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A NEW STRATEGY FOR THE PREPARATION OF 11-OXYGENATED STEROIDS SYNTHESIS OF (±)-ADRENOSTERONE

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Abstract: Conjugate 1,4-addition of 1-[(*tert*-butyldimethylsilyl)oxy]-2-methyl-1,3-cyclohexadiene (**5**) to 2-methylcyclopentenone in highly polar media and subsequent alkylation of the resultant silyl enol ether (**4**) with phenylthiodienyl carbonate **10** in 5.0 M $LiClO_4$·Et_2O provides substrate **2**. Exposure of **2** to TMSOTf/ $TMSOCH_2CH_2OTMS$ affords tetracyclic bis-ketal **3**, which is converted into (±)-adrenosterone (**1**) in four steps.
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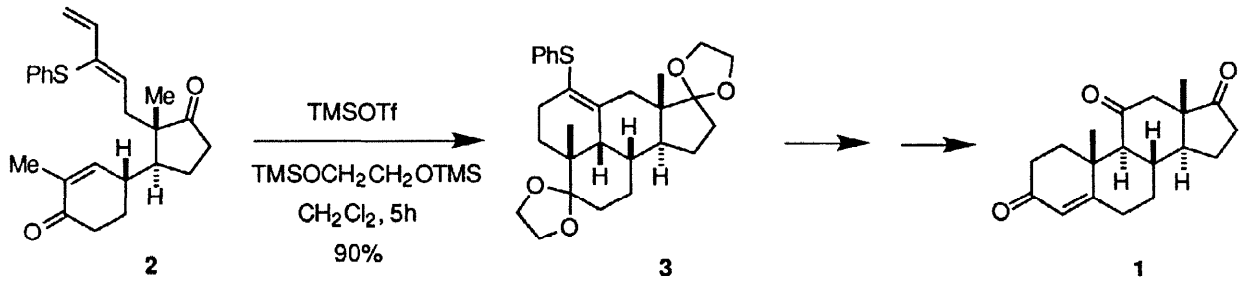
The importance and role of corticosteroids in medicine has, in part, been responsible, over the years, for the evolution of new strategies for the synthesis of 11-oxygenated steroids. In addition, 11-oxygenated steroids have served as useful targets during the development of new synthetic methodology.[1] We detail below a new strategy for the synthesis of 11-oxygenated steroids [cf. adrenosterone (**1**)] which features: (1) 5.0 M lithium perchlorate-diethyl ether mediated formation of substrate **2** *via* a 1,4 Michael addition to 2-methylcyclopentenone followed by subsequent alkylation of the resultant silyl enol ether and (2) tandem intramolecular Diels-Alder cycloaddition/olefin isomerization reaction leading to the formation of tetracyclic bis-ketal **3** (cf. **2** → **3**).



2 **3** **1**

Central to our strategy for constructing 11-oxygenated steroids was the need to add a silyl dienol ether to an unreactive Michael acceptor (cf. **4** + **5** → **6**) and the requirement that substrate **2** undergo an intramolecular ionic Diels-Alder reaction with formation of diastereoisomer **7** followed by complete equilibration of the enol phenyl thioether to the desired, more stable isomer **3**.[2,3] With regards to the formation of **2**, it was anticipated, based on previous work from our Laboratory,[4] that use of a polar medium would dramatically lower the barrier for the Michael addition and give rise to the corresponding silyl enol ether **6** which would allow for subsequent alkylation. Concerning the [4 + 2] cycloaddition, analysis of the four transition states reveals that only the transition state leading to **7** is relatively free of torsional strain and steric crowding. Thus, approach of the diene from the α face of the dienophile *via* an exo transition state should lead directly to **7**. In the corresponding endo transition state, there is a severe steric interaction between the phenylthio group and the eventual C(7) axial hydrogen (steroid numbering).

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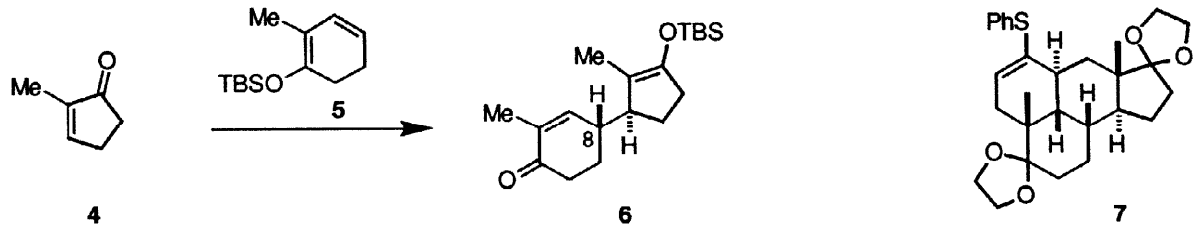
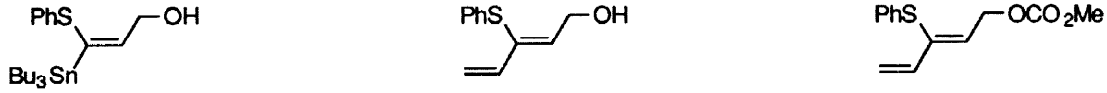


4 6 7

The highly polar medium, 5.0 M $LiClO_4$·Et_2O, has been shown to be very effective in promoting the 1,4 Michael addition of silyl ketene acetals to hindered, unreactive enones.[4] Use of this unique solvent system to hasten the 1,4 addition of the known, less reactive silyl dienol ether **5**[5] to 2-methylcyclopentenone was examined since efforts to promote the addition under conventional thermal and Lewis acid catalysis failed. Use of lithium cobalt-bis-dicarbollide, which we have shown[6] catalyzes the conjugate addition of silyl ketene acetals to hindered α,β-unsaturated carbonyl compounds, failed to give rise to any 1,4 product. However, exposure (ambient temperature, 14h) of 2-methylcyclopentenone (0.2 M in 5.0 M $LiClO_4$·Et_2O) to 1.5 equiv of **5** provided silyl enol ether **6** in 51% yield along with the undesired C(8) (steroid numbering) epimeric compound.

With silyl enol ether **6** in hand, we set out to alkylate **6** with phenylthiodienyl carbonate **10** which was synthesized from the known vinyl stannane **8**.[7] Iodostannylation (I_2, CH_2Cl_2, 0 °C, 15 min) of **8** followed by coupling of the resultant vinyl iodide with vinyl tri-*n*-butyltin under Stille conditions [$Cl_2Pd(CH_3CN)_2$, THF, reflux, 12h][8] provided, in 75% overall yield, 3-phenylthiopentadienol **9**. Exposure (1h) of **9** to methyl chloroformate in methylene chloride/pyridine at 0 °C afforded **10** in 96% yield.



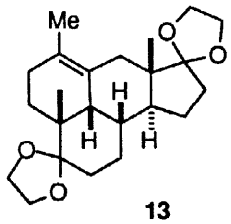
8 9 10

The direct alkylation of silyl enol ether **6** employing dienyl carbonate **10** was also realized in highly polar media. Treatment of a 0.2 M solution of **6** in 5.0 M $LiClO_4$·Et_2O at ambient temperature with 1.5 equiv of **10** gave rise, after 2h, to an 81% yield of **2** in which the olefinic geometry of the enol thioether was a mixture of isomers. The ***Z*** and ***E*** isomers were equilibrated in benzene containing 10 mol% of diphenyldisulfide upon exposure (2h) to light. An 87% yield of the equilibrated dienes was obtained in which the ***Z*:*E*** ratio was improved to ca. 3:1. The ***Z*** and ***E*** olefins were separated by chromatography giving rise to pure **2** and **11**.

11 12

With the availability of both **2** and **11**, we set out initially to examine the intramolecular Diels-Alder reaction of **2** under a variety of conditions. In principle, one need not separate the mixture of dienes since if the desired bond migration occurs after the Diels-Alder reaction, both cycloadducts should give rise to **3** or its equivalent. Attempts to promote the [4 + 2] cycloaddition of **2** thermally (toluene, 120 °C, 12h) failed to provide any cycloadducts. Equally disturbing was the fact that use of either trimethylsilyl triflate, boron trifluoride etherate or 5.0 M $LiClO_4$·Et_2O led to rapid degradation of **2** with no cycloadducts being detected. Much to our delight, *in situ* generation of the oxycarbenium ion **12**[9] employing modified Noyori conditions[10] (1.0 equiv TMSOTf, 8.0 equiv $TMSOCH_2CH_2OTMS$, CH_2Cl_2, ambient temperature, 5h) gave rise to a 90% yield of **3**, mp 147-149 °C, in which the double bond had migrated into the desired position.[11] Note that the initially formed Diels-Alder adduct **7** could not be detected. All efforts to induce the ***E***-isomer **11** to undergo cycloaddition were not successful.

The transformation of tetracyclic enol phenyl thioether **3** into (±)-adrenosterone (**1**) necessitated replacement of the thiophenyl group with a methyl. This was accomplished by treatment of a 0.1 M solution of **3** in tetrahydrofuran containing 3 mol% bis(triphenylphosphine)nickel(II) chloride with 3.0 equiv of a 3.0 M solution of methylmagnesium bromide in tetrahydrofuran.[12] After heating at reflux for 5h, an 84% yield of crystalline **13**, mp 128-130 °C, was obtained. Removal (acetone, *p*-TsOH, 8h) of the ketal groups provided tetracyclic diketone **14**, mp 173 °C, which upon ozonolysis (O_3, CH_2Cl_2, MeOH, -78 °C; PPh_3) afforded **15**, mp 130-131 °C, in 69% yield. Exposure (30 min) of **15** to 4% methanolic potassium hydroxide solution at 40 °C afforded (58%) crystalline (±)-adrenosterone (**1**), mp 183-184 °C (lit.[1d] mp 184-185 °C).



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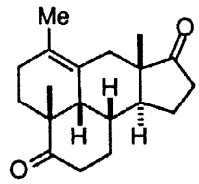

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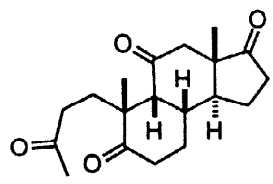

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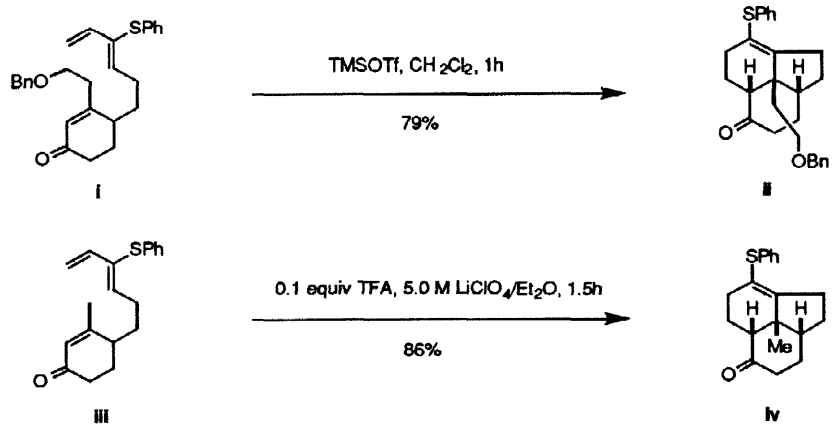
2. MMX calculations indicate that **3** is 6.6 kcal lower in energy than cycloadduct **7**.
3. During the course of this study, we observed similar double bond migrations of enol phenyl thioethers which were generated *in situ* during intramolecular Diels-Alder reactions. For example, exposure (ambient temperature, 1h) of substrate **i** to trimethylsilyl triflate in methylene chloride gave rise (79%) to cycloadduct **ii**, exclusively. Similarly, treatment (ambient temperature, 1.5h) of substrate **iii** with 0.1 equiv of TFA in 5.0 M $LiClO_4$·Et_2O afforded (86%) tricyclic ketone **iv** with no trace of the anticipated cycloadduct being

detected. Also, in the case of **iii** → **iv**, this transformation could be brought about in 81% yield employing 0.1 equiv of boron trifluoride etherate in methylene chloride at 0 °C (1h).



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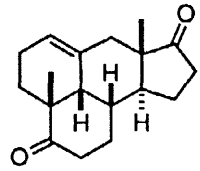
11. The structure of **3** was confirmed by conversion [(a) acetone, *p*-TsOH, 24h; (b) Raney Ni, EtOH, 0 °C, 1h] into crystalline diketone **v**, mp 127 °C, whose structure was unambiguously established by single-crystal x-ray analysis. Diketone **v** crystallizes in space group P2/n with cell dimensions of a = 6.171 (2) Å, b = 31.719 (14) Å, c = 7.503 (3) Å, β = 105.23 (2) Å, V = 1417.00 Å^3 and ρ_{calcd} = 1.277 g/cm^{-3} (Z = 4). For more information, contact Dr. John C. Huffman, Indiana University, Department of Chemistry, Molecular Structure Center, Bloomington, Indiana 47405, Report # 96118.



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