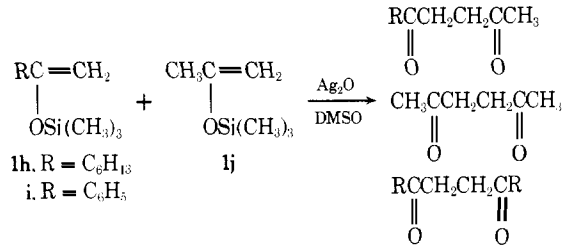
stituted α-position have been done with much difficulty; *e.g.*, the radical-induced dimerization[3,9] of unsymmetrical ketones produces mainly the most crowded 1,4-diketone, and the reductive coupling[3] of unsymmetrical α,α'-dibromo ketones with zinc–copper couple produces a mixture of all possible isomers of 1,4-diketones.

The present method is successfully applicable to some cross couplings leading to unsymmetrical 1,4-diketones, as exemplified by the synthesis of undecan-2,5-dione, a precursor of dihydrojasmone. Treatment of a mixture of trimethylsilyl enol ether **1h** and a threefold exess of trimethylsilyl enol ether **1j** with Ag_2O in dimethyl sulfoxide afforded undecan-2,5-dione (80% isolated yield based upon the starting **1h**) with hexan-2,5-dione and hexadecan-7,10-dione (yield <5%). Similarly, cross coupling of **1i** and **1j** gave 1-phenylpentan-1,4-dione in 60% isolated yield.



A detailed understanding of the reaction mechanism must await further mechanistic study. Now, we would like to propose an intermediate of silver(I) enolate (**2**) generated regiospecifically from silyl enol ether and Ag_2O, whose oxidative coupling may lead to the formation of 1,4-diketone. Oxidative couplings of organosilver[10] and organocopper compounds[11] are well known. We are currently exploring the full scope of the utility of silver(I) enolate in synthesis.

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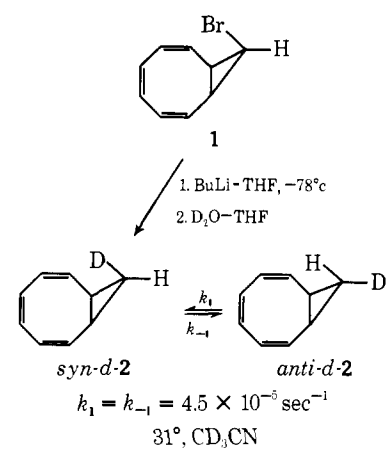
Epimerization of Bicyclo[6.1.0]nonatriene

Sir:

Since the initial observation of the thermal rearrangement of bicyclo[6.1.0]nonatriene by Vogel[1] in 1961, much effort has been directed toward unraveling the complex mechanistic details of the thermal isomerizations of bicyclo[6.1.0]nonatriene systems.[2] Epimerizations at C_9 have recently been observed for *syn*-9-carbomethoxy,[3] -cyano,[4] -fluoro,[5] and -methoxy[5] substituted systems, for which two different mechanisms have been proposed.[3,5] Since anti-9-substituted systems in general undergo skeletal rearrangements more rapidly than the corresponding syn-9-substituted systems, isomerizations of 9-syn systems may proceed *via* epimerization through 9-anti systems. Such an isomerization *via* the 9-anti epimer has been clearly demonstrated for *syn*-9-cyanobicyclo[6.1.0]nonatriene[4] and most likely occurs in other syn-9-substituted systems[3,5] but is an unsettled question for *syn*-9-methylbicyclo[6.1.0]nonatriene.[3,6]

We wish to report the stereospecific synthesis of bicyclo[6.1.0]nonatriene-*syn*-9-*d* and an investigation of its facile epimerization. This study clearly reveals the mechanism of epimerization of the unsubstituted bicyclo[6.1.0]nonatriene and suggests an alternative mechanism to those previously proposed for epimerization of syn-9 substitued systems.[3,5]

syn-9-Bromobicyclo[6.1.0]nonatriene (**1**) was prepared in a method similar to procedures used by Katz.[7a] A tetrahydrofuran (THF) solution of potassium cyclooctateaenide was added slowly to a stirred solution of bromoform in THF at −20°. Fractional distillation of the resulting mixture of products afforded a *ca.* 15% yield of **1** (32° (10^{-4} Torr)).[7] The syn bromide **1** was metalated with butyl lithium in THF at −78° and quenched with a D_2O–THF solution. Distillation at 0° gave in *ca.* 90% yield bicyclo[6.1.0]nonatriene-*syn*-9-*d* (*syn*-*d*-**2**).[8] On warming to 30°, *syn*-*d*-**2** epimerizes to *anti*-*d*-**2** and after several hours an equilibrium mixture of 50% *syn*-*d*-**2** and 50% *anti*-*d*-**2** is obtained with neglible skeletal rearrangement to 8,9-dihydroindenes.[1,2]

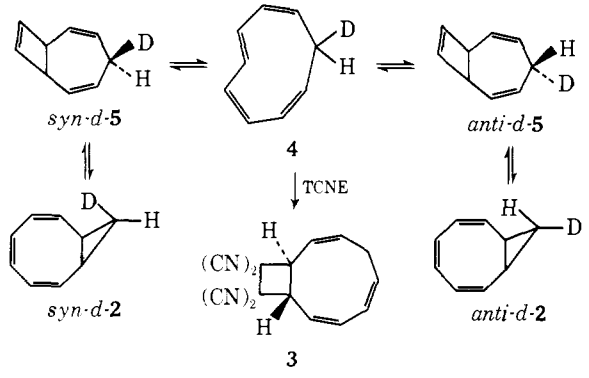


The rate of epimerization was determined by quenching at 15-min intervals and monitoring the pmr signal integrals at −25°. Treating the epimerization as a simple reversible first-order case ($k_1 = k_{-1}$), k_1 was determined as (4.5 ± 0.2) $\times 10^{-5}$ sec^{-1} at 31.3° in CD_3CN ($\Delta G^* = 23.9$ kcal/mol) and (4.7 ± 0.2) $\times 10^{-5}$ sec^{-1} at 35° in $CDCl_3$ ($\Delta G^* = 24.1$ kcal/mol).

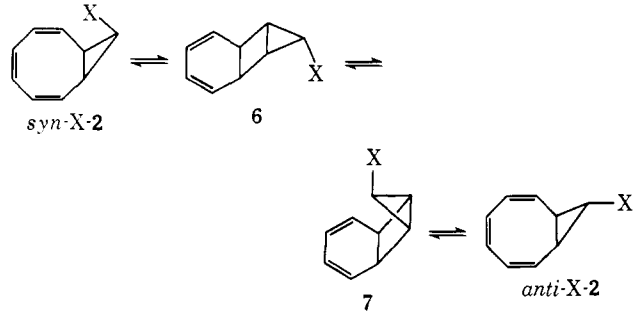
When these data are combined with data recently reported by Boche, Weber, and Benz,[9] the mechanism of epimerization becomes obvious. Boche has presented strong evidence that the reaction of TCNE with **2** to yield adduct **3** occurs through formation and trapping of (*ZEZZ*)-cyclononatetraene **4** as an intermediate. At high concentrations of TCNE in CH_3CN, the rate of formation of **4** becomes rate limiting, the first-order rate constant for its formation being *ca.* 9×10^{-5} sec^{-1} at 31.3°. Presuming **4** to be the intermediate responsible for epimerization of **2**, the rate of formation of **4** should be twice the rate of epimerization of

2, since **4** is symmetrical and half of all **4** formed returns to *syn-d*-**2** with no net epimerization.[10] Comparison of Boche's rate constant for formation of **4** of 9×10^{-5} sec^{-1} and $2k_1$ for epimerization, $(9.0 \pm 0.4) \times 10^{-5}$ sec^{-1}, both at 31.3° in acetonitrile, shows this to be the case within experimental error. Further support for **4** as the epimerization intermediate is the observation by Boche that **4** generated independently thermally rearranges exclusively to **2** at −28°. The complete scheme (Scheme I) proposed for epimerization is summarized below.

Scheme I



Brown[5] has recently suggested that the epimerizations of *syn*-9-fluoro- and *syn*-9-methoxybicyclo[6.1.0]nonatrienes to the anti derivatives, which occur with free energies of activation of 23.2 kcal/mol (35°) and 25.9 kcal/mol (50°), respectively, proceed *via* the tricyclic intermediates as outlined below. This mechanism can be ruled out in the case of



the unsubstituted system for two reasons. First, the free energy of activation for closure of **2** (X = H) to **6** (X = H) can be estimated as *ca.* (27.5 ± 1.0) kcal/mol,[11] considerably greater than ΔG^* for epimerization, and secondly, the activation energy for inversion of the bicyclopentane moiety (**6** to **7**, X = H) can be predicted to fall in the range of 37–45 kcal/mol.[12]

We further suggest that syn-9-substituted systems probably epimerize *via* (*ZEZZ*)-cyclononatetraene intermediates. The ΔG^* of 23.2 kcal/mol for epimerization of syn-F-**2** seems too low to be compatible with the tricyclic mechanism[5] in that ΔG^* for closure of *syn*-F-**2** should exceed 26 kcal/mol.[11] In addition, it is clear that ΔG^* for ring opening of the tricyclic diene with syn stereochemistry[13] (**7**) exceeds that of the diene with anti stereochemistry (**6**),[14] and thus the free energy of formation of the transition state between **7** (X = F) and *anti*-F-**2** would be expected to be even greater than for the transition state between *syn*-F-**2** and **6** (X = F). In the same respects, the feasibility of the tricyclic mechanism for *syn*-9-methoxybicyclo[6.1.0]nonatriene can be regarded as marginal considering the low ΔG^* of 25.9 kcal/mol.

The generally higher activation energies for epimerization of syn-9-substituted systems relative to the unsubstituted system is compatible with a (*ZEZZ*)-cyclononatetraene intermediate. This intermediate very likely forms from bicyclo[5.2.0]nonatriene (**5**) which is produced from Cope rearrangement of the folded conformer of **2**.[6a-c,15,16] This folded conformer and the transition state for the Cope rearrangement are certainly sterically destabilized by syn substituents as previously pointed out by others.[6a-d,15,16]

Other cases to which this mechanism may apply are the epimerizations of the *syn*-9-cyano-[4] and *syn*-9-carbomethoxybicyclo[6.1.0]nonatriene.[3] Since these derivatives have weakened peripheral bonds and strenghthened cross-links,[4] they may well undergo epimerization *via* external bond cleavage as suggested by Jones[3] for the carbomethoxy derivative; however, the present mechanism represents a reasonable alternative which must be considered for these cases.

The present observations bear on the question of possible involvement of the anti epimer in the thermal rearrangement of *syn*-CH_3-**2**.[3,6] Whereas 9,9 dimethyl-**2** thermolyzes predominately to a *trans*-dihydroindene product,[16] the *syn*-CH_3-**2**, which might be expected to behave similarly in the absence of epimerization, yields *ca.* 7:3 ratio of *cis*- and *trans*-dihyroindenes on thermolysis.[6a-c,16,17] Anastassiou has clearly shown that *syn*- and anti-CH_3-**2** yield different product ratios with *anti*-CH_3-**2** giving a *ca.* 9:1 ratio of *cis* and *trans*-dihydroindenes.[6a-c]

We feel a plausible explanation for the origin of *cis*-dihydroindenes from the *syn*-CH_3-**2** isomer is as follows. In the rate determining step, *syn*-4-methylbicyclo[5.2.0]nonatriene (*syn*-CH_3-**5**) is formed which opens to (*ZEZZ*)-1-methylcyclononatetraene. This *ZEZZ* monocycle can then equilibrate with *anti*-4-methylbicyclo[5.2.0]nonatriene (*anti*-CH_3-**5**) and *anti*-CH_3-**2**. This equilibrating system will then lead irreversibly (probably *via anti*-4-methylbicyclo[5.2.0]nonatriene[2b]) to the *cis*-dihydroindenes. Clearly such a mechanism involves generation of the *anti*-CH_3-**2** epimer during thermolysis of *syn*-CH_3-**2**, although it should be noted that formation of the *anti*-CH_3-**2** epimer arises after the rate determining step.[18]

Acknowledgment. This work was supported in part by the National Science Foundation (Grant GP-29580) and by the Research Corporation.

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(17) These facts have been rationalized by postulating that a methyl group of a dimethyl substituted bridge will be "sterically larger" than that in a monomethyl substituted bridge.[16]
(18) The ΔG^* for thermolysis of anti-CH_3-2 is 27.4 kcal/mol[6b] while ΔG^* for the formation of cis-dihydroindenes from syn-CH_3-2 can be estimated as 31.6 kcal/mol. Using this mechanistic model and these values of ΔG^* it can be estimated that ca. 0.4% of the anti-CH_3-2 epimer is present after thermolysis of syn-CH_3-2 for one half-life at 151°.

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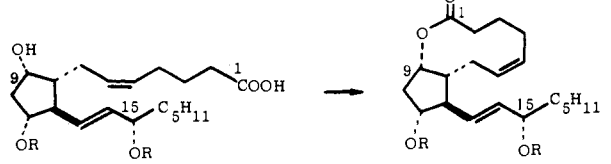
Synthesis of Novel Macrocyclic Lactones in the Prostaglandin and Polyether Antibiotic Series

Sir:

A highly effective method has recently been described for the conversion of a series of ω-hydroxyalkanoic acids to macrocyclic lactones under neutral, aprotic conditions.[1] The method is based on the strategy of forming from the hydroxy acid an ester which is subject to activation of *both* carboxyl and hydroxyl functions by internal proton transfer so as to result in an electrostatically driven cyclization to form the lactone. The extraordinary efficiency of this "double activation" process coupled with its operation without the need for basic or acidic catalysts opens for the first time the possibility of synthesizing a wide variety of complex and highly functionalized macrocyclic lactones. These include not only important naturally occurring lactones (*e.g.*, macrolide antibiotics) but also novel substances formed by lactonization of biologically active hydroxy acids. This communication discloses results on the synthesis of macrolactones in the prostaglandin series which are of special interest as stabilized *in vivo* equivalents of these easily metabolized and medically important substances. In addition, the conversion of the polyether antibiotic monensin to a novel and potentially useful cyclic form is described.

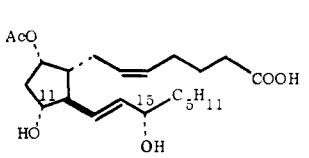
Prostaglandin $F_{2\alpha}$-11,15-bis(tetrahydropyranyl) (THP) ether (**1**),[2] upon treatment with 2,2′-dipyridyl disulfide (1.5 equiv) and triphenylphosphine (1.5 equiv)[1,3] in concentrated dry xylene solution for 15 hr at 25° followed by dilution with xylene and reluxing for 5 hr under an air-free (nitrogen) atmosphere, afforded the protected 1 → 9-lactone derivative of prostaglandin $F_{2\alpha}$ **2** in 90% yield. Removal of the protecting groups (HOAc-H_2O-THF, 3:1:1; 50°; 7 hr) proceeded smoothly to give prostaglandin $F_{2\alpha}$ 1 → 9-lactone **3** (ir_{max} 1740 cm^{-1}, $[\alpha]^{20}D$ + 80.87° (*c* 4 in $CHCl_3$)) as a colorless oil (92%) which solidifies upon refrigeration.[4] In agreement with the assigned structure, **3** underwent selective oxidation with manganese dioxide to form the corresponding 15-ketone,[4] uv_{max} 228 nm (ε 20,000) (EtOH). Apart from being of considerable interest with regard to biological activity, the lactone **3** represents an internally protected form of prostaglandin $F_{2\alpha}$ which allows a variety of useful selective transformations.[5]



1, R = THP

2, R = THP
3, R = H

Reaction of the 9-acetate of prostaglandin $F_{2\alpha}$[4,6] (**4**) with 2,2′-dipyridyl disulfide (2 equiv) and triphenylphosphine (2 equiv) in concentrated xylene solution at 25° for 15 hr followed by dilution with xylene and heating at reflux for 15 hr afforded an oily acetoxy lactone (74%) which gave upon deacetylation (1 equiv of K_2CO_3 in methanol at 25° for 2.5 hr) and chromatography the 1→15-lactone of prostaglandin $F_{2\alpha}$ (**5**):[4] mp 111–112° (from ether-pentane); ir_{max}



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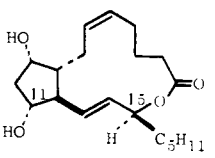


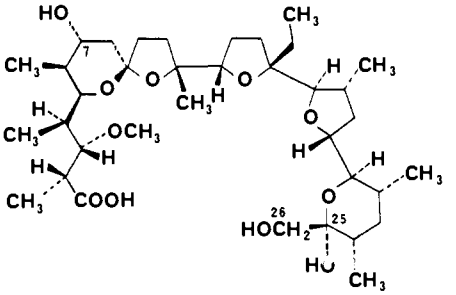
5

1730 cm^{-1}; $[\alpha]^{20}D$ −92.40° (*c* 1.2 in $CHCl_3$) (67%). The lactone **5** was unaffected by treatment with activated manganese dioxide under conditions which converted **3** to the corresponding 15-ketone providing chemical confirmation of the 1→15-lactone formulation (**5**) as opposed to a 1→11-lactone structure.[7]

Application of the lactonization method to prostaglandin $F_{2\alpha}$ itself (1.66 equiv of 2,2′-dipyridyl disulfide, 1.66 equiv of triphenylphosphine in concentrated xylene solution at 25° for 15 hr followed by dilution with xylene and heating at reflux for 8 hr) produced the 1→9-lactone **3** (60% yield) and the 1→15-lactone **5** (16% yield) as major products after chromatographic separation. The R_f values found for **3** and **5** on silica gel thin layer plates using 15% acetone in methylene chloride for development were 0.11 and 0.21, respectively.

Starting from the 15-(*R*) epimer of **1** and using the same procedure as applied for the sequence **1→2→3**, there was produced in 91% overall yield the 15-(*R*) epimer of **3**[4] mp 117–118°, $[\alpha]^{20}D$ + 80.0° (*c* 2.6 in $CHCl_3$). Similarly starting from the 15-(*R*) epimer of **4** there was obtained the 15-(*R*) epimer of **5**, [4]oil, $[\alpha]^{20}D$ + 62.9° (*c* 0.4 in $CHCl_3$) (50% overall).

To illustrate the application of the macrolactonization process in an even more complex case, the cyclization of the polyether antibiotic monensin (**6**)[8] was chosen for study.



6

Treatment of monensin (free acid) with 2.5 equiv of 2,2′-dipyridyl disulfide and 2.5 equiv of triphenylphosphine in benzene for 17 hr at 25° followed by dilution with benzene and heating at reflux for 17 hr afforded the lactone **7**[4] as a clear, colorless oil soluble in all organic solvents, carbonyl absorption at 1726 ($CHCl_3$) or 1733 cm^{-1} (CCl_4), $[\alpha]^{23}D$ +41.8° (*c* 0.70 in CH_3OH), in 95% yield. The attachment