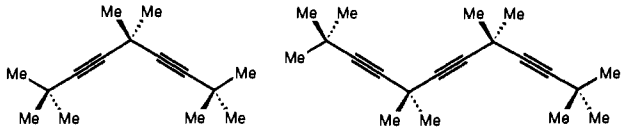
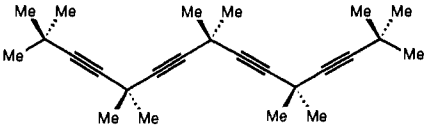
cyclic contribution to homoconjugation. Toward this end we synthesized the homoconjugated acyclic pentayne **5** by the route summarized in Scheme I. Completely analogous reactions likewise provided the lower homologues in this new family of reference compounds, i.e., the acyclic diyne **2**, triyne **3**, and tetrayne **4**.[11]



2 **3**



4

By using the calorimeter and methods we have previously described,[7] we found the heats of hydrogenation for acyclic homoconjugated polyacetylenes **2**, **3**, **4**, and **5** to be -130 ± 1, -201 ± 1, -271 ± 1, and -339 ± 2 kcal/mol, respectively (duplicate runs on each).[12] A plot of these values versus the number of triple bonds gives a remarkably good straight line (Figure 1). Linear least-squares treatment of the eight independent experimental results shows the standard deviation of all points about the linear function to be only 0.8 kcal/mol. These data provide an additivity value for the enthalpy increment per homoconjugated triple bond of -69.8 kcal/mol. Consequently, the heat of hydrogenation predicted for compound **1** in the absence of any special effects associated with closing the cycle of homoconjugation is -69.8×5 or -349.0 ± 0.8 kcal/mol.

The experimental heat of hydrogenation for decamethyl[5]-pericyclyne (**1**) was found to be -340.7 kcal/mol with a standard deviation of the mean of 2.2 kcal/mol from the pooled experimental data.[13] This value is significantly smaller ($\Delta\Delta H = 8.3$ kcal/mol), though not dramatically so, than the value predicted on the basis of acyclic model compounds which have an equivalent degree of homoconjugation but lack the cyclic component.

Before attributing this entire $\Delta\Delta H$ to homoaromaticity in **1**, one must first consider the possible presence of *extra* strain in the cyclic hydrogenation product derived from **1** relative to that in the saturated acyclic models. Any *de*stabilization in the cyclic hydrogenation product would have the same effect on $\Delta\Delta H$ as would an electronic stabilization of the cyclic pentayne. To probe this aspect of the problem, we carried out molecular mechanics calculations[14] on the hydrogenation products of all the polyacetylenes **1**-**5** and found that the reduced 15-membered ring suffers from no more than 2 kcal/mol of extra strain over that present in the saturated acyclics. After correcting for the strain increase on hydrogenation, enthalpy lowering relative to the model remains statistically significant at the 0.99 confidence level. We attribute this enthalpy lowering to stabilization of the cyclic pentayne, i.e., to homoaromaticity.

The recent discovery[7] of a 4.5 kcal/mol stabilization energy in triquinacene (a *trishomo*benzene) has been interpreted as the first evidence that cyclic homoconjugation can actually have thermodynamic consequences in neutral systems. Our results with decamethyl[5]pericyclyne(**1**) reinforce this conclusion. The fact that the thermodynamic effects are small in magnitude reflects, we believe, the highly "bond-alternate" character of these homoconjugated cycles.

Finally, it should be emphasized that the absence of a large thermodynamic stabilization (homoaromaticity) does *not* necessarily imply that orbital interactions (homoconjugation) must also be small. Triquinacene and decamethyl[5]pericyclyne are characterized by strong homoconjugative orbital interactions, as revealed by PES and other spectroscopic measurements, yet they exhibit only a modest degree of homoaromaticity, by the thermodynamic criterion. Cyclic homoconjugation is a necessary condition for homoaromaticity but does not guarantee that the effects of homoaromaticity will be large.[15]

Acknowledgment. We thank the National Science Foundation and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for financial support of this work.

Registry No. **1**, 88057-40-3; **2**, 116503-39-0; **3**, 116503-40-3; **4**, 116503-41-4; **5**, 116503-42-5.

(11) Complete experimental details can be found in the M.S. Thesis of M. J. Cooney, University of Nevada-Reno, 1987.

(12) Uncertainties are given as twice the standard deviation of the mean, according to the usual thermochemical convention.

(13) This standard deviation includes a 0.7 kcal/mol estimate of errors due to weighing and handling small samples.

(14) The Macintosh version of the MMX program distributed by Serena Software, Bloomington, IN (March 1988 edition) was used for these calculations and is very reliable for acyclic saturated hydrocarbons. This program has no means for finding the global minimum energy conformation, so 2 kcal/mol must be considered an upper limit for the strain energy.

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A Novel Asymmetric Synthesis of Substituted Cyclopropanes†

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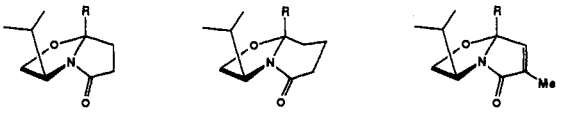
Received July 8, 1988

During the past several years, we have been studying the synthetic utility of chiral nonracemic bicyclic lactams such as **1**-**3**.



1 **2** **3**

These readily accessible materials have led to efficient syntheses of enantiomerically pure compounds containing a quaternary stereocenter.[1] Thus, routes to chiral 4,4-disubstituted cyclopentenones, 4,4-disubstituted cyclohexenones, 2,2-disubstituted-4-keto acids, and various natural products were achieved. For instance, photoaddition of ethylene to **3** led to a chiral cyclobutane synthesis and the pheromone, grandisol.

We now describe how these versatile chiral bicyclic lactams may be utilized as a starting point to various chiral, nonracemic cyclopropanes, an area with rather few general synthetic approaches.[2] The wide variety of important natural products[3] and currently employed insecticides (e.g., permethrinic acid) containing the cyclopropane ring in a chiral environment provide further

† This paper is dedicated to Professor Harry M. Walborsky on the occasion of his 65th birthday.

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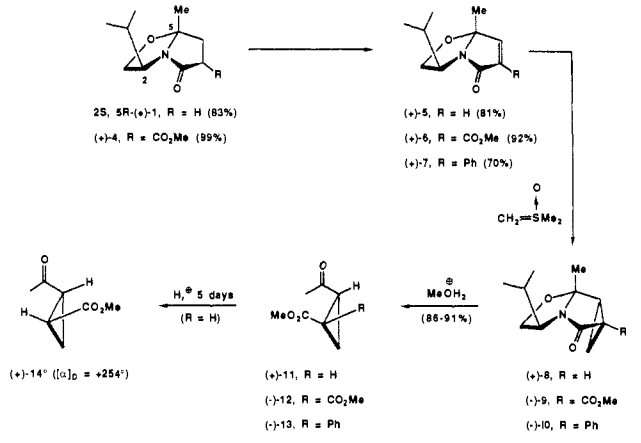
Table I. Chiral Cyclopropanes from Lactams **5–7**

cyclopropane adducts					cyclopropanes			
compd	% yield	$[\alpha]_D$[a] (deg)	% de	mp[b] (°C)	compd	% yield	$[\alpha]_D$[a,c] (deg)	mp
8	64	+58.3	95	47–48	**11**	88	+48.7	oil
9	65	−69.0	99	98–99	**12**	86	−149.7	72–73 °C
10	58	−72.5	93	106–108	**13**	81	−175.7	oil

[a] All rotations taken as *c*, 1–4 in THF. [b] Pure, single diastereomer. [c] Rotations for pure enantiomer, based on pure lactams, **8–10**.

impetus for having viable synthetic routes available.

The starting materials were **1**, previously described,[1] and 2-carbomethoxy derivative (+)-**4** prepared by metalation and



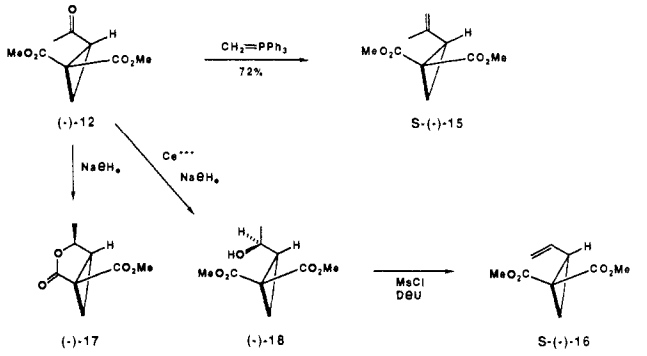
acylation (LDA, $ClCO_2Me$, as a 1:1 mixture of epimers). These were transformed into the α,β-unsaturated lactams **5** (mp 38–40 °C, $[\alpha]_D$ +21.4°) and **6** (oil, $[\alpha]_D$ +13.5°) by metalation, selenation, and oxidative elimination (LDA, PhSeBr, H_2O_2). A third unsaturated lactam **7** was smoothly formed by heating equimolar quantities of *S*-valinol and methyl 4-oxo-2-phenyl-2-pentenoate in toluene with removal of water (16 h, mp 59–61 °C, $[\alpha]_D$ +44.8°).

With these three chiral substrates (**5–7**) in hand, we proceeded to test the nucleophilic addition and its stereoselectivity. To our delight, when dimethylsulfoxonium methylide, generated according to Corey,[4] was added to each of the chiral unsaturated lactams, the cyclopropanated adducts (+)-**8**, (−)-**9**, and (−)-**10** were formed in greater than 93% de (Table I). The small quantity of exo-cyclopropanated material was easily removed by flash chromatography or crystallization. Confirmation of the endo approach to form *endo*-cyclopropane derivatives was obtained by comparison with known cyclopropanes (vide infra). The cyclopropanated bicyclic lactams, purified as shown in Table I, were subjected to hydrolysis (10% H_2SO_4–methanol reflux, 96 h) and produced cyclopropanes **11–13** in 81–88% yields (Table I). Thus, a new and efficient entry into enantiomerically pure cyclopropanes has been demonstrated.

Some interesting and useful extensions of this work are also worthy of note. For example, prolonged heating (5–6 days) of **11** in the methanolic sulfuric acid solution resulted in complete epimerization of the trans-disubstituted cyclopropane (+)-**14**. Since no epimerization was observed for the carbomethoxy (**12**), or pheny (**13**), substituted cyclopropanes, we are assuming that the acyl groups and not the carbomethoxy was affected. To date, we have not rigorously established the absolute configuration of **14**.

In order to further demonstrate the utility of this method and, of equal importance, to assess that the cyclopropanes shown in Table I were indeed of high optical purity, we elected to prepare vinyl cyclopropanes **15** and **16**. These highly useful chiral synthons were employed by Quinkert in the total synthesis of (−)-methyl jasmonate,[5] (+)-confertin,[6] (−)-norgestrel,[7] and (+)-estrone.[8]

Furthermore, the absolute configuration of **15** and **16** was established by X-ray crystallography.[6b] Our approach to **15** and **16** required that we start with (+)-**6** to prepare (−)-**12** as described



above. Standard Wittig olefination gave *S*-(−)-**15** in 72% yield; the opposite antipode reported by Quinkert. Comparison of rotation data ($[\alpha]_D$ −119° versus Quinkert's[6a] value +128°) was consistent with very high optical purity[9] and the *S*-configuration for our product, resulting from endo entry of the sulfoxonium ylide. Formation of the vinyl cyclopropane **16** was more eventful. Reduction of **12** in the hope of reaching the carbinol **18** was not possible with sodium borohydride under a variety of conditions. In each case, good yields (90%) of the lactone **17** (mp 97.5–99 °C, $[\alpha]_D$ −56.85°, *c* 1.08, THF) were obtained. Attempts to open lactone **17** and give the vinyl derivative **16** failed. It was subsequently found that addition of 1.0 equiv of $CeCl_3 \cdot 7H_2O$[10] to an aqueous ethanol solution of **12** gave a single carbinol **18** (99%, $[\alpha]_D$ −19.4°, *c* 1.4, THF). The stereochemistry of the latter was the same as the lactone **17** by interconvertive comparison. Mesylation of **18** (MsCl, CH_2Cl_2, 0 °C), followed by elimination (DBU, benzene, DMAP, reflux, 48 h), gave the vinyl cyclopropane diester **16** (49%, oil, $[\alpha]_D$ −46.1°, *c* 0.3, CCl_4).[11]

A final comment regarding endo entry of the sulfoxonium ylid to **5–7** is appropriate. We currently favor the notion, advanced by Cieplek[12] and supported by LeNoble[13] and Johnson and Cieplek[14] that nucleophilic approach to the π-system generates a $\sigma^*_\ddagger$ orbital in the transition state (A) that is anti to the electronegative C–O bond and syn to the angular methyl. The latter may also aid in stabilization of the $\sigma^*_\ddagger$ via hyperconjugative transmission of electron density. Ylide entry from the top face (B) generates a $\sigma^*_\ddagger$ which is syn to the C–O bond such that no stabilization is

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(9) Although our rotation was ~10% lower than that reported by Quinkert (ref 6a), the enantiomeric purity determined by hplc and NMR of the precursor (−)-**9** (>99%) stands as more reliable than that determined by the polarimeter.
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(11) The volatility of **16** made solvent removal difficult, and, thus, the rotation when compared to Quinkert's value ($[\alpha]_D$ +54.6°) was low.
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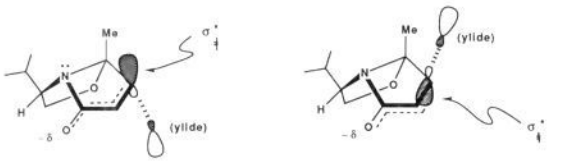

available in the formation of the $\sigma^*_\ddagger$ orbital. Thus, the idea of stabilization of $\sigma^*_\ddagger$ orbitals in the transition state may prove to be a useful guide to understanding some unexpected stereoelectronic effects. These and others will be reported in more detail in the future.

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DNA Cleavage by a Synthetic Mimic of the Calicheamicin–Esperamicin Class of Antibiotics

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DNA cleavage is currently a topic of intense research investigations.[1] Both naturally occurring[2] and synthetic[3] compounds have demonstrated the ability to cleave DNA under appropriate conditions which often include metal ions, thiols, photolysis and/or oxygen as cofactors. The recently reported calicheamicin[4] (represented by calicheamicin $\gamma_{1\alpha}{}^{I}$) and esperamicin[5] class of antibiotics have shown striking capacities to induce DNA scission[6,7] via a proposed mechanism that involves hydrogen abstraction from the phosphate backbone of DNA by benzenoid diradicals.[4-6]

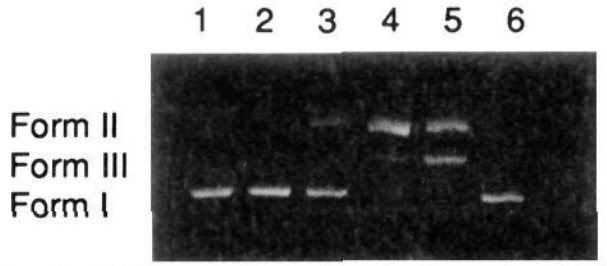


Figure 1. ΦX174 Form I DNA (50 μM per base) was incubated with compound **1** in Tris-acetate buffer (pH 8.5, 50 mM) at 37 °C for 12 h and analyzed by agarose gel electrophoresis. Lane 1, DNA alone; lanes 2–5, DNA + **1** at 1.0, 10, 100, and 500 μM, respectively; lane 6, DNA + **3** at 2 mM.

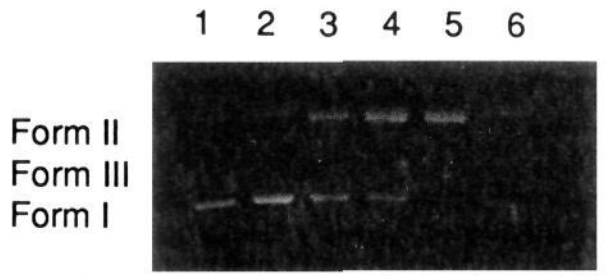
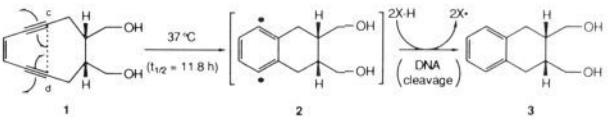


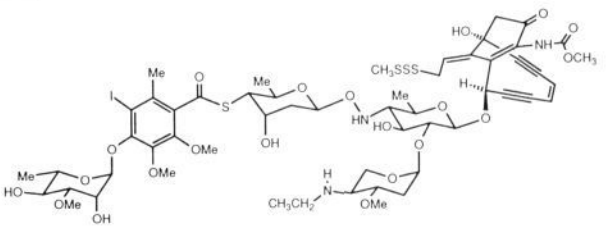
Figure 2. ΦX174 Form I DNA (50 μM per base) was incubated with compound **1** (20 μM) for various times at 37 °C and analyzed as described under Figure 1. Lanes 1–5, 0, 6, 12, 24, and 48 h, respectively; lane 6, DNA alone.

Scheme I[a]



[a] Presumed mechanism of DNA cleaving action of compound **1**.

According to this mechanistic proposal, a cascade reaction sequence, triggered upon DNA binding of the molecules, generates the reactive diradical species from the cyclodecaenediyne moiety present in these complex structures. Inspired by this fascinating hypothesis, we recently initiated a program directed toward the design, synthesis, and evaluation of simple structures that might mimic the biological action of these natural products. In this communication, we report the first synthetic mimic of the calicheamicin–esperamicin class of antibiotics and its DNA-cleaving properties.



calicheamicin $\gamma_{1\alpha}{}^{I}$

On the basis of previous calculations and experimental results from these laboratories,[8] the conjugated cyclodecaenediyne diol **1** (Scheme I) was designed as a potential DNA-cleaving molecule. The crucial expectation was that **1** would be sufficiently stable at ambient temperatures to allow its isolation and handling, but that it would undergo Bergman cyclization[9] at 37 °C (body

† Merck Sharp and Dohme Postdoctoral Fellow, 1988.
‡ Dean's Graduate Fellow, University of Pennsylvania, 1988.
§ Visiting scientist from Nippon Zeon Co., Japan, 1987–1989.

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