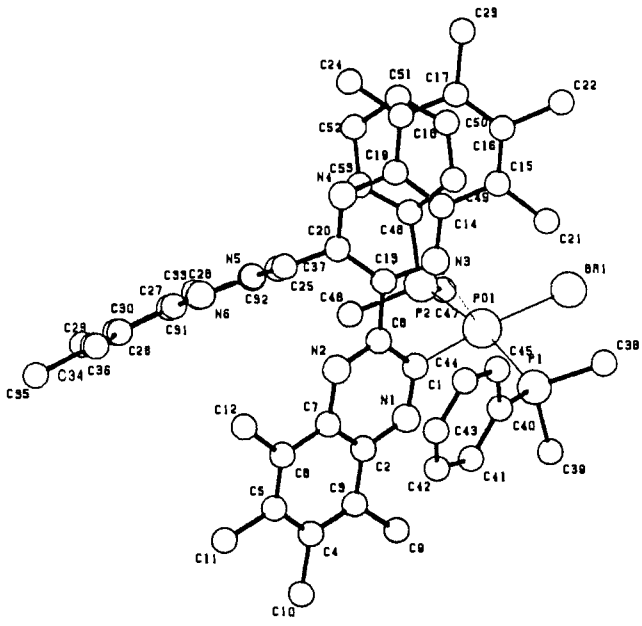

Figure 2. Structure of **3c**. Two crystallographically independent molecules are present in the asymmetric unit; only one is shown. Selected interatomic distances (angstroms) and angles (degrees) are as follows: Pd-Br, 2.534 (1); Pd-P(1), 2.329 (2); Pd-P(2), 2.314 (2); Pd-N(3), 2.942 (5); Pd-C(1), 1.987 (5); Br-Pd-P(1), 92.0 (1); Br-Pd-C(1), 174.7 (1); Br-Pd-N(3), 115.1 (1); P(1)-Pd-N(3), 94.2 (1); C(1)-Pd-N(3), 69.8 (2).

the higher feeding ratio of **1a/2**. Although further polymerization also proceeded with the feeding ratio of over 7, insoluble polymers were produced.

The living polymerization mentioned above should be propagated via (quinoxalinyl)palladium complexes, which undergo successive insertion of ortho isocyano groups on 1,2-diisocyanoarene into their carbon-palladium linkage. Indeed, treatment of (biquinoxalinyl)palladium complex **3b** once isolated[7] with **1a** (2 equiv) resulted in the propagation to form a mixture of terquinoxaline (**3c**; 27%), quaterquinoxaline (**3d**; 28%), quinquequinoxaline (**3e**; 17%), and sexiquinoxaline (**3f**; 4%).[8] The structure of (terquinoxalinyl)palladium complex **3c**[7] was determined by X-ray crystallography (Figure 2).[9] Noteworthy is that the (terquinoxalinyl)palladium complex exists in distorted square-pyramidal five-coordination[10] in which nitrogen atom of the second quinoxaline unit coordinates to palladium atom at an axial position. It is of much interest that the reactive propagating species of living polymerization can be isolated and fully characterized.[4]

Finally, a soluble higher polymer with regular poly(2,3-quinoxaline) structure was successfully synthesized by use of 1,2-diisocyano-3,6-bis[(trimethylsilyl)methyl]benzene (**1b**); the reaction of **1b** with **2** (**1b/2** = 19) proceeded at reflux in THF to afford quinoxaline polymer **5** of $\bar{M}_n$ = 4830 as determined by VPO in 65% isolated yield, which was soluble in common organic solvents such as chloroform and THF. **5**: yellow powder, UV (CH_2Cl_2 solution) λ_{max} 275 nm (ϵ 171 000). It should be noted that GPC using polystyrene as the standard indicated a very sharp distribution of molecular weight $\bar{M}_w/\bar{M}_n$ = 1.08.

This method for controlled living polymerization offers a new entry to poly(heteroaromatics), which have attracted increasing attention owing to their interesting properties.

Supplementary Material Available: Experimental procedure for the reaction of **1a** with **2**, spectral and analytical data for **3b**, **3c**, and **4b-h**, and tables of crystal data, atomic coordinates, isotropic and anisotropic thermal parameters, and bond lengths and bond angles for **3a** and **3c** (18 pages). Ordering information is given on any current masthead page.

Samarium-Catalyzed Intramolecular Tishchenko Reduction of β-Hydroxy Ketones. A Stereoselective Approach to the Synthesis of Differentiated Anti 1,3-Diol Monoesters

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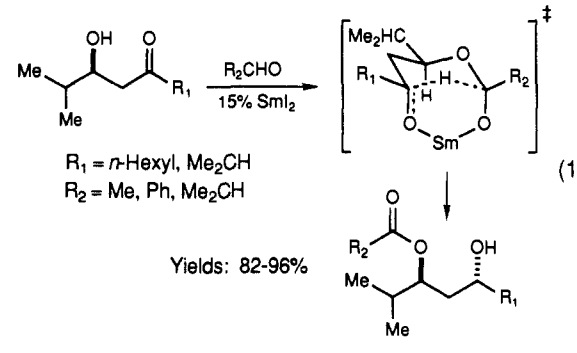
Those carbonyl and olefin addition reactions in which the reagent is "directed" through the active participation of functionality contained within the substrate provide the opportunity for both unique site selectivity and stereocontrol. Recent examples of directed hydrogenation,[1] hydride reduction,[2] and conjugate addition[3] complement the more traditional reactions in this class such as the Simmons-Smith reaction[4] and the Henbest and Sharpless allylic alcohol epoxidations.[5] In connection with our interest in the development of stereoselective reactions that may be employed in the synthesis of polyketide-derived natural products, we have evaluated a number of hydride reagents that might effect reduction of hydroxy ketones wherein the proximate heteroatom functionality strictly controls the facial selectivity of hydride delivery.[2b] We now report our findings on the samarium-catalyzed intramolecular Tishchenko reduction of β-hydroxy ketones (eq 1);[6,7] this transformation affords the corresponding



anti diol monoesters in high yield and with excellent levels of stereochemical control.[8]

(7) (Biquinoxalinyl)- and (terquinoxalinyl)palladium complexes (**3b** and **3c**) were isolated by TLC (silica gel) of the reaction mixture of **1a** with **2** (**1a/2** and 2 and 3, respectively) followed by recrystallization from dichloromethane-hexane.

(8) Produced oligomers were isolated after conversion to **4c-f** by the reaction with [(trimethylsilyl)methyl]magnesium chloride (reflux in THF for 15 min).

(9) **3c**: triclinic, space group $P\bar{1}$, a = 16.178 (3) Å, b = 24.714 (5) Å, c = 13.037 (1) Å, α = 90.81 (1)°, β = 94.08 (1)°, γ = 106.77 (2)°, V = 4975 (2) Å^3, Z = 4, λ (Cu Kα) = 1.541 78 Å, μ = 50.8 cm^{-1}, R = 0.048, R_w = 0.072 excluding hydrogen atoms.

(10) Collier, J. W.; Mann, F. G.; Watson, D. G.; Watson, H. R. *J. Chem. Soc.* **1964**, 1803.

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(2) (a) Saksena, A. K.; Mangiaracina, P. *Tetrahedron Lett.* **1983**, *24*, 273-276. (b) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560-3578.

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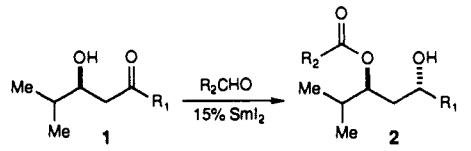
0002-7863/90/1512-6447$02.50/0

Table I. Reduction of Unsubstituted Hydroxy Ketones **1**



	R_1	R_2[a]	yield,[b] %	anti:syn
1a	*n*-Hexyl	Me	96	>99:1
	n-Hexyl	Me_2CH	95	>99:1
	n-Hexyl	Ph	94	>99:1
1b	Me_2CH	Me	85	>99:1
	Me_2CH	Ph	99	>99:1

[a] In all experiments 4–8 equiv of R_2CHO was employed. Reaction temperature of −10 °C (30–45 min) was employed. [b] Isolated yields of purified **2**.

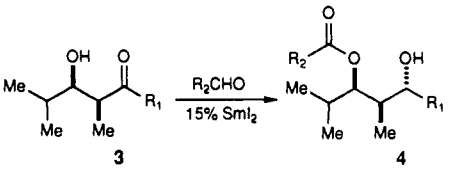
As is illustrated in Table I, treatment of β-hydroxy ketones **1a** and **1b** with 4–8 equiv of aldehyde and 15 mol % SmI_2[9] in THF at −10 °C results in the rapid formation of the anti 1,3-diol monoesters **2**.[10] A variety of aldehydes, such as acetaldehyde, isobutyraldehyde, and benzaldehyde, are effective hydride donors, and transformations typically proceed to completion within an hour. Use of excess aldehyde is not mandatory but leads to enhanced rates of reaction.[11] The diastereoselectivities observed in all reactions carried out in this study exceed the limits of capillary GLC detection, and the estimate of >99:1 diastereoselection noted in the tables could be as high as 300–500:1. In addition, these reactions show little propensity for subsequent acyl migration (<5%).

A typical experimental procedure is as follows: The β-hydroxy ketone **1b** (2.58 g, 16.3 mmol) is dissolved in 45 mL of anhydrous THF under nitrogen. To this solution is added 6.90 mL (65.3 mmol) of freshly distilled benzaldehyde. The solution is cooled to −10 °C (methanol–ice bath) and covered with aluminum foil, and 24.5 mL (2.45 mmol) of a 0.1 M stock solution of SmI_2 in THF[12] is added dropwise (1 min). The initial blue color disappears within 15 s. After 10 min, the reaction mixture is quenched by the addition of diethyl ether and saturated aqueous $NaHCO_3$. The ethereal solution is washed with saturated aqueous $NaHCO_3$, dried, and concentrated. Silica gel chromatography (6:1, hexane–diethyl ether) affords 4.28 g (16.2 mmol, 99% yield) of the hydroxybenzoate as a pale yellow oil. Analysis of the corresponding bisacetate and comparison with authentic samples of syn and anti diol monoesters indicate the presence of only the anti isomer within the limits of capillary GLC detection (>99:1, anti:syn).

The reductions of both syn and anti α-methyl β-hydroxy ketones follow the same stereochemical course with equally high levels of asymmetric induction. In analogy with our earlier studies on the reduction of the same substrates with triacetoxyborohydride,[2b] asymmetric induction from the distal hydroxy stereocenter dominates any bias induced by the α-methyl-bearing center (Tables II and III).

Hindered ketones are also readily reduced, and representative cases are illustrated in Scheme I. Ketone **7** affords the fully differentiated triol in 89% yield with 40 mol % SmI_2, and **9** and **11** are smoothly reduced to the anti derivatives with 30 mol % SmI_2. It is noteworthy that reduction of substrate **9** leads to the concomitant removal of the oxazolidinone auxiliary and formation of dioxalone **10**. Our preliminary studies indicate that the samarium-catalyzed Tishchenko reduction can be sensitive to subtle structural variations. Whereas the δ-benzyloxy β-hydroxy ketone **13** is reduced smoothly within 45 min to afford the anti reduction product, the γ-benzyloxy β-hydroxy ketone **15** is recovered unchanged when even more than stoichiometric amounts of SmI_2 are employed. A control experiment demonstrates that the observed lack of reactivity is not due to catalyst inactivation. After 90 min of exposure to 60 mol % SmI_2 and excess acetaldehyde, **15** remains unaffected, but when substrate **5b** is added to this mixture, the latter is reduced within 20 min. The reason for this difference in reactivity is unclear and is presently under investigation.

Table II. Reduction of Hydroxy Ketones **3**



	R_1	R_2[a]	yield,[b] %	anti:syn
3a	Et	Me_2CH	95	>99:1
3b	Me_2CH	Me	85	>99:1

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

A plausible mechanism for the samarium-catalyzed reduction might involve coordination of the aldehyde and the hydroxy ketone to the catalyst, hemiacetal formation, and intramolecular hydride transfer. As illustrated in eq 1, the proposed transition structure bears a close resemblance to that suggested earlier by us for the triacetoxyborohydride reductions of analogous substrates.[2b] The higher level of stereochemical control observed in the samarium-catalyzed reductions may be attributed to the coordination of samarium to *both* carbonyl and hemiacetal oxygens. In conjunction with an aldol addition reaction of carbon-bound nickel enolates with benzaldehyde, Burkhardt, Bergman, and Heathcock have recently documented a similar intramolecular Tishchenko reduction mediated by nickel complexes; in this study, product acyl migration is reported to be significant.[13] Their projections on the mechanism and probable transition state are similar to those presented here.[14]

Reduction of **1b** with CD_3CDO results in complete incorporation of deuterium at the newly generated carbinol center; this finding demonstrates that the aldehyde is the exclusive source of hydride. When an excess of an equimolar mixture of CH_3CHO and CD_3CDO is used in the reduction of **3b**, a 1:1 mixture of the deuterated and nondeuterated reduction products is obtained ($k_H/k_D \approx 1$), implying that hydride transfer is not the rate-limiting step.

Our studies indicate that the active samarium catalyst may well be some Sm(III) entity. Upon addition of SmI_2 to the mixture of β-hydroxy ketone and excess aldehyde, the blue color of Sm(II) is quickly replaced by the yellow-orange hue of Sm(III), resulting from the Sm(II)-mediated aldehyde pinacol reduction.[15] Indeed,

(8) For other examples of anti reduction of β-hydroxy ketones and derivatives, see: (a) Rreference 2b. (b) Anwar, S.; Davis, A. P. *Tetrahedron* **1988**, *44*, 3761–3770. (c) Bloch, R.; Gilbert, L.; Girard, C. *Tetrahedron Lett.* **1988**, *29*, 1021–1024.

(9) Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693–2698.

(10) Stereochemical assignments of all the products have been determined through comparison with authentic syn and anti isomers, and by analysis of ^1H NMR coupling constants and nuclear Overhauser experiments on the corresponding formal or acetonide derivatives. See the supplementary material for details.

(11) For example, 1.0 equiv of isobutyraldehyde was employed to reduce substrate **5b** (Table II) in 90 min (88% yield, >99:1).

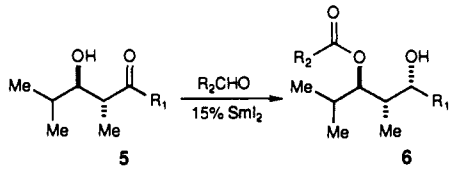
(12) To obtain high yield and stereoselectivity, it is imperative that the SmI_2 be freshly prepared. In addition, the diiodoethane used in the preparation of the catalyst must be prewashed with a saturated solution of sodium thiosulfate. See the supplementary material for details.

(13) Burkhardt, E. R.; Bergman, R. G.; Heathcock, C. H. *Organometallics* **1990**, *9*, 30–44.

(14) The transition state proposed herein is also similar in constitution to the transition structure reported recently for intramolecular Reformatsky reactions promoted by samarium iodide: Molander, G. A.; Etter, J. B. *J. Am. Chem. Soc.* **1987**, *109*, 6556–6558.

(15) Namy, J. L.; Souppe, J.; Kagan, H. B. *Tetrahedron Lett.* **1983**, *24*, 765–766.

Table III. Reduction of Hydroxy Ketones 5

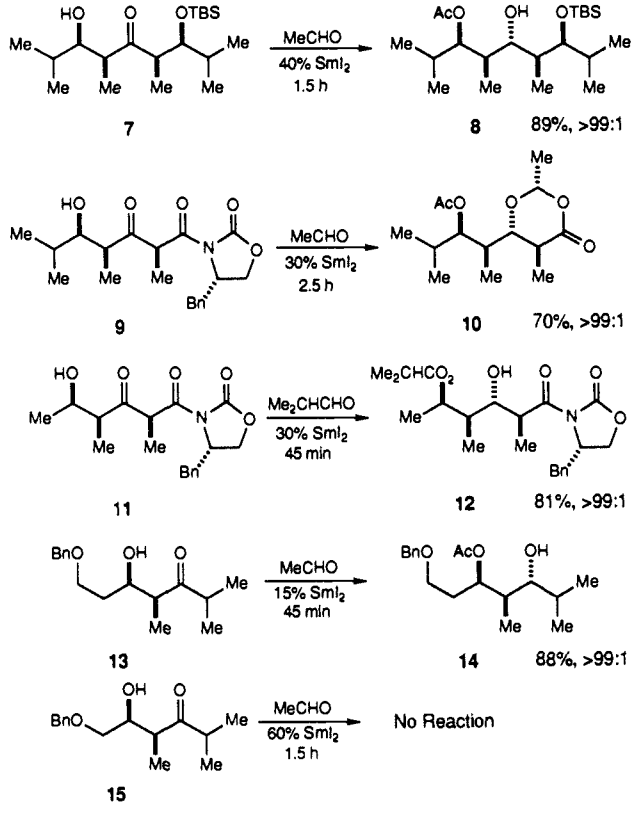


5 6

	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

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(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.

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