Total Synthesis of (–)-Voacinol and (–)-Voacandimine C

Kristen M. Flynn,[1] In-Soo Myeong,[1] Taylor Pinto,[1] and Mohammad Movassaghi*[1]

[1]Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, United States

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ABSTRACT: We describe the first total synthesis of complex aspidosperma alkaloids (–)-voacinol and (–)-voacandimine C via a late-stage C7-methylenation strategy inspired by a biogenetic hypothesis. We envisioned rapid access to these natural alkaloids from a common, symmetrical precursor assembled by methylenation of a D-ring-oxidized variant of the structurally related natural product (–)-deoxoapodine. Chemoselective N9-oxidation of a pentacyclic deoxoapodine precursor enabled the synthesis of the corresponding hexacyclic C8-aminonitrile. Stereocontrolled methylenation of a C8-enamine derivative of deoxoapodine, accessed by ionization of the C8-aminonitrile, afforded a symmetrical dodecacyclic bisaminonitrile as a versatile precursor to these bisindole alkaloids. Final-stage, biosynthesis-inspired, controlled reductive opening of the oxolane substructures of this dodecacyclic intermediate provided a unified approach to (–)-voacinol and (–)-voacandimine C, while direct reduction of the same intermediate afforded the structurally related (–)-methylenebisdeoxoapodine.

■ INTRODUCTION

The aspidosperma alkaloids are a structurally diverse family of monoterpene indole alkaloids with a characteristic pentacyclic skeleton (Figure 1; rings A–E) containing multiple stereogenic centers and varying levels of oxidation.[1,2] Their complex molecular structures and biological activities have attracted significant interest and has prompted the development of innovative syntheses.[3–24] The bisindole alkaloid (–)-voacinol (**1**), first isolated from *Voacanga grandifolia* in 1987 (Figure 1),[25] is a member of a distinct set of aspidosperma alkaloids with a methylene bridge connecting two aspidosperma units.[1] Alkaloid **1** was isolated again in 2013 along with the structurally related (–)-voacandimine C (**2**) from *Voacanga africana*.[26] Despite advancements in the total synthesis of related bisindole alkaloids,[20–24] there are no reported syntheses of C7,C7'-methylene–adjoined aspidosperma alkaloids. Alkaloids **1** and **2** have significant structural similarities with (–)-deoxoapodine (**4**),[27,28] a hexacyclic alkaloid isolated from *Tabernae armeniaca* in 1975, exhibiting a C2-vinylogous urethane along with C21-oxygenation.[1] Inspired by our observations concerning the reactivity of a transiently formed D-ring iminium ion[29] *en route* to (–)-deoxoapodine (**4**),[30–33] we hypothesized that alkaloids **1** and **2** may be biogenetically accessed by derivatization of (–)-deoxoapodine (**4**). Given prior isolation of natural alkaloids comprised of simpler aspidosperma alkaloids adjoined by a methylene, such as (–)-methylenebismehranine (**6**),[34,35] we posited that (–)-methylenebisdeoxoapodine (**3**) may be of interest as a congener of alkaloids **1** and **2**. Herein we report the first total synthesis of (–)-voacinol (**1**) and (–)-voacandimine C (**2**) by leveraging the reactivity of a D-ring oxidized variant of (–)-deoxoapodine (**4**). Our final-stage diversification of a versatile dodecacyclic intermediate, inspired by consideration of a plausible unified biosynthetic hypothesis, provides both natural alkaloids (–)-**1** and (–)-**2**, in addition to (–)-methylenebisdeoxoapodine (**3**). Samples of the corresponding (+)-*ent*-voacinol (**1**) and (+)-*ent*-voacandimine C (**2**) were also accessed to assist with structure confirmation studies.

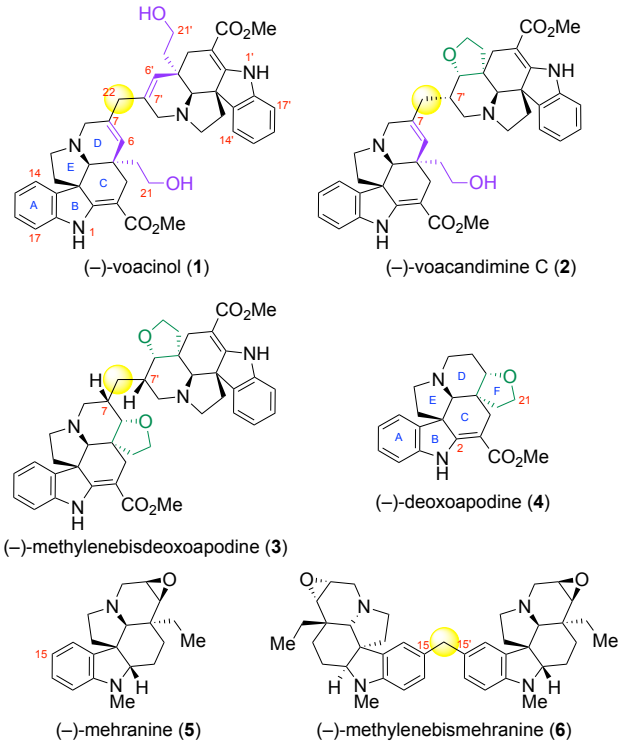
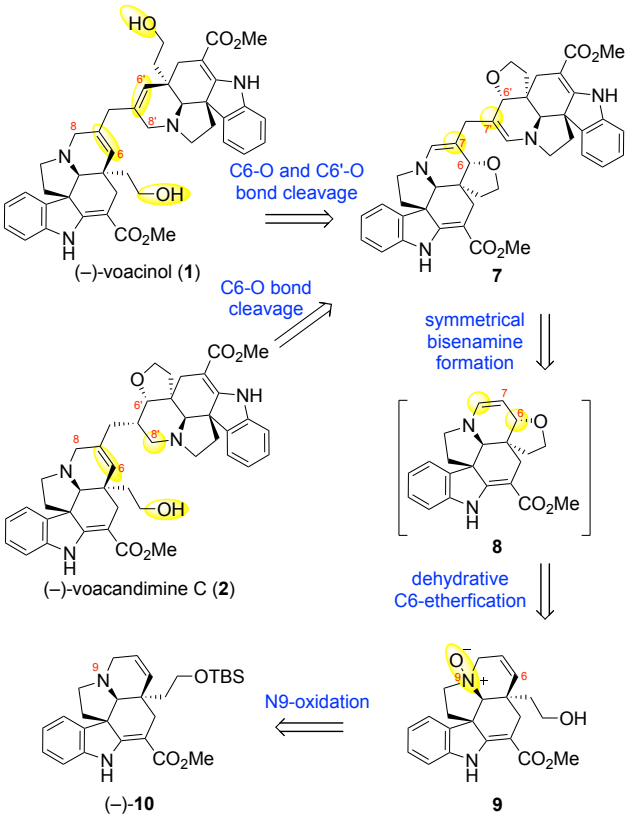


Figure 1. Structures of (–)-voacinol (1), (–)-voacandimine C (2), (–)-methylenebisdeoxoapodine (3), and related aspidosperma alkaloids.

■ RESULTS AND DISCUSSION

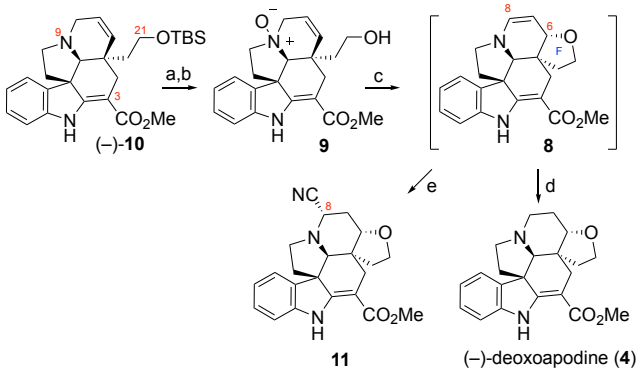
Our retrosynthetic analysis for (–)-voacinol (**1**) and (–)-voacandimine C (**2**) is illustrated in Scheme 1. We envisioned accessing alkaloids (–)-**1** and (–)-**2** through a common symmetrical intermediate **7**. We hypothesized that opening of the two oxolane substructures of dodecacyclic bisenamine **7** and subsequent C8/C8' reduction of the corresponding unsaturated iminium ions would provide (–)-voacinol (**1**, Scheme 1). Furthermore, we speculated that the unsymmetrical, bisindole alkaloid (–)-voacandimine C (**2**) could be accessed through desymmetrization of dodecacycle **7** via reductive opening of a single oxolane substructure. We anticipated that electrophilic activation of one ethereal oxygen of intermediate **7** may allow for generation of the corresponding unsaturated iminium ion, that upon subsequent C8- and C8'-reduction would give (–)-voacandimine C (**2**). We hypothesized that bisenamine **7** could be accessed through an initial C7-methylenation of enamine **8**, yielding an unsaturated iminium ion, followed by nucleophilic addition of a second equivalent of enamine **8**. Enamine **8** could be obtained from N9-oxide alcohol **9** through a biogenesis-inspired dehydrative etherification.[29] We envisioned accessing the pentacyclic N-oxide **9** via chemoselective oxidation of vinylogous urethane (–)-**10**, an advanced intermediate used in our synthesis of kopsifolines A and E.[36]

Scheme 1. Retrosynthetic analysis of (–)-voacinol (1) and (–)-voacandimine C (2).



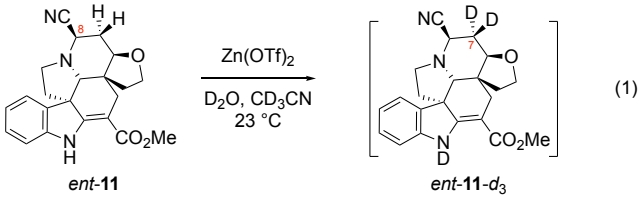
Our synthesis of the key hexacyclic enamine **8** commenced with derivatization of vinylogous urethane (–)-**10** (Scheme 2), a C21-oxygenated variant of tabersonine[37] that we have previously prepared in enantiomerically enriched form in ten steps from a readily available indole derivative.[29,36,38] We found that treatment of vinylogous urethane (–)-**10** (90% ee) with peracetic acid (1.3 equiv)[29,39] provided the desired N9-oxidation (70%) while minimizing a competitive C3-oxidation.[40] Subsequent unveiling of the primary alcohol afforded the N-oxide alcohol **9** in 96% yield (Scheme 2). Exposure of N-oxide **9** to trifluoroacetic anhydride (4.0 equiv) and polystyrene-bound 2-*tert*-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine (PS-BEMP, 6.0 equiv) led to formation of the corresponding unsaturated C8-iminium ion,[29] which upon methanolysis of the primary trifluoroacetate gave the desired F-ring formation and offered the desired hexacyclic enamine **8** (Scheme 2). This strategy provides a new route to (–)-deoxoapodine (**4**) by application of this biosynthesis-inspired dehydrative-etherification on a more advanced pentacyclic substrate containing the C2-vinylogous urethane to introduce the F-ring.[29] Treatment of enamine **8** with excess sodium triacetoxyborohydride (10 equiv) afforded (–)-deoxoapodine (**4**) in 64% yield from alcohol **9**, significantly increasing the overall yield for alkaloid **4** from 21% to 29% from a common tetracyclic precursor.[29,36] Given the sensitivity of enamine **8** toward isolation, we considered its conversion to the corresponding α-aminonitrile as a more stable surrogate.[41–46] Exposure of enamine **8** to *in situ* generated hydrogen cyanide in hexafluoroisopropanol afforded the C8-aminonitrile **11** (*ca*. 10:1 C8-epimers) in 79% yield over two steps (Scheme 2).

Scheme 2. Synthesis of hexacyclic aminonitrile 11.[a]



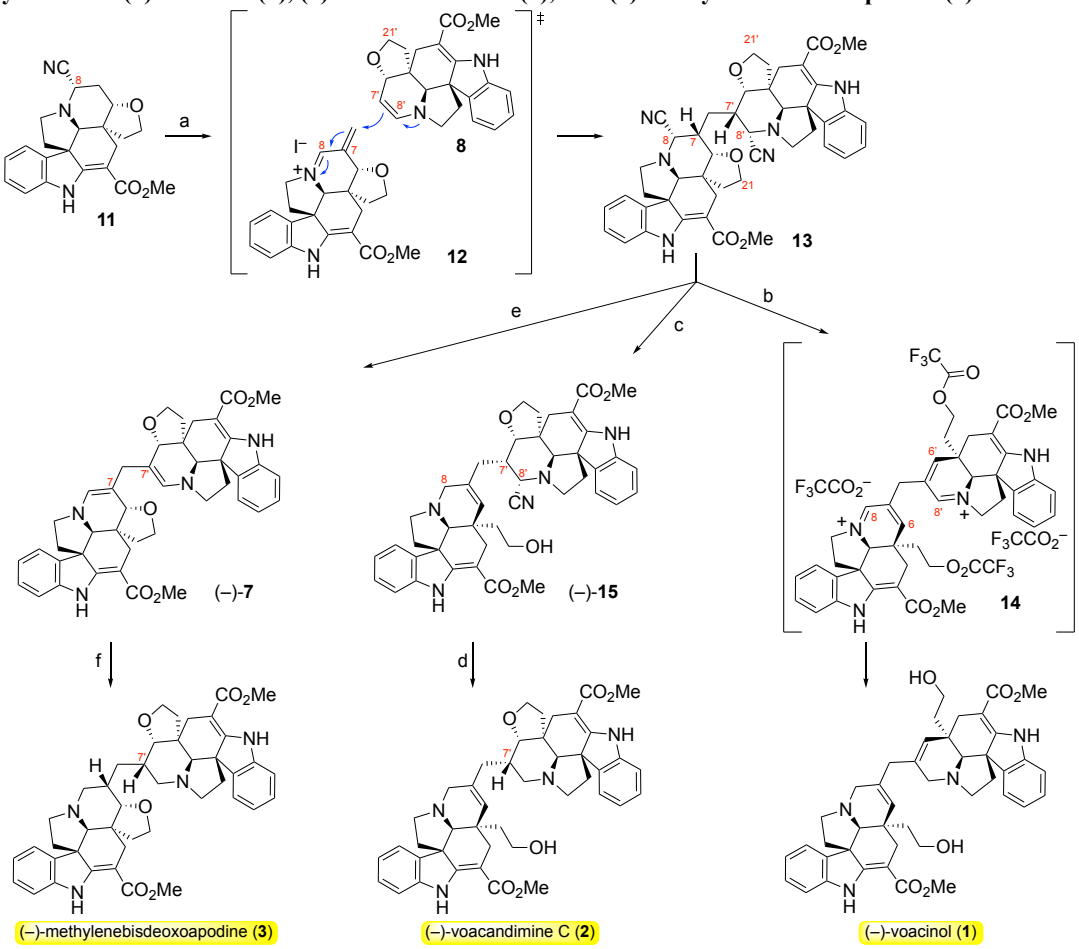
[a] Reagents and conditions: (a) AcO_2H (32 wt. %) in dilute AcOH, K_2CO_3, CH_2Cl_2, 0 ºC, 70%; (b) 20% TFA, CH_2Cl_2; 20% Et_3N, MeOH, 23 ºC, 96%. (c) TFAA, PS-BEMP, CH_2Cl_2, 23 ºC; PS-BEMP, MeOH, 23 ºC; (d) $NaBH(OAc)_3$, AcOH, Et_3N, CH_2Cl_2, 0 → 23 ºC, 64% over two steps; (e) TMSCN, H_2O, HFIP, 0 → 23 ºC, 79% over two steps, 10:1 dr of C8-epimers, major shown.

The utility of C8-aminonitrile **11** as a latent C8-enamine **8** was demonstrated by treatment of *ent*-aminonitrile **11** with zinc trifluoromethanesulfonate (1.0 equiv) in deuterium oxide–acetonitrile-d_3 (1:10 v/v) at 23 °C, resulting in double deuterium incorporation at C7 (>97% *d*-incorporation) over 31 h (eq. 1).



(1)

Scheme 3. Synthesis of (–)-voacinol (1), (–)-voacandimine C (2), and (–)-methylenebisdeoxoapodine (3).[a]



[a] Reagents and conditions: (a) $Zn(OTf)_2$, Eschenmoser's salt, TFE, 1,2-dichloroethane, 23 ºC, 73%, 9:1 dr of C7' epimers, major shown; (b) TFAA, $Zn(OTf)_2$, DTBMP, CH_2Cl_2, 23 ºC; $NaBH_4$, 0 → 23 ºC then Et_3N, MeOH, 95% over two steps; (c) TFAA, CH_2Cl_2, 23 ºC; $NaBH_4$, 0 → 23 ºC then Et_3N, MeOH, 23% over two steps; (d) $Zn(OTf)_2$, $NaBH(OAc)_3$, CH_2Cl_2, 23 ºC, 63%; (e) $AgBF_4$, DTBMP, THF, 23 ºC, 73%; (f) AcOH, $NaBH(OAc)_3$, CH_2Cl_2, 23 ºC, 91%, 1.75:1 dr of C7'-epimers, major C7'-epimer shown.

Monitoring the C7-deuterium-incorporation into *ent*-aminonitrile **11** by ^{1}H NMR spectroscopy measured the rate of electrophilic trapping of the corresponding C8-enamine as evidenced by the convergence of the C8-methine (δ 4.27, dd, J = 6.4, 2.6 Hz) resonance into a singlet. Interestingly, gradual deuterium incorporation was observed at both C7-H_α and C7-H_β, surpassing 50% total *d*-incorporation at C7 in 15 h without observing resonances that correspond to a persistent enamine. Continued exposure to the reaction conditions led to *ent*-aminonitrile **11**-d_3 (*ca.* 10:1 C8-epimers). These observations are consistent with a reversible formation of the C8-enamine from the corresponding C8-aminonitrile, fast electrophilic trapping of the transiently formed C8-enamine, and retention of the C8-stereochemistry. These findings formed the basis of our approach to securing the desired C7-stereochemistry in (–)-voacandimine C (**2**) and related precursors.

Our observations regarding the reactivity and superior stability of aminonitrile **11** compared to enamine **8** compelled us to consider a bisaminonitrile variant of bisenamine **7** *en route* to alkaloids **1**-**2**. We envisioned accessing the dodecacyclic bisaminonitrile **13** (Scheme 3) through activation of aminonitrile **11** in the presence of an electrophilic methylene reagent. Treatment of aminonitrile **11** with zinc(II) trifluoromethanesulfonate (1.0 equiv) in the presence of Eschenmoser's salt (0.50 equiv) led to generation of the exo-methylene conjugated iminium ion **12.** Interception of the iminium ion **12** by a second equivalent of enamine **8** led to the formation of the dodecacyclic bisaminonitrile **13** over 3 h in 73% yield with a high level of stereoselection for the desired (C7*S*,C7'*S*)-diastereomer (C7*S*,C7'*S*-**13**:C7S,C7'*R*-**13**, *ca.* 9:1, major epimer shown in Scheme 3). This strategy proved highly effective for introduction of the C7,C7'-methylene and securing four new stereogenic centers in dodecacycle **13**. Interestingly, while the ratio of C8-epimers of the aminonitrile **11** used to access dodecacycle **13** was found to be inconsequential, the observed level of C7'-diastereoselection for product **13** diminishes with an extended reaction time (6 h, C7*S*,C7'*S*-**13**:C7S,C7'*R*-**13**, *ca.* 2:1). From our observation concerning the formation of *ent*-aminonitrile **11**-d_3 (eq. 1), the erosion of selectivity likely arises from C7'-epimerization via intermediacy of the corresponding C8'-enamine dodecacycle. To further support this, the C8'-enamine dodecacycle could be accessed in 23% yield through exposure of the major (C7*S*,C7'*S*)-diastereomer **13** to zinc(II) trifluoromethanesulfonate (1.0 equiv) in trifluoroethanol and 1,2-dichloroethane (23 ºC, 3 h). These observations are consistent with kinetic preference for the formation of the (C7*S*,C7'*S*)-**13** diastereomer over the (C7S,C7'*R*)-**13** diastereomer.

The versatility of bisaminonitrile **13** to access (–)-voacinol (**1**) and (–)-voacandimine C (**2**) is illustrated in Scheme 3. Addition of zinc (II) trifluoromethanesulfonate (1.0 equiv) and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP, 2.0 equiv) to bisaminonitrile **13** led to opening of both oxolane rings in the presence of trifluoroacetic anhydride (10 equiv), likely via C8- and C8'-enamines, to

give bisiminium ion **14**. The formation of the symmetrical bisiminium ion **14** was supported through observation of key ^{1}H and ^{13}C NMR resonances (600 MHz, $CDCl_3$) including the downfield shift of the C8/C8'- and C6/C6'-methine signals to δ9.02 (s, 2H) and δ7.13 (s, 2H), respectively, and the corresponding downfield shifts for the C8- and C6-carbon resonances at δ162.6 (2C) and δ151.2 (2C), respectively. In-situ reduction of bisiminium ion **14** with sodium borohydride (20 equiv) followed by methanolysis of the trifluoroacetates provided (–)-voacinol (**1**) in 95% yield (2 steps, Scheme 3). All spectroscopic data for our synthetic (–)-voacinol (**1**) was consistent with literature data.[25] The optical rotation data for our synthetic sample of alkaloid (–)-**1** [observed $[\alpha]_D^{23} = -290$ (c = 0.131, $CHCl_3$); lit. $[\alpha]_D^{25} = -105.5$ ($CHCl_3$)] indicated the correct sign with an increased magnitude compared with the literature report.[25] For comparison, a sample of (+)-*ent*-voacinol (**1**) was also prepared using this approach starting with *ent*-vinylogous urethane (+)-**10** (99% ee), and the optical rotation for the enantiomer of the natural product was found to be of similar magnitude but opposite rotation [observed $[\alpha]_D^{23} = +323$ (c = 0.134, $CHCl_3$)].

During optimization of our synthetic route to access (–)-voacinol (**1**), we noted optimal opening of the two oxolanes of bisaminonitrile **13** to form intermediate **14** in the presence of both Lewis acid ($Zn(OTf)_2$) and base (DTBMP). We leveraged the slower rate of oxolane opening without these additives to allow for the planned desymmetrization of dodecacycle **13** (Scheme 3). Treatment of bisaminonitrile **13** with excess trifluoroacetic anhydride (15 equiv), in the absence of other additives, favors activation of a single aminonitrile, leading to a single oxolane ring-opening, likely due to preference for formation of a monocationic intermediate. Exposure of the resulting iminium ion to sodium borohydride (30 equiv) led to C8-reduction, which upon methanolysis afforded allylic amine (–)-**15** as a *single* diastereomer in 23% yield with the majority of the mass balance as recovered (C7*S*,C7'*S*)-**13** starting material (57%) along with (–)-voacinol (**1**) in 10% yield as a minor component.[40] This specific sequence was developed to avoid an undesired C7'-epimerization in synthesis of allylic amine (–)-**15**. The propensity of (C7'*S*)-aminonitrile (–)-**15** to epimerize was noted when it was treated with silver tetrafluoroborate (1.5 equiv) to give the corresponding C8'-enamine, that upon C8'-aminonitrile reformation resulted in recovery of aminonitrile **15** as a mixture of C7'-epimers (C7'*S*:C7'*R*, *ca*. 2:1). Under optimal conditions, treatment of (C7'*S*)-aminonitrile (–)-**15** with $Zn(OTf)_2$ (1.0 equiv) and sodium triacetoxyborohydride (20 equiv) provided (–)-voacandimine C (**2**) as a single diastereomer in 63% yield (Scheme 3). All spectroscopic data for our synthetic (–)-voacandimine C (**2**) were consistent with literature reports.[26,40] The circular dichroism data for our synthetic sample of alkaloid (–)-**2** were consistent with the data points available in the literature.[40] While the optical rotation for (–)-voacandimine C (**2**) has not been reported, we measured the optical rotations of both our synthetic sample of (–)-**2** [observed $[\alpha]_D^{23} = -304$ (c = 0.036, $CHCl_3$)] and a synthetic sample of (+)-*ent*-voacandimine C (**2**) prepared from *ent*-vinylogous urethane (+)-**10** (97% ee) in an earlier stage of our synthetic campaign [observed $[\alpha]_D^{23} = +331$ (c = 0.035, $CHCl_3$)] for comparison. Our synthesis of (–)-voacandimine C (**2**) with complete (C7'*S*)-stereochemical control highlights the functionality of bisaminonitrile **13**.

In addition to the studies described above using dodecacycle **13** as the key intermediate in the synthesis of (–)-voacinol (**1**) and (–)-voacandimine C (**2**), we also pursued the synthesis of the corresponding dodecacyclic bisenamine **7** to evaluate its potential utility in accessing these alkaloids based on our original retrosynthetic analysis (Scheme 1). Our initial attempts to access bisenamine **7** involved treatment of a solution of enamine **8** with Eschenmoser's salt (0.5 equiv) to afford C7/C7'-methylene-dodecacycle **7** in ~30% yield from pentacycle **9**. The capricious formation of bisenamine **7** directly from enamine **8** prompted the examination of an alternative route to bisenamine **7**. Treatment of bisaminonitrile **13** with silver tetrafluoroborate (1.5 equiv) and DTBMP (3.0 equiv) provided the bisenamine (–)-**7** in 73% yield (Scheme 3). Notably, the C7,C7'-methylene substitution of bisenamine (–)-**7** provides greater stability toward isolation as compared to the hexacyclic enamine **8**. Sequential exposure of bisenamine (–)-**7** to acetic acid (15 equiv) followed by addition of sodium triacetoxyborohydride (15 equiv) afforded (–)-methylenebisdeoxoapodine (**3**) along with the corresponding minor C7'-epimer in 91% yield (C7*S*,C7'*S*-**3**: C7*S*,C7'*R*-**3**, *ca*. 1.75:1, major epimer shown in Scheme 3).[40] The formation of the (–)-(C7'*S*)-methylenebisdeoxoapodine (**3**) as the major product is consistent with protonation of bisenamine (–)-**7** occurring from the less hindered *si*-face of the C8- and C8'-enamines, leading to the diastereomer calculated to be more stable.[40] Parallel experiments conducted using *ent*-bisenamine (+)-**7** not only offered further insights into its reactivity and relation to alkaloids **1** and **2**, but also provided enantiomeric samples of these alkaloids for comparison as described above. Exposure of *ent*-bisenamine (+)-**7** to trifluoroacetic anhydride (1.0 equiv) and subsequent reduction of both the C8-iminium ion and the C8'-enamine, requiring excess sodium borohydride (30 equiv) as the reductant, led to formation of (+)-*ent*-voacandimine C (**2**) and its C7'-epimer in 48% yield (C7'*S*:C7'*R*, *ca*. 1:6) along with (+)-*ent*-voacinol (**1**) in 24% yield. Furthermore, sequential treatment of *ent*-bisenamine (+)-**7** with trifluoroacetic anhydride (5.0 equiv) and sodium borohydride (30 equiv) led to formation of (+)-*ent*-voacinol (**1**) in 89% yield (two steps), confirming our hypothesis for direct conversion of dodecacycle **7** to alkaloid **1** (Scheme 1). These observations support the possible involvement of bisenamine **7**, or a hydrated variant as the corresponding C8/C8'-hemiaminal, in the biogenesis of alkaloids (–)-**1** and (–)-**2** (Scheme 1), and further highlight the utility of bisaminonitrile **13** in providing exquisite C7'-stereochemical control.

■ CONCLUSIONS

In summary, we have reported the first total synthesis of bisindole alkaloids (–)-voacinol (**1**) and (–)-voacandimine C (**2**). Late-stage diversification of a common dodecacyclic intermediate, accessed via C7-methylenation of a D-ring oxidized variant of the related alkaloid (–)-deoxoapodine (**4**), formed the basis of our approach to these alkaloids inspired by a plausible unified biosynthetic lineage. Detailed examination of key transformations, including reversible formation of enamine **8** from aminonitrile **11**, reactivity of bisaminonitrile **13**, and the controlled net reductive ring opening of its oxolane substructure, and *in situ* observation of the bisiminium ion **14**, informed our development of optimal conditions for the concise and stereocontrolled synthesis of (–)-voacinol (**1**) and (–)-voacandimine C (**2**) from pentacycle **10**[36] in seven and eight steps, respectively. This approach provided the first synthetic samples of bisindole alkaloids (–)-**1** and (–)-**2**, along with the corresponding enantiomers and derivatives of interest, including (–)-methylenebisdeoxoapodine (**3**), for detailed structural analysis. Furthermore, we demonstrate the viability of the dodecacyclic bisenamine (–)-**7** as a plausible biosynthetic precursor to (–)-voacinol (**1**) and (–)-voacandimine C (**2**, Scheme 1), and highlight factors that influence control of stereochemistry in these C7,C7'-methylene–adjoined bisindole aspidosperma alkaloids.

ASSOCIATED CONTENT

The Supporting Information is available free of charge.

Experimental procedures, spectroscopic data, and copies of ^{1}H, and ^{13}C NMR spectra (PDF)

AUTHOR INFORMATION

Corresponding Author

*Email: movassag@mit.edu

ORCID

Mohammad Movassaghi: 0000-0003-3080-1063

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Notes

The authors declare no competing financial interest.

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