# Total Synthesis of $(\pm)$ -Cortisone. Double-Hydroxylation Reaction for Corticoid Synthesis

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Abstract: Total syntheses of  $(\pm)$ -cortisone and  $(\pm)$ -adrenosterone have been achieved in 18 steps with the aid of metal-assisted new synthetic sequences, in particular, ene reaction and homoenolate chemistry. A novel double-hydroxylation reaction of enol silvl ethers leading to a single step construction of the dihydroxyacetone side chain in corticoids has been developed and applied to the synthesis of cortisone, cortexolone, and  $16\alpha$ -methylcortexolone.

Cortical steroids,<sup>1</sup> of which cortisone (1),<sup>2,3</sup> cortisol (2),<sup>4</sup> cortexolone (3),<sup>5</sup> and aldosterone  $(4)^6$  are prominent instances of active substances, are secreted by the cortex of the adrenal glands in mannals. They exhibit a broad range of physiological activities



from the control of sodium content in blood to the regulation of carbohydrate metabolism. The enone moiety in the A ring as well as the ketol in the side chain has been considered necessary for these biological activities. Dexamethasone  $(5)^7$  and betamethasone (6),<sup>8</sup> the 16-methyl group of which has been introduced to retard the metabolic loss of the ketol side chain, represent a typical structure of the commercialized drugs. Over the years, corticosteroids have been the subjects of extensive pharmacological, chemical, and synthetic investigations.<sup>1</sup> In particular, cortisone's six contiguous chiral centers, coupled with its physiological importance, have made this prominent member of steroids an attractive target of synthetic activities over the last three decades.

Historically, several different strategies<sup>1,9</sup> have provided chemical access to the corticosteroids.<sup>10</sup> Among these, the CD

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→ ABCD approach has come to gain considerable recent success mainly owing to the excellent strategies presented by Stork<sup>11</sup> for elaboration of the CD ring as well as the AB ring portion of the molecule.

In spite of the myriad of efforts directed toward the preparation of cortisone, only three classical examples<sup>3</sup> have actually achieved the total synthesis of the final target structure. Instead, a vast majority of syntheses terminated at the stage of adreno-sterone<sup>11a,b,c,12</sup> (7) or 11-ketoprogesterone<sup>11d,13</sup> (8), onto which the oxygenated side chain is to be installed with the aid of established several-step procedures<sup>9,14</sup> that accompany suitable protection/ deprotection processes.



The design and analysis of new reactions and development of efficient strategies for natural product synthesis have long been major forces of research in these laboratories, and the considerable challenge of creating a stream-lined approach to the corticosteroids

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emerged as an attractive objective. We have focused on the synthesis of cortisone, in particular, on the development of efficient access for the construction of the dihydroxyacetone side chain, during the pursuit of which we hoped to devise new strategies for corticoid synthesis as well as to develop new concepts in the designing of new reactions. Herein are reported the details of the 18-step total synthesis of  $(\pm)$ -cortisone (1),<sup>15</sup>  $(\pm)$ -adrenosterone (7) as well as partial synthesis of cortexolone (3), and congeners. Aspects of computational analysis of some crucial stereochemical results are also described.

### **Results and Discussion**

(A) Total Synthesis of  $(\pm)$ -Cortisone and  $(\pm)$ -Adrenosterone. In planning the synthesis of cortisone, the decision was made to adopt an excellent strategy developed by Stork for the AB ring construction,<sup>11c,d</sup> which converts the partial structure A into the 3-enone B in only five steps in good overall yield (Scheme I). This scheme should provide the most straightforward access to the steroidal AB ring, if an efficient route to the starting 1,6-keto ester A could be secured.

With these considerations in mind, the keto acid C was viewed as the logical precursor. The homoallylic alcohol portion on the D ring serves for introduction of the dihydroxyacetone side chain through appropriate refunctionalization. For this specific problem, a novel double-hydroxylation procedure (vide infra) has been developed.

Given a chance of the availability of the copper homoenolate D, whose conjugate addition was then studied in these laboratories,<sup>16</sup> our initial effort was concentrated on efficacious preparation of the enone E that would act as a viable Michael acceptor.

A common problem in the CD  $\rightarrow$  ABCD ring strategy, namely stereoselectivity in the construction of a *trans*-hydrindan, emerges in the preparation of E. On the basis of related studies by us<sup>17</sup> and others,<sup>18</sup> we have chosen to rely upon the stereoselective conjugate addition of an organocopper reagent to enone F.

The enone 11 that represents a pro-C ring was conveniently prepared in two steps (81% overall yield) from the commercially available enone 9 as previously reported.<sup>17,19</sup> In order for in-



troduction of the latent D ring side chain, the enone 11 was treated with a variety of organocopper reagents derived from (2methyl-1-propenyl)magnesium bromide (12). Owing to the steric impediment at C(13) exercised by the (*tert*-butoxycarbonyl)methyl appendage, the desired conjugate addition proceeded only when a large amount (>3-fold excess) of a copper reagent with a cuprate-type stoichiometry was employed (maximum 78% yield of 13). The reaction was, however, frustrated by its poor reproducibility, often producing considerable amounts of 1,2-adducts. Me<sub>3</sub>SiCl acceleration of the conjugate addition of catalytic organocopper reagents, then investigated in our laboratories,<sup>16,20,21</sup>



Figure 1. Assignment of C-16 stereochemistry.

provided an effective solution to this problem. Thus, when a mixture of the enone 11 and Me<sub>3</sub>SiCl was added to a cooled THF solution of a mixture of 1.5 equiv of the Grignard reagent 12 and a catalytic amount of CuBr·Me<sub>2</sub>S, the conjugate reaction was found to proceed very rapidly to give the desired adduct as a single isomer after aqueous workup. Despite the use of a nearly stoichiometric amount of the Grignard reagent, reproducibility of the reaction was excellent, and the yield was comparable to that of the foregoing stoichiometric reaction. The stereochemistry of the adduct 13 was assigned to be trans on the basis of related examples<sup>17</sup> and was confirmed at a later stage. The keto ester was then converted to olefinic aldehyde 14 in two steps (LiAlH<sub>4</sub>, Swern oxidation, 78%).

With the stereochemistry of the CD ring juncture thus secured, the task of closing the D ring remained to be done. Internal ene reaction is known to be a reliable procedure for the formation of five-membered rings, which gives rise to 1,2-cis-disubstituted isomers.<sup>22</sup> Thus, the ring closure of 14 by the ene reaction was expected to mainly produce either 15 or 16. Although the formation of the  $16\beta$ ,  $17\beta$ -isomer 16 was desired in view of the C(17) stereochemistry of natural steroids, it was not clear if the ene reaction actually provides such stereochemistry. The difficulty in making predictions on an empirical ground arose from the competing A<sup>1,2</sup>- and A<sup>1,3</sup>-strain in the highly substituted allylic system found in 14. In the last section of this article is discussed the ground-state and transition-state analysis of 14 by a computational method that correctly predicts both the sense and the degree of the stereoselectivity.

Initial attempts to effect thermal ene reaction failed. Heating 14 either neat or as a solution in a sealed tube at 150-300 °C gave a complex mixture from which products perhaps due to internal aldol condensation were isolated. We next examined Snider's Me<sub>2</sub>AlCl-catalyzed ene reaction<sup>23</sup> that could be carried out under much milder conditions. In contrast to the simple cases reported, the Lewis acid catalyzed reaction of 14 was slow at low temperature, and the use of excess reagent invariably gave a tertiary chloride 17 as a major product.

Only in the presence of 1 equiv of the aluminum reagent at 0 °C, however, did very clean reaction take place to afford the desired *trans*-hydrindanone 15 in 85% yield as a mixture of isomers, in which the major isomer constituted 85% of the total with the other three isomers constituting about 5% each. The stere-ochemistry of the reaction remained unaffected by variation of the reaction conditions.

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#### Scheme II





To determine the C(16) and C(17) stereochemistry, the cyclized product (containing about 5% of an isomer) was acetylated and then subjected to further transformation (Scheme II). The acetoxy ketone 18 was converted through a sequence of standard reactions to 21. The ketone 21, which contained a small amount of 22 (ratio 94:6), was treated with KOH in methanol. After 18 h at room temperature, the 21 to 22 ratio changed to 28:72. Since the  $\beta$ -oriented 17-acetyl group is thermodynamically more favored than the  $\alpha$ -oriented one,<sup>9</sup> the acetyl group in 21 must have been  $\alpha$ -oriented and so must have been the isopropenyl group in 18.

For further confirmation of the assignment, the ketal in 22 was hydrolyzed to obtain the diketone 23, which was identical with the material prepared by catalytic hydrogenation of enone 24, which is to occur from the less hindered  $\alpha$ -side as amply demonstrated in the steroid chemistry.9

With the C(17) stereochemistry assigned, the 16-hydroxyl group was shown to be also  $\alpha$ -oriented on the basis of 500-MHz <sup>1</sup>H NMR analysis of the (*tert*-butyldimethyl)silylated derivative 28 obtained at a later stage. Careful decoupling experiments and spectrum simulation (LAOCOON)<sup>24</sup> coupled with conformational analysis by molecular mechanics (MM2)<sup>25</sup> served to show that the C(16) methyne and the C(17) methyne are cis to each other. The observed coupling constant of  $J_{16,17} = 6.4$  Hz was especially diagnostic (Figure 1). Thus, the major product of the ene reaction was shown to be 15.

While the stereochemistry of C(16) and C(17) is erased at a later stage, the major isomer 15 was separated for the sake of experimental simplicity and used for the subsequent reactions. The CD ring portion with an appropriate side chain at C(17)completed, our attention was next focused on the introduction of the  $\alpha$ -oriented propionate appendage onto C(8). To this end, the ketone 15 was converted first to enol silvl ether 25 and then to the enone 26.26 A high level of the regioselectivity was achieved during silvlation either with Me<sub>3</sub>SiCl/NaI<sup>27</sup> or ethyl (trimethylsilyl)acetate/TBAF.28

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Among a variety of functionalized three-carbon nucleophiles that might undergo conjugate addition to 26, the catalytic copper homoenolate D that had just been developed was the most suitable candidate.<sup>16</sup> We anticipated that the addition reaction selectively would afford the desired  $8\alpha$ -isomer 27, since the addition of organocopper reagents onto trans-fused bicyclic compounds such as 26 would take place from the less hindered  $\alpha$ -side.<sup>12b,29,30</sup> In fact, conjugate addition of Me<sub>2</sub>CuLi to 26b proceeded highly selectively to give a product that exhibited a high-field 18-methyl signal typical for an  $8\alpha$ -isomer.<sup>30</sup>

In sharp contradiction with the above expectation, the conjugate addition of the homoenolate under our standard conditions of using Me<sub>3</sub>SiCl as a promoter (note that no reaction takes place without a Lewis acid additive)<sup>16</sup> turned out to be more  $\beta$ -face selective, affording a disappointing 1/1 mixture of stereoisomers 27b and 29 (100% yield). The readily discernible angular methyl signals on <sup>1</sup>H NMR serve to distinguish these isomers (27b,  $\delta = 0.92$ ;

(30) The following correlation has been observed for the stereochemistry at the pro-C(8) and the <sup>1</sup>H NMR spectrum. The signals due to the angular methyl group in 8a-substituted pro-CD rings and congeners appear at an upper field (by ca. 0.1 ppm) than those due to the  $\beta$ -substituted isomer, and the parent enones show their angular methyl signals in between: (a) Stork, G.; Spiess, E. J., Columbia University, unpublished results. Spiess, E. J. Ph.D. Thesis, 1980. (b) Reference 12b.

Chemical Shift Values of Angular Methyl Groups



(c) There have been found some evidence that conjugate additions of cuprates to some enones are reversible.<sup>21b</sup> The observed equatorial selectivity in the precedents<sup>12b,29,30a</sup> as well as in the addition of Me<sub>2</sub>CuLi to **26** is very likely due to the reversibility (cf. formula i wherein the copper moiety takes the less hindered equatorial position). Me<sub>3</sub>SiCl-mediated addition, on the other hand, has been proposed to be kinetically controlled with its stereochemistry being controlled at an early stage of the addition,<sup>21b</sup> and this is likely to result in the enhanced axial approach in the present Me<sub>3</sub>SiCl-mediated reaction. One possible rationalization thus involves a stereochemistry-determining step represented by ii, in which the conjugation between the forming carbon-copper bond and the enolate severely distorts the fused bicyclic structure (estimated by MM2 to give several kilocalories per mole strain). Another interpretation in a similar vein involves a four-membered intermediate iii proposed recently: Corey, E. J.; Hannon, F. J.; Boaz, N. W., to be submitted for publication. E.N. thanks Professor Corey for the provision of the manuscript.



**29**,  $\delta = 1.12$ ). The propensity of the Me<sub>3</sub>SiCl to relatively favor the  $\beta$ -attack was found very prominent. For instance, despite the strong steric impediment due to its angular [(tert-butyldimethyl)siloxy]methyl group, the 18-siloxy enone 30 related to a projected synthesis of aldosterone (4) also afforded a 1/1 mixture of diastereoisomers.

Despite the lack of reasoning for the selectivity of the Me<sub>3</sub>SiCl-mediated reaction,<sup>30e</sup> we examined various other conditions, to find that  $BF_3 \cdot OEt_2^{31}$  not only accelerates the reaction but also improves the stereoselectivity to afford the desired adduct 27a with over 97% selectivity in 80-85% yield.

The keto ester 27a was then converted eventlessly to the keto acid 28 through protection of the 16-hydroxyl group by (tertbutyldimethyl)silylation followed by hydrolysis of the ester group. The overall yield from the hydrindanone 15 to 28 was 35%. It should be noted that the silvlation just mentioned is the only protective operation in our 18-step synthesis, and the silvl group installed herein acts as a leaving group at a later step.

The stereochemistry of C(8), C(13), and C(14) was confirmed at this point by chemical correlation to Stork's intermediate, 3411d (Scheme III). The ester 31 prepared from 27a was reduced to the alcohol 32 and then converted to the  $17-\beta$ -acetyl compound 33. Ketalization of the 20-keto group, followed by oxidation of the 11-hydroxyl group and hydrolysis of the ester group, afforded the keto acid 34. The <sup>1</sup>H NMR of this material compared favorably with that of an authentic spectrum.

Conversion of 28 to the steroid nucleus 39 was achieved through the internal Diels-Alder route.<sup>11c,d</sup> The keto acid 28 was subjected



to Stork's three-step protocol to obtain the tetracyclic ketone 37 in 68% overall yield, together with two minor structural isomers. One of these isomers was assigned by <sup>1</sup>H NMR as an olefinic regioisomer 40 (12% yield), which formed during the dehydration reaction, and another as a stereoisomer 41 (8%) formed in the cycloaddition reaction. Attempted isomerization (RhCl<sub>3</sub>·H<sub>2</sub>O/ EtOH)<sup>11d,33</sup> of the regioisomer 40 resulted in the formation of a complex mixture due to destruction of the homoallylic alcohol moiety in the D ring. Ozonolysis of the tetracycle 37 gave the tetraketone 38 (80% yield), which was then subjected to aldolization to form the A ring. Stork's original conditions  $(4\% \text{ KOH/MeOH}, 0.015 \text{ M})^{11e}$  gave the desired product **39** in a moderate yield (50%), accompanied by the methanol adduct 42 (10%). Cyclization could not be achieved in isopropyl alcohol or in *tert*-butyl alcohol. Interestingly, base treatment of the tetraketone 43 possessing a methoxymethyl (MOM) group produced a complex mixture perhaps due to formaldehyde in situ generated from the MOM group. An observation that 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) converts the methanol adduct 42 to the desired triketone 39 suggested possible use of this base

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for the conversion of 38 to 39. Indeed, heating a (0.03 M) benzene solution of 38 and DBU (10 equiv) in a sealed tube at 230 °C for 3 h afforded **39** in over 75% vield.<sup>34</sup> The two-step conversion from 37 to 39 not only completed the AB ring but also set the D ring ready for the final hydroxylation of the side chain.

At this point, completion of synthesis of  $(\pm)$ -cortisone requires only the introduction of the two hydroxyl groups at C(17) and C(21) to 39 possibly by selective manipulation of the D ring enone. At the outset, this task appeared to be a formidable challenge, since the compound possesses an equally reactive A ring enone. Recourse to the manipulation of the side-chain portion at an earlier stage thus emerged as a reasonable alternative. In an attempt to selectively hydroxylate the latent C(21) methyl group, the keto ester 44 was epoxidized to 45, which was then submitted to



isomerization conditions (Al(O<sup>i</sup>Pr)<sub>3</sub>,<sup>35</sup> Al(O<sup>i</sup>Bu)<sub>3</sub>, Ti(O<sup>i</sup>Pr)<sub>4</sub>,<sup>36</sup>  $Et_2AITMP$ ,<sup>37</sup> Me<sub>3</sub>SiOTf/amine,<sup>38</sup> and TBSOTf/amine). Although the reaction of **45b** with Ti(O'Pr)<sub>4</sub> afforded **46b** in ca. 60% yield, the reaction was poorly reproducible. Alternative attempts to directly convert 44 to 46 by SeO<sub>2</sub>/AcOH failed presumably because of the preferential oxidation of the 11-keto group. It is notable that a substantial level of diastereoselection (83:17) occurred during the mCPBA epoxidation of the homoallylic alcohol 44a. The overwhelming preference of the conformer G over H



(by MM2) combined with the Henbest rule suggests the stereochemistry of the epoxide 45a as indicated. In support of such reasoning, a much lower level of stereoselectivity was seen for the silyl ether 44b.

Focusing again on the selective hydroxylation of the D ring enone at the stage of the triketone 39, we envisioned taking ad-



vantage of its steric environment. In light of literature precedents on the selective hydrogenation of the  $\Delta^{16}$ -olefin in the presence of the more hindered  $\Delta^4$ -olefin,<sup>9</sup> the Rh-catalyzed hydrosilation reaction<sup>39</sup> was examined. The reaction of 39 with 1.0 equiv of

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tripropylsilane and a catalytic amount of RhCl(PPh<sub>3</sub>)<sub>3</sub> in THF at 60-65 °C for 82 h proceeded expectantly to give enol silvl ether 47 as the predominant product (89% yield on 74% conversion). The next objective entailed the standard oxygenation of the enol silvl ether moietv<sup>40</sup> to introduce the 17-oxygen function (48), which was hoped to act as cornerstone for selective oxygenation of the C(21) methyl group.

In the first step toward this endeavor, we encountered a truly remarkable transformation. When the enol silyl ether was oxidized with slight excess of mCPBA in the presence of excess NaHCO<sub>3</sub> in CH<sub>2</sub>Cl<sub>2</sub> at 0 °C, a considerable amount of 17-hydroxy-21-siloxy ketone, the silvl ether of the target molecule, was formed, whereas none of the expected 17-siloxy ketone 48 was detected. To our great surprise, use of 2.5 equiv of mCPBA in the presence of powdered KHCO<sub>3</sub> was found to convert 47 directly into cortisone silyl ether, which smoothly lost its silyl group upon acidic workup to afford cortisone (1) in isolated 83% yield. Thus, the synthesis of the target molecule has been achieved from the triketone 39 in a remarkably short, two steps. The synthetic, racemic cortisone was identical with an authentic sample of natural 1 by 200-MHz <sup>1</sup>H NMR, 50-MHz <sup>13</sup>C NMR, and TLC mobility under several different conditions. An 18-step total synthesis of (±)-cortisone has thus been achieved in ca. 5% overall yield.

A very slight modification of the final oxidation step (i.e., order of the addition of the reagents; see the Experimental Section) converts the enol silvl ether 47 directly into  $(\pm)$ -adrenosterone (49). Thus, treatment of 47 with a mixture of 2.5 equiv of mCPBA and excess KHCO<sub>3</sub> at room temperature produced 49 in 50% yield.

(B) Double Hydroxylation: General Synthesis of the Dihydroxyacetone Side Chain in Corticoids. There have been several methods for introduction of the dihydroxyacetone function onto a steroid nucleus, which start(s) either from a 17-keto or 20-keto compound requiring three to several steps 9,14 Although the stereochemistry of the 17-hydroxyl group is generally well taken care of by the presence of the 18-methyl group, the chemoselectivity is not always very high, usually necessitating suitable protective operations.

The double-hydroxylation reaction described above has two unique advantages over the existing ones, its extreme brevity and the notable chemoselectivity owing to the neutrality of the conditions. Investigation of the general potential of this reaction in the synthesis of corticoids was without doubt worthwhile.

In order to define the scope of the reaction, dienone 50 (Scheme IV) was studied in some detail. The hydrosilation reaction has proven not only highly regioselective so far as the reaction was not forced to go completion but also stereoselective with respect to the geometry of the enol double bond (unassigned, however). Thus, with 1.0 equiv of tripropylsilane, enol silyl ether 51 was obtained as a single product in 79% yield upon 92% conversion.

The remarkable ease of the double hydroxylation led us to examine its generality in corticoid synthesis. Oxidation of 51 with 1.0 equiv of mCPBA in the presence of excess powdered KHCO<sub>3</sub> in  $CH_2Cl_2$  produced enol silvl ether **52** in a surprising 91% yield. The reaction enables regio- and chemoselective activation of the C(21) position under practically neutral conditions. If KHCO<sub>3</sub> was omitted, a considerable amount of 17-hydroxy ketone 54 formed, presumably owing to protonolysis of an intermediary epoxide 53. Alternatively 51 could be oxidized in 88% yield to cortexolone  $(3)^5$  by slow addition of a solution of ca. 2.5 equiv of mCPBA. Interestingly, when 51 was added to mCPBA, androsterone 55 was obtained in 68% yield presumably due to Baeyer-Villiger oxidation of either 54 or 3.

In another example, the acetoxy enone 56 (Scheme V) was hydrosilated in the presence of Wilkinson's catalyst (88%), and the resultant silyl ether 57 was double-hydroxylated to 58, the triacetate 59 of which has been used as an intermediate of com-

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Scheme IV



Scheme V



<u>60</u>

5<u>0</u>

mercial production of corticosteroids.<sup>10</sup>

As mentioned in a previous paragraph, Me<sub>3</sub>SiCl dramatically accelerates conjugate addition of catalytic organocopper reagent, thereby greatly improving the chemoselectivity.<sup>20</sup> Combined use of the Me<sub>3</sub>SiCl-acceleration technology and the doublehydroxylation procedure led to the rapid construction of pharmacologically important 16-methyl-17,21-dihydroxy structure found in some corticoid drugs (cf. 5 and 6). Thus, the dienone 50 was treated with 1.2 equiv of MeMgBr in the presence of Cu<sup>+</sup>(cation)/Me<sub>3</sub>SiCl/HMPA to obtain a 98:2 geometrical mixture of the silvl ethers 60 in 94% isolated yield, whose double-bond geometry has not been assigned. The isomeric relationship between these products was established by conversion of each separated isomer to the same double-hydroxylation product 61 (86%). The stereochemistry of the 16 $\alpha$ -methyl group was assigned on the basis of the well-established steric bias in the D ring.9

(C) Stereochemistry of the Ene Reaction of the CD Ring Precursor. Although the intramolecular ene reaction is one of the most important ring-forming reactions that provides access to 1,2-cis-disubstituted cyclopentanes,<sup>22</sup> rules that could predict the preferential formation of the  $16\alpha$ , $17\alpha$ -isomer **15** have been lacking.

61 ~

Since molecular models are virtually incapable of handling the effects of bond distortions and long-range steric interactions, analysis of the stereochemistry of the ene cyclization of 14 using molecular models offered only poor rationalization of experimental results. Computational models being able to keep track of these factors,  $^{41,42}$  we have examined this case by using molecular mechanics calculation.

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Ground-state analysis  $(MM2)^{25}$  of the CD ring precursor 14 indicated that the conformers leading to the formation of 15 (e.g., I) are more stable than those affording 16 (i.e., J) by 1–2 kcal/mol mainly due to the greater A<sup>1,3</sup>-strain between C(18) and C(21) methyl groups in J than the A<sup>1,2</sup>-strain in I.



The ground-state consideration was thus in line with the experimental observations. Nonetheless, we felt that use of a more transition-state-oriented calculation, which may incorporate the spirit of Houk's ab initio MM2 method,<sup>43,44</sup> should give us a more reliable picture of the stereoselectivity. The ene cyclization catalyzed by 1 equiv of Me<sub>2</sub>AlCl at low temperature has been considered to be kinetically controlled.<sup>23</sup>

Transition-state structures of the ene reaction of propene with ethylene and with formaldehyde have recently been calculated.<sup>45</sup> They are remarkably similar to each other, implying that the transition structure of the ene reaction is relatively insensitive to variation of the nature of the reactants: the lengths of the forming  $C_{sp^2}-C_{sp^2}$  bond in the transition state of the reaction of propene with formaldehyde and that with ethylene have been calculated to be 2.016 and 2.11 Å, respectively.

We postulated "reactive conformations" leading to 15 and 16, wherein two reacting sp2 carbons (pro-C(16) and C(17)) in the stable ground-state conformers, I and J, are forced to stay at a distance of 2.016 Å (a 2.11-Å distance gave essentially the same conclusion). These structures were then optimized with this constraint to obtain stable conformers,  $16\alpha$ , $17\alpha$ -conformer (K) and its alternative (L), the latter being less stable by 0.95 kcal/mol. In both of the optimized "reactive conformers", the distance between the aldehyde oxygen and the starred methyl carbons bearing the transferred hydrogen needs only decrease from 3.05-3.16 to 2.56 Å to attain the ab initio transition-state geometry. Thus, the calculated energy difference of 0.95 kcal/mol that represents a 85:15 ratio at 0 °C provides a reasonable estimate of the steric effects in the two diastereomeric transition states leading to 15 and 16.

The reasonable correlation between the experimental and the computational results is rather surprising in view of the rather arbitrary choice of parameters. There is little doubt however that computational models, used in a discrete fashion for comparison of closely related diastereoisomeric structures, would help chemists make synthetic plans with greater confidence than simple manipulation of molecular models.

### **Experimental Section**

Keto Ester 13. A THF solution of (2-methyl-1-propenyl)magnesium bromide (0.47 M, 8.5 mL, 4.0 mmol) was added to a suspension of CuBr Me<sub>2</sub>S (78 mg, 0.38 mmol) in THF (5 mL) at -78 °C. A mixture of 4-[(tert-butoxycarbonyl)methyl]-3-methyl-2-cyclohexen-1-one (11; 0.542 g, 2.53 mmol) and trimethylsilyl chloride (2.2 mL, 17 mmol) in 2 mL of THF was added to the suspension over a period of 5 min. The mixture was stirred at -78 °C for 40 min, quenched by addition of 1 N HCl (3 mL) and THF (3 mL), and diluted with methanol until a homogeneous solution was obtained. After the solution was stirred for 2 h at room temperature, solid sodium chloride and hexane was added. The organic layer was separated and washed twice with 1 N HCl, and the aqueous layer was extracted twice with hexane. The combined organic extracts were washed with a saturated sodium bicarbonate and with brine, dried over magnesium sulfate, and concentrated to obtain a crude product. Chromatographic purification on silica gel (10% ethyl acetate/hexane) afforded the desired keto ester 13 (0.55 g, 78%). The product was homogeneous by GLC analysis: IR (neat) 1714 (s) cm<sup>-1</sup>; H NMR (60 MHz, CCl<sub>4</sub>) δ 0.97 (s, 3 H), 1.2-2.6 (envelope, 24 H, including s, 9 H at 1.42 and m, 6 H at 1.63-1.77), 4.85-5.04 (m, 1 H); GLC (PEG-20M, CT 170 °C) retention time 29.2 min. Anal. Calcd for C<sub>17</sub>H<sub>28</sub>O<sub>3</sub>: C, 72.82; H, 10.06. Found: C, 72.98; H, 10.10.

Olefinic Aldehyde 14. Lithium aluminum hydride (85 mg, 2.2 mmol) was added to an ethereal solution (5 mL) of the keto ester 13 (191 mg, 0.681 mmol) at 0 °C, and the mixture was stirred at room temperature for 1 h. The standard workup for LAH reaction gave the crude diol, which was used in the next step without purification. To a cooled (-55 °C) solution of oxalyl chloride (0.20 mL, 2.3 mmol) in methylene chloride (5 mL) was added dimethyl sulfoxide (0.32 mL, 4.5 mmol). After 2 min the crude diol in methylene chloride (2 mL) was added slowly during 3 min. The mixture was stirred at that temperature for 20 min, and triethylamine (1.3 mL, 9.3 mmol) was added in one portion. The reaction mixture was warmed to room temperature, washed with water and with brine, dried, and concentrated to obtain a crude product. Chromatographic purification on silica gel (30% ethyl acetate/hexane) yielded 110 mg of the olefinic aldehyde 14 (78%) as a colorless oil: IR (neat) 1710 (s) cm<sup>-1</sup>; <sup>1</sup>H NMR (60 MHz, CCl<sub>4</sub>) δ 1.00 (s, 3 H), 1.2-2.8 (m, 15 H, including m, 6 H at 1.70-1.83), 4.90-5.13 (m, 1 H), 9.63-9.77 (m, 1 H). Anal. Calcd for C<sub>13</sub>H<sub>20</sub>O<sub>2</sub>: C, 74.96; H, 9.68. Found: C, 75.10: H. 9.54.

trans-Hydrindanone 15. To a methylene chloride solution (20 mL) of the olefinic aldehyde 14 (383 mg, 1.84 mmol) was added a hexane solution of dimethylaluminum chloride (1.4 M, 1.35 mL, 1.9 mmol) at 0 °C during 10 min, and the reaction mixture was kept at that temperature for 15 min. After slow addition of 1 N HCl, the mixture was diluted with ether. The organic layer was washed twice with 1 N HCl, with saturated sodium bicarbonate and then with brine. Column chromatography on silica gel eluted by 40% ethyl acetate/hexane gave the trans-hydrindanone 15 as a brownish oil (277 mg, 72%): IR (neat) 3340 (br), 1700 (s), 890 (m) cm<sup>-1</sup>; <sup>1</sup>H NMR (60 MHz, CCl<sub>4</sub>)  $\delta$  0.90 (s, 3 H), 1.4–2.6 (envelope, 14 H, including br s, 3 H at 1.79), 4.10–4.50 (m, 1 H), 4.83–5.07 (m, 2 H).

Keto Ester 27a Due to Homoenolate Addition. To an acetonitrile solution of sodium iodide (19.1 g, 127 mmol) were added an acetonitrile solution (20 mL) of the hydrindanone 15 (6.7 g, 32 mmol), triethylamine (22.7 mL, 163 mmol), and chlorotrimethylsilane (16.0 mL, 126 mmol). The mixture was stirred at room temperature for 40 min and extracted four times with hexane. The extract was then washed with saturated sodium bicarbonate and with brine and dried, and the solvent was removed under reduced pressure. The crude enol silyl ether 25 was dissolved in acetonitrile (50 mL), to which palladium acetate (7.0 g, 31 mmol) was added, and the mixture was stirred at room temperature for 5 h. Most of the solvent was removed in vacuo, and the residue was extracted with ethyl acetate/ether. The extract was filtered through silica gel, and the filtrate was concentrated to obtain the enone 26a, which was used for the next step after simple purification by short silica gel column chromatography (30% ethyl acetate/hexane). To a cooled (0 °C) mixture of the enone 26a and CuBr Me<sub>2</sub>S (813 mg, 3.95 mmol) in THF (100 mL) were added sequentially a THF (10 mL) solution of zinc homoenolate<sup>16</sup> (58 mmol), HMPA (10 mL, 57.5 mmol), and BF<sub>3</sub>·OEt<sub>2</sub> (13 mL, 106 mmol). After stirring at room temperature for 3 h, the reaction mixture was poured into a column of alumina and kept there for 5 h at room temperature. The column was eluted by ether to obtain a mixture of 27a and its 16-trimethylsilyl ether. Treatment of the mixture with aqueous HCl afforded pure 27a, which was used for the next step without purification: <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) δ 0.952 (s, 3 H),

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1.236 (d, 6 H, J = 6.4 Hz), 1.86–2.54 (envelope, 17 H, including s, 3 H at 1.84), 4.34–4.49 (m, 1 H), 4.964 (br s, 1 H), 5.006 (qq, 1 H, J = 6.3 Hz), 5.137 (br s, 1 H).

(tert-Butyldimethyl)silyl Ether of 27a. The crude homoenolate adduct 27a, 4-(dimethylamino)pyridine (507 mg, 4.2 mmol), triethylamine (3.6 mL, 25.8 mmol), and (tert-butyldimethyl)silyl chloride (4.3 g, 28.5 mmol) were dissolved in DMF (30 mL) and stirred at 60 °C for 5 h. The reaction mixture was poured into a vigorously stirred, ice-cooled mixture of hexane and aqueous sodium bicarbonate. The aqueous layer was separated and extracted three times with ether, and the combined organic extracts were washed with brine, dried, and concentrated to obtain a crude product. Chromatographic purification on silica gel eluted by 25% ethyl acetate/hexane afforded the (tert-butyldimethyl)silyl ether of 27a (6.16 g, 44%, four steps from 15): IR (neat) 1720 (s), 1710 (s) cm<sup>-1</sup>; <sup>1</sup>H NMR (60 MHz, CCl<sub>4</sub>) δ 0.02 (s, 3 H), 0.03 (s, 3 H), 0.90 (s, 9 H), 0.97 (s, 3 H), 1.0-2.6 (envelope, 22 H, including d, 6 H, J = 7 Hz at 1.25and br s, 3 H at 1.80), 4.2-4.5 (m, 1 H), 4.6-5.2 (m, 3 H); <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>) δ 210.16, 172.39, 140.62, 114.75, 73.56, 67.40, 62.21, 54.48, 52.35, 46.08, 46.08, 37.91, 35.29, 31.38, 29.83, 25.69, 25.57, 21.64, 17.76, 15.48, -4.59, -5.17,

Keto Acid 28. The silvlated keto ester (4.28 g, 9.8 mmol) and potassium hydroxide (1.9 g, 34 mmol) were dissolved in water (50 mL)/ ethanol (150 mL) and warmed to 45 °C for 1.5 h. The reaction mixture was neutralized by addition of tartaric acid (2.5 g, 17 mmol) and most of ethanol removed under reduced pressure. The residue was diluted with methylene chloride and water, and additional tartaric acid (5.0 g) was added to make the mixture acidic (ca. pH 2). The aqueous layer was extracted three times with methylene chloride, and the combined organic extracts were washed with water. Tartaric acid was removed by filtration to obtain a yellow oil. Chromatographic purification on silica gel (ethyl acetate/hexane/acetic acid (30:70:1)) yielded the keto acid 28 (3.1 g, 80%) as white crystals. A portion was recrystallized from hexane to obtain white plates, which melted at 122-123 °C: IR (neat) 2250-3500 (s), 1730 (m), 1705 (m), 1665 (s), 1250 (m), 1210 (m), 835 (m), 775 (m), 730 (m) cm<sup>-1</sup>; <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>)  $\delta$  0.01 (s, 3 H), 0.04 (s, 3 H), 0.86 (s, 9 H), 0.97 (s, 3 H), 1.02-2.54 (envelope, 16 H, including s, 3 H at 1.78), 4.34-4.46 (m, 1 H), 4.88 (br s, 1 H), 4.95 (br s, 1 H), 10.03 (br s, 1 H); <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>) δ 210.93, 179.11, 140.69, 114.96, 73.63, 62.31, 54.61, 52.45, 46.26, 46.12, 37.95, 35.47, 31.04, 29.61, 25.82, 25.73, 17.91, 15.66, -4.46, -5.05. Anal. Calcd for C22H38O4Si: C, 66.96; H, 9.71. Found: C, 66.71; H, 9.81.

Tertiary Alcohol 35 Due to Addition of Isopropenyllithium to 28. To a cooled (-78 °C) THF solution of the keto acid 28 (166 mg, 0.42 mmol) was added isopropenvllithium in ether (0.45 M, 3.7 mL, 1.7 mmol), and the reaction mixture was stirred for 20 min at that temperature before removal of the cooling bath. After stirring at room temperature for 1 h, the reaction mixture was added rapidly to a stirred solution of acetic acid (1 mL) in ethyl acetate (4 mL). Water was added and the aqueous phase extracted twice with ether. The combined organic extracts were then dried and concentrated to obtain the tertiary alcohol 35. Chromatographic purification on silica gel (15% ethyl acetate/hexane) afforded the pure 35 (172 mg, 89%) as a colorless oil: IR (neat) 3480 (br), 1670 (s), 1630 (sh), 1250 (w), 1095 (m), 925 (w), 835 (m), 770 (w) cm<sup>-1</sup>; <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) & 0.000 (s, 3 H), 0.020 (s, 3 H), 0.839 (s, 9 H), 1.07-1.89 (envelope, 23 H, including s, 3 H at 1.274, s, 3 H at 1.753, s, 3 H at 1.769, and s, 3 H at 1.856), 2.23-2.39 (m, 1 H), 2.63-2.79 (m, 2 H), 4.26-4.40 (m, 1 H), 4.764 (br s, 1 H), 4.854 (br s, 2 H), 5.010 (br s, 1 H), 5.745 (br s, 1 H), 5.942 (br s, 1 H). Anal. Calcd for C<sub>28</sub>H<sub>48</sub>O<sub>3</sub>Si: C, 72.99; H, 10.50. Found: C, 73.01; H, 10.53.

Diels-Alder Adduct 37. The tertiary alcohol 35 (48.0 mg, 0.104 mmol) was dissolved in 1 mL of THF. A THF (0.5-mL) solution of Burgess' salt (Et<sub>3</sub>N<sup>+</sup>SO<sub>2</sub>N<sup>-</sup>CO<sub>2</sub>Me, 34.0 mg, 0.144 mmol) was added and the reaction mixture stirred for 30 min at room temperature. Phosphate buffer (0.1 N, pH 7.4) was added, and the solvent was removed in vacuo. The residue was partitioned between ether and brine and the aqueous layer extracted four times with ether. The combined organic extracts were washed three times with brine, dried, and concentrated to obtain a colorless oil. TLC showed that a small amount of the Diels-Alder adduct had been formed during workup. The oil was quickly dissolved in methylene chloride (3 mL) and cooled to 0 °C. Trifluoroacetic acid (0.015 mL, 0.10 mmol) was added, and the mixture was stirred for 35 min. After addition of triethylamine (0.015 mL, 0.11 mmol), the mixture was diluted with ether and washed with saturated aqueous sodium bicarbonate. The aqueous phase was extracted four times with ether, and the combined organic extracts were washed with brine, dried, and concentrated to obtain a yellow oil. Chromatographic purification on silica gel (3-5% ethyl acetate/hexane) afforded an inseparable mixture of the Diels-Alder adduct 37 and 41 (37.8 mg, 82% from 35, 37:41 = 93:7 based on the GLC area,  $R_f = 0.26$  for 5% ethyl acetate/hexane), accompanied by an uncyclized olefinic regioisomer 40 (6.2 mg, 13%,  $R_f = 0.35$  for 5% ethyl acetate/hexane) formed during the initial dehydration reaction: GLC (OV-101, CT 240 °C) retention times 27.2 min (40), 44.1 min (37), 48.9 min (41).

**37** + **41**: IR (neat) 1690 (s), 1245 (m), 1080 (w) cm<sup>-1</sup>; <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>)  $\delta$  0.007 (s, 3 H), 0.022 (s, 3 H), 0.858 (s, 9 H), 1.057 (s, 3 H), 1.243 (s, 3 H), 1.49–2.57 (envelope, 22 H, including br s, 3 H at 1.576 and s, 3 H at 1.812), 4.353 (dt, 1 H, J = 3.1, 7.0 Hz), 4.884 (br s, 1 H), 4.926 (br s, 1 H), characteristic signal of **41** 1.023 (s). Anal. Calcd for C<sub>28</sub>H<sub>46</sub>O<sub>2</sub>Si: C, 75.96; H, 10.47. Found: C, 76.03; H, 10.48.

**40**: IR (CHCl<sub>3</sub> solution) 1668 (s), 1624 (w), 1600 (w), 1372 (m), 1252 (m), 1090 (s), 892 (m) cm<sup>-1</sup>; <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>)  $\delta$  0.00 (s, 3 H), 0.02 (s, 3 H), 0.861 (s, 9 H), 1.075 (s, 3 H), 1.11–1.93 (envelope, including br s, 3 H, at 1.836 and br s, 6 H, at 1.885), 1.98 (d, 1 H, J = 7.1 Hz), 2.20–2.60 (m, 2 H), 2.76 (dt, 2 H, J = 6.0, 10 Hz), 4.392 (dt, 1 H, J = 3.1, 7.1 Hz), 4.852 (br s, 1 H), 4.945 (br s, 2 H), 4.976 (br s, 1 H), 5.791 (br s, 1 H), 5.995 (br s, 1 H), 6.134 (br s, 1 H).

Tetraketone 38. The Diels-Alder adducts (37 and 41; 93:7, 75.2 mg, 0.170 mmol) were dissolved in a mixture of methanol (4 mL) and methylene chloride (4 mL) and cooled to -78 °C. A stream of ozone in oxygen was bubbled until the solution turned blue. Excess ozone was purged by nitrogen gas and dimethylsulfide (1 mL) added. The solution was warmed to room temperature and then stirred for 1 h. The solvent was removed in vacuo, leaving a brown oil, which was purified by column chromatography on silica gel (30-40% ethyl acetate/hexane) to obtain the tetraketone 38 as white crystals (64.8 mg, 80% containing ca. 5% of the C-10 epimer). Recrystallization from hexane gave pure 38 (white needles, mp 141-143 °C), which was used in the next step: IR (CHCl<sub>3</sub>) 1704 (s), 1366 (m), 1165 (m), 1078 (m) cm<sup>-1</sup>; <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) & 0.097 (s), 0.849 (s), 1.106 (s), 1.228 (s), 1.31-1.51 (m), 1.77-2.57 (envelope, including s at 2.099 and s at 2.131), 2.660 (d, J = 8.0 Hz), 2.979 (d, J = 14.3 Hz), 4.857 (dt, J = 3.4, 7.0 Hz); <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>) δ 213.12, 210.55, 207.63, 204.75, 72.49, 69.75, 65.75, 57.23, 56.42, 49.12, 49.04, 43.84, 38.68, 38.48, 35.76, 33.08, 30.42, 30.10, 29.81, 25.61, 21.85, 17.62, 15.31, 15.31, -3.73, -5.34. Anal. Calcd for C27H44O5Si: C, 68.03; H, 9.30. Found: C, 67.88; H, 9.16.

11-Keto-16-dehydroprogesterone (39). A benzene (1.1 mL) solution of the tetraketone 38 (15.4 mg, 0.0323 mmol) and DBU (0.050 mL, 0.33 mmol) in a sealed tube was degassed by several freeze/thaw cycles and heated at 230 °C for 3 h. The reaction mixture was diluted with methylene chloride and washed three times with 1 N HCl. The combined organic extracts were washed with saturated aqueous sodium bicarbonate and with brine, dried, and concentrated to obtain a crude product. Chromatographic purification on silica gel eluted with 50% ethyl acetate/hexane gave the desired compound 39 (white crystals, 7.9 mg, 75%). A portion was recrystallized from ether, giving white needles with mp 199–201 °C: IR (CHCl<sub>3</sub>) 1696 (s), 1660 (s) cm<sup>-1</sup>; <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>)  $\delta$  0.885 (s), 1.422 (s), 1.43–2.60 (envelope, including s at 2.281), 2.77–2.91 (m), 3.123 (d, J = 12.0 Hz), 5.714 (br s), 6.73–6.79 (m). Anal. Calcd for  $C_{21}H_{26}O_3$ : C, 77.27; H, 8.03. Found: C, 77.17; H, 8.05.

Enol Silyl Ether 47. A mixture of 39 (22.4 mg, 0.0686 mmol), tripropylsilane (0.0144 mL, 0.0689 mmol), and Wilkinson's catalyst (4.1 mg, 0.0044 mmol) was dissolved in THF (0.4 mL) and heated in a sealed tube at 65 °C for 38 h. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (20% ethyl acetate/hexane) to obtain the enol silyl ether 47 (21.9 mg, 89% on 74% conversion), accompanied by the recovery of the starting material (5.9 mg, 26%): IR (neat) 1700 (s), 1670 (s), 1232 (m) cm<sup>-1</sup>; <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>)  $\delta$  0.54-0.69 (m), 0.830 (s), 0.965 (d,  $J \approx$  7.1 Hz), 1.14-2.54 (envelope, including s at 1.409 and br s at 1.792), 2.79 (d, J = 13 Hz), 5.73 (br s).

Cortisone (1) via Double-Hydroxylation Reaction of 47. To a cooled (0 °C) mixture of finely powdered, dry potassium bicarbonate (85 mg, 0.85 mmol) and the enol silvl ether 47 (21.0 mg, 0.0433 mmol) in methylene chloride (3 mL) was added a methylene chloride (1 mL) solution of mCPBA (85%, 22.3 mg, 0.129 mmol) over a period of 1 h. After the solution was stirred at 0 °C for 15 min, aqueous sodium thiosulfate was added and the mixture stirred at room temperature for 10 min. The aqueous phase was separated and extracted three times with methylene chloride. The combined organic extracts were concentrated, and the resultant oil was dissolved in THF (1 mL) and acidified to ca. pH 1 with 1 N HCl. After 15 min at room temperature most of THF was removed and the residue partitioned between methylene chloride and saturated aqueous sodium bicarbonate. The aqueous layer was separated and extracted three times with methylene chloride. The combined organic extracts were washed with brine, dried, and concentrated to yield a crude product. Recrystallization from ethanol/benzene gave cortisone (1; 8.1 mg) as white crystals. The mother liquid was then concentrated and purified by column chromatography on silica gel (5% methanol/ chloroform) to obtain an additional crop of 1 (4.8 mg, total 12.9 mg, 83%). A portion was recrystallized from ethyl acetate to obtain white

needles with mp 212–215 °C dec (lit.<sup>2</sup> mp 215 °C for (+)-cortisone). The synthetic material was identical with an authentic (optically active) sample by 200-MHz <sup>1</sup>H NMR and 50-MHz <sup>13</sup>C NMR and TLC mobility under different conditions (50% ethyl acetate/hexane × 3,  $R_f = 0.29$ ; 75% ether/hexane × 7,  $R_f = 0.26$ ; 40% ethyl acetate/benzene × 3,  $R_f = 0.29$ ).

Adrenosterone 49. To a stirred mixture of potassium bicarbonate (88 mg, 0.88 mmol) and mCPBA (80%, 17.2 mg, 0.080 mmol) in methylene chloride (1 mL) was added a methylene chloride solution of the enol silyl ether 47 (16.5 mg, 0.034 mmol) at 0 °C over a period of 30 min. After the solution was stirred at 0 °C for 4 h, aqueous sodium thiosulfate was added, and then the mixture was stirred at room temperature. The aqueous phase was extracted three times with methylene chloride, and the combined organic extracts were washed with brine, dried, and concentrated to obtain a crude mixture, which was purified by column chromatography on silica gel (50% ethyl acetate/hexane) to obtain

(±)-adrenosterone (49; 5.1 mg, 50%) as white crystals. The synthetic material was identical with authentic sample by IR, 200-MHz <sup>1</sup>H NMR, and TLC mobility ( $R_f = 0.40$  for 50% ethyl acetate/hexane × 2;  $R_f = 0.28$  for 30% ethyl acetate/benzene × 3).

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Supplementary Material Available: General data and details of experiments for the synthesis of 3, 51, 52, 57, 58, 60, and 61 and the structural assignment of intermediates (15 pages). Ordering information is given on any current masthead page.

# Atom Transfer Cyclization Reactions of Hex-5-ynyl Iodides: Synthetic and Mechanistic Studies<sup>†</sup>

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Abstract: Atom transfer cyclization reactions provide a nonreductive complement to the tin hydride method for conducting radical cyclizations. Three useful sets of reaction conditions (portionwise or syringe pump addition of catalytic tributyltin hydride and photolysis with catalytic hexabutylditin) for the isomerization of hex-5-ynyl iodides to (iodomethylene)cyclopentanes have been developed. To illustrate the generality of this new reaction, a series of mono- and polycyclic derivatives (both fused and spiro) has been prepared. All evidence indicates that a two-step chain mechanism operates. In addition to the requirement for a normal initiation step, a trap for iodine must be present for the reaction to proceed. This important function is performed by the tin additive. The first-formed hexynyl radical closes in a 5-exo fashion to provide a cyclopentylidene radical. This vinyl radical then rapidly abstracts an iodine atom from the starting alkyl iodide ( $k_1 \approx (2-5) \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$  at 30 °C). Stereochemical trends in the formation of (E)- and (Z)-vinyl iodides are analyzed with the aid of a Curtin-Hammett kinetic scheme. The observation of identical ratios of stereoisomers from isomeric starting iodides provides strong evidence for this mechanistic picture and demonstrates that the inversion of the intermediate radicals is more rapid than iodine atom transfer. In the formation of the spiro rings, products derived from 1,5-hydrogen atom transfer have been isolated along with the expected vinyl iodides, and a proposal that the atom-transfer reactions of intermediate vinyl radicals are faster than chair-chair interconversions of substituted cyclohexanes is considered. Cyclizations of a series of 4-tert-butylcyclohexane derivatives have demonstrated that hexynyl radicals have a small preference for equatorial attack, while hexenyl radicals have a small preference for axial attack.

The trialkyltin hydride mediated cyclization of hex-5-enyl and hex-5-ynyl halides (and related radical precursors) has rapidly become an important method for the formation of carbocyclic and heterocyclic rings (Figure 1).<sup>2</sup> Tin hydride is a valuable reagent to mediate radical chain reactions because it (1) generates radicals site-selectively, (2) provides these radicals with some solution lifetime to undergo desired reactions, and (3) traps the product radicals by hydrogen atom transfer before nonproductive radical-radical or radical-molecule reactions can occur. Inherent limitations of tin hydride reagents are well recognized and include (1) the difficulty to conduct slow cyclization or addition reactions due to competing reduction of the starting radical, (2) the difficulty to establish different lifetimes for intermediate radicals<sup>3</sup> due to similarities in rates for the reaction of many radicals with tin hydride, and (3) the necessity to terminate a radical sequence by hydrogen atom transfer (a net reduction always results). This last limitation is particularly troublesome if functionality is required in the cyclic product for subsequent synthetic transformations (Figure 1). Reagents that mediate the "nonreductive" cyclization and addition reactions of radicals have been the focus of recent research.2,4

Scheme I



The atom transfer addition (or cyclization) of a C-X bond across a carbon-carbon multiple bond (Figure 2) is a Khar-

<sup>&</sup>lt;sup>+</sup>Taken in part from the Ph.D. theses of M.-H.C. (1987) and D.K. (1988).

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