

Figure 2. Negative derivatives of the potential of mean force (dashed line) and its entropic component (solid line), in kcal mol⁻¹ Å⁻¹. Error bars correspond to 1 standard deviation.

Again this is in qualitative agreement with the estimate of Yaacobi and Ben-Naim.²³ The noise in the data is too great to determine which of the entropic and energetic effects is larger in the solvent-separated region of the PMF.

Our formula for calculating the entropic contribution to the free energy of association is straightforward. To our knowledge, a calculated PMF between two solutes has never before been decomposed directly into its energetic and entropic components either by theory or by computer simulation. The entropic component is

$$-TS(r) = -TS(r_0) + \frac{1}{kT} \int_{r_0}^r dR \left[\left\langle E \frac{\partial E}{\partial R} \right\rangle_R - \langle E \rangle_R \left\langle \frac{\partial E}{\partial R} \right\rangle_R \right] \quad (1)$$

where $TS(r_0)$ is an additive constant, E is the total configurational energy, and $\langle \dots \rangle_R$ denotes the ensemble average with the solute-solute separation fixed at R . We set both $-TS(r)$ and the free energy of association to 0 at 8.0-Å separation. Similar formulas have been published,^{18,24} but apparently not used to calculate the entropy of association.

Our MD calculations simulate a periodically replicated collection of 106 SPC water molecules and two methane molecules at 1.0 g cm⁻³ and 25 °C, using the program SOLVENT 1.0,²⁵ described elsewhere. The PMF and entropy of association are calculated for solute separations between 3.25 and 8.00 Å. The total simulation time is approximately 60 ns. The simulations measure directly the derivatives of the quantities plotted in Figure 1b. The negative derivatives of the free energy (i.e., the solvent averaged force) and its entropic component ($-kT^{-1}$ times the integrand in eq 1) are shown in Figure 2. Uncertainties ($\pm\sigma$) are displayed for the entropy derivative, while the average uncertainty for the mean force is 0.05 kcal mol⁻¹ Å⁻¹.

The entropy contribution in Figure 2 is clearly negative for separations shorter than 5.5 Å. This provides statistical validation of our central result, that entropy drives the hydrophobic solutes together. A rather small (108 molecule) system is simulated here due to the large statistical uncertainty in the entropy calculation. Alternative methods of calculation provide no improvement in accuracy. The "direct" method of calculating the configurational energy of the system as a function of solute separation shows a large uncertainty which grows with the system size. Differencing of PMFs at different temperatures is equally inefficient. System size effects on the free energy have been determined and are found to be minimal.²⁰ Further applications of this technique are underway.

Acknowledgment. This research is supported by the Australian Research Council (ARC) (Grant No. A29131271). Supercomputer calculations were performed on the Fujitsu VP2200 computer at AST, to whom grateful acknowledgment is made.

(24) Guillot, B.; Guissani, Y.; Bratos, S. *J. Chem. Phys.* **1991**, *95*, 3643-3648.

(25) Smith, D. E.; Haymet, A. D. J. *J. Chem. Phys.*, in press.

Coherence Transfer Involving Quadrupolar Nuclei in Solids: ²⁷Al ↔ ³¹P Cross-Polarization NMR in the Molecular Sieve VPI-5

C. A. Fyfe,* H. Grondy,† K. T. Mueller, K. C. Wong-Moon, and T. Markus

Department of Chemistry
University of British Columbia
2036 Main Mall, Vancouver
British Columbia, Canada V6T 1Z1
Received February 26, 1992

During the last 15 years there have been significant advances in solid-state chemistry and materials research which derive directly from the application of high-resolution solid-state NMR spectroscopy.¹ Typically a dilute spin-1/2 nucleus such as ¹³C is observed, while interactions from protons are removed by dipolar decoupling and the carbon chemical shift anisotropy is averaged using magic-angle spinning (MAS). A spectrum with sharp lines is then observed which is similar to that obtained from the same material in the liquid state or dissolved in solution.² Problems inherent in the study of dilute nuclei, namely, the low signal-to-noise ratio, are overcome by cross-polarization of spin magnetization from an abundant spin reservoir such as protons.³

Historically, cross-polarization has been used to transfer spin coherence from abundant spins to a dilute spin system. Protons (¹H) have been used almost exclusively as the source of strong nuclear polarization for cross-polarization experiments, although there have been some examples where other abundant nuclei such as ¹⁹F have been used.^{4,5} Another notable exception is found in the studies of Schaefer and co-workers involving magnetization transfer between ¹³C and ¹⁵N in isotopically enriched materials.^{6,7}

For quadrupolar nuclei with nonintegral spins such as ¹¹B, ¹⁷O, and ²⁷Al, the second-order quadrupolar broadening of the readily observed central (+1/2 ↔ -1/2) transition is not completely averaged by MAS.⁸⁻¹⁰ The NMR lines from quadrupolar spins are shifted and distorted in single-axis spinning experiments, but the recently introduced techniques of dynamic-angle spinning^{11,12} and double rotation¹³ can achieve averaging of these resonances. Very few examples exist of cross-polarization experiments involving quadrupolar nuclei, and they all involve magnetization transfer from protons to quadrupolar nuclei.¹⁴⁻²² Recently, a description

* To whom correspondence should be addressed.

† Present address: Max-Planck-Institut für Kohlenforschung, Mülheim an der Ruhr, Germany.

(1) Fyfe, C. A. *Solid State NMR for Chemists*; CFC Press: Guelph, 1984.

(2) Schaefer, J.; Stejskal, E. O. *J. Am. Chem. Soc.* **1976**, *98*, 1031-1032.

(3) Pines, A.; Gibby, M. G.; Waugh, J. S. *J. Chem. Phys.* **1973**, *59*, 569-590.

(4) Fleming, W. W.; Fyfe, C. A.; Kendrick, R. D.; Lyerla, J. R.; Vanni, H.; Yannoni, C. S. *ACS Symp. Ser.* **1980**, *142*, 206-209.

(5) Sebald, A.; Merwin, L. H.; Schaller, T.; Knöller, W. *J. Magn. Reson.* **1992**, *96*, 159-164.

(6) Schaefer, J.; McKay, R. A.; Stejskal, E. O. *J. Magn. Reson.* **1979**, *34*, 443-447.

(7) Schaefer, J.; Skokut, T. A.; Stejskal, E. O.; McKay, R. A.; Varner, J. E. *J. Biol. Chem.* **1981**, *256*, 11574-11579.

(8) Behrens, H. J.; Schnabel, B. *Physica* **1982**, *114B*, 185-190.

(9) Samoson, A.; Kundla, E.; Lippmaa, E. *J. Magn. Reson.* **1982**, *49*, 350-357.

(10) Ganapathy, S.; Schramm, S.; Oldfield, E. *J. Chem. Phys.* **1982**, *77*, 4360-4365.

(11) Llor, A.; Virlet, J. *J. Chem. Phys. Lett.* **1988**, *152*, 248-253.

(12) Mueller, K. T.; Sun, B. Q.; Chingas, G. C.; Zwanziger, J. W.; Terao, T.; Pines, A. *J. Magn. Reson.* **1990**, *86*, 470-487.

(13) Samoson, A.; Lippmaa, E.; Pines, A. *Mol. Phys.* **1988**, *65*, 1013-1018.

(14) Blackwell, C. S.; Patton, R. L. *J. Phys. Chem.* **1984**, *88*, 6135-6139.

(15) Morris, H. D.; Ellis, P. D. *J. Am. Chem. Soc.* **1989**, *111*, 6045-6049.

(16) Morris, H. D.; Bank, S.; Ellis, P. D. *J. Phys. Chem.* **1990**, *94*, 3121-3129.

(17) Kellberg, L.; Linsten, M.; Jakobsen, H. *J. Chem. Phys. Lett.* **1991**, *182*, 120-126.

(18) Woessner, D. E. *Z. Phys. Chem. (München) N.F.* **1987**, *152*, 51-58.

(19) Bryant, R. G.; Ganapathy, S.; Kennedy, S. D. *J. Magn. Reson.* **1987**, *78*, 376-378.

(20) Harris, R.; Nesbitt, G. J. *J. Magn. Reson.* **1988**, *78*, 245-256.

(21) Walter, T. H.; Turner, G. L.; Oldfield, E. *J. Magn. Reson.* **1988**, *76*, 106-120.

(22) Edwards, J. C.; Ellis, P. D. *Magn. Reson. Chem.* **1990**, *28*, S59-67.

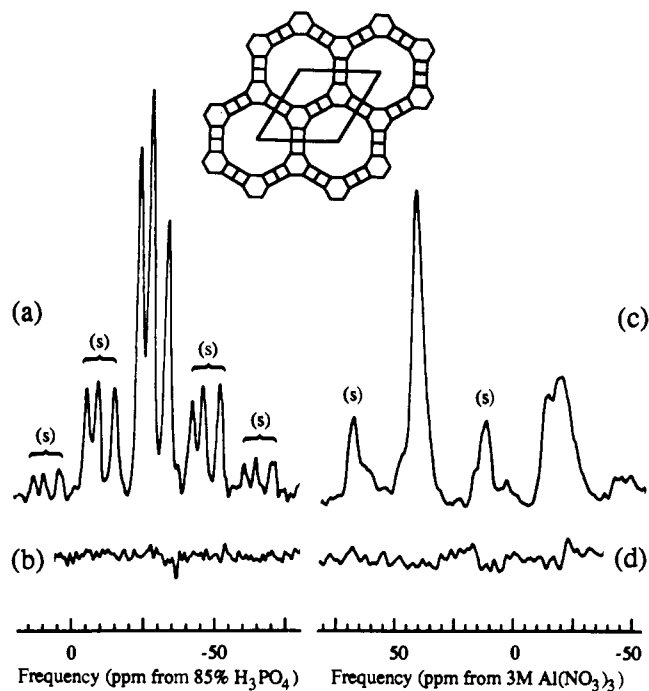


Figure 1. Demonstration of $^{27}\text{Al} \rightarrow ^{31}\text{P}$ and $^{31}\text{P} \rightarrow ^{27}\text{Al}$ cross-polarization in VPI-5 (the schematic at the top shows a projection of the three-dimensional hexagonal unit cell in which the AlO_4 and PO_4 tetrahedra at the vertices are strictly alternating). (a) $^{27}\text{Al} \rightarrow ^{31}\text{P}$ CP experiment taking 16 732 scans with a contact time of 0.8 ms, a recycle delay of 0.5 s, and a 90° pulse time of $9.0 \mu\text{s}$ for the central transition of the ^{27}Al . Resonances from the three inequivalent phosphorus sites are observed with spinning sidebands (marked with an s) at multiples of the rotor frequency. (b) $^{27}\text{Al} \rightarrow ^{31}\text{P}$ experiment as in part (a) with no irradiation of the ^{27}Al nuclei. (c) $^{31}\text{P} \rightarrow ^{27}\text{Al}$ CP experiment taking 3200 scans with a contact time of 1.6 ms, a recycle delay of 30 s, and a 90° pulse time of $9.0 \mu\text{s}$ for the ^{31}P . (d) $^{31}\text{P} \rightarrow ^{27}\text{Al}$ experiment as in part (c) with no irradiation of the ^{31}P nuclei.

of the behavior of quadrupolar spins under spin-locking (an important part of cross-polarization experiments) and magic-angle spinning conditions has been presented by Vega,²³ as well as a report on cross-polarization from $I = 1/2$ to $S = 3/2$ nuclei under MAS conditions.²⁴ In all cases involving quadrupolar nuclei, the importance of modifications to the Hartmann-Hahn matching condition for radiofrequency irradiation field strengths,²⁵ necessary to obtain efficient polarization transfer, must be examined.

Inorganic systems such as zeolites, gels, and ceramics are of great technological importance and interest and contain many quadrupolar nuclei but very few protons. We have undertaken a study to determine the feasibility of polarization transfer experiments between spin pairs in these systems, particularly between ^{31}P ($I = 1/2$) and ^{27}Al ($I = 5/2$). Our preliminary results show that these experiments are indeed possible.

The attainment of cross-polarization from quadrupolar nuclei is particularly important in materials chemistry and materials research as they usually have very short T_1 relaxation times. Spin- $1/2$ nuclei in dense inorganic systems may have T_1 values ranging from many seconds to hours, effectively precluding their observation in many instances. By using cross-polarization from the quickly relaxing quadrupolar spins, spectra of the spin- $1/2$ nuclei could be obtained in a relatively short time. Additional information regarding the local structure and bonding in these systems might also be obtained through the distance dependence of the cross-polarization process.

The sample chosen for study was the very large pore molecular sieve VPI-5, an aluminophosphate dihydrate containing 18-membered rings²⁶ as shown in Figure 1. NMR experiments were

performed under MAS conditions in a 9.4-T superconducting magnet where the resonance frequencies for ^{31}P and ^{27}Al are 161.98 and 104.26 MHz, respectively. The spectra in Figure 1 demonstrate the transfer of magnetization in both directions between the ^{27}Al and ^{31}P spins in the Al-O-P bonding units in VPI-5. The cross-polarization is accomplished with an appropriate spin-locking pulse sequence³ after a preparation pulse creates spin coherence for the nuclei used as the polarization source. For the ^{27}Al spins this corresponds to a pulse only $1/3$ as long as a 90° pulse in solution as we are only irradiating and observing the central transition.²⁷ The Hartmann-Hahn condition is then altered, resulting in a match of the enhanced central transition nutation radiofrequency field strength.^{14-22,24} The free induction decays of the nuclear magnetization are digitized and alternately added and subtracted from memory following a reversal of rotating frame spin temperature.²⁸ With MAS the ^{31}P chemical shift anisotropies are averaged to their isotropic values for the three crystallographically inequivalent ^{31}P sites in the unit cell. For the ^{27}Al nuclei, MAS partially averages the second-order quadrupolar interaction and two resonances are seen: One from the tetrahedrally coordinated aluminum sites (41 ppm) and a second from the octahedrally coordinated aluminum (approximately -18 ppm). Since no preparation pulses were applied to the nuclei observed in each experiment, the appearance of resonances in spectra (a) and (c) of Figure 1 represents the transfer of magnetization between the two spin systems by cross-polarization. The observed signal is solely due to cross-polarization and not caused by direct irradiation during the spin-lock as proven by a series of cross-check experiments, of which spectra (b) and (d) of Figure 1 are representative.

A two-dimensional heteronuclear correlation experiment²⁹ using cross-polarization is performed by preparing the aluminum spins with a 90° pulse (for the central transition) and then encoding their evolution frequencies in an initial time period. The aluminum polarization is subsequently transferred to the phosphorus spins with a spin-locking sequence, and a phosphorus free induction decay is accumulated after each of a set of aluminum evolution times. Two-dimensional Fourier transformation provides the correlation spectrum of Figure 2. The data were accumulated using time proportional phase incrementation (TPPI) in order to obtain pure-absorption-phase line shapes in both spectral dimensions.^{30,31} From the two-dimensional spectrum it is evident that each of the three ^{31}P resonances is connected to both tetrahedral and octahedral ^{27}Al resonances, in agreement with the proposed crystal structure of VPI-5.³²

Other experiments that depend on the dipolar interaction such as those of Veeman and coworkers,³³ where spin echoes are observed under magic-angle-spinning and double-resonance conditions, have been accomplished. Rotational echo double resonance (REDOR) experiments^{34,35} and transferred-echo double resonance (TEDOR) experiments³⁶ have also been performed on this system and will be reported in a future communication.

In summary, cross-polarization to and from quadrupolar nuclei has been experimentally verified using the ^{31}P and ^{27}Al spin systems in an aluminophosphate molecular sieve. This bodes well

(26) Davis, M. E.; Saldarriaga, C.; Montes, C.; Garces, J.; Crowder, C. *Nature (London)* **1988**, *331*, 698-699.

(27) Schmidt, V. H. *Pulsed Magn. Opt. Reson., Proc. Ampère Int. Summer Sch., 2nd, 1971* **1972**, 75-83.

(28) Stejskal, E. O.; Schaefer, J. *J. Magn. Reson.* **1975**, *18*, 560-563.

(29) Caravatti, P.; Bodenhausen, G.; Ernst, R. R. *Chem. Phys. Lett.* **1982**, *89*, 363-367.

(30) Marion, D.; Wüthrich, K. *Biochem. Biophys. Res. Commun.* **1983**, *113*, 967-974.

(31) Drobny, G.; Pines, A.; Sinton, S.; Weitekamp, D.; Wemmer, D. *Faraday Symp. Chem. Soc.* **1979**, *13*, 49-55.

(32) McCusker, L. B.; Baerlocher, Ch.; Jahn, E.; Bülow, M. *Zeolites* **1991**, *11*, 308-313.

(33) van Eck, E. R. H.; Janssen, R.; Maas, W. E. J. R.; Veeman, W. S. *Chem. Phys. Lett.* **1990**, *174*, 428-432.

(34) Gullion, T.; Schaefer, J. *J. Magn. Reson.* **1989**, *81*, 196-200.

(35) Pan, Y.; Schaefer, J. *J. Magn. Reson.* **1990**, *90*, 341-345.

(36) Hing, A. W.; Vega, S.; Schaefer, J. *J. Magn. Reson.* **1992**, *96*, 205-209.

(23) Vega, A. J. *J. Magn. Reson.* **1992**, *96*, 50-68.

(24) Vega, A. J. *Solid State NMR* **1992**, *1*, 17-32.

(25) Hartmann, S. R.; Hahn, E. *Phys. Rev.* **1962**, *128*, 2042-2053.

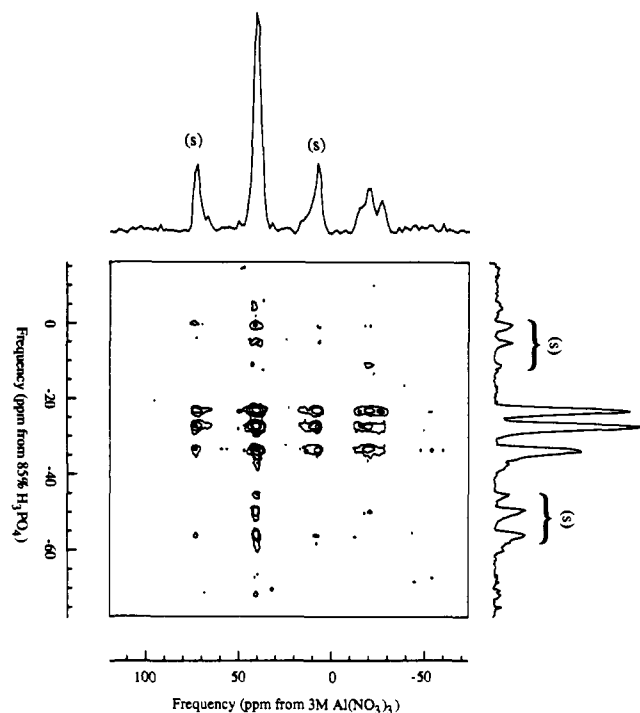


Figure 2. Two-dimensional heteronuclear correlation spectrum of ^{27}Al and ^{31}P in VPI-5. The data were accumulated as described in the text with 640 scans from each of 256 cross-polarization experiments with an incremental increase in the ^{27}Al evolution time of 12.5 μs .

for the use of heteronuclear correlations for further investigations of local microstructure in solids.

Acknowledgment. C.A.F. acknowledges the financial assistance of the NSERC of Canada in the form of operating and equipment grants. K.C.W.-M. thanks the NSERC for the award of a postgraduate fellowship, and K.T.M. thanks both the NSERC and the Killam Foundation for postdoctoral fellowships. We acknowledge helpful discussions with Dr. J. Schaefer and thank Dr. P. Grobet and Dr. M. Davis for kindly providing samples of VPI-5.

A New and Practical Approach to the Synthesis of Taxol and Taxol Analogues: The Pinene Path

Paul A. Wender* and Thomas P. Mucciario

Department of Chemistry, Stanford University
Stanford, California 94305

Received April 15, 1992

The natural product taxol (1) has shown remarkable potential in recent clinical trials for the treatment of breast and ovarian cancer.^{1,2} Unfortunately, the limited supply of taxol from its currently approved source,³⁻⁶ the Pacific yew tree, has hampered

(1) For a review of the clinical biology of taxol, see: Rowinsky, E. K.; Cazenave, L. A.; Donehower, R. C. *J. Natl. Cancer Inst.* **1990**, *82*, 1247.
(2) For recent clinical results, see: Holmes, F. A.; Walters, R. S.; Theriault, R. L.; Forman, A. D.; Newton, L. K.; Raber, M. N.; Buzdar, A. U.; Frye, D. K.; Hortobagyi, G. N. *J. Natl. Cancer Inst.* **1991**, *83*, 1797.

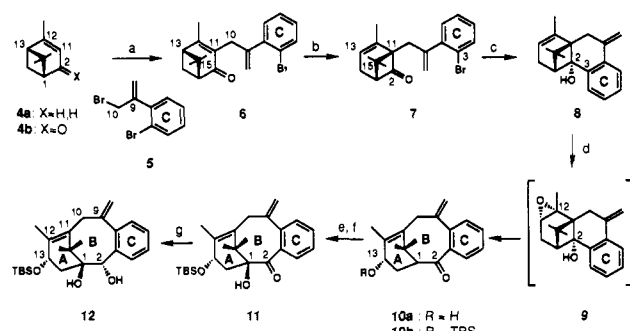
(3) Wani, M. C.; Taylor, H. L.; Wall, M. E.; Coggon, P.; McPhail, A. T. *J. Am. Chem. Soc.* **1971**, *93*, 2325.

(4) For environmental and supply reasons, extraction of taxol from the Pacific yew is expected to be phased out in the next few years. Replacement sources are under evaluation.

(5) Witherup, K. M.; Look, S. A.; Stasko, M. W.; Ghiorzi, T. J.; Muschik, G. M.; Cragg, G. M. *J. Nat. Prod.* **1990**, *53*, 1249.

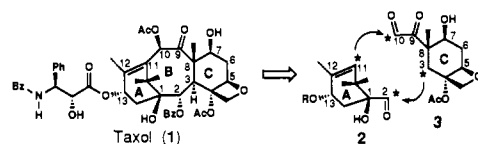
(6) Vidensek, N.; Lim, P.; Campbell, A.; Carlson, C. *J. Nat. Prod.* **1990**, *53*, 1609.

Scheme 1^a



^a (a) KOtBu , DME, 0 $^{\circ}\text{C}$ (50–60%). (b) $h\nu$, C_6H_{12} (85%). (c) $t\text{-BuLi}$, TMEDA, THF, -78 $^{\circ}\text{C}$ (67%). (d) i. $\text{Ti}(\text{O}i\text{Pr})_4$, $t\text{BuOOH}$, CH_2Cl_2 , 0 $^{\circ}\text{C}$; ii. DABCO, CH_3CN reflux (50–60% overall). (e) TBSOCl , imid., DMF, 60 $^{\circ}\text{C}$ (98%). (f) KOtBu , O_2 , DMSO, THF, 60 $^{\circ}\text{C}$ (80%). (g) Na , EtOH, Et_2O , 0 $^{\circ}\text{C}$ (60%).

the development of this promising chemotherapeutic lead. To alleviate this supply problem, an impressive range of science is being investigated; major efforts to secure taxol, its analogues, and possible precursors include botanical,⁵ cell culture,⁷ biosynthetic, and synthetic⁸ approaches. We describe here a new and practical synthetic route to tricyclic analogues of taxol that could serve in the synthesis of taxol itself. The underlying strategy allows for the preparative and routine formation of analogues and potential precursors of taxol in the correct enantiomeric form in a uniquely concise sequence based on an abundant and inexpensive starting material, pinene (4a).



Our approach to this problem was guided by the goal of producing a practical synthesis of taxol that could also be used to make analogues as needed to elucidate the novel mode of action of taxol at the molecular level⁹ and to develop second generation drugs. It was reasoned that this goal could best be realized through the convergence of variable A and C ring precursors (e.g., 2 and 3) in a process that produces the taxane B ring, affording overall access to systematically varied ABC tricycles. Toward these ends, a novel and flexible strategy was fashioned around the use of α -pinene, a constituent of pine and a major component of industrial solvents such as turpentine. Available in either enantiomeric form and possessing 10 of the 20 carbons of the taxol core, pinene was viewed as a superb building block for a variety of approaches to the taxanes.

Our first objective in the elaboration of pinene (4a) focused on the attachment of a suitable C ring precursor to its C11 center (Scheme I).¹⁰ For this purpose, the readily available air-oxidation product of pinene,¹¹ verbenone (4b), was seen to possess a carbonyl group ideally situated for bond formation at C11 through the use

(7) Christen, A. A.; Bland, J.; Gibson, D. M. *Proc. Am. Assoc. Cancer Res.* **1989**, *30*, 566, A2252.

(8) Over 30 groups have made impressive contributions to the literature on the synthesis of taxanes. These include the following: Berkowitz, Bleichert, Clark, Fetizon, Frejd, Funk, Gadwood, Ghosh, Greene, Holton, Hua, Hudlicky, Inouye, Jenkins, Kato, Kende, Kitagawa, Kraus, Kuwajima, Lange, Martin, Oishi, Paquette, Pattenden, Potier, Sakan, Shea, Snider, Swindell, Trost, Wender, Winkler, Yadav, Yamada, Zucker. For reviews, see: (a) Snapper, M. L. Ph.D. Dissertation, Stanford University, Stanford, CA, 1990. (b) Swindell, C. S. *Org. Prep. Proced. Int.* **1991**, *23*, 465.

(9) (a) Schiff, P. B.; Horwitz, S. B. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 1561. (b) Schiff, P. B.; Fant, J.; Horwitz, S. B. *Nature* **1979**, *277*, 665.

(10) The numbering used in this paper refers to the corresponding centers of taxol. This sequence has been performed in both enantiomeric series.

(11) Kizlink, J.; Hronec, M.; Cvengrosova, Z.; Kuruc, L.; Kriz, M.; Oblozinsky, A.; Ilavsky, J. *Czech CS 258 634*, 1986; *Chem. Abstr.* **1989**, *111*, 214768r.