$$Co^{2+} + 2H_2O \overset{K_2}{\rightleftharpoons} Co(OH)_2 + 2H^+ \qquad (2)$$

$$Co(OH)_2 + Ru(III) \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} Co(OH)_2^+ + Ru(II) \qquad (3)$$

$$Co(OH)_2^+ + Ru(III) \xrightarrow[k_4]{\text{slow}} CoO^{2+} + Ru(II) + H_2O \qquad (4)$$

$$CoO^{2+} \xrightarrow[H_2O]{k_5} Co^{2+} + H_2O_2 \qquad (5)$$

$$CoO^{2+} + Co(II) \xrightarrow{k_6} CoOCo^{4+} \rightarrow \text{ppt.} \qquad (6)$$

$$2Ru(III) + H_2O_2 \rightarrow 2Ru(II) + O_2 + 2H^+ \qquad (7)$$

as part of the catalytic sequence.[2a,8] The net reaction, Ru(II) formation and Co(III) precipitation, found when [Ru(III)] and [Co(II)] are equal, results from eq 2–4 and 6 (or its equivalent).[9,10] The diminished catalyst activity at high Ru(III) is also ascribed to eq 6; this reaction converts part of the Co(IV) and Co(II) to an inactive Co(III) species each cycle. Thus the effective catalyst concentration is diminished at high [Co(II)] and high [Ru(III)]/[Co(II)] ratios. The production of peroxide in eq 5 is chemically reasonable and receives some support from electrochemical studies of Co(II).[11] The oxidation of H_2O_2 by $Ru(bpy)_3^{3+}$ (eq 7) is sufficiently rapid ($k_{eff} = 5 \times 10^2$ M^{-1} s^{-1} at pH 7[3]) when [Ru(II)] > 5[Ru(III)] to quantitatively oxidize H_2O_2 to O_2.

The sequence eq 2–5 and 7 provides a mechanism for Co(II) catalysis of eq 1. It gives rise to a rate law of the observed form when reaction 4, oxidation of Co(III) to Co(IV), is the slow step preceded by equilibria 2 and 3. Provided that Co^{2+} and $Co(OH)_2^+$ are the dominant forms of Co(II) and Co(III), respectively, a is equal to $nK_2K_3k_4$ where n is 4 when reaction 7 is rapid. From the $Co(H_2O)_6^{3+/2+}$ reduction potential (1.86 V[12]) and estimated Co^{n+} hydrolysis constants,[13] $K_2K_3/[H^+]^2$ is $\sim 1 \times 10^{-2}$ at pH 7 (i.e., $K_2 = 10^{-18.8}$ and $E°(Co(OH)_2^+/Co(OH)_2) = 1.1$ V), giving k_4 $(=a/4K_2K_3) \sim 1 \times 10^6$ M^{-1} s^{-1} and $k_5 \geq 100$ s^{-1}. The formation of Co(IV) is thus implicated to be rate determining in the Co(II) catalysis of eq 1 at pH ~7. At present the rate constant for the reaction of Co(IV) with water (hydroxide ion) can only be estimated as ≥100 s^{-1} at pH 7. Future experiments may provide greater insight into the details of O–O bond formation on Co(IV).

Acknowledgment. We thank E. Norton for performing the cobalt analyses. This work was carried out at Brookhaven National Laboratory under contract with the U.S. Department of Energy and supported by its Office of Basic Energy Sciences.

Registry No. H_2O, 7732-18-5; Co, 7440-48-4; $Ru(bpy)_3^{3+}$, 18955-01-6.

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(8) Note that this mechanism is not unique. The following (and variants) are also consistent with the observed rate law:

$$2Ru(III) \rightleftharpoons Ru(IV) + Ru(II)$$

$$Ru(IV) + Co(OH)_2 \rightarrow Ru(II) + Co(IV) \text{ etc.}$$

This interpretation seems less attractive than the scheme considered because of the very positive $E°$ for the Ru(IV)/Ru(III) couple. See: Gaudiello, J. G.; Sharp, P. R.; Bard, A. J. *J. Am. Chem. Soc.* **1982**, *104*, 6373.

(9) The time profiles of high Ru(III) runs have been successfully simulated with $k_6 \sim (1 \times 10^4)$ k_5. In addition, eq 6 finds precedent in the $VO^{2+}/V^{2+}{}_{aq}$[10a] and $FeO^{2+}/Fe^{2+}{}_{aq}$[10b] systems. Equation 6 is not, however, a unique "catalyst suicide" mechanism. Direct oligomerization also likely occurs at high Co(III) concentrations (as in the stopped-flow runs).

(10) (a) Newton, T. W.; Baker, F. B. *Inorg. Chem.* **1964**, *3*, 569. (b) Conochiolli, T. J.; Hamilton, E. J., Jr.; Sutin, N. *J. Am. Chem. Soc.* **1965**, *87*, 926.

(11) Shafirovich, V. Ya.; Strelets, V. V. *Nouv. J. Chim.* **1978**, *2*, 199, footnote 10.

(12) Warnquist, B. *Inorg. Chem.* **1970**, *9*, 682.

(13) Baes, C. F., Jr.; Mesmer, R. E. "The Hydrolysis of Cations"; Wiley-Interscience: New York, 1976; p 238. K_{nh} is defined as the equilibrium constant for $M^+ + nH_2O \rightleftharpoons M(OH)_n^{(1-n)+} + nH^+$. The following log K_{nh} values were used here: Co(II) −9.65 (n = 1), −18.8 (n = 2); Co(III) −2.5 (n = 1), −5.9 (n = 2). The Fe(III) values (p 230) were used for Co(III). Note that the potential complication of phosphate complexing has been neglected.

1,3-Asymmetric Induction in Addition Reactions of Chiral β-Alkoxy Aldehydes: Efficient Chelation Control via Lewis Acidic Titanium Reagents

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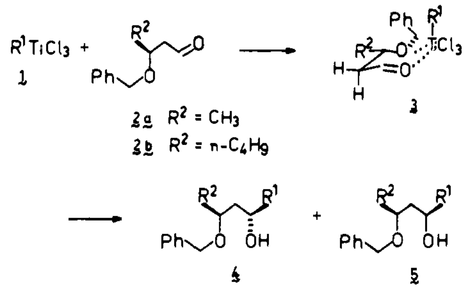
Controlling 1,3 asymmetric induction in Grignard- and aldol-types of additions to acyclic carbonyl compounds remains a challenge.[1] Since ketones and aldehydes devoid of additional heteroatoms generally show poor degrees of diastereofacial selectivity in stereochemically relevant cases,[1] chiral β-alkoxy derivatives have been tested in hope of potential chelation control. However, such reagents as RMgX,[2] RLi,[2] and R_2CuLi[3] failed to perform well, in spite of the fact that they chelate efficiently in systems involving 1,2 asymmetric induction.[3,4] We report that Lewis acidic titanium reagents[5] provide a solution to this long-pending problem.

Since compounds of the type $RTiCl_3$ (**1**) are known to form bis-etherates as well as other octahedral six-coordinate adducts,[6] we speculated that they might react with chiral β-alkoxy aldehydes **2** to form the chelation-controlled products **4** via intermediates **3**.[7] We also thought that $TiCl_4$ could interact similarly, so that addition of proper carbon nucleophiles that do not destroy chelation should likewise afford **4** preferentially.



Indeed, the reaction of **2a** and **b** with CH_3TiCl_3[8] in CH_2Cl_2 at −78 °C yielded compounds **4** with unprecedented levels of 1,3 asymmetric induction (Table I). Furthermore, complexation of **2a** and **b** using $TiCl_4$ followed by addition of allylsilanes[9] or dibutylzinc[10] at −78 °C also resulted in stereoselectivities of ≥90% (Table I).[11] In these cases we are not certain whether the or-

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(1) (a) Bartlett, P. A. *Tetrahedron* **1980**, *36*, 3. (b) Morrison, J. D.; Mosher, H. S. "Asymmetric Organic Reactions"; Prentice Hall: Englewood Cliffs, NJ, 1971.

(2) Leitereg, T. J.; Cram, D. J. *J. Am. Chem. Soc.* **1968**, *90*, 4011, 4019.

(3) Still, W. C.; Schneider, J. A. *Tetrahedron Lett.* **1980**, *21*, 1035.

(4) (a) Cram, D. J.; Kopecky, K. R. *J. Am. Chem. Soc.* **1959**, *81*, 2748. (b) Wolfrom, M. L.; Hanessian, S. *J. Org. Chem.* **1962**, *27*, 1800. (c) Nakati, T.; Kishi, Y. *Tetrahedron Lett.* **1978**, 2745. (d) Eliel, E. L.; Koskimies, J. K.; Lohri, B. *J. Am. Chem. Soc.* **1978**, *100*, 1615. (e) Still, W. C.; McDonald, J. H. *Tetrahedron Lett.* **1980**, *21*, 1031. (f) Bernardi, R. *Ibid.* **1981**, *22*, 4021.

(5) Reviews of organotitanium reagents in organic synthesis: (a) Reetz, M. T. *Top. Curr. Chem.* **1982**, *106*, 1. (b) Weidmann, B.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 31.

(6) Reetz, M. T.; Westermann, J. *Synth. Commun.* **1981**, 647 and references therein.

(7) **3** is simply an operation model. Half-chair conformations lead to the same results. Also, the benzyl group may be axial.

(8) CH_3TiCl_3 was prepared by reacting $Zn(CH_3)_2$ with $TiCl_4$ in CH_2Cl_2: Reetz, M. T.; Westermann, J.; Steinbach, R. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 900.

(9) Allylsilanes are known to add to aldehydes in the presence of $TiCl_4$: (a) Hosomi, A.; Sakurai, M. *Tetrahedron Lett.* **1976**, 1295. (b) Trost, B. M.; Coppola, B. P. *J. Am. Chem. Soc.* **1982**, *104*, 6879.

(10) Aldehydes react smoothly with ZnR_2 in the presence of $TiCl_4$: Reetz, M. T.; Steinbach, R.; Wenderoth, B. *Synth. Commun.* **1981**, 261.

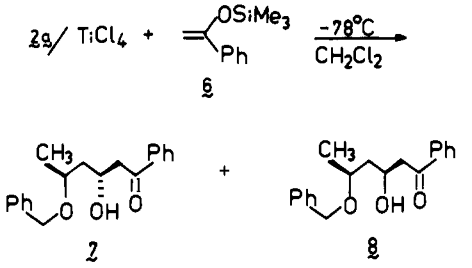
0002-7863/83/1505-4833$01.50/0

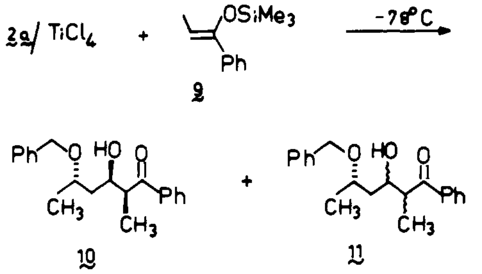
Table I

reagent	aldehyde	R^1	R^2	4:5
CH_3TiCl_3	2a	CH_3	CH_3	90:10
$TiCl_4/CH_2{=}CHCH_2SiMe_3$	2a	$CH_2{=}CHCH_2$	CH_3	95:5
$TiCl_4/CH_2{=}C(CH_3)CH_3SiMe_3$	2a	$CH_2{=}C(CH_3)CH_2$	CH_3	95:5
$TiCl_4/Zn(n\text{-}C_4H_9)_2$	2a	$n\text{-}C_4H_9$	CH_3	90:10
CH_3TiCl_3	2b	CH_3	$n\text{-}C_4H_9$	91:9
$TiCl_4/CH_2{=}CHCH_2SiMe_3$	2b	$CH_2{=}CHCH_2$	$n\text{-}C_4H_9$	95:5
$TiCl_4/CH_2{=}C(CH_3)CH_2SiMe_3$	2b	$CH_2{=}C(CH_3)CH_2$	$n\text{-}C_4H_9$	99:1

ganometallics used are in fact the reacting species or whether rapid metal/titanium exchange first generates $RTiCl_3$, which then reacts via **3**. The yields in all cases amounted to >90%. The reaction of allylmagnesium chloride with **2a** in THF affords a 40:60 ratio of **4**:**5**, in agreement with related nonselective processes.[3]

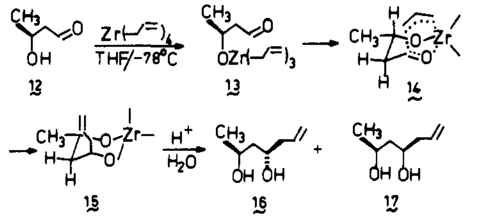
Diastereofacial selectivity in the Mukaiyama-type of aldol addition[12] of **6** to **2a**/$TiCl_4$ is also noteworthy (**7**:**8** = 92:8, 95% conversion).[11] Interestingly, addition of prochirally pure silyl enol ether **9** not only results in excellent 1,3 asymmetric induction, but also in high syn selectivity. The crude product (conversion >95%) contains at least 92% or **10**[13] in addition to traces of two or possibly three other diastereomers. Simple diastereoselectivity in Mukaiyama aldol additions involving normal aldehydes is generally low,[14] e.g., we found that **9** adds to propanal at −78 °C to afford a 66:34 mixture of syn and anti diastereomers. Thus, in the case of **2a** chelation exerts a pronounced effect on stereoselection at the two neighboring chiral centers, a fortuitous finding that extends the scope of the present methodology considerably.[15]





We also discovered that chiral β-acetoxy aldehydes such as β-acetoxybutanal react analogously with $TiCl_4/CH_2{=}CHCH_2SiMe_3$, although the degree of diastereofacial selectivity is somewhat lower (88:12). In the benzyloxy cases, chelation of the type **3** followed by axial attack of the carbonyl nucleophile is plausible.[16] It is important to note that reactions of **2a** with less Lewis acidic titanium reagents such as $CH_3Ti(O\text{-}i\text{-}Pr)_3$, $CH_2{=}CHCH_2Ti(O\text{-}i\text{-}Pr)_3$, and $CH_2{=}CHCH_2Ti(NEt_2)_3$ resulted in negligible 1,3 asymmetric induction (generally ~1:1 diastereomer ratios), in line with earlier observations pertaining so similar reactions of allylboron reagents in the absence of Lewis acids.[17] Furthermore, adding $CH_3Ti(O\text{-}i\text{-}Pr)_3$ to a solution of the **2a**/$TiCl_4$ complex lowered the **4**:**5** ratio to 70:30. It is likely that rapid ligand exchange between complexed $TiCl_4$ and the added reagent sets in, which partially destroys the chelating properties of the system.[18]

We have also explored the possibility of stereoselective *intramolecular* transfer of alkyl groups by reacting β-hydroxy aldehydes with polyalkylmetal compounds.[19] For example, the reaction of **12** with tetraallylzirconium afforded a diastereomer ratio for **16**:**17** of 81:19. Assuming initial deprotonation to form propene and the intermediate **13**, intramolecular transfer of an allyl group via the bicyclic[1.3.3] transition state **14** is one possible explanation. It remains to be seen whether covalently bonded metals other than zirconium (e.g., Si, Sn, Ti) perform better in similar situations.



In summary, Lewis acidic titanium reagents $RTiCl_3$[20] and $TiCl_4$ provide an efficient means of controlling stereochemistry in the

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[11] (a) Stereochemical assignments were made as follows: The methyl adducts of **2a** were deprotected by hydrogenolysis and the resulting diols compared with authentic samples (Cazaux, L.; Maroni, P. *Bull. Soc. Chim. Fr.* **1972**, 773). The allyl adducts of **2a** were compared with authentic samples (Hoffmann, R. W., private communication. Geueke, K.-J. Dissertation, Universität Marburg, 1981).[14] By analogy the methallyl adducts of **2a** as well as the reactions involving **2b** should afford the chelation products. In fact, *all* of the products in Table I show characteristic patterns in the ^{13}C NMR spectra. For example, the signals of the carbon atoms bearing the benzyloxy and hydroxy groups in **4** consistently appear at higher field than the corresponding signals observed for **5**. The same applies to the aldol adducts **7** and **8**. (b) Since some of the diastereomers have similar R_f values, flash chromatography does not separate them efficiently. Low-pressure liquid chromatography can be used for purification.

[12] Mukaiyama, T. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 817.

[13] It is possible to Kugelrohr-distill the crude product (64% isolated) or to use low-pressure liquid chromatography for purification. The ^{13}C NMR ($DCCl_3$) signals are as follows: δ 11.8, 19.4, 41.1, 45.2, 68.7, 70.4, 72.4, 127.3, 127.5, 127.8, 128.1, 128.4, 132.9, 136.0, 138.4, 204.8. The tentative assignment regarding syn selectivity is based on analogy to the syn-selective reaction of **9** with propanal as well as on the small coupling constant for the vicinal protons of the two neighboring stereocenters (J_{vic} = 4.1 Hz). The latter is in line with Heathcock's observation regarding the syn configuration of aldols in other cases: Heathcock, C. H.; Pirrung, M. C.; Sohn, J. E. *J. Org. Chem.* **1979**, *44*, 4294.

[14] Mukaiyama, T.; Banno, K. B.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503.

[15] The reason for the dramatic increase in simple diastereoselection must be related to chelation of the type **3** but is presently a matter of speculation. Assuming the traditional Zimmerman–Traxler chair transition state as well as silicon as the metal in the pericycle, the enolate can allign with the chelated aldehyde function from the axial direction in two basically different ways. One results in syn selectivity via a *trans*-decalin type of transition state, the other in anti selectivity via the *cis*-decalin analogue. In the latter case, the two possible chair/chair geometries are both energetically unfavorable. See also footnote 7.

[16] A boat conformer can also be invoked. In the $NaBH_4$-induced reduction of chiral β-hydroxy ketones related transition states have been proposed: Narasaka, K.; Pai, H. C. *Chem. Lett.* **1980**, 1415.

[17] For example, **2a** is known to react with allyldimethoxyborane to yield a **4**:**5** (R^1 = allyl, R^2 = methyl) product ratio of 63:37. The assignments were made by deprotection, acetalization using benzaldehyde, and analysis of the ^1H NMR spectrum of the cyclic acetal according to Gerlach's method (Gerlach, H.; Wetter, H. *Helv. Chim. Acta* **1974**, *57*, 2306). We thank Professor R. W. Hoffmann for providing the data and for helpful discussions.[11]

[18] Sporadic reports of chelation control in 1,2 asymmetric induction using Lewis acids have appeared: (a) Izawa, T.; Mukaiyama, T. *Chem. Lett.* **1978**, 409. (b) Maruyama, K.; Ishihara, Y.; Yamamoto, Y. *Tetrahedron Lett.* **1981**, *22*, 4235. (c) See also ref 9b.

[19] Here we mean intermediates with normal covalently bonded metal centers, in contrast to chelated species of the type **3**. The latter may also react "intramolecularly" by a 1,3-shift.

[20] CH_3TiCl_3 and $(CH_3)_2TiCl_2$ are also highly stereo- and chemoselective in other systems: (a) Reetz, M. T.; Westermann, J.; Steinbach, R. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 901. (b) Reetz, M. T.; Steinbach, R.; Westermann, J.; Peter, R. *Ibid.* **1980**, *19*, 1011. (c) Reetz, M. T.; Westermann, J. *J. Org. Chem.* **1983**, *48*, 254.

construction of 1,3-diols. We are currently testing the use of other carbon nucleophiles such as propargylsilanes, crotylstannanes, aryltitanium trichlorides, and alkylaluminum reagents[21] with **2a** and **b** and related aldehydes having an additional chiral center at the α-position.

Acknowledgment. We thank the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie for support of this work.

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(21) We have discovered that certain alkylaluminum reagents add to aldehydes in the presence of $TiCl_4$: Reetz, M. T.; Kesseler, K., unpublished results.

Amphimedine, New Aromatic Alkaloid from a Pacific Sponge, *Amphimedon* sp. Carbon Connectivity Determination from Natural Abundance ^{13}C–^{13}C Coupling Constants

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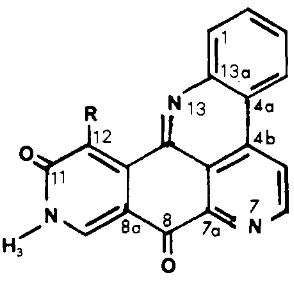
Although a wide variety of novel natural products have been isolated from marine organisms, relatively few alkaloids have been reported.[1] We report here a new, cytotoxic fused pentacyclic aromatic alkaloid obtained from a Pacific sponge. Owing to the paucity of protons in the molecule, extensive use was made in the structure elucidation of long-range proton–^{13}C couplings and also natural-abundance ^{13}C–^{13}C couplings obtained from a two-dimensional double-quantum coherence experiment.[2-4] The latter technique has been used rarely for structure elucidations to date,[5] but it is extremely useful for highly fused systems such as the one described herein.

The new alkaloid, amphimedine (**1**), a sparingly soluble yellow solid, mp >360 °C, was isolated from an *Amphimedon* sp. of sponge collected at Guam Island at −3 m. Room-temperature (CH_2Cl_2; $CHCl_3$–MeOH; MeOH) and hot Soxhlet extracts ($CHCl_3$) of freeze-dried specimens were chromatographed sequentially over silica gel and alumina ($CHCl_3$–MeOH) to give pure amphimedine. High-resolution mass spectral analysis established the formula $C_{19}H_{11}N_3O_2$ (*m/e* 313.08547, +0.35 mass error) and indicated a very stable structure, since only a few fragment ions were observed, corresponding to losses of CH_3, CO, CHO, and HCN. The UV absorption of **1** [absolute ethanol, λ_{max} 210 nm (19690), 233 (39393), 281 (9099), 341 (6060)] changed significantly upon addition of $NaBH_4$ [λ_{max} nm 235 (12879), 280 (9090)], indicating the presence of conjugated ketone. Two intense carbonyl absorptions, 1690 and 1640 cm^{-1}, were thus attributed to α,β-unsaturated ketone and amide functionalities, respectively; no OH or NH absorptions were observed in the IR.



1 R = H
2 R = Br

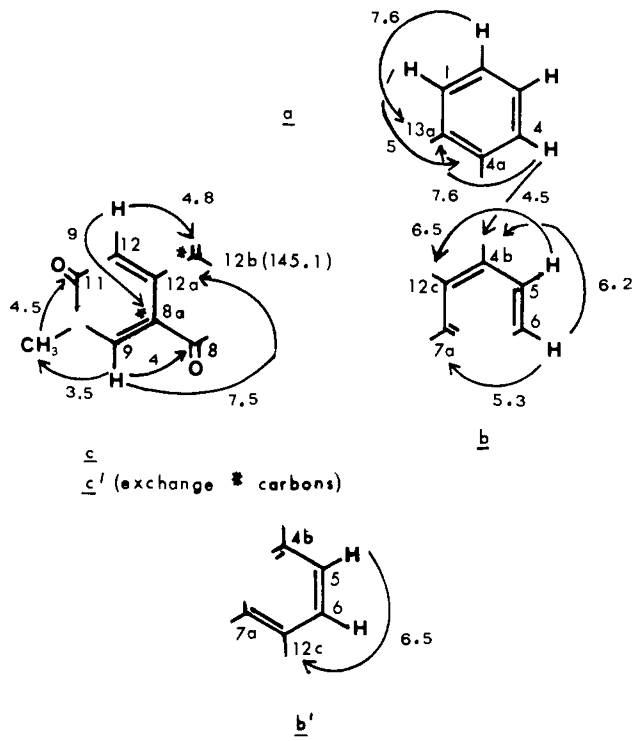


Figure 1. Partial structures from proton–proton and H–C–C–C coupling.

Owing to the very limited solubility of **1** in common organic solvents, most NMR spectral data were obtained in trifluoroacetic acid-*d* (TFA-*d*) and TFA-*d*–$CDCl_3$ (2:1); these data are summarized in Table I. Proton homonuclear decoupling confirmed that protons on carbons 1–4 were on contiguous atoms of an aromatic ring, that protons at C-5 and -6 constituted an isolated vicinal pair, and that protons at C-8 and -12 were each isolated. NOE enhancements were observed between H-4 and -5 and also between H-9 and the *N*-methyl protons (H-14). The ^{13}C data confirmed the presence of an amide carbonyl (C-11, δ 165.9) and a cross-conjugated ketone (C-8, δ 175.0).[6]

Since over half of the carbons in amphimedine were nonprotonated, further information regarding the skeletal network was sought from three-bond proton–carbon couplings, which were identified by a series of single-frequency decoupling experiments; see Table I and Figure 1. Analysis of these data confirmed the presence of partial structures a, b (or b′), and c (or c′), Figure 1, but did not provide evidence for joining the fragments. A link between carbons 4a and 4b was indicated by a three-bond coupling between H-4 and C-4b, but an H-5 to C-4a coupling was not observed.

When maximum use of proton and proton–carbon coupling did not unambiguously resolve the structure, attention was turned to determination of natural-abundance ^{13}C–^{13}C one-bond couplings

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(1) Fenical, W. *Science* (*Washington, D.C.*) **1982**, *215*, 923.

(2) Bax, A.; Freeman, R.; Kempsell, S. P. *J. Am. Chem. Soc.* **1980**, *102*, 4849.

(3) Bax, A.; Freeman, R.; Frenkiel, T. A.; Levitt, M. H. *J. Magn. Reson.* **1981**, *43*, 478.

(4) Mareci, T. H.; Freeman, R. *J. Magn. Reson.* **1982**, *48*, 158.

(5) (a) Cf.: Pinto, A. C.; Gonçalves, M. L. A.; Filho, R. B.; Neszmelyi, A.; Lukacs, G. *J. Chem. Soc., Chem. Commun.* **1982**, 293. (b) Freeman, R., Frenkiel, T. A. *J. Am. Chem. Soc.* **1982**, *104*, 5545.

(6) Levy, G. C.; Lichter, R. L.; Nelson, G. L. "Carbon-13 Nuclear Magnetic Resonance Spectroscopy"; Wiley: New York, 1980; Chapter 5.

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