the 7.7-, 9.5-, and 10.3-eV bands as (2.0):0.6:0.94 as shown. Calculations on **4** with a modified version of HAM3 (HAM3/CI), which included the lowest 50 KT_i* configurations and in which the HOMO-LUMO gap (ΔE_{HOMO}^{LUMO}) was varied, gave the results shown by the bars under the spectrum of **4** in Figure 1. The ΔE_{HOMO}^{LUMO} value obtained by this procedure (2.95 eV, lower limit) gives vertical bound electronic transitions for **4** at 371 ($^1B_2$), 325 ($^1A_1$) and 318 nm ($^1A_1$**). The latter values are in superficial agreement with observations[8] for neutral **4**. This procedure demonstrates one way a PE spectrum and the NKM view can be related to electronic properties of the corresponding neutral system.

In summary, the present results provide new experimental information that supports the view that shake-up phenomena[6a] are important in the low-lying ionic states of polyenes and may in some cases be comparable to through bond-through space effects.[14] We hope the present results will help to foster the wider view of the information implicit in photoelectron spectra of such systems.

Acknowledgment. This work was partially supported in part by the National Science Foundation. We are grateful to Dr. R. A. Wielesek for help in figure preparation.

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Cation-Stabilizing Auxiliaries: A New Concept in Biomimetic Polyene Cyclization

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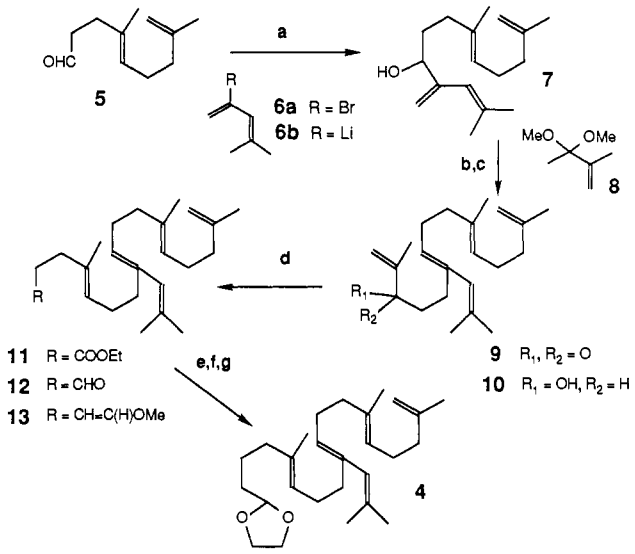
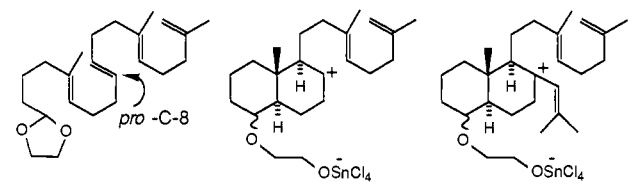
The one-step formation of two or three new rings by cyclization of polyenic substrates is now such a well-established art that very high yields can be achieved in favorable cases.[2] However, for more than 20 years serious effort has been directed toward a more ambitious and hitherto unattainable goal: the production of *four* new rings in one high-yielding, stereoselective step from acyclic polyenes. Such a reaction, involving the formation of six asymmetric centers at the bridgeheads, could seriously be compared to the biological conversion of squalene epoxide to protolanosterol. Most of the attempts in this direction have given incompletely cyclized products: for example, the nonenzymic cyclization of squalene epoxide affords tricyclic material with a five-membered C-ring as the only isolable polycycle.[3a] There have been only three partially successful experiments: tetracyclic products have been obtained with high *stereoselectivity*; yields, however, have been modest (2%,[3b] 30%,[4] and 34%[5]). Numerous attempts to improve upon these results, including the use of solid supports or ultrahigh pressures, have been abortive.[6] Consequently the feeling has emerged that the search for a *high-yielding* reaction may be a hopeless one without the help of the enzyme to overcome the unfavorable entropy of activation. Now we disclose a promising test case of a conceptually new approach to this problem: the modification of an internal double bond of the substrate by introduction of an auxiliary, so as to enhance the propagation of the cyclization process.

Formation of tetracyclic material from a substrate such as **1**[4] may be thought of as arising from two bicyclization reactions occurring in tandem. In this model, the first two rings would be expected to be formed in high yield;[2a] however, the resulting secondary cation **2** would not be sufficiently stabilized for efficient initiation of a second bicyclization.[7] Modification of cation **2** to a type known to be a good initiator was therefore envisaged. Introduction of a cation-stabilizing auxiliary (for example, an isobutenyl group) at *pro*-C-8 in polyene **1** would lead, after formation of the first two rings, to a tetrasubstituted allylic cation **3** which would be predicted to be an effective initiator for further cyclization[8] (the stereochemical consequence was not assured, however; see below). In the absence of conclusive mechanistic information on tetracyclizations this rationale was necessarily speculative, although the detection of bicyclic material resulting from elimination of a proton from a cation related to **3** in a similar

Scheme I[a]



[a] (a) 2.5 mol equiv of **6a**, 2.3 mol equiv of 1.6 M *n*-BuLi/hexanes, THF, -78 °C, 30 min, then 1 mol equiv of **5**; 75%. (b) 2 mol equiv of **8**, 0.4 mol equiv of 2,4-dinitrophenol, toluene, reflux, 17 h; 74%. (c) **9**, 1.5 mol equiv of 1 M DIBAL/hexanes, CH_2Cl_2, -78 °C, 30 min; 91%. (d) Excess triethylorthoacetate, catalytic propionic acid, reflux, 1 h; 90%. (e) 1.5 mol equiv of 1 M DIBAL/hexanes, ether, -90 °C, 15 min, then excess MeOH, -90 °C; 95% mass recovery, used without purification. (f) 3.5 mol equiv of methoxymethyltriphenylphosphonium chloride, 3.5 mol equiv of *s*-BuLi/cyclohexane, THF, -78 °C, 45 min, then 1 mol equiv of **12**, -78 - 20 °C; 51%. (g) **13**, excess ethylene glycol, 0.01 mol equiv of *p*-TsOH, DME, 21 °C, 17 h; 77%.



1 **2** **3**

(1) The X-ray analyses reported herein were performed by Professor Schubert, Institut für Anorganische Chemie der Universität Würzburg.

(2) For reviews, see: (a) Johnson, W. S. *Acc. Chem. Res.* **1968**, *1*, 1-8. Johnson, W. S. *Bioorg. Chem.* **1976**, *5*, 51-98. (b) Speckamp, W. N. *Recl. Trav. Chim. Pays-Bas* **1981**, *100*, 345-354. (c) Bartlett, P. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1984; Vol. 3, pp 341-409.

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(4) (a) Johnson, W. S.; Wiedhaup, K.; Brady, S. F.; Olson, G. L. *J. Am. Chem. Soc.* **1968**, *90*, 5277-5279. (b) Johnson, W. S.; Wiedhaup, K.; Brady, S. F.; Olson, G. L. *J. Am. Chem. Soc.* **1974**, *96*, 3979-3984.

(5) Johnson, W. S.; Chen, Y.-Q.; Kellogg, M. S. *J. Am. Chem. Soc.* **1983**, *105*, 6653-6656.

(6) Johnson, W. S., unpublished results.

(7) The activation energy for reaction of the destabilized cationic site of **2** with the adjacent double bond is probably low relative to that for conformational reorganization of the remaining polyene chain. Significant participation by the terminal olefinic bond is therefore unlikely to occur. For an undesirable result from a polyene cyclization initiated by an inadequately stabilized cation, see: Peters, J. A. M.; Posthumus, T. A. P.; van Vliet, N. P.; Zeelen, F. J.; Johnson, W. S. *J. Org. Chem.* **1980**, *45*, 2208-2214.

(8) Johnson, W. S.; Schaaf, T. K. *J. Chem. Soc. Chem. Commun.* **1969**, 611-612.

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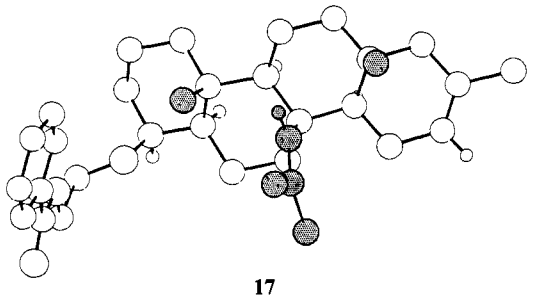
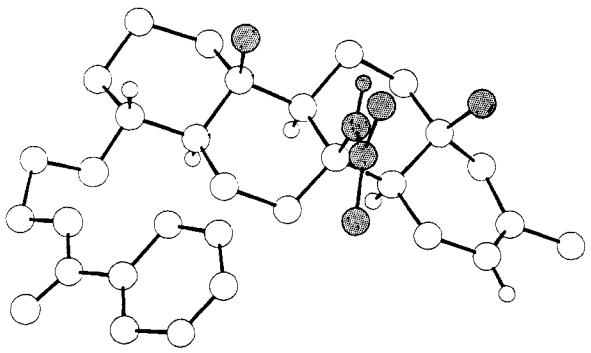


17



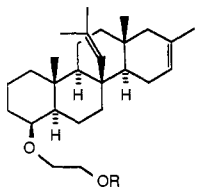
18

Figure 1. ORTEP plots of X-ray analyses with angular axial groups shaded.

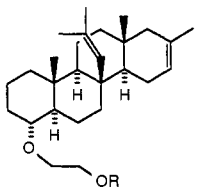
system is at least consistent with our hypothesis.[9]

The modified substrate **4** bearing the isobutenyl auxiliary at *pro*-C-8 was synthesized as shown in Scheme I; aldehyde **5**[10] was condensed with lithio diene **6b** (from bromo diene **6a**[11] and butyllithium) to give dienic alcohol **7**,[12] which was heated with olefinic ketal **8**[13] in the presence of an acid catalyst to afford enone **9**[12] by Claisen rearrangement. Reduction of **9** to alcohol **10**[12] followed by ortho ester Claisen rearrangement provided ester **11**.[12] Reduction of **11** with DIBAL and treatment of the resulting aldehyde **12** with methoxymethyltriphenylphosphosphorane gave the homologated enol ether **13**,[12] which was readily converted to the required pentadienic acetal **4**.[12,14]

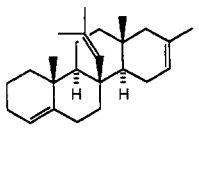
Cyclization of 4. Treatment of **4** with stannic chloride (pentane, 0 °C, 15 min)[15] gave two tetracyclic alcohols **14**,[12] mp 105–108 °C, and **15**[12] (in a ratio of approximately 2.5:1, accompanied by minor amounts of D-ring double-bond positional isomers)[16] in a combined yield of 67% after silica gel chromatography. Hydrocarbon **16**[12a,17] was also produced in 10% yield, *bringing the combined yield of tetracyclic products to 77%, as compared with 30% for the substrate* **1** *without the auxiliary*.[4] Unequivocal proof of the configurations of the tetracyclic products was essential since



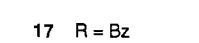
14 R = H



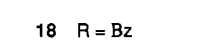
15 R = H



16



17 R = Bz



18 R = Bz

there is a precedent for cis ring fusion resulting from cyclization of a polyene containing a trans double bond bearing a bulky substituent.[18] The necessary confirmation was provided by X-ray analysis of the benzoates **17**,[12,19] mp 121–122 °C, and **18**,[12] mp 93–95 °C (see Figure 1).

In conclusion, a new principle has been proposed: the enhancement of polyene cyclizations by a cation-stabilizing auxiliary appropriately positioned on the substrate, which in a test case has given a dramatic increase in yield. A new methodology is thus suggested for the stereospecific, one-step synthesis of polycyclic natural products having four or more rings starting with acyclic substrates; for the first time, one can design such syntheses with reasonable expectation of realizing satisfactory conversions in the cyclization step. Of course, plans have to be included for manipulation of the angular auxiliary. The isobutenyl group, as in **14**, might either be removed (by ozonolysis–decarbonylation) or converted to substituents found in natural products, such as an aldehydo or methyl group, A promising alternative is the substrate with an isopropylidene auxiliary located at *pro*-C-7 which has been prepared for cyclization studies. As to other types of auxiliary, a methyl group at *pro*-C-8 evidently does not stabilize the cation sufficiently to effect significant yield improvement in a model system,[20] A thioether substituent at *pro*-C-8, on the other hand, is a good candidate, since the sulfide-stabilized carbenium ion has been shown to serve as a fairly good cyclization initiator.[21] Finally, it is interesting to consider the speculative hypothesis that cation stabilizers play a role in the enzymic process.[22]

Acknowledgment. We thank the National Institutes of Health and the National Science Foundation for their support of this work.

Supplementary Material Available: Figure representing the enzyme model proposed in ref 22 (1 page). Ordering information is given on any current masthead page.

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(10) Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T.-t.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741–743.

(11) Grob, C.A.; Spaar, R. *Helv. Chim. Acta* **1970**, *53*, 2119–2129.

(12) (a) ^{1}H NMR and IR spectra were consistent with the assigned structure. (b) A satisfactory combustion analysis was obtained for an appropriately purified specimen of this compound.

(13) (a) Wertheman, L.; Johnson, W. S. *Proc. Nat. Acad. Sci. U.S.A.* **1970**, *67*, 1810–1813. (b) Johnson, W. S.; Brocksom, T. J.; Loew, P.; Rich, D. H.; Werthemann, L.; Arnold, R. A.; Li, T.-t.; Faulkner, D. J. *J. Am. Chem. Soc.* **1970**, *92*, 4463–4464.

(14) **4** was obtained in 97% purity (estimated by VPC, 15-m SE54 capillary column) after purification by HPLC on a (reversed phase) Du Pont Zorbax ODS column with 1:30 H_2O/MeOH eluant. The single detectable impurity (3%) was assumed to be the *pro*-C-8,9 cis isomer.

(15) These conditions are essentially the same as those used in the cyclization of **1**.[4]

(16) Constitution of these products[12a] was presumed by analogy to established minor products in a related case.[4b]

(17) Proof of the configuration of **16** was provided by correlation with material produced from **14**. Submission of **14** to the cyclization conditions led to elimination of the axial hydroxy ether side chain to form a product which was shown to be identical with **16** by ^{1}H NMR, VPC coinjection, and MS (identical molecular ion and fragmentation pattern). The isomer **15** in which the side chain is equatorial was unaffected by this treatment.

(18) Kano, S.; Yokomatsu, T.; Yuasa, Y.; Shibuya, S. *J. Org. Chem.* **1985**, *50*, 3449–3453.

(19) The benzoates **17** and **18** were purified by HPLC using the conditions of ref 14 (although **18** was eluted with methanol) followed by crystallization from methanol.

(20) Johnson, W. S.; Ilton, M. A., unpublished work. See: Ilton, M. A. Ph.D. Dissertation, Stanford University, 1967.

(21) Brinkmeyer, R. S. *Tetrahedron Lett.* **1979**, *20*, 207–210.

(22) The enzyme could possibly provide external negative point-charge sites (cf.: Honig, B.; Nakanishi, K.; et al. *J. Am.. Chem. Soc.* **1979**, *101*, 7084–7086) which would stabilize developing cationic centers in the substrate by ion pairing. The cyclization of squalene epoxide might thus be assisted according to the principle established above. The plant enzyme that produces the dammarane triterpenoids could be envisaged as delivering these point charges to the *pro*-β (axial) face of the reacting substrate, allowing for equatorial closure of the rings and extrusion of the product as the axial angular methyl groups are formed. In the case of the liver enzyme that produces protolanosterol the critical point charges are delivered, instead, to the α-face. In a forthcoming disclosure it is shown that the isobutenyl auxiliary at *pro*-C-8 gives a large rate enhancement in the closure of the B-ring. Therefore the boat closure of the B-ring could be promoted by delivery of a point charge to the α-face at *pro*-C-8, thereby lowering the activation energy of the boat relative to the chair closure. (The difference in activation energies for the two processes must in any case be relatively small since a signficant proportion of the boat product is formed in the nonenzymic cyclization of a squalene epoxide analogue: van Tamelen, E. E.; Anderson, R. J. *J. Am. Chem. Soc.* **1972**, *94*, 8225–8228). The ubiquitous but enigmatic non-Markovnikov biological closure of the C-ring (cf. ref 3a and: van Tamelen, E. E. *J. Am. Chem. Soc.* **1982**, *104*, 6480–6481) may be favored by delivery of a point charge at *pro*-C-13. Thus the enzyme, instead of having to impose a profound and highly restrictive conformational influence on the substrate, may provide an electronic environment which guides and sustains processes that are already inherent in it, i.e., the Stork–Eschenmoser principle. An attractive feature of this model is its simplicity.