22.45, 22.75, 26.3, 27.8, 34.9, 35.0, 37.4, 40.9, 49.2, 72.2, 72.7, 116.5, 135.65; MS 208 (M^+, 1), 167 (61), 149 (100), 67 (46), 55 (30), 41 (44). Anal. Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.7; H, 11.3.

2-Methyl-1-oxaspiro[5.5]undecane-2-carbonitrile (43b): t_r = 10.47 min (B), R_f = 0.44 (19/1); IR 2240 (C≡N), 1080, 980 (CO) cm^{-1}; ^1H NMR (300 MHz) δ 1.15–2.10 (m with a s at 1.56, all H); ^{13}C NMR δ 16.8, 21.75, 22.0, 26.05, 30.25, 31.55, 34.5, 36.9, 41.25, 66.7, 75.45, 123.15; MS 194 (M^+, 2), 151 (38), 150 (100), 137 (98), 55 (39), 41 (34).

In Situ Oxidation of Hydroxytetrahydropyrans of the Type 27a. Isolation of δ-Lactones 44–57. For general procedure[18b] and details for the analytical and spectral characterization of compounds **44**,[57] **45**,[36] **46**,[38] **47**,[58] **48**, **49**, **50**,[59] **51**,[38] **52**, **53**, **54**,[38] **55**,[60] **56**,[33] and **57** (see eq 4), see the the supplementary material.

Acknowledgment. We are grateful for support of this research by DGICYT (No. PB88-0287) and partially by LILLY S.A. D.J.R. thanks the Conselleria de Cultura Educació i Ciencia de la Generalitat Valenciana for a fellowship. We thank Dr. C. Nájera and Dr. C. Gómez for NMR and mass spectrometry determinations, respectively.

Registry No. **4a**, 129471-18-7; **4b**, 133549-41-4; **4c**, 133549-42-5; **9a**, 16686-11-6; **9b**, 5978-08-5; **9c**, 3308-98-3; **10a**, 3390-13-4; **10b**, 4352-98-1; **10c**, 133549-21-0; **11a**, 130518-96-6; **11b**, 129847-08-1; **11c**, 133549-22-1; **12a**, 59985-72-7; **12b**, 56341-93-6; **12c**, 133549-23-2; **13a**, 133549-18-5; **13b**, 58568-17-5; **13c**, 133549-24-3; **14a**, 133549-19-6; **14b**, 58568-20-0; **14c**, 133549-25-4; **15a**, 129847-03-6; **15b**, 129847-09-2; **15c**, 133549-26-5; **16a**, 133549-20-9; **16b**, 53857-10-6; **17a**, 24175-21-1; **17b**, 42991-09-3; **18a**, 130518-97-7; **18b**, 38338-80-6; **19a**, 129847-04-7; **19b**, 944-27-4; **20a**, 129847-05-8; **20b**, 129847-10-5; **21a**, 129847-06-9; **21b**, 129864-57-9; **22a**, 129847-07-0; **22b**, 129847-11-6; **23**, 133549-37-8; **24a**, 78-94-4; **24b**, 930-68-7; **25a**, 75506-74-0; **25b**, 133549-27-6; **25c**, 133549-28-7; **26b**, 133578-17-3; **27a**, 133549-38-9; **28a**, 133549-38-9; **29a**, 133549-39-0; **30b**, 36452-81-0; **31b**, 133549-40-3; **32c**, 6263-83-8; **33c**, 133578-18-4; **34a**, 180-79-0; **35a**, 133549-29-8; **36a**, 133549-30-1; **37a**, 133549-31-2; **38a**, 133549-32-3; **39a**, 133549-33-4; **40a**, 133549-34-5; *cis*-**41a**, 124469-06-3; *trans*-**41a**, 124469-07-4; **42b**, 133549-35-6; **43b**, 133549-36-7; **44**, 28525-62-4; **45**, 705-86-2; **46**, 2610-95-9; **47**, 2319-32-6; **48**, 2610-93-7; **49**, 129665-07-2; **50**, 28771-65-5; **51**, 102540-91-0; **52**, 129665-08-3; **53**, 129665-09-4; **54**, 115407-73-3; **55**, 20127-07-5; **56**, 4481-78-1; **57**, 120375-26-0; DMF, 68-12-2; *i*-PrCHO, 78-84-2; PhCHO, 100-52-7; MeCOEt, 78-93-3; $(\overline{CH_2})_4CO$, 120-92-3; $(\overline{CH_2})_5CO$, 108-94-1; $(\overline{CH_2})_7CO$, 502-49-8; PhCOMe, 98-86-2; c-C_3H_5COPh, 3481-02-5; PhCN, 100-47-0; $PhCON(\overline{CH_2})_4$, 3389-54-6; PhCOCl, 98-88-4; PhNCS, 103-72-0; PhCHNPh, 538-51-2; $(PhCH_2S)_2$, 150-60-7; $PrCON(\overline{CH_2})_4$, 33527-93-4; EtOCOCl, 541-41-3; CuBr·Me_2S, 54678-23-8; EtCOEt, 96-22-0; *n*-$C_5H_{11}CHO$, 66-25-1; MeCOMe, 67-64-1; *i*-BuCOMe, 108-10-1; *t*-BuCOMe, 75-97-8; EtCOPh, 93-55-0; *n*-PrCOPh, 495-40-9; PhCOPh, 119-61-9; triethylsilane, 617-86-7; trimethylsilyl cyanide, 7677-24-9; allyltrimethylsilane, 762-72-1.

Supplementary Material Available: Full analytical and spectral data for compounds **10a**, **12a**, **17a**, **10b**, **13b**, **16b**, **17b**, **19b**, **25a**, **44–57**; experimental procedure for compounds **44–57**; and copies of ^1H (300 MHz) and ^{13}C (75 MHz) NMR of compounds **10c**, **11c–14c**, **25c**, **33c**, **35a–37a**, **39a**, **40a**, ***trans*-41a**, ***cis*-41a**, **43b**, **48**, **49**, **52**, and **53** (44 pages). Ordering information is given on any current masthead page.

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Cyclopentenyllithium Additions to Chiral Aldehydes. Diastereofacial Selectivity Indicating the Absence of a Pronounced Neighboring Carboxylate Anion Effect

Dirk Friedrich[1] and Leo A. Paquette*

Evans Chemical Laboratories, The Ohio State University, Columbus, Ohio 43210

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The 1,2-addition of cyclopentenyllithium to a series of three five-membered aldehydo esters and their hemiacylals has been examined in order to assess the level and direction of facial selectivity surrounding nucleophilic attack at the aldehyde carbonyl and to clarify possible electronic and steric contributions stemming from neighboring functional groups. Neither methyl substitution of the acetic acid (ester) side chain nor the interchange of ester for carboxylate anion serve as important diastereocontrol elements. Instead, diastereofacial selectivity in these and related cyclic carboxaldehydes is governed by the inherent structural features of the ring system to which the functional group is attached. The convenient preparation of a complete subset of isomerically pure bicyclic lactones carrying five stereogenic centers is reported.

Major uncertainties persist in understanding the diastereofacial selectivities associated with addition reactions involving *cyclic* carboxaldehydes. Sound predictive knowledge concerning, and reasonable control of, the stereochemical outcomes underlying such nucleophilic processes is an unsolved problem. The specific issue is exemplified by (+)-1, a compound believed to be blocked from nucleophilic capture along that direction cofacial with the dithioketal.[2] However, the illustrated Grignard addition proceeds with formation of a 1:1 mixture of **2** and **3**.

The three observations grouped in Scheme I hold similar interest. The addition of 3-furyllithium to aldehydo ester

(1) Postdoctoral Fellow, Wigner-Stiftung der Technischen Universität Berlin (1989–1990) and the Deutsche Forschungsgemeinschaft (1990–1991).

(2) Paquette, L. A.; Wiedeman, P. E.; Bulman-Page, P. C. *J. Org. Chem.* **1988**, *53*, 1441.

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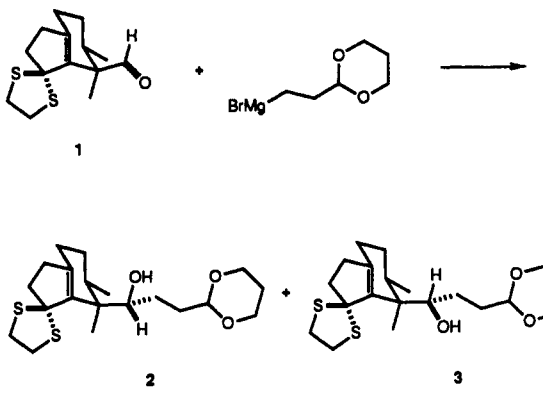
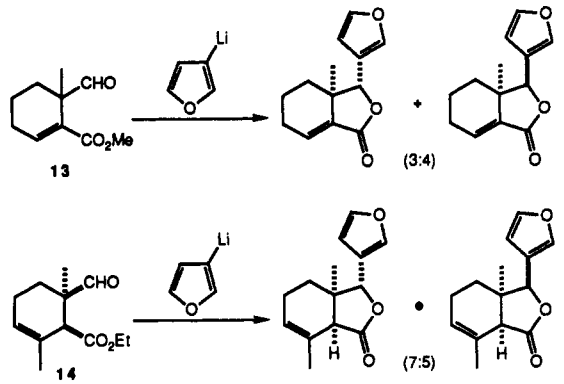


1 2 3

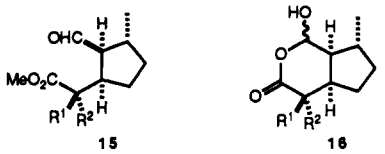
4[3] leads to a 1:4 mixture of lactone diastereomers 5 and 6. Similar treatment of hemiacylal 7 gives rise predominantly to the R^* diastereomer 8 (7:3),[4] while 10 is converted only to 11.[5] The crossover in diastereofacial preference may be linked to the locus and degree of unsaturation present in the starting materials, to solvent effects, or, more intriguingly, to the chemical composition of the oxygenated substituent flanking the aldehyde carbonyl. For 4, the neighboring group is carbomethoxy. When 7 and 10 are concerned, the pendant side chain incorporates a carboxylate anion. Does the presence of a negatively charged residue in close proximity to the seat of nucleophilic attack exert significant influence on diastereofacial selectivity?

Related chemistry involving 13 and 14 has been reported. Despite the change in relative positioning of the double bond within the six-membered ring, product distributions are not greatly imbalanced.[6]



13 (3:4) 14 (7:5)

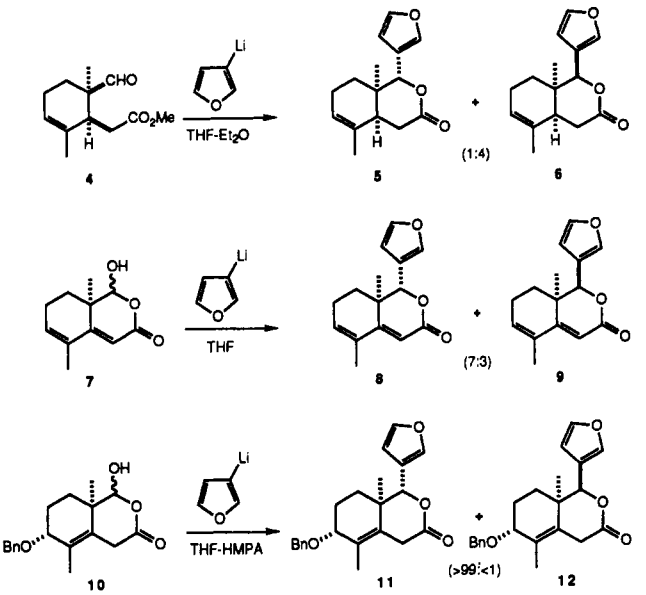
The primary goal of this investigation was to elucidate whether a neighboring carboxylate anion exerts control of aldehyde capture in a diastereofacial manner opposite that observed with the ester derivative. A second objective was to ascertain if alkyl substitution of the acetic acid unit can contribute diastereocontrol elements independent of those of the ring to which the reaction centers are attached (see 15 and 16).



15 16

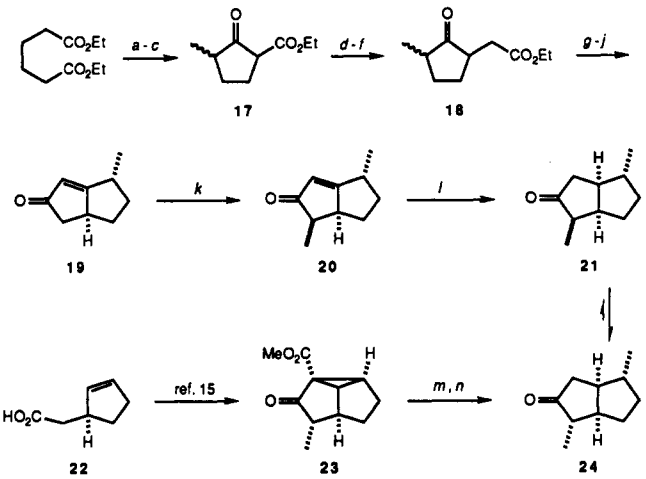
a, $R^1=R^2=H$; b, $R^1=H$, $R^2=CH_3$; c, $R^1=CH_3$, $R^2=H$

Scheme I



4 5 6 (1:4) 7 8 9 (7:3) 10 11 12 (>99:<1)

Scheme II[a]



17 18 19 20 21 22 23 24

[a] Key: [a] NaOEt, toluene; [b] CH_3I; [c] NaOEt; [d] $ClCH_2CO_2Et$, K_2CO_3, acetone; [e] H_3O^+, Δ; [f] H^+, EtOH; [g] 2-methoxy-1,3-dioxolane, H^+; [h] $(MeO)_2P(O)CH_2Li$; [i] H_3O^+; [j] $Bu_4N^+OH^-$, C_6H_6; [k] LDA, CH_3I; [l] Dibal-H, [CH_3Cu]; [m] $(CH_3)_2CuLi$. [n] H^+, Δ or $LiI\cdot 3H_2O$, DMF, Δ.

Synthesis of the Functionalized Cyclopentanecarboxaldehydes. Following improvement of the original routes to 17,[7] the conversion to 19 proceeded by functionalization of keto ester 18[8,9] so as to allow for subsequent Horner–Emmons cyclization[10] (Scheme II). The unfavorable diastereomeric ratio (ca. 2:1) present in the monocyclic precursors to 19 was of little consequence since equilibration occurs following ring closure[11] to provide enone of 95% diastereomeric purity. While monomethylation product 20 was configurationally stable, saturated ketone 21, obtainable in pure condition by conju-

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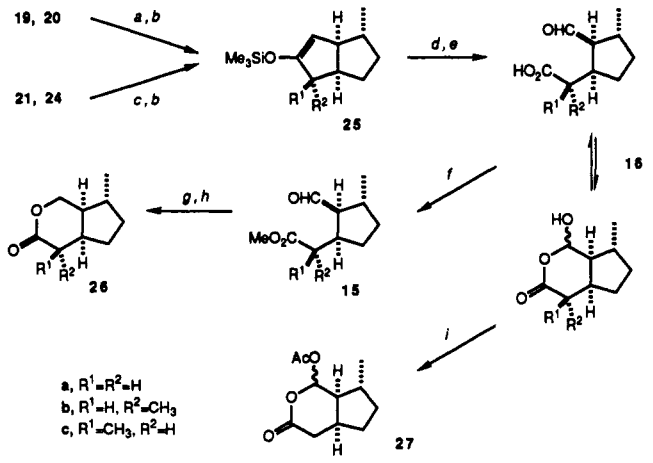
Scheme III[a]



[a] Key: [a] Dibal-H, [CH_3Cu]; [b] Me_3SiCl, NEt_3; [c] LDA. [d] O_3, CH_3OH; [e] Me_2S; [f] CH_2N_2; [g] $NaBH_4$; [h] LDA, CH_3I. [i] Ac_2O, [BF_3].

gate reduction of **20**,[12] underwent ready epimerization to **24**. An efficient preparation of **24** from commercially available 2-cyclopentenylacetic acid has been reported recently.[13] However, the acidic decarboxylation conditions described for the final step afforded an 83:17 mixture of **24** and **21**. This ratio was subsequently shown to be the thermodynamic equilibrium value by independent base-catalyzed equilibration of the stereoisomers. An improvement in the maintenance of stereochemical integrity was realized by making recourse instead to hydrated lithium iodide in dimethylformamide.[14] Heating at 160 °C for 30 min reproducibly led to a 95:5 mixture of **24** and **21**.

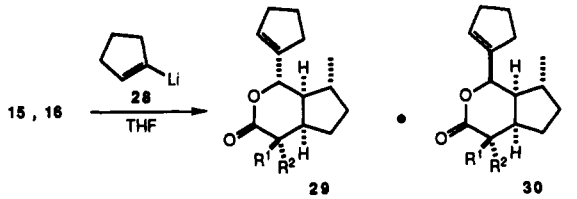
Sequential treatment of **19** with the Dibal-H/methylcopper complex[12] and trimethylsilyl chloride in the presence of triethylamine under carefully controlled conditions delivered **25a** (Scheme III). Ozonolytic cleavage of this silyl enol ether and reductive workup with dimethyl sulfide led to **16a**, whose ^1H and ^{13}C NMR spectra are very broad and ill-defined in appearance because of the aldehyde–hemiacylal equilibrium. Nonetheless, its smooth conversion into **15a** and **27** by reaction with diazomethane and acetic anhydride (BF_3 catalysis), respectively, leaves little doubt regarding its purity. Relative stereochemistry was confirmed at this stage by conversion to the known **26a**.[15] Transformation into its monomethyl homologues isoiridomyrmecin (**26b**) and iridomyrmecin (**26c**) was also effected.[13b,15a,b,16]

The β-stereoselective course of the regiospecific methylation of **19** differs in direction from the characteristic α-preference exhibited by saturated diquinane systems.[17]

Table I. Percent Distribution of Diastereomeric Lactonic Products 29 and 30 (Formula Designation)

	lactone, %	
precursor	29	30
15a	13 (a)	87 (a)
15b	7 (b)	93 (b)
15c	14 (b)	86 (c)
16a	17 (a)	83 (a)
16b	23 (b)	77 (b)
16c	10 (c)	90 (c)

Scheme IV[a]



[a] Key: a, $R^1 = R^2 = H$; b, $R^1 = H$, $R^2 = CH_3$; c, $R^1 = CH_3$, $R^2 = H$.

Fortunately, the stereochemistry present in **20** can be preserved during conversion to **25c** provided that proper care is exercised.[18] The availability of **25b** rests on the excellent regioselectivity that can be reliably achieved during kinetic deprotonation–O-silylation of **24**.[13b] Processing of these two unsaturated intermediates in the manner already discussed afforded the remaining members of the **15** and **16** series.

Stereochemical Investigation of Cyclopentenyllithium Additions to 15 and 16. In order to facilitate the assessment of diastereofacial selectivity, 1-cyclopentenyllithium (**28**) was selected as the common nucleophile because of its ready availability[19] and achiral nature. Coupling of **15a** to **28** in cold tetrahydrofuran with inverse addition resulted in predominant formation of crystalline lactone **30a** (Scheme IV, Table I). The diastereomer ratios were determined by careful integration of ^1H NMR spectra recorded directly on unpurified lactonization products. The absorptions due to the allylic α-acyloxy protons are well-separated and particularly amenable to quantitative measurement. Unequivocal stereochemical information was gained from the precise determination of coupling constants and supporting NOE measurements as detailed in the following text.

The condensation of **28** and **16a** proceeded smoothly without requiring inverse addition. After heating of the resultant hydroxy acids in benzene to complete the lactonization, ^1H NMR analysis revealed the product distribution to parallel that observed earlier, but with a small enhancement in the proportion of minor diastereomer **29a** (from 13 to 17%).

The increased steric bulk generated by the presence of an α-methyl group adjacent to the carbomethoxy substituent as in **15b** is seen to exert only a modest cooperative effect. The β-methyl group in **15c** had no apparent effect on stereoinduction. Interestingly, whereas the R^* lactone

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(18) An alternative preparation of **21** and its conversion via **25c** to **26c** have been described in a communication[16g] (no data or experimental). The same authors give ^{13}C data for **21** in a study of carbon chemical shifts for bicyclo[3.3.0]octanes: Whitesell, J. K.; Matthews, R. S. *J. Org. Chem.* **1977**, *42*, 3878.

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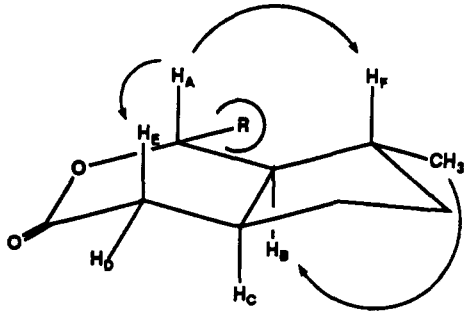
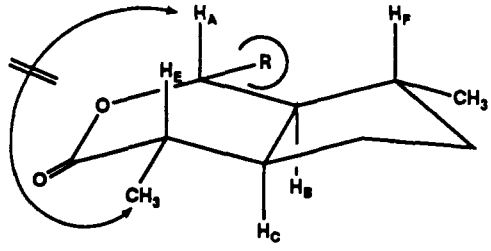


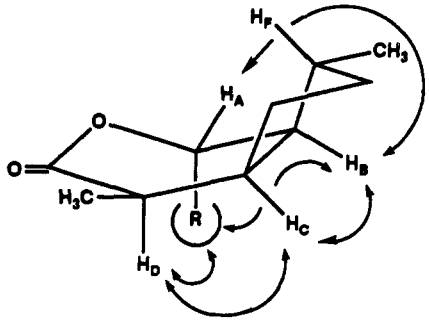
29a

J_{AB} = 9.5; J_{BC} = 8; J_{BF} = 11; J_{CD} = 6.5; J_{CE} = 10



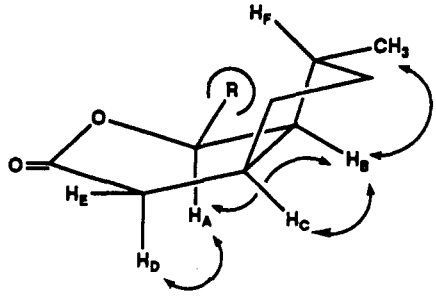
29b

J_{AB} = 10.5; δ 2.6 - 1.8 region seriously overlapped



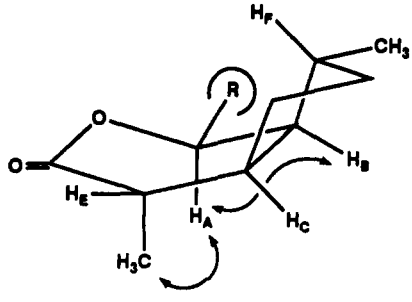
29c

$J_{AB} \leq 1$; J_{BC} = 11; J_{BF} = 9; J_{CD} = 7



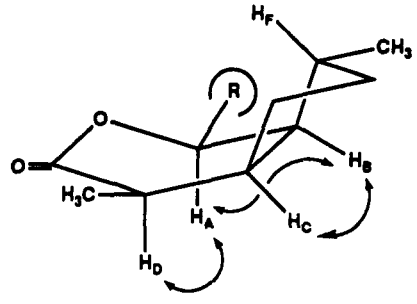
30a

J_{AB} = 3.5; J_{BC} = 10.5; J_{BF} = 8.5; J_{CD} = 7; J_{CE} = 1.5



30b

J_{AB} = 3.5; J_{BC} = 9; J_{BF} = 9; J_{CE} = 2.5



30c

J_{AB} = 3.5; J_{BC} = 10; J_{BF} = 10; J_{CD} = 6.5

Figure 1. Relative configurations and conformations of lactones **29** and **30**.

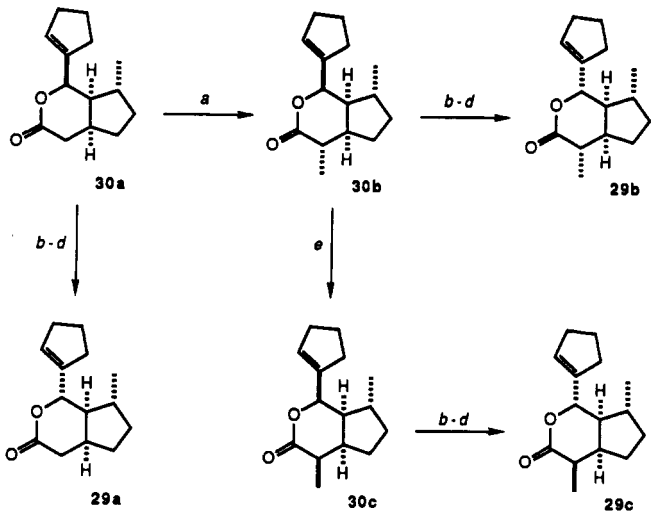
produced from **15c** was the expected **30c**, the minor *S** lactone was determined to be **29b** and not **29c** (Table I)! No epimerization occurs when any of the four pure lactones (**29b,c**; **30b,c**) are simply heated in benzene. In fact, **29b**, **30b**, and **30c** are also recovered unchanged following saponification with dilute KOH in aqueous methanol, acidification, and relactonization in hot benzene. However, **29c** is transformed completely into **29b** under these conditions. Since the hydroxy esters formed by cyclopentenyllithium addition to **15b,c** are converted to **29** and **30** by treatment in this fashion, the epimerization phenomenon can be traced to this phase of the workup. Comparable treatment of **16b** proved to be somewhat attenuating in the relative proportion of diastereomer **30**. The 90% selectivity witnessed for **16c** approximates closely the values encountered earlier.

Thus, a uniform preference is exhibited for nucleophilic addition to that carbonyl face that leads ultimately to formation of lactones **30**. This diastereoselective bias is neither uniformly decreased when the transition is made from ester (viz. **15**) to carboxylic acid derivative (**16**) nor enhanced by increased steric bulk on the neighboring acetic acid side chain. The changes made within the immediate environment of the aldehyde group are such that they do not ever cause lactones **29** to surface as dominant condensation products.

NMR Analysis of the Relative Configurations and Conformations of Lactones 29 and 30. Homonuclear decoupling experiments performed on **29a** showed J_{AB}, J_{CE}, and J_{BF} to be large, indicating these five protons to be positioned axially on the lactone framework (see Figure 1). This cis relationship of H_A to both H_E and H_F also rests securely on NOE difference experiments, which also established H_B to be in close spatial proximity to methyl. These data are uniquely consistent with a boat-chair conformation for this molecule. The spatial arrangement adopted by **29a** is shared by **29b** because of the unique opportunity offered for projecting all three framework constituents equatorially.

The situation changes dramatically in epimer **29c**. The

Scheme V[a]



[a] Key: [a] LDA; CH_3I; [b] KOH, MeOH; [c] H_3O^+; [d] $Me_2NCH[OCH_2C(CH_3)_3]_2$, $CHCl_3$; [e] LDA; *t*-BuOH, −110 °C.

cis-fused nature of this bicycle is clearly evident on the basis of the large observed value of J_{BC} (11 Hz). A diaxial relationship must exist between H_B and H_F (J_{BF} = 9 Hz) and the dihedral angle between H_C and H_D must approach 0° (J_{CD} = 7 Hz). These features can be accommodated by the alternative boat-chair arrangement shown. The axial disposition of the cyclopentenyl unit is supported by the observation of NOE effects from H_B and H_D to its vinyl proton.

In order for the two substituents in **30a** to become equatorial, this lactone must adopt a geometry very similar to that of **29c**. The magnitudes of the H_A/H_B and H_C/H_D interactions agree with their relative cis dispositions. The trans placement of H_C and H_E is similarly indicated by the small J_{CE} value of 1.5 Hz. The additional multiplicity reflected in the H_B signal that stems from its involvement with H_F is large (J = 8.5 Hz), in line with their axial orientation on the fused cyclopentane ring. No change in geometry occurs on proceeding to **30b** or **30c** nor is one expected (see Figure 1).

Regiospecific Configurational Inversion within the Epimeric Lactones. Although the predescribed reactions constitute a reasonably serviceable entry to lactones **30**, an ability to fix all *five contiguous stereogenic centers* in a predictable way was lacking. The following protocol provides for the efficient preparation of **29b,c** and **30b,c** as pure configurational isomers.

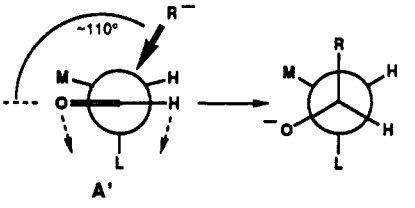
When the anion of **30a**, generated by reaction with lithium diisopropylamide (LDA) at low temperature, was treated with methyl iodide, **30b** was produced to the virtual exclusion of its epimer. Brief exposure of **30b** in turn to LDA and kinetically controlled reprotonation with *tert*-butyl alcohol at −110 °C[20] was equally successful in providing pure **30c** (Scheme V). These observations constitute convincing experimental evidence for the belief that the enolate anions of **30a** and **30b** adopt a ground-state conformation closely related to that of their neutral precursors (Figure 1). Furthermore, these enolates appear constrained to react with electrophiles from their convex surface, stereoelectronic factors contributing to axial entry with high selectivity.

The cyclopentenyl-substituted sites in **30a–c** were inverted by treatment of their derived hydroxy acids, obtained by saponification and controlled acidification, with the dineopentyl acetal of dimethylformamide.[21] Lactones **29a–c** were formed in good yield in rapid and very convenient fashion. Due to the ease with which these hydroxy acids undergo simple relactonization, small amounts of unchanged starting materials are always recovered. However, the minor constituents are easily removed by medium-pressure liquid chromatography.

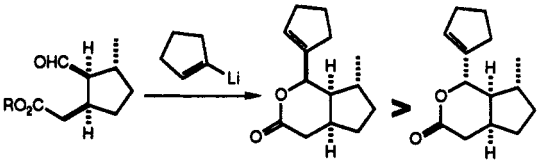
In addition to its synthetic promise, the foregoing constitutes a complete chemical correlation of all lactones involved in the diastereofacial selectivity aspect of this investigation. Any diastereomer of **29** or **30** may now be reached conveniently.

Aldehyde Geometry and Transition-State Analysis. Control of the stereochemistry of 1,2-carbonyl addition reactions has important implications for synthesis. Herein, aldehydes **15** and **16** have been allowed to react with cyclopentenyllithium. The ensuing coupling reactions proceed under kinetic control via a pair of diastereomeric transition states. The high discrimination shown by **15a** for production of the *R** lactone, viz. **30a**, is mirrored by **16a**. Furthermore, the favored approach is in the same direction and similar in extent to that adopted by **4**. In light of the close parallel in the distribution of **29** and **30** exhibited by esters (i.e., **15**) and hemiacylals (i.e., **16**) alike, one must conclude that *the neighboring carboxylate anion effect has no pronounced impact on diastereomer ratios if all other factors are kept constant.* The crossover in diastereofacial selectivity exhibited by **7** and **10** must therefore stem from other structural characteristics.

Discussions of diastereoselectivity in nucleophilic additions to open-chain aldehydes having a chiral center next to the carbonyl function are often based on the "revised Cram model".[22] This generalization defines the relevant reactive conformation A′ on the basis of minimum steric



interactions along the *entire* reaction coordinate as well as the optimal attack angle for bond development. Additional considerations are required for proper assessment, based on the same model, of nucleophilic addition involving cycloalkyl carboxaldehydes. In particular, the M and L assignments to the α-substituents are not obvious, since bridging prevents them from being free and independently rotating. Also, different ring conformations now gain importance.

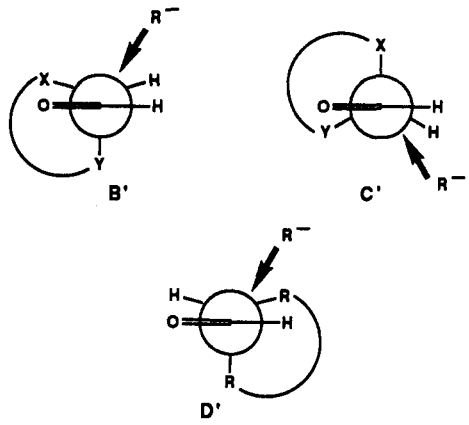


Nevertheless, for each fundamental conformation of the ring system that compares to A′, the relevant reactive conformation has to be selected uniquely from the two possible alternatives B′ and C′:

(20) Friedrich, D.; Bohlmann, F. *Tetrahedron* **1988**, *44*, 1369.

(21) (a) Vorbrüggen, H. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 211. (b) Brechbühler, H.; Büchi, H.; Hatz, E.; Schreiber, J.; Eschenmoser, A. *Ibid.* **1963**, *2*, 212. (c) Brechbühler, H.; Büchi, H.; Hatz, E.; Schreiber, J.; Eschenmoser, A. *Helv. Chim. Acta* **1965**, *48*, 1746. (d) Vorbrüggen, H.; Krolikiewicz, K. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 876.

(22) Eliel, E. L. In *Asymmetric Synthesis*; Morrison, J. D., Ed., Academic Press, New York, 1983; Vol. 2.



Consequently, consideration of the two envelope conformations available to a cyclopentanecarboxaldehyde causes four alternatives to emerge as the prime candidates for the relevant reactive conformation(s). These appear as A–D in Figure 2.

Options B and D are quickly excluded a priori since they correspond to a less than favorable trajectory of attack as reflected in D'.

Option C is, in contrast, a clearly defined example of good stereochemical control. Thus, scrutiny of the steric interactions arising from H vs CH_2CO_2R leads to the prediction that frontside attack should prevail, in complete agreement with the experimental observations.

The options surrounding option A are less obvious. Recourse to an argument analogous to that applied in the C case would give rise to backside attack, but this is not seen. To arrive at the correct alternative prediction requires proper weighting of those steric interactions involving the carbonyl oxygen (see Figure 2). Nonbonded compressions stemming from this source are assumed to be less important in option C because its CHO group is disposed axially. If considered, however, the effect would cooperate with the reaction trajectory already defined. As concerns option A, these same steric considerations are contradictive (Figure 2). Consequently, more weight must necessarily be accorded to those steric interactions involving the carbonyl group.

This entire issue could be skirted if the conformation with an axial CHO group would prove subject to a faster reaction rate than an equatorial aldehyde conformer. Such a scenario would result in exclusive focus on C. While there is no evidence on this point,[22] it is useful to recall that methyl substitution of the acetic acid chain in either configurational sense has little effect on the final distribution of **29** and **30**.

A very significant conclusion of this analysis is that diastereofacial selectivity in these cyclic carboxaldehydes as well as **4**, **7**, **10**, **13**, and **14** is governed rather strictly by the structural features of the particular ring system to which the functional group undergoing reaction is attached.

Experimental Section

Melting points are uncorrected. The IR and NMR spectra were recorded in CCl_4 and $CDCl_3$, respectively, unless noted. ^1H NMR spectra were recorded at 300 MHz and ^{13}C NMR spectra at 75 or 20 MHz. Elemental analyses were performed at the Scandinavian Microanalytical Laboratory, Herlev, Denmark. All MPLC separations were conducted with Merck Lobar columns (Lichroprep Si-60) with a Fluid Metering INC pump and a Waters Associates Model R403 differential refractometer detector. The organic extracts were dried over anhydrous $MgSO_4$. Solvents were reagent grade and in many cases dried prior to use (PE is petroleum ether; E refers to ethyl ether; EA is ethyl acetate).

Ethyl 3-Methyl-2-oxocyclopentanecarboxylate (17). Sodium ethoxide was freshly prepared from sodium metal (35 g, 1.52 mmol) in dry ethanol (500 mL) followed by removal of most of the solvent in vacuo. Dry toluene (650 mL) was introduced and another 350 mL was distilled out at atmospheric pressure. Diethyl adipate (250 g, 1.24 mol) and toluene (1000 mL) were added, and the mixture was refluxed. During a period of 5–8 h, a total of 1 L of solvent was distilled while more toluene (total of 1400 mL) was added in portions to permit stirring. After the mixture was cooled to 35 °C, methyl iodide (250 g, 1.76 mol) was introduced and refluxing was resumed for 12 h. Toluene (ca. 1600 mL) was removed by distillation at normal pressure before a solution of sodium ethoxide (from 32 g (1.39 mol) of sodium) in dry ethanol (450 mL) was introduced all at once. After 10 h of heating, toluene (1500 mL) was added and solvent was again removed (ca. 1500 mL). The cooled residue was treated with ether and dilute aqueous HCl until all solids were dissolved and the aqueous phase was acidic. Following washing of the organic layer with water and brine, these solutions were reextracted with ether. The combined ethereal solutions were dried and evaporated. Distillation of the residue gave 135.6 g (64%) of **17** as a yellowish liquid: bp 75–80 °C (1 Torr) [lit.[7b] bp 87–92 °C (5 Torr)]; ^1H and ^{13}C NMR indicated the material to be a 2:1 mixture of diastereomers (minor isomer in parentheses); ^{13}C NMR (75 MHz) δ 213.3 (213.0) (s), 168.9 (168.9) (s), 60.4 (60.4) (t), 53.8 (53.1) (d), 43.5 (42.7) (d), 28.9 (29.2) (t), 24.6 (24.3) (t), 13.3 (14.0) (q), 13.5 (13.5) (q).

Ethyl 3-Methyl-2-oxocyclopentaneacetate (18). Keto ester **17** (135.5 g, 0.796 mol) and methyl chloroacetate (120 g, 1.106 mol) were dissolved in a suspension of K_2CO_3 (330 g, 2.39 mol) in acetone (600 mL), and the mixture was refluxed for 6 h while stirred mechanically. After an overnight period of stirring at 25 °C, the insoluble salts were removed by filtration and rinsed with ether. The combined filtrates were evaporated and the solids again filtered. Following removal of the excess methyl chloroacetate, the residual oil was refluxed overnight with 20% HCl (650 mL) and the resulting mixture was continuously extracted with ether. The crude γ-keto acid was esterified by heating overnight with ethanol (80 g) and *p*-toluenesulfonic acid monohydrate (2.5 g) in benzene (300 mL) under a Dean–Stark trap. The cooled solution was washed with $NaHCO_3$ solution, dried, and freed of solvent. The residue was purified by distillation, bp 109 °C (3.8 Torr). The colorless liquid (128.7 g, 88%) consisted of a 2:1 mixture of diastereomers. An analytical sample was obtained by flash chromatography (silica gel, elution with 2:1 PE–E) and 2-fold Kugelrohr distillation: IR (cm^{-1}) 1740; ^1H NMR (major) δ 4.09 (q, J = 7 Hz, 2 H), 2.73–2.02 (series of m, 4 H), 1.72–0.98 (series of m, 4 H), 1.21 (t, J = 7 Hz, 3 H), 1.09 (d, J = 6.5 Hz, 3 H); (minor) δ 4.10 (q, J = 7 Hz, 2 H), 2.73–2.02 (series of m, 4 H), 1.72–0.98 (series of m, 4 H), 1.22 (t, J = 7 Hz, 3 H), 1.05 (d, J = 7 Hz, 3 H); ^{13}C NMR (75 MHz) δ (minor diastereomer in parentheses) 220.1 (220.0) (s), 171.6 (171.5) (s), 60.1 (60.1) (t), 44.9 (44.2) (d), 43.3 (41.5) (d), 34.2 (34.0) (t), 29.6 (28.3) (t), 27.0 (26.0) (t), 14.1 (14.9) (q), 13.8 (13.8) (q); MS m/z (M^+) calcd 184.1099, obsd 184.1088. Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.23; H, 8.73.

(4*R,6a*S**)-4,5,6,6a-Tetrahydro-4-methyl-2(1*H*)-pentalenone (19).** A solution of **18** (20.0 g, 108.6 mmol) and 2-methoxy-1,3-dioxolane (15.0 g, 144.1 mmol) in dry CH_2Cl_2 (100 mL) was treated with *p*-toluenesulfonic acid (1.0 g) and stirred at room temperature. Another portion of acid (600 mg) was introduced at this time and again after 48 h (200 mg). After 62 h, approximately 20% of the ketalized material had also undergone conversion to the methyl ester. Saturated $NaHCO_3$ solution was introduced, and the separated organic phase was dried and evaporated to leave a dark oil (26 g) that was directly carried forward.

n-Butyllithium in hexanes (190 mL of 1.4 M, 266 mmol) was added to a solution of dimethyl methylphosphonate (35.0 g, 282 mmol) in dry tetrahydrofuran (500 mL) at −78 °C during 15 min. After a 30-min period of stirring, the above ketal in THF (100 mL) was introduced during 10 min at −78 °C. Stirring was maintained for 1 h and the mixture was allowed to warm to 20 °C. One hour later, the reaction mixture was poured into ice-cold 5% HCl (500 mL), vigorously stirred at room temperature overnight, and submitted to continuous ether extraction for 24 h. The crude diketophosphonate obtained after evaporation was

dissolved in benzene (600 mL), treated with water (600 mL) and aqueous tetra-*n*-butylammonium hydroxide solution (78 mL of 40%, 119 mmol), and stirred vigorously at room temperature. The pH of the aqueous phase was checked periodically, and more Bu_4NOH solution was added as needed in small portions to maintain alkalinity. After 4 h, the organic layer was washed with water and brine, and the aqueous solutions were back-extracted with ether. The combined organic solutions were dried and concentrated to leave an oil, flash chromatography of which on silica gel (elution with 1:1 PE–E) gave **19** (12.52 g, 85%) as a colorless oil. ^1H NMR and GC showed ca. 5% of the epimer to be present. An analytical sample of **19** was prepared by 2-fold Kugelrohr distillation (≤100 °C (1 Torr)): IR (cm^{-1}) 1710; ^1H NMR δ 5.85 (dd, J = 2, 1 Hz, 1 H), 2.96 (m, 1 H), 2.83 (br ddq, J = 7.5, 7.5, 7 Hz, 1 H), 2.58 (dd, J = 17.5, 6 Hz, 1 H), 2.26 (dddd, J = 13, 7.5, 7.5, 1 Hz, 1 H), 2.12 (br ddd, J = 12, 6.5, 6.5 Hz, 1 H), 2.04 (dd, J = 17.5, 3 Hz, 1 H), 1.52 (dddd, J = 13, 11.5, 7.5, 6.5 Hz, 1 H), 1.22 (d, J = 7 Hz, 3 H), 1.12 (dddd, J = 12, 12, 11.5, 7.5 Hz, 1 H); ^{13}C NMR (20 MHz) δ 210.2 (s) 195.2 (s), 123.4 (d), 44.8 (d), 42.0 (t), 34.8 (t), 33.3 (d), 30.7 (t), 19.8 (q); MS m/z (M^+) calcd 136.0888, obsd 136.0880. Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.13; H, 8.87.

(1*R,4*R**,6a*S**)-4,5,6,6a-Tetrahydro-1,4-dimethyl-2-(1*H*)-pentalenone (20).** To a solution of LDA (prepared from diisopropylamine (4.0 mL, 28.5 mmol) and *n*-BuLi in hexanes (18.0 mL of 1.5 M, 27.0 mmol)) in dry THF (40 mL) was added **19** (2.50 g, 18.4 mmol) in THF (8 mL) during 10 min at −78 °C. After 40 min, a solution of methyl iodide (3.2 mL, 51.4 mmol) and HMPA (3.0 mL) in THF (5 mL) was introduced during 5 min. After 2 h at −78 °C, the reaction mixture was warmed to 0 °C during 30 min, treated with saturated NH_4Cl solution, and treated with ether. The organic phase was washed with 5% HCl, water, and brine, and then dried and evaporated. Purification by flash chromatography (silica gel, elution with 6:5 PE–E) afforded **20** as a pale yellow oil (2.37 g, 86%). An analytically pure sample of **20** was obtained by FC and distillation (<100 °C (0.5 Torr)): IR (cm^{-1}) 1705, 1630; ^1H NMR δ 5.78 (dd, J = 2.5, 1 Hz, 1 H), 3.06 (ddddd, J = 12.5, 7, 6, 2.5, 2 Hz, 1 H), 2.79 (br ddq, J = 8, 6, 7 Hz, 1 H), 2.55 (dq, J = 7.5, 7 Hz, 1 H), 2.25 (br ddd, J = 12.5, 8, 7 Hz, 1 H), 1.85 (br ddd, J = 11.5, 8, 6 Hz, 1 H), 1.50 (dddd, J = 12.5, 11.5, 8, 6 Hz, 1 H), 1.28 (dddd, J = 12.5, 11.5, 11.5, 7 Hz, 1 H), 1.21 (d, J = 7 Hz, 3 H), 1.01 (d, J = 7.5 Hz, 3 H); ^{13}C NMR (20 MHz) δ 214.5 (s), 194.5 (s), 121.7 (d), 49.8 (d), 43.9 (t), 34.9 (t), 34.1 (d), 25.6 (t), 20.0 (q), 13.6 (q); MS m/z (M^+) calcd 150.1045, obsd 150.1042. Anal. Calcd for $C_{10}H_{14}O$: C, 79.96; H, 9.39. Found: C, 79.70; H, 9.45.

(1*R,3a*S**,4*R**,6a*R**)-1,4-Dimethyl-3,3a,4,5,6,6a-hexahydro-2(1*H*)-pentalenone (21).** Methylcopper was prepared from copper(I) iodide (150 mg, 5.8 mol %) and ethereal methyllithium (0.45 mL of 1.5 M, 5.3 mol %) in dry THF (50 mL) under nitrogen at 0 °C for 15 min. The yellow, turbid mixture was cooled to −60 °C, at which point HMPA (3.5 mL) and Dibal-H in hexanes (16.0 mL of 1.0 M, 16.0 mmol) were sequentially introduced over 5 min. The clear, dark brown solution was kept below −50 °C for 70 min. A solution of **20** (1.90 g, 12.65 mmol) in 20 mL of THF was *slowly* introduced below −50 °C (15 min), and this temperature was maintained for 45 min. The mixture was cooled to −78 °C, quenched with 5% HCl, and diluted with ether. The ethereal layer was washed with water and brine, and then dried and concentrated. Flash chromatography of the residue (silica gel, elution with 4:1 PE–E) gave **21** (1.43 g, 74%) as a colorless oil. An analytical sample of **21** was obtained by rechromatography and Kugelrohr distillation (<100 °C (0.5 Torr)): IR (cm^{-1}) 1735; ^1H NMR δ 2.76 (br dddd, J = 9, 8.5, 8.5, 8 Hz, 1 H), 2.58 (ddd, J = 18.5, 10.5, 2 Hz, 1 H), 2.45 (ddq, J = 9, 2, 7 Hz, 1 H), 2.18 (dddd, J = 10.5, 8, 6, 4.5 Hz, 1 H), 1.94–1.82 (m, 1 H), 1.83 (dd, J = 18.5, 6 Hz, 1 H), 1.77–1.62 (m, 2 H), 1.26–1.03 (m, 2 H), 1.03 (d, J = 7 Hz, 3 H), 1.01 (d, J = 7 Hz, 3 H); ^{13}C NMR (75 MHz) δ 220.8 (s), 46.8 (d), 44.7 (d), 44.5 (d), 43.1 (t), 42.2 (d), 34.4 (t), 27.3 (t), 20.9 (q), 10.4 (q); MS m/z (M^+) calcd 152.1201, obsd 152.1209. Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 78.91; H, 10.67.

(1*S,3a*S**,4*R**,6a*R**)-1,4-Dimethyl-3,3a,4,5,6,6a-hexahydro-2(1*H*)-pentalenone (24). A. Cuprate Addition–Decarboxylation of 23.** Keto ester **23**[13] (5.97 g, 30.74 mmol) in dry ether (30 mL) was added to a solution of lithium dimethylcuprate in ether (prepared from CuI (9.60 g, 50.4 mmol) and ethereal methyllithium (65 mL of 1.5 M, 97.5 mmol) in ether (150 mL) during 10 min below −40 °C. The mixture was stirred for 2 h below −30 °C prior to the quench (5% HCl) and filtration through a pad of Celite. After dilution with ether, the organic solution was washed with 5% HCl, water, and brine, and then dried and evaporated.

The residual oil was stirred with $LiI{\cdot}3H_2O$ (17.5 g, 93.1 mmol) in dimethylformamide (90 mL) in a preheated (160 °C) oil bath for 30 min, cooled, and diluted with ether. Following an analogous workup and flash chromatography (silica gel, elution with 4:1 PE–E), there was isolated 3.97 g (85%) of **24** as a pale yellow oil contaminated with ca. 5% of **21**.[13]

B. Epimerization of 21. Storage of **21** (neat) at room temperature for several days resulted in conversion to an ca. 1:1 mixture of **21** and **24** (^1H and ^{13}C NMR analysis). When 50 mg samples of various **21**/**24** mixtures were stirred with 10% aqueous KOH (0.5 mL) in methanol (2 mL) at 20 °C for 48 h, GC analysis indicated thermodynamic equilibrium to have been reached at 83% of **24** and 17% of **21**.

Copper Hydride Reduction and O-Silylation of 19 and 20. A. (3a*S,4*R**,6a*S**)-1,3a,4,5,6,6a-Hexahydro-4-methyl-2-[(trimethylsilyl)oxy]pentalene (25a).** Analogous to the preparation of **21**, the conjugate reduction of enone **19** (3.0 g, 22.0 mmol) was performed using CuI (250 mg, 6 mol %) and ethereal methyllithium (0.75 mL of 1.5 M, 5.1 mol %) in dry THF (120 mL), followed by HMPA (6 mL) and Dibal-H (27.0 mL of 1.0 M in hexanes). After 45 min at −55 to −45 °C, the reaction mixture was cooled to −70 °C, whereupon chlorotrimethylsilane (4.2 mL, 33.1 mmol) and then triethylamine (5.1 mL, 36.6 mmol) were introduced sequentially. After 10 min, the cooling bath was removed and the mixture was allowed to warm to room temperature (30 min), where stirring was maintained (90 min). Triethylamine (5 mL) and PE (100 mL) were added, and the volatiles were removed by evaporation. The residue was taken up in PE (50 mL), slurried with silica gel (12 g) in PE (50 mL), applied to a silica gel column (50 g), and eluted with PE (500 mL). Solvent removal left **25a** (4.26 g, 92%) as a clear, colorless oil of ≥98% purity (GC analysis): IR (cm^{-1}) 1640; ^1H NMR (C_6D_6) δ 4.77 (dddd, J = 2, 2, 1.5, 1.5 Hz, 1 H), 2.69 (dddd, J = 15.5, 9, 2, 2 Hz, 1 H), 2.68–2.50 (m, 2 H), 2.11 (dddd, J = 15.5, 2.5, 2.5, 1.5 Hz, 1 H), 2.01–1.88 (m, 1 H), 1.87–1.66 (m, 2 H), 1.38–1.24 (m, 1 H), 1.21–1.07 (m, 1 H), 1.02 (d, J = 7 Hz, 3 H), 0.22 (s, 9 H); ^{13}C NMR (75 MHz, C_6D_6) δ 153.5 (s), 106.4 (d), 55.6 (d), 42.1 (d), 42.1 (t), 38.8 (d), 34.7 (t), 34.5 (t), 20.3 (q), 0.1 (q, 3 C); MS m/z (M^+) calcd 210.1440, obsd 210.1439.

B. (1*R,3a*S**,4*R**,6a*R**)-1,3a,4,5,6,6a-Hexahydro-1,4-dimethyl-2-[(trimethylsilyl)oxy]pentalene (25c).** Enone **20** (380 mg, 2.53 mmol) was reduced and O-silylated in entirely comparable fashion to give **25c** as a colorless oil (359 mg, 63%): IR (cm^{-1}) 1635; ^1H NMR (C_6D_6) δ 4.71 (dd, J = 2.5, 1.5 Hz, 1 H), 2.82 (dddq, J = 9, 2.5, 2.5, 7 Hz, 1 H), 2.71–2.55 (m, 2 H), 1.85–1.55 (m, 4 H), 1.22–1.08 (m, 1 H), 1.13 (d, J = 7 Hz, 3 H), 1.06 (d, J = 6.5 Hz, 3 H), 0.22 (s, 9 H); ^{13}C NMR (75 MHz, C_6D_6) δ 156.5 (s), 104.8 (d), 53.9 (d), 43.5 (d), 42.2 (d), 41.4 (d), 35.5 (t), 27.1 (t), 20.5 (q), 13.7 (q), 0.0 (q, 3 C); MS m/z (M^+) calcd 224.1596, obsd 224.1606.

Regioselective Deprotonation and O-Silylation of 21 and 24. A. (1*S,3a*S**,4*R**,6a*R**)-1,3a,4,5,6,6a-Hexahydro-1,4-dimethyl-2-[(trimethylsilyl)oxy]pentalene (25b).** The conditions developed by Vandewalle et al.[13] for 24 were adopted to obtain, after isolation as in the previous text, **25b** as a colorless oil in 94% yield (this compound had previously been prepared as an unpurified intermediate): IR (cm^{-1}) 1640; ^1H NMR (C_6D_6) δ 4.68 (dd, J = 2.5, 1.5 Hz, 1 H), 2.62 (dddd, J = 8.5, 5, 2.5, 1.5 Hz, 1 H), 2.23 (dddq, J = 3, 1.5, 1.5, 7 Hz, 1 H), 2.19 (dddd, J = 8.5, 8.5, 6, 3 Hz, 1 H), 1.97 (dddd, J = 12, 8.5, 6, 6 Hz, 1 H), 1.82 (dddd, J = 11.5, 6, 6, 6 Hz, 1 H), 1.73 (dddq, J = 6.5, 6, 5, 6.5 Hz, 1 H), 1.38 (dddd, J = 12, 7.5, 6, 6 Hz, 1 H), 1.23 (d, J = 7 Hz, 3 H), 1.17 (dddd, J = 11.5, 7.5, 6.5, 6 Hz, 1 H), 1.01 (d, J = 6.5 Hz, 3 H), 0.22 (s, 9 H); ^{13}C NMR (20 MHz, C_6D_6) δ 157.5 (s), 105.0 (d), 53.7 (d), 48.6 (d), 48.3 (d), 41.6 (d), 34.4 (t), 33.3 (t), 20.3 (q), 19.9 (q), 0.9 (q, 3 C); MS m/z (M^+) calcd 224.1596, obsd 224.1584.

B. Use of a 1:1 Mixture of 21 and 24. Ketones **21** and **24** (1:1, 1.03 g, 6.76 mmol) were transformed into a corresponding mixture of **25b** and **25c** (1.25 g, 82%) under conditions identical

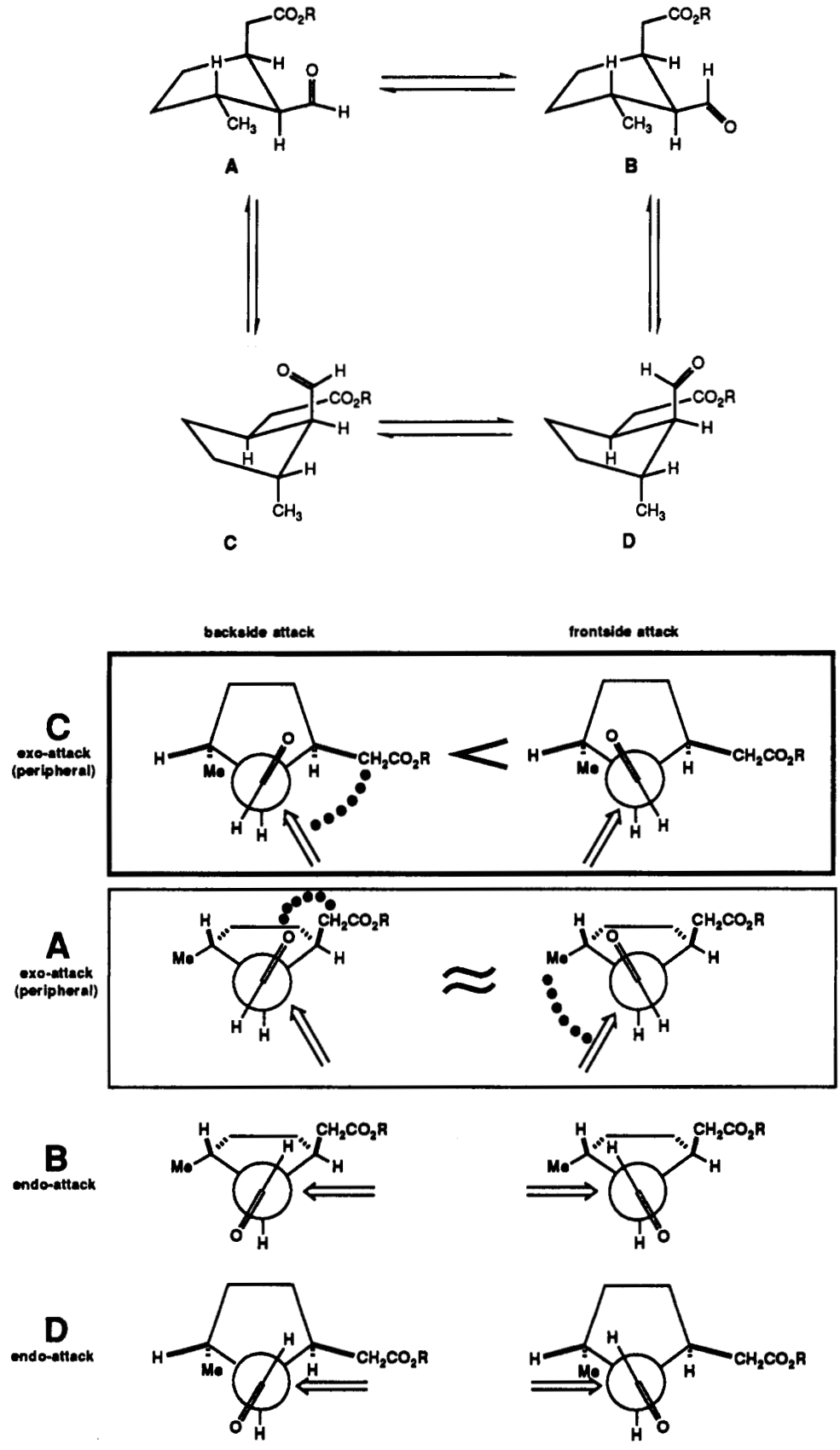


Figure 2. Minimum energy conformations for **15a** together with possible reaction trajectories for nucleophilic attack.

with those employed in part A. This mixture was utilized in further experiments to be described without separation.

Ozonolysis of the Silyl Enol Ethers 25a–c. A. Preparation of 15a. A solution of **25a** (3.0 g, 14.26 mmol) in cold (−78 °C), dry methanol (80 mL) was treated with a stream of ozone until a blue color persisted. The excess ozone was removed by nitrogen purging, and methyl sulfide (10 mL) was added at −78 °C. The solution was warmed to 20 °C during 1 h, stirred for an additional 2 h, and then evaporated. The residual material was dissolved in ether and treated with a slight excess of ethereal diazomethane. After removal of the ether, the resulting oil was immediately subjected to flash chromatography (silica gel, elution with 7:3 PE–E). There was isolated 2.26 g (86%) of **15a** as a colorless oil: IR (cm^{-1}) 1740, 1725; ^1H NMR δ 9.73 (d, J = 3 Hz, 1 H), 3.64 (s,

3 H), 2.75 (ddddd, J = 8.5, 8.5, 8, 7, 7 Hz, 1 H), 2.50 (dd, J = 16, 7 Hz, 1 H), 2.49 (ddd, J = 8.5, 7, 3 Hz, 1 H), 2.36 (dddq, J = 8, 7, 7, 7 Hz, 1 H), 2.34 (dd, J = 16, 8 Hz, 1 H), 2.05–1.85 (m, 2 H), 1.45–1.15 (m, 2 H), 1.03 (d, J = 7 Hz, 3 H); ^{13}C NMR (75 MHz) δ 240.1 (d), 173.0 (s), 61.2 (d), 51.6 (q), 39.3 (d), 35.6 (t), 34.5 (d), 33.4 (t), 32.4 (t), 20.4 (q); MS m/z (M^+ + 1) calcd 185.1178, obsd 185.1113.

B. Aldehydo Ester 15b. Ozonolytic cleavage of **25b** (1.50 g, 6.68 mmol) as in the previous text, followed directly by esterification with diazomethane and silica gel chromatography (elution with 1:2 PE–E), gave **15b** (1.26 g, 95%) as a colorless oil: IR (cm^{-1}) 1735, 1720; ^{1}H NMR δ 9.71 (d, J = 3 Hz, 1 H), 3.64 (s, 3 H), 2.59 (dq, J = 10.5, 7 Hz, 1 H), 2.55–2.36 (m, 2 H), 2.32 (dddq, J = 8, 7, 5, 7 Hz, 1 H), 2.03–1.86 (m, 2 H), 1.43–1.18 (m, 2 H), 1.17 (d, J = 7 Hz, 3 H), 1.03 (d, J = 7 Hz, 3 H); ^{13}C NMR (75 MHz) δ 203.9 (d), 176.5 (s), 60.6 (d), 51.6 (q), 45.5 (d), 40.8 (d), 35.2 (d), 33.4 (t), 30.4 (t), 20.9 (q), 17.3 (q); MS m/z (M^+ – H) calcd 197.1178, obsd 197.1225.

C. Aldehydo Ester 15c. Ozonolysis of **25c** (320 mg, 1.43 mmol) in the predescribed manner afforded 223 mg (79%) of **15c** after flash chromatographic purification (silica gel, elution with 2:1 PE–E): IR (cm^{-1}) 1740, 1720; ^{1}H NMR δ 9.69 (d, J = 4 Hz, 1 H), 3.65 (s, 3 H), 2.60 (dq, J = 10.5, 7 Hz, 1 H), 2.47–2.25 (m, 3 H), 2.02 (dddd, J = 12.5, 8, 7.5, 2 Hz, 1 H), 1.85–1.74 (m, 1 H), 1.55–1.39 (m, 1 H), 1.25 (dddd, J = 12.5, 10.5, 7.5, 7 Hz, 1 H), 1.17 (d, J = 7 Hz, 3 H), 1.05 (d, J = 7 Hz, 3 H); ^{13}C NMR (75 MHz) δ 203.3 (d), 176.4 (s), 59.7 (d), 51.5 (q), 46.3 (d), 40.4 (d), 34.7 (d), 33.5 (t), 30.9 (t), 21.1 (q), 16.8 (q); MS m/z (M^+ – H) calcd 197.1178, obsd 197.1179.

Reductive Cyclization of 15a. Solid $NaBH_4$ (300 mg, 7.93 mmol) was added during 10 min to a solution of **15a** (1.0 g, 5.43 mmol) in methanol (40 mL) at –10 °C. After being warmed to room temperature during 1 h and stirred for another 30 min, the reaction mixture was quenched with 5% HCl. The methanol was evaporated, and the residue was taken up in ether, washed with 5% HCl and brine, dried, and evaporated prior to flash chromatography (silica gel, elution with 1:2 PE–E). There was isolated 794 mg (95%) of **26a** as a colorless oil: IR (cm^{-1}) 1755; ^{1}H NMR δ 4.26 (dd, J = 11.5, 4 Hz, 1 H), 4.09 (dd, J = 11.5, 4.5 Hz, 1 H), 2.68–2.51 (m, 2 H), 2.39–2.27 (m, 1 H), 2.08–1.94 (m, 1 H), 1.94–1.65 (m, 3 H), 1.30–1.05 (m, 2 H), 1.04 (d, J = 6 Hz, 3 H); ^{13}C NMR (75 MHz) δ 173.6 (s), 68.9 (t), 44.5 (d), 37.5 (d), 34.8 (t), 34.8 (d), 34.6 (t), 33.4 (t), 18.7 (q); MS m/z (M^+) calcd 154.0994, obsd 154.1019. Anal. Calcd for $C_9H_{14}O_2$: C, 70.10, H, 9.15. Found: C, 70.09; H, 9.18.

Isoiridomyrmecin (26b) and Iridomyrmecin (26c). To an LDA solution (from 0.22 mL (1.57 mmol) of diisopropylamine and 0.90 mL of 1.5 M n-butyllithium in hexanes (1.35 mmol)) in dry THF (8 mL) was added (10 min) at –78 °C a solution of **26a** (125 mg, 0.81 mmol) in THF (2 mL). There followed a mixture of methyl iodide (340 mg, 2.40 mmol) and HMPA (0.5 mL). The reaction mixture was kept at –78 °C for 2 h prior to being quenched with saturated NH_4Cl solution. The products were extracted into ether and washed in sequence with 5% HCl, water, and brine. After drying and concentration, the residue was subjected to flash chromatography (silica gel, 2:3 PE–E) to give 118 mg (87%) of a 4:1 mixture (^{1}H NMR analysis) of **26b** and **26c** as a colorless oil. These lactones were identified by ^{1}H NMR comparisons.

Hemiacylal Formation. A 2.45-g (11.65-mmol) sample of silyl enol ether **25a** was ozonolyzed as before. Half of the material obtained after treatment with methyl sulfide and evaporation of methanol was immediately purified by flash chromatography on silica gel (ether elution) to give **16a** as a viscous, colorless oil (732 mg, 74%): IR (cm^{-1}) 3500–3200 (br), 3200–2600 (br), 1750–1710 (br); ^{1}H NMR (80 MHz, C_6D_6) extremely broad at room temperature; δ 9.52 (br s, *CHO*), 5.40 (br s, OC*H*OH), 3.00–0.60 (br m); MS m/z (M^+) calcd 170.0943, obsd 170.0938.

A solution of **16a** (138 mg 0.811 mmol) and acetic anhydride (0.40 mL, 4.24 mmol) in CH_2Cl_2 (4 mL) was treated with boron trifluoride etherate (1 drop) and stirred at room temperature overnight. After dilution of the reaction mixture with ether, the solution was washed with saturated $NaHCO_3$ solution, water, and brine. The residue obtained after drying and concentration was purified by flash chromatography (silica gel, elution with 1:2 PE–E) to give 135 mg (74%) of **27** as a colorless oil consisting of a 3:2 mixture of diastereomers: IR (cm^{-1}) 1760 (br); ^{1}H NMR (major) δ 6.33 (d, J = 2 Hz, 1 H), 2.90–2.30 (m, 3 H), 2.10 (s, 3 H), 2.16–1.78 (m, 4 H), 1.35–1.13 (m, 2 H), 1.09 (d, J = 6.5 Hz, 3 H); (minor) δ 6.50 (d, J = 4 Hz, 1 H), 2.90–2.30 (m, 3 H), 2.12 (s, 3 H), 2.16–1.78 (m, 4 H), 1.35–1.13 (m, 2 H), 1.07 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (75 MHz) δ (isomers not distinguished) 170.6/170.5 (s), 168.6/168.5 (s), 94.8/93.2 (d), 47.5/46.8 (d), 38.0/35.3, 34.0/33.2 (d), 35.2/35.0, 34.7/34.4, 33.9/33.6 (t), 20.9/20.8, 19.8/18.7 (q); MS m/z (M^+) calcd 212.1049, obsd 212.1094.

Compounds **16b** and **16c** were prepared analogously and used directly as obtained.

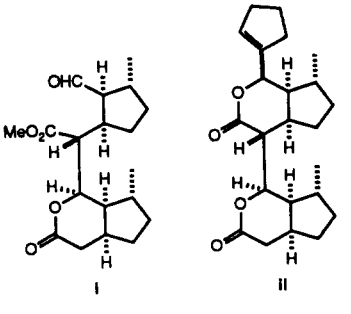
Cyclopentenyllithium Additions to the Aldehydo Esters. A. General Procedure. *tert*-Butyllithium in pentane (17.0 mL of 1.7 M, 28.9 mmol) was added during 10 min to a cold (–78 °C) solution of 1-iodocyclopentene (3.00 g, 15.46 mmol) in dry THF (120 mL) under nitrogen. After 90 min, the resulting suspension was slowly introduced via syringe (10 min) into a cold (–78 °C), magnetically stirred solution of **15a** (3.30 g, 17.91 mmol) in dry THF (80 mL). After 2 h at –78 °C, the reaction mixture was quenched with saturated ammonium chloride solution. The products were taken up in ether, and the organic solution was washed with 2% HCl, water, and brine. After drying and solvent evaporation, the crude product was triturated with ether to give 305 mg (6%) of a colorless solid, mp 254–256 °C (benzene):[23] IR ($CHCl_3$, cm^{-1}) 1745 (br); ^{1}H NMR δ 5.86 (ddddd, J = 2, 2, 2, 2, 2 Hz, 1 H), 5.12 (br s, 1 H), 4.54 (dd, 11, 2.5 Hz, 1 H), 3.04 (br d, J = 11 Hz, 1 H), 2.76 (br ddddd, J = 10.5, 9.5, 8, 7, 1.5 Hz, 1 H), 2.59 (dd, J = 15, 7 Hz, 1 H), 2.54 (br ddd, J = 9.5, 9.5, 8.5 Hz, 1 H), 2.42–2.22 (m, 4 H), 2.38 (dd, J = 15, 1.5 Hz, 1 H), 2.22–2.07 (m, 2 H), 2.03 (ddd, J = 10.5, 8.5, 3.5 Hz, 1 H), 2.05–1.70 (m, 7 H), 1.38–1.02 (m, 4 H), 1.09 (d, J = 6 Hz, 3 H), 0.92 (d, J = 6 Hz, 3 H); ^{13}C NMR (20 MHz) δ 171.8 (s), 170.0 (s), 139.1 (s), 126.6 (d), 77.2 (d), 76.2 (d), 49.5 (d), 45.7 (d), 45.4 (d), 37.9 (d), 35.9 (d), 35.3 (d), 34.7 (t, 2C), 34.4 (t), 34.1 (d), 33.3 (t), 33.2 (t, 2C), 32.3 (t), 22.9 (t), 21.5 (q), 20.4 (q); MS m/z (M^+) calcd 372.2301, obsd 372.2286. Anal. Calcd for $C_{23}H_{32}O_4$: 74.16; H, 8.66. Found: C, 74.18; H, 8.74.

Separation of the remaining material by flash chromatography (silica gel, elution with 3:2 PE–E) followed by MPLC (silica gel, elution with 3:1 PE–EA) afforded pure **30a** (1.14 g, 36%) as a colorless solid: mp 86.5–87.5 °C (from pentane–ether); IR (cm^{-1}) 1755; ^{1}H NMR δ 5.84 (ddddd, J = 2, 2, 2, 2, 2 Hz, 1 H), 4.80 (br s, 1 H), 2.73 (ddddd, J = 10.5, 9.5, 8, 7, 1.5 Hz, 1 H), 2.61 (dd, J = 15, 7 Hz, 1 H), 2.39 (dd, J = 15, 1.5 Hz, 1 H), 2.43–2.22 (m, 4 H), 2.02 (ddd, J = 10.5, 8.5, 3.5 Hz, 1 H), 2.00–1.79 (m, 4 H), 1.76–1.67 (m, 1 H), 1.19 (dddd, J = 12, 12, 9.5, 5.5 Hz, 1 H), 1.07 (dddd, J = 12, 11, 10, 5.5 Hz, 1 H), 0.91 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (75 MHz) δ 173.4 (s), 139.1 (s), 126.3 (d), 78.3 (d), 46.6 (d), 35.5 (d), 34.8 (d), 34.8 (t), 34.7 (t), 33.2 (t), 32.9 (t), 32.4 (t), 23.0 (t), 20.4 (q); MS m/z (M^+) calcd 220.1463, obsd 220.1450. Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.18; H, 9.13.

The smaller amount of **29a** also produced in this reaction is characterized in the following text.

B. Condensation Involving 15b. Comparable treatment of **15b** (1.12 g, 5.65 mmol) with cyclopentenyllithium gave rise to a crude product mixture that was saponified with 10% aqueous KOH (20 mL) in methanol (50 mL) at room temperature overnight, freed of solvent, and worked up as before. The resulting

(23) This lactone, believed to be ii, is probably formed by addition of cyclopentenyllithium to i, which results from self-condensation of **15a** during the reaction.



I II

hydroxy acids were lactonized by heating overnight in dry benzene (100 mL) at reflux. ^{1}H NMR analysis of the concentrate showed **30b** and **29b** to be present in a 93:7 ratio. A portion of this material (1.167 g) was separated by MPLC (silica gel, elution with 4:1 PE–EA) to afford in order of elution 195 mg (16%) of a colorless oily mixture of these lactones and 742 mg (62%) of pure **30b**, a colorless solid: mp 63–64 °C (from PE); IR (cm^{-1}) 1740; ^{1}H NMR δ 5.79 (ddddd, J = 2, 2, 2, 2, 2 Hz, 1 H), 5.08 (br s, 1 H), 2.50 (dq, J = 2.5, 7.5 Hz, 1 H), 2.40–2.16 (m, 5 H), 2.00 (ddd, J = 9.5, 8.5, 3.5 Hz, 1 H), 1.97–1.78 (m, 4 H), 1.76–1.65 (m, 1 H), 1.32 (d, J = 7.5 Hz, 3 H), 1.28–1.02 (m, 2 H), 0.89 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (75 MHz) δ 175.6 (s), 139.8 (s), 126.3 (d), 76.9 (d), 46.3 (d), 43.5 (d), 41.1 (d), 34.3 (t), 33.8 (t), 33.2 (t), 32.2 (t), 23.0 (t), 20.7 (q), 18.1 (q); MS m/z (M$^+$) calcd 234.1620, obsd 234.1625. Anal. Cacld for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.93; H, 9.45.

The minor constituent **29b** is fully characterized in the following text.

C. Condensation Involving 15c. Comparable treatment of **15c** (145 mg, 0.73 mmol) with cyclopentenyllithium afforded a product mixture that was likewise subjected to saponification and lactonization. ^{1}H NMR analysis of the pale yellow oil (178 mg) showed the **30c**:**29b** ratio to be 86:14. MPLC (silica gel, elution with 4:1 PE–EA) afforded 126 mg (79%) of colorless, semisolid lactone mixture from which **30c** could be isolated pure as colorless crystals: mp 93–94 °C (from PE); IR (cm^{-1}) 1755; ^{1}H NMR δ 5.84 (ddddd, J = 2, 2, 2, 2, 2 Hz, 1 H), 4.87 (br s, 1 H), 2.78 (dq, J = 6.5, 6.5 Hz, 1 H), 2.69–2.55 (m, 1 H), 2.42–2.25 (m, 4 H), 2.04 (ddd, J = 11, 9, 3.5 Hz, 1 H), 2.01–1.69 (m, 5 H), 1.16 (d, J = 6.5 Hz, 3 H), 1.07–0.96 (m, 2 H), 0.91 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (75 MHz) δ 175.8 (s), 139.0 (s), 126.3 (d), 77.5 (d), 47.6 (d), 42.0 (d), 37.2 (d), 35.3 (d), 34.7 (t), 33.3 (t), 29.2 (t), 23.0 (t), 20.2 (q), 12.8 (q); MS m/z (M$^+$) calcd 234.1620, obsd 234.1637. Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.86; H, 9.42.

Characterization of the minor constituent as **29b** and not **29c** was clearly evident by ^{1}H NMR comparison once **29c** also became available (see the following text).

Cyclopentenyllithium Additions to the Hemiacylals. A. General Procedure. Cyclopentenyllithium was prepared in the predescribed manner from 1.40 g (7.22 mmol) of 1-iodocyclopentene. To the cold (−78 °C), white suspension in THF was added **16a** (518 mg, 3.04 mmol) in the same solvent (5 mL) during 5 min. After 2 h at −78 °C, the reaction mixture was quenched by addition of saturated NH_4Cl solution and processed as in the previous text. The resulting product was refluxed in dry benzene (30 mL) for 5 h. Evaporation of the solvent gave a semisolid mixture of lactones (580 mg), ^{1}H NMR analysis of which revealed **30a** and **29a** to be present in an 83:17 ratio. A portion of this mixture (478 mg) was subjected to MPLC (silica gel, elution with 3:1 PE–EA) to afford 139 mg (25%) of a 1:1 mixture of the two lactones and 218 mg (40%) of pure **30a**.

B. Condensation Involving 16b and 16c. These reactions were performed in an entirely analogous manner with the results compiled in Table I. The isolated yields were in the 55–60% range.

Direct Methylation of 30a. (1*S,2*R**,5*S**,6*R**,9*R**)-2-Cyclopentenyl-5,9-dimethyl-3-oxa-4-oxobicyclo[4.3.0]nonane (30b).** To a cold (−78 °C) solution of LDA (from 0.75 mL (5.35 mmol) of diisopropylamine and 3.10 mL of 1.5 M *n*-butyllithium in hexanes (4.65 mmol)) in dry THF (20 mL) was added during 10 min a solution of **30a** (708 mg, 3.21 mmol) in the same medium. After 30 min, a solution of methyl iodide (1.15 g, 8.10 mmol) and HMPA (1.0 mL) in THF was introduced. The reaction mixture was stirred for 2 h at −78 °C prior to quenching with saturated NH_4Cl solution. The product was taken up in ether and washed sequentially with 5% HCl, water, and brine. After drying and solvent evaporation, final purification was achieved by flash chromatography (silica gel, elution with 1:1 PE–E) to give 683 mg (91%) of **30b**, the spectral properties of which were identical with those described earlier.

(1*S,2*R**,5*R**,6*R**,9*R**)-2-Cyclopentenyl-5,9-dimethyl-3-oxa-4-oxobicyclo[4.3.0]nonane (30c).** A solution of **30b** (168 mg, 0.72 mmol) in dry THF was added during 5 min to a cold (−78 °C), magnetically stirred solution of LDA (4.95 mmol) in the same solvent (20 mL) under nitrogen. After 30 min, the temperature was lowered to −110 °C and a solution of *tert*-butyl alcohol (1.20 g, 16.2 mmol) in THF was introduced during 1 min with vigorous stirring. After 5 min, saturated NH_4Cl solution was added and the usual workup followed. Purification by flash chromatography (silica gel, elution with 1:1 PE–E) afforded pure **30c** (163 mg, 97%), the spectral properties of which were identical with those described earlier.

(1*S,2*S**,5*S**,6*R**,9*R**)-2-Cyclopentenyl-5,9-dimethyl-3-oxa-4-oxobicyclo[4.3.0]nonane (29b).** Lactone **30b** (468 mg, 2.0 mmol) in methanol (20 mL) was saponified by stirring with 10% aqueous KOH (20 mL) at room temperature overnight. After evaporation of the methanol, the alkaline solution was diluted with water and ether and carefully acidified to pH 4–6 by addition of 5% HCl with stirring. The liberated hydroxy acid was quickly isolated by partitioning between ether and brine, drying of the ethereal phase, and concentration. The residue was immediately dissolved in acid-free $CHCl_3$ (50 mL) and treated with a $CHCl_3$ solution of the dineopentylacetal of dimethylformamide (5 equiv). After 15 min, the reaction mixture was diluted with ether, stirred with 5% HCl (100 mL) for 15 min, diluted with ether, and washed sequentially with 5% HCl, water, and brine. Separation by MPLC (silica gel, elution with 4:1 PE–EA) afforded in order of elution 269 mg (57%; 64% based on recovered **30b**) of **29b** and 49 mg (10%) of **30b**.

For 29b: colorless solid; mp 71–72 °C (from PE); IR (cm^{-1}) 1750; ^{1}H NMR δ 5.74 (dddd, J = 2, 2, 2, 2 Hz, 1 H), 4.68 (br d, J = 10.5 Hz, 1 H), 2.56–2.20 (m, 5 H), 2.17–1.98 (m, 2 H), 1.98–1.80 (m, 4 H), 1.60 (dddq, J = 9.5, 7, 7, 6.5 Hz, 1 H), 1.35–1.15 (m, 2 H), 1.19 (d, J = 6.5 Hz, 3 H), 0.90 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (20 MHz) δ 176.1 (s), 140.6 (s), 130.8 (d), 80.1 (d), 47.8 (d), 43.8 (d), 39.2 (d), 38.5 (t), 35.8 (t), 33.1 (t), 32.2 (t), 30.3 (t) 23.2 (t), 19.5 (q), 14.0 (q); MS m/z (M$^+$) calcd 234.1620, obsd 234.1635. Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.84; H, 9.48.

(1*S,2*S**,5*R**,6*R**,9*R**)-2-Cyclopentenyl-5,9-dimethyl-3-oxa-4-oxobicyclo[4.3.0]nonane (29c).** Comparable treatment of **30c** (120 mg, 0.512 mmol) and MPLC purification (silica gel, elution with 4:1 PE–EA) gave 62 mg (52%; 65% based on recovered **30c**) of **29c** and 20% of recovered starting material.

For 29c: colorless oil; IR (cm^{-1}) 1750; ^{1}H NMR δ 5.60 (ddddd, J = 2, 2, 2, 2, 2 Hz, 1 H), 4.75 (br s, 1 H), 2.81 (dq, J = 7, 7 Hz, 1 H), 2.57 (dddd, J = 11, 11, 7, 7 Hz, 1 H), 2.45–2.25 (m, 4 H), 2.10 (br dd, J = 11, 9 Hz, 1 H), 2.00–1.72 (m, 5 H), 1.17–0.97 (m, 2 H), 1.05 (d, J = 7 Hz, 3 H), 1.03 (d, J = 6 Hz, 3 H); ^{13}C NMR (75 MHz) δ 175.9 (s), 143.3 (s), 127.2 (d), 79.3 (d), 47.0 (d), 40.8 (d), 39.6 (d), 36.3 (d), 34.2 (t), 33.3 (t), 32.6 (t), 29.7 (t) 23.2 (t), 18.4 (q), 12.8 (q); MS m/z (M$^+$) calcd 234.1620, obsd 234.1644.

(1*S,2*S**,6*R**,9*R**)-2-Cyclopentenyl-9-methyl-3-oxa-4-oxobicyclo[4.3.0]nonane (29a).** Analogous treatment of **30a** (200 mg, 0.908 mmol) and separation by MPLC (silica gel, elution with 3:1 PE–EA) afforded in order of elution pure **29a** (144 mg, 72%; 83% based on recovered **30a**) and **30a** (26 mg, 13%).

For 29a: colorless solid; mp 64–65 °C (from PE); IR (cm^{-1}) 1755; ^{1}H NMR δ 5.74 (ddddd, J = 2, 2, 2, 2, 1 Hz, 1 H), 4.66 (br d, J = 9.5 Hz, 1 H), 2.65 (dd, J = 14.5, 6.5 Hz, 1 H), 2.58–2.28 (m, 5 H), 2.25 (dd, J = 14.5, 10 Hz, 1 H), 2.10–2.02 (m, 1 H), 2.00–1.80 (m, 4 H), 1.75–1.61 (m, 1 H), 1.35–1.15 (m, 2 H), 0.95 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (75 MHz) δ 173.5 (s), 140.6 (s), 130.2 (d), 80.4 (d), 47.0 (d), 38.0 (d), 35.4 (d), 35.0 (t), 34.9 (t), 33.5 (t), 32.1 (t), 30.7 (t), 23.0 (t), 19.4 (q); MS m/z (M$^+$) calcd 220.1463, obsd 220.1486. Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.30; H, 9.18.

Equilibration of 29c with 29b. Treatment of **29c** (10 mg) with 10% aqueous KOH (0.5 mL) in methanol (5 mL) with stirring for 4 h at room temperature, followed by acidification, isolation of the hydroxy acid, and relactonization by heating in benzene led to the recovery of **29b** (8 mg). No residual **29c** was detected by ^{1}H NMR analysis.

Lactones **29b**, **30b**, and **30c** were stable to these reaction conditions.

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Supplementary Material Available: ^{1}H or ^{13}C NMR spectra of those compounds for which elemental analyses are not available (10 pages). Ordering information is given on any current masthead page.