lished mesoionic compounds[12] and heteroaromatic betaines.[2,9,10,13]

Work is currently underway in this laboratory defining the scope and limitations of these unique compounds, as well as studying their physical and chemical properties.

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(4) Satisfactory analytical data were obtained for all compounds reported.
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(14) On leave from (a) Yamaguchi University, Japan; (b) Hebrew University, Jerusalem.

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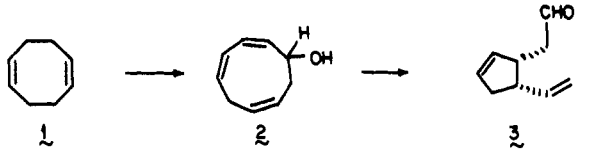
A Stereocontrolled Synthetic Entry to the Primary Prostaglandins from Butadiene. Oxy Anionic Substituent Effects on [1,5]-Hydrogen Sigmatropy

Sir:

Many of the elegant schemes devised to gain access to the prostaglandins have capitalized on the availability of starting materials which contain a suitably functionalized five-membered ring.[1] Herein we describe a new direct approach to this challenging problem which (1) enjoys the economic advantage of being based on butadiene as raw material, (2) provides access to all of the primary prostaglandins and a number of analogues from a single precursor, and (3) allows for optical resolution at a pivotal early stage. The crux of the present strategy lies in efficient overriding by anionic [3,3]-carbon sigmatropy of the normal predilection of a polyunsaturated medium-sized ring for thermal [1,5]-hydrogen sigmatropy.

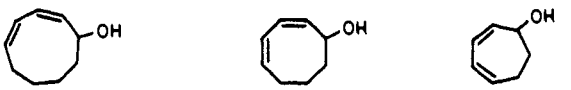
A product of butadiene cyclodimerization,[2] the commercially plentiful *cis*[2]-1,5-cyclooctadiene (**1**) was efficiently transformed into *cis*[3]-2,4,7-cyclononatrienol (**2**) by a previously described procedure.[3] When solutions of **2** in benzene were heated at 160 °C for 3 h in sealed tubes, smooth conversion into a mixture of *cis*[2]-3,7-cyclononadienone (80%) and aldehyde **3** (20%) was observed. The undesirable dominant formation of the dienone, which is in accord with kinetically favored [1,5]-hydrogen shift within **2**, was totally overcome by alternate treatment with 1.2 equiv of oil-free potassium hydride in anhydrous tetrahydrofuran at room temperature.[4] Under these conditions, quantitative conversion into **3**, homogeneous by TLC and VPC analysis, materialized. A noteworthy feature of this reaction is that it represents the first example where the process favored upon thermal activation does not continue to dominate under anionic conditions. Unanswered, however, is the question of whether [1,5]-hydrogen sigmatropy is affected by a substituent change from R = H to R = K. Since this reaction class had not previously been given attention, we have carried out quantitative kinetic studies on **2** and several additional prototypical dienols. *The present findings indicate that the general effect of oxy substitution on neighboring center chemistry remains substantial, although appreciably less so for [1,5]-H than for [3,3]-C sigmatropy.*



1 **2** **3**

The energetics of thermal [1,5]-H migration in neutral **2**, including the activation parameters (Table I), are seen to be slightly more elevated than those associated with comparable processes in unsaturated seven-[5] and eight-membered rings.[6] This somewhat heightened barrier to rearrangement is likely the end result of a less than ideal stereoelectronic alignment between the C–H bond and the pπ components of the flanking diene moiety. Conversion into the lithium alkoxide did not appear to result in marked acceleration of either rearrangement. The situation for the oxy-Cope process improved when M = Na^+; however, the behavior of the potassium alkoxide was truly spectacular (Table I). The rate enhancement for [3,3]-C shift proved to be very large (10^{10} at 25 °C), in agreement with precedent.[4]

The systems chosen for assessment of counterion-controlled [1,5]-H sigmatropy were the cyclic dienols **4–6**, prepared by photooxygenation of *cis*[2]-1,4-cyclononadiene[6c] and 1,4-cyclooctadiene,[7] as well as diisobutylaluminum hydride reduction of 2,4-cycloheptadienone,[8] respectively. In each of the three examples, thermal activation proceeded smoothly to provide the corresponding β,γ-unsaturated ketone exclusively. First-order rate constants for the formation of 3-cyclononenone,[9] 3-cyclooctenone,[9] and 3-cycloheptenone[9] afforded linear Arrhenius plots and the activation parameters shown in Table II. From these rate data, it can be seen that the ease of [1,5]-H shift increases as the ring is decreased in size, as expected from the stereoelectronic considerations mentioned earlier.



4 **5** **6**

When **4** was treated with 1.1 equiv of potassium hydride in dry tetrahydrofuran at room temperature, clean, high yield conversion into 3-cyclononenone (post quench) occurred in a short time. The behavior of **5** was entirely analogous. An exception to this trend was found in the case of **6** which rearranged to mixtures of 3-cycloheptenone (major) and 3,5-cycloheptadienol (minor) in ratios which proved to be temperature dependent. Quantitative kinetic examination of these reactions at three temperatures confirmed that the potassium alkoxides were experiencing [1,5]-H migration at significantly enhanced rates (Table II). Important observations are the 10^5–10^6 rate accelerations common to all three systems, irrespective of their ring size, and the overcoming of substantially more negative $\Delta S^{\ddagger}$ values by appreciable decreases in $\Delta H^{\ddagger}$ (9–14 kcal/mol). In the presence of 5 equiv of 18-crown-6, a limiting ninefold additional rate acceleration was seen. For [3,3]-C migration, this factor is 180.[4] Under these conditions, **6**-O^-K^+ is converted *only* into 3,5-cycloheptadienol. This may arise from an enhanced predilection on the part of the increasingly "naked" alkoxide anion to experience intramolec-

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Table I. Rate Constant and Activation Parameter Data for Rearrangement of **2** and Several of its Alkoxide Salts[a]

substrate	temp, °C	k[3,3], s^{-1} [b]	k[1,5], s^{-1} [b]	thermodynamic parameters for oxy-Cope process (25 °C)
4	169.5	7.44×10^{-5}	2.76×10^{-4}	E_a = 34.5 kcal/mol
	159.5	2.97×10^{-5}	1.25×10^{-4}	$\Delta H^{\ddagger}$ = 33.9 kcal/mol
	149.5	1.16×10^{-5}	5.43×10^{-5}	$\Delta G^{\ddagger}$ = 34.4 kcal/mol
	25[c]	4.02×10^{-13}	1.62×10^{-11}	$\Delta S^{\ddagger}$ = −1.4 eu
K^+ salt	15	6.62×10^{-4}		E_a = 15.4 kcal/mol
	5	2.52 ± 10^{-4}		$\Delta H^{\ddagger}$ = 14.8 kcal/mol
	−3.5	1.05×10^{-4}		$\Delta G^{\ddagger}$ = 21.3 kcal/mol
	25[c]	1.63×10^{-3}		$\Delta S^{\ddagger}$ = −21.7 eu
Na^+ salt	66	5.3×10^{-4}		
Li^+ salt	66	too slow to measure		

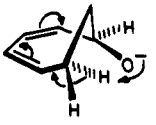
[a] Anhydrous tetrahydrofuran was employed as solvent in all runs. [b] Average value derived from duplicate runs. [c] Extrapolated values based upon the activation parameters.

Table II. Kinetic and Thermodynamic Parameters for [1,5]-Hydride Shifting in **4–6** and Their Potassium Alkoxides (25 °C)[a]

substrate	k(25 °C),[b] s^{-1}	E_a, kcal/mol	$\Delta H^{\ddagger}$, kcal/mol	$\Delta G^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu	$\frac{k_{anionic}}{k_{thermal}}$ (25 °C)
4-OH	2.94×10^{-11}	29.0	28.4	31.8	−11.4	
						2.3×10^6
4-O^-K^+	6.87×10^{-5}	14.7	14.1	23.1	−30.3	
5-OH	1.33×10^{-8}	24.8	24.2	28.2	−13.3	
						1.8×10^5
5-O^-K^+	2.39×10^{-3}	15.6	15.1	21.0	−20	
6-OH	2.87×10^{-8}	24.6	24.0	27.7	−12.5	
						1.4×10^5
6-O^-K^+	4.0×10^{-3} [c]	13.8	13.2	20.7	−25.1	

[a] Anhydrous tetrahydrofuran was employed as solvent in all runs. [b] Extrapolated values based upon the activation parameters. [c] Rate data apply only to 3-cycloheptenone production.

ular hydride transfer as in A, although intermolecular proton transfers are as likely in light of the nature of the data.[10]



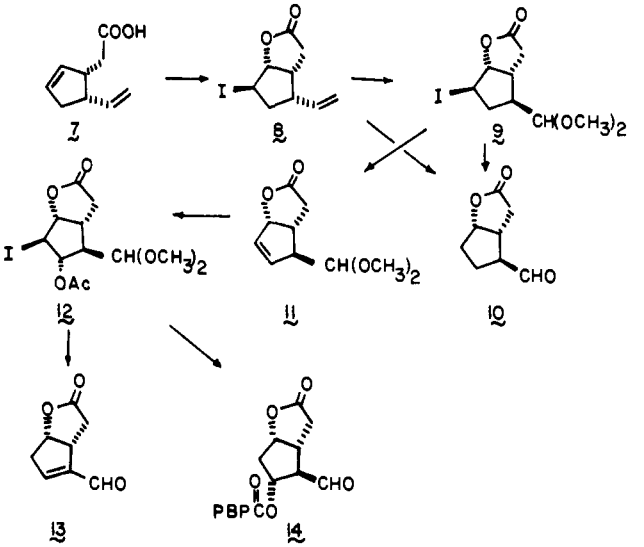
A

Oxidation of **3** with silver oxide (1.2 equiv) and sodium hydroxide (7 equiv) in aqueous solution[11] produced the oily carboxylic acid **7** (75% yield) which was efficiently cyclized to **8**, mp 71–71.5 °C, using standard iodolactionization methodology.[12] The regiospecific formation of **8** stems principally from the kinetic ramifications of γ- vs. δ-lactone formation.[13] Ozonolysis of **8** was effected at −78 °C in dichloromethane solution containing 5 equiv of methanol. Subsequent reductive workup with dimethyl sulfide (1.5 equiv) delivered an aldehyde whose epimerization was efficiently accomplished in a two-phase system of concentrated hydrochloric acid and 2% isopropyl alcohol in chloroform. Following addition of trimethyl orthoformate (9 equiv) and passage of an additional 24 h, oily iodo acetal **9** was isolated in 70% overall yield from **7**. Conversion of **9** into the desired aldehyde **10** was effected by heating (80 °C) in toluene with 1.1 equiv of tri-*n*-butyltin hydride[14] and subsequent hydrolysis with 4 N hydrochloric acid and chloroform under two-phase conditions. A shorter alternative route to **10** consisted of reductive dehalogenation of **8** and ozonolysis followed by acidic epimerization (75%). In light of the prior elaboration of several 11-deoxy prostaglandins from **10**,[15,16] a formal synthesis of these substances is achieved.

Dehydroiodination of **9** with DBU (1.25 equiv) in tetrahydrofuran (reflux, 5 h) resulted in regiospecific introduction of a double bond to give oily lactone **11** in 90% yield. The ready availability of the latter opens a direct access route to the A prostaglandins.[17]

Further, **11** can be converted into **12** (80%) by reaction with iodine (1 equiv) and silver acetate (1.2 equiv) in acetic acid at room temperature for 20 h.[18] Reductive deiodination of this intermediate furnished a trans-locked β-acetoxy acetal which underwent facile elimination in the presence of 4 N hydrochloric acid–chloroform (two phase) to give **13** (81%), a well-established precursor to the C prostaglandins[19] and thromboxane B_2.[20] Usefully, the same deiodination product was easily transformed into the well-known Corey aldehyde **14** in three steps (K_2CO_3, CH_3OH, 20 °C, 0.5 h; *p*-phenylbenzoyl chloride (2 equiv), pyridine, toluene, 20 °C, 24 h;[14] concentrated HCl, $CHCl_3$ containing 2% 2-propanol) and an overall yield of 60%. The successful elaboration of F prostaglandins from **14** has been reported previously.[21,22]

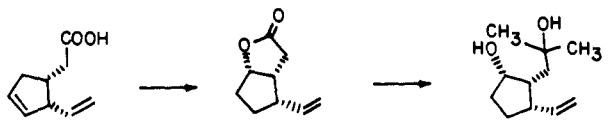
In anticipation of an effective resolution of carboxylic acid **7**, a spectroscopic technique which would permit accurate and convenient assessment of its enantiomeric purity was sought. To this end, **7** was transformed via **8** to the unsaturated lactone



7 8 9 10 11 12 13 14

15 (Bu_3SnH, toluene, 80 °C) with 95% efficiency. Exposure of **15** to 3 equiv of methyllithium afforded diol **16** which was directly subjected to NMR examination ($CDCl_3$ solution).[23] In the presence of ~30 mol % of tris[(trifluoromethyl)hydroxymethylene-*d*-camphorato]europium(III), the diastereotopic methyl groups appear as two equally intense sets of twinned singlets at δ 4.0, 3.8, 2.7, and 2.5, sufficiently separated for accurate integration. Evidently, coordination to the lanthanide ion is adequate to cause restricted rotation about the tertiary hydroxyl bearing carbon.

The resolution of (±)-**7** with *endo*-bornylamine[24] afforded a diastereomeric crystalline salt, mp 107–108 °C, $[\alpha]^{22}_D$ +114° (*c* 2.72, C_2H_5OH), after several recrystallizations from acetone. Recovery of the free acid from this salt gave an oily



7 **15** **16**

product, $[\alpha]^{22}_D$ +151° (*c* 3.22, C_2H_5OH). The sequential conversion of this material into optically active **8**, $[\alpha]^{22}_D$ −21.5° (*c* 2.34, C_2H_5OH), and then into **16**, followed by $Eu(tfc)_3$ analysis, revealed that enantiomeric enrichment had progressed to a level of >98% ee. That the desired antipode had been obtained was established by conversion of the acid into (+)-**13**, $[\alpha]^{23}_D$ +236° (*c* 1.06, $CHCl_3$). When allowance is made for optical purity, the extrapolated rotation for (+)-**13** becomes 241°, in excellent agreement with the $[\alpha]_D$ of an authentic pure sample.[25]

Thus, a preparatively useful route to a wide selection of prostaglandin hormones from the simplest of achiral conjugated dienes has become available. A noteworthy feature of this synthesis, apart from its simplicity, is the unambiguous placement of four contiguous chiral centers about a cyclopentane ring without the benefit of a stereodirecting group in either **1** or **2**.

Acknowledgment. The authors are indebted to the National Institutes of Health for partial financial support of this work (Grant AI-11490), to Robert Henderson of the Cities Service Co. for a generous quantity of *cis*,*cis*-1,5-cyclooctadiene, and to Professor E. J. Corey, Dr. Norman A. Nelson, and Dr. Edward D. Brown for ^1H NMR spectra, certain physical constants, and (in the last instance) an authentic sample of **14**.

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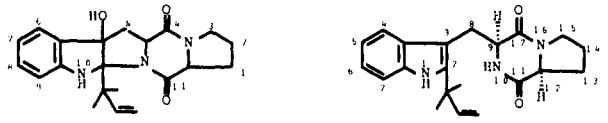
Asymmetric Total Synthesis of Brevianamide E

Sir:

The structure of brevianamide E, isolated from the culture medium of *Penicillium brevicompactum*, was assigned as **1** mainly on the basis of spectroscopic evidence and plausible biogenetic argument.[1] More recently a degradation product of brevianamide E, deoxybrevianamide E [L-prolyl-2-(1′,1′-dimethylallyl)tryptophyldiketopiperazine (**2**)], was found in a toxigenic fungi, *Aspergillus ustus*,[2] and synthesized.[3]



1 **2**

However the stereochemistry of brevianamide E remained obscure. We here report the first total synthesis of optically active brevianamide E, which determines the relative stereochemistry and the absolute configuration.

Schotten-Baumann reaction of the acid chloride of *N*-benzyloxycarbonyl-L-proline (**3**) with dimethyl aminomalonate[4] gave the amide **4** (Scheme I), mp 75.5–76 °C, $[\alpha]^{18}_D$ −43° (*c* 0.1, EtOH), in 69% yield. After debenzyloxycarbonylation of **4**, using 20% palladium/charcoal under 2 atm of hydrogen in methanol, the resulting amine **5** was heated at 120 °C for 1 h to afford the diketopiperazine **6** in 40% yield. Furthermore this cyclization was found to be effectively catalyzed by 2-hydroxypyridine.[5] Thus **6** was obtained as a single stereoisomer, mp 64–65 °C, $[\alpha]^{18}_D$ −54° (*c* 0.111, MeOH), in 93% yield from **4**, by heating **5** at 70 °C for 1 h in the presence of a catalytic amount of 2-hydroxypyridine.

Condensation of **6** with 3-dimethylaminomethyl-2-(1′,-

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