

one of the enolate groups would be required for a closed transition state aldol reaction involving the tetramer.¹⁵ Molecular mechanics calculations (MM2) performed on the 4:3 complex indeed indicate unhindered rotation of the enolate ligands, so coordination of a fourth group is expected to be sterically accessible without prior deaggregation of the tetramer.¹⁶ Seebach has proposed that aldol reactions of tetrameric Lewis base-coordinated enolates may take place via a ligand dissociative process, and although our data do not provide definitive evidence for such a mechanism, they certainly support the viability of a coordinatively unsaturated reactive tetramer.¹⁷ On the basis of these results, experiments to evaluate the relative reactivities of the ligand-free, 3:4, and 4:4 complexes¹⁸ and of related lithium enolates bearing chiral ligands are currently underway in our laboratories.

Acknowledgment. We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the National Science Foundation PYI program (CHE 90-47740) for financial support of this work. Helpful discussions with Professors D. Collum, P. Willard, and D. Seebach are also gratefully acknowledged. E.N.J. thanks the David and Lucille Packard Foundation, the Lilly Grantee program, the Alfred P. Sloan Foundation, and the Camille and Henry Dreyfus Foundation Teacher-Scholar program for awards.

Supplementary Material Available: Experimental procedures, titration procedures, and details of the aggregation measurements and X-ray diffraction studies (35 pages). Ordering information is given on any current masthead page.

(15) Denmark, S. E.; Henke, B. R. *J. Am. Chem. Soc.* 1991, 113, 2177 and references cited therein.

(16) Jackman has provided strong evidence for a reactive tetramer in transesterification by lithium aryloxides. Jackman, L. M.; Petrei, M. M.; Smith, D. B. *J. Am. Chem. Soc.* 1991, 113, 3451.

(17) Seebach, D.; Amstutz, R.; Dunitz, J. D. *Helv. Chim. Acta* 1981, 64, 2622.

(18) For discussions on the relative reactivity of partially solvated alkyl-lithium aggregates, see: (a) Hay, D. R.; Song, Z.; Smith, S. G.; Beak, P. *J. Am. Chem. Soc.* 1988, 110, 8145. (b) Collum, D. B. *Acc. Chem. Res.*, in press.

Miyakolide: A Bryostatin-like Macrolide from a Sponge, *Polyfibrospongia* sp.

Tatsuo Higa,* Jun-ichi Tanaka, and Masaru Komesu

Department of Marine Sciences
University of the Ryukyus
Nishihara, Okinawa 903-01, Japan

Dolores Garcia Gravalos and José Luis Fernández Puentes

PharmaMar Research Institution
28046 Tres Cantos, Madrid, Spain

Gérald Bernardinelli and Charles W. Jefford*

Laboratory of Crystallography and
Department of Organic Chemistry
University of Geneva, 1211 Geneva 4, Switzerland
Received June 5, 1992

We recently discovered that a sponge of the genus *Polyfibrospongia* contained a novel class of bis-oxazoles, one of which, hennoxazole A, displayed significant antiviral activity.¹ This finding prompted us to examine the sponge further to determine whether other biologically active constituents were present. We

(1) Ichiba, T.; Yoshida, W. Y.; Scheuer, P. J.; Higa, T.; Garcia Gravalos, D. *J. Am. Chem. Soc.* 1991, 113, 3173.

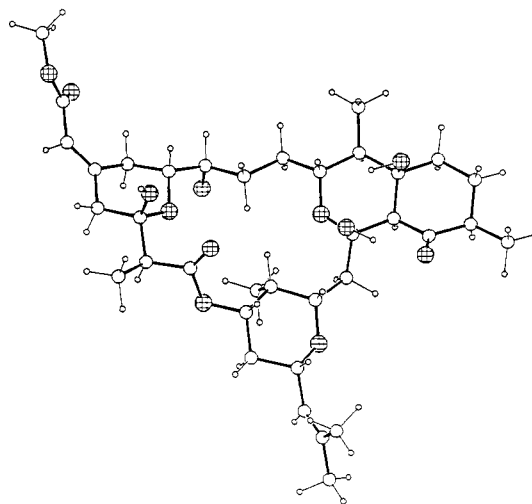


Figure 1. Perspective drawing of the relative configuration of miyakolide (1) as determined by X-ray analysis. The oxygen atoms are hatched.

now report on the isolation and characterization of a new macrolide, miyakolide (1),² which is structurally similar to the bryostatins, an important class of anti-cancer compounds.³

Polyfibrospongia sp. (8.4 kg) was collected at the same site off the island of Miyako and processed in the same manner as previously described.¹ The fractions obtained by initial chromatography, which showed TLC spots different from those of the hennoxazoles, were separated by Sephadex LH-20 (CH₂Cl₂/MeOH 1:2). The resulting fractions were repeatedly separated by HPLC (RP-8, MeOH/H₂O 5:1; Si-60, hexane/EtOAc 3:2) to give 97 mg (0.0012%) of miyakolide (1).⁴ Recrystallization (CH₂Cl₂/MeOH) furnished colorless crystals: mp 197–199 °C; [α]_D²⁴ –24° (c 1.05, CHCl₃). The molecular formula C₃₆H₅₄O₁₂ was established by HRFABMS on a fragment ion at *m/z* 661.3606 (M – OH, C₃₆H₅₃O₁₁ requires 661.3624). The presence of four rings in 1 was inferred from the unsaturation requirement of the molecule and from the ¹³C NMR data,⁴ which pointed to a ketone (δ 215.0), two ester carbonyl functions (δ 176.0, 166.5), and two C=C double bonds (δ 154.5, 136.1, 124.9, 116.9).

Analysis of the ¹H, ¹³C, and 2D spectra (H–H and C–H COSY, COLOC) enabled the structures of rings A–D and their substituents to be deduced. All connections, except that between rings B and D for which there are two possibilities, were also established by 2D NMR spectroscopy. Since this ambiguity could not be resolved by the NMR method, recourse was made to X-ray analysis. A suitable crystal was grown from a solution in Et-

(2) The compound was named after the island Miyako where the sponge was collected.

(3) Pettit, G. R.; Gao, F.; Sengupta, D.; Coll, J. C.; Herald, C. L.; Doubek, D. L.; Schmidt, J. M.; Van Camp, J. R.; Rudloe, J. J.; Nieman, R. A. *Tetrahedron* 1991, 47, 3601 and references cited therein.

(4) 1: UV (MeOH) λ_{max} 225 nm (ε 21000); IR (KBr) 3450, 2930, 1705, 1650, 1190, 1150 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 5.74 (1 H, s, H34), 5.18 (ddd, *J* = 12, 5, 5 Hz, H13), 5.15 (1 H, d, *J* = 8.3 Hz, H29), 5.02 (1 H, d, *J* = 2 Hz, C18-OH), 4.48 (1 H, s, C9-OH), 4.13 (1 H, ddd, *J* = 10, 9, 2 Hz, H15), 3.88 (1 H, br d, *J* = 10 Hz, H11), 3.84 (1 H, dd, *J* = 12, 1 Hz, H22), 3.74 (1 H, d, *J* = 13 Hz, H21), 3.63 (3 H, s, OCH₃), 3.54 (1 H, dd, *J* = 11, 11 Hz, H1), 3.51 (1 H, d, *J* = 1 Hz, OH), 3.40 (1 H, dd, *J* = 10, 10 Hz, H23), 2.70 (1 H, q, *J* = 7 Hz, H17), 2.56 (1 H, s, H8), 2.48 (1 H, m, H6), 2.47 (1 H, m, H12), 2.42 (1 H, d, *J* = 13 Hz, H19), 2.34 (1 H, dd, *J* = 13, 12 Hz, H21), 2.09 (1 H, d, *J* = 13 Hz, H19), 2.02 (1 H, br d, *J* = 12 Hz, H4), 1.98 (1 H, m, H10), 1.96 (1 H, m, H5), 1.76 (2 H, m, H24, H5), 1.70 (1 H, m, H10), 1.70 (3 H, s, H31), 1.68 (1 H, m, H14), 1.68 (3 H, s, H32), 1.62 (1 H, m, H25), 1.52 (1 H, m, H14), 1.49 (1 H, m, H2), 1.48 (1 H, m, H25), 1.47 (1 H, m, H4), 1.22 (3 H, d, *J* = 7 Hz, H33), 1.21 (1 H, m, H24), 0.96 (3 H, d, *J* = 7 Hz, H27), 0.92 (3 H, d, *J* = 7 Hz, H28), 0.86 (3 H, d, *J* = 7 Hz, H26); ¹³C NMR (67.5 MHz, CDCl₃) δ 215.0 (C7), 176.0 (C16), 166.5 (C35), 154.5 (C20), 136.1 (C30), 124.9 (C29), 116.9 (C34), 99.4 (C18), 96.1 (C9), 78.9 (C3), 73.6 (C11), 73.6 (C23), 73.4 (C22), 73.3 (C15), 73.2 (C13), 71.2 (C1), 60.4 (C8), 50.9 (OCH₃), 47.4 (C17), 45.6 (C6), 43.9 (C2), 42.9 (C19), 41.1 (C10), 34.3 (C4), 34.3 (C12), 32.9 (C24), 32.3 (C7), 31.7 (C14), 31.6 (C21), 30.5 (C25), 25.6 (C31), 18.3 (C32), 13.7 (C27), 12.5 (C33), 10.0 (C26), 5.6 (C28); LR FABMS *m/z* 678 (M⁺), 677, 661, 307, 289.

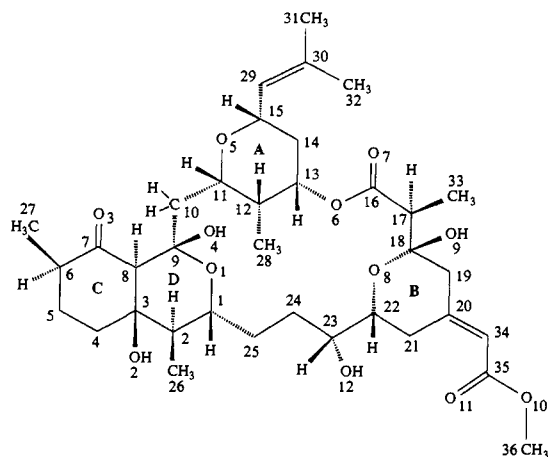


Figure 2. Numbered structure of miyakolide (1).

OAc/CCl₄ and measured on a Nonius CAD4 diffractometer at 220 K. It exhibited an ordered structure, from which the relative configuration of the whole molecule was determined (Figure 1).⁵ The perspective drawing of **1** shows that it is a macrolide possessing three hydroxyran rings, two hemiketal functionalities, and a methyl ethylidenoate substituent attached to a hydroxyran ring (Figure 2). All of the 6-membered rings exist in chair conformations, while rings C and D are trans-fused. The 16-membered ring of the macrolide portion adopts a quinquangular conformation [4*4*4*4*4].^{8,9}

Unlike the bryostatins, which possess potent anti-neoplastic properties, miyakolide only displayed weak in vitro (IC₅₀ 17.5 μg/mL) and in vivo antitumor activity (T/C 127% at 800 μg/kg) against P388 mouse leukemia.¹¹ The disparity in activity may be due to subtle differences between the macrolide portions of the two molecules. Both bryostatin-1 and miyakolide are bound by outer perimeters of 26 atoms. However, the inner perimeters consist of 20 and 16 atoms, respectively. In bryostatin-1, the hydroxyran rings are all cis-substituted at the 2,6-positions. Interestingly, although the corresponding 6-membered rings are similarly cis-substituted in miyakolide, one of the hydroxyrans, ring A, is not incorporated as an ether link in the 16-membered macrocycle since it is joined by the C(11) and C(13) atoms (Figure 2). Consequently, miyakolide may not bind cations so well, which may possibly account for its diminished activity.

Supplementary Material Available: Tables of crystallographic data, including positional parameters, isotropic and anisotropic displacement parameters, bond distances and angles, and dihedral angles (9 pages); table of observed and calculated structure factors (9 pages). Ordering information is given on any current masthead page.

(5) Crystallographic data for **1**: C₃₆H₅₄O₁₂ (C₄H₈O), *M_w* = 678.9/72.0, orthorhombic, *P*2₁2₁2₁, *a* = 12.717 (3), *b* = 15.264 (4), *c* = 20.591 (4) Å, *V* = 3997 (2) Å³, *Z* = 4, *D_c* = 1.25 g cm⁻³, *F*(000) = 1624, μ(Mo Kα) = 0.086 mm⁻¹; *R* = ω*R* = 0.081 (ω = 1) for 2414 observed reflections (*|F_o*| > 4σ(*F_o*)). The structure was solved by direct methods (Multan-87)⁶ and refined by full-matrix least-squares (X-TAL).⁷ All the coordinates of the H atoms were calculated, except those of the three hydroxyl groups which were determined by a difference electron density map.

(6) Main, P.; Fiske, S. J.; Hull, S. E.; Lessinger, L.; Germain, G.; Declercq, J.-P.; Woolfson, M. M. *A System of Computer Programs for the Automatic Solution of Crystal Structures from X-Ray Diffraction Data*; Universities of York and Louvain: England, and Louvain-la-Neuve, Belgium, 1987.

(7) Hall, S. R.; Stewart, J. M., Eds. *XTAL-3.0 User's Manual*; Universities of Western Australia (Nedlands, WA) and Maryland (College Park, MD), 1987.

(8) Bernardinelli, G.; Gerdl, R. *Helv. Chim. Acta* **1982**, *65*, 558.

(9) This notation seems to be more appropriate than that of Dale¹⁰ on account of the presence of four strain-free anti-gauche-anti sequences in the macrocycle.

(10) Dale, J. *Acta Chem. Scand.* **1973**, *27*, 115.

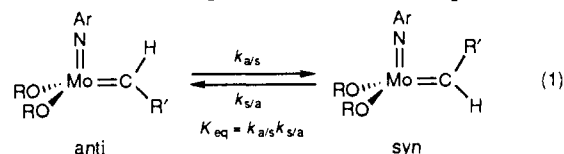
(11) Other in vitro bioassay results are IC₅₀ 17.1 μg/mL (A-549 human lung carcinoma cells) and >20 μg/mL (HT-29 human colon adenocarcinoma cells) and in vivo activity T/C 123% at 400 μg/kg against B-16 melanoma.

Rate of Interconversion of Syn and Anti Rotamers of Mo(CHCMe₂Ph)(NAr)(OR)₂ and Relative Reactivity toward 2,3-Bis(trifluoromethyl)norbornadiene

John H. Oskam and Richard R. Schrock*

Department of Chemistry, 6-331
Massachusetts Institute of Technology
Cambridge, Massachusetts 02139
Received May 5, 1992

Alkylidene complexes of the type M(CHR')(NAr)(OR)₂ (M = Mo or W; R' = alkyl, aryl, etc.; Ar = 2,6-C₆H₃-*i*-Pr₂) are useful initiators for the polymerization of cyclic olefins,¹⁻⁶ in some cases in a living manner¹ and stereoselectively.⁶ Syn and anti rotamers of such species have been observed in solution when OR is a phenoxide ligand, and they have been shown to interconvert with Δ*G*[‡] = 16–18 kcal mol⁻¹ (eq 1).⁷ We have now acquired such



data for molybdenum compounds that contain OR = OCMe₃ (OR_{F0}), OCMe₂(CF₃) (OR_{F3}), OCMe(CF₃)₂ (OR_{F6}), and OC(CF₃)₂(CF₂CF₂CF₃) (OR_{F13}) ligands. We find that the rate of interconversion of rotamers and their reactivities can vary by many orders of magnitude, and that under at least some circumstances the rotamer that is present in vanishingly small quantities is the most reactive toward 2,3-bis(trifluoromethyl)norbornadiene.

An alkylidene H_α resonance for *anti*-Mo(CHCMe₂Ph)(NAr)(OR)₂ compounds (OR = OR_{F3}, OR_{F6}, or OR_{F13}) can be observed upon photolysis at 366 nm in toluene-*d*₈ or THF-*d*₈ at -80 °C for several hours. Photostationary mixtures that contain up to 35% of the anti rotamer usually are obtained after approximately 4 h of photolysis. The anti H_α resonance appears downfield of the syn H_α resonance and has a characteristic^{7,8} relatively large value for ¹J_{CH_α (140–155 Hz; see supplementary material). The H_α resonance for *anti*-Mo(CHCMe₂Ph)(NAr)(O-*t*-Bu)₂ could not be observed in similar experiments.}

The first-order rate of conversion of the anti rotamer to the syn rotamer was determined by ¹H NMR at several appropriate temperatures versus an internal standard (25 runs; see Table V in supplementary material). (Most rate constants so far have been determined over a range of only ~15 °C, so the accuracy of some of the more extreme values found in Table I (calculated at 25 °C employing the Eyring equation) may not be high.) We find that in toluene-*d*₈ the rate of rotamer isomerization slows dramatically as the alkoxide ligands become more electron withdrawing, decreasing by approximately 3 orders of magnitude in the series 2–4. Since *anti*-1 could not be observed upon photolysis of *syn*-1 (in either THF-*d*₈ or toluene-*d*₈) at -80 °C, we can only estimate that the rate of conversion of *anti*-1_{tol} to *syn*-1_{tol} is probably at least 2 orders of magnitude faster than that of *anti*-2_{tol} to *syn*-2_{tol}. Therefore the rate of conversion of anti to syn rotamer decreases approximately 5 orders of magnitude in the series 1_{tol}–4_{tol}.

The H_α resonance in the anti rotamer could be located at room temperature (for OR_{F3}, OR_{F6}, and OR_{F13}) or 0 °C (for OR =

(1) Schrock, R. R. *Acc. Chem. Res.* **1990**, *23*, 158.

(2) Bazan, G. C.; Schrock, R. R.; Cho, H.; Gibson, V. C. *Macromolecules* **1991**, *24*, 4495.

(3) Bazan, G. C.; Oskam, J. H.; Cho, H.-N.; Park, L. Y.; Schrock, R. R. *J. Am. Chem. Soc.* **1991**, *113*, 6899.

(4) Sailor, M. J.; Ginsburg, E. J.; Gorman, C. B.; Kumar, A.; Grubbs, R. H.; Lewis, N. S. *Science* **1990**, *249*, 1146.

(5) Wu, Z.; Wheeler, D. R.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 146.

(6) Bazan, G.; Khosravi, E.; Schrock, R. R.; Feast, W. J.; Gibson, V. C.; O'Regan, M. B.; Thomas, J. K.; Davis, W. M. *J. Am. Chem. Soc.* **1990**, *112*, 8378.

(7) Schrock, R. R.; Crowe, W. E.; Bazan, G. C.; DiMare, M.; O'Regan, M. B.; Schofield, M. H. *Organometallics* **1991**, *10*, 1832.

(8) Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875.