Separate Measurements of Heteronuclear *J* Coupling Constants by Manipulated Polarization Transfer in Two-Dimensional NMR

V. Rutar*†

Department of Chemistry, University of Missouri Columbia, Missouri 65211

Received February 24, 1983

Scalar spin–spin (*J*) coupling constants between ^{13}C and ^{1}H nuclei are very important for molecular identification and conformational analysis. It has been shown[1-5] that two-dimensional (2-D) *J*-resolved spectroscopy separates chemical shifts and coupling constants, thus avoiding the overlapping of multiplets that occurs in one-dimensional coupled NMR spectra. Although the 2-D approach simplifies interpretation and also improves resolution, only few practical applications have been reported, because typically 1000 data sets have to be acquired and processed to obtain competitive results. Measuring times can be shortened by approximately 10 times by adopting the new strategy that is described in this communication together with the first successful application.

$^{1}J_{CH}$ coupling constants between ^{13}C and directly attached protons are found between 125 and 250 Hz, while the coupling through two or more bonds ($^{2}J_{CH}$, $^{3}J_{CH}$, etc.) is significantly smaller (usually less than 20 Hz). Simultaneous measurements of all couplings evidently need too much time, therefore the distinctive difference between attached and distant protons has to be utilized for spin "manipulations" and subsequent separation of $^{1}J_{CH}$ vs. $^{2}J_{CH}$, $^{3}J_{CH}$, etc. As a first step toward this general goal a pulse sequence for manipulated polarization transfer (MPT) of CH groups will be considered:

$$\pi/2(x,H)-\tau-\pi/2(x,C),\pi(x,H)-\tau-\pi(x,C),\pi/2(y,H)-\tau-t_1/2-\pi/2(x,H)-\tau-\pi(x,C),\pi(y,H)-\tau-\pi/2(x,H)-t_1/2\text{–acquire C, decouple H} \quad (A)$$

Here radiofrequency pulses are applied on ^{13}C and ^{1}H spins, and their phases are denoted by directions in the doubly rotating frame. The first part of (A) contains five pulses and three fixed delays $\tau = 1/(2^{1}J_{CH})$, and it is equivalent to the DEPT pulse sequence[6] with the variable pulse $\theta(y,H) = \pi/2(y,H)$. In the present experiment polarization transfer[7,8] is merely used to establish ^{13}C magnetization along the x direction of the rotating frame.

^{13}C spins are then allowed to evolve during the variable time t_1, which is increased systematically to create data sets for further 2-D processing. The basic novelty becomes apparent, if we simplify the description by ignoring $\pi(x,C)$ and $\pi(y,H)$ pulses which are used to refocus precession from chemical shifts and inhomogeneous magnetic field:

$$\text{DEPT}-t_1/2-\pi/2(x,H)-1/^{1}J_{CH}-\pi/2(x,H)-t_1/2\text{–acquire C, decouple H} \quad (B)$$

At the middle of the evolution time two $\pi/2(x,H)$ pulses are applied. The first one turns protons from the $\pm z$ into $\pm y$ directions of the rotating frame. If they are directly attached to ^{13}C spins, one-bond coupling $^{1}J_{CH}$ flips them for 180° from the $\pm y$ to $\mp y$ directions during the interval $2\tau = 1/^{1}J_{CH}$ and the second $\pi/2(x,H)$ pulse turns them back to the *original* ($\pm z$) directions. On the other hand distant protons experience only couplings that are supposed to be small compared to $^{1}J_{CH}$; therefore, their evolution is negligible and they are *inverted* by two $\pi/2(x,H)$ pulses.

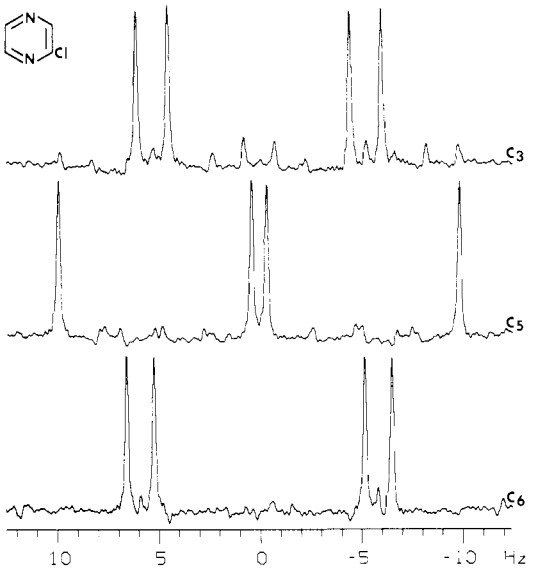


Figure 1. Cross sections of 2-D spectra of 2-chloropyrazine as obtained by the MPT pulse sequence; 128 data sets were created by systematically increasing the evolution time t_1 in steps of 40 ms. Signals of three chemically nonequivalent CH groups were found as a function of t_1 and Fourier transformed. Since coupling with the directly attached proton ($^{1}J_{CH}$) has been eliminated in this experiment, only couplings with two distant ones are revealed for each ^{13}C nuclear site. Total measuring time was only 30 min.

The new pulse sequence clearly separates directly attached and distant protons. This manipulation selectively refocuses precession from one-bond coupling and significantly modifies spectra.

As an example 2-chloropyrazine has been studied. One-dimensional coupled spectra[9] show signals of three chemically nonequivalent CH groups, and each of them is split into eight lines due to coupling with one attached and two distant protons. Application of the MPT pulse sequence (A) eliminates $^{1}J_{CH}$ from the F_1 dimension of 2-D data sets (Figure 1), and cross sections reveal only couplings with distant protons. The band width has been reduced to ±12.5 Hz, and even a small number of signal accumulations has improved resolution (line width ≤0.2 Hz) far beyond the specification for the static magnetic field (0.5 Hz). Carbons C_3 and C_6 have first-order spectra with coupling constants $^{3}J_{C_3H_5} = 10.52$ Hz, $^{4}J_{C_3H_6} = 1.56$ Hz, $^{2}J_{C_6H_5} = 11.73$ Hz, and $^{4}J_{C_6H_3} = 1.35$ Hz, while $^{2}J_{C_5H_6}$ and $^{3}J_{C_5H_3}$ are approximately equal (10.26 and 9.50 Hz); therefore, the inner peaks of C_5 signals are only 0.7 Hz apart. Since their separation can hardly be determined in one-dimensional spectra, the advantage of the increased resolution and superiority of the MPT pulse sequence become evident from Figure 1.

The above approach to 2-D NMR represents the most efficient solution when someone wants to determine long-range coupling constants, but traditional ^{13}C spectra show overlapping multiplets or insufficient resolution.

If the phase of the last proton pulse $\pi/2(x,H)$ in (A) is reversed [$\pi/2(-x,H)$], attached protons are *inverted* at the middle of the time t_1. Distant protons experience two opposite $\pi/2$ pulses and almost no evolution between them; therefore, they are turned back to the *original* directions. Precession from coupling between ^{13}C spins and distant protons is refocused during the second half of the evolution time and only $^{1}J_{CH}$ is revealed along the F_1 dimension. This manipulation is also very useful, because each multiplet is compressed into only two peaks, and their separation

† On leave of absence from J. Stefan Institute, Ljubljana, Yugoslavia.
* Address correspondence to this author at the University of Missouri.

(1) Bodenhausen, G.; Freeman, R.; Niedermeyer, R.; Turner, D. L. *J. Magn. Reson.* **1976**, *29*, 291–294.
(2) Bodenhausen, G.; Freeman, R.; Turner, D. L. *J. Chem. Phys.* **1976**, *65*, 839–840.
(3) Thomas, D. M.; Bendall, M. R.; Pegg, D. T.; Doddrell, D. M.; Field, J. *J. Magn. Reson.* **1981**, *42*, 298–306.
(4) Jin-shan, W.; De-zheng, Z.; Tao, J.; Xiu-wen, H.; Guo-bao, C. *J. Magn. Reson.* **1982**, *48*, 216–224.
(5) Garbow, J. R.; Weitekamp, D. P.; Pines, A. *Chem. Phys. Lett.* **1982**, *93*, 504–509.
(6) Pegg, D. T.; Doddrell, D. M.; Bendall, M. R. *J. Chem. Phys.* **1982**, *77*, 2745–2752.
(7) Morris, G. A.; Freeman, R. *J. Am. Chem. Soc.* **1979**, *101*, 760–762.
(8) Pegg, D. T.; Bendall, M. R.; Doddrell, D. M. *J. Magn. Reson.* **1981**, *44*, 238–249.
(9) Turner, C. J.; Cheeseman, G. W. H. *Org. Magn. Reson.* **1974**, *6*, 663–666.

0002-7863/83/1505-4095$01.50/0

can be determined easily. In 2-chloropyrazine 64 data sets were sufficient to find the values $^1J_{C_3H_3}$ = 192.57 Hz, $^1J_{C_5H_5}$ = 185.67 Hz, and $^1J_{C_6H_6}$ = 186.41 Hz, which agree with one-dimensional results within ±0.05 Hz. Since increments of t_1 were 10 ms, the lines folded in only once.

If small changes of $^1J_{CH}$ (such as solvent effects) must be measured very accurately, the spectral band width can be reduced by increasing the evolution time in large steps. The lines will fold in several times, but their relative positions will be measured with superior resolution.

Spin manipulations can be extended to CH_2 and CH_3 groups as well as some other pairs of nuclei. Details will be published in a subsequent paper together with practical applications.

Acknowledgment. Stimulating discussions with Professor T. C. Wong are greatly appreciated. The NT-300 spectrometer was purchased partially through a grant from the National Science Foundation (PCM-8115599).

Stereoselective Total Synthesis of Pyrrolizidine Alkaloid Bases: (−)-Rosmarinecine and (−)-Isoretronecanol

Kuniaki Tatsuta,* Hideaki Takahashi, Yoshiya Amemiya, and Mitsuhiro Kinoshita

Department of Applied Chemistry, Keio University Hiyoshi, Kohoku, Yokohama 223, Japan

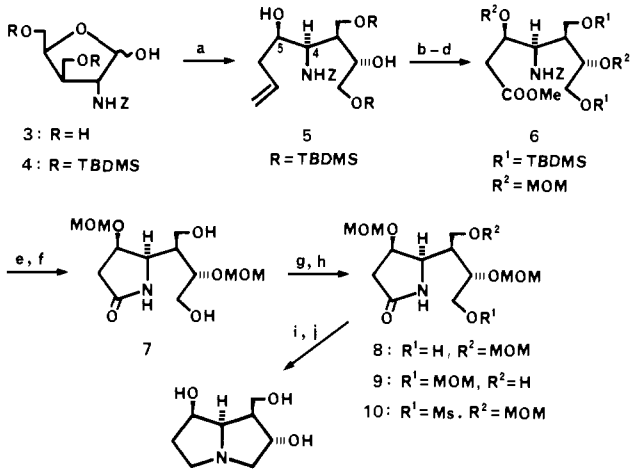
Received January 17, 1983

The pyrrolizidine alkaloids, which occur naturally in various plant species, in general consist of a pyrrolizidine ("necine") base and a carboxylic ("necic") acid. Their structures, syntheses, and physiological properties have been continuously and amply reviewed;[1] however, completely stereoselective syntheses of optically active necine bases have not been reported to date.[2]

Thus, we focused on the stereoselective total synthesis of "natural" necine bases, (−)-rosmarinecine (**1**)[3] and (−)-isoretronecanol (**2**)[2,4] from D-glucosamine.

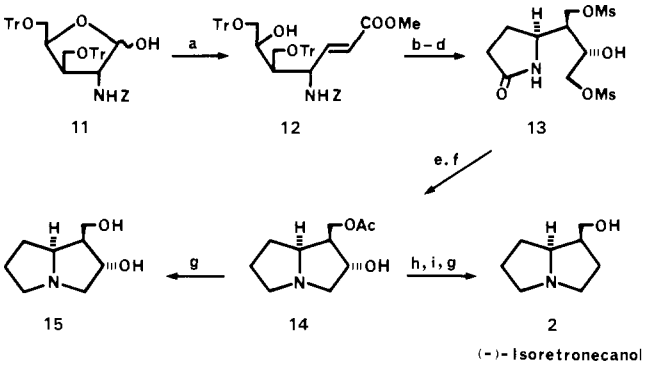
The first target was (−)-rosmarinecine (**1**, Scheme I). Methyl 2-amino-2,3-dideoxy-3-*C*-formyl-α-D-xylofuranoside-(3′*R*)-5-hemiacetal,[5] which has been already derived for the synthesis in three steps from methyl α-D-glucosaminide through the skeletal rearrangement of the *N*,*O*-*o*-benzenedisulfonyl derivative in our laboratories, was converted to the corresponding furanose **3**[6] successively by N-benzyloxycarbonylation [benzyl *S*-(4,6-dimethylpyrimidin-2-yl)thiocarbonate,[7] aqueous methanol, 1.5 h],

Scheme I[a]



[a] Key: (a) from 4, CH_2=$CHCH_2MgBr$, ether, 5 °C, 30 min; 20 °C, 30 min; reflux, 3 h; (b) $NaIO_4$, $KMnO_4$, aqueous *t*-BuOH and then 5% K_2CO_3, 15 h; (c) CH_2N_2, ether, 30 min; (d) MOMCl, *i*-Pr_2EtN, $CHCl_3$, 60 °C, 5 h; (e) 3 atm of H_2, 5% Pd–C, THF, AcOH, 3 h; (f) Bu_4NF, THF, 5 °C, 30 min; (g) 7 → 8 + 9, MOMCl, *i*-Pr_2EtN, THF, 6 h; (h) 8 → 10, MsCl, Py, 1 h; (i) from 10, BH_3·Me_2S, THF, 60 °C, 5 h; (j) 0.5 N HCl, dioxane, 80 °C, 6 h.

Scheme II[a]



[a] Key: (a) Ph_3P=CHCOOMe, toluene, 60 °C, 62 h; (b) 3 atm of H_2, 5% Pd–C, THF, AcOH, 5 h; (c) Amberlyst 15, MeOH, 60 °C, 5 h; (d) MsCl, py, 0 °C, 2 h; (e) BH_3·Me_2S, THF, 60 °C, 12 h; (f) KOAc, DMSO, 80 °C, 4 h; (g) NH_3, MeOH, 40 h; (h) $SOCl_2$, reflux, 3 h; (i) 3 atm H_2, Raney Ni, EtOH, 15 h.

hydride reduction (sodium borohydride, methanol), and acid hydrolysis (6 N hydrochloric acid, 1 h). Compound **3** contains already felicitously placed functional groups and an anomeric carbon of potential value for the stereoselective introduction of a hydroxyl group and carbon chain.

Silylation of **3** [*tert*-butyldimethylsilyl (TBDMS) chloride, pyridine, 15 h] gave the disilyl furanose **4** (87%), which was submitted to Grignard reaction with 7 equiv of allylmagnesium bromide in ether to afford the single *threo*[8] amido alcohol **5** [92%, oil, $[\alpha]^{19}_D$ −10° ($CHCl_3$)]. The *R* configuration of the newly formed alcohol at C-5 is assigned on the presumption of a stereoselectively chelation-controlled approach[8c,d] of the reactant to the anomeric carbon of **4** and is confirmed by the successful transformation to natural rosmarinecine (**1**). Oxidation[9] of **5** (5 equiv of sodium metaperiodate and 1.5 equiv of potassium per-

(1) For examples, see: Bull, L. B.; Culvenor, C. C. J.; Dick, A. T. "The Pyrrolizidine Alkaloids"; North-Holland: Amsterdam, 1968. Wood, H. C. S.; Wrigglesworth, R. "Rodd's Chemistry of Carbon Compounds"; Coffey, S., Ed.; Elsevier: Amsterdam, 1977; Vol. IVB, pp 7–62. Robins, D. J. *Adv. Heterocycl. Chem.* **1979**, *24*, 247–291.

(2) Three syntheses affording optically active (−)-isoretronecanol have been reported [(a) Rüeger, H.; Benn, M. *Heterocycles* **1982**, *19*, 1677–1680. (b) Robins, D. J.; Sakdarat, S. *J. Chem. Soc., Perkin Trans. 1*, **1981**, 909–913. Robins, D. J.; Sakdarat, S. *J. Chem. Soc., Chem. Commun.* **1979**, 1181–1182. (c) Takano, S.; Ogawa, N.; Ogasawara, K. *Heterocycles* **1981**, *16*, 915–916] with >90%, 90%, and 33% optical purity, respectively. A synthon for some necines has been synthesized with 99% optical purity: Rüeger, H.; Benn, M. *Heterocycles* **1982**, *19*, 23–25.

(3) (a) Richardson, M. F.; Warren, F. L. *J. Chem. Soc.* **1943**, 452–454. (b) Porter, L. A.; Geissman, T. A. *J. Org. Chem.* **1962**, *27*, 4132–4134. (c) The natural alkaloid rosmarinine, from which (−)-rosmarinecine (**1**) could be obtained by alkaline hydrolysis, was provided by Prof. S. E. Drewes, University of Natal, S. Africa; see ref 3a.

(4) Adams, R.; Hamlin, K. E., Jr. *J. Am. Chem. Soc.* **1942**, *64*, 2597–2599. Recent synthesis of the racemate: Iwashita, T.; Kusumi, T.; Kakisawa, H. *J. Org. Chem.* **1982**, *47*, 230–233 and references therein.

(5) Tatsuta, K.; Miyashita, S.; Akimoto, K.; Kinoshita, M. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 3254–3256.

(6) All new compounds reported have been fully characterized by IR, ^1H NMR, and high-resolution mass spectroscopy and/or combustion analysis.

(7) Purchased from Aldrich Chemical Co. See also: (a) Nagasawa, T.; Kuroiwa, K.; Narita, K.; Isowa, Y. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 1269–1272. (b) Ikeda, D.; Miyasaka, T.; Yoshida, M.; Horiuchi, Y.; Kondo, S.; Umezawa, H. *J. Antibiot.* **1979**, *32*, 1365–1366.

(8) (a) Still, W. C.; McDonald, J. H., III *Tetrahedron Lett.* **1980**, *21*, 1031–1034. (b) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1–115. (c) Tsuda, Y.; Nunozawa, T.; Yoshimoto, K. *Chem. Pharm. Bull.* **1980**, *28*, 3223–3231. (d) Kinoshita, M.; Ohsawa, N.; Gomi, S. *Carbohydr. Res.* **1982**, *109*, 5–23.

(9) ApSimon, J. W.; Chau, A. S. Y.; Craig, W. G.; Krehm, H. *Can. J. Chem.* **1967**, *45*, 1439–1445.

0002-7863/83/1505-4096$01.50/0