CLAISEN-REARRANGEMENT-MEDIATED RING CONTRACTION OF MACROCYCLIC LACTONES

A NEW APPROACH TO CARBOCYCLES AND HETEROCYCLES

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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-benzoylmethreoquinine 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 Dieckmann cyclization, 15 acyloin condensation, 16 Story synthesis, 12 titanium-induced dicarbonyl-coupling reactions, 14 intramolecular Wittig-type reactions, 17 among others, come close to fulfilling this goal. Unfortunately, the potential for introducing asymmetric 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 1 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 1 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 46, 46 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 4b, 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 = CH2). 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, cis-d-ester 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. 5c, 5d In addition, many alternative synthetic routes to macrolides had been developed, for example, ring expansion of cycloalkanones, 5b, 8a transacylation reactions, 8b, 8c and fragmentation reactions. 8a

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 of this reaction, that is, the stereo-relationship of the carboxyl and vinyl moieties as they emerge on the newly created hetero- or carbocycles. This stereocorelationship is of course a function of the ketene acetal and olefin stereochemistries as well as the
conformation of the transition state. Subsequent to these studies, the relative asymmetric induction 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 α-hydroxy acids using the Mukaiyama reagent (2-chloro-1-methylpyridinium iodide). It was hoped that the cis double bond in 6 would facilitate the lactonization reaction by removing potential transannular interactions in the resulting macrocycles 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 and other procedures for the saturated nine-membered lactone. The requisite hydroxy acids were prepared according to previously reported procedures.

We were pleased to discover that the ketene acetals prepared from the lactone 7a-c enolates, using the standard procedure, rearranged smoothly before or during workup to the corresponding silyl esters, which were then hydrolyzed with HF (2 equiv) in CH3CN. The remarkable ease of these rearrangements is noteworthy. For example, the ketene acetal derived from lactone 7a rearranged at -60°C (t1/2 ≈ 57 h). However, the large ring ketene acetals prepared from lactones 7d and 7e required heating in toluene at 110°C (t1/2 ≈ 6 h) and 80°C (t1/2 ≈ 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, stereoselective kinetic alkylations of similar nine- and thirteen-membered lactone enolates, 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. The vinyl proton and alkoxymethylene proton resonances (360 MHz 1H-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.

The fact that only one ketene acetal is produced from these lactones is responsible, to a large degree, for the high stereoselectivity of the Claisen rearrangements. The product stereochemical integrity for cycloalkanecarboxylic acids 7a-d was established by the 13C-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 7e and 7f rest on transformation to the corresponding dimethyl cis-cycloheptane and cis-cyclooctane diesters (1. CH2N2; 2. RuCl3(H2O)n, NaIO4, CCl4, CH3CN, H2O; 3. CH2N2) and comparison of the 13C-NMR data with the previously reported 13C-NMR data for these diesters. Acids & 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 acetal (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.
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,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 WOW 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.

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

RELATIVE ASYMMETRIC INDUCTION

The high internal asymmetric induction observed in the rearrangements of the ketene acetics 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 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, 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 (C₆H₅)₂BH] of 19a with oxidative workup (NaOH, H₂O₂) to provide two terpenes isolated previously from Nepeta cataria (catnip oil), namely, (±)-dihydroneptalactone (20a) and (±)-isodihydroneptalactone (20b) in a 93:7 ratio, respectively (75%). The 1H-NMR and IR spectra of our samples were identical with authentic spectra. 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,‡
Scheme 4.

Fig. 3.
a modified version of the MM2 molecular mechanics program. 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. 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 (13C-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-
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 pseudo-equatorial 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°C, 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. CH₂N₂; 2. RuCl₃, NaIO₄ 3. CH₃N₃) with dimethyl ester 30, in turn prepared by stereospecific hydrogenation of the Diels–Alder cyclo adduct of maleic anhydride and isoprene (29).†

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

Again, these stereochemical results can be ap-
Fig. 4.—continued
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 pseudo-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).
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). At first glance this might appear to be a trivial exercise. However, examination of previous syntheses of 37 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 (Scheme 7). Alkylation of the dianion of 31 (2 equiv of NaH, DMF, 0°) with cis - 1 - chloro - 2 - butene - 4 - tetrahydropyranl ether (1.2 equiv) (32) 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, CH₂CN, reflux) to provide the key lactone 34 in good yield after column chromatography (73%). Subjection of lactone 34 to the typical rearrangement conditions 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 ¹³C-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 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 (NEt₃, MeOH, 0°) to provide ester 37 in 77% overall yield. Our synthetic material was identical with an authentic sample generously provided by Dr Uskokovic of Hoffmann-La Roche Inc.

In summary, this single example signifies that this
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 acyclic 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 1H-NMR spectra were recorded on a Varian EM 390, 200 MHz 1H-NMR spectra were recorded on a Varian XL200, and 360 MHz 1H-NMR spectra were recorded on a Nicolet NMC360. Data are reported as follows: chemical shifts, in ppm downfield of internal TMS (multiplicity, coupling constant(s), number of protons). 13C-NMR spectra were obtained on either a Varian XL100, XL200 or on a Nicolet NMC360. Chemical shifts are referenced to the central peak of the CDCl3, triplet (77.00 ppm). IR absorption spectra were obtained on a Perkin–Elmer model 283 and were referenced to polyethylene (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 x 1/4 in glass 10% SE-30 on Chromosorb Q conditioned at 210°C (column A) or an 8 ft x 1/4 in glass 10% UCQ952 on Chromosorb Q 80/100 conditioned at 250°C (column B). All HPLC was performed on a Waters 590 pump equipped with an R401 differential refractometer 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). Solvents were dried by distillation over an appropriate drying agent under N2 atmosphere and stored under N2 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 N2. Evaporation of solvents was performed first at aspirator pressure on a Buchi rotoevaporator and then at c.a.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 Et3N (8 equiv), and the resulting soln was added slowly (over 24–40 h) via a syringe pump to a refluxing soln of Z-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 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.

(2Z)-8-Hydroxy-6-octenoic acid lactone (7a). Hydroxy acid 6a (927 mg, 5.86 mmol) gave 336 mg (41%) of an oil. Rf 0.42 (EtOAc–hexanes, 1: 19). IR(neat)3020, 2930, 2860, 1736, 1446, 1365, 1213, 1135, 1020, 700 cm⁻¹; 'H-NMR (90 MHz, CDCl₃) δ 5.97–5.46 (m, 2H), 4.75 (d, J = 4 Hz, 2H), 2.47–2.10 (m, 4H), 2.05–1.60 (m, 2H), 1.60–1.15 (m, 4H). Exact mass calc for C₉H₁₃O₂ (M⁺): 140.0837; found: 140.0835.

(2Z)-9-Hydroxy-7-nonenoic acid lactone (7b). Hydroxy acid 6b (613 mg, 3.56 mmol) gave 268 mg (49%) of an oil. Rf 0.39 (EtOAc–hexanes, 1: 19). IR(neat)3020, 2925, 2860, 1755, 1655, 1460, 1150, 1030, 715 cm⁻¹; 'H-NMR (90 MHz, CDCl₃) δ 5.80–5.30 (m, 2H), 4.67 (d, J = 3 Hz, 2H), 2.47–2.10 (m, 4H), 1.95–1.60 (m, 2H), 1.60–1.15 (m, 4H).

(2Z)-10-Hydroxy-8-decenoic acid lactone (7e). Hydroxy acid 6e (613 mg, 3.56 mmol) gave 268 mg (49%) of an oil. Rf 0.39 (EtOAc–hexanes, 1: 19). IR(neat)3020, 2925, 2860, 1755, 1655, 1460, 1150, 1030, 715 cm⁻¹; 'H-NMR (90 MHz, CDCl₃) 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).
with ethyl vinyl ether and pyridinium gtoluettesulfonate (13.37). 125 (14.52X 124 (14.10), 108 (21.43), 98 (25.18). Exact mass cal for C_{12}H_{20}O_{2} (M+): 182.1150; found: 182.1149.

(Z)-4-Hydroxy-12,14-tetradecenoic acid lactone (7e). Hydroxy acid 6d (1.66 g, 6.6 mmol) gave 1.16 g (82%) of an oil. R, 0.68 (EtOAc–hexanes, 1: 1). IR (neat) 3020, 2925, 2855, 1730, 1650, 1550, 1450, 1320, 1135, 1065, 970, 775 cm⁻¹; 'H-NMR (90 MHz, CDCl₃) 6 5.27 (br t, J = 10.5 Hz, 1H), 4.56 (br s, 2H), 2.00-1.25 (m, 14H), 0.90 (d, J = 7 Hz, 3H), 0.89 (d, J = 6 Hz, 3H). Exact mass cal for C₁₂H₁₄O₂ (M+): 182.1150; found: 182.1149.

(Z)-5,9-Dimethyl-6-hydroxyhexanoic acid lactone (18). Hydroxy acid 17 (315 mg, 1.69 mmol) gave 204 mg (72%) of an oil. R, 0.67 (EtOAc–hexanes). IR (neat) 3030, 2930, 2855, 1730, 1650, 1550, 1450, 1320, 1135, 1065, 970, 775 cm⁻¹; 'H-NMR (90 MHz, CDCl₃) 6 5.90-5.31 (m, 3H), 4.57 (d, J = 7 Hz, 2H), 2.10-1.17 (m, 5H), 0.90 (d, J = 7 Hz, 3H), 0.89 (d, J = 6 Hz, 3H). Exact mass cal for C₁₀H₁₆O₂ (M+): 168.1150; found: 168.1149.

(Z)-5,9-Dimethyl-6-hydroxyhexanoic acid lactone (22). To a soln of 4-methylcyclohexanone (3.3 g, 30 mmol) in CH₂Cl₂ (20 ml) was added an organolithium reagent (1.47 g, 7.4 mmol) and the mixture was heated at 40°C for 2 h. The reaction mixture was cooled to -78°C and 2-iodopropanol (1.2 g, 7.4 mmol) was added. The soln was then stirred for 30 min at -78°C. The mixture was then quenched with an aqueous NH₄Cl and diluted with Et₂O. The aq layer was then extracted twice with Et₂O and then carefully neutralized with aq Na₂CO₃ and then back-extracted with Et₂O. The organic phase was washed with sat NaHCO₃ aq, then brine and dried (MgSO₄). Flashation and removal of solvent provided 1.38 g of a yellow oil. Exact mass cal for C₁₀H₁₆O₂ (M+): 168.0838; found: 168.0837. To 6-hydroxy-4-methylhexanoic acid lactone (2.5 g, 20 mmol) was added an eq soln of Na₂O (11 ml, 60%), and the mixture was heated at 100°C for 1 h. The soln was diluted with Et₂O and the aq layer extracted twice with Et₂O. The organic layer was washed twice with a sat soln of Na₂SO₄, then with brine (Me₂SO₄). Filtration and removal of solvent in vacuo provided 1.38 g of a yellow oil. Exact mass cal for C₁₀H₁₆O₂ (M+): 168.0838; found: 168.0837. To 6-hydroxy-4-methylhexanoic acid lactone (2.5 g, 20 mmol) was added an eq soln of HCl (11 ml, 60%), and the mixture was heated at 100°C for 1 h. The soln was diluted with Et₂O and the aq layer extracted twice with Et₂O. The organic layer was washed twice with a sat soln of Na₂SO₄, then with brine (Me₂SO₄). Filtration and removal of solvent in vacuo provided 1.38 g of a yellow oil. Exact mass cal for C₁₀H₁₆O₂ (M+): 168.0838; found: 168.0837.
and/or silyl ester by removal of solvents via atmospheric distillation, as these products were quite volatile. For the standard workup described above was used, affording 141 mg (41%) of a clear, colorless oil. R, 0.22 (EtOAc-petroleum ether, 1: 19). IR (neat) 3010, 2950, 2920, 2870, 2860, 2970, 2800, 1705, 1640 cm⁻¹; 1H-NMR (90 MHz, CDCl₃) δ 3.92 (d, J = 6.6 Hz, 3H); MS m/z (rel. int.) M⁺ 168.1150; found: 168.1150.

(Z)-Hydroxy-4,7-dimethyl-6-oxocyclohexane (23). Hydroxy acid 22 (708 mg, 3.8 mmol) was lactonized using the standard conditions described above, affording 141 mg (41%) of a clear, colorless oil. R, 0.27 (EtOAc-petroleum ether, 1: 49). IR (neat) 3024, 2950, 2920, 2870, 2860, 1710, 1455, 1410, 1380, 1090, 1050, 1100, 850 cm⁻¹; 1H-NMR (90 MHz, CDCl₃) δ 6.89 (brs, 1H), 5.52 (brt, 1H), 4.53 (brs, 2H), 4.02 (brs, 2H), 3.22-2.05 (m, 4H), 1.77-1.26 (m, 4H), 0.88 (d, J = 6 Hz, 3H). The IR spectrum was consistent with the expected product. The mass spectrum was consistent with the expected product. The mass spectrum was consistent with the expected product. The mass spectrum was consistent with the expected product.

Distillation, as these products were quite volatile. For the standard workup described above was used, affording 141 mg (41%) of a clear, colorless oil. R, 0.22 (EtOAc-petroleum ether, 1: 19). IR (neat) 3010, 2950, 2920, 2870, 2860, 1710, 1455, 1410, 1380, 1090, 1050, 1100, 850 cm⁻¹; 1H-NMR (90 MHz, CDCl₃) δ 3.92 (d, J = 6.6 Hz, 3H); MS m/z (rel. int.) M⁺ 168.1150; found: 168.1150.

(Z)-Hydroxy-4,7-dimethyl-6-oxocyclohexane (23). Hydroxy acid 22 (708 mg, 3.8 mmol) was lactonized using the standard conditions described above, affording 141 mg (41%) of a clear, colorless oil. R, 0.27 (EtOAc-petroleum ether, 1: 49). IR (neat) 3024, 2950, 2920, 2870, 2860, 1710, 1455, 1410, 1380, 1090, 1050, 1100, 850 cm⁻¹; 1H-NMR (90 MHz, CDCl₃) δ 6.89 (brs, 1H), 5.52 (brt, 1H), 4.53 (brs, 2H), 4.02 (brs, 2H), 3.22-2.05 (m, 4H), 1.77-1.26 (m, 4H), 0.88 (d, J = 6 Hz, 3H). The IR spectrum was consistent with the expected product. The mass spectrum was consistent with the expected product. The mass spectrum was consistent with the expected product. The mass spectrum was consistent with the expected product.

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Exact mass calc for C₆H₁₀O₂ (M⁺): 122.0993; found: 122.1002.

cis-2-Ethynylcyclooctane-2-carboxylic acid (8e) and cis-2-ethynylcycloheptane-2-carboxylic acid (8f). Lactone 26 (10 mg, 0.06 mmol) was silylated by dissolving in 

Chaisen-rearrangement-mediated ring contraction of macrocyclic lactones

Workup provided 76 mg (76%) of a colorless viscous oil. HPLC on a 5 μL ATEX cyan column (1:2 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) 3500–2600, 2930, 2920, 2910, 2860, 1710, 1650, 1460, 1340, 1260, 1250, 1200, 1150, 1120, 990, 900 cm⁻¹ - H-NMR (360 MHz, CDCl₃): δ 5.98 (ddd, J = 17.4, 10.8, 8.7 Hz, 1H), 4.95 (ddd, J = 10.8, 1.2, 0.9 Hz, 1H), 4.91 (ddd, J = 17.4, 8.1, 0.9 Hz, 1H), 4.47 (ddd, J = 10.2, 1.2, 0.9 Hz, 1H), 3.0–2.4 (m, 2H), 1.90–1.1 (m, 7H), 0.95 (d, J = 6 Hz, 0.9 Hz), 0.94 (d, J = 6 Hz, 2.2 Hz), 2.0–1.1 (m, 1H), 0.95 (d, J = 6 Hz, 0.9 Hz), 0.94 (d, J = 6 Hz, 2.2 Hz).

Exact mass calc for C₆H₁₁O₂ (M⁺): 124.0676; found: 124.0675.

To a soln of 28b in Et₂O (1 ml) was added ethereal diazomethane until a yellow color remained. R₂' = 0.55, 0.62 (EtOAc–hexanes, 1:1). IR (neat) 3080, 2930, 2920, 2830, 1735, 1640, 1540, 1430, 1380, 1320, 1250, 1160, 1040, 1000, 915 cm⁻¹ - H-NMR (90 MHz, CDCl₃): δ 10.57 (d, J = 10.8, 8.7 Hz, 1H), 5.99 (s, 3H), 3.0–2.4 (m, 2H), 1.90–1.1 (m, 7H), 0.95 (d, J = 6 Hz, 0.9 Hz), 0.94 (d, J = 6 Hz, 2.2 Hz), 2.0–1.1 (m, 1H), 0.95 (d, J = 6 Hz, 0.9 Hz), 0.94 (d, J = 6 Hz, 2.2 Hz).

Exact mass calc for C₃H₆O₂ (M⁺): 91.0146; found: 91.0150.

Methyl 2-(1H-inden-1-yl)-2,4-cyclohexadiene-2-carboxylate (32b). Lactone 26 (50 mg, 0.39 mmol) was silylated in Ref. 6 (vide supra). The mixture was then warmed to 30°C and stirred at this temp for 2 h. Standard workup followed by purification with HFL as described previously gave 26 mg (43%) of a viscous oil. IR (neat) 3500–2600, 3070, 2940, 2920, 2860, 1710, 1640, 1540, 1530, 1370, 1270, 1230, 1180, 1120, 990, 900 cm⁻¹ - H-NMR (90 MHz, CDCl₃): δ 6.45 (d, J = 6 Hz, 0.9 Hz), 2.8–2.1 (m, 2H), 2.15–1.9 (m, 1H), 1.78 (br s, 3H), 1.11 (d, J = 6 Hz, 2.2 Hz), 1.02 (d, J = 6 Hz, 2.2 Hz), 0.9 (d, J = 6 Hz, 0.9 Hz), 0.87 (d, J = 6 Hz, 2.2 Hz).

Exact mass calc for C₇H₁₆O₂ (M⁺): 119.0800; found: 119.0802.

Methyl 2-(1-methyl-1H-inden-1-yl)-2,4-cyclohexadiene-2-carboxylate (32c). Lactone 26 (50 mg, 0.39 mmol) was silylated as described in Ref. 6 (vide supra). The mixture was then warmed to 30°C and stirred at this temp for 2 h. Standard workup followed by purification with HFL as described previously gave 19 mg (18%) of a viscous oil. IR (neat) 3500–2600, 3070, 2940, 2920, 2860, 1710, 1640, 1540, 1530, 1370, 1270, 1230, 1180, 1120, 990, 900 cm⁻¹ - H-NMR (90 MHz, CDCl₃): δ 6.45 (d, J = 6 Hz, 0.9 Hz), 2.8–2.1 (m, 2H), 2.15–1.9 (m, 1H), 1.78 (br s, 3H), 1.11 (d, J = 6 Hz, 2.2 Hz), 1.02 (d, J = 6 Hz, 2.2 Hz), 0.9 (d, J = 6 Hz, 0.9 Hz), 0.87 (d, J = 6 Hz, 2.2 Hz).

Exact mass calc for C₇H₁₆O₂ (M⁺): 119.0800; found: 119.0802.

5-Methyl-2-(1H-inden-1-yl)-2,4-cyclohexadiene-2-carboxylate (32a). Lactone 26 (50 mg, 0.39 mmol) was silylated as described in Ref. 6 (vide supra). The mixture was then warmed to 30°C and stirred at this temp for 2 h. Standard workup followed by purification with HFL as described previously gave 19 mg (18%) of a viscous oil. IR (neat) 3500–2600, 3070, 2940, 2920, 2860, 1710, 1640, 1540, 1530, 1370, 1270, 1230, 1180, 1120, 990, 900 cm⁻¹ - H-NMR (90 MHz, CDCl₃): δ 6.45 (d, J = 6 Hz, 0.9 Hz), 2.8–2.1 (m, 2H), 2.15–1.9 (m, 1H), 1.78 (br s, 3H), 1.11 (d, J = 6 Hz, 2.2 Hz), 1.02 (d, J = 6 Hz, 2.2 Hz), 0.9 (d, J = 6 Hz, 0.9 Hz), 0.87 (d, J = 6 Hz, 2.2 Hz).

Exact mass calc for C₇H₁₆O₂ (M⁺): 119.0800; found: 119.0802.
Dimethyl (1R, 2S*, 3R*) - 5 - methyl - cyclohexane - 1, 2 - di carbamate (30). Substitution of the methyl - 2 - ethynyl - 5 - methylcyclohexanoates of 28a,b (47 mg, 0.26 mmol) to Sharpless oxidation using RuO₄ provided the corresponding carbonyl acids. The esters were prepared by reaction with ethereal diazomethane, R, 0.23 (EtOAc, hexanes, 1: 9). IR (film) 3560 - 3000, 2950, 2890, 2830, 1735, 1715, 1575, 1505, 1450, 1425, 1300, 1250, 1195, 1170, 1070, 1005, 950, 970, 950, 905, 890, 845, 820, 770, 755, 730 cm⁻¹; 1H-NMR (90 MHz, CDCl₃) δ 3.68 (s, 6H), 3.3-3.1 (m, 2H), 2.5-1.1 (m, 7H) (9.8/6 (J = 6 Hz), 9.09 (d, J = 6 Hz), 56:44, 3H); MS m/z (rel. int.) M⁺ 214 (0.7), 183 (35), 182 (31), 154 (54), 123 (24), 92 (22), 96 (14), 95 (100), 94 (79), 81 (33), 79 (29), 67 (29), 59 (23). Exact mass cal for C₁₇H₂₂O₂N (M⁺): 291.1605; found: 291.1606. (Found: C, 69.38; H, 6.74; N, 5.27. 2844

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 recrystallized from MeOH (90 ml) to afford 4.67 g (92%) of a yellow oil. The methyl esters were prepared by reaction with methyl chloride in ether with concomitant formation of the crude methyl ester. The crude methyl ester was purified by column chromatography using isolute alcohol-hexanes (1: 9) to afford 1.10 g (53%) of a white solid. The methyl esters were prepared by reaction with methyl chloride in ether with concomitant formation of the crude methyl ester. The crude methyl ester was purified by column chromatography using isolute alcohol-hexanes (1: 9) to afford 1.10 g (53%) of a white solid.

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) 3560-3300, 3020, 2920, 1710, 1610, 1570, 1500, 1460, 1340, 1260, 1104, 1025, 785, 695 cm⁻¹; 1H-NMR (90 MHz, CDCl₃) δ 8.05-7.60 (m, 2H, 7.30 (s, 5H), 5.07-5.17 (m, 2H), 4.37-3.67 (m, 4H), 3.65-3.03 (m, 3H), 2.51-2.05 (m, 2H, 2H), 2.05-1.62 (m, 2H).

4 - (N - Z) - 4 - Hydroxy - 2 - butenylbenzamido]butyric acid lactone (28). The mixture was partitioned between Et₂O (200 ml) and H₂O (100 ml). The organic layers were washed with Na₂CO₃, and the aqueous layer was extracted with Et₂O (previously dried over KOH pellets followed by drying over Na₂SO₄). The resulting yellow oil was stirred vigorously at room temperature for 1 h before being subjected to excess diazomethane.

The residue was taken up in Et₂O (100 ml) and washed with half sat brine (50 ml), brine (50 ml) and dried (MgSO₄). 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) 3560-3300, 3020, 2920, 1710, 1610, 1570, 1500, 1460, 1340, 1260, 1104, 1025, 785, 695 cm⁻¹; 1H-NMR (90 MHz, CDCl₃) δ 8.05-7.60 (m, 2H, 7.30 (s, 5H), 5.07-5.17 (m, 2H), 4.37-3.67 (m, 4H), 3.65-3.03 (m, 3H), 2.51-2.05 (m, 2H, 2H), 2.05-1.62 (m, 2H).

† Compound 29 was kindly produced by Professor D. M. S. Wheeler at the University of Nebraska.
The crude diazoketone (90.0 mg, 0.316 mmol) was dissolved in MeOH (20 ml) and to this solution was added a suspension of AgNO₃ (10 mg, 0.071 mmol) and the mixture was cooled to 0 °C. The mixture was poured into CH₂Cl₂ (100 ml) and washed with 10%, HCl aq (2 x 20 ml), HzO (20 ml), sat. Na₂CO₃ aq (2 x 20 ml), and dried (Na₂SO₄). The crude hydrolysis product (7) - cis - N-benzoyl meroquinone methyl ester (37). The crude product was identified by comparison with the authentic sample provided by Dr. M. Uskokovic of Hoffmann-La Roche Inc. for the major product obtained from the treatment of the mixture of acids 24 and 25 with 1. CH₃OH; 2. O₂, MeOH.

REFERENCES


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. Ac₂O, Pyr]. For details, see: J. Wolinsky, T. Gibson, D. Chan and H. Wolf, *Tetrahedron* 21, 1247 (1965).


