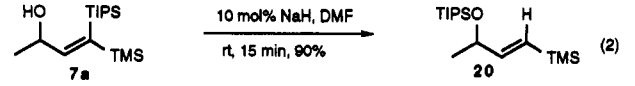
agent.[20] Another challenge in preparing (*Z*)-trisubstituted vinylsilanes is the sluggishness of the hydrometalated intermediate toward alkylation with electrophiles which are less reactive than methyl or allyl halides. A significant amount of the protonated product often accompanies the desired products and separation of these products can be difficult. Utilization of a silyl migration on a (*Z*)-vinylstannane, prepared via the Piers palladium-catalyzed conjugate addition of a tin group to an ynone, provides a simple solution to these problems.[21] Transmetalation and migration occurs to give **13** in 79% yield, entry 4.

Although these migrations are formally reversible, no starting material was recovered after workup. Under these conditions the equilibrium clearly lies completely on the side of the lithium alkoxide. The driving force for this reaction may be the formation of a covalent O–Li bond (hard–hard) rather than a C–Li bond (soft–hard).[9] Replacement of lithium by sodium should cause reversal of the migration and that process is well documented.[13] We found that treatment of **7a** with 10 mol % NaH in DMF caused a carbon–oxygen migration providing **20** in 90% yield.



(2)

In conclusion, we have shown that 1,4-silyl migrations of stereochemically defined vinylstannanes can be utilized in the synthesis of a variety of (*Z*)-vinylsilanes and hetero- and homobimetallic compounds. This sequence provides additional substrates for hydrogenation and cyclopropanation reactions, the results of which will be reported shortly.

Acknowledgment. This research was supported by the Alfred P. Sloan Foundation, the Natural Science and Engineering Research Council (NSERC) of Canada, the Merck Frosst Centre for Therapeutic Research, and BioMega (Canada). We thank a reviewer for bringing refs 9 and 10 to our attention.

Supplementary Material Available: General experimental procedures, details for specific representative reactions, and compound characterization data (17 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(20) (a) Soderquist, J. A.; Colberg, J. C.; Del Valle, L. *J. Am. Chem. Soc.* **1989**, *111*, 4873. (b) Soderquist, J. A.; Colberg, J. C. *Synlett.* **1989**, 25.

(21) Piers, E.; Tillyer, R. D. *J. Chem. Soc., Perkin Trans 1* **1989**, 2124 and references cited therein.

A Microscale NMR Method of Determining Absolute Stereochemistries in β-Amino Alcohols by Enantioselective Complexation and the Mode of Action of Their Oxidative Resolution

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Summary: By reactions of six examples of the title compounds with the Katsuki–Sharpless catalyst, enantioselective complexation was found to be at the origin of the oxidative resolution of the *N,N*,α-trisubstituted β-amino alcohols and provides a means of assigning absolute stereochemistries to the title compounds.

In 1983, the Sharpless group[1] described a kinetic resolution of *N,N*-dialkyl β-amino alcohols (Scheme I) based on the preferred oxidation of one enantiomer (that related to (*S*)-1-amino-2-propanol) by ^{t}BuOOH, promoted by 2 equiv of $Ti(O^iPr)_4$ in the presence of 1.2–1.5 equiv[2] of (*R,R*)-diisopropyl tartrate (H_2DIPT), with isolation of the unreacted antipode in high ee. These reactions were not catalytic, as is the Katsuki–Sharpless asymmetric epoxidation,[3] but were nonetheless a useful alternative to classical resolutions that depend on diastereomers possessing different physical properties, especially because the absolute stereochemistries of the products were consistently the same, as is true of the epoxidation system. For quite unrelated purposes, I had occasion to examine the

Scheme I

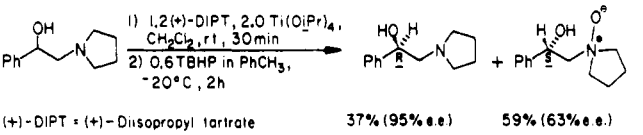

Table I. Spreads in Chemical Shifts in ppm (Δδ) and H–H Coupling Constants in Hz (*J*) for Tartrate Signals in the NMR Spectra of $Ti_2DIPT_2A(O^iPr)_3$

	first type			second type		
HA	$\Delta\delta_H$	$\Delta\delta_C$	*J*	$\Delta\delta_H$	$\Delta\delta_C$	*J*
HDMAE	0.13	1.73	9.3	0.55	0.51	7.2
HEPY	0.10	1.40	9.1	0.64	0.94	8.0
HDMAP	0.06	1.42	9.15	0.52	0.37	7.3
HDMAC	0.082	1.52	9.25	0.51	0.25	7.33
l-ephedrine	0.27	1.58	9.4	0.72	0.75	8.6

reactions of such amino alcohols with the parent Katsuki–Sharpless catalyst, $Ti_2DIPT_2(O^iPr)_4$. This has led to an explanation of the mode of action of this remarkable resolution and to a microscale method of assigning absolute stereochemistries to such amino alcohols.

N,N-Dimethyl-2-aminoethanol (HDMAE) and *N,N*-dimethyl-1-amino-2-propanol (HDMAP) were known to form the monomeric, pentacoordinate complexes $TiDMAE(O^iPr)_3$ and $TiDMAP(O^iPr)_3$.[4] These and analogous complexes of other amino alcohols (generically represented by HA) are reactive toward alkoxide substitutions, as 1:1

(1) Miyano, S.; Lu, L. D.-L.; Viti, S. M.; Sharpless, K. B. *J. Org. Chem.* **1983**, *48*, 3608.

(2) Miyano, S.; Lu, L. D.-L.; Viti, S. M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 4350.

(3) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974. Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765. Reviews: Sharpless, K. B.; Woodard, S. S.; Finn, M. G. *Pure Appl. Chem.* **1983**, *55*, 1823. Finn, M. G.; Sharpless, K. B. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1985; Vol. 5, p 247. Johnson, R. A.; Sharpless, K. B. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: New York, 1991; Vol. 7, Chapter 3.2.

(4) Alyea, E.; Merrell, P. H. *Inorg. Nucl. Chem. Lett.* **1973**, *9*, 69.

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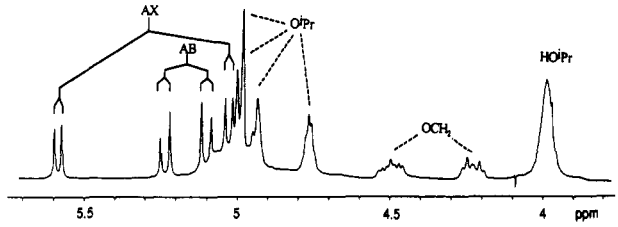
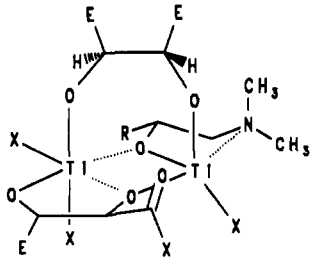


Figure 1. OC*H* region of the ^{1}H-NMR spectrum of $TiDIPT_2DMAE(O^iPr)_3$ with irradiation of the CCH_3 region.

mixtures with $Ti(O^iPr)_4$ showed severely broadened NMR signals due to TiO^iPr–HO^iPr exchange. Treatment of $TiDMAE(O^iPr)_3$ with 1 equiv of H_2DIPT gave a new, nonfluxional and less reactive complex fitting the formula $Ti_2DIPT_2DMAE(O^iPr)_3$, with liberation of 0.5 equiv of HDMAE, whose signals were only somewhat broadened by exchange. This same complex also arose by treatment of the fluxional $Ti_2DIPT_2(O^iPr)_4$[5] with 0.5 equiv of HDMAE.

A detailed spectral analysis is given here only for the DMAE complex but analogous $Ti_2DIPT_2A(O^iPr)_3$ complexes formed with four other amino alcohols and the NMR data relevant to their detection are tabulated in Table I.[6] In the NMR spectra, there were two equally populated but asymmetric types of tartrate but no sign of carbonyl coordination (four *C*=O and four ester O*C*H peaks appeared at positions close to those with H_2DIPT, whereas coordination induces strong downfield shifts[5]). The first type exhibited moderate shift differences between skeletal O*CH* ($\Delta\delta_H$ = 0.13 ppm), appearing as an AB pattern with strong H–H coupling (J = 9.3 Hz) as depicted in Figure 1, and moderately well separated O*C*H signals ($\Delta\delta_C$ = 1.73 ppm), as is typical of a chelating tartrate unit lacking carbonyl coordination.[7] In the second type, one skeletal O*CH* was strongly deshielded (to 5.62 ppm), giving rise to an unusually large $\Delta\delta_H$ (0.52 ppm) for the resulting AX pair of doublets, but showed a small $\Delta\delta_C$ (0.37 ppm) and more moderate (and more variable) coupling (J = 7.2 Hz). Excepting the deshielding, these characteristics were typical of a nonchelating mode of tartrate ligation.[5a,7] There were three equally intense sets of TiO^iPr O*C*H peaks (the corresponding OCH signals overlapped with ester O*C*H signals). The DMAE methylene protons gave rise to a clear ABXY system, and there were paired NCH_3 and NCH_3 signals due to prochirality befitting amino-group coordination. In accord with the expectation that the relatively basic and primary alkoxide of DMAE can bridge two metals better than DIPT, structure 1 fully accounts for the spectra. The downfield shift of one O*CH* can be explained by an interaction between one O*CH* on the nonchelating tartrate unit with a carbonyl group on the other, but other explanations might apply as chemical shifts are subject to many influences.

By either mode of mixing, 2-(2-hydroxyethyl)pyridine (HEPY) gave rise to the very same NMR patterns, confirming that the aforementioned deshielding was not due to the amino moiety. Similarly, racemic HDMAP formed *a single diastereomer* of an analogous complex (**2**) and,



X:O^{i}Pr E:COO^{i}Pr
1 R:H
2 R:CH$_3$

consequently, a full equiv was required to produce the same spectral clarity obtained with 0.5 equiv of HDMAE or HEPY. Again, the unreacted HDMAP showed broadened signals due to exchange, probably on the pentacoordinate metal. By irradiation of the CH_3 region, a single and large OC*H*–NC*H* coupling constant was measurable (10.6 Hz) and the O*CH* was assigned the pseudoaxial disposition depicted in **2**, assuming an envelope form for the chelate ring. Racemic *trans-N,N*-dimethyl-2-aminocyclohexanol (HDMAC)[2] behaved in entirely the same way, as did also *l*-ephedrine.[8] With *d*-ephedrine, substitution of O^{i}Pr groups occurred, but an indecipherable and complex mixture resulted and no useful assignments could be made. These experiments, along with the absence of a second well-defined complex with racemic HDMAP or HDMAC in the presence of excess $Ti_2DIPT_2(O^iPr)_4$, allowed the assignment of the *R* configuration to the DMAP and DMAC units in their ternary complexes. The secondary alkoxide oxygens of the chiral amino alcohols, also more basic than in DIPT, evidently can also bridge two Ti centers when not sterically impeded. The reaction of *l*-ephedrine also revealed that secondary amino groups could be similarly coordinated, as also occurred in the reactions of the ephedrines with $Ti(O^iPr)_4$ alone.

These reactions therefore obeyed eq 1. In the oxidative resolution 2 equiv of $Ti(O^iPr)_4$ were used. According to the foregoing, both the ternary complex of the *R* enantiomer and the binary complex of the *S* antipode should then arise (eq 2). Reaction of HEPY with 1 equiv of

$$2rac\text{-HA} + 2Ti(O^iPr)_4 + 2H_2DIPT \rightarrow Ti_2DIPT_2(R\text{-A})(O^iPr)_3 + (S)\text{-HA} + 5HO^iPr \quad (1)$$

$$2rac\text{-HA} + 4Ti(O^iPr)_4 + 2H_2DIPT \rightarrow Ti_2DIPT_2((R)\text{-A})(O^iPr)_3 + Ti((S)\text{-A})(O^iPr)_3 + Ti(O^iPr)_4 + 6HO^iPr \quad (2)$$

$$Ti((S)\text{-A})(O^iPr)_3 + {}^t\text{BuOOH} \rightarrow Ti((S)\text{-AO})(O^iPr)_3 + {}^t\text{BuOH (fast)} \quad (3)$$

$$Ti_2DIPT_2((R)\text{-A})(O^iPr)_3 + {}^t\text{BuOOH} \rightarrow Ti_2DIPT_2((R)\text{-AO})(O^iPr)_3 + {}^t\text{BuOH (slow)} \quad (4)$$

$Ti(O^iPr)_4$ and 0.5 equiv of H_2DIPT confirmed this. One can surmise that the oxidation to the *N*-oxide (HAO) takes place on the more reactive binary template to deplete the mixture of (*S*)-HA (eq 3), leaving the *R* enantiomer relatively intact. This is consonant with the observation that, with just 1 equiv of $Ti(O^iPr)_4$ (i.e., eq 1), only slow oxi-

(5) (a) Potvin, P. G.; Gau, R.; Kwong, P. C. C.; Bianchet, S. *Can. J. Chem.* **1989**, *69*, 1523. (b) Finn, M. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1990**, *113*, 113.

(6) See supplementary material for full spectra. All attempts at isolation resulted in further reaction, probably to $Ti_2DIPT_2A_2(O^iPr)_2$, and air-sensitive, glassy solids. This also occurred during mass spectrometry: the EI spectra of the DMAC mixture showed a peak at 761 (corresponding to $Ti_2DIPT_2DMAC(O^iPr)_2$) as well as higher mass fragments arising from $Ti_2DIPT_2DMAC_2(O^iPr)_2$.

(7) Potvin, P. G. *J. Org. Chem.*, submitted for publication.

(8) This material also produced a second, more minor complex showing a few sets of separate signals, especially for the ephedrine and the nonchelating tartrate O*CH*. The minor product was therefore probably a conformer of the major complex and, as such, was estimated to constitute some 20% of the total.

dation of the *R* enantiomer took place,[1] with the less reactive ternary complex as the only available template (eq 4).

For certain substrates, additional H_2DIPT (up to 1.5 equiv total) was beneficial.[2] A probable explanation is that the unreacted $Ti(O^iPr)_4$ in equation 2 constitutes an alternative site for (*R*)-HA in cases of incomplete formation of the ternary complex. An additional 0.5 equiv of H_2DIPT would preclude this. This might also be avoided if, as eq 2 suggests, only the 1.5 equiv of $Ti(O^iPr)_4$ actually required for the oxidative resolution were used. On the other hand, eq 1 suggests that no chemical transformation of HA would be needed if a method of isolating the free (*S*)-HA could be found, with subsequent release of the (*R*)-HA by the standard workup.[2] Indeed, careful gel permeation chromatography of the *rac*-HDMAC mixture (Bio-rad Biobeads SX-8/CH_2Cl_2) was accompanied by some decomposition of the ternary species (H_2DIPT was detected in the early fractions) but provided a 25% yield of (*S*)-HDMAC in 75% ee[2] in the later fractions. Further work in this vein is currently underway.

Thus, it is the complexation, not the oxidation, which is enantioselective. The (*R,R*)-DIPT-based Katsuki-Sharpless complex will give well-defined complexes with α,*N*-disubstituted and α,*N*,*N*-trisubstituted β-amino alcohols related to *l*-ephedrine. With the proven generality and the predictable enantioselectivity of the oxidative resolution (13 successful examples of *N*,*N*,α-trisubstituted β-amino alcohols including HDMAC[2,9]), probably extendable also to substrates with α-substituents as small as methyl and/or with only secondary amino groups, this reaction could be used to reliably assign the absolute stereochemistries of homochiral materials, even on a very small scale, according to which tartrate antipode will give signals fitting the patterns of Table I.

Acknowledgment. The author is grateful to Mr. Benjamin Fieldhouse for the work with HEPY, to Mr. Stephen Bianchet for the gel permeation work, and to the Natural Sciences and Engineering Research Council of Canada for financial support.

Supplementary Material Available: General procedure for the preparation of NMR samples, NMR peak listings with assignments, and ^1H and ^{13}C spectra (13 pages). Ordering information is given on any current masthead page.

(9) Kihara, M.; Ohnishi, K.; Kobayashi, S. *J. Heterocycl. Chem.* **1988**, *25*, 161.

A Straightforward Route to Functionalized Intermediates Containing the CD Substructure of Taxol

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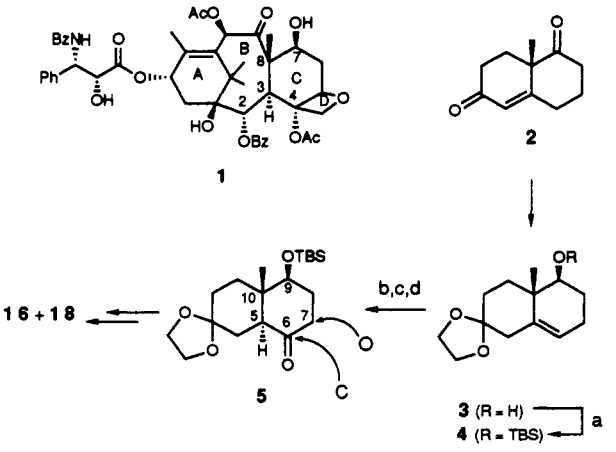
Summary: The Wieland-Miescher ketone lends itself to conversion, in a few steps, to intermediates which could well be useful for a synthesis of taxol (1) and analogs thereof.

The chemistry and pharmacology of the potent anticancer diterpenoid taxol (1; Scheme I)[1] have been reviewed extensively.[2] After isolation from the yew tree, *Taxus brevifolia*, taxol is only available in limited quantities. The therapeutic promise of this compound for the treatment of certain cancers, combined with its limited availability, have made it the subject of intensive synthetic and hemisynthetic study.[2]

We began by taking note of the possibility that the commercially available Wieland-Miescher ketone **2**[3] might be exploited to secure much of the functionality required for embarking upon a synthesis of taxol. The relationship of the angular methyl group and its vicinal ketone in **2** bear obvious homology with the corresponding C-7,8 region of **1**. Moreover, transformations reported by Heathcock[4] provide access to **3** which by modest adaptation allowed for the preparation of **5**. Thus, the equatorial secondary alcohol of **3**[5] was readily converted to **4**.[6] Hydroboration and oxidation analogous to the reported protocol gave a mixture of diastereomeric alcohols. Tetrapropylammonium perruthenate catalyzed oxidation[7] of this

Scheme I[a]



[a] Conditions: (a) TBSOTf/2,6-lutidine/CH_2Cl_2/0 °C; 97%; (b) (i) BH_3-THF, (ii) H_2O_2/NaOH; (c) 6 mol % TPAP/NMO/powdered 4-Å molecular sieves/CH_2Cl_2; (d) NaOMe/MeOH; 62% from **4**.

(1) Wani, M. C.; Taylor, H. L.; Wall, M. E.; Coggan, P.; McPhail, A. T. *J. Am. Chem. Soc.* **1971**, *93*, 2325.
(2) (a) Swindell, C. S. *Org. Prep. Proc. Int.* **1991**, *23*, 465. (b) Blechert, S.; Guenard, D. *Taxus* Alkaloids. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: San Diego, 1990; Vol. 39, pp 195-238. (c) Rowinsky, E. K.; Cazenave, L. A.; Donehower, R. C. *J. Natl. Cancer Inst.* **1990**, *82*, 1247. (d) Chabner, B. A. *Princ. Prac. Oncol.* **1991**, *5*, 1.
(3) Wieland, P.; Miescher, K. *Helv. Chim. Acta* **1950**, *33*, 2215.
(4) Heathcock, C. H.; Ratcliffe, R. *J. Am. Chem. Soc.* **1971**, *93*, 1746.
(5) (a) Boyce, C. B. C.; Whitehurst, J. S. *J. Chem. Soc.* **1960**, 2680. (b) Ward, D. E.; Rhee C. K.; Zoghaib, W. M. *Tetrahedron Lett.* **1988**, *29*, 517.
(6) Corey, E. J.; Cho, H.; Rücker, C.; Hua, D. H. *Tetrahedron Lett.* **1981**, *22*, 3455.

0022-3263/92/1957-3274$03.00/0