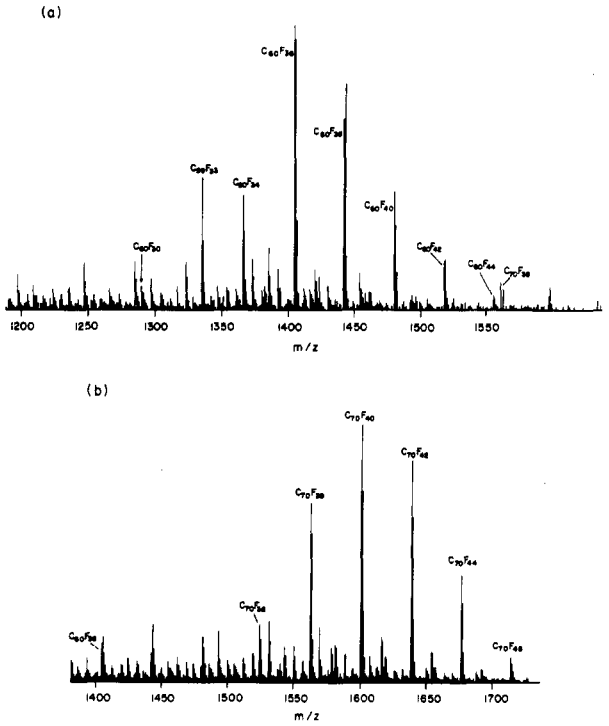

Figure 1. Mass spectra of fluorinated fullerenes: (a) a C_{60}-rich sample at a probe temperature of 200 °C; (b) a C_{70}-rich sample at a probe temperature of 300 °C.

Fluorinations were performed on a Sartorius magnetic suspension balance, Model 4201. This allowed us to monitor in situ weight uptake (±0.1 mg) while the sample was exposed to a fluorine pressure of several hundred Torr. Usually fluorine uptake was almost complete within a few minutes and then continued very slowly for up to 20 h to constant weight. Weight uptakes were measured ex situ with 0.01-mg precision. Results varied from sample to sample but usually indicated $F/C_{60} > 30$. A 9.22-mg sample of pure C_{60} gave a weight increase upon fluorination of 9.24 mg corresponding to $F/C_{60} = 38.0 \pm 0.1$. Small amounts of pure C_{60} were fluorinated separately in an IR cell. By following the absorption at 1283 cm^{-1}, we could see that small amounts of CF_4 were slowly liberated. Thus, the weight uptakes represent lower limits. A few samples were analyzed for fluorine content by igniting weighed portions in oxygen in a Schoniger flask and titrating with $La(NO_3)_3$. The results agree roughly with the weight uptake measurements, although usually showing somewhat lower fluorine content, a problem generally encountered with molecules of high fluorine content.

Mass spectra were run on a ZAB-2F (VG-Analytical) double-focusing instrument of reverse geometry. The samples were introduced into the mass spectrometer by using the direct-insertion probe, which was heated up to 400 °C. The EI mass spectrometry conditions were as follows: electron-ionizing energy, 70 eV; emission current, 1 mA; source temperature, 250 °C; and resolution, 2000 (10% valley definition). Typical mass spectra are presented in Figure 1. Part a shows the spectrum for a C_{60}-rich sample at a probe temperature of 200 °C, and part b shows the spectrum for a C_{70}-rich sample at a probe temperature of 300 °C. The spectra show mass groups with intervals of 2F = 38. The most intense peak in fluorinated C_{60} occurs at m/z = 1404, indicating a particularly stable molecule, $C_{60}F_{36}$, analogous to the product of the Birch reduction, $C_{60}H_{36}$.[3] MIKE (mass analyzed ion kinetic energy) and CAD (collisionally activated dissociation) spectra were run on several of the major ions, including $C_{60}F_{36}^+$, $C_{60}F_{38}^+$, $C_{60}F_{40}^+$, $C_{60}F_{42}^+$, and $C_{60}F_{44}^+$, in order to find out whether some of these ions are due to fragmentation. No F_2 elimination was observed from any of these ions, clearly indicating that these are all parent ions of the corresponding neutral fluorinated compounds ($C_{60}F_{36}$, $C_{60}F_{38}$, etc.). The characteristic fragmentations of these ions are F• and CF_3• and C_2F_5• eliminations. As a result, the ion $C_{59}F_{33}^+$ in the mass spectrum (Figure 1a) is a major fragment from $C_{60}F_{36}^+$ due to CF_3• loss. At higher probe temperature (400 °C), the C_{60}-rich sample gave peaks at $C_{60}F_{46}^+$, $C_{60}F_{48}^+$, $C_{60}F_{50}^+$, and $C_{60}F_{52}^+$. The most intense peak in the C_{70} spectrum (Figure 1b) is at m/z = 1600, corresponding to $C_{70}F_{40}^+$, although higher fluorinated C_{70} ions up to $C_{70}F_{46}^+$ are clearly present.

Infrared spectra show a strong, broad absorption at 1165 cm^{-1} characteristic of a C–F stretch with partial ionic character (the C–F absorption in covalent graphite fluoride occurs at 1215 cm^{-1}).[7] A TGA experiment on a C_{60}-rich sample showed decomposition at 320 °C; a major constituent in the downstream mass spectrum was CO_2, suggesting that the relatively poor thermal stability is due to air exposure of the product. The fluorinated material is brown to tan colored. Most of the products appeared inhomogeneous under the microscope, suggesting the presence of several phases, possibly with different degrees of fluorination. In a few cases, small amounts of a yellow-white material were observed.

After fluorination, an X-ray powder profile exhibits only a few broad peaks characteristic of a liquid or glass with short-range positional correlations and no long-range order. The starting material is highly crystalline.[8] In monatomic glasses the near-neighbor distance is simply and directly related to the position of the first diffuse scattering maximum. No such relationship exists for disordered molecular solids. However, the fact that the first diffuse maximum after fluorination occurs at about $2\theta = 9°$ is consistent with an increased near-neighbor intermolecular distance relative to the pristine structure. An amorphous structure is also consistent with differential scanning calorimetry, which shows a broad glass transition near 20 °C and no first-order transitions in the range −140 to 200 °C.

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Unusually Stable γ-Lactone Ring Fused Norcaradienes from Intramolecular Cyclization of Vinylcarbenes

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Intermolecular carbenoids addition to benzene ring is the most commonly used method to prepare norcaradienes.[1] But an intramolecular version of this reaction has never been successful in affording stable norcaradienes of tricyclic structures. Since 1970, intramolecular cyclization of aryl diazoketones has been

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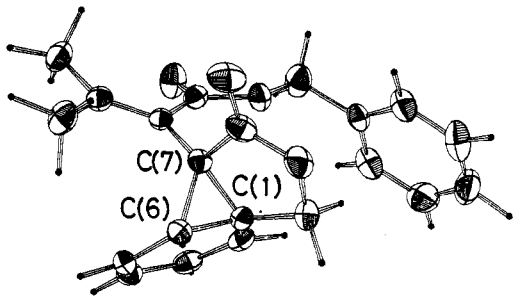
A



B

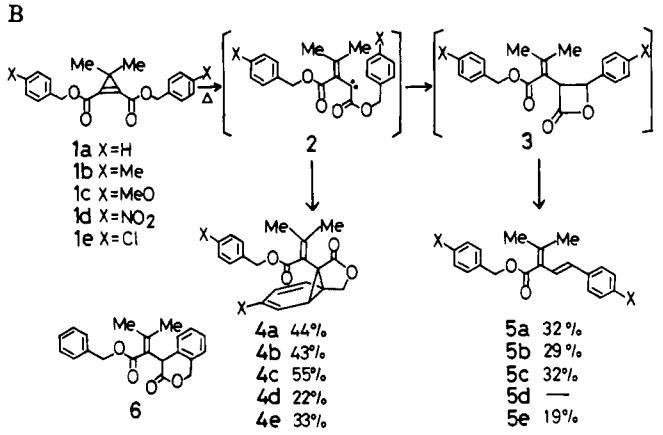


Figure 1. (A) ORTEP view of **4a** and (B) an illustration of the synthesis process.

applied to the syntheses of dihydroazulene[2] and azadihydroazulene derivatives[3] and cycloheptabenzofuran.[4] In all cases, norcaradienes were proposed to be the transient species. Quite recently, Saba[5] reported the first example of detection of tricyclononcaradienoic structures derived from the above-mentioned intramolecular carbene addition as a tautomeric equilibrium mixture with the corresponding cycloheptatriene derivatives by low-temperature NMR study. Hoffmann[6] and Günther[7] pointed out that an efficient conjugation of the occupied cyclopropane Walsh orbital with an unoccupied π-acceptor orbital at C(7) resulted in the strengthening of the C(1)–C(6) bond. On the basis of this explanation, we designed an intramolecular vinylcarbene cyclization by thermolysis of cyclopropenes[8] to prepare the stable tricyclo-[5.3.0.0^{1,6}]deca-2,4-diene skeleton.

Thermolysis of a benzene solution of cyclopropene **1a** which was prepared by the photolysis of the corresponding 3*H*-pyrazole at 130 °C in a sealed tube for 15 h gave two products. The major crystalline compound **4a** (44%) was a hitherto unknown type of tricyclic norcaradiene whose structure was elucidated by its single-crystal X-ray analysis,[9] as shown in Figure 1. To our surprise, even in solution **4a** existed completely as norcaradiene which was confirmed by the inspection of its ^{1}H and ^{13}C NMR spectrum.[10] Intermolecular reaction of **2** with the solvent benzene hardly occurred in this case, although a stabilized vinylcarbene was known to afford a norcaradiene derivative from the intermolecular reaction with benzene.[11] The minor compound obtained was the diene **5a** (32%) via decarboxylation of the β-lactone intermediate **3**. In a similar manner, thermolysis of the para-substituted cyclopropenes **1b–1e** gave the corresponding norcaradienes **4b–4e** and dienes **5b,c,e**, respectively. In the case of the *p*-nitro-substituted compound **1d**, C–H insertion occurred on the opposite side chain resulting in the formation of γ-lactone (6%) together with **4d**. The present success of the isolation of stable tricyclic norcaradienes is brought about by the two C(7) substituents, the vinyl group, and the lactone linkage.[12] The orthogonal orientation of the dimethylvinyl group, which makes it a net σ-electron-withdrawing group, may be important.[13] The requirement for stabilization of norcaradienes of this type seems to be very delicate, since an intramolecular cyclization of aryl diazo esters with the C(7) carbomethoxy substituent[14] was unsuccessful in affording the corresponding norcaradienes bearing the identical tricyclic skeleton as **4**. Moreover, an intramolecular cyclization of vinylcarbene to a phenyl substituent[15] only resulted in a formation of a cycloheptatriene derivative.

The unusual stability of **4a** and also the lack of the equilibrium between **4a** and the corresponding cycloheptatriene form were demonstrated by its thermolysis. It was stable under heating at 180 °C for 6 h in toluene in a sealed tube. Pyrolysis of crystalline **4a** at 190 °C for 3 h without solvent resulted in the formation of δ-lactone **6**, (35%) together with the recovery of **4a** (50%). Flash pyrolysis of **4a** (300 °C, 3 s) also afforded a 35% yield of **6**. Hence, an aromatization is then preferred to a cycloheptatriene formation.

The present findings that a vinyl group substitution at C(7) increases the stability of norcaradienes will help to construct norcaradienes of unknown types which are considered to be unstable at the present time.

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(12) MNDO calculations have shown that norcaradiene is more unstable than cycloheptatriene by 8.1 kcal/mol. However, this energy differece is reduced to 4.4 kcal/mol between the C(7) dimethylvinyl-substituted and C(1)–C(7) γ-lactone ring fused norcaradiene and the corresponding cycloheptatriene. More interestingly, the two-atom energy term (cf.; Sawada, H.; Kikuchi, O.; Yokoyama, Y. *J. Fluorine Chem.* **1990**, *50*, 393. Fischer, H.; Kollmar, H. *Theor. Chim. Acta* **1970**, *16*, 163–174.) between the C(1) and C(6) atoms is significantly stabilized (–12.31 eV) in the substituted norcaradiene compared with that of norcaradiene (–11.99 eV). These results indicate strongly that the three-membered ring in the substituted norcaradiene is more stable than norcaradiene against the ring-opening process with the C(1)–C(6) bond cleavage.

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Supplementary Material Available: Spectral data for norcaradienes **4a–4e** and X-ray crystallographic data for **4a** including tables of fractional atomic coordinates, bond distances, and bond angles (9 pages); listing of observed and calculated structure factor amplitudes (10 pages). Ordering information is given on any current masthead page.

Novel Macrolactonization Strategy for the Synthesis of Erythromycin Antibiotics

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Erythromycins B (**1**) and A (**2**) (Scheme I) are the archetypal representatives of the clinically important family of 14-membered, macrolide antibiotics.[1,2] Owing to the challenges posed by their densely functionalized and stereochemically complex architecture, these compounds have elicited intense interest, and a number of elegant syntheses of derivatives of the aglycons of **1** and **2** and their respective seco acids, as well as of the natural antibiotic **2** itself, have been recorded.[3] In this context, we recently reported a facile, asymmetric synthesis of the erythronolide B seco-acid derivative **5** and have extended that work to the preparation of the related erythronolide A analogue **6**,[4] but the significant challenge of elaborating **5** and **6** into the corresponding natural antibiotics **1** and **2** remained. After consideration of a number of potential options, we were particularly intrigued by one exciting, albeit speculative, strategy for the end game of the syntheses of **1** and **2** that had not been previously explored. Namely, we envisaged that macrolactonization of glycosylated seco-acid derivatives related to **3** and **4**, which should be accessible from **5** and **6**, might serve as a key step in a novel and concise route to **1** and **2** and biologically interesting analogues thereof. However, prior to embarking upon a venture to convert synthetic **5** and **6** into intermediates analogous to **3** and **4**, it seemed prudent to establish first that such glycosylated seco acids would undergo macrolactonization; there was no precedent for such a cyclization.[5]

In previous formulations of strategies for the synthesis of erythromycin antibiotics, macrocyclization of a seco-acid derivative of the aglycon has been generally perceived as the primary subgoal. Significantly, the subsequent glycosylation of the hydroxyl groups at C(3) and C(5) of an intermediate macrolide leading eventually to a natural target has only been achieved in Woodward's seminal total synthesis of **2**.[3e] Critical to the success of the macrolactonization step in all cases thus far reported is the reduction of conformational space available to the seco-acid backbone, typically in two different regions. Rigidification of the segment between C(2) and C(6) has been most commonly achieved by formation of a cyclic protecting group involving the hydroxyl groups at C(3) and C(5). Conformational restriction of a second segment of the carbon framework has been most frequently accomplished by construction of a cyclic, six-membered protecting group array incorporating the functionality at C(9) and C(11).[3e-i,m-r] Other useful devices to rigidify the backbone include insertion of a double bond at strategic sites such as between C(10) and C(11)[3a-c] or between C(8) and C(9)[3s] or by incorporation of a conjugated enone between C(7) and C(5) in tandem with a double bond between C(11) and C(12).[3k]

The preceding investigations delineated some of the key structural features that must be embodied within the seco-acid matrix in order to optimize the prospects for successful macrolactonization. After careful consideration of these factors, we concluded that the critical question of whether glycosylated seco-acid derivatives of the erythromycins might be induced to undergo macrolactonization could be most expeditiously resolved by using conformationally constrained substances related to **3** and **4**. We reasoned that rigidity could be imparted to the C(9)–C(13) segment of the framework in a conventional manner by forming a cyclic derivative between the C(11) and C(9) hydroxyl groups. We further anticipated that the steric buttressing interactions between the two carbohydrate residues at C(3) and C(5) of **3** and **4** would advantageously reduce conformational mobility along the C(1)–C(8) subunit to facilitate cyclization. However, since one might also envision that unfavorable steric interactions between the two sugar residues could dramatically disfavor those conformers of **3** and **4** that were capable of undergoing cyclization, we undertook exploratory experiments to establish the viability of effecting macrolactonization of a fully glycosylated derivative of erythromycin B. We now report the details of some of those investigations.

In the first phase of these feasibility studies, erythromycin B (**1**) was converted into **9** according to Scheme II.[6] Transformation of **1** into **7** proceeded in 53% overall yield according to modifications of known procedures for N-demethylation, carbonyl reduction, and acetal formation in the erythromycin area.[7] Although the stereochemistry at the acetal carbon in **7** could not be unambiguously established, the equatorial orientation of the

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