progress to further elucidate this mechanism by varying the electronic and steric properties of the metalloporphyrin. We also plan to examine Ru_2(DPB) as a possible hydrogen electrode catalyst.

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(26) Equilibria between dihydrogen complexes and dihydrides of a single metal center are well-known. (a) Kubas, G. J.; Unkefer, C. J.; Swanson, B. I.; Fukushima, E. *J. Am. Chem. Soc.* **1986**, *108*, 7000-7009. (b) Heinekey, D. M.; Chinn, M. S. *J. Am. Chem. Soc.* **1987**, *109*, 5865-5867. (c) Khalsa, G. R. K.; Kubas, G. J.; Unkefer, C. J.; Van Der Sluys, L. S.; Kubat-Martin, K. A. *J. Am. Chem. Soc.* **1990**, *112*, 3855-3860.

Stereoselective Synthesis of Olefins from Silylated Sulfonylhydrazones

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Contribution No. 8133, Arnold and Mabel Beckman Laboratories of Chemical Synthesis California Institute of Technology Pasadena, California 91125

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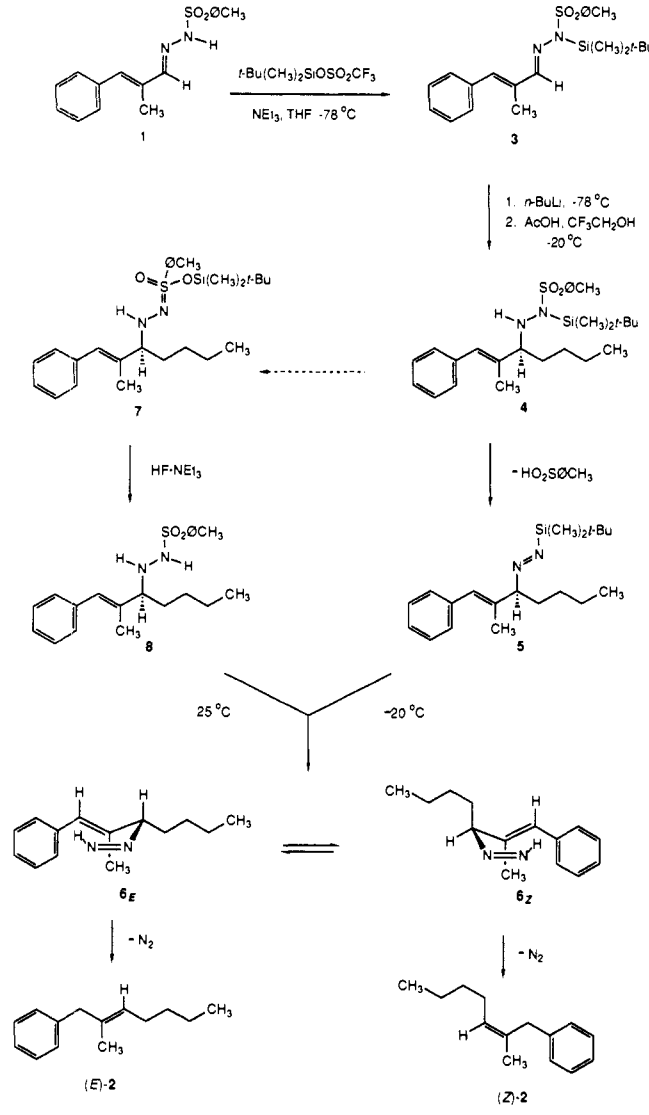
Aldehyde tosylhydrazones have previously been shown to react with alkyllithium or cuprate reagents to form anionic addition products. The reaction requires 2 equiv or more of the organometallic reagent to proceed to completion and is presumed to occur by the elimination of dinitrogen from an intermediate dianion.[1] We find that aldehyde tosylhydrazones can be transformed into stable *N-tert*-butyldimethylsilyl derivatives which undergo smooth 1,2-addition with equimolar quantities of organolithium reagents.[2] The resulting adducts can be induced to decompose along a different pathway than previously observed, by sigmatropic rearrangement of a proposed allylic diazene intermediate, to afford olefinic products.[3] The method and mechanistic details pertinent to the process are illustrated in the conversion of (*E*)-α-methylcinnamaldehyde tosylhydrazone (**1**)[4] to the *E*-trisubstituted olefin **2** (Scheme I).

Triethylamine (1.25 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (1.15 mmol) are added sequentially to a solution of tosylhydrazone **1** (1.0 mmol)[4] in anhydrous tetrahydrofuran (THF, 5 mL) at -78 °C. Methanol (1.25 mmol) is added after 30 min, and the cold reaction mixture is partitioned between hexanes and saturated aqueous sodium bicarbonate solution to afford, upon concentration of the organic layer, the *N-tert*-butyldimethylsilyl sulfonylhydrazone **3** in near quantitative yield. These derivatives vary in their stability toward silica gel and, in general, are used directly without purification. That silylation occurs on nitrogen and not a sulfonamide oxygen is ascertained by ^{15}N NMR spectroscopy (**3**: δ -42.2, -209.9 vs external HNO_3, $CDCl_3$, 0.03 M $Cr(acac)_3$).[5] The conversion of **3** to olefin **2** is accomplished in a single operation, as follows. A deoxygenated solution of crude **3** in THF (5 mL) is cooled to -78 °C and treated with *n*-butyllithium (1.15 mmol, 1.6 M in hexanes). Acetic acid (1.2 mmol) is added after 15 min followed by the cosolvent 2,2,2-trifluoroethanol (10 mL), and the mixture is brought to -20 °C and held at that temperature for 12 h. Extractive isolation and flash column chromatography provide the olefin **2** as a 12:1 mixture of *E* and *Z* isomers, respectively, in 88% yield from **1**.

The formation of **2** from **3** is believed to proceed by the sequence **3** → **4** → **5** → **6** → **2** (Scheme I), a conclusion drawn from the following observations. Intermediate **4** rearranges upon attempted isolation to form **7**, the product of N → O silyl migration. This rearrangement is not observed in the reaction medium described, but does occur if excess acetic acid is employed in the quenching step. Unlike **4**, **7** is stable under the conditions of olefin formation and can be purified by flash column chromatography. Inter-

Scheme I



(1) (a) Vedejs, E.; Stolle, W. T. *Tetrahedron Lett.* **1977**, 135. (b) Bertz, S. H. *Tetrahedron Lett.* **1980**, *21*, 3151.

(2) Organolithium additions to cinnamaldehyde tosylhydrazone proceed in 1,4 fashion (ref 1a).

(3) The sigmatropic rearrangement of an allylic or propargylic diazene intermediate has been invoked in numerous organic transformations. Reduction of tosylhydrazones: (a) Hutchins, R. O.; Milewski, C. A.; Maryanoff, B. E. *J. Am. Chem. Soc.* **1973**, *95*, 3662. (b) Hutchins, R. O.; Kacher, M.; Rua, L. *J. Org. Chem.* **1975**, *40*, 923. (c) Kabalka, G. W.; Yang, D. T. C.; Baker, J. D., Jr. *J. Org. Chem.* **1976**, *41*, 574. (d) Kabalka, G. W.; Chandler, J. H. *Synth. Commun.* **1979**, *9*, 275. Elimination of *p*-toluenesulfinic acid from an allylic tosylhydrazine: (e) Sato, T.; Homma, I.; Nakamura, S. *Tetrahedron Lett.* **1969**, 871. (f) Corey, E. J.; Cane, D. E.; Libit, L. *J. Am. Chem. Soc.* **1971**, *93*, 7016. Wolff-Kishner reduction of α,β-unsaturated ketones: (g) Reusch, W. In *Reduction*; Augustine, R. L., Ed.; Marcel Dekker: New York, 1968; p 182. Oxidation of alkylhydrazines: (h) Corey, E. J.; Wess, G.; Xiang, Y. B.; Singh, A. K. *J. Am. Chem. Soc.* **1987**, *109*, 4717. (i) Myers, A. G.; Finney, N. S.; Kuo, E. Y. *Tetrahedron Lett.* **1989**, *30*, 5747.

(4) (*p*-Tolylsulfonyl)hydrazine (2.10 mmol) and (*E*)-α-methylcinnamaldehyde (2.00 mmol) were combined in tetrahydrofuran (10 mL) at 23 °C, the mixture was stirred at 23 °C for 1 h, and the solution was concentrated. Recrystallization of the solid residue (ether-petroleum ether-methanol, 20:5:1) afforded pure **1** (0.58 g, 93%, mp 124-126 °C dec).

(5) Martin, G. J.; Martin, M. L.; Gouesnard, J.-P. *^{15}N-NMR Spectroscopy*; Springer-Verlag: New York, 1981; p 165.

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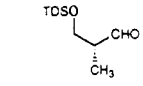
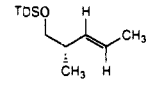
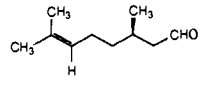
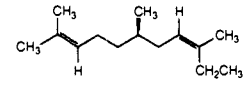
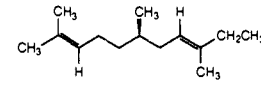
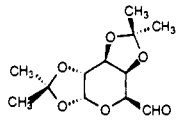
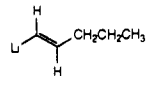
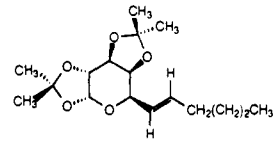
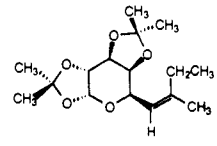
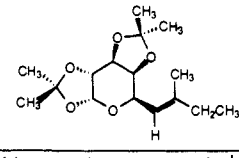
Table I. Olefin Synthesis by Coupling of *N-tert*-Butyldimethylsilyl Aldehyde Tosylhydrazones with Organolithium Reagents[a]

entry	aldehyde[b]	organolithium reagent[c]	product	%yield[d] (stereoselectivity)[e]
1[f,g]				77 (>20:1)
2				90 (2:1)
3[f]	-			83 (>20:1)
4[h]				86 (>20:1)
5[h]	-			79 (1:1)
6[h]	-			81 (>20:1)

[a] Olefin syntheses were conducted as described in the text. Deviations from this procedure are noted. [b] Experiments were carried out with optically active aldehydes. Procedures for their synthesis from commercially available materials appear in the supplementary material. For entries 1–3, tosylhydrazone formation and silylation were carried out sequentially in a single flask. For entries 4–6, these steps were conducted separately. [c] Prepared from the corresponding tributylstannyl derivatives by transmetalation with *n*-butyllithium in tetrahydrofuran at −78 → 0 °C. Experimental procedures for the preparation of each vinylstannane appear in the supplementary material. Vinyllithium (entry 1) was prepared from equimolar quantitites of commercial tetravinyltin and *n*-butyllithium. [d] Entries 1–3: overall yield from the aldehyde. Entries 4–6: overall yield from the tosylhydrazone (details for its preparation appear in the supplementary material). [e] Stereoselectivity ">20:1" indicates that the stereoisomeric product could not be detected by (400-MHz) ^{1}H NMR spectroscopy. Stereochemical assignments are confirmed by multiple difference NOE measurements. Where appropriate, NMR spectra were obtained in more than one solvent. [f] The olefin-forming step was carried out at −10 °C. [g] Vinyllithium was added at −60 °C in ethyl ether as solvent. TDS = *tert*-butyldiphenylsilyl. [h] The olefin-forming step was carried out initially at 0 °C with warming to 23 °C.

estingly, **7** displays fluxional behavior (^{1}H NMR, $\tau_c \sim 40$ °C, 400 MHz, $CDCl_3$), which we attribute to rapid intramolecular exchange of the *tert*-butyldimethylsilyl group between the sulfonimidate oxygens.[6] Quantitative desilylation of **7** can be achieved with triethylamine–hydrogen fluoride complex to provide the sulfonylhydrazine **8**. When **8** is subjected to the conditions of olefin formation (THF:CF_3CH_2OH, 1:2, −20 °C), no significant production of **2** is observed. Olefin formation does occur from **8** at higher temperatures ($t_{1/2} \sim 12$ h at 25 °C), albeit with attenuated stereoselectivity ((*E*)-**2**:(*Z*)-**2** ~ 7:1 at 25 °C). Clearly, **8** is not kinetically competent to be an intermediate in the formation of **2** from **3**, which leads us to propose that elimination of *p*-toluenesulfinic acid occurs directly from **4** to produce the *tert*-butyldimethylsilyl diazene **5**. Desilylation of **5** is then believed to occur rapidly in situ to form the allylic diazene **6**, which spontaneously loses dinitrogen by 1,5-sigmatropic rearrangement.[7]

The selective formation of (*E*)-**2** is simply rationalized by consideration of allylic 1,3-strain within transition states resembling $\mathbf{6}_E$ and $\mathbf{6}_Z$.[8] Additional support for this transition-state description and further demonstration of the scope and utility of the method are revealed in experiments summarized in Table I.

Several features of the transformations depicted in Table I are worthy of comment. These examples show that the method is equally effective in olefin formation between a saturated aldehyde and a vinyl anion as from an α,β-unsaturated aldehyde and a saturated organolithium reagent (illustrated above with α-methylcinnamaldehyde and butyllithium). Entries 1 and 4 demonstrate the value of the method in the constructive synthesis of *E*-disubstituted olefins, an important methodological problem with few efficient and reliable solutions.[9] Importantly, the nonracemic aldehydes of these examples form the corresponding *E*-disub-

(6) Silyl nitronates similarly exhibit fluxional behavior: Colvin, E. W.; Beck, A. K.; Bastani, B.; Seebach, D.; Kai, Y.; Dunitz, J. D. *Helv. Chim. Acta* **1980**, *63*, 697.

(7) For a review of the chemistry of silyl diazenes, see: Wiberg, N. *Adv. Organomet. Chem.* **1984**, *23*, 131.

(8) For a recent review of $A_{1,3}$ strain as a controlling factor in stereoselective transformations, see: Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841.

(9) For the synthesis of complex *E*-disubstituted olefins, the Julia olefin synthesis is, by far, the most frequently employed method: (a) Julia, M.; Paris, J.-M. *Tetrahedron Lett.* **1973**, 4833. (b) Kocienski, P. J.; Lythgoe, B.; Ruston, S. *J. Chem. Soc., Perkin Trans. 1* **1978**, 829.

stituted olefins without detectable epimerization at the adjacent stereogenic center, suggesting potential for application of the method in asymmetric synthesis. Entries 2, 3, 5, and 6 illustrate syntheses of trisubstituted olefins and further define the requirements for selectivity in olefin formation. Thus, additions with 2-lithio-1-butene (entries 2 and 5) exhibit little or no selectivity while additions with (*E*)-2-lithio-2-butene (entries 3 and 6) produce a single stereoisomer, within the limits of detection. The transformations exemplified in the latter entries are particularly significant; we are unaware of another means by which to accomplish this bond construction with the observed selectivity and efficiency. Together these examples reinforce the notion that $A_{1,3}$ steric interactions dominate the transition state for diazene rearrangement (see entries 3 and 6), but caution that $A_{1,2}$ terms can become important where $A_{1,3}$ interactions diminish (see entries 2 and 5).

In conclusion, *N*-*tert*-butyldimethylsilyl tosylhydrazones are demonstrated to be valuable precursors for the constructive synthesis of carbon–carbon double bonds. The method is efficient and offers unique solutions to problems in the stereoselective synthesis of di- and trisubstituted olefins.

Acknowledgment. We are indebted to Mr. Narayanan Kurur and Professor John D. Roberts for their assistance in obtaining ^{15}N NMR spectra. This research was generously supported by the Caltech Consortium in Chemistry and Chemical Engineering; members: E. I. du Pont de Nemours & Co., Inc., Eastman Kodak Company, and Minnesota Mining and Manufacturing Company. Financial support from the National Science Foundation is also gratefully acknowledged.

Supplementary Material Available: Experimental procedures for the preparation of the optically active aldehydes and organolithium precursors of Table I (6 pages). Ordering information is given on any current masthead page.

Synthesis of the Antitumor Bisindole Alkaloid Vinblastine: Diastereoselectivity and Solvent Effect on the Stereochemistry of the Crucial C-15–C-18′ Bond

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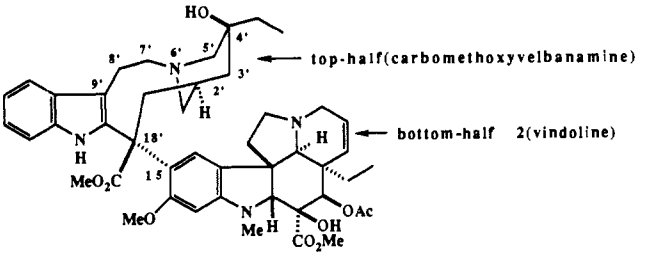
The clinically valuable antitumor agent vinblastine (**1**) has been the object of intensive chemical and pharmacological investigations for the past 25 years.[1] Synthetic studies have focused on how to control the absolute stereochemistry of the crucial C-15–C-18′ bond linking the bottom half, vindoline (**2**), and the top half, carbomethoxyvelbanamine, Scheme I.[2] Potier[3] and Kutney[4] have described a solution to this problem using the Polonovski reaction to fragment catharanthine *N*-oxide to a putative bis iminium ion which is trapped by **2** to give anhydrovinblastine **3** after hydride reduction. The control of the C-15–C-18′ stereochemistry is highly temperature dependent. At −50 °C the C-18′ *S* natural stereoisomer is formed, whereas at 0 °C the C-18′ *R* isomer predominates. More recently, Kuehne has described extensive studies that utilize a variant on the chloroindolenine approach to establish the correct absolute stereochemistry at C-18′.[5]

Scheme I



1(Vinblastine), **3**(3′,4′-anhydrovinblastine)

Despite the formidable and extensive literature in this area, there has not been a systematic examination of how the various stereogenic centers in the top half influence the stereochemistry of the C-15–C-18′ bond. Previously, we had reported that treatment of (+)-**4** with *m*-$MeOC_6H_4NMe_2$/*p*-nitrobenzyl chloroformate-/CH_2Cl_2 gave **6** with 60% ee (retention of C-18′ configuration). Coupling with more nucleophilic aryl components, such as 3,5-$(MeO)_2C_6H_3NMe_2$ gave **7** with >90% ee.[6] The same reaction with vindoline (**2**) gave **8** as a 1:1 mixture of diastereomers at C-18′, indicating that the more slowly the putative iminium ion **5** is captured by the aromatic nucleophile, the more conformational isomerization, in this case racemization, can take place. The transition states leading to **6**/**7** are enantiomeric, whereas for **8** they are diastereomeric. Starting with (−)-**4**, the antipodes of **6**/**7** are formed, whereas coupling with vindoline gave the same result, namely **8** (1:1, 18′-epimers), Scheme II.

We reasoned that a substituent at C-2′ in **4**,[7] fashioned to eventually become the piperidine ring (C-3′, -4′, and -5′), would sufficiently slow the conformational inversion of the nine-membered ring to allow coupling with vindoline to proceed with retention of configuration at C-18′. To ascertain the effect of C-18′/C-2′/C-4′ stereochemistry, we made all possible stereoisomers (only three are shown); the epimers at the C-4′ position correspond to the leurosidine series and did not affect the stereochemical outcome at C-18′. The details of the syntheses of **9**, **10**, and **11**, Scheme III, will be reported in a full account of this research.

Treatment of **9** with $ClCO_2CH_2C_6H_4NO_2$-*p*/vindoline/CH_2Cl_2/25 °C for 72 h gave two compounds, **12** (52%) and **13** (42%). The structure of **12** was established by converting it into 18′-epivinblastine **17**, via **14** (80%), **15** (89%) and **16**, to give **17** (92%) (structure by X-ray).[8] To establish the unprecedented structure of the C-9′ coupled adduct **13**, it was hydrolyzed to the

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[‡] Indiana University.

(1) For a comprehensive review of this area, see: The Alkaloids. *Antitumor Bisindole Alkaloids from Catharanthus roseus (L.)*; Brossi, A., Suffness, M., Eds.; Academic Press Inc.: San Diego, 1990; Vol. 37.

(2) 3′,4′-Anhydrovinblastine has been converted into vinblastine. Mangeney, P.; Andriamialisoa, R. Z.; Langlois, N.; Langlois, Y.; Potier, P. *J. Am. Chem. Soc.* **1979**, *101*, 2243. For a biomimetic equivalent, see reference 10.

(3) Langlois, N.; Gueritte, F.; Langlois, Y.; Potier, P. *J. Am. Chem. Soc.* **1976**, *98*, 7017. Potier, P. *J. Nat. Prod.* **1980**, *43*, 72. For a review, see: Lounasmaa, M.; Nemes, A. *Tetrahedron* **1982**, *38*, 223.

(4) Kutney, J. P. *Lloydia* **1977**, *40*, 107. This paper discusses the effect of solvent and temperature on the C-18′ *S*/*R* ratio in the Polonovski coupling reaction.

(5) For a modification of the chloroindolenine route that produces the correct 18′ configuration, see: Kuehne, M. E.; Zebovitz, T. C.; Bornmann, W. G.; Marko, I. *J. Org. Chem.* **1987**, *52*, 4340. Kuehne, M. E.; Bornmann, W. G. *J. Org. Chem.* **1989**, *54*, 3407. For earlier examples of the chloroindolenine approach that produces the C-18′ *R* stereochemistry, see: Neuss, N.; Gorman, M.; Cone, N. J.; Huckstep, L. L. *Tetrahedron Lett.* **1968**, 783. Kutney, J. P.; Beck, J.; Bylsma, F.; Cook, J.; Cretney, W. J.; Fuji, K.; Imhof, R.; Treasurywala, A. M. *Helv. Chim. Acta* **1975**, *58*, 1690. Rahmann, ur-A.; Basha, A.; Ghazala, M. *Tetrahedron Lett.* **1976**, 2351. Recent work using the chloroindolenine method has been applied to analogues: Schill, G.; Priester, C. U.; Windhovel, U. F.; Fritz, H. *Tetrahedron* **1987**, *43*, 3747.

(6) Magnus, P.; Ladlow, M.; Elliott, J.; Kim, C. S. *J. Chem. Soc., Chem. Commun.* **1989**, 518.

(7) The compound **4** and C-2′-substituted derivatives are made from D- or L-tryptophan: Magnus, P.; Ladlow, M.; Kim, C. S.; Boniface, P. *Heterocycles* **1989**, *28*, 951.

(8) The full details of the single-crystal X-ray crystallographic structure determination of **17** and **19** will be given in a full account of this research.

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