Rate Enhancement of Biomimetic Polyene Cyclizations by a Cation-Stabilizing Auxiliary

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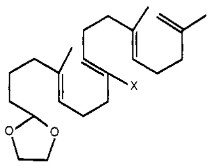
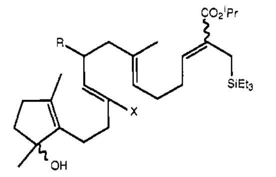
Received May 11, 1987

Recently we reported a more than twofold improvement in yield of a polyene tetracyclization mediated by a cation-stabilizing ("C-S") auxiliary. Thus the polyene **1b** underwent stereoselective



1a X = H
1b X = -CH=CMe$_2$



2a R = OH, X = H
2b R = OH, X = CH=CMe$_2$
2c R = X = H

ring closure to give D-homosteroidal products in 77% yield as compared with 30% for **1a**.[1] We now disclose an enormous rate acceleration attended by a fourfold increase in yield in a cyclization involving formation of three rings mediated by this same (isobutenyl) auxiliary. This discovery not only has practical potential for the synthesis of corticoids but may also have biological significance.

Substrates like **2a** with a hydroxyl group at *pro*-C-11 are potentially important corticoid precursors.[2] Unfortunately the rate of cyclization of such functionalized substrates is attenuated by several orders of magnitude,[3] presumably a result of the low nucleophilicity of the *pro*-C-8,9 olefinic bond induced by the electron-withdrawing allylic heteroatom. These slow cyclizations result in poor yield due to the involvement of competing processes, presumably dimerization of the substrate[2d] and destruction of the double bonds by acid, particularly in the terminator. The aim of the present study was to see if this difficulty could be obviated by use of an appropriately placed cation stabilizer. Accordingly, we elected to compare the cyclization of **2a**, bearing the newly established carbalkoxyallylsilane terminator,[4] with the modified version **2b** having the isobutenyl auxiliary at *pro*-C-8. The results of this study are delineated below.

Synthesis of the related substrates **2a,b** was envisaged from a common intermediate **5**[5] (Scheme I) prepared by reaction of the known diketal **3**[2a] with the aldehyde **4**.[5a,6] Reduction of **5** with Red-Al[2d] afforded only the *E,E* diene **6a**,[5] whereas a modification of the Corey reductive iodination[7] stereoselectively converted **5**

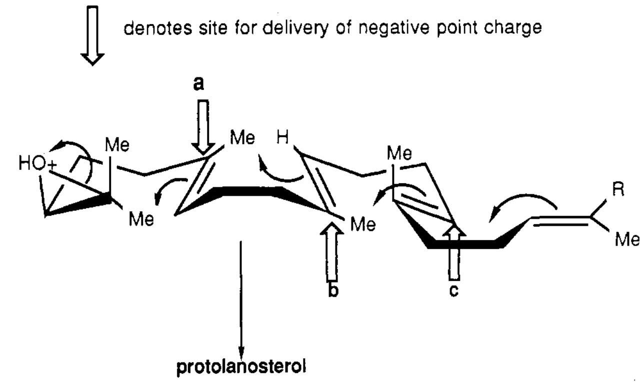
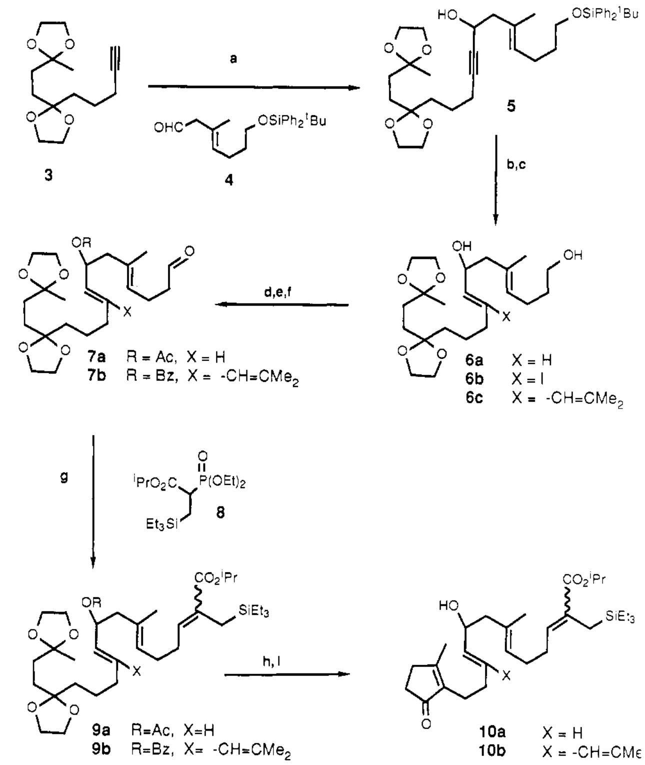


Figure 1. Proposed enzyme model.

Scheme I



(a) BuLi/hexanes (1.2 mol equiv, 1.6 M), DME, −23 °C then 1 mol equiv of **4**; 76%. (X = H): (b) Red-Al-toluene (4 mol equiv, 3.4 M), THF, reflux; 92%. (d) Ac_2O, Et_3N, catalytic DMAP, CH_2Cl_2, 24 °C; 99%. (e) Excess K_2CO_3, methanol-water, 24 °C; 49% (71% after recycling diol **6a**). (f) CrO_3, pyridine (each 6 mol equiv), CH_2Cl_2, 22 °C; 75%. (g) **8** (1.2 mol equiv), 1.2 mol equiv of BuLi, DME, −20 °C then 1 mol equiv of **7a**; 61%. (h) Pyridinium tosylate (1 mol equiv), acetone-water reflux; 97%. (i) Excess 2% NaOH, ethanol-water-THF, reflux; 82%. (X = -CH:CMe$_2$): (b) $LiAlH_4$ (3 mol equiv), 30 mol equiv of LiOMe, THF, reflux then 20 mol equiv of iodine, −78 °C; 55%. (c) (2-Methylpropenyl)bromozinc (10 mol equiv), catalytic Pd-$(Ph_3P)_4$, THF, reflux; 78%. (d) Benzoyl chloride, pyridine, 20 °C; 91%. (e) Excess KOH, isopropanol, 22 °C; 97%. (f) As above; 87%. (g) As above; 76%. (h) As above; 99%. (i) As above; 52%.

to the (*Z*)-vinyl iodide **6b**.[5a] (It is noteworthy that the silyl ether suffered hydrogenolysis under these reducing conditions.) Palladium-catalyzed coupling of **6b** with (2-methylpropenyl)-bromozinc[8] efficiently generated the requisite triene **6c**.[5] Transformation of **6a,c** to the aldehydes **7a,b**[5a] paved the way for incorporation of the terminator by Horner–Emmons reaction with

(1) Johnson, W. S.; Telfer, S. J.; Cheng, S.; Schubert, U. *J. Am. Chem. Soc.* **1987**, *109*, 2517–2518.
(2) (a) Johnson, W. S.; Escher, S.; Metcalf, B. W. *J. Am. Chem. Soc.* **1976**, *98*, 1039–1041. (b) Johnson, W. S.; Brinkmeyer, R. S.; Kapoor, V. M.; Yarnell, T. M. *J. Am. Chem. Soc.* **1977**, *99*, 8341–8343. (c) Johnson, W. S.; Frei, B.; Gopalan, A. S. *J. Org. Chem.* **1981**, *46*, 1512–1513. (d) Johnson, W. S.; Lyle, T. A.; Daub, G. W. *J. Org. Chem.* **1982**, *47*, 161–163.
(3) For example, compare ref 2d with Johnson, W. S.; Daub, G. W.; Lyle, T. A.; Niwa, M. *J. Am. Chem. Soc.* **1980**, *102*, 7800–7802. Also compare the cyclization of **2a** to give **11a** in the present paper with that of **2c**, ref 4.
(4) Johnson, W. S.; Newton, C.; Lindell, S. D. *Tetrahedron Lett.* **1986**, 6027–6030. Note that this new terminator yields products, as established in the cyclization of **2c**, that promise to be particularly useful for the development of the C-17 corticoid side chain.
(5) (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.
(6) Aldehyde **4** was prepared in four steps from 5-methylhex-5-ene-1,4-diol (Hughes, L. R.; Schmid, R.; Johnson, W. S. *Bioorg. Chem.* **1979**, *8*, 513–518) as follows: (a) 1 mol equiv of Ph_2-*t*-BuSiCl, 1.2 mol equiv of imidazole, DMF; 100%. (b) $SOCl_2$, CCl_4; 83%. (c) 1,3-Dithiane, BuLi, THF; 87%. (d) MeI, $CaCO_3$, DMF–H_2O; 78%. Steps b–d are based on established art (ref 2).
(7) (a) Corey, E. J.; Katzenellenbogen, J. A.; Posner, G. H. *J. Am. Chem. Soc.* **1967**, *89*, 4245–4247. (b) Corey, E. J.; Katzenellenbogen, J. A.; Gilman, N. W.; Roman, S. A.; Erickson, B. W. *J. Am. Chem. Soc.* **1968**, *90*, 5618–5620.
(8) On the basis of Corey methodology (ref 7) as modified by Negishi, E.; Okukado, N.; King, A. O.; Van Horn, D.; Spiegel, B. I. *J. Am. Chem. Soc.* **1978**, *100*, 2254–2256. Also, see: Jabri, N.; Alexakis, A.; Normant, J. F. *Tetrahedron Lett.* **1981**, *22*, 959–962.
(9) Johnson, W. S. *Bioorg. Chem.* **1976**, *5*, 51–98.

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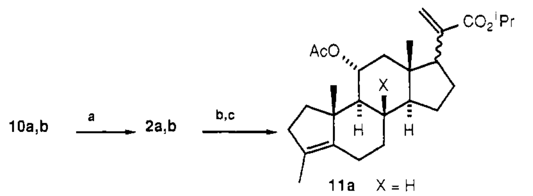
Scheme II



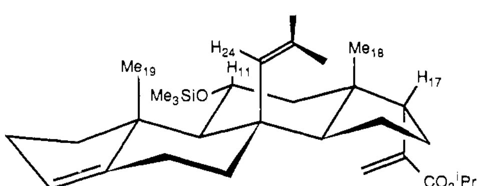
11a X = H
11b X = -CH=CMe$_2$

(a) To give **2a**: 2 mol equiv of MeLi in Et_2O, −78 °C then repeat; 91% crude. To give **2b**: 10 mol of equiv MeLi, −40 °C; 99% crude. (b) See under "**Cyclizations**" in text. (c) Ac_2O (10 mol equiv), 0.1 mol equiv of DMAP, 1:2 Et_3N/C_6H_6.

the phosphonate **8**,[4] the products **9a,b**[5] both being isolated as 2:3 mixtures of *E* and *Z* isomers. Conversion to the enones **10a,b**[5] and thence to the desired carbinols **2a,b**[5a,10] (see Scheme II) was achieved by established methodology.[2,9]

Cyclizations. The optimal cyclization conditions[10] were applied in the following preparative experiments. The dehydration product of **2a** (i.e., the cyclopentadiene[10]) was treated with 20% TFA in 1:1 CF_3CH_2OH/CH_2Cl_2 at −20 °C for 24 h to produce, after acetylation followed by HPLC, **11a**[5] in 20% yield as a 1:1 mixture of C-17 epimers. It is particularly noteworthy that *only 1–2% of **11a** was formed after a reaction time of 1 h, whereas the cyclization of **2b** appeared to be complete within 1 min*, even though the conditions (5% TFA, CH_2Cl_2, −20 °C) were milder. Also in striking contrast, no side products were observed in the cyclization of either **2b** or its dehydration product.[10] After a reaction time of 1 h, the procorticoid **11b**[5] was isolated, after acetylation and flash chromatography, in 80–83% yield as a 9:1 mixture of C-17 α:β isomers.

The 17α-epimer of **11b** was separated from the β-isomer by HPLC[11] and crystallized from ethanol as very fine needles (mp 148–151 °C) which, unfortunately, proved to be unsuitable for single-crystal X-ray structure analysis. However, the validity of structure **11b** is supported by the unambiguously established constitution of the analogous compound derived from **1b**[1] as well as of related C-11-hydroxy cyclization products.[2] Moreover, strong corroborative evidence was obtained by use of the nuclear Overhauser effect. Thus, the trimethylsilyl ether **12**[5] afforded the NOE data displayed in Table I. The enhancements are fully consistent with the relative stereochemistry assigned to **12**. Particularly significant is the transannular enhancement observed at H_{11} upon irradiation of the C-S auxiliary's vinyl proton (H_{24}) and vice versa.



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In conclusion, the unprecedented high yield for the cyclization of a *pro*-C-11-OH polyene substrate, namely **2b**, points to the potential of applying the concept to the synthesis of corticoids. To this end, removal of the auxiliary is under investigation, as is the use of alternative (e.g., heteroatom) auxiliaries.[12] The enormous cyclization rate enhancement of **2b** is a first-order anchimeric effect due to the C-S auxiliary. In forthcoming disclosures relatively small rate increases, due to second-order effects,[13] are observed when the C-S auxiliary is at the once-removed position from the initiator. Thus the rate of cyclization was enhanced by >10-fold when the methyl at *pro*-C-13 of **2c** was replaced by an isobutenyl group.[14] These first- and second-order rate effects indicate that there is considerable cationic character at *pro*-C-8 and *pro*-C-13 in the transition state, otherwise the isobutenyl auxiliary would not be effective in lowering the activation energy. The same argument applies to the effect of external point-charge stabilization in the proposed mechanism of the enzymic cyclization.[15]

Table I. NOE Enhancements for **12** at 400 MHz

site of irradiation	observed (+%)				
	H_{11}	H_{24}	H_{17}	Me_{18}	Me_{19}
H_{11}		13	0	1	0
H_{24}	19		2	2	2
H_{17}	4	0		2	0
Me_{18}	7	7.3	7		0
Me_{19}	7	5.3	2	0	

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

Registry No. 2a, 109787-69-1; **2a** (dehydration product, *Z*), 109801-33-4; **2a** (dehydration product, *E*), 109801-31-2; **2b**, 109787-70-4; **2b** (dehydration product, *Z*), 109801-34-5; **2b** (dehydration product, *E*), 109801-32-3; **3**, 43001-29-2; **4**, 109787-71-5; **5**, 109787-72-6; **6a**, 109787-73-7; **6a** (diacetate), 109787-84-0; **6a** (monoacetate), 109787-85-1; **6b**, 109787-79-3; **6c**, 109787-80-6; **6c** (dibenzoate), 109787-86-2; **6c** (monobenzoate), 109787-87-3; **7a**, 109787-74-8; **7b**, 109787-81-7; **8**, 109271-06-9; **9a** (*E*), 109801-29-8; **9a** (*Z*), 109787-88-4; **9a** (diketone, *E*), 109801-30-1; **9a** (diketone, *Z*), 109787-92-0; **9b** (*E*), 109787-82-8; **9b** (*Z*), 109787-89-5; **9b** (diketone, *E*), 109787-93-1; **9b** (diketone, *Z*), 109787-94-2; **10a** (*E*), 109787-75-9; **10a** (*Z*), 109787-90-8; **10b** (*E*), 109787-83-9; **10b** (*Z*), 109787-91-9; **11a** (α), 109787-76-0; **11a** (β), 109837-92-5; **11b** (α), 109787-77-1; **11b** (β), 109837-93-6; **12**, 109787-78-2; (2-methylpropenyl)bromozinc, 109801-35-6; 5-methylhex-5-ene-1,4-diol, 100590-28-1.

(10) Attempts to chromatograph the carbinols **2a,b** generally resulted in variable amounts of dehydration of the tertiary allylic alcohol giving the corresponding cyclopentadienes which are intermediates in the cyclization of the carbinols (see p 69 of ref 9 for evidence in a related series). Yield optimization was carried out on the crude carbinols **2a,b** by using a 15-m, SE54 capillary column (hydrogen as carrier) for VPC analysis. The methyl ether of either cholestanol or stigmasterol was used as internal standard.

(11) HPLC separation was performed on a DuPont Zorbax SIL, normal phase column with use of 5% ether in hexanes as eluant.

(12) Cf. ref 1.

(13) Cf. Barlett, P. A.; Brauman, J. I.; Johnson, W. S.; Volkmann, R. A. *J. Am. Chem. Soc.* **1973**, *95*, 7502–7504.

(14) Johnson, W. S.; Newton, C., unpublished observation.

(15) Cf. ref 1, footnote 22. The concept as applied to the enzymic conversion of 2,3-oxidosqualene to protolanosterol involves axial delivery of negative point-charge stabilizers by the enzyme as depicted in Figure 1. The expected transition state stabilization, as inferred from our rate data, nicely accounts for the (otherwise disfavored) boat ring-B as well as the non-Markownikov ring-C cyclization. Thus the charges **b** (directed to *pro*-C-8) and **c** (directed to *pro*-C-13) guide the course of the reaction by being delivered only to the α-face of the substrate. It is further postulated that stabilization by charge **a**, delivered to the β-face at *pro*-C-10, may be important in enhancing the rate and efficiency of the overall process by a first-order effect of the sort disclosed in the present paper.

$(Me_5C_5)_2Yb(\mu\text{-}Me)Be(C_5Me_5)$: A Model for Methane Coordination?

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Received May 11, 1987

The concept of NH_3 or CH_3^- acting as a classical Lewis base by donating a pair of electrons in a σ-symmetry orbital to a vacant

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