# *Communications to the Editor*

## Cyclozirconation of a Computationally-Designed Diene: Synthesis of (−)-Androst-4-ene-3,16-dione

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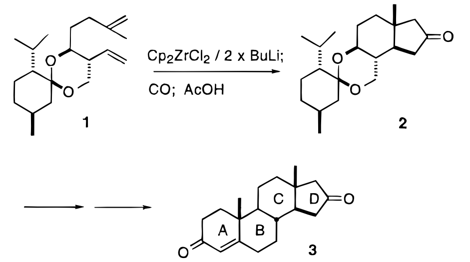
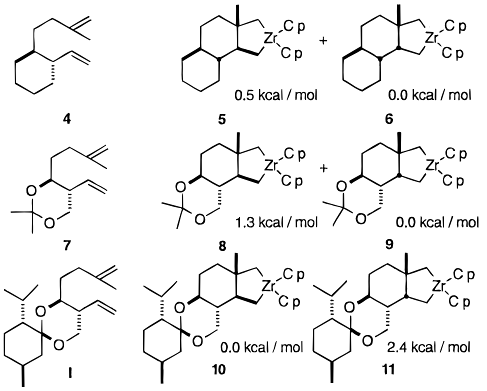
We report a new approach to the stereoselective construction of polycyclic systems, illustrated by the cyclozirconation/carbonylation[1] of a *computationally*-designed diene **1** to give the tetracyclic ketone **2**. Ketone **2** was converted over several steps to (−)-androst-4-ene-3,16-dione (**3**).[2]

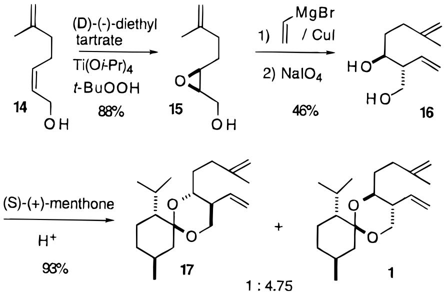


We[3] and others[4] have reported that intramolecular diene cyclozirconation can be carried out under conditions of either kinetic or thermodynamic control. We have also shown[3b,c] that semiempirical calculations (ZINDO)[5] can be used to predict the relative stabilities of diastereomeric zirconacycles. We describe here a computational approach to the design of a diene such that cyclozirconation is *directed* toward a desired diastereomer.

**Scheme 1**



**Scheme 2**



Our initial objective was the construction of the steroid skeleton (e.g., **3**) with control of both relative and absolute configuration. We first considered a B → BCD construction, starting with diene **4**. Unfortunately (Scheme 1), computational analysis (ZINDO)[5] predicted that the undesired cis-fused zirconacycle **6** would be *more* stable than the desired trans-fused zirconacycle **5**. The prospects did not improve with the acetonide **7**. Again (Scheme 1), computational analysis (ZINDO) predicted that the cis-fused **9** would be more stable than the desired trans-fused **8**.

It was clear that the protecting group on the diol had to introduce steric bulk underneath the ring system of the tricyclic zirconacycle, to destabilize the cis diastereomer. After considering several other alternatives, we settled on the menthonide **1**. This introduced steric interactions such the desired trans-fused **10** was predicted to be *more* stable than the cis-fused **11**. For each of these three dienes (**1**, **4**, and **7**), the other two diastereomeric zirconacycles were predicted to be significantly less stable (from **1**, the other trans-fused diastereomer (**12**) was calculated at 9.6 kcal/mol, and the other cis-fused diastereomer (**13**) was calculated at 9.9 kcal/mol, compared to **10**).

The cis allylic alcohol **14**[6] (Scheme 2) was prepared by coupling (*Z*)-4-chloro-2-buten-1-ol[7] with methallyl magnesium chloride. Epoxidation with D-(−)-diethyl tartrate[8] gave the enantiomerically enriched epoxide **15**. Grignard opening followed by

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† X-ray crystallography.

[1] (a) For an overview of carbonylative diene and enyne cyclometalation, see: Hegedus, L. S. *Transition Metals in the Synthesis of Complex Organic Molecules*, 2nd ed; University Science Books: Sausalito, 1999. For other recent references to carbonylative cyclometalation, see: (b) Zhao, Z.; Ding, Y.; Zhao, G. *J. Org. Chem.* **1998**, *63*, 9285. (c) Negishi, E.-I.; Montchamp, J.-L.; Anastasia, L.; Elizarov, A.; Choueiry, D. *Tetrahedron Lett.* **1998**, *39*, 2503. (d) Shiu, Y.-T.; Madhushaw, R. J.; Li, W.-T.; Lin, Y.-C.; Lee, G.-H.; Peng, S.-M.; Liao, F.-L.; Wang, S.-L.; Liu, R.-S. *J. Am. Chem. Soc.* **1999**, *121*, 4066. (e) Murakami, M.; Itami, K.; Ito, Y. *J. Am. Chem. Soc.* **1999**, *121*, 4130. (f) Hicks, F. A.; Kablaoui, N. M.; Buchwald, S. A. *J. Am. Chem. Soc.* **1999**, *121*, 5881.

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[5] Both ZINDO and molecular mechanics were used as implemented on the Tektronix CAChe workstation (ref 3b).

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10.1021/ja992491x CCC: $19.00

**Table 1:** Cyclozirconation/Carbonylation of **1**

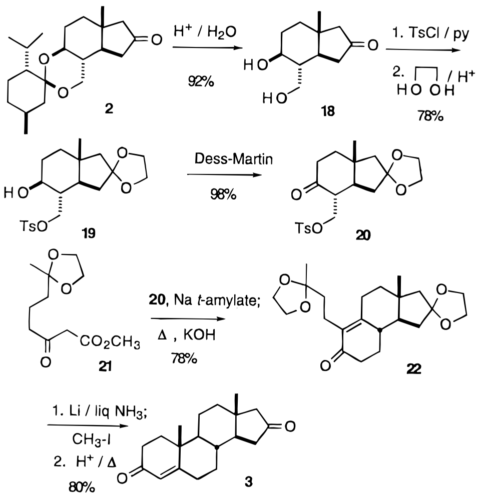
| | *T* (°C) | *t* (h) | % yield | 2 | $\delta$ 72.3 | $\delta$ 63.2 | $\delta$ 61.6 |
|---|---|---|---|---|---|---|---|
| 1 | 80 | 5 | 28 | 49 | 20 | 10 | 21 |
| 2 | 80 | 12 | 42 | 58 | 10 | 7 | 25 |
| 3 | 90 | 2 | 48 | 47 | 20 | 12 | 21 |
| 4 | 100 | 1 | 19 | 60 | 14 | 13 | 13 |
| 5 | **80** | **10** | **63** | **52** | 21 | 8 | 19 |
| 6 | 80 | 14 | 26 | 47 | 19 | 10 | 24 |
| 7 | 80 | 24 | 10 | 56 | 8 | 5 | 31 |

periodate cleavage of the minor 1,2-diol product[9] gave the 1,3-diol **16**.[10] Ketalization with (*S*)-(+)-menthone then gave the readily separable[11] menthonides **17** and **1**, in a 1:4.75 ratio.

Cyclozirconation conditions were varied (Table 1) to optimize the yield of **2**. In each case, the crude diastereomeric mixture of zirconacycles was carbonylated,[12] and the yield and the ratios of the mixture of four product ketones (easiily discerned by their oxygenated methines, $^{13}$C NMR $\delta$ 73.1 (**2**), $\delta$ 72.3, $\delta$ 63.2, $\delta$ 61.6) were recorded. At temperatures in excess of 80 °C (entries 1−4), substantial thermal degradation set in. Returning to 80 °C (Entries 2, 5−7), it was apparent that while the proportion of **2** was still increasing at 12 h, thermal degradation was again competing, lowering the overall yield. Pure **2** was isolated from the mixture of four ketones by crystallization, and the structure was established by X-ray crystallography.[10b]

With ZINDO, we are calculating the *heat of formation* of the diastereomeric zirconacycles, at absolute zero in the gas phase. When the difference between the two most stable diastereomeric zirconoacycles is <2 kcal/mol, the calculations are not expected to be predictive. In the event, cyclozirconation (80 °C, 10 h) of the diol **16** gave mainly (5:1) the cis-fused ketone, while cyclozirconation (80 °C, 10 h) of the acetonide **7** gave mainly (4:1) the trans-fused ketone.

**Scheme 3**



To prepare (−)-androst-4-ene-3,16-dione (**3**), the menthonide **2** was hydrolyzed[13] (Scheme 3) to give the crystalline diol **18**. Room-temperature ketalization[14] of the monotosylate proceeded efficiently. Oxidation[15] then gave the ketone **20**.

The Robinson annulation[16] of substrates such as **20** with the $\beta$-ketoester **21**[17] has been well developed.[18] To complete the synthesis, the tricyclic enone **22** was reduced[18d] with lithium in liquid ammonia, and the intermediate enolate was alkylated with methyl iodide. The resulting ketone was hydrolyzed and cyclized to give (−)-androst-4-ene-3, 16-dione (**3**). Synthetic **3** was identical with authentic material[19] by TLC, $^1$H NMR, $^{13}$C NMR, IR, MS, melting point, and optical rotation.

Using this computationally guided approach, we have designed a diene **1** such that the desired angularly substituted *trans*-fused zirconacycle was more favored than its diastereomers (ZINDO). The crystalline trans-fused ketone **2**, the major product from the cyclization, could easily be isolated in diastereomerically and enantiomerically pure form. We expect that ketone **2** will be a useful chiron for steroid total synthesis.

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**Supporting Information Available:** Experimental details, full characterization data, and figure of the X-ray structure of a derivative of **2** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Diene **16** is the product of opening of the epoxide with retention (or double inversion) of absolute configuration. For a recent precedent, see: Casalnuovo, J. A.; Scott, R. W.; Harwood: E. A.; Schore, N. E. *Tetrahedron Lett.* **1994**, *35*, 1153. (b) The relative and absolute configurations of **16** were confirmed by X-ray analysis of a derivative of the enantiomer of **2**. See Supporting Information for details.

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