matographed on a silica gel column with ether–petroleum ether (1:1) as an eluant to give 0.15 g of (±)-α-multistriatin (70% from starting acetate).

This compound was identical with an authentic sample by VPC, and the ^{1}H NMR, IR, and ^{13}C NMR spectra were consistent with literature data.[6a] VPC analysis revealed that the synthetic material was at least 99.5% pure.

Acknowledgment. We are grateful to the doners of the Petroleum Research Fund, administered by the American Chemical Society, and to the National Cancer Institute (Grant No. CA 22237) for partial support of this research. We are also grateful to Professor R. M. Silverstein for authentic samples, of the four multistriatin isomers.

Registry No. **5**, 21889-89-4; **6**, 10276-21-8; **7**, 79722-56-8; **8**, 79722-57-9; **9**, 79722-58-0; **10**, 79722-59-1; **11**, 79722-60-4; **12**, 79722-61-5; **13**, 54815-06-4; **15**, 77067-72-2; **16**, 79767-70-7; **17**, 79722-62-6; **18**, 79722-63-7; **19**, 79722-64-8; **20**, 79768-50-6; **21**, 79722-65-9; diethyl chlorophosphonate, 814-49-3; (±)-2β,3β-epoxy-4α,6α-dimethylcyclohexan-1β-ol, 79722-66-0; (±)-2β,3β-epoxy-4α,6α-dimethylcyclohexanone, 79767-71-8; (±)-1β-acetoxy-3-ethyl-4α,6α-dimethyl-2-cyclohexene, 79722-67-1.

Synthetic Approach to Cytochalasins[1]

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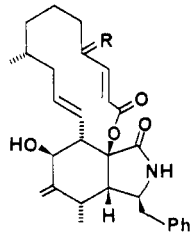
Studies directed toward total synthesis of cytochalasin B (1) and A (2) are described. A simple acyclic unit, **12**, intended for incorporation into the macrolactone ring of the cytochalasins has been prepared in seven steps from citronellol (**5**). The isoindolone nucleus **36** has been prepared by a Diels–Alder strategy via adduct **31**. Conversion of this adduct to methoxy lactam **33** and coupling with tribenzylaluminum afforded lactam **34**. Hydroxylation of the enolate of **34** gave isoindolone **35** containing the five chiral centers necessary for preparation of **1** and **2**. Debenzylation of **35** produced diol **36**, which will be combined with fragment **12** to ultimately complete a cytochalasin total synthesis.

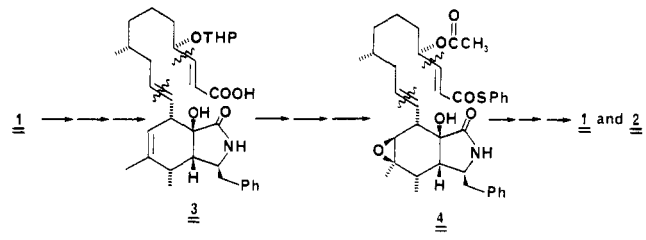
The extensive range of biological activity displayed by the cytochalasins, coupled with their unique structural features,[3] has prompted several research groups to explore synthetic approaches to these fungal metabolites.[1,4-10] Recently, Stork et al. completed the first total synthesis of cytochalasin B (**1**), the most abundant and most thoroughly studied member of this group.[11] During the past few years, we have also been attempting to develop syntheses of cytochalasins B (**1**) and A (**2**),[1,4] and we now report some details of our progress.



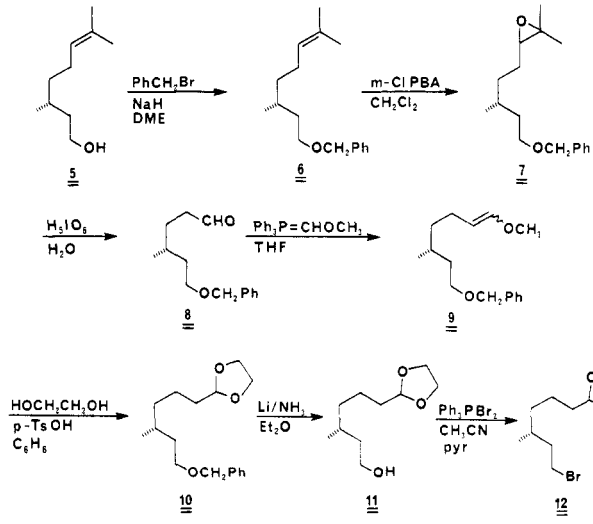
1 R = α-OH, β-H

2 R = O

Scheme I



Scheme II



Our synthetic plan was designed with the knowledge that Masamune et al.[7] had transformed cytochalasin B (**1**) in several steps to the seco acid **3**, which was then successfully converted back to **1** via intermediate epoxy thioester **4** (Scheme I). Turner et al. previously described

(1) (a) Taken from the Ph.D. Thesis of M.Y.K., Fordham University, 1980. (b) A preliminary account of a part of this work has appeared: Kim, M.; Weinreb, S. M. *Tetrahedron Lett.* **1979**, 579.

(2) Fellow of the A. P. Sloan Foundation, 1975–1979; recipient of a Research Career Development Award from the National Institutes of Health (HL-00541), 1975–1980. Address correspondence to this author at The Pennsylvania State University.

(3) (a) Tanenbaum, S. W., Ed. "Cytochalasins, Biochemical and Cell Biological Aspects"; North-Holland Publishing Co.: Amsterdam, 1978. (b) Carter, S. B. *Endeavour*, **1972**, *113*, 77. (c) Binder, M.; Tamm, C. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 370.

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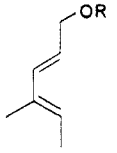
0022-3263/81/1946-5383$01.25/0

oxidation of cytochalasin B (1) to cytochalasin A (2).[12] Thus, synthesis of 3 or 4 (or any of the other Masamune intermediates[7]) would constitute total syntheses of both cytochalasins A and B. It was our intention to construct 3 and/or 4 by coupling a bicyclic isoindolone moiety, a central eight-carbon aliphatic fragment, and a three-carbon "acrylate" unit (see wavy line in 3 and 4). Described below are syntheses of the former two segments which we hope to incorporate into a cytochalasin total synthesis.

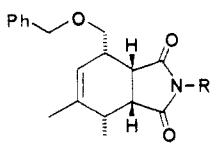
As in the Stork synthesis,[11] our starting material for preparation of the desired acyclic carbon chain containing a single chiral center was citronellol (5). Although (+)-citronellol having the proper absolute chirality for synthesis of cytochalasins is available,[13] the sequence outlined here (Scheme II) was developed by using commercial racemic 5. O-Benzylation of citronellol gave ether 6, which was degraded to aldehyde 8 in two steps via periodic acid cleavage of epoxide 7.[14] Homologation of 7 by a Wittig reaction provided enol ether 8 as a 7:6 mixture of *E* and *Z* isomers, respectively. Without separation, this mixture was treated with ethylene glycol and a catalytic amount of *p*-toluenesulfonic acid to give acetal 10. Debenzylation of 10 was effected with lithium in ammonia to afford alcohol 11. The overall yield of 11 from citronellol was about 50%. Bromide 12 was prepared from alcohol 11 by using triphenylphosphine dibromide,[15] and we hope to eventually join this compound with one of the synthetic isoindolone units described below.

Diels–Alder chemistry seemed ideally suited for construction of the cytochalasin isoindolone system both in terms of incorporating the necessary functionality and establishing the proper relative configuration of substituents. In fact, since our initial demonstration[4] of the feasibility of a Diels–Alder approach to the cytochalasin isoindolone nucleus, essentially all synthetic work in this area has been based on such a strategy.[5,6,8-11]

Our preparation of the bicyclic portion of 3 and 4 began with readily synthesized diene alcohol 13[4,10] which was



13 R=H
14 R=OCH$_2$Ph

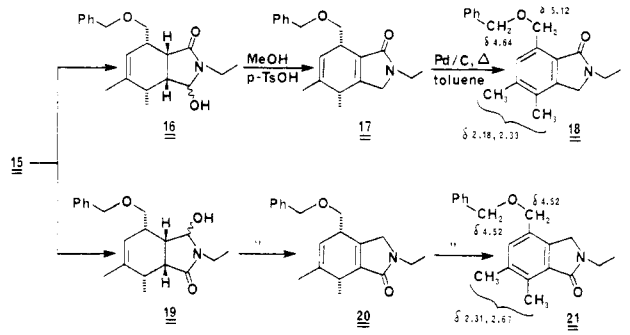


15 R=CH$_2$CH$_3$

benzylated (PhCH$_2$Br/NaH/glyme) to afford 14. This diene combined smoothly with commercially available *N*-ethylmaleimide, giving Diels–Alder adduct 15. The major part of our exploratory work was done in the *N*-ethyl series of compounds with the aim of eventually preparing a requisite isoindolone having a more easily removable nitrogen protecting group (vide infra).

Introduction of a β-*C*-benzyl group into adduct 15 was our next goal, and thus it was necessary to first selectively differentiate between the two carbonyl groups of this molecule. Reduction of imide 15 with excess sodium borohydride[16] gave a mixture of starting material (25%) and

Scheme III



what proved to be hydroxy lactams 16 (12%) and 19 (23%). Both 16 and 19 appear to be single stereoisomers, but we have not yet been able to establish the configurations of these relatively unstable intermediates. The structures of these products were firmly established by the route shown in Scheme III. Treatment of 16 and 19 with a trace of *p*-TsOH in methanol led to unsaturated lactams 17 and 20, respectively. These two compounds were easily aromatized on heating with Pd/C to yield 18 and 21. A comparison of the ^{1}H NMR spectra of 18 and 21, in particular the characteristic downfield shifts resulting from the magnetic anisotropy of the lactam carbonyl group, clearly supported the structural assignments indicated in Scheme III.

Since the desired hydroxy lactam 16 was unfortunately the minor product from the sodium borohydride reduction, we investigated reduction of imide 15 with diisobutylaluminum hydride (dibal). With this reagent the major hydroxy lactam proved to be the desired compound 16 (65%) along with a small amount of the regioisomer 19 (10%). Interestingly, although the desired hydroxy lactam 16 isolated here was identical with material obtained from the sodium borohydride reduction, the minor isomer of the dibal reaction appears to be the hydroxyl group epimer of the corresponding regioisomer 19 produced in the borohydride procedure. As anticipated, this epimer also formed unsaturated lactam 20 on treatment with a trace of *p*-toluenesulfonic acid in methanol. It should be mentioned that all attempts to reduce the N–H imide corresponding to 15 with sodium borohydride or dibal gave complex product mixtures.

We believe that the imide reduction with diisobutylaluminum hydride may involve an initial complexation of the aluminum with the benzyloxy oxygen of 15. Inspection of models suggests that delivery of hydride directly from this complex along the preferred reaction path for nucleophilic addition to imides would lead to selective reduction of the lower carbonyl group and formation of 16.[17] On the other hand, the borohydride reduction of 15 is more "normal",[16,17] leading to preferential attack of hydride at the carbonyl adjacent to the bulkier substituent (i.e., (benzyloxy)methyl > methyl), giving mainly 19. We are unable at present to extend the above arguments to explain the stereochemistry of the hydroxy lactams produced in these reductions since, as mentioned above, we have not established the hydroxyl configurations, nor do we know whether the isolated products are in fact the kinetic stereoisomers of the reactions.

It was our intention to introduce a benzyl group into hydroxy lactam 16 via an alkylation reaction which we had developed a few years ago, namely, treatment of an amide "methylol" such as 22 with an excess of a trialkyl alane

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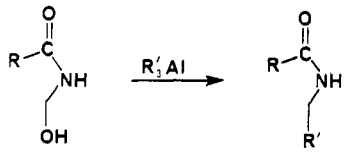
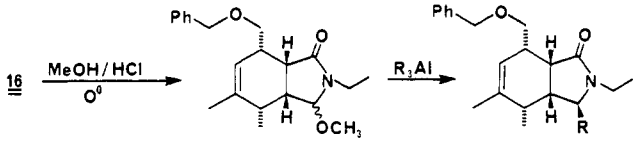


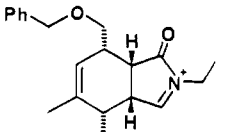
22 23

to produce a homologated amide **23**.[18] However, all efforts to couple **16** directly with alkyl aluminum reagents failed. Alternatively, hydroxy lactam **16** was first converted to methyl ether **24** on treatment with cold methanol con-



24 25 R = CH_3; 26 R = CH_2CH_3; 27 R = CH_2Ph

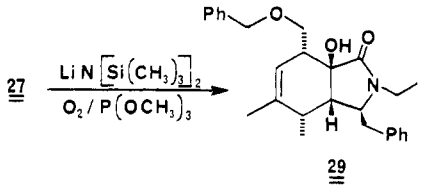
taining a trace of hydrochloric acid, and this compound was found to combine with various alanes as desired. Thus, treatment of methoxy lactam **24** with commercial trimethyl- and triethylaluminum gave the coupled products **25** and **26**, respectively. Similarly, reaction of **24** with tribenzylaluminum, generated in situ from benzylmagnesium chloride and aluminum chloride,[19] produced **27** in 40% yield. In all three cases, single stereoisomers were isolated which probably have the β configuration shown. We believe that this alkylation probably involves transfer of a ligand from an alanate complex to the less hindered β face of the electrophilic acyliminium species **28**. The stereochemistry of these products was more



28

firmly established by the results of a later series of experiments (vide infra). Several attempts were also made to effect the analogous coupling reactions with Grignard reagents, but only unsaturated lactam **17** was produced in these cases.

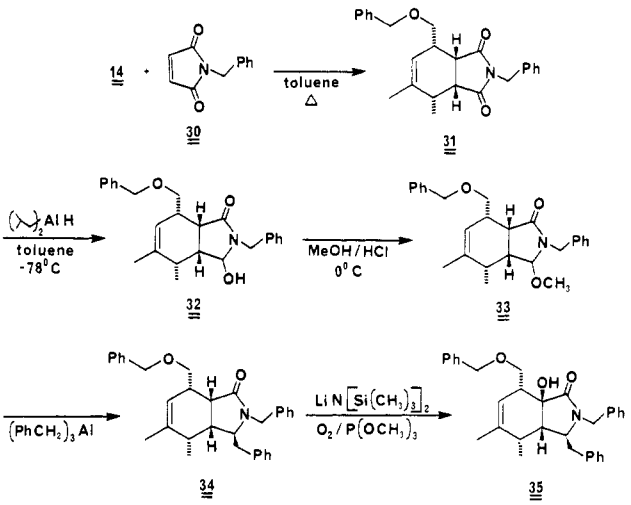
Angular hydroxylation of lactam **27** proved straightforward by using standard methodology.[20] Deprotonation of **27** with lithium hexamethyldisilazide, followed by addition of oxygen gas and trimethyl phosphite, produced a single alcohol, **29**, believed to arise from attack of oxygen



29

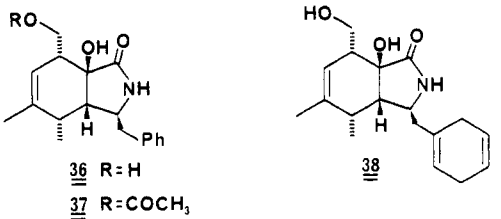
on the unhindered β side of the intermediate lactam enolate. The alcohol stereochemistry produced in this oxygenation was established later in a related compound (vide infra).

Scheme IV



With the functionalized isoindolone **29** now in hand, it was necessary to repeat the successful sequence in an alternate series of compounds containing a readily removable nitrogen protecting group. Thus, diene **14** and *N*-benzylmaleimide (**30**)[21] were converted in five steps to isoindolone **35** as shown in Scheme IV. Yields and reaction conditions in this route were essentially identical with those in the *N*-ethyl series.

We next turned our attention to removal of the *N*- and *O*-benzyl protecting groups of **35**. Reduction of **35** with lithium in ammonia, followed by addition of water to destroy excess lithium, gave a mixture of the desired deprotected diol **36** and the overreduced compound **38**. Since

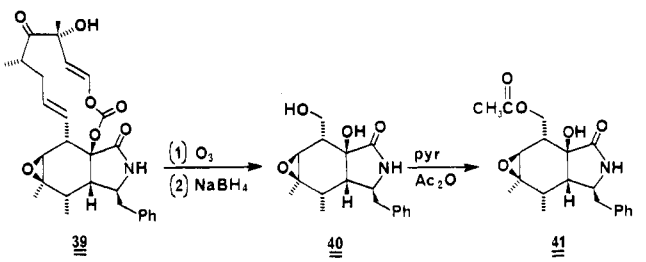


36 R = H; 37 R = $COCH_3$

38

we believed that conversion of **36** to **38** might be occurring *after* addition of the proton source,[22] the reaction was instead quenched with diphenyl ether before addition of a protic solvent, giving **36** in 80% yield.

In order to unambiguously establish the structure and stereochemistry of isoindolone **36**, we made a direct correlation with a cytochalasin degradation product. Ozonolysis of cytochalasin E (**39**) was found by Turner, Ald-



39 40 41

rich, et al. to produce an isoindolone fragment **40**.[23,24] An

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(20) Cf. Wasserman, H. H.; Lipshutz, B. H. *Tetrahedron Lett.* **1975**, 1731.
(21) Mehta, N. B.; Philips, A. P.; Lui, F. F.; Brooks, R. E. *J. Org. Chem.* **1960**, *25*, 1012.
(22) For a nice discussion of dissolving metal reductions see: House, H. O. "Modern Synthetic Reactions"; W. A. Benjamin: Menlo Park, CA, 1972. Because of the small scales on which we were working, it was impossible to use stoichiometric quantities of lithium metal.
(23) Aldridge, D. C.; Burrows, B. F.; Turner, W. B. *J. Chem. Soc., Chem. Commun.* **1972**, 148; Aldridge, D. C.; Greatbanks, D.; Turner, W. B. *Ibid.* **1973**, 551.

authentic sample of this compound[25] was acetylated to yield epoxy acetate **41**. Our synthetic isoindolone **36** was acetylated to afford **37**, and oxidation of this compound with *m*-chloroperbenzoic acid gave epoxide **41** containing a trace of the corresponding α-epoxide. Direct TLC and NMR comparison of synthetic and naturally derived compound **41** established their identity.

We are currently attempting to devise a method for joining bromo acetal **12** and isoindolone **36** or **41** to ultimately produce **3** or **4**. In addition, work is in progress on synthesis of **36** in optically active form.

Experimental Section

Melting points were taken on a Fisher-Johns hot-stage apparatus and are uncorrected. Boiling points are uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer Model 137 or 197 spectrophotometer. Proton magnetic resonance spectra at 60 MHz were recorded on either a Varian A60-A or a Perkin-Elmer R-12 spectrometer. ^{1}H NMR spectra at 100 MHz were obtained on a Varian XL-100 spectrometer and at 270 MHz on a Brucker 270-HX spectrometer at Yale University. Chemical shifts are reported in δ units with tetramethylsilane as an internal standard. All spectra were taken in deuteriochloroform unless otherwise noted. Carbon-13 magnetic resonance (^{13}C NMR) spectra were obtained on JEOLCO PH-100 FT NMR spectrometer. Mass spectra were recorded by electron impact (EI) on an Associated Electrical Industries MS-902 double-focusing mass spectrometer on which both low- and high-resolution spectra were obtained. Chemical ionization (CI) mass spectra were obtained on a Finnigan 3300 mass spectrometer using methane or isobutane as a carrier gas. Combustion analyses were performed by Micro-Tech Laboratories, Inc. Analytical and preparative thin-layer chromatography (TLC) was done on silica gel 60 PF-254 (E. M. Merck). Column chromatography was carried out by using 70–230-mesh silica gel 60 (E. M. Merck).

2,6-Dimethyl-8-(benzyloxy)-2-octene (6). To a suspension of 16.89 g (0.35 mol) of a 50% dispersion of sodium hydride in mineral oil (prewashed with dry hexane) in 300 mL of dimethoxyethane was added dropwise 50 g (0.32 mol) of Fluka (±)-citronellol (**5**) under a nitrogen atmosphere at 0 °C, and the mixture was stirred at room temperature for 2 h. Benzyl bromide (54.73 g, 0.32 mol) was added dropwise at 0 °C, and the resulting mixture was stirred at room temperature for 40 h under nitrogen. After excess sodium hydride was carefully destroyed with water, the reaction mixture was diluted with ether. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, and the solvent was evaporated in vacuo. Distillation of the crude product under vacuum [132 °C (0.4 torr)] gave 73.17 g (93%) of benzyl ether **6**: ^{1}H NMR δ 0.91 (3 H, d, J = 6 Hz), 1.63 (3 H, br s), 1.72 (3 H, br s), 1.16–2.33 (7 H, m), 3.57 (2 H, t, J = 6.5 Hz), 4.57 (2 H, s), 5.18 (1 H, m) 7.45 (5 H, s); IR (film) 2970, 2940, 2860, 1455, 1380, 1370, 1100, 740, 700 cm^{-1}.

2,6-Dimethyl-2,3-epoxy-8-(benzyloxy)octane (7). To a solution of 20 g (0.08 mol) of benzyl ether **6** in 200 mL of methylene chloride was added dropwise a solution of 18.1 g (0.09 mol) of *m*-chloroperbenzoic acid in 100 mL of methylene chloride at 0 °C. The mixture was stirred at room temperature for 1 h and was filtered. The filtrate was washed successively with saturated $NaHSO_3$, saturated $NaHCO_3$, water, and brine and dried over anhydrous $MgSO_4$. Evaporation of the solvent in vacuo gave 21.3 g (100%) of epoxide **7**, homogeneous by TLC, which was used in the next step without purification: ^{1}H NMR δ 0.92 (3 H, d, J = 5.7 Hz), 1.27 (3 H, s), 1.3 (3 H, s), 1.22–1.8 (7 H, m), 2.71 (1 H, t, J = 5 Hz), 3.54 (2 H, t, J = 6 Hz), 4.53 (2 H, s), 7.4 (5 H, s).

3-Methyl-6-(benzyloxy)-1-hexanal (8). A mixture of 121 mg (0.46 mmol) of the epoxide **7**, 112 mg (0.49 mmol) of periodic acid, and 4 mL of water was stirred at 40 °C for 4 h. The mixture was extracted with ether, and the organic layer was washed with saturated $NaHCO_3$ solution, water, and brine. The extract was dried over anhydrous $MgSO_4$, and evaporated in vacuo to give 90 mg (89%) of aldehyde **8** homogeneous by TLC and of sufficient purity for the next step: ^{1}H NMR δ 0.9 (3 H, d, J = 6 Hz), 1.2–1.9 (5 H, m), 2.43 (2 H, dt, J = 7, 2 Hz), 3.55 (2 H, t, J = 6.2 Hz), 4.55 (2 H, s), 7.45 (5 H, s), 10.02 (1 H, t, J = 2 Hz); IR (film) 2970, 2940, 2860, 1720, 1450, 1370, 1100, 740, 700 cm^{-1}.

1-Methoxy-5-methyl-7-(benzyloxy)-1-heptene (9). To a suspension of 8.52 g (0.025 mol) of methoxymethyltriphenylphosphonium chloride in 100 mL of dry THF was added dropwise 13.3 mL (0.021 mol) of 1.62 M *tert*-butyllithium in hexane at −78 °C under argon. After 25 min, a solution of 3.65 g (0.017 mol) of aldehyde **8** in 15 mL of dry THF was added dropwise to the deep red ylide solution, and the mixture was stirred for 1.5 h at −78 °C. The reaction mixture was quenched with water and diluted with ether. The organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, and evaporated in vacuo. The crude product was directly transformed into acetal **10** without purification: ^{1}H NMR δ 0.85 (3 H, d, J = 5.7 Hz), 1.08–2.3 (7 H, m), 3.45 and 3.52 (3 H, 2 s), 3.48 (2 H, t, J = 6.2 Hz), 4.48 (2 H, s), 4.12–5.1 (1 H, m), 5.85 (d, J = 6.5 Hz), 6.29 (2 d, J = 13 Hz, 1 H total, 6:7 ratio), 7.35 (5 H, s).

1-[2-(1,3-Dioxalanyl)]-4-methyl-6-(benzyloxy)hexane (10). A solution of crude enol ether **9**, 8 mL of ethylene glycol, and a crystal of *p*-toluenesulfonic acid in 30 mL of benzene was heated at reflux overnight. The reaction mixture was diluted with ether and washed successively with saturated $NaHCO_3$, saturated $CaCl_2$, water, and brine. The extract was dried over anhydrous $MgSO_4$ and was evaporated in vacuo. The crude product was purified by column chromatography, eluting with ethyl acetate/hexane (1/19) to give 2.7 g (61% from aldehyde **8**) of the oily acetal **10**: ^{1}H NMR δ 0.9 (3 H, d, J = 5.7 Hz), 1.15–1.9 (9 H, m), 3.55 (2 H, m), 3.93 (4 H, m), 4.55 (2 H, s), 4.91 (1 H, t, J = 4.5 Hz), 7.43 (5 H, s); IR (film) 2950, 2850, 1450, 1400, 1360, 1110, 740, 700 cm^{-1}; mass spectrum, m/e (relative intensity) 278 (M$^+$, 1.6), 187 (16.0), 125 (16.7), 110 (13.7), 107 (43.1), 92 (25.2), 81 (13.3); calcd for $C_{16}H_{26}O_3$ m/e 278.1882, found m/e 278.1856 (9.3 ppm error).

3-Methyl-6-[2-(1,3-dioxalanyl)]hexan-1-ol (11). To a solution of 100 mg of lithium metal in distilled liquid ammonia was added a solution of 1.28 g of acetal **10** in 3 mL of dry ether. After 10 min, ethanol was added dropwise to the reaction mixture until the blue color disappeared. Ammonia was allowed to evaporate, and the residue was diluted with ether. The organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, and evaporated in vacuo to give 814 mg (96%) of alcohol **11** which showed a single spot on TLC. The product was purified by distillation under vacuum [120 °C (1.3 torr)]: ^{1}H NMR δ 0.93 (3 H, d, J = 5.3 Hz), 1.2–1.83 (9 H, m), 1.73 (1 H, s, exchangeable), 3.73 (2 H, t, J = 6.7 Hz), 3.97 (4 H, m), 4.93 (1 H, t, J = 4 Hz); IR (film) 3340, 2900, 1460, 1410, 1120, 1040 cm^{-1}.

1-[2-(1,3-Dioxalanyl)]-4-methyl-6-bromohexane (12). To a suspension of triphenylphosphine dibromide complex [prepared by adding 0.027 mL (84.97 mg, 0.53 mmol) of bromine to a solution of 142.8 mg (0.53 mmol) of triphenylphosphine in 3 mL of acetonitrile at 0 °C and stirring for 15 min] was added dropwise a solution of 100 mg (0.53 mmol) of the alcohol **11** and 42 mg (0.53 mmol) of pyridine in 1 mL of acetonitrile at room temperature. The mixture was stirred for 2 h and was evaporated to dryness. The residue was taken up in ether, washed with saturated $NaHCO_3$, water, and brine, and dried over anhydrous $MgSO_4$. The ether was evaporated in vacuo, and the crude product was purified by column chromatography, eluting with ethyl acetate/hexane (1/4) to give 92 mg (70%) of bromide **12**: ^{1}H NMR δ 0.93 (3 H, d, J = 6 Hz), 1.1–2.2 (9 H, m), 3.48 (2 H, t, J = 7 Hz), 3.97 (4 H, m), 4.93 (1 H, t, J = 4 Hz); IR (film) 2950, 2870, 1460, 1400, 1380, 1260, 1220, 1130, 1030, 940 cm^{-1}; mass spectrum, m/e 250, 252.

3-Methyl-6-(benzyloxy)-2,4-hexadiene (14). To a suspension of 2.35 g (48 mmol) of a 50% sodium hydride dispersion in mineral oil in 80 mL of dimethoxyethane (distilled from $LiAlH_4$) was added dropwise 5 g (45 mmol) of diene alcohol **13** at 0 °C under nitrogen. The mixture was stirred for 2 h at room temperature and was cooled in an ice bath. Benzyl bromide (7.6 g, 45 mmol) was added dropwise to the mixture, and stirring was continued overnight at room temperature. Excess sodium hydride was destroyed by careful addition of water at 0 °C, and the mixture was extracted

(24) The revised structure **39** determined for cytochalasin E does not affect the assignment of structure to isoindolone **40**: Büchi, G.; Kitaura, Y.; Yuan, S.-S.; Wright, H. E.; Clardy, J.; Demain, A. L.; Glinsukon, T.; Hunt, N.; Wogan, G. N. *J. Am. Chem. Soc.* **1973**, *95*, 5423.

(25) We are very grateful to Dr. D. C. Aldridge for an authentic sample of **40** derived from cytochalasin E.

with ethyl acetate. The organic phase was washed with water and brine, dried over anhydrous $MgSO_4$, and evaporated in vacuo. The residue was purified by filtration through silica gel with chloroform as the eluant, followed by distillation of the product under vacuum [97 °C (2 torr)] to give 8 g (89%) of diene benzyl ether **14**: ^1H NMR (100 MHz) δ 1.72 (3 H, d, J = 6 Hz), 1.74 (3 H, s), 4.06 (2 H, d, J = 6 Hz), 4.50 (2 H, s), 5.54 (1 H, m), 6.25 (1 H, d, J = 15 Hz), 5.62 (1 H, dt, J = 15, 6 Hz), 7.32 (5 H, s); IR (film) 2900, 1700, 1460, 1380, 1320, 1280, 1080, 750, 705 cm^{-1}.

2-Ethyl-5α,6-dimethyl-8α-(benzyloxy)-2,4β,5β,8β,9β-pentahydro-1*H*-isoindole-1,3-dione (15). To a solution of 5 g (24.7 mmol) of diene benzyl ether **14** in 45 mL of toluene was added 3.2 g (25.5 mmol) of *N*-ethylmaleimide, and the mixture was heated at reflux for 5 h. The solvent was evaporated in vacuo, and the residue was purified by column chromatography on silica gel, eluting with ethyl acetate/hexane (1/9) to give 7 g (87%) of Diels–Alder adduct **15**: ^1H NMR (100 MHz) δ 1.04 (3 H, t, J = 8 Hz), 1.47 (3 H, d, J = 8 Hz), 1.72 (3 H, br s), 2.5 (2 H, m), 2.92 (1 H, dd, J = 6, 8 Hz), 3.18 (1 H, dd, J = 6, 8 Hz), 3.44 (2 H, q, J = 8 Hz), 3.79 (1 H, dd, J = 7, 9 Hz), 4.04 (1 H, dd, J = 7,9 Hz), 4.62 (2 H, s), 5.44 (1 H, br s), 7.32 (5 H, s); IR (film) 2930, 2840, 1760, 1700, 1660, 1440, 1400, 1350, 1220, 1080, 720, 680 cm^{-1}.

2-Ethyl-3-hydroxy-5α,6-dimethyl-8α-[(benzyloxy)methyl]-2,3,4β,5β,8β,9β-hexahydro-1*H*-isoindol-1-one (16) and 1-Hydroxy-2-ethyl-5α,6-dimethyl-8α-[(benzyloxy)methyl]-1,2,4β,5β,8β,9β-hexahydro-3*H*-isoindol-3-one (19). (A) Diisobutylaluminum Hydride Reduction. To a solution of 178 mg (0.544 mmol) of imide **15** in 2.5 mL of toluene (distilled from CaH_2) was added dropwise at −78 °C 0.7 mL of 1 M diisobutylaluminum hydride in hexane (0.7 mmol) under a nitrogen atmosphere, and the mixture was kept for 15 min at −78 °C. Several drops of water were added to the mixture which was stirred 1 h longer at room temperature. The reaction mixture was diluted with ethyl acetate, washed successively with saturated sodium potassium tartrate solution, water, and brine, and dried over anhydrous $MgSO_4$. The solvent was evaporated in vacuo, and the residue was chromatographed on silica gel, eluting with ethyl acetate/hexane (3/7) to give 116 mg (65%) of hydroxy lactam **16** and 18 mg (10%) of isomeric hydroxy lactam **19**.

Hydroxy lactam **16**: ^1H NMR (100 MHz) δ 1.1 (3 H, t, J = 7 Hz), 1.28 (3 H, d, J = 7 Hz), 1.8 (3 H, br s), 2.44 (2 H, m), 2.72 (1 H, m), 3.0 (1 H, dq, J = 7, 14 Hz), 3.0 (1 H, dd), 3.5 (1 H, dq, J = 7, 14 Hz), 3.53 (1 H, dd, J = 4, 9 Hz), 3.58 (1 H, d, J = 12 Hz, exchangeable), 3.9 (1 H, dd, J = 3, 9 Hz), 4.31 (1 H, d, J = 12 Hz), 4.48 (1 H, d, J = 12 Hz), 4.9 (1 H, dd, J = 4, 12 Hz), 5.26 (1 H, br s), 7.26 (5 H, s); IR (film) 3400, 3000, 2950, 2880, 1675, 1450, 1430, 1360, 1320, 1140, 1100, 1070, 1030, 1000 cm^{-1}.

Regioisomeric hydroxy lactam **19**: ^1H NMR (100 MHz), δ 1.12 (3 H, t, J = 7 Hz), 1.28 (3 H, d, J = 7 Hz), 1.75 (3 H, br s), 2.6 (4 H, m), 3.04 (1 H, d, J = 9 Hz, exchangeable), 3.34 (2 H, m), 3.74 (2 H, d, J = 6 Hz), 4.56 (2 H, s), 4.96 (1 H, dd, J = 4, 9 Hz), 5.64 (1 H, br s), 7.32 (5 H, s); IR (film) 3350, 2950, 1660, 1450, 1370, 1330, 1220, 1080 cm^{-1}.

(B) Sodium Borohydride Reduction. To a solution of 215 mg (0.657 mmol) of imide **15** in 4 mL of ethanol at 0 °C was added 360 mg (9.3 mmol) of sodium borohydride, and the mixture was stirred for 5 h at 0 °C. At 20-min intervals 2 drops of a 2 N HCl/ethanol solution were added to the reaction mixture. The mixture was poured into ice–water and was extracted with chloroform. The organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, and evaporated to dryness in vacuo. The residue was chromatographed on 10 g of silica gel with ethyl acetate/hexane (3/7) as the eluant to give 82.8 mg (25%) of starting imide **15**, 26 mg (12%) of hydroxy lactam **16**, and 50 mg (23%) of the isomer **19** which was epimeric with the same regioisomer obtained from the dibal reduction: ^1H NMR (100 MHz) δ 1.05 (3 H, t, J = 7 Hz), 1.21 (3 H, d, J = 8 Hz), 1.73 (3 H, br s), 2.6 (4 H, m), 3.16 (1 H, m), 3.4 (1 H, d, J = 6 Hz, exchangeable), 3.48 (1 H, m), 3.69 (2 H, d, J = 7 Hz), 4.57 (2 H, s), 4.90 (1 H, dd, J = 4, 6 Hz), 5.28 (1 H, br s), 7.34 (5 H, s); IR (film) 3400, 3000, 2940, 2870, 1675, 1450, 1380, 1360, 1080 cm^{-1}.

2-Ethyl-5α,6-dimethyl-8α-[(benzyloxy)methyl]-1,2,5β,8β-tetrahydro-3*H*-isoindol-3-one (20). A solution of 30 mg (0.91 mmol) of hydroxy lactam **19** (derived from either the diisobutylaluminum hydride reduction or from the sodium borohydride reduction) in 2 mL of methanol containing a few crysals of *p*-toluenesulfonic acid was stirred overnight at room temperature, and the methanol was evaporated. The residue was extracted with ethyl acetate, washed with saturated $NaHCO_3$, water, and brine, dried over anhydrous $MgSO_4$, and evaporated to dryness in vacuo. The crude product was purified by column chromatography on 1 g of silica gel, eluting with ethyl acetate/hexane (3/7) to give 18 mg (63%) of unsaturated lactam **20**: ^1H NMR (100 MHz) δ 1.17 (3 H, t, J = 7 Hz), 1.28 (3 H, d, J = 7 Hz), 1.78 (3 H, br s), 2.94 (1 H, m), 3.2–3.7 (5 H, m), 3.78 (1 H, d, J = 3 Hz), 4.02 (1 H, d, J = 18 Hz), 4.5 (2 H, s), 5.34 (1 H, br s), 7.28 (5 H, s); IR (film) 2950, 1660, 1460, 1320, 1270, 1100, 800, 740 cm^{-1}.

2-Ethyl-5α,6-dimethyl-8α-[(benzyloxy)methyl]-2,3,5β,8β-tetrahydro-1*H*-isoindol-1-one (17). This compound was prepared from hydroxy lactam **16** in a manner identical with that described above for synthesis of lactam **20**: ^1H NMR (100 MHz) δ 1.19 (3 H, t, J = 7 Hz), 1.23 (3 H, d, J = 7 Hz), 1.83 (3 H, br s), 2.89 (1 H, m), 3.3–3.68 (4 H, m), 3.76 (1 H, d, J = 3 Hz), 3.94 (1 H, dd, J = 3, 8 Hz), 3.97 (1 H, d, J = 18 Hz), 4.52 (2 H, s), 5.68 (1 H, br s), 7.25 (5 H, s); IR (film) 3000, 2970, 1665, 1450, 1420, 1360, 1320, 1270, 1230, 1100 cm^{-1}.

2-Ethyl-5,6-dimethyl-8-[(benzyloxy)methyl]-2,3-dihydro-1*H*-isoindol-1-one (18). To a solution of 22 mg (0.7 mmol) of the lactam **17** in 3 mL of toluene was added 5 mg of 5% palladium on carbon, and the mixture was heated at reflux 5 h. The mixture was filtered, and the filtrate was evaporated to dryness. The residue was purified by column chromatography on 1 g of silica gel, eluting with ethyl acetate/hexane (3/7) to give 12 mg (55%) of aromatized compound **18**: ^1H NMR (100 MHz) δ 1.24 (3 H, t, J = 7 Hz), 2.18 (3 H, s), 2.33 (3 H, s), 3.61 (2 H, q, J = 7 Hz), 4.22 (2 H, s), 4.64 (2 H, s), 5.12 (2 H, s), 7.3 (5 H, m); IR (film) 2920, 2850, 1665, 1440, 1410, 1350, 1190, 1120, 1050, 1020, 860, 770, 720 cm^{-1}.

2-Ethyl-5,6-dimethyl-8-[(benzyloxy)methyl]-1,2-dihydro-3*H*-isoindol-1-one (21). This compound was prepared as described above for compound **18**: ^1H NMR (100 MHz) δ 1.23 (3 H, t, J = 7 Hz), 2.31 (3 H, s), 2.67 (3 H, s), 3.61 (2 H, q, J = 7 Hz), 4.23 (2 H, s), 4.52 (4 H, s), 7.28 (5 H, m); IR (film) 3000, 2930, 2860, 1670, 1460, 1450, 1420, 1240, 1190, 1090, 1060, 900 cm^{-1}.

2-Ethyl-3-methoxy-5α,6-dimethyl-8α-[(benzyloxy)methyl]-2,3,4β,5β,8β,9β-hexahydro-1*H*-isoindol-1-one (24). To a solution of 10 mg (0.3 mmol) of hydroxy lactam **16** in 3 mL of methanol was added 1 drop of dilute HCl, and the mixture was stirred for 30 min at 0 °C. A drop of saturated $NaHCO_3$ solution was added to the mixture to neutralize the acid, and the methanol was evaporated in vacuo. The residue was taken up in ethyl acetate, washed with water, brine, and dried over anhydrous $MgSO_4$. The solvent was evaporated in vacuo, and the crude product was purified by column chromatography on 1 g of silica gel, eluting with ethyl acetate/hexane (3/7) to give 12 mg (100%) of methyl ether **24**: ^1H NMR (100 MHz) δ 1.02 (3 H, t, J = 7 Hz), 1.26 (3 H, d, J = 7 Hz), 1.7 (3 H, br s), 2.4 (3 H, m), 2.96 (1 H, m), 2.92 (1 H, dq, J = 7, 14 Hz), 3.14 (3 H, s), 3.46 (1 H, dq, J = 7, 14 Hz), 3.84 (1 H, dd, J = 9, 9 Hz), 4.06 (1 H, dd, J = 6, 9 Hz), 4.56 (1 H, m), 4.56 (2 H, s), 5.47 (1 H, br s), 7.28 (5 H, s); IR (film) 3000, 2975, 2940, 1680, 1450, 1380, 1365, 1325, 1280, 1230, 1070 cm^{-1}.

2-Ethyl-3β-methyl-5α,6-dimethyl-8α-[(benzyloxy)methyl]-2,3,4β,5β,8β,9β-hexahydro-1*H*-isoindol-1-one (25). To a solution of 397 mg (1.16 mmol) of methyl ether **24** in 14 mL of benzene at 5 °C was added 3 mL of a solution of 25% trimethyl aluminum in hexane (10.4 mmol). The mixture was heated at reflux for 48 h under a nitrogen atmosphere and was cooled to room temperature. To this solution was added 3 mL of water, and the mixture was stirred for 20 min. The reaction mixture was diluted with ethyl acetate, washed with saturated sodium potassium tartrate solution, water, and brine, dried over anhydrous $MgSO_4$, and evaporated in vacuo. The crude product was purified by column chromatography on 20 g of silica gel, eluting with ethyl acetate/hexane (3/7) to give 248 mg (66%) of the C-methylated product **25**: ^1H NMR (100 MHz) δ 1.0 (3 H, t, J = 7 Hz), 1.18 (6 H, d, J = 7 Hz), 1.74 (3 H, br s), 2.28 (3 H, m), 2.84 (1 H, dq, J = 7, 14 Hz), 2.94 (1 H, m), 3.16 (1 H, dd, J = 5, 10 Hz), 3.54 (1 H, dq, J = 7, 14 Hz), 3.84 (1 H, dd, J = 9, 9 Hz), 4.08 (1 H, dd, J = 5, 9 Hz), 4.58 (2 H, s), 5.56 (1 H, br s), 7.28 (5 H, m); IR (film) 2975, 2930, 2880, 1665, 1455, 1380, 1360, 1325, 1080 cm^{-1}.

2,3β-Diethyl-5α,6-dimethyl-8α-[(benzyloxy)methyl]-

2,3α,4β,5β,8β,9β-hexahydro-1*H*-isoindol-1-one (26). This compound was prepared as described for compound **25** from 105 mg of methyl ether **24** and 2 mL of a 25% triethyl aluminum/hexane solution in toluene at reflux for 4 h to give 23 mg (22%) of the C-ethylated compound **26**: ^{1}H NMR (100 MHz) δ 0.77 (3 H, t, J = 7 Hz), 0.96 (3 H, t, J = 7 Hz), 1.14 (3 H, d, J = 7 Hz), 1.5 (2 H, m), 1.7 (3 H, br s), 2.32 (3 H, m), 2.69 (1 H, m), 2.9 (1 H, dd, J = 5, 9 Hz), 3.22 (1 H, m), 3.58 (1 H, m), 3.9 (1 H, dd, J = 8, 8 Hz), 4.09 (1 H, dd, J = 6, 8 Hz), 4.58 (2 H, s), 5.52 (1 H, br s), 7.28 (5 H, m).

2-Ethyl-3β-benzyl-5α,6-dimethyl-8α-[(benzyloxy)methyl]-2,3α,4β,5β,8β,9β-hexahydro-1*H*-isoindol-1-one (27). To a solution of 380 mg (2.84 mmol) of anhydrous aluminum chloride in 2 mL of dry THF was added dropwise 5.5 mL of 1.6 M benzylmagnesium chloride in THF (8.8 mmol) of 0 °C under a nitrogen atmosphere. The mixture was stirred at room temperature overnight, and heated at reflux for 1 h. The mixture was cooled to room temperature, and 6 mL of toluene and then a solution of 100 mg (0.29 mmol) of methyl ether **24** in 2 mL of toluene were added. Most of the THF was removed under vacuum, and the mixture was heated at reflux for 2 h under a nitrogen atmosphere. Water (1 mL) was added, and the mixture was stirred for 20 min. The reaction mixture was diluted with ethyl acetate, washed with saturated sodium potassium tartrate solution, water, and brine, dried over anhydrous $MgSO_4$, and evaporated in vacuo. The crude product was purified by column chromatography on 20 g of silica gel, eluting with ethyl acetate/hexane (3/7), followed by preparative TLC developed with ethyl acetate/hexane (1/9) to give 47 mg (40%) of the C-benzylated lactam **27**: ^{1}H NMR (100 MHz) δ 0.84 (3 H, d, J = 7 Hz), 1.0 (3 H, t, J = 7 Hz), 1.66 (3 H, br s), 2.32 (3 H, m), 2.74 (4 H, m), 3.48 (1 H, m), 3.7 (1 H, m), 3.98 (1 H, dd, J = 9, 8 Hz), 4.06 (1 H, dd, J = 6, 8 Hz), 4.54 (2 H, s), 5.48 (1 H, br s), 7.24 (10 H, m); IR (film) 3040, 2975, 2940, 2855, 1680, 1495, 1450, 1380, 1280, 1100, 1080, 800, 760, 740, 705 cm^{-1}.

2-Ethyl-3β-benzyl-5α,6-dimethyl-8α-[(benzyloxy)methyl]-9β-hydroxy-2,3α,4β,5β,8β,9-hexahydro-1*H*-isoindol-1-one (29). To a solution of 100 mg (0.62 mmol) of hexamethyldisilazane in 2 mL of dry THF was added dropwise 0.2 mL (0.48 mmol) of 2.4 M n-butylithium in hexane at −78 °C under a nitrogen atmosphere, and the mixture was stirred for 30 min. A solution of 24 mg (0.06 mmol) of lactam **27** in 0.5 mL of THF was added to the mixture, and stirring was continued at 0 °C for 1 h. Oxygen gas was passed through this solution for 1 h at 0 °C, and a few drops of trimethyl phosphite were added. The mixture was stirred for 2 h at room temperature and was diluted with ethyl acetate. The organic layer was washed with water, brine, dried over anhydrous $MgSO_4$, and evaporated to dryness in vacuo. The residue was purified by column chromatography on 4 g of silica gel, eluting with ethyl acetate/hexane (3/7) to give 15 mg (60%) of the hydroxylated compound **29**: ^{1}H NMR (100 MHz) δ 0.78 (3 H, d, J = 7 Hz), 1.0 (3 H, t, J = 7 Hz), 1.7 (3 H, br s), 2.2 (1 H, t, J = 4 Hz), 2.6 (2 H, m), 2.9 (3 H, m), 3.28 (1 H, m), 3.68 (1 H, m), 3.82 (1 H, dd, J = 3, 10 Hz), 4.3 (1 H, dd, J = 1, 10 Hz), 4.5 (1 H, d, J = 11 Hz), 4.74 (1 H, d, J = 11 Hz), 4.54 (1 H, s, exchangeable), 5.1 (1 H, br s), 7.3 (10 H, m); IR (film) 3430, 3000, 2975, 2940, 1678, 1600, 1500, 1455, 1380, 1280, 1230, 1090, 1070, 1030, 810 cm^{-1}.

2-Benzyl-5α,6-dimethyl-8α-[(benzyloxy)methyl]-2,4β,5β,8β,9β-hexahydro-1*H*-isoindole-1,3-dione (31). This compound was synthesized by the procedure described above for preparation of adduct **15** from 5.4 g of the diene benzyl ether **14** and 5 g of N-benzylmaleimide (**30**)[21] to give 8.6 g (83%) of the Diels–Alder adduct **31**. A sample recrystallized from ethanol had the following: mp 70–72 °C; ^{1}H NMR (100 MHz) δ 1.42 (3 H, d, J = 7 Hz), 1.56 (3 H, br s), 2.5 (2 H, m), 2.94 (1 H, dd, J =6, 9 Hz), 3.20 (1 H, dd, J = 6, 8 Hz), 3.76 (1 H, dd, J = 9, 8 Hz), 4.0 (1 H, dd, J = 9, 6 Hz), 4.54 (2 H, s), 4.58 (2 H, s), 5.36 (1 H, br s), 7.22 (5 H, s), 7.30 (5 H, s); IR (film) 3030, 2935, 2900, 2850, 1760, 1690, 1500, 1400, 1340, 1175, 1100, 1080, 1030, 965, 925, 830, 780, 740, 700 cm^{-1}; mass spectrum, m/e (relative intensity) 390 (M$^+$ + 1, 0.5), 389 (M$^+$, 0.4), 298 (63.6), 283 (45.7), 268 (75.4), 267 (31.5), 188 (18.1), 121 (13.9), 119 (17.9), 110 (30.8), 107 (91.2), 92 (31), 91 (100). Anal. Calcd for $C_{24}H_{27}NO_3$: C, 77.09; H, 6.99; N, 3.60. Found: C, 76.86; H, 6.65; N, 3.64.

2-Benzyl-3-hydroxy-5α,6-dimethyl-8α-[(benzyloxy)methyl]-2,3,4β,5β,8β,9β-hexahydro-1*H*-isoindol-1-one (32). This compound was prepared as described for compound **16** by starting from 1 g of the Diels–Alder adduct **31** and 4 mL of 1 M diisobutylaluminum hydride solution to give 640 mg (64%) of the desired hydroxy lactam **32**. A sample recrystallized from ethyl acetate/hexane had the following: mp 109–110 °C; ^{1}H NMR (100 MHz) δ 1.2 (3 H, d, J =6.5 Hz), 1.8 (3 H, br s), 2.4 (2 H, m), 2.62 (1 H, m), 2.94 (1 H, dd, J = 8, 12 Hz), 3.6 (1 H, dd, J =3, 9 Hz), 3.62 (1 H, d, J = 12 Hz, exchangeable), 3.74 (1 H, d, J = 14 Hz), 3.98 (1 H, dd, J = 3, 9 Hz), 4.36 (1 H, d, J = 12 Hz), 4.48 (1 H, d, J = 14 Hz), 4.72 (1 H, dd, J = 4, 12 Hz), 4.8 (1 H, d, J = 14 Hz), 5.3 (1 H, br s), 7.22 (5 H, s), 7.3 (5 H, s); IR (film) 3400, 3000, 2900, 2850, 1675, 1490, 1440, 1350, 1200, 1140, 1100, 1060, 1020, 940, 840, 740, 700 cm^{-1}; mass spectrum, m/e (relative intensity) 391 (M$^+$, 10.2), 358 (6.6), 329 (10.6), 300 (5.8), 283 (3.9), 282 (14.1), 270 (29.3), 267 (10.8), 253 (16.0), 252 (72.2), 251 (16.9), 236 (7.1), 198 (7.8), 160 (12.6), 133 (26.2), 120 (24.2), 119 (94.8), 107 (30.5), 105 (15.6), 91.0 (100.0), 65.0 (18.2). Anal. Calcd for $C_{25}H_{29}NO_3$: C, 76.70; H, 7.47. Found: C, 76.32; H, 7.43.

2-Benzyl-3-methoxy-5α,6-dimethyl-8α-[(benzyloxy)methyl]-2,3,4β,5β,8β,9β-hexahydro-1*H*-isoindol-1-one (33). As described for preparation of **24**, 160 mg of hydroxy lactam **32** gave 153 mg (93%) of methoxy lactam **33**: ^{1}H NMR (CCl_4 + acetone-d_6, 100 MHz) δ 1.12 (3 H, d, J = 6.5 Hz), 1.5 (3 H, br s), 2.4 (3 H, m), 3.0 (1 H, dd, J = 6, 10 Hz) 3.12 (3 H, s), 3.82 (1 H, dd, J = 8, 8 Hz), 4.06 (1 H, dd, J = 7, 8 Hz), 3.72 (1 H, d, J = 14 Hz), 4.24 (1 H, s), 4.54 (2 H, s), 4.84 (1 H, d, J = 14 Hz), 5.46 (1 H, br s), 7.2 (10 H, m); IR (film) 3050, 2950, 2860, 1690, 1440, 1380, 1280, 1180, 1090, 1040, 960, 820, 740, 700 cm^{-1}.

2,3β-Dibenzyl-5α,6-dimethyl-8α-[(benzyloxy)methyl]-2,3α,4β,5β,8β,9β-hexahydro-1*H*-isoindol-1-one (34). Anhydrous aluminum chloride (2.5 g, 18.75 mmol) was dissolved with cooling (ice bath) in 50 mL of anhydrous ether, and the resulting solution was treated with 35 mL (56 mmol) of 1.6 M benzylmagnesium chloride in THF over a 1-h period. The resulting suspension was stirred overnight at room temperature and was heated at reflux for 3 h. Benzene (60 mL, distilled from CaH_2) was added to the mixture, and most of the ether and THF was removed. The remaining suspension was filtered through a fritted-glass "airlessware" funnel, and the filtrate was evaporated. The residue was taken up in 40 mL of toluene and refiltered. To the filtrate was added a solution of 385 mg (0.95 mmol) of methoxy lactam **33** in 1 mL of toluene. The mixture was heated at reflux for 2.5 h, cooled to room temperature, and treated with 2 mL of water. The mixture was stirred for 30 min and was diluted with ethyl acetate. The organic phase was washed with saturated sodium potassium tartrate solution, water, and brine, dried over anhydrous $MgSO_4$, and the solvent was evaporated in vacuo to give a residue which contained the desired coupled product **34** contaminated with bibenzyl and benzyl alcohol. Bibenzyl was easily removed by an initial column chromatography, eluting with ethyl acetate/hexane (2/8). The remaining material from the chromatography was treated with acetic anhydride/pyridine at room temperature to convert the benzyl alcohol to benzyl acetate. The product was then purified by silica gel column chromatography, eluting with ethyl acetate/hexane (2/8) to give 195 mg (44%) of lactam **34**: ^{1}H NMR (270 MHz) δ 0.61 (3 H, d, J = 7 Hz), 1.47 (3 H, br s), 2.14 (1 H, m), 2.36 (2 H, m), 2.72 (1 H, dd, J = 7, 12 Hz), 2.82 (1 H, dd, J = 6, 12 Hz), 2.85 (1 H, m), 3.2 (1 H, m), 3.76 (1 H, d, J = 14 Hz), 4.18 (1 H, dd, J = 9, 9 Hz), 4.04 (1 H, dd, J = 9, 6 Hz), 4.6 (2 H, s), 5.2 (1 H, d, J = 14 Hz), 5.58 (1 H, br s), 7.2 (15 H, m); IR (film) 3000, 2900, 2830, 1670, 1440, 1360, 1260, 1090, 1020, 810, 740, 700 cm^{-1}; ^{13}C NMR δ 13.44, 20.06, 34.07, 38.38, 40.14, 41.60, 43.78, 44.27, 57.86, 71.75, 73.57, 125.99, 126.96, 127.63, 128.05, 128.42, 128.54, 128.78, 129.93, 136.36, 137.21, 139.76, 175.19; mass spectrum, m/e (relative intensity) 465 (M$^+$, 10.1), 374 (100), 283 (10.1), 268 (22.7), 264 (21.9), 254 (18.1), 192 (0.5), 181 (15.1), 172 (14.1), 119 (15.0), 92 (21.7), 91 (79.9); calcd for $C_{32}H_{35}NO_2$ m/e 465.2668, found m/e 465.2656 (2.4 ppm error).

2,3β-Dibenzyl-5α,6-dimethyl-8α-[(benzyloxy)methyl]-9β-hydroxy-2,3α,4β,5β,8β,9-hexahydro-1*H*-isoindol-1-one (35). Compound **34** was hydroxylated as described above for lactam **27**. From 100 mg of lactam **34** was obtained 52 mg (50%) of alcohol **35**: ^{1}H NMR (270 MHz) δ 0.55 (3 H, d, J = 7 Hz), 1.46 (3 H, br s), 2.2 (1 H, m), 2.64 (3 H, m), 3.0 (2 H, m), 3.8 (1 H, m), 3.84 (1 H, d, J = 14 Hz), 4.4 (1 H, m), 4.5 (1 H, d, J = 11 Hz),

4.78 (1 H, br s, exchangeable), 4.8 (1 H, d, J = 11 Hz), 5.16 (1 H, br s), 5.2 (1 H, d, J = 14 Hz), 7.2 (15 H, m); IR (film) 3400, 3000, 2900, 2840, 1670, 1440, 1360, 1260, 1080, 1030, 810, 740, 700 cm^{-1}; mass spectrum, m/e (relative intensity) 481 (M^+, 0.3), 462 (1.4), 408 (10.2), 407 (10.9), 406 (3.1), 391 (8.7), 390 (30.7), 372 (10.3), 344 (4.4), 298 (9.7), 284 (9.4), 280 (25.2), 278 (3.1), 270 (10.5), 254 (5.8), 250 (4.3), 210 (3.3), 188 (10.6), 181 (10.2), 160 (4.3), 147 (3.2), 135 (3.9), 91 (100); calcd for $C_{32}H_{35}NO_3$ m/e 481.2617, found m/e 481.2592 (5.3 ppm error).

3β-Benzyl-5α,6-dimethyl-8α-(hydroxymethyl)-9β-hydroxy-2,3α,4β,5β,8β,9-hexahydro-1*H*-isoindol-1-one (36). To a solution of 5 mg (0.83 mmol) of lithium metal in 3 mL of ammonia was added a solution of 12 mg (0.03 mmol) of **35** in 1 mL of dry THF. A solution of 100 mg of dibenzyl ether in 2 mL of THF was added to the reaction mixture, followed by water, and the mixture was evaporated. The residue was taken up in ethyl acetate, washed with water, brine, dried over anhydrous $MgSO_4$, and evaporated in vacuo. The crude product was purified by column chromatography, eluting with THF/hexane (1/1) to give 6 mg (80%) of crystalline diol **36**: mp 189–190 °C; ^{1}H NMR (100 MHz) δ 1.38 (3 H, d, J = 7 Hz), 1.8 (3 H, br s), 2.5 (4 H, m), 3.06 (2 H, m), 3.9 (2 H, m), 4.12 (1 H, br s, exchangeable), 4.32 (1 H, br s, exchangeable), 5.12 (1 H, br s), 5.96 (1 H, br s), 7.2 (5 H, m); ^{13}C NMR δ 14.812, 20.090, 33.741, 44.844, 46.179, 55.765, 56.372, 63.228, 81.672, 120.623, 127.054, 128.813, 128.934, 137.428, 141.554, 177.350; IR ($CHCl_3$) 3400, 2920, 2840, 1680, 1485, 1450, 1430, 1370, 1320, 1270, 1100, 1020 cm^{-1}; mass spectrum, m/e (relative intensity) 301 (M^+, 1.6), 300 (0.2), 283 (13.9), 210 (100), 192 (62.5), 182 (26.6), 172 (18), 164 (28.5), 162 (37.2), 120 (20), 119 (69), 95 (57.8), 94 (38.0), 91 (92.8), 83 (24.2), 79 (22.1), 70 (70.0); calcd for $C_{16}H_{23}NO_3$ m/e 301.1678, found m/e 301.1679 (0.4 ppm error).

3β-Benzyl-5α,6-dimethyl-8α-(acetoxymethyl)-9β-hydroxy-2,3α,4β,5β,8β,9-hexahydro-1*H*-isoindol-1-one (37). A mixture of 8 mg (0.026 mmol) of alcohol **36**, 0.5 mL of pyridine, and 0.2 mL of acetic anhydride was stirred at room temperature for 2 h. Pyridine and acetic anhydride were evaporated under vacuum to give 8 mg (89%) of acetate **37** which was used directly in the next step: ^{1}H NMR δ 1.38 (3, H, d, J = 6.5 Hz), 1.9 (3 H, br s), 2.16 (3 H, s), 2.4–3.3 (6 H, m), 3.4 (1 H, br s), 4.36 (1 H, dd, J = 6.5, 11 Hz), 4.68 (1 H, dd, J = 7.6, 11 Hz), 5.42 (1 H, br s), 5.56 (1 H, br s), 7.35 (5 H, m); mass spectrum, m/e (relative intensity) 343 (M^+, 100), 301 (8), 283 (23), 282 (10), 90 (6).

3β-Benzyl-5α,6α-dimethyl-6β,7β-epoxy-8α-(acetoxymethyl)-9β-hydroxy-2,3α,4β,5β,6,7α,8β,9-octahydro-1*H*-isoindol-1-one (41). Method A. To a solution of 8 mg (0.023 mmol) of alkene **37** in 1 mL of methylene chloride was added 6 mg (0.03 mmol) of *m*-chloroperbenzoic acid. The mixture was stirred overnight at room temperature and was filtered. The filtrate was washed with saturated $NaHSO_3$ solution, saturated $NaHCO_3$, water, and brine and dried over anhydrous $MgSO_4$. Evaporation of the solvent in vacuo gave the β-epoxide **41** containing a trace of the α-epoxide. Epoxide **41** was purified by preparative TLC developed with ethyl acetate/hexane (3/1): ^{1}H NMR δ 1.11 (3 H, d, J = 7 Hz), 1.3 (3 H, s), 2.1 (3 H, s), 2.26 (2 H, m), 2.8 (3 H, m), 3.65 (1 H, m), 4.5 (1 H, dd, J = 8.6, 11.4 Hz), 4.73 (1 H, dd, J = 6.3, 11.4 Hz), 5.65 (1 H, br s), 7.25 (5 H, m).

Method B. A mixture of 0.75 mg (0.002 mmol) of authentic cytochalasin E degradation product **40**,[25] 5 drops of pyridine, and 2 drops of acetic anhydride was stirred for 2 h at room temperature. Pyridine and acetic anhydride were evaporated under vacuum, and the residue was purified by preparative TLC, eluting with ethyl acetate/hexane (3/1) to give acetate **41** identical in NMR and TLC with the synthetically derived material prepared in method A.

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Direct and Efficient Synthesis of β-L-Rhamnopyranosides†

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Methyl α-L-rhamnopyranoside (1) was converted in a single-stage procedure to crystalline methyl 4-*O*-benzoyl-2,3-*O*-cyclohexylidene-α-L-rhamnopyranoside (**2**). This compound served as a stable derivative from which 4-*O*-benzoyl-2,3-*O*-cyclohexylidene-α-L-rhamnopyranosyl bromide (**3**) could be derived in essentially quantitative yield by reaction with dibromomethyl methyl ether. The glycosyl halide **3** was used to prepare three β-L-rhamnopyranosides by reaction with the selectively blocked glycosides methyl 2,3-*O*-isopropylidene-α-L-rhamnopyranoside (**4**), methyl 4-*O*-acetyl-2-*O*-benzoyl-α-L-rhamnopyranoside (**5**), and methyl 3,4-di-*O*-benzyl-α-L-rhamnopyranoside (**6**). Good to moderate yields of the corresponding β-linked rhamnose disaccharides **7–9** were obtained. The yields and stereospecificity of the glycosylation reaction were highest for the relatively reactive secondary hydroxyl groups HO-4 and HO-3. Reduced stereospecificity and moderate yield of the β anomer were associated with the most unreactive hydroxyl group HO-2.

L-Rhamnose occurs in plant glycosides,[1,2] glycolipids,[3] and immunologically important polysaccharides.[4,5] Several groups including our own have synthesized di-[6-8] and oligosaccharides[9-11] containing two or three α-linked rhamnopyranoside residues as models for immunodeterminants of polysaccharide antigens. It is unusual to find naturally occurring L-rhamnose in other than the α-L-

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