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Progress toward the Total Synthesis of (+)-Aldosterone: Synthesis of the A–D Rings

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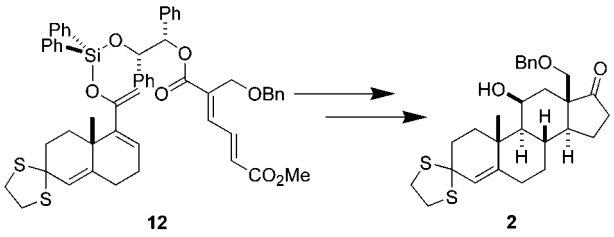
ABSTRACT



Synthesis of the A–D rings of the cortical hormone (+)-aldosterone is described. The key step incorporates a chiral tether in a type 2 intramolecular Diels–Alder reaction that establishes the absolute configuration of four contiguous asymmetric centers. This approach provides an efficient route for either enantiomer of the steroid skeleton.

Synthesized in the adrenal cortex, the cortical hormones play a vital role in the biochemistry of man.[1] Aldosterone (**1**), the most common mineralocorticoid, was isolated in 1953.[2] It maintains proper blood pressure and blood volume by regulating the reabsorption of water and sodium ions from urine. This and other steroids have provided an arena for testing synthetic strategy and methodology for over fifty years. (±)-Aldosterone was first synthesized by Wettstein[3] in 1955, and later by Johnson.[4] Barton's three-step partial synthesis of (+)-aldosterone from commercially available corticosterone acetate provided a method for producing quantities of aldosterone.[5] Other total and partial syntheses are given in ref 6.

We have developed procedures for controlling stereo- and regiochemistry in Diels−Alder cycloaddition reactions.[7] An application of these efforts to the synthesis of (+)-aldosterone is illustrated in Scheme 1. The overall strategy is an ascending synthesis of the tetracyclic steroid core starting from the AB rings and building the C and D rings in subsequent steps.

We envisioned the hormone to be derived from the steroid core **2**. This precursor could in turn arise from a D-ring forming Dieckman-demethoxycarbonylation sequence of bridged bicycle **3**.

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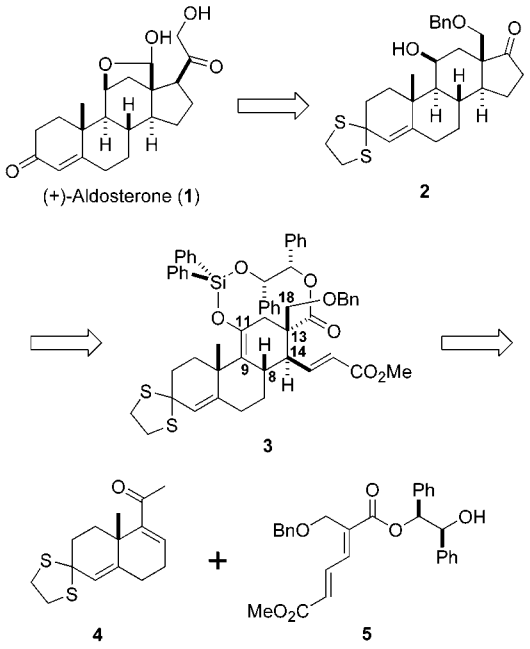
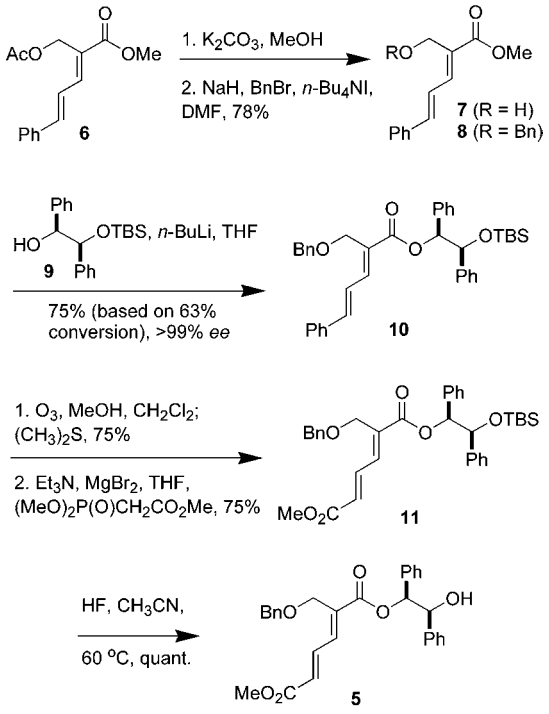
Scheme 1. Retrosynthetic Plan for the Synthesis of Advanced Intermediate **2** and (+)-Aldosterone (**1**)



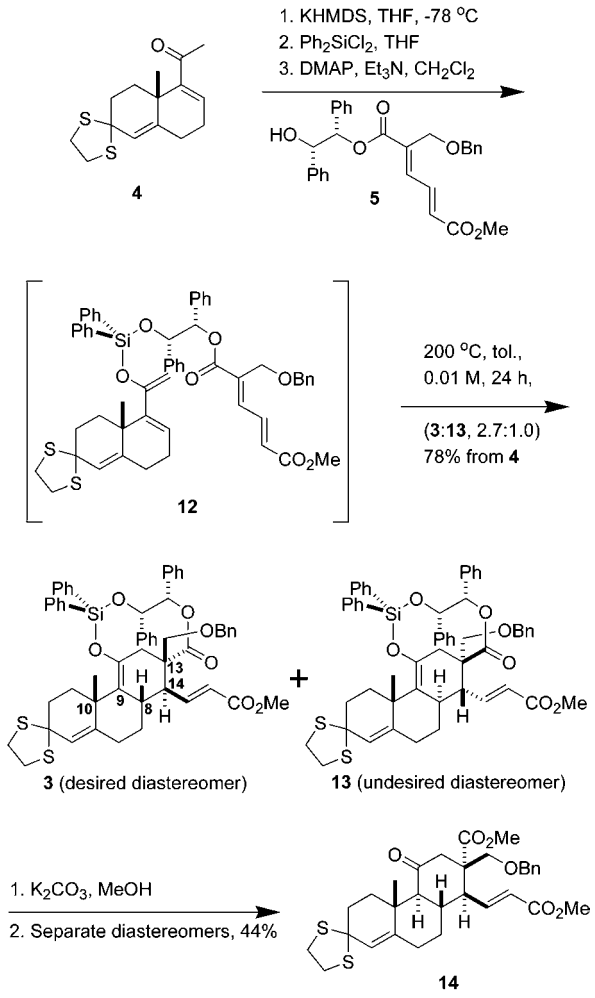
Bridged pentacycle **3** arises from a type 2 intramolecular Diels−Alder reaction (IMDA).[7] The cycloaddition, which can form up to eight diastereomeric products, requires control of regiochemistryand stereochemistry, as well as π facial selectivity, to provide the isomer required for the synthesis.

This key intramolecular cycloaddition can be staged by temporarily uniting latent diene **4**[8,9] and dienophile **5** through

Scheme 2. Synthesis of Dienophile **5**



Scheme 3. Type 2 IMDA Reaction of Silyl Acetal **12** Leading to the Diastereoselective Synthesis of Intermediate **14**



a chiral silyl acetal tether.[10] A related synthesis of adrenosterone demonstrated that the (*S*, *S*)-hydrobenzoin auxiliary in the bridging group induced formation of the cycloadducts, favoring the α-approach of the dienophile to generate the natural steroid stereochemistry at C8, C9, C11, C13, and C14, respectively.[10] This work culminated in the total synthesis of (+)-adrenosterone.[11]

This same strategy was employed to bias the π facial selectivity for the critical construction of the C-ring of (+)-aldosterone. The aldosterone synthesis requires a dienophile with the C18 carbon (steroid numbering) in an elevated oxidation state. Having identified an approach to the target steroid in Scheme 1, the synthesis of chiral dienophile **5** was undertaken. A major challenge in the synthesis of **5** was differentiating the two ester groups. The solution to this

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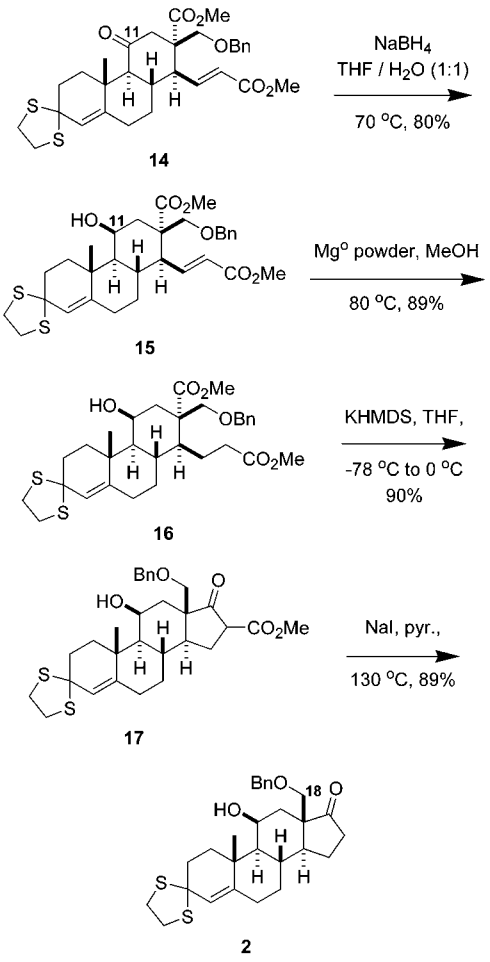
Scheme 4. Stereoselective Synthesis of Advanced Aldosterone Intermediate **2** Containing A−D Rings



problem can be found in Scheme 2. Acetate **6**[12,13] was saponified to allylic alcohol **7**, which was protected to give benzyl ether **8**. Methyl ester **8** was transesterified[14] with TBS-protected (*S*,*S*)-hydrobenzoin **9**[15] to furnish ester **10**. Selective γ,δ-olefin ozonolysis[16] of **10** provided the aldehyde, which was converted to conjugated diester **11** under modified Horner−Wadsworth−Emmons conditions.[17] Fluoride-assisted desilylation of **11** completed the synthesis of dienophile **5**.

A three-component coupling procedure was used to set the stage for the key type 2 IMDA cycloaddition (Scheme 3). Diene precursor **4**[11,18] (derived from (+)-Wieland−Miescher ketone) was kinetically deprotonated and *O*-silylated with dichlorodiphenylsilane. Dienophile **5** was coupled with the silyl chloride intermediate to produce hydrobenzoin tethered cycloaddition precursor **12**. It was found that upon addition of the dienophile to the chlorosiloxy intermediate, the acid byproduct caused trans-silylation from the hexamethyldisilazane to the dienophile **5**, capping the alcohol with a TMS group and rendering it inactive for coupling. By simply concentrating the reaction mixture and then subjecting the residue to high vacuum after coupling the dichlorosilane to the diene derived from **4**, excess hexamethyldisilazane was removed. This modification enhanced the yield of the coupling step.

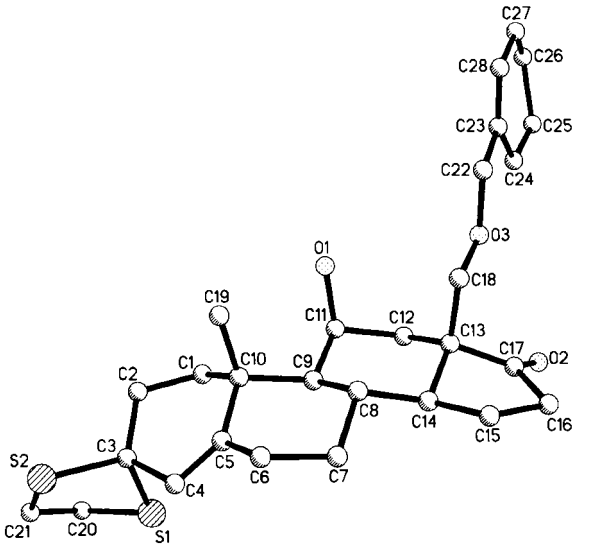


Figure 1. Molecular structure of advanced intermediate **2**.

Heating a dilute solution of **12** in toluene produced a 2.7:1.0 mixture of diastereomeric cycloadducts **3** and **13** in 78% combined yield where the major product, **3**, arose from an α-approach of the dienophile. Cycloadduct **3** has the necessary stereochemistry at C8, C10, C13, and C14 for completion of the enantioselective synthesis of aldosterone. Following removal of the chiral disposable tether, the diastereomeric products could be separated to provide intermediate **14** where the trans-stereochemistry of the B−C ring junction is established during the cleavage process. The type 2 IMDA reaction of **12** established the four contiguous stereocenters (C8, C9, C13, and C14) within the C-ring of the steroid core relative to C10.

Construction of the D-ring of the steroid skeleton is outlined in Scheme 4. Selective reduction of the C11 ketone of **14** with $NaBH_4$ provided β-C11 alcohol **15**.[19] Reduction of α,β-unsaturated ester **15** gave diester **16**,[20] which under-

(12) Compound **6** was prepared by coupling methyl acrylate and *trans*-cinnamaldehyde under Baylis−Hillman conditions followed by acetylation of the resulting alcohol and an acetate transposition procedure developed by Foucaud and El Guemmout. See Supporting Information and ref 13.

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went Dieckman cyclization to furnish β-keto ester **17** as a 3:1 mixture of epimers. Demethoxycarbonylation of **17** resulted in the formation of intermediate **2**.[21] This advanced intermediate incorporates the A−D rings of the steroid aldosterone as well as an elevated oxidation state of the C18 carbon.

The absolute stereochemistry of intermediate **2** was confirmed by X-ray analysis (Figure 1). The molecular structure of **2** proves the stereochemistry of the six stereocenters including the β-orientation of the C11 hydroxyl group.

In summary, we have developed a concise route into the A−D rings of the cortical steroid aldosterone. The key step in the synthesis of advanced intermediate **2** was a type 2 intramolecular Diels−Alder reaction that sets the four contiguous stereocenters of the C-ring. Further elaboration of **2** should allow for the enantioselective total synthesis of (+)-aldosterone.

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Supporting Information Available: X-ray crystal structure and crystallographic data for **2** and experimental procedures and full characterization data for **2**, **3**, **5**, **6**−**8**, **10**−**11**, and **14**−**17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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