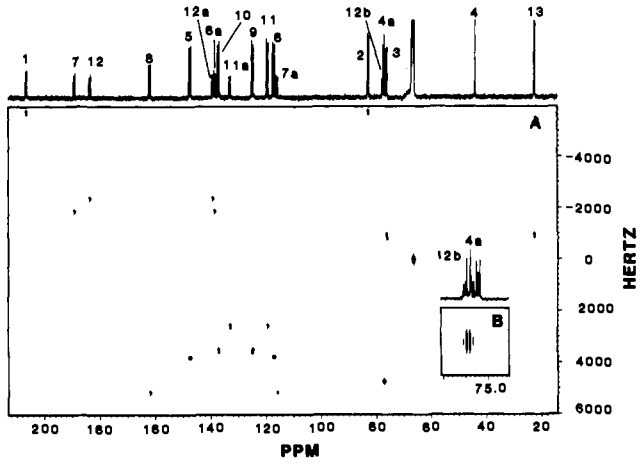
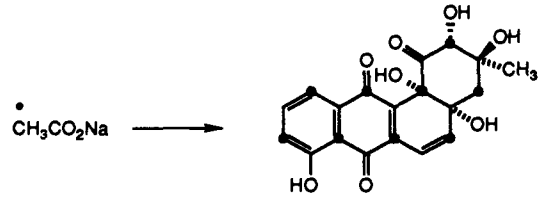



Figure 1.

of Silicar CC-4.[14] The column was eluted with $CH_2Cl_2$, 10% EtOAc/$CH_2Cl_2$, and 35% EtOAc/$CH_2Cl_2$. **2** eluted in the last fraction and was further purified by flash chromatography ($SiO_2$), eluting with 20% EtOAc/$CH_2Cl_2$, and then recrystallized from EtOAc (148 mg, mp 216–218 °C dec).

The data obtained by workers at Warner-Lambert yielded a structure, exclusive of stereochemistry, identical with yoronomycin.[13] Through a series of 1D and 2D NMR experiments (including LR-HETCOSY,[15] difference NOE, and NOESY), we have confirmed the structure of **2** and determined its relative stereochemistry, as shown.[16]

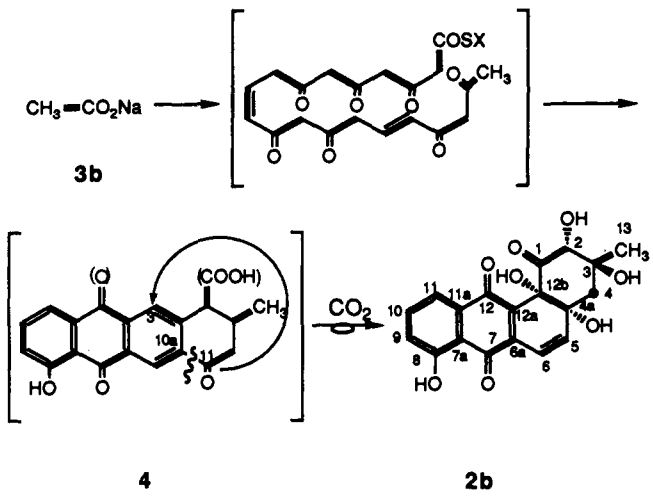
Initial biosynthetic experiments with tracer amounts of sodium [2-$^{14}$C]acetate fed to production broths at 18 h, alone and mixed with unlabeled acetate, established conditions for feedings of acetate labeled with stable isotopes. Sodium [2-$^{13}$C]acetate (481 mg), **3a**, mixed with sodium [2-$^{14}$C]acetate (0.5 μCi), was fed to two production broths. The crude product (138 mg) was purified as described to yield 9.5 mg of **2a** (1.6% incorporation of **3a**), which was analyzed by $^{13}$C NMR spectroscopy (100.6 MHz, dioxane-$d_8$),[17] yielding the labeling pattern indicated in Table I. Based on a 25% recovery of the **2a**, an average enrichment of 9.2% was anticipated.[18]




**3a** **2a**

The labeling pattern of **2a** was consistent with the paradigm represented by Scheme I. To confirm this, Na[1,2-$^{13}C_2$]OAc, **3b**, was next fed. A total of 721 mg of **3b**, mixed with 0.65 μCi of Na[2-$^{14}$C]OAc, was fed to three production broths, and this yielded 10.7 mg of pure **2b** (1% incorporation of **3b**). The $^{13}$C NMR spectrum (Figure 1) of **3b** showed 18 resonances with doublets flanking the natural abundance singlets, indicating nine intact precursor acetate units, and one lone enriched singlet. However, contrary to expectations, the singlet was due to C-4, and on the basis of pairing resonances from their $J_{CC}$ values (Table I), the D-ring labeling pattern was clearly inconsistent with Scheme I! The coupling patterns for C-4a and C-12b were not first order, due to the closeness of their chemical shifts (76.9 and 77.5 ppm, respectively), and were diagnostic for their being coupled to each other. The correctness of all the assigned pairings was confirmed by both $^{13}$C{$^{13}$C}COSY and $^{13}$C 2D INADEQUATE (spectrum shown in Figure 1) experiments.

Scheme II




**4** **2b**

PD 116198 clearly is not derived by a simple folding and condensation of a decaketide directly to the angular benz[*a*]-anthraquinone skeleton. This is in direct contrast to the pathway previously reported for three other benz[*a*]anthraquinones.[7-10] The data presented here are consistent with initial condensation to a linear tetracyclic structure, schematically represented by **4**, and subsequent cleavage of the C-10a/C-11 bond (between two precursor acetates) followed by bond formation between C-3 and C-11 (Scheme II). A more detailed understanding of this unusual pathway is being pursued.

**Acknowledgment.** Dr. James C. French is thanked for arranging receipt of a slant of *S. phaeochromogenes* WP 3688 and an authentic sample of PD 116198 from the Warner-Lambert Company. This work was supported by U.S. Public Health Service Grant GM 31715 to S.J.G. The Bruker AM 400 NMR spectrometer was purchased in part by grants from the National Science Foundation (CHE-8216190) and the M. J. Murdock Charitable Trust to Oregon State University.

(14) Silicar CC-4 was obtained from Mallinkrodt (7086).
(15) Sato, Y.; Geckle, M.; Gould, S. J. *Tetrahedron Lett.* **1985**, *26*, 4019.
(16) Gould, S. J.; Halley, K. A., unpublished results.
(17) Spectral width 25 000 Hz; 64K data points; 35° pulse angle; 1.31-s acquisition time; 3.0-Hz line broadening; 38 096 scans.
(18) The average $^{13}$C enrichment per position was 7.3%.

## A Catalytic Method for the Reduction of Esters to Alcohols†

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*Received February 7, 1991*

While transition-metal catalysis has been successfully applied to the hydrosilylation of olefins, alkynes, and many carbonyl compounds,[2] the hydrosilylation of esters remains relatively unknown. Investigations using γ-irradiation[3a] and metal halides such

† This paper is dedicated to our friend and colleague Professor K. Barry Sharpless on the occasion of his 50th birthday.
(1) (a) National Science Foundation Predoctoral Fellow, 1989–1992. (b) Recipient of a fellowship from the Division of Organic Chemistry of the American Chemical Society, sponsored by the Dow Chemical Company.
(2) (a) For a recent review of the hydrosilylation reaction, see: Ojima, I. In *The Chemistry of Organic Silicon Compounds*; Patai, S., Rappoport, Z., Eds.; John Wiley & Sons: New York, 1989. (b) Cf.: Nakano, T.; Nagai, Y. *Chem. Lett.* **1988**, 498.
(3) (a) Nagata, Y.; Dohmaru, T.; Tsurugi, J. *J. Org. Chem.* **1973**, *38*, 795. (b) Calas, R. *Pure Appl. Chem.* **1966**, *13*, 61 and references therein. (c) Boyer, J.; Corriu, R. J. P.; Perz, R.; Poirier, M.; Reyé, C. *Synthesis* **1981**, 558. (d) Chuit, C.; Corriu, R. J. P.; Perz, R.; Reyé, C. *Synthesis* **1982**, 981. (e) Corriu, R. J. P.; Perz, R.; Reyé, C. *Tetrahedron* **1983**, *39*, 996.

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**Scheme I**

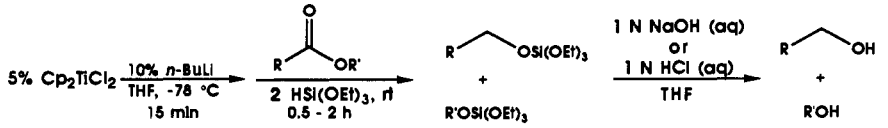
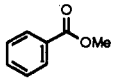
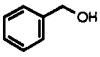
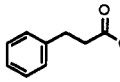
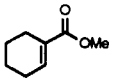
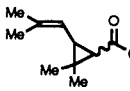
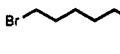
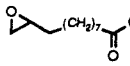
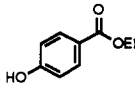
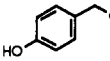
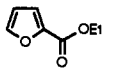
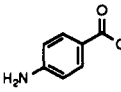
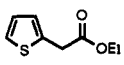
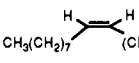
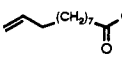
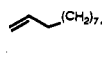
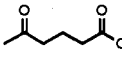
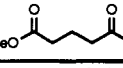



**Table I.** Titanium-Catalyzed Reduction of Esters to Alcohols

| Entry | Ester | Procedure[a] | Workup | Product | Yield (%)[b] |
|---|---|---|---|---|---|
| 1 |  | A | conc. HCl |  | 93[c] |
| 2 |  | A<br>1.2 equiv. $H_2SiPh_2$ | 1 N NaOH in MeOH |  | 82 |
| 3 |  | A | 1 N NaOH in $H_2O$ |  | 71 |
| 4 |  | A | 1 N NaOH in EtOH |  | 83 |
| 5 |  | B<br>-20 °C → r.t., 8 h | 1 N NaOH in $H_2O$ |  | 78 |
| 6 |  | B<br>(EBTHI)$TiCl_2$ / 2 n-BuLi | 1 N NaOH in $H_2O$ |  | 67 |
| 7 |  | A<br>3.3 equiv. $HSi(OEt)_3$ | 1 N NaOH in $H_2O$<br>extract with EtOAc |  | 88 |
| 8 |  | A | 1 N NaOH in $H_2O$ |  | 75 |
| 9 |  | A<br>4.8 equiv. $HSi(OEt)_3$ | 1 N NaOH in $H_2O$<br>extract with EtOAc |  | 81 |
| 10 |  | A | 1 N NaOH in $H_2O$ |  | 88 |
| 11 |  | A | 1 N NaOH in $H_2O$ |  | 90 |
| 12 |  | B<br>(EBTHI)$TiCl_2$ / 2 n-BuLi | 1 N NaOH in $H_2O$ |  | 62 |
| 13 |  | A<br>3.3 equiv. $HSi(OEt)_3$ | 1 N NaOH in $H_2O$<br>extract with EtOAc |  | 78 |
| 14 |  | A | 1 N NaOH in $H_2O$ |  | 87 |

[a] Procedure A: Silane and ester are added to the precatalyst mixture simultaneously. Procedure B: Silane is added to the precatalyst mixture, and the reaction mixture is warmed to room temperature, during which time gas evolution is observed. The ester is added after gas evolution ceases. See the supplementary material for full experimental procedures. [b] Isolated yields of >95% pure material. All compounds are known and were characterized by IR, $^1H$ NMR, and $^{13}C$ NMR spectroscopy. [c] One hundred millimole scale.

as $ZnCl_2$,[3b] $NiCl_2$,[3b] CsF,[3c,e] and KF[3d,e] as catalysts have been successful, but harsh reaction conditions or stoichiometric amounts of the metal salt are necessary in order for the transformations to proceed. We now report a titanium-catalyzed hydrosilylation of esters that proceeds in high yields under mild conditions, using readily available, inexpensive materials.

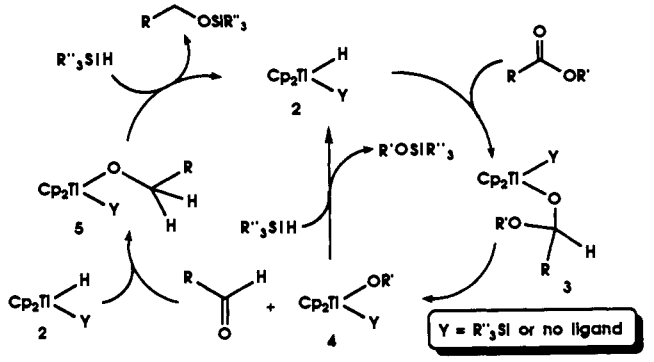
Addition of 5 mol % of bis(trimethylphosphine)titanocene[4] to a solution containing 1 equiv of diphenylsilane produces a hydrosilylation catalyst that converts 1 equiv of ethyl acetate to diphenyldiethoxysilane rapidly and in 94% yield. Alternatively, an active catalyst system can be conveniently generated by the reaction of 2 equiv of n-BuLi with $Cp_2TiCl_2$,[5] as shown in Scheme I. This simple procedure was used for the reduction of a great variety of ester substrates (see Table I).[6]

(4) Kool, L. B.; Rausch, M. D.; Alt, H. G.; Thewalt, U. *J. Organomet. Chem.* **1987**, *320*, 37.

(5) Binger, P.; Muller, P.; Benn, R.; Rufinska, A.; Gabor, B.; Kruger, C.; Betz, P. *Chem. Ber.* **1989**, *122*, 1035.

(6) (a) Typical Procedure: To a dry Schlenk tube under argon was added $Cp_2TiCl_2$ (38 mg, 0.15 mmol) and 2 mL of THF. The slurry was cooled to −78 °C and a 1.6 M hexane solution of n-butyllithium (188 μL, 0.3 mmol) was added. After the solution was stirred for 15 min, triethoxysilane (1.4 mL, 7.5 mmol) and the ester (3.0 mmol) were added, and the cold bath was removed. As the reaction mixture warmed, gas evolution was apparent and a significant amount of heat was generated which, in certain cases, was enough to reflux the THF. For large-scale reactions, it is recommended that a room temperature water bath be used in order to avoid excess heating. After 0.5–2 h, GC analysis of an aliquot taken from the reaction mixture showed complete disappearance of the starting material. The catalyst was deactivated by exposure to air for 15 min. Then, THF (5 mL) and 1 N aqueous NaOH (15 mL) were added, and the reaction mixture was stirred for 1 h. Standard workup afforded crude (≥90% pure) product. Further purification could be accomplished by flash chromatography or distillation, if necessary. (b) An extra equivalent of silane is required for compounds with acidic protons.

Scheme II




A surprising degree of selectivity is seen with this catalyst system. For example, ethyl 6-bromohexanoate is cleanly converted to 6-bromo-1-hexanol at −20 °C. Likewise, α,β-unsaturated esters and esters containing phenolic, amino, or cyclopropyl groups, as well as di- and trisubstituted olefins, are efficiently transformed into the corresponding primary alcohols.[6b] For substrates containing a terminal olefin or an epoxide, use of the more hindered titanocene dichloride species ethylene-1,2-bis($\eta^5$-4,5,6,7-tetrahydro-1-indenyl)titanium dichloride,[7] (EBTHI)$TiCl_2$, is required for a successful transformation. Selective hydrosilylation of an ester in the presence of a ketone was not possible. However, *a methyl ester can be selectively reduced in the presence of a tert-butyl ester.*

The system is relatively insensitive to the presence of adventitious moisture or small amounts of oxygen. The reaction proceeds cleanly, even when the substrate is premixed with 10 mol % of $H_2O$ (excess silane is used to scavenge water, which is silylated under the reaction conditions) or if the reaction is carried out in a solvent that has not been rigorously deoxygenated. Moreover, while the examples shown in Table I use 5 mol % of inexpensive $Cp_2TiCl_2$, the amount of titanium reagent can be reduced to as low as 0.5 mol % with no noticeable decrease in yield.

While we have not yet undertaken detailed mechanistic studies, a plausible pathway for the reaction is shown in Scheme II. Our hypothesis that the active catalyst is probably in the +3 oxidation state is based on the known propensity of Ti(IV) to be reduced,[8] on the observation of partial deoxygenation of the terminal epoxide substrate (entry 6) to the corresponding olefin,[9] and on the observed disappearance of $^1H$ NMR signals of the titanium species. The initial interaction of the catalyst **2** with the ester substrate leads to intermediate **3**, which expels aldehyde with concomitant production of **4**. The aldehyde reacts with a second equivalent of **2** to produce **5**. Finally, the silyl ethers of the product alcohols are liberated via a σ-bond metathesis process[10] to regenerate the catalyst. Further work is obviously necessary to verify this hypothesis.

In summary, we have developed a new catalytic hydrosilylation system for the conversion of esters to primary alcohols which utilizes inexpensive silanes as the stoichiometric reductant.[11] This procedure is efficient and selective and may represent a safer and more convenient alternative to the use of reducing agents such as $LiAlH_4$ and DIBAL on a large scale.[12] Further work is in progress to utilize this and related systems for other functional group interconversions and to map out the mechanistic course of these reaction processes.

**Acknowledgment.** This work was supported by the National Institutes of Health (GM 34917), the National Science Foundation (CHE-9000482), and W. R. Grace, to whom we are grateful. S.L.B. is a Fellow of the Alfred P. Sloan Foundation and a Camille & Henry Dreyfus Teacher-Scholar. We are indebted to Professors K. Barry Sharpless and Julius Rebek, Dr. Alberto Gutiêrrez, and Robert Grossman for their insightful comments.

**Supplementary Material Available:** Detailed experimental procedures for the preparation of and spectroscopic characterization for the products given in Table I (7 pages). Ordering information is given on any current masthead page.

(12) CAUTION! Methoxysilanes should not be used in this reaction, as they are volatile and are known to cause blindness. Additionally, while we have performed this reaction ca. 200 times without incident using the combination *n*-BuLi/$Cp_2TiCl_2$ in a ratio of ~2, we note that in two reactions in which *n*-BuLi/$Cp_2TiCl_2$ = 4, opening of the reaction vessel to the air caused the appearance of a flame, presumably due to the known disproportionation of $(EtO)_3SiH$ to $SiH_4$ (see: Xin, S.; Aikten, C.; Harrod, J. F.; Mu, Y.; Samuel, E. *Can. J. Chem.* **1990**, *68*, 471). A control experiment in which *n*-BuLi was allowed to react with $(EtO)_3SiH$ in the absence of $Cp_2TiCl_2$ gave similar results. We have found that the liquid polymer, polymethylhydrosiloxane (a commodity material produced by Dow-Corning and available from Huls America), is a suitable substitute for $(EtO)_3SiH$; its use eliminates the chance of generating $SiH_4$.

## Polymer-Supported Solution Synthesis of Oligosaccharides[1]

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*Received February 14, 1991*

The efficient preparation of oligosaccharides, as well as their elaboration into glycopeptides and glycolipids, is of central importance for the application of these compounds in biological sciences and medicine.[2] In an effort to develop a fundamentally new approach to oligosaccharide synthesis, we have been exploring a polymer-supported method combining the anomeric control of solution chemistry with the ease and speed of solid-state-supported workup. The solid-state-based procedure eliminates time-consuming workups and potentially reduces the time required for the synthesis of an oligosaccharide from months to days or weeks.

Despite recent dramatic advancements in the solution methodology of oligosaccharide synthesis,[3,4] yields in the key glycosidic

(1) Supported through the Protein Engineering Network of Centres of Excellence, Canada.

(2) E.g.: *Carbohydrate Recognition in Cellular Function*; Bock, G., Harnett, S., Eds.; Ciba Foundation Symposium 145; Wiley: Chichester, 1989.

(3) (a) Paulsen, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 155; (b) **1990**, *29*, 823.

(4) (a) Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 212. (b) Fugedi, P.; Garegg, P. J.; Lonn, H.; Norberg, T. *Glycoconjugate J.* **1987**, *4*, 97. (c) Mootoo, D. R.; Date, V.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1988**, *110*, 2662. (d) Konradsson, P.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1989**, 1124. (e) Fraser-Reid, B.; Wu, Z.; Udodong, U. K.; Ottoson, H. *J. Org. Chem.* **1990**, *55*, 6068. (f) Veeneman, G. H.; Van Leeuwen, S. H.; Zuurmond, H.; Van Boom, J. H. *J. Carbohydr. Chem.* **1990**, *6*, 783. (g) Kanie, O.; Kiso, M., Hasegawa, A. *J. Carbohydr. Chem.* **1988**, *7*, 501. (h) Reddy, G. V.; Kulkarni, V. R.; Mereyala, H. B. *Tetrahedron Lett.* **1989**, *30*, 4283. (i) Friesen, R. W.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 6656. (j) Friesen, R. W.; Danishefsky, S. J. *Tetrahedron* **1990**, *46*, 103.

(7) (a) Wild, F. W. R. P.; Zsolnai, L.; Huttner, G.; Brintzinger, H. H. *J. Organomet. Chem.* **1982**, *232*, 233. (b) Collins, S.; Kuntz, B. A.; Taylor, N. J.; Ward, D. G. *J. Organomet. Chem.* **1988**, *342*, 21.

(8) (a) Long, W. P.; Breslow, D. S. *J. Am. Chem. Soc.* **1960**, *82*, 1953. (b) For examples of Ti(III) hydrides, see: Bercaw, J. E.; Marvich, R. H.; Bell, L. G.; Brintzinger, H. H. *J. Am. Chem. Soc.* **1972**, *94*, 1219. Samuel, E.; Harrod, J. F. *J. Am. Chem. Soc.* **1984**, *106*, 1859.

(9) RajanBabu, T. V.; Nugent, W. A.; Beattie, M. S. *J. Am. Chem. Soc.* **1990**, *113*, 6408.

(10) (a) Woo, H.-G.; Tilley, T. D. *J. Am. Chem. Soc.* **1989**, *111*, 3757. (b) Woo, H.-G.; Tilley, T. D. *J. Am. Chem. Soc.* **1989**, *111*, 8043.

(11) Esters can be reduced by using catalytic $Cp_2TiCl_2$ and stoichiometric *i*-PrMgBr: Sato, F.; Jinbo, T.; Sato, M. *Tetrahedron Lett.* **1980**, *21*, 2175. Sato, F.; Jinbo, T.; Sato, M. *Synthesis* **1981**, 871.

0002-7863/91/1513-5095$02.50/0 