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Total Synthesis of Pentacyclic (–)-Ambiguine P Using Sequential Indole Functionalizations

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Abstract

The first synthesis of a pentacyclic ambiguine (ambiguine P) is reported. The synthesis takes advantage of sequential alkylations of an indole core to rapidly construct the pentacyclic framework of the natural product. Key to the success of the synthesis was the use of a Nicholas reaction to alkylate at C2, crafting a fused seven-membered ring that is characteristic of the pentacyclic ambiguines, as well as the use of an amidedirected functionalization at C12 to set a requisite quaternary center. A versatile late-stage intermediate was prepared that may be applicable to the synthesis of the other pentacyclic ambiguines.

The ambiguine natural products,[1] selected examples of which are shown in Figure 1, are a subset of a larger family of indole secondary metabolites known as the hapalindoles.[2] With the exception of four ambiguines, including A (**1**) and H (**2**), which are tetracyclic, the ambiguines possess a fused pentacyclic scaffold featuring a characteristic seven-membered ring moiety. Since the first reported isolation of ambiguine congeners in 1992 from *Fischerella ambigua*,[1a] there have been continued efforts aimed at their total synthesis[3–5] given their intriguing structures. In addition, some members of the hapalindole family, such as the fischerindoles[6] and welwitindolinones,[6b,7] exert a broad spectrum of biological activities, including antimicrobial, antifungal, insecticidal, and anticancer activity as well as phytotoxicity.[1a,c,2a,c,d,6b,8] Therefore, there has also been interest in exploring the function of the ambiguines in a biological context. While preliminary bioactivity studies on the ambiguines have been conducted,[1c–f] comprehensive studies have yet to be undertaken. It is our anticipation that structurally related derivatives of the ambiguines, which may be accessed en route to their chemical preparation, may also possess interesting activity. As such, a total synthesis of the pentacyclic ambiguines could unveil their biological potential

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Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b13388.

Experimental details and spectroscopic data (PDF)

Crystallographic data for **31** (CIF)

Crystallographic data for **S3** (CIF)

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as well as set the stage for an understanding of their biosynthesis, especially the poorly understood late-stage oxidations of the fused seven-membered ring.[9a–c]

No syntheses exist for the pentacyclic ambiguines (**3**–**11**) despite numerous reported attempts.[3] On the other hand, successful syntheses of tetracyclic ambiguine H (**2**) were disclosed by the Baran group in 2007[4] and the Maji group in 2018.[5] Presumably, the seven-membered E ring that is resident in the pentacyclic ambiguines poses an added synthetic challenge. Herein we report a strategy for the preparation of the pentacyclic ambiguines that has culminated in the total synthesis of (−)-ambiguine P (**11**).

In our retrosynthesis (Scheme 1), we envisioned that ambiguine P and related pentacyclic congeners could arise from common intermediate **14** via late-stage oxidation and/or chlorination. Pentacyclic isocyanide **14** could be accessed from **15**, which in the forward sense would require olefination of the formyl group and conversion of the angular nitrile group to an isonitrile group. The C12 quaternary center in **15** would be installed using the primary amide of **16** as a directing group. To access the pentacyclic core of **16**, we envisioned sequential indole C3, C2, and C4 functionalizations, which would ultimately allow the use of readily available starting materials (see **16** ⇒ **19** + **20** + **21**). Notably, to forge the seven-membered ring of the pentacyclic framework, a cobaltmediated Nicholas alkylation at C2 of **18** would be employed, followed by Friedel–Crafts cyclization at C4 to build the C ring.

The key synthetic challenge that had to be considered in preparing the pentacyclic ambiguine natural products lay in the diastereoselective α-functionalization at C12 (see the structure of **5** in Figure 1 for numbering). The stereochemical outcome of this α-functionalization on related systems[10] is dictated by the stereochemistry at C15 leading to the cis-disposed stereodiad, whereas the trans-disposed grouping is required in our case (see the relative stereochemistry between C12 and C15 in **5**). In our approach, we take advantage of a directed α-functionalization using the amide group in **16** to overcome this challenge.[11]

Our synthesis commenced with the elegant Cu(II)-mediated oxidative coupling of indole (**20**) with (*S*)-carvone (**21**) to afford C3-functionalized indole **22** (Scheme 2), following the precedent of Baran.[10] Subsequent 1,2-addition of propargylic alcohol **19** to the enone carbonyl of **22** and Babler–Dauben oxidative transposition[12] afforded enone **18** in 44% yield over the two steps. Cyclization to forge the seven-membered ring that is characteristic of the pentacyclic ambiguines was accomplished in excellent yield through an intramolecular Nicholas reaction[13] wherein the indole C2 site preferentially reacted over C3 and C4. While site-selective Friedel–Crafts alkylation at C4 of the indole nucleus is often challenging because of competition with C2 and C3,[14] with the seven-membered E ring in place in **23**, we found that the combination of 15 equiv each of aluminum chloride and methanol successfully furnished the C ring in the desired pentacycle **17**. Conjugate addition of cyanide to the enone moiety using Nagata's reagent[15] installed a nitrile group that would later serve both as a directing group and a surrogate for the isonitrile moiety. Concomitant trapping of the enolate that resulted from conjugate addition of the cyanide with trimethylsilyl chloride (TMSCl) accomplished in situ protection of the carbonyl group. At this stage, reductive

removal of the dicobalt group using tributyltin hydride[16] yielded pentacycle **24** in 49% yield over three steps.

With access to the key pentacycle **24** in gram quantities over a seven-step sequence from carvone, we sought to address the challenge of setting the C12 quaternary center. Not surprisingly, direct α-vinylation at C12[17] yielded the transdisposed vinyl group (with respect to C15) in accord with Fürst–Plattner selectivity.[18] To overcome this undesired diastereoselectivity, we sought to employ the nitrile group as a directing group. Thus, Rh(I)-catalyzed nitrile hydration[19] gave a mixture of **25** and **16** (Scheme 3). Treatment of this mixture with methyl formate under basic conditions afforded the hemiaminal ether in 54% yield, setting the C12 quaternary center with complete selectivity for the desired stereochemistry. Reduction of the ketone group with sodium borohydride generated alcohol **26**.[20]

Ring opening of hemiaminal ether **26** to give β-cyano aldehyde **27** occurred in 51% yield using triflic anhydride.[21] Presumably, the triflate is ejected upon aqueous workup, which leads to opening of the hemiaminal ether ring.[22] At this stage, transforming **27** by Barton–McCombie deoxygenation[23] of the corresponding thiocarbamate intermediate gave **15** in 43% yield over two steps. While exploring the olefination and nitrile hydration sequence, we discovered that these two transformations could be achieved in a single step. In the event, treatment of **15** with $TMSCH_2Li$ produced the secondary alcohol, which engaged the nitrile group in the presence of pyridinium *p*-toluenesulfonate (PPTS)[24] under microwave irradiation. Subsequent cleavage of the TMS group with tetrabutylammonium fluoride (TBAF) yielded the primary amide and the vinyl group, resulting in an effective marriage of a Peterson-type olefination[25] and nitrile hydration. At this stage, it was necessary to convert the primary amide at C11 to an isonitrile, a functional group that is present in the majority of ambiguine natural products. Hypervalent iodine-mediated Hofmann rearrangement[26] of amide **29** progressed in 39% yield to give the desired tertiary amine **30** along with indolenine **31**, which presumably arose from competing aziridination of the indole C2–C3 double bond[27] followed by ring opening. Subjecting the intermediate tertiary amine (**30**) to a formylation–dehydration sequence yielded pentacyclic isonitrile **14**. Sequential elimination of the isonitrile and allylic oxidation using selenium dioxide gave ambiguine P (**11**) as a mixture of diastereomers (1.5:1 ratio in favor of **11**).

In summary, the first total synthesis of a pentacyclic ambiguine has been achieved in 20 steps from C3-functionalized indole **22**, which is readily available in multigram quantities in a single step from commercial materials.[10] Overall, our approach to the pentacyclic ambiguines highlights rapid construction of the pentacyclic skeleton through sequential alkylative functionalizations of indole using robust C–C bond-forming reactions as well as a novel application of an amide group to accomplish a stereoselective C12 functionalization. With ready access to pentacyclic isonitrile **14**, current efforts are being directed toward its late-stage derivatization to access other pentacyclic members of the ambiguine family that retain the isonitrile group.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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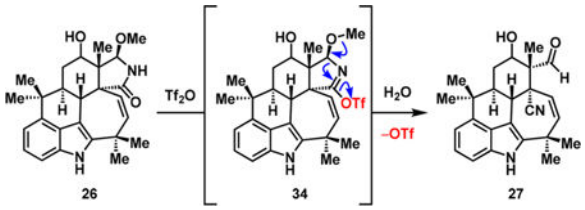

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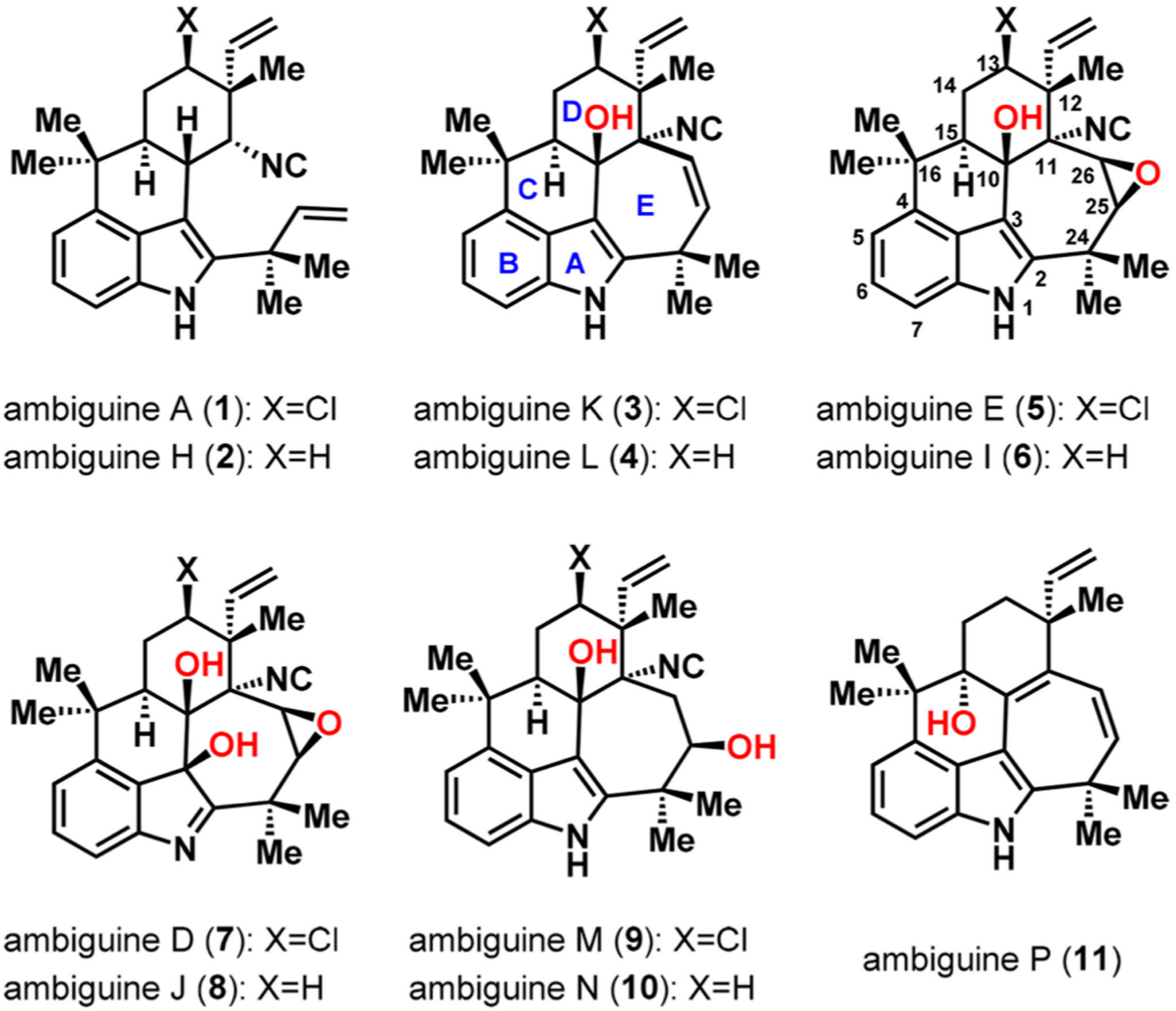
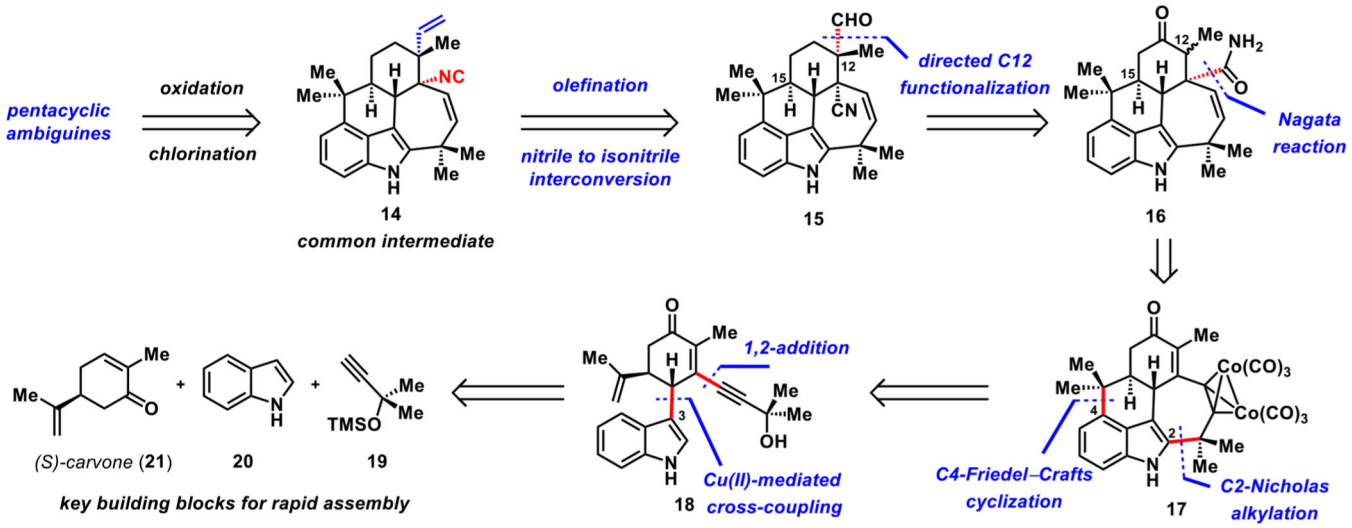
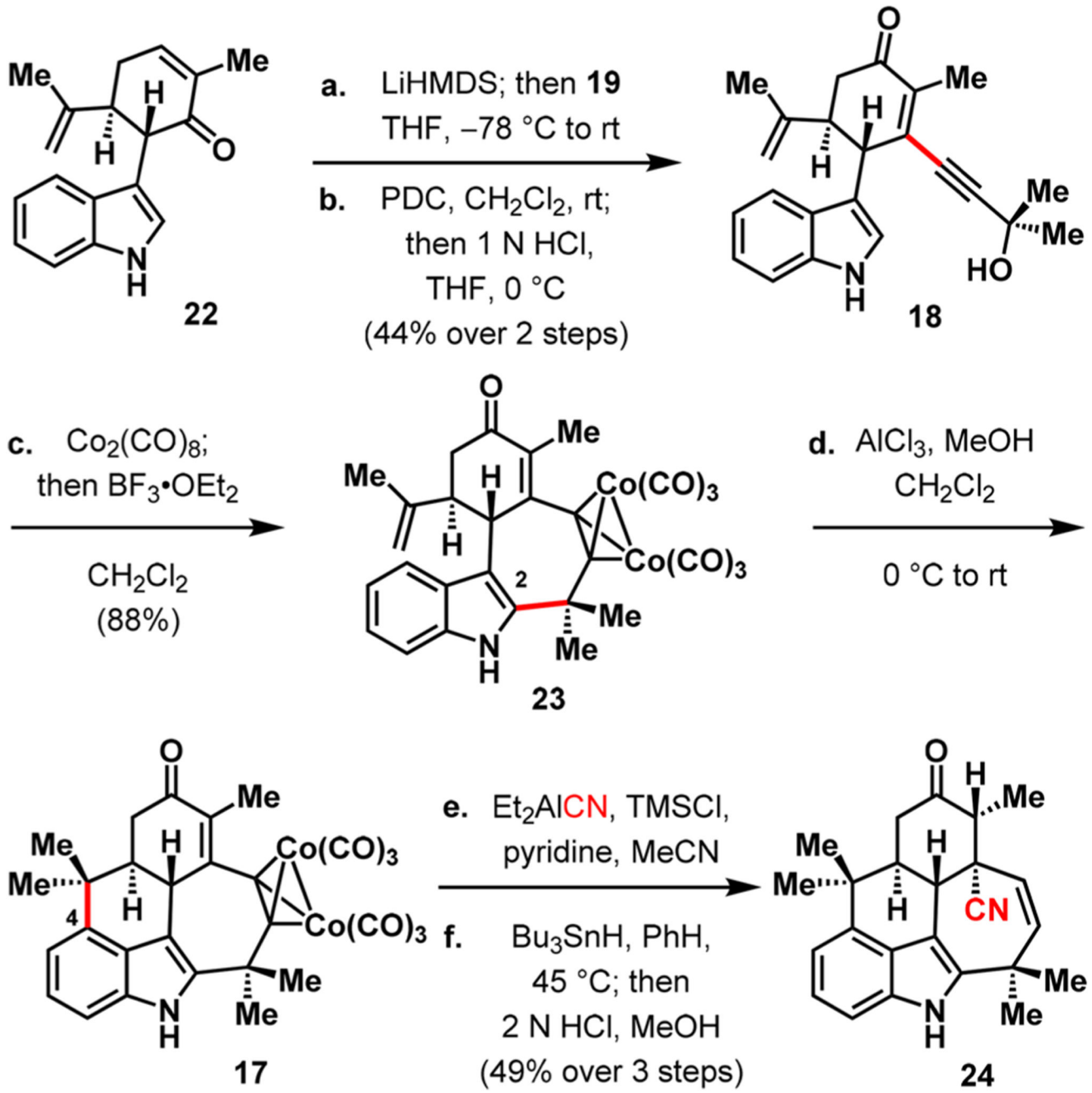


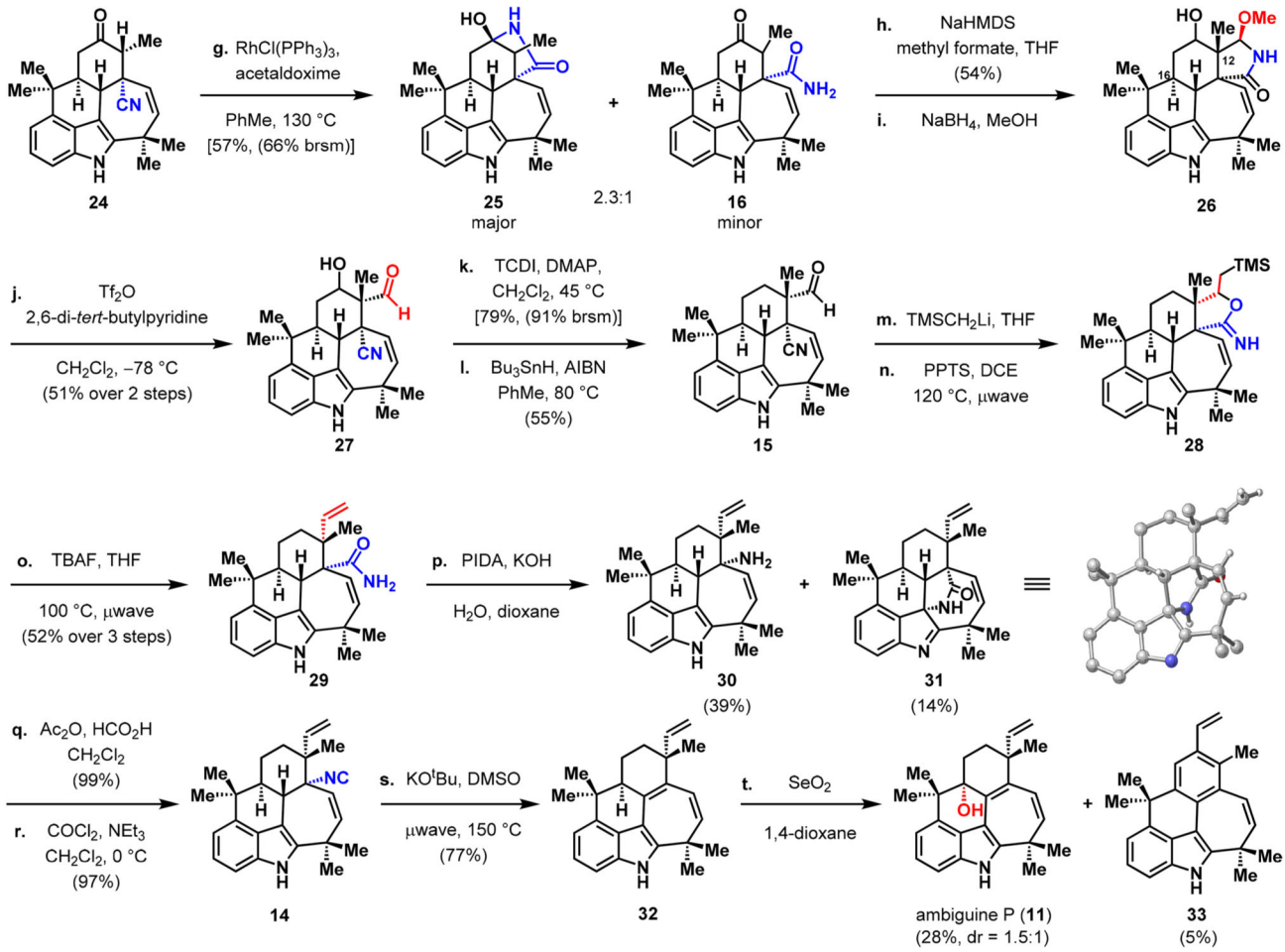
Figure 1.
Selected ambiguine natural products.



Scheme 1.
Retrosynthesis



Scheme 2.
Construction of the Pentacyclic Core



Scheme 3.

Setting the Quaternary Center at C12 and Completion of Ambiguine P