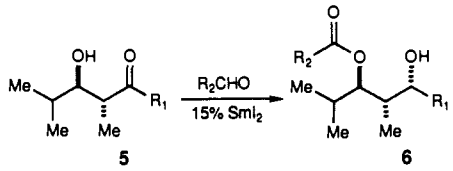
Table III. Reduction of Hydroxy Ketones 5

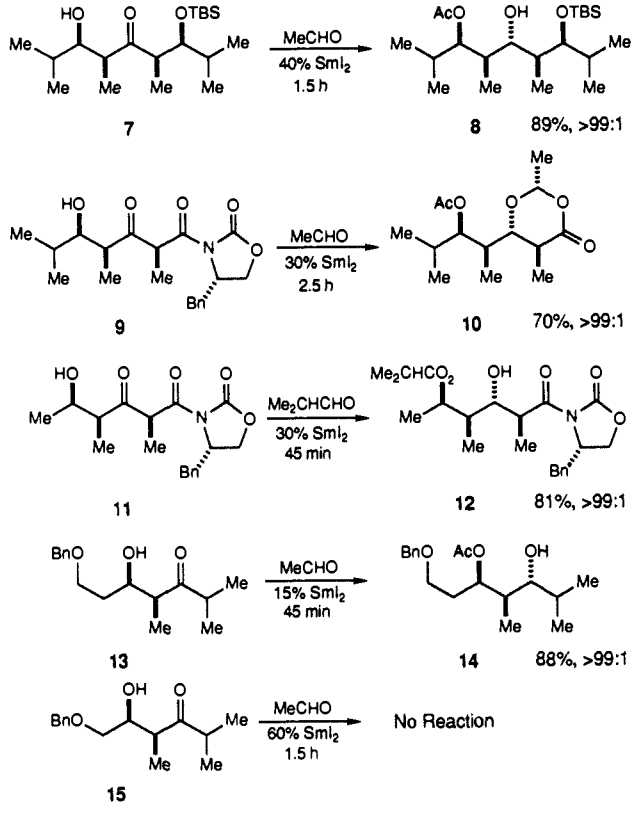


5 6

	R_1	R_2[a]	yield,[b] %	anti:syn
5a	Et	Me	86	>99:1
5b	Me_2CH	Ph	95	>99:1

[a] See Table I. [b] See Table I.

Scheme I



a 1:1 mixture of SmI_2 and PhCHO, which presumably consists of the pinacol adduct $(PhHCO)_2SmI$ and SmI_3, is equally effective as a catalyst (ca. 15 mol %) in reductions with benzaldehyde or isobutyraldehyde.[16] Whether the pinacol-samarium(III) complex, SmI_3, or the combination of the two is the active catalyst remains to be determined; however, we find SmI_3[17] to be less efficient and $SmCl_3$ and $Sm(acac)_3$ entirely ineffective as catalysts. Additional studies with regard to the scope of this and related reactions are under current study.

Acknowledgment. Support has been provided by the National Institutes of Health and Merck. The NIH BRS Shared Instrumentation Grant Program 1 S10 RR01748-01A1 is acknowledged for NMR facilities.

Supplementary Material Available: Experimental procedures and spectral and analytical data for all reaction products (6 pages). Ordering information is given on any current masthead page.

(16) Control experiments were performed to establish that the Sm(III)-pinacol adduct is stable and does not revert to SmI_2 and PhCHO. When **3b** is treated with 1.0 equiv of the Sm(III)pinacolate-SmI_3 mixture, the corresponding anti isobutyrate is obtained in 40% yield within 45 min (>99:1). Presumably, the catalyst first initiates a retro-aldol reaction, and the resulting isobutyraldehyde is subsequently consumed in the reduction of the remaining β-hydroxy ketone.

(17) Prepared according to the method of Imamoto. See: Imamoto, T.; Ono, M. *Chem. Lett.* **1987**, 501-502.

Intramolecular Cyanohydrin Elaboration. Construction of Corticosteroids from 17-Ketosteroids

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The microbial degradation of naturally occurring sterols provides an inexpensive source of 17-ketosteroids, such as androst-4-ene-3,17-dione (AD, **1**).[1] The elaboration of 17-ketosteroids to commercially important pregnanes, such as corticosteroids (**5**) and 17α-hydroxyprogesterones (**6**), is thus of considerable economic consequence and has inspired the development of much new synthetic methodology.[2] Herein is reported a particularly efficient solution to this problem.

One of the few methods for creating a carbon-carbon bond to C-17 that achieves the correct relative stereochemistry in one step is formation of the cyanohydrin of the 17-ketone (Scheme I).[3] If conditions of concomitant equilibration and selective crystallization are established, a wide variety of steroid 17β-cyanohydrins, such as **2**, can be prepared in high yield.[4] Protection of the 3-ketone and 17-hydroxyl, addition of methyllithium or methylmagnesium halide to the nitrile, and oxidation of the 21-carbon to the corticosteroid classically requires four steps.[2k,4c] Attempts to combine the latter operations by adding various oxymethyl anion synthons[5] to this hindered nitrile generally fail because of competing destruction of the reagent.[6]

We have found that intramolecular addition of such a synthon results in efficient construction of the corticosteroid side chain (Scheme I). Specifically, the 17-hydroxyl is first protected as the (chloromethyl)dimethylsilyl ether **3**.[7] Deprotonation[8] of the

(1) (a) Marsheck, W. J.; Kraychy, S.; Muir, R. D. *Appl. Microbiol.* **1972**, *23*, 72-77. (b) Wovcha, M. G.; Antosz, F. J.; Knight, J. C.; Kominek, L. A.; Pyke, T. R. *Biochim. Biophys. Acta* **1978**, *531*, 308-321. For a recent reference in this area, see: (c) Wang, K. C.; Young, L.-H.; Wang, Y.; Lee, S.-S. *Tetrahedron Lett.* **1990**, *31*, 1283-1286, and references therein.

(2) (a) Redpath, J.; Zeelen, F. J. *Chem. Soc. Rev.* **1983**, *12*, 75-98. (b) Nitta, I.; Ueno, H. *Org. Synth. Chem.* **1987**, *45*, 445-461. (c) VanRheenen, V.; Shephard, K. P. *J. Org. Chem.* **1979**, *44*, 1582-1584. (d) Neef, G.; Eder, U.; Seeger, A.; Wiechert, R. *Chem. Ber.* **1980**, *113*, 1184-1188. (e) Barton, D. H. R.; Motherwell, W. B.; Zard, S. Z. *J. Chem. Soc., Chem. Commun.* **1981**, 774-775. (f) *Ibid.* **1982**, 551-552. (g) Barton, D. H. R.; Motherwell, W. B.; Zard, S. Z. *Nouv. J. Chim.* **1982**, *6*, 295. (h) Daniewski, A. R.; Wojciechowska *J. Org. Chem.* **1982**, *47*, 2293-2995. (i) Daniewski, A.; R.; Wojciechowska *Synthesis* **1984**, 132-134. (j) van Leusen, D.; van Leusen, A. M. *Tetrahedron Lett.* **1984**, *25*, 2581-2584. (k) Nitta, I.; Fujimori, S.; Ueno, H. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 978-980. (l) *Ibid.* **1985**, *58*, 981-986. (m) Barton, D. H. R.; Zard, S. Z. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2191-2192. (n) Hofmeister, H.; Annen, K.; Laurent, H.; Wiechert, R. *Liebigs Ann. Chem.* **1987**, 423-426. (o) Solyom, S.; Szilagy, K.; Toldy, L. *Liebigs Ann. Chem.* **1987**, 153-160. (p) Ciattini, P. G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1990**, *31*, 1889-1892.

(3) (a) Ercoli, A.; de Ruggieri, P. *J. Am. Chem. Soc.* **1953**, *75*, 650-653. (b) Kuhl, H.; Taubert, H.-D. *Steroids* **1976**, *28*, 89-99.

(4) Yields of 17β-cyanohydrins are typically 90-98% by this method, depending on the steroid. See: References 2k and 6. (a) Gasc, J. C.; Nedelec, L. *Tetrahedron Lett.* **1971**, 2005-2008. (b) Teichmueller, G.; Haessler, G.; Barnikol-Oettler, K.; Grinenko, G. S.; Dolginova, E. M.; Jenapharm, V. E. B. East Germany Patent DD 147, 669 April 15, 1981; *Chem. Abstr.* **1982**, *96*, 20370f. The surprising generality of the method is further exemplified in: (c) Van Rheenen, V. H.; Upjohn Co., U.S. Patents 4,500,461 February 19, 1985; 4,548,748 October 22, 1985; 4,585,590 April 29, 1986; *Chem. Abstr.* **1985**, *103*, 22844a.

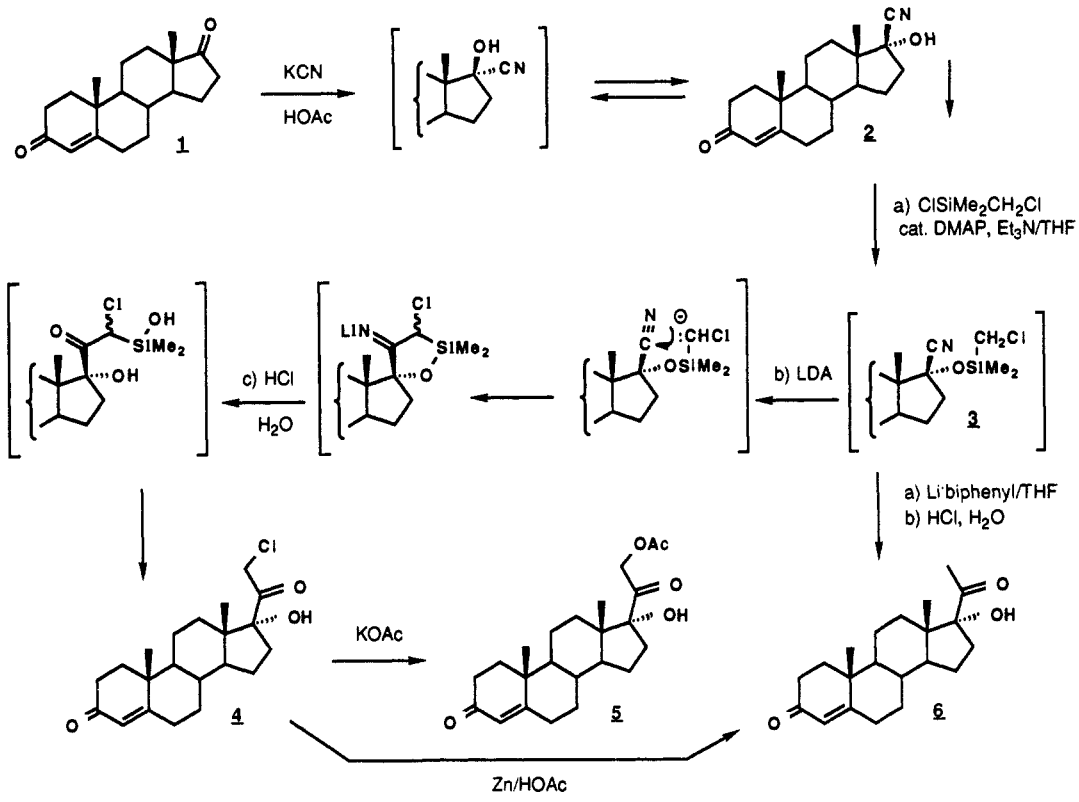
(5) (a) Krief, A. *Tetrahedron* **1980**, *36*, 2531-2640. (b) Beak, P.; Reitz, D. B. *Chem. Rev.* **1978**, *78*, 275-316. (c) Sawyer, J. S.; Kucerovy, A.; Macdonald, T. L.; McGarvey, G. J. *J. Am. Chem. Soc.* **1989**, *110*, 842-853. (d) Katritzky, A. R.; Sengupta, S. *Tetrahedron Lett.* **1987**, *28*, 1847-1850. (e) Corey, E. J.; Eckrich, T. M. *Tetrahedron Lett.* **1983**, *24*, 3163-3164. (f) *Ibid.* **1983**, *24*, 3165-3168.

(6) An interesting approach to this problem involves prior conversion of the nitrile to the more electrophilic aldehyde: Reid, J. G.; Debiak-Krook, T. *Tetrahedron Lett.* **1990**, *31*, 3669-3672.

(7) This readily available spacer group has shown its utility in nucleophilic, intermolecular additions to ketones: (a) Tamao, K.; Ishida, N. *Tetrahedron Lett.* **1984**, *25*, 4245-4248. In radical, intramolecular additions to olefins: (b) Stork, G.; Sofia, M. J. *J. Am. Chem. Soc.* **1986**, *108*, 6828-6829. (c) Stork, G.; Kahn, M. *J. Am. Chem. Soc.* **1985**, *107*, 500-501. (d) Nishiyama, H.; Kitajima, T.; Matsumoto, M.; Itoh, K. *J. Org. Chem.* **1984**, *49*, 2298-2300. To acetylenes: (e) Magnol, E.; Malacria, M. *Tetrahedron Lett.* **1986**, *27*, 2255-2256.

0002-7863/90/1512-6449$02.50/0

Scheme I



chloromethyl group with strong base, such as lithium diisopropylamide, results in spontaneous cyclization onto the nitrile. Quenching the reaction mixture with an excess of aqueous acid effects hydrolysis of the resulting imine, cleavage of the silyl ether, and protiodesilylation. The resulting 21-chloro corticoid generally crystallizes directly from the reaction mixture in high yield and purity. Members of this class of corticoid derivatives are anti-inflammatory agents;[9] the commercially more important corticosteroid 21-acetates, such as **5**, are prepared by subsequent displacement with potassium acetate.[2c,k,1] Alternately, the 17α-hydroxyprogesterones, such as **6**, are obtained by reduction of the 21-chloro group.

Note that under the conditions, certain functionality in the molecule need not be protected, which allows short synthetic sequences. The following example using an unprotected 3-ketone is illustrative. 17β-Cyanohydrin **2**[4] was silylated ($ClSiMe_2CH_2Cl$, catalytic DMAP, Et_3N/THF), and the resulting mixture was added directly to 3.5 equiv of lithium diisopropylamide (THF/hexane, −80 °C) and then warmed to −30 °C. After quenching with excess aqueous hydrochloric acid, the 21-chloroketone **4** crystallized spontaneously, giving 93% overall yield after purification by trituration in methanol. Displacement of the 21-chloride with potassium acetate gave cortexolone acetate (**5**).[10] Zinc/acetic acid reduction of **4** yielded 17α-hydroxyprogesterone (**6**), quantitatively.

Cyclization can also be induced by reductive cleavage of the carbon–halogen bond, for instance with lithium biphenylide,[11] giving the 17α-hydroxyprogesterone directly upon quenching with acid (**3** to **6** in Scheme I). In this case, the 3-ketone must be suitably protected, e.g., as the methyl enol ether or ethylene ketal. Progress in the area of these reductive cyclizations will be reported in due course.

Acknowledgment. This methodology originated from stimulating discussions with Bruce Pearlman and Scott Denmark, whose insights are sincerely appreciated.

(8) (a) Burford, C.; Cooke, F.; Roy, G.; Magnus, P. *Tetrahedron* **1983**, *39*, 867–876. (b) Magnus, P.; Roy, G. *J. Chem. Soc., Chem. Commun.* **1978**, 297–298. (c) Olofson, R. A.; Hoskin, D. A.; Lotts, K. D. *Tetrahedron Lett.* **1978**, 1677–1680. (d) Magnus, P.; Cooke, F. *J. Chem. Soc., Chem. Commun.* **1977**, 513. (e) Burford, C.; Cooke, F.; Ehlinger, E.; Magnus, P. *J. Am. Chem. Soc.* **1977**, *99*, 4536–4537.

(9) For example: Mitsukuchi, M.; Nakagami, J.; Ikemoto, T.; Higuchi,, S.; Tarumoto, Y.; Yasui, H.; Sota, K. *Chem. Pharm. Bull.* **1989**, *37*, 1534–1539.

(10) Cortexolone acetate (Reichstein's "Substance S" acetate, **5**) is a commercial precursor of important glucocorticoids such as hydrocortisone (cortisol) acetate, via microbial 11β-hydroxylation using *Curvularia lunata*. See, for example: Zuidweg, M. H. J. *Biochim. Biophys. Acta* **1968**, *152*, 144–158. Alternatively, the sequence beginning with 11β-hydroxy-AD gives hydrocortisone acetate directly. Note that in this case, the 11-hydroxyl also does not need protection, providing that enough LDA is used to generate the trianion. Colleagues J. Gregory Reid, Therese Debiak-Krook, and William Perrault worked out this alternative. We have also performed the analogous sequence in the $\Delta^{(9,11)}$ series, i.e., to $\Delta^{(9,11)}$-**5**, which was converted into hydrocortisone acetate via a known hydroxybromination–debromination sequence; see: Reference 2c.

(11) Freeman, P. K.; Hutchinson, L. L. *J. Org. Chem.* **1980**, *45*, 1924–1930.