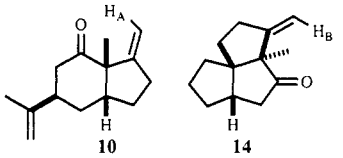
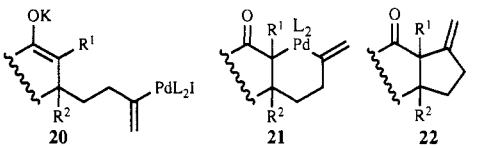
the conjugate addition products **8**, **12**, and **16b** derived from the enones **7**, **11**,[10] and **15b**, respectively, could be assigned with confidence. The Pd(0)-catalyzed ring closures of **9** and **13** were expected to produce the corresponding cis-fused products (**10**, **14**, respectively), and these predictions were confirmed by ^{1}H NMR spectroscopy. Thus, in a NOE difference experiment, irradiation at δ 1.25 (angular Me signal) in the ^{1}H NMR spectrum of **10**, caused enhancement of the signal (δ 4.84) due to H_A. Similarly, saturation of the signal (δ 1.08) due to the angular Me group in the ^{1}H NMR spectrum of **14** increased the intensity of the resonance (δ 4.93) due to H_B. Molecular models show clearly that these signal enhancements are possible only if the substances **10** and **14** have the stereochemistry indicated. In the corresponding trans-fused isomers, the angular methyl protons and the designated olefinic protons (H_A, H_B) are spatially remote and nuclear Overhauser enhancements would be very unlikely.



10 **14**

The initially formed annulation products (e.g. **18a-c**) derived from keto iodides (e.g. **17a-c**) that do not contain an α-substituent at C-2 are unstable under the reaction conditions necessary for ring closure. Not surprisingly, the presence of base (*t*-BuOK) causes isomerization of these substances to the more stable conjugated ketones (e.g. **19a-c**).

Although a detailed mechanistic discussion is beyond the scope of this paper, it may be proposed that the novel Pd(0)-catalyzed cyclization[11] of **9**, **13**, and **17a-c** occurs, in each case, via an intermediate of general structure **20**. The latter species would be formed from the substrate keto iodide by a combination of oxidative addition of the Pd(0) catalyst to the carbon-iodide bond and the formation of an enolate anion by proton abstraction by base (*t*-BuOK). Intramolecular "transmetalation" of **20** would afford the six-membered palladocycle **21**, which, upon reductive elimination of Pd(0) would provide the cyclized product **22**.



20 **21** **22**

It is interesting to note explicitly that the new methylenecyclopentane annulation method described herein (see **1** → **4**) is regiochemically opposite (and therefore complementary) to that developed earlier in our laboratory.[12] Extensions to this work, including the application of the newly developed annulation sequence to natural product synthesis, are in progress.

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Supplementary Material Available: Experimental procedures for the preparation of, and spectral data for, compounds **8-10**; ^{1}H NMR spectra of compounds **8-10**; ^{13}C NMR spectrum of compound **10**; spectral data for compounds **12-14**, **16a-c**, **17a-c**, and **19a-c** (9 pages). Ordering information is given on any current masthead page.

(9) Ziegler, F. E.; Reid, G. R.; Studt, W. L.; Wender, P. L. *J. Org. Chem.* **1977**, *42*, 1991.

(10) The enone **11** was prepared from the *N,N*-dimethylhydrazone of cyclopentanone via the following four-step sequence (see: Corey, E. J.; Enders, D. *Chem. Ber.* **1978**, *111*, 1362): LDA, THF, 0 °C, then 1,2-epoxybutane; $NaIO_4$, THF, H_2O; pyridinium chlorochromate, CH_2Cl_2; KOH, EtOH. For an alternative preparation, see: Begley, M. J.; Cooper, K.; Pattenden, G. *Tetrahedron* **1981**, *37*, 4503.

(11) For examples of Pd(0)-catalyzed intramolecular coupling of *aryl* iodides with soft enolate anions, see: Ciufolini, M. A.; Qi, H.-B.; Browne, M. E. *J. Org. Chem.* **1988**, *53*, 4149 and citations therein. For examples of transition metal catalyzed intramolecular carbonylative coupling of aryl and vinyl iodides with soft enolate anions, see: Negishi, E.; Zhang, Y.; Shimoyama, I.; Wu, G. *J. Am. Chem. Soc.* **1989**, *111*, 8018.

(12) Piers, E.; Karunaratne, V. *J. Chem. Soc., Chem. Commun.* **1983**, 935; *Tetrahedron* **1989**, *45*, 1089.

Acceleration of Cope Rearrangement by a Remote Carbenium Ion Center: Theoretical Elucidation of the Electronic Origin

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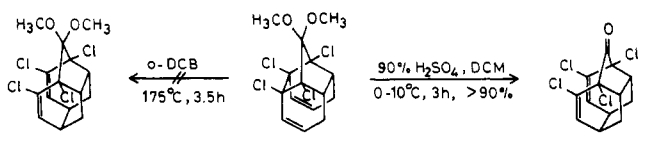
Summary: MNDO calculations on model systems reveal a stepwise process via classical carbocation intermediates as well as a pathway involving a pyramidal, bis-olefin π-complex of CH^+ as being responsible for the acid catalysis of Cope rearrangement found recently in a rigid tetracyclic system.

Recently a remarkable acceleration of Cope rearrangement by a remote carbenium ion center was found in a rigid tetracyclic molecule, **1** (Scheme I).[2] Direct conjugation at the transition state cannot be the driving force in this system, unlike in the previously known acid-catalyzed Cope rearrangements (Scheme II).[3] However, there

Scheme I



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(1) (a) Indian Institute of Science. (b) University of Hyderabad.

(2) Mehta, G.; Padma, S. *J. Org. Chem.* **1988**, *53*, 4892.

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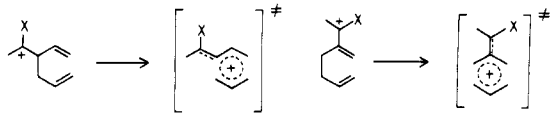
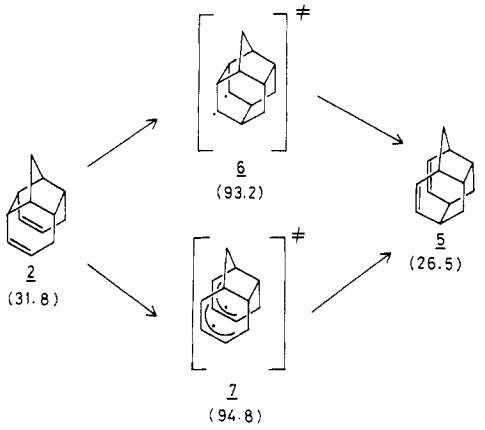
Scheme II[a]



[a] X = H, C, O.

Scheme III[a]

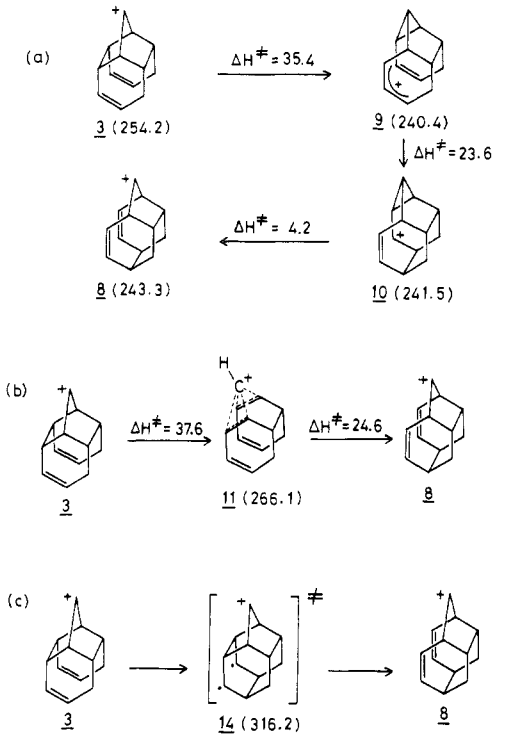


[a] MNDO heats of formation (kcal/mol) in parentheses.

is the intriguing possibility of homoconjugation, involving a σ-bond of the norbornyl skeleton, providing the necessary stabilization to the transition state of the cation. In order to unravel the electronic origin of acceleration of Cope rearrangement by a remote carbenium ion center, reaction energy profiles were computed in detail for two model systems, **2** and **3**. The MNDO method,[4] which makes an accurate prediction of the activation enthalpies and entropies in the prototypical Cope system, 1,5-hexadiene, **4** (both in the chair and the boat forms), was employed.[5-10]

In each system several pathways were examined using different reaction coordinates (e.g., lengthening the 3–4 bond of the hexadiene unit, shortening the 1,6 bond, as well as a combination of the two by linear interpolation between the reactant and product geometries), with full optimization of the remaining geometric parameters. From each of the highest energy points, transition-state structures were optimized by minimizing the gradient norm.[11] Transition structures so obtained as well as the various minima were thoroughly characterized by computing their

Scheme IV[a]



[a] MNDO heats of formation (in parentheses) and activation enthalpies in kilocalories/mole.

vibrational frequencies and Hessian indices.

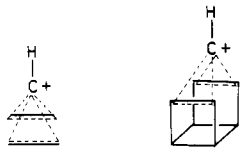
Two reaction pathways requiring similar activation barriers were computed for the Cope rearrangement of **2** → **5**. One process proceeds via a 1,4-diradical (cyclohexadiyl derivative), **6**, while the other involves a bis-allylic species, **7** (Scheme III). These results are rather similar to those obtained for the Cope rearrangement of boat hexadiene, **4**.[5,6,9,10] However, there are subtle differences. The diradical structures are not intermediates, but transition structures in the case of **2**. Thus, both reaction profiles in Scheme III correspond to single-step processes, unlike in **4**. The calculated activation enthalpies are also greater in **2**. The rigid polycyclic framework is probably responsible for producing these changes in the potential energy surfaces involving **2**.

In contrast to **2** and **4**, the Cope rearrangement of the cation, **3** → **8**, is fundamentally different. The minimum energy reaction pathway (MERP) involves a multistep rearrangement (Scheme IVa). The first step is a C–C bond shift leading to the allyl cation, **9**. This is followed by the formation of a new C–C bond and a higher energy localized carbenium ion, **10**. Finally, **10** rearranges to give the eventual Cope product, **8**. Each of these steps requires progressively smaller barriers. The overall activation energy is determined by the transition state of the first rearrangement step. In complete accord with the experimentally found acid catalysis of the Cope rearrangement in 1,[2] the enthalpy of activation calculated for **3** is 26.0 kcal/mol less than that for **2**.

Another pathway involving a more dramatic σ-participation was computed for **3** (Scheme IVb). In this two-step reaction, **3** first rearranges to a pyramidal carbocation, **11**. This remarkable species, computed to be a true minimum on the potential energy surface, is essentially a π-complex between CH^+ and two olefin fragments. Such complexes have been postulated earlier in other contexts, with rather indirect experimental support, e.g., in the carbon skeletal scrambling in the cyclopentyl cation (**12**)[12] and in the re-

(3) (a) Breslow, R.; Hoffmann, J. M., Jr. *J. Am. Chem. Soc.* **1972**, *94*, 2111. (b) Lutz, R. P. *Chem. Rev.* **1984**, *84*, 205.
(4) Dewar, M. J. S.; Thiel, W. *J. Am. Chem. Soc.* **1977**, *99*, 4906.
(5) For the Cope rearrangement of the chair form of hexadiene, the activation enthalpy in kcal/mol calculated using the MNDO method is 39.0[6] (exp: 33.5[7]). The corresponding value for the boat form obtained in this study, 45.6, shows an even better agreement with experiment, 44.7.[8] The performance of the MNDO method for this problem is as impressive as those of the related semiempirical methods, AM1[9] and MINDO/3.[10]
(6) Dewar, M. J. S.; Healy, E. F.; Stewart, J. J. P. *J. Chem. Soc., Faraday Trans. 2* **1984**, *80*, 227.
(7) Doering, W. v.E.; Toscano, V. G.; Beasley, G. H. *Tetrahedron* **1971**, *27*, 5299.
(8) Goldstein, M. J.; Benzon, M. S. *J. Am. Chem. Soc.* **1972**, *94*, 7147.
(9) (a) Dewar, M. J. S.; Jie, C. *J. Am. Chem. Soc.* **1987**, *109*, 5893. (b) Dewar, M. J. S.; Jie, C. *J. Chem. Soc. Chem. Commun.* **1987**, 1451. (c) Dewar, M. J. S. *Int. J. Quant. Chem. Symp.* **1988**, *22*, 557.
(10) Dewar, M. J. S.; Ford, G. P.; McKee, M. L.; Rzepa, H. S.; Wade, L. E. *J. Am. Chem. Soc.* **1977**, *99*, 5069.
(11) For some applications of the transition structure optimization methodology used in this work, see: Poppinger, D. *Chem. Phys. Lett.* **1975**, *35*, 550. Schwarz, H.; Franke, W.; Chandrasekhar, J.; Schleyer, P. v. R. *Tetrahedron* **1979**, *35*, 1969. Bowen, R. D.; Chandrasekhar, J.; Frenking, G.; Schleyer, P. v. R.; Schwarz, H.; Wesdemiotis, C.; Williams, D. H. *Chem. Ber.* **1980**, *113*, 1084.

arrangement of the homocubyl cation (13).[13] Of course,



12 13

complexes like 11 become familiar structures when the isolobal analogy between CH^+ and the $Fe(CO)_3$ fragment (or CoCp, RhCp, etc.) is invoked.[14] The energy profile connecting 3 and 8 via 11 is rather symmetrical with an overall barrier of 37.6 kcal/mol. However, the highest energy structures are calculated to have a Hessian index of 2 and hence are not true transition structures. Nevertheless, a C_s trajectory via the complex, 11, is available for the Cope rearrangement of 3 requiring only a slightly greater energy than the MERP. More importantly, this trajectory requires less energy than the MERP for the Cope rearrangement of the neutral parent, 2.

An independent measure of the homoconjugative driving force was obtained by obtaining a diradical saddle point for the process 3 → 8 (Scheme IVc). This structure, 14, with a Hessian index of 1, resembles the diradical transition structure, 6,[15] but with a localized carbocation center. The corresponding activation enthalpy of 61.9 kcal/mol is also similar to that in the rearrangement of 2 → 5 (and 26.5 kcal/mol higher than that for the MERP of 3).

In summary, MNDO calculations reveal the possibility of both classical and nonclassical ion participation in the Cope rearrangement of 3.[16] We are currently examining experimentally and theoretically, with appropriately chosen systems, the role of the norbornyl skeleton and the rigid endocyclic bonds in enhancing such homoconjugative interactions.

Acknowledgment. S.L. thanks the CSIR (New Delhi) for an SRF.

(12) (a) Franke, W.; Schwarz, H.; Thies, H.; Chandrasekhar, J.; Schleyer, P. v. R. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 485. (b) Franke, W.; Schwarz, H.; Thies, H.; Chandrasekhar, J.; Schleyer, P. v. R.; Hehre, W. J.; Saunders, M.; Walker, G. *Chem. Ber.* **1981**, *114*, 2808. (c) Schwarz, H.; Thies, H.; Franke, W. *Ionic Processes in the Gas Phase* **1984**, 267.

(13) Jorgensen, W. L. *J. Am. Chem. Soc.* **1977**, *99*, 4272.

(14) Hoffmann, R. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 711.

(15) Since some of the structures are diradicaloid in nature, the energy of each stationary point was recomputed with the Half Electron method including 3 × 3 C.I. As suggested by Dewar in his exhaustive studies on the Cope rearrangement,[9] the HE energy requires correction by ca. 20 kcal/mol, to compensate for overestimation of electron correlation effects. As in 4, both the RHF and the corrected HE estimates yield virtually identical barriers for all the diradicaloid pathways.

(16) As suggested by a reviewer, the relative preferences of classical and nonclassical structures may vary (probably in favor of the latter) if other theoretical methods like the MINDO/3 are used. Detailed results using this method would be presented in due course. Another reviewer has wondered whether the nonclassical participation involves a conceptually simpler bis-(or a tris-)homotropylium cation, rather than the π-complex structure proposed in this study. Comparison of geometries and charge distribution unambiguously prove that 11 is closer to the symmetrical diolefin complex[12] of CH^+ than to a homoconjugative species like the 7-norbornenyl cation.

Total Synthesis of Myxovirescin B

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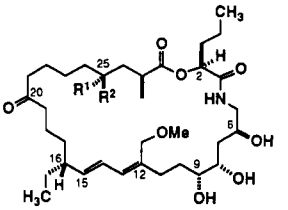
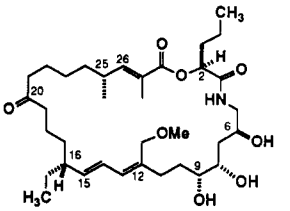
Summary: A high convergent total synthesis of optically active myxovirescin B, a 28-membered macrolactam lactone (1c), is presented. Ring closure of the macrocycle was efficiently accomplished via an intramolecular Horner–Emmons reaction of the sensitive aldehydic phosphonate 18b.

In 1982, researchers at the Gesellschaft für Biotechnologische Forschung reported the isolation of a new family of antibiotics from the myxobacterium, *Myxococcus virescin* (Mx v 48).[1] The myxovirescins, consisting of 31 structurally related macrocycles, appear to be ubiquitous among related strains of these gliding bacteria.[2,3] A postulated biological mechanism of action suggests interference with cell wall synthesis by blocking incorporation of *N*-acetylglucosamine.[1] The predominant component, myxovirescin A, was determined to be the mixture of 28-membered macrolactam–lactone diastereoisomers 1a,b by X-ray crystallography of the bisacetonide of diastereomer 1a in conjunction with degradation experiments.[2,4] Subsequently, myxovirescin B (1c) was identified as the C_{26}–C_{27} unsaturated derivative of myxovirescin A_1 (1a).[4,5] Very recently, the relative and absolute stereoassignments of the entire myxovirescin family have been resolved by Trowitzsch and co-workers.[6] Herein, we report a highly convergent synthetic pathway which has led to the first preparation of any member of these unique antibiotics with formation of optically active myxovirescin B (1c).



	R^1	R^2
1a - A_1	Me	H
1b - A_2	H	Me



1c - Myxovirescin-B

(1) Gerth, K.; Irschik, H.; Reichenbach, H.; Trowitzsch, W. *J. Antibiot.* **1982**, *35*, 1454.

(2) Trowitzsch, W.; Wray, V.; Gerth, K.; Höfle, G. *J. Chem. Soc., Chem. Commun.* **1982**, 1340. Kunze, B.; Kuhl, W.; Höfle, G.; Reichenbach, H. *J. Antibiot.* **1985**, *38*, 1649. For biosynthetic studies: Trowitzsch, W.; Gerth, K.; Wray, V.; Höfle, G. *J. Chem. Soc., Chem. Commun.* **1983**, 1174.

(3) The megovalicins appear to be identical to the myxovirescins. Miyashiro, S.; Yamanaka, S.; Takayama, S.; Shibai, H. *J. Antibiot.* **1988**, *41*, 433.

(4) Trowitzsch, W.; Burgschulte, K.; Wray, V.; Schomburg, D.; Höfle, G. *Justus Liebigs Ann. Chem.* **1985**, 1629.

(5) Onishi, N.; Izaki, K.; Takahashi, H. *J. Antibiot.* **1984**, *37*, 13.

(6) Trowitzsch-Kienast, W.; Schober, K.; Wray, V.; Gerth, K.; Reichenbach, H.; Höfle, G. *Justus Liebigs Ann. Chem.* **1989**, 345.

0022-3263/90/1955-3457$02.50/0