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Total syntheses of indolactam alkaloids (–)-indolactam V, (–)-pendolmycin, (–)-lyngbyatoxin A, and (–)-teleocidin A-2

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Abstract

We report the total syntheses of (–)-indolactam V and the C7-substituted indolactam alkaloids (–)-pendolmycin, (–)-lyngbyatoxin A, and (–)-teleocidin A-2. The strategy for preparing indolactam V relies on a distortion-controlled indolyne functionalization reaction to establish the C4–N linkage, in addition to an intramolecular conjugate addition to build the conformationally-flexible nine-membered ring. The total synthesis of indolactam V then sets the stage for the divergent synthesis of the other targeted alkaloids. Specifically, late-stage sp^2–sp^3 cross-couplings on an indolactam V derivative are used to introduce the key C7 substituents and the necessary quaternary carbons. These challenging couplings, in addition to other delicate manipulations, all proceed in the presence of a basic tertiary amine, an unprotected secondary amide, and an unprotected indole. Thus, our approach not only enables the enantiospecific total syntheses of four indolactam alkaloids, but also serves as a platform for probing complexity-generating and chemoselective transformations in the context of alkaloid total synthesis.

Introduction

Natural products belonging to the family of indolactam alkaloids[1] (e.g., **1**–**4**, Figure 1) have been widely studied for their pharmacological properties. The most well-known of these compounds is indolactam V (**1**), which was first isolated in 1984.[2] Indolactam V (**1**) functions as an efficient tumor promoter as a result of its ability to bind to protein kinase C (PKC). Accordingly, **1** has been used in a variety of studies to better understand mammalian tumor growth.[3,4] Similarly, C7-substituted indolactams **2**–**4** have been valued for their tumor-promoting abilities. It should be noted that each of **1**–**4** and their derivatives exhibit biological functions which range from stem-cell differentiation[5] to anti-bacterial,[6] anti-malarial[7] and anti-cancer[8] activities.

The attractive biological profiles of indolactam alkaloids have prompted numerous synthetic investigations. These efforts have led to several total syntheses of **1**,[9,10] as well as completed syntheses of **2**–**4**.[11,12] A central challenge to accessing each of these alkaloids involves assembly of the parent 3,4-disubstituted indole framework possessing a conformationally-

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flexible[13] 9-membered lactam. To this end, most strategies to access the medium-sized ring have involved amide bond formation as the key step.[9] With regard to **2**–**4**, introduction of the C7 sp^2–sp^3 linkage presents an additional challenge. The few successful approaches to **2**–**4** all involve early introduction of the C7-linked quaternary carbon, followed by assembly of the indole core.[11,12] We envisioned a strategically distinct approach to indolactam V (**1**) and related C7-substituted alkaloids **2**–**4**, which is summarized in Scheme 1. Specifically, the 9-membered ring would be introduced through two key steps from an appropriate indole building block: namely, intermolecular assembly of the C4–N bond and ring closure at C3. This would be implemented in practice by accessing an indolyne in situ,[14,15,16] which would undergo selective C4-trapping by an amine nucleophile (**5**→**6**). Elaboration of adduct **6** to ester **7** would be followed by a challenging conjugate addition at C3 to forge the 9-membered ring en route to **1**. We hypothesized that **1** could be used as a precursor to the C7-substituted indolactam alkaloids, without the use of *N*-protecting groups. Our unique divergent strategy would require the use of efficient cross-couplings to build the sp^2–sp^3 C–C linkages and introduce the quaternary carbons (**1**→**8**→**2**–**4**). Achieving alkylative cross-couplings at C7 of indoles can be difficult, and only a few such examples are known in the presence of unprotected indole nitrogens.[17] Moreover, to our knowledge, there are no examples of sp^2–sp^3 cross-couplings to introduce quaternary C7 substituents on indole substrates in the literature.

We herein describe the enantiospecific total syntheses of indolactam alkaloids **1**–**4**. As we have previously reported a formal total synthesis of **1**,[10] aside from a brief discussion of optimization of key steps, this manuscript focuses on C7 functionalization studies and the divergent total syntheses of the less well-studied targets **2**–**4**. This study not only leads to the generation of several natural products enantiospecifically, but also serves as an exercise aimed at probing complexity-generating and chemoselective transformations in alkaloid total synthesis.

Results and discussion

Optimization of the total synthesis of indolactam V (1)

Although our previous studies toward **1** validated our approach, we sought to improve several key steps of our formal synthesis[10] and render the route suitable for scale-up (Scheme 2). We first optimized the synthesis of indolyne precursor **9**, which can now be obtained in 7 steps from commercially available materials in 62% overall yield (previously 27% yield, over 7 steps).[18] Next, treatment of silyltriflate **9** with peptide **10** in the presence of CsF in acetonitrile efficiently furnished indolyne adduct **11** and established the key C4–N linkage.[19,20] The regioselectivity in the indolyne trapping is governed by aryne distortion,[15a,b] which arises from the presence of the inductively-withdrawing C6 bromide substituent.[10] After elaborating **11** to α,β-unsaturated ester **7**, $ZrCl_4$-mediated cyclization[21] provided **12** as a single diastereomer in 90% yield.[22] As **12** possesses the undesired stereochemical configuration at C9, we developed optimal conditions to facilitate its epimerization based on the protocol reported by Nakatsuka.[9c] Treatment of **12** with $NaHCO_3$ in MeOH at 40 °C delivered a separable mixture of recovered **12** and the desired epimer **13**. Reduction of **13** delivered indolactam V (**1**), which was subsequently protected

to give silyl ether **14** in 90% yield over two steps. Using our optimized route, we have prepared over 500 mg of **14** for use in subsequent functionalization efforts.

Cross-coupling to introduce the C7 sp^2–sp^3 linkage and the key quaternary carbon

With access to late-stage compound **14**, we turned our attention to the previously unexplored divergent approach to alkaloids **2**–**4**. One of the most challenging aspects of this strategy involves functionalization of C7. Importantly, the methodology would have to build a new sp^2–sp^3 C–C linkage, containing a quaternary center, on an unprotected indole. In general, sp^2–sp^3 couplings are far less common compared to their sp^2–sp^2 counterparts and, as mentioned previously, no examples of such couplings to introduce quaternary carbons at C7 of indoles are available.

We tested the viability of our alkylative coupling strategy using readily available unprotected bromoindole substrate **15** (Table 1). Enolate precursors **19**–**22** were examined, as the carbonyls in the presumed products could plausibly be elaborated to the olefins present in **2**–**4**. Unfortunately, attempts to use isobutyraldehyde (**19**) as the coupling partner[23] led predominantly to the recovery of starting material **15** with or without formation of desbromo indole **17** (entries 1[24] and 2, respectively). We also tested ester **20** as a coupling partner,[25] but only observed recovered substrate **15** (entries 3 and 4). Next, silylketene acetal **21** was employed in the desired coupling.[26] To our delight, using 1 mol% $Pd(dba)_2$, some of the desired product **16b** was formed, albeit with recovered substrate **15** (entry 5). By simply increasing the catalyst loading to 5 mol%, full conversion to product **16b** was observed (entry 6). Zinc enolate **22**, which was generated in situ from the corresponding α-bromoamide, was also evaluated as a potential coupling partner using Hartwig's methodology.[27] Although no reaction was observed using literature conditions (entry 7), we found that the desired product **16c** could be obtained under more forcing conditions (i.e., 15 mol% Pd and 80 °C) (entry 8). It should be noted that desbromo compound **17** and dimer **18** were also formed in minor quantities. To our knowledge, the successful formation of **16b** and **16c** represents the first simultaneous formation of an sp^2–sp^3 bond and quaternary center at the C7 position of an indole with an unprotected nitrogen.

Total synthesis of (–)-pendolmycin (2)

Our promising results for the cross-coupling on the model system prompted us to shift our efforts to the complex indolactam scaffold (Scheme 3). Treatment of **14** with NBS led to C7 bromination to furnish **24**.[28] Next, the critical coupling reactions using the aforementioned conditions (see Table 1, entries 6 and 8) were tested. Despite our previous success in coupling silylketene acetal **21**, attempts to effect the corresponding coupling on indolylbromide **24** led to no reaction. However, the coupling of bromide **24** with zinc enolate **22** delivered cross-coupled product **25** in 61% yield. As this complexity-generating transformation proceeds on an advanced late-stage intermediate in the presence of two free NHs and a tertiary amine to introduce an sp^2–sp^3 linkage with a quaternary carbon, its success demonstrates the exceptional tolerance and utility of Hartwig's parent methodology.[27]

Having installed the necessary C7 substituent and the key quaternary carbon, we were able to complete the total synthesis of pendolmycin (**2**), as shown in Scheme 4. The morpholine amide of **25**, which neighbors the sterically-congested quaternary carbon, was selectively reduced with the Schwartz reagent (i.e., $Cp_2Zr(H)Cl$)[29] to furnish aldehyde **26**. Of note, competitive reduction of the secondary amide was not observed.[30] Subsequent Wittig olefination of **26** provided the penultimate compound **27**. Finally, exposure of **27** to TBAF in THF revealed the primary alcohol to deliver (–)-pendolmycin (**2**). This three-step sequence provides a concise means to convert amide **25** to the natural product (**2**), without the use of *N*-protecting groups.

Total synthesis of lyngbyatoxin A and teleocidin A-2

Although structurally similar to pendolmycin (**2**), lyngbyatoxin A (**3**) and teleocidin A-2 (**4**) present additional degrees of complexity. Specifically, the sidechains appended to C7 of the indole each contain a quaternary stereocenter, in addition to an electron-rich olefin. We envisioned that both natural products **3** and **4** could be obtained from bromoindole **24** (see Scheme 3) and a prochiral cross-coupling partner.

To enable this approach, we prepared amide **29** and tested the key cross-coupling reaction (Figure 2). Ester **28**, which was obtained from commercial sources, first underwent α-bromination under standard conditions.[31] Subsequent saponification,[32] followed by CDI-mediated coupling with morpholine, afforded amide **29**.[33] Reaction of amide **29** with Zn metal resulted in conversion to the corresponding zinc enolate **30**. Gratifyingly, treatment of bromoindole **24** with in situ-generated enolate **30** under Pd-catalyzed coupling conditions gave the desired diastereomeric products **31** and **32** in 75% combined yield (d.r. = 1:1 by ^{1}H NMR analysis).[34] Isomers **31** and **32** were separable by silica gel chromatography.[35] The formation of **31** and **32** represents the first implementation of Hartwig's amide enolate coupling methodology in the assembly of stereogenic quaternary carbons.[27]

With coupled products **31** and **32** in hand, we completed the total syntheses of (–)-lyngbyatoxin A (**3**) and (–)-teleocidin A-2 (**4**), respectively (Schemes 5 and 6). Amide **31** was reduced to aldehyde **33**, which in turn, underwent Wittig homologation to give **34** (Scheme 5). To complete the total synthesis of (–)-lyngbyatoxin (**3**), it was necessary to deprotect the primary alcohol in **34**. Although attempts to employ TBAF led to decomposition, we found that exposure of **34** to $LiBF_4$ and camphorsulfonic acid (CSA) in THF at ambient temperature afforded natural product **3**.[28,36] We were delighted to find that the analogous 3-step reaction sequence facilitated the conversion of diastereomer **32** to (–)-teleocidin A-2 (**4**) as summarized in Scheme 6. Spectral data for our synthetic samples of natural products **2**–**4** matched literature reports.[11,12]

Conclusions

We have completed the total syntheses of four indolactam alkaloids: (–)-indolactam V, (–)-pendolmycin, (–)-lyngbyatoxin A, and (–)-teleocidin A-2. Our approach to these alkaloids features a number of key features, including: a) a distortion-controlled indolyne functionalization reaction to assemble a key C–N bond; b) a Lewis acid-mediated

cyclization to assemble the nine-membered lactam; and specifically, for the divergent syntheses of **2**–**4**: c) late-stage sp^2–sp^3 cross-couplings to introduce the C7 sidechains and the challenging quaternary carbons; and d) a series of delicate functional group manipulations in the absence of *N*-protecting groups. Our studies demonstrate that indolynes serve as valuable electrophilic indole surrogates and provide an unconventional tactic for use in total synthesis. Moreover, these efforts showcase a series of complexity-generating (e.g., sp^2–sp^3 cross-couplings) and chemoselective transformations in the context of alkaloid synthesis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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18. The transformations used to prepare **9** are identical to those previously developed in our laboratory, but with modified procedures to improve the yields. See the ESI for details.

19. Our previously reported yield for the formation of **11** from **9** and **10** was 62%; see reference 10.

20. Less than 5% of the corresponding C5-substituted product was detected.

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34. The addition of LiBr helped to suppress the competitive formation of des-bromo compound **14**.

35. The stereochemical configurations at the newly formed quaternary centers of **31** and **32** were assigned after conversion to the natural products **3** and **4**.

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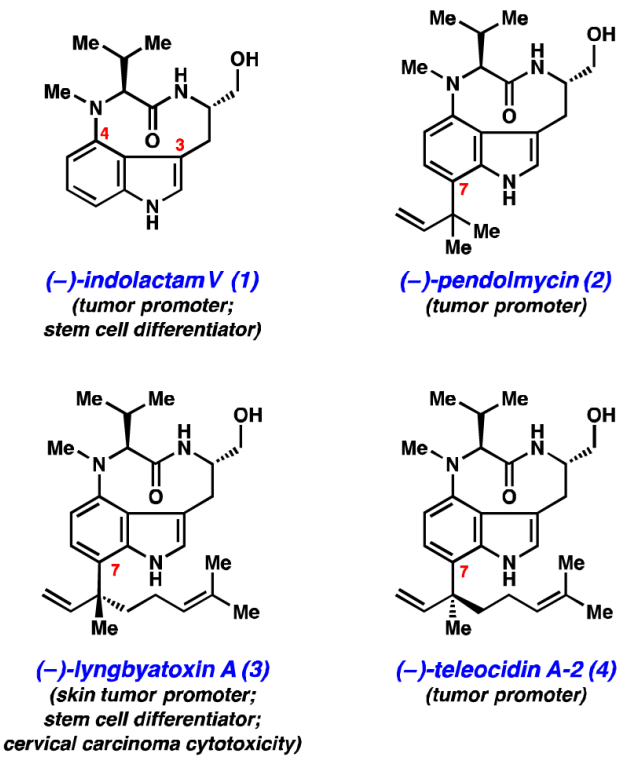


Fig. 1.
Indolactam alkaloids **1**–**4**.

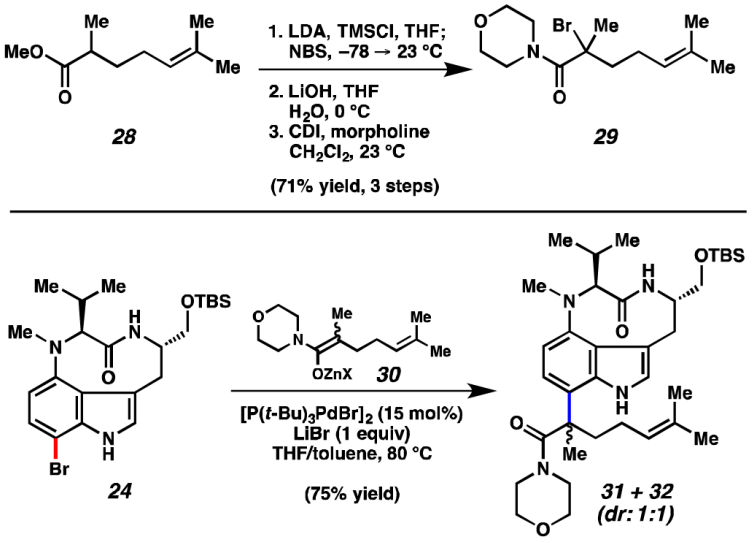
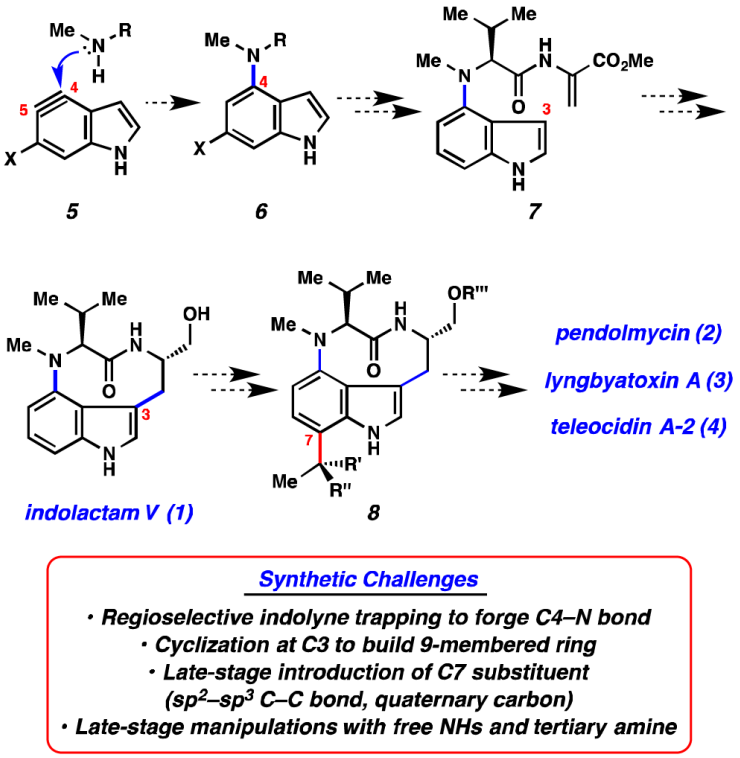


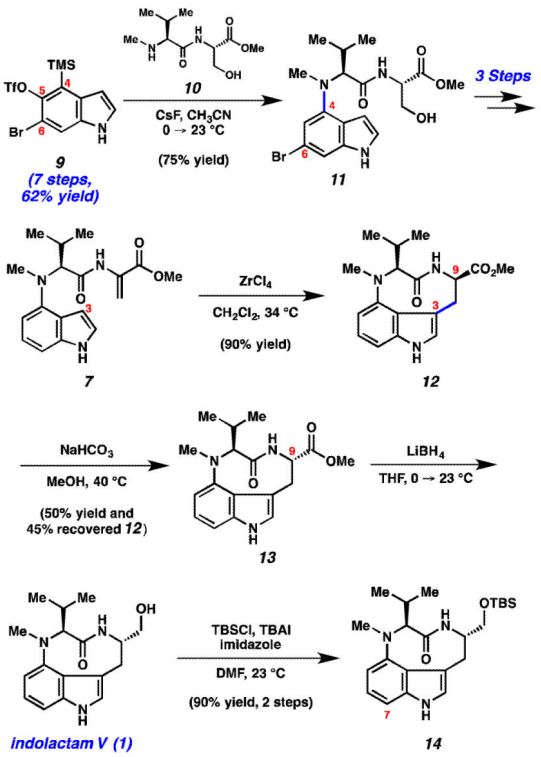
Fig. 2.

Synthesis of morpholine amide **29** and cross-coupling to access diastereomeric adducts **31** and **32** possessing the necessary all-carbon quaternary stereocenters.

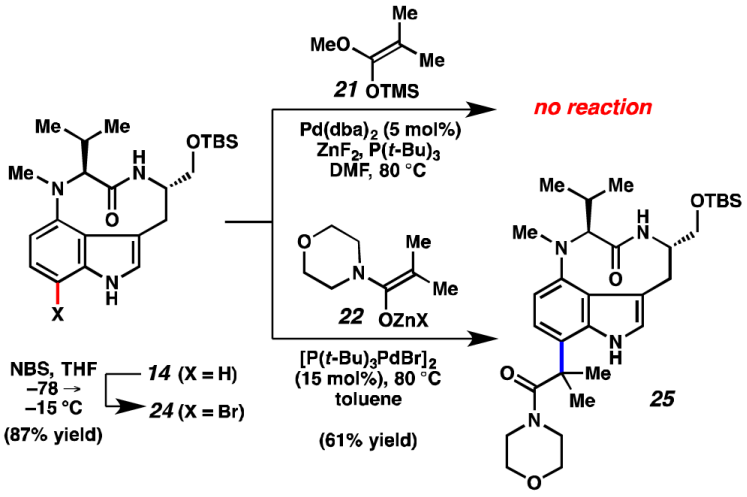


Scheme 1.

Synthetic strategy toward **1** and C7 substituted indolactam alkaloids **2**–**4**.

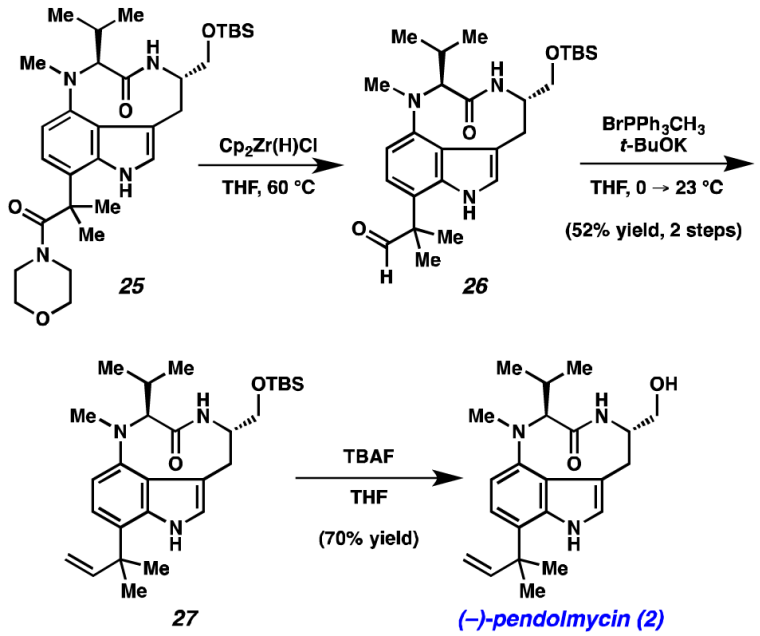


Scheme 2.
Optimized synthesis of indolactam V (**1**) and **14**.



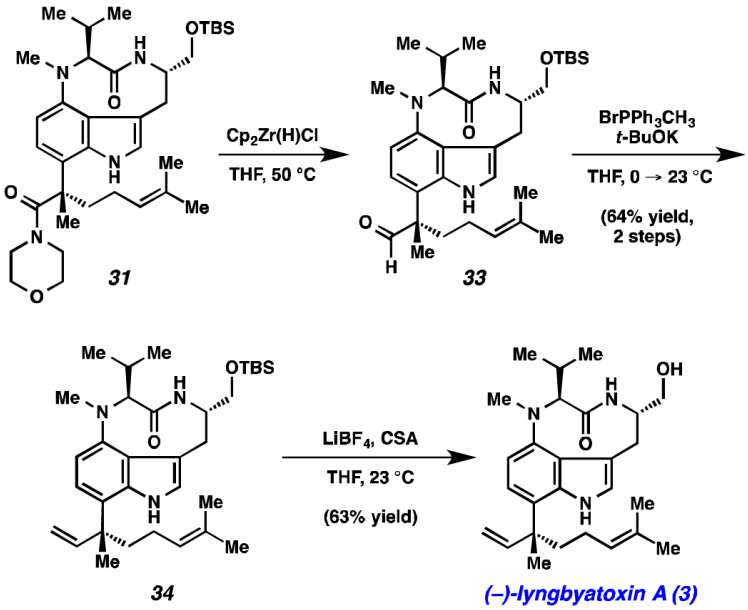
Scheme 3.

C7 functionalization of **14** and introduction of key sp^2–sp^3 linkage with a quaternary carbon substituent.



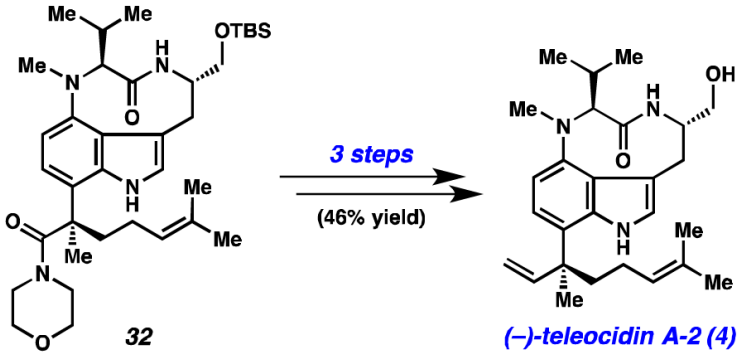
Scheme 4.

Total synthesis of (–)-pendolmycin (**2**).



Scheme 5.

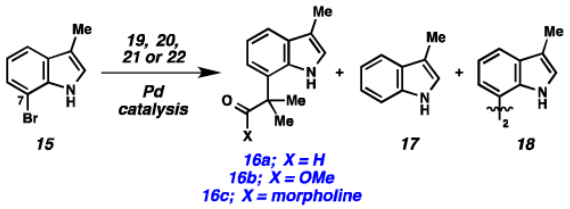
Total synthesis of (–)-lyngbyatoxin A (**3**).

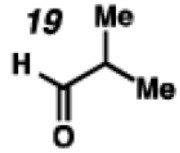
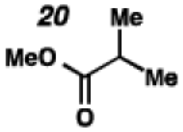
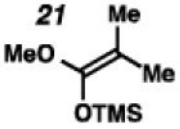
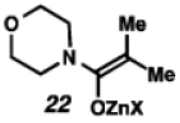


Scheme 6.
Total synthesis of (–)-teleocidin A-2 (**4**).

Table 1

C7 sp^2–sp^3 cross-coupling on model substrate **15**.



entry	cross-coupling partner	conditions[a]	ratio[b] 15:16:17:18
1		2 mol% $Pd(OAc)_2$, LIgand *23*[c] Cs_2CO_3, dioxane, 80 °C	3.7 : 0 : 1 : 0
2		2 mol% $Pd(OAc)_2$, Ligand *23*[c] $LINCy_2$, dioxane, 80 °C	1 : 0 : 0 : 0
3		1 mol% $Pd(dba)_2$, P(*t*-Bu)$_3$ $LiNCy_2$, toluene, 23 °C	1 : 0 : 0 : 0
4		5 mol% $Pd(dba)_2$, P(*t*-Bu)$_3$ $LiNCy_2$, toluene, 23 °C	1: 0 : 0 : 0
5		1 mol% $Pd(dba)_2$, P(*t*-Bu)$_3$ ZnF_2, DMF, 80 °C	1: 3 : 0 : 0
6		5 mol% $Pd(dba)_2$, P(*t*-Bu)$_3$ ZnF_2, DMF, 80 °C	0: 1 : 0 : 0
7		2.5 mol% $[P(t\text{-Bu})_3PdBr]_2$ toluene, 23 °C	1 : 0 : 0 : 0
8		15 mol% $[P(t\text{-Bu})_3PdBr]_2$ toluene, 80 °C	0 : 11.3 : 2.1 : 1

[a] For detailed reaction conditions, see the ESI.

[b] Ratios determined by ^1H NMR analysis of the crude reaction mixtures.

[c] Ligand **23** = diisopropyl[2′-methoxy-1,1′-binaphthalen]-2-yl.