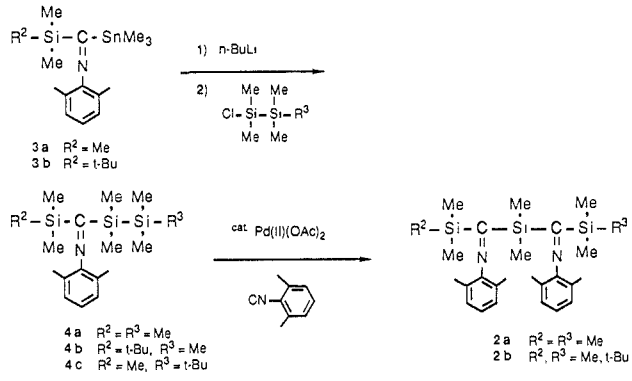
and 0.70 at room temperature, which split into two slightly broad singlets at δ −0.03 and 0.32 with a relative intensity of 3:1 at 90 °C. The temperature dependence of the ^{1}H NMR spectra shows that the syn–anti interconversion of *N*-2,6-xylylimines is rapid enough to sharpen the $(CH_3)_3Si$ and $(CH_3)_2Si$ signals at 90 °C.

2,4-Bis(2,6-xylylimino)-1,3,5-trisilapentane (**2a**) (yield 60%)[3] was also obtained by a palladium-catalyzed reaction of 2,6-xylyl isocyanide with 1-[(trimethylsilyl)(2,6-xylylimino)methyl]-1,1,2,2,2-pentamethyldisilane (**4a**),[4] which was prepared from [(trimethylsilyl)(2,6-xylylimino)methyl]trimethylstannane (**3a**) and chloropentamethyldisilane according to the reported procedure.[5]



3a R^2 = Me
3b R^2 = t-Bu

4a $R^2 = R^3$ = Me
4b R^2 = t-Bu, R^3 = Me
4c R^2 = Me, R^3 = t-Bu

2a $R^2 = R^3$ = Me
2b R^2, R^3 = Me, t-Bu

Similarly, 1-*tert*-butyl-1,1,2,2,3,3,3-heptamethyltrisilane (**1b**) reacted with 2,6-xylyl isocyanide in the presence of palladium(II) acetate to afford 1-*tert*-butyl-1,1,3,3,5,5,5-heptamethyl-2,4-bis-(2,6-xylylimino)-1,3,5-trisilapentane (**2b**) (yield 82%),[3] which was recrystallized from ethanol. **2b** (mp 79–81 °C): IR (KBr) 1546 cm^{-1}; UV (cyclohexane solution) λ_{max} 410 nm (ϵ 620).

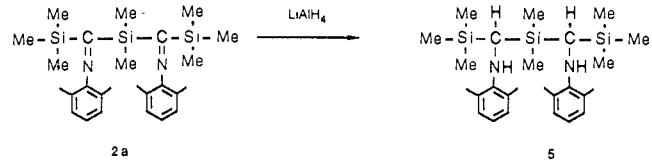
The same 2,4-bis(2,6-xylylimino)-1,3,5-trisilapentane (**2b**) was prepared by palladium-catalyzed insertion of 2,6-xylyl isocyanide into either 1-[(*tert*-butyldimethylsilyl)(2,6-xylylimino)methyl]-1,1,2,2,2-pentamethyldisilane (**4b**)[4] or 1-[(trimethylsilyl)(2,6-xylylimino)methyl]-2-*tert*-butyl-1,1,2,2-tetramethyldisilane (**4c**).[4] These findings excluded the possibility of successive insertion of two 2,6-xylyl isocyanides into the silicon–silicon linkage of polysilane.

The palladium-catalyzed regular insertion of isocyanides into polysilane was successfully applied to tetrasilane; e.g., the reaction of decamethyltetrasilane (**1c**) with 2,6-xylyl isocyanide produced the expected 1,1,1,3,3,5,5,7,7,7-decamethyl-2,4,6-tris(2,6-xylylimino)-1,3,5,7-tetrasilaheptane (**2c**)[3] in 34% isolated yield as a yellow crystalline solid. **2c** (mp 110–112 °C): IR 1544 cm^{-1}; UV (cyclohexane solution) λ_{max} 407 nm (ϵ 540).

Further extension of the poly-insertion of 2,6-xylyl isocyanide into permethylhexasilane (**1d**) afforded a mixture that included the expected poly[sila(*N*-2,6-xylyl)imine] (**2d**), whose mass spectrum gave the corresponding molecular ion peak.

An experimental procedure for the palladium-catalyzed regular insertion of 2,6-xylyl isocyanide into polysilane is exemplified with octamethyltrisilane. A mixture of 2,6-xylyl isocyanide (0.89 g, 6.8 mmol), octamethyltrisilane (0.46 g, 2.2 mmol), and palladium(II) acetate (0.05 g, 0.2 mmol) in toluene (8 mL) was heated at reflux for 3 h under a nitrogen atmosphere. In order to remove the remaining 2,6-xylyl isocyanide, the reaction mixture was stirred with copper(I) chloride (2.1 g, 21 mmol) for 5 h at room temperature and then subjected to flash chromatography (hexane–toluene solvent) on Florisil, which was pretreated with triethylamine. The solvent was evaporated and the remaining yellow solid was crystallized from ethanol to give **1a** (0.58 g, 56%).

Reduction of the imino groups of **2a** was readily performed by treatment with $LiAlH_4$ in Et_2O at room temperature to afford 1,1,1,3,3,5,5,5-octamethyl-2,4-bis(*N*-2,6-xylylamino)-1,3,5-trisilapentane (**5**)[6] in 85% yield.



2a 5

The poly-insertion of isocyanides into polysilanes of high molecular weight is being undertaken in this laboratory.

Acknowledgment. The work was supported in part by the Ministry of Education, Science, and Culture (Grant-in-Aid for Special Project Research, No. 62115003).

(4) **4a**: IR (KBr) 1594, 1544 cm^{-1}; ^{1}H NMR δ −0.30–0.50 (br, 24 H), 1.95 (s, 6 H), 6.67–7.02 (m, 3 H); mass spectrum, *m/z* 335 (M^+). Anal. Calcd for $C_{17}H_{33}NSi_3$: C, 60.82; H, 9.91; N, 4.17. Found: C, 60.63; H, 10.04; N, 4.13. **4b**: IR (KBr) 1594, 1540 cm^{-1}; ^{1}H NMR δ −0.15 (s, 6 H), 0.02 (s, 9 H), 0.24 (s, 6 H), 1.02 (s, 9 H), 1.98 (s, 6 H), 6.60–7.00 (m, 3 H); mass spectrum, *m/z* 377 (M^+). **4c**: IR (KBr) 1594, 1542 cm^{-1}; ^{1}H NMR δ −0.12 (br s, 9 H), 0.10 (s, 6 H), 0.40 (br s, 6 H), 0.93 (s, 9 H), 1.97 (s, 6 H), 6.63–7.02 (m, 3 H); mass spectrum, *m/z* 377 (M^+).

(5) Ito, Y.; Matsuura, T.; Murakami, M. *J. Am. Chem. Soc.* **1987**, *109*, 7888.

(6) **5** (mp 86–87 °C): IR (KBr) 3428, 1594 cm^{-1}; ^{1}H NMR δ −0.05 (br s, 24 H), 2.23 (br s, 12 H), 2.97–3.23 (m, 4 H), 6.50–6.90 (m, 6 H); mass spectrum, *m/z* 470 (M^+).

Cycloaddition Reactions of Silyloxyacetylenes with Ketenes: Synthesis of Cyclobutenones, Resorcinols, and Δ-6-Tetrahydrocannabinol

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Received February 2, 1988

The utility of alkyoxyacetylenes (R—C≡C—OR′) in synthesis[2] has been limited by lack of simple, general methods for their preparation with widely varied R groups.[3] Recently we reported a single-pot preparation of triisopropylsilyloxyacetylenes **4** from esters **1**.[4] Herein we report that such silyloxyacetylenes are useful substitutes for alkoxyacetylenes in 2 + 2 cycloaddition reactions with both ketenes and cyclobutenone-derived vinylketenes, affording cyclobutenone **2** and resorcinol **6** products, respectively.

In parallel with precedents for alkoxyacetylenes,[5] it was found that on bubbling ketene[6] through solutions of silyloxyacetylenes **4** at 0 °C, 3-silyloxycyclobutenones **2** were formed. Yields were high whether the R group in **4** and **2** had a primary, secondary, or tertiary center as its point of attachment (Chart I, entries 1–3);[7]

(1) Smith Kline & French Postdoctoral Research Scientist, 1985–1987.

(2) Brandsma, L.; Bos, H. J. T.; Arens, J. F. In *Chemistry of Acetylenes*; Viehe, H. G., Ed.; Marcel Dekker: New York, 1969; pp 751–860. See also ref 12 below as well as footnote 2 of ref 3e.

(3) While a number of alkoxyacetylene preparations have been published, most lack generality in the nature of possible attachments to the acetylenic carbon, and/or require multiple steps, and/or utilize explosive intermediates. See: (a) Jones, E. R. H.; Eglington, G.; Whiting, M. C.; Shaw, B. L. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. 4, p 404. (b) Newman, M. S.; Geib, J. R.; Stalick, W. M. *Org. Prep. Proc. Int.* **1972**, *4*, 89. (c) Moyano, A.; Charbonnier, F.; Greene, A. *J. Org. Chem.* **1987**, *52*, 2919. (d) Raucher, S.; Bray, B. L. *J. Org. Chem.* **1987**, *52*, 2332. (e) Pericas, M. A.; Serratosa, F.; Valenti, E. *Tetrahedron* **1987**, *43*, 2311 and numerous citations provided in ref 3c–e.

(4) Kowalski, C. J.; Lal, G. S.; Haque, M. S. *J. Am. Chem. Soc.* **1986**, *108*, 7127.

(5) See ref 2, pp 805–807.

(6) Ketene was generated via pyrolysis of acetone, see: Hanford, W. E.; Sauer, J. C. *Org. React.* **1946**, *3*, 109.

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Scheme I

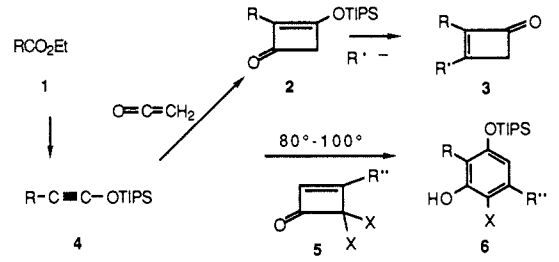
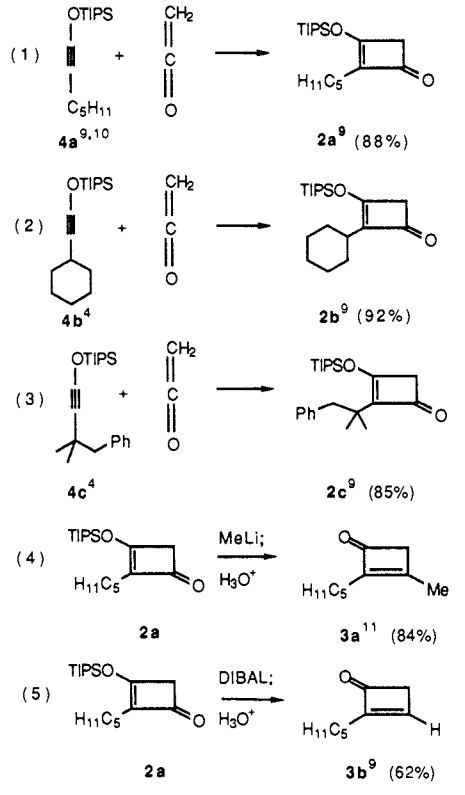


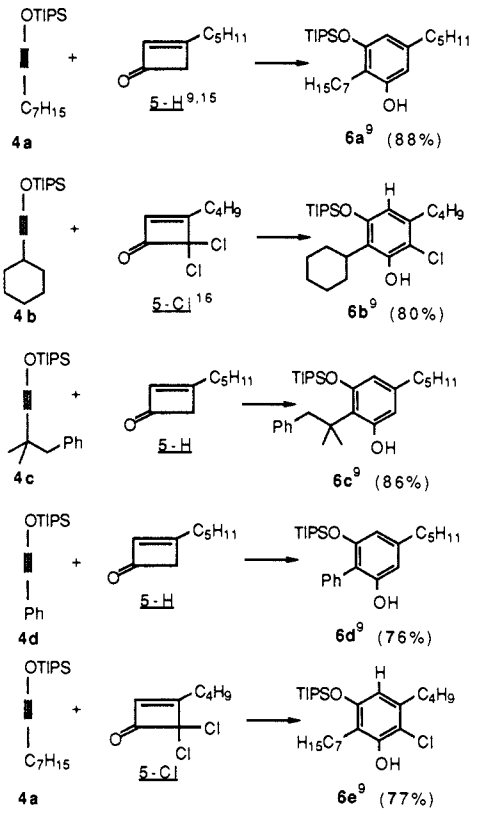
Chart I. Cyclobutenone Synthesis[7]



the reaction failed, however, when R = Ph. When 1-ethoxyheptyne[3b] was used in place of 1-triisopropylsilyloxyheptyne, the reaction required 5 h (versus 3 h) suggesting that silyloxyacetylenes are actually more reactive than the corresponding alkoxy analogues toward ketene; yields of product were the same (88%) in both cases. On treatment with nucleophiles such as methyllithium or diisobutylaluminum hydride, 3-silyloxycyclobutenones **2** underwent carbonyl addition rather than silicon–oxygen bond cleavage, affording 2,3-disubstituted cyclobutenones **3** after acid treatment, (Chart I, entries 4 and 5). Analogous chemistry based on alkoxyacetylenes has been shown in the literature to be useful.[8]

Danheiser has reported some very elegant chemistry in which vinylketenes, generated upon heating cyclobutenones, underwent 2 + 2 cycloadditions with alkoxyacetylenes; after subsequent electrocyclic ring opening, closing, and tautomerization, resorcinol products were formed.[12] In the present work, when silyloxyacetylenes **4** were heated with cyclobutenones **5** in toluene or xylene, monosilylated resorcinol products **6** were formed in yields of 76–88% (Chart II).[13] The substitution pattern generated using 4,4-dichlorocyclobutenones (e.g., in preparing **6b**)[14] was the same as that obtained by Danheiser in such reactions with alkoxyacetylenes and is thus consistent with his proposed mechanistic pathway.[12a] Important to note from Chart II is the wide variation permitted in substitution at the carbon directly attached to the acetylenic moiety; thus secondary, tertiary, and aromatic carbon attachments (never before demonstrated in reactions of alkoxyacetylenes) all work quite well. Unlike the alkoxyacetylene reactions with cyclobutenones, however, the 2-position of the cyclobutenone partner must be unsubstituted in the current chemistry (e.g., cyclobutenones **3a** and **3b** would not react successfully with silyloxyacetylenes **4b** and **4a**, respectively).

Chart II. Resorcinol Synthesis[13]



The net effect of the overall two-step transformation from ester **1** to cyclobutenone **2** or resorcinol **6** is to regiospecifically attach the R group from ester **1** to the 2-position of the newly formed four- or six-membered ring. The tremendous chemical literature surrounding ester synthesis makes available for such processes a wide variety of potentially complex R groups, prepared via regio-, stereo-, and even enantiocontrolled methods. In order to illustrate this concept, we have applied the resorcinol chemistry described above to preparation of the minor, physiologically active cannabinoid isomer, Δ-6-tetrahydrocannabinol (**11**).

Reaction of isoprene (2 equiv) with keto ester **7**[17] (room tem-

(7) 3-Triisopropylsilyloxycyclobutenones, **2a–c**, were prepared by bubbling ketene[6] into 0 °C solutions of silyloxyacetylenes **4a–c** in methylene chloride (about 0.1 M) for 3, 5, and 12 h, respectively. Evaporation of solvent and flash chromatography on silica gel afforded purified products in yields given in Chart I.

(8) Ficini, J.; Genet, J. P. *Tetrahedron Lett.* **1975**, 2633 and references therein.

(9) All new compounds afforded satisfactory spectral and analytical data.

(10) Prepared according to the procedure described in ref 4.

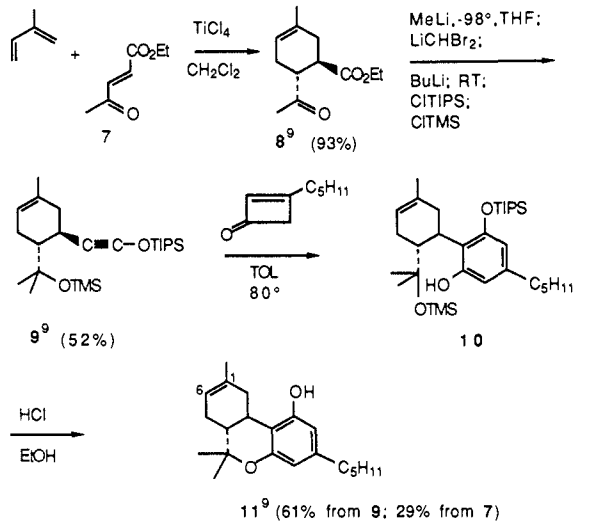
(11) Ficini, J.; Besseyre, J.; Claeys, M. *Bull. Soc. Chim. Fr.* **1975**, 1809.

(12) (a) Danheiser, R. L.; Gee, S. K. *J. Org. Chem.* **1984**, *49*, 1674. (b) Danheiser, R. L.; Gee, S. K.; Perez, J. J. *J. Am. Chem. Soc.* **1986**, *108*, 806.

(13) The procedure for preparing resorcinols **6a,c,d** involved heating approximately 0.2 M solutions of the corresponding silyloxyacetylenes **4** in toluene with 1.2 equiv (1 equiv for **4d**) of cyclobutenone 5-H, at 80 °C for 1–1.5 h under an N_2 atmosphere. Resorcinols **6b** and **6e** were prepared by heating xylene solutions of **4b** and **4a** with 1.0 equiv of cyclobutenone **5–Cl** in the presence of 1 equiv of 2,4,6-tri-*tert*-butylphenol,[12a] at 135 °C for 1.5 h. In all cases the reaction mixtures were cooled, diluted with diethyl ether, washed with aqueous sodium bicarbonate solution, dried, concentrated, and purified with flash chromatography (silica gel in petroleum ether).

(14) The substituent between the triisopropylsilyloxy and *n*-butyl groups on the resorcinol ring of **6b** was shown to be hydrogen, and not chlorine, by NOE enhancement of both the triisopropyl methyl and methine proton signals upon irradiation of the aromatic ring hydrogen.

Scheme II



perature, 0.1 equiv of titanium tetrachloride, in methylene chloride) afforded the Diels–Alder product **8** in 93% yield, as a 20:1 mixture of regioisomers (major isomer shown).[18] This ester was converted into silyloxyacetylene **9** in a second step,[4] via successive treatment in tetrahydrofuran with methyllithium (1 equiv, −90 °C), dibromomethyllithium (2.2 equiv, −78 °C), and *n*-butyllithium (7 equiv, −78 °C), warming to room temperature, cooling, and then silylating first the ynolate anion oxygen with triisopropylsilyl chloride (7 equiv, −78 °C → room temperature) and then the more hindered tertiary alkoxide with trimethylsilyl chloride (10 equiv, −78 °C → room temperature). The homologation/rearrangement reaction central to this step was expected to proceed with retention of stereochemistry,[19] and indeed the trans substituted product **9** was obtained (52% yield after flash chromatography). Heating a 1:1 mixture of silyloxyacetylene **9** and 3-pentylcyclobutenone[15] in toluene at 80 °C for 1 h smoothly afforded the desired resorcinol product **10**. Without purification, this tertiary silyl ether was treated with refluxing acidic ethanol to afford Δ-6-tetrahydrocannabinol (**11**)[20,22] in 61% yield for two steps from **9**. This novel four-step synthesis, proceeding in 29% overall yield from ester **7**, nicely illustrates the potential utility of ester-derived silyloxyacetylenes in 2 + 2 cycloadditions with vinylketenes.

Acknowledgment. We thank Dr. Steven Carr and Walter Johnson of the Physical and Structural Chemistry Department for determination of exact mass spectra as well as Dr. Charles DeBrosse and Pricilla Offen of the Analytical Chemistry Department for NOE and COSY NMR experiments reported herein.

(15) Cyclobutenone **5-H** was prepared in 70% yield from 3-ethoxycyclobutenone by addition of *n*-pentylmagnesium bromide in ether, followed by treatment with aqueous hydrochloric acid; see ref 8 and 11.

(16) Danheiser, R. L.; Savariar, S. *Tetrahedron Lett.* **1987**, *28*, 3299.

(17) McMurry, J. E.; Blaszczak, L. C. *J. Org. Chem.* **1974**, *39*, 2217.

(18) When the reaction was performed in toluene at 60 °C, with no catalyst, a nearly 1:1 mixture was obtained. The high degree of regioselectivity observed in the Lewis acid catalyzed reaction with isoprene surprised us, although some enhancement of the desired product was expected. See: (a) Lee, I.; Rhyu, K. B.; Jeon, Y. K. *J. Korean Chem. Soc.* **1979**, *23*, 286. (b) Kakushima, M.; Scott, D. G. *Can. J. Chem.* **1979**, *57*, 1399. (c) Kahn, S. D.; Pan, C. F.; Overman, L. E.; Hehre, W. J. *J. Am. Chem. Soc.* **1986**, *108*, 7381.

(19) Kowalski, C. J.; Haque, M. S.; Fields, K. W. *J. Am. Chem. Soc.* **1985**, *107*, 1429.

(20) Spectral data for product **11** was identical with that reported in the literature,[21] and COSY NMR clearly showed that the olefinic ring hydrogen at C-6 was separated from the benzylic hydrogen by two intervening carbon centers (not one, as would be expected if the methyl were at C-6 and the hydrogen at C-1).

(21) (a) Binder, M.; Franke, I.; Schmidt, B.; Dietrich, W. *Helv. Chem. Acta* **1982**, *65*, 807. (b) Taylor, E. C.; Lenard, K.; Shvo, Y. *J. Am. Chem. Soc.* **1966**, *88*, 367. (c) Fahrenholtz, K. E.; Lurie, M.; Kierstead, R. W. *J. Am. Chem. Soc.* **1967**, *89*, 5934.

(22) For a review of cannabinoid total synthesis, see: Razdan, R. K. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; John Wiley: New York, 1981; Vol. 4, p 185.

Hydride Transfer Catalyzed by Lactate Dehydrogenase Displays Absolute Stereospecificity at C_4 of the Nicotinamide Ring

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The stereospecificity of hydride transfer to and from C_4 of the nicotinamide ring catalyzed by dehydrogenases has been intensively studied,[1] and recent controversy surrounding the mechanistic importance of the stereospecificity has renewed interest in this topic.[2] This communication reports the results of an experiment designed to detect rare nonstereospecific hydride transfer to or from the nicotinamide ring. In determining the energy difference between the two diastereomeric transition states each 1.35 Kcal/mol of stabilization energy results in a factor of 10 increase in the stereospecificity of the reaction. Thus, the over 10^4 increase in sensitivity afforded by this measurement expands the accessible energy range by over 5 Kcal/mol. The absolute stereospecificity of enzyme catalyzed reactions has been discussed by Cornforth who suggested experiments similar to the one described in this communication.[3]

The inability of ^{1}H NMR to detect trace (<1%) contaminants[4] and the uncertainty of the purity of chiral [4-^{3}H]NADH[5] limits the sensitivity of the methods commonly used to determine NADH stereochemistry. The initial work of Westheimer and co-workers using deuterium isotope ratio mass spectrometry was only accurate to ±2% at best.[6] In careful radioactive studies there has been evidence of nonstereospecific hydride transfers.[7] ^{1}H NMR studies utilizing nuclear Overhauser effects have shown that the nicotinamide ring of NAD(P) can bind in either a syn or anti fashion to glucose-6-phosphate dehydrogenases.[8] The ability of dehydrogenases to utilize both the α and arabino configurations at the C_1' and C_2' positions of the ribose ring, respectively,[2d] suggests the active site can accommodate altered nucleotide structures.

If 10 μM [4-^{3}H]NAD is added to a solution containing 50 mM (*S*)-lactate and 5 mM pyruvate in the presence of lactate dehydrogenase from pig heart (Sigma), any nonstereospecific hydride transfer either to or from the nicotinamide ring results in the appearance of ^{3}H in the (*S*)-lactate. The rate of hydride transfer in the dynamic equilibrium established by the presence of the enzyme can be monitored by the increase in the intensity of the pyruvate signal in the ^{1}H NMR if [3-$^2H_3$]pyruvate is present initially. After a fixed incubation time, when each NAD molecule has undergone an average of 10^5 turnovers, carrier lactate is added, the tritiated nucleotides removed by filtration through charcoal, and the lactate recrystallized to constant specific activity as the Zn^{2+} salt. The radioactivity derived from [4-^{3}H]NAD that ap-

(1) (a) For reviews, see: You, K. *Meth. Enzymol.* **1982**, *87*, 101. (b) You, K. *CRC Crit. Rev. Biochem.* **1985**, *17*, 313.

(2) (a) Nambiar, K. P.; Stauffer, D. M.; Kolodziej, P. A.; Benner, S. A. *J. Am. Chem. Soc.* **1983**, *105*, 5886. (b) Oppenheimer, N. J. *J. Am. Chem. Soc.* **1984**, *106*, 3032. (c) Benner, S. A.; Nambiar, K. P.; Chambers, G. K. *J. Am. Chem. Soc.* **1985**, *107*, 5513. (d) Oppenheimer, N. J.; Marshner, T. M.; Malver, O.; Kam, B. L. In *Mechanisms of Enzymatic Reactions: Stereochemistry*; Frey, P. A., Ed.; Elsevier: New York, 1986; p 15. (e) Benner, S. A.; Nambiar, K. P. In *Mechanisms of Enzymatic Reactions: Stereochemistry*; Frey, P. A., Ed.; Elsevier: New York, 1986; p 29.

(3) Cornforth, J. In *Structures of Complexes between Biopolymers and Low Molecular Weight Molecules*; Bartmann, W., Snatzke, G., Eds.; John Wiley and Sons: New York, **1982**; pp 1–16.

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(5) Jarabak, J.; Talalay, P. *J. Biol. Chem.* **1960**, *235*, 2147.

(6) (a) Fisher, H. F.; Conn, E. E.; Vennesland, B.; Westheimer, F. H. *J. Biol. Chem.* **1953**, *202*, 687. (b) Fisher, H. F.; Lowes, F. A.; Ofner, P.; Westheimer, F. H.; Vennesland, B. *J. Biol. Chem.* **1953**, *202*, 699.

(7) (a) Walton, D. J. *Biochemistry* **1973**, *12*, 3472. (b) Chan, P. C.; Bielski, B. H. J. *J. Biol. Chem.* **1975**, *250*, 7266.

(8) (a) Levy, H. R.; Ejchart, A.; Levy, G. C. *Biochemistry* **1983**, *22*, 2792. (b) Groneborn, A. M.; Clore, G. M.; Hobbs, L.; Jeffrey, J. *Eur. J. Biochem.* **1984**, *145*, 365.

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