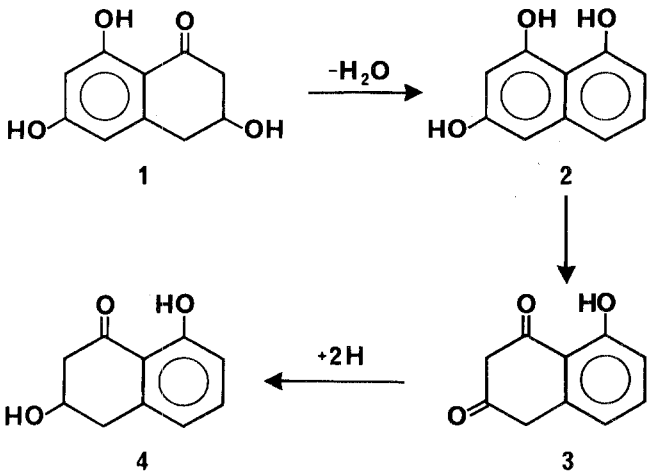

Figure 1. Probable biosynthetic pathway for the conversion of (+)-scytalone (1) to (−)-vermelone (4).

light. Compound 4 also formed a red-brown chelate when chromatograms were sprayed with 1% $FeCl_3$ and a gray spot with DMB reagent (equal volumes of 1% 2,4-dimethoxybenzaldehyde in ethanol and concentrated HCl, freshly mixed). Bands of silica gel containing 4 were scraped from TLC plates, packed in 1-cm chromatography columns, and eluted with ethyl ether.

(−)-Vermelone formed crystals from cyclohexane: mp 91–94 °C; $[\alpha]^{25}D$ −18° (*c* 0.36, EtOH); MS *m/e* (%) 178.062345 (98, M^+; $C_{10}H_{10}O_3$ requires 178.062980), 161 (20), 160 (100, M − H_2O), 135 (25), 134.037171 (98, M − CH_2=CHOH; $C_8H_6O_2$ requires 134.036770), 132 (44), 131 (20), 107 (13), 106 (62), 105 (32), 104 (28), 103 (16), 78 (54), 77 (44), 63 (13), 52 (19), 51 (31); uv-visible λ_{max} (EtOH) (ε) 333.5 nm (4000), 259 (10 600); λ_{max} (EtONa) (ε) 374 (5500), 346 (5200), 333 (sh), 266 (sh).

Chemical Conversions of (−)-Vermelone (4). Compound 4 was oxidized with Jones reagent[7] to give a single orange quinone. The R_f values and uv-visible spectra of this quinone agreed with those[1] of synthetic 2-hydroxyjuglone.[8] (−)-Vermelone (4) was dehydrated with 50% aqueous KOH by the methods described for (+)-scytalone.[3] The uv-visible and mass spectra of the phenol obtained from 4 agreed with those of 1,8-DHN synthesized from 8-hydroxy-1-naphthalenesulfonic acid (sodium salt) according to Tanaka et al.[9]

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Maytansinoids. Synthesis of a Fragment of Known Absolute Configuration Involving Chiral Centers C-6 and C-7

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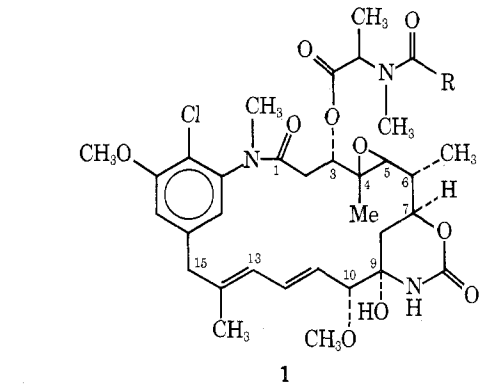
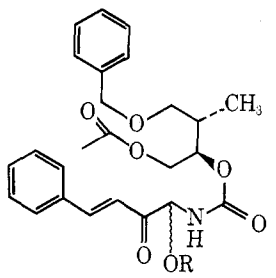
An efficient, stereocontrolled synthesis is described for compound **2**, which represents a fragment corresponding to carbons 5–12 of the maytansinoid ring skeleton. The total yield from (*Z*)-2-butene-1,4-diol is 78%. The dioxepane **6** has been resolved via the α-phenethylurethane and the absolute configuration of the enantiomers determined by the Horeau method. The specific rotations of all intermediates are reported.

The maytansinoids[1–4] are a group of structurally related ansa macrolides isolated from *Maytenus* and *Colubrina* species, which are of great current interest because of their high antileukemic potency and cytotoxicity. They are characterized by structure **1**, in which R may be CH_3 (maytansine),[1] C_2H_5 (maytanprine),[2] $CH(CH_3)_2$ (maytanbutine),[2] or $CH_2CH(CH_3)_2$ (maytanvaline).[3] 15ξ-Hydroxymaytanbutine (colubrinol)[4] and its acetate have also been described. More recently,[3] maytansine, the most thoroughly investigated representative of this class of compounds, has also been found to possess significant activity against solid murine tumor systems, and it is presently undergoing clinical trials.

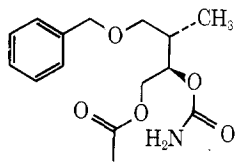
Sparked by our interest in the unusual biological properties of these structurally interesting natural products, whose isolated yields from their respective plant sources are in the order of 10^{-4}% or less, we have initiated a synthetic program aimed at the natural products themselves as well as at structurally related substances, which might retain the biological properties of the former. Two groups, Meyers et al.[5–7] and Corey and Bock,[8] have recently reported on their approaches to this problem. In this paper we wish to describe the synthesis of compound **2**, which represents a fragment corresponding to carbon atoms 5–12 of the maytansinoid ring skeleton. The final intermediate **3** has also been prepared in optically active form of known absolute configuration. The elaboration of this intermediate which contains the chiral centers corresponding to C-6 and C-7 in maytansine in the correct relative configuration seemed to us an appropriate point of departure since such a precursor could in turn direct the development of stereochemistry of all the remaining chiral centers, C-3, C-4, C-5, and C-10. The synthesis of **3**, which follows a plan similar to that of Corey and Bock,[8] and is identical with the latter up to compound **7**, had been completed when that paper appeared. Interestingly, the further utilization of that intermediate proceeds along quite different lines. It was envisioned that the relative stereochemistry at C-6 and C-7 could be created by a methyllithium opening of a suitably protected (*Z*)-2,3-epoxybutane-1,4-diol. Thereafter the vicinal hydroxyl



1



2, R = H
2a, R = CH_3

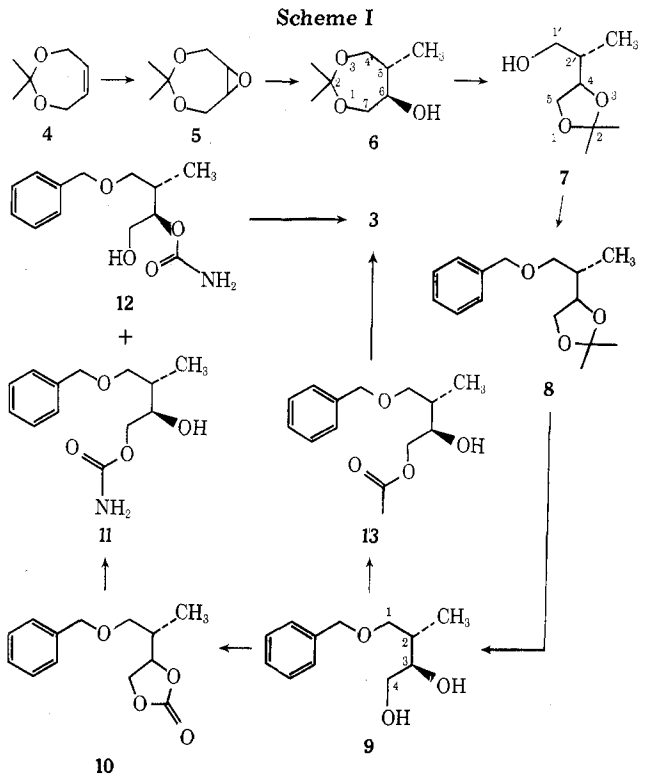


3

groups could be protected as a ketal, followed by benzylation of the free hydroxyl group. After hydrolysis of the ketal and reaction of the resulting glycol with phosgene, ammonolysis of the cyclic carbonate should produce a hydroxyethyl carbamate, which could be acetylated to produce compound **3**. The expected regioselectivity of carbamate formation was based on previous studies of unsymmetrical 1,3-dioxolane-2-ones.[9,10] A crucial point here is the purity of the required *cis*-2-butene-1,4-diol, since contaminating trans diol would lead to the undesirable erythro product, thereby creating purification problems. Moreover, the inherent stereospecificity of epoxide ring openings would be wasted on a mixture of the cis and trans epoxides, in that both the (2*RS*, 3*SR*) and (2*RS*,3*RS*) isomers would result. Since the difficulties in obtaining pure *cis*-2-butene-1,4-diol are well known,[12] it seemed advantageous to incorporate this compound in a small ring system which would dictate the configuration of the double bond. Theoretical possibilities include 2,5-dihydrofuran, 4,5-dehydro-1,2-dioxane, and a 4,7-dihydro-1,3-dioxepin. This last structure not only fixes the configuration of the double bond, but also contains another advantage: it incorporates the ketal protecting group for the future 1,2-glycol. Since the acetone ketal 2,2-dimethyl-4,7-dihydro-1,3-dioxepin (**4**) had already been prepared in high yield,[13] it was chosen as the starting material.

The synthetic pathway to compound **2** is summarized in Scheme I. Reaction of the dioxepin **4** (prepared according to Monroe[13] in better than 90% yield) with *m*-chloroperbenzoic acid in CH_2Cl_2 for 6 h at reflux gave the acid-labile epoxide **5** in 99% yield. According to previous work,[11] lithium dimethylcuprate is the reagent of choice for effecting trans opening of epoxides without rearrangement. When the epoxide **5** was treated with 0.52 molar equiv of Me_2CuLi in ether, first at −78 °C for 30 min and then at room temperature for 18 h, the enantiomeric pair represented by **6** [14] was produced in 94% yield. This hydroxydioxepane was easily hydrolyzed with aqueous acid, but could be rearranged directly to the dioxolane ring system **7** in 99% yield either by *p*-toluenesulfonic acid catalysis in benzene or more conveniently with a trace of concentrated HCl, followed by distillation through a Vigreux column. The structure of the rearranged product was shown to be **7** rather than the isomeric 2,2,5-trimethyl-4-hydroxymethyl-1,3-dioxane by ^1H NMR double resonance

Scheme I



measurements at 270 MHz. Thus, the doublet corresponding to the carbinol hydrogens collapsed upon irradiation of the septet at about δ 2 ($CHCH_3$), consistent with dioxolane structure **7**, but not the dioxane structure. Had the latter been correct, the doublet corresponding to the carbinol hydrogens should have collapsed upon irradiation of a quartet at about δ 3.5 (CHOC). The free alcohol in **7** was benzylated in 91–95% yield by treatment with NaH and benzyl chloride in dimethylformamide. The resulting benzyl ether ketal **8** was then hydrolyzed to the glycol **9** by 1 N HCl in 2:1 acetonitrile–H_2O in 91% yield. The benzyl ether glycol **9** was converted to the cyclic carbonate **10** in 70% yield by treatment with phosgene in toluene–pyridine. When **10** was ammonolyzed, two compounds were isolated in a 3:1 ratio. Since the major product had ^1H NMR signals at δ 4.11 (AB pattern, 2 H) and 3.99 (X of ABX, 1 H), and showed a doublet at δ 4.73 for the alcohol proton in Me_2SO-d_6, while the minor product had ^1H NMR signals at δ 4.77 (quartet, 1 H) and 3.72 (broad doublet, 2 H) and a triplet at δ 4.76 for the alcohol proton in Me_2SO-d_6, the major and minor products were assigned structures **11** and **12**, respectively. Corroborative evidence was also obtained from the mass spectra and ^{13}C spectra of the two compounds. This finding is at variance with two previous reports,[9,10] in which unsymmetrical 1,3-dioxolane-2-ones were ammonolyzed to give urethanes similar to **12**. Since the major product **11** leads not to **3**, but to an isomer, this route was not considered a viable method for the synthesis of **3**.

When glycol **9** was treated with 0.95 equiv of acetic anhydride for 2 days in pyridine, the monoacetate **13** was formed in about 80% yield, with the starting material comprising the other 20% of the mixture. These could be easily separated by chromatography and **13** characterized. Structure **13**, rather than the isomeric 3-acetoxy structure, was assigned to this substance on the basis of spectral evidence: ^1H NMR in $CDCl_3$, which showed an AB pattern at δ 4.09 and an X of ABX at δ 4.01, very similar to that of compound **11**; ^1H NMR in Me_2SO-d_6, which showed a doublet at δ 4.87 coupled to the quintet at δ 3.76; mass spectrum, which showed a peak at *m/e* 179, corresponding to loss of CH_2OAc, and no peak at *m/e* 221, corresponding to loss of CH_2OH; and ^{13}C spectra. The 3-acetoxy-4-hydroxy compound was later synthesized by trit-

ylation of **9** in pyridine, addition of acetic anhydride, and detritylation with ethanol. It had all the expected properties, which were different than those of **13**. When monoacetate **13** was treated in benzene with 2 equiv each of NaOCN and CF_3CO_2H,[15] the desired urethane **3**, mp 112–113 °C, was formed in 96% yield after one recrystallization from benzene–ether, identical in all respects with the product obtained by acetylation of the urethane **12**.

In order to effect the linkage of the urethane nitrogen of **3** with the carbon chain extending from C-9 to the aromatic ring, thereby generating the carbinolamide functionality at C-9 and providing at the same time an oxygen function at C-10, we have condensed the urethane **3** with styrylglyoxal to form the adduct **2** in quantitative yield. Carbinolamides of highly electrophilic aldehydes have been known since 1874, when Bischoff[16] condensed chloral hydrate with ethyl urethane under strong acid catalysis. More recently Vail et al.[17] prepared the 1,2-biscarbinolamide of glyoxal and ethyl urethane using a bicarbonate alkaline medium. In contrast to either of these two sets of conditions we have effected the condensation without external catalyst in refluxing benzene. The reversibility of the condensation reaction could be observed when the NMR spectrum of the crystalline adduct was taken in $CDCl_3$ at 270 MHz. Peaks corresponding to free urethane and aldehyde hydrate were identified, which accounted for approximately 5% of the sample. This reversibility could be arrested by conversion of **2** into the methyl ether **2a** in boiling methanol for 5 min. The conditions for both the condensation reaction and the protection of the carbinolamide by methylation are thus compatible with a wide variety of functionality and protecting groups that could be built into the precursor molecules.

In a lengthy synthetic scheme, it is generally accepted that separation of enantiomers, or resolution, is most advantageously carried out at the earliest possible stage. In the case of the above scheme, attempts at resolution of the alcohol **6** seemed most likely to succeed, in that the hydroxyl group to be derivatized is bonded to an asymmetric carbon atom, and compound **6** occupies an early position in the synthetic sequence. Standard attempts at resolution through hemiphthalate esters provided low yields of derivatives, since the acidic carboxyl group catalyzed hydrolysis and decomposition of the acetonide. On the other hand, reaction of the alcohol **6** with (+)-(*R*)-α-phenethylamine isocyanate resulted in conversion to the diastereomeric urethanes, which could be separated by crystallization from hexane–toluene (10:1). The higher melting diastereomer melted at 103–103.5 °C after two or three recrystallizations and had $[\alpha]^{23}D$ −1.9°,[18] which did not improve upon further crystallization. The lower melting diastereomer could be obtained by chromatography on silica gel; it had mp 74–74.5 °C and $[\alpha]^{23}D$ 78.4°. Both disastereomers were judged to be at least 99% pure by FT ^1H NMR at 270 MHz. Samples composed of the two diastereomers in a 98:2 ratio displayed two distinct and separate signals at δ 0.98 and 0.93. In pure samples the complete absence of one signal was observed even after a large number of pulses. Reduction of the urethanes with lithium aluminum hydride in refluxing THF for 5 h, followed by nonacidic, nonaqueous workup, gave the parent alcohols having $[\alpha]^{23}D$ 43.4° from the lower melting urethane and $[\alpha]^{23}D$ −43.5° from the higher melting diastereomer in 96% yield. Esterification of the two antipodes with *rac*-α-phenylbutyric anhydride according to the method of Horeau[19] provided the absolute configuration of (+)-**6** as (5*S*, 6*R*) and that of (−)-**6**[20] as (5*R*,6*S*). The "optical yields" in these reactions were 16.7 and 13.9%, respectively. These were corroborated by the 270-MHz ^1H NMR spectra of the isolated esters, which showed, for instance, two signals at δ 2.11 and 1.81 in the ratio of 58:42 corresponding to the diastereomeric hydrogens at C-3 of the butyric esters.

The synthetic sequence leading to **3** was repeated with (−)-**6** to give the following yields and $[\alpha]^{23}D$ values:[18] (−)-**7**, 95%, −5.1°; (−)-**8**, 95%, −7.7°; (−)-**9**, 91%, −3.7°; (+)-**13**, 68%, (80% conversion), +4.9°; (−)-**3**, 68%, (75% conversion), −5.4°.

Experimental Section

Ir spectra were recorded on a Perkin-Elmer Model 137 spectrophotometer. Liquid samples were run as a thin film between NaCl plates and solid samples in KBr disks. NMR spectra were determined as solutions in $CDCl_3$ with Me_4Si as an internal standard. Chemical shifts are reported in δ, coupling constants (*J*) are reported in hertz; the abbreviations s, d, t, q, and m signify singlet, doublet, triplet, quartet, and multiplet, respectively. ^1H NMR spectra were recorded on a Bruker HX-270 (270 MHz) spectrometer operating in the pulsed Fourier transform mode. ^{13}C NMR spectra were recorded on a Bruker HX-90E spectrometer operating at 22.63 MHz in the pulsed Fourier transform mode. Free induction decay data were accumulated and processed with a Nicolet 1089 computer. Mass spectra were determined using a Finnigan 1015 quadrupole mass spectrometer equipped with VPC, gas and solid probe inlets; the data were recorded and processed by a Systems Industries Computer Interface System/150, and plotted as bar graphs. Optical rotations were measured with a Perkin-Elmer Model 141 polarimeter. Melting points are uncorrected. High-pressure liquid chromatography was carried out using Quantum Industries TLC grade silica gel (no binder) in glass columns. Microanalyses were performed by Baron Consulting Co., Orange, Conn. All compounds are racemic unless otherwise specified.

2,2-Dimethyl-4,7-dihydro-1,3-dioxepin (4).[13] 2-Butene-1,4-diol (91% cis, 22.00 g, 250 mmol) was combined with 2,2-dimethoxypropane (55.00 g, 530 mmol) in a 100-ml flask. *p*-Toluenesulfonic acid monohydrate (2 mg) was added and the solution stirred magnetically during distillation at atmospheric pressure. Fractions collected were bp 63–65 °C (MeOH, 50 ml); bp 78–85 °C (excess dimethoxypropane, 13 ml); bp 144–146 °C (product, 28.27 g, 89% yield based on 100% cis diol, 97% based on 91% cis diol). ^1H NMR δ 5.67, t, J = 1.65 Hz, 2 H (olefinic protons); 4.26, d, J = 1.65 Hz, 4 H (CH_2); 1.44, s, 6 H (CH_3). ^{13}C NMR δ 129.5, d (C-5 + 6); 101.9, s (C-2); 61.4, t (C-4 + 7); 24.0, q (methyls). Ir 1381, 1372 (methyls); 1217 (acetonide); 1176, 1086, 1073 (ether C–O); 735, 725 cm^{-1} (olefins). Mass spectrum (10% cutoff) *m/e* 128, 0.05% (M^+); 70, 17% ($CH_2{=}CHCH_2CHO^+$); 59, 88% [$CH_3C(OH)CH_3$]; 43, 100% ($CH_3C{\equiv}O^+$); 39, 30%.

4,4-Dimethyl-3,5,8-trioxabicyclo[5.1.0]octane (5). A solution of 10.00 g (78 mmol) of 2,2-dimethyl-4,7-dihydro-1,3-dioxepin (**4**) in 50 ml of CH_2Cl_2 was added over a 30-min period to a solution of 18.00 g of 85% pure *m*-chloroperbenzoic acid (89 mmol) in 150 ml of CH_2Cl_2 and the addition funnel rinsed with 50 ml of CH_2Cl_2. The mixture was allowed to reflux for 6 h, and then the flask was cooled to 0 °C to precipitate the *m*-chlorobenzoic acid present. The solid was filtered, and the CH_2Cl_2 solution washed with 2 × 250 ml of 10% K_2SO_3, 3 × 250 ml of saturated $NaHCO_3$, 200 ml of 5% NaOH, and 200 ml of saturated NaCl and dried over $MgSO_4$. Removal of solvent in vacuo left 15 g of slightly yellow oil, which was distilled with a 10-cm Vigreux column. Only one fraction distilled; it had bp 85–88 °C (17 Torr) and weighed 11.10 g (99% yield). ^1H NMR δ 4.02, AB of ABX, $|J_{AB}|$ = 14.4, $|J_{AX} + J_{BX}|$ = 39 Hz, 4 H (–CH_2–); 3.22, X of ABX, 2 H (epoxide protons); 1.38, s, 3 H (CH_3); 1.32, s, 3 H (CH_3). ^{13}C NMR δ 101.8, s (C-4); 59.9, t (C-2 + 6); 56.1, d (C-1 + 7); 24.4, q (C-4 methyl cis to epoxide); 23.1, q (C-4 methyl trans to epoxide). Ir 1380, 1370 (methyls); 1218 (acetonide); 1086 (ether C–O); 834, 796 cm^{-1} (epoxide). Mass spectrum (10% cutoff) *m/e* 129, 25% ($M^+ - CH_3$); 99, 12%; 59, 18% [$CH_3C(OH)^+$–CH_3]; 43, 100% ($CH_3C{\equiv}O^+$); 31, 11% ($^+CH_2OH$); 29, 12% ($HC{\equiv}O^+$).

Anal. Calcd for $C_7H_{12}O_3$: C, 58.31; H, 8.39. Found: C, 58.59; H, 8.17.

(5*RS*,6*SR*)-2,2,5-Trimethyl-6-hydroxy-1,3-dioxepane (6). Purified cuprous iodide (5.00 g, 26 mmol) and a stirring bar were placed in an oven-dried 250-ml flask, and the flask was evacuated and purged with N_2 (ten times). Dry ether (10 ml) was added by syringe and the flask cooled to −78 °C. Then 40 ml of 1.38 M methyllithium (55 mmol) was added and the solution allowed to stir for 10 min. 4,4-Dimethyl-3,5,8-trioxabicyclo[5.1.0]octane (**5**, 7.50 g, 52 mmol) was placed in a 25-ml test tube, which was capped, evacuated, and purged with N_2 (ten times). Dry ether (10 ml) was added by syringe and the solution mixed. The epoxide solution was added over 20 min to the cuprate, giving a slight yellow color to the reaction mixture. The solution was kept at −78 °C for 30 min and then allowed to warm to room temperature. After 18 h, no starting material was seen by NMR of an aliquot. The mixture was quenched with 15 ml of MeOH and added to 250 ml of saturated NH_4Cl, followed by extraction with 5 × 250 ml of ether (only first extract is yellow). The ether solution was washed with 250 ml of saturated NaCl and dried over $MgSO_4$, and the

solvent was removed in vacuo. Distillation through a 10-cm Vigreux column afforded 7.82 g of compound boiling at 102–104 °C (13–14 Torr) (94% yield). ^{1}H NMR δ 3.70, d of d, J = 3, 13 Hz, 1 H (C-7 H); 3.68, d of d, J = 3, 13 Hz, 1 H (C-4 H); 3.59, d of d, J = 6, 13 Hz, 1 H (C-7 H); 3.37, d of d, J = 7, 13 Hz, 1 H (C-4 H); 3.31, t of d, J = 6, 3 Hz, 1 H (C-6 H); 3.06, broad s, 1 H (OH); 1.68, sextet of d, J = 7, 3 Hz, 1 H (C-5 H); 1.34, s, 3 H (CH_3 of acetonide); 1.32, s, 3 H (CH_3 of acetonide); 0.98, d, J = 7 Hz, 3 H (CH_3CH). ^{13}C NMR δ 101.1, s (C-2); 74.0, d (C-6); 63.4, t (C-7); 62.4, t (C-4); 40.7, d (C-5); 24.6, q (C-2 methyls); 14.6, q (C-5 methyl). Ir broad 3600–3200 (OH); 1381, 1370 (methyls); 1215 (acetonide); 1080 (ether C–O); 850 cm^{-1}. Mass spectrum (10% cutoff) m/e 145, 3% ($M^+ - CH_3$); 72, 67%; 59, 100% [$CH_3C(OH)^+CH_3$]; 57, 71%; 43, 95% ($CH_3C{\equiv}O^+$).

Anal. Calcd for $C_8H_{16}O_3$: C, 59.98; H, 10.07. Found: C, 59.84; H, 10.01.

Acetate: bp 85–88 °C (4 Torr).

Anal. Calcd for $C_{10}H_{18}O_4$: C, 59.38; H, 8.97. Found: C, 59.11; H, 8.71.

(2′*RS*,4*SR*)-2′-(2,2-Dimethyl-1,3-dioxacyclopent-4-yl)-1′-propanol (7). (5*RS*, 6*SR*)-2,2,5-Trimethyl-6-hydroxy-1,3-dioxepane (**6**, 4.00 g, 25 mmol) was placed in a 5-ml flask along with 2 drops (30 μl) of concentrated HCl and a stirring bar. The mixture was distilled through a 10-cm Vigreux column, giving only one fraction, bp 112–114°C (20 Torr), weighing 3.95 g (98% yield). ^{1}H NMR δ 4.12, q, J = 6.5 Hz, 1 H (CHO); 4.03, t, J = 7.1 Hz, 1 H ($CHOCH_2O$); 3.71, t, J = 7.9 Hz, 1 H ($CHOCH_2O$); 3.66, s, 1 H (OH); 3.53, d, J = 6.3 Hz, 2 H (CH_2OH); 1.85, septet, J = 6.5 Hz, 1 H (CH_3CH); 1.41, s, 3 H (acetonide CH_3); 1.32, s, 3 H (acetonide CH_3); 0.96, d, J = 7.5 Hz, 3 H (CH_3CH). ^{13}C NMR δ 108.5, s (C-2); 78.0, d (C-4); 67.2, t (C-5); 65.2, t (C-1′); 38.2, d (C-2′); 26.4, q (C-2 methyl cis to alkyl group); 25.3, q (C-2 methyl trans to alkyl group); 12.1, q (C-3′). Ir broad 3600–3200 (OH); 1380, 1370 (methyls); 1212 (acetonide); broad 1060–1040 (C–O); 860 cm^{-1}. Mass spectrum (50% cutoff) m/e 145, 69% ($M^+ - CH_3$); 101, 62% (2,2-dimethyl-1,3-dioxacyclopent-4-yl ion); 85, 94%; 72, 89%; 59, 51% [$CH_3C(OH)^+$-CH_3]; 57, 59%; 55, 59%; 43, 100% ($CH_3C{\equiv}O^+$); 41, 70%; 31, 50% ($^+CH_2OH$).

Anal. Calcd for $C_8H_{16}O_3$: C, 59.98; H, 10.07. Found: C, 60.26; H, 9.79.

(2′*RS*,4*SR*)-2′-(2,2-Dimethyl-1,3-dioxacyclopent-4-yl)-1′-propyl Benzyl Ether (8). Sodium hydride (4.18 g, 55% in oil, 95 mmol) was placed in a 100-ml flask with a stirring bar and washed with 3 × 20 ml of hexane. Freshly distilled (from CaH_2) DMF (20 ml) was added, and the flask was sealed with a septum, evacuated, and flushed ten times with N_2. (2′*RS*,4*SR*)-2′-(2,2-dimethyl-1,3-dioxacyclopent-4-yl)-1′-propanol (**7**, 7.73 g, 48.2 mmol) was placed in 10 ml of distilled DMF and added dropwise to the stirred NaH suspension by syringe while cooling in an ice bath. The ice bath was removed after all the alcohol had been added, and the solution stirred at room temperature for 30 min. Freshly distilled and degassed benzyl chloride (6.39 g, 50.6 mmol) was dissolved in 10 ml of DMF and this solution added dropwise to the alcoholate solution while cooling in an ice bath. The reaction mixture was then stirred for 48 h at room temperature. For workup 50 ml of ether was added followed by 30 ml of MeOH, to destroy excess hydride, and 150 ml more of ether. The combined ether layers were washed with 5 × 100 ml of H_2O (only first H_2O layer is yellow) and dried over $MgSO_4$, and the ether was removed in vacuo. Distillation of the slightly yellow residue afforded only one fraction, bp 174–176 °C (19 Torr), weighing 11.52 g (94.4% yield). ^{1}H NMR δ 7.31, m, 5 H (aromatic protons); 4.47, s, 2 H (benzylic protons); 4.03, t, J = 10.8 Hz, 1 H ($CHOCH_2O$); 4.01, q, J = 5.2 Hz, 1 H ($CHOCH_2O$); 3.68, t, J = 10.8 Hz, 1 H ($CHOCH_2O$); 3.36, d, J = 6 Hz, 2 H ($CHCH_2OCH_2$); 1.92, septet, J = 7 Hz, 1 H (CH_3CH); 1.39, s, 3 H (acetonide CH_3); 1.36, s, 3 H (acetonide CH_3); 1.01, d, J = 7 Hz, 3 H (CH_3CH). ^{13}C NMR δ 138.4, s (quaternary phenyl C); 128.3, d (meta C's); 127.4, d (ortho + para C's); 108.1, s (C-2); 78.2, d (C-4); 73.1, t (benzylic C and C-1′); 68.1, t (C-5); 37.2, d (C-2′); 26.6, q (C-2 methyl cis to alkyl group); 25.6, q (C-2 methyl trans to alkyl group); 13.2, q (C-3′). Ir 1385, 1372 (methyls); 1215 (acetonide); 1100, 1058 (ether C–O); 862; 738, 700 cm^{-1} (monosubstituted benzene). Mass spectrum (5% cutoff) m/e 235, 5% ($M^+ - CH_3$); 101, 10%, (2,2-dimethyl-1,3-dioxacyclopent-4-yl ion); 91, 100% ($PhCH_2^+$); 43, 32% ($CH_3C{\equiv}O^+$).

Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.70; H, 8.63.

(2*RS*,3*SR*)-2-Methylbutane-1,3,4-triol 1-*O*-Benzyl Ether (9). To 30 ml of 2:1 (v/v) CH_3CN–H_2O was added 2.6 ml of concentrated HCl, making the solution 1 N HCl. (2′*RS*,4*SR*)-2′-(2,2-dimethyl-1,3-dioxacyclopent-4-yl)-1′-propylbenzyl ether (**8**, 3.56 g) was added and the mixture was stirred for 7 days. The mixture was then poured into 50 ml of saturated NaCl and extracted with 5 × 30 ml of ether. The combined ether layers were washed with 50 ml of saturated $NaHCO_3$ and dried over $MgSO_4$, and the ether was evaporated in vacuo. The residue was distilled, first at 20 mm to remove traces of ether, and then at ~1 Torr, where only one fraction was collected, having bp 142–147 °C and weighing 2.99 g (91% yield). ^{1}H NMR δ 7.35, m, 5 H (aromatic protons); 4.50, s, 2 H (benzylic protons); 3.73, broad m, 1 H (CHOH); 3.60, br d, 2 H (CH_2OH); 3.48, eight-line AB of ABX, $|J_{AB}|$ = 9, $|J_{AX} + J_{BX}|$ = 22 Hz, 2 H (C-1 H_2); 2.87, br d, 1 H (CHOH); 2.51, br s, 1 H (CH_2OH); 1.96, complex septet, 1 H (CH_3CH); 0.96, d, J = 7 Hz, 3 H (CH_3CH). ^{13}C NMR δ 138.1, s (quaternary phenyl C); 128.3, d (meta C's); 127.6, d (ortho + para C's); 73.6, d (C-3); 73.1, t (C-1 and benzylic C); 64.8, t (C-4); 36.0, d (C-2); 12.0, q (C-2 methyl). Ir 3600–3200 (OH); 1375 (methyl); 1100, 1060 (ether C–O); 738, 701 cm^{-1} (monosubstituted benzene). Mass spectrum (25% cutoff) m/e 210, 2.5% (M^+); 179, 8% ($M^+ - CH_2OH$); 108, 31%; 107, 51% ($^+OCH_2Ph$); 91, 100% ($PhCH_2^+$); 65, 35%; 43, 41% ($CH_3C{\equiv}O^+$); 31, 28% ($^+CH_2OH$).

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.39; H, 8.61.

2′-(1,3-Dioxacyclopent-2-on-4-yl)-1′-propyl Benzyl Ether (10). To a solution of 905 mg (4.3 mmol) of 2-methylbutane-1,3,4-triol 1-*O*-benzyl ether in 15 ml of pyridine was added 3 ml of a 2.07 M phosgene solution in toluene (6.2 mmol) with vigorous stirring and cooling with an ice bath. After stirring for 1 h at room temperature, the solution was poured into 50 ml of ice–H_2O–concentrated HCl (~3:1:1), which was extracted with 5 × 30 ml of ether. The ether layer was washed with 3 × 50 ml of saturated $NaHCO_3$ and dried over $MgSO_4$, and the ether was evaporated. The residue was distilled; only one fraction was collected at bp 164–167 °C (1 Torr) weighing 700.6 mg (69% yield, not optimized). ^{1}H NMR δ 7.32, m, 5 H (aromatic protons); 4.68, q, J = 8 Hz, 1 H ($CHOCH_2O$); 4.48, t, J = 9 Hz, 1 H ($CHOCH_2O$); 4.47, s, 2 H (benzylic protons); 4.26, t, J = 9 Hz, 1 H ($CHOH_2O$); 3.47, d of d, J = 4.5, 9 Hz, 1 H ($CHCH_2O$); 3.33, t, J = 9 Hz, 1 H ($CHCH_2O$); 2.11, m, 1 H (CH_3CH); 1.02, d, J = 7 Hz, 3 H (CH_3CH). ^{13}C NMR δ 155.1, s (C-2); 137.8, s (quaternary phenyl C); 128.5, d (meta C's); 127.8, d (para C); 127.6, d (ortho C's); 79.1, d (C-4); 73.3, t (benzyl C); 71.7, t (C-1′); 68.8, t (C-5); 37.5, d (C-2′); 11.6, q (C-3′). Ir 1812 (carbonate C=O); 1370 (methyl); 1176, 1091, 1066 (C–O); 740; 694 cm^{-1} (monosubstituted benzene). Mass spectrum (10% cutoff) m/e 236, 0.9% (M^+); 235, 1.6% ($M^+ - H$); 159, 10% ($M^+ - C_6H_5$); 107, 18% ($PhCH_2O^+$); 91, 100% ($PhCH_2^+$); 68, 23%; 65, 20%; 43, 29%.

Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.08; H, 6.83. Found: C, 66.26; H, 6.89.

3-Carbamoyl-2-methylbutane-1,3,4-triol 1-*O*-Benzyl Ether (12) and 4-Carbamoyl-2-methylbutane-1,3,4-triol 1-*O*-Benzyl Ether (11). To a solution of 1.37 g of 2′-(1,3-dioxacyclopent-2-on-4-yl)-1′-propyl benzyl ether (**10**) dissolved in 1 ml of dioxane, 5 ml of concentrated NH_4OH was added and the solution stirred for 15 h. The reaction mixture was poured into 50 ml of H_2O and extracted with 5 × 30 ml of ether. The ether layers were combined, washed with 2 × 100 ml of 10% HCl, 3 × 100 ml of saturated $NaHCO_3$, and 100 ml of saturated NaCl, and dried over $MgSO_4$. The ether was then evaporated, leaving 1.52 g of residue. This was chromatographed on 108 g of silica gel, giving 108.6 mg of 2-methylbutane-1,3,4-triol 1-*O*-benzyl ether (**10**, 8.8% yield, eluted with 20% EtOAc in benzene); 854.6 mg of pure 4-carbamoyl-2-methylbutane-1,3,4-triol 1-*O*-benzyl ether (**11**, 57.5%, 25% EtOAc in benzene); 278.8 mg of pure 3-carbamoyl-2-methylbutane-1,3,4-triol 1-*O*-benzyl ether (**12**, 18.9%, 25% EtOAc in benzene); as well as 181 mg of mixed fractions. An integrated 270-MHz ^{1}H NMR spectrum of the reaction mixture showed the ratio of primary (**11**) to secondary carbamate (**12**) to be 73:27. The products isolated were in the ratio 75:25.

Properties of **11**: ^{1}H NMR δ 7.30, m, 5 H (aromatic protons); 5.50, br s, 2 H (NH_2); 4.45, s, 2 H (benzylic protons); 4.03, AB of ABX, $|J_{AB}|$ = 9 Hz, 2 H (CH_2OCONH_2]; 3.93, X of ABX, 1 H (CHOH); 3.66, br s, 1 H (OH); 3.43, CD of CDY, $|J_{AB}|$ = 10, $|J_{AX} + J_{BX}|$ = 30 Hz, 2 H ($CHCH_2OCH_2$); 1.91, m, 1 H (CH_3CH); 0.92, d, J = 7 Hz, 3 H (CH_3CH). In Me_2SO-d_6, a pentet appears at δ 3.81, J ~ 4 Hz, 1 H (CHOH), that is coupled to a signal at δ 4.79, d, J = 5 Hz, 1 H (OH). ^{13}C NMR δ 157.2, s (urethane C=O); 137.9, s, (quaternary phenyl C); 128.4, d (meta C's); 127.7, d (para C); 127.6, d (ortho C's); 73.7, t (benzyl C*); 73.4, t (C-1*); 71.9, d (C-3); 67.8, t (C-4); 35.9, d (C-2); 11.3, q (C-2's methyl). Ir 3600–3200 (OH); 2850 (C–H); 1727–1740 (C=O); 1390 (methyl); 1080 (C–O); 740, 700 cm^{-1} (monosubstituted benzene). Mass spectrum (30% cutoff) m/e 254, 0.8% ($M^+ + 1$); 179, 5% ($M^+ - CH_2OCONH_2$); 147, 50% ($M^+ - OCH_2Ph + 1$); 108, 29% ($PhCH_2OH^+$); 107, 31% ($PhCH_2O^+$); 104, 27% ($HO^+{=}CHCH_2O$-$CONH_2$); 103, 28% ($O{=}CHCH_2OCONH_2$); 92, 44% ($PhCH_2^+ + 1$); 91, 100% ($PhCH_2^+$); 77, 13% (Ph^+); 44, 34% (NH_2CO^+).

Anal. Calcd for $C_{13}H_{19}NO_4$: C, 61.64; H, 7.56; N, 5.53. Found: C, 61.37; H, 7.31; N, 5.79.

Properties of **12**: ^{1}H NMR δ 7.32, m, 5 H (aromatic protons); 5.04, br s, 2 H (NH_2); 4.77, q, J = 5 Hz, 1 H ($CHOCONH_2$); 4.50, s, 2 H (benzylic protons); 3.72, d, J = 4 Hz, 2 H (CH_2OH); 3.40, AB of ABX, $|J_{AB}|$ = 9 Hz, 2 H ($CHCH_2OCH_2$); 3.24, br s, 1 H (OH); 2.16, septet,

$J \sim 7$ Hz, 1 H (CH_3CH); 0.97, d, $J = 7$ Hz, 3 H (CH_3CH). In Me_2SO-d_6, a signal appeared at δ 4.76, t, $J \sim 5$ Hz, 1 H (OH), that was coupled to a signal at δ 3.46, obscured by H_2O peak (CH_2OH). ^{13}C NMR δ 157.6, s (urethane C=O); 137.8, s (quaternary phenyl C); 128.4, d (meta C's); 127.7, d (ortho + para C's); 77.7, d (C-3); 73.3, t (benzyl C); 71.9, t (C-1); 63.2, t (C-4); 34.9, d (C-2); 12.9, q (C-2's methyl). Ir 3600–3200 (OH); 2940–2850 (C–H); 1718 (C=O); 1380 (methyl); 1100, 1050, 1020 (C–O); 740, 697 cm^{-1} (monosubstituted benzene). Mass spectrum (30% cutoff) *m/e* 254, 0.8% ($M^+ + 1$); 223, 0.6% ($M^+ - CH_2OH + 1$); 192, 32% ($M^+ - NH_2CO_2H$); 107, 48% ($PhCH_2O^+$); 92, 48% ($PhCH_2^+ + 1$); 91, 100% ($PhCH_2^+$); 44, 32% (CO_2^+ or NH_2CO^+).

Anal. Calcd for $C_{13}H_{19}NO_4$: C, 61.64; H, 7.56; N, 5.53. Found: C, 61.48; H, 7.47; N, 5.55.

(2*RS*,3*SR*)-4-Acetoxy-2-methylbutane-1,3-diol 1-*O*-Benzyl Ether (13). A solution of 1.00 g (4.7 mmol) of (2*RS*,3*SR*)-2-methylbutane-1,3,4-triol 1-*O*-benzyl ether (**9**) in 15 ml of pyridine and 0.44 ml (4.6 mmol) of acetic anhydride was stirred at room temperature for 48 h, and then poured into an ice–H_2O–concentrated HCl (3:3:1) mixture. This was extracted with 5 × 30 ml of ether, and the combined ether extracts washed with 2 × 100 ml of 5% HCl and 3 × 100 ml of saturated $NaHCO_3$, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was applied to a high-pressure column chromatographic system and these fractions eluted: 925 mg of product (80% conversion, 96% yield, eluted with 10–15% EtOAc in benzene) and 201 mg of starting material (20%, eluted with 50% EtOAc in benzene). ^1H NMR δ 7.32, m, 5 H (aromatic protons); 4.50, s, 2 H (benzyl protons); 4.09, AB of ABX, $|J_{AB}| = 10.5$, $|J_{AX} + J_{BX}| = 36$ Hz, 2 H (CH_2OAc); 4.01, br X of ABX, 1 H (CHOH); 3.51, complex d, 2 H ($CHCH_2OCH_2$); 2.83, br s, 1 H (OH); 2.10, s, 3 H (CH_3CO); 2.00, m, 1 H (CH_3CH); 0.97, d, $J = 7$ Hz, 3 H (CH_3CH). In Me_2SO-d_6, a signal appeared at δ 4.87, d, $J \sim 6$ Hz, 1 H (CHOH), that was coupled to a signal at δ 3.76, pentet, $J \sim 5.2$ Hz, 1 H (CHOH). ^{13}C NMR δ 171.1, s (carbonyl C); 138.0, s (quaternary phenyl C); 128.3, d (meta C's); 127.5, d (ortho + para C's); 73.1, t (benzyl C + C-1); 70.6, d (C-3); 67.0, t (C-4); 35.9, d (C-2); 20.8, q (acetate methyl); 11.2, q (C-2 methyl). Ir 3600–3200 broad, (OH); 1745 (acetate C=O); 1380 (methyl); 1242 (C–O–C of acetate); 1095, 1060 (ether C–O); 740, 694 cm^{-1} (monosubstituted benzene). Mass spectrum (3% cutoff) *m/e* 252, 0.05% (M^+); 179, 1.0% ($M^+ - CH_2OAc$); 91, 100% ($PhCH_2^+$); 43, 87% ($CH_3C{\equiv}O^+$).

Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.64; H, 7.99. Found: 66.67; H, 7.72.

When 1.2 molar equiv of acetic anhydride was used, 26% of the diacetate of **9** was isolated by HPLC.

Anal. Calcd for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53. Found: C, 65.54; H, 7.55.

(2*RS*,3*SR*)-4-Acetoxy-3-carbamoyl-2-methyl-1-butanol 1-*O*-Benzyl Ether (3). A solution of 331 mg (1.31 mmol) of 4-acetoxy-2-methylbutane-1,3-diol 1-*O*-benzyl ether in 5 ml of CH_2Cl_2 was added to a 10-ml flask containing 173 mg (2.62 mmol) of NaOCN, and 314 mg (2.62 mmol) of CF_3CO_2H was added dropwise with very slow stirring. The flask was stoppered and allowed to stir slowly for 2 days. The reaction mixture was then poured into 50 ml of CH_2Cl_2, to which 50 ml of H_2O was added. The H_2O layer was extracted with 4 × 25 ml of CH_2Cl_2 and washed with 2 × 50 ml of 5% HCl and 3 × 50 ml of saturated $NaHCO_3$, and the CH_2Cl_2 was evaporated, leaving 382 mg of solid, which was recrystallized from ether–benzene to give 371 mg (96%) of white solid with mp 112–113 °C. ^1H NMR δ 7.32, m, 5 H (aromatic protons); 5.08, m, 1 H (CHO); 4.73, br s, 2 H (NH_2); 4.50, s, 2 H (benzylic protons); 4.27, d of d, $J = 3$, 12 Hz, 1 H (CH_2OAc); 4.17, d of d, $J = 12$, 15 Hz, 1 H (CH_2OAc); 3.38, complex d, 2 H ($CHCH_2OCH_2$); 2.11, m, 1 H (CH_3CH); 2.06, s, 3 H (CH_3C=O); 1.00, d, $J = 7$ Hz, 3 H (CH_3CH). ^{13}C NMR δ 170.9, s (acetate C=O); 156.6, s (urethane C=O); 138.1, s (quaternary phenyl C); 128.3, d (meta C's); 127.6, d (ortho + para C's); 73.2, t + d (benzyl C + C-3); 71.8, t (C-1); 64.2, t (C-4); 35.1, d (C-2); 20.8, q (acetate methyl); 12.3, q (C-2-methyl). Ir 3401, 3279 (NH_2); 1745 (acetate C=O); 1701 (urethane C=O); 1647 (amide I band); 1235 (C–O–C of acetate); 1050 (ether C–O); 740, 695 cm^{-1} (monosubstituted benzene). Mass spectrum (10% cutoff) *m/e* 295, 0.09% (M^+); 128, 15%; 91, 69% ($^+CH_2Ph$); 71, 18%; 68, 32%; 65, 19%; 43, 100% ($CH_3C{\equiv}O^+$).

Anal. Calcd for $C_{15}H_{21}NO_5$: C, 61.00; H, 7.17; N, 4.74. Found: C, 60.82; H, 6.96; N, 4.48.

(2*RS*,3*SR*)-3-Acetoxy-2-methylbutane-1,4-diol 1-*O*-Benzyl Ether. To a solution of 1.00 g of (2*RS*,3*SR*)-2-methylbutane-1,3,4-triol 1-*O*-benzyl ether in 15 ml of pyridine was added 1.44 g of trityl chloride. The solution was stirred for 48 h at room temperature following which 0.45 ml of acetic anhydride was added, and the solution stirred 2 more days at room temperature. After addition of 50 ml of ether the mixture was washed with 2 × 50 ml of H_2O. The H_2O layer was extracted with 3 × 50 ml of ether and the combined ether extracts washed with 2 × 50 ml of 5% HCl and 3 × 100 ml of saturated $NaHCO_3$ and dried over $MgSO_4$. The residue after solvent evaporation was subjected to HPLC on 108 g of slightly acidic silica gel. In addition to trityl compounds, eluted with benzene, there were obtained 345 mg of diacetate (25%, eluted with 5% EtOAc in benzene), 170 mg of 4-acetoxy-2-methylbutane-1,3-diol 1-*O*-benzyl ether (14%, eluted with 10% EtOAc in benzene), and 673 mg of 3-acetoxy-2-methylbutane-1,4-diol 1-*O*-benzyl ether (56%, eluted with 15–20% EtOAc in benzene). ^1H NMR δ 7.32, m, 5 H (aromatic protons); 4.91, d of t, $J = 4.5$, 6.3 Hz, 1 H (CHOAc); 4.50, AB quartet, $|J_{AB}| = 16.2$ Hz, 2 H (benzylic protons); 3.72, br t, $J \sim 6$, 2 H (CH_2OH); 3.42, d of d, $J = 4.8$, 19.5 Hz, 1 H (CH_3CHCH_2O); 3.34, d of d, $J = 7.4$, 9.5 Hz, 1 H (CH_3CHCH_2O); 2.69, t, $J \sim 6$ Hz, 1 H (CH_2OH); 2.18, m, 1 H (CH_3CH); 2.07, s, 3 H (CH_3C=O); 0.94, d, $J = 7$ Hz, 3 H (CH_3CH). Ir 3600–3200 broad (OH); 1745 (acetate C=O); 1380 (methyl); 1245 (C–O–C of acetate); 1095, 1060 (ether C–O); 740, 694 cm^{-1} (monosubstituted benzene). Mass spectrum (5% cutoff) *m/e* 235, 0.2% ($M^+ - OH$); 222, 0.3% ($M^+ - CH_2OH + 1$); 209, 0.3% ($M^+ - CH_3C{\equiv}O$); 192, 12% ($M^+ - CH_3CO_2H$); 191, 2.2% ($M^+ - CH_3CO_2$); 161, 3% ($M^+ - CH_2Ph$); 108, 31% ($PhCH_2^+OH$); 107, 17% ($PhCH_2O^+$); 91, 100% ($PhCH_2^+$); 65, 14%; 43, 76% ($CH_3C{\equiv}O^+$).

Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.64; H, 7.99. Found: C, 66.45; H, 7.82.

Preparation of the Carbinolamide 2. To a solution of 57.9 mg (0.2 mmol) of 3-carbamoyl-4-acetoxy-2-methylbutanol 1-*O*-benzyl ether (**3**) in 1 ml of hot benzene was added a solution of 32.0 mg (0.2 mmol) of styrylglyoxal[21,22] in hot benzene. The solution was stirred for 48 h under reflux and the solvent evaporated in vacuo. It was replaced with 2 ml of hexane–toluene (10:1) and the mixture kept at −25 °C for 2 days. Crystals (88.0 mg, 98%) having mp 80–82 °C were collected after centrifugation and washing with cold hexane (1 ml). The melting point of these crystals was not changed after a further recrystallization from the same solvent mixture. They may consist of a mixture of diastereomers. ^1H NMR δ 7.86, d, $J = 15$ Hz, 1 H (=CHCO); 7.62, d of d, $J = 6$, 2 Hz, 2 H (meta H's of PhCH=); 7.38, br m, 3 H (ortho and para H of PhCH=); 7.27, m, 5 H ($PhCH_2$); 7.03, d, $J = 15$ Hz, 1 H (PhCH=); 6.10, br d $J \sim 6$ Hz, 1 H (OCHNH); 5.75, br d, $J \sim 6$ Hz, 1 H (OCHNH); 5.20, m, 1 H (CHOCONH); 4.78, br m (HOCHNH); 4.47, s, 2 H (CH_2Ph); 4.28, m, 2 H (CH_2OAc); 3.40, d, $J = 6$ Hz, 2 H (CH_3CHCH_2O); 2.03, s, 3 H ($COCH_3$); 1.98, m, 1 H (CH_3CH); 1.02, d, $J = 6$ Hz, 3 H (CH_3CH). The doublet at δ 1.02 is really two doublets (in about a 60:40 ratio) separated by less than 2 Hz at 270 MHz, possibly resulting from this being a diastereomeric mixture. In addition to the peaks reported above, there are present clear peaks at δ 6.98 (styrylglyoxal) and 5.11, 4.90, and 4.49 (urethane **3**) comprising roughly 5% of the mixture, possibly resulting from dissociation in the NMR tube. Ir 3400 (NH); broad 3600–3300 (OH); 1745 ($OCOCH_3$); 1701 (CH=CHCO); 1227; br 1064 (C–O–C); 754, 712 cm^{-1} (monosubstituted benzene). Mass spectrum (20% cutoff) *m/e* 192, 3.1%; 174, 67%; 159, 23%; 131, 100% ($PhCH{=}CHCO^+$); 99, 23%; 91, 87% ($PhCH_2^+$); 43, 53% (CH_3CO^+).

Anal. Calcd for $C_{25}H_{29}NO_7$: C, 65.92; H, 6.42; N, 3.08. Calcd for hemihydrate: C, 64.64; H, 6.51; N, 3.02. Found: C, 64.91, 65.02; H, 6.31, 6.36; N, 3.40, 3.36.

Preparation of the Carbinolamide Methyl Ether 2a. A solution of 40 mg of the carbinolamide **2** in 1 ml of distilled methanol was heated in an oil bath until boiling occurred. The boiling was continued for 1 min and then the excess methanol evaporated in vacuo. This yielded 40.2 mg of a clear oil homogeneous by TLC and NMR. ^1H NMR δ 7.86, d, $J = 12$ Hz, 1 H (=CHCO); 7.61, d of d, $J = 6$, 2 Hz, 2 H (meta H's of PhCH=); 7.38, br m, 3 H (ortho and para H of PhCH=); 7.28, m, 5 H ($PhCH_2$); 7.01, d, $J = 12$ Hz, 1 H (PhCH=); 6.32, d, $J \sim 6$ Hz, 1 H (OCHNH); 6.02, br d, $J \sim 6$ Hz, 1 H (OCHNH); 5.20, m, 1 H (CHOCONH); 4.48, s, 2 H (CH_2Ph); 4.29, m, 2 H (CH_2OAc); 3.50, s, 3 H (CH_3O); 3.40, d, $J = 6$ Hz, 2 H (CH_3CHCH_2O); 2.05, s, 3 H ($OCOCH_3$); 1.98, m, 1 H (CH_3CH); 1.02, d, $J = 6$ Hz, 3 H (CH_3CH). Ir 3350 (NH); 1730 ($OCOCH_3$); 1689 (PhCH=CHCO); 1215; 1100, 1062 (C–O–C); 750, 712 cm^{-1} (monosubstituted benzene). Mass spectrum (20% cutoff) *m/e* 338, 19% ($M^+ - PhCHCHCO$); 131, 100% ($PhCHCHCO^+$); 91, 37% ($PhCH_2^+$); 57, 22%; 43, 42% (CH_3CO^+).

Anal. Calcd for $C_{26}H_{31}NO_7$: C, 66.51; H, 6.66; N, 2.98. Found: C, 66.23; H, 6.57; N, 3.02.

(−)-(5*R*,6*S*)-2,2,5-Trimethyl-6-[(*R*)-*N*-α-phenylethylcarbamoyloxy]-1,3-dioxepane and (+)-(5*S*,6*R*)-2,2,5-Trimethyl-6-[(*R*)-*N*-α-phenylethylcarbamoyoxy]-1,3-dioxepane. Into a flame-dried 100-ml flask containing a stirring bar and 60 ml of freshly distilled hexane was added by syringe 5.63 g (35.2 mmol) of (5*RS*,6*SR*)-2,2,5-trimethyl-6-hydroxy-1,3-dioxepane, followed by 4.93 g (33.5 mmol) of (+)-(*R*)-α-phenethyl isocyanate (Norse Laboratories). The flask was fitted with a reflux condenser and flushed with N_2. After 4 days at reflux, TLC showed no isocyanate remaining, and

the solvent was removed in vacuo. The resulting yellow oil was dissolved in 90 ml of hexane + 15 ml of toluene + 1 ml of pyridine and left in the freezer for 5 days, during which time crystallization occurred. After three recrystallizations from hexane–toluene (9:1 to 5:1), there was obtained 2.32 g (22.5%, 45% of theory) of a solid having mp 103–103.5 °C and $[\alpha]^{23}D$ −1.96° (*c* 1.0, $CHCl_3$). Prior experiments had shown that the rotation of such material does not improve upon further recrystallization. ^1H NMR δ 7.31, m, 5 H (phenyl H); 5.11, br d, 1 H (NH); 4.82, pentet, $J \sim 6.6$ Hz, 1 H (CHN); 4.42, br m, 1 H (CHO); 3.73, two d, J = 12, 2 Hz, 2 H (one H each from C-4 and C-7); 3.61, d of d, J = 12, 6 Hz, 1 H (C-7 H); 3.40, d of d, J = 12, 5.4 Hz, 1 H (C-4 H); 1.86, m, 1 H (CH_3CHCH_2); 1.49, d, J = 7 Hz, 3 H (CH_3CHN); 1.33, s, 3 H (CH_3CCH_3); 1.31, s, 3 H (CH_3CCH_3); 0.98, d, J = 7 Hz, 3 H (CH_3CHCH_2). ^{13}C NMR δ 155.3, s (urethane C=O); 143.9, s (quaternary phenyl C); 128.5, d (meta C's); 127.2, d (para C); 125.9, d (ortho C's); 101.1, s (C-2); 76.4, d (C-6); 62.6, t (C-7); 61.3, t (C-4 of dioxepane); 50.9, d (benzyl C); 38.6, d (C-5 of dioxepane); 24.8, q (methyl of C-2); 24.4, q (methyl of C-2); 22.6, q (methyl β to phenyl); 14.4, q (methyl of C-5). Ir 3322 (NH); 1724 (C=O); 1370, 1380 (methyls); 1233, 1214 (acetonide); 846; 704, 763 cm^{-1} (monosubstituted benzene). Mass spectrum (10% cutoff) *m/e* 308, 0.5% (M^+ + 1); 307, 0.05% (M^+); 292, 1.8% ($M^+ - CH_3$); 250, 10% ($M^+ - CH_2COCH_3$); 249, 11% ($M^+ - CH_3COCH_3$); 105, 100% ($PhCHCH_3^+$); 84, 26%; 77, 10% (Ph^+); 72, 18%; 58, 56% ($CH_3COCH_3^+$); 43, 36% ($CH_3C{\equiv}O^+$).

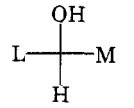
Anal. Calcd for $C_{17}H_{25}NO_4$: C, 66.42; H, 8.20; N, 4.56. Found: C, 66.50; H, 8.00; N, 4.71.

The mother liquors from the first crystallization were chromatographed on silica gel using 1–4% EtOAc in benzene containing 0.1% pyridine, which afforded slight separation of the diastereomers. After four passes through a HPLC column of 108 g silica gel, there was obtained 321 mg (23%, 47% of theory) of the diastereomer melting at 74.5–75.0 °C after crystallization from hexane. This diastereomer had $[\alpha]^{23}D$ 78.44° (*c* 1.0, $CHCl_3$). ^1H NMR δ 7.31, m, 5 H (phenyl H); 5.20, br d, $J \sim 6$ Hz, 1 H (NH); 4.82, pentet, J = 6.6 Hz, 1 H (CHN); 4.44, br d of t, 1 H (OCH); 3.78, br d, 2 H (one H each from C-4 and C-7); 3.67, br d of d, J = 12, 5.4 Hz, 1 H (C-7 H); 3.38, d of d, J = 12, 6 Hz, 1 H (C-4 H); 1.80, sextet of d, J = 6.6, 2 Hz, 1 H (C-5 H); 1.48, d, J = 7.2 Hz, 3 H (CH_3CHN); 1.33, s, 3 H (CH_3CCH_3); 1.31, 3 H (CH_3CCH_3); 0.93, d, J = 7.2 Hz, 3 H (CH_3CHCH_2). ^{13}C NMR δ 155.2, s (urethane C=O); 143.8, s (quaternary phenyl C); 128.6, d (meta C's); 127.2, d (para C); 125.9, d (ortho C's); 101.2, s (C-2 of dioxepane); 76.3, d (C-6 of dioxepane); 62.6, t (C-7 of dioxepane); 61.2, t (C-4 of dioxepane); 50.8, d (benzyl C); 38.6, d (C-5 of dioxepane); 24.8, q (C-2's methyl); 24.4, q (C-2's methyl); 22.4, q (methyl β to phenyl); 14.5, q (C-5's methyl). Ir 3330 (NH); 1689 (C=O); 1368 (methyls); 1239, 1218 (acetonide); 847; 777, 703 cm^{-1} (monosubstituted benzene). Mass spectrum (10% cutoff) *m/e* 292, 2.7% ($M^+ - CH_3$); 249, 17% ($M^+ - CH_3COCH_3$); 164, 17%; 132, 27%; 130, 23%; 120, 10% ($PhCHNHCH_3^+$); 105, 100% ($PhCHCH_3^+$); 91, 20% ($PhCH_2^+$); 84, 62%; 79, 16%; 77, 18% (Ph^+); 71, 42%; 59, 65% ($CH_3^+COHCH_3$); 43, 42% ($CH_3C{\equiv}O^+$).

Anal. Calcd for $C_{17}H_{25}NO_4$: C, 66.42; H, 8.20; N, 4.56. Found: C, 66.18; H, 7.95; N, 4.33.

(−)-(5*R*,6*S*)-2,2,5-Trimethyl-6-hydroxy-1,3-dioxepane (Enantiomer of 6). To 1.06 g (31.1 mmol) of lithium aluminum hydride suspended in 20 ml of THF (freshly distilled from $LiAlH_4$) was added with stirring over a period of 10 min a solution of 1.96 g (6.4 mmol) of (−)-(5*R*,6*S*)-2,2,5-trimethyl-6-[(*R*)-*N*-α-phenylethylcarbamoyl]-1,3-dioxepane in 10 ml of THF, while cooling in an ice bath. The mixture was then heated at reflux under N_2 for 5 h. The flask was cooled in an ice bath and 2.5 ml of saturated Na_2SO_4 solution added dropwise with stirring. The resulting white precipitate was filtered and washed with 10 × 6 ml of Et_2O. The filtrate was dried over $MgSO_4$ and evaporated, leaving 1.94 g of a mixture of the alcohol and α-phenethylamine. These were separated by a rapid filtration through silica gel. For this purpose the mixture was dissolved in 5 ml of hexane, applied to 15 g of silica gel, and 45 ml of hexane filtered through and discarded. Elution with 20 ml of ether, followed by 30 ml of EtOAc, afforded 1.03 g of the alcohol. Further elution with EtOAc (50 + 100 ml) eluted only amine in small quantities. The alcohol was distilled in a microstill to give 988.3 mg (96%) of pure (−)-**6** having $[\alpha]^{23}D$ −43.46° (*c* 1.0, $CHCl_3$). The ir, ^1H NMR, and mass spectra of this material were identical with those of the racemate.

Determination of Absolute Configuration of (+)-2,2,5-Trimethyl-6-hydroxy-1,3-dioxepane (6). (+)-(5*S*,6*R*)-2,2,5-Trimethyl-6-hydroxy-1,3-dioxepane (32.0 mg, 0.20 mmol) having $[\alpha]^{22}D$ = +42.39° (*c* 1.0, $CHCl_3$) and 124.0 mg (0.40 mmol) of α-phenylbutyric anhydride[23] were dissolved in dry pyridine to make 1.00 ml of solution. Previous work had established that the reaction is complete in 8 h at room temperature. The reaction mixture was allowed to remain at room temperature for 16 h after which 50.0 μl of H_2O was added to effect hydrolysis of excess anhydride. After 45 min a rotation was taken of the solution: α_1 2.346°. The solution was removed from the cell, mixed with 100 μl of Et_3N, and a second rotation taken immediately: α_2 2.529°. According to the method of Horeau[19] one obtains $\alpha_1 - 1.1\ \alpha_2 = -0.436°$ and thus the alcohol has the "configuration":



In this case, this translates to 5*S*,6*R* for the absolute configuration of the alcohol **6** and 16.7% for the optical yield in the acylation reaction. The ester was isolated by pouring the solution into 20 ml of Et_2O, washing with 2 × 20 ml of $NaHCO_3$, drying over $MgSO_4$, and evaporating the solvents. The residue weighed 52.3 mg (86% yield) and had a rotation of 2.426° when dissolved in 1.00 ml of dry pyridine + 50.0 μl of H_2O ($[\alpha]^{23}D$ 48.7°) and 2.224° when dissolved in 1.00 ml of dry pyridine + 50.0 μl of H_2O + 100 μl of Et_3N ($[\alpha]^{23}D$ 48.9°). Thus the assumption of little change in $[\alpha]D$ of ester upon addition of Et_3N is correct in this case (cf. ref 19). ^1H NMR δ 7.32, s, + 7.30 (ratio 58:42), s, 5 H (phenyl H); 4.50, d of t, J = 6.6, 3.6 Hz, 1 H (OCH); 3.65, d, J = 4.2 Hz, 1 H ($OCHCH_2$); 3.59,[24] d of d, J = 9.6, 3.0 Hz, and 3.42,[24] d of d, J = 12, 7.8 Hz, 1 H ($CHCO_2$); 3.50,[24] d of d, J = 24, 7.2 Hz, 1 H ($OCHCH_2O$); 3.49,[24] d of d, J = 14.4, 12.6 Hz, 1 H ($CHCH_2$); 3.32,[24] d of d, J = 12.6, 7.2 Hz, 1 H ($CHCH_2O$); 2.11, d of quintets, J = 7.2 Hz, and 1.81, d of quintets, J = 7.2 Hz (ratio 58:42), 2 H (CH_3CH_2); 1.68, d of sextets, J = 7.2, 3.0, 1 H (CH_3CH); 1.32, s, 3 H (CH_3CCH_3); 1.31, s, 3 H (CH_3CCH_3); 0.91, d of d, J = 7.2 Hz, and 0.89, d of d, J = 7.2, 13.6 Hz (ratio 58:42), 3 H (CH_3CH_2); 0.73, d, J = 7.2 Hz, 2 H (CH_3CH). Ir 1730 (C=O); 1370, 1366 (methyl); 1220 (acetonide) 846; 698, 770 cm^{-1} (monosubstituted benzene). Mass spectrum (10% cutoff) *m/e* 291, 8% ($M^+ - CH_3$); 147, 15% [$PhC(CH_2CH_3){=}COH^+$]; 119, 100% ($PhCHC_2H_5^+$); 91, 46% ($PhCH_2^+$); 84, 15%, 59, 18% ($CH_3^+COHCH_3$); 43, 12% ($CH_3C{\equiv}O^+$).

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Registry No.—**2a,** 59005-35-5; **2a,** 59005-36-6; **3,** 59005-37-7; **4,** 1003-83-4; **5,** 57280-22-5; **6,** 59005-38-8; **6** acetate, 59005-39-9; (−)-(5*R*,6*S*)-**6,** 59042-52-3; (+)-(5*S*,6*R*)-**6,** 59042-53-4; **7,** 58967-01-4; **8,** 59005-40-2; **9,** 59005-41-3; **10,** 59005-42-4; **11,** 59005-43-5; **12,** 59005-44-6; **13,** 59005-45-7; *cis*-2-butene-1,4-diol, 6117-80-2; 2,2-dimethoxypropane, 77-76-9; NaOCN, 917-61-3; CF_3CO_2H, 76-05-1; (2*RS*,3*SR*)-3-acetoxy-2-methylbutane-1,4-diol 1-*O*-benzyl ether, 59005-46-8; styrylglyoxal, 6784-05-0; (−)-(5*R*,6*S*)-2,2,5-trimethyl-6-[(*R*)-*N*-α-phenylethylcarbamoyloxy]-1,3-dioxepane, 59005-47-9; (+)-(5*S*,6*R*)-2,2,5-trimethyl-6-[(*R*)-*N*-α-phenylethylcarbamoyloxy]-1,3-dioxepane, 59042-54-5; (+)-(*R*)-δ-phenethyl isocyanate, 33375-06-3.

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(14) The threo stereochemistry established for **6** on mechanistic grounds has been confirmed by converting this compound into *threo*-3-methylmalic acid, mp 127–128 °C, by benzylation followed by hydrolysis of the acetonide grouping in aqueous HCl, oxidation of the primary alcohol groups with Jones reagent, and debenzylation with Pd/H_2. Y. Izumi, S. Tatsumi, and M. Imaida [*Bull. Chem. Soc. Jpn.*, **39,** 1818 (1966)] reported mp 129

°C for the threo acid and mp 115 °C for the erythro isomer. Stereoisomeric purity of **6** was shown by elution of a single peak on GLC under conditions that separated the (5*RS*,6*SR*) and (5*RS*,6*RS*) isomers, obtained by Collins oxidation of **6** and reduction of the resulting ketone by $NaBH_4$.

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Stereocontrolled Synthesis of α-Multistriatin, an Essential Component of the Aggregation Pheromone for the European Elm Bark Beetle

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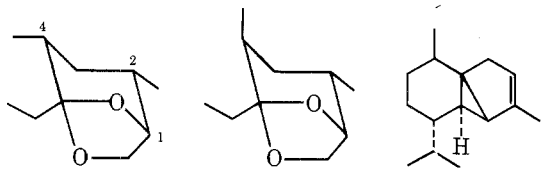
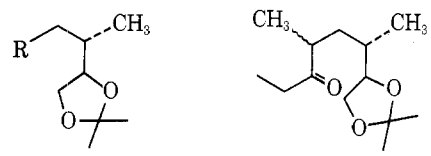
A practical stereocontrolled synthesis of an 85:15 equilibrium mixture of α- and γ-multistriatin (**1**) in an overall yield of 73% is described. α-Multistriatin is one of the three essential components of the aggregation pheromone of the European elm bark beetle. The dioxolane **3** which is available in 90% yield from (*Z*)-2-butene-1,4-diol in both the racemic and enantiomeric forms is converted as the racemate to the iodide **5** and the latter used in the alkylation of the anion of 3-pentanone. Hydrolytic cleavage of the resulting acetonide **6** furnishes the racemic multistriatins in 80% yield from **3**. The use of optically active **3** in this synthesis should furnish the as yet unknown absolute configuration of the natural pheromone.

The aggregation pheromone for the European elm bark beetle, *Scolytus multistriatus* (Marsham), which is the principal vector of Dutch elm disease in the United States, has recently been characterized as a three-component mixture by Silverstein et al.[1] One of the active components has been named α-multistriatin by these authors and has been assigned structure **1**.[2] The other two components are (−)-4-methyl-3-heptanol and (−)-α-cubebene (**2**). The first two components are beetle-produced pheromones, the third a host-produced synergist. The possible uses of a mixture of the three as a control of the elm bark beetle makes α-multistriatin an interesting target for chemical synthesis.



1α **1γ** **2**



3, R = OH
4, R = tosyl
5, R = I

6

Of the two previous syntheses by Silverstein and associates the first, a nonstereospecific approach, served to elucidate and confirm the structure of the molecule; the second was designed to prove its stereochemistry. Although stereocontrolled, it proceeded in less than 2.5% overall yield.[2]

The synthesis reported in this paper yields multistriatin as an 85:15 mixture of α and γ isomers (as does that of Silverstein et al.[2]) in an overall yield of 73% from commercially available (*Z*)-2-butene-1,4-diol. The crucial step is the alkylation of 3-pentanone with the iodide **5**, which possesses the correct threo configuration at C-1 and C-2 of both α- and γ-multistriatin.[3] The iodide **5** was obtained in quantitative yield by classical procedures from the dioxolane **3**. The synthesis of the latter in four steps in 90% yield is described in the preceding paper.[4,5] The alkylation reaction of 3-pentanone with the iodide **5** could be accomplished in low yield via the pyrrolidine enamine,[6] or the magnesium salt of the *tert*-butylimine.[7] The preferred method was reaction of the enolate (5 equiv; prepared from the ketone with lithium diisopropylamide) and the iodide in THF for 3 days at room temperature. This method afforded approximately 85% of the mixture of diastereomeric ketones **6**, and 15% of recovered iodide. The acetonide grouping was removed and the molecule cyclized by treatment with 1 N HCl in 2:1 acetonitrile–H_2O for 18 h, which provided multistriatin (**1**) in quantitative yield in an 85:15 ratio of α and γ isomers, shown by ^1H NMR at 270 MHz and GLC to be identical with the equilibrium mixture obtained by Silverstein et al.[2]

That no detectable amounts of the β or δ isomers were formed in this sequence of reactions attests to the stereospecificity of the epoxide opening reaction with dimethyllithium cuprate,[4,5] a key reaction in the synthesis of the dioxolane **3**.

Since this compound has been obtained in optically active form of known absolute configuration,[4] this synthesis also constitutes a total synthesis of optically active α- and γ-multistriatin. Completion of the synthesis with optically active **3** will at the same time establish the as yet unknown absolute configuration of the natural pheromone.

Experimental Section

Ir spectra were recorded on a Perkin-Elmer Model 137 spectrophotometer. Liquid samples were run as a thin film between NaCl plates. NMR spectra were determined as solutions in $CDCl_3$ with Me_4Si as an internal standard. Chemical shifts are reported in δ, coupling constants (*J*) are reported in hertz; the abbreviations s, d, t, q, and m signify singlet, doublet, triplet, quartet, and multiplet, respectively. ^1H NMR spectra were recorded on a Bruker HX-270