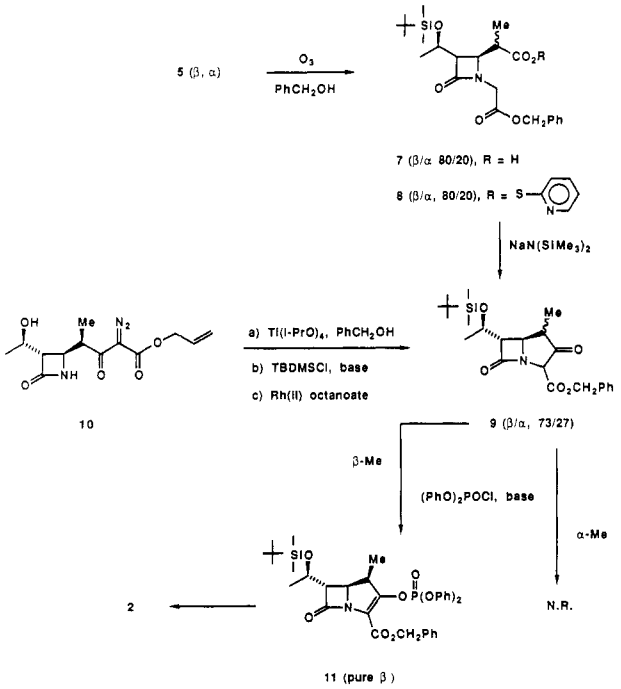
this would occur spontaneously at a later stage. The Dieckmann cyclization to **9** was performed by using exactly



2.0 equiv of sodium hexamethyldisilazide rapidly added to a THF solution of **8** at −30 °C. Lower temperatures, slow addition of base, and excess base all produced cyclic ketone **9**, but with 50–80% epimerization. The fast addition at higher temperature produced **9** in 85% yield in a 73:27 ratio of β- to α-methyl epimers. Thus, ~7% epimerization took place as evidenced by NMR integration of the C-1 proton. All attempts to purify the bicyclic ketone **9** by chromatography resulted in total epimerization to the 1α-methyl isomer. Proof of structure and stereochemistry for **9** was gathered by transforming the known β-lactam **10**[14] into **9** using the Merck protocol.[2] Although **9** from the present route was a 73:27 mixture, the pure material obtained from **10** coincided spectroscopically in every way with the major epimer in our mixture.

Due to the extreme lability of the C-1 methyl group when positioned on the β-face of **9**, this material was directly transformed[2] into the stable enol phosphonate and furnished only the pure β-methyl derivative **11**.[15] The Merck group had observed[3] this fortunate behavior regarding the relative rates of reaction for the α- and β-methyl epimers in the phosphorylation step. Thus, a kinetic separation of diastereomers was performed affording our target **11**, in 87% yield (based upon 73% of the β-epimer in **9**). Since further elaboration to a variety of thiovinyl derivatives is proprietary and involves many different side chains, we felt that the acquisition of **11** in five steps and 27% overall yield would be a prudent place to terminate this study.

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(14) Kindly supplied by Dr. R. A. Partyka of Bristol-Myers.

(15) Colorless oil, moisture sensitive; $[\alpha]^{22}_D$ +41.50° (*c* 1.33, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.45–7.12 (m, 15 H), 5.25, 5.18 (AB q, *J* = 12.6 Hz, CH_2Ph), 4.21, (dq, 1 H, *J* = 12.3, 6.2 Hz, CH_3CHOSi), 4.14 (dd, 1 H, *J* = 10.3, 2.8 Hz, *H*-6), 3.44 (dq, 1 H, 5.4, 2.8 Hz, *H*-1), 3.25 (dd, 1 H, *J* = 6.1, 3.0 Hz, *H*-5), 1.22 (d, 3 H, *J* = 6.2 Hz), 1.18 (d, 3 H, *J* = 7.3 Hz), 0.85 (s, 9 H), 0.07 (s, 3 H), 0.06 (s, 3 H); mass spectrum (Cl) *m/e* (relative intensity) 664 (M + 1, 5.4), 663 (M^+, 11.7), 500 (14.7), 432 (15.4), 286 (100). IR (neat) 2953, 2928, 2884, 2855, 1783 (C=O), 1724 (C=O), 1636, 1589, 1488, 1185, 1071, 1025, 971.

Supplementary Material Available: Complete experimental details and spectral data for all steps and products respectively (21 pages). Ordering information is given on any current masthead page.

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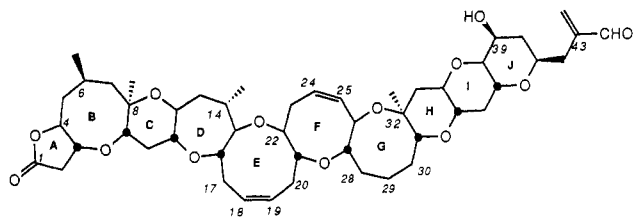
Assignment of ^{13}C NMR Peaks of Brevetoxin A: Application of Two-Dimensional Hartmann–Hahn Spectroscopy

Summary: Brevetoxin A, $C_{49}H_{50}O_{13}$ (BTX-A), the most potent toxin produced by the dinoflagellate *Gymnodinium breve*, consists of a 10 trans-fused oxacarbocyclic skeleton. The inherent problem when dealing with the NMR of molecules like BTX-A arises from the flexible nature of the molecule which is caused by the presence of medium-sized rings. This can be serious in terms of its lack of ^1H–^{13}C correlation in the spectra. A pulse scheme, Hartmann–Hahn (HOHAHA) type heteronuclear experiment for displaying RELAY cross peaks is described for direct detection of ^{13}C-nuclei. This pulse sequence leads to an improvement in resolution and sensitivity. The two dimensional (2D) ^1H–^{13}C correlation spectra which this pulse scheme produces has been applied in the assignment of carbon peaks in BTX-A.

Sir: Despite the numerous pulse sequences for obtaining 2D heteronuclear RELAY[1] as well as 2D heteronuclear chemical-shift correlation spectroscopy,[2] flexible molecules that cause severe broadening of peaks may lead to problems. This can be serious in terms of its lack of ^1H–^{13}C correlation, as exemplified by a molecule such as brevetoxin A (BTX-A, **1**).[3] In this paper, a pulse scheme for



BTX-A (1)

direct detection of ^{13}C nuclei which is superior in resolution and sensitivity to other currently available methods is described. The pulse scheme described here is a Hartmann–Hahn (HOHAHA)[4-6] type heteronuclear experiment

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which represents a modified version of the scheme developed by Bax et al.[7] for displaying RELAY cross peaks. This modified method utilizes a MLEV-17[8] composite pulse scheme for achieving net magnetization transfer among protons via a homonuclear Hartmann–Hahn (HOHAHA) type cross polarization. This net homonuclear magnetization is then relayed to the ^{13}C nuclei via an INEPT sequence and processed to provide pure phase absorption spectra. The altered sequence and phase cycling are as follows:

^{13}C:		$180°\theta$			$180°\theta$		$90°2\theta$	acq
^1H:	$90°\phi t_{1/2}$		$t_{1/2}$	MLEV 17_y	Δ_1	$180°\theta$ Δ_1	$90°\varphi$	Δ_2 decouple

$\phi = x; \theta = x, x, -x, -x; \varphi = y, -y; 2\theta = x, x, x, x, y, y, y, y, -x, -x, -x, -x, -y, -y, -y, -y$; acquisition = $x, -x, x, -x, y, -y, y, -y, -x, x, -x, x, x -y, y, -y, y$ with ϕ being alternated between x and y on alternative scans and storing the data from odd and even numbered scans separately for later processing via the standard hypercomplex method[17] to provide 2D phase-sensitive spectra.

The MLEV-17_y represents a composite pulse scheme of an integer number of repeats, N, of the sequence *ABBA BBAA BAAB AABB* 60_y, where $A = 90_x180_y90_x$ and $B = 90_{-x}180_{-y}90_{-x}$, which spin locks the proton magnetization along the y axis. Our reason for incorporating the MLEV-17 sequence are twofold:[9] (1) the MLEV-17 cycle covers a larger chemical shift range for a given amount of R_f power and (2) the MLEV-17 cycle minimizes magnetization loss due to relaxation processes making the pulse scheme attractive for peaks having short T_2 values (broad lines). Since the experiment did not require suppression of large solvent lines, the two trim pulses were omitted.[8] Also, we reduced the last 17th pulse from 180° to 60°.[10]

We demonstrate this HOHAHA type heteronuclear experiment as applied to BTX-A, $C_{49}H_{70}O_{13}$ (1), a potent neurotoxin produced by the dinoflagellate *Gymnodinium breve*.[11] In our ongoing biosynthetic studies of the BTX's,[12] the assignments of carbon peaks for BTX-A became necessary. Previously, full proton assignment of BTX-A was only made possible by use of the HOHAHA experiment.[13] The problem in dealing with molecules like BTX-A as experienced by the authors arises from the flexible nature of the molecule, which is caused by the presence of medium-sized rings. The presence of medium-sized rings not

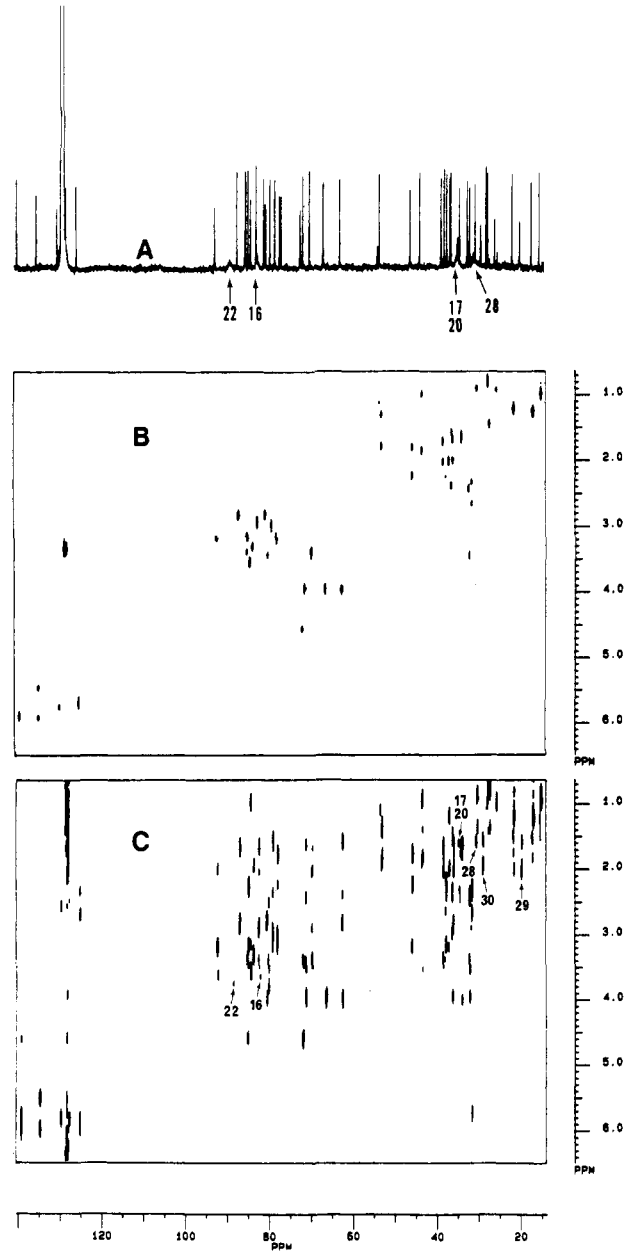

Figure 1. Partial ^{13}C NMR spectra using 8.7 mM solution of BTX-A in benzene-d_6 at 45 °C. The spectra were recorded on a Bruker AM-400 spectrometer equipped with digital phase shifters. Chemical shifts are referenced to internal benzene-d_6 at δ 7.15 and δ 128.0 for proton and carbon respectively. (A) 1D ^{13}C NMR of BTX-A. (B) Conventional 2D heteronuclear ^1H–^{13}C shift correlation. (C) 2D heteronuclear HOHAHA type RELAY correlation. For this experiment; Δ_1 = 18.5 ms, Δ_2 = 1.3 ms, 19 ms MLEV-17 mixing time at a field strength of 6.0 kHz (6-W R_f power) was used. Although some three-bond relay peaks are present, for other experiments using longer MLEV-17 mixing times the direct one-bond correlations between the broadened proton and carbon signals were not observed. The spectrum was recorded in the pure-phase absorption mode[17] by storing the data in odd- and even-numbered scans in separate memory locations to allow a hypercomplex 2D Fourier transformation. Both 2D experiments were recorded for identical time periods (26 h), identical acquisition times in F_2, and identical increments and transients per increment in F_1. A slightly larger sweep width was used in F_1 for the HOHAHA experiment, thus accounting for the slight difference in digital resolution in F_1. For processing, 6-Hz Lorentzian line broadening was used in F_2 and a 23° shifted sine bell window function was used in F_1 for both sets of data. The conventional HETCOR experiment is in absolute value display while that for the HOHAHA experiment is in phase-sensitive display.

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Table I. Carbon Assignments of BTX-A[a]

carbon	ppm	carbon	ppm	carbon	ppm
1	170.86	18	127.41 or 129.35[b]	34	77.96
2	37.59	19	129.35 or 127.41[b]	35	79.07
3	84.93	20	34.50	36	36.27
4	84.26	21	80.08	37	62.51
5	43.48	22	88.49	38	80.57
6	27.35	23	31.61	39	66.41
7	53.17	24	124.80	40	33.99
8	76.80	25	139.05	41	71.13
9	86.94	26	71.90	42	32.20
10	36.02	27	85.10	43	149.10
11	82.33	28	30.85	44	193.34
12	69.74	29	19.72	45	134.00
13	38.28	30	29.00	6-Me	27.55
14	37.05	31	83.76	8-Me	15.04
15	92.25	32	76.38	14-Me	21.40
16	82.00	33	45.83	32-Me	16.89
17	34.50				

[a] Measurements were performed with Bruker AM-400 in benzene-d_6 at 45 °C. Although the carbon assignments described here is done in benzene-d_6, partial carbon assignments for BTX-A has been carried out in CD_2Cl_2.[3a] Here we note carbon peaks whose assignments differ with those reported by Shimizu et al.;[3a] namely, C-10, C-15, C-33, and C-34 correspond to δ's at 45.36, 77.72, 35.83, and 83.63 or 87.18, respectively, in CD_2Cl_2, whereas in Table I (as shown above) the said carbons correspond to δ 36.02, 92.25, 45.83, and 77.96, respectively. [b] The broad olefinic protons at C-18 and C-19 overlap as well as protons represented by H-17b and H-20a,-b.[13] Thus, even with the presence of RELAY, the problem of overlap in proton region for this olefinic carbons could not be surmounted to ensure its assignment.

only broadens peaks in proton NMR but leads to broadening of the carbons effected by this system as well. The use of conventional ^1H–^{13}C COSY (HETCOR)[2] resulted in partial assignment of carbon peaks in BTX-A. The remaining carbons could not be assigned by use of conventional HETCOR techniques due to either extensive overlap of the proton region or, more importantly, due to the broad peaks resulting from the inherent flexibility of the molecule.

A major problem was the broadening of both proton and carbon signals, which was most apparent in rings E and G of BTX-A. Thus in some cases the low intensity and severely broadened carbon peaks almost led to the erroneous assumption of treating the peak as an artifact. For example, this aspect of ^{13}C NMR peak is best shown by the 1D ^{13}C spectrum of BTX-A (Figure 1A); C-22 at δ 88.49 and C-16 at δ 82.00. The COLOC sequence[12a,14] was then used in an attempt to find long-range coupling, but the results from this sequence were disappointing in that no new information was secured except for the assignments of the quaternary centers at C-8 and C-32.

The power of the heteronuclear HOHAHA technique as applied to BTX-A is demonstrated in Figure 1. Thus in Figure 1C, cross peaks are observed for C-29 at δ 19.72, C-30 at δ 29.00, C-28 at δ 30.85, overlapping carbon peaks of C-17 and C-20 at δ 34.50, C-16 at δ 82.00, and C-22 at δ 88.49. For comparison, a conventional HETCOR experiment, used previously for partial ^{13}C NMR peak assignment of a protein,[15] is also shown (Figure 1B). Both 2D experiments shown in Figure 1 were acquired with identical parameters in F_2 (experimental time, acquisition time, digital resolution) and processed with identical window functions in F_1 and F_2. More importantly, one bond ^1H–^{13}C coupling cross peaks are present for all of the broadened carbon signals in the HOHAHA data; in contrast most of these cross peaks are absent in the HETCOR data. The carbon assignments for BTX-A are shown on Table I.

The heteronuclear HOHAHA technique was instrumental in assigning carbons in rings E and G and other carbons that were problematic due to ring flexibility as well as severe overlapping in the proton region. Although the experiment described here is by no means an alternative to the more sensitive experiments like heteronuclear multiple quantum coherence (HMQC),[16] it clearly provides an improvement in sensitivity and resolution over other currently available experiments for detecting the less sensitive ^{13}C nuclei. More importantly this technique represents a powerful method of dealing with molecules containing severely broadened peaks as shown by BTX-A.

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The Preparation of [1-(Arylimino)alkyl]zinc by the α-Addition of Organozinc to Isocyanide

Summary: Organozinc underwent α-addition to aryl isocyanide in toluene at 40–95 °C to afford [1-(arylimino)-alkyl]zinc (3), whose structure was spectroscopically assigned.

Sir: Acylmetals are important intermediates in transition metal catalyzed carbonylation reaction, and there has been much interest in the chemistry of acylmetals, especially in the utilization of acylmetals as acyl anion equivalents in the field of synthetic chemistry.[1] N-Substituted (α-iminoalkyl)metal compounds, nitrogen analogue of acylmetals, are also expected to act as acyl anion equivalents. However, the use of N-substituted (α-iminoalkyl)metal compounds for the nucleophilic introduction of acyl group has been so far limited,[2] mainly because of the paucity of convenient methods for their preparation. Lithium aldimines developed by Walborsky are useful, but of synthetically limited applicability.[2b] Recently, we have reported the synthesis and reactions of N-substituted organo(silyliminomethyl)stannanes, which may serve as synthetic equivalents to organosilylcarbonyl anion and carbonyl dianion.[3] In this paper, we describe a facile

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