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Synthesis studies on the *Melodinus* alkaloid meloscine

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ABSTRACT

The pentacyclic *Melodinus* alkaloid (±) meloscine was synthesized in 19 chemical steps from 2 bromobenzaldehyde through a route featuring an allenyl azide cyclization cascade to deliver the core azabicyclo[3.3.0]octane substructure. Peripheral functionalization of this core included a Tollens type aldol condensation to set the quaternary center at C(20) and a diastereoselective ring closing metath esis to forge the tetrahydropyridine ring.

1. Introduction

The *Melodinus* alkaloids comprise a small class of plant derived pentacyclic compounds isolated from either Apocynaceae or Kopsia species.[1] Among the 14 members of this family, three related iso lates all extend from the melodan skeleton, Fig. 1. The complex and compact framework of scandine (**3**) has been hypothesized to emerge from rearrangement of the more common tabersonine species.[1,2] Scandine then can serve as the direct precursor to both meloscine (**1**) and epimeloscine (**2**) via decarboxymethylation. Permissive evidence for this biosynthesis proposal was garnered by Palmisano et al., who documented a high yield (72%) pinacol type shift in a system related to **4**→**3**.[3a] Alternatively, Hugel and Lévy have described a high temperature rearrangement process that passes through an aziridine intermediate en route to the melodan skeleton from a tabersonine derivative.[3b,5a]

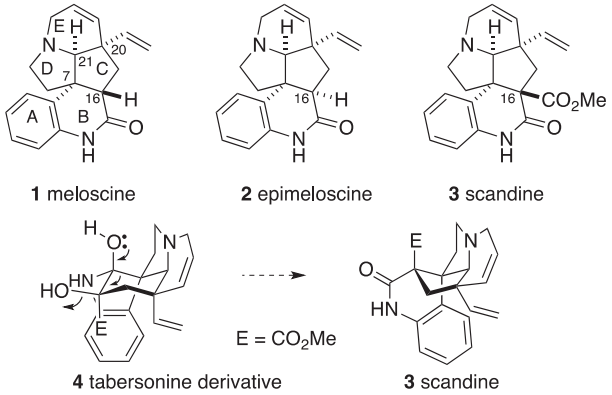

Fig. 1. Alkaloids with the melodan skeleton from Apocynaceae *Melodinus*; a bio-synthetic hypothesis for the formation of the melodan structure from a tabersonine precursor.

The melodan alkaloids have remained an enduring challenge for chemical synthesis, with reports spanning the last three decades that describe either approaches to,[3,4] or syntheses of,[5] one or more members of this family. The melodan alkaloids' congested bicyclic core, featuring four contiguous stereogenic carbon atoms about a cyclopentane ring, two of which are all carbon quaternary cen ters, poses a formidable test for stereoselective synthesis. Not sur prisingly, this challenge has been addressed through widely differing synthesis strategies, and four total syntheses have been recorded prior to our work, Scheme 1. The initial success in this area was reported by Overman et al.,[5b] who relied on an aza Cope–Mannich sequence (**5**→**6**) for the elaboration of the racemic meloscine core. This work stood as the only total synthesis of meloscine for almost 20 years, when in 2008 Bach et al. described a synthesis of natural (+) meloscine through an enantioselective [2π+2π] photocycloaddition of **7** and methyl 2 (trimethylsiloxy) acrylate to furnish the cyclobutyl containing species **8**.[5c,d] Neither the Overman work nor the Bach work delivered the core cyclo pentyl C ring directly; in the former case, a Wolff reaction mediated ring contraction was utilized to formulate this ring, whereas in the latter case, a pinacol like ring expansion served the same strategic function. More recently, Mukai et al. have completed a synthesis of (±) meloscine through Pauson–Khand cyclization of

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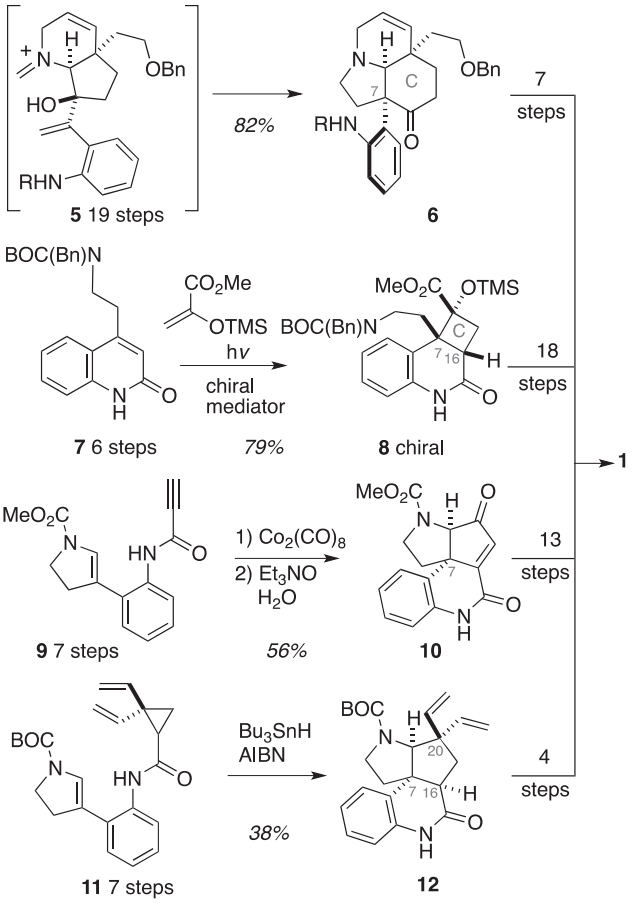
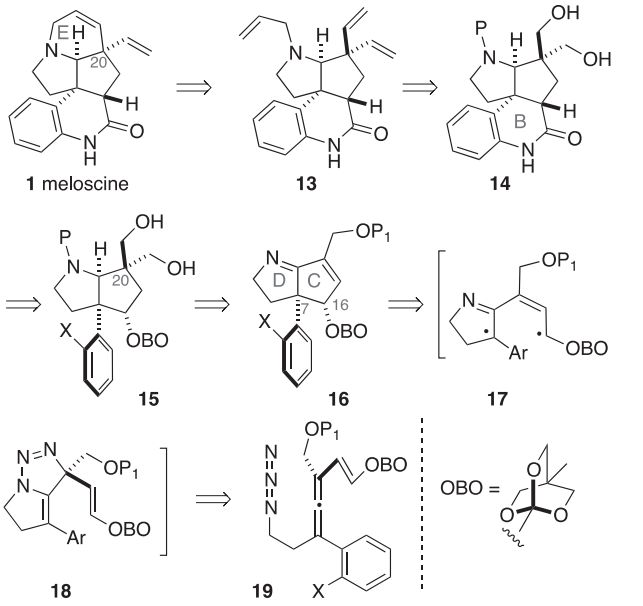


Scheme 1. Prior art in the total synthesis of meloscine.



Scheme 2. Retrosynthetic analysis of meloscine via allenyl azide cascade cyclization chemistry.

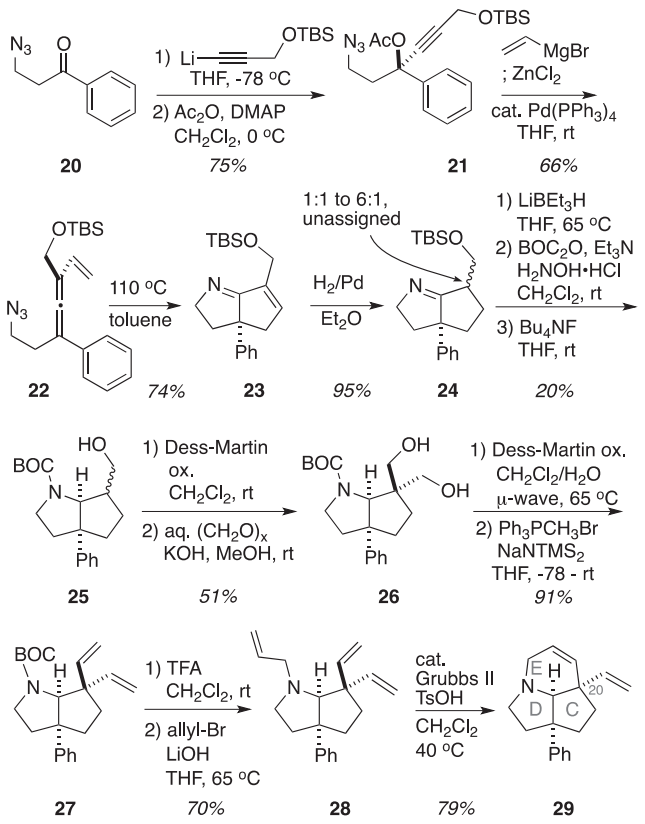
the propynoylamide **9** to furnish the tetracyclic core of meloscine **10**.[5e] Soon thereafter, Curran et al. detailed the most efficient construction of meloscine to date through a radical mediated [3 atom+2 atom] addition within divinyl cyclopropane **11** to afford tetracycle **12**.[5f] Both the Mukai and the Curran approaches do deliver the central cyclopentanoid C ring directly and with the correct stereochemistry for meloscine at C(7) and C(21). The Curran cyclization chemistry furnishes the product tetracycle with the correct stereochemistry at C(16) for epimeloscine but not meloscine. However, the ready epimerization of the epimeloscine skeleton to meloscine is not problematic per the earlier observations of Bernauer et al.[1a] Thus, Curran's synthesis delivers not only epimeloscine but meloscine as well.

A different conceptualization of the meloscine problem can be envisioned, Scheme 2. Advances in allenyl azide cascade cyclization chemistry[6] has enabled the development of a synthesis strategy for meloscine that features efficient formation of the C/D ring azabicyclo[3.3.0]octane core with complete relative stereochemical control at C(7) and C(16). In this strategy, allenyl azide **19** plays a pivotal role; thermolysis of this species is expected to proceed through a reaction sequence involving first [3+2] cycloaddition to deliver an unisolable triazoline **18** whose subsequent fragmentation is driven by release of strain.[6d,g] Loss of N_2 from **18** should furnish the singlet diyl **17**, which is poised for formal electrocyclization through a conrotatory pathway to provide the C/D ring bicyclic product **16** as the diastereomer shown.[6d,g] Two further operations are required in order to convert **16** into the target meloscine; (1) union of the aryl ring with a carboxylic acid derivative, which would be revealed by deprotecting the OBO function, to deliver lactam ring B, and (2) construction of tetrahydropyridine ring E from the extant C(20) and nitrogen substituents. At the outset of this work, it was not obvious, which of these two operations should be executed first, so maintaining flexibility to pursue both options via appropriate choice of P and P_1 was built into the plan. In addition, formation of the C(20) quaternary center (**16**→**15**) was anticipated to be a difficult transformation, given the steric hindrance in the local environment of the C ring, and so several different options were envisioned. Finally, the ultimate operation of the synthesis route was anticipated to be a diastereoselective ring closing metathesis between the *N* allyl fragment and the β face vinyl appendage of **13**. At the initial planning stages, the expectation for diastereoselectivity in this transformation was undergirded by nothing more than density functional calculations on **1** and its C(20) epimer. While this work was in progress, both the Mukai and the Curran syntheses of meloscine were published; each utilized this same metathesis based ring closure, and no evidence for a C(20) epimer was reported. A preliminary account of this work has been published;[7] this report elaborates on that disclosure and details the detours, derailments, and dead ends encountered along the way to meloscine.

2. Results and discussion

Three issues were paramount at the outset of the meloscine synthesis effort as delineated in Scheme 2: (1) Would the ring closing metathesis to form the E ring proceed with satisfactory diastereoselectivity? (remembering that neither the Mukai nor the Curran precedents were reported yet) (2) What X group at the *ortho* position of the aryl ring would be tolerated during the chemistry used to prepare an advanced intermediate B ring precursor? (3) Should the E ring or the B ring be closed first? Either option has the potential to rigidify the resultant molecular skeleton and thereby influence the facility of the second choice ring closure.

The first issue (metathesis diastereoselectivity) was addressed with a model system that explicitly tested the metathesis based closure of the E ring but avoided any issues associated with the nature of the 'X' substituent or its use in lactam ring closure, Scheme 3. In this model system, the simple unfunctionalized benzoyl derivative **20**[8] served as the launch point. Acetylide addition to **20** and acetylation of the resulting alcohol delivered the activated



Scheme 3. A meloscine model system to validate the E-ring assembly strategy.

propargyl system **21**, which was vinylated using Vermeer's[9] Zn/Pd based protocol. This allene forming procedure has proven quite reliable and robust for forming allenyl azide cyclization substrates.[6d] The product allenyl azide exhibited only marginal stability and so it was heated immediately in refluxing toluene to initiate the cascade cyclization sequence and furnish the meloscine model system C/D bicyclic core **23** in good yield.

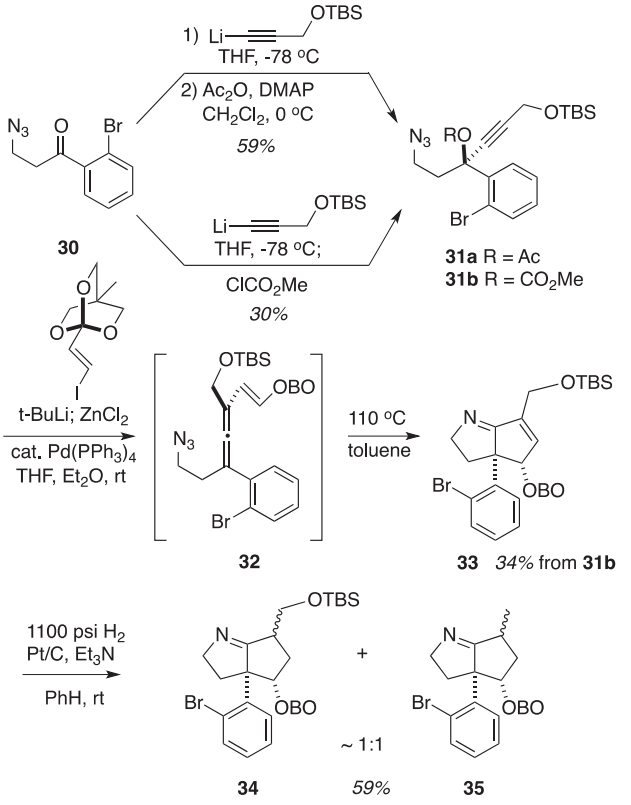
Hydrogenation of the cyclopentenyl alkene within **23** provided the partially saturated system **24** as an inconsequential mixture of diastereomers whose ratio varied from run to run. Reduction of the imine function could not be realized through hydrogenation under a variety of conditions, presaging one of the more unexpectedly difficult transformations of the sequence. Many hydride sources and reaction conditions were examined (i.e., L Selectride, $NaBH_3CN$/CSA, allyl iodide, then $NaBH_3CN$) before a successful and reproducible reduction procedure utilizing superhydride at elevated temperature was identified. Steric hindrance is plausibly the culprit, a conclusion consistent with the subsequent failure to attach a Boc group to the secondary amine formed from **24** under standard (Boc_2O, DMAP) conditions. Recourse to the more forcing conditions of Harris,[10] which feature a transient *O* Boc hydroxylamine intermediate, did proceed in only modest yield. Desilylation of the TBS ether in **24** and then oxidation of the resulting primary alcohol in **25** affords an intermediate aldehyde that serves as input for one of the key transformations of the synthesis; introduction of the quaternary all carbon center at C(20). One potential concerning aspect of the plan to generate a C(20) dialdehyde from **25** extends from the propensity of such systems (or a precursor α hydroxymethyl aldehyde) to suffer facile deformylation or decarbonylation. Fortunately, a well precedented workaround presented itself; use of a Tollens type aldol reaction,[11] which generates a dialcohol product and thereby avoids all deformylation (decarbonylation) triggers. Thus, simply treating the aldehyde derived by oxidation of the alcohol within **25** with aqueous formaldehyde and base furnished the diol **26** in moderate yield and free of byproducts. The structure and stereochemistry of diol **26** were verified by single crystal X ray analysis.[12]

The anticipated problems with a C(20) dialdehyde became real when the next operation was attempted; the double oxidation of the diol within **26** to give the corresponding dialdehyde. Initial failures with standard oxidation protocols (Swern, PCC, Dess–Martin, Parikh–Doering all resulted in formation of only traces of aldehyde containing products) led to a rethinking of the problem. TLC evidence indicated that in each case, starting diol **26** was readily consumed but complex product mixtures, whose mass spectrometric analysis was consistent with the presence of compounds containing CH(CHO) and C(CH_2OH)(CHO) units, resulted. If product dialdehyde instability was the issue, then a procedure that minimized the time that the product was exposed to nucleophilic/basic media might be advantageous. Toward this end, the rate accelerating effects of water in Dess–Martin oxidations have been noted.[13] This modification was attempted, but the reaction still produced complex mixtures of aldehyde containing products. Microwave irradiation of reactions also can provide rate acceleration, and so that experimental modification was employed, finally to great consequence. The dialdehyde derived from diol **26** could be prepared in relatively clean form and in good yield by a brief microwave assisted water saturated Dess–Martin oxidation protocol, but all attempts to concentrate, isolate, and characterize this dialdehyde were accompanied by extensive decomposition. Thus, the dialdehyde was used as a crude material. Exposure of this sensitive dialdehyde to a large excess of preformed methylenetriphenylphosphorane proceeded smoothly to deliver the C(20) divinyl product **27** in overall excellent yield.

Conversion of the *N* Boc moiety within **27** into the corresponding *N* allyl derivative proceeded uneventfully, and the triene **28** was in hand to test the final C–C bond forming transformation. Density functional calculations[14] suggested that the desired C(20) vinyl epimer **29** should be more stable than the C(20) epimeric alternative by 12 kcal/mol. Use of the Grubbs II metathesis reagent should permit the system to reach equilibrium, thus exploiting this energy difference to achieve the desired diastereoselectivity. In the event, treatment of triene **28** with a catalytic amount of Grubbs II catalyst in refluxing methylene chloride sufficed to deliver only the desired C(20) epimer of tricycle **29**, with an intact E ring as per the ultimate meloscine synthesis goal. Thus, this model system addresses the first strategic concern and sets the stage for exploration of the other two issues en route to the authentic target meloscine.

The second questions raised above regarding the identity of the aryl substituent 'X' in cyclization substrate **19** was addressed in a simpler model system ($H_3C{-}C{\equiv}C{-}Li$ addition rather than $TBSOCH_2C{\equiv}C{-}Li$ addition to $ArC(=O)CH_2CH_2N_3$) in an earlier study.[6d] Attempts to prepare and cyclize allenyl azide substrates related to **22** with either *ortho* NO_2 or *ortho* BocHN groups on the aryl ring did not afford any bicyclic product. These failures left the *ortho* bromo alternative as the most attractive option, as detailed below. This choice of aryl substituent places constraints on the type of carboxylic acid derivative that can be employed in B ring formation, and also on the type of amide forming chemistry planned for the closure of the B ring (vide infra).

The first implementation of these lessons learned began with the acetate **31a**, prepared from the *ortho* bromoaryl substituted azide **30**,[6d] Scheme 4. However, this apparently routine beginning became less than auspicious as this acetate was unreactive in the Vermeer palladium mediated zincate addition that served so reliably in all earlier studies. The presence of the OBO group on the alkene initially was assumed to be responsible for the failure to react, given that the simple ethylene zincate $H_2C{=}CH{-}ZnCl$ did work with a similar arylbromide containing substrate[6d] and with

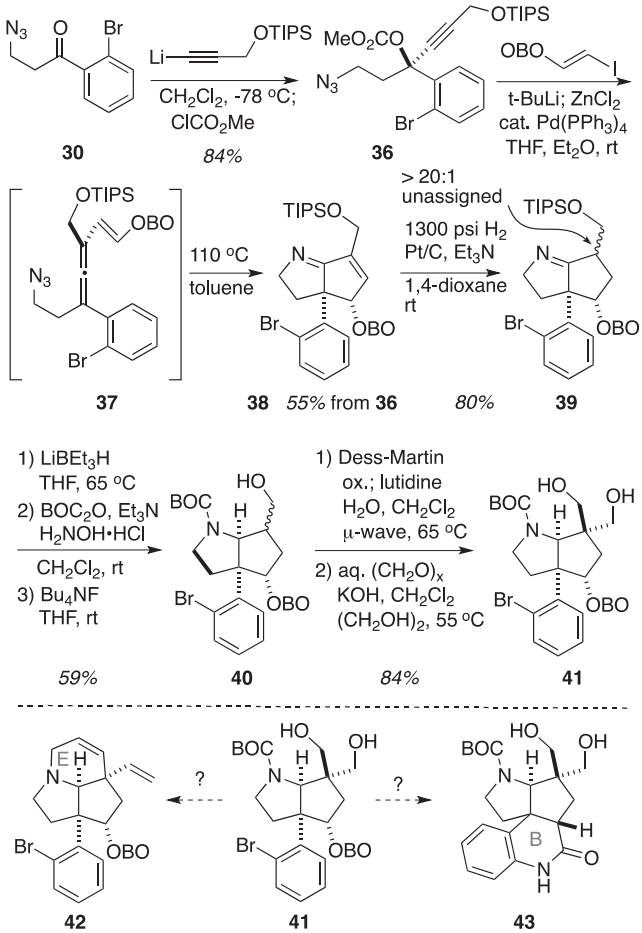


Scheme 4. Synthesis of the meloscine C/D bicyclic core via allenyl azide cascade cyclization chemistry first attempt.

31a as well.[15] An additional control experiment documented that the OBO bearing zincate (prepared from the corresponding known lithiate)[16] did react smoothly with the des bromo substrate **21** to give allene product.[15] Thus, neither the OBO group nor the presence of the aryl bromide per se appears sufficient to shut down the Vermeer chemistry. However, their combination apparently is deadly to the prospects of forming **32** from **31a**. A suitable compromise between reactivity and stability was found with the carbonate **31b**,[17] which did engage the OBO bearing zincate in productive allene formation and produced the desired cascade cyclization substrate **32** in good yield. Unfortunately, this allenyl azide was not stable to isolation and purification by chromatography, and so the crude allene formed from the zincate addition was subjected to immediate thermolysis in toluene to afford the expected azabicyclo[3.3.0]octane core of the meloscine structure, **33**, with the key C(7)/C(16) stereochemical relationship set as anticipated (vide supra).

Standard palladium mediated hydrogenation of the cyclopentenyl alkene of **33** via the same procedure used in the des bromo model system **23** was not an option, given the facility of palladium mediated Ar–Br hydrogenolysis. In addition, the acid lability of the OBO group might render even trace production of HBr (from minor hydrogenolysis of the Ar–Br bond) problematic. Therefore, an extensive catalyst screening effort was undertaken with **33** and various Pd, Pt, Ni, and Ir based systems in protic and non protic solvents, at a range of H_2 pressures (15–1100 psi), and with various basic additives. In the end, the only satisfactory conditions identified involved Pt/C with Et_3N as additive at 1100 psi of H_2 in benzene. Under these specified conditions, the cyclopentenyl system **33** was converted to an equal mixture of the desired hydrogenated product **34** and the overreduced hydrogenolysis product **35**. The Br moiety survived intact, but the OTBS ether did not. This observation led to a minor rerouting of the meloscine synthesis approach in order to remove the silyl ether vulnerability.

Apparently, access to the C–O bond of silyl ether **33** by the Pt surface is competitive with simple alkene hydrogenation, leading to the mixture of **34** and **35**. That observation suggests that discouraging such access, perhaps by increasing the steric profile of the silyl ether, may suffice to turn the product distribution toward the desired hydrogenated species. A test of this simple premise was executed with the TIPS ether analogue of propargyl alcohol, Scheme 5. Optimization studies of carbonate formation led to the discovery that performing the initial alkynyl lithiate addition to **30** in CH_2Cl_2 rather than in THF resulted in far superior yields of the intermediate alcoholate, and hence better yields of the derived carbonate **36**. The remainder of the azabicyclo[3.3.0]octane preparation proceeded without event, and the key C/D ring synthon **38** was formed in overall good yield from carbonate **36**. The structure and stereochemistry of **38** were confirmed by single crystal X ray analysis.[7] In the critical departure from the failed Scheme 4 chemistry, hydrogenation of **38** at high pressure under Pt catalysis produced the alkene hydrogenation product **39** with only trace amounts of a hydrogenolysis byproduct detected. At this point, reliance on the chemistry developed with the model system (Scheme 3) sufficed to push the hydrogenation product **39** through to the C(20) quaternary diol **41**. The conversion of monoalcohol **40** into the diol **41** benefited from some optimization efforts relative to the model system work. Application of the 'standard' (model system, **25**→**26**) Dess–Martin oxidation conditions to **40** proceeded in 32–78% yield to **41**, but application of the newly formulated superior conditions to the oxidation of **40** (microwave assisted, water saturated CH_2Cl_2 solvent, heating to 65 °C) led to yield improvement. In addition, initial application of the model

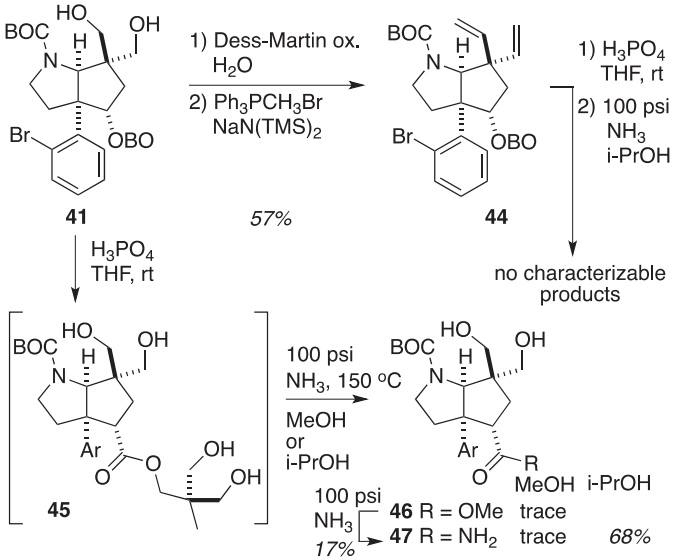


Scheme 5. Synthesis of the meloscine C/D bicyclic core via allenyl azide cascade cyclization chemistry second attempt introduction of the C(20) quaternary center.

system Tollens aldol conditions (KOH, methanol, aqueous formaldehyde, room temperature) to the aldehyde derived from **40** was not successful; complete consumption of the aldehyde with no product diol formation was observed. However, simply elevating the reaction temperature to 55 °C and using ethylene glycol and CH_2Cl_2 as co solvents overcame whatever problems derailed the room temperature reaction, and the desired diol **41** was formed in excellent yield.

At this juncture, a strategic decision was at hand; should B ring formation (**41**→**43**) or should E ring formation (**41**→**42**) be pursued first? Furthermore, the precise timing of OBO hydrolysis factored into this decision, as the OBO group's acid sensitivity might limit some approaches to either target **42** or **43**. Following the best traditions of natural product synthesis, all options were pursued simultaneously, with the winning approach to be identified only in retrospect.

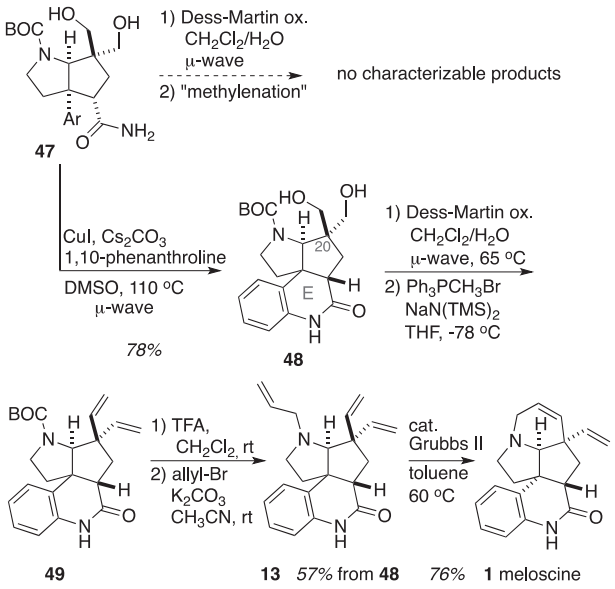
Initial scouting experiments designed to probe the 'E ring first' strategy with the OBO group intact are shown in Scheme 6. The diol **41** could be oxidized under standard Dess–Martin conditions and the resulting sensitive dialdehyde was immediately methylenated with a large excess of Wittig reagent to provide the divinyl species **44**. Partial hydrolysis of the OBO unit in **44** under mild acid catalysis appeared by ^{1}H NMR spectroscopic analysis to provide an intermediate 2 methyl 2 (hydroxymethyl)propane 1,3 diol ester. Unfortunately, all attempts at aminolysis of this intermediate ester met with either recovery of the ester or complete decomposition. A reordering of operations seemed justified after this disappointing result, and so initial hydrolysis/aminolysis of the OBO unit prior to diol functionalization was pursued next. Acid mediated hydrolysis of OBO diol **41** again provided an intermediate ester **44**, which resisted aminolysis under anything less than forcing conditions. High pressures of ammonia maintained in a Parr bomb apparatus in methanol solvent at 150 °C provided the first glimpse of success, as small amounts of the desired amide **47** along with methyl ester **46** were isolated. Resubmission of the methyl ester **46** to aminolysis conditions led to some conversion to the amide **47**, but the yield remained low even after extended reaction times. These observations undermined one of the assumptions underlying this experimental approach; passage through an intermediate methyl ester was initially presumed to be a favorable (or at least not unfavorable) event, as aminolysis of methyl esters are typically facile.[18] Rather, it appeared that methyl ester **46** was actually a 'trap' for



Scheme 6. Functionalization along the C/D core periphery.

substrate from which formation of the desired primary amide was difficult at best. The obvious workaround was to remove the offending methanol from the reaction medium. Substitution of isopropanol as solvent throughout but otherwise maintaining the vigorous Parr bomb conditions led to formation of the desired primary amide **47** in good yield, and free of any ester byproduct.

The acquisition of primary amide **47** provided a new substrate upon which to revisit the earlier question, 'E ring first or B ring first?' An 'E ring first' strategy requires conversion of the diol in **47** into a divinyl derivative, Scheme 7. Oxidation of this diol under the modified Dess–Martin conditions did furnish the unstable dialdehyde as a clean compound that, like the related dialdehydes discussed earlier, resisted chromatographic purification. As in the earlier studies (Scheme 3, **25**→**26** and Scheme 5, **40**→**41**), a large excess of preformed methylenetriphenylphosphorane was added to this crude dialdehyde. Unfortunately, only dialdehyde decomposition ensued, and no characterizable compounds were isolated. Exploration of alternative methylenation procedures (Tebbe's reagent, Cp_2TiMe_2, $TMSCH_2Li$, even a few phosphonates) was no more successful. The primary amide function appeared to be incompatible with any methylenation conditions attempted. Thus, the 'E ring first' strategy was put to rest.



Scheme 7. Completion of the synthesis of (±)-meloscine.

The 'B ring first' approach commenced with a transition metal mediated amidation reaction between the primary amide nitrogen and the aryl bromide within **47**. Many variants of this formal aza Ullmann coupling have been described, but the simplicity and reliability of a Goldberg type Cu mediated recipe stood out.[19] In fact, exposure of **47** to CuI/1,10 phenanthroline in DMSO under both heating and microwave irradiation[19c] delivered the intact lactam ring in excellent yield. No evidence for any debrominated material was forthcoming. With the E ring installed, attention turned to the C(20) diol moiety, whose oxidation/methylenation now had to transpire with the added constraint of the presence of the secondary amide. Fortunately, this sequence proceeded without any interference from the amide unit, and the C(20) divinyl containing product **49** was formed in good yield. The large excess of Wittig reagent necessary to push the bis methylenation to completion had in this case a deleterious side effect; it proved impossible to purify the divinyl compound **49** from byproducts from the excess Wittig species. Therefore, it was expedient at this point to simply carry the

impure **49** through the Boc removal/N allylation sequence and purify triene product **13**. Triene **13** was subjected to the same Grubbs ring closing metathesis conditions observed to be successful in the model series (Scheme 3, **28**→**29**) in order to close off the E ring and deliver (±) meloscine (**1**) free of any C(20) epimeric material.

3. Conclusions

The *Melodinus* alkaloid meloscine was prepared by total chemical synthesis over 19 steps from *ortho* bromobenzaldehyde in 2.2% yield overall. This route compares favorably with the earlier approaches of Overman (26 steps), Bach (25 steps), and Mukai (22 steps), but is less efficient than Curran's strategy (13 steps). Notable transformations that emerged from this chemistry include (1) a completely diastereoselective diradical cyclization at the terminus of an allenyl azide cyclization cascade, (2) a Tollens type aldol to install an all carbon quaternary center in a sterically congested environment, and, as per the Mukai and Curran work, (3) a diastereoselective ring closing metathesis to deliver the final ring of this pentacyclic target.

4. Experimental

4.1. General experimental

All moisture and oxygen sensitive reactions were carried out in flame dried glassware under a nitrogen atmosphere unless otherwise stated. Dry solvents such as acetonitrile, dichloromethane, diethyl ether, tetrahydrofuran, toluene, and triethylamine were obtained by passing the commercial solvent through activated alumina columns. Unless otherwise stated, reagents were purchased at the highest commercial quality and used without further purification. Thin layer chromatography was carried out on EMD 0.25 mm silica gel plates with UV visualization or by staining with potassium permanganate or ceric ammonium molybdate. Purification of products via flash chromatography was performed with the indicated solvent system using 40–63 μm silica gel. Melting points are uncorrected. High resolution mass spectra were obtained according to the technique specified and were performed at the Pennsylvania State University Proteomics and Mass Spectrometry Core Facility, University Park, PA. X ray data were obtained at Pennsylvania State University X ray Crystallography Facility, University Park, PA.

4.2. Acetic acid 1-(2-azido-ethyl)-4-(*tert*-butyldimethylsilanyloxy)-1-phenyl-but-2-ynyl ester (21)

A solution of *tert* butyldimethyl 2 propynyloxysilane (13.9 g, 81.6 mmol) in THF (150 mL) was cooled to 78 °C and *n* butyl lithium (2.5 M in hexanes, 30.1 mL, 75.4 mmol) was added dropwise. The reaction mixture was stirred for 1 h at 78 °C, after which a solution of 3 azido 1 phenylpropan 1 one (**20**) (11.0 g, 62.8 mmol) in THF (150 mL) was added via cannula. The mixture was stirred at 78 °C for 1.5 h, and then treated with saturated aqueous NH_4Cl (150 mL). The organic layer was separated and the aqueous phase was extracted with diethyl ether (3×150 mL). The combined organics were washed with water (2×200 mL), brine (150 mL), and then dried over Na_2SO_4. The solution was concentrated in vacuo to give a clear yellow oil.

The crude oil was dissolved in CH_2Cl_2 (300 mL), cooled to 0 °C, and treated with 4 dimethylaminopyridine (26.1 g, 214 mmol) and acetic anhydride (10.9 g, 107 mmol). The reaction solution was allowed to warm to room temperature while stirring for 16 h. The reaction mixture was then treated with 1 M H_3PO_4 (100 mL). The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (3×75 mL). The combined organics were washed with water (2×100 mL), brine (100 mL), and dried over Na_2SO_4. The solution was filtered and concentrated in vacuo. The crude mixture was purified by column chromatography on SiO_2 (5% ethyl acetate in hexanes) to give acetate **21** as a yellow oil (18.4 g, 75%). IR (thin film) 2099, 1754 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.53 (d, J 8.3 Hz, 2H), 7.38–7.27 (m, 3H), 4.49 (s, 2H), 3.53 (ddd, J 12.4, 10.0, 5.8 Hz, 1H), 3.34 (ddd, J 12.5, 9.9, 5.4 Hz, 1H), 2.46 (ddd, J 13.4, 9.6, 5.6 Hz, 1H), 2.21 (ddd, J 13.6, 9.8, 5.6 Hz, 1H), 2.07 (s, 3H), 0.96 (s, 9H), 0.17 (s, 6H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 167.8, 140.5, 128.4, 128.0, 124.8, 88.0, 81.5, 76.8, 51.6, 47.0, 42.9, 25.6, 21.4, 18.1, 5.3; HRMS (TOF MS ES$^+$) [M+H$^+$] calcd for $C_{20}H_{30}N_3O_3Si$ 388.2056, found 388.2050.

4.3. (6-Azido-4-phenyl-2-vinylhexa-2,3-dienyloxy)-*tert*-butyldimethylsilane (22)

To a solution of $ZnCl_2$ (2.81 g, 2.84 mmol) in THF (150 mL) was added vinyl magnesium bromide (1.0 M in THF, 20.6 mL, 21 mmol). The solution was stirred at room temperature for 80 min. Solutions of $Pd(PPh_3)_4$ (0.596 g, 0.516 mmol) in THF (25 mL) and acetate **21** (4.00 g, 10.3 mmol) in THF (25 mL) were added sequentially via cannula. The mixture was stirred for 1 h, then saturated NH_4Cl solution (150 mL) and Et_2O (150 mL) were added. The organic layer was separated and the aqueous layer was extracted with Et_2O (3×150 mL). The combined organic layers were washed with water (2×100 mL) and brine (150 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by column chromatography on SiO_2 using hexanes as the eluent to give allene **22** (2.44 g, 66%) as a clear oil. IR (thin film) 2097, 1930 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37–7.22 (m, 5H), 6.28 (dd, J 17.7, 10.9 Hz, 1H), 5.32 (d, J 17.7 Hz, 1H), 5.13 (d, J 10.9 Hz, 1H), 4.35 (s, 2H), 3.47 (t, J 7.1 Hz, 1H), 2.76 (t, J 7.2 Hz, 1H), 0.86 (s, 9H), 0.03 (d, J 8.0 Hz, 6H); ^{13}C NMR (75 Hz, $CDCl_3$) δ 206.2, 135.7, 131.9, 128.5, 127.2, 126.1, 114.5, 109.9, 105.1, 61.2, 49.8, 29.7, 25.7, 18.2, 5.4; HRMS (TOF MS ES$^+$) [M N_2+H$^+$] calcd for $C_{20}H_{30}NOSi$ 328.2097, found 328.2093.

4.4. 6-(((*tert*-Butyldimethylsilyl)oxy)methyl)-3a-phenyl-2,3,3a,4-tetrahydrocyclopenta[*b*]pyrrole (23)

Allene **22** (1.73 g, 4.87 mmol) was dissolved in toluene (300 mL, 0.016 M) and sparged with a stream of nitrogen for 30 min. The solution was heated to 110 °C for 1 h and then concentrated in vacuo to give a yellow oil. The oil was purified by column chromatography on SiO_2 (2–5% ethyl acetate/hexanes) to give **23** (1.08 g, 68%) as a clear oil. IR (thin film) 2359, 1637 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.29–7.15 (m, 5H), 6.63 (s, 1H), 4.63 (d, J 2.7 Hz, 2H), 4.12 (dd, J 14.9, 7.2 Hz, 1H), 3.79 (ddd, J 18.0, 10.5, 4.8 Hz, 1H), 2.70 (m, 2H), 2.21 (dd, J 11.8, 4.7 Hz, 1H), 2.05 (td, J 11.2, 7.2 Hz, 1H), 0.93 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (75 Hz, $CDCl_3$) δ 188.7, 144.4, 144.0, 140.0, 128.2, 126.41, 126.40, 64.4, 64.0, 58.9, 43.3, 41.1, 25.8, 18.3, 5.0; HRMS (TOF MS ES$^+$) [M+H$^+$] calcd for $C_{20}H_{30}NOSi$ 328.2097, found 328.2099.

4.5. 6-(((*tert*-Butyldimethylsilyl)oxy)methyl)-3a-phenyl-2,3,3a,4,5,6-hexahydrocyclopenta[*b*]pyrrole (24)

To a solution of **23** (1.00 g, 3.05 mmol) in Et_2O (30 mL) was added 10% palladium on carbon (0.300 g 0.156 mmol, 5 mol %). The suspension was stirred under 1 atm H_2 for 72 h, then filtered through Celite and concentrated in vacuo to give a yellow oil. This crude oil was purified by column chromatography on SiO_2 (2–5% ethyl acetate in hexanes) to give imine **24** (0.959 g, 95%, 1:1 mixture of diastereomers) as a clear oil. IR (thin film) 1665 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31–7.26 (m, 2H), 7.21–7.16 (m, 3H), 4.13 (m, 1H), 4.00 (dd, J 9.9, 4.3 Hz, 1H), 3.90 (m, 1H), 3.68 (dd, J 9.8, 7.9 Hz,

1H), 2.74 (m, 1H), 2.29 (ddd, *J* 12.3, 6.7, 1.5 Hz, 1H), 2.08–1.95 (m, 4H), 1.74 (dt, *J* 11.7, 8.4 Hz, 1H), 0.88 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (both diastereomers, $CDCl_3$, 90 MHz) δ 190.9, 143.1, 128.5, 126.4, 126.0, 66.1, 64.9, 64.0, 41.5, 38.6, 36.0, 29.2, 25.8, 18.1, 5.5; HRMS (TOF MS ES$^+$) $[M+H]^+$ calcd for $C_{20}H_{32}NOSi$ 330.2253, found 330.2250.

4.6. *tert*-Butyl 6-(hydroxymethyl)-3a-phenylhexahydrocyclopenta[*b*]pyrrole-1(2*H*)carboxylate (25)

A solution of super hydride (1.0 M in THF, 9.1 mL, 9.1 mmol) was added dropwise to a solution of imine **24** (1.00 g, 3.0 mmol) in THF (30 mL). There was an initial vigorous evolution of gas that subsided quickly. The mixture was heated at 65 °C for 48 h, then cooled to 0 °C, and the excess hydride was neutralized by the slow addition of ice. Ethyl acetate (20 mL) and water (30 mL) were added and the organic layer was drawn off. The aqueous layer was extracted with ethyl acetate (3×20 mL) and the combined organic layers were washed with brine (1×30 mL) and dried over Na_2SO_4. The solution was filtered and concentrated in vacuo to give the secondary amine as a clear oil.

The crude amine was dissolved in CH_2Cl_2 (30 mL) and triethyl amine (2.9 mL, 21 mmol), Boc_2O (2.3 g, 11 mmol), and hydroxyl amine hydrochloride (0.42 g, 6 mmol) were added sequentially. The mixture was stirred for 24 h at room temperature and an additional 1 equiv of Boc_2O (0.66 g, 3.0 mmol) was added. The solution was stirred for an additional 48 h and then concentrated in vacuo to give a yellow oil. This crude oil was dissolved in hexanes and passed through a short plug of SiO_2 (2% ethyl acetate in hexanes) to remove the bulk of the contaminants and then concentrated in vacuo to give a clear oil. The oil was dissolved in THF (30 mL) and Bu_4NF (1.0 M in THF, 10 mL, 10 mmol) was added. The solution was stirred for 18 h at room temperature then was diluted with water (30 mL) and ethyl acetate (20 mL) was added. The layers were separated and the aqueous layer was extracted with ethyl acetate (1×20 mL) and CH_2Cl_2 (2×20 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated in vacuo to give a yellow oil. The crude alcohol was purified by column chromatography on SiO_2 (5–10–15% ethyl acetate/hexanes) to give alcohol **25** (0.20 g, 20%, mixture of rotamers) as a yellow oil. IR (thin film) 3432, 1667 cm^{-1}; ^{1}H NMR (major rotamer, 300 MHz, $CDCl_3$) δ 7.34–7.18 (m, 5H), 4.72 (dd, *J* 11.3, 2.9 Hz, 1H), 4.63 (d, *J* 6.1 Hz, 1H), 3.73 (ddd, *J* 11.6, 7.5, 5.4 Hz, 1H), 3.60 (td, *J* 11.5, 3.7 Hz, 1H), 3.47 (td, *J* 10.9, 3.5 Hz, 1H), 3.29 (dt, *J* 11.5, 7.6 Hz, 1H), 2.49 (m, 1H), 2.21–1.93 (m, 4H), 1.76 (dd, *J* 12.6, 6.4 Hz, 1H), 1.49 (s, 9H), 1.33 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.5, 148.5, 128.5, 126.1, 125.4, 80.6, 67.8, 62.3, 58.1, 49.7, 47.5, 40.1, 39.8, 28.4, 28.3; HRMS (TOF MS ES$^+$) $[M+H]^+$ calcd for $C_{19}H_{27}NO_3$ 318.2069, found 318.2060.

4.7. *tert*-Butyl 6,6-bis(hydroxymethyl)-3a-phenylhexahydrocyclopenta[*b*]pyrrole-1(2*H*)carboxylate (26)

To a solution of alcohol **25** (0.114 g, 0.359 mmol) in CH_2Cl_2 (15.0 mL) was added Dess–Martin periodinane (0.457 g, 1.08 mmol) in one portion. The reaction mixture was stirred at room temperature for 45 min. A 1:1 solution (10.0 mL) of saturated aqueous $NaHCO_3$/saturated aqueous $Na_2S_2O_3$ was added and the biphasic mixture was stirred until all of the solids had dissolved and the mixture was clear. The mixture was poured into a separatory funnel and the organic layer was drawn off. The aqueous layer was extracted with dichloromethane (3×15.0 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo to give a yellow oil. The oil was dissolved in methanol (7 mL), and aqueous formaldehyde (37% w/w, 1.43 mL, 19.1 mmol) and potassium hydroxide (0.371 g, 5.62 mmol) were added sequentially. The solution was stirred at room temperature for 48 h. The reaction solution was diluted with brine (15.0 mL) and extracted with dichloromethane (4×10.0 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to give a yellow oil. The oil was purified by column chromatography (10–15–30–35% ethyl acetate/hexanes) to give diol **26** (0.064 g, 51%) as a clear oil. IR (thin film) 3398, 1660 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (app t, *J* 7.5 Hz, 2H), 7.23–7.18 (m, 3H), 4.27 (s, 1H), 3.90 (s, 1H), 3.68 (app t, *J* 9.6 Hz, 1H), 3.51–3.31 (m, 4H), 2.21–2.10 (m, 2H), 2.03–1.85 (m, 2H), 1.69–1.64 (m, 2H), 1.49 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.3, 147.3, 128.5, 126.3, 125.4, 80.8, 70.7, 66.3, 65.1, 58.7, 52.7, 46.6, 38.5, 34.9, 30.5, 28.4; HRMS (TOF MS ES$^+$) $[M+H]^+$ calcd for $C_{20}H_{30}NO_4$ 348.2175, found 348.2194.

4.8. *tert*-Butyl-3a-phenyl-6,6-divinylhexahydrocyclopenta[*b*]pyrrole-1(2*H*)carboxylate (27)

A microwave reaction tube was charged with alcohol **26** (0.055 g, 0.158 mmol) and water saturated dichloromethane (1.5 mL). Dess–Martin periodinane (0.336 g, 0.791 mmol) was added in a single portion and the tube was flushed with nitrogen and then sealed with a Teflon cap. The reaction mixture was heated via microwave irradiation at 65 °C for 30 min and then cooled to room temperature. A 1:1 solution of saturated aqueous $NaHCO_3$/saturated aqueous $Na_2S_2O_3$ (6 mL) was added and the biphasic mixture was stirred until all of the solids had dissolved and the mixture was clear. The mixture was poured into a separatory funnel and the organic layer was drawn off. The aqueous layer was extracted with dichloromethane (3×5 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo to give the desired dialdehyde as a pale yellow oil.

A suspension of methyltriphenylphosphonium bromide (0.565 g, 0.1.58 mmol) in THF (0.200 mL) was cooled to 78 °C and a solution of NaHMDS (1.0 M in THF, 1.50 mL, 1.50 mmol) was added dropwise. The suspension was stirred at 78 °C for 1.5 h. The crude dialdehyde was dissolved in 0.200 mL of THF and added via cannula to the ylide suspension, rinsing the flask with an additional 0.150 mL of THF. The reaction mixture was allowed to warm to room temperature and stirred at that temperature for 72 h. Saturated aqueous ammonium chloride (5 mL) and ethyl acetate (5 mL) were added. The organic layer was drawn off and the aqueous layer was extracted with ethyl acetate (1×5.00 mL) and CH_2Cl_2 (2×5.00 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated in vacuo to give a brown oil. The oil was purified by SiO_2 column chromatography (hexanes to 1–5% EtOAc/hexanes) to give **27** as a clear oil (0.049 g, 91%, 1:2 mixture of rotamers). IR (thin film) 1894 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, major rotamer) δ 7.34–7.20 (m, 5H), 6.17–5.92 (m, 2H), 5.10–5.00 (m, 4H), 4.35 (s, 1H), 3.65–3.36 (m, 2H), 2.21–1.92 (m, 6H), 1.49 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, both rotamers) δ 154.3, 148.4, 148.3, 144.3, 143.9, 141.3, 128.4, 126.1, 125.7, 125.5, 113.2, 112.5, 112.4, 112.2, 79.9, 79.2, 75.3, 75.0, 59.1, 58.0, 55.3, 54.7, 46.4, 46.1, 39.0, 38.0, 36.4, 36.0, 33.4, 32.6, 29.7, 28.5; HRMS (TOF MS ES$^+$) $[M+H]^+$ calcd for $C_{22}H_{30}NO_2$ 340.2277, found 340.2279.

4.9. 1-Allyl-3a-phenyl-6,6-divinyloctahydrocyclopenta[*b*]pyrrole (28)

Carbamate **27** (0.012 g, 0.035 mmol) was dissolved in 10% trifluoroacetic acid/CH_2Cl_2 (1 mL) and stirred for 16 h at room temperature. The reaction mixture was concentrated in vacuo to give a brown oil. This oil was redissolved in CH_2Cl_2 (5 mL), washed with saturated sodium bicarbonate (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give the crude amine as a brown oil. This crude oil was dissolved in THF (0.5 mL). Allyl bromide (0.040 mL, 0.53 mmol) and lithium hydroxide

monohydrate (0.106 g, 1.41 mmol) were added sequentially. The resulting solution was heated at 65 °C for 18 h. The reaction mixture then was cooled to room temperature and diluted with water (5 mL) and EtOAc (5 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3×5 mL), washed with water (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give a brown oil. This oil was purified by SiO_2 column chromatography to give **28** as a clear oil (0.007 g, 70%). IR (thin film) 2360 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34–7.27 (m, 4H), 7.18 (m, 1H), 6.26 (dd, *J* 17.7, 10.7 Hz, 1H), 5.94 (dddd, *J* 15.1, 10.1, 7.9, 4.9 Hz, 1H), 5.70 (dd, *J* 17.8, 11.0 Hz, 1H), 5.21 (d, *J* 12.8 Hz, 1H), 5.11–5.01 (m, 4H), 4.92 (d, *J* 13.3 Hz, 1H), 3.55 (dd, *J* 13.5, 4.9 Hz, 1H), 3.36 (s, 1H), 3.03–2.98 (m, 2H), 2.39 (ddd, *J* 12.2, 9.0, 5.3 Hz, 1H), 2.18–1.89 (m, 5H), 1.71 (dd, *J* 12.1, 5.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.1, 143.3, 142.8, 136.3, 128.0, 126.3, 125.4, 116.3, 114.6, 113.2, 80.8, 59.0, 58.9, 55.1, 52.5, 41.6, 38.3, 34.4; HRMS (TOF MS ES$^+$) $[M+H]^+$ calcd for $C_{20}H_{26}N$ 280.2065, found 280.2051.

4.10. 8a-Phenyl-6a-vinyl-1,2,3[1],4,6a,7,8,8a-octahydrocyclopenta[*hi*]indolizine (29)

To a solution of bicycle **28** (0.007 g, 0.025 mmol) in CH_2Cl_2 (2 mL) was added tosic acid (0.006 g, 0.03 mmol), followed by Grubbs second generation metathesis catalyst (0.004 g, 0.005 mmol). The solution was heated to 40 °C for 16 h, then cooled to room temperature. Saturated aqueous sodium bicarbonate (5 ml) was added and the resulting biphasic mixture was stirred for 1 h. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3×5 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated in vacuo to give a brown residue. This residue was purified by column chromatography on SiO_2 (1–5–10–20% EtOAc/hexanes) to give **29** as a clear oil (0.005 g, 79%). ^1H NMR (600 MHz, toluene) δ 7.44 (d, *J* 8.0 Hz, 2H), 7.17 (d, *J* 7.6 Hz, 2H), 7.05 (t, *J* 7.6 Hz, 1H), 5.71 (dd, *J* 10.1, 2.2 Hz, 1H), 5.61 (dd, *J* 17.4, 10.6 Hz, 1H), 5.57 (dd, *J* 10.1, 4.9 Hz, 1H), 4.90 (d, *J* 17.5 Hz, 1H), 4.80 (d, *J* 4.8 Hz, 1H), 3.52 (s, 1H), 3.32 (d, *J* 17.0 Hz, 1H), 3.07 (dd, *J* 17.0, 5.0 Hz, 1H), 2.96 (q, *J* 7.9 Hz, 1H), 2.72 (td, *J* 8.4, 3.4 Hz, 1H), 2.21–2.14 (m, 2H), 1.86 (dd, *J* 12.5, 6.0 Hz, 1H), 1.83–1.71 (m, 3H); ^{13}C NMR (150 MHz, toluene) δ 151.7, 144.7, 137.1, 132.2, 126.1, 125.7, 123.1, 111.9, 77.8, 58.3, 53.4, 48.0, 47.2, 45.2, 38.4, 37.3; HRMS (TOF MS ES$^+$) $[M+H]^+$ calcd for $C_{18}H_{22}N$ 252.1752, found 252.1766.

4.11. 1-Azido-3-(2-bromophenyl)-6-((*tert*-butyldimethylsilyl)oxy)hex-4-yn-3-yl acetate (31a)

A solution of *tert* butyldimethyl 2 propynyloxysilane (7.58 g, 44.5 mmol) in THF (175 mL) was cooled to 78 °C and *n* butyl lithium (2.5 M in hexanes, 16.4 mL, 41 mmol) was added dropwise. The reaction mixture was stirred for 1 h at 78 °C and then a solution of 3 azido 1 (2 bromophenyl)propan 1 one (**30**, 6.00 g, 34.2 mmol) in THF (50 mL) was added via cannula. The mixture was stirred at 78 °C for 1.5 h and then treated with saturated aqueous NH_4Cl (150 mL). The organic layer was separated and the aqueous was extracted with diethyl ether (3×150 mL). The combined organic layers were washed with water (2×200 mL), brine (150 mL), and dried over Na_2SO_4. The solution was concentrated in vacuo to give the crude lithiate addition product a clear yellow oil.

This crude alcohol was dissolved in CH_2Cl_2 (200 mL), cooled to 0 °C, and treated with 4 dimethylaminopyridine (14.2 g, 116 mmol) and acetic anhydride (5.50 mL, 58.2 mmol). The solution was stirred for 16 h, warming to room temperature. The reaction mixture was then treated with 1 M H_3PO_4 (100 mL). The organic layer was drawn off and the aqueous phase was extracted with CH_2Cl_2 (3×75 mL). The combined organics were washed with water (2×100 mL), brine (100 mL), and dried over Na_2SO_4. The solution was filtered and concentrated in vacuo. The crude reaction mixture was purified by column chromatography on SiO_2 (5% ethyl acetate in hexanes) to give acetate **31a** as a yellow oil (7.82 g, 59%). IR (thin film) 2098, 1754 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.94 (dd, *J* 7.9, 1.7 Hz, 1H), 7.57 (dd, *J* 7.9, 1.3 Hz, 1H), 7.32 (td, *J* 7.6, 1.3 Hz, 1H), 7.14 (td, *J* 7.6, 1.7 Hz, 1H), 4.48 (s, 2H), 3.59 (ddd, *J* 12.4, 9.6, 5.9 Hz, 1H), 3.39 (ddd, *J* 12.4, 9.5, 5.7 Hz, 1H), 2.79 (ddd, *J* 13.7, 9.5, 5.9 Hz, 1H), 2.38 (ddd, *J* 13.7, 9.6, 5.6 Hz, 1H), 2.11 (s, 3H), 0.93 (s, 9H), 0.14 (s, 6H); ^{13}H NMR (75 MHz, $CDCl_3$) δ 168.1, 138.1, 137.5, 135.5, 130.3, 129.6, 127.4, 118.6, 88.5, 81.5, 77.7, 51.7, 47.3, 38.9, 25.7, 21.1, 18.2, 5.2; HRMS (TOF MS ES$^+$) $[M+H]^+$ calcd for $C_{20}H_{29}N_3O_3SiBr$ 466.1162, found 466.1166.

4.12. 1-Azido-3-(2-bromophenyl)-6-((*tert*-butyldimethylsilyl)oxy)hex-4-yn-3-yl methyl carbonate (31b)

A solution of *tert* butyldimethyl(prop 2 yn 1 yloxy)silane (12.7 g, 62.8 mmol) in THF (100 mL) was cooled to 78 °C and *n* butyllithium (2.5 M in hexanes, 23.9 mL, 60 mmol) was added dropwise. The reaction mixture was stirred for 0.5 h at 78 °C, after which time a solution of 3 azido 1 (2 bromophenyl)propan 1 one (7.60 g, 29.9 mmol) in CH_2Cl_2 (150 mL) was added via cannula. The mixture was stirred for 1.5 h at 78 °C, and then methyl chloroformate (14.1 g, 149 mmol, 11.6 mL) was added dropwise. The solution was allowed to warm to room temperature while stirring for 16 h. Water (100 mL) was added and the organic layer was separated. The aqueous layer was extracted with EtOAc (3×150 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated in vacuo to give a dark yellow oil that was purified by column chromatography on SiO_2 (5% ethyl acetate in hexanes) to give carbonate **31b** as a pale yellow oil (3.59 g, 30%). IR (thin film) 2096, 1760 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.93 (dd, *J* 7.9, 1.7 Hz, 1H), 7.59 (dd, *J* 7.9, 1.3 Hz, 1H), 7.33 (td, *J* 7.6, 1.3 Hz, 1H), 7.18 (td, *J* 7.6, 1.7 Hz, 1H), 4.49 (s, 2H), 4.49 (s, 3H), 3.59 (ddd, *J* 12.4, 9.8, 5.7 Hz, 1H), 3.41 (ddd, *J* 12.4, 9.6, 5.7 Hz, 1H), 2.82 (ddd, *J* 13.7, 9.6, 5.7 Hz, 1H), 2.47 (ddd, *J* 13.7, 9.7, 5.7 Hz, 1H), 0.93 (s, 9H), 0.15 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.7, 136.9, 135.6, 130.3, 130.0, 127.3, 118.7, 89.0, 81.0, 80.0, 54.8, 51.7, 47.1, 38.9, 25.7, 18.2, 5.3; (TOF MS ES$^+$) $[M+H]^+$ calcd for $C_{20}H_{29}N_3O_4$ 482.1111, found 482.1111.

4.13. 3a-(2-bromophenyl)-6-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)-2,3,3a,4-tetrahydrocyclopenta[*b*]pyrrole (33)

A solution of 1 [(*E*) 2 iodoethenyl] 4 methyl 2,6,7 trioxabicyclo[2.2.2]octane[16] (1.10 g, 3.90 mmol) in Et_2O (20 mL) was cooled to 78 °C and *tert* butyllithium (1.7 M in *n* pentane, 5.30 mL, 9.0 mmol) was added dropwise. The reaction mixture was stirred for 1 h, at which time a solution of zinc chloride (0.611 g, 4.48 mmol) in THF (10 mL) was added via cannula. The cooling bath was removed and the solution was allowed to warm to room temperature and then stirred for 1 h. A solution of $Pd(PPh_3)_4$ (0.225 g, 0.195 mmol) in THF (5 mL) and carbonate **31b** (0.941 g, 1.95 mmol) in THF (5 mL) were added sequentially via cannula. The reaction mixture was stirred at room temperature until TLC (10:90 ethyl acetate/hexanes) indicated that the starting material was consumed. The reaction mixture was poured into a separatory funnel containing ice and saturated aqueous ammonium chloride (40 mL). The organic layer was drawn off and the aqueous layer was extracted with Et_2O (3×20 mL), washed with brine (1×40 mL), and dried over Na_2SO_4. The solution was filtered and concentrated in vacuo at a bath temperature not exceeding 40 °C to give unstable allene **32**.

The crude allene mixture was dissolved in toluene (750 mL, 0.003 M) and sparged with a stream of nitrogen for 30 min. The

solution was heated at 110 °C for 1.5 h and then concentrated in vacuo. The residue was purified by column chromatography on SiO_2 (5–10% EtOAc/3% triethylamine/hexanes) to give a yellow solid. The solid was triturated with hexanes and the crystals were collected by vacuum filtration to give **33** (0.350 g 34%) as a white solid. Mp 150–153 °C; IR (thin film) 1638 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, J 7.9 Hz, 1H), 7.38 (br s, 1H), 7.11 (td, J 7.6, 1.0 Hz, 1H), 6.93 (td, J 7.6, 1.6 Hz, 1H), 6.64 (s, 1H), 4.63 (s, 2H), 3.93 (dd, J 14.6, 6.7 Hz, 1H), 3.66–3.48 (m, 7H), 3.33 (br s, 1H), 3.03 (d, J 2 Hz, 1H), 1.93 (m, 1H), 0.90 (s, 9H), 0.64 (s, 3H), 0.08 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.1, 142.6, 141.3, 138.9, 134.5, 133.5, 127.5, 125.5, 122.9, 108.1, 72.0, 66.1, 63.4, 59.3, 58.9, 42.7, 30.2, 25.8, 18.2, 14.3, 5.5; HRMS (TOF MS ES$^+$) $[M+H]^+$ calcd for $C_{26}H_{37}NO_4SiBr$ 534.1675, found 534.1669.

4.14. Hydrogenation of cyclopentenylated dihydropyrrole 33

A Parr bomb was charged with **33** (0.050 g, 0.094 mmol), benzene (5.0 mL), triethylamine (0.014 mL, 0.10 mmol), and 5% platinum on carbon (0.010 g). The bomb was sealed, purged with hydrogen gas three times, and then pressurized with hydrogen gas (1100 psi), and stirred at 40 °C for 18 h. The gas was vented and an additional 0.010 g of 5% platinum on carbon was added. The bomb was then resealed, purged with hydrogen gas three times, pressurized to 1100 psi of hydrogen gas, and stirred at 40 °C for 18 h. This sequence was repeated until TLC (10:90 ethyl acetate/hexanes) indicated that the starting material was completely consumed. The reaction mixture was filtered through Celite, rinsing with EtOAc, and concentrated in vacuo to give a light yellow oil, which was purified by column chromatography on SiO_2 (5–10% EtOAc/3% triethylamine/hexanes) to give **34** (0.014 g, 28%) as a clear oil and **35** (0.012 g, 31% 6:1 dr) as a yellow oil.

*4.14.1. Compound **34**.* IR (thin film) 1662 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.53 (dd, J 7.9, 1.4 Hz, 1H), 7.32 (dd, J 8.0, 1.5 Hz, 1H), 7.17 (td, J 7.6, 1.4 Hz, 1H), 7.01 (td, J 7.0, 1.7 Hz, 1H), 4.02–3.93 (m, 2H), 3.79–3.71 (m, 6H), 3.68–3.57 (m, 2H), 3.21 (dd, J 12.8, 4.8 Hz, 2H), 2.30–2.14 (m, 3H), 2.04 (td, J 12.2, 7.6 Hz, 1H), 0.90 (s, 9H), 0.74 (s, 3H), 0.07 (d, J 3 Hz, 6H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 191.1, 138.5, 134.9, 132.4, 127.9, 125.8, 124.2, 108.7, 72.3, 66.9, 64.8, 64.2, 53.4, 41.8, 31.0, 30.0, 25.9, 25.6, 18.3, 14.6, 5.4, 5.3; (TOF MS ES$^+$) $[M+H]^+$ calcd for $C_{26}H_{39}NO_4SiBr$ 536.1832, found 536.1815.

*4.14.2. Compound **35**.* IR (thin film) 1665 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.53 (dd, J 7.9, 1.4 Hz, 1H), 7.29 (dd, J 7.9, 1.6 Hz, 1H), 7.16 (td, J 7.6, 1.3 Hz, 1H), 7.01 (td, J 7.6, 1.7 Hz, 1H), 3.96 (dd, J 14.3, 7.5 Hz, 1H), 3.80–3.67 (m, 6H), 3.61 (m, 1H), 3.25 (dd, J 12.8, 4.9 Hz, 1H), 3.12 (m, 1H), 2.36–2.23 (m, 2H), 2.06 (m, 1H), 1.74 (m, 1H), 1.24 (app s, 3H), 0.71 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 194.9, 138.5, 134.8, 132.3, 127.8, 125.7, 124.6, 108.9, 72.2, 66.6, 63.7, 52.5, 42.3, 35.6, 33.5, 30.0, 18.9, 14.6; (TOF MS ES$^+$MS ES$^+$) $[M+H]^+$ calcd for $C_{20}H_{25}NO_3Br$ 406.1018, found 406.1010.

4.15. 1-Azido-3-(2-bromophenyl)-6-(triisopropylsilyloxy)hex-4-yn-3-yl methyl carbonate (36)

n Butyllithium (2.5 M in hexanes, 18.4 mL, 46 mmol) was added dropwise to a solution of triisopropyl(prop 2 ynyloxy)silane (9.78 g, 46.0 mmol) in CH_2Cl_2 (150 mL) at 78 °C. The reaction mixture was stirred for 1.5 h at that temperature, after which time a solution of 3 azido 1 (2 bromophenyl)propan 1 one (**30**) (9.00 g, 35.4 mmol) in CH_2Cl_2 (150 mL) was added via cannula. The mixture was allowed to warm to room temperature over 18 h with continual stirring. The mixture was cooled to 0 °C followed by dropwise addition of methyl chloroformate (11.7 g, 123 mmol, 9.58 mL). The cooling bath was removed and the solution was allowed to warm to room temperature over 18 h with continual stirring. Water (100 mL) was added, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3×150 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated in vacuo to give a dark yellow oil. Purification of this oil by column chromatography on SiO_2 (5% ethyl acetate in hexanes) gave carbonate **36** as a pale yellow oil (14.0 g, 84%). IR (thin film) 2099, 1762 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.94 (dd, J 7.9, 1.7 Hz, 1H), 7.59 (dd, J 7.9, 1.3 Hz, 1H), 7.33 (dt, J 7.6, 1.3 Hz, 1H), 7.18 (td, J 7.6, 1.7 Hz, 1H), 4.57 (s, 2H), 3.73 (s, 3H), 3.60 (m, 1H), 3.41 (m, 1H), 2.82 (m, 1H), 2.47 (m, 1H), 1.21–1.05 (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.7, 137.0, 135.6, 130.4, 130.0, 127.3, 118.8, 89.1, 80.8, 80.0, 54.8, 52.0, 47.2, 38.9, 17.9, 11.9; HRMS (TOF MS ES$^+$) $[M+NH_4^+]$ calcd for $C_{23}H_{38}N_4O_4SiBr$ 541.1846, found 541.1866.

4.16. 3a-(2-bromophenyl)-4-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)-6-((triisopropylsilyloxy)methyl)-2,3,3a,4-tetrahydrocyclopenta[*b*]pyrrole (38)

tert Butyllithium (1.7 M in *n* pentane, 2.0 mL, 2.0 mmol) was added dropwise to a solution of 1 [(*E*) 2 iodoethenyl] 4 methyl 2,6,7 trioxabicyclo[2.2.2]octane[16] (0.200 g, 0.709 mmol) in Et_2O (3 mL) at 78 °C. After 1 h of stirring at that temperature, a solution of zinc chloride (0.106 g, 0.780 mmol) in THF (3 mL) was added via cannula. The cooling bath was removed and the solution was allowed to warm to room temperature over 1 h with continual stirring. Solutions of $Pd(PPh_3)_4$ (0.041 g, 0.036 mmol) in THF (1 mL) and carbonate **36** in THF (1 mL) were added sequentially via cannula. The reaction mixture was stirred at room temperature until TLC indicated that the starting material was consumed (10:90 EtOAc/hexanes). The reaction mixture was poured into a mixture of ice and saturated aqueous ammonium chloride (10 mL). The organic layer was removed and the aqueous layer was extracted with Et_2O (3×5 mL), washed with brine (1×10 mL), and the combined organic phases were dried over Na_2SO_4. The combined organics were filtered and concentrated in vacuo at a bath temperature not exceeding 40 °C to give crude unstable allene **37**.

The crude allene was dissolved in toluene (75 mL, 0.003 M) and sparged with a stream of nitrogen for 30 min. This solution was heated at 110 °C for 1.5 h and then concentrated in vacuo. The residue was purified by column chromatography on SiO_2 (5–10–20% EtOAc/3% triethylamine/hexanes) to give a yellow solid. The solid was triturated with hexanes and the resulting crystals were collected by vacuum filtration to give 0.069 g (55%) of **38** as a white solid. Conducting the above reaction on the following scale: 1 [(*E*) 2 iodoethenyl] 4 methyl 2,6,7 trioxabicyclo[2.2.2]octane (3.10 g, 11.0 mmol), *tert* butyllithium (1.7 M in *n* pentane, 17.1 mL, 29 mmol), zinc chloride (1.94 g, 14.3 mmol), $Pd(PPh_3)_4$ (0.63 g, 0.55 mmol), **36** (3.75 g, 7.15 mmol) gave **38** (0.98 g, 43%). Mp 159–163 °C; IR (thin film) 1639 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, J 7.9 Hz, 1H), 7.39 (br s, 1H), 7.12 (t, J 7.4 Hz, 1H), 6.94 (td, J 7.5, 1.3, 1H), 6.70 (s, 1H), 4.74 (s, 2H), 3.94 (dd, J 14.6, 6.7 Hz, 1H), 3.64–3.51 (m, 7H), 3.32 (br s, 1H), 3.05 (s, 1H), 1.93 (td, J 11.4, 6.8 Hz, 1H), 1.19–1.07 (m, 21H), 0.66 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.8, 143.2, 141.9, 139.5, 135.0, 134.1, 128.0, 126.0, 123.5, 108.7, 72.5, 66.7, 63.9, 60.2, 59.5, 43.5, 30.7, 18.4, 14.9, 12.3; HRMS (TOF MS ES$^+$) $[M+NH_4^+]$ calcd for $C_{29}H_{43}NO_4BrSi$ 576.2145, found 576.2128.

4.17. 3a-(2-Bromophenyl)-4-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)-6-(((triisopropylsilyl)oxy)methyl)-2,3,3a,4,5,6-hexahydrocyclopenta[*b*]pyrrole (39)

A Parr pressure vessel was charged with **38** (0.700 g, 1.21 mmol), 1,4 dioxane (12.0 mL), triethylamine (0.085 mL, 0.61 g, 0.61 mmol), and 5% platinum on carbon (0.311 g, 0.061 mmol, 5 mol %). The

vessel was sealed, purged with hydrogen gas three times, and then pressurized with hydrogen gas (1400 psi), and stirred for 18 h at 40 °C. The gas was vented and a further 0.05 equiv of 5% platinum on carbon was added. The vessel was then resealed, purged with hydrogen gas three times, pressurized to 1400 psi of hydrogen gas, and stirred at 40 °C for 18 h. This sequence was repeated until TLC analysis (10:90 EtOAc/hexanes) indicated that the starting material was completely consumed. The reaction mixture was filtered through Celite, which was rinsed with EtOAc, and the combined organics were concentrated in vacuo to give a light yellow oil. This oil was purified by column chromatography on SiO_2 (5% EtOAc/3% triethylamine/hexanes) to give imine **39** (0.566 g, 80%) as a clear oil. IR (thin film) 2246, 2215, 1667 cm^{-1}; ^1H NMR (major isomer, 300 MHz, $CDCl_3$) δ 7.52 (dd, *J* 7.9, 1.4 Hz, 1H), 7.32 (d, *J* 8.0, 1.5 Hz, 1H), 7.17 (app td, *J* 7.6, 1.4 Hz, 1H), 7.01 (app td, *J* 7.6, 1.6 Hz, 1H), 4.07 (dd, *J* 9.7, 4.3 Hz, 1H), 3.96 (dd, *J* 14.4, 7.6 Hz, 1H), 3.79–3.60 (m, 8H), 3.21 (app dd, *J* 12.8, 3.2 Hz, 2H), 2.12–2.35 (m, 3H), 2.05 (m, 1H), 1.12–1.04 (m, 21H), 0.73 (s, 3H); ^{13}C (major isomer, 75 MHz, $CDCl_3$) δ 191.1, 138.5, 134.9, 132.3, 127.8, 125.7, 124.2, 108.7, 72.2, 66.8, 65.0, 64.2, 53.4, 41.9, 41.7, 31.0, 29.9, 18.0, 14.6, 12.0; HRMS (TOF MS ES$^+$) [M+H$^+$] calcd for $C_{29}H_{45}NO_4BrSi$ 578.2301, found 578.2298.

4.18. *tert*-Butyl-3a-(2-Bromophenyl)-6-(hydroxymethyl)-4-(4-methyl-2,6,7-trioxabicyclo [2.2.2] octan-1-yl)hexahydrocyclopenta[*b*]pyrrole-1(2*H*)carboxylate (40)

Superhydride (1.0 M in THF, 10 mL, 10 mmol) was added dropwise to a solution of **39** (0.586 g, 1.01 mmol) in THF (10.1 mL). An initial vigorous evolution of gas subsided quickly. The mixture was heated at reflux for 72 h and then cooled to 0 °C, and the excess hydride reagent was destroyed by the slow addition of ice. Saturated ammonium chloride solution (10 mL) was added and the biphasic solution was stirred for 1 h at room temperature. EtOAc (10 mL) was added and the organic layer was drawn off. The aqueous layer was extracted with EtOAc (3×10 mL) and the combined organics were washed with brine (1×15 mL) and dried over Na_2SO_4. The solution was filtered and concentrated in vacuo.

The crude amine prepared above was dissolved in CH_2Cl_2 (10.0 mL) and triethylamine (0.706 mL, 0.512 g, 5.06 mmol), Boc_2O (0.442 g, 2.03 mmol), and hydroxylamine hydrochloride (0.035 g, 0.506 mmol) were added sequentially. The reaction mixture was stirred at room temperature for 24 h and an additional portion of Boc_2O (0.111 g, 0.506 mmol) was added. The solution was stirred for an additional 48 h at room temperature and then concentrated in vacuo to give a white oil. The crude *N* Boc product mixture was dissolved in acetonitrile (10 mL) and extracted with hexanes (5×10 mL). The combined hexanes extracts were concentrated in vacuo to give a clear oil.

The crude *N* Boc species was dissolved in THF (10 mL) and *n*Bu_4NF solution (1.0 M in THF, 5.0 mL, 5.0 mmol) was added. The reaction mixture was stirred at room temperature for 18 h, diluted with water (20 mL), and EtOAc (15 mL) was added. The layers were separated and the aqueous layer was extracted with EtOAc (1×10 mL) and CH_2Cl_2 (2×10 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude alcohol was purified by column chromatography on SiO_2 (1–4–10% ethyl acetate/3% triethylamine/hexanes) to give alcohol **40** (0.317 g, 59%) as white crystals. Mp 82–86 °C; IR (thin film) 3441, 2244, 1667 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* 7.8 Hz, 1H), 7.23 (d, *J* 7.7 Hz, 1H), 7.14 (app. t, *J* 7.5 Hz, 1H), 6.99 (app t, *J* 7.4 Hz, 1H), 5.17 (d, *J* 9.5, 1H), 3.51–3.37 (m, 9H), 3.30 (d, *J* 7.2 Hz, 1H), 3.21 (t, *J* 9.5 Hz, 1H), 2.88–2.75 (m, 3H), 2.31 (dd, *J* 8.8, 6.9 Hz, 1H), 1.94 (app. q, *J* 11.7 Hz, 1H), 1.57 (m, 1H, overlapping with H_2O), 1.43 (s, 9H), 0.56 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5, 141.1, 134.1, 129.0, 127.1, 126.0, 125.8, 109.5, 80.3, 71.8, 65.3, 64.4, 61.4, 47.6, 45.1, 42.3, 34.8, 30.0, 28.3, 28.1, 14.2; HRMS (TOF MS ES$^+$) [M+H$^+$] calcd for $C_{25}H_{35}NO_6Br$ 524.1648, found 524.1657.

4.19. *tert*-Butyl-3a-(2-Bromophenyl)-6,6-bis(hydroxymethyl)-4-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)-hexahydrocyclopenta[*b*]pyrrole-1(2*H*)carboxylate (41)

A microwave reaction tube was charged with alcohol **40** (0.167 g, 0.318 mmol), water saturated CH_2Cl_2 (3.20 mL), and 2,6 lutidine (0.184 mL, 0.171 g, 1.59 mmol). Dess–Martin periodinane (0.405 g, 0.955 mmol) was added in a single portion and the tube was purged with nitrogen and then sealed with a Teflon cap. The reaction mixture was heated via microwave irradiation at 65 °C for 0.5 h and then cooled to room temperature. A 1:1 solution (3 mL) of saturated aqueous $NaHCO_3$/saturated aqueous $Na_2S_2O_3$ was added and the biphasic mixture was stirred at room temperature until all of the solids had dissolved and the mixture was clear. The organic layer was drawn off and the aqueous layer was extracted with CH_2Cl_2 (3×5 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo to give a pale yellow oil.

This crude aldehyde prepared above was dissolved in ethylene glycol (3.18 mL) and CH_2Cl_2 (0.100 mL). Aqueous formaldehyde (37% w/w, 1.43 mL, 1.56 g, 19.1 mmol) and KOH (0.371 g, 5.62 mmol) were added sequentially. The reaction solution was heated to 55 °C and stirred for 48 h at that temperature. After this time period, the reaction solution was cooled to room temperature, diluted with brine (15 mL), and extracted with CH_2Cl_2 (4×10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to give a white foam. This foam was purified by column chromatography (1–5–10% MeOH/CH_2Cl_2) to give diol **41** (0.149 g, 84%, mixture of rotamers) as a white solid. Mp 208–212 °C; IR (thin film) 3492, 1659 cm^{-1}; ^1H NMR (major rotamer, 300 MHz $CDCl_3$) δ 7.54 (app dd, *J* 7.8, 1.0 Hz, 1H), 7.21–7.11 (m, 2H), 7.01 (app dt, *J* 7.3, 2.0 Hz, 1H), 4.9 (s, 1H), 4.55 (d, *J* 11.2 Hz, 1H), 4.02 (d, *J* 10.8 Hz, 1H), 3.82 (dd, *J* 11.0, 6.0 Hz, 1H), 3.61 (app t, *J* 11.1 Hz, 1H), 3.48–3.38 (m, 7H), 3.32 (dd, *J* 6.7, 3.0 Hz, 1H), 3.23 (app t, *J* 9.9 Hz, 1H), 2.99 (dd, *J* 13.1, 6.7 Hz, 1H), 2.88 (dt, *J* 11.2, 7.0 Hz, 1H), 2.42 (t, *J* 6.1 Hz, 1H), 2.14, (dt, *J* 12.3, 9.5 Hz, 1H), 2.07–1.98 (m, 2H), 1.43 (s, 9H), 0.59 (s, 3H); ^{13}C NMR (major rotamer, 75 MHz, $CDCl_3$) δ 155.6, 140.6, 134.1, 129.1, 127.2, 126.1, 126.0, 109.3, 80.4, 71.8, 69.6, 68.1, 67.9, 61.7, 49.1, 47.1, 45.0, 34.3, 31.8, 30.1, 28.4, 14.3; HRMS (TOF MS ES$^+$) [M+H$^+$] calcd for $C_{26}H_{37}NO_7Br$ 554.1753, found 554.1773.

4.20. *tert*-Butyl 3a-(2-bromophenyl)-4-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)-6,6-divinylhexahydrocyclopenta[*b*]pyrrole-1(2*H*)carboxylate (44)

A microwave reaction tube was charged with diol **41** (0.030 g, 0.54 mmol), lutidine (0.144 g, 1.35 mmol, 0.156 mL), and water saturated CH_2Cl_2 (1.5 mL). Dess–Martin periodinane (0.229 g, 0.541 mmol) was added in a single portion and the tube was purged with nitrogen and then sealed with a Teflon cap. The reaction mixture was heated via microwave irradiation for 0.5 h at 65 °C and then cooled to room temperature. A 1:1 solution of saturated aqueous $NaHCO_3$/ saturated aqueous $Na_2S_2O_3$ (3 mL) was added and the biphasic mixture was stirred at room temperature until all of the solids had dissolved and the mixture was clear. The organic layer was drawn off and the aqueous layer was extracted with CH_2Cl_2 (3×5 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo to give the crude dialdehyde as a pale yellow oil.

THF (1 mL) was added to a commercially available 1:1 mixture of methyltriphenylphosphonium bromide/sodium amide (0.264 g, 0.739 mmol). The resulting mixture was stirred for 1 h at room

temperature, at which time a solution of the dialdehyde prepared above in THF (1 mL) was added via cannula to the ylide suspension. The resulting mixture was stirred at room temperature for 16 h. The solution was poured into EtOAc (5 mL) and saturated aqueous NH_4Cl (5 mL). The organic layer was separated and the aqueous phase was extracted with EtOAc (3×5 mL). The combined organic layers were washed with water (1×5 mL), brine (1×5 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give a brown oil. This oil was purified by SiO_2 column chromatography (1–5% EtOAc/hexanes) to give **44** as a clear oil (0.017 g, 57%, mixture of rotamers). IR (thin film) 2358, 1692 cm^{-1}; ^1H NMR (850 MHz, toluene d_8, major rotamer) δ 7.51 (d, J 7.7 Hz, 1H), 7.15–7.11 (m, 2H), 6.99 (q, J 6.3 Hz, 1H), 6.35 Hz (dd, J 17.4, 10.6 Hz, 1H), 5.89 (ddd, J 16.8, 10.9, 6.6 Hz, 1H), 5.18–4.97 (m, 5H), 3.51–3.32 (m, 7H), 3.15 (t, J 9.7 Hz, 1H), 2.91–2.79 (m, 2H), 2.47–2.39 (m, 2H), 2.06 (m, 1H), 1.41 (s, 9H), 0.58 (s, 3H); ^{13}C NMR (212 MHz, $CDCl_3$, all rotamers) δ 154.7, 154.3, 146.7, 143.5, 142.8, 141.1, 141.0, 134.1, 133.9, 132.2, 131.5, 129.8, 129.3, 128.5, 127.0, 125.9, 125.8, 112.65, 111.8, 110.6, 109.4, 79.7, 79.0, 74.0, 71.6, 61.6, 60.8, 51.1, 51.0, 47.5, 44.8, 44.4, 34.1, 33.4, 32.8, 32.2, 30.1, 29.7, 28.6, 28.4, 14.3; HRMS (TOF MS ES^+) $[M+H]^+$ calcd for $C_{28}H_{37}NO_5Br$ 546.1855, found 546.1833.

4.21. *tert*-Butyl-3a-(2-bromophenyl)-4-carbamoyl-6,6-bis(hydroxymethyl)- hexahydrocyclopenta[*b*]pyrrole-1(2*H*)carboxylate (47)

Orthoester diol **41** (0.119 g, 0.214 mmol) was dissolved in 10% (v/v) H_3PO_4/THF (3.00 mL). The solution was stirred at room temperature until consumption of the orthoester was indicated by TLC (10% MeOH/CH_2Cl_2). This solution of crude ester was transferred to a Parr pressure vessel and isopropyl alcohol (5 mL) was added. The vessel was purged with NH_3 gas three times, pressurized with NH_3 gas at 100 psi, and stirred for 0.5 h while connected to the NH_3 tank. The vessel was sealed and heated at 110 °C for 20 h. The Parr vessel was cooled to room temperature, the ammonia gas was vented, and the reaction solution remained unperturbed for 1 h to give a milky suspension. The suspension was filtered through Celite and the filtrate was concentrated in vacuo to give a yellow solid. This solid was purified via column chromatography on SiO_2 (1–5–10% MeOH/CH_2Cl_2) to give **47** as a white solid, as a 2:1 mixture of rotamers (0.068 g, 68%). Mp 206 °C (decomp.); IR (solid) 3331, 2151, 1662 cm^{-1}; ^1H NMR (major rotamer, 300 MHz, CD_3OD) δ 7.59 (d, J 8.0 Hz, 1H), 7.25 (m, 1H), 7.14–7.07 (m, 2H), 4.95 (s, 1H, overlapping with HOD), 4.17 (d, J 8.9 Hz, 1H), 3.95 (m, 1H), 3.71 (d, J 10.7 Hz, 1H), 3.61 (d, J 10.7 Hz, 1H), 3.48 (m, 1H), 3.36 (m, 1H), 2.87 (m, 1H), 2.64–2.26 (m, 3H), 1.66 (d, J 14.9 Hz, 1H), 1.48 (s, 9H); ^{13}C NMR (both rotamers, 75 MHz, CD_3OD) δ 179.6, 179.4, 157.1, 156.2, 143.1, 142.9, 136.4, 130.1, 130.0, 129.5, 129.4, 128.3, 128.2, 123.0, 122.9, 82.0, 81.9, 72.0, 71.3, 68.6, 67.9, 67.2, 66.3, 65.3, 63.2, 62.9, 51.4, 50.5, 50.4, 50.3, 46.5, 46.3, 36.4, 34.9, 34.1, 34.1, 28.9, 28.7; HRMS (TOF MS ES^+) $[M+H^+]$ calcd for $C_{21}H_{30}N_2O_5Br$ 469.1361, found 469.1338.

4.22. *tert*-Butyl-4,4-bis(hydroxymethyl)-6-oxo-3a,4,5,5a,6,7-hexahydro-1*H*-pyrrolo[3′,2′:2,3]cyclopenta[1,2-*c*]quinoline-3(2*H*)carboxylate (48)

Cs_2CO_3 (0.650 g, 0.198 mmol), copper(I) iodide (0.004 g, 1.98×10^{-2} mmol), and 1,10 phenanthroline (0.007 g, 3.97×10^{-2} mmol) were added to a solution of primary amide **47** (0.008 g, 0.02 mmol) in DMSO (0.200 mL) in a microwave reactor tube. The tube was purged with N_2, sealed with a Teflon cap, and heated at 110 °C for 0.5 h under microwave irradiation. The reaction solution was cooled to room temperature and filtered through Celite, which was rinsed with CH_2Cl_2. The combined organics were concentrated in vacuo to give a blue residue. The residue was purified by preparative TLC on SiO_2 (5% MeOH/CH_2Cl_2, applying the crude mixture to the TLC plate using no more than 10% MeOH/CH_2Cl_2) to give lactam **48** as a yellow solid (0.006 g, 78%, mixture of rotamers). Mp 218–221 °C; IR (thin film) 3241, 1661 cm^{-1}; ^1H NMR (both rotamers, 500 MHz, CD_3OD) δ 7.30 (m, 1H), 7.19 (t, J 6.9 Hz, 1H), 7.10 (t, J 7.5 Hz, 1H), 6.87 (d, J 7.9 Hz, 1H), 4.46 (s, 0.6H, major rotamer), 4.42 (s, 0.4H, minor rotamer), 3.99 (t, J 9.9 Hz, 1H), 3.59 (d, J 12.8 Hz, 1H), 3.54–3.37 (m, 3H), 2.98 (dd, J 12.0, 6.6 Hz, 1H), 2.30 (dd, J 12.9, 6.6 Hz, 1H), 2.19–1.80 (m, 3H), 1.64 (t, J 12.5 Hz, 1H), 1.51 (s, 6H), 1.28 (s, 3H); ^{13}C NMR (both rotamers, 125 MHz, CD_3OD) δ 173.6, 173.1, 156.7, 155.9, 136.8, 129.2, 129.0, 128.0, 127.6, 125.3, 125.1, 116.9, 116.8, 82.0, 81.9, 76.6, 75.0, 68.0, 67.2, 64.0, 62.0, 60.0, 58.9, 53.4, 52.6; 48.2, 47.9 (overlapping with CD_3OD), 40.5, 39.8, 37.2, 36.5, 30.8, 28.8, 28.6; HRMS (TOF MS ES^+) $[M+H^+]$ calcd for $C_{21}H_{29}N_2O_5$ 389.2076, found 389.2103.

4.23. 3-Allyl-4,4-divinyl-2,3,3a,4,5,5a-hexahydro-1*H*-pyrrolo[3′,2′:2,3]cyclopenta[1,2-*c*]quinolin-6(7*H*)-one (13)

Dess–Martin periodinane (0.076 g, 0.18 mmol) was added to a solution of lactam diol **48** (0.007 g, 0.02 mmol) in water saturated CH_2Cl_2 (0.180 mL) in a microwave reactor tube. The tube was purged with nitrogen, sealed with a Teflon cap, and heated to 65 °C for 0.5 h under microwave irradiation. The reaction mixture was cooled to room temperature and 3 mL of a 1:1 mixture of saturated aqueous sodium bicarbonate/saturated aqueous $Na_2S_2O_3$ was added. The biphasic solution was stirred until all of the solids had dissolved and the mixture was clear. The organic layer was removed, and the aqueous layer was extracted with CH_2Cl_2 (3×5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to give the unstable 1,3 dialdehyde as a pale yellow oil.

A suspension of methyltriphenylphosphonium bromide (0.129 g, 0.360 mmol) in THF (0.3 mL) was cooled to 78 °C and a solution of NaHMDS (1.0 M in THF, 0.34 mL, 0.34 mmol) was added dropwise. This suspension was stirred at 78 °C for 1.5 h. The crude 1,3 dialdehyde prepared above was dissolved in 0.15 mL of THF and added via cannula to the ylide suspension, rinsing the flask with an additional 0.15 mL of THF. The reaction mixture was allowed to warm to room temperature and stirred for 72 h at that temperature. Saturated aqueous ammonium chloride (5 mL) and EtOAc (5 mL) were added. The organic layer was removed and the aqueous layer was extracted with EtOAc (1×5 mL) and CH_2Cl_2 (2×5 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated in vacuo to give **49** as a brown oil.

This crude oil was dissolved in 10% (v/v) TFA/CH_2Cl_2 (3 mL) and stirred at room temperature for 4 h. The reaction solution was concentrated in vacuo and saturated aqueous sodium bicarbonate (3 mL) and CH_2Cl_2 (5 mL) were added to the residue. The organic layer was removed and the aqueous layer was extracted with CH_2Cl_2 (3×5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to give the crude free amine as a brown oil.

This crude amine was dissolved in MeCN (0.5 mL), and K_2CO_3 (0.015 g, 0.11 mmol) and allyl bromide (0.010 mL, 0.11 mmol) were added sequentially. The reaction mixture was stirred at room temperature for 24 h and then water (3 mL) and CH_2Cl_2 (3 mL) were added. The organic layer was drawn off, and the aqueous layer was extracted with CH_2Cl_2 (3×3 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to give a brown residue. The residue was purified on SiO_2 (5–15% EtOAc/hexanes) to give **13** as a colorless oil (0.004 g, 57% from **48**). IR (thin film) 1674 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.79 (br s, 1H), 7.31 (d, J 7.2 Hz, 1H), 7.15 (td, J 7.6, 1.4 Hz, 1H), 7.05 (td, J 7.5, 1.3 Hz, 1H), 6.65 (dd, J 7.8, 1.2 Hz, 1H), 6.24 (dd, J 17.7, 10.9 Hz, 1H), 5.93 (dddd, J 17.4, 10.2, 7.5, 5.1 Hz, 1H), 5.74 (dd, J 17.5, 10.8 Hz, 1H), 5.30–5.09

(m, 4H), 4.94 (dd, *J*=10.8, 0.8 Hz, 1H), 4.88 (dd, *J*=17.6, 0.8 Hz, 1H), 3.51 (m, 1H), 3.43 (s, 1H), 3.29 (dt, *J*=10.1, 5.0 Hz, 1H), 3.04 (dd, *J*=13.7, 7.5, 1H), 2.94 (dd, *J*=8.8, 7.0 Hz, 1H), 2.84 (dt, *J*=10.0, 8.1 Hz, 1H), 2.41 (dd, *J*=12.6, 6.9 Hz, 1H), 2.17 (dd, *J*=12.6, 8.9 Hz, 1H), 2.02–1.97 (m, 2H); ^{13}C (150 Hz, $CDCl_3$) δ 171.5, 143.0, 140.6, 135.8, 134.4, 130.0, 127.7, 127.3, 123.7, 116.9, 115.3, 114.4, 113.7, 87.6, 58.6, 56.9, 55.6, 53.4, 50.5, 43.7, 41.4; HRMS (TOF MS ES$^+$) [M+H$^+$] calcd for $C_{21}H_{25}N_2O$ 321.1967, found 321.1961.

4.24. (±)-Meloscine (1)

Hoveyda–Grubb's second-generation catalyst (0.00023 g, 0.00036 mmol) in toluene (0.10 mL) was added to a solution of **13** (0.0023 g, 0.0072 mmol) in toluene (2.0 mL). The reaction mixture was heated for 24 h at 60 °C and then cooled to room temperature and concentrated in vacuo to give a brown residue. The residue was purified via column chromatography on SiO_2 (hexanes/1–2–4% MeOH/CH_2Cl_2) to give **1** as a white solid (0.0014 g, 76%). Mp 205–210 °C (lit.[5e] 208–209); IR (thin film) 1672 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (s, 1H), 7.39 (d, *J*=7.9 Hz, 1H), 7.15 (t, *J*=7.7 Hz, 1H), 7.05 (t, *J*=7.6 Hz, 1H), 6.65 (d, *J*=7.9 Hz, 1H), 6.01 (ddd, *J*=10.0, 5.5, 2.2 Hz, 1H), 5.72 (dd, *J*=9.9, 2.4 Hz, 1H), 5.53 (dd, *J*=17.4, 10.5 Hz, 1H), 4.91 (d, *J*=17.3 Hz, 1H), 4.79 (d, *J*=10.5 Hz, 1H), 3.51 (s, 1H), 3.30 (dd, *J*=16.1, 5.5 Hz, 1H), 3.25–3.08 (m, 2H), 2.96 (t, *J*=8.8 Hz, 1H), 2.88 (td, *J*=8.0, 4.5 Hz, 1H), 2.31 (dd, *J*=12.7, 8.3 Hz, 1H), 2.22–2.08 (m, 2H), 1.96 (dt, *J*=12.8, 7.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4, 143.2, 135.0, 132.4, 127.9, 127.7, 127.6, 127.0, 123.9, 115.1, 112.6, 82.5, 56.8, 53.0, 51.0, 48.1, 46.8, 43.4, 42.2; HRMS (TOF MS ES$^+$) [M+H$^+$] calcd for $C_{19}H_{21}N_2O$ 293.1654, found 293.1643.

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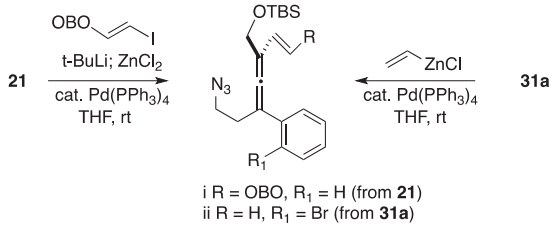

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