teractions with water, its relative inflexibility in linkage conformation may play a role in its particular effectiveness.

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Synthesis of Bryostatin 7

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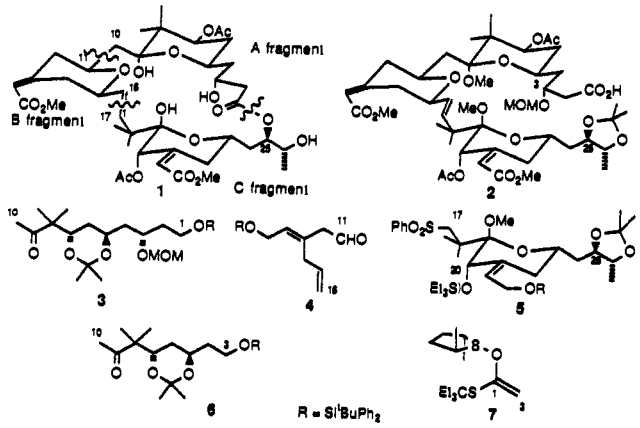
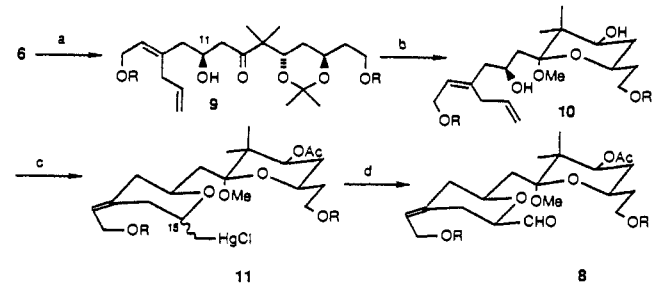
We record herein the synthesis of bryostatin 7 (**1**), a representative member of potent antileukemic agents isolated from the invertebrate filter feeder *Bugula neritina*.[1,2] As previously documented,[3] our earlier efforts toward this objective reached seco-acid derivative **2** corresponding to **1** through the connection of fragments A (**3**), B (**4**), and C (**5**). Unfortunately, deprotection of the C(3)-OMOM group (of **2**), which had been introduced at an early stage and had served well by surviving throughout the course of the synthesis of **2**, turned out to be problematic.[4] This led to a revision of the synthetic route that placed the creation of the C(3) stereogenic center at the end of the seco-acid synthesis. Thus, sequential connection of fragment A′ (**6**) [C(3)–C(10)] [instead of A (**3**) [C(1)–C(10)]], B (**4**), C (**5**), and a C(1)–C(2) unit (**7**) in this order, followed by macrolactonization, completed the synthesis of **1**. All of these fragments were available in our earlier work.[3]

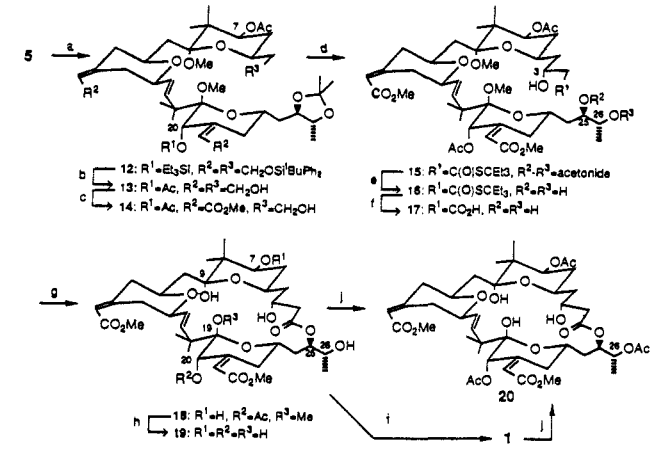


Scheme I[a]



[a] R = SiᵗBuPh₂. (a) (*R,R*)-2,5-Dimethylborolanyl triflate, $^{i}Pr_2EtN$, Et_2O, then **4** (86%, 11*S*:11*R* = 8:1); (b) MeOH, PPTS, $(MeO)_3CH$ (84%); (c) (i) $Hg(OAc)_2$, THF–MeOH, then KCl, (ii) Ac_2O, pyridine, DMAP (93%, two steps, 15*S*:15*R* = 1:1); (d) (i) $NaBH_4$, O_2, DMF–CH_2Cl_2 (77%), (ii) $(COCl)_2$, DMSO, CH_2Cl_2, then Et_3N, −78 °C, (iii) Al_2O_3 (3% H_2O), CH_2Cl_2 (60%, two steps).

Scheme II[a]



[a] (a) (i) PhLi, THF, −78 °C, then **8**, then PhCOCl and DMAP, −78 °C → 25 °C, (ii) Na–Hg, MeOH–EtOAc, Na_2HPO_4, −20 °C (60%, two steps); (b) (i) $^{n}Bu_4NF$, THF, (ii) $^{t}BuMe_2SiCl$, DMF, imidazole, (iii) Ac_2O, pyridine, DMAP, (iv) $^{n}Bu_4NF$, THF (100%, four steps); (c) MnO_2, THF, then MeOH, NaCN, and AcOH (61%); (d) (i) $(COCl)_2$, DMSO, CH_2Cl_2, then Et_3N, −78 °C → 0 °C, (ii) **7**, $^{i}Pr_2EtN$, Et_2O, −100 °C → −78 °C (83%, two steps, 3*R*:3*S* = 3:1); (e) CSA, MeOH (40%); (f) (i) Et_3SiOTf, CH_2Cl_2, lutidine, 0 °C, (ii) $Hg(O_2CCF_3)_2$, Na_2HPO_4, THF, (iii) HF·pyridine, THF, −20 °C (64%, three steps); (g) DCC, PPTS, pyridine, $ClCH_2CH_2Cl$, reflux (51%); (h) K_2CO_3, MeOH, then 5% HCl aqueous workup (54%); (i) (i) $^{t}BuMe_2SiCl$, DMF, Et_3N, DMAP, (ii) Ac_2O, pyridine, (iii) HF–MeCN (40%, two steps); (j) Ac_2O, pyridine.

Synthesis of the A′B Fragment (8). The aldol reaction of **4** with the enolate derived from **6** and (*R,R*)-2,5-dimethylborolanyl triflate proceeded with a stereoselection of 8:1 to provide the desired diastereomer **9** as the major product (Scheme I). The two chiral components, **6** and the triflate, constitute a matched pair.[5] With all the carbons in place, **9** was further modified to fragment A′B (**8**). Construction of the two pyran rings was accomplished by deacetonization (step b) to secure **10** followed by Hg-mediated cyclization (step c). The stereorandomness of the latter process as shown in **11** was not critical as this pyran side chain was equilibrated to become equatorial at the aldehyde stage (see **8** and step d, reaction iii) in the manner already detailed for the synthesis of fragment AB.[3b]

Connection of Fragment A′B, C, and the C(1)–C(2) Unit. The synthesis of fragment C (**5**) has been described elsewhere,[3a] and the characterization of its precursors and an updated synthetic route are provided in the supplementary material. The stereostructure assigned to **5** was confirmed by X-ray analysis of its C(20) hydroxyl compound generated from **5**.[6]

(1) (a) Pettit, G. T.; Herald, C. L.; Doubek, D. L.; Herald, D. L.; Arnold, E.; Clardy, J. *J. Am. Chem. Soc.* **1982**, *104*, 6846. (b) Pettit, G. R.; Leet, J. E.; Herald, C. L.; Kamano, Y.; Boettner, F. E.; Baczynskyj, L.; Nieman, R. A. *J. Org. Chem.* **1987**, *52*, 2854 and references cited therein.

(2) For the physiological activity of bryostatins, see: Wender, P. A.; Cribbs, C. M.; Koehler, K. F.; Sharkey, N. A.; Herald, C. L.; Kamano, Y.; Pettit, G. R.; Blumberg, P. M. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 7197.

(3) (a) Masamune, S. *Pure Appl. Chem.* **1988**, *60*, 1587. (b) Blanchette, M. A.; Malamas, M. S.; Nantz, M. H.; Roberts, J. C.; Somfai, P.; Whritenour, D. C.; Masamune, S.; Kageyama, M.; Tamura, T. *J. Org. Chem.* **1989**, *54*, 2817. (c) Duplantier, A. J.; Nantz, M. H.; Roberts, J. C.; Short, R. P.; Somfai, P.; Masamune, S. *Tetrahedron Lett.* **1989**, *30*, 7357.

(4) Model experiments carried out prior to our selection of MOM for the C(3) hydroxyl group protection showed that a *β*-OMOM *carboxylic acid* could be removed under mild acidic conditions, e.g., acetic acid, under which **2** underwent extensive side reactions.

(5) For a double asymmetric synthesis, see: Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1.

(6) We thank Dr. O. Yamashita and Mr. J. Okada for carrying out this analysis, which is detailed in the supplementary material.

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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.
(11) For the reaction of β-hydroxy carboxylic acid thiol esters, see: (a) Masamune, S.; Hayase, Y.; Chan, W. K.; Sobczak, R. L. *J. Am. Chem. Soc.* **1976**, *98*, 7874. (b) Masamune, S.; Lu, L. D.-L.; Jackson, W. P.; Kaiho, T.; Toyoda, T. *Ibid.* **1982**, *104*, 5523.
(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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