Optimization of the Julia-Lythgoe procedure[7] used to couple the two fragments **5** and **8** required extensive experimentation (Scheme II). Phenyllithium was found to be the base of choice for deprotonation of **5** selectively at C(17). The use of weaker bases, e.g., LDA and Et_2NLi, and stronger bases, e.g., *tert*- and *n*-butyllithium, resulted in insufficient deprotonation and concomitant formation of arylic anions,[8] respectively. The presence of Na_2HPO_4 in the reductive elimination (the second reaction of step a) served to retain the C(7) acetate in product **12**.[9] After selective acetylation at C(20), affording triol **13** (step b), and conversion of this bis allylic alcohol to the corresponding bis ester (**14**) (step c), the remaining C(3) hydroxyl group was oxidized and the product aldehyde was treated with chiral enolate reagent **7** (step d, reaction ii) to provide as the major product the 3-hydroxy (instead of MOM-protected 3-hydroxy) seco-acid thiol ester **15**. The two reactants, the aldehyde derived from **14** and enolate **7**, constitute a mismatched pair,[5] and in this context, the stereoselectivity of 3:1 observed in this aldol reaction should be appreciated.

Macrolactonization and Functional Group Manipulation. Thiol ester **15** was sensitive toward acid, but selective removal of its acetonide was achieved with the retention of the methyl acetal functionalities to provide **16** as one diastereomer. This compound was the seco-acid derivative originally designed for macrolactonization at the risk that there are three sites [the C(3), C(25), and C(26) hydroxyl groups] available for lactonization. Since all attempts at the direct lactonization of **16** with a thiophilic metal cation[10] failed, **16** was converted to carboxylic acid **17** with temporary protection of the three hydroxyl groups.[11] It was only after numerous experiments that **17** was macrolactonized in a yield of 51% with a combination of DCC (10 equiv), pyridine (100 equiv), and PPTS (10 equiv).[12,13] Spectral inspection of the product **18** indicated that the lactonization site was indeed C(25)[14] and that the C(9) methyl acetal and C(7) acetate were hydrolyzed under the reaction conditions. After macrolactonization there still remained a problem: the C(19) methoxy group[15] resisted acid hydrolysis probably because of the presence of the electron-withdrawing C(20) acetate group in addition to the excessive steric congestion around the C(19) center. Surprisingly, removal of the acetate followed by acidification solved the problem to give **19**.[16] The triacetate **20** derived from **19** was found to be identical with the acetate of **1**[17] isolated from the natural source to establish the correctness of the stereostructures assigned to all the synthetic intermediates. Selective silation of the C(26) hydroxyl group of **19** followed by acetylation and desilation completed the synthesis of **1** and confirmed as identical the two samples of synthetic and natural origin.[18,19]

(7) Julia, M. *Pure Appl. Chem.* **1985**, *57*, 763.
(8) Gais, H.-J.; Ball, W. A.; Bund, J. *Tetrahedron Lett.* **1988**, *29*, 781.
(9) For instance, see: Greck, C.; Grice, P.; Jones, A. B.; Ley, S. V. *Tetrahedron Lett.* **1987**, *28*, 5759.
(10) (a) Masamune, S.; Bates, G. S.; Corcoran, J. W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 585. (b) Masamune, S.; Hirama, M.; Mori, S.; Ali, S. A.; Garvey, D. S. *J. Am. Chem. Soc.* **1981**, *103*, 1568. (c) Park, P.; Broka, C. A.; Johnson, B. F.; Kishi, Y. *Ibid.* **1987**, *109*, 6205.
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(12) Haslam, E. *Tetrahedron* **1980**, *36*, 2409. Boden, E. P.; Keck, G. E. *J. Org. Chem.* **1985**, *50*, 2394. Use of DMAP instead of pyridine gave an intractable mixture.
(13) Model studies were carried out with 3,16-dihydroxyhexadecanoic acid.
(14) An unidentified product isolated in minute quantities could possibly be the C(1)-C(26) lactone. The preference of the C(25) over C(26) was anticipated from molecular models of the seco acid.
(15) In the construction of the C fragment, this methyl acetal was prepared under forcing anhydrous conditions: MeOTMS, TMSOTf (Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357), or $(MeO)_3CH$, $BF_3{\cdot}OEt_2$. Therefore this resistance to hydrolysis was anticipated.
(16) For a similar observation, see, inter alia: Kishi, Y. *J. Am. Chem. Soc.* **1989**, *111*, 7530.
(17) Pettit, G. R.; Herald, C. L.; Kamano, Y.; Gust, D.; Aoyagi, R. *J. Nat. Prod.* **1983**, *46*, 528.
(18) NMR spectra (C_6D_6) of bryostatins and their derivatives are often concentration-dependent probably due to the expected intermolecular hydrogen bonding, and each comparison must be made under identical conditions. See also ref 1b.

Supplementary Material Available: Spectral data for all new compounds, detailed experimental procedures for selected reactions, and details of an X-ray analysis of **5** (24 pages). Ordering information is given on any current masthead page.

(19) We thank Professors G. R. Pettit and Y. Kamano for their generous supply of samples of bryostatin 1 and 7 and helpful suggestions, Dr. K. Furihata of Professor H. Seto's laboratory for the measurement of 500-MHz ^1H NMR spectra of advanced intermediates and final products, and the National Institutes of Health for financial support (CA 48175) of the work carried out at MIT. J.C.R. is an NIH predoctoral trainee (NCI T32-CA 09112).

Metal-Encapsulated Porphyrazines: Synthesis, X-ray Crystal Structure, and Spectroscopy of a Tetratin-*star*-Ni(porphyrazine)S_8 Complex

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We report that octakis(alkylthio)porphyrazines, which we prepared previously,[1] can be converted to porphyrazineoctathiolate, **4**, a new polynucleating ligand that is capable of binding metal ions to the periphery of the macrocyle as well as at the center. We describe the synthesis, structure, and spectroscopic properties of an unprecedented metal-encapsulated porphyrazine complex **6**, $[Sn(t\text{-}Bu)_2]_4$-*star*-Ni(porphyrazine)S_8.

Nickel(II) porphyrazineoctathiolate, **5**, was prepared according to Scheme I. The reaction of **1** with benzyl bromide gave **2**, which was cyclized via template condensation.[1] Compound **4** was debenzylated to give the highly air sensitive sodium salt of *star*-Ni(porphyrazine)S_8 octaanion **5**. Complex **6** was synthesized by reacting **5** with di-*tert*-butyltin dinitrate and was isolated as deep green-black needles.

The X-ray crystal structure of **6** shows that it crystallizes in space group $C2/c$ (No. 15) with four macrocycles and four ordered toluene molecules per unit cell.[2] We expected that each of the four tin atoms complexed by **4** would be chelated to the two adjacent sulfur atoms of a single pyrrole ring, as seen in tetrahedral dialkyltin dithiolene complexes.[3] Instead, each tin atom not only is coordinated to two thiolates of different pyrrole rings but also presents the first example of metal ion coordination by the meso nitrogen of a porphyrazine (Figure 1). In this tridentate S-N-S coordination mode, the average Sn-N and Sn-S distances are 2.311 and 2.588 Å, respectively. The tin atoms have nearly square-pyramidal geometry with one *tert*-butyl group at the apex. The two independent tin atoms are adjacent and lie 0.73 and 0.54 Å above the plane of the planar porphyrazineoctathiolate ligand; the other two tin atoms are related by inversion and lie below this plane, resulting in a quasi-chair conformation. In contrast, both ^1H and ^{119}Sn NMR show all four di-*tert*-butyltin groups to be equivalent in solution at 20 °C,[4] presumably because of rapid conformational interconversion. The two sulfur atoms on a given pyrrole ring are unusually far apart as a result of their coordination to different tin atoms. Typical sulfur-sulfur distances in met-

(1) Schramm, C. J.; Hoffman, B. M. *Inorg. Chem.* **1980**, *19*, 383-385.
(2) Crystallographic data for $6{\cdot}(C_7H_8){\cdot}1.25(CH_2Cl_2)$: monoclinic, $C2/c$ (No. 15), a = 21.911 (3) Å, b = 21.265 (2) Å, c = 14.822 (3) Å, β = 94.44 (2)°, V = 6885 (3) Å^3, Z = 4; CAD-4 diffractometer, T = -120 °C, Mo Kα radiation, data was collected to 2θ = 50°. The structure was solved by direct methods using TEXSAN 4.0. Final full-matrix least-squares refinement of 339 parameters gave $R(F)$ = 0.0288 and $R_w(F)$ = 0.0420 for 4794 absorption-corrected reflections with $F^2 \geq 3\sigma(F^2)$.
(3) Abel, E. W.; Jenkins, C. R. *J. Chem. Soc. A* **1967**, 1344-1347.
(4) ^1H NMR: δ 1.48 ppm singlet ($CDCl_3$-TMS). ^{119}Sn NMR: δ 4.50 singlet ($CDCl_3$, external $SnMe_4$).

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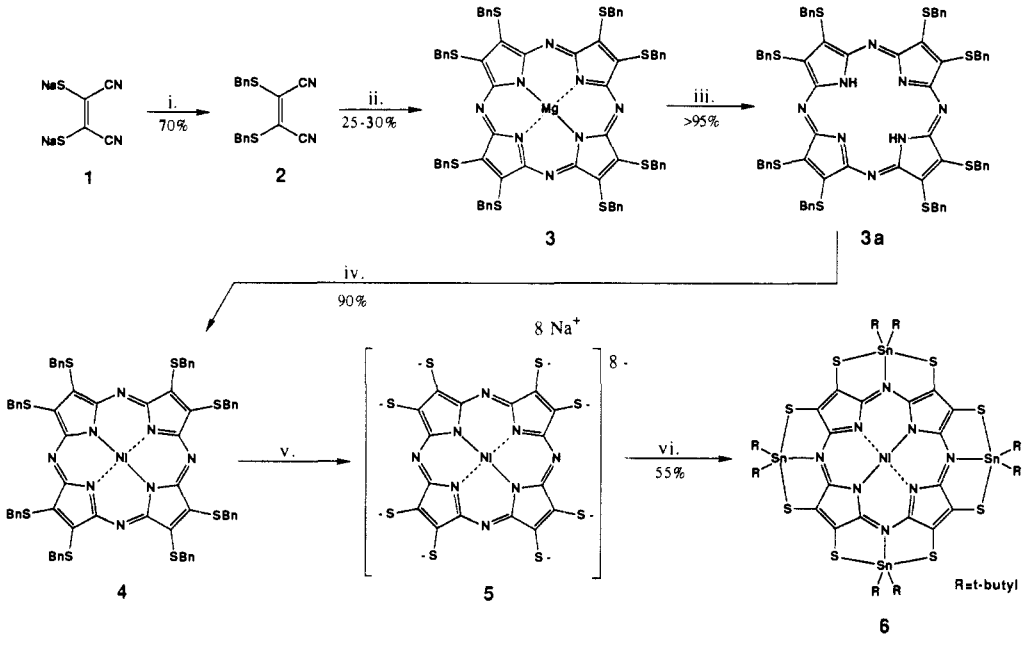
Scheme I[a]



[a] (i) BnBr, MeOH, 0 °C; (ii) $Mg(OPr)_2$, PrOH, 100 °C, 12 h; (iii) CF_3COOH, 25 °C, 16 h; (iv) $Ni(OAc)_2$, PhCl, 4 h; (v) Na (24 equiv), NH_3, THF, -33 °C, not isolated; (vi) $(t\text{-}Bu)_2Sn(NO_3)_2$, MeOH, H_2O, 25 °C, 1 h.

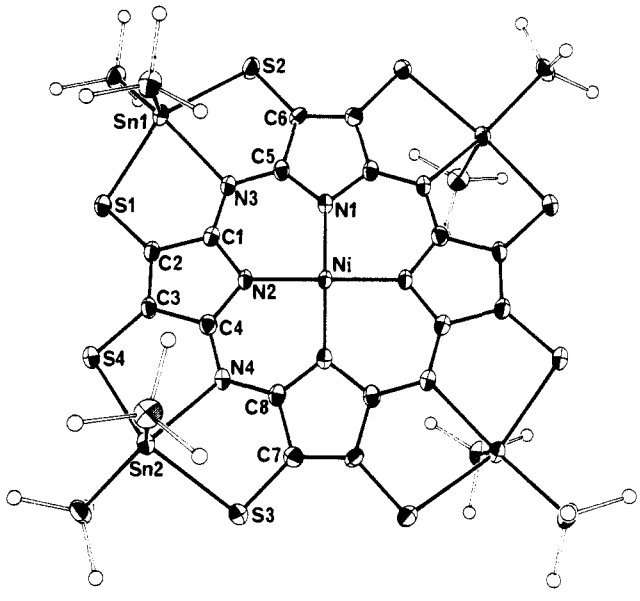


Figure 1. ORTEP diagram of **6** showing 50% probability ellipsoids. For clarity, the hydrogen atoms have been omitted and the methyl carbons have been drawn arbitrarily small.

al–dithiolene complexes[5] are 3.1–3.3 Å whereas in **6** the distance between two sulfurs on a pyrrole is 3.73 Å. Likewise the C=C—S bond angle has increased from about 120° in metal–dithiolene complexes to 133° in complex **5**.

Optical spectroscopy reveals that the coordination of the dialkyltin group to the meso nitrogen exerts a profound effect on the electronic structure of the porphyrazine system. The optical spectrum of **4** is typical for the porphyrazine system. It includes the following: an intense peak (Q) at 672 nm (log ϵ = 4.63) that, by comparison to the spectra of unsubstituted porphyrazine,[6] may be assigned to an $a_2 \rightarrow e$ transition between π MOs of the ring;

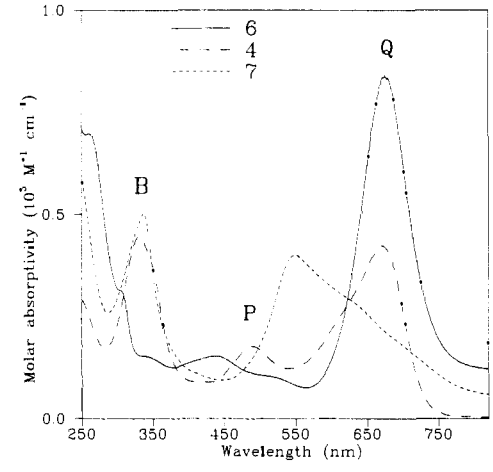


Figure 2. Optical spectra of *star*-Ni(porphyrazine) derivatives in dichloromethane (20 μM).

the Soret (B) band at 330 nm (log ϵ = 4.65) that corresponds to an $a_1 \rightarrow e$ transition of the ring π MOs,[7] in addition there is a less intense peak (P) at 490 (log ϵ = 4.26) (Figure 2). Coordination of the dialkyltin group leaves peak Q unshifted (676 nm) but doubles the absorbance. However, the B (and P) peak is absent in **6**, apparently having shifted to higher energy. This phenomenon is attributed to the stabilization of the porphyrazine a_1 MO, which has a high orbital density on the meso nitrogens, by N → Sn σ-donation and/or Sn($d\pi$)–N($p\pi$) interaction.[8]

Addition of $NBu_4^+X^-$ (X^- = F^-, Cl^-, Br^-, CN^-) to a solution of **6** causes a conspicuous color change (green to purple) that is essentially complete with the addition of eight F^- ions per macrocycle. The resulting solution is air stable, and thus the color change cannot be attributed to the regeneration of **5**, which is air sensitive, but rather to the formation of a new species, **7**, in which eight fluoride ions are coordinated to the four tin atoms of **6**. If the tin atoms of **7** were to retain the tridentate coordination seen

(5) (a) Bousseau, M.; Valade, L.; Legros, J.-P.; Cassoux, P.; Garbauskas, M.; Interrante, L. V. *J. Am. Chem. Soc.* **1966**, *108*, 1908, 1916. (b) Underhill, A. E.; Tonge, J. S.; Clemenson, P. I.; Wang, H.-H.; Williams, J. M. *Mol. Cryst. Liq. Cryst.* **1985**, *125*, 439–446. (c) Alvarez, S.; Vincente, R.; Hoffmann, R. *J. Am. Chem. Soc.* **1985**, *107*, 6253–6277 and references therein.

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in **6**, the addition of two F^- ions per Sn would require that the metal ions become seven-coordinate, which is unlikely.[9] Moreover, the spectrum of **7** shows a normal porphyrazine Soret band B, indicating that the Sn–N bond is broken. Therefore, we tentatively suggest that the addition of F^- causes the tin atoms to undergo a linkage isomerization and move to the bidentate dithiolene site, where each tin atom could easily accommodate two additional F^- ligands in an octahedral geometry. In support of this, the Q peak of **7** is blue-shifted, split, and broadened, indicating a stabilization of the porphyrazine a_2 MO through a stronger perturbation at the pyrrole rings.

It is clear from these observations that peripheral metalation of porphyrinic macrocycles has a profound influence on the properties of these compounds. Additional investigations of these novel *star*-porphyrazines will be published in due course.

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Supplementary Material Available: Tables of fractional coordinates, thermal parameters, and intramolecular bond distances and angles for $6\cdot(C_7H_8)\cdot 1.25(CH_2Cl_2)$ and analytical data (microanalysis, melting point, NMR, optical spectrum, and FAB-MS) on compounds **2–4**, **3a**, and **6** (10 pages). Ordering information is given on any current masthead page.

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Transannular Diels–Alder Route to Systems Related to Dynemicin A

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The enediyne-containing antibiotics[1-4] have been the subject of many recent research efforts owing to their remarkable properties.[5] Reported herein are synthetic pathways that provide facile access to molecules equipped with many of the structural features that are characteristic of the most recently discovered member of this class, dynemicin A (**1**).

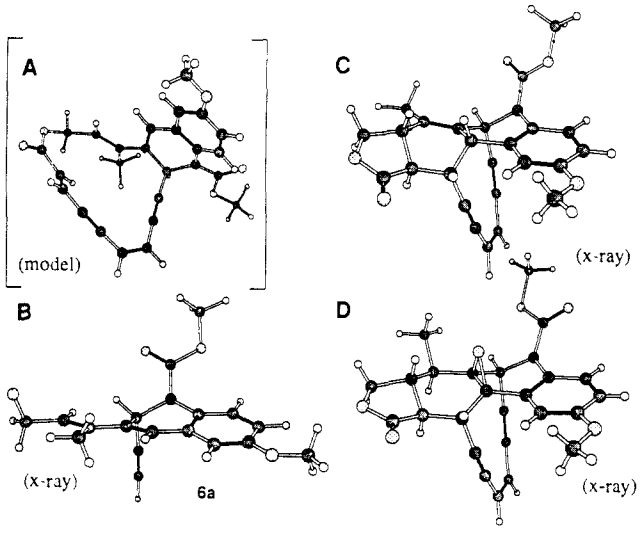
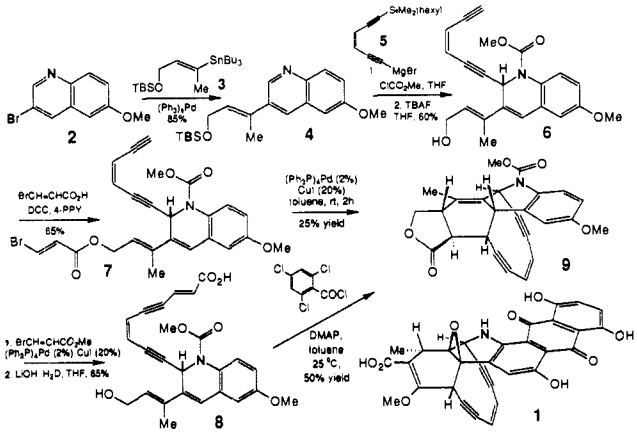


Figure 1. (A) Model of presumed macrolactone intermediate. X-ray structures of (B) trisubstituted quinoline **6a**, (C) polycyclization product **9**, and (D) epoxide **13**.

Scheme I



The bicyclic ring systems of the esperamicin and calicheamicin aglycons have been synthesized by a Diels–Alder based strategy, but not without the use of a pinacol reaction that rearranges the isomeric skeleton that was initially obtained.[6] A new Diels–Alder based strategy that reverses the previously observed regiochemistry and results in a remarkably facile polycyclization route to dynemicin-type molecules is illustrated in Scheme I. A Stille coupling reaction[7] of 3-bromo-6-methoxyquinoline[8] (**2**) and vinylstannane[9] **3** resulted in the formation of the 3-alkenylquinoline **4** (85% yield). Application of the Yamaguchi protocol[10] for the 1,2-addition of acetylide anions to pyridinium salts with quinoline **4** proved highly successful. In situ generation of the quinolinium salt of **4** with methyl chloroformate, addition of the bromomagnesium salt **5**,[11] and subsequent silyl deprotection (TBAF,

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‡ Cornell University.

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

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