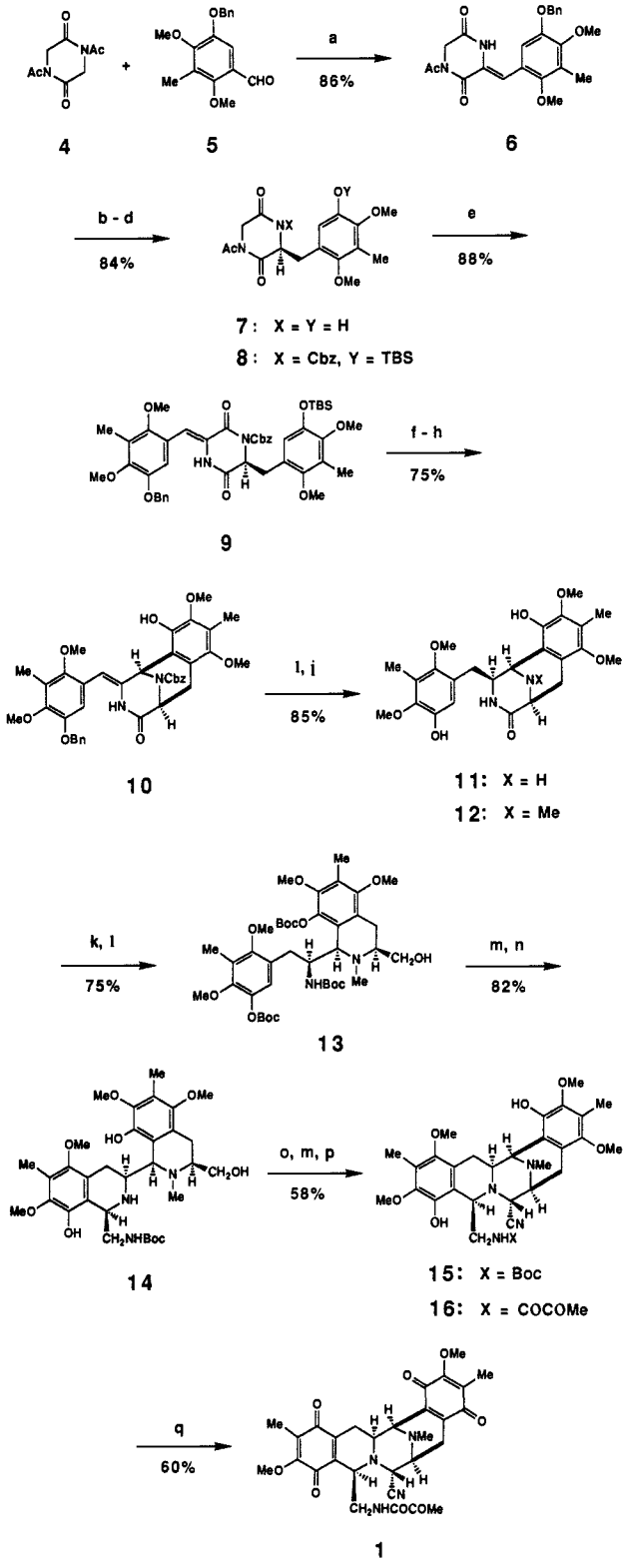
Scheme I[a]



[a] The reagents and reaction conditions were the following: (a) *t*-BuOK/*t*-BuOH, THF, 0 °C. (b) H_2 (1000 psi), 10% Pd/C, EtOAc, 80 °C. (c) TBSCl, Et_3N, CH_2Cl_2, reflux. (d) $PhCH_2OCOCl$, Et_3N, DMAP, CH_2Cl_2, −15 °C. (e) **5**, *t*-BuOK/*t*-BuOH (1 equiv), THF, −78 °C, then DBU, 0 °C. (f) $NaBH_4$, AcOH, EtOH, −25 °C. (g) HCOOH, 23 °C. (h) *n*-Bu_4NF, THF, 23 °C. (i) H_2 (1500 psi), Raney Ni-W2, EtOH, 120 °C. (j) 37% HCHO, $NaBH_3CN$, TFA, MeOH, 23 °C. (k) *t*-Boc_2O, DMAP, DMF, 60 °C. (l) $NaBH_4$, EtOH, 0 °C. (m) TFA, 23 °C. (n) *t*-$BocNHCH_2CHO$, MeOH, 60 °C. (o) $(COCl)_2$ (2.2 equiv), DMSO (4.4 equiv), CH_2Cl_2, −78 °C; Et_3N (8 equiv) warmed to 23 °C then NaCN, MeOH, 23 °C. (p) MeCOCOCl, $NaHCO_3$, CH_2Cl_2, 23 °C. (q) DDQ (3 equiv), acetone−H_2O (10:1), 0 °C.

synthetic saframycin A was identical with an authentic sample in both TLC and spectroscopic properties.

Acknowledgment. This work was supported by the National Institutes of Health (Grant CA28119). We thank Prof. T. Arai of Chiba University for providing a sample of natural saframycin A.

Supplementary Material Available: NMR spectra and a listing of high-resolution mass spectroscopic data of key intermediates (13 pages). Ordering information is given on any current masthead page.

Amphiphilic Carbene Complexes: Both Electrophiles and Nucleophiles Attack the Carbene Carbon of $C_5H_5(CO)_2Re{=}CHR$

Charles P. Casey,* Paul C. Vosejpka, and Fredric R. Askham

Department of Chemistry, University of Wisconsin Madison, Wisconsin 53706

Received November 21, 1989

Metal carbene complexes have been discussed in terms of a dichotomy between electrophilic "Fischer carbene complexes" and nucleophilic "Schrock carbene complexes".[1,2] Metal–carbon double bonds of Fischer carbene complexes such as $(CO)_5W{=}C(OCH_3)C_6H_5$[3] typically have an electron-rich late transition metal in a low oxidation state bonded to an electron-poor carbene carbon (often but not necessarily stabilized by an electron-donor heteroatom). Many of the reactions of Fischer carbene complexes such as replacement of a methoxy group by an amine group are initiated by attack of a nucleophile at the carbene carbon.[4] In contrast, metal–carbon double bonds in Schrock carbene complexes such as $Cp_2ClTa{=}CHR$[5] typically have an electron-poor early transition metal in a high oxidation state bonded to an electron-rich carbene carbon. The reactions of Schrock carbene complexes with substrates such as ketones are initiated by nucleophilic attack of the carbene carbon on the carbonyl carbon of the ketone.[6] We and others[7] have considered it possible to synthesize metal carbene complexes of intermediate reactivity. To our knowledge, the only metal carbene complex that has been shown to have amphiphilic reactivity at the carbene carbon is Roper's $(CO)_2(Ph_3P)_2Ru{=}CF_2$,

(1) (a) Fischer, E. O. *Adv. Organomet. Chem.* **1976**, *14*, 1. (b) Schrock, R. R. *Acc. Chem. Res.* **1979**, *12*, 98. (c) Schrock, R. R. *Science* **1983**, *219*, 13. (d) Gallop, M. A.; Roper, W. R. *Adv. Organomet. Chem.* **1986**, *25*, 121. (e) Dötz, K. H.; Fischer, H.; Hofmann, P.; Kreissl, F. R.; Schubert, U.; Weiss, K. *Transition Metal Carbene Complexes*; Verlag Chemie: Deerfield Beach, FL, 1984. (f) Dötz, K. H. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 587. (g) Wulff, W. D.; Tang, P. C.; Chan, K. S.; McCallum, J. S.; Yang, D. C.; Gilbertson, S. R. *Tetrahedron* **1985**, *41*, 5813. (h) Dötz, K. H.; Popall, M.; Müller, G. *J. Organomet. Chem.* **1987**, *334*, 57. (i) Wulff, W. D. In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI Press Inc.: Greenwich, CT, 1988; Vol. 1.

(2) To emphasize the distinctive character of his complexes (and to conform to IUPAC nomenclature), Schrock refers to his compounds as metal alkylidene complexes.

(3) Fischer, E. O.; Maasböl, A. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 380.

(4) Werner, H.; Fischer, E. O.; Heckl, B.; Kreiter, C. G. *J. Organomet. Chem.* **1971**, *28*, 367.

(5) Schrock R. R.; Messerle, L. W.; Wood, C. D.; Guggenberger, L. J. *J. Am. Chem. Soc.* **1978**, *100*, 3792.

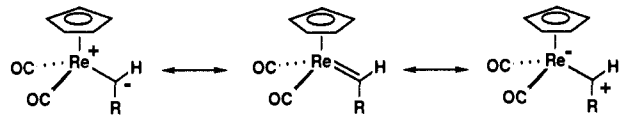
(6) (a) Schrock, R. R. *J. Am. Chem. Soc.* **1976**, *98*, 5399. (b) Hartner, F. W.; Schwartz, J.; Clift, S. M. *J. Am. Chem. Soc.* **1983**, *105*, 640. (c) Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611. (d) Brown-Wensley, K. A.; Buchwald, S. L.; Cannizzo, L.; Clawson, L.; Ho, S.; Meinhardt, D.; Stille, J. R.; Straus, D.; Grubbs, R. H. *Pure Appl. Chem.* **1983**, *55*, 1733. (e) Cannizzo, L. F.; Grubbs, R. H. *J. Org. Chem.* **1985**, *50*, 2316.

(7) (a) Fenske, R. F. In *Organometallic Compounds: Synthesis, Structure, and Theory*; Shapiro, B. L., Ed.; Texas A & M University Press: College Station, TX, 1983; p 305. (b) Hofmann, P. In *Transition Metal Carbene Complexes*; Verlag Chemie: Weinheim, 1983; p 113.

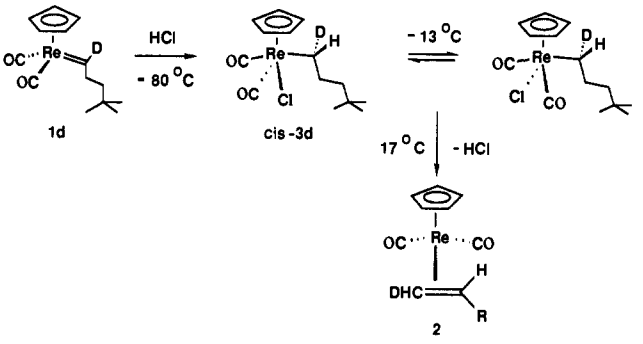
0002-7863/90/1512-3713$02.50/0

which reacts with HCl to produce $(CO)_2(Ph_3P)_2Ru(CF_2H)Cl$ and with CH_3NH_2 to produce $(CO)_2(Ph_3P)_2RuCNCH_3$ although it is inert toward C_6H_5Li.[8,9] A third type of reactivity involving electron transfer and radical intermediates has been observed by Grubbs in the reaction of a $Cp_2Ti{=}CH_2$ reactive intermediate with benzyl chloride.[10]

Here we report that the carbene carbon of $C_5H_5(CO)_2Re{=}CHCH_2CH_2C(CH_3)_3$[11] (**1**) is attacked by both electrophiles and nucleophiles. We believe that the high polarizability of the Re=C double bond of **1** is responsible for the amphiphilic reactivity of **1**. Moreover, we have found that the addition of HCl to **1** is stereospecific and that the resulting alkylrhenium chloride compound is an intermediate in the acid-catalyzed isomerization of the carbene ligand to an alkene ligand.



The rhenium alkylidene complex **1** undergoes acid-catalyzed rearrangement to rhenium alkene complex $C_5H_5(CO)_2Re[\eta^2\text{-}CH_2{=}CHCH_2C(CH_3)_3]$ (**2**).[12] Treatment of **1** with dry HCl in $C_6D_5CD_3$ at room temperature for 2 h led to **2** in 60% NMR yield and 41% isolated yield. In the course of examining the mechanism of this rearrangement, we found that HCl reacts with **1** in $C_6D_5CD_3$ at −80 °C to produce the alkylrhenium chloride compound *cis*-$C_5H_5(CO)_2(Cl)ReCH_2CH_2CH_2C(CH_3)_3$ (**3**),[12] which then loses HCl to produce **2**, upon warming to 17 °C, with a half-life of 70 min. The observation of separate ^1H NMR resonances for the diastereotopic α-CH_2 protons of **3** at δ 2.65 and 2.49 establishes the cis arrangement of the alkyl and chloride ligands.



The reaction of $C_5H_5(CO)_2Re{=}CDCH_2CH_2CMe_3$[13] (**1d**) (82% D at the carbene carbon) with HCl in $C_6D_5CD_3$ at −53 °C led to formation of predominately one diastereomer of *cis*-**3d**, which had a 1.00:0.35 ratio of the δ 2.65:2.49 resonances of the ReCHDR group. This observation requires greater than 85% stereospecificity for the addition of HCl to a single rotamer about the Re=CDR bond.[14] We do not know whether the syn or anti rotamer is the reactive species, and we do not know whether the stereochemistry of the HCl addition is cis or trans, but our current hypothesis is that cis addition occurs to the more stable anti rotamer.[15]

Upon warming to −13 °C for 2 h, the initially formed diastereomer of *cis*-**3d** rearranges to a 1:1 mixture of the two possible diastereomers of *cis*-**3d** without significant loss of deuterium label.[16] Possible mechanisms for isomerization of *cis*-**3d** include (1) intramolecular interconversion of the cis alkyl and chloride ligands by a pseudorotation process[17] and (2) ionization of chloride. Because of the rapid interconversion of the two diastereomers of *cis*-**3d** in $C_6D_5CD_3$, the deuterium label in the rhenium–alkene complex **2** is equally distributed between the cis and trans positions on the terminal carbon of the alkene.[18]

Protonation of the carbene carbon is a characteristic reaction of nucleophilic carbene complexes.[1b,19,20] For example, $[(CH_3)_3CCH_2]_3Ta{=}CHC(CH_3)_3$ reacts with HCl to produce $Ta[CH_2C(CH_3)_3]_4Cl$.[1b] The possibility that **1** reacts with HCl by initial protonation at rhenium cannot be discounted; Dixneuf has observed that $(PMe_2Ph)_2(CO)_2Fe{=}CSC(CO_2Me){=}C(CO_2Me)S$ reacts with CF_3CO_2H to initially produce $(PMe_2Ph)_2(CO)_2(H)Fe{=}CSC(CO_2Me){=}C(CO_2Me)S^+CF_3CO_2^-$, which then rearranges to $(PMe_2Ph)_2(CO_2)Fe(\eta^2\text{-}CH{=}SC(CO_2Me){=}C(CO_2Me)S]^+CF_3CO_2^-$.[20-22] We have not observed any resonances in the hydride region of the ^1H NMR spectrum at −80 °C that would provide evidence for an intermediate metal hydride.

The rhenium carbene complex **1** reacted with nucleophiles and bases in a manner similar to that seen for electrophilic carbene complexes. PMe_3 reacted with **1** rapidly in diethyl ether at −78 °C to produce the zwitterionic complex $C_5H_5(CO)_2ReCH(PMe_3)CH_2CH_2C(CH_3)_3$ (**4**)[12] in 91% yield. Similarly, $LiCuMe_2$ reacted with **1** to produce $Li^+C_5H_5(CO)_2ReCH(CH_3)CH_2CH_2C(CH_3)_3^-$ (**5**).[12]

Electrophilic carbene complexes are mildly acidic.[24] **1** was readily deprotonated by treatment with $KOCMe_3$ in THF at room temperature, which led to the isolation of the vinyl rhenium anion $K^+C_5H_5(CO)_2Re[(E)\text{-}CH{=}CHCH_2C(CH_3)_3]^-$ (**6**).[12] Low-tem-

(8) Clark, G. R.; Hoskins, S. V.; Jones, T. C.; Roper, W. R. *J. Chem. Soc., Chem. Commun.* **1983**, 719.

(9) In a review, Roper has suggested that the reaction with HCl occurs by initial protonation at Ru. Brothers, P. J.; Roper, W. R. *Chem. Rev.* **1988**, *88*, 1293.

(10) Buchwald, S. L.; Anslyn, E. V.; Grubbs, R. H. *J. Am. Chem. Soc.* **1985**, *107*, 1766.

(11) Casey, C. P.; Nagashima, H. *J. Am. Chem. Soc.* **1989**, *111*, 2352.

(12) See supplementary material for full characterization.

(13) $C_5H_5(CO)_2Re{=}CDCH_2CH_2C(CH_3)_3$ (**1d**) was prepared from $(C_5H_5)_2Zr(Cl)COCH_2CH_2C(CH_3)_3$ and $K^+C_5H_5(CO)_2ReD^-$. ^1H NMR integrations indicate 82% deuterium on the carbene carbon.

(14) (a) Kiel, W. A.; Tin, G.-Y.; Constable, A. G.; McCormick, F. B.; Strouse, C. E.; Eisenstein, O.; Gladysz, J. A. *J. Am. Chem. Soc.* **1982**, *104*, 4865. (b) Kiel, W. A.; Tin, G.-Y.; Badner, G. S.; Gladysz, J. A. *J. Am. Chem. Soc.* **1983**, *105*, 4958.

(15) Attempts to observe more than one rotamer of **1** by ^1H NMR at −50 °C were unsuccessful.

(16) When an excess of HCl is added to **1d**, the sum of the integrals for the α protons of **3d** remained constant relative to one of the β protons. If HCl addition were reversible, exchange of deuterium out of **3** would have increased the α integrations relative to another signal.

(17) (a) Faller, J. W.; Anderson, A. S. *J. Am. Chem. Soc.* **1970**, *92*, 5852. (b) Brunner, H. *Top. Curr. Chem.* **1975**, *56*, 67. (c) Henrich, K.; McPartlin, M.; Horton, A. D.; Mays, M. J. *J. Chem. Soc., Dalton Trans.* **1988**, 1083. (d) Flood, T. C.; Rosenberg, E.; Sarhangi, A. *J. Am. Chem. Soc.* **1977**, *99*, 4334. (e) Bailey, N. A.; Dunn, D. A.; Forcraft, C. N.; Harrison, G. R.; Winter, M. J.; Woodward, S. *J. Chem. Soc., Dalton Trans.* **1988**, 1449. (f) Carrē, F.; Colomer, E.; Corrin, R. J. P.; Vioux, A. *Organometallics* **1984**, *3*, 1272.

(18) When the reaction of **1** with CF_3CO_2D was studied in CD_3OD, a slower isomerization to **2** was observed, no intermediate similar to **3** was seen, and deuterium was unequally distributed between the trans (60%) and cis (33%) positions on the terminal alkene carbon. This suggests that scrambling of an intermediate Re alkyl species similar to **3** is slower than stereospecific elimination of CF_3CO_2H from the intermediate.

(19) (a) Hill, A. F.; Roper, W. R.; Waters, J. M.; Wright, A. H. *J. Am. Chem. Soc.* **1983**, *105*, 5939. (b) Clark, G. R.; Roper, W. R.; Wright, A. H. *J. Organomet. Chem.* **1984**, *273*, C17. (c) Klein, D. P.; Bergman, R. G. *J. Am. Chem. Soc.* **1989**, *111*, 3079.

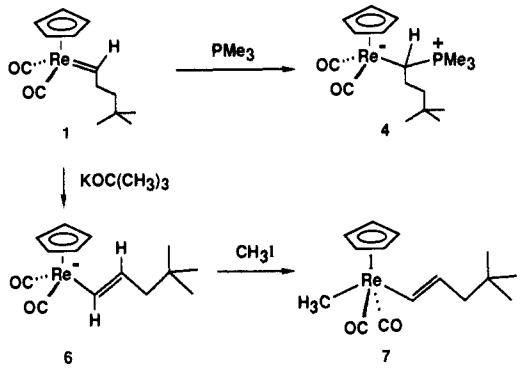
(20) The reaction of **1** with Cp_2ZrHCl which produces $Cp_2Zr(\mu\text{-}CHR)(\mu\text{-}CO)Re(CO)Cp$ has been explained in terms of attack of the electrophilic Zr at the carbene carbon of **1**. Casey, C. P.; Askham, F. R.; Petrovich, L. M. *J. Organomet. Chem.*, in press.

(21) LeBozec, H.; Fillant, J.-L.; Dixneuf, P. H. *J. Chem. Soc., Chem. Commun.* **1986**, 1182.

(22) Osborne, V. A.; Parker, C. A.; Winter, M. J. *J. Chem. Soc., Chem. Commun.* **1986**, 1185.

(23) For electrophilic additions to the carbyne carbon of M≡C complexes, see: (a) Holmes, S. J.; Clark, D. N.; Turner, H. W.; Schrock, R. R. *J. Am. Chem. Soc.* **1982**, *104*, 6322. (b) Green, M.; Orpen, A. G.; Williams, I. D. *J. Chem. Soc., Chem. Commun.* **1982**, 493. (c) Clark, G. R.; Marsen, K.; Roper, W. R.; Wright, L. J. *J. Am. Chem. Soc.* **1980**, *102*, 6570. (d) Kreissl, F. R.; Sieber, W. J.; Wolfgruber, M. *J. Organomet. Chem.* **1984**, *270*, C45. (e) Kreissl, F. R.; Keller, H. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 904. (f) Kreissl, F. R.; Sieber, W. J.; Wolfgruber, M.; Riede, J. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 640.

(24) Casey, C. P.; Brunsvold, W. R. *J. Organomet. Chem.* **1976**, *118*, 309 and references therein.



perature protonation of **6** in CH_3OD led to regeneration of carbene complex **1**, which subsequently underwent acid-catalyzed isomerization to **2** at room temperature. Unlike other anions of electrophilic carbene complexes, which undergo C-alkylation, **6** is alkylated at rhenium.[25] For example, reaction of CH_3I with **6** produces *trans*-$C_5H_5(CO)_2(CH_3)Re[(E)$-$CH{=}CHCH_2C(CH_3)_3]$ (**7**).[12] The tendency of **6** to undergo alkylation at rhenium is related to the stability of $C_5H_5(CO)_2ReR_2$ systems.[26]

In summary, **1** is only the second example of a carbene complex that reacts with both nucleophiles and electrophiles at the carbene carbon atom. Derivatives of **1** are being synthesized to modulate the reactivity of the Re=C multiple bond.

Acknowledgment. Support from the National Science Foundation is gratefully acknowledged. P.C.V. thanks BP America for a fellowship.

Supplementary Material Available: Full spectral characterization of compounds **1-7** (3 pages). Ordering information is given on any current masthead page.

(25) (a) Casey, C. P.; Anderson, R. L. *J. Organomet. Chem.* **1974**, *73*, C28. (b) Hegedus, L. S.; McGuire, M. A.; Schultze, L. M.; Yijun, C.; Anderson, O. P. *J. Am. Chem. Soc.* **1984**, *106*, 2680. (c) Bodner, G. S.; Smith, D. E.; Hatton, W. G.; Heah, P. C.; Georgion, S.; Rheingold, A. L.; Geib, S. J.; Hutchinson, J. P.; Gladysz, J. A. *J. Am. Chem. Soc.* **1987**, *109*, 7688.

(26) (a) Goldberg, K. I.; Bergman, R. G. *J. Am. Chem. Soc.* **1989**, *111*, 1285. (b) Hoyano, J. K.; Graham, W. A. G. *Organometallics* **1982**, *1*, 783.

Crystal and Molecular Structure of Dynemicin A: A Novel 1,5-Diyn-3-ene Antitumor Antibiotic

Masataka Konishi,* Hiroaki Ohkuma, Takashi Tsuno, and Toshikazu Oki

Bristol-Myers Research Institute, Tokyo Research Center 2-9-3, Shimo-Meguro, Meguro-Ku, Tokyo 153, Japan

Gregory D. VanDuyne and Jon Clardy*

Department of Chemistry, Baker Laboratory Cornell University, Ithaca, New York 14853-1301

Received December 18, 1989

The antitumor antibiotics of the esperamicin[1] and calicheamicin[2] families have aroused considerable interest because of their exceptional potency,[3] the structural novelty of their 1,5-diyne-3-ene core, and their intriguing mode of action.[4] In this paper, we report the structure of another 1,5-diyn-3-ene antibiotic: dynemicin A (**1**) from *Micromonospora chersina*.[5] Dynemicin A (**1**) has potent inhibitory activity against a wide range of bacteria and tumor cell lines, a structurally novel fusion of an anthraquinone with a tetracyclo 1,5-diyn-3-ene, and a putative mode of action similar to the esperamicins and calicheamicins.

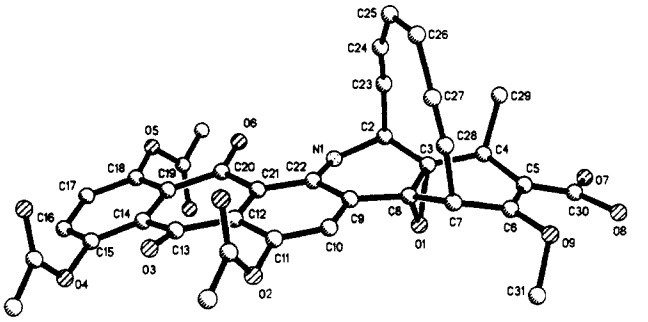
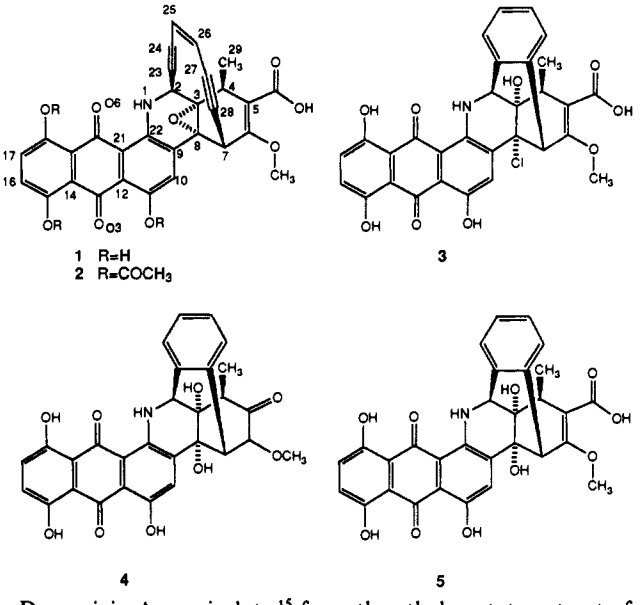


Figure 1. A computer-generated perspective drawing of the final X-ray model of dynemicin A triacetate (**2**). Hydrogens are omitted for clarity, and no absolute configuration is implied.



Dynemicin A was isolated[5] from the ethyl acetate extract of *M. chersina* as a lipophilic violet solid: HRMS *m/z* 538.1132 $(M + H)^+$; $C_{30}H_{19}NO_9$ + H requires 538.1138; mp 208-210 °C dec; $[\alpha]_D$ +270° (*c* 0.01, DMF); IR (KBr) 3420, 3350, 2930, 1660, 1630, 1587, 1480, 1385, 1300, 1280, 1180, and 785 cm^{-1}; UV (MeOH) λ_{max} 239 (ϵ 24 900), 282 (sh), 569 (10 800), and 599 nm (10 100). The UV spectrum and the absorption shifts observed in weakly acid and alkaline solution[6] suggested a 1,4,5,8-tetrahydroxyanthraquinone chromophore. Poor solubility hampered spectral characterization of **1**,[7] but conversion to its triacetate **2** (acetic anhydride-pyridine, 25 °C) provided a more tractable material. The ^{13}C NMR spectrum of **2** revealed a 1,2,4,5,8-pentasubstituted anthraquinone (δ_C 146.9, s, C18; 130.6, d, C17; 131.0, d, C16; 146.4, s, C15; 125.9, s, C14; 180.6, s, C13;

(1) (a) Golik, J.; Clardy, J.; Dubay, G.; Groenewold, G.; Kawaguchi, H.; Konishi, M.; Krishnan, B.; Ohkuma, H.; Saitoh, K.; Doyle, T. W. *J. Am. Chem. Soc.* **1987**, *109*, 3461-3462. (b) Golik, J.; Dubay, G.; Groenewold, G.; Kawaguchi, H.; Konishi, M.; Krishnan, B.; Ohkuma, H.; Saitoh, K.; Doyle, T. W. *J. Am. Chem. Soc.* **1987**, *109*, 3462-3464.

(2) (a) Lee, M. D.; Dunne, T. S.; Siegel, M. M.; Chang, C. C.; Morton, G. O.; Borders, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 3464-3466. (b) Lee, M. D.; Dunne, T. S.; Chang, C. C. Ellestad, G. A.; Siegel, M. M.; Morton, G. O.; McGahren, W. J.; Borders, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 3466-3468.

(3) Maiese, W. M.; Lechevalier, M. P.; Lechevalier, H. A.; Korshalla, J.; Kuck, N.; Fantini, A.; Wildey, M. J.; Thomas, J.; Greenstein, M. *J. Antibiot.* **1989**, *42*, 558-563.

(4) (a) Zein, N.; Sinha, A. M.; McGahren, W. J.; Ellestad, G. A. *Science* **1988**, *240*, 1198-1201. (b) Long, B. H.; Golik, J.; Forenza, S.; Ward, B.; Rehfuss, R.; Dabrowiak, J. C.; Catino, J. J.; Musial, S. T.; Brookshire, K. W.; Doyle, T. W. *Proc. Natl. Acad. Sci. U.S.A.* **1989**, *86*, 2-6.

(5) Konishi, M.; Ohkuma, H.; Matsumoto, K.; Tsuno, T.; Kamei, H.; Miyaki, T.; Oki, T.; Kawaguchi, H.; VanDuyne, G. D.; Clardy, J. *J. Antibiot.* **1989**, *42*, 1449-1452.

(6) UV: λ_{max} in 0.01 N HCl-MeOH 240 (ϵ 26 300), 284 (sh), 572 (10 100), and 596 nm (10 300); in 0.01 N NaOH-MeOH 247 (ϵ 22 600), 278 (5400), 598 (11 500), and 644 nm (11 300). See: Oki, T.; Yoshimoto, A.; Matsuzawa, Y.; Takeuchi, T.; Umezawa, H. *J. Antibiot.* **1980**, *33*, 1331-1340.

(7) ^1H NMR of **1** (400 MHz in DMSO d_6): δ 1.30 (3 H, d, J = 7.3), 3.57 (1 H, q, J = 7.3), 3.82 (3 H, s), 4.89 (1 H, s), 5.08 (1 H, d, J = 4.3), 6.06 and 6.09 (AB quartet, J = 9.8), 7.33 (1 H, d, J = 8.9), 7.38 (1 H, J = 8.9), 8.03 (1 H, s), 9.86 (1 H, d, J = 4.3), 12.15 (1 H, br s), 12.30 (1 H, v br s), 12.70 (1 H, br s), 13.10 (1 H, br s).

0002-7863/90/1512-3715$02.50/0