Tetrahedron Vol. 42, No. 11, pp. 2831 to 2846, 1986
Printed in Great Britain.

0040-4020/86 $3.00+.00
Pergamon Journals Ltd.

CLAISEN-REARRANGEMENT-MEDIATED RING CONTRACTION OF MACROCYCLIC LACTONES

A NEW APPROACH TO CARBOCYCLES AND HETEROCYCLES

RAYMOND L. FUNK,*† MATTHEW M. ABELMAN and JOHN D. MUNGER, JR.‡
Department of Chemistry, University of Nebraska, Lincoln, NE 68588-0304, U.S.A.

(*Received in U.S.A.* 1 *July* 1985)

Abstract—Macrocyclic ketene acetals **3** undergo Claisen rearrangements smoothly and constitute a viable and general approach to hetero- or carbocyclic ring systems **4**. This novel ring contraction process is subject to high internal asymmetric induction (cf. lactones **7** → carbocycles **8**) as well as relative asymmetric induction in the rearrangements of ketene acetals derived from lactones **18**, **23** and **27**. Finally, N-benzoylmeroquinene methyl ester (**37**) was prepared to demonstrate the potential of this methodology in heterocycle synthesis.

INTRODUCTION

The development of new synthetic methodology for the construction of hetero- and carbocyclic ring systems has been a long standing goal of synthetic organic chemists. However, most methodology has been targeted for a particular ring size or limited range of sizes. Indeed, no truly general method for hetero- and carbocycle synthesis from acyclic precursors has, heretofore, been reported although the Dieckman cyclization,[1a] acyloin condensation,[1b] Story synthesis,[1c] titanium-induced dicarbonyl-coupling reactions,[1d] intramolecular Wittig-type reactions,[1e] among others, come close to fulfilling this goal. Unfortunately, the potential for introducing asymmetic centers concomitant with ring formation is limited or impossible in a number of these existing methods. The realization of the latter subgoal is especially useful in the context of total synthesis of polycarbocyclic natural products which typically embody several asymmetric centers.

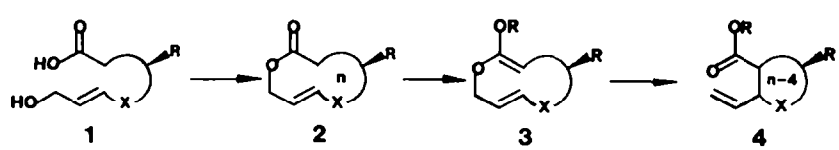
In this paper we describe in detail[2] a new and general strategy for hetero- and carbocycle synthesis which meets these goals. Our basic strategy (Scheme 1) was based on the expectation that the *n*-membered macrocyclic lactones **2**, readily available from the corresponding hydroxy acids **1**, could be contracted to the $n-4$ membered hetero- (X = O, N, etc.) or carbocycles (X = C) **4** by Claisen rearrangement[3] of intermediate ketene acetals **3**. The general success of this plan seemed well assured. Danishefsky had reported on the rearrangement of ketene acetals derived from vinyl lactones[4a,b] and, indeed, was the genesis of this idea. Our Claisen substrates differ only by incorporation of the olefinic moiety within the ketene acetal ring system. Moreover, several examples of the analogous Cope rearrangements[3a,5] leading to substituted cyclopentanes and cyclohexanes had been reported in the literature. However, the Cope analogy of this rearrangement for $n = 1, 2$ proceeds in the opposite direction, that is, both *cis*-divinylcyclopropane and *cis*-divinylcyclobutane readily rearrange to 1,4-cycloheptadiene and 1,4-cyclooctadiene, respectively.[3a] Therefore, the most uncertain example in our projected methodology was the rearrangement of a seven-membered ketene acetal **3** (X = CH_2). Nonetheless, we were confident that this rearrangement would also be successful considering the relative facility of the Ireland-ester–enolate Claisen rearrangement,[6] the observation that 2,5-dihydrooxepin and *cis*-2-ethenylcyclopropane carboxaldehyde form a 5:95 equilibrium mixture,[7] and the expectation that a more favorable equilibrium would be observed when the more stable ester functionality, *vis-à-vis* aldehyde, is produced.

Finally, the viability of this methodology rested on the availability of the lactones **2**. Fortunately, a number of reagents for effecting macrolactonization of hydroxy acids were available, a consequence of the intense synthetic activity directed towards macrolide antibiotics.[8a–c] In addition, many alternative synthetic routes to macrolides had been developed, for example, ring expansion of cycloalkanones,[8d–i] transacylation reactions,[8j,k] and fragmentation reactions.[8k–m]

Although the potential generality of this rearrangement process was quite appealing, the stereochemical implications were even more intriguing. At the outset, we planned to investigate the internal asymmetric induction[9] of this reaction, that is, the stereorelationship of the carboxyl and vinyl moieties as they emerge on the newly created hetero- or carbocycles. This stereocontrol is of course a function of the ketene acetal and olefin stereochemistries as well as the

† Eli Lilly Grantee, 1982–84.

‡ Maude Hammond Fling Fellow, 1982–84, University of Nebraska-Lincoln.



Scheme 1.

conformation of the transition state. Subsequent to these studies, the relative asymmetric induction[9] was targeted for investigation, for example, the relative disposition of the carboxyl and vinyl groups with regard to a pre-existing asymmetric center in **3**. Our studies on these aspects of this novel strategy for hetero- and carbocycle synthesis are described herein.

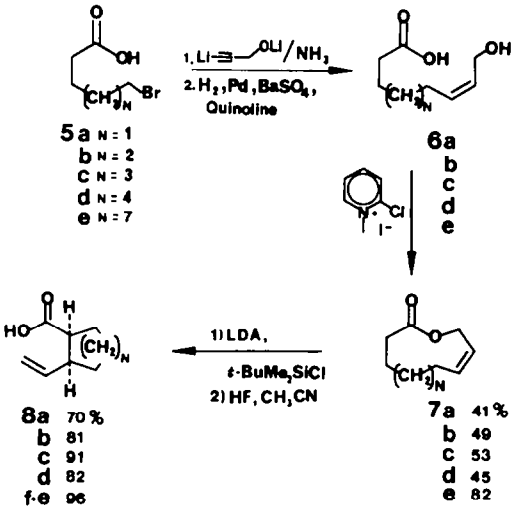
SCOPE AND INTERNAL ASYMMETRIC INDUCTION

Our first investigation of this method began with the preparation of the series of medium and large ring lactones **7** shown in Scheme 2. The lactones were prepared by cyclization of the corresponding ω-hydroxy acids using the Mukaiyama reagent (2-chloro-1-methylpyridinium iodide).[10] It was hoped that the *cis* double bond in **6** would facilitate the lactonization reaction by removing potential transannular interactions in the resulting macrocycles[11] in addition to the obvious entropic advantage over the saturated counterpart. Indeed, only trace amounts of diolides are formed and the yield for the nine-membered lactone **7a** is considerably higher than those reported by this[10] and other procedures for the saturated nine-membered lactone.[8] The requisite hydroxy acids were prepared according to previously reported procedures.[8d,12]

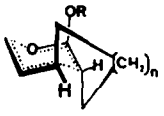
We were pleased to discover that the ketene acetals prepared from the lactone **7a–c** enolates, using the standard procedure,[6] rearranged smoothly before or during workup to the corresponding silyl esters, which were then hydrolyzed with HF (2 equiv) in CH_3CN. The remarkable ease of these rearrangements is noteworthy. For example, the ketene acetal derived from lactone **7a** rearranged at $-60°$ ($t_{1/2} \approx 57$ h). However, the large ring ketene acetals prepared from lactones **7d** and **7e** required heating in toluene at 110° ($t_{1/2} \approx 6$ h) and 80° ($t_{1/2} \approx 7$ h), respectively, to effect rearrangement. Moreover, only one silyl ketene acetal isomer was produced, presumably the isomer with an additional *cis* double bond within the ring. This assignment is based on the preference for the (*Z*)-enolate in acyclic ester enolizations under these conditions,[6] stereoselective kinetic alkylations of similar nine- and thirteen-membered lactone enolates,[11] and our observation that relatively small amounts of the other ketene acetal isomer (1 : 3.2 for **7d** and 1 : 1.3 for **7e**) could be generated when the enolizations were conducted in the presence of HMPA (HMPA–THF, 23 : 77), conditions known to provide predominantly the *E*-enolate isomer with acyclic esters.[6] The vinyl proton and alkoxymethylene proton resonances (360 MHz ^{1}H-NMR) of the new ketene acetal isomer were at higher field than analogous resonances in the major ketene acetal isomer, consistent with the trends established with the acyclic *Z*, *E* silyl ketene acetal isomers. Finally, it should be noted here that the degree of control over the stereochemistry of the ketene acetal functionality with these two systems is significantly less than with the acyclic systems.[6]

The fact that only one ketene acetal is produced from these lactones is responsible, to a large degree (*vide infra*), for the high stereoselectivity of the Claisen rearrangements. The product stereochemical integrity for cycloalkanecarboxylic acids **7a–d** was established by the ^{13}C-NMR spectra as well as by HPLC and GC analysis of the derived methyl esters. The stereochemical assignments for **7a** and **7b** are based on epimerization (NaOMe, MeOH) of the methyl esters to the more stable *trans* isomers. The assignments for **7c** and **7d** rest on transformation to the corresponding dimethyl *cis*-cycloheptane and *cis*-cyclooctane diesters (1. CH_2N_2; 2. $RuCl_3 \cdot (H_2O)n$, $NaIO_4$, CCl, CH_3CN, H_2O;[13] 3. CH_2N_2) and comparison of the ^{13}C-NMR data with the previously reported ^{13}C-NMR data for these diesters.[14] Acids **8e** and **8f** were produced as a 76 : 24 mixture and the stereochemical assignment is unknown.

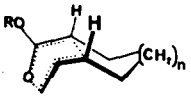
The preferential formation of the *cis*-2-alkenylcycloalkanecarboxylic acids **8a–d** can be readily understood by examining the two distinct diastereotopic transition states for rearrangement of the ketene acetals (Fig. 1). Molecular models indicate the chair-like transition state **A** to be much more strained than the twist boat-like transition state **B**. Transition state **A** is apparently accessible only when the diaxially bridging methylene chain becomes sufficient in length ($n = 7$) and hence two isomers, **8e, f** are observed.



Scheme 2.

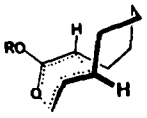


A

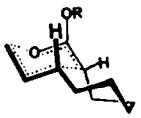


B

Fig. 1.



C



D

Fig. 2.

We examined two additional Claisen substrates, **9** and **13** (Scheme 3), to delineate further the scope and generality of this method. Subjection of lactone **9** to the standard silylation conditions gave the silyl ketene acetal **10** (R = t-BuMe$_2$Si) in 97% yield. As anticipated, the rearrangement of **10** proceeded *completely* to the cyclopropane **11** when heated in chloroform at 65°. This investigation, in conjunction with the aforementioned cases, demonstrates that all ring sizes are, in principle, accessible via this methodology and also provides an efficient synthetic route to *cis*-chrysanthemic acid.†

The preparation and rearrangement of the lactone **13** were studied in order to assess the effect a *trans* double bond would have upon the rearrangement. If the enolate geometry is preserved and the boat-like transition state **C** (Fig. 2) is still preferred over the analogous chair-like transition state **D**, then one would predict a reversal of stereochemistry, i.e. *trans*-2-ethenylcycloheptanecarboxylic acid (**14**). In this case, the boat-like transition state **C** is marginally favored and a 59:41 *trans*:*cis* ratio of isomers is obtained. Moreover, the yield for lactonization is markedly suppressed (28%) and no lactone was isolated from an attempt to lactonize the hydroxy acid which would give rise to the analogous ten-membered lactone. These results indicate that the preparation of common ring sized carbocycles is best achieved beginning with *cis*-allylic alcohols. However, it may be possible, if not advantageous, to prepare large rings by rearrangement of lactones incorporating *trans* double bonds. Studies to investigate this possibility are under way.

RELATIVE ASYMMETRIC INDUCTION

The high internal asymmetric induction observed in the rearrangements of the ketene acetals derived from the unsubstituted lactones **7** set the stage for an investigation of relative asymmetric induction. Thus, when a pre-existing asymmetric center is present at some position in the macrocyclic ketene acetal, *diastereotopic* boat-like transition states are possible. The preference of one boat-like transition state over another is a function of relative transition state conformational energies.

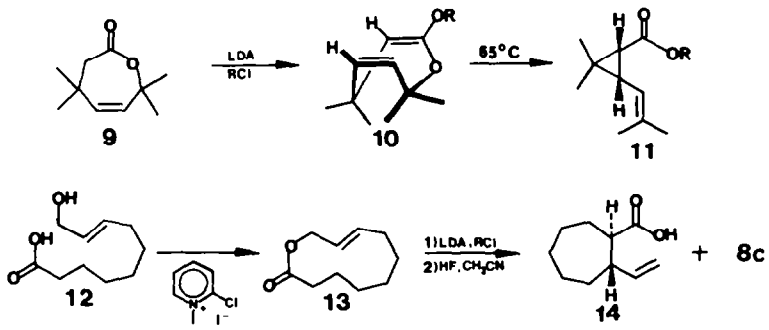
A. 1,2-*Relative asymmetric induction*

Synthesis of (±)-*dihydroneptalactone.* We chose as our first case to investigate a substrate wherein this effect would be most profound, e.g. 1,2-relative asymmetric induction during rearrangement of lactone **18** (Scheme 4). The hydroxy acid precursor to lactone **18** was prepared in 52% overall yield from ethyl-5-iodo-3-methylpentanoate (**15**) by the three-step sequence shown in Scheme 4. Lactonization of **17** using the Mukaiyama reagent[10] proceeded satisfactorily (72%) to afford lactone **18**. We were gratified to find that the silyl ketene acetal, prepared from lactone **18** in the standard fashion,[6] rearranged before isolation and gave a single stereoisomer, cyclopentanecarboxylic acid **19a**. None of the alternative stereoisomer, the *cis*,*cis*-isomer **19b**, was detected. The stereochemical assignment for **19a** was proven by stereoselective hydroboration [2 equiv of $(C_6H_{11})_2BH$] of **19a** with oxidative workup (NaOH, H_2O_2) to provide two terpenes isolated previously from *Nepeta cataria* (catnip oil),[15] namely, (±)-dihydronepetalactone (**20a**) and (±)-isodihydroneptalactone (**20b**) in a 93:7 ratio, respectively (75%). The ^{1}H-NMR and IR spectra of our samples were identical with authentic spectra.[16]

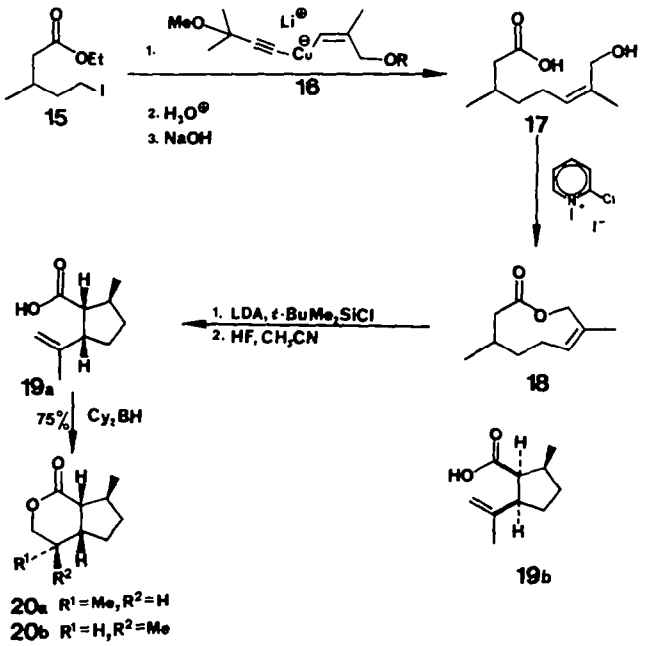
Inspection of molecular models indicates that four boat-like transition states (Fig. 3) are possible for the rearrangement of the ketene acetal prepared from lactone **18**. Moreover, the relative energy differences of these transition states can be estimated by calculating the transition state strain energies (SE) using MMPM.‡

† For full experimental details, see Ref. 2*c*.

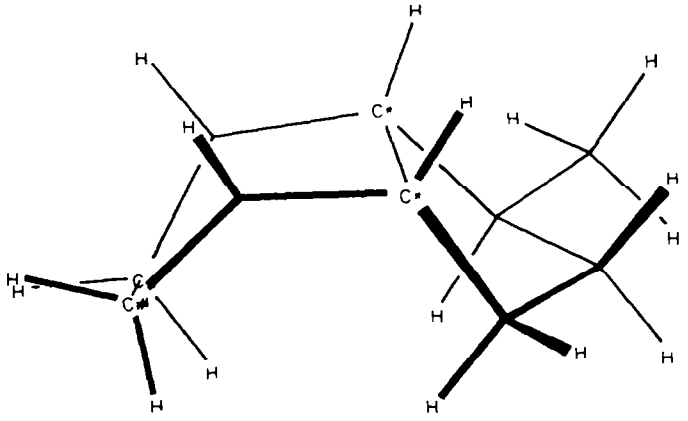
‡ We used the MMPM program as parameterized, available from Serena Software, 489 Serena Lane, Bloomington, IN 47401, U.S.A. Calculations were performed on an IBM-XT with 640K core and an 8087 chip. We are indebted to Professor J. Gajewski of the University of Indiana for many fruitful discussions and helpful advice.



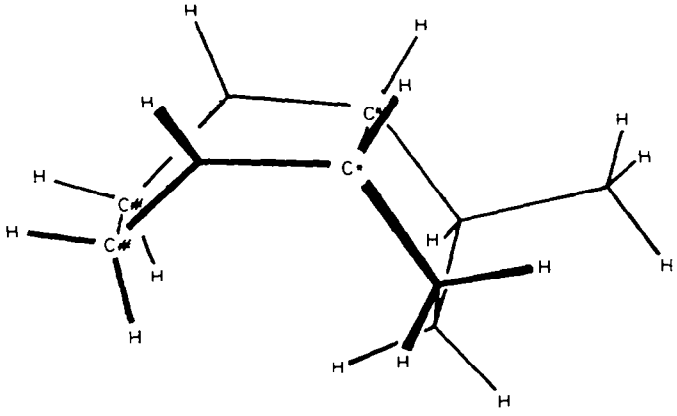
Scheme 3.



Scheme 4.

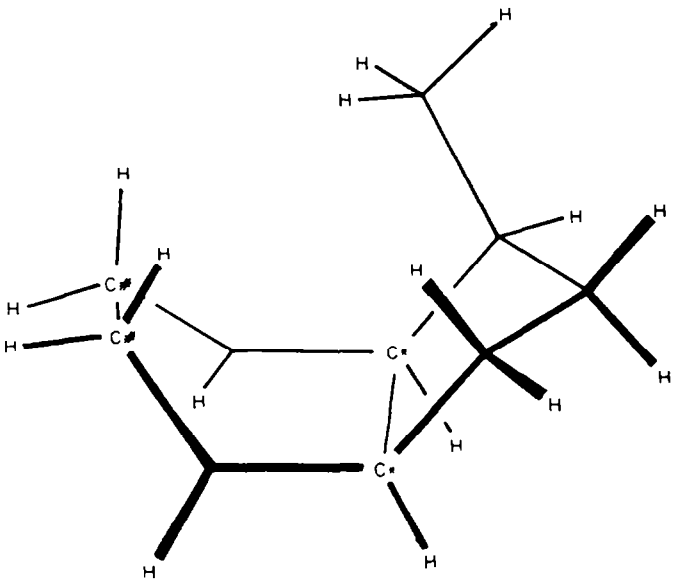


E ΔSE = 0

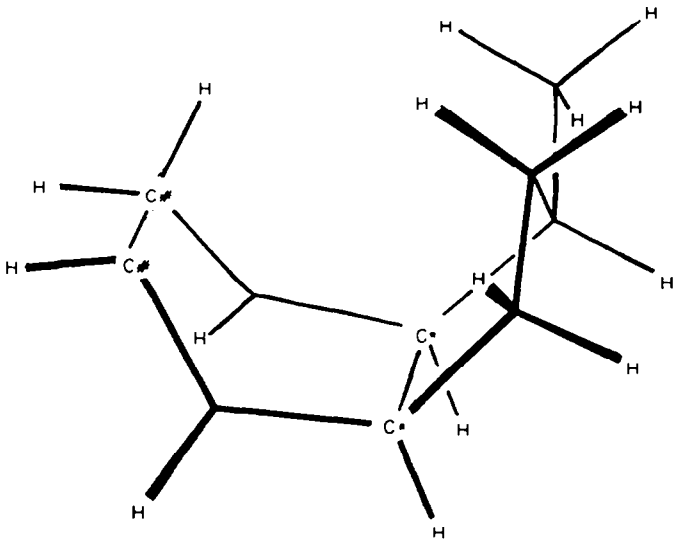


F ΔSE = 1.97

Fig. 3.



G ΔSE = 2.92

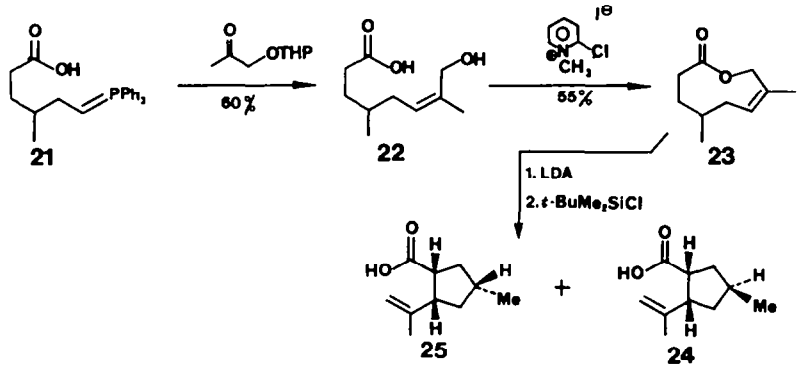


H ΔSE = 2.07

Fig. 3.—*continued*

a modified version of the MM2 molecular mechanics program.[17] The analogous Cope transition states **E–H** were used to model the four boat-like Claisen transition states since the MMPM program is currently parameterized only for transition-state carbons (C*, C#) and hydrogen or carbon substituents on the central carbon (C.) of the allylic π-system. Transition-state bond orders of 0.8 (1.67 Å) for the bond breaking (C#—C#) and 0.2 (2.48 Å) for the bond forming (C*—C*) were entered in order to approximate the early reactant-like transition states of Claisen rearrangements.[18] At the very least, these computations provide a qualitative insight about various transition-state conformers. Thus, for the rearrangement of the ketene acetal derived from **18**, a transition-state conformer similar to **E** is clearly preferred and would give rise to the observed *cis,trans*-isomer **19a**. The *cis,cis*-isomer **19b** would be produced by rearrangement through either transition state **G** or **H**. Interestingly, the calculations predict the boat, boat-like conformer **H** to be the preferred over the boat, chair-like conformer **G** which has a serious $A^{(1,3)}$-type interaction between the endocyclic oxygen atom and the pseudo-axial methyl substituent. However, the ΔSE between transition-state conformers **H** and **E** is still significant (2.07 kcal mol^{-1}) and a Boltzmann distribution at 0° gives a predicted ratio of 98:2 for **19a**:**19b**, which is exactly the limit of detection of our product ratio analysis (^{13}C-NMR).

The consequences of this stereochemical investigation are considerable. Indeed, we submit that the same stereochemical pattern should emerge regardless of ring size (for the larger rings the $A^{(1,3)}$ interaction mutates into an equally serious transannular interac-



Scheme 5.

tion which cannot be eliminated by rotation into a conformer similar to **H**). This recognition is a key element in syntheses for guaianolides, taxanes and germacranes currently under investigation in our laboratories.

B. 1,3-*Relative asymmetric induction*

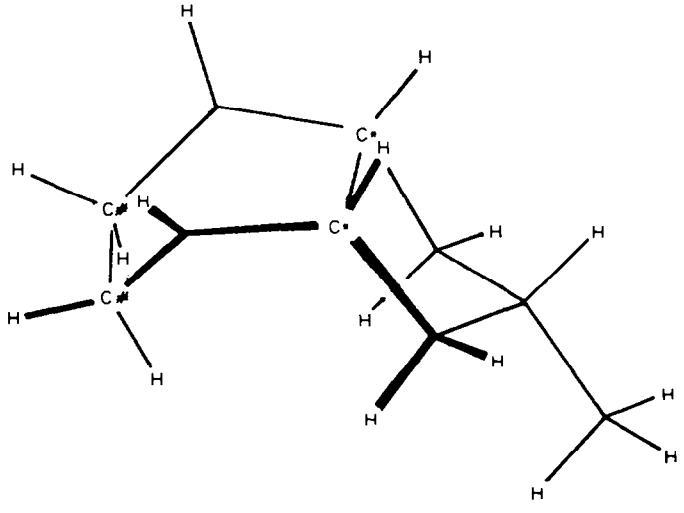
We next turned our attention to the preparation of lactone **23** (Scheme 5) with the intention to investigate 1,3-relative asymmetric induction in the Claisen rearrangement process. Lactone **23** was prepared in good yield (55%) from the hydroxy acid **22**, in turn available via a stereospecific Wittig olefination reaction using ylid **21** and the tetrahydropyranyl ether of acetol following reaction conditions described previously.[19] The rearrangement of lactone **23** proceeded smoothly to deliver a mixture of cyclopentanecarboxylic acids **24** and **25** in a 10:90 ratio, respectively. The stereochemical assignments are tentative but are based on the secure stereochemical assignments for the products obtained from the analogous ten-membered lactone, e.g. **26** (*vide infra*).

Four possible transition states for the rearrangement of the ketene acetal derived from lactone **23** are illustrated in Fig. 4. As in the previously described example involving 1,2-relative asymmetric induction, the preferred transition state is a boat, chair-like conformer with a pseudoequatorial methyl substituent, namely **I**. However, the preference for transition state **I** is not as profound in this case. Transition state **K**, which leads ultimately to the minor carboxylic acid **24**, suffers only from two additional pseudo-gauche butane-type interactions. The predicted ratio, assuming a rearrangement temperature of 0°, is precisely the experimentally observed ratio.

The rearrangement of the ten-membered lactones **26** and **27** was also subject to 1,3-relative stereocontrol (Scheme 6). Lactones **26** and **27** were prepared using sequences similar to those employed for lactones **7**. Subjection of lactone **26** to the standard silylation conditions provided upon hydrolysis a mixture of two carboxylic acids, **28a** and **28b** (44:56), whereas lactone **27** afforded a single diastereomer, **28d**. The stereochemical assignment for **28b** was based on correlation (1. CH_2N_2; 2. $RuCl_3$, $NaIO_4$;[13] 3. CH_2N_2) with dimethyl ester **30**, in turn prepared by stereospecific hydrogenation of the Diels–Alder cyclo adduct of maleic anhydride and isoprene (**29**).†

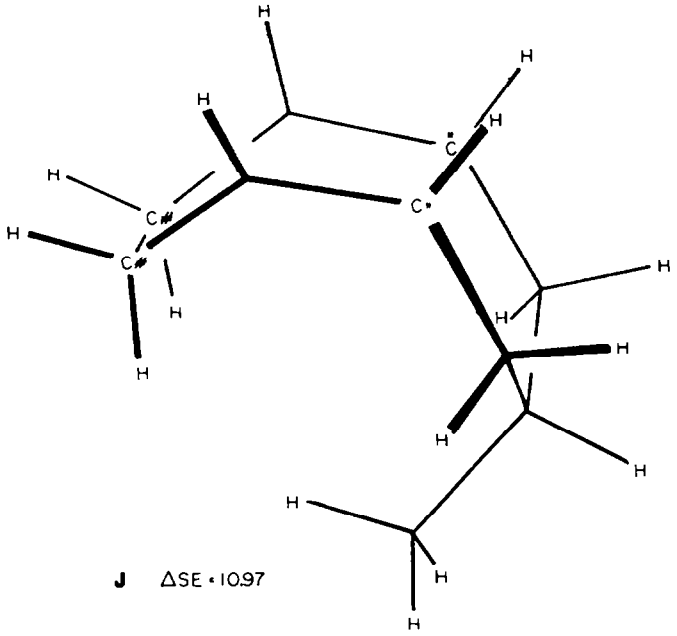
Again, these stereochemical results can be ap-

† Compound **29** was kindly provided by Professor D. M. S. Wheeler at the University of Nebraska.

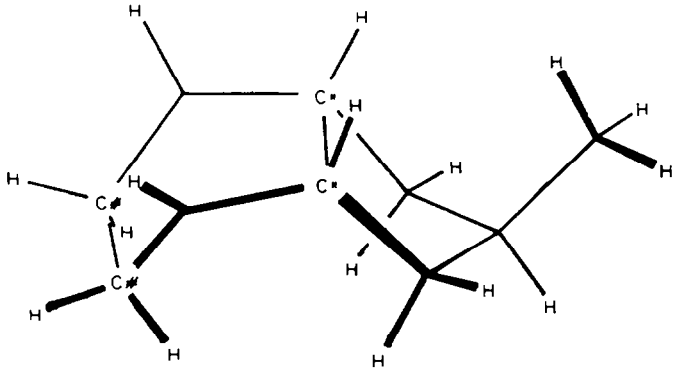


I ΔSE = 0

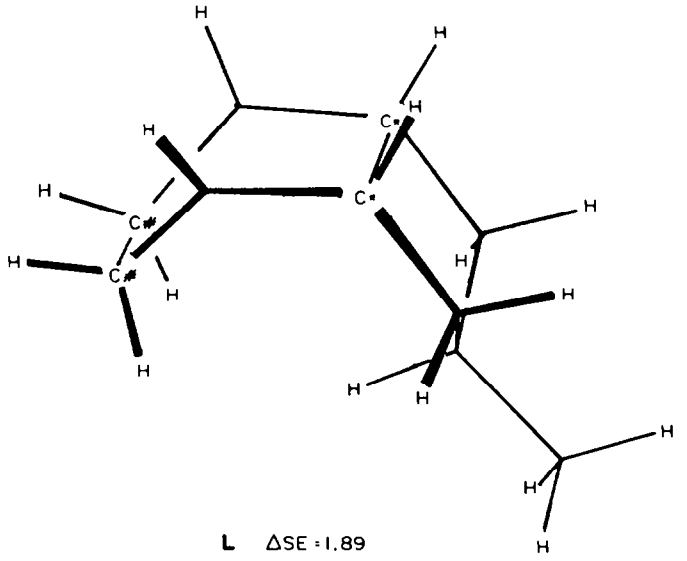
Fig. 4.



J ΔSE = 10.97

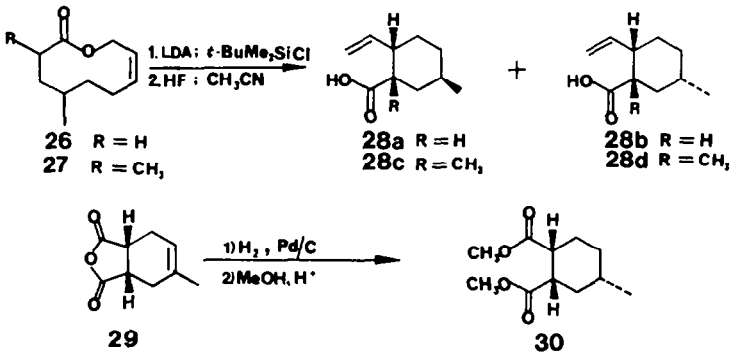


K ΔSE = 1.21



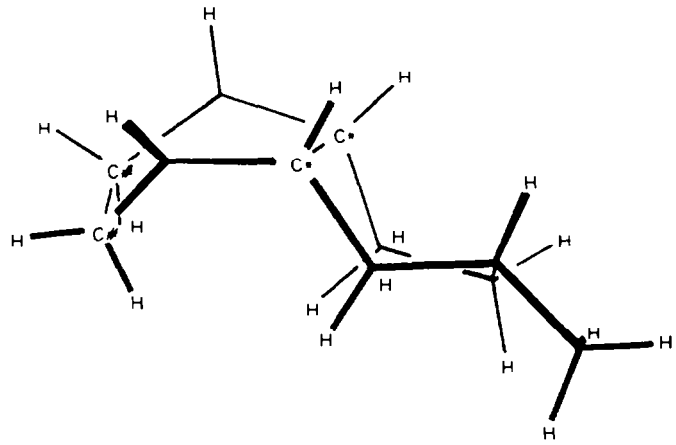
L ΔSE = 1.89

Fig. 4.—*continued*

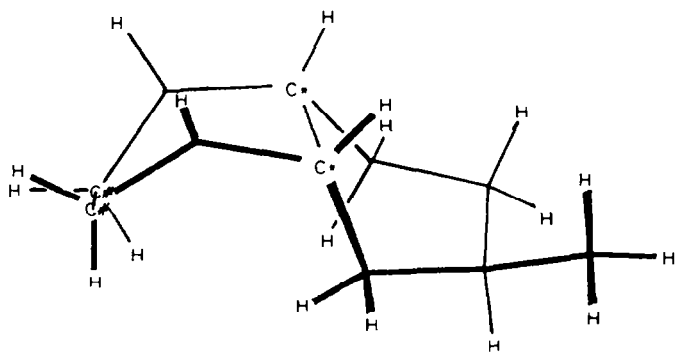


Scheme 6.

preciated by computational evaluation of possible transition states (Fig. 5). Transition states **M** and **N** are the apparent minima for rearrangement of the ketene acetal produced from lactone **26** and differ little in strain energy (predicted product ratio at 0° of 52:48, **28b**:**28a**). The twist-boat, twist-boat conformation of **N** appreciably minimizes the gauche butane-like interaction of the methyl substituent with the vinyl carbon, as well as a vicinal torsional interaction, and hence effectively competes with the pseudo-equatorial twist-boat, twist-boat conformer **M**. However, in the analogous transition states for rearrangement of the lactone **27**, a psuedo-1,3-diaxial-like interaction cannot be entirely relieved in conformer **P** and therefore precludes rearrangement through this transition state (predicted ratio 96:4, **28d**:**28c**).

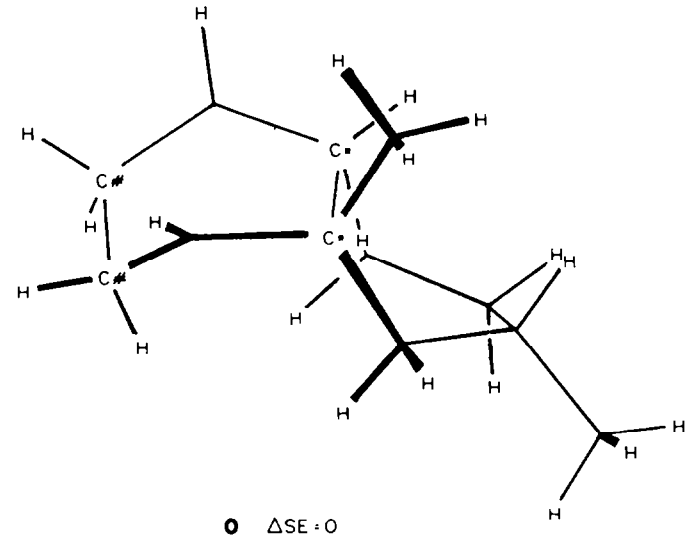


M ΔSE = 0

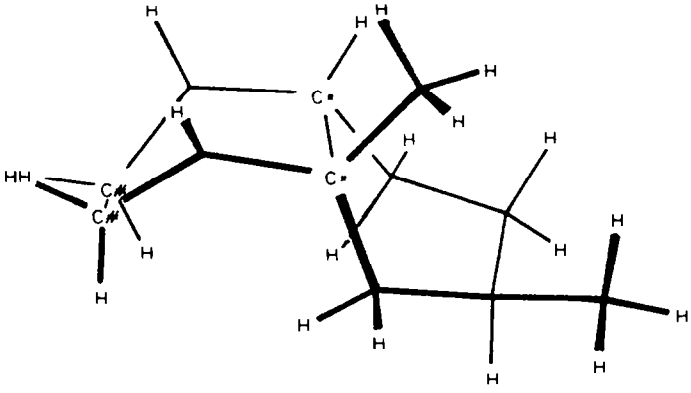


N ΔSE = 0.05

Fig. 5.



O ΔSE = 0



P ΔSE = 1.76

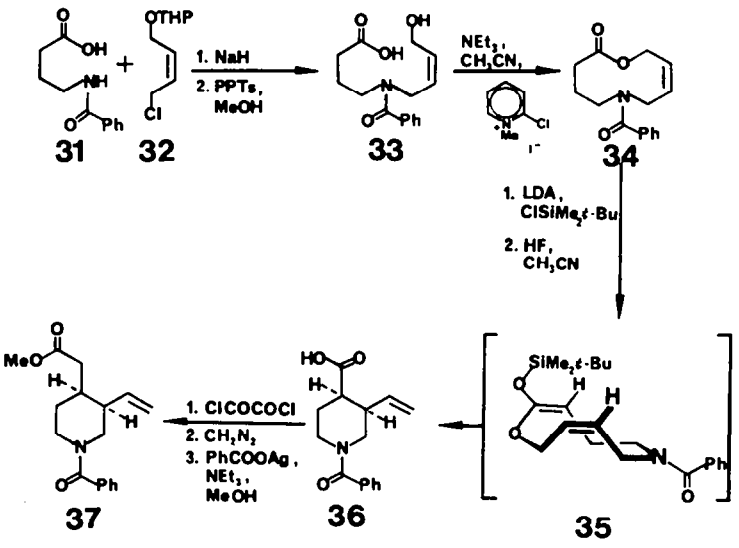
Fig. 5.—*continued*

SYNTHESIS OF HETEROCYCLES

The utility of this method in heterocycle synthesis remained to be tested. We chose as our objective for this purpose N-benzoylmeroquinene methyl ester (**37**).[20] At first glance this might appear to be a trivial exercise. However, examination of previous syntheses of **37**[20] reveals that the *cis* stereochemistry was introduced by catalytic hydrogenation, necessitating subsequent unravelling of the vinyl group, albeit by rather ingenious schemes. Our method offers the unique opportunity to establish the *cis* stereorelationship of the vinyl and carboxymethyl substituents while simultaneously constructing the piperidine ring. Thus, we anticipated that the rearrangement of the ketene acetal would provide the carboxylic acid **36**, which requires only carbonyl homologation to complete the synthesis.

Accordingly, we developed an expedient synthesis of lactone **34** from N-benzoyl-4-aminobutyric acid **31**[21] (Scheme 7). Alkylation of the dianion of **31** (2 equiv of NaH, DMF, 0°) with *cis* - 1 - chloro - 2 - butene - 4 - tetrahydropyranyl ether (1.2 equiv) (**32**)[22] followed by hydrolysis of the THP protecting group provided the carboxylic acid **33** in good yield (61%). Lactonization was accomplished using the standard protocol (2-chloro-N-methylpyridinium iodide, CH_3CN, reflux)[10] to provide the key lactone **34** in good yield after column chromatography (73%). Subjection of lactone **34** to the typical rearrangement conditions[6] delivered the carboxylic acid **36** in 86% yield after hydrolysis of the intermediate silyl ester. We did not detect the ketene acetal **35** and the reaction product is stereochemically homogeneous by ^{13}C-NMR, results that are consistent with the analogous carbocyclic system (e.g. **7b** → **8b**). That this stereochemical assignment was indeed correct was verified by homologation of acid **36** to the methyl ester **37**. The acid chloride required for the Wolff rearrangement reaction[23] was prepared by treating the sodium carboxylate of acid **36** (NaH, benzene) with oxalyl chloride (ether, 0°). The crude reaction mixture was added to excess ethereal diazomethane to afford a diazoketone which, without purification, was treated with silver benzoate (NEt_3, MeOH, 0°) to provide ester **37** in 77% overall yield. Our synthetic material was identical with an authentic sample generously provided by Dr Uskoković of Hoffmann-La Roche Inc.

In summary, this single example signifies that this



Scheme 7.

methodology can also assist the preparation of heterocyclic natural products provided the heteroatom is judiciously placed within the macrocyclic ketene acetal ring system.

CONCLUSION

We have described a general strategy for the preparation of hetero- and carbocycles by a route involving four-atom-ring contractions of macrolides. This strategy might be initially perceived as unusual, if not amusing. That is, some of the macrolide precursors are, perhaps, more complex from a synthetic perspective than the product carbocycles. Surely the gross structure of 2-ethenyl cyclohexene carboxylic acid can be accessed more rapidly by alternative methodology. However, the stereochemical dividend of the alicyclic Claisen rearrangement may be the most meritorious aspect of this method. In the preliminary studies discussed herein we concentrated on the synthesis of natural products which are comprised of small or common rings, primarily for the facilitation of structural and stereochemical assignments. It is now our objective to apply this methodology in the stereocontrolled syntheses of natural products incorporating medium rings, for which synthetic methodology is relatively lacking.

EXPERIMENTAL

General methods. 60 MHz ^{1}H-NMR spectra were recorded on a Varian T-60, 90 MHz ^{1}H-NMR spectra were recorded on a Varian EM 390, 200 MHz ^{1}H-NMR spectra were recorded on a Varian XL200, and 360 MHz ^{1}H-NMR spectra were recorded on a Nicolet NMC 360. Data are reported as follows: chemical shifts, in ppm downfield of internal TMS (multiplicity, coupling constant(s), number of protons). ^{13}C-NMR spectra were obtained on either a Varian XL100, XL200 or on a Nicolet NMC 360. Chemical shifts are referenced to the central peak of the $CDCl_3$ triplet (77.00 ppm). IR absorption spectra were obtained on a Perkin–Elmer model 283 and were referenced to polystyrene (1601 cm^{-1}). High-resolution mass spectra were provided by the Midwest Center for Mass Spectrometry of the University of Nebraska, Lincoln, Nebraska. Elemental analyses were provided by Galbraith Laboratories Inc., Knoxville, Tennessee. M.ps were determined in open Pyrex capillary tubes on a Thomas–Hoover Unimelt apparatus. M.ps and b.ps are uncorrected. Gas chromatography was performed on a Varian Aerograph model 920 with an 8 ft × 1/4 in glass 10% SE-30 on Chromosorb Q conditioned at 210° (column A) or an 8 ft × 1/4 in glass 10% UCQ982 on Chromosorb Q 80/100 conditioned at 250° (column B). All HPLC was performed on a Waters 590 pump equipped with an R401 differential refractomer and a UK6 injector. All chromatography was carried out on E. M. Reagents silica gel (400–230 mesh) according to the method of Still, and all TLC on commercial silica gel plates (Analtech Silica HLF 250 m). Solvents were dried by distillation over an appropriate drying agent under N_2 atmosphere and stored under N_2 over Linde molecular sieves (4 Å). All reactions involving organometallics, air-sensitive reagents and Claisen rearrangements were carried out in apparatus that was flame-dried and cooled under a stream of dry N_2. Evaporation of solvents was performed first at aspirator pressure on a Buchi rotoevaporator and then at *ca* 0.050 mmHg at room temp until a constant weight was obtained.

General procedure for lactonization of hydroxy acids. To the appropriate hydroxy acid was added acetonitrile (20 ml per mmol) and Et_3N (8 equiv), and the resulting soln was added slowly (over 24–40 h) via a syringe pump to a refluxing soln of 2-chloro-1-methylpyridinium iodide (4 equiv per mmol of hydroxy acid, from Fluka Chem. Corp.) in acetonitrile (200 ml per mmol of hydroxy acid). The typically red mixtures were heated at reflux for an additional 4 h, followed by the removal of the acetonitrile by distillation. The residue was chromatographed on silica gel using EtOAc–hexanes as eluant and the lactones were isolated after removal of the solvents by careful distillation at atmospheric pressure.

(Z)-8-Hydroxy-6-octenoic acid lactone (**7a**). Hydroxy acid **6a**[8d] (927 mg, 5.86 mmol) gave 336 mg (41%) of an oil. R_f 0.42 (EtOAc–hexanes, 1 : 19). IR (neat) 3020, 2930, 2860, 1736, 1448, 1365, 1215, 1135, 1020, 700 cm^{-1}; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 5.97–5.46 (m, 2H), 4.75 (d, J = 4 Hz, 2H), 2.47–2.10 (m, 4H), 2.05–1.53 (m, 4H); MS *m/z* (rel. int.) M$^+$ 140 (8.45), 111 (21.03), 96 (46.60). Exact mass calc for $C_8H_{12}O_2$ (M$^+$): 140.0837; found: 140.0835.

(Z)-9-Hydroxy-7-nonenoic acid lactone (**7b**). Hydroxy acid **6b**[8d] (613 mg, 3.56 mmol) gave 268 mg (49%) of an oil. R_f 0.39 (EtOAc–hexanes, 1 : 19). IR (neat) 3020, 2925, 2860, 1755, 1655, 1460, 1150, 1030, 715 cm^{-1}; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 5.80–5.30 (m, 2H), 4.67 (d, J = 3 Hz, 2H), 2.50–2.05 (m, 4H), 1.95–1.60 (m, 2H), 1.60–1.15 (m, 4H).

(Z)-10-Hydroxy-8-decenoic acid lactone (**7c**). Hydroxy acid

6c[14] (949.5 mg, 5.10 mmol) gave 455 mg (53%) of an oil. R_f 0.48 (EtOAc–hexanes, 1 : 19). IR (neat) 3020, 2925, 2855, 1730, 1645, 1450, 1240, 1215, 1185, 1140, 1060, 745 cm^{-1}; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 5.97–5.43 (m, 2H), 4.53 (d, J = 4.5 Hz, 2H), 2.57–1.97 (m, 4H), 1.95–1.13 (m, 8H); MS *m/z* (rel. int.) M^+ 168 (13.37), 125 (14.52), 124 (14.10), 108 (21.43), 98 (25.18). Exact mass calc for $C_{10}H_{16}O_2$ (M^+): 168.1151; found: 168.1151.

(*Z*)-11-*Hydroxy*-9-*undecenoic acid lactone* (**7d**). Hydroxy acid **6d**[12] (2.04 g, 10.21 mmol) gave 836 mg (45%) of an oil. R_f 0.36 (EtOAc–hexanes, 1 : 19). IR (neat) 3020, 2925, 2855, 1725, 1655, 1445, 1365, 1260, 1230, 1155, 1060, 995, 970, 725 cm^{-1}; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 6.05–5.48 (m, 2H), 4.49 (d, J = 7 Hz, 2H), 2.47–1.94 (m, 4H), 1.90–1.03 (m, 10H); MS *m/z* (rel. int.) M^+ 182 (2.69), 138 (1.79), 111 (2.42), 98 (6.87), 97 (3.23), 95 (4.63), 94 (2.77), 93 (2.42), 81 (10.56), 74 (61.86). Exact mass calc for $C_{11}H_{18}O_2$ (M^+): 182.1308; found: 182.1308.

(*Z*)-14-*Hydroxy*-12-*tetradecenoic acid lactone* (**7e**). Hydroxy acid **6e**[12] (1.66 g, 6.86 mmol) gave 1.164 g (82%) of an oil. R_f 0.68 (EtOAc–hexanes, 1 : 9). IR (neat) 3020, 2910, 2835, 1730, 1650, 1455, 1360, 1240, 1165, 970, 780, 755, 710 cm^{-1}; ^{1}H-NMR (90 MHz, C_6D_6) δ 5.9–5.33 (m, 2H), 4.57 (d, J = 7.2 Hz, 2H), 2.37–1.87 (m, 4H), 1.87–1.08 (m, 16H); MS *m/z* (rel. int.) M^+ 224 (1.12), 195 (1.25), 181 (5.01), 111 (17.03), 109 (17.36), 98 (30.31), 95 (39.39). Exact mass calc for $C_{14}H_{24}O_2$ (M^+): 224.1759; found: 224.1754.

(*E*)-10-*Hydroxy*-8-*decenoic acid lactone* (**13**). Hydroxy acid **12** (2.61 g, 14.03 mmol) gave 649 mg (28%) of an oil. R_f 0.66 (EtOAc–hexanes, 1 : 9). IR (neat) 3030, 2930, 2855, 1735, 1655, 1455, 1355, 1230, 1135, 975, 715 cm^{-1}; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 6.03–5.79 (m, 2H), 4.70–4.37 (m, 2H), 2.43–1.97 (m, 4H), 1.87–1.10 (m, 8H); MS *m/z* (rel. int.) M^+ 168 (8.88), 123 (65.89), 114 (15.08), 113 (18.13), 107 (12.76), 100 (30.18). Exact mass calc for $C_{10}H_{16}O_2$ (M^+): 168.1150; found: 168.1143.

(*Z*)-8-*Hydroxy*-3,7-*dimethyl*-6-*octenoic acid* (**17**). The ethoxyethyl ether of (*Z*)-3-iodo-2-methyl-2-propen-1-ol† (4.065 g, 15 mmol) in Trapp solvent (25 ml, THF–Et_2O–pentane, 4 : 1 : 1) was cooled to −90° (internal temp) using a nitrogen slurry (consisting of ligroin–isopropanol–Me_2CO, 4 : 1 : 1) and then t-BuLi (14.28 ml of a 2.1 M soln in pentane, 30 mmol) was added dropwise. After stirring at −90° for 1 h, the soln was allowed to warm to −50° and then cooled to −78°. In a separate flask, n-butyllithium (9.375 ml of a 1.6 M soln in pentane, 15 mmol) was added dropwise to a soln of 3-methyl-3-methoxy-1-butyne[26] (1.47 g, 15 mmol) in dry THF (6 ml) at 0°. After stirring for 45 min at 0°, the clear, colorless soln was added via cannula to a precooled suspension (0°) of cuprous iodide (2.85 g, 15 mmol) in dry THF (15 ml). This was stirred at 0° until all the cuprous iodide dissolved and a red–orange copper acetylide[26] soln was obtained (*ca* 30 min). The copper acetylide was added via cannula to the soln of the vinyl lithium compound and stirred at −78° for 30 min. The soln was warmed to −50° and ethyl-5-iodo-3-methylpentanoate (prepared from ethyl-4-bromo-3-methylpentanoate[27] by treatment with NaI (3 equiv) in Me_2CO) (1.088 g, 4.03 mmol) was added dropwise. The mixture was stirred at −30° for 1 h, warmed to room temp over a period of 3 h and then stirred for an additional 10 h. The mixture was quenched with an alkaline (pH 9) soln of sat aq NH_4Cl and NH_4OH. The aq layer was extracted with Et_2O (2 × 50 ml), washed with brine and dried (Na_2SO_4). Evaporation of the solvents under reduced pressure provided a dark oil which was treated with pyridinium tosylate[25] (126 mg, 0.5 mmol) and heated at reflux with anhydrous EtOH for 3 h. Standard workup provided 650 mg of a dark oil which was chromatographed on silica gel affording 442.5 mg (51%) of a clear, yellow oil. R_f 0.37 (EtOAc–petroleum ether, 3 : 7). IR (neat) 3400, 2940, 2860, 1730, 1450, 1370, 1290, 1025 cm^{-1}; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 5.22 (br t, 1H), 4.10 (q, J = 6 Hz, 2H), 4.07 (br s, 2H), 2.3–1.1 (m, 14H), 1.79 (br s, 3H), 1.23 (t, J = 6 Hz, 3H), 0.94 (d, J = 6 Hz, 3H); MS *m/z* (rel. int.) $M^+ - H_2O$ 196 (9.57), 169 (3.89), 151 (17.41), 122 (29.82), 108 (100), 95 (18.97), 93 (81.31), 81 (25.22), 55 (31.70). Exact mass calc for $C_{12}H_{20}O_2$ ($M^+ - H_2O$): 196.1463; found: 196.1461. The ethyl ester was saponified by dissolving the ester in MeOH (2.4 ml) and 3 M KOH (2.4 ml). After stirring for 4 h at room temp, standard acidic workup provided 317 mg (82%) of a colorless oil. IR (neat) 3400–2600, 2950, 2860, 1710, 1440, 1400, 1380, 1290, 1000 cm^{-1}; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 6.82 (br s, 2H), 5.24 (br t, 1H), 4.07 (br s, 2H), 2.12 (m, 4H), 1.73 (br s, 3H), 1.26 (m, 3H), 0.98 (d, J = 6 Hz, 3H); MS *m/z* (rel. int.) $M^+ - H_2O$ 168 (36.71), 153 (3.94), 140 (1.80), 109 (100), 108 (97.66). Exact mass calc for $C_{10}H_{16}O_2$ ($M^+ - H_2O$): 168.1151; found: 168.1149. (Found: C, 64.23; H, 9.96. Calc for $C_{10}H_{16}O_2$: C, 64.48; H, 9.74%.)

(*Z*)-3,7-*Dimethyl*-8-*hydroxy*-6-*nonenoic acid lactone* (**18**). Hydroxy acid **17** (315 mg, 1.69 mmol) gave 204 mg (72%) of an oil. R_f 0.27 (EtOAc–hexanes, 1 : 49). IR (neat) 2920, 1735, 1440, 1270, 1220, 1170, 1140, 1065, 1000 cm^{-1}; ^{1}H-NMR (90 MHz, C_6D_6) δ 5.27 (br t, J = 9 Hz, 1H), 4.56 (br s, 2H), 2.10 (m, 4H), 1.61 (s, 3H), 1.33 (m, 3H), 0.78 (d, J = 6 Hz, 3H); MS *m/z* (rel. int.) M^+ 168 (68.24), 139 (90.75), 124 (19.44), 109 (26.42), 98 (54.32), 93 (39.13), 81 (76.58), 69 (100), 55 (71.58). Exact mass calc for $C_{10}H_{16}O_2$ (M^+): 168.1151; found: 168.1149.

(*Z*)-8-*Hydroxy*-4,7-*dimethyl*-6-*octenoic acid* (**22**). To a soln of 4-methylcyclohexanone (3.3 g, 30 mmol) in $CHCl_3$ (50 ml) was added *m*-chloroperbenzoic acid (9.8 g, 57 mmol) in several portions. The reaction was heated to reflux for 1.5 h and then cooled to 0°. The mixture was then filtered through a Buchner funnel and the white ppt rinsed with cold $CHCl_3$. The filtrate was then washed four times with sat $NaHCO_3$ aq, brine and dried (K_2CO_3). The soln was filtered and the solvent removed *in vacuo* to yield 2.55 g (85%) of a clear oil, 6-hydroxy-4-methylhexanoic acid lactone. IR (neat) 2960, 2920, 2870, 1735, 1475, 1450, 1390, 1340, 1280, 1250, 1180, 1160, 1095, 1080, 1070, 1005, 930, 860 cm^{-1}; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 4.17 (m, 2H), 2.6 (m, 2H), 2.05–1.1 (m, 5H), 0.95 (d, J = 5 Hz, 3H); MS *m/z* (rel. int.) M^+ 128 (7), 98 (24), 83 (8), 70 (5), 69 (61), 56 (100), 55 (33). Exact mass calc for $C_7H_{12}O_2$ (M^+): 128.0837; found: 128.0838. To 6-hydroxy-4-methylhexanoic acid lactone (2.56 g, 20 mmol) was added an aq soln of HI (11 ml, 60 mmol) and the mixture was heated at 100° for 12 h. The soln was diluted with Et_2O and the aq layer extracted twice with Et_2O. The organic layer was washed twice with a sat soln of $Na_2S_2O_3$, brine and dried ($MgSO_4$). Filtration and removal of solvents *in vacuo* provided 6-iodo-4-methylhexanoic acid, 4.6 g (90%), as a clear oil. ^{1}H-NMR (90 MHz, $CDCl_3$) δ 10.9 (br s, 1H), 3.3–3.0 (m, 2H), 2.45–2.25 (m, 2H), 1.9–1.4 (m, 5H), 0.89 (d, J = 6 Hz, 3H). The 6-iodo-4-methylhexanoic acid (4.6 g, 18 mmol) was dissolved in dry CH_3CN (30 ml) and triphenylphosphine (5 g, 19 mmol) was added. The soln was heated at reflux for 12 h. Washing the resulting mixture with hexanes to remove any excess triphenylphosphine provided (3-methyl-5-carboxypentyl)triphenylphosphonium iodide, 9.3 g (100%). IR (neat) 3600–2500, 3060, 2960, 2930, 2880, 1980, 1910, 1820, 1730, 1588, 1488, 1440, 1385, 1340, 1320, 1270, 1220, 1185, 1160, 1115, 995, 905, 790, 730, 690 cm^{-1}; ^{1}H-NMR (90 MHz, acetone-d_6) δ 8.1–7.5 (m, 15H), 4.2 (br s, 1H), 3.62 (m, 2H), 2.2 (br t, 2H), 1.9–1.3 (m, 5H), 1.0 (d, J = 6 Hz, 3H). To a soln of (3-methyl-5-carboxypentyl)triphenylphosphonium iodide (3.85 g, 7.4 mmol, dried *in vacuo* at 50°, 0.5 mmHg) in THF (15 ml) and HMPA (6 ml) was added at 25° via cannula a soln of potassium hexamethyldisilazide (14.8 mmol) in THF (15 ml) (prepared from KH and hexamethyldisilazane). The soln turned bright red and was stirred at 25° for 30 min at which time the reaction mixture was cooled to −78° and 2-tetrahydropyranyloxyacetone (1.2 g, 7.4 mmol) in THF (3 ml) was added dropwise. The mixture was stirred at −78° for 1 h and then warmed to 25° over 2 h. The reaction was quenched by partitioning between H_2O and Et_2O. The aq layer was extracted twice with Et_2O and then carefully neutralized with 1 N HCl under a layer of Et_2O. The aq layer was then extracted twice more with Et_2O and the organic phase washed with brine and dried (Na_2SO_4). Filtration and evaporation of the organic phase *in vacuo* provided 1.38 g of a yellow oil.

† Reaction of (*Z*)-3-iodo-2-methyl-2-propen-1-ol[24] with ethyl vinyl ether and pyridinium *p*-toluenesulfonate (PPTS)[25] gave the ethoxyethyl derivative.

Flash chromatography on silica gel using 1:19 isopropanol–hexanes provided 1.2 g (60%) of (*Z*)-8-tetrahydropyranyloxy-4,7 - dimethyl - 6 - octenoic acid. R_f 0.5 (isopropanol–hexanes, 1:9). ^{1}H-NMR (90 MHz, $CDCl_3$) δ 8.9 (br s, 1H), 5.32 (br t, 1H), 4.5 (br s, 1H), 4.02 (br s, 2H), 4.0–3.3 (m, 2H), 2.28 (br t, 3H), 2.1–1.0 (m, 10H), 1.75 (br s, 3H), 0.88 (d, J = 6 Hz, 3H). The tetrahydropyranyl ether was hydrolyzed with pyridinium tosylate (126 mg, 0.5 mmol) in MeOH at 25° for 12 h. Standard workup provided 744 mg (91%) of a colorless oil. IR (neat) 3300, 2960, 2920, 2870, 1710, 1455, 1410, 1380, 1090, 1050, 1010, 950, 880 cm^{-1}; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 6.1 (br s, 2H), 5.32 (br t, 1H), 4.1 (br s, 2H), 2.3 (br t, 2H), 2.1–1.2 (m, 3H), 1.8 (br s, 3H), 0.9 (d, J = 6 Hz, 3H); MS *m/z* (rel. int.) $M^+ - H_2O$ 168 (38), 151 (23), 109 (100), 108 (29), 107 (24), 95 (36), 93 (27), 81 (22), 71 (18), 69 (31), 68 (24), 67 (31). Exact mass calc for $C_{10}H_{16}O_2$ ($M^+ - H_2O$): 168.1150; found: 168.1147.

(Z)-8-Hydroxy-4,7-dimethyl-6-octenoic acid lactone (**23**). Hydroxy acid **22** (708 mg, 3.8 mmol) was lactonized using the standard conditions described above, affording 348 mg (55%) of a colorless, volatile oil. R_f 0.49 (EtOAc–hexanes, 1:19). IR (neat) 2950, 2920, 2860, 1740, 1450, 1380, 1345, 1325, 1270, 1250, 1235, 1170, 1160, 1130, 1115, 1095, 1085, 1060, 1040, 1030, 980 cm^{-1}; ^{1}H-NMR (360 MHz, $CDCl_3$) δ 5.4 (br t, J = 8.92 Hz, 1H), 4.73 (d, J = 13.24 Hz, 1H), 4.55 (d, J = 13.24 Hz, 1H), 2.40 (ddd, J = 13, 7.9, 3.3 Hz, 1H), 2.24 (ddd, J = 13, 9.7, 3.3 Hz, 1H), 2.10 (br dd, J = 9, 5.5 Hz, 2H), 1.86–1.64 (m, 3H), 1.78 (br s, 3H), 1.0 (d, J = 7 Hz, 3H); MS *m/z* (rel. int.) M^+ 168 (81), 167 (34), 153 (10), 151 (31), 123 (22), 121 (21), 109 (100), 108 (55), 107 (99), 99 (19), 95 (58), 93 (50), 83 (23), 79 (28), 71 (29), 70 (17), 69 (83), 68 (62), 67 (80), 57 (58), 56 (24), 55 (98), 53 (25). Exact mass calc for $C_{10}H_{16}O_2$ (M^+): 168.1150; found: 168.1150.

(Z)-9-Hydroxy-4-methyl-7-nonenoic acid lactone (**26**). (*Z*)-9-Hydroxy-4-methyl-7-nonenoic acid (950 mg, 5.0 mmol) was lactonized using the standard conditions described above, affording 125 mg (15%) of a volatile, colorless oil. R_f 0.27 (EtOAc–petroleum ether, 1:49). IR (neat) 3020, 2950, 2920, 2870, 1740, 1465, 1370, 1275, 1240, 1210, 1190, 1160, 1105, 1090, 1030 cm^{-1}; ^{1}H-NMR (90 MHz, C_6D_6, benzene (7.20 ppm) as internal ref.) δ 5.68–5.28 (m, 2H), 4.90 (dd, J = 12, 5 Hz, 1H), 4.34 (br d, 1H), 2.8–1.0 (m, 9H), 0.9 (d, J = 6 Hz, 3H); MS *m/z* (rel. int.) M^+ 168 (20), 140 (21), 139 (36), 114 (11), 108 (16), 107 (11), 98 (11), 97 (13), 96 (13), 95 (36), 94 (21), 93 (27), 84 (13), 83 (100), 82 (13), 81 (48), 79 (16), 71 (11), 70 (35), 69 (50), 68 (35), 67 (48), 57 (12), 56 (15), 55 (83), 54 (68), 53 (19). Exact mass calc for $C_{10}H_{16}O_2$ (M^+): 168.1150; found: 168.1149.

(Z) - 9 - Hydroxy - 2,4 - dimethyl - 7 - nonenoic acid lactone (**27**). (*Z*) - 9 - Hydroxy - 2,4 - dimethyl - 7 - nonenoic acid (382 mg, 1.9 mmol) was lactonized using the standard conditions described above, affording 141 mg (41%) of a clear, colorless oil. R_f 0.22 (Et_2O–petroleum ether, 1:19). IR (neat) 3010, 2950, 2910, 2870, 1740, 1455, 1375, 1285, 1270, 1250, 1190, 1170, 1140, 1125, 1080, 1030, 820 cm^{-1}; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 5.5 (m, 2H), 4.8 (dd, J = 12, 5 Hz, 1H), 4.42 (br d, J = 12 Hz, 1H), 2.85–1.55 (m, 4H), 1.45–1.0 (m, 4H), 1.12 (d, J = 6 Hz, 3H), 0.89 (m, 3H); MS *m/z* (rel. int.) M^+ 182 (3), 140 (3), 127 (6), 122 (9), 109 (11), 107 (11), 95 (13), 93 (12), 85 (9), 84 (100), 83 (15), 82 (27), 81 (29), 79 (11), 69 (24), 68 (35), 67 (31), 57 (12), 56 (26), 55 (38), 54 (45). Exact mass calc for $C_{11}H_{18}O_2$ (M^+): 182.1306; found: 182.1310.

General procedure for silylation and rearrangement of lactones. The silylations were performed exactly as described in Ref. 6. Great care was taken to isolate all ketene acetals and/or silyl ester by removal of solvents via atmospheric distillation, as these products were quite volatile. For the ketene acetals that were isolable at room temp, the rearrangements were effected by dissolving the ketene acetal in an appropriate inert, dry, degassed solvent and heating. A small amount (*ca* 10–30 mg) of the ketene acetal was placed in an NMR tube, the appropriate deuterated solvent added, and the tube heated simultaneously with the rest of the sample. The reaction progress as well as the determination of half life was monitored by obtaining spectra at regular intervals. The rearrangement products were then hydrolyzed by dissolving the appropriate silyl ester in acetonitrile (5 ml per mmol), cooling the soln to 0°, and adding a soln of hydrofluoric acid in acetonitrile (2 equiv of a 3 M soln in acetonitrile, prepared from 48% HF aq). The disappearance of the silyl ester was monitored by TLC, and the reaction quenched at the appropriate time by addition of 3 M K_2CO_3 aq. The aq layer was washed with Et_2O, neutralized with conc HCl, and extracted with Et_2O. The organic phase was dried ($MgSO_4$) and the solvents were removed *in vacuo* to afford the carboxylic acids.

cis-2-*Ethenylcyclopentanecarboxylic acid* (**8a**). Lactone **7a** (46.6 mg, 0.33 mmol) was silylated and kept at −60° until *ca* half of the ketene acetal rearranged to the silyl ester (57 h). Isolation at 25° completed the rearrangement, and hydrolysis gave 32.6 mg (70%) of an oil. R_f 0.28 (EtOAc–hexanes, 1:9). IR (neat) 3650–3200, 3080, 2970, 2880, 1705, 1610 cm^{-1}; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 5.82 (ddd, J = 17.4, 9.5, 7.6 Hz, 1H), 5.13 (ddd, J = 17.4, 2.1, 1 Hz, 1H), 5.01 (ddd, J = 9.5, 2.1, 0.9 Hz, 1H), 3.05–2.8 (m, 2H), 2.2–1.5 (m, 6H); ^{13}C-NMR on methyl ester (90 MHz, $CDCl_3$) δ 138.459, 114.945, 51.133, 48.683, 47.256, 31.481, 27.838, 24.035; MS *m/z* (rel. int.) M^+ 140 (3.57), 125 (3.95), 111 (5.10), 96 (7.43), 95 (100.0). Exact mass calc for $C_8H_{12}O_2$ (M^+): 140.0836; found: 140.0836.

cis-2-*Ethenylcyclohexanecarboxylic acid* (**8b**). Lactone **7b** (135 mg, 0.88 mmol) was silylated and isolation gave the rearrangement product, which was hydrolyzed to afford 108 mg (81%) of an oil. R_f 0.25 (EtOAc–hexanes, 1:9). IR (neat) 3600–3100, 2930, 2860, 1705, 1635, 1450, 1425, 1255, 1220, 915 cm^{-1}; ^{1}H-NMR (90 MHz, CCl_4) δ 5.93 (ddd, J = 18, 9.6, 7.2 Hz, 1H), 5.02 (ddd, J = 18, 1.8, 0.9 Hz, 1H), 4.99 (ddd, J = 9.6, 1.8, 0.8 Hz, 1H), 2.77–2.40 (m, 2H), 2.00–1.10 (m, 8H); ^{13}C-NMR (25.2 MHz, $CDCl_3$) δ 180.478, 133.062, 115.591, 45.817, 41.077, 30.122, 24.574, 24.174, 22.037; MS *m/z* (rel. int.) M^+ 154 (8.13), 136 (14.45), 125 (16.74), 109 (100.0), 99 (4.64), 94 (15.26), 82 (12.98), 81 (23.46). Exact mass calc for $C_9H_{14}O_2$ (M^+): 154.0997; found: 154.0997.

cis-2-*Ethenylcycloheptanecarboxylic acid* (**8c**). Lactone **7c** (83.6 mg, 0.49 mmol) was silylated and variable amounts of ketene acetal and rearrangement products were observed. Warming to 40° gave exclusively the rearrangement product, which was hydrolyzed to afford 76.5 mg (91%) of an oil. R_f 0.22 (EtOAc–hexanes, 1:9). IR (neat) 3600–3100, 3060, 2925, 2850, 1705, 1635, 1450, 1415, 1190, 910, 715 cm^{-1}; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 5.83 (ddd, J = 16.5, 9.6, 7.8 Hz, 1H), 4.95 (ddd, J = 16.5, 1.9, 0.8 Hz, 1H), 4.90 (ddd, J = 9.6, 1.9, 0.8 Hz, 1H), 2.93–2.57 (m, 2H), 2.13–1.13 (m, 10H); ^{13}C-NMR (25.2 MHz, $CDCl_3$) δ 180.592, 139.596, 144.868, 48.682, 44.303, 32.509, 29.061, 27.133, 26.303, 25.315; MS *m/z* (rel. int.) M^+ 168 (4.49), 150 (4.91), 139 (14.93), 125 (38.50), 123 (53.95), 122 (25.59), 108 (20.18), 99 (10.37), 96 (23.84), 95 (31.98), 94 (10.49), 93 (29.17), 81 (100.0), 79 (26.22). Exact mass calc for $C_{10}H_{16}O_2$ (M^+): 168.1150; found: 168.1150.

cis-2-*Ethenylcyclooctanecarboxylic acid* (**8d**). Lactone **7d** (120 mg, 0.66 mmol) was silylated to afford 164 mg (82%) of a single ketene acetal. ^{1}H-NMR (90 MHz, toluene-d_8, benzene (7.20 ppm) as internal ref.) δ 6.03–5.30 (m, 2H), 4.30 (d, J = 7.5 Hz, 2H), 3.77 (t, J = 7.6 Hz 1H), 2.40–1.95 (m, 4H), 1.77–1.20 (m, 8H), 1.02 (s, 9H), 0.23 (s, 6H); ^{1}H-NMR (90 MHz, $CDCl_3$) δ 5.94–5.29 (m, 2H), 4.10 (d, J = 7.5 Hz, 2H), 3.50 (t, J = 7.6 Hz, 1H), 2.45–1.85 (m, 4H), 1.67–1.08 (m, 8H), 0.89 (s, 9H), 0.12 (s, 6H). Heating this ketene acetal in refluxing toluene effected the rearrangement. The half life was determined by observing the disappearance of the peak at δ 0.12 (CH_3Si of ketene acetal) and concomitant appearance of a peak at δ 0.25 (CH_3Si of silyl ester). The half life of the rearrangement (equal peak heights) was found to be 6 h. Heating the mixture for an additional 48 h gave the silyl ester, which was hydrolyzed to give 99 mg (82%) of an oil: R_f 0.23 (EtOAc–hexanes, 1:9). IR (neat) 3600–3100, 3000, 2920, 2850, 1710, 1635, 1445, 1415, 1240, 990, 910, 800 cm^{-1}; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 5.80 (ddd, J = 18, 9.6, 7.2 Hz, 1H), 5.0 (ddd, J = 18, 1.8, 0.6 Hz, 1H), 4.97 (br dd, J = 9.6, 2.1 Hz, 1H), 3.0–2.5 (m, 2H), 2.16–1.2 (m, 12H); ^{13}C-NMR (25.2 Hz, $CDCl_3$) δ 181.949, 139.490, 114.872, 45.083, 43.657, 30.112, 28.243, 26.358, 26.288, 25.214, 24.509; MS *m/z* (rel. int.)

M^+ 182 (6.74), 164 (4.32), 153 (10.16), 137 (12.23), 126 (11.57), 125 (42.91), 122 (17.89), 114 (11.53), 112 (17.75), 110 (21.02), 109 (20.49), 107 (15.50), 95 (70.52), 81 (100.0). Exact mass calc for $C_{11}H_{18}O_2$ (M^+): 182.1309; found: 182.1309.

cis-2-*Ethenylcycloundecanecarboxylic acid* (**8e**) *and* trans-2-*ethenylcycloundecanecarboxylic acid* (**8f**). Lactone **7e** (260 mg, 1.16 mmol) was silylated to give 381 mg (97%) of the corresponding ketene acetal. ^{1}H-NMR (90 MHz, $CDCl_3$) δ 5.80–5.40 (m, 2H), 4.27 (br d, 2H, J = 6.8 Hz), 3.67 (t, J = 7.5 Hz, 1H), 2.27–1.67 (m, 4H), 1.65–1.27 (m, 18H), 0.97 (s, 9H), 0.19 (s, 6H). The rearrangement was effected by heating a toluene soln of the ketene acetal at 80°. The peak at δ 0.19 (CH_3Si of the ketene acetal) was observed to disappear with the concomitant appearance of a new peak at δ 0.28. The half-life (observance of equal peak heights) was found to be 7 h. Heating for an additional 56 h, completed the rearrangement, and the resulting silyl ester was hydrolyzed to afford 249 mg (96%) of an oil which consisted of two components as determined by GC (column A, temp 155°, retention times 144 and 132 min, respectively). R_f 0.25 (EtOAc–hexanes, 1:9). IR (neat) 3500–3100, 3080, 2930, 2860, 1705, 1640, 1470, 1445, 1415, 1245, 995, 910 cm^{-1}; ^{1}H-NMR (360 MHz, $CDCl_3$) δ 5.75 (ddd, J = 17.14, 10.28, 8.06 Hz, 0.76H), 5.69 (ddd, J = 17.16, 10.09, 8.79 Hz, 0.24H), 5.06–4.94 (m, 2H), 2.76–2.28 (m, 2H), 1.90–1.00 (m, 18H); ^{13}C-NMR (90 MHz, $CDCl_3$) δ 181.433, 181.366, 139.767, 139.446, 115.305, 114.878, 45.783, 43.938, 43.750, 29.951, 29.063, 28.790, 27.597, 26.642, 26.411, 26.276, 26.074, 25.764, 25.535, 25.435, 25.269, 24.395, 23.798, 23.124, 22.905; MS *m/z* (rel. int.) M^+ 224 (3.32), 195 (3.16), 164 (2.85), 149 (9.12), 125 (19.15), 123 (14.39), 112 (16.06), 110 (10.23), 99 (24.33), 95 (64.69). Exact mass calc for $C_{14}H_{24}O_2$ (M^+): 224.1766; found: 224.1763.

trans-2-*Ethenylcycloheptanecarboxylic acid* (**14**) *and* cis-2-*ethenylcycloheptanecarboxylic acid* (**8c**). Lactone **13** (50 mg, 0.27 mmol) was silylated to give 60.2 mg (79%) of the silyl ester, which was hydrolyzed in quantitative yield affording an oil, which was a mixture of two compounds. R_f = 0.15, 0.26 (EtOAc–hexanes, 1:9). ^{1}H-NMR (90 MHz, $CDCl_3$) δ 5.83 (ddd, J = 16.5, 9.6, 7.8 Hz, 0.41H), 5.70 (ddd, J = 17.4, 9.6, 7.2 Hz, 0.59H), 5.13–4.77 (m, 2H), 2.90–2.17 (m, 2H), 2.05–1.13 (m, 10H); ^{13}C-NMR (25.2 MHz, $CDCl_3$) δ 182.065, 142.080, 113.409, 50.907, 45.867, 32.787, 29.878, 28.584, 26.203, 25.775, those resonances of **8c** previously reported; relative intensities of comparable resonances were found to be in a ratio of 41:59 **8c**:**14**, respectively. IR (neat) and mass spectra were identical to those reported for **8c**.

(1*R**,2*S**,5*S**)-5-*Methyl*-2-(*methylethenyl*)*cyclopentanecarboxylic acid* (**19**). Lactone **18** (204 mg, 1.21 mmol) was silylated and warmed slowly to room temp over 4 h. The isolated silyl ester (341 mg, 1.14 mmol) was hydrolyzed to afford 133 mg (71%) of an oil. R_f 0.29 (EtOAc–hexanes, 1:9). IR (neat) 3500–2500, 2960, 2865, 1710, 1450, 1375, 1220, 890 cm^{-1}; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 8.72 (br s, 1H), 4.71 (br s, 2H), 2.9–1.8 (m, 6H), 1.68 (br s, 3H), 1.25 (m, 1H), 1.02 (d, J = 6 Hz, 3H); ^{13}C-NMR (90 MHz, $CDCl_3$) δ 180.705, 144.915, 111.112, 55.735, 49.937, 37.084, 33.793, 29.847, 22.778, 21.298; MS *m/z* (rel. int.) M^+ 168 (6.82), 123 (55.01), 113 (17.85), 108 (13.21), 100 (31.08), 93 (16.71), 87 (23.49), 81 (48.41), 69 (100), 55 (20.40). Exact mass calc for $C_{10}H_{16}O_2$ (M^+): 168.1151; found: 168.1149.

4-*Methyl*-2-(*methylethenyl*)*cyclopentanecarboxylic acids* **24** *and* **25**. To a soln of lithium hexamethyldisilazide (0.71 mmol) (prepared from n-BuLi and hexamethyldisilazane at 0° in THF) and t-butyldimethylsilyl chloride (107 mg, 0.71 mmol) chilled to −78° was added **23** (100 mg, 0.59 mmol) dropwise as a soln in THF (1 ml). The soln was stirred at −78° for 1 h and then allowed to warm to 0° over 2 h. The reaction was quenched by partitioning between H_2O and Et_2O. The two phases were separated and the aq phase was extracted twice with Et_2O and the combined organic layers were dried (Na_2SO_4). The solvents were removed *in vacuo* to provide 159 mg of a clear oil. R_f 0.27 (EtOAc–hexanes, 1:49). The crude product was diluted with THF (1 ml) and 3 N HCl (0.1 ml) added. The soln was stirred at 25° for 1 h. Standard extractive workup provided 76 mg (76%) of a colorless viscous oil. HPLC on a 5μ ALTEX cyano column (1:24 isopropanol–hexanes), retention time of 5 min at a flow rate of 3 ml min^{-1} provided 46 mg of a clear oil. IR (neat) 3600–2500, 3090, 2960, 2880, 1710, 1650, 1460, 1430, 1375, 1228, 890 cm^{-1}; ^{1}H-NMR (360 MHz, $CDCl_3$) δ 4.82 (br s, 1H), 4.78 (br s, 1H), 3.08 (m, 1H), 2.75 (m, 1H), 2.15 (dd, J = 21, 8.34 Hz, 1H), 2.08–1.95 (m, 1H), 1.84–1.76 (m, 2H), 1.78 (br s, 3H), [1.11 (d, J = 6.5 Hz), 1.02 (d, J = 6.5 Hz), 9:1, 3H]; MS *m/z* (rel. int.) M^+ 168 (5), 153 (6), 125 (50), 123 (41), 108 (24), 107 (20), 100 (12), 96 (27), 95 (11), 93 (15), 81 (100). Exact mass calc for $C_{10}H_{16}O_2$ (M^+): 168.1150; found: 168.1155.

5-*Methyl*-2-*ethenylcyclohexanecarboxylic acids* **28a,b**. Lactone **26** (65 mg, 0.39 mmol) was silylated as described in Ref. 6 (*vide supra*). The mixture was then warmed to −30° and stirred at this temp for 2 h. Standard workup followed by hydrolysis with HF as described previously gave 26 mg (43%) of a viscous oil. IR (neat) 3500–2600, 3070, 2940, 2920, 2860, 1705, 1640, 1455, 1415, 1375, 1340, 1270, 1230, 1180, 1125, 990, 910 cm^{-1}; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 11.0 (br s, 1H), 5.9 (ddd, J = 17.4, 10.2, 8.7 Hz, 1H), 5.05 (ddd, J = 17.4, 1.8, 0.9 Hz, 1H), 4.97 (ddd, J = 10.2, 1.2, 0.9 Hz, 1H), 3.0–2.42 (m, 2H), 1.98–1.1 (m, 7H), [0.98 (d, J = 6 Hz), 0.94 (d, J = 6 Hz), 3:2, 3H]; MS *m/z* (rel. int.) M^+ 168 (3), 150 (7), 139 (10), 125 (19), 123 (82), 122 (39), 108 (16), 107 (15), 99 (18), 96 (16), 95 (50), 93 (54), 91 (13), 81 (97), 79 (30). Exact mass calc for $C_{10}H_{16}O_2$ (M^+): 168.1150; found: 168.1146.

To a soln of **28a,b** in Et_2O (1 ml) was added ethereal diazomethane until a yellow color remained. R_f 0.53, 0.62 (EtOAc–hexanes, 1:9). IR (neat) 3080, 2940, 2920, 2850, 1735, 1640, 1570, 1450, 1435, 1380, 1265, 1200, 1160, 1040, 1000, 915 cm^{-1}; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 5.9 (ddd, J = 18, 10, 7 Hz, 1H), 4.95 (ddd, J = 18, 3, 1 Hz, 1H), 4.91 (ddd, J = 10, 3, 1 Hz, 1H), 3.58 (s, 3H), 2.98–2.4 (m, 2H), 2.0–1.1 (m, 7H), [0.95 (d, J = 6 Hz), 0.9 (d, J = 6 Hz), 3:2, 3H]; MS *m/z* (rel. int.) M^+ 182 (5), 167 (2), 151 (7), 150 (14), 139 (9), 127 (4), 126 (5), 124 (7), 123 (72), 122 (65), 113 (5), 108 (14), 107 (19), 96 (7), 95 (29), 94 (16), 93 (53), 91 (12), 87 (22), 81 (100), 80 (14), 79 (35), 77 (16), 69 (18), 67 (54). Exact mass calc for $C_{11}H_{18}O_2$ (M^+): 182.1306; found: 182.1303. The ratio of the esters was found to be 44:56, respectively, as determined by integration of GLC peaks (column A, temp 140°, retention times 12 and 12.6 min, respectively).

(1*S**,2*S**,5*R**)-1,5-*Dimethyl*-2-*ethenyl*-1-*cyclohexanecarboxylic acid* (**28d**). Lactone **27** (95.0 mg, 0.52 mmol) was silylated as described in Ref. 6 (*vide supra*). Standard workup and hydrolysis as described above gave 38 mg (40%) of fine, white crystals, m.p. 97–98°. IR ($CHCl_3$) 3500–2600, 3080, 3030, 2990, 2960, 2940, 2870, 1705, 1635, 1465, 1445, 1420, 1400, 1380, 1280, 1225, 1130, 990, 920 cm^{-1}; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 5.98 (ddd, J = 17.4, 10.2, 8.4 Hz, 1H), 5.0 (ddd, J = 17.4, 1.2, 0.6 Hz, 1H), 4.98 (ddd, J = 8.4, 1.2, 0.6 Hz, 1H), 2.5–2.3 (m, 1H), 2.1–1.12 (m, 7H), 1.32 (s, 3H), 0.92 (d, J = 6 Hz, 3H); MS *m/z* (rel. int.) M^+ 182 (4), 167 (11), 153 (9), 138 (10), 137 (100), 136 (23), 126 (6), 125 (6), 122 (9), 115 (7), 110 (10), 109 (24), 108 (13), 107 (12), 96 (31), 95 (47), 93 (12), 87 (29), 83 (19), 82 (14), 81 (60), 79 (14), 69 (26), 68 (16), 67 (33), 55 (53), 54 (38). Exact mass calc for $C_{11}H_{18}O_2$ (M^+): 182.1306; found: 182.1306.

To a soln of **28d** in Et_2O (1 ml) was added excess ethereal diazomethane. Evaporation of the solvent *in vacuo* provided a clear oil, methyl(1*S**,2*S**,5*R**)-1,5-dimethyl-2-ethenylcyclohexanecarboxylate. R_f 0.43 (EtOAc–hexanes, 1:9). IR (neat) 2940, 2920, 2850, 1735, 1455, 1370, 1250, 1215, 1110, 1010 cm^{-1}; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 5.95 (ddd, J = 18, 10.8, 9.0 Hz, 1H), 4.96 (ddd, J = 18, 1.8, 0.6 Hz, 1H), 4.92 (ddd, J = 10.8, 2.4, 0.6 Hz, 1H), 3.58 (s, 3H), 2.5–2.2 (m, 1H), 2.0–1.1 (m, 7H), 1.3 (s, 3H), 0.9 (d, J = 6 Hz, 3H); ^{13}C-NMR (90 MHz, $CDCl_3$) δ 177.876, 138.852, 115.635, 51.354, 46.248, 45.691, 37.211, 29.714, 29.368, 27.287, 26.931, 22.752; MS *m/z* (rel. int.) $M^+ - CO_2Me$ 137 (17), 136 (8), 125 (10), 123 (13), 119 (13), 111 (18), 109 (17), 97 (31), 96 (11), 95 (28), 91 (14), 87 (11), 85 (32), 83 (36), 82 (14), 81 (37), 71 (50), 70 (18), 69 (59), 67 (19), 57 (100), 56 (28), 55 (54). Exact mass calc for $C_{10}H_{17}$ ($M^+ - CO_2Me$): 137.1330; found: 137.1326.

Dimethyl (1R,2S*,5R*) - 5 - methyl - cyclohexane - 1,2 - dicarboxylate* (**30**). Subjection of the methyl-2-ethenyl-5-methylcyclohexanoates of **28a,b** (47 mg, 0.26 mmol) to Sharpless oxidation using RuO_4 provided the corresponding carboxylic acids. The methyl esters were prepared by reaction with ethereal diazomethane. R_f 0.23 (EtOAc–hexanes, 1:9). IR (neat) 3000, 2950, 2860, 1735, 1650, 1440, 1375, 1360, 1335, 1300, 1265, 1200, 1160, 1130, 1085, 1060, 1015, 995, 970, 950, 905, 890, 845, 825, 800, 770, 755, 730 cm^{-1}; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 3.68 (s, 6H), 3.3–3.1 (m, 2H), 2.5–1.1 (m, 7H) [0.98 (d, J = 6 Hz), 0.90 (d, J = 6 Hz), 56:44, 3H]; MS *m/z* (rel. int.) M^+ 214 (0.7), 183 (35), 182 (21), 154 (54), 123 (24), 122 (42), 96 (14), 95 (100), 94 (79), 81 (33), 79 (29), 67 (27), 59 (23). Exact mass calc for $C_{11}H_{18}O_4$ (M^+): 214.1205; found: 214.1201. ^{13}C-NMR (90.6 MHz, $CDCl_3$) δ 51.590, 51.511, 43.586, 43.243, 41.667, 40.959, 36.213, 33.812, 32.327, 32.006, 30.560, 28.094, 28.055, 23.948, 22.213, 21.898. An authentic sample of the major isomer was prepared in 3 steps: (a) Diels–Alder reaction of isoprene and maleic anhydride;† (b) atmospheric hydrogenation in EtOAc using Pd/C; (c) hydrolysis of the anhydride with MeOH and catalytic CF_3CO_2H. ^{1}H-NMR (90 MHz, $CDCl_3$) δ 3.65 (s, 3H), 3.62 (s, 3H), 3.22 (m, 2H), 2.5–1.1 (m, 7H), 0.98 (d, J = 6 Hz, 3H); ^{13}C-NMR (90.6 MHz, $CDCl_3$) δ 174.185, 173.71, 51.594, 51.494, 43.563, 40.960, 32.341, 31.990, 30.575, 28.027, 22.219.

4 - [N - (Z) - 4 - Tetrahydropyranyloxy - 2 - butenylbenzamido]butanoic acid. NaH (1.71 g of a 50% dispersion in mineral oil, 35.6 mmol) was placed in a dry 250 ml round-bottomed flask equipped with a magnetic stir bar and the mineral oil was removed by washing with dry hexanes and decanting the organic phase (3 × 20 ml). NaH was suspended in 75 ml of dry DMF and the reaction mixture cooled to 0–5°. To this rapidly stirring mixture was added a soln of **31** (3.36 g, 16.2 mmol) in DMF (15 ml) dropwise over 15 min. After 30 min the H_2 gas evolution ceased, the mixture was warmed to room temp briefly and recooled to 0–5°. A soln of freshly chromatographed (*Z*)-**32** (3.70 g, 19.44 mmol) in DMF (10 ml) was added quickly at 0–5° and the resultant suspension was allowed to warm to room temp. After 5.5 h at room temp, the mixture was partitioned between Et_2O (200 ml) and H_2O (100 ml). The separated organic layer was extracted with sat $NaHCO_3$ aq (50 ml), and the combined aq layers were neutralized with conc HCl, saturated with NaCl, and extracted with Et_2O (4 × 150 ml). The combined organic layers were dried ($MgSO_4$) and solvents were removed *in vacuo* to give an oil, which was judged to be the alkylated product mixed with a small amount of DMF. The total yield was 4.75 g, of which *ca* 3.92 g (67%) was the alkylated product. Although purification by chromatography could be effected using silica gel and isopropyl alcohol–hexanes (1:5), it was more convenient to take the mixture on to the next step and purify. For spectral analysis, 116 mg was chromatographed using isopropanol–hexanes (1:4) as eluent to afford 91 mg of an oil. IR (film) 3700–2350, 3010, 2940, 2880, 1725, 1630, 1612, 1600, 1575, 1495, 1440, 1260, 1200, 1180, 1130, 1115, 1070, 1020, 970, 900, 865, 785, 695 cm^{-1}; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 10.05–9.32 (br s, 1H), 7.30 (s, 5H), 5.90–5.27 (br m, 2H), 4.53 (br s, 1H), 4.37–3.11 (br m, 8H), 2.53–2.00 (br m, 2H), 2.00–1.73 (br m, 2H), 1.73–1.37 (br m, 6H).

4 - [N - (Z) - 4 - Hydroxy - 2 - butenylbenzamido]butanoic acid (**33**). Into a 100 ml round-bottomed flask equipped with a magnetic stir bar and reflux condenser was placed the 4 - [N - (*Z*) - 4 - tetrahydropyranyloxy - 2 - butenyl - benzamido]butanoic acid (3.75 g, 10.38 mmol) and MeOH (50 ml) added. To this soln was added pyridinium *p*-toluenesulfonate (261 mg, 1.04 mmol) and the soln set to reflux for 4 h. The mixture was cooled, and the MeOH removed *in vacuo*. The residue was taken up in Et_2O (500 ml) and washed with half sat brine (50 ml), brine (50 ml) and dried ($MgSO_4$). The solvents were removed *in vacuo* and the residue was kept under vacuum (0.01 mmHg) for 12 h, which gave an oil, yield 2.65 g (92%). IR (film) 3650–2360, 3020, 2920, 1720, 1610, 1600, 1570, 1500, 1460, 1430, 1260, 1140, 1025, 785, 695 cm^{-1}; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 8.05–7.60 (br s, 2H), 7.30 (s, 5H), 5.97–5.17 (br m, 2H), 4.37–3.67 (br m, 4H), 3.65–3.03 (br m, 2H), 2.51–2.05 (br m, 2H), 2.05–1.62 (br m, 2H).

4 - [N - (Z) - 4 - Hydroxy - 2 - butenylbenzamido]butanoic acid lactone (**34**). Hydroxy acid **33** (1.146 g, 4.13 mmol) was lactonized using the standard conditions described previously to afford 784.5 mg (73%) of a clear yellow oil. R_f 0.64 (EtOAc–hexanes, 7:3). IR (film) 3055, 3025, 2930, 2870, 1748, 1635, 1572, 1490, 1443, 1428, 1395, 1375, 1325, 1280, 1240, 1195, 1157, 1135, 1080, 1055, 1031, 1024, 790, 719, 695, 655 cm^{-1}; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 7.33 (br s, 5H), 5.90–5.43 (m, 2H), 4.67 (m, 2H), 4.11 (br d, J = 7.5 Hz, 2H), 3.26 (br t, J = 5.0 Hz, 2H), 2.50–2.27 (m, 2H), 2.13–1.83 (m, 2H); MS *m/z* (rel. int.) M^+ 259 (0.21), 216 (1.74), 215 (11.27), 214 (2.10), 187 (3.81), 186 (3.54), 159 (1.00), 158 (2.01), 105 (100.0), 82 (1.28), 78 (2.38), 77 (25.48), 74 (6.32), 69 (1.22), 59 (9.42), 55 (1.27), 54 (1.23), 51 (3.80). Exact mass calc for $C_{15}H_{17}O_3N$ (M^+): 259.1209; found: 259.1200. (Found: C, 69.36; H, 6.79; N, 5.49. Calc for $C_{15}H_{17}O_3N$: C, 69.48; H, 6.61; N, 5.41%.)

(±) - cis - N - Benzoyl - 3 - ethenyl - 4 - piperidinecarboxylic acid (**36**). Lactone **34** (136 mg, 0.525 mmol) was silylated as described in Ref. 6 to afford 182 mg (93%) of a clear oil. ^{1}H-NMR (90 MHz, $CDCl_3$) δ 7.27 (br s, 5H), 5.77 (ddd, J = 17.2, 10.4, 7.6 Hz, 1H), 5.23–4.87 (m, 2H), 4.37–3.69 (br m, 2H), 3.37–2.52 (m, 4H), 2.13–1.57 (m, 2H), 0.93 (s, 9H), 0.25 (s, 6H). This silyl ester (153 mg, 0.41 mmol) was hydrolyzed with HF as described above to afford 99 mg of a clear oil. Subjection of this compound to HPLC purification and analysis (Beckman–Altex Ultrasphere Cyano HPLC column, dp 5, i.d. 10 mm × 25 cm, using isopropyl alcohol–hexanes, 1:19, operating at 5 ml min^{-1} flow rate) gave a single compound (retention time = 15.4 min), yield 98 mg (92%), which crystallized upon standing, m.p. 48–49°. IR (film): 3650–2850, 3040, 3025, 2995, 2925, 2855, 1720, 1595, 1575, 1465, 1450, 1305, 1255, 1180, 1018, 915, 785, 730 cm^{-1}; ^{1}H-NMR (360 MHz, $CDCl_3$, 22°) δ 7.39 (br s, 5H), 5.84 (ddd, J = 17.13, 10.23, 8.11 Hz, 1H), 5.41–4.96 (br m, 2H), 4.62–4.28 (br m, 1H), 3.87–3.65 (br s, 1H), 3.36 (br d, J = 12.4 Hz, 1H), 3.36–3.08 (br m, 1H), 3.05–2.62 (br m, 2H), 2.14–1.66 (br m, 2H); ^{1}H-NMR (360 MHz, $CDCl_3$, 60°) δ 7.39 (br s, 5H), 5.85 (ddd, J = 17.21, 10.38, 7.65 Hz, 1H), 5.25–5.07 (m, 2H), 4.44–3.73 (m, 2H), 3.41 (dd, J = 13.12, 2.56 Hz, 1H), 3.26 (br t, J = 8.81 Hz, 1H), 2.90–2.75 (m, 2H), 2.04–1.89 (m, 1H), 1.88–1.74 (m, 1H); ^{13}C-NMR (50.31 MHz, $CDCl_3$, 50°) δ 177.11, 171.11, 135.86, 134.59, 129.66, 128.41, 126.96, 118.04, 44.46, 40.90, 24.33; MS *m/z* (rel. int.) M^+ 259 (2.69), 218 (2.39), 154 (2.73), 122 (2.93), 106 (4.11), 105 (60.22), 77 (17.87), 51 (2.89), 40 (7.89). Exact mass calc for $C_{15}H_{17}O_3N$ (M^+): 259.1209; found: 259.1216. (Found: C, 69.40, H, 6.74; N, 5.27. Calc for $C_{15}H_{17}O_3N$: C, 69.48; H, 6.61; N, 5.41%.)

(±) - cis - N - Benzoyl - 3 - ethenyl - 4 - piperidine diazomethyl ketone. To a dry, 50 ml round-bottomed flask equipped with a magnetic stir bar was placed NaH (21.1 mg of a 50% dispersion in mineral oil, 0.44 mmol) and dry C_6H_6 (5 ml). To this suspension was added (±) - *cis* - N - benzoyl - 3 - ethenyl - 4 - piperidinecarboxylic acid (104 mg, 0.40 mmol) in C_6H_6 (10 ml) and the mixture was stirred until H_2 gas evolution stopped. The resulting suspension was cooled to 5° and oxalyl chloride (127 mg, 1.0 mmol) added and the rapidly stirring suspension allowed to warm slowly to room temp over 30 min. The C_6H_6 soln was decanted from the ppt formed during the reaction, and the ppt washed with C_6H_6 (2 × 20 ml). The combined organic phases were placed in a 100 ml round-bottomed flask and the C_6H_6 removed by distillation under N_2 to ensure dryness of the acid chloride intermediate. The acid chloride was dissolved in dry Et_2O (15 ml), and the resulting soln was added dropwise to a cold (0–5°), stirring soln of diazomethane in Et_2O (previously dried over KOH pellets followed by drying over Na metal, 15 mmol). The resulting yellow soln was stirred for 1 h at 0–5° and the excess diazomethane removed *in vacuo*. The residue was taken up in Et_2O (100 ml), washed with H_2O (20 ml), brine, dried (Na_2SO_4), and the solvents were removed to give 94.5 mg (83%) of a yellow oil. IR (film) 3060, 2920,

† Compound **29** was kindly produced by Professor D. M. S. Wheeler at the University of Nebraska.

2840, 2092, 1628, 1440, 1340, 1145, 1005, 915, 780, 725, 700 cm^{-1}; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 7.37 (s, 5H), 5.98–5.53 (m, 1H), 5.23 (s, 1H), 5.30–4.90 (m, 2H), 4.37–3.05 (br m, 4H), 2.87–2.46 (br m, 2H), 2.13–1.54 (br m, 2H).

(±)-N-*Benzoylmeroquinene methyl ester* (**37**). The crude diazoketone (90.0 mg, 0.318 mmol) was dissolved in MeOH (20 ml) and to this soln was added a suspension of Ag benzoate (1.0 g, 4.37 mmol, previously dried at 25°, 0.01 mmHg, 12 h) and Et_3N (10 ml, 71.7 mmol) and the resultant soln stirred at room temp for 6 h. The mixture was poured into CH_2Cl_2 (100 ml) and washed with 10% HCl aq (2 × 20 ml), H_2O (20 ml), sat $NaHCO_3$ aq (2 × 20 ml), brine, and dried ($MgSO_4$). Evaporation of the solvents gave 75 mg of an oil, which was purified by HPLC (Beckman–Altex Ultrasphere Cyano HPLC column, dp 5, i.d. 10 mm × 25 cm, using isopropyl alcohol–hexanes, 1:9, flow rate 4 ml min^{-1}, retention time 10.5 min) to give 70.5 mg (77%) of a clear oil. IR (film) 3050, 2990, 2920, 2845, 1732, 1630, 1575, 1492, 1435, 1365, 1310, 1290, 1260, 1200, 1165, 1140, 1070, 1005, 920, 785, 725, 695 cm^{-1}; ^{1}H-NMR (360 MHz, $CDCl_3$) δ 7.37 (s, 5H), 5.83 (ddd, J = 16.50, 10.43, 8.48 Hz, 1H), 5.25–4.86 (br m, 2H), 4.74–4.40 (br m, 1H), 3.67 (s, 3H), 3.44–2.76 (br m, 2H), 2.59–2.07 (br m, 5H), 1.87–1.34 (br m, 2H); ^{13}C-NMR (50.31 MHz, $CDCl_3$, 50°) δ 172.76, 170.86, 136.21, 134.51, 129.41, 128.28, 126.97, 118.24, 51.41, 42.67, 37.26, 35.69, 27.51; MS *m/z* (rel. int.) M^+ 287 (3.61), 286 (4.05), 246 (2.19), 214 (4.99), 182 (10.59), 168 (2.56), 148 (1.85), 134 (1.36), 105 (100.0), 82 (1.02), 77 (23.98), 51 (1.87). Exact mass calc for $C_{15}H_{17}O_3N$ (M^+): 287.1521; found: 287.1517. These spectral data were identical to those obtained from an authentic sample provided by Dr M. Uskoković. In addition, mobilities on TLC plates were compared and found to be identical for the following solvent systems: EtOAc–hexanes, 1:1, R_f 0.35; Et_2O, R_f 0.56; isopropyl alcohol–hexanes, 1:9, R_f 0.40.

(±)-*Methyl* cis - N - *benzoyl* - 3 - *ethenyl* - 4 - *piperidine carboxylate*. To the crude hydrolysis product (±) - *cis* - N - benzoyl - 3 - ethenyl - 4 - piperidinecarboxylic acid (97 mg) was added dry Et_2O (5 ml) and the mixture was cooled to 0° and a soln of diazomethane in Et_2O (*ca* 1 M in Et_2O, 5 ml) was added dropwise and stirred for 30 min. The excess diazomethane was removed *in vacuo* and the residue passed through a short plug of silica gel and subjected to HPLC analysis and purification (Beckman–Altex Ultrasphere-Si column, dp 5, i.d. 10 mm × 25 cm, elution with 1:1 EtOAc–hexanes). The minor fraction (retention time 1.25 min) gave 17.5 mg of t-butyl dimethylsilanol. The major fraction (retention time 5.44 min) afforded 68.5 mg of an oil. IR (film) 3060, 3000, 2940, 2845, 1732, 1630, 1575, 1490, 1430, 1370, 1325, 1305, 1250, 1190, 1170, 1150, 1045, 1015, 995, 920, 782, 700 cm^{-1}; ^{1}H-NMR (360 MHz, $CDCl_3$) δ 7.38 (br s, 5H), 5.83 (ddd, J = 17.21, 10.47, 7.93 Hz, 1H), 5.33–4.94 (m, 2H), 4.60–4.31 (m, 1H), 3.92–3.73 (m, 1H), 3.63 (s, 3H), 3.49–3.16 (m, 2H), 3.02–2.68 (m, 2H), 2.18–1.54 (m, 2H).

Acknowledgements—We appreciate the financial and material support provided by the National Institutes of Health (Grant No. BM2866301). High-field (360 MHz) ^{1}H- and ^{13}C-NMR spectra were obtained on a spectrometer purchased with funds provided, in part, by the National Science Foundation (Grant No. CHE-80-24328). Mass spectra were obtained through the National Science Foundation Regional Mass Spectroscopy Center at the University of Nebraska (Grant No. CHE-82-11164). We also thank Professor Wolinsky, Purdue University, for spectra of (±)-dihydronepetalactone (**20a**), and Dr Uskoković of Hoffmann–La Roche Inc. for an authentic sample of N-benzoyl meroquinene methyl ester (**37**).

Note added in proof—The stereochemical assignments for cyclopentanecarboxylic acids **24** and **25** have been confirmed by an independent synthesis. Thus, subjection of 3-isobutoxy-2-cyclopenten-1-one to the following synthetic sequence: 1. 2LDA; 2. $CH_2C(CH_2Cl)_2$; 3. $CoCl_2$, $NaBH_4$; 4. MeLi; 5. H_3O^+; 6. $RuCl_3$, $NaIO_4$; 7. CH_2N_2 afforded the all-*cis* isomer of methyl 2-(1-oxoethyl)-4-methylcyclopentanecarboxylate as the major product. This compound was identical to the major product obtained from the treatment of the mixture of acids **24** and **25** with 1. CH_2N_2; 2. O_3, Me_2S.

REFERENCES

[1a] J. P. Shaefer and J. J. Bloomfield, *Org. React.* (*N.Y.*) **15**, 1 (1967); [b] J. J. Bloomfield, D. C. Owsley and J. M. Nelke, *Org. React.* (*N.Y.*) **23**, 259 (1976); [c] P. R. Story and P. Busch, *Adv. Org. Chem.* **8**, 67 (1972); [d] J. E. McMurry, *Accts Chem. Res.* **16**, 405 (1983); [e] A. Maercker, *Org. React.* (*N.Y.*) **14**, 270 (1965); K. B. Becker, *Tetrahedron* **36**, 1717 (1980).

[2] For a preliminary account of this work, see: [a] M. M. Abelman, R. L. Funk and J. D. Munger Jr., *J. Am. Chem. Soc.* **104**, 4030 (1982); [b] R. L. Funk and J. D. Munger Jr., *J. Org. Chem.* **49**, 4319 (1984); [c] R. L. Funk and J. D. Munger Jr., *J. Org. Chem.* **50**, 707 (1985).

[3] For reviews on the Claisen rearrangement, see: [a] S. J. Rhoads and N. R. Raulins, *Org. React.* (*N.Y.*) **22**, 1 (1975); [b] F. Ziegler, *Accts Chem. Res.* **10**, 227 (1977); [c] G. B. Bennett, *Synthesis* 589 (1977).

[4a] S. Danishefsky, R. L. Funk and J. R. Kerwin Jr., *J. Am. Chem. Soc.* **102**, 6889 (1980); [b] S. Danishefsky and K. Tsuzuki, *Ibid.* **102**, 6891 (1980). For recent exploitation of this methodology, see: [c] M. J. Begley, A. G. Cameron and D. W. Knight, *J. Chem. Soc. Chem. Commun.* 827 (1984); [d] R. K. Brunner and H.-J. Borschber, *Helv. Chim. Acta* **66**, 2608 (1983); [e] S. D. Burke, D. M. Armistead and F. J. Schoenen, *J. Org. Chem.* 4320 (1984); [f] S. D. Burke, D. M. Armistead and J. M. Fevig, *Tetrahedron Lett.* **26**, 1163 (1985).

[5a] L. A. Paquette, J. A. Colapret, D. R. Andrews, *J. Org. Chem.* **50**, 201 (1985); [b] W. C. Still, *J. Am. Chem. Soc.* **101**, 2493 (1979); [c] S. L. Schreiber and C. Sautini, *J. Am. Chem. Soc.* **106**, 4038 (1984).

[6] R. E. Ireland, R. H. Mueller and A. K. Willard, *J. Am. Chem. Soc.* **98**, 2868 (1976).

[7] S. J. Rhoads, R. D. Cockroft, *J. Am. Chem. Soc.* **91**, 3126 (1969).

[8] For a review on the preparation of macrolides, see: [a] T. Mukaiyama, *Angew. Chem. Int. Ed. Engl.* **18**, 707 (1979); [b] K. C. Nicolaou, *Tetrahedron* **33**, 683 (1977); [c] S. Masamune, G. S. Bates and J. W. Corcoran, *Angew. Chem. Int. Ed. Engl.* **16**, 585 (1977). For alternative ways to prepare macrolides, see: [d] R. G. Carlson, J. H.-A. Huber and D. E. Henton, *J. Chem. Soc. Chem. Commun.* 223 (1973); [e] R. C. Cookson and V. Bhat, *J. Chem. Soc. Chem. Commun.* 1123 (1981); [f] R. C. Cookson and P. S. Ray, *Tetrahedron Lett.* **23**, 3521 (1982); [g] K. Kostova and M. Hesse, *Helv. Chim. Acta* **66**, 741 (1983); [h] Y. Nakashita and M. Hesse, *Ibid.* **66**, 845 (1983); [i] N. Ono, H. Miyake and A. Kaji, *J. Org. Chem.* **49**, 4997 (1984); [j] E. Vedejs, *Accts Chem. Res.* **17**, 358 (1984); [k] E. J. Corey, D. J. Brunelle and K. C. Nicolaou, *J. Am. Chem. Soc.* **99**, 7359 (1977); [l] A. Escheumoser, M. Shibuya and F. Jaisli, *Angew. Chem. Int. Ed. Engl.* **18**, 636 (1979); [m] S. L. Schreiber and W.-F. Liew, *J. Am. Chem. Soc.* **107**, 2950 (1985) and refs cited therein.

[9] For a definition of this term, see: P. A. Bartlett, *Tetrahedron* **36**, 2 (1980).

[10] T. Mukaiyama, M. Usui and K. Saigo, *Chem. Lett.* 49 (1976).

[11] W. C. Still and I. Galynker, *Tetrahedron* **37**, 3981 (1981).

[12] D. E. Ames, A. N. Covell and T. G. Goodburn, *J. Chem. Soc.* 5889 (1963).

[13] P. H. J. Carlsen, R. Katsuki, V. S. Martin and K. B. Sharpless, *J. Org. Chem.* **46**, 3936 (1981).

[14] D. E. James and J. K. Stille, *J. Org. Chem.* **46**, 3936 (1981).

[15a] J. Wolinsky, D. Dickerson, M. Slabaugh, D. Nelson, T. Sakan, S. Isoe, S. B. Hyeas and R. Katsumura, *Tetrahedron Lett.* **46**, 4097 (1965); [b] I. Fleming and N. K. Terrett, *Tetrahedron Lett.* 5103 (1984); [c] J. Wolinsky and E. J. Eustace, *J. Org. Chem.* **37**, 3376 (1972).

[16] Authentic spectra were kindly provided by Professor J.

Wolinsky of Purdue University. Acid **19a** was also converted to the Wolinsky iridomyrmecin synthetic intermediate [1. LAH; 2. Ac_2O, Pyr]. For details, see: J. Wolinsky, T. Gibson, D. Chan and H. Wolf, *Tetrahedron* **21**, 1247 (1965).

[17] N. L. Allinger, *J. Am. Chem. Soc.* **99**, 8127 (1977).

[18a] J. J. Gajewski, *Accts Chem. Res.* **13**, 142 (1980); [b] J. J. Gajewski and J. Emrani, *J. Am. Chem. Soc.* **106**, 5733 (1984).

[19] W. C. Still, K. P. Darst and C. Sreekamar, *J. Org. Chem.* **45**, 4260 (1980).

[20] For the synthesis of **37**, see the elegant work of the Hoffmann-La Roche group; M. R. Uskoković, T. Henderson, C. Reese, H. L. Lee, G. Grethe and J. Gutzwiller, *J. Am. Chem. Soc.* **100**, 571 (1978).

[21a] R. E. Steiger, *J. Org. Chem.* **9**, 396 (1944); [b] D. T. Elmore and J. R. Ogle, *J. Chem. Soc.* 1141 (1958).

[22] G. E. Keck, E. Boden and U. Sonnewald, *Tetrahedron Lett.* **22**, 2615 (1981).

[23a] M. S. Newman and P. F. Beal III, *J. Am. Chem. Soc.* **72**, 63 (1950); [b] T. Hudlicky and J. P. Sheth, *Tetrahedron Lett.* 2667 (1979).

[24] J. G. Duboudin, B. Jousseaume, A. Bonakdar and A. Saux, *J. Organometal. Chem.* **168**, 227 (1979).

[25] M. Miyashita, A. Yoshikoshi and P. A. Grieco, *J. Org. Chem.* **42**, 3773 (1977).

[26] E. J. Corey, D. Floyd and B. H. Lipshutz, *J. Org. Chem.* **43**, 3418 (1978).

[27] J. Gootjes and W. Th. Nauta, *Rec. Trav. Chim.* **84**, 1427 (1965).