Bruker AM-500 instruments.[24]

Synthesis of 2-Methoxy-3-methyl-2-cyclopenten-1-one (1).[25] Dimethyl sulfate (13 g) was added during 30 min to a stirred solution of 3-methylcyclopentane-1,2-dione (12 g) in dry acetone (150 mL) containing anhydrous potassium carbonate (15 g) maintained under gentle reflux. The mixture was heated under reflux for 2 h, cooled, and filtered. Evaporation of the acetone left a residue which was distilled, bp 55–59 °C/10 mm (lit.[25] bp 45–47 °C/0.4 mm). ^{1}H NMR ($CDCl_3$): δ 2.01 (3 H, s), 2.42–2.57 (4 H, m), 3.85 (3 H, s). ^{13}C NMR ($CDCl_3$): 203.2 (C=O), 154.3 (s), 152.7 (s), 58.2 (q), 34.1 (t), 23.8 (t), 6.8 (q), ppm. IR (film): 1695 (C=O), 1640 cm^{-1}.

Photooxygenation of 1. A solution of 1 in dichloromethane containing TPP was irradiated under oxygen in the standard manner, and the products were separated by column chromatography. Methyl 2,5-dioxohexanoate (4),[9] ^{1}H NMR ($CDCl_3$, TMS): δ 2.21 (3 H, s), 2.83 (2 H, t, J = 6.1 Hz), 3.09 (2 H, t, J = 6.0 Hz), 3.88 (3 H, s). IR ($CHCl_3$): 1760–1700 (C=O), 1210, 1165, 1085 cm^{-1}. Compound 5, ^{1}H NMR ($CDCl_3$, TMS): δ 9.51 (br d, OH), 6.24 (1 H, s), 5.70 (1 H, s), 3.86 (3 H, s), 2.72 (4 H, m). ^{13}C NMR ($CDCl_3$): 178.13 (C=O), 167.12 (C=O), 138.53 (s), 126.09 (t), 51.69 (q), 32.76 (t), 26.98 (t) ppm. IR (film): 1720, 1625, 1434, 1210, 1160 cm^{-1}. High-resolution MS calcd for $C_7H_{10}O_4$ m/z 158.0579, found m/z 158.0574. Cleavage product 5 reacted with diazomethane to give 6. ^{1}H NMR ($CDCl_3$): δ 4.62 (2 H, m), 3.86 (3 H, s), 3.78 (3 H, s), 2.8–2.1 (4 H, m), 1.7–1.3 (2 H, m). IR (film): 1547 (N=N) cm^{-1}. Compound 6 slowly decomposed at room temperature.

Photooxygenation of 1 in Methyl Alcohol. Freshly distilled 1 (4 mmol) in 20 mL of dry methyl alcohol (containing 5×10^{-4} M rose bengal) was irradiated at −20 °C with bubbling oxygen. After 2.5 h, the solvent was evaporated under vacuum, and compounds 7 and 8 were detected by ^{1}H NMR spectroscopy in $CDCl_3$. The acids were converted to ester 10[11] and lactone 9 by reaction with diazomethane and chromatography on a SiO_2 column. Lactone 9, ^{1}H NMR ($CDCl_3$): δ 3.83 (3 H, s), 2.7–2.4 (3 H, m), 2.3–2.1 (1 H, m), 1.68 (3 H, s). ^{13}C NMR ($CDCl_3$): 176.2 (C=O), 171.8 (C=O), 83.6 (s), 53.7 (q), 33.5 (t), 28.1 (t), 23.7 (q) ppm. IR (film): 1795, 1740 (C=O), 1200, 1110, cm^{-1}. High-resolution MS calcd for $C_7H_{10}O_4$ m/z 158.0579, found m/z 158.0579. Methyl 4-oxopentanoate 10,[11] ^{1}H NMR ($CDCl_3$): δ 3.72 (3 H, s), 2.81 (2 H, t, J = 4.2 Hz), 2.71 (2 H, t, J = 4.1 Hz), 2.21 (3 H, s).

Low-Temperature Photooxygenation of 1. A stock solution of 5 mg of rose bengal in 3 mL of CD_3OD or mixed solvent with acetone-d_6 or CD_2Cl_2 was prepared. For good resolution ^{1}H NMR spectra, mixed solvent was used because the high viscosity of CD_3OD at low temperatures causes broad peaks; 26 mg of 1 was dissolved in a 5-mm NMR tube in 1 mL of the stock solution. The NMR tube was cooled to −70 °C in a temperature-controlled cell[23] and photolyzed with a Varian Eimac lamp as light source and a filter solution (cutoff below 460 nm) until no more 1 was detected by TLC (usually 3 h). The NMR tube was transferred as quickly as possible to the precooled probe of the Bruker AM 360 NMR instrument. The ^{1}H NMR spectra were immediately obtained at −60 °C. The ^{1}H NMR spectrum at −50 °C showed that the reaction mixture contained compound 3 (≪5%), 11 (minor), and 12 (major). The ^{1}H NMR spectra were scanned repeatedly as the temperature was increased. Decomposition to product 8 was initially detected around −20 °C. When the reaction mixture was warmed to around 0 °C, the spectrum was too complicated to assign the peaks. The sample was warmed to room temperature, the solvent was evaporated, and then the residue was dissolved in $CDCl_3$. The NMR spectrum showed that all intermediates were converted to 7 (60%), 8 (20%), and 9 (20%). ^{1}H NMR (3, CD_3OD and $(CD_3)_2CO$, at −50 °C): δ 6.22 and 5.68 (olefinic methylene). ^{1}H NMR (11, CD_3OD and $(CD_3)_2CO$, at −50 °C): δ 3.16 (3 H, s), 2.4–1.9 (4 H, m), 1.43 (3 H, s). ^{1}H NMR (12, CD_3OD, at −50 °C): δ 3.38 (3 H, s), 2.4–1.9 (4 H, m), 1.43 (3 H, s). ^{13}C NMR (12, CD_3OD, at −50 °C): 210.32 (C=O), 99.76 (s), 88.45 (s), 51.07 (q), 32.96 (t), 30.76 (t), 19.18 (q) ppm.

Acknowledgment. Supported by NIH Grant No. GM-20080.

Supplementary Material Available: Spectral data of compounds 4, 5, 6, and 9 and low-temperature ^{1}H and ^{13}C NMR spectra of compound 12 are available (17 pages). Ordering information is given on any current masthead page.

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Stereocontrolled Functionalization of Cycloheptadiene Using Organometallic Chemistry: Synthesis of the (+)-Prelog-Djerassi Lactone and a Tylosin Subunit

Anthony J. Pearson,*[1a] Yen-Shi Lai,[1a] Wenyuan Lu,[1b] and A. Alan Pinkerton[1b]

Department of Chemistry, Case Western Reserve University, Cleveland, Ohio 44106, and Department of Chemistry, The University of Toledo, 2801 W. Bancroft Street, Toledo, Ohio 43606

Received April 3, 1989

Stereospecifically substituted cyclohepta-1,3-diene derivatives, prepared via nucleophile addition to dicarbonyl(cycloheptadienyl)(triphenyl phosphite)iron hexafluorophosphate, have been converted to the (+)-Prelog-Djerassi lactone 5 and to the racemic lactone 7, which is related to the known tylosin intermediate 6. Stereocontrolled dioxygenation of the cylcoheptadienes, using singlet oxygen addition or Bäckvall's palladium(II)-catalyzed 1,4-diacetoxylation procedure, is described. These methods are complementary in that singlet oxygen addition occurs trans to the existing substituents, while the Bäckvall procedure leads to all-cis compounds. A study of methyl cuprate additions to protected 4-hydroxycycloheptenone derivatives revealed a pronounced cis-directing effect from a benzoyloxy group, while other protecting groups led to a more stereorandom addition of methyl group. The use of enzymes for the stereospecific hydrolysis of 1,4-diacetoxycycloheptene derivatives was studied. Coupled with the Pd-catalyzed diacetoxylation of *cis*-5,7-dimethyl-1,3-cycloheptadiene, this has led to a 13-step conversion of 1,3-cycloheptadiene to the (+)-Prelog-Djerassi lactone.

The macrolide antibiotics provide interesting and useful target molecules with which to illustrate new methods of stereocontrolled carbon–carbon bond formation.[2] A number of successful total syntheses of, and approaches

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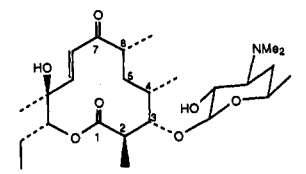
Table I. Decomplexation of 8 To Give 10

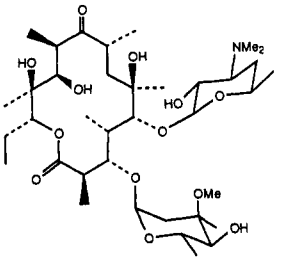
reagent	solvent	reactn time, h	temp, °C	yield, %
Me_3NO	DMA[a]	72	55–60	47
Me_3NO	benzene	48	reflux	19
Me_3NO	benzene	72	reflux	20
Me_3NO	DMA[a]	72	ca. 35, ultrasonication	38
$CuCl_2$	EtOH	24	ambient	44
Jones' reagent	acetone	24	ambient	51
PCC[b]	CH_2Cl_2	24	ambient	20
Collins' reagent	CH_2Cl_2	24	reflux	76–78

[a] *N,N*-Dimethylacetamide. [b] Pyridinium chlorochromate.

to, compounds such as methymycin (**1**),[3] erythromycin (**2**),[4] tylosin (**3**),[5] and carbomycin B (**4**),[6] and/or their aglycons, have been reported in recent years.[7] The Prelog–Djerassi lactonic acid (**5**) was isolated in 1956 as a degradation product of methymycin (representing C-1–C-7) and the related compounds narbomycin, picromycin, and neomethymycin,[8] and this compound has proven to be an exceptionally popular target for the demonstration of methods for stereoselective functionalization of various carbon frameworks.[9] The structurally related lactone **6** has been used by Grieco and co-workers as an intermediate in a total synthesis of tylonolide hemiacetal, a known synthetic precursor for tylosin.[10]



1



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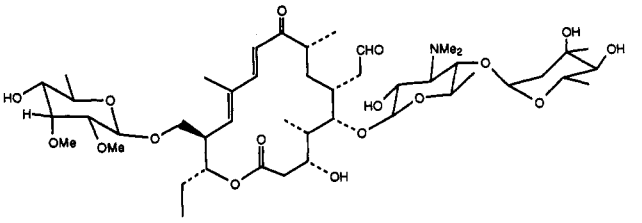

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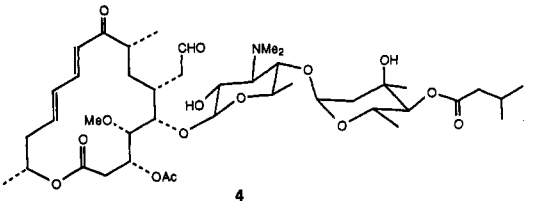

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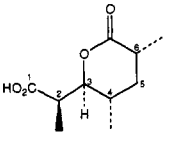

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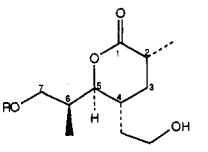

6 R = Bu^tPh_2Si

7 R = CH_3OCH_2

Recent work in our laboratory has focused on the use of transition metals attached to cyclic polyenes as templates for controlling relative stereochemistry during sequential carbon–carbon bond formations.[11] Examples pertinent to the present study are the conversions of dicarbonyl(triphenyl phosphite)(cycloheptadienyl)iron hexafluorophosphate to the symmetrical dimethyl-substituted derivative **8** and the ester **9**. These complexes have substitution corresponding to C-4 and C-6 of lactone **5**, and C-2 and C-4 of lactone **6**, respectively, and are obvious precursors to these valuable intermediates, provided the diene can be further manipulated in a stereocontrolled fashion. This paper describes our efforts along these lines,

(1) (a) Case Western Reserve University. (b) Authors to whom correspondence should be addressed regarding the X-ray structure of the DNP derivative of **28b**, at the University of Toledo.

(2) For reviews on the chemistry and biochemistry of macrolide antibiotics, see: Masamune, S.; Bates, G. S.; Corcoran, J. W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 585. Westley, J. W. *Adv. Appl. Microbiol.* **1977**, *22*, 177. Pressman, B. C. *Annu. Rev. Biochem.* **1976**, *45*, 501.

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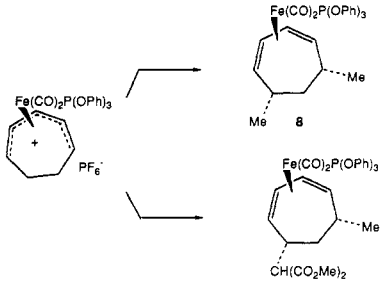
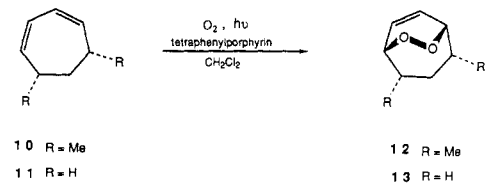
which have culminated in an asymmetric synthesis of optically pure **5** and a synthesis of (racemic) lactone **7**, which differs from **6** only in the nature of the C-7 hydroxyl protecting group.[12]



Results and Discussion

1. Prelog–Djerassi Lactone Synthesis. a. General Studies on Cycloheptadiene Functionalization. Oxidative demetalation of complexes of type **8** was effected in our earlier studies[11] using trimethylamine *N*-oxide,[13] though the reaction was much more sluggish than with diene–$Fe(CO)_3$ systems, owing to the poorer π-acceptor capacity of the triphenylphosphite ligand, which leads to deactivation of CO ligands toward nucleophilic addition (of trimethylamine *N*-oxide). This reaction has proven somewhat capricious on complex **8**, and so alternative methods for conversion of **8** to **10** were examined in order to obtain reproducibly high yields. The results of this study are given in Table I, from which it is seen that the method of choice for this conversion is the use of Collins' reagent.[14] This routinely gave **10** in 76–78% yield on a scale of ca. 60 g.

With substantial quantities of **10** in hand, we carried out a general study of methods for 1,4-dioxygenation, in anticipation that the two methyl groups would direct the stereochemistry of such reactions. Consequently, it was gratifying to find that singlet oxygen addition to **10**, using the method of Adams,[15] proceeded cleanly to give a single endoperoxide **12**, which was assigned the stereochemistry depicted on the basis of NMR spectral data of products from its subsequent manipulation (see later). Since we also required a more readily accessible model system for studying the enzyme-mediated reactions and cuprate additions described later, we subjected 1,3-cycloheptadiene (**11**) to singlet oxygen addition to generate the endoperoxide **13**.



The endoperoxides **12** and **13** were manipulated in two ways. Treatment with base effected their conversion to hydroxy enones **14** and **15**, while reduction gave diols **16** and **17**, which were converted to their acetates **18** and **19**. The assignment of relative stereochemistry for diacetate **18** is readily made from the ^1H NMR spectrum, which showed diaxial coupling of 9.8 Hz between H-3,7 and H-4,6.

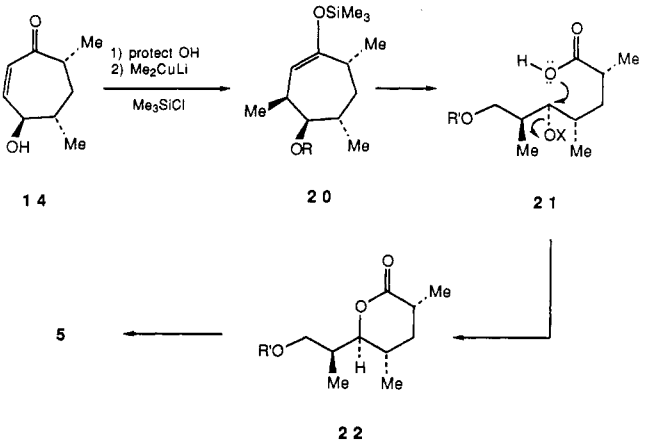
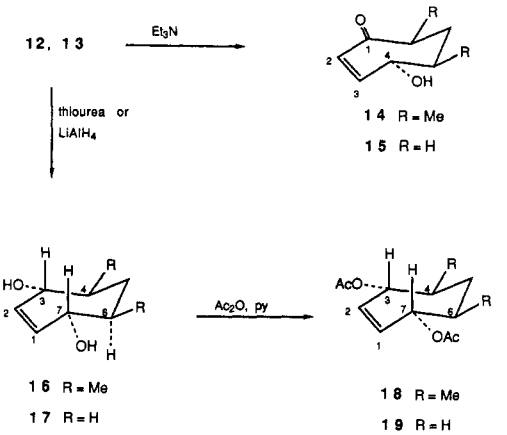
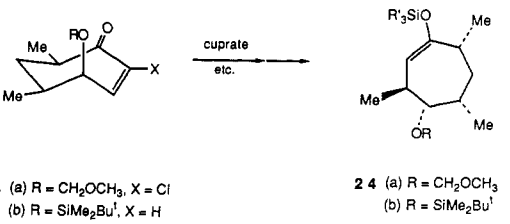


Figure 1.



With compounds **14** and **18** readily accessible, we considered a possible strategy for their conversion to the Prelog–Djerassi lactone **5**. Clearly, this would require the introduction of a methyl group cis to the 4-hydroxy functionality in **14**, e.g., via cuprate addition. Figure 1 shows a potential route for the conversion of **14** to **5**, which involves a lactonization step by internal S_N2 displacement of an activated hydroxyl group (**21** → **22**). Earlier work from the groups of Stork[16] and White[17] had shown that cuprate addition to the epimeric protected hydroxycycloheptenone derivatives **23** proceeded stereospecifically to give compounds **24**, which were converted to the Prelog–Djerassi lactone. We considered it of interest to determine



if this stereoselectivity was due only to steric hindrance from the OR group, or if stereoelectronic effects (quasi-axial addition) are important. Consequently, a number of hydroxyl-protected derivatives of both **14** and **15** were prepared, and their reactions with (dimethylcopper)lithium

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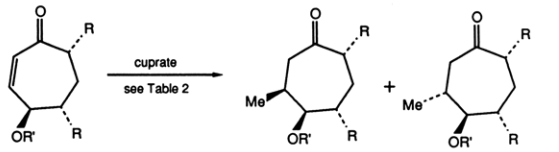
Table II. Results of Addition of Methyl Cuprate Reagents to Enones 25 and 26

enone substrate	reactn condtns	products isolated (% of mixture)	combined yields, %
25b	Me_2CuLi, Et_2O, −78 °C	**27b** (100)	26
25g	Me_2CuLi, Et_2O, −78 °C	**27g** (50) + **29g** (50)	61
26a	2 equiv of Me_2CuLi, Et_2O, 0 °C	**28a** (65) + **30a** (35)	34
26b	2 equiv of Me_2CuLi, Et_2O, 0 °C	**28b** (83) + **30b** (17)	28
26b	2 equiv of Me_2CuLi, Et_2O, −78 °C	**28b** (100)	30[a]
26b	4 equiv of Me_2CuLi, Et_2O, −78 °C	**28b** (100)	40[b]
26b	2 equiv of Me_2CuLi, TBDMS-Cl, −78 °C, 30 min	**28b** (100)	29[c]
26b	2 equiv of $Me_5Cu_2Li_3$, Et_2O, −78 °C, 60 min	**28b** (100)	14
26b	2 equiv of $Me_2Cu(CN)Li_2$, Et_2O, 0 °C, 60 min	1-cyclohepten-4-one	30
26c	2 equiv of Me_2CuLi, Et_2O, 0 °C	**28c** (80) + **30c** (20)	13
26d	2 equiv of Me_2CuLi, Et_2O, 0 °C	**28d** (75) + **30d** (25)	<10
26e	2 equiv of Me_2CuLi, Et_2O, 0 °C	**28e** (33) + **30e** (67)	68
26f	2 equiv of Me_2CuLi, Et_2O, 0 °C	**28f** (14) + **30f** (86)	60
26g	2 equiv of Me_2CuLi, Et_2O, 0 °C	**28g** (20) + **30g** (80)	70
26h	2 equiv of Me_2CuLi, Et_2O, 0 °C	**28h** (33) + **30h** (67)	27

[a] This result was somewhat unreproducible. [b] 1-Cyclohepten-4-one was also isolated in 35% yield. [c] The presumed enol silane intermediate did not survive the workup conditions (aqueous NH_4Cl).

were examined under a variety of conditions, for the overall transformation of **25(26)** to **27(28)** and/or **29(30)**. The



25 R = Me; **26** R = H **27** R = Me ; **28** R = H **29** R = Me; **30** R = H

(a) R' = $COCH_3$ (e) R' = CH_2OCH_3
(b) R' = COPh (f) R' = CH_2Ph
(c) R' = COC_6H_4OMe-p (g) R' = $SiMe_2Bu^t$
(d) R' = COC_6H_4OMe-o (h) R' = $CH_2OCH_2CH_2OCH_3$

results of this investigation are summarized in Table II. Since the unsubstituted derivatives **26** could be prepared more directly, cuprate addition to these compounds was studied more thoroughly. Pertinent ^1H NMR data for the products of these reactions are given in Table III.

The ^1H NMR spectra for all pairs of compounds showed the same characteristics for H-4 and the methyl group. Thus, a doublet of triplets (J = ca. 6, 2 Hz) is usually observed for H-4 of compound **28**, at lower field than the triplet of doublets (J = ca. 7, 2 Hz) for compound **30**, while the methyl doublet is usually at lower field for **28** than for **30**. The data are consistent with the conformations shown in Figure 2, where **28** would show only one "diaxial" coupling for H-4, while **30** would show two such couplings. However, since these couplings are smaller than diaxial couplings in the cyclohexane ring and rather variable, and

Table III. Relevant ^1H NMR Spectral Data for Products 28 and 30[a]

compd	H-4[b]	CH_3[b]
28a	5.02 (dt, 6.4, 3)	0.94 (d, 7.0)
30a	4.77 (tm, 7)	0.93 (d, 6.9)
28b	5.33 (dt, 6.2, 2)	1.07 (d, 6.9)
30b	5.04 (td, 7.9, 2.4)	1.06 (d, 7.0)
28c	5.31 (dt, 4.3, 1.7)	1.07 (d, 6.9)
30c	5.01 (td, 7.7, 1.7)	1.05 (d, 6.9)
28d	5.36 (dm, 5.8)	1.08 (d, 7)
30d	5.09 (td, 4.1, 1.2)	1.07 (d, 6.8)
28e	3.76 (dt, 5.9, 2.2)	1.05 (d, 7)
30e	3.53 (td, 6, 3.3)	1.0 (d, 7.1)
28f	3.93 (dm, 7)	0.97 (d, 6.9)
30f	3.68 (td, 5.9, 3.1)	0.95 (d, 7)
28g	3.85 (dm, 5.2)	obscured
30g	3.43 (td, 8.9, 5.3)	obscured
28h	obscured	1.03 (d, 7.1)
30h	obscured	0.99 (d, 7.2)

[a] See Experimental Section for compounds **27** and **29**. [b] Shieldings are quoted in δ ppm downfield from tetramethylsilane internal standard, couplings in Hz. All spectra were run at 200 MHz in $CDCl_3$ solution.

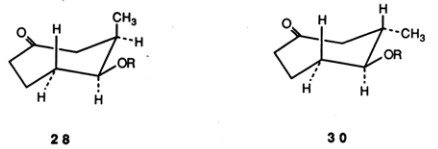


Figure 2. Solution conformations of compounds **28** and **30** used to assign stereochemistry based on NMR data.

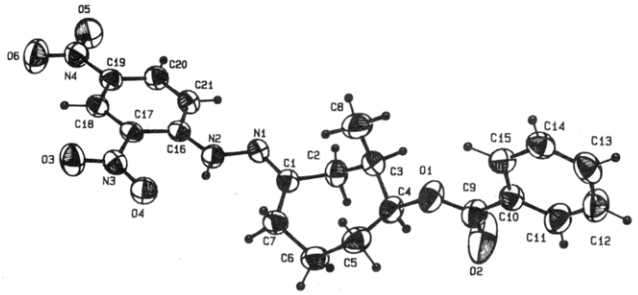


Figure 3. X-ray structure of the (2,4-dinitrophenyl)hydrazone derivative of compound **28b**, showing 50% probability ellipsoids. The compound crystallized in the triclinic space group $P\bar{1}$. Selected bond lengths are as follows (Å): C-1–C-2, 1.503 (4); C-2–C-3, 1.534 (4); C-3–C-4, 1.523 (4); C-4–O, 1.458 (3). Selected torsional angles are as follows (deg): C-1–C-2–C-3–C-4, 82.06 (0.31); C-1–C-2–C-3–CH_3, −46.44 (0.35); CH_3–C-3–C-4–O, −57.01 (0.30); H-3–C-3–C-4–H-4, −52.25 (2.25); H-4–C-4–C-5–H-5(ax.), 175.74 (2.40); H-4–C-4–C-5–H-5(eq), 60.03 (2.29).

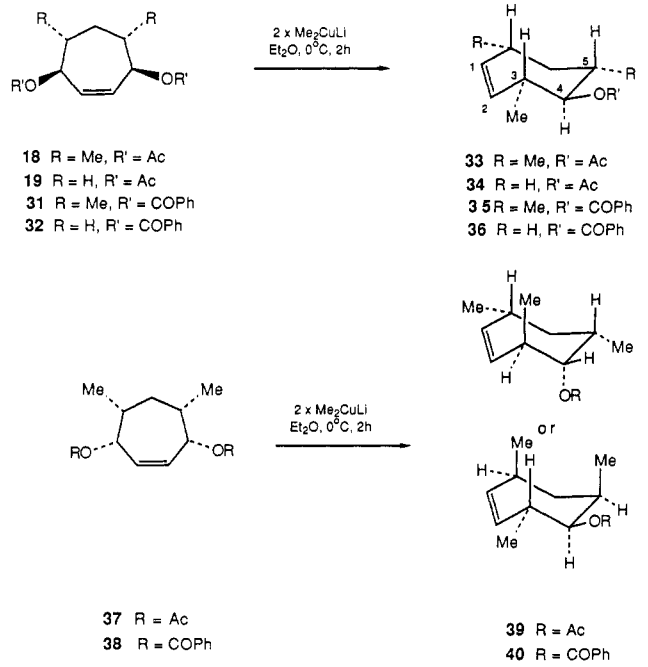
since the conformations of substituted cycloheptanones are not at all well-understood,[13] we decided to confirm the stereochemical assignments by X-ray crystallographic analysis. Accordingly, **28b** was converted to its crystalline (2,4-dinitrophenyl)hydrazone derivative, the X-ray structure of which is shown in Figure 3; this is in close agreement with the conformation shown in Figure 2.

Perhaps the most interesting observation from the results in Table II is the fact that cuprate addition to the benzoate derivatives **25b** and **26b** occurs stereospecifically cis to the benzoyloxy group under certain reaction conditions. In view of the greater preponderance of trans addition to, e.g., **26e**, it is unlikely that stereoelectronic control is responsible for this effect, but rather the benzoate appears to direct the incoming cuprate, possibly via a weak coordinating effect. Several modifications were chosen (Table II) in an attempt to improve both selectivity and yield, but without success.

Table IV. Addition of Lithium Dimethylcuprate to Bis(acyloxy)cycloheptene Derivatives

substrate	product	yield, %
19	**35**	<5
32	**36**	59
31	**34**	65
37	**39**	42
38	**40**	70

Thus, it appears possible to effect the construction of an intermediate of type **20**, that was considered as a precursor to the Prelog–Djerassi lactone (Figure 1). However, the low yields that were obtained, which could not be improved by variation of reaction conditions, led us to investigate alternative tactics. Accordingly, a survey was conducted of methyl cuprate additions to the diacetates **18** and **19** and related epimeric compounds. As can be seen from Table IV, displacement of allylic acetate and benzoate, using lithium dimethylcuprate, occurs in a completely anti sense, in agreement with the literature observations.[19] This was readily deduced from ^{1}H NMR spectral data, assuming the conformation shown, the cycloheptene system being more reliable than cycloheptanone.[13] Thus, H-4 of product **36** appears as a triplet, J = 10.1 Hz, at δ 4.57, fully consistent with diaxial coupling to two protons. The stereochemical assignment was confirmed by converting compound **36** to **30b**, which was spectroscopically identical with the *minor* product from cuprate addition to **26d**. Similar correlation of **35** with **29b** was not reliable owing to nonregioselectivity of the hydroboration reaction on **35**.



18 R = Me, R' = Ac
19 R = H, R' = Ac
31 R = Me, R' = COPh
32 R = H, R' = COPh

33 R = Me, R' = Ac
34 R = H, R' = Ac
35 R = Me, R' = COPh
36 R = H, R' = COPh

37 R = Ac
38 R = COPh

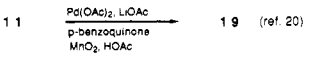
39 R = Ac
40 R = COPh

Thus, it can be seen that, while cuprate addition to compounds **18**, **19**, **31**, and **32** is highly stereoselective, the products have incorrect relative stereochemistry to allow further elaboration to the target lactone **5**. However, in view of the success of this reaction, we decided to investigate alternative methods for 1,4-dioxygenation of the cycloheptadiene precursor **10**. Bäckvall has reported[20] that

Table V. Enzymatic Hydrolyses of Compounds 18, 19, and 37

substrate	enzyme (reactn time)	products (yield, %)	hydroxy acetate abs config	hydroxy acetate enantiomeric excess: % ee
19	lipase (30 h)	**41** (40), **19** (50), **17**	*R* alcohol	44
19	acetylcholinesterase	**41** (39), **19** (50–55), **17** (ca. 5)	*R* alcohol	>98
18	acetylcholinesterase	no reaction		
18	lipase (30 h)	**43** (61), **18** (35), **16** (2–3)	*S* alcohol	>98
37	lipase (48 h)	**44** (48), **37** (35), **45** (15)	*S* alcohol	>98

palladium(II)-catalyzed 1,4-diacetoxylation of cycloheptadienes proceeds highly stereoselectively, as illustrated by the conversion of **11** to **19**. These conditions were used



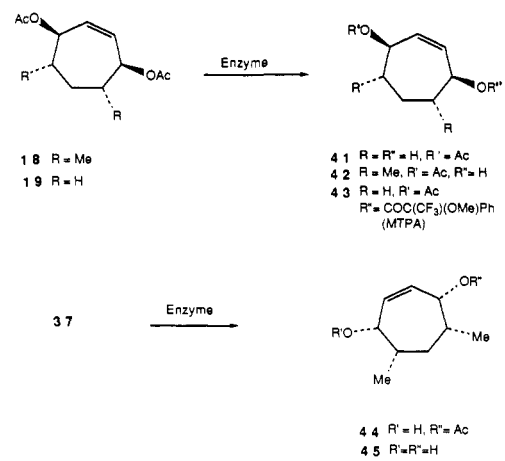
for the conversion of **10** to **37**, which was obtained as a single product in 63% yield. The diacetate **37** could be converted via hydrolysis and benzoylation to the dibenzoate **38**, and the latter compound was also prepared by double Mitsunobu inversion[21] of diol **16**, thus confirming the stereochemical assignment. As expected, cuprate addition to **37** and **38** occurred stereospecifically (anti displacement) to give **39** and **40**, respectively, and the results are summarized in Table IV.

Comparison of the products **39** and **40** with **24**, shown earlier, reveals that these compounds have relative stereochemistry that should allow their conversion to the Prelog–Djerassi lactone, using tactics similar to those employed by Stork[16] or White.[17] The symmetrical nature of the diacetoxy derivative **37** invites an application of enzyme-mediated hydrolysis[22] in the hope of achieving asymmetric induction, leading to the Prelog–Djerassi lactone as its natural antipode. Accordingly, completion of the synthesis was set aside while a study of enzymatic hydrolysis was conducted.

b. Enzyme-Mediated Hydrolysis of Diacetoxycycloheptene Derivatives. Compounds **18**, **19**, and **37** were employed in this study. Treatment of the unsubstituted diacetate **19** with lipase from *Candida cylindracea*, according to the procedure of Eichberger et al., [22] using a reaction time of 30 h, resulted in the formation of monoacetate **41**, diol **17**, and recovered diacetate **19**. The enantiomeric excess of **41** was estimated by ^{19}F NMR spectroscopy of the (*R*)-MTPA ester, and the absolute stereochemistry was determined by using Mosher's method.[23] The results for enzymatic hydrolysis of all three compounds, using lipase as well as electric eel acetylcholinesterase (following the method of Deardorff et al.[22]), are summarized in Table V.

In none of the cases studied could the reaction be driven to give hydroxy acetate exclusively; after a prolonged reaction time, diol began to appear, as monitored by thin-layer chromatography. Consequently, each reaction was

(18) Eliel, E. L.; Allinger, N. L.; Angyal, S. J.; Morrison, G. A. *Conformational Analysis*; American Chemical Society: Washington, DC, 1981.
(19) Goering, H. L.; Tseng, C. C. J. *J. Org. Chem.* **1983**, *48*, 3986 and references cited therein.
(20) Bäckvall, J.-E.; Byström, S. E.; Nordberg, R. E. *J. Org. Chem.* **1984**, *49*, 4619.
(21) Mitsunobu, O.; Wada, M.; Sano, J. *J. Am. Chem. Soc.* **1972**, *94*, 680. Mitsunobu, O. *Synthesis* **1981**, 1.
(22) Deardorff, D. R.; Matthews, A. J.; McMeekin, D. S.; Craney, C. L. *Tetrahedron Lett.* **1986**, *27*, 1255. Laumen, K.; Schneider, M. *Tetrahedron Lett.* **1984**, *25*, 5875. Johnson, C. R.; Penning, T. D. *J. Am. Chem. Soc.* **1986**, *108*, 5655. For a review on ester hydrolysis using enzymes, see: Jones, J. B. *Tetrahedron* **1986**, *42*, 3403.
(23) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.



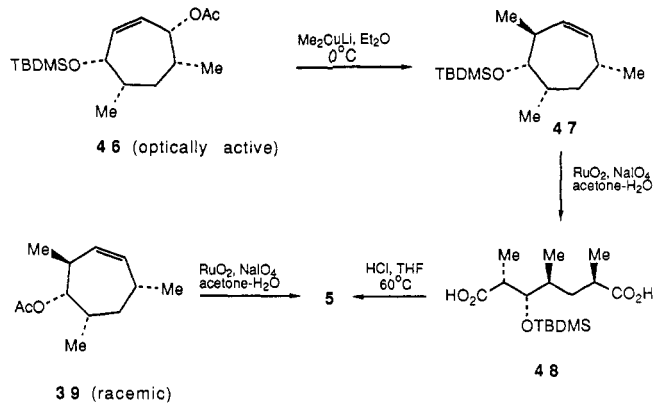
worked up after ca. 50% conversion, and the products were separated chromatographically. Recovered diacetate and diol could then be recycled. Lipase hydrolysis of **18** and **37** gave exclusively *S* alcohol, as expected by comparison with literature data for analogous diacetoxycyclopentene derivatives.[22] Acetylcholinesterase hydrolysis of **19** gave exclusively *R* alcohol, again as expected, while lipase hydrolysis of **19** unexpectedly gave predominantly R alcohol, at variance with the literature and with the results on **18** and **37**, although the enantiomeric excess was rather low. For the most part, then, enzymatic hydrolysis of symmetrical diacetoxycycloalkenes is predictable, but in view of the results of **19**, we recommend that the absolute stereochemistry of products from enzymatic hydrolysis of new substrates be independently established. The conversion of **37** to **44** clearly allows an asymmetric synthesis of the Prelog–Djerassi lactone, which will now be described.

c. Synthesis of the (+)-Prelog–Djerassi Lactone. Protection of the hydroxy group of **44** as its *tert*-butyldimethylsilyl ether **46**, followed by cuprate displacement of the allylic acetate, afforded **47** in 75% overall yield. Oxidative cleavage of the double bond using ruthenium tetraoxide, generated in situ, gave the diacid **48**, along with small amounts of the desired lactone **5**, which results from loss of the silyl protecting group during olefin scission. Since deprotection and lactonization were the desired final steps, this mixture was treated directly with acid to yield the lactone **5** in 66% overall yield from **47**. This compound was spectroscopically identical with the literature material[8,9,24] and, moreover, showed a rotation indicating very high optical purity: $[\alpha]_D$ +32° (*c* 1.0, $CHCl_3$) (lit.[8] $[\alpha]_D$ +33° (*c* 0.797, $CHCl_3$)). The racemic lactone could also be prepared directly from **39**, by ring scission using $RuO_2/NaIO_4$, as shown in Scheme I.

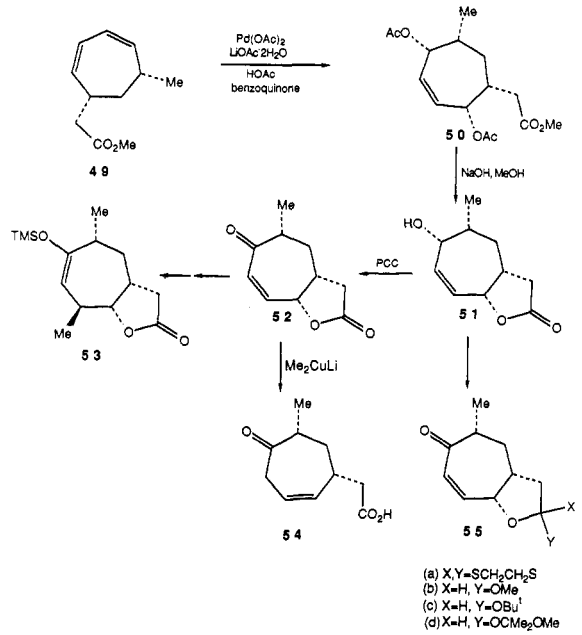
2. Synthesis of a Tylosin Precursor: Lactone 6. With the above protocol developed, we anticipated a relatively easy task in the synthesis of Grieco's lactone **6**, commencing with the readily prepared[11] ester **49**. This compound was converted to the diacetate **50**, in 59–63% yield via the Bäckvall reaction, and **50** was readily converted to the lactone **51** in quantitative yield, thereby differentiating the two hydroxy groups. Oxidation of **51** afforded the enone **52**, which we anticipated would serve as an appropriate substrate for cuprate addition to give **53**. This in turn would be converted to lactones of general type **6** or **7**. However, reaction of **52** with Me_2CuLi under a variety of conditions led only to the carboxylic acid derivative **54** (72% yield). Several attempts were made to circumvent this problem; a range of protected lactone and

(24) Rickards, R. W.; Smith, R. M. *Tetrahedron Lett.* **1970**, 1025.

Scheme I



Scheme II



lactol derivatives **55** were examined in the cuprate reaction, but all of these gave multiple products, and only minor amounts of material corresponded to the desired adduct (Scheme II).

Therefore, the lactone **51** was converted, via **56**, to the diol **57**, which was in turn converted to diol-protected enone derivatives **60** and **61** (Scheme III). Cuprate addition was found to be problematic for the methoxymethyl (MOM) protected derivative **60**, which gave exclusively **62**, the product of reductive cleavage, on treatment with Me_2CuLi. However, the bis(*tert*-butyldiphenylsilyl ether) **61** was well-behaved and gave **63** as a single product in 82% yield. Modification of the cuprate reaction to effect enolate trapping allowed conversion of **61** to **64**, which was subjected, without purification, to ozonolytic cleavage to give the hydroxy acid **65** in 65% overall yield from **61**. Protection of **65** as the methoxymethyl ether ester **66**, followed by removal of the silyl protecting groups, gave the lactone **7** in stereochemically homogeneous form, showing a ^1H NMR spectrum analogous to that of lactone **6**.[25] Comparison of **7** with **6**, which was used by Grieco et al.[10] as an intermediate in the synthesis of the right-hand section of tylosin, indicates that manipulation of substi-

(25) We wish to thank Professor Paul A. Grieco for providing a copy of the ^1H NMR spectrum of lactone **6**.

tuted cycloheptadienes, which are readily available via nucleophile addition to cycloheptadienyliron complexes (e.g., **7** gives **8** and **9**), allows general methodology appropriate for the construction of important macrolide antibiotic subunits.

Conclusions. To conclude, a few comments on the syntheses of lactones **5** and **7** are in order. The route to **5** from 1,3-cycloheptadiene requires 13 synthetic steps and leads to optically pure lactone. The overall yield is ca. 19%, based on starting material consumed during the enzymatic hydrolysis of **37**, and so this is a very respectable asymmetric synthesis of the Prelog–Djerassi lactone. The synthesis of lactone **7** requires 18 steps from 1,3-cycloheptadiene and proceeds in ca. 15% overall yield. This compares very favorably with Grieco's synthesis of **6**, which requires 24 steps from norbornadiene, including an optical resolution. Furthermore, we have recently shown[26] that enolate nucleophiles bearing chiral auxiliaries add to complex **7** in an asymmetric fashion, allowing the preparation of diene **49** in ca. 50% enantiomeric excess. This bodes well for future asymmetric synthesis using such organoiron complexes, although there is clearly a need to improve the asymmetric induction. Such improvements are currently under investigation in our laboratory.

Experimental Section

General. All reactions were carried out under dry, oxygen-free nitrogen or argon, unless otherwise noted. Solvents used in all reactions were purified immediately prior to use by distillation as follows: tetrahydrofuran (THF) from Na/benzophenone; CH_2Cl_2 from CaH_2; Et_2O from $LiAlH_4$. All solvents used for chromatography were purified by in-house distillation of commercially available materials. Residual solvent was removed from oils after chromatography by exposing a film of the material to high vacuum (10^{-3} mmHg) for 16–24 h. Infrared spectra were recorded for solutions in chloroform on a Perkin-Elmer 1420 spectrophotometer and were referenced to polystyrene at 1601 cm^{-1}. ^1H NMR spectra were recorded for solutions in deuteriochloroform, unless otherwise noted, at 200 MHz on a Varian XL-200 instrument, referenced to a tetramethylsilane internal standard. Mass spectra were run either at the Midwest Center for Mass Spectrometry at the University of Nebraska—Lincoln, an NSF Regional Facility, or in-house on a Kratos MS25A instrument. Optical rotations were measured on a Perkin-Elmer 141 digital polarimeter at room temperature. Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Combustion analyses were obtained through Galbraith Laboratories, Inc., Knoxville, TN. Preparative thin-layer chromatography was performed on commerically available UNIPLATE 20 × 20 cm plates (0.5-mm layer) or on similarly proportioned plates (1.0-mm layer) prepared in-house with Kieselgel 60 PF_{254} silica gel. Unless otherwise stated, all compounds are racemic.

Crystal Structure Determination of (2,4-Dinitrophenyl)hydrazone Derivative of 28b. An orange needle crystal of $C_{21}H_{22}N_4O_6$, having approximate dimensions of 0.30 × 0.14 × 0.08 mm, was mounted on a glass fiber in a random orientation. Preliminary examination and data collection were performed on an Enraf-Nonius CAD4 computer-controlled κ-axis diffractometer equipped with a graphite-crystal, incident-beam monochromator. The space group was determined to be $P\bar{1}$ (No. 2). The crystal data, structure solution, and refinement methods are summarized in the supplementary material. The structure was solved by direct methods and refined by full-matrix least squares. Hydrogen atoms were located and their positions and isotropic thermal parameters refined.

All calculations were carried out on a VAX 11/750 apparatus using VAXSDP.[27] Scattering factors for the neutral atoms and anomalous scattering coefficients were taken from standard literature sources.[28] Final atomic coordinates and bond lengths and angles are reported in the supplementary material. A perspective drawing of the molecule is shown in the supplementary material.

Endoperoxide 13. To a solution of 1,3-cycloheptadiene (3 g, 31.2 mmol) in 300 mL of dry CH_2Cl_2 was added 15 mg of tetraphenylporphyrin. The resultant deep purple solution was irradiated with a 100-W tungsten halogen lamp at room temperature for 2 h while oxygen was continuously bubbled through it. The solvent was removed on the rotary evaporator to give the endoperoxide (3.9 g, 100%) contaminated with tetraphenylporphyrin. This raw material was usually used for the next reaction without further purification, and tetraphenylporphyrin was removed at that stage. A crystalline analytical sample was prepared by chromatography and recrystallization from CH_2Cl_2 at 4 °C, mp 87–89 °C. IR (cm^{-1}): ν_{max} 3005, 2920, 1450, 1380, 1270. ^1H NMR: δ 6.36 (dd, J = 5.2, 3.9 Hz, 2 H), 4.74 (m, 2 H), 1.88 (m, 4 H), 1.26–1.62 (m, 2 H). HRMS calcd for $C_7H_{11}O_2$ (M + H): 127.0758. Found: 127.0775.

Endoperoxide 12. In the same procedure as for **13**, irradiation of *cis*-5,7-dimethyl-1,3-cycloheptadiene (1 g, 8.2 mmol) for 5 h gave the endoperoxide (1.13 g, 90%) as a colorless oil. IR (cm^{-1}): ν_{max} 2950, 2920, 1460, 1380, 1280, 1130, 1070. ^1H NMR: δ 6.42 (dd, J = 4.9, 3.1 Hz, 2 H), 4.41 (t, J = 4 Hz, 2 H), 2.16 (m, 2 H), 1.56 (m, 1 H), 1.31 (m, 1 H), 0.9 (d, J = 7.2 Hz, 6 H). HRMS calcd for $C_9H_{15}O_2$ (M + H): 155.1071. Found: 155.1005.

General Procedure for the Preparation of Hydroxy Enones 14 and 15 via Base-Catalyzed Isomerization of Endoperoxides 12 and 13. An ca. 0.2 M solution of the endoperoxide in dry CH_2Cl_2 was cooled with an ice bath. To this solution was added 2 equiv of Et_3N dropwise over 20 min. The mixture was stirred for 1 h at 0 °C and 12 h at room temperature and washed with 10% aqueous HCl and then water. The organic phase was dried ($MgSO_4$) and evaporated. Chromatography of the residue on silica gel gave the hydroxy enone.

5α,7α-Dimethyl-4β-hydroxycyclohept-2-en-1-one (14). The endoperoxide **12** (500 mg, 3.2 mmol) gave **14** (350 mg, 70%). IR (cm^{-1}): ν_{max} 3410, 1710, 1650, 1445, 1100. ^1H NMR: δ 6.35 (dd, J = 12.3, 3 Hz, 1 H), 5.91 (dd, J = 12.3, 1.9 Hz, 1 H), 3.93 (m, 1 H), 2.7 (m, 1 H), 1.93 (m, 1 H), 1.69 (ddd, J = 14, 4.6, 2.1 Hz, 1 H), 1.48 (dt, J = 14, 1.2 Hz, 1 H), 1.16 (d, J = 6.7 Hz, 3 H), 1.1 (d, J = 7 Hz, 3 H). Anal. Calcd for $C_9H_{14}O_2$: C, 70.08; H, 9.16. Found: C, 70.18; H, 8.94.

4-Hydroxycyclohept-2-en-1-one (15). The endoperoxide **13** (1 g, 7.8 mmol) gave **15** (830 mg, 82%). IR (cm^{-1}): ν_{max} 3400, 2920, 1700, 1450, 1130, 1105. ^1H NMR: δ 6.62 (dd, J = 12.4, 3.2 Hz, 1 H), 5.93 (dd, J = 12.4, 2.0 Hz, 1 H), 4.57 (m, 1 H), 3.81 (m, 1 H), 2.58 (m, 2 H), 2.23 (m, 1 H), 1.72–1.96 (m, 3 H). Anal. Calcd for $C_7H_{10}O_2$: C, 66.63; H, 7.99. Found: C, 67.18; H, 7.93.

General Procedure for the Preparation of Dihydroxycycloheptenes 16 and 17 via Reduction of Endoperoxides 12 and 13 with Thiourea. Thiourea (1 equiv) was added in portions to an ca. 0.5 M solution of the endoperoxide in MeOH. The mixture was stirred at room temperature for 12–15 h, and reaction was monitored by TLC. After completion, the mixture was filtered and evaporated, and the residue was chromatographed to give the dihydroxy compound.

3β,7β-Dihydroxy-4α,6α-dimethylcycloheptene (16). The endoperoxide **12** (500 mg, 3.2 mmol) gave **16** (292 mg, 58%) as white needles, mp 125–126 °C. IR (Cm^{-1}): ν_{max} 3430, 2950, 1450, 1370, 1130, 1010. ^1H NMR: δ 5.64 (s, 2 H), 3.84 (d, J = 9.4 Hz, 2 H), 1.59–1.80 (m, 3 H), 1.27 (td, J = 9.9, 7.6 Hz, 1 H), 1.0 (d, J = 6.6 Hz, 3 H). HRMS calcd for $C_9H_{16}O_2$: 156.1149. Found: 156.1146.

3,7-*cis*-Dihydroxycycloheptene (17). The endoperoxide **13** (1 g, 7.8 mmol) gave **17** (690 mg, 68%) as a white powder, mp

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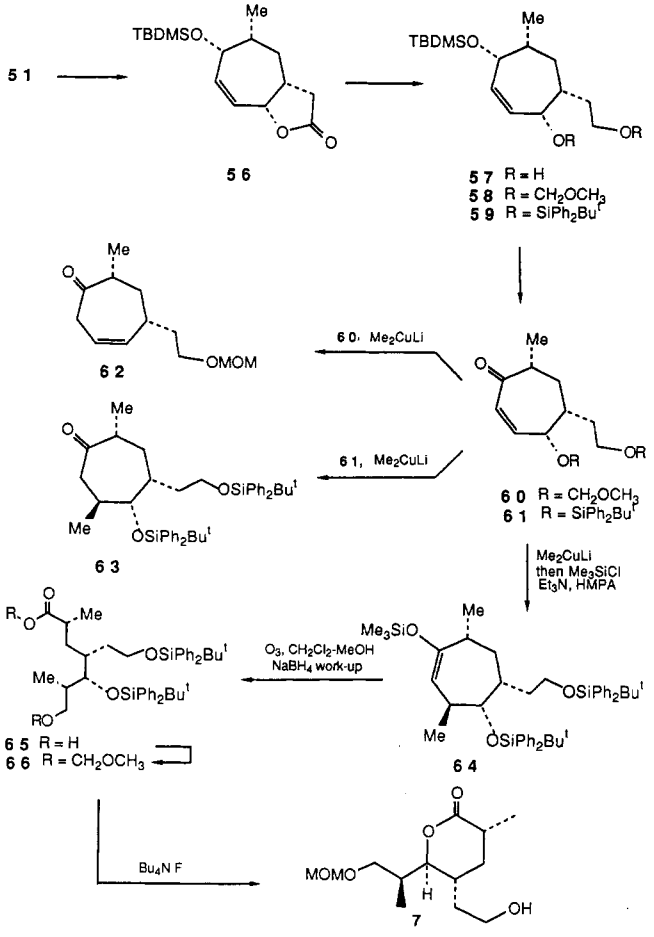
Scheme III



96–98 °C. IR (cm^{-1}): ν_{max} 3420, 2920, 2870, 1440, 1130, 1015. ^1H NMR: δ 5.76 (s, 2 H), 4.29 (dm J = 8.8 Hz, 2 H), 2.02–2.15 (m, 2 H), 1.73–1.85 (m, 2 H), 1.55–1.72 (m, 2 H). Anal. Calcd for $C_7H_{12}O_2$: C, 65.58; H, 9.44. Found: C, 65.27; H, 9.58.

Preparation of 16 via Reduction of 12 with $LiAlH_4$. A suspension of $LiAlH_4$ (740 mg, 19.5 mmol) in THF (20 mL) was cooled with an ice bath, and the endoperoxide **12** (1.59, 9.8 mmol) in THF (5 mL) was added dropwise over 15 min. The mixture was stirred at 0 °C for $1^1/_2$–2 h. The reaction was quenched by cautious addition of saturated NH_4Cl (5 mL), and the resultant mixture was filtered through a Celite pad. The filtrate was extracted with CH_2Cl_2, and the combined extracts were dried ($MgSO_4$), evaporated, and chromatographed to give the dihydroxy compound **16** (1.1 g, 72%).

General Procedure for the Peracetylation of Diols 16 and 17. The diol (2 mmol) and acetyl chloride (0.32 mL, 4.5 mmol) were dissolved in 2 mL of dry CH_2Cl_2 and cooled to 0 °C. To this solution was added 0.32 mL of dry pyridine dropwise over 10 min, and the mixture was allowed to warm to room temperature and stirred overnight. The mixture was diluted with 3 mL of CH_2Cl_2, washed with 10% HCl and H_2O, dried ($MgSO_4$), and evaporated to give essentially pure diacetate. Analytical samples were prepared by chromatography and recrystallization.

3β,7β-Diacetoxy-4α,6α-dimethylcycloheptene (18). Diol **16** gave **18** (97%) as colorless flakes, mp 53–55 °C. IR (cm^{-1}): ν_{max} 2960, 1745, 1365, 1225, 1030, 1015. ^1H NMR: δ 5.48 (s, 2 H), 5.09 (d, J = 9.8 Hz, 2 H), 2.05 (s, 6 H), 1.73–1.84 (m, 3 H), 1.42 (td, J = 11.2, 3.5 Hz, 1 H), 0.87 (d, J = 6.7 Hz, 6 H). HRMS calcd for $C_{11}H_{17}O_3$ (M – $COCH_3$): 197.1176. Found: 197.1182.

3,7-*cis*-Diacetoxycycloheptene (19). Diol **17** gave **19** (97%) as a white powder, mp 78–79 °C. IR (cm^{-1}): ν_{max} 2960, 1740, 1360, 1230, 1030, 1015. ^1H NMR: 5.65 (s, 2 H) 5.35 (dm, J = 9.9 Hz, 2 H), 2.05 (s, 6 H), 1.55–2.02 (m, 6 H). Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.23; H, 7.60. Found: C, 62.45; H, 7.55.

General Procedure for the Reaction of Enones 25b, 25g, 26b, and 26g with Lithium Dimethylcuprate. To a freshly prepared ethereal solution of Me_2CuLi (2 equiv, ca. 1 M) cooled to the indicated temperature was added dropwise the enone (0.5 mmol) in 1 mL of ether. The mixture was stirred at the indicated temperature, and the reaction was monitored by TLC. After all starting material was consumed (30–40 min), 2 mL of saturated NH_4Cl was added and the mixture was brought to room temperature and stirred for 30 min. Ether was added, and the phases were separated. The aqueous layer was extracted three times with ether, and the combined ether layers were washed with saturated NH_4Cl and H_2O, dried ($MgSO_4$), and evaporated. The residue was chromatographed on silica gel to give the products.

4β-(Benzoyloxy)-3β,5α,7α-trimethylcycloheptanone (27b). Benzoyloxy enone **25b** reacted at −78 °C to give **27b** (26%) as the sole stereoisomer. IR (cm^{-1}): ν_{max} 1730, 1700, 1380, 1265, 1165. ^1H NMR: δ 7.96–8.01 (m, 2 H), 7.35–7.51 (m, 3 H) 4.93 (dd, J = 8.8, 3.5 Hz, 1 H), 2.73 (d, J = 12.7 Hz, 1 H), 2.41 (d, J = 12.7 Hz, 1 H), 2.4 (m, 1 H), 2.18 (m, 1 H), 1.71 (ddd, J = 15.2, 4.3, 2.5 Hz, 1 H), 1.52 (m, 1 H), 1.06 (d, J = 7.2 Hz, 3 H), 0.97 (d, J = 6.8 Hz, 3 H), 0.96 (d, J = 6.9 Hz, 3 H). HRMS calcd for $C_{17}H_{22}O_3$: 274.1568. Found: 274.1597.

***cis*-4-(Benzoyloxy)-3-methylcycloheptanone (28b).** Benzoyloxy enone **26b** reacted at −78 °C with 4 equiv of Me_2CuLi to give **28b** (40%), as the sole methyl adduct, together with 1-cyclohepten-4-one (35%). IR (cm^{-1}): ν_{max} 2940, 1710, 1260, 1105. ^1H NMR: δ 8.02–8.06 (m, 2 H), 7.41–7.62 (m, 3 H), 5.33 (dt, J = 6.2, 2 Hz, 1 H), 2.91 (dd, J = 15, 10.8 Hz, 1 H), 2.51–2.57 (m, 2 H), 2.41 (dd, J 15, 2.8 Hz, 1 H), 2.16–2.34 (m, 2 1.63–2.0 (m, 3 H), 1.07 (d, J = 6.9 Hz, 3 H). HRMS calcd for $C_{15}H_{19}O_3$: 246.1255. Found: 246.1266.

1-Cyclohepten-4-one. Benzoyloxy enone **26b** reacted with Me_2CuLi in THF at −78 °C to give exclusively this compound (54%). IR (cm^{-1}): ν_{max} 2420, 2380, 2230, 1700, 1425, 1220. ^1H NMR: δ 6.65 (m, 1 H), 5.45 (m, 1 H), 3.13–3.18 (m, 2 H), 2.47–2.53 (m, 2 H), 2.21–2.32 (m, 2 H), 1.83–1.95 (m, 2 H). HRMS calcd for $C_7H_{10}O$: 110.0731. Found: 110.0728.

***trans*-4-(Benzoyloxy)-3-methylcycloheptanone (30b).** Benzoyloxy enone **26b** reacted at 0 °C to give **30b** (5%) together with **28b** (25%) and 1-cyclohepten-4-one. The two stereoisomers were separated by TLC with multiple development. IR (cm^{-1}): ν_{max} 2940, 1720, 1710, 1270, 1110. ^1H NMR: δ 8.04–8.08 (m, 2 H), 7.4–7.52 (m, 3 H), 5.04 (td, J = 7.9, 2.4 Hz, 1 H), 2.78 (dd, J = 13.3, 2.4 Hz, 1 H), 2.56 (d, J = 13.2 Hz, 1 H), 2.46–2.53 (m, 2 H), 2.06–2.34 (m, 2 H), 1.78–1.88 (m, 3 H), 1.06 (d, J = 7 Hz, 3 H). HRMS calcd for $C_8H_{12}O$ (M – $PhCO_2H$): 124.0888. Found: 124.0889.

4β-[(*tert*-Butyldimethylsilyl)oxy]-3β,5α,7α-trimethylcycloheptanone (27g) and 4β-[(*tert*-Butyldimethylsilyl)oxy]-3α,5α,7α-trimethylcycloheptanone (29g). Silyloxy enone **25g** reacted at 0 °C to give **27g** and **29g** as a 1:1 mixture, total yield 61%. IR (cm^{-1}): ν_{max} 1695 (br). ^1H NMR shows two sets of equally integrated peaks. Diagnostic resonances are δ 3.39 (dd, J = 6.4, 2.9 Hz) and 3.48 (dm, J = 4.1 Hz). HRMS calcd for $C_{16}H_{32}O_2Si$: 284.2170. Found: 284.2169.

***cis*- and *trans*-4-[(*tert*-Butyldimethylsilyl)oxy]-3-methylcycloheptanone (28g and 30g).** Silyloxy enone **26g** reacted at 0 °C to give **28g** and **30g** as a 1:4 mixture in 70% total yield. IR (cm^{-1}): ν_{max} 1685 (br). ^1H NMR (partial): **28g** δ 3.85 (dm, J = 5.2 Hz, 1 H), 2.85 (dd, J = 14.8, 11 Hz, 1 H), **30g** δ 3.43 (td, J = 8.9, 5.3 Hz, 1 H), 2.92 (dd, J = 10.8, 2.3 Hz, 1 H). HRMS calcd for $C_{14}H_{28}O_2Si$: 256.1857. Found: 256.1786.

Preparation of the (2,4-Dinitrophenyl)hydrazone of 28b. A solution of 1 g of (2,4-dinitrophenyl)hydrazine was prepared by warming in 30 mL of diglyme and allowed to stand at room temperature for 2 days. This solution (10 mL) was added at room temperature to 200 mg of **28b** in 2 mL of EtOH. Concentrated HCl (3 drops) was then added, and the mixture was stirred at room temperature until no starting material could be detected by TLC. The product was isolated by chromatography. Recrystallization from pentane/CH_2Cl_2 gave orange yellow crystals (194 mg, 56%), mp 274–275 °C. IR (cm^{-1}): ν_{max} 1950, 1870, 1720, 1615, 1515, 1335. ^1H NMR: δ 10.97 (s, 1 H), 9.03 (d, J = 2.6 Hz, 1 H), 8.21 (d, J = 2.6 Hz, 1 H), 7.91–8.02 (m, 2 H), 7.35–7.89 (m, 3 H), 5.24 (dm, J = 7.6 Hz, 1 H), 2.92 (dd, J = 14.1, 9.7 Hz, 1 H), 2.48–2.54 (m, 3 H), 2.01–2.21 (m, 3 H), 1.71–1.97 (m, 2 H), 1.02 (d, J = 7.2 Hz, 3 H). HRMS calcd for $C_{21}H_{22}O_6N_6$: 426.1538. Found: 426.1542.

General Procedure for the Reaction of 31, 32, 37, and 38 with Lithium Dimethylcuprate. To a freshly prepared ethereal solution of Me_2CuLi (2 equiv, ca. 1 M), at 0 °C, was added dropwise the diacetate or dibenzoate (100 mg in 1 mL of ether, 0.5-mL wash). The resultant mixture was stirred at 0 °C for 2 h and then quenched with 4 mL of saturated NH_4Cl. Ether was added, and the phases were separated. The aqueous phase was extracted three times with ether, and the combined ether extracts were washed with NH_4Cl and H_2O, dried ($MgSO_4$), and evaporated to give essentially pure product. Analytical samples were prepared by chromatography.

4β-(Benzoyloxy)-3α,5α,7α-trimethylcycloheptene (35). This compound was obtained from dibenzoate **31** as the sole product in 65% yield. IR (cm^{-1}): ν_{max} 2970, 1740, 1270, 1118, 960. ^1H NMR: δ 7.98–8.02 (m, 2 H), 7.32–7.48 (m, 3 H), 5.53 (dm, J = 10.7 Hz, 1 H), 5.24 (dm, J = 10.7 Hz, 1 H), 4.57 (t, J = 10.1 Hz, 1 H), 2.67 (m, 1 H), 2.36 (m, 1 H), 1.99 (m, 1 H), 0.96 (2 d, overlapping, J = 6.1 Hz, 6 H), 0.85 (d, J = 6.7 Hz, 3 H). Anal. Calcd for $C_{17}H_{22}O_2$: C, 79.02; H, 8.59. Found: C, 79.34; H, 8.49.

***trans*-4-(Benzoyloxy)-3-methylcycloheptene (36).** This compound was obtained from dibenzoate **32** as the sole product in 59% yield. IR (cm^{-1}): ν_{max} 2930, 1720, 1315, 1275, 1110. ^1H NMR: δ 7.95–8 (m, 2 H), 7.32–7.47 (m, 3 H), 5.8 (m, 1 H), 5.35 (m, 1 H), 4.76 (td, J = 6.4, 3.5 Hz, 1 H), 2.74 (m, 1 H), 2.03–2.14 (m, 3 H), 1.67–1.79 (m, 2 H), 1.48 (m, 1 H), 1.02 (d, J = 7.1 Hz, 3 H). Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.22; H, 7.88. Found: C, 77.55; H, 7.65. HRMS calcd for C_8H_{12} (M − $PhCO_2H$): 108.0938. Found: 108.0939.

4α-Acetoxy-3β,5α,7α-trimethylcycloheptene (39). This compound was obtained from the diacetate **37** as the sole product in 42% yield. IR (cm^{-1}): ν_{max} 2960, 1730, 1510, 1240, 1090. ^1H NMR: δ 5.33 (s, br, 2 H), 4.8 (dd, J = 10.1, 3.9 Hz, 1 H), 2.54 (m, 1 H) 2.28 (m, 1 H), 2.0 (m, 1 H), 1.98 (s, 3 H), 0.96 (d, J = 6.3 Hz, 6 H), 0.84 (d, J = 6.9 Hz, 3 H). HRMS calcd for $C_{10}H_{17}O$ (M − $COCH_3$): 153.1278. Found: 153.1268.

4α-(Benzoyloxy)-3β,5α,7α-trimethylcycloheptene (40). This compound was obtained from the dibenzoate **38** as the sole product in 70% yield. IR (cm^{-1}): ν_{max} 2960, 2880, 1720, 1505, 1275, 1118. ^1H NMR: δ 7.96–8.0 (m, 2 H), 7.33–7.49 (m, 3 H), 5.4 (m, 2 H), 5.08 (dd, J = 6.3, 2.8 Hz, 1 H), 2.73 (m, 1 H), 2.40 (m, 1 H), 2.23 (m, 1 H), 1.43 (m, 2 H), 1.02 (d, J = 7.3 Hz, 3 H), 1.01 (d, J = 7.1 Hz, 3 H), 0.92 (d, J = 6.9 Hz, 3 H). HRMS calcd for $C_{16}H_{19}O_2$ (M − CH_3): 243.1384. Found: 243.1378.

Hydroboration and Subsequent Oxidation of 36. To a solution of disiamylborane (0.23 mmol, prepared by using the literature procedure)[29] in 1.5 mL of Et_2O was added **36** (50 mg, 0.22 mmol) in 1 mL of Et_2O. The mixture was stirred at room temperature for 4 h, and the ether was removed under aspirator vacuum at room temperature with flushing of Ar. The residue was dissolved in 1.5 mL of CH_2Cl_2, and pyridinium chlorochromate (376 mg, 1 mmol) was added while the mixture was cooled in an ice bath. The resultant mixture was allowed to warm to room temperature and was stirred for 15 h. It was diluted with Et_2O and filtered through Celite. The filtrate was washed with brine and water, dried, and evaporated. Chromatography of the residue on silica gel gave **30b** (26 mg, 48%).

Enzymatic Hydrolysis of Diacetate 19. 1. With Acetylcholinesterase. To a slowly stirred suspension of acetylcholinesterase[30] (ca. 1 mg, 250 units, from electric eel) and NaN_3 (3 mg, 0.046 mmol) in aqueous phosphate buffer (0.2 M, pH 6.8, 20 mL) was added **19** (500 mg, 2.36 mmol) in one portion. The resultant mixture was stirred at room temperature for 15 h and then extracted five times with EtOAc. The combined EtOAc extract was dried ($MgSO_4$), evaporated, and chromatographed to give **41** (156 mg, 39%), **17** (53.9, 18%), and recovered **19** (13 mg, 2.5%).

***cis*-3-Acetoxy-7-hydroxycycloheptene (41)** gave the following data. IR (cm^{-1}): ν_{max} 3440, 2920, 1440, 1330, 1020. ^1H NMR: δ 5.77 (dt, J = 12.2, 2.1 Hz, 1 H), 5.58 (dt, J = 12.2, 2.3 Hz, 1 H), 5.29 (ddd, J = 9.7, 2.3, 2 Hz, 1 H), 5.29 (ddd, J = 10.1, 2.1, 1 Hz, 1 H), 2.22 (m, 1 H), 2.06 (s, 3 H), 1.8–2.05 (m, 3 H), 1.26–1.78 (m, 2 H). HRMS calcd for $C_7H_{11}O_2$ (M − CH_3CO) 127.0758. Found: 127.0760.

2. With Lipase. To a vigorously stirred solution of lipase (1.06 g, from *C. cyclindracea*) in aqueous phosphate buffer (0.2 M, pH 7.5, 90 mL) was added **19** (500 mg, 2.36 mmol) in one portion. The mixture was stirred at room temperature for 15 h and then extracted with EtOAc (5 × 50 mL). The combined EtOAc extracts were dried ($MgSO_4$), evaporated, and chromatographed to give **41** (168 mg, 38%), **17** (51 mg, 17%), and recovered **19** (23 mg, 5%).

Enzymatic Hydrolysis of Diacetate 18 with Lipase. To a vigorously stirred solution of lipase[31] (200 mg, from *C. cylindracea*) in aqueous phosphate buffer (0.2 M, pH 7.5, 18 mL) was added **18** (130 mg, 0.54 mmol) in one portion, and the mixture was stirred at room temperature. Two portions of lipase (10 mg each) were added after 3 and 6 h of stirring. The reaction was monitored with TLC and was stopped when traces of diol **16** were detected (30 h). The same workup as for **19** gave **42** (70 mg, 62%) and recovered **18** (53 mg, 38%).

(3*R*,4*S*,6*R*,7*S*)-3-Acetoxy-4,6-dimethyl-7-hydroxycycloheptene (42) gave the following data. IR (cm^{-1}): ν_{max} 3470, 2980, 1740, 1370, 1225, 1140. ^1H NMR: δ 5.66 (dt, J = 12.5, 2.7 Hz, 1 H), 5.43 (dt, J = 12.5, 2.7 Hz, 1 H), 5.01 (dm, J = 10.1, 1 H), 3.89 (dm, J = 9.3 Hz, 1 H), 2.06 (s, 3 H), 1.68–1.85 (m, 3 H), 1.33 (m, 1 H), 0.999 (d, J = 6.6 Hz, 3 H), 0.86 (d, J = 6.6 Hz, 3 H). HRMS calcd for $C_9H_{15}O_2$ (M − $COCH_3$): 155.1071. Found: 155.1068.

Enzymatic Hydrolysis of Diacetate 37. Reaction of **37** (150 mg, 0.62 mmol) with lipase in the same manner as for **18** for 48 h gave **44** (59 mg, 48%), diol **45** (15 mg, 15%), and recovered **37** (50 mg, 33%).

(3*R*,4*R*,6*S*,7*S*)-3-Acetoxy-4,6-dimethyl-7-hydroxycycloheptene (44): $[\alpha]^{23}_D$ +78.7 (c 6, CH_2Cl_2). IR (cm^{-1}): ν_{max} 3460, 1735, 1430, 1350. ^1H NMR: δ 5.99 (dd, J = 11.7, 6.2 Hz, 1 H), 5.77 (dd, J = 11.7, 6.3 Hz, 1 H), 5.25 (dd, J = 6.2, 4.1 Hz, 1 H), 4.06 (dd, J = 6.1, 1.3 Hz, 1 H), 2.35 (m, 1 H), 2.05 (s, 3 H), 1.72–2.0 (m, 3 H), 1.47 (dt, J = 14, 3.5 Hz, 1 H), 0.99 (d, J = 6.7 Hz, 3 H), 0.92 (d, J = 6.3 Hz, 3 H). HRMS calcd for $C_9H_{14}O$ (M − CH_3CO_2H): 138.1089. Found: 138.1049. Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.62; H, 9.16. Found: C, 66.4; H, 9.02.

(3*R*,4*R*,6*S*,7*S*)-3-Acetoxy-4,6-dimethyl-7-[(*tert*-butyldimethylsilyl)oxy]cycloheptene (46). To a solution of **44** (32 mg, 0.16 mmol) and diisopropylethylamine (206 mg, 1.6 mmol) in 1.5 mL of dry *N,N*-dimethylformamide was added *tert*-butylchlorodimethylsilane (120 mg, 0.8 mol) in one portion. The mixture was stirred at 60 °C for 24 h. It was cooled to room temperature, diluted with Et_2O, and washed with 10% HCl. The organic layer was dried ($MgSO_4$), evaporated, and chromatographed to give **46** (49 mg, 98%). $[\alpha]_D$: +2.7 (c 3, CH_2Cl_2). IR (cm^{-1}): ν_{max} 2940, 2840, 1730, 1455, 1365, 1235, 1070, 1040. ^1H NMR: δ 5.63 (m, 1 H), 5.47 (m, 1 H), 5.44 (m, 1 H), 4.34 (m, 1 H), 2.05 (s, 3 H), 1.88 (m, 1 H), 1.68 (m, 2 H), 1.17 (m, 1 H), 0.96 (d, J = 6.7 Hz, 6 H), 0.87 (s, 9 H), 0.32 (s, 6 H). HRMS calcd for $C_{15}H_{28}OSi$ (M − CH_3CO_2H): 252.1908. Found: 252.1921. Anal. Calcd for $C_{17}H_{32}O_3Si$: C, 65.34; H, 10.33. Found: C, 65.30; H, 10.55.

(3*R*,5*S*,6*S*,7*S*)-6-[(*tert*-Butyldimethylsilyl)oxy]-3,5,7-trimethylcycloheptene (47). To a suspension of CuI (60 mg, 0.32 mmol) in dry Et_2O (1 mL), at 0 °C, was added a 1.4 M ethereal solution of MeLi (0.46 mL) dropwise. The resultant clear solution was stirred at 0 °C for 15 min, and **46** (4.9 mg, 0.16 mmol) in 1 mL of Et_2O was then added dropwise. The mixture was stirred at 0 °C for 2 h. Saturated NH_4Cl (3 mL) was added, followed by 2 mL of Et_2O. The phases were separated, and the aqueous phase was extracted twice with Et_2O. The combined Et_2O extracts were washed with aqueous NH_4Cl and H_2O, dried ($MgSO_4$), and evaporated to give essentially pure **47** (29 mg, 68%). An analytical sample was prepared by chromatography. $[\alpha]_D$: +32.8 (c 1, CH_2Cl_2). IR (cm^{-1}): ν_{max} 2940, 2880, 2850, 1460, 1250, 1050, 1040. ^1H NMR: δ 5.36–5.41 (m, 2 H), 3.62 (dd, J = 4.3, 2.8 Hz, 1 H), 2.46 (qd, J = 7.9, 2.7 Hz, 1 H), 2.32 (m, 1 H), 2.0 (m, 1 H), 1.43 (dd, J = 11.9, 11.2 Hz, 1 H), 1.25 (m, 1 H), 0.99 (d, J = 7.2 Hz, 3 H), 0.98 (d, J = 7.4 Hz, 3 H), 0.92 (d, J = 7.90 Hz, 3 H), 0.89

(29) Brown, H. C. *Organic Synthesis via Boranes*; John Wiley & Sons: New York, 1975; p 29.

(30) From Sigma, No. C-3389, from electric eel, E.C. 3.1.1.7.

(31) From Sigma, No. L-1754, from *C. cylindracea*, E.C. 3.1.1.3.

(s, 9 H), 0.03 (s, 6 H). HRMS calcd for $C_{16}H_{32}OSi$: 268.2221. Found: 268.2236.

(2*R*,3*S*,4*S*,6*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-2,4,6-trimethyl-1,7-heptanedioic Acid (48). To a suspension of RuO_2 (14 mg, 0.11 mmol) in 0.5 mL of acetone was added a solution of $NaIO_4$ (55 mg, 0.26 mmol) in H_2O (0.5 mL). The black suspension of RuO_2 disappeared, and the whole became yellow. To this yellow mixture was added a solution of **47** (29 mg, 0.11 mmol) in acetone (0.5 mL). The mixture turned black immediately, and another 55 mg of $NaIO_4$ in the minimum amount of acetone/H_2O (1:1) was added. This was repeated twice during the course of the reaction when the mixture became black. The reaction was monitored with TLC, and the mixture was stirred at room temperature for an additional 10 h after the starting material was no longer detected. It was then filtered through a Celite pad, and the filtrate was made basic with 10% NaOH and washed with hexane. The aqueous phase was then acidified with concentrated HCl and extracted with EtOAc. The combined EtOAc extracts were washed with brine, dried ($MgSO_4$), and concentrated to give diacid **48** contaminated by a small amount of lactone **5** (total 20 mg, ca. 73%). Compound **39** was similarly treated to give racemic **5** in 42% yield. Spectral data for **48** are as follows. IR (cm^{-1}): ν_{max} 3060, 2940, 2880, 2855, 1700, 1100, 1060, 1040. ^1H NMR: δ 3.68 (dd, J = 7.8, 1.7 Hz, 1 H), 2.72 (qd, J = 6.8 1.7 Hz, 1 H), 2.48 (m, 1 H), 1.88 (m, 2 H), 1.56 (m, 1 H), 1.23 (d, J = 5.3 Hz, 3 H), 1.2 (d, J = 5 Hz, 3 H), 1.02 (d, J = 6.8 Hz, 3 H), 0.88 (s, 9 H), 0.08 (s, 6 H).

Prelog–Djerassi Lactone 5. Without further purification, the mixture of **48** and **5** obtained above (25 mg, ca. 0.08 mmol) was heated at 70 °C with 10% HCl (0.5 mL) in THF (1 mL) for 2 h. Ether (2 mL) was added, and the phases were separated. The aqueous layer was extracted twice with CH_2Cl_2, and the combined organic extract was dried ($MgSO_4$) and evaporated. Recrystallization of the residue from pentane/CH_2Cl_2 gave pure **5** (14 mg, 90%) as a white solid, mp 125–127 °C (lit.[8] mp 124–125 °C). $[\alpha]_D$: +32 (c 1, $CHCl_3$). IR (CM^{-1}): ν_{max} 3050, 1730, 1380, 1190, 1090. ^1H NMR: δ 4.53 (dd, J = 10.4, 1.9 Hz, 1 H), 2.70 (qd, J = 7.2, 1.9 Hz, 1 H), 2.43 (m, 1 H), 1.87–2.05 (m, 2 H), 1.47 (apparent t, J = 12.2 Hz, 1 H), 1.23 (d, J = 7.2 Hz, 3 H), 1.13 (d, J = 7.2 Hz, 3 H), 0.95 (d, J = 6.2 Hz, 3 H). HRMS calcd for $C_{10}H_{16}O_4$: 200.1048. Found: 200.1113.

3α,7α-Diacetoxy-4α-methyl-6α-(methoxycarbonyl)cycloheptene (50). To a solution of LiOAc·$2H_2O$ (2.8 g, 27.6 mmol), 1.4-benzoquinone (592 mg, 5.52 mmol), and $Pd(OAc)_2$ (67 mg, 0.3 mmol) in HOAc (10 mL) was added **49** (500 mg, 2.76 mmol). The mixture was stirred for 27 h at room temperature and filtered through a Celite pad, and the filtrate was diluted with brine (10 mL) and extracted with pentane (5 × 20 mL). The combined pentane extract was washed with 5% NaOH, brine, and H_2O, dried ($MgSO_4$e, and evaporated to give essentially pure **50** (59–63% yield). An analytical sample was prepared by chromatography. IR (cm^{-1}): ν_{max} 1710, 1360, 1015. ^1H NMR: δ 5.65 (d, J = 4.7, 1 H), 5.63 (d, J = 4.1 Hz, 1 H), 5.45 (dd, J = 4.1, 1.4 Hz, 1 H), 5.34 (dd, J = 4.7, 2 Hz, 1 H), 3.62 (s, 3 H), 2.46 (m, 1 H), 2.34 (dd, J = 11.2, 6 Hz, 2 H), 2.07 (m, 1 H), 2.0 (s, 3 H), 1.98 (s, 3 H), 1.71 (t, J = 6.2 Hz, 2 H), 0.91 (d, J = 6.9 Hz, 3 H). HRMS calcd for $C_{14}H_{19}O_5$ (M - OCH_3): 267.1231. Found: 267.1227. Anal. Calcd for $C_{15}H_{22}O_6$: C, 60.37; H, 7.44. Found: C, 60.35; H, 7.38.

Hydroxy Lactone 51. A mixture of **50** (500 mg, 1.66 mmol) and 10% methanolic NaOH (6.5 g) was stirred at 40 °C for 4 h. The pH was then adjusted to ca. 3 by addition of 10% HCl, and the mixture was allowed to cool to room temperature and stirred for 20 min. It was extracted with $CHCl_3$ (3 × 10 mL), and the combined extract was washed with brine and H_2O, dried ($MgSO_4$), and evaporated to give **51** (332 mg, 100%). IR (cm^{-1}): ν_{max} 3585, 3460, 1760, 1335, 1190. ^1H NMR: δ 5.56 (s, 2 H), 5.33 (d, J = 7.7 Hz, 1 H), 4.46 (d, J = 5.6 Hz, 1 H), 2.73 (dd, J = 12.5, 2.9 Hz, 1 H), 2.68 (m, 1 H), 2.14 (d, J = 12.5 Hz, 1 H), 2.06 (m, 1 H), 1.54 (d, J = 7.7 Hz, 1 H), 1.51 (dd, J = 7.5, 2.1 Hz, 1 H), 0.88 (d, J = 6.8 Hz, 3 H). HRMS calcd for $C_{10}H_{14}O_3$: 182.0942. Found: 182.0928. Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.90; H, 7.75. Found: C, 66.23; H, 7.88.

Lactonic Enone 52. Compound **51** (50 mg, 0.27 mmol) was dissolved in 2 mL of CH_2CL_2. To this solution, at room temperature, was added pyridinium chlorochromate (174 mg, 0.81 mmol) in portions. The mixture was stirred at room temperature for 15 h and then filtered through Celite. The filtrate was washed with H_2O, dried ($MgSO_4$), evaporated, and chromatographed on silica gel to give **52** (44 mg, 91%) was a colorless solid, mp 88–89 °C. IR (cm^{-1}): ν_{max} 1700, 1668, 1155, 1015, 900. ^1H NMR: δ 6.39 (dd, J = 12.6, 2.6 Hz, 1 H), 6.0 (dd, J = 12.6, 2.3 Hz, 1 H), 5.31 (dt, J = 8.6, 2.4 Hz, 1 H), 3.02 (m, 1 H), 2.68 (dd, J = 17.5, 8.3 Hz, 1 H), 2.35 (m, 1 H), 2.18 (dd, J = 17.5, 10.2 Hz, 1 H), 1.9 (ddt, J = 16.2, 5.7, 1.7 Hz, 1 H), 1.71 (t, J = 11 Hz, 1 H), 1.12 (d, J = 6.9 Hz, 3 H). HRMS calcd for $C_{10}H_{12}O_3$: 180.0786. Found: 180.0775.

5α-(Carboxymethyl)-7α-methylcyclohept-3-en-1-one (54). To a suspension of CuI (984 mg, 0.44 mmol) in Et_2O (1 mL) at 0 °C was added 1.4 M ethereal MeLi (0.63 mL, 0.88 mmol) dropwise. The clear solution was stirred at 0 °C for 15 min and then cooled to −78 °C. To this solution was added **52** (40 mg, 0.22 mmol) in 1 mL of Et_2O dropwise. The mixture was stirred at −78 °C for 30 min followed by the addition of 3 mL of saturated NH_4Cl. The mixture was extracted with Et_2O, and the combined ether extract was washed with NH_4Cl and H_2O, dried, and evaporated to give to **54** (29 mg, 72%). IR (cm^{-1}): ν_{max} 3440, 1770, 1695, 1160. ^1H NMR: δ 5.55 (m, 1 H), 5.54 (m, 1 H), 3.37 (dd, J = 13, 3.6 Hz, 1 H), 2.89 (dd, J = 13, 3.7 Hz, 1 H), 2.83 (m, 1 H), 2.56 (m, 1 H), 2.42 (d, J = 7 Hz, 1 H), 2.40 (d, J = 7 Hz, 1 H), 1.71 (d, J = 8.6 Hz, 1 H), 1.69 (m, obscured, 1 H) 0.88 (d, J = 7 Hz, 3 H). HRMS calcd for $C_{10}H_{14}O_3$: 182.0942. Found: 182.0943.

(*tert*-Butyldimethylsilyl)oxy Lactone 56. To a solution of **51** (500 mg, 2.5 mmol) and imidazole (512 mg, 7.5 mmol) in dry DMF (3 mL) was added TbDMS-Cl (565 mg, 3.75 mmol). The mixture was stirred under Ar at room temperature for 5 h. The mixture was partitioned between Et_2O and aqueous $NaHCO_3$. The aqueous layer was extracted with ether, and the combined ether extract was washed with 10% HCl and H_2O, dried ($MgSO_4$), and evaporated. Chromatography of the residue gave **56** (783 mg, 100%). IR (cm^{-1}): ν_{max} 1765, 1090, 870. ^1H NMR: δ 5.55 (s, 2 H), 5.31 (d, J = 6.2 Hz, 1 H), 4.44 (d, J = 5.6 Hz, 1 H), 2.81 (dd, J = 16.2, 9.3 Hz, 1 H), 2.75 (m, 1 H), 2.18 (dd, J = 16.2, 3.4 Hz, 1 H), 1.92 (m, 1 H), 1.56 (d, J = 9.3 Hz, 1 H), 1.53 (m, obscured, 1 H), 0.89 (s, 9 H), 0.88 (d, J = 9.7 Hz, 3 H), 0.04 (s, 6 H). Anal. Calcd for $C_{16}H_{28}O_3Si$: C, 64.82; H, 9.53. Found: C, 65.03; H, 9.51.

3α-Hydroxy-4α-(2-hydroxyethyl)-6α-methyl-7α-[(*tert*-butyldimethylsilyl)oxy]cycloheptene (57). To a suspension of $LiAlH_4$ (76 mg, 2 mmol) in THF (10 mL) at −78 °C was added **56** (313 mg, 1 mmol) in 2 mL of THF. The mixture was stirred at −78 °C for 2 h and 0 °C for 45 min, and 10% HCl (5 mL) was added to the mixture, followed by cautious addition of 10 mL of $CHCl_3$. The mixture was allowed to warm to room temperature and stirred for 30 min, the phases were separated, and the aqueous layer was extracted three times with $CHCl_3$. The combined $CHCl_3$ extract was dried (MgSO4) and evaporated to give **57** (288 mg, 91%). IR (cm^{-1}): ν_{max} 3600, 3370, 1460, 1090, 990. ^1H NMR: δ 6.21 (dd, J = 11.6, 7.8 Hz, 1 H), 5.99 (dd, J = 11.6, 7.2 Hz, 1 H), 4.48 (br, 1 H), 3.96 (apparent d, J = 6.83, 2 H), 3.76 (quint, J = 5.8 Hz, 1 H), 3.59 (quint, J = 5.4 Hz, 1 H), 3.14 (br, 1 H) 2.07 (t, J = 11.9 Hz, 1 H), 1.78–1.89 (m, 2 H), 1.67 (apparent q, J = 6.6 Hz, 2 H) 1.28 (dm, J = 13.7 Hz, 1 H), 0.97 (d, J = 6.8 Hz, 3 H), 0.91 (s, 9 H), 0.07 (s, 6 H). HRMS calcd for $C_{16}H_{32}O_3Si$: C, 63.95; H, 10.74. Found: C, 64.08; H, 10.46.

3α-(Methoxymethoxy)-4-[2-(methoxymethoxy)ethyl]-6α-methyl-7-[(*tert*-butyldimethylsilyl)oxy]cycloheptene (58). To a solution of **57** (150 mg, 0.47 mmol) and *N*,*N*-diisopropylethylamine (1 mL, 5.64 mmol) in CH_2Cl_2 (5 mL) was added dropwise chloromethyl methyl ether (227 mg, 2.82 mmol). The mixture was stirred at reflux for 15 h, diluted with 5 mL of CH_2Cl_2, and washed with 10% HCl and H_2O. The organic phase was dried ($MgSO_4$), evaporated, and chromatographed to give **58** (156 mg, 82%). IR (cm^{-1}): ν_{max} 2950, 1450, 1390, 1090. ^1H NMR: δ 5.55 (s, 1 H), 5.54 (s, 1 H), 4.59 (d, J = 10.6 Hz, 2 H), 4.58 (d, J = 5.4 Hz, 2 H), 4.32 (apparent t, J = 2.03, 2 H), 3.57 (d, J = 6.3 Hz, 1 H), 3.53 (d, J = 6.3 Hz, 1 H), 3.32 (s, 3 H), 3.31 (s, 3 H), 2.28 (m, 1 H), 1.6–1.88 (m, 5 H), 0.93 (d, J = 6.9 Hz, 3 H), 0.84 (s, 9 H), 0 (s, 6 H). HRMS calcd for $C_{20}H_{40}O_5Si$: 388.2643. Found: 388.2645.

3α-[(*tert*-Butyldiphenylsilyl)oxy]-4α-[2-[(*tert*-butyldiphenylsilyl)oxy]ethyl]-6α-methyl-7α-[(*tert*-butyldimethylsilyl)oxy]cycloheptene (59). Compound **57** (317 mg, 1 mol) and

imidazole (408 mg, 5 mmol) were dissolved in 2 mL of dry DMF. To this solution was added dropwise *tert*-butylchlorodiphenylsilane (0.78 mL, 3 mmol) via a syringe. The mixture was stirred under Ar at room temperature for 20 h, diluted with Et_2O (10 mL), and washed with saturated $NaHCO_3$, 10% HCl, and H_2O. The organic phase was dried ($MgSO_4$), evaporated, and chromatographed on silica gel to give **59** (710 mg, 92%). IR (cm^{-1}): ν_{max} 2980, 1470, 1430, 1390, 1115, 1010. ^1H NMR: δ 7.63–7.73 (m, 8 H), 7.29–7.47 (m, 12 H), 5.54 (dm, J = 11 Hz, 1 H), 5.38 (dm, J = 11 Hz, 1 H), 4.90 (m, 1 H), 4.22 (m, 1 H), 3.65–3.88 (m, 2 H), 2.05 (m, 2 H), 1.45–1.86 (m, 4 H), 1.08 (s, 9 H), 1.06 (s, 9 H), 0.92 (d, J = 7 Hz, 3 H), 0.88 (s, 9 H), 0 (s, 6 H). Anal. Calcd for $C_{48}H_{68}O_3Si$: C, 74.18; H, 8.83. Found: C, 74.03; H, 8.94.

4α-(Methoxymethoxy)-5α-[2-(methoxymethoxy)ethyl]-7α-methylcyclohept-2-en-1-one (60). **58** (150 mg, 0.37 mmol) in 1.5 mL of THF was treated with tetrabutylammonium fluoride (0.7 mL, 1 M in THF) at room temperature for 15 h. The mixture was partitioned between CH_2Cl_2 and H_2O. The aqueous layer was extracted twice with CH_2Cl_2, and the combined organic phase was dried ($MgSO_4$), evaporated, and chromatographed to give the desilylated product (96 mg, 90%). IR (cm^{-1}): ν_{max} 3420, 1440, 1340, 1000, 890. ^1H NMR: δ 6.27 (dd, J = 11.4, 7.4 Hz, 1 H), 6.0 (dd, J = 11.4, 7.0 Hz, 1 H), 4.75 (d, J = 6.8 Hz, 1 H), 4.6 (s, 2 H), 4.56 (d, J = 6.7 Hz, 1 H), 4.03 (d, J = 7.0 Hz, 1 H), 3.81 (dd, J = 11.3, 7 Hz, 1 H), 3.59 (d, J = 6.3, 1 H), 3.56 (d, J = 6.3 Hz, 1 H), 3.36 (s, 3 H), 3.34 (s, 3 H), 1.51–2.0 (m, 6 H), 1.0 (d, J = 8.6 Hz, 3 H). HRMS calcd for $C_{14}H_{25}O_4$ (M – OH): 257.1752. Found: 257.1748.

Treatment of this material with 3 equiv of pyridinium chlorochromate in CH_2Cl_2 at room temperature for 10 h gave **60** in 85% yield. IR (cm^{-1}): ν_{max} 1653, 1440, 1130, 1090. ^1H NMR: δ 6.53 (dd, J = 12.2, 3.9 Hz, 1 H), 6.03 (dd, J = 12.3, 1.7 Hz, 1 H), 4.71 (s, 2 H), 4.61 (d, J = 7.9 Hz, 1 H), 4.59 (s, 2 H), 3.54 (m, br, 2 H), 3.39 (s, 3 H), 3.34 (s, 3 H), 2.56 (m, 1 H), 2.4 (m, 1 H), 1.87–1.98 (m, 2 H), 1.29–1.34 (m, 2 H), 1.12 (d, J = 6.4 Hz, 3 H). HRMS calcd for $C_{14}H_{24}O_5$: 272.1622. Found: 272.1630.

4α-[(*tert*-Butyldiphenylsilyl)oxy]-5α-[2-[(*tert*-butyldiphenylsilyl)oxy]ethyl]-7α-methylcyclohept-2-en-1-one (61). To a solution of **59** (388 mg, 0.5 mmol) in 5 mL of acetone were added, at 0–5 °C, KF (60 mg, 1 mmol) and freshly prepared 8 N Jones' reagent (0.5 mL). The mixture was stirred at 0 °C for 15–20 h, diluted with H_2O (5 mL), and extracted with CH_2Cl_2. The combined CH_2Cl_2 extract was dried ($MgSO_4$), evaporated, and chromatographed to give **61** (307 mg, 93%). IR (cm^{-1}): ν_{max} 1652, 1460, 1450, 1410, 1380, 1100. ^1H NMR: δ 7.52–7.6 (m, 8 H), 7.24–7.36 (m, 12 H), 6.9 (dd, J = 11.8, 3.6 Hz, 1 H), 5.72 (dd, J = 11.8, 2.2 Hz, 1 H), 4.65 (m, 1 H), 3.59 (m, 2 H), 2.04–2.21 (m, 3 H), 1.57 (m, 1 H), 1.14–1.25 (m, 2 H), 1.01 (s, 9 H), 0.97 (s, 9 H), 0.88 (d, J = 6.6 Hz, 3 H). HRMS calcd for $C_{42}H_{52}O_3Si_2$: 660.3452. Found: 660.3456. Anal. Calcd for $C_{42}H_{52}O_3Si_2$: C, 76.32; H, 7.94. Found: C, 76.69; H, 7.52.

5α-[2-(Methoxymethoxy)ethyl]-7α-methylcyclohept-3-en-1-one (62). Reaction of **60** with Me_2CuLi (2 equiv, Et_2O, –78 °C, 80 min, NH_4Cl work up) gave **62** as the sole product, yield 72–75%. IR (cm^{-1}): ν_{max} 2895, 1680, 1440, 1130, 1085. ^1H NMR: δ 5.49–5.55 (m, 2 H) 4.56 (s, 2 H), 3.55 (t, J = 6.6 Hz, 2 H), 3.3 (s, 3 H), 2.89 (dd, J = 12.5, 7.6 Hz, 1 H), 2.49–2.6 (m, 2 H), 2.36 (m, 1 H), 1.6–1.77 (m, 4 H), 1.06 (d, J = 6.9 Hz, 3 H). HRMS calcd for $C_{12}H_{20}O_3$: 212.1411. Found: 212.1406.

4α-[(*tert*-Butyldiphenylsilyl)oxy]-5α-[2-[(*tert*-butyldimethylsilyl)oxy]ethyl]-7α-methyl-1-[(trimethylsilyl)oxy]-cycloheptene. To a suspension of CuI (260 mg, 1.24 mmol) in dry Et_2O (1.5 mL) at 0 °C was added 1.8 mL of ethereal MeLi (1.4 M). The solution formed was stirred at 0 °C for 15 min, and then **61** (400 mg, 0.62 mmol) in 2 mL of Et_2O was added dropwise. The mixture was stirred at 0 °C for 40 min and then treated consecutively at 0 °C with HMPA (0.2 mL, 1.2 mmol), Et_3N (0.2 mL, 1.4 mmol), and TMS-Cl (0.4 mL, 3 mmol). The mixture was allowed to warm to room temperature and stirred for 2 h. It was diluted with 2 mL of dry pentane and filtered quickly through a silica gel pad under aspirator vacuum, and the silica gel pad was washed with more pentane. The combined filtrate was evaporated to give a colorless oil (455 mg) essentially free of HMPA and Et_3N. This material was used in the next step without further purification. IR (cm^{-1}): ν_{max} 1640, 1450, 1420, 1375, 1100. ^1H NMR: δ 7.44–7.56 (m, 8 H), 7.24–7.32 (m, 12 H), 4.57 (d, J = 7.1 Hz, 1 H), 3.43 (dd, J = 6.4, 1.5 Hz, 1 H), 3.35 (m, 2 H), 2.22 (m, 2 H), 1.6–1.7 (m, 2 H), 1.42 (d, J = 5.8 Hz, 1 H), 1.40 (d, J = 5.4 Hz, 1 H), 1.11 (dd, J = 9.4, 2.6 Hz, 1 H), 0.92 (s, 9 H), 0.87 (s, 9 H), 0.61 (d, J = 7.2 Hz, 3 H), 0 (s, 9 H), one methyl doublet obscured.

4α-[(*tert*-Butyldiphenylsilyl)oxy]-5α-[2-[(*tert*-butyldiphenylsilyl)oxy]ethyl]-3β,7α-dimethylcycloheptanone (63). When, instead of treatment with TMS-Cl, the above reaction was quenched with saturated NH_4Cl, **63** was obtained in 89% yield after chromatography. IR (cm^{-1}): ν_{max} 2970, 1690, 1380, 1102. ^1H NMR: δ 7.44–7.6 (m, 8 H), 7.3–7.38 (m, 12 H), 3.26–3.39 (m, 3 H), 1.88–2.12 (m, 3 H), 1.65 (qt, J = 5, 0.9 Hz, 1 H), 1.31–1.5 (m, 2 H), 1.01 (s, 9 H), 0.89 (s, 9 H), 0.58 (d, J = 7 Hz, 3 H), one methyl doublet obscured. Anal. Calcd for $C_{43}H_{56}O_3Si_2$: C, 76.29; H, 8.34. Found: C, 76.58; H, 8.51.

Hydroxy Carboxylic Acid 65. Crude **64** (455 mg) was dissolved in 0.6 mL of CH_2Cl_2 and cooled in a dry ice/acetone bath when 0.6 mL of MeOH was added. The solution was treated with excess O_3/O_2 mixture at –78 °C until a blue color persisted. The reaction flask was purged with Ar, and $NaBH_4$ (47 mg, 1.24 mmol) was added in one portion. The mixture was stirred at –78 °C for 1 h and room temperature for 1 h. It was then partitioned between 10% HCl and $CHCl_3$. The aqueous phase was extracted with $CHCl_3$ (3 × 5 mL), and the combined $CHCl_3$ extract was washed with brine, dried ($MgSO_4$), evaporated, and chromatographed (silica gel, eluted with 1% HOAC in 6:4 EtOAc/hexane) to give **65** (286 mg, 65% from **61**). IR cm^{-1}): ν_{max} 3490, 3060, 1690, 1450, 1415, 1090. ^1H NMR: δ 7.51–7.6 nm, 8 H), 7.21–7.4 (m, 12 H), 3.75 (t, J = 1.8 Hz, 1 H), 3.32 (obscured, 2 H), 3.25 (d, J = 7 Hz, 2 H), 2.15 (dd, J = 12.7, 6 Hz, 1 H), 1.69–1.82 (m, 2 H), 1.63 (dm, J = 6.4 Hz, 1 H), 1.58 (dm, J = 6.4 Hz, 1 H), 1.14–1.36 (m, 2 H), 0.97 (s, 9 H), 0.93 (s, 9 H), 0.86 (d, J = 7.9 Hz, 3 H), 0.77 (d, J = 6.9 Hz, 3 H). Anal. Calcd for $C_{43}H_{58}O_5Si_2$: C, 72.64; H, 8.23. Found: C, 73.01; H, 8.13.

Alkoxy Ester 66. Compound **65** (178 mg, 0.25 mmol) was stirred with iPr_2NEt (0.52 mL, 3 mmol) and chloromethyl methyl ether (0.12 mL, 1.5 mmol) in CH_2Cl_2 (1.5 mL) at room temperature for 15 h. It was diluted with 5 mL of CH_2Cl_2 and washed with 10% HCl, saturated $NaHCO_3$, and H_2O. The organic phase was dried ($MgSO_4$), evaporated, and chromatographed to give **66** (180 mg, 90%). IR (cm^{-1}): ν_{max} 1720, 1095. ^1H NMR: δ 7.43–7.59 (m, 8 H), 7.15–7.36 (m, 12 H), 5.0 (d, J = 5.9 Hz, 1 H), 4.9 (d, J = 5.9 Hz, 1 H), 4.25 (d, J = 6.4 Hz, 1 H), 4.19 (d, J = 6.4 Hz, 1 H), 3.66 (t, J = 2.5 Hz, 1 H), 3.28 (d, J = 6.9 Hz, 1 H), 3.22 (s, 3 H), 3.20 (d, J = 6.9 Hz, 1 H), 3.1 (s, 3 H), 2.08–3.15 (obscured, 2 H), 2.17 (m, 1 H), 1.62–1.88 (m, 2 H), 1.49 (m, 2 H), 1.05–1.34 (m, 2 H), 0.92 (s, 9 H), 0.88 (s, 9 H), 0.78 (d, J = 6.8 Hz, 3 H), 0.77 (d, J = 6.9 Hz, 3 H). HRMS calcd for $C_{31}H_{47}O_7Si$ (M – TBDPS): 559.3088. Found: 559.0321. Anal. Calcd for $C_{47}H_{66}O_7Si_2$: C, 70.64; H, 8.33. Found: C, 70.76; H, 7.98.

Hydroxy Lactone 7. Compound **66** (100 mg, 0.125 mmol) in 1 mL of dry THF was treated with tetrabutylammonium fluoride (0.38 mmol) at room temperature for 12 h. The mixture was diluted with CH_2Cl_2, washed with brine, dried ($MgSO_4$), evaporated, and chromatographed to give **7** (32 mg, 92%). IR (cm^{-1}): ν_{max} 3460, 1710, 1095. ^1H NMR: δ 4.56 (s, 2 H), 4.27 (dd, J = 10.6, 1.7 Hz, 1 H), 3.65–3.79 (m, 2 H), 3.56 (t, J = 9.4 Hz, 1 H), 3.4 (dd, J = 9.5, 5.9 Hz, 1 H), 3.29 (s, 3 H), 2.39 (m, 1 H), 1.9–2.16 (m, 3 H), 1.6 (m, 1 H), 1.32 (m, 2 H), 1.22 (d, J = 7.1 Hz, 3 H), 0.84 (d, J = 7 Hz, 3 H). HRMS calcd for $C_{12}H_{21}O_4$ (M – OCH_3): 229.1439. Found: 229.1438. Anal. Calcd for $C_{13}H_{24}O_5$: C, 59.96; H, 9.30. Found: C, 59.49; H, 9.35.

Acknowledgment. A.J.P. thanks the U.S. Public Health Service, National Institutes of Health, for financial support (Grant GM 32114) and the National Institutes of Health (RR-01689 and RR-03574) and the National Science Foundation (CHE 80-24633) for shared instrumentation grants toward the purchase of NMR and mass spectrometer facilities. We also thank Dr. Harjinder S. Bansal for preliminary work on the enzymatic hydrolyses. A.A.P. thanks the College of Arts and Sciences, University of Toledo, for supporting of the X-ray crystallographic facility.

Supplementary Material Available: Structural report for the (2,4-dinitrophenyl)hydrazone of **28b**, including anisotropic thermal parameters, a detailed description of data collection, structure solution, and refinement, and 200-MHz ^{1}H NMR spectra of the (2,4-dinitrophenyl)hydrazone of **28b** and of compounds **5**, **12**, **13**, **16** (R = Me), **18** (R = Me), **19** (R = H), **27** + **29** (R = Me, R′ = TBS), **27** (R = Me, R′ = COPh), **28** + **30**, **39–41**, **47**, **48**, **52**, **54**, **58**, **60**, **62**, and **64** (37 pages); tables of observed and calculated structure factors (11 pages). Ordering information is given on any current masthead page.

Chemistry of Fruit Flies. Composition of the Rectal Gland Secretion of (Male) *Dacus cucumis* (Cucumber Fly) and *Dacus halfordiae*. Characterization of (*Z*,*Z*)-2,8-Dimethyl-1,7-dioxaspiro[5.5]undecane

William Kitching,*[†] Judith A. Lewis,[†] Michael V. Perkins,[†] Richard Drew,[‡] Christopher J. Moore,[‡] Volker Schurig,[§] Wilfried A. König,[∥] and Wittko Francke[∥]

Department of Chemistry, University of Queensland, St. Lucia, Queensland, Australia 4067, Department of Primary Industries, Brisbane, Australia 4067, Institut für Organische Chemie, Universität Tübingen, Auf der Morgenstelle 18, D7400, Federal Republic of Germany, and Institut für Organische Chemie der Universität, Martin-Luther-King Platz 6, D-2000, Hamburg, Federal Republic of Germany

Received December 30, 1988

Combined gas chromatography–mass spectrometry and synthesis have established that the major components of the rectal gland secretion of adult male cucumber flies (*Dacus cucumis*) are the *E*,*E*, *E*,*Z*, and *Z*,*Z* diastereomers of 2,8-dimethyl-1,7-dioxaspiro[5.5]undecane, which have been synthesized utilizing organomercury chemistry from 1,10-undecadien-6-one. The thermodynamically least stable *Z*,*Z* diastereomer has been characterized for the first time, by ^{1}H and ^{13}C NMR measurements and mass spectrometry. Minor amounts of 3-hydroxy-2,8-dimethyl-1,7-dioxaspiro[5.5]undecane and various derivatives of the 1,6-dioxaspiro[4.5]decane and 1,7-dioxaspiro[5.6]dodecane systems are also present. 1,3-Nonanediol occurs in significant amounts, and both enantiomers have been acquired by Sharpless asymmetric epoxidation of (*E*)-2-nonen-1-ol followed by Red-Al (Aldrich) reduction of the chiral epoxy alcohols. Chiral gas chromatographic analysis of the diols (as their cyclic carbonates) has demonstrated that the natural material is the *R*-(−) enantiomer. Natural (*E*,*Z*)-2,8-dimethyl-1,7-dioxaspiro-[5.5]undecane is shown to be racemic, whereas the more abundant *E*,*E* diastereomer is enantiomerically highly pure, possessing the 2*S*,6*R*,8*S* configuration. The major volatile component of the rectal gland secretion of male *Dacus halfordiae* (Tryon) is also (*E*,*E*)-2,8-dimethyl-1,7-dioxaspiro[5.5]undecane, with no detectable levels of the *E*,*Z* or *Z*,*Z* isomers. Other spiroacetals present were 2-ethyl-7-methyl-1,6-dioxaspiro[4.5]decane and the unusual even carbon-numbered (*E*,*E*)-2-ethyl-8-methyl-1,7-dioxaspiro[5.5]undecane. 6-Oxo-1-nonanol, diethyl succinate, and 2-methyl-6-pentyl-3,4-dihydro-2*H*-pyran were also identified.

Introduction

Fruit flies are destructive pests of horticulture in the tropical and temperate world and elaborate detection systems are employed for population monitoring and timing of eradication programs.[1] In recent years, more attention has been directed to the possible use of pheromone-based attractants, following the demonstration[2,3] that male tephritids store the pheromone in a reservoir and secrete it from a sac, both glands being located in the rectal region and appearing in the male (e.g., of Queensland fruit fly, *Dacus tryoni*) 2 days after the pupal–adult apolysis.[2] As the flies mature, droplets of yellowish material form.[2] In only one species, *D. oleae* (olive fly) does the female release the sac pheromone,[4] whereas male-produced pheromones have been identified in several species of tephritid fruit flies including *D. tryoni*,[5] *D. dorsalis*,[6] *D. cucurbitae*,[6] *Anastrepha suspensa*,[7] *A. ludens*,[8] and *Ceratitis capitata*.[9] These secretions are multicomponent in nature. What appear to be sex pheromones have also been found in the males of *Dirioxa pornia* (Walker),[10] *Rhagholitis pomonella* (Walsh),[11] and *R. cerasi L*,[12] but chemical information is lacking. The release of the pheromone is generally accompanied by courting behavior and the females may respond to other visual, auditory, or gustatory stimuli.[1]

Bellas and Fletcher[13] conducted the first chemical examination of the reservoir secretion of a Dacine species, and this work concerned *D. tryoni* (Froggatt) (Queensland fruit fly) and the taxonomically close *D. neohumeralis*, both very serious pests of fruit and vegetable crops in eastern Australia. The same set of six relatively simple amides was found in each species, although in different proportions. Since that report, studies of a number of

[†] University of Queensland.
[‡] Department of Primary Industries.
[§] Universität Tübingen.
[∥] Institut für Organische Chemie der Universität.

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