

All Natural: The Renaissance of Natural Products Chemistry

Historically, natural products have been drivers in the evolution of organic chemistry; “engines of its development and as links to the domain of biology”, as E. J. Corey put it.¹ The central importance of natural products in organic chemistry can be seen in the development of synthetic methodology, refinements of frontier orbital theory, biochemistry of primary and secondary metabolism, astounding breakthroughs in drug development and, more recently, advances in chemical biology. More than 40% of today’s prescription drugs, and even more of anticancer agents, can trace their origins or underlying synthetic design principles to the discovery of a natural product.² The preeminence of organic chemistry, the maturation of allied scientific fields, not to mention more than a few Nobel prizes, were enabled by natural products. Without natural products, the study of conformational analysis,³ developments in circular dichroism (CD),⁴ nuclear magnetic resonance (NMR),⁵ mass spectrometry (MS),⁶ “the art of organic synthesis”,⁷ and of course, logical frameworks for total synthesis of natural products of high molecular complexity⁸ may have followed very different paths.

Most would agree that the legacy of natural products is decorated with a substantive, significant, and colorful history, but in recent times a quiet renaissance in natural products has been underway. This new wave of accomplishments is inspired and propelled by contemporary developments in the methodology of isolation–purification, structure elucidation, high-throughput targeted screening, molecular genetic analysis, and even computational chemistry. The synergism of these progressive scientific endeavors has elevated the profile and practical significance of natural products to society in our modern age.

Natural products remain an important source of therapeutic drug leads and continue to inspire new approaches to problems in organic chemistry. An exciting contemporary field of endeavor is development of therapeutics from marine natural products.⁹ To date, three marine natural products have been approved as prescription drugs: the analgesic peptide ω -conotoxin MVIIa (ziconotide, Prialt) from the venom of the textile cone snail *Conus magus* and two anticancer drugs—the alkaloid ET-743 (trabectedin, Yondelis) from the Caribbean ascidian *Ecteinascidia turbinata* and the antibody–drug conjugate (ADC) brentuximab-vedotin (Adcetris), based on the highly cytotoxic linear peptide dolastatin-10 from *Dolabella auricularia*.¹⁰ The anticancer drug eribulin mesylate (Halaven),¹¹ approved in 2010 and today manufactured by multistep synthesis, is a truncated analogue of halichondrin B, a macrolide first isolated almost 30 years ago by Hirata and Uemura from the sponge *Halichondria okadai*¹² and synthesized by Kishi and co-workers.¹³ Other marine natural products or their synthetic analogues have also been approved or are in late-phase clinical trials.^{5b}

Past ACS Virtual Issues on the subject of natural products—edited by William Roush (“Total Synthesis of Biologically Active Natural Products”, <http://pubs.acs.org/JACSbeta/jvi/issue1.html>)¹⁴ and Karl Hale (“Terpenoid- and Shikimate-

Derived Natural Product Total Synthesis”, http://pubs.acs.org/page/vi/2013/total_synthesis.html)¹⁵—nicely showcased applications of contemporary synthetic chemistry to the total synthesis of natural products. In this Virtual Issue, I have selected 22 articles published between 2012 and 2014 in *Organic Letters*, *The Journal of Organic Chemistry*, and *Journal of the American Chemical Society* that serve to illustrate the dimensions of discovery, structure elucidation, biological activity, and modernity of natural products chemistry. These include structure elucidation facilitated by computer-assisted applications, the sequencing of the entire genome of a newly discovered microbe to explain a decades-old chemical mystery, and new alkaloid structures of surprising complexity that will galvanize efforts in total synthesis and challenge the creativity of synthetic organic chemists. These fine papers reveal how the science of natural products is now networked to new developments in allied fields. Here, we read how molecular genomics is applied to discovery and decoding the biosynthesis of natural products. Computational chemistry, coupled with chiroptical methods, lends power and reliability to stereochemical assignments. Advanced NMR methods bring tools of unprecedented sensitivity and surgical precision to structure elucidation. Alkaloids of astonishing molecular architecture continue to be found; some as promising leads for treatment of the global scourge of malaria and other diseases. Even repurposing inexpensive compounds from the “pool” of chiral feedstocks for complex synthesis is demonstrated—and it is “all natural”.

Natural products are important sources for leads in drug discovery. An outstanding example is the discovery, by Cuevas and co-workers, of PM050489 (**1**, Figure 1) and PM060184 (**2**) – two likely products of nonribosomal peptide synthase–polyketide synthase genes (NRPS-PKS) – from the Madagascar marine sponge, *Lithoplocamia lithistoides*.¹⁶ The two analogues, differing by a single Cl atom, bear some resemblance to the well-known antimetabolite (+)-discodermolide (+)-**3** from *Discodermia dissoluta*.¹⁷ Notably, they exhibit subnanomolar activity against a panel of cultured cancer cell lines through a tubulin-binding mechanism¹⁸ that is distinct from that of (+)-**3**. The “once-in-a-decade” finding of compounds like **1** and **2** is made more remarkable by the early completion of several milestones: total synthesis and advancement of **2** into phase-I clinical trials¹⁹ in humans as an anticancer agent.

Historically, antibacterial natural products were first obtained from bacteria at the beginning of a time often called the ‘Golden Age of antibiotics’. In a paper published in *Organic Letters*, MacMillan and co-workers describe a new alkaloid, hunanamycin (**4**), from a cultured marine bacterium *Bacillus hunanensis* SNA-048 from the Bahamas that exhibits selective activity against the pathogen *Salmonella enterica*.²⁰ Compound **4** resembles a bacterial degradation product of riboflavin. Interestingly, the only susceptible bacterium among the four

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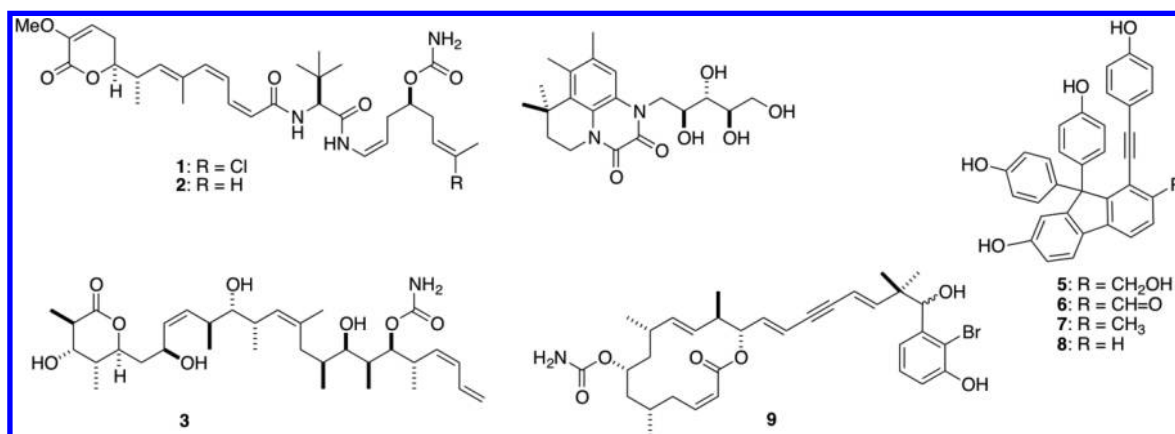


Figure 1. Polyketide and other natural products from marine sponges, bacteria, and plants: PM050489 (1) and PM060184 (2) from the sponge *Lithoplocamia lithistoides*,¹⁶ (+)-discodermolide from *Discodermia dissoluta*,¹⁷ hunanamycin (4) from *Bacillus hunanensis*,²⁰ selaginpulvilins A–D (5–8) from *Selaginella pulvinata*,²¹ and callyspongiolide (9) from *Callyspongia* sp.²²

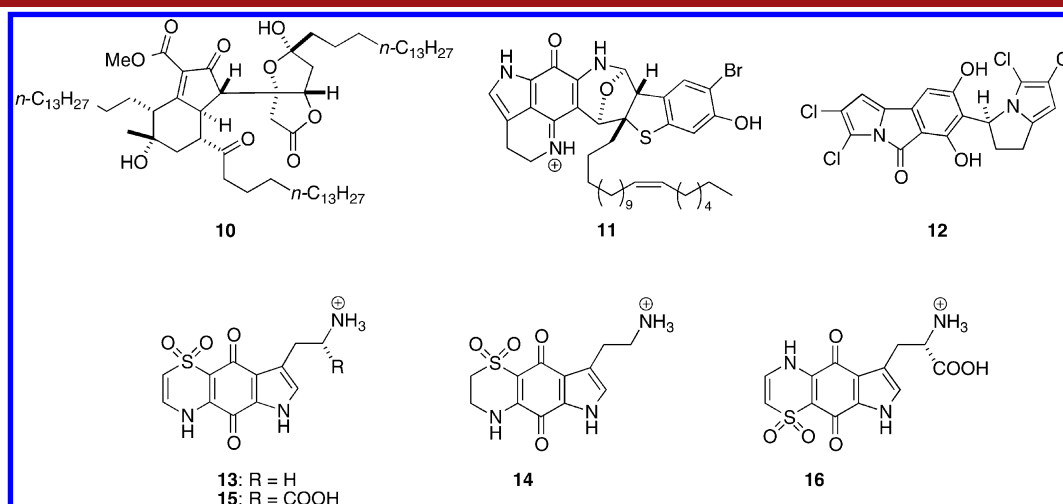


Figure 2. Manzamenone O (10),²³ atkamine (11),²⁵ chlorizidine (12),²⁶ and thiaplakortones A–D (13–16).²⁸

tested against the natural product lacks the riboflavin transporter.

The natural products of Chinese traditional medicines have become the subject of intense study in the People's Republic of China and elsewhere. Selaginpulvilins A–D (5–8) are potent new phosphodiesterase 4 inhibitors from the terrestrial plant *Selaginella pulvinata*, a traditional Chinese herbal.²¹ Yin and co-workers determined the structures, which contain a rare diphenyl-9H-fluorene core, from integrated analysis of MS and NMR data. Final completion of the structure of 5 was achieved by X-ray crystallography.

Lai, Proksch, and co-workers describe a new polyketide derivative, callyspongiolide (9), from the sponge *Callyspongia* sp. collected in Indonesia.²² Callyspongiolide is a rare polyketide containing a carbamate moiety and terminated with a bromophenol ring, but the structure is incomplete. The configuration of the benzylic alcohol stereocenter in 9 and the interrelationship of all stereocenters in the molecule remain to be defined, making the compound a potential target for total synthesis and structural assignment. Callyspongiolide induces caspase-independent apoptosis in Jurkat J16T and Ramos B lymphocytes.²²

Alkaloids and oxa-heterocycles with unusual frameworks continue to be described from marine invertebrates. The complexity of structures derived from highly oxidized, relatively

simple long-chain fatty acids or “sphingoid” bases often belies their simple biosynthetic origins. The remarkable polyheterocyclic core of manzamenone O (10, Figure 2) from the Okinawan sponge *Plakortis* sp.,²³ an octahydroindenone ring system, appears to arise from an unusual biosynthetic confluence of three independently modified fatty acid chains. Kobayashi and co-workers provide detailed spectroscopic evidence for the structure of 10, but the absolute configuration remains to be assigned. Manzamenone O (10) exhibits in vitro antibacterial and antifungal activity against several strains of microbes.

The pyrroloiminoquinones, such as the discorhabdins, are familiar alkaloids from marine sponges.²⁴ The newly described atkamine (11), from the deep-water *Latrunculia* sp., collected in the Aleutian Islands, elevates the level of constitutional and stereochemical complexity of this family. Hamann and Zou²⁵ elucidated the structure of the title compound by integrated 1D and 2D NMR spectroscopic data, measurement of the electronic circular dichroism spectrum (ECD), and assignment of the absolute configuration by computation of the ECD spectrum using time-dependent density functional theory (TD-DFT). No significant activity is reported, but this ornate alkaloid with an unprecedented 5H-pyrrolo[2,1-a]isoindol-5-one moiety is a challenging target for synthesis.

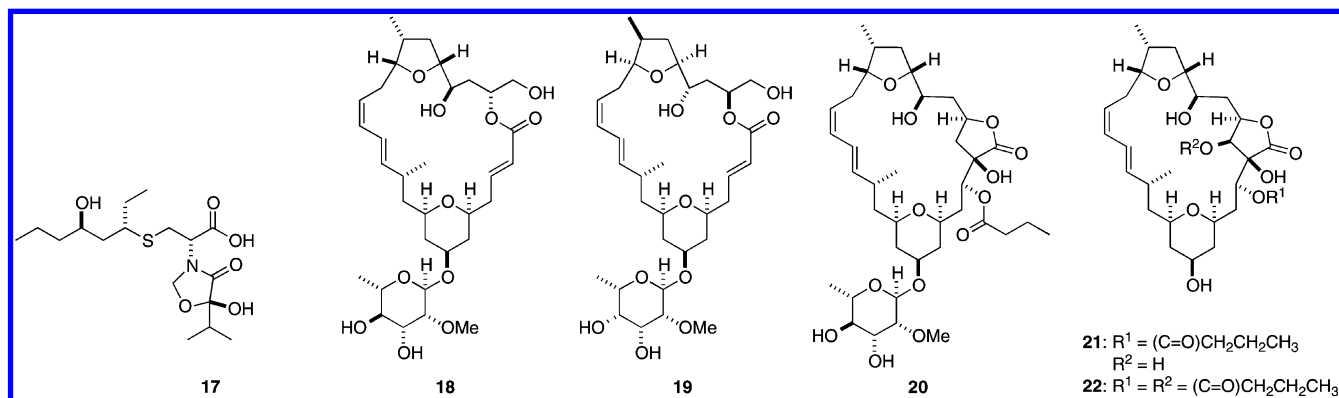


Figure 3. Structures of theleпамиде (17),³¹ the originally assigned structure of mandelalide A (18)³² and its corrected structure (19),³⁵ and mandelalides B–D (20–22).

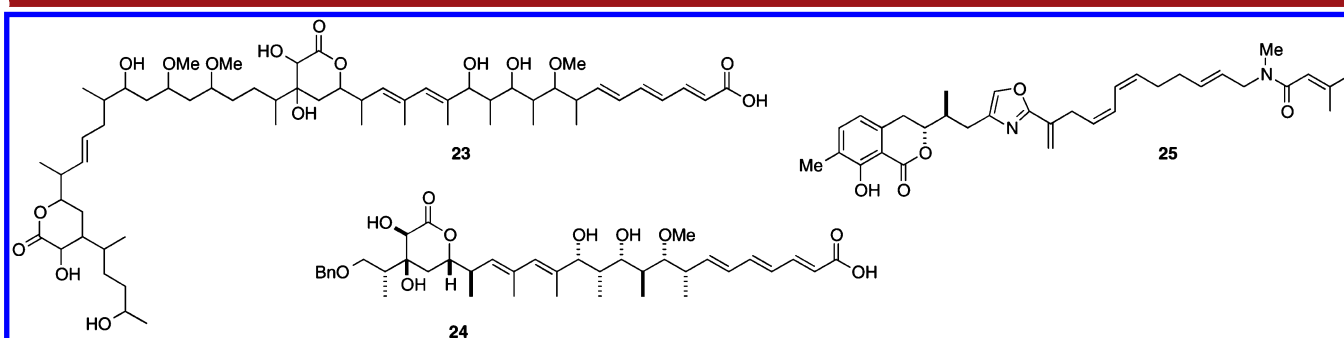


Figure 4. Hemicalide (23, planar structure),³⁶ synthetic intermediate 24,³⁷ and a synthetic stereoisomer 25³⁸ of deshydroxyajudazol A.

Chlorizidine (12), obtained by Hughes and workers²⁶ by cultivation of a marine *Streptomyces* sp. isolated in marine media, is a highly cytotoxic alkaloid with in vitro activity against cultured human colon tumor cells (HCT-116). The structure of 12, which was solved by single-crystal X-ray crystallography, embodies a pyrroloisindolone core that deviates from other natural bis-pyrrole alkaloids in many ways but bears a possible relationship to marinopyrrole A, a C₂-symmetric atropisomeric bis-pyrrole from a different sediment-derived *Streptomyces* sp.²⁷ Compound 12 is particularly susceptible to C–N bond cleavage of the acylpyrrole moiety by nucleophilic addition–elimination, a property that may play a role in the cytotoxic activity.

Thiaplakortones A–D (13–16), from the Australian sponge *Plakortis lita*,²⁸ are benzothiazines discovered through a directed high-throughput screening (HTS) campaign for antimalarial compounds. Quinn and co-workers showed that the four natural products exhibit high in vitro potency against chloroquine-sensitive strains of malaria parasite *Plasmodium falciparum* while inducing only mild cytotoxicity against cultured human HEK293 cell lines. Thiaplakortone A (13), which is the subject of a recently published synthesis and SAR study that improved the compound's pharmacodynamic properties,²⁹ resembles anti-inflammatory thiazines from a New Zealand ascidian *Aplidium* sp. isolated by Copp and co-workers.³⁰

Among the unexpected structures of recently discovered alkaloids from marine organisms is theleпамиде (17, Figure 3). This compound is a singular member within a novel “chemical space”, a thioether-ketide fused oxazolidone from the tidal annelid worm, *Thelepus crispus*, collected in the temperate latitudes of the San Juan Islands.³¹ Rodríguez, Jiménez, and co-

workers proposed the structure of 17—which appears to derive from cysteine, valine, and a lipid of uncertain origin—based on integrated MS and NMR data. The stereoassignment of 17 relied on ROESY correlations and DFT calculations of a purported hydrogen-bonded conformation obtained from a search of energy minimized structures. Theleпамиде shows modest cytotoxicity against cultured CCRF-CE leukemia cells.

Cytotoxic macrolides are a common feature of marine-derived natural products from sponges and ascidians. Mandelalides A–D are remarkably cytotoxic macrolides isolated by McPhail and co-workers from the South African ascidian *Lissoclinum* sp. and are characterized by a glycosylated macrolide ring that embeds a highly complex tetrahydrofuran moiety.³² The structure of 18 for mandelalide A was proposed on the basis of extensive analysis of 2D NMR data and includes an inventive application of “TOCSY matching”³³ to assign the sugar configuration. Degradation of 18 to 2-O-methyl- α -L-rhamnose and stereocorrelation of the sugar to the macrolide ring completed the absolute configuration, but some inconsistencies became evident. Recent syntheses of the proposed structure 18 by Fürstner³⁴ and Ye,³⁵ and two of its stereoisomers, gave compounds with NMR properties that did not match those of mandelalide A. Stereoisomer 19, prepared by Ye³⁵ with inverted configurations at C-17, C-20, C-21, and C-23 compared to 18, was shown to be identical to mandelalide A by ¹H and ¹³C NMR. Mandelalide A exhibits submicromolar cytotoxicity against cultured human lung cancer (NCI-H460) and murine neuroblastoma cell lines.³² Mandelalide B (20) is an *n*-butyrate ester of an oxidatively modified macrolide core and epimeric at C-4' in the sugar, while mandelalides C and D (21 and 22) are deglycosylated analogues.

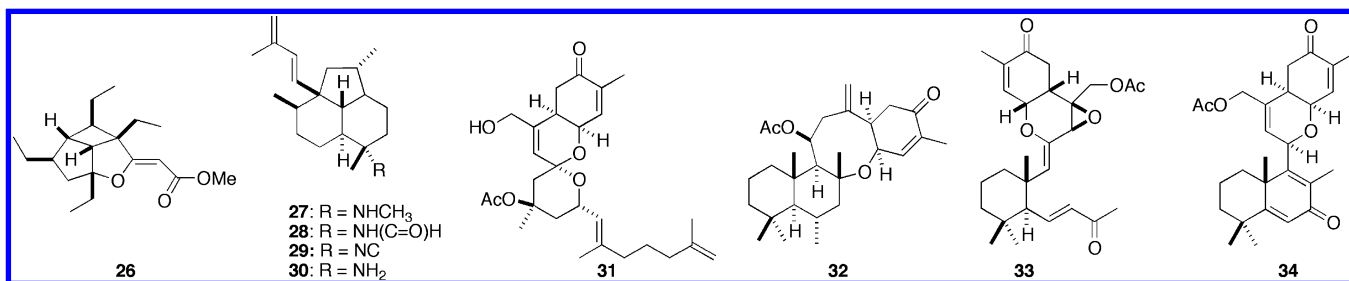


Figure 5. Structures of sponge terpenoids: hippolachnin A (**26**) from *Hippospongia lachne*,⁴⁰ amphilectanes (**27–29**)⁴¹ from the Caribbean *Svenzea flava*, the derived primary amine **30**, and rearranged diterpenes **31–34** from a *Phorbas* species⁴³ from British Columbia.

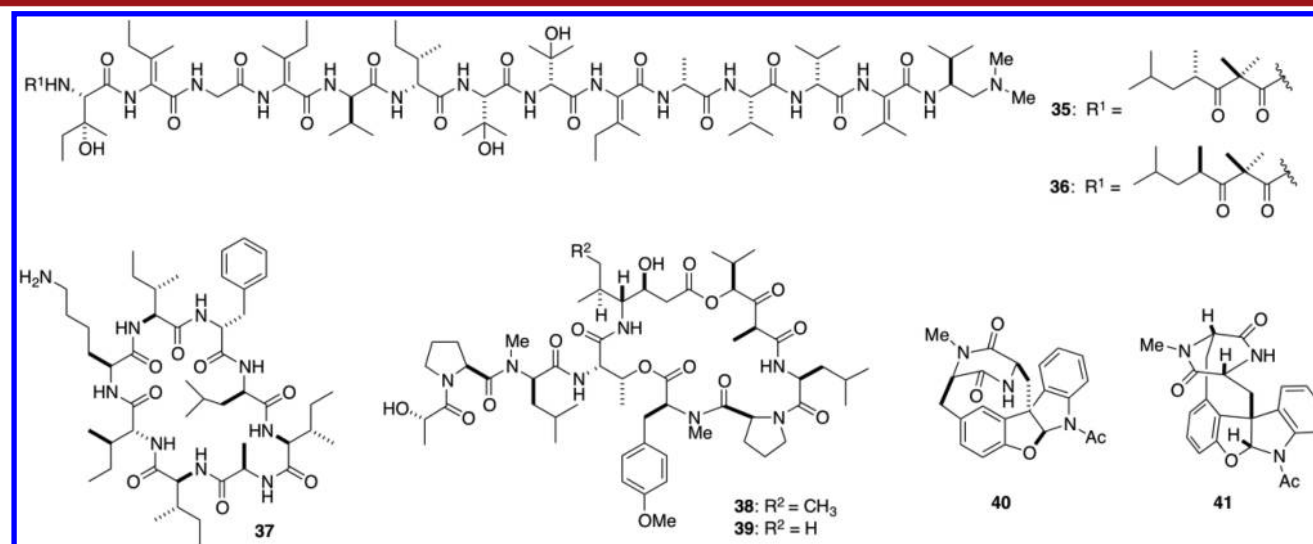


Figure 6. Structures of yaku'amides A (**35**)⁴⁴ and 4-*epi*-yaku'amide A (**36**),⁴⁵ surugamide A (**37**),⁴⁶ didemnin B (**38**), nor-didemnin B (**39**),⁴⁷ proposed structure of (+)-azonazine (**40**),⁵⁰ and the reassigned structure of (–)-*ent*-azonazine (**41**).⁵²

Assignment of stereocenters in complex polyketides is often challenging due to the difficulty relating remote “islands of stereochemistry”. Several recent reports describe how synthesis and deductive analysis can be applied to resolve such issues. Hemicalide (**23**, partial stereochemistry only, Figure 4) is a highly cytotoxic polyketide from the sponge *Hemimycale* sp. from Vanuatu.³⁶ In ongoing synthetic efforts, the stereochemistry of hemicalide, a δ -lactone fused on an oxidized long-chain polyketide, was addressed by Ardisson and co-workers³⁷ using an iterative deductive approach involving synthesis, computational conformational analysis, and NMR comparisons with the natural product that converged on **24**, a synthetic fragment embodying the likely absolute stereostructure of C-8–C-24. In contrast, the completion by Rizzacasa and co-workers³⁸ of a rational synthesis of the proposed structure of 8-deshydroxyajudazol A (**25**), one of several nanomolar mitochondrial respiration inhibitors in the ajudazol series from the myxobacterium *Chondromyces crocatus*,³⁹ allowed comparison of the NMR data with those of the natural product. Discrepancies of chemical shift values between the natural product and **25** remain, leading the authors to conclude that the “composition of natural material remains to be achieved beyond reasonable doubt”.³⁸

Terpenoids are conventionally associated with several phyla of marine invertebrates, but sponges are the canonical source of the widest variety of structures. A few have exceptional bioactivity. Hippolachnin A (**26**, Figure 5) is a remarkable polyketide obtained from the South China sea sponge,

Hippospongia lachne, by Han, Lin and co-workers.⁴⁰ The structure **26**, which is composed of three fused rings—an oxabicyclo[3.3.0]heptane further fused to a cyclobutane ring, was elucidated by a combination of NMR and MS analysis. The absolute configuration of **26** was assigned by calculation of the electronic CD spectrum by TD-DFT and matching of the measured and calculated spectra. Hippolachnin A exhibited potent antifungal activity (mostly submicromolar) against several yeast pathogens.

Rodriguez and co-workers have isolated, from the Caribbean sponge *Svenzea flava*, new isoneoamphilectanes **27** and **28**,⁴¹ corresponding to the substituted *N*-methylamine and *N*-formamide derivatives, respectively, of the putative precursor isonitrile **29**.⁴² The latter compound was previously described from the Pacific sponge *Cymbastella hooperi* by König and coworkers. Compound **27** exhibited significant antimycobacterial activity. Most notable in this study is the use of vibrational circular dichroism (VCD) for the assignment of absolute configuration of **30**, the primary amine derived from alkaline hydrolysis of **28**, after DFT calculation of the expected VCD spectra.⁴¹ Although less sensitive than ECD, VCD is gaining in popularity for assignment of configuration due to the ease of ab initio calculation of the theoretical vibronic spectra, especially in the “fingerprint region” and independence of the need for a chromophore.

Remarkably, new terpenoid carbon skeleta continue to be discovered from marine sources. Andersen and co-workers described alotaketal C (**31**), along with ansellone B (**32**),

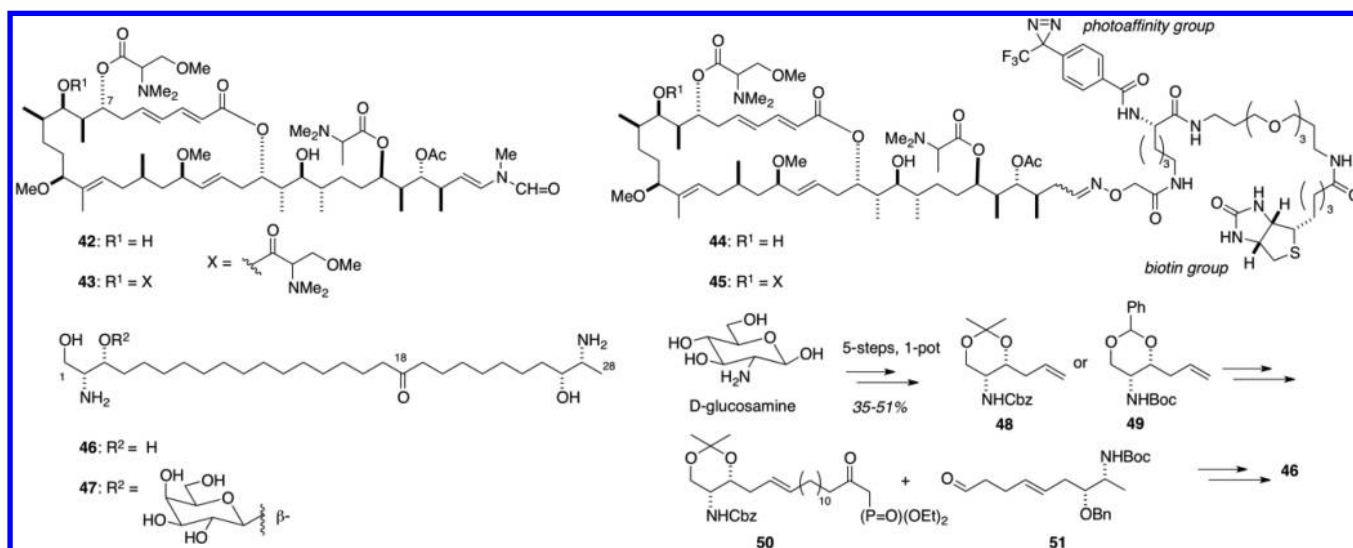


Figure 7. Structures of aplyronine A (42) and C (43)⁵⁵ and derived affinity probes 44 and 45,⁵⁴ rhizochalinin C (46) and its β -galactoside, rhizochalin C (47),⁵⁹ L-sphingolipid synthons 48 and 49, and intermediates 50 and 51 in the synthesis of 46.⁶⁰

secoepoxyansellone A (33), phorbadiolone (34), and four other sesterterpenes from the Northeastern Pacific sponge, *Phorbasp. sp.*⁴³ Alotaketol C activates cyclic-AMP signaling in HEK293 cells.

Nonribosomal peptides are frequently encountered in marine-derived bacteria, invertebrates, and other sources. Often the structures are surprisingly different from proteinogenic peptides and require some innovative approaches for sequencing, assignment of configuration of amino acid residues, and synthesis. The deep-sea sponge *Ceratopsion sp.* collected in the East China sea sequesters yaku'amides A (35, Figure 6) and B, highly cytotoxic (P388 murine leukemia cells, IC₅₀ 14 and 4 ng·mL⁻¹, respectively) modified linear peptides which contain an unusual number and variety of α,β -dehydroamino acids.⁴⁴ Inoue and co-workers have adapted an innovative approach⁴⁵ to assembly of a triad of dehydroisoleucine residues through a series of Cu(I) promoted amidations of vinyl iodides and completion of the total synthesis of 35 and 4-*epi*-yaku'amide A (36), thus defining the C-4 configuration and enabling further structure–activity relationships. Matsunaga and co-workers describe the octapeptides, surugamides A (37) and B–E from a marine *Streptomyces*,⁴⁶ and a stereoassignment of the amino acid configurations using liquid chromatography–mass spectrometry (LCMS) that represents a creative solution to a difficult but reasonably common problem: location, in the peptide sequence, of pairs of D- and L-amino acids of the same constitution.

The didemnins are highly modified depsipeptides incorporating a statin residue. Didemnin B (38), first discovered from the ascidian, *Trididemnum solidum*, by Ken Rinehart in the early 1980s,⁴⁷ was among the first marine natural products to enter human clinical trials as anticancer drugs. In a surprise finding, published in early 2012, by the Tsukumoto group,⁴⁸ the pelagic marine bacterium *Tistrella mobilis* was shown to produce 38 under conventional fermentation conditions. Later, Moore, Qian and coworkers showed⁴⁹ *T. bauzanensis* also biosynthesizes 38 and 39, but this work also included a comprehensive genetic study of *T. mobilis* that led to the sequencing of the entire genome, annotation of the putative gene functions and revelation of a modular NRPS biosynthesis of 38 and 39. Time-course studies show that the fatty acylglutamine conjugates,

didemnins X and Y,⁴⁷ appear to be precursor peptides, also produced by *Tistrella sp.*, that are cleaved by an as-yet unidentified mechanism to liberate the more potent cytotoxic peptides 38 and 39.

(+)-Azonazine, first described from the fermentation of a marine-derived fungus,⁵⁰ is an interesting oxidatively dimerized diketopiperazine derived from an *N*-methyl-Tyr-Trp dipeptide. The heterocyclic core of the proposed structure of (+)-azonazine (40), a dihydro-5aH-benzofuro[2,3-*b*]indole ring system, is familiar: it is also found in the central heterocyclic core of the potent cytotoxin diazonamide A from the ascidian *Diazona chinensis*.⁵¹ Yao and co-workers completed a biomimetic synthesis, and reassigned both the relative and absolute configurations, of the enantiomer, (–)-*ent*-azonazine (41),⁵² through a hypervalent iodine-promoted oxidative phenolic coupling of the diketopiperazine precursor followed by reductive remodeling.

Natural products are also well-known sources of biological probes for cell biology. Many have become standard tools in study of cell physiology, e.g., the phosphatase inhibitor okadaic acid, first isolated from the marine sponge *Halichondria okadaei*.⁵³ Desirable properties of biological probes for macromolecules usually combine potent bioactivity with specificity toward their cognate receptors. Kita, Kigoshi, and co-workers demonstrate this elegantly with a study⁵⁴ of inhibition of microtubule assembly with probes prepared from two macroclides obtained from the sea hare, *Aplysia kurodai*: aplyronine A (42, Figure 7), a potent cytotoxin (HeLa S3 cells, IC₅₀ 0.1 nM), and the co-occurring compound aplyronine C (43), which lacks the C-7 *N,N,O*-trimethylserinyl unit.⁵⁵ Both 42 and 43 inhibit actin polymerization, but 43 is 1000 times less cytotoxic than 42. Affinity probes, including 44 and 45, were constructed from 42 and 43, respectively, and bifunctional linkers fitted with photoaffinity and biotin arms, and then used to uncover a new motif of protein–protein assembly involving the cytoskeletal proteins actin and tubulin.

While many similar macrolides have been shown to inhibit actin polymerization by binding to G-actin, the remarkable discovery revealed here is binding of aplyronine A (42) and the derived affinity probe 44 leads to a 1:1:1 heterotrimeric complex with actin and tubulin, with a primary binding site on

tubulin and concomitant inhibition of tubulin polymerization. Aplyronine C (**43**) and the conjugated probe **45**, on the other hand, bind only to actin.⁵⁴

Some of the articles highlighted here describe sophisticated instrumental or computational approaches to solving stereochemical problems, but in some cases “less is more”. Rychnovsky and Wagner demonstrate a delightfully simple method⁵⁶ for assignment of the absolute configuration of benzylic, allylic, and propargylic secondary alcohols along with related carbinols by kinetic resolution using propionic anhydride and Birman’s catalyst.⁵⁷ A direct empirical model for kinetic resolution allows a clear assignment of *S* or *R* carbinol by matching the configuration of Birman’s chiral catalyst to the observed rate of acylation and requires no elaborate kinetics instrumentation; this method can be run on a simple TLC plate and gives a clear reading. In fact, the method has been deployed as a university undergraduate laboratory experiment (over 1000 students); experimenters were able to make reliable assignments of unknowns with a 93.6% success rate!⁵⁸

Finally, total synthesis of natural products has long-relied on starting materials from the “pool” of chiral substrates. Rhizochalinin C (**46**, Figure 7)⁵⁹ is one of about a dozen “two-headed” C₂₇ to C₃₀ sphingoid bases, derived mostly from the sponges *Oceanapia philipensis* and *Rhizochalina incrustata*. These unusual sphingoid bases often have antipodal configurations with respect to mammalian *D*-erythro-sphingosine. Sphingolipid (**46**) and the *O*- β -galactoside, rhizochalin C (**47**),⁵⁹ are functionalized at both termini: one is an *L*-threo-2-amino-1,3-alkanol and the other an *L*-threo-2-amino-3-alkanol. In the first synthesis of a member of these long-chain sphingosines,⁶⁰ inexpensive *D*-glucosamine, which has been used before as an *L*-serine synthon,⁶¹ is repurposed for the preparation of antipodal *L*-sphingolipid synthons by a five-step, one-pot transformation in good overall yields (35–51%). In⁰-promoted Barbier reaction of *D*-glucosamine with allyl bromide, followed by *N*-protection, oxidative cleavage (NaIO₄), reductive workup (NaBH₄), and *O*-protection, gives the key precursors **48** and **49** of the aminoalkanol termini. The latter compounds are expanded to give phosphonate **50** and aldehyde **51**, respectively, for final assembly by Horner–Wadsworth–Emmons reaction and global deprotection to complete the synthesis of rhizochalinin C (**46**).⁶⁰

In summary, natural products inspire not only elegant syntheses but also cross-disciplinary investigations that uncover and clarify profound biological phenomena. I encourage you to visit and read these articles, admire their exotic and chemically complex structures, and embrace the diversity and exciting discoveries that frame modern day natural products chemistry.

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Notes

Views expressed in this editorial are those of the author and not necessarily the views of the ACS.

REFERENCES

- (1) Editorial review for *Natural Products Chemistry*; Barton, D. H. R., Nakanishi, K., Meth-Cohn, O., Eds., Elsevier: New York, 1999.
- (2) (a) Newman, D. J.; Cragg, G. M. *J. Nat. Prod.* **2012**, *75*, 311–335. (b) Newman, D. J.; Cragg, G. M.; Snader, K. M. *J. Nat. Prod.* **2003**, *66*, 1022–1037.
- (3) Barton, D. H. R. Noble prize in chemistry, 1969.
- (4) (a) *Circular Dichroism. Principles and Applications*, 2nd ed.; Berova, N., Nakanishi, K., Woody, R. W., Eds.; Wiley-VCH: Toronto, 2000. (b) Crabbé, P. *Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry*; Holden-Day: San Francisco, 1965.
- (5) Molinski, T. F. *Nat. Prod. Rep.* **2010**, *27*, 321–329.
- (6) Dorrestein, P. C. *Nat. Prod. Rep.* **2014**, *31*, 704–705 and articles cited within this special issue..
- (7) Woodward, R. B. Nobel Prize in chemistry, 1965.
- (8) Corey, E. J. Nobel Prize in chemistry, 1990.
- (9) (a) Molinski, T. F.; Dalisay, D. S.; Lievens, S. L.; Saludes, J. P. *Nat. Rev. Drug. Discovery* **2009**, *8*, 69–85. (b) Newman, D. J.; Cragg, G. M. *Mar. Drugs* **2014**, *12*, 255–278.
- (10) (a) Pettit, G. R.; Kamano, Y.; Herald, C. L.; Fujii, Y.; Kizu, H.; Boyd, M. R.; Boettner, F. E.; Doubek, D. L.; Schmidt, J. M.; Chapuis, J.-C.; Michel, C. *Tetrahedron* **1993**, *49*, 9151–9170. (b) Luesch, H.; Moore, R. E.; Paul, V. J.; Mooberry, S. L.; Corbett, T. H. *J. Nat. Prod.* **2001**, *64*, 907–910.
- (11) Yu, M. J.; Kishi, Y.; Littlefield, B. A. In *Anticancer Agents from Natural Products*; Cragg, G. M., Kingston, D. G. I., Newman, D. J., Eds.; Taylor and Francis: Boca Raton, 2005; pp 241–265.
- (12) Hirata, Y.; Uemura, D. *Pure Appl. Chem.* **1986**, *58*, 701–710.
- (13) Aicher, T. D.; Buszek, K. R.; Fang, F. G.; Forsyth, C. J.; Jung, S. H.; Kishi, Y.; Matelich, M. C.; Scola, P. M.; Spero, D. M.; Yoon, S. K. *J. Am. Chem. Soc.* **1992**, *114*, 3162–3164.
- (14) Roush, W. R. *J. Am. Chem. Soc.* **2008**, *130*, 6654–6656.
- (15) Hale, K. J. *Org. Lett.* **2013**, *15*, 3181–3198.
- (16) Martín, M. J.; Coello, L.; Fernández, R.; Reyes, F.; Rodríguez, A.; Murcia, C.; Garranzo, M.; Mateo, C.; Sánchez-Sancho, F.; Bueno, S.; de Eguilior, C.; Francesch, A.; Munt, S.; Cuevas, C. *J. Am. Chem. Soc.* **2013**, *135*, 10164–10171.
- (17) (a) Gunasekera, S. P.; Gunasekera, M.; Longley, R. E.; Schulte, G. K. *J. Org. Chem.* **1990**, *55*, 4912–4915. The absolute stereostructure of (+)-**3** was established from total synthesis of the enantiomer (–)-**3**. (b) Nerenberg, J. B.; Hung, D. T.; Somers, P. K.; Schreiber, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 12621–12622.
- (18) Martínez-Díez, M.; Guillén-Navarro, M. J.; Pera, B.; Bouchet, B. P.; Martínez-Leal, J. F.; Barasoain, I.; Cuevas, C.; Andreu, J. M.; García-Fernández, L. F.; Díaz, J. F.; Avilés, P.; Galmarini, C. M. *Biochem. Pharmacol.* **2014**, *88*, 291–302.
- (19) <http://clinicaltrials.gov/show/NCT01299636> (accessed Jul 2, 2014).
- (20) Hu, Y.; Wang, K.; MacMillan, J. B. *Org. Lett.* **2013**, *15*, 390–393.
- (21) Liu, X.; Luo, H.-B.; Huang, Y.-Y.; Bao, J.-M.; Tang, G.-H.; Chen, Y.-Y.; Wang, J.; Yin, S. *Org. Lett.* **2014**, *16*, 282–285.
- (22) Pham, C.-D.; Hartmann, R.; Böhrer, P.; Stork, B.; Wesselborg, S.; Lin, W.; Lai, D.; Proksch, P. *Org. Lett.* **2014**, *16*, 266–269.
- (23) Tanaka, N.; Asai, M.; Takahashi-Nakaguchi, A.; Gono, T.; Fromont, J.; Kobayashi, J. *Org. Lett.* **2013**, *15*, 2518–2521.
- (24) Molinski, T. F. *Chem. Rev.* **1993**, *93*, 1825–1838.
- (25) Zou, Y.; Hamann, M. T. *Org. Lett.* **2013**, *15*, 1516–1519.
- (26) Alvarez-Mico, X.; Jensen, P. R.; Fenical, W.; Hughes, C. C. *Org. Lett.* **2013**, *15*, 988–991.
- (27) (a) Hughes, C. C.; Prieto-Davo, A.; Jensen, P. R.; Fenical, W. *Org. Lett.* **2008**, *10*, 629–631. (b) Hughes, C. C.; Kauffman, C. A.; Jensen, P. R.; Fenical, W. *J. Org. Chem.* **2010**, *75*, 3240–3250.
- (28) Davis, R. A.; Duffy, S.; Fletcher, S.; Avery, V. M.; Quinn, R. J. *J. Org. Chem.* **2013**, *78*, 9608–9613.
- (29) Pouwer, R. H.; Deydier, S. M.; Le, P. V.; Schwartz, B. D.; Franken, N. C.; Davis, R. A.; Coster, M. J.; Charman, S. A.; Edstein, M. D.; Skinner-Adams, T. S.; Andrews, K. T.; Jenkins, I. D.; Quinn, R. J. *ACS Med. Chem. Lett.* **2014**, *5*, 178–182.
- (30) Pearce, A. N.; Chia, E. W.; Berridge, M. V.; Clark, G. R.; Harper, J. L.; Larsen, L.; Maas, E. W.; Page, M. J.; Perry, N. B.; Webb, V. L.; Copp, B. R. *J. Nat. Prod.* **2007**, *70*, 936–940.

- (31) Rodríguez, J.; Nieto, R. M.; Blanco, M.; Valeriote, F. A.; Jiménez, C.; Crews, P. *Org. Lett.* **2014**, *16*, 464–467.
- (32) Sikorska, J.; Hau, A. M.; Anklin, C.; Parker-Nance, S.; Davies-Coleman, M. T.; Ishmael, J. E.; McPhail, K. L. *J. Org. Chem.* **2012**, *77*, 6066–6075.
- (33) Gheysen, K.; Mihai, C.; Conrath, K.; Martins, J. C. *Chem.—Eur. J.* **2008**, *14*, 8869–8878.
- (34) Willwacher, J.; Fürstner, A. *Angew. Chem., Int. Ed.* **2014**, *53*, 4217–4221.
- (35) Lei, H.; Yan, J.; Yu, J.; Liu, Y.; Wang, Z.; Xu, Z.; Ye, T. *Angew. Chem., Int. Ed.* **2014**, *53*, 6533–6537.
- (36) Carletti, I.; Massiot, G.; Debitus, C. WO 2011/051380A1, 2011.
- (37) Fleury, E.; Sorin, G.; Prost, E.; Pancrazi, A.; Sautel, F.; Massiot, G.; Lannou, M.-I.; Ardisson, J. *J. Org. Chem.* **2013**, *78*, 855–864.
- (38) Birkett, S.; Ganame, D.; Hawkins, B. C.; Meiries, S.; Quach, T.; Rizzacasa, M. A. *J. Org. Chem.* **2013**, *78*, 116–123.
- (39) Jansen, R.; Kunze, B.; Reichenbach, H.; Höfle, G. *Eur. J. Org. Chem.* **2002**, 917–921.
- (40) Piao, S.-J.; Song, Y.-L.; Jiao, W.-H.; Yang, F.; Liu, X.-F.; Chen, W.-S.; Han, B.-N.; Lin, H.-W. *Org. Lett.* **2013**, *15*, 3526–3529.
- (41) Avilés, E.; Rodríguez, A. D.; Vicente, J. *J. Org. Chem.* **2013**, *78*, 11294–11301.
- (42) König, G. M.; Wright, A. D.; Angerhofer, C. K. *J. Org. Chem.* **1996**, *61*, 3259–3267.
- (43) Daoust, J.; Chen, M.; Wang, M.; Williams, D. E.; Chavez, M. A. G.; Wang, Y. A.; Merchant, C. E.; Fontana, A.; Kieffer, T. J.; Andersen, R. J. *J. Org. Chem.* **2013**, *78*, 8267–8273.
- (44) Ueoka, R.; Ise, Y.; Ohtsuka, S.; Okada, S.; Yamori, T.; Matsunaga, S. *J. Am. Chem. Soc.* **2010**, *132*, 17692–17694.
- (45) Kuranaga, T.; Sesoko, Y.; Sakata, K.; Maeda, N.; Hayata, A.; Inoue, M. *J. Am. Chem. Soc.* **2013**, *135*, 5467–5474.
- (46) Takada, K.; Ninomiya, A.; Naruse, M.; Sun, Y.; Miyazaki, M.; Nogi, Y.; Okada, S.; Matsunaga, S. *J. Org. Chem.* **2013**, *78*, 6746–6750.
- (47) (a) Rinehart, K. L., Jr.; Gloer, J. B.; Cook, J. C., Jr.; Mizsak, S. A.; Scahill, T. A. *J. Am. Chem. Soc.* **1981**, *103*, 1857–1859. (b) Sakai, R.; Stroh, J. G.; Sullins, D. W.; Rinehart, K. L. *J. Am. Chem. Soc.* **1995**, *117*, 3734–3748. (c) Rinehart, K. L. U.S. Patent 5,294,603, Mar 15, 1994. (d) Rinehart, K. L.; Lithgow-Bertelloni, A. M. PCT Int. Pat. Appl. WO91.04985, Apr 18, 1991.
- (48) Tsukimoto, M.; Nagaoka, M.; Shishido, Y.; Fujimoto, J.; Nishisaka, F.; Matsumoto, S.; Harunari, E.; Imada, C.; Matsuzaki, T. *J. Nat. Prod.* **2012**, *74*, 2329–2331.
- (49) Xu, Y.; Kersten, R. D.; Nam, S.-J.; Lu, L.; Al-Suwailem, A. M.; Zheng, H.; Fenical, W.; Dorrestein, P. C.; Moore, B. S.; Qian, P.-Y. *J. Am. Chem. Soc.* **2012**, *134*, 8625–8632.
- (50) Wu, Q.-X.; Crews, M. S.; Draskovic, M.; Sohn, J.; Johnson, T. A.; Tenney, K.; Valeriote, F. A.; Yao, X.-J.; Bjeldanes, L. F.; Crews, P. *Org. Lett.* **2010**, *12*, 4458–4461.
- (51) (a) Lindquist, N.; Fenical, W.; Van Duyne, G. D.; Clardy, J. *J. Am. Chem. Soc.* **1991**, *113*, 2303–2304. The original structure assignment was incorrect and later revised by Haran and co-workers through synthesis. (b) Li, J.; Jeong, S.; Esser, L.; Harran, P. G. *Angew. Chem., Int. Ed.* **2001**, *40*, 4765–4769. (c) Li, J.; Burgett, A. W. G.; Esser, L.; Amezcua, C.; Harran, P. G. *Angew. Chem., Int. Ed.* **2001**, *40*, 4770–4773.
- (52) Zhao, J.-C.; Yu, S.-M.; Liu, Y.; Yao, Z.-J. *Org. Lett.* **2013**, *15*, 4300–4303.
- (53) (a) Tachibana, K.; Scheuer, P. J.; Tsukitani, Y.; Kikuchi, H.; Van Engen, D.; Clardy, J.; Gopichand, Y.; Schmitz, F. J. *J. Am. Chem. Soc.* **1981**, *103*, 2469–2471. (b) Takai, A.; Murata, M.; Torigoe, K.; Isobe, M.; Mieskes, G.; Yasumoto, T. *Biochem. J.* **1992**, *284*, 539–544.
- (54) Kita, M.; Hirayama, Y.; Yoneda, K.; Yamagishi, K.; Chinen, T.; Usui, T.; Sumiya, E.; Uesugi, M.; Kigoshi, H. *J. Am. Chem. Soc.* **2013**, *135*, 18089–18095.
- (55) Yamada, K.; Ojika, M.; Ishigaki, T.; Yoshida, Y.; Ekimoto, H.; Arakawa, M. *J. Am. Chem. Soc.* **1993**, *115*, 11020–11021.
- (56) Wagner, A. J.; Rychnovsky, S. D. *J. Org. Chem.* **2013**, *78*, 4594–4598.
- (57) Birman, V. B.; Li, X. *Org. Lett.* **2008**, *10*, 1115–1118.
- (58) Wagner, A. J.; Miller, S. M.; Nguyen, S.; Le, G. Y.; Rychnovsky, S. D.; Link, R. D. *J. Chem. Educ.* **2014**, *91*, 716–721.
- (59) Makarieva, T. N.; Dmitrenok, P. S.; Zakharenko, A. M.; Denisenko, V. A.; Guzii, A. G.; Li, R. H.; Skepper, C. K.; Molinski, T. F.; Stonik, V. A. *J. Nat. Prod.* **2007**, *70*, 1991–1998.
- (60) Ko, J.; Molinski, T. F. *J. Org. Chem.* **2013**, *78*, 498–505.
- (61) Giannis, A.; Henk, T. *Tetrahedron Lett.* **1990**, *31*, 1253–1256.