tylstannyl cyanocuprate and acetylene) to cyclohexenone.[6] The intermediate enolate was trapped in situ with triethylsilyl chloride at −78 °C. The enol ether/vinyl stannane **3** can be isolated in 80–85% yield after flash chromatography (silica gel). The attachment of the vinyl sulfone unit in a stereospecific manner was efficiently achieved by a Stille reaction[7] involving *trans*-2-tosylvinylphenyl sulfone[8] **4** and a Pd(II) complex.[9] The resulting dienyl sulfone **5** was produced in yields of 65–70%. After chemoselective cyclopropanation of the enol ether double bond of **5** [ethyl diazoacetate and bis(*N*-benzylsalicylaldiminato)copper(II) catalyst, 65% yield], the stage was set for the key cyclization process. The reaction of **6** with cesium fluoride in refluxing acetonitrile did in fact trigger a facile cyclopropane cleavage and subsequent Michael addition to the vinyl sulfone, in 75–87% yields, in a completely stereoselective manner to install four contiguous chiral centers! This remarkable stereoselectivity is presumably controlled by the cis double bond of the dienyl sulfone and a preferred approach of the enolate to the geometrically accessible vinyl sulfone double bond.

The stereochemical assignments of the asymmetric centers in adduct **1** were confirmed both by high field ^{1}H NMR[5b,10] and by a single-crystal X-ray analysis[11] (Figure 1, see Supplementary Materials for details). The new synthon **1** was readily converted to a known dihydrocompactin relay compound **2**[5b] by stereospecific reduction of the ketone with L-Selectride (63% yield) and subsequent desulfonylation with concomitant ester exchange with sodium amalgam and disodium hydrogen phosphate in dry methanol (75% yield).[12]

In summary, the salient, new features of this convergent synthesis of the dihydrocompactin synthon **1** are (1) a new *cis*-2-stannylvinyl cuprate reagent, (2) the 2-tosylvinyl sulfone coupling, and most importantly (3) the intramolecular cyclization of an ester enolate on a vinyl sulfone in a stereospecific fashion.

Acknowledgment. This research is based upon work supported under an NSF Fellowship to J.K.L. We gratefully acknowledge Dr. William Butler and Myoung Soo Lah of the Chemistry Department of The University of Michigan for the X-ray structure analysis.

Supplementary Material Available: Summary of crystal data, fractional coordinates, thermal parameters, and perspective drawings for compound **1** (9 pages). Ordering information is given on any current masthead page.

(6) For a typical procedure: To a stirred solution of 5.25 mmol of LDA in 5 mL of dry THF was added 5.0 mmol of freshly distilled *n*-Bu_3SnH at −78 °C. After 30 min, the solution of anion was transferred via cannula into a stirred solution of 5.5 mmol of CuCN and 12 mmol of dry LiCl[13] in 20 mL of THF at −45 °C, producing a deep red solution of *n*-$Bu_3SnCuCNLi$. After 30 min, acetylene gas, 6.0 mmol (146 mL at 24 °C) was bubbled in. After stirring 30 min at −45 °C to −30 °C, the greenish brown solution was cooled to −78 °C. Successive additions of 6.0 mmol of Et_3N, 5.0 mmol of Et_3SiCl,[14] and 1.0 mmol of cyclohex-2-en-1-one were carried out. The reaction mixture was allowed to warm slowly to 0 °C over 2 h and was quenched by addition to a rapidly stirred mixture of 50 mL of Et_2O and 20 mL of aqueous NH_4Cl/NH_4OH (4:1). Flash column chromatography of the crude product on silica gel, with 1% Et_3N/hexane eluant followed by 1% Et_3N/1% EtOAc/hexane, gave the desired adduct as the silyl enol ether, 437 mg (83%). To the best of our knowledge, this constitutes the first preparation of this *cis*-2-stannylvinyl cuprate.

(7) See: Scott, W. J.; Crisp, G. T.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 4630) for the analogous reactions of vinyl triflates.

(8) This compound was readily prepared by LDA deprotonation of methylphenyl sulfone in THF at −20 °C, followed by addition of DMF (see: Kozerski, L., et al. *Tetrahedron* **1986**, *42*, 1469) for the analogous reaction with methylphenyl sulfoxide). Treatment of the filtered solid with 1.05 equiv of TsCl in THF gave the *trans*-2-tosylvinyl sulfone, separable from the minor cis isomer by flash chromatography.

(9) We found it convenient to use a minor modification of the catalyst, the use of 2–3 mol% of $PdCl_2(PPh_3)_2$ and 6–10 mol% of CuI. See: Hagiwara, N. *Synthesis* **1980**, 627.

(10) Key 360 MHz ^{1}H NMR data ($CDCl_3$): δ 2.50 (t, J = 11.5 Hz, 1 H) confirmed the trans ring juncture, and 2.86 (dd, J = 11.5, 5.7 Hz, 1 H) confirmed the configuration at the ester and methylene sulfone groups, with an axial and an equatorial proton, respectively.

(11) Compound **1** crystallized in the monoclinic space group $P2_1$, with a = 14.191 (4) Å, b = 20.835 (16) Å, c = 13.110 (4) Å, and β = 91.12 (4)°; four molecules of composition $C_{20}H_{24}O_5S$ formed the asymmetric unit. The structure was solved with direct methods and refined to a R = 0.089 with a final R_w of 0.075.

(12) Trost, B. M.; Arndt, H. C.; Strege, P. E.; Verhoeven, T. R. *Tetrahedron Lett.* **1976**, 3477.

(13) Knochel, P.; Yeh, M. C.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390.

(14) For conjugate additions in the presence of trimethylsilyl chloride, see: (a) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6019. (b) Alexakis, A.; Berlan, J.; Besace, Y. *Tetrahedron Lett.* **1986**, *27*, 1047.

The Effect of Substitution and Stereochemistry on Ion Binding in the Polyether Ionophore Monensin

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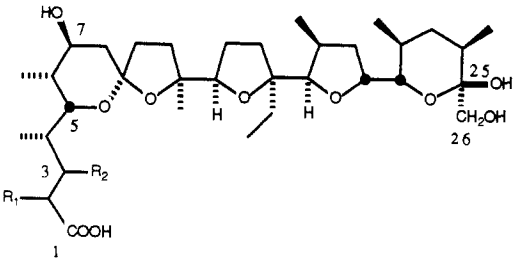
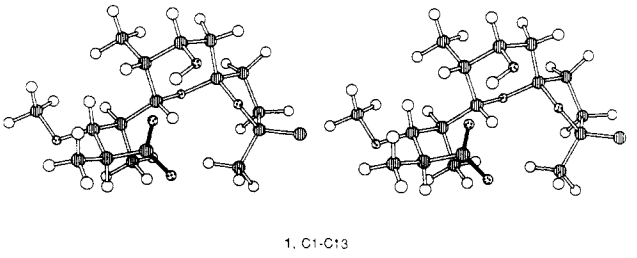
One of the most striking features of the polyether ionophores is their incorporation of specific substitutional and stereochemical arrays which appear to stabilize ion-binding conformations.[1] These conformations in the acyclic segments of the polyethers appear to be rigidified by avoidance of alternative conformers having relatively high-energy +gauche/−gauche (+g/−g) pentane interactions. In monensin[2] (**1**) with its particular substitution and



1, R_1 = β-Me, R_2 = β-OMe
2a, R_1 = H, R_2 = β-iPr
2b, R_1 = H, R_2 = α-iPr
2c, R_1 = H, R_2 = β-Me
2d, R_1 = H, R_2 = H

stereochemical pattern at C2–C7, the avoidance of +g/−g interactions leaves little opportunity for the acyclic C1–C5 segment to adopt conformations other than that found in the crystal structures of monensin and its salts. This conclusion follows from examination of the C1–C13 conformation of monensin shown



1, C1-C13

below in stereo. The reader will note that no rotation about C3–C4, C4–C5, or the C3–OMe is possible without creating new +g/−g interactions and that C2–C3 has at least one +g/−g interaction in all three of its conformations. The C2–C3 conformer shown would appear to be the least strained of the three possibilities since it uniquely places the planar C1 carbon in nonbonded contact with C5, allows formation of stabilizing hydrogen bonds,

(1) Still, W. C.; Cai, D.; Lee, D.; Hauck, P.; Bernardi, A.; Romero, A. *Lectures in Hetero. Chem.* **1987**, *9*, 33. Still, W. C.; Hauck, P.; Kempf, D. *Tetrahedron Lett.* **1987**, *28*, 2817.

(2) Agtarap, A.; Chamberlain, J. W.; Pinkerton, M.; Steinrauf, L. *J. Am. Chem. Soc.* **1968**, *89*, 5737.

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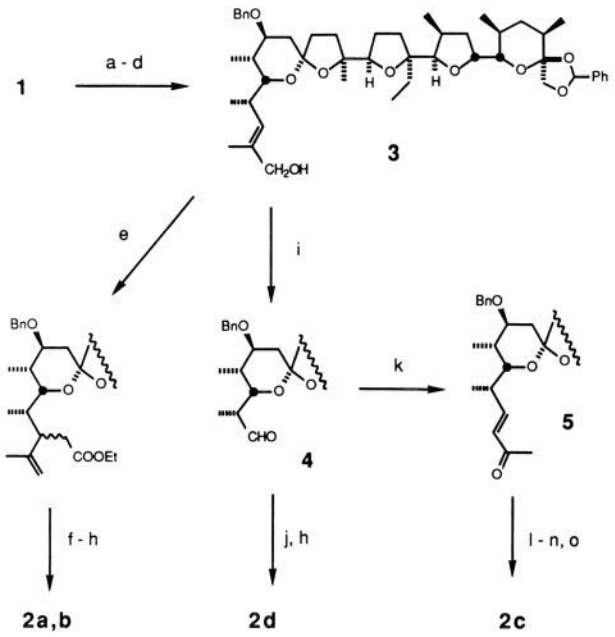
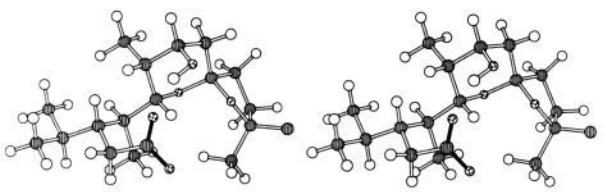
Scheme I[a]



[a] Note: a. PhCHO, $ZnCl_2$; b. Bu_4NOH, MeOH, then MeI; c. BnBr, NaH, THF; d. $LiAlH_4$, THF; e. $(EtO)_3CMe$, EtCOOH, reflux; f. NaOH, H_2O–MeOH–THF; g. silica gel separation; h. H_2, $Pd(OH)_2$/C, EtOAc; i. O_3, MeOH, then Me_2S; j. $Ph_3PCHCOOBn$, C_6H_6, reflux; k. $Ph_3PCHCOCH_3$, C_6H_6, reflux; l. Me_2CuLi, Et_2O; m. Br_2, NaOH, dioxane–H_2O; n. H_2, Pd-black, MeOH; o. $HClO_4/CHCl_3$.

and positions the anionic C1 carboxylate near to the bound metal cation. If such rigidifying features are important in stabilizing the binding conformation and thus enhancing binding, then it should be possible to use them to construct new substitutional and stereochemical derivatives of monensin which would also be effective ionophores. One such compound is a 3-isopropyl derivative (**2a**) whose C1–C13 segment is shown below in stereo. Like

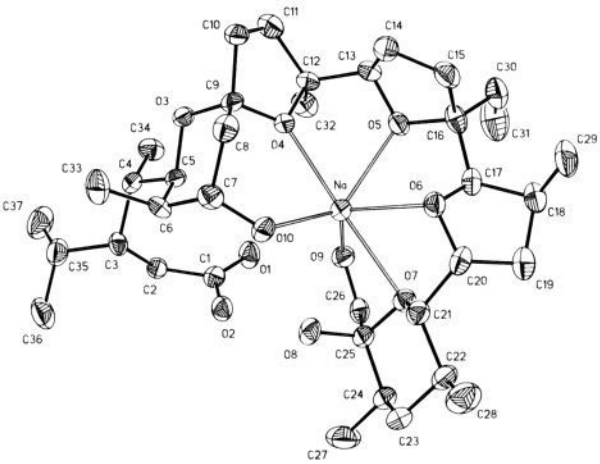


2a, C1-C13

monensin, its C1–C5 chain is highly preorganized for ion binding by the avoidance of +g/−g interactions. In this communication we describe syntheses of **2a–d** and show how the substituents at C2 and C3 effect metal ion binding.

Synthesis of **2a–d** began with monensin A. As shown in Scheme I, monensin was converted to the C25,C26-benzylidene methyl ester, and the 3-OMe was eliminated with simultaneous benzylation of the C7 hydroxyl. Ester reduction then gave the key intermediate **3** (41% overall from monensin). To prepare **2a** and **2b**, we used an ortho ester Claisen followed by saponification and hydrogenation which converted C1, C2, and the C2 methyl to the desired isopropyl substituent. The 3–4:1 diastereomeric product resulting from the Claisen rearrangement was separated by silica gel chromatography and led to **2a** and **2b** (40% and 10%, respectively). Compounds **2c** and **2d** were prepared by ozonolysis of **3** to aldehyde **4** (81%) followed by addition of the desired C1,C2 chain. While preparation of **2d** was straightforward (70% from **4**), we were unable to obtain **2c** by the obvious 1,4-addition of methyl to the intermediate α,β-unsaturated ester. We therefore turned to the corresponding methyl ketone **5** which smoothly reacted with lithium dimethyl cuprate with ≥20:1 stereoselectivity. The resulting saturated methyl ketone was then oxidized to the desired acid with a bromoform reaction. Hydrogenolysis gave **2c** (44% from **4**).

Compounds **2a** and **2c** crystallized from aqueous MeOH and were subjected to X-ray crystallographic analysis.[3] Although **2a** and **2c** had been prepared in the form of the free acids, their chromatography apparently resulted in extraction of sodium from the silica gel used. The crystal structures we obtained were thus of the sodium complexes and showed the expected natural C1–C5 conformation. The structure of **2a** (below) had one unexpected feature. The C3 isopropyl has rotated from the strain-free conformation shown above to one having a +g/−g interaction between an isopropyl methyl (C37) and the C4 substituent (C34) at an energetic cost of 1.4 kcal/mol according to gas-phase AMBER[4] molecular mechanics. Crystal packing forces appear responsible for the orientation. In the crystallographic unit cell of **2a**, the C3-isopropyl is closely packed against adjacent molecules, and alternative conformations appear to create serious intermolecular nonbonded interactions. The presence of this novel structural feature supports the suggestion[1] that acyclic +g/−g interactions are substantially less strained than they are in related diaxial-1,3-dimethylcyclohexanes.



The association energies of monensin (Bu_4N salt) and **2a–d** were measured by the fluorescence method of Haynes[5] by using thallium(I) perchlorate in methanol. The sodium binding energies were measured as differences between thallium and sodium by titrating thallium(I) with the sodium salt. The results are summarized in Table I. As anticipated by the above discussion, **2a** gives binding energies with metal ions which are similar to those found with natural monensin. The binding trends observed with thallium(I) are also seen with sodium. Compounds **2c** and **2d** have sequentially fewer conformational restraints and show corresponding reductions in binding energy. Finally, **2b**, the epimer of **2a**, shows still further reduction in ion affinity as expected from its destabilization of the natural binding conformation. While the expected changes in binding are thus found, it is clear that structures having poorly organized C1–C5 chains (e.g., **2d**) still bind cations reasonably well. Even neutral methyl monensin with its partially disrupted C1 to C25,C26 hydrogen bonding network still binds thallium(I) with an association constant of >100.

Thus substitution and stereochemistry have predictable effects on binding which appear to follow from simple conformational considerations. The observation that the isopropyl derivative **2a** and monensin have similar binding energies for metal ions suggests that conformational preorganization is more important to binding

(3) Chang, M. Columbia University, to be published elsewhere.

(4) United atom monensin sodium calculation using the MacroModel V2.0 AMBER force field. Parameters: Weiner, S. J.; Kollman, P. A.; Case, D. A.; Singh, U. C.; Chio, C.; Alagona, G.; Profeta, S.; Weiner, P. *J. Am. Chem. Soc.* **1984**, *106*, 765. Wipff, G.; Weiner, P.; Kollman, P. *J. Am. Chem. Soc.* **1982**, *104*, 3249.

(5) Cornelius, G.; Gartner, W.; Haynes, D. H. *Biochemistry* **1974**, *13*, 3052.

Table I. Association Energies (kcal/mol) of Monensin and Derivatives for Metal Ions in Methanol at 20 °C

compd	thallium(I)	sodium
1	−6.5 (±0.5), −6.0[5]	−8.1 (±0.8), −7.0[5], −8.5[6]
2a	−6.3 (±0.4)	−7.9 (±0.7)
2b	−4.6 (±0.2)	−6.3 (±0.5)
2c	−6.0 (±0.4)	−7.5 (±0.6)
2d	−5.3 (±0.3)	
1 methyl ester	−3.2 (±0.2)	

than any specific substituent or stereochemical array. The preorganization of the C2–C3 and C3–C4 bonds appears to contribute ~1 kcal/mol to binding (**1** or **2a** versus **2d**); however, conformational restraints which disfavor the native binding conformation can give larger reductions in binding energy (**1** or **2a** versus **2b**). It should also be noted that major modifications to the polyether structure can be made without elimination of ionophoric properties. These results are compatible with the view that the ion binding properties of the polyethers result from an accumulation of smaller effects which depend upon the properties of the component substructures. Finally, these molecules illustrate that the avoidance of +g/−g interactions can create an effective mechanism for an acyclic conformational lock and control the geometry of otherwise flexible structures.[7]

(6) Cox, B. G.; van Truong, N.; Rzeszotarska, J.; Schneider, H. *J. Chem. Soc., Faraday Trans. 1* **1984**, *80*, 3275.

(7) This work was supported by NIH Grant HL25634 and an SERC/NATO postdoctoral fellowship to P.W.S.

Patellazole C: A Novel Cytotoxic Macrolide from *Lissoclinum patella*

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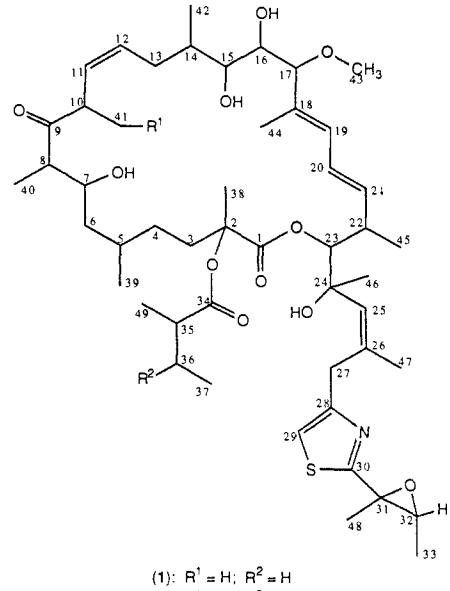
The didemnid tunicate *Lissoclinum patella* collected in Palau has previously been shown to produce a family of unique, cytotoxic cyclic peptides, all containing thiazole amino acids.[2] In contrast, we now report that *L. patella* from the Fiji Islands produces a new family of novel thiazole-containing polyketide metabolites, the patellazoles A–C (**1–3**).[3] The patellazoles were potent cytotoxins in the NCI human cell line protocol with mean IC_{50}'s of 10^{-3}–10^{-6} μg/mL and antifungal against *Candida albicans*. Solvent partition of a MeOH extract of 220 g of freeze dried and pulverized *L. patella* resulted in concentration of activity in the CCl_4 fraction. Gravity column chromatography of this fraction on a silica gel 62 bed followed by successive RP and silica gel HPLC afforded 97 mg of **1**, 143 mg of **2**, and 313 mg of **3**. We now wish to report the structure determination of patellazole C (**3**) (spectral data and assignments for patellazoles A and B are provided in the Supplementary Material).

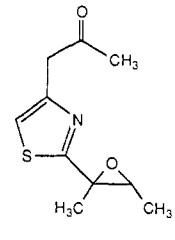
Patellazole C (**3**): $[\alpha]_D$ −100° (*c* 1.06, CH_2Cl_2); UV (MeOH) λ_{max} 241 nm (ε 26 000); IR (neat) ν_{max} 3474, 1728, 1708 cm^{-1} was



(1): R^1 = H; R^2 = H
(2) R^1 = H, R^2 = OH
(3) R^1 = OH; R^2 = OH

assigned molecular formula $C_{49}H_{77}NO_{13}S$ by FABMS mass measurement of the MH^+ ion (920.5179; requires 920.5197). All 49 carbons were visible in the ^{13}C NMR spectrum (Table I), and DEPT[4] experiments established the presence of 71 carbon bound protons (13 methyls, 6 methylenes, and 20 methines); D_2O exchange FABMS and ^1H NMR experiments indicated the presence of six active protons.

A double quantum filtered phase sensitive COSY[5] and a ^1H–^{13}C chemical shift correlation experiment[6] established all one bond ^1H–^{13}C connectivities and partial structures representing C3–C8, C10–C15, C16–C17, C18–C23, C25–C26, C32–C33, and C35–C37. The presence and position of an epoxy thiazole was indicated by NMR data (Table I) which compared favorably with 2-*tert*-butyl-4-methylthiazole.[7] The J_{CH} of 186.7 Hz for C29 is consistent with published data for thiazoles.[7] Similarly, the J_{CH} of 172.6 Hz for C32 is indicative of a small ring heterocycle. These assignments were confirmed by treatment of patellazole C with O_3 in CH_2Cl_2 followed by a reductive workup to give thiazole **4**.[8] These partial structures plus three carbonyls account for all sp^2 atoms indicating the remaining unsaturation must be a ring.



(4)

The connection of partial structures in **3** was established by a combination of INAPT,[9] COLOC,[10] and 2D INADEQUATE[11]

[†] Department of Medicinal Chemistry.
[‡] Department of Chemistry.

(1) Alfred P. Sloan Foundation Fellow, 1985–1989. NIH Career Development Awardee, 1987–1992.

(2) Sesin, D. F.; Gaskell, S. J.; Ireland, C. M. *Bull. Soc. Chim. Belg.* **1986**, *95*, 853–67, plus references therein.

(3) The tunicate was identified as *Lissoclinum patella* (Gottschatt, 1898) by Dr. Francoise Monniot, Museum National d'Histoire Naturelle Paris, France.

(4) Doddrell, D. M.; Pegg, D. T.; Bendall, M. R. *J. Magn. Reson.* **1982**, *48*, 323.

(5) (a) Rance, M.; Sorenson, O. W.; Bodenhausen, G.; Wagner, G.; Ernst, R. R.; Wuthrich, K. *Biochem. Biophys. Res. Commun.* **1983**, *117*, 479. (b) Piantini, U.; Sorenson, O. W.; Ernst, R. R. *J. Am. Chem. Soc.* **1982**, *104*, 6800.

(6) Bax, A.; Morris, G. A. *J. Magn. Reson.* **1981**, *42*, 501.

(7) (a) Babadjamian, A.; Metzger, J. *Bull. Soc. Chim. Fr.* **1968**, 4878. (b) Garnier, R.; Faure, R.; Babadjamian, A.; Vincent, E. J. *Bull. Soc. Chim. Fr.* **1972**, 1040: UV (MeOH) λ_{max} 246.3 nm (ε 4390); ^1H NMR (CCl_4) δ 6.52 (s, H5); ^{13}C (CCl_4) δ 178.9 (s, C2), 151.5 (s, C4), 111.4 (d, J_{CH} = 185.5 Hz, C5).

(8) UV (MeOH) λ_{max} 251 nm (ε 4200); ^1H NMR (C_6D_6) δ 6.46 (s, 1 H), 3.42 (dd, 2 H, *J* = 16.1 Hz), 2.82 (q, 1 H, *J* = 5.4 Hz), 1.73 (s, 3 H), 1.63 (s, 3 H), 0.88 (d, 3 H, *J* = 5.4 Hz); HREIMS, $C_{10}H_{13}NOS$ (obsd 211.0675, req. 211.0667).

(9) Bax, A. *J. Magn. Reson.* **1984**, *57*, 314.

0002-7863/88/1510-7919$01.50/0