88; I, 17.35. Found: C, 37.54; H, 7.01; N, 9.48; O, 29.54; I. 17.62.

Acknowledgments. We wish to extend our thanks to Messrs. L. Spangle and T. Elzey of our Physical Chemistry group, who measured the ^1H NMR spectra; to Dr. J. Occolowitz and Mr. J. Hettle for the mass spectra; to Mr. D. W. Smith for computer assistance; to Dr. E. Flynn, who suggested the problem; and to our colleagues at the Lilly Research Laboratories for helpful discussions.

Registry No.—Apramycin, 37321-09-8; apramycin hydriodide, 58617-23-5; penta-*N*-acetylapramycin, 58581-37-6; acetic anhydride, 108-24-7; *N,O*-permethylpenta-*N*-acetylapramycin, 58581-38-7; methyl iodide, 74-88-4; 2-deoxystreptamine, 2037-48-1; aprosamine tetrahydrochloride, 58581-39-8; dihydroaprosamine, 58581-40-1; methyl-4-amino-4-deoxy-α-D-glucopyranoside, 4097-95-4; methyl-4-amino-4-deoxy-α-D-glucopyranoside tetraacetate, 2595-35-9; methyl-4-amino-4-deoxy-β-D-glucopyranoside tetraacetate, 21209-55-2; methyl α-aprosaminide, 58617-24-6; methyl β-aprosaminide, 58068-66-9.

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(9) Melting points are uncorrected. NMR spectra were measured in D_2O with $TSPD_4$ as internal reference on Varian HA-100 and HR-200 spectrometers. In several of the spectra the signal due to the internal reference has been offset so as to appear in the spectrum. TLC was carried out on Brinkmann silica gel G using MeOH, $CHCl_3$, NH_4OH (28%) mixtures. Visualization was by ninhydrin (0.3% in EtOH) for amines and by hypochlorite, ethanol, starch–iodide for both amines and amides. All solvents were reagent grade and were used as received except where noted. Where given oxygen analyses are by direct measurement. Mass spectra were measured on a CEC 21-110, EI, 70 eV. High-resolution spectra were obtained using photoplate recording. Periodate oxidations were monitored by treatment of aliquots of the reaction mixture with 2 N KI solution and titrating the liberated iodine with standardized sodium arsenite solution.
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Nitrones as Intermediates in the Synthesis of *N*-Hydroxyamino Acid Esters

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A new method of synthesis of *N*-hydroxyamino acid esters as substrates for *N*-hydroxy peptides is reported. Esters of amino acid *N*-benzylidene *N*-oxides (nitrones) were obtained by alkylation of *anti*-benzaldoxime with corresponding bromo acid esters or by reaction of triethylammonium salts of nitrone amino acid derivatives with benzyl or *p*-nitrobenzyl bromides. The nitrones were converted into *N*-hydroxyamino acid esters by treatment with hydroxylamine salts (or, in the case of *tert*-butyl esters, with free hydroxylamine), without hydroxylaminolysis of the ester group.

Hydroxyamic acids are known to occur in nature.[1] Some of them are structurally related to peptides. New compounds with *N*-hydroxyamide bonds are still being isolated.[2] They have various physiologic activities, but their biochemical function is not quite clear. They usually occur as metabolites of microorganisms,[1] although the presence of oxidized peptide bonds in cancer protein[3] has also been reported.

Therefore, the synthesis of *N*-hydroxy peptides seems to be of interest. In our program, which aims at elaborating special methods, we are using two routes.

The first consists of an unambiguous synthesis through *O*-benzyl hydroxylamine derivatives.[4] Since the second makes use of standard methods of peptide synthesis for selective N-acylation of *N*-hydroxyamino acid esters, it is, therefore, necessary to obtain these esters.

To date several synthetic methods have been described. Esterification of the *N*-hydroxyamino acid molecule is possible in alcohol in the presence of sulfuric acid,[5] hydrogen chloride[6] or, better, by using diazomethane.[6] All these methods call for substrates that are not readily available, or do not permit the synthesis of the widely employed *tert*-butyl, benzyl, and *p*-nitrobenzyl esters.

Another possibility of obtaining these esters is through formation of the hydroxylamine group in the ester molecule, as, e.g., nitro ester reduction[6] or amino acid ester oxidation.[7]

Of the numerous methods employed in the synthesis of hydroxylamine derivatives, the ones using nitrones seem to be most convenient.[8]

N-Hydroxyglycine was obtained as far back as 1896 from the nitrone prepared from chloroacetic acid and *anti*-benzaldoxime.[9] In 1967, Buehler[10] extended this procedure to other *N*-hydroxyamino acids and found sodium *syn*-benzaldoximate to be O-alkylated by various alkyl halides, whereas *anti*-benzaldoximate was readily N-alkylated.[11] He obtained several nitrones from α-bromocarboxylic acids and hydrolyzed these compounds under drastic conditions with concentrated hydrochloric acid to the corresponding *N*-hydroxyamino

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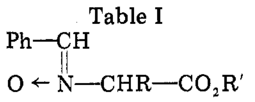
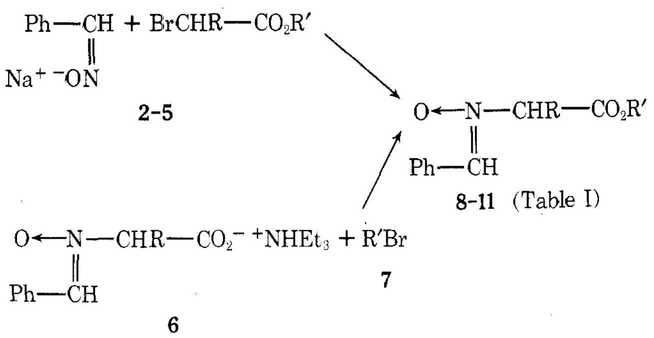
Table I



Nitrone	R	R′	Procedure	Yield, %	Mp, °C	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
8a	H	CMe_3	A	70	99	$C_{13}H_{17}NO_3$	66.36	7.28	5.95	66.54	7.36	5.75
8b	H	CH_2Ph	B	66	96	$C_{16}H_{15}NO_3$	71.36	5.61	5.20	71.16	5.64	5.30
8c	H	CH_2-*p*-$C_6H_4NO_2$	B	77	143–144	$C_{16}H_{14}N_2O_5$	61.14	4.49	8.91	60.74	4.60	8.64
9a	Me	Me	A	72	160	$C_{11}H_{13}NO_3$	63.76	6.32	6.76	63.84	6.49	6.63
9b	Me	Et	A	68	114	$C_{12}H_{15}NO_3$	65.14	6.83	6.33	65.27	6.72	6.51
9c	Me	CMe_3	A	72	118	$C_{14}H_{19}NO_3$	67.45	7.68	5.62	67.58	7.61	5.78
9d	Me	CH_2Ph	B	81	85–86	$C_{17}H_{17}NO_3$	72.07	6.05	4.94	72.08	6.04	5.08
9e	Me	CH_2-*p*-$C_6H_4NO_2$	B	89	113	$C_{17}H_{16}N_2O_5$	62.19	4.91	8.53	62.22	4.99	8.88
10	CH_2CHMe_2	Et	A	62	90–91	$C_{15}H_{21}NO_3$	68.42	8.04	5.32	68.52	8.06	5.60
11	CH_2Ph	Me	A	67	142	$C_{17}H_{17}NO_3$	72.07	6.05	4.94	72.04	6.14	4.82

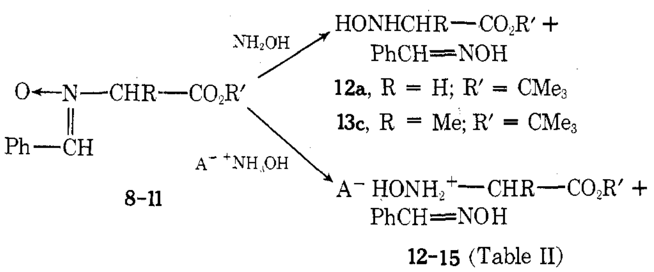
acids. Several authors have adopted this method for the synthesis of hydroxylamine derivatives.[12–15]

In this paper we present a new general method for the synthesis of esters of *N*-hydroxyamino acids which is also based on this procedure. Reaction of alkyl bromocarboxylate **2** with sodium *anti*-benzaldoximate (**1**) in an appropriate alcohol[16] gives the corresponding nitrones **5–15** in good yields (Table I) as easily crystallizing species. We also obtained benzyl and *p*-nitrobenzyl esters of amino acid *N*-benzylidene *N*-oxides from the triethylammonium salts of the corresponding nitrone derivatives **3** and appropriate benzyl bromides **4** in dimethylformamide solution.

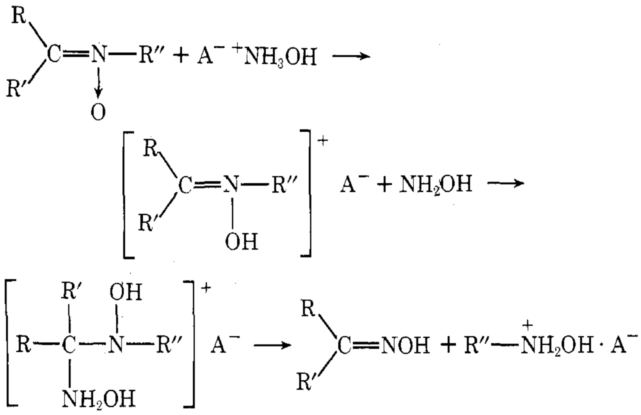


2, R = H; R′ = CMe_3 — **5**, R = CH_2Ph; R′ = Me
3a, R = Me; R′ = Me — **6a**, R = H;
3b, R = Me; R′ = Et — **6b**, R = Me;
3c, R = Me; R′ = CMe_3 — **7a**, R′ = CH_2Ph
4, R = CH_2CHMe_2; R′ = Et — **7b**, R′ = CH_2-*p*-$C_6H_4NO_2$

It is obvious that acidic hydrolysis of nitrones has not been utilized in the synthesis of *N*-hydroxyamino acid esters. Cleavage of nitrones can be achieved by means of acids,[10,12,14,15] by hydrazinolysis,[12] or by hydroxylaminolysis.[13,15,17] The use of phenylhydrazine permitted Hjeds et al.[18] to retain the lactone ring in the molecule. However, Testa et al.[19] reported that the ester group undergoes hydrazinolysis during the nitrone cleavage. We have employed hydroxylaminolysis to split the nitrones derived from *tert*-butyl esters **8a** and **9c**, although this variant makes product separation somewhat difficult, and calls for column chromatography to isolate the ester from benzaldoxime. We propose a new method using hydroxylamine salts which avoids hydroxylaminolysis of the ester group, and achieves cleavage of the nitrones. The reaction is carried out under very mild conditions and its products are *N*-hydroxyamino acid ester salts and benzaldoxime.



This method utilizes specially chosen hydroxylamine salts to obtain readily crystallizing *N*-hydroxyamino acid ester salts. In the study here described were used hydroxylamine hydrochloride, *p*-toluenesulfonate, and oxalate. The course of cleavage is presumably as follows:



Cleavage with hydroxylamine salts can, of course, be applied also to other types of nitrones and seems to be a general way for the synthesis of hydroxylamine derivatives. The properties of the *N*-hydroxyamino acid esters are summarized in Table II. The structure of all these compounds has been confirmed by NMR and ir spectroscopy (typical spectra are included in the Experimental Section).

Experimental Section

Melting points are uncorrected. The NMR spectra were obtained on a Tesla BS-487 spectrometer (80 MHz) with Me_4Si as internal standard. The infrared spectra were recorded on a Zeiss IR-10 spectrophotometer.

The *anti*-benzaldoxime (**1**) was prepared by modified literature methods.[12,20] The *N*-benzylideneglycine (**6a**) and -alanine (**6b**) *N*-oxides were synthesized by Buehler's[10] procedure. The preparation described below of materials **9b, 9c, 13c,** and **12b** is illustrative of procedures A, B, C, and D used to produce the materials appearing in Tables I and II. Minor variations in the procedures are not critical for good yield and product purity. Determination of NHOH% was performed iodometrically.[6]

***anti*-Benzaldoxime (1).** *syn*-Benzaldoxime (0.33 mol, 40 g) was added under cooling to 70 ml of concentrated hydrochloric acid and cooled to −5 °C. The precipitated benzaldoxime hydrochloride was collected and immediately added in small portions to 600 ml of 20% sodium carbonate solution under vigorous stirring. The resulting product was extracted twice with 300-ml portions of ether, dried over magnesium sulfate, and evaporated. To the residue was added 200

Table II
HONH—CHR—CO_2R'

Ester	R	R'	Procedure	Yield, %	Mp, °C	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Calcd, % NHOH	Found, % C	Found, % H	Found, % N	Found, % NHOH
12a	H	CMe_3	C	76	45–46	$C_6H_{13}NO_3$	48.97	8.90	9.52	21.77	48.92	8.88	9.50	21.8
12b	H	CH_2Ph	D	91	147–148[a]	$C_{16}H_{19}NO_6S$	54.39	5.42	3.96	9.07	54.70	5.50	4.13	9.1
12c	H	CH_2-*p*-$C_6H_4NO_2$	D	92	168–170[a,b]	$C_{16}H_{18}N_2O_8S$	48.25	4.55	7.03	8.04	48.53	4.45	7.11	8.3
13a	Me	Me	D	92	99–100[c]	$C_4H_{10}NO_3Cl$	30.83	6.49	9.01	20.52	30.98	6.34	8.84	20.2
13b	Me	Et	D	83	127[d]	$C_7H_{13}NO_7$	37.67	5.87	6.28	14.35	37.55	5.94	6.27	14.3
13c	Me	CMe_3	C	88	70–71[e]	$C_7H_{15}NO_3$	52.16	9.38	8.69	19.89	52.26	9.20	8.61	19.9
13d	Me	CH_2Ph	D	86	65–67[c]	$C_{10}H_{14}NO_3Cl$	51.83	6.06	6.04	13.81	52.00	6.12	6.22	13.7
13e	Me	CH_2-*p*-$C_6H_4NO_2$	D	92	125–126[a]	$C_{17}H_{20}N_2O_8S$	49.52	4.89	6.79	7.53	49.66	4.68	6.77	7.4
14	CH_2CHMe_2	Et	D	78	77–79[a]	$C_{15}H_{25}NO_6S$	51.87	7.25	4.03	9.22	51.59	7.49	4.18	9.6
15	CH_2Ph	Me	D	90	107–109[a]	$C_{15}H_{21}NO_6S$	55.58	5.76	3.81	8.72	55.49	5.72	3.75	8.8

[a] *p*-Toluenesulfonate. [b] With decomposition. [c] Hydrochloride. [d] Oxalate. [e] C. Shin, K. Nanjo, E. Ando, and J. Yoshimura, *Bull. Chem. Soc. Jpn.*, **47**, 3109 (1974); reported mp 70.5–71.5 °C.

ml of light petroleum ether. The crystals were collected and washed with petroleum ethers, yield 32 g (80%), mp 128 °C (lit.[20] mp 130 °C).

Procedure A. *N*-Benzylidene-DL-alanine *N*-Oxide Ethyl Ester (9b). Sodium (40 mmol, 0.92 g) was dissolved in 40 ml of ethanol; to it was added 40 mmol (4.84 g) of **1** and 44 mmol (8.0 g) of ethyl α-bromopropionate (**3b**). The mixture was allowed to stand until pH 7 was reached (2 h), evaporated to dryness, and, after 30 ml of water was added, extracted with 40 ml of chloroform. The organic layer was dried with magnesium sulfate, evaporated to dryness, and crystallized from ethanol–ether: yield 6.0 g (68%); mp 114 °C; NMR ($CDCl_3$) δ 8.18 (2 H, m, ArH), 7.50 [1 H, s, CH=N(O)–], 7.30 (3 H, m, ArH), 4.75 (1 H, q, $C_\alpha H$), 4.13 (2 H, q, $CO_2CH_2CH_3$), 1.67 (3 H, d, $C_\alpha HCH_3$), 1.13 (3 H, t, $CO_2CH_2CH_3$); ir (KBr) 1740 (CO), 1580 (C=N), 1220 cm^{-1} (N–O).

Procedure B. *N*-Benzylidene-DL-alanine *N*-Oxide *p*-Nitrobenzyl Ester (9c). To a solution of *N*-benzylidene-DL-alanine *N*-oxide (**6b**, 10 mmol, 1.79 g) in 5 ml of DMF was added 10 mmol (1.4 ml) of triethylamine, and the resulting mixture was treated with 10 mmol (2.15 g) of *p*-nitrobenzyl bromide (**7b**) in 5 ml of DMF. The reaction mixture was allowed to stand overnight, then poured into water and extracted twice with 20-ml portions of chloroform. The chloroform extracts were dried with magnesium sulfate. The residue was evaporated and crystallized from ethyl acetate–ethyl ether: yield 2.9 g (89%); mp 113 °C; NMR ($CDCl_3$) δ 8.1 (4 H, complex, ArH), 7.49 [1 H, s, –CH=N(O)–], 7.30 (5 H, complex, ArH), 4.73 (1 H, q, $C_\alpha H$), 4.65 (2 H, s, $ArCH_2$), 1.72 (3 H, d, $C_\alpha HCH_3$); ir (KBr) 1750 (CO), 1585 (C=N), 1520 and 1348 (NO_2), 1220 cm^{-1} (N–O).

Procedure of C. *N*-Hydroxy-DL-alanine *tert*-Butyl Ester (13c). To 15 ml of a 1.2 N solution of hydroxylamine in methanol prepared from hydroxylamine hydrochloride and sodium methanolate[21] was added 15 mmol (3.6 g) of *N*-benzylidene-DL-alanine *tert*-butyl *N*-oxide (**9c**) and the mixture was heated until the solid material dissolved (2 min). The resulting mixture was evaporated to dryness, and the residue was dissolved in benzene. The reaction mixture was evaporated and chromatographed on 50 g of Merck silica gel. The benzaldoxime was eluted with benzene–ethyl acetate (10:1) and the product **13c** was eluted with benzene–ethyl acetate (1:1). The fraction containing **13c** was evaporated and the residue crystallized from ether–light petroleum ether: yield 2.1 g (88%); mp 70–71 °C, NMR (CCl_4) δ 6.20 (2 H, s, NHOH), 3.40 (1 H, q, C_α H), 1.38 [9 H, s, $C(CH_3)_3$], 1.12 (3 H, d, $C_\alpha HCH_3$); ir (KBr) 3285, 3180 (br), 2900 (br), 1750 cm^{-1} (CO).

Procedure D. *N*-Hydroxyglycine Benzyl Ester *p*-Toluenesulfonate (12b). Nitrone **8b** (5 mmol, 1.35 g) and 5 mmol (1.02 g) of hydroxylamine *p*-toluenesulfonate were dissolved by heating in 10 ml of ethanol and evaporated. The residue was dissolved in chloroform, filtered, and evaporated. The residue was crystallized from ethanol–ether: yield 1.6 g (91%); mp 147–148 °C; NMR (Me_2SO-d_6) N δ 7.8 and 7.35 (4 H, complex, ArH), 7.75 (5 H, s, ArH), 5.51 (2 H, s, $ArCH_2$), 4.5 (2 H, s, $C_\alpha H_2$), 2.52 (3 H, s, $ArCH_3$); ir (KBr) 3180 (br), 2920 (br), 2780 (br), 1751 cm^{-1} (CO).

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Registry No.—**1**, 622-31-1; **2**, 5292-43-3; **3a**, 5445-17-0; **3b**, 535-11-5; **3c**, 39149-80-9; **4**, 35657-97-7; **5**, 3196-22-3; **6a**, 3884-90-0; **6b**, 58617-25-7; **7a**, 100-39-0; **7b**, 100-11-8; **8a**, 58581-41-2; **8b**, 58581-42-3; **8c**, 58581-43-4; **9a**, 58581-44-5; **9b**, 58581-45-6; **9c**, 58581-46-7; **9d**, 58581-47-8; **9e**, 58581-48-9; **10**, 58581-49-0; **11**, 58581-50-3; **12a**, 58581-51-4; **12b**, 58581-53-6; **12c**, 58581-55-8; **13a**, 58581-56-9; **13b**, 58581-58-1; **13c**, 21653-09-8; **13d**, 58581-59-2; **13e**, 58581-61-6; **14**, 58581-63-8; **15**, 58581-64-9; hydroxylamine HCl, 5470-11-1; hydroxylamine *p*-toluenesulfonate, 53933-48-5; hydroxylamine oxalate, 26217-76-5.

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Synthesis of Cuauhtemone

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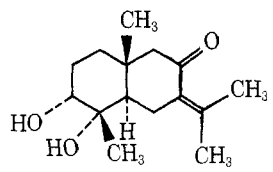
The sesquiterpenoid growth inhibitor cuauhtemone (1) has been synthesized starting from the monoethylene ketal of cyclohexane-1,4-dione. The stereochemistry of the ring A diol system has been introduced by osmium tetroxide hydroxylation. This reaction though stereoselective appears to be less susceptible to steric hindrance than the corresponding epoxidation process. The isopropylidene side chain of cuauhtemone is introduced by addition of methyllithium to the enolate of a β-keto ester followed by dehydration.

Cuauhtemone is a sesquiterpenoid dihydroxy ketone isolated from the Mexican medicinal shrub "Cuauhtematl" [*Pluchea odorate* (compositae)].[1,2] It has been reported to inhibit the growth of corn and bean seeds. The structure of the natural product was proven by a combination of magnetic resonance[1] and x-ray spectroscopic[2] techniques leading to the formulation 1 for cuauhtemone. This report describes a total synthesis of racemic 1.



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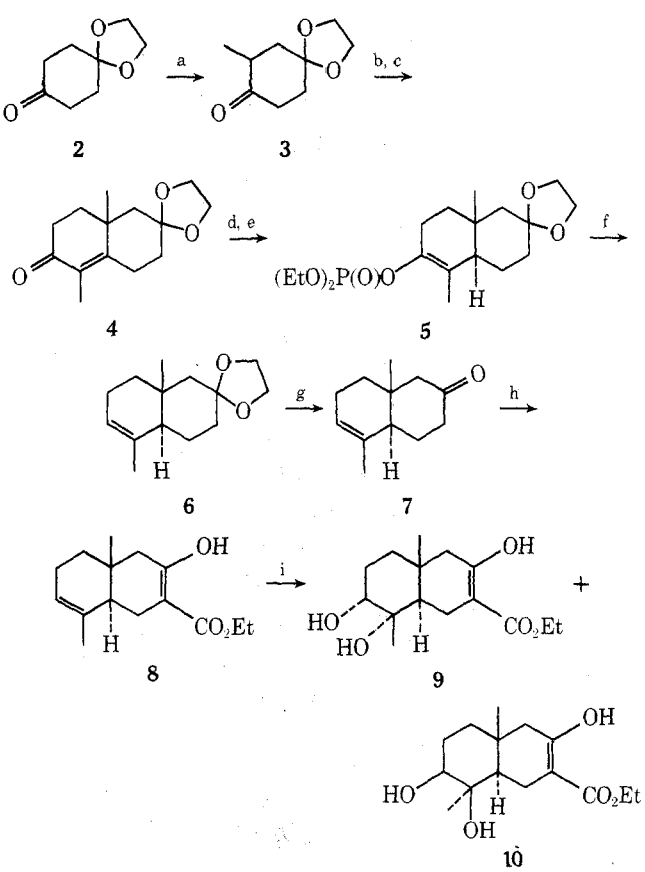
Our initial synthetic goal was the bicyclic olefin ketal 6 shown in Scheme I. This intermediate incorporates the necessary trans-fused ring system and it provides appropriate sites for the introduction of both the diol function and the isopropylidene groups of the cuauhtemone molecule. The preparation of 6 was carried out as shown in Scheme I starting from the monoethylene ketal of cyclohexane-1,4-dione (2).[3] Monomethylation of 2 in the form of its pyrrolidine enamine[4] afforded 3. The latter was annelated with ethyl vinyl ketone employing potassium hydroxide in methanol for the Michael stage and pyrrolidine in refluxing benzene for the aldol closure step. The product 4 has been previously prepared by Narang and Dutta[5] using a β-chloro ketone as the vinyl ketone equivalent, and subsequent to the onset of our work its preparation and that of ketal 6 as well have also been described by Miller and Behare.[6] The latter workers carried out the annelation using a β-dialkylamino ketone as the source of the vinyl ketone. In all cases, however, the percent conversion of 3 is less than 40%.

We established the trans fusion for the ring junction of cuauhtemone in a manner similar to that later reported by Miller and Behare.[6] The ketal enone 4 was reduced with lithium in ammonia and the resulting enolate was trapped as the enolphosphonate 5.[7] Further reduction of 5 with lithium in ammonia–ethylamine–*tert*-butyl alcohol[7] gave the desired olefin ketal 6.

Scheme I



Step a, C_4H_9N, CH_3I; b, $CH_3CH_2COCH{=}CH_2$, KOH, CH_3OH; c, C_4H_9N; d, Li, NH_3; e, $(EtO)_2POCl$; f, Li, NH_3, $EtNH_2$, *t*-BuOH; g, H_2O–HOAc; h, $(EtO)_2CO$, NaH; i, OsO_4

The cis α-diol moiety of cuauhtemone was introduced by osmium tetroxide oxidation. The reaction of a double bond