J. Am. Chem. Soc. 1982, 104, 3758-3759

Efficient de Novo Construction of the Indanpropionic Acid Precursor of 11-Keto Steroids. An Improved Internal Diels-Alder Sequence

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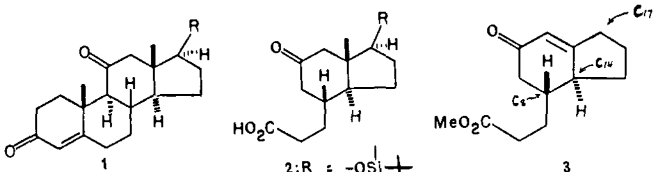
Received February 1, 1982

Our recent demonstration[1] that 11-keto steroids (**1**) typical of



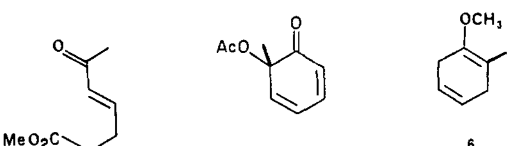
1 2:R = -OSi— 3 14:R =

cortical hormones could be constructed in just five steps from the indanonepropionic acid **2** required an efficient, stereospecific synthesis of that substance.[2] This has now been achieved: this communication describes the conversion of cyclopentanone to **14**, in nine steps and stereospecifically.

It seemed to us that a very short synthesis would be possible if three problems could be solved: (1) annulation of cyclopentanone to the simple indenone ester **3** with the anti stereochemistry of the hydrogens at C_8 and C_{14} (steroid numbering); (2) introduction of a suitable precursor to the corticosteroid side chain at C_{17}; and (3) introduction of the "angular" methyl group so as to produce the (normally less stable) *trans*-hydrindan system.

We now describe the solution of these problems.

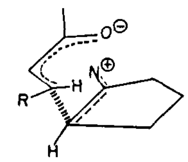
The simplest construction of **3** would appear to involve enamine annulation[3] of cyclopentanone with the unsaturated keto ester **4**.



4 5 6

This was attractive because of the ready availability of **4** by either of two routes, both starting from *o*-cresol: Photolysis (sun lamp) of the acetoxydienone **5**[4] in ether-methanol gave the intermediate acetoxydienic ester,[5] which was then refluxed with methanol and Dowex 50[6] to give **4** in ~50% yield (overall from *o*-cresol). Alternatively, ozonolysis of the Birch reduction product **6** from the methyl ether of *o*-cresol followed by refluxing with Dowex 50 in tetrahydrofuran gave the unsaturated keto ester **4** [bp 135-136 °C (12 mm)] (NMR δ 6.7 (dt J = 12.5 Hz, 1 H); 6.0 (d, J = 16 Hz, 1 H)) in ~60% overall yield (from *o*-cresol).

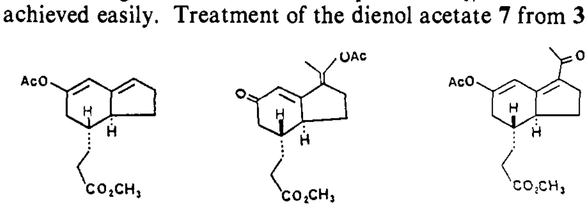
Annulation was simply effected by reaction of the pyrrolidine enamine of cyclopentanone with **4**: refluxing in ethanol for 5 min, followed by the usual buffer hydrolysis[3] gave, in 60-70% yield the bicyclic keto ester **3**. The indenone ester **3** appeared stereochemically homogeneous (NMR δ 5.9 (s, 1 H), IR 1740, 1660 cm^{-1}; MS (CI, ethyl ester) $(M + 1)^+$ 237). We did not have at this point rigorous evidence for the desired anti stereochemistry shown in **3**. Our hope that, possibly via the less crowded of the transition states involving attraction between incipient immonium and enolate ions (cf. A), the stereochemistry would indeed be as



A

shown in **3** was eventually confirmed (vide infra) by X-ray analysis of a later intermediate.

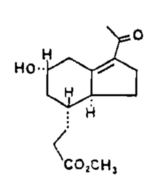
The next goal, introduction of the potential C_{17} substituent, was achieved easily. Treatment of the dienol acetate **7** from **3** (iso-



7 8 9

propenyl acetate, trace of sulfuric acid, overnight, room temperature) with acetic anhydride and 1 equiv of boron trifluoride etherate (5 min at 0 °C) gave, in quantitative yield, the mixture of enol acetates **8** and **9** (4:1). The isomer **9** (NMR δ 6.9, 1 H) could easily be separated from **8** (NMR δ 6.2, 1 H), into which it could be converted by resubmission to the acetylation procedure.[9] Subsequent steps were carried out with **8** (mp 98.5-100 °C).[10]

There now remained the demanding task of transforming **8** into **14**. This required stereocontrolled conjugate addition to either one or the other of the potential α,β-unsaturated ketone systems of **8** and selective protection of the resulting 20-keto system. We solved both problems in the following way: Reduction with sodium borohydride (absolute ethanol, 10 min, room temperature) to the cyclohexenol (80% yield)[11] was followed by enol acetate cleavage and conjugation (sodium carbonate methanol, 2.5 h room temperature) to the acetylcyclopentene **10** (mp 86-86.5 °C)[10] (92% yield), the structure of which was rigorously confirmed by X-ray analysis.[12]



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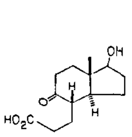
The stage was now set for the last—and crucial—introduction of the missing methyl group in the correct orientation. Various schemes based on direct conjugate addition of methyl failed—not

(1) Stork, G.; Clark, G.; Shiner, C. S. *J. Am. Chem. Soc.* **1981**, *103*, 4948.

(2) The previous work, being concerned with establishing the validity of the **2** → **1** scheme, had not addressed the problem of an efficient construction of **2**. It had served our purpose simply to transform the readily available isomeric keto acid i into the necessary **2** by a serviceable, but cumbersome, carbonyl migration.



(3) Stork, G.; Brizzolara, A.; Landesman, H.; Szmuszkovicz, J.; Terrell, R. *J. Am. Chem. Soc.* **1963**, *85*, 207.

(4) Wessely, F.; Sinwel, S. *Monatsh. Chem.* **1950**, *81*, 1055.

(5) Cf.: Barton, D. H. R.; Quinkert, G. *J. Chem. Soc.* **1960**, 1. These authors were first to achieve the photochemical rearrangement of the acetoxycyclohexadienone **5** to 6-acetoxy-3,5-heptadienoic acid. We operated in more concentrated solution (0.1 M) and obtained the ester in the presence of methanol.

(6) Newman, M. S. *J. Am. Chem. Soc.* **1953**, *75*, 7540.

(7) All NMR spectra were taken at 250 MHz in deuteriochloroform. Purifications were by flash chromatography: Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(8) Cf.: Gorodetsky, M.; Levy, E.; Youssefieh, R. D.; Mazur, Y. *Tetrahedron* **1966**, *22*, 2039.

(9) A catalytic amount of boron trifluoride was sufficient for the isomerization.

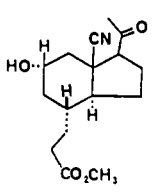
(10) Satisfactory C and H analyses were obtained for this substance.

(11) Simple conjugated acetoxydienes undergo cleavage via ester exchange under these conditions. The (very useful) survival of the system here probably reflects steric hindrance.

(12) Carried out by Dr. John Dewan, to whom we express our thanks.

surprisingly—to provide the proper C/D trans stereochemistry.[13]

The possibility of using a sequence starting with the conjugate addition of a cyano group was difficult to evaluate, since the only reported case with the parent acetylhydrindene corresponding to **10** involves potassium cyanide[14] and results in a predominance of the *cis*-indan derivative.[15] Our initial results, using the *tert*-butyldimethylsilyl ether of **10** and diethylaluminum cyanide in benzene,[16] gave a disappointing 4:1 ratio of trans to cis products. The stereochemical difficulty was resolved, however, when it was found that the same reaction (excess Et_2AlCN, dry benzene, room temperature, 5 min) on the *free* hydroxy compound[17] gave the single adduct **11** in 81% yield. The corresponding dioxolane **12** (mp 131–132 °C) had its structure unambiguously confirmed by X-ray analysis.[18]



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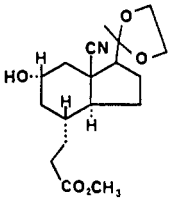

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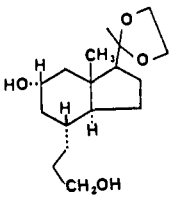

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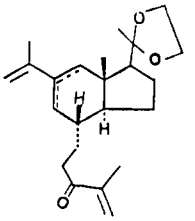
All centers of the target **14** had now been correctly introduced, and it remained only to perform some simple group transformations. Reduction of the cyano group to the imine (lithium aluminum hydride, refluxing tetrahydrofuran, 2.5 days, 90% yield) and Wolff–Kishner reduction (84% yield) of either the imine[19] or the corresponding aldehyde (excess 15% acetic acid) gave the diol **13** (mp 104–105 °C),[10] which was finally oxidized to the required **14** (pyridinium dichromate,[20] 88% yield) (mp 133–135 °C);[10] NMR δ 0.7 (s, 3 H), 1.24 (s, 3 H).

The efficiency of the construction of the indan derivative **14** prompted us to attempt the correction of two minor drawbacks of the previously reported sequence[1] by which we had converted **2** to **1**. The first problem in that conversion came from the production of a small amount of isomeric diene in the dehydration of the lithium isopropenyl reaction product from **14**: this problem disappeared when we found that the undesired diene contaminant was converted to the correct cycloadduct **16** in the presence of a catalytic amount of rhodium chloride.[21] The diene *mixture* **15** (40% from **14**) thus gave **16** in 93% yield when refluxed in ethanol in the presence of a trace of rhodium chloride trihydrate.[22] The second problem, formation of a small amount of undesired exo adduct in the Diels–Alder reaction, simply did not arise in the present series, which starts with **14** rather than with **2**: only the desired endo adduct **16** could be detected. It was transformed, as in the previous series, into (±)-11-keto progesterone **17** (mp 159–161 °C), which gave NMR, IR, and mass spectral data identical with those of a sample of authentic "natural" material. The overall yield from the indanonepropionic acid **14** was 60%.



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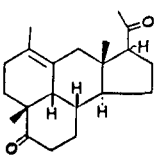

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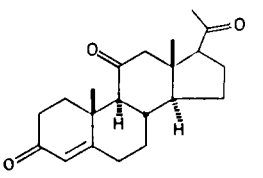

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This sequence represents a rather concise synthesis of 11-keto progesterone, in which the 21 carbons (originating from 1 mol each of *o*-cresol, cyclopentanone, acetic acid, hydrogen cyanide, and 2 mol of 2-bromopropene) all appear in the 21 carbons of 11-keto progesterone.[23]

Acknowledgment. We thank the National Institutes of Health and the National Science Foundation for their support of this work.

Registry No. (±)-**3**, 81768-79-8; **4**, 81768-80-1; (±)-**5**, 70682-37-0; **6**, 69697-74-1; (±)-**7**, 81768-81-2; (±)-**8**, 81768-82-3; (±)-**8** alcohol, 81768-83-4; (±)-**9**, 81768-84-5; (±)-**10**, 81768-85-6; (±)-**11**, 81768-86-7; (±)-**12**, 81768-87-8; (±)-**12** imine, 81768-88-9; (±)-**13**, 81768-89-0; (±)-**14**, 81768-90-3; (±)-**15**, isomer 1, 81768-91-4; (±)-**15**, isomer 2, 81768-92-5; (±)-**16**, 81768-93-6; (±)-**17**, 81800-93-3; cyclopentanone, 120-92-3; isopropenyl acetate, 108-22-5.

(13) Including attempts to direct conjugate addition to the β-face by treatment of the (axial) hydroxy epimer of **10** (obtained together with **10** (1:1) by L-Selectride reduction of **8** with trimethylaluminum and nickel acetylacetonate) (cf.: Bagnell, L.; Meisters, A.; Mole, T.; *Aust. J. Chem.* **1975**, *28*, 817.)

(14) Meyer, W. L.; Wolfe, J. F. *J. Org. Chem.* **1964**, *29*, 170.

(15) Nagata, W.; Yioshioka, M. "Organic Reactions"; Wiley: New York, 1977; Vol. 25, Chapter 3.

(16) Predominant, or exclusive, formation of *trans*-hydrindans, but in cases when the acetylhydrindene was part of a rigid tetracyclic system, has been observed previously: Nagata, W.; Terasawa, T. *Tetrahedron Lett.* **1963**, 865, and other instances in ref 15.

(17) It may be that the free hydroxyl group stops the addition at the kinetic product. It may also be the result of directional influence by the hydroxyl; see: Barlett, P. A.; Green, F. R., III *J. Am. Chem. Soc.* **1978**, *100*, 4858.

(18) We thank Dr. Peter Corfield for this determination.

(19) Cf.: Nagata, W.; Itazaki, H. *Chem. Ind. (London)* **1964**, 1194.

(20) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399.

(21) Cf.: Grieco, P.; Nishizawa, M.; Marinovic, N.; Ehmann, W. J. *J. Am. Chem. Soc.* **1976**, *98*, 7102. Cramer, R. *Ibid.* **1966**, *88*, 2272.

(22) The dioxolane protecting group is hydrolyzed under these conditions. Alternatively, the diene mixture **15** can be refluxed for 1 h with Merck 40-63 silica gel 60 in methylene chloride. Under these conditions, although it was necessary to chromatograph the reaction product to remove the small amount of undesired diene in **15**, the adduct (cf. **16**) was then obtained, still protected as its 20-dioxolane (90% yield).

(23) Of course, any practical application of this route would require solving the problem of chirality induction in the formation of **3**.

On the Mechanism of Hydrogenolysis of Linear Hydrocarbons and Its Relationship to the Fischer–Tropsch Reaction

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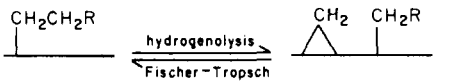
Received January 20, 1982

The hydrogenolysis of linear hydrocarbons over heterogeneous transition-metal catalysts converts the initial alkane, in the presence of H_2, to lower chain hydrocarbons (eventually methane).

Sinfelt[1] has proposed that the hydrogenolysis of ethane to methane proceeds via a dehydrogenated 1,2-adsorbed intermediate, which next undergoes C–C bond cleavage to produce C_1 fragments that are rapidly hydrogenated to methane. In contrast, the hydrogenolysis of higher alkanes was suggested to proceed via a dehydrogenated 1,3-adsorbed intermediate.

As opposed to the earlier mechanisms, we consider that the C–C bond cleavage involves the rearrangement of a metal alkyl linkage (i.e., deinsertion) to form a surface-bound methylene and the next lower homologous metal alkyl. This mechanism for C–C bond cleavage is the reverse of our recently proposed mechanism for C–C bond formation in the Fischer–Tropsch reaction (eq 1).[2,3]



(1)

We have constructed two theoretical models for the hydrogenolysis of linear hydrocarbons. In the first case we assume a metal *n*-alkyl species is formed by the selective cleavage of a

† Deceased, December 10, 1981.

(1) Sinfelt, J. H. *Adv. Catal.* **1973**, *23*, 91.

(2) Brady, R. C.; Pettit, R. *J. Am. Chem. Soc.* **1980**, *102*, 6181.

(3) Brady, R. C.; Pettit, R. *J. Am. Chem. Soc.* **1981**, *103*, 1287.

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