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A Systematic Investigation of Quaternary Ammonium Ions as Asymmetric Phase-Transfer Catalysts. Synthesis of Catalyst Libraries and Evaluation of Catalyst Activity

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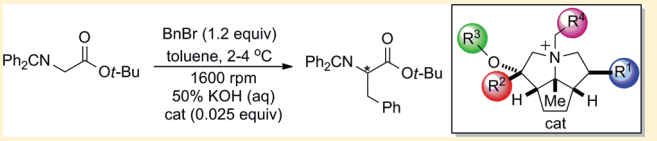
Supporting Information

ABSTRACT: Despite over three decades of research into asymmetric phase-transfer catalysis (APTC), a fundamental understanding of the factors that affect the rate and stereoselectivity of this important process are still obscure. This paper describes the initial stages of a long-term program aimed at elucidating the physical organic foundations of APTC employing a chemoinformatic analysis of the alkylation of a protected glycine imine with libraries of enantiomerically enriched quaternary ammonium ions. The synthesis of the quaternary ammonium ions follows a diversity-oriented approach wherein the tandem inter-[4 + 2]/intra[3 + 2] cycloaddition of nitroalkenes serves as the key transformation. A two-part synthetic strategy comprised of (1) preparation of enantioenriched scaffolds and (2) development of parallel synthesis procedures is described. The strategy allows for the facile introduction of four variable groups in the vicinity of a stereogenic quaternary ammonium ion. The quaternary ammonium ions exhibited a wide range of activity and to a lesser degree enantioselectivity. Catalyst activity and selectivity are rationalized in a qualitative way on the basis of the effective positive potential of the ammonium ion.



INTRODUCTION

Phase-transfer catalysis (PTC) is an extremely useful method for performing nearly any type of reaction involving an ionic starting material or intermediate. A number of characteristics of PTC reactions make them especially attractive for industrial applications including, ease of scalability, their intrinsic "green nature", and potential for extension to asymmetric variants (APTC).[1] One of the most useful aspects of APTC is the ability to catalyze a wide variety of reaction types, ranging from redox processes to many carbon−carbon bond-forming reactions. However, despite over three decades of research into APTC, a fundamental understanding of the factors that affect catalyst activity and stereoselectivity is still obscure. The purpose of this report is to describe the initiation of a research program to elucidate the structural features that govern the activity and enantioselectivity of quaternary ammonium ion phase-transfer catalysts. The research program consists of two separate components described in this and the accompanying paper.[2] In this report we describe the development of suitably flexible synthesis of chiral, nonracemic, quaternary ammonium ions by solution-phase parallel synthesis as well as the collection of a large set of catalyst activity and selectivity data. In the accompanying report (DOI 10.1021/jo2005457), the data sets are analyzed by developing many quantitative structure−activity and selectivity-relationships (QSAR and QSSR). An enolate alkylation reaction was chosen to initiate these studies for three reasons: (1) it is one of the oldest and most useful methods to form carbon−carbon bonds, (2) many examples of PTC enolate alkylations are on record, and (3) the methods to perform enolate alkylations in a catalytic enantioselective manner are very limited.

The requirements for a catalytic, enantioselective enolate alkylation are the in situ generation of an enolate, alkylation in the presence of a stereochemical controlling element, and stereochemical stability of the product (Scheme 1). Although auxiliary-based methods for the diastereoselective alkylation of enolates truly revolutionized the practice of organic synthesis beginning in the 1970s,[3,4] a general and selective processes for catalytic enantioselective alkylations remains elusive.[5] In contrast to other carbon−carbon bond-forming reactions of enolates (compare to, e.g., aldol and Michael reactions), the rate of enolate alkylation is significantly less than addition to a π-system; thus, the use of soft-enolization techniques which are crucial for catalytic π-addition reactions cannot be utilized for enolate alkylations.[6] The use of more reactive enolates, and strong bases to generate them, introduces a host of compatibility issues, thus preventing the implementation of similar stereocontrol elements under catalytic conditions.

Nevertheless, notable successes have been achieved that represent creative solutions to some of the challenges described above. For example, a lithio cycloalkanone enolate alkylation has been cleverly engineered using a triamine catalyst.[7,8] Transition-metal-catalyzed allylations are the most intensely investigated class of asymmetric alkylation reactions and have been extensively reviewed.[9] Ligand development has been critical in facilitating many α-aryl and α-alkenylations of carbonyl compounds under palladium catalysis, although they are typically limited to generation of quaternary centers to avoid product racemization.[10] Two

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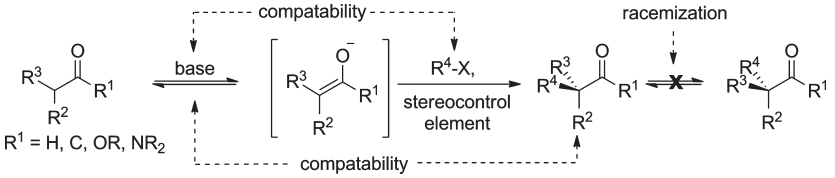
Scheme 1



alternative strategies have recently been reported, the asymmetric alkylation of ketone-derived tributyltin enolates in the presence of chromium(salen) complexes[11] and asymmetric dimethoxymethylation of *N*-acylthiazolidinethiones with an orthoester under catalysis by a nickel(BINAP) complex.[12] A single report of intramolecular alkylation of an enamine generated from a proline derivative is on record, but extension to intermolecular versions is unknown.[13] Perhaps the most imaginative extension of enamine catalysis for alkylation-type reactions is the enantioselective α-allylation, α-enolation, α-vinylation, and α-arylation of aldehydes via the intermediacy of chiral enaminium radicals.[14]

To date, PTC is the only catalytic process capable of reducing to practice the simplest of enolate alkylations, such as methylation, ethylation, and benzylation (vide infra).[5] As a synthetic tool APTC is complementary to the recently developed transition-metal coupling methods that are well suited for coupling with C-sp^2 electrophiles.[15] The mode of operation of APTC is unique in that the base and electrophile are in separate phases, thereby allowing the generation of highly active chiral nucleophiles in the presence of an electrophile. The broad electrophile scope of APTC reactions developed thus far suggests that APTC will eventually be a general method for performing strong base chemistry catalytically and enantioselectively.

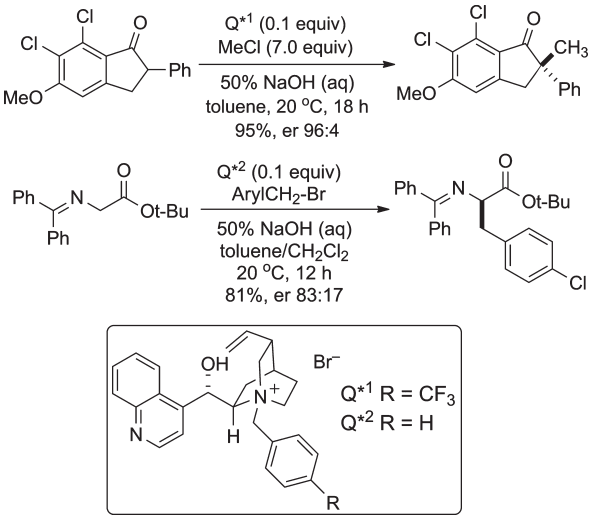
The state of the art of APTC stands at an interesting crossroad. On one hand, impressive advances have been achieved in the ability to execute catalytic reactions that involve reactive carbanions and tremendous potential still exists. On the other hand, without testable hypotheses about what structural features are dominant in conferring high activity and selectivity to phase-transfer catalysts, researchers are constrained to make and test catalysts without guiding principles to aide in the process. Accordingly, rationalization of activity and selectivity of APTC is currently done ad hoc, with little understanding of the observed trends. This dilemma is not surprising. The rates and selectivities of APTC reactions are governed by interfacial transport, desolvation, and a host of nonbonded interactions which are difficult to study. Still more challenging is the a priori design of asymmetric phase transfer catalysts. In fact, the most readily available and successful APTCs to date are the cinchona alkaloid derivatives. Unfortunately, these structures offer little opportunity for systematic modification.[16,17]

If anything has been learned about asymmetric catalysis over the past 30 years it is that major advances in the state of the art are inexorably tied to the development of a solid, physical organic foundation upon which greater and greater improvements can be built.[18] Therefore, we sought to establish a research strategy capable of elucidating the fundamental origins of the structure—activity and selectivity of asymmetric phase-transfer catalysts. *To emphasize, the goals of this research were not simply to discover a new enantioselective catalyst but rather to investigate a new method for catalyst development.* The approach we have adopted is analogous to a drug design process consisting of iterations of synthesis, evaluation, and modeling. Reported herein are the first iterations of synthesis (160 catalysts) followed by evaluation (activity and selectivity) and finally modeling (in the accompanying paper).[2]

BACKGROUND

1. APTC Enolate Alkylations and Known Catalyst Motifs. Phase-transfer catalysis has already proven to be a broadly applicable and general method to perform strong base chemistry catalytically.[19] In a landmark publication, the Merck Process Group reported the enantioselective methylation of an indanone under PTC conditions employing an *N*-4-trifluoromethylbenzyl cinchona alkaloid derivative.[20] A second critical advance appeared in 1989 when O'Donnell demonstrated the selective alkylation of glycine imines under similar conditions (Scheme 2).[21] O'Donnell's alkylation is an operationally simple method for α-amino acid synthesis and has since served as a benchmark for the development of new asymmetric phase-transfer catalysts.[22]

Scheme 2



In the intervening 20 years, many variations of cinchona alkaloid catalysts have been reported. The first notable advances were from independent studies by Lygo[23] and Corey,[24] in which the incorporation of a 9-anthracenylmethyl moiety as the nitrogen substituent markedly improved the enantioselectivity (Chart 1). Analogously, Park and Jew developed a trifluorinated *N*-benzyl quaternary ammonium catalysts[25a] and dimeric, meta-bridged cinchoninium catalysts.[25b] In recent years, Maruoka and Ooi have introduced a large number of novel, non-cinchona alkaloid catalyst

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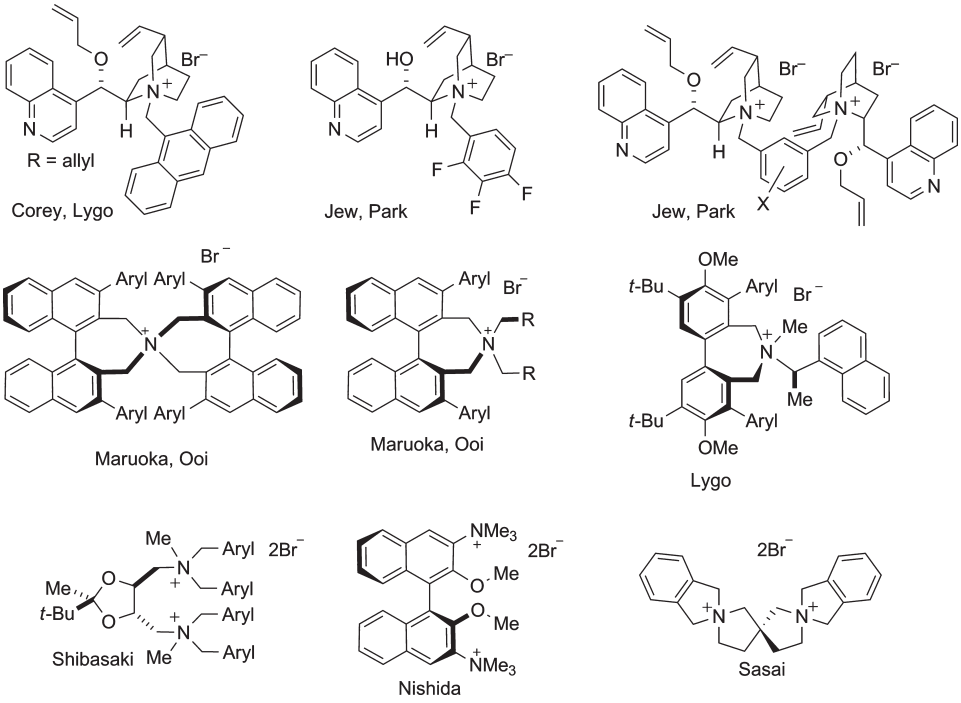
Chart 1



systems based on a binaphthyl scaffold which allows introduction of substituents in the 3,3′ positions.[26] Similarly, employing an in situ generation and screening process, Lygo has discovered a useful locally C_2 (at the nitrogen)-symmetric catalyst.[23c] Shibasaki/Ohshima,[27] Sasai,[28] Arai/Nishida,[29] and others have independently developed two-centered (and higher) APTC's by incorporation of quaternary ammonium ions about a C_n axis. In addition to extensive catalyst development, significant advances in other typically strong-base-promoted reactions have been recorded including double alkylation of glycine imines, ketone alkylations, Michael, aldol, Mannich, and Darzens reactions, as well as epoxidations and aziridinations.[19k−n]

2. Catalyst Activity. *2.1. Mechanisms of Hydroxide-Initiated PTC.* The broad utility of PTC has motivated numerous investigations from fields as far reaching as synthetic chemistry, chemical engineering, computational chemistry, physical chemistry, and chemoinformatics. PTC reactions that use aqueous bases to generate carbanions are termed hydroxide-initiated PTC.[30] The mechanism of hydroxide-initiated PTC reactions is an intensely investigated subject that has been thoroughly reviewed from both a chemical[31] and engineering[32] perspective. Pioneering studies by Makosza[33] and Starks[34] led to two distinct mechanistic descriptions, later termed the interfacial (Makosza) and extraction (Starks) mechanisms. The mechanisms differ in the mode in which the substrate·ammonium ion pair enters the organic phase (Figure 1). Numerous studies have provided experimental support for *both* the extraction[35,36] and interfacial mechanisms.[37−39] These studies have accumulated a number of phenomenological observables that are used as indicators to decipher which mechanism is dominant.[31b] Reactions governed by the extraction mechanism show little dependence on stirring rate and first order kinetic behavior in substrate and catalyst. On the other hand, PTC reactions governed by the interfacial mechanism show a strong dependence on stirring rate, complex kinetic order in substrate, and fractional order in catalyst. The current understanding of hydroxide-initiated PTC reactions suggests a mechanistic continuum that is strongly dependent on substrate pK_a and catalyst structure.[31b] To summarize, the extraction mechanism is dominant at the two extremes of substrate acidity (pK_a < 16 and pK_a > 23) and the interfacial mechanism is dominant when the pK_a of the substrate is between 16 and 23. The rational is that reactions with highly acidic substrates are rate limited in extraction of the substrate enolate and nonacidic substrates are rate limited by the rate of hydroxide extraction. Thus, the interfacial mechanism is proposed to be most relevant for enolate alkylations.[40]

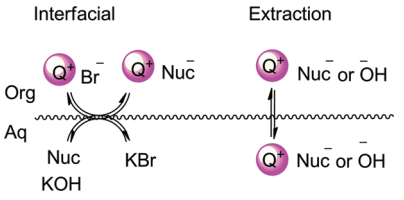


Figure 1. Two mechanisms of nucleophile transfer in hydroxide-initiated PTC Reactions.

2.2. Guidelines for the Design of Active Catalysts. The quaternary ammonium ion catalyst is obviously the most critical element of a PTC reaction, and as is the case for any catalytic reaction, the selection of the "optimal" catalyst is crucial.[41,31b] The fact that there are two possible mechanisms, in combination with the possibility of many "off-cycle" pre-equilibria, all of which are a function of substrate and catalyst combination, has made identifying simple structure−activity relationships difficult.[31a] For reactions strictly following an extraction mechanism (e.g., S_N2 displacements with N_3^-, CN^-, SCN^-, etc.), catalyst activity correlates well with lipophilicity.[36,35,42] No such generalizable structure−activity relationships exist for hydroxide-initiated PTC reactions.

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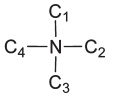
For hydroxide-initiated PTC reactions, small hydrophilic ammonium ions are often superior catalysts, which is a compounding source of confusion.[43,44] For example, triethylbenzylammonium, a small hydrophilic quaternary ammonium ion, is an efficient catalyst for a myriad of PTC enolate alkylations (e.g., nitriles, esters, ketones, etc.).[45] One approach has been to correlate a macroscopic observable such as interfacial surface tension to catalytic activity which unfortunately does not address the question of what catalyst attributes confer high activity.[46] In the most advanced SAR to date, the ammonium ion accessibility (or size) *and* solubility were varied simultaneously, and the most active symmetrical catalyst for alkylations was tetraethylammonium bromide.[47] A useful quantitative correlation of structure to catalyst activity was subsequently derived, namely the structural parameter, q (eq 1, where C_n is the number of carbons in C_i).[48] The q parameter is defined as the sum of the reciprocals of the number of carbons on each chain.[49] For hydroxide-initiated PTC reactions, such as the alkylation of enolates, q values between 1.5 and 2.0 are optimal. This analysis is useful for simple quaternary ammonium ions containing only alkyl chains (C_{1-4}) but extension to catalysts containing functional groups, changes in hybridization, rings, branch points, or stereogenic centers has not been reported.

$$q = \frac{1}{\#C_1} + \frac{1}{\#C_2} + \frac{1}{\#C_3} + \frac{1}{\#C_4}$$



3. Structural Considerations for Catalyst Enantioselectivity. The rationalization of enantioselectivity and reduction to design criteria is of preeminent importance to the study of catalytic processes.[50] The alkylation of O'Donnell's imine is by far the most studied enolate alkylation, and two models have been proposed to rationalize the enantioselectivity observed with cinchona alkaloid derived catalyst (Figure 2).[51] In a thorough computational study, O'Donnell and Lipkowitz analyzed the enolate molecular recognition event and origin of stereoselectivity of this important transformation.[52] Computational results suggest selective binding of the catalyst to the *Si* face of the *Z*-enolate (Figure 2a). Subsequently, it has been proposed that catalysts bearing a 9-methylanthracenyl group on nitrogen react through the *E*-enolate (Figure 2b).[23,24]

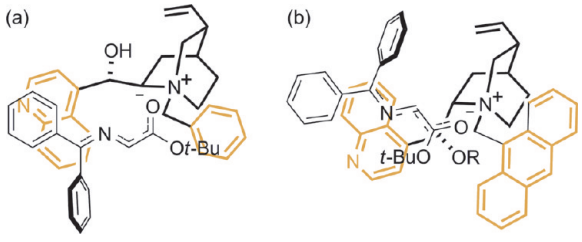


Figure 2. Models to rationalize the enantioselectivity of cinchona-derived PTC catalysts.

The binding site of cinchona alkaloid derived catalysts has been probed by intermolecular NOE correlations between ammonium borohydrides and fluorides and indicates two "front-face" binding regions (Figure 3a).[53] These studies provide good support for strong hydrogen-bonding interactions of the type $N^+CH\cdots O^-$ in solution which has also been identified in the solid state by X-ray crystallographic analysis of quaternary ammonium−enolate ion pairs.[54] High-level calculations further corroborate that, in solution, ammonium ion ester enolates tend to orient "face-on" to one of the faces of the ammonium (Figure 3b).[51b] The combination of these analyses lends to a useful design mnemonic by inscribing the ammonium nitrogen in a tetrahedron (red) where the vertices are the four carbons bound to it. The face proximal to the oxygen is proposed to lead to more selective reaction of the substrate bound to it.

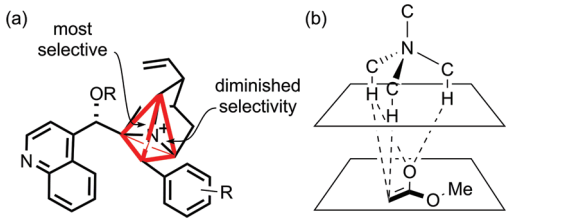


Figure 3. Two potentially generalizable levels of analysis for ammonium ion enolate binding.

4. Objectives of this Study. Our initial survey of the literature revealed a few significant trends. First, while a myriad of APTC methods have been developed for enolate π-addition reactions, the reports on analogous alkylation reactions remains limited, largely O'Donnell's glycine imine substrate.[19m] It is not clear whether the lack of reports on new hydroxide-initiated PTC enolate alkylations is because known catalysts are insufficiently active, insufficiently selective, or both. What is clear, however, is that a more rational, systematic manner to develop quaternary ammonium ion catalysts is needed. Specifically, to elevate APTC to the state of rational design available to other catalytic enantioselective methods, two unique challenges need to be addressed. First, a method to estimate the activity of catalysts a priori is needed. This capacity would greatly alleviate the synthetic investment currently required to study APTC and, in so doing, facilitate discovery. Second, a clearer picture of structural features that confer high selectivity to asymmetric phase-transfer catalysts is needed.

Each of these aspects is a daunting task because they require systematically varying the topology of a quaternary ammonium ion catalyst, which is difficult to synthesize in enantiopure form. Fortunately, the pharmaceutical drug discovery model provides close analogy for both of these challenges.[55] Thus, the first phase of these studies has been initiated in analogy to a phenotypic screening assay where catalyst activity will be evaluated as a function of molecular "pharmacodynamic" properties.[56] The intermolecular enantiotopic face discrimination event is analogous to molecular recognition of a substrate (or drug) by an enzyme, except that the synthetic effort is tantamount to building the enzyme binding pocket rather than the substrate.

We therefore set out to devise a research strategy that would provide a proof of principle as a catalyst development methodology. The key objectives were to develop *quantitative* analyses of both catalyst activity and enantioselectivity, in order to probe the underlying hypothesis that a quantitative treatment of catalyst activity and selectivity as a function of catalyst structure would naturally lend to a more facile catalyst development process. To emphasize, the motivational factors for this study were *to probe the manner in which catalyst development is done and not simply to develop a catalyst*. We therefore made two decisions before initiating this study. First, the alkylation of O'Donnell's imine would serve as the benchmark reaction for catalyst screening, thereby foregoing a methodological development period.

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Second, an arbitrary, and modest, enantioselectivity threshold of ~80:20 was set as the point at which random catalyst screening would stop and a more systematic, QSAR-guided investigation would begin. After all, developing a QSAR model on a data set where catalyst selectivities exceed 99:1 is, in many ways, a moot point because the end goal has already been reached. No limit for range of activity data was set initially, but the preliminary survey readily identified catalysts with activity differences up to 4 orders of magnitude, which is well suited for a QSAR study. The design and synthesis of a suitably diverse libraries of quaternary ammonium ion catalysts and collection of activity and selectivity data for this initial data set is described below. A qualitative analysis of the observed trends follows which are reduced to quantifiable changes in the catalysts and interpreted mechanistically in the accompanying paper.[2] Ongoing studies (data not shown) indicate that these, quantitative models are readily utilized as a methodological tool for further catalyst optimization.

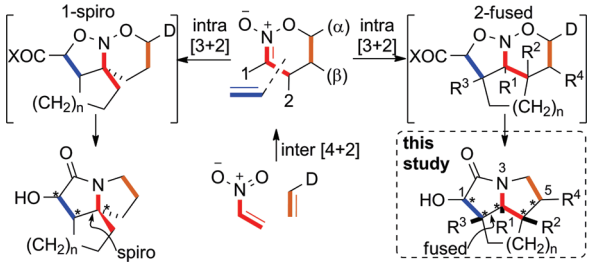
RESULTS

1. Research Plan and Design. *1.1. Scaffold Synthesis Method.* Without testable hypothesis about what structural features will dominant in conferring high catalyst activity and selectivity, this endeavor was necessarily initiated as a discovery-oriented program. The initial focus was set on (1) identifying a suitable scaffold (or scaffolds) that could be prepared in enantiopure fashion and would allow for substitution in multiple positions followed by (2) developing suitably flexible parallel synthesis procedures for the elaboration of the scaffold to a diverse library of quaternary ammonium ions. Concurrently the scaffold and most easily substituted positions were evaluated in the context of known quaternary ammonium design principles. The tandem [4 + 2]/[3 + 2] cycloaddition of nitroalkenes, a methodology extensively studied in these laboratories, was quickly identified as a reaction that embodies all of the requisite characteristics for scaffold preparation.[57]

In the tandem cycloaddition of nitroalkenes, three key components, a nitroalkene, a dienophile, and a dipolarophile, combine to construct a new six-carbon unit forging four bonds, up to six contiguous stereogenic centers, and four rings. Lastly, the newly minted skeleton is transformed by hydrogenolysis, which proceeds by reductive N−O bond cleavage followed by intramolecular reductive amination and finally closure of the remaining ring to construct a pyrrolizidine ring system. Of the four possible permutations of inter- and intramolecularity, the tandem inter [4 + 2]/intra [3 + 2] family wherein the dipolarophile and nitroalkene are covalently tethered is the most powerful (Scheme 3).[58] Tethering the dipolarophile to either the α- or β-position of the dienophile results in bridged cycloadducts and generates primary amines after hydrogenolysis. Tethering the dipolarophile to the nitroalkene results in either a spiro-mode (1-position) or a fused-mode (2-position) cycloaddition and generates tertiary lactams after hydrogenolysis. Extensive investigation of this family has revealed many advantages, including (1) ease of preparation of the precursors, (2) flexibility in the electronic nature and configuration of the components, (3) high levels of absolute stereocontrol with chiral dienophiles, and (4) diversity of product structure.[59]

1.2. Scaffold Selection. A key challenge to systematic investigation of APTC is the availability of catalyst scaffolds that allow for facile modification of sites proximal to the quaternary ammonium ion center.[51c,60] Both the spiro- and fused-mode cycloadditions create skeletons where the nitrogen is fixed in a central position of a rigid ring system, thereby providing potential for the controlled installation of groups in the vicinity of the nitrogen. The fused mode, tandem inter [4 + 2]/intra [3 + 2] cycloaddition with a two-carbon tether was chosen for initial studies. In this mode, the tandem cycloaddition/hydrogenolysis sequence generates a tricyclic cyclopentapyrrolizidin-2-one ring system bearing a hydroxy group at C(1) and a substituent at C(5) (Scheme 3). Prior to elaboration of a detailed parallel synthesis strategy, the local environment around the ammonium nitrogen was considered in the context of known design principles.

Scheme 3



1.3. Scaffold Shape and Ammonium Ion Accessibility. By connecting the nitroalkene and the dipolarophile with a two-carbon tether, the ring fusions (C(7b)−N, C(7b)−C(5a), C(7b)−C(7a)) are dictated to all be cis, giving the scaffold a bowl shape (Figure 4). Library design efforts were initiated by inscribing the central ammonium nitrogen of the scaffold in a regular tetrahedron (red) to determine which faces will be accessible for Coulombic interactions. Clearly, the concave face inscribed by C(2)−C(4)−C(7b) is shielded by the C(6)−C(7) methylenes rendering it sterically inaccessible. Initial molecular modeling[61] indicated that a nitrogen substituent (R^4) would occupy the face defined by C(2)−C(4)−C(9) to avoid steric interaction with a group at C(8). Therefore, the two most accessible faces of the ammonium ion tetrahedron appear to be the two situated on the convex face of the scaffold inscribed by C(2)−C(9)−C(7b) and C(4)−C(9)−C(7b), respectively.

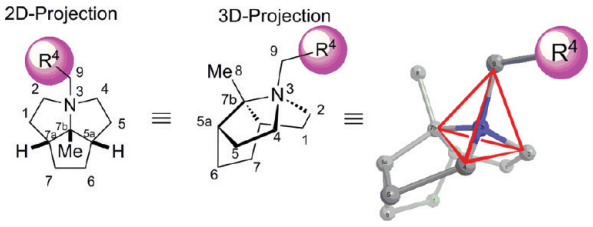


Figure 4. Steric environment the pyrrolizidine scaffold.

1.4. Parallel Synthesis Design. The tandem inter [4 + 2]/intra [3 + 2] cycloaddition of nitroalkenes in the fused mode allows for the stereoselective introduction of groups at C(5) (R^1) and a hydroxy group at C(1) while preserving the relative configuration of the scaffold ring system (Scheme 4). The variable groups R^1, R^2, and R^4 are situated on the convex face allowing for the evaluation of many different combinations of substituents. Because the C(5)-substituent (R^1) is the first point of diversification its variation was limited (either H or Me), thereby reducing the synthetic investment required for this initial survey. Moreover, the configuration of the C(1) center is dictated by the geometry of the dipolarophile thus introducing an additional element for diversification. After

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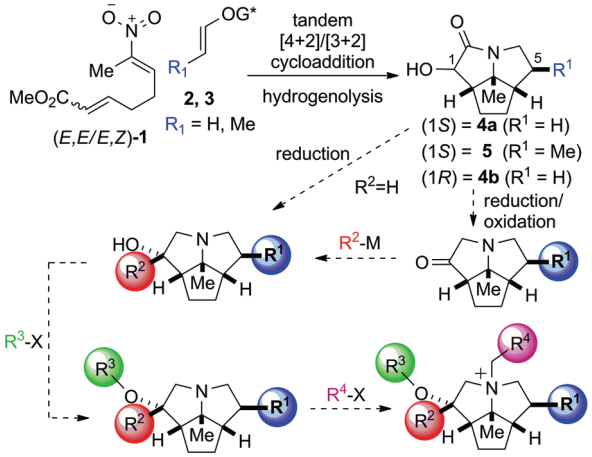
introduction of groups at C(1) and C(5) the scaffolds will be elaborated by means of parallel synthesis.

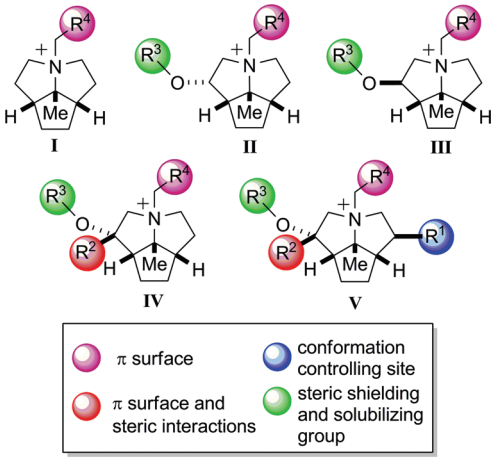
The forward synthetic analysis from the scaffold is outlined in Scheme 4. The hydroxyl group at C(1) was targeted for the next two points of diversification. Simple oxidation followed by addition of an organometallic reagent (R^2-M) would allow for the introduction of groups directly in the vicinity of the C-(2)−C(7b)−C(9) face. Also, alkylation of the resulting alcohol (or the original secondary alcohol) with simple alkyl halides (R^3-X) would serve as a facile method for introducing groups on the concave face. Lastly, the nitrogen substituent (R^4) is installed by a second alkylation to afford the final quaternary ammonium salts. This analysis served as a general framework from which the order of synthetic steps suitable for parallel synthesis was worked out experimentally.

Scheme 4



1.5. Focused Libraries. To facilitate description of the libraries, the catalysts are divided into focused sets of increasing substitution (**I**−**V**). The R^1 substituent (H, Me) served to influence the position of the R^4 substituent and to differentiate the accessibility of the two convex faces inscribed by C(3)−C(7b)−C(9) and C(2)−C(7b)−(C9). The R^2 substituent would play a complementary role in terms of accessibility and interaction of the counterion. This group could be more extensively diversified because of its later stage of introduction in the synthesis. Because R^3 is more distal to the nitrogen atom, the primary focus for this substituent was to serve as a lipophilicity modifier. The residue R^4 was restricted primarily to groups of varying π-surfaces. Additionally, because this group is introduced last, a larger degree of synthetic flexibility is available, thus facilitating a systematic investigation of the role of steric and electronic factors for these aryl rings. The proximity of this substituent to the positively charged nitrogen means that the character of this group should have a larger influence (through dipole and field effects) on the localized positive potential encompassing the nitrogen than any of the other groups. The overall degree of modification in the scaffold as outlined here should lead to sufficient variation in the catalyst structural properties for a QSAR analysis (Chart 2). The simplest members of this group (library **I**) bear no oxygen-containing functionality and vary only in the nitrogen substituent (R^4). Oxygen functionality is introduced in libraries **II** and **III**, whereas additional steric and conformation influencing groups are introduced in libraries **IV** and **V**. Quaternary ammonium

Chart 2

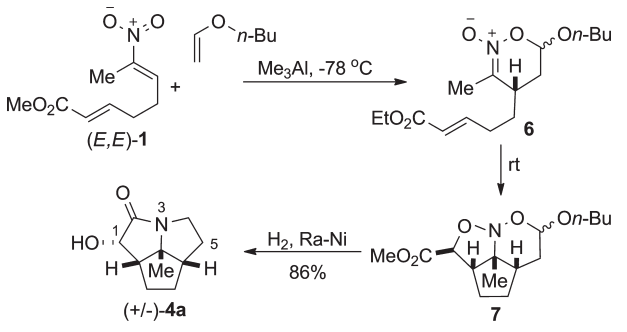


ion library members will be referred to by roman numerals (libraries **I**−**V**) followed by a braced number set designating the order and number of groups introduced {*X*−*X*,*X*−*X*}. For example, in Scheme 6 the intermediate free amine **X**{R^1,R^2,R^3} will be converted to library **V**{R^1,R^2,R^3,*X*−*X*} through the action of reagents {*X*−*X*}.

2. Library Syntheses. *2.1. Preparation of Tandem Cycloaddition Precursors.* To accurately determine the activity and enantioselectivity for each catalyst (ca. three runs/catalyst), approximately 30 mg of each quaternary ammonium salt would be required, thus mandating the synthesis of gram quantities of the scaffolds for libraries **I**−**V**. Thus, the first phase of this investigation was to develop robust, scalable routes to the cycloaddition precursors (nitroalkenes (*E*,*E*)-**1** and (*E*,*Z*)-**1** and chiral vinyl ethers **2** and **3**, above) in decagram quantities. Each of these cycloaddition precursors were readily prepared either directly following the known route or with small changes upon scale-up.[62] The preparation of the cycloaddition precursors **1**−**3** is detailed in the Supporting Information.

2.2. Scaffold Preparation by Tandem Cycloaddition of Nitroalkenes. The centerpiece of the library synthesis was the use of the tandem cycloaddition of nitroalkenes to cast the polycyclic skeletons that will serve as parallel synthesis scaffolds. Known α-hydroxy lactam **4** was prepared in racemic form by tandem [4 + 2]/[3 + 2] cycloaddition of nitroalkene (*E*,*E*)-**1** with *n*-butyl vinyl ether via the intermediacy of nitronate **6** and nitroso acetal **7** (Scheme 5). Reductive hydrogenolysis afforded the tricyclic lactam (±)-**4a** in excellent overall yield (86% over three steps).

Scheme 5



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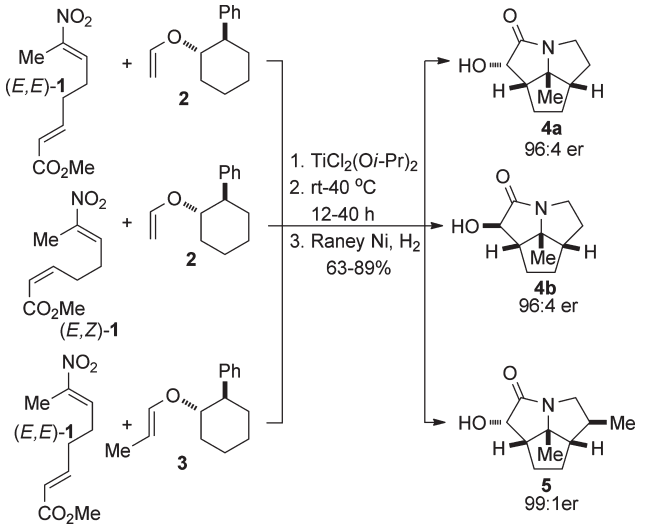
Likewise, enantiomerically enriched α-hydroxy lactams **4a** and **5** were readily prepared on scale in nonracemic form via the tandem cycloaddition with chiral vinyl and propenyl ethers **2** and **3**, respectively (Scheme 6).[62] In this process, a standard set of reaction conditions was employed, namely exposure of a solution of nitroalkene and dienophile to $TiCl_2(O\text{-}i\text{-}Pr)_2$ at −78 °C to afford the intermediate nitronate. Subsequent thermal cycloaddition occurred over the course of 2−3 h upon standing at room temperature. The resulting nitroso acetals were immediately subjected to hydrogenolysis with Raney nickel in methanol to afford the lactams in 76% and 89% respectively (three steps) with high enantioselectivity (er 96:4).[63] The epimeric α-hydroxy lactam **4b** (not previously described) was readily prepared in 63% yield following the standard protocol (er 96:4). The elaboration of these scaffolds to the libraries **I**−**V**, respectively, is detailed in the next section.

2.3. Preparation of Library ***I***. The next phase of these studies involved the development of a suitably versatile parallel synthesis route to allow for the introduction of various substituents on the core scaffold. The simplest scaffold (library **I**), containing only a single site of variation, was first targeted to address the introduction of groups in the key N-alkylation step.

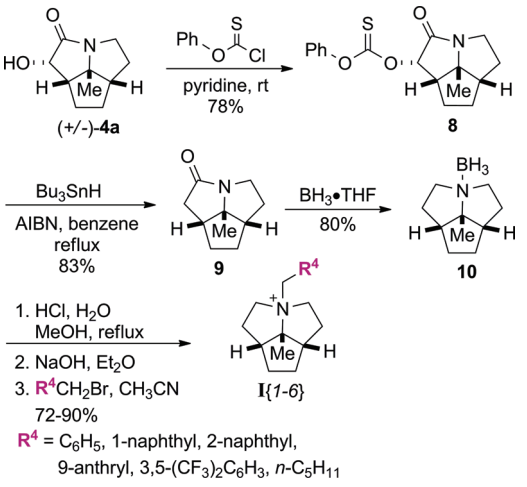
Scheme 6



To complete the synthesis of the C_s symmetric scaffold, reduction of the two oxygen functional groups was required. Removal of the hydroxyl group was accomplished by activation as a phenyl(thiono)carbonate **8** followed by Barton-type deoxygenation under the action of Bu_3SnH/AIBN to afford lactam **9** in good overall yield (64%, two steps) (Scheme 7).[64] Reduction of lactam **9** with borane·THF afforded the fully deoxygenated scaffold **16** for library **I** as its borane adduct in 80% yield. With large quantities of borane adduct **10** in hand, N-quaternization conditions suitable for parallel synthesis could be investigated.

To facilitate the throughput of material, a method for the direct conversion of the amine borane adduct to the desired quaternary ammonium salts was sought that avoided the need for purification of intermediates. Heating amine·borane **10** in methanol in the presence of 1 M aq HCl led cleanly to the intermediate amine hydrochloride. The free base was liberated by partitioning the salt between 0.1 M aq NaOH and ether. Exposure of the free amine to a slight excess of benzylic and primary aliphatic bromides {*1*−*6*} in acetonitrile at room temperature led smoothly to the quaternary ammonium ions **I**{*1*−*6*} in 72−90%. The excess electrophile could easily be removed by either filtration through silica gel or trituration with ether analogous to the methods of Dehmlow[65] and Maruoka,[66] respectively. Ultimately, it was decided that silica gel plug filtration followed by trituration with ether could be used as the general conditions for purification for other ammonium salts.

Scheme 7



2.4. Preparation of Libraries ***II*** *and* ***III***. The next level of complexity called for the synthesis of libraries of chiral, nonracemic ammonium salts to study their effectiveness as asymmetric phase-transfer catalysts. The construction of libraries **II** and **III** introduces a second parallel synthesis step, namely O-alkylation. These two libraries embodied three objectives aimed at investigating *both* enantioselectivity and rate (1) to introduce groups with variable solubilizing abilities (rate), (2) introduce variable π-surfaces and steric bulk (selectivity), and (3) investigate the effect of configuration at C(1) (selectivity).

The diastereomeric lactams **4a** and **4b** were reduced to the pyrrolizidines **11a** and **11b** with BH_3·THF (>10 equiv) in good to excellent yield (Scheme 8). These amines were also isolated as their borane adducts, thus protecting the amine from air oxidation[67] and subsequent alkylation in the next step. This sequence allowed for the preparation of multigram quantities of borane complexes **11a** and **11b** as crystalline solids which was a convenient stage for storage of material. Application of standard Williamson ether synthesis conditions[68] (NaH, DMF) to borane complexes **11a** and **11b** allowed for facile elaboration to intermediates **II**{*1*−*5*} and **III**{*1*−*5*}. The introduction of simple hydrophobic groups (*n*-hexyl), hydrophilic groups (methoxyethoxymethyl, MEM) as well as aromatic carbocycles and heterocycles, is readily achieved in good yield under a standard set of reaction conditions. It is noteworthy that the inclusion of a MEM ether in these series required the use of either neutral or base-promoted deborylation conditions because of the acid lability of this group. Accordingly, aq HCl was replaced with aq Na_2CO_3

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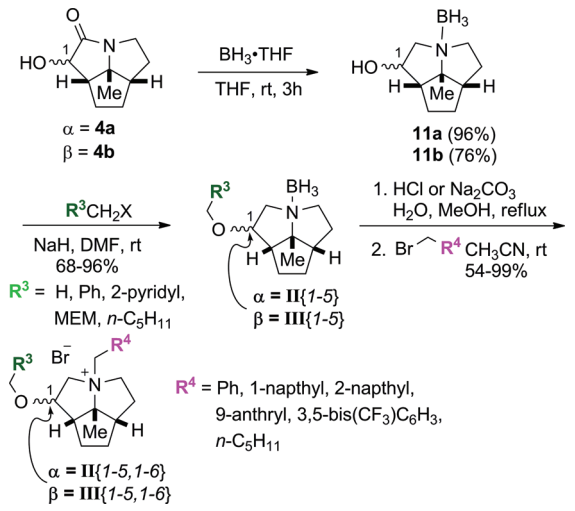
under otherwise identical reaction conditions. Elaboration of the intermediate borane adducts as described previously proceeded smoothly to afford quaternary ammonium salt libraries **II**{*1−5,1−6*} and **III**{*1−5,1−6*} in good yields over the three step process.

Scheme 8



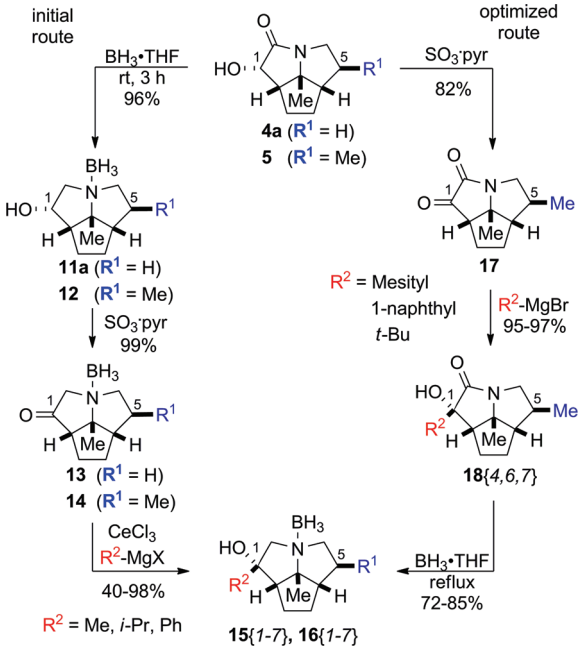
*2.5. Preparation of Libraries **IV** and **V***

2.5.1. Introduction of R^2 Substituents. The presence of the hydroxyl group at C(1) allows for further diversification. This site was targeted for the introduction of different aliphatic and aromatic groups by organometallic addition to the corresponding C(1) ketone. Accordingly, Parikh−von Doering oxidation of **11a** furnished the desired ketone **13** in 98% yield (Scheme 9).[69] However, ketone **13** was not stable and was immediately carried on to the organometallic addition step. The increased acidity of the α-hydrogens, likely as a consequence of nitrogen complexation,[70] required the use of softer, less Brønsted basic organocerium reagents.[71] The resulting additions took place (40−98% yield) to form **15**{*1−7*} with complete *β*-diastereoselection as a consequence of the bowl shape of the core scaffold. Likewise, ketone **14** (an inseparable 12:1 mixture of C(5) diastereomers from cycloaddition with a propenyl ether) underwent the cerium-mediated addition to afford the tertiary alcohols **16**{*1−7*} in similar yields.

However, the inability to introduce bulky groups as well as poor reproducibility led to a modification of the synthetic route. Oxidation of alcohol **5** to α-keto lactam **17** afforded two important benefits over the initial route. First, the addition of Grignard reagents to this highly active dicarbonyl compound proceeded reproducibly and in excellent yields (95−97%) even with bulky nucleophiles. Second, the minor C(5) diastereomer could be removed by a single recrystallization. Reduction of the resulting lactams **18**{*4,6,7*} required elevated temperatures, presumably a consequence of the additional steric bulk proximal to the site of reduction. In this way, the corresponding amine·borane adducts **15** and **16** could be isolated in respectable yields (72−85%) without increasing the number of steps in the synthetic route.

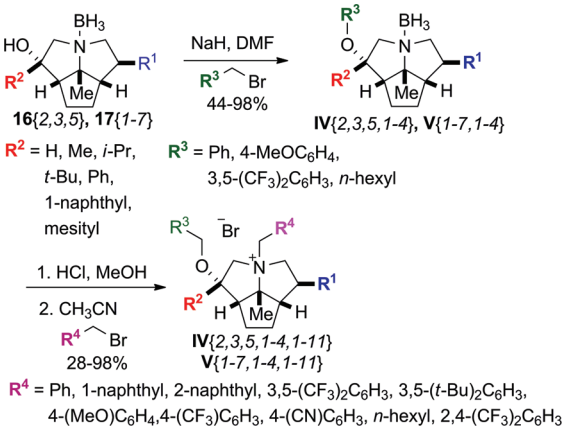
*2.5.2. Parallel Synthesis toward Libraries **IV** and **V**.* Extension of the developed parallel synthesis route to the more hindered tertiary alcohol at C(1) found in libraries **IV** and **V** was straightforward (Scheme 10) and readily accomplished

Scheme 9



following the previously developed protocol. The R^3 substituents in libraries **IV** and **V** were limited to unfunctionalized aliphatic groups and electron-rich (4-$MeOC_6H_4$) and electron-deficient (3,5-$(CF_3)_2C_6H_3$) aromatic groups. Also, the 9-anthrylmethyl group at R^4 was removed from this set,[72] but a larger number of groups of varying electronic makeup and size were introduced for R^4 in libraries **IV** and **V**.

Scheme 10



2.6. Summary of Library Syntheses. A library of over 160 catalysts sharing the same core scaffold has been generated that incorporates the substituents below (Figure 5). Although this number represents only a small fraction of the complete matrix of ∼1100 catalysts, the library represents a good approximation of the total structural space occupied by the complete matrix on the basis of preliminary data. The groups shown reflect the need to evaluate the roles of steric and electronic contributions, *π*-surface, lipophilicity, and polar surface area on the catalyst structure for a given phase-transfer-catalyzed reaction.

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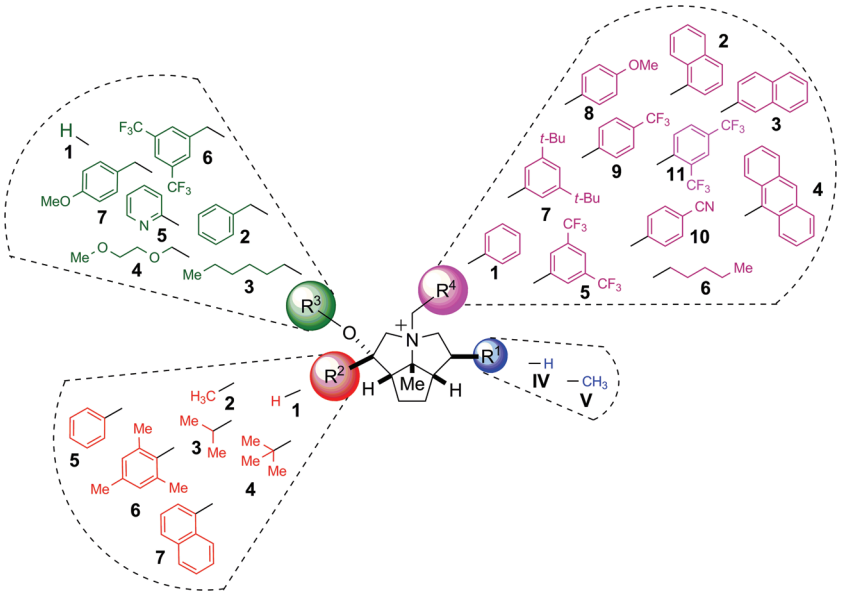


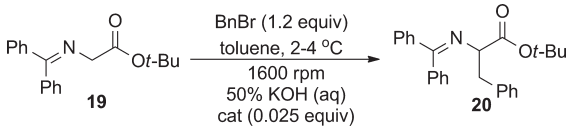
Figure 5. Substituents included in the catalyst library.

3. Collection of Kinetic Data. *3.1. Refining a Kinetic Analysis.* The base-promoted benzylation of glycine benzophenone imine *tert*-butyl ester **19** has become the benchmark reaction for investigation of new catalyst structures.[19m] As such, a standard set of reaction conditions has been established, namely the use 50% aq KOH solution and toluene.[22] Given the intrinsic biphasic nature of PTC reactions, efficient mixing is essential to promote efficient transport and to minimize the errors associated with precipitation. For these reasons, a 4 mL (1 cm ×3.5 cm) cylindrical vial was chosen as the reaction vessel together with a 1.5 cm egg-shaped stir bar. This stir bar was large enough such that it traversed the interface and yet was small enough to ensure mixing as a consistent shearing motion.[47,73,74] The scale of the reactions was dictated by the need to conduct multiple kinetic runs using 80−120 mg of starting ester **19** (thus dictating a minimally measurable amount of catalyst (4−8 mg)) and to maintain a reaction concentration of 0.33 M.

Under these conditions, orienting experiments utilizing 5 mol % of a catalyst at room temperature resulted in rapid reaction; most were complete within 1−3 min! Clearly, this range of rates was not amenable to providing reproducible results. Decreasing the catalyst loading to 2.5 mol % and decreasing the temperature to 2−4 °C successfully slowed the reaction to a point where a range of rates could be observed (Scheme 11).[75]

Initial experiments with tetrabutylammonium bromide allowed for an examination of sampling methods to ensure reproducibility. Sampling from the bulk mixture gave inconsistent results and the sampling needle clogged frequently. A more reliable protocol involved stopping the agitation momentarily to allow the biphasic mixture to separate (∼2 s) and sampling from the organic layer. When this protocol was used, the reaction profile was reproducible, typically to within 1−2%, but always within 5% (see the Supporting Information).

Scheme 11



An important decision was an appropriate value to represent the rate data (e.g., k_i, k_{obs}, $t_{1/2}$, etc). Upon initial testing of catalyst **I**{*1*}, a significant induction period was observed over the course of the first 5% conversion. This type of behavior has previously been reported as a function of ammonium counterion and is indicative of an interfacial mechanism.[40,76] The induction period was seen under the protocol wherein the base was added last. However, if the order of addition of reagents was changed such that the alkylating agent was added last, then the converse was observed and appearance of product was rapid at first, but quickly declined (a kinetic "burst"). Most importantly, regardless of the order of operations, the "time course" of the two reactions converges to a single rate. Given the significant variation at the onset of the reaction, it was decided to extract data that would be independent of the initial rate, namely $t_{1/2}$. Although this determination is labor intensive, since it would require monitoring each reaction to greater than 50% conversion, it has the added advantage of showing the entire reaction profile.

3.2. Stir Rate Dependence. The last critical decision to be made was a stirring rate that would sufficiently minimize errors from precipitation and still allow for the differences in catalyst activities to be observed. Hydroxide-initiated PTC reactions can exhibit a rate dependence on stirring speed in excess of ∼2000 rpm. At high enough stirring speeds there is little dependence which is consistent with the proposal that the influence of mixing is to increase the surface area to volume ratio (effectively concentration) of the biphase[39a] and that phase-transfer reagents can decrease the interfacial surface tension.[46a]

To determine a suitable stirring speed for application to the standard protocol, the dependence of catalytic activity on stirring speed was determined for a variety of variably active quaternary ammonium ions. Reaction half-lives were determined following the experimental parameters noted above employing a range of stir rates (1038−2500 rpm). The resulting observed half-lives are plotted as a log/log in analogy

to a dose−response graph (Figure 6).[55,56] The top two curves represent catalysts with low catalytic activity while the two lower curves represent catalysts among the highest activity. Importantly, there is a sufficient range of stirring speeds, along which the activities of all of the catalysts surveyed are dependent (nonzero slope) on mixing rate. In choosing the stir rate with which all of the kinetic experiments were to be carried out, the important considerations were as follows: (1) there was sufficient and consistent mixing, (2) the experiments were operationally accessible, and (3) the stir rate existed in a region where a reaction rate dependence was still observed. The stir rate of 1600 rpm fit within all three of these criteria (represented by the black vertical dotted line in Figure 6), and therefore, all of the remaining kinetic data were collected at this stir rate.

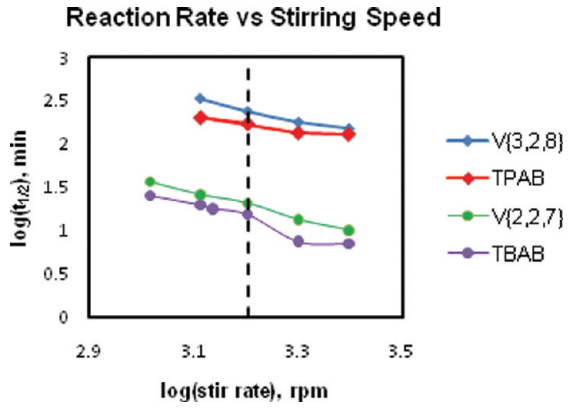


Figure 6. Effect of stir rate on reaction half-life with catalysts of varying structure and activity.

4. Summary of the Kinetic Data. *4.1. Statistical Description.* With a working analytical method in hand, a large subset of the ammonium salts was evaluated for their kinetic competence, represented as half-lives. The half-lives were determined by interpolation of the kinetic plot of percentage of product formation as a function of time. The reported half-life values represent averages over two runs with an average error of 4.5%.[77] Data from kinetic runs that resulted in errors exceeding 20% was discarded and repeated until an error of less than 20% was observed.

To date, half-lives for 102 of the 160 catalysts have been collected. The observed half-life data cover 4 orders of magnitude of activity that was deemed suitable for the initial investigation of the structural effects of catalyst on rate. The half-life data collected from these experiments ranged from 5 min to over 15 h and are summarized in logarithmic scale below (Figure 7). Of the 102 catalysts surveyed to date, 52 of them exhibited half-lives of 20 min or less. Twenty-three catalysts make up the data between 20 min and 1 h, and the half-lives of the remaining 27 catalysts range from 1 to 15 h.

4.2. Catalytic Activity of Library ***I***. The half-life data for library **I** is summarized in Table 1. These ammonium ions showed fairly poor catalytic activity exhibiting half-lives in the range of 5−12 h. The one exception was the catalyst containing an *n*-hexyl nitrogen substituent. In this case, the half-life observed was only 13 min.

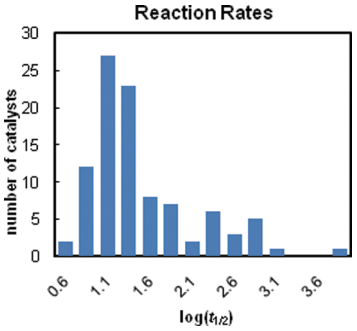


Figure 7. Histogram of $t_{1/2}$ data in logarithmic form.

Table 1. Half-life Data for Library I

entry	library no.	R^4	$t_{1/2}$, min
1	**I**{*1*}	C_6H_5	940
2	**I**{*2*}	1-naphthyl	730
3	**I**{*3*}	2-naphthyl	na
4	**I**{*4*}	9-anthryl	324
5	**I**{*5*}	3,5-$(CF_3)_2C_6H_3$	na
6	**I**{*6*}	*n*-hexyl	12.8

4.3. Catalytic Activity of Libraries ***II*** *and* ***III***. The half-life data for libraries **II** and **III** is summarized in Table 2. These ammonium salts are generally more active catalysts than those lacking an oxygen substituent and exhibited half-life ranges from 6 min to 5.7 h. Catalysts containing a non-hydrogen substituent at R^3 are generally more active than the corresponding catalysts with hydrogen at R^3. However, no clear dependence of the nature of the R^3 substituent on catalyst activity was discernible. When R^3 = H, the rate was markedly dependent on the configuration at C(1) (entries 5 vs 6). However, when $R^3 \neq$ H, the half-life was nearly independent of the C(1) configuration (entries 10 vs 11, 12 vs 13, 16 vs 17, 21 vs 22, and 23 vs 24).

4.4. Catalytic Activity of Libraries ***IV*** *and* ***V***. The half-life data for libraries **IV** and **V** is summarized in Table 3. The activity of these catalysts appears to be largely dependent on the R^2 substituent within the series. Comparing catalysts with fixed R^1, R^3, and R^4 substituents, but with varying R^2 substituents, the following trend in rates holds: R^2 = *i*-Pr > Me > Ph. However, there are important exceptions. For example, catalysts containing R^4 = 3,5-$(CF_3)_2C_6H_3$, R^1 = Me, R^3 = benzyl, the following trend in half-life holds for R^2: Me > *i*-Pr > *t*-Bu > Ph (entries 13, 26, 35, 39). Evidently, a compelling, but complex dependence of the bis-(trifluoromethyl)phenyl group at R^4 on the catalyst activity is observed. Moreover, ammonium salts containing R^3 = *n*-hexyl are generally more active than catalysts with $R^3 \neq$ *n*-hexyl with all other substituents held constant, which suggests a dependence on lipophilicity.

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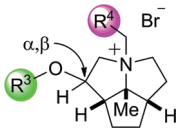
Table 2. Half-life Data for Library II and III



entry	library no.	R^3	R^4	C(1) configuration	$t_{1/2}$, min
1	**II**{*1,1*}	H	C_6H_5	α	181
2	**II**{*1,2*}	H	1-naphthyl	α	179
3	**II**{*1,4*}	H	9-anthryl	α	298
4	**II**{*1,5*}	H	3,5-$(CF_3)_2C_6H_3$	α	346
5	**II**{*1,3*}	H	2-naphthyl	α	245
6	**III**{*1,3*}	H	2-naphthyl	*β*	72
7	**II**{*2,1*}	C_6H_5	C_6H_5	α	10
8	**II**{*2,2*}	C_6H_5	1-naphthyl	α	18
9	**II**{*2,3*}	C_6H_5	2-naphthyl	α	12.1
10	**II**{*3,1*}	*n*-hexyl	C_6H_5	α	11.7
11	**III**{*3,1*}	*n*-hexyl	C_6H_5	*β*	14.8
12	**II**{*3,2*}	*n*-hexyl	1-naphthyl	α	6.6
13	**III**{*3,2*}	*n*-hexyl	1-naphthyl	*β*	9.5
14	**III**{*3,3*}	*n*-hexyl	2-naphthyl	*β*	13.5
15	**II**{*3,5*}	*n*-hexyl	3,5-$(CF_3)_2C_6H_3$	α	12.7
16	**II**{*3,6*}	*n*-hexyl	*n*-hexyl	α	4.6
17	**III**{*3,6*}	*n*-hexyl	*n*-hexyl	*β*	5.5
18	**II**{*4,1*}	MEM	C_6H_5	α	17.5
19	**II**{*4,2*}	MEM	1-naphthyl	α	12.3
20	**II**{*4,3*}	MEM	2-naphthyl	α	22.8
21	**II**{*5,1*}	2-pyridyl	C_6H_5	α	17.1
22	**III**{*5,1*}	2-pyridyl	C_6H_5	*β*	11.1
23	**II**{*5,2*}	2-pyridyl	1-naphthyl	α	6.6
24	**III**{*5,2*}	2-pyridyl	1-naphthyl	*β*	11
25	**II**{*5,3*}	2-pyridyl	2-naphthyl	α	12.7
26	**II**{*5,4*}	2-pyridyl	9-anthryl	α	21.1
27	**II**{*5,5*}	2-pyridyl	3,5-$(CF_3)_2C_6H_3$	α	31.8

4.5. Other Quaternary Ammonium Ions. Varying the substituents on a common scaffold allowed for observation of a large range of rates. To determine how much of the "total possible" range of activity was being sampled, tetramethylammonium bromide (TMAB, q = 4.0) was tested and exhibited a half-life of 1200 min (Table 4).[78] The similarly hydrophilic, but less accessible, tetraethylammonium bromide (q = 2.0) exhibited a 20-fold rate increase over TMAB. The more lipophilic, but similarly accessible cation cetyltrimethyl (C_{19} total, q = 3.06) ammonium bromide was only three times faster than TMAB (entry 3). The rate increase from tetramethyl- to tetraethylammonium bromide was also seen in the use of tributylbenzylammonium bromide, which caused a further 20-fold rate increase. To directly address this dramatic effect of ammonium accessibility with catalysts more closely related to the common scaffold, one other small set of quaternary ammonium ions was constructed that replaces one of the pyrrolidine rings of the scaffold with an azetidine.[79] As expected, the ammonium ions containing an azetidine ring exhibited overall poor catalytic activity with half-lives ranging from 900 to 1000 min.

5. Enantioselectivity of the Catalysts. In addition to determining the substituent effects on rate, those structural features that most strongly affect enantioselectivity were of equal interest. Summarized below is the enantioselectivity data for all 143 chiral, nonracemic catalysts constructed to date. The enantiomeric ratio of benzylated product **20** was measured by purifying a sample by silica gel chromatography from a separate experiment at 2−4 °C with 2.5 mol % catalyst loading. The enantiomeric ratios were determined by CSP-HPLC by a known protocol.[80]

*5.1. Enantioselectivity for Libraries **II** and **III**.* The enantioselectivity data for the α-series (library **II**, $R^1 = R^2 = H$) and the *β*-series (library **III**, $R^2 = H$) are summarized in Table 5. For the α-series (library **II**), little to no stereoinduction was observed, regardless of the combination of substituents (entry 1). In the *β*-series (library **III**), catalysts with R^3 = H produced low to moderate enrichment of the *S* enantiomer of **20** with R^4 = 3,5-$(CF_3)_2C_6H_3$ (entry 5, er 57:43) exhibiting the largest selectivity. Relative to the α-series, catalysts with R^3 = aliphatic consistently produced the *S* enantiomer in slightly greater enrichment (entries 8−13). Additionally, moderate enantioselectivity was observed in catalysts containing a 2-pyridyl group (where the point of attachment is the sp^2 carbon of the heteroaromatic ring) at R^3 (entries 20, 23, and 25) with the largest selectivity observed when R^4 = 1-naphthyl. Similar results were observed in catalysts with R^3 = benzyl within this series, apart from when R^4 = Ph (entry 19) which resulted in decreased selectivity. Overall, the enantioselectivity data for the catalysts in library **III** were greater than their diastereomeric counterparts in library **II**.

*5.2. Enantioselectivity for Libraries **IV** and **V**.* The enantioselectivities for catalysts with variable R^2, R^3, and R^4 groups while holding R^1 constant as a methyl group (excluding entry 1) are summarized in Table 6. See the Supporting Information for a fully tabularized list. Entries with the highest selectivities are shown in bold type. Introducing a methyl group at R^1 while maintaining a hydrogen and a benzyl group at R^2 and R^3, respectively, did not lead to significant differences in the enantioselectivity apart from when the R^4 group was a 3,5-substituted aryl ring (entries 2−4). In this case, inversion of the C(1) configuration resulted in a comparable enantioselectivity (entries 5 and 6).

The results for the catalysts with R^2 = Me are similar to those catalysts with R^2 = H. Likewise, catalysts with a 3,5-substitution pattern on the aryl ring of R^4 consistently resulted in the highest selectivities independent of the R^3 substituent (compare entry 7 to entries 8−12). Increasing the size of the R^2 substituent to isopropyl and *tert*-butyl resulted in a reversal in the selectivity (entries 13). As was the case with catalysts with R^2 = Me, the catalysts exhibiting a 3,5-substitution pattern on the aryl ring of R^4 with R^2 = *i*-Pr and *t*-Bu produced the highest selectivities (entry 14). Catalysts containing R^2 = phenyl were variably selective for either the *S* or *R* enantiomer, apart from when R^4 was a 3,5-disubstitued aryl group (entries 15 and 16). However, the maximum enantioselectivity was observed when R^4 = 3,5-$(CF_3)C_6H_3$ (entries 19, 20, 22, and 25). This effect is independent of the oxygen substituent (R^3). Additionally, the substitution pattern of the trifluoromethyl groups on the aryl ring (R^4) proved to be important, as having groups at the 3- and 5- aryl positions consistently resulted in greater enantioselectivity than having substituents at the 2- and 4-aryl positions or just the 4-aryl position (entry 23 and 24). Moreover, the presence of an alkyl group at R^1 (Me) is imperative as the analogous catalyst with R^1 = H afforded significantly decreased enantioselectivity (entry 1).

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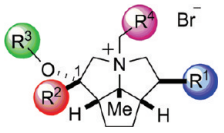
Table 3. Half-life Data for Library IV and V



entry	library no.	R^1	R^2	R^3	R^4	C(1) configuration	$t_{1/2}$, min
1	**IV**{*2,2,1*}	H	Me	C_6H_5	C_6H_5	α	93.5
2	**IV**{*2,2,2*}	H	Me	C_6H_5	1-naphthyl	α	51.1
3	**IV**{*3,2,1*}	H	*i*-Pr	C_6H_5	C_6H_5	α	19.5
4	**IV**{*3,2,5*}	H	*i*-Pr	C_6H_5	3,5-$(CF_3)_2C_6H_3$	α	26.1
5	**IV**{*5,2,5*}	H	C_6H_5	C_6H_5	3,5-$(CF_3)_2C_6H_3$	α	16.3
6	**V**{*1,2,1*}	Me	H	C_6H_5	C_6H_5	α	32.5
7	**V**{*1,2,8*}	Me	H	C_6H_5	4-(MeO)C_6H_4	α	51.8
8	**V**{*1,2,8*}	Me	H	C_6H_5	4-(MeO)C_6H_4	*β*	53.9
9	**V**{*1,2,7*}	Me	H	C_6H_5	3,5-(*t*-Bu)$_2C_6H_3$	*β*	9.78
10	**V**{*1,2,6*}	Me	H	C_6H_5	*n*-hexyl	α	24.7
11	V{*2,2,1*}	Me	Me	C_6H_5	C_6H_5	α	20.7
12	**V**{*2,2,3*}	Me	Me	C_6H_5	2-naphthyl	α	23.0
13	**V**{*2,2,5*}	Me	Me	C_6H_5	3,5-$(CF_3)_2C_6H_3$	α	899.7
14	**V**{*2,2,8*}	Me	Me	C_6H_5	4-(MeO)C_6H_4	α	19.9
15	**V**{*2,2,7*}	Me	Me	C_6H_5	3,5-(*t*-Bu)$_2C_6H_3$	α	15.1
16	**V**{*2,2,6*}	Me	Me	C_6H_5	*n*-hexyl	α	28.1
17	**V**{*2,3,1*}	Me	Me	*n*-hexyl	C_6H_5	α	23.0
18	**V**{*2,3,2*}	Me	Me	*n*-hexyl	1-naphthyl	α	75.8
19	**V**{*2,3,3*}	Me	Me	*n*-hexyl	2-naphthyl	α	30.7
20	**V**{*2,3,5*}	Me	Me	*n*-hexyl	3,5-$(CF_3)_2C_6H_3$	α	236.0
21	**V**{*2,3,8*}	Me	Me	*n*-hexyl	4-(MeO)C_6H_4	α	26.5
22	**V**{*2,3,7*}	Me	Me	*n*-hexyl	3,5-(*t*-Bu)$_2C_6H_3$	α	28.9
23	**V**{*2,3,6*}	Me	Me	*n*-hexyl	*n*-hexyl	α	21.1
24	**V**{*2,7,1*}	Me	Me	4-(MeO)C_6H_4	C_6H_5	α	17.9
25	**V**{*3,2,1*}	Me	*i*-Pr	C_6H_5	C_6H_5	α	132.1
26	**V**{*3,2,5*}	Me	*i*-Pr	C_6H_5	3,5-$(CF_3)_2C_6H_3$	α	122.1
27	**V**{*3,2,7*}	Me	*i*-Pr	C_6H_5	3,5-(*t*-Bu)$_2C_6H_3$	α	28.6
28	**V**{*3,3,1*}	Me	*i*-Pr	*n*-hexyl	C_6H_5	α	41.8
29	**V**{*3,3,3*}	Me	*i*-Pr	*n*-hexyl	2-naphthyl	α	20.3
30	**V**{*3,3,5*}	Me	*i*-Pr	*n*-hexyl	3,5-$(CF_3)_2C_6H_3$	α	62.4
31	**V**{*3,3,8*}	Me	*i*-Pr	*n*-hexyl	4-(MeO)C_6H_4	α	42.7
32	**V**{*3,2,6*}	Me	*i*-Pr	C_6H_5	*n*-hexyl	α	86.0
33	**V**{*3,7,5*}	Me	*i*-Pr	4-(MeO)C_6H_4	3,5-$(CF_3)_2C_6H_3$	α	60.9
34	**V**{*3,7,8*}	Me	*i*-Pr	4-(MeO)C_6H_4	4-(MeO)C_6H_4	α	249.4
35	**V**{*4,2,5*}	Me	*t*-Bu	C_6H_5	3,5-$(CF_3)_2C_6H_3$	α	95.8
36	**V**{*5,2,1*}	Me	C_6H_5	C_6H_5	C_6H_5	α	10.6
37	**V**{*5,2,2*}	Me	C_6H_5	C_6H_5	1-naphthyl	α	12.2
38	**V**{*5,2,3*}	Me	C_6H_5	C_6H_5	2-naphthyl	α	10.3
39	**V**{*5,2,5*}	Me	C_6H_5	C_6H_5	3,5-$(CF_3)_2C_6H_3$	α	9.5
40	**V**{*5,2,8*}	Me	C_6H_5	C_6H_5	4-(MeO)C_6H_4	α	17.5
41	**V**{*5,2,9*}	Me	C_6H_5	C_6H_5	(4-CF_3)C_6H_4	α	16.0
42	**V**{*5,2,10*}	Me	C_6H_5	C_6H_5	(4-CN)C_6H_4	α	14.4
43	**V**{*5,3,1*}	Me	C_6H_5	*n*-hexyl	C_6H_5	α	9.5
44	**V**{*5,3,2*}	Me	C_6H_5	*n*-hexyl	1-naphthyl	α	18.7
45	**V**{*5,3,3*}	Me	C_6H_5	*n*-hexyl	2-naphthyl	α	13.1
46	**V**{*5,3,5*}	Me	C_6H_5	*n*-hexyl	3,5-$(CF_3)_2C_6H_3$	α	4.9
47	**V**{*5,3,8*}	Me	C_6H_5	*n*-hexyl	4-(MeO)C_6H_4	α	9.9
48	**V**{*5,3,7*}	Me	C_6H_5	*n*-hexyl	3,5-(*t*-Bu)$_2C_6H_3$	α	8.5

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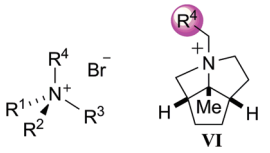
Table 3. Continued

entry	library no.	R^1	R^2	R^3	R^4	C(1) configuration	$t_{1/2}$, min
49	**V**{*5,6,1*}	Me	C_6H_5	3,5-$(CF_3)_2C_6H_3$	C_6H_5	α	7.9
50	**V**{*5,6,5*}	Me	C_6H_5	3,5-$(CF_3)_2C_6H_3$	3,5-$(CF_3)_2C_6H_3$	α	7.0
51	**V**{*5,6,8*}	Me	C_6H_5	3,5-$(CF_3)_2C_6H_3$	4-(MeO)C_6H_4	α	6.9
52	**V**{*5,7,1*}	Me	C_6H_5	4-(MeO)C_6H_4	C_6H_5	α	19.9
53	**V**{*5,7,2*}	Me	C_6H_5	4-(MeO)C_6H_4	1-naphthyl	α	19.2
54	**V**{*5,7,3*}	Me	C_6H_5	4-(MeO)C_6H_4	2-naphthyl	α	12.0
55	**V**{*5,7,5*}	Me	C_6H_5	4-(MeO)C_6H_4	3,5-$(CF_3)_2C_6H_3$	α	18.6
56	**V**{*5,7,7*}	Me	C_6H_5	4-(MeO)C_6H_4	3,5-(*t*-Bu)$_2C_6H_3$	α	14.6
57	**V**{*7,2,1*}	Me	1-naphthyl	C_6H_5	C_6H_5	α	13.7
58	**V**{*7,2,5*}	Me	1-naphthyl	C_6H_5	3,5-$(CF_3)_2C_6H_3$	α	28.7
59	**V**{*7,2,8*}	Me	1-naphthyl	C_6H_5	4-(MeO)C_6H_4	α	11.3
60	**V**{*7,2,9*}	Me	1-naphthyl	C_6H_5	(4-CF_3)C_6H_4	α	11.8
61	**V**{*7,2,10*}	Me	1-naphthyl	C_6H_5	(4-CN)C_6H_4	α	48.6
62	**V**{*6,2,1*}	Me	2,4,6-$(CH_3)_2C_6H_2$	C_6H_5	C_6H_5	α	12.2
63	**V**{*6,2,8*}	Me	2,4,6-$(CH_3)_2C_6H_2$	C_6H_5	4-(MeO)C_6H_4	α	11.8

Table 4. Half-life Data for other Quaternary Ammonium Ions



VI

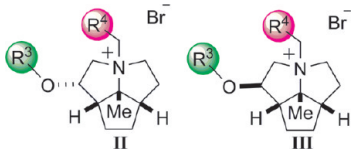
entry	library no.	catalyst	R^4	$t_{1/2}$, min
1		Me_4N		12,000
2		Et_4N		480
3		$Me_3NC_{16}H_{33}$		2800
4		*n*-Bu_3NBn		21
5	**VI**{*1*}		C_6H_5	890
6	**VI**{*2*}		1-naphthyl	1000
7	**VI**{*3*}		2-naphthyl	1090

The installation of different groups at R^2 with π-surfaces while maintaining R^3 = 3,5-$(CF_3)C_6H_3$ produced similar results (entries 25 and 26). When R^2 = isopropyl or *tert*-butyl (entreis 13 and 14), the enantioselectivity is significantly diminished in comparison to catalysts that contain an aromatic group is in this position. Together these results attest to the importance of π-surface rather than steric bulk at R^2 for higher enantioselectivity.

DISCUSSION

1. Analysis of Ammonium Ion Preparations. *1.1. Synthetic Strategy.* Since the discovery of asymmetric phase-transfer catalysis with cinchona alkaloid derivatives, a significant level of effort has been devoted to the introduction of novel synthetic catalyst structures. Most of the synthetic endeavors fall into one of the following two synthetic strategies: (1) elaboration of a readily available source of chiral material by appending a nonstereogenic quaternary ammonium ion or (2) incorporation of a quaternary ammonium into a molecule in such a way that it lies on a symmetry axis. Although each of these approaches has seen some success, the synthetic strategy presented herein is significantly different and warrants discussion.

Table 5. Enantioselectivity of Libraries II and III[a]



II **III**

entry	library no.	R^3	R^4	er, *S*/*R*
1	**II**{*1−5,1−6*}			50:50 ± 3
2	**III**{*1,2*}	H	1-naphthyl	48:52
3	**III**{*1,3*}	H	2-naphthyl	55:45
4	**III**{*1,4*}	H	9-anthryl	50:50
5	**III**{*1,5*}	H	3,5-$(CF_3)_2C_6H_3$	57:43
6	**III**{*1,6*}	H	*n*-hexyl	52:48
7	**III**{*1,1*}	H	C_6H_5	55:45
8	**III**{*3,2*}	*n*-hexyl	1-naphthyl	48:52
9	**III**{*3,3*}	*n*-hexyl	2-naphthyl	55:45
10	**III**{*3,4*}	*n*-hexyl	9-anthryl	47:53
11	**III**{*3,5*}	*n*-hexyl	3,5-$(CF_3)_2C_6H_3$	52:48
12	**III**{*3,6*}	*n*-hexyl	*n*-hexyl	53:47
13	**III**{*3,1*}	*n*-hexyl	C_6H_5	54:46
14	**III**{*2,2*}	C_6H_5	1-naphthyl	64:36
15	**III**{*2,3*}	C_6H_5	2-naphthyl	48:52
16	**III**{*2,4*}	C_6H_5	9-anthryl	44:56
17	**III**{*2,5*}	C_6H_5	3,5-$(CF_3)_2C_6H_3$	57:43
18	**III**{*2,6*}	C_6H_5	*n*-hexyl	58:42
19	**III**{*2,1*}	C_6H_5	C_6H_5	53:47
20	**III**{*5,2*}	2-pyridyl	1-naphthyl	64:36
21	**III**{*5,3*}	2-pyridyl	2-naphthyl	48:52
22	**III**{*5,4*}	2-pyridyl	9-anthryl	54:46
23	**III**{*5,5*}	2-pyridyl	3,5-$(CF_3)_2C_6H_3$	58:42
24	**III**{*5,6*}	2-pyridyl	*n*-hexyl	57:43
25	**III**{*5,1*}	2-pyridyl	C_6H_5	60:40

[a] This is a representative summary. For a full tabular listing, see the Supporting Information.

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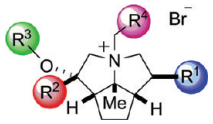
Table 6. Enantioselectivity of Libraries IV and V[a]



entry	library no.	R^1	R^2	R^3	R^4	C(1) configuration	er, *S*/*R*
1	**IV**{*1,2,5*}	H	Ph	C_6H_5	3,5-$(CF_3)_2C_6H_3$	α	56:44
2	**V**{*1,2,X*}	Me	H	C_6H_5	*1−3,6 or 8*	α	50:50 ± 4
3	**V**{*1,2,5*}	Me	H	C_6H_5	3,5-$(CF_3)_2C_6H_3$	α	56:44
4	**V**{*1,2,7*}	Me	H	C_6H_5	3,5-(*t*-Bu)$_2C_6H_3$	α	60:40
5	**V**{*1,2,2*}	Me	H	C_6H_5	*1−3* or *6−8*	*β*	50:50 ± 5
6	**V**{*1,2,5*}	Me	H	C_6H_5	3,5-$(CF_3)_2C_6H_3$	*β*	63:37
7	**V**{*2,X,X*}	Me	Me	*2,3,7*	*1−6,8*	α	50:50 ± 4
8	**V**{*2,3,7*}	Me	Me	*n*-hexyl	3,5-(*t*-Bu)$_2C_6H_3$	α	58:42
9	**V**{*2,2,5*}	Me	Me	C_6H_5	3,5-$(CF_3)_2C_6H_3$	α	57:43
10	**V**{*2,2,7*}	Me	Me	C_6H_5	3,5-(*t*-Bu)$_2C_6H_3$	α	57:43
11	**V**{*2,7,5*}	Me	Me	4-(MeO)C_6H_4	3,5-$(CF_3)_2C_6H_3$	α	59:41
12	**V**{*2,7,7*}	Me	Me	4-(MeO)C_6H_4	3,5-(*t*-Bu)$_2C_6H_3$	α	57:43
13	**V**{*3,X,X*}	Me	*i*-Pr	*2,3,7*	*1−8*	α	41:59 ± 5
14	**V**{*4,2,5*}	Me	*t*-Bu	C_6H_5	3,5-$(CF_3)_2C_6H_3$	α	37:63
15	**V**{*5,X,X*}	Me	C_6H_5	*2,3*	*1,2,3,8*	α	50:50 ± 6
16	**V**{*5,3,5*}	**Me**	**C_6H_5**	***n*-hexyl**	**3,5-$(CF_3)_2C_6H_3$**	**α**	**79:21**
17	**V**{*5,3,7*}	Me	C_6H_5	C_6H_5	3,5-(*t*-Bu)$_2C_6H_3$	α	61:39
18	**V**{*5,2,X*}	Me	C_6H_5	C_6H_5	*2,3*	α	50:50 ± 5
19	**V**{*5,2,5*}	**Me**	**C_6H_5**	**C_6H_5**	**3,5-$(CF_3)_2C_6H_3$**	**α**	**81:19**
20	**V**{*5,6,5*}	**Me**	**C_6H_5**	**3,5-$(CF_3)_2C_6H_3$**	**3,5-$(CF_3)_2C_6H_3$**	**α**	**81:19**
21	**V**{*5,X,X*}	Me	C_6H_5	*6,7*	*1,2,3,8*	α	50:50 ± 5
22	**V**{*5,7,5*}	**Me**	**C_6H_5**	**4-(MeO)C_6H_4**	**3,5-$(CF_3)_2C_6H_3$**	**α**	**81:19**
23	**V**{*5,7,7*}	Me	C_6H_5	4-(MeO)C_6H_4	3,5-(*t*-Bu)$_2C_6H_3$	α	63:37
24	**V**{*X,2,X*}	Me	*5,7*	C_6H_5	*1,8,9,10,11*	α	50:50 ± 6
25	**V**{*7,2,5*}	**Me**	**1-naphthyl**	**C_6H_5**	**3,5-$(CF_3)_2C_6H_3$**	**α**	**81:19**
26	**V**{*6,2,5*}	**Me**	**mesityl**	**C_6H_5**	**3,5-$(CF_3)_2C_6H_3$**	**α**	**76:24**

[a] This is a representative summary. For a full tabular listing, see the Supporting Information.

The approach presented here is unique in that the synthetic effort was focused on systematically varying the steric and electronic environment around a central stereogenic quaternary ammonium ion. To this end, the synthetic investment was divided into two different parts. The first part involved preparation of a nitrogen containing scaffold (a cyclopentapyrrolizidine) on a significant scale which was readily accomplished by application of the tandem inter [4 + 2]/intra [3 + 2] cycloaddition of nitroalkenes with only minor changes to the previously published routes. Notably, the tandem cycloaddition also served as a diversifying element in that it was in this step that the configuration at C(1) was set (libraries **II** and **III**) and the R^1 group was introduced stereoselectively, which subsequently proved to be a critical catalyst structural feature.

The second synthetic component involved development of procedures amenable to parallel synthesis that introduced a variety of groups in the vicinity of the ammonium nitrogen. Ultimately, three operationally simple bond-forming reactions were utilized to accomplish this goal that allowed for the catalysts to be prepared in a parallel fashion. The tandem cycloaddition naturally installs a hydroxyl group at C(1) which served as a functional handle for two parallel synthesis steps, a Grignard addition and an O-alkylation, leaving only N-quaternization as the final parallel synthesis step. Including the previously installed R^1 substituent, a total of four variable groups were introduced. The diversity and number of groups utilized was greatest for the positions that could be incorporated in parallel (R^2, 6; R^3, 7; R^4, 11) and the least for the group that required a recast skeleton (R^1, 2). A good appreciation for the shape of the catalyst(s) and disposition of the variable groups in relation to the ammonium nitrogen is necessary to facilitate a thorough analysis of the effect of each group (and combinations thereof) on catalytic activity and selectivity.

1.2. Catalyst Shape and Position of Groups. Library **I** is a logical starting point because the inherent symmetry simplifies the analysis. Figure 8 shows a plot of the relative conformer energies as a function of a double dihedral driver about bonds C(5a)−C(6)−C(7)−C(7a) and C(7b)−N(3)−C(9)−C(10) for catalyst **I**{*1*}.[81] A full 360 degree rotation about the C(7b)−N(3)−C(9)−C(10) bond constitutes a full range of motion of the R^4 substituent, in this case, a phenyl group. The R^4 substituent can be found in two local sparsely populated minima corresponding to gauche conformations (± 60°), which, in the

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case of library **I**, are a pair of diastereomeric conformers. A single, highly populated, global minimum is found when the R^4 substituent is projected 180° away from the N(3)−C(9) bond. A small energetic barrier separates the global and local minima, but a "full range of motion" of the R^4 substituent is prohibited because of steric interactions with the C(8)- methyl group. For the remainder of this discussion the R^4 group will be projected in its global minimum of ∼180°.

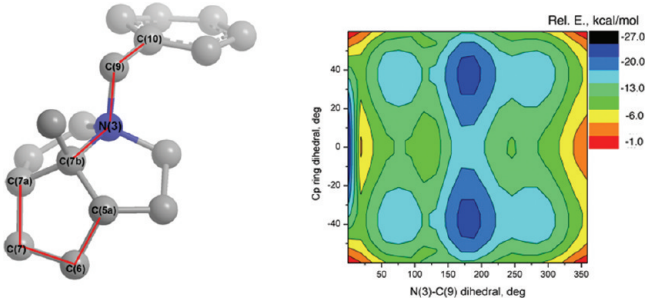

Figure 8. Conformer energy as a function of N−C(9) rotation and C(6)−C(7) bond rotation.

Substitution of the ring system in any way removes the symmetry plane in the scaffold of library **I**; therefore, all catalysts (except library **I**) consist of at least six diastereomeric conformers. Because only one or two of these conformers are highly populated, in any projections or analysis from this point on the lowest energy conformer of the ring system will be depicted. The remaining three variable groups each reside in different faces of the central ammonium nitrogen (R^1 and R^2). The R^1 and R^2 groups are placed directly on the right and left convex faces (Figure 9), and the R^3 group resides in the concave face of the scaffold (see Figure 12).

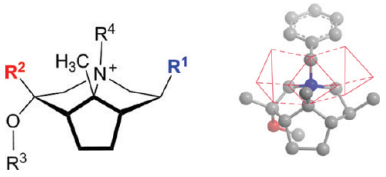

Figure 9. Representation of the convex faces of the ammonium scaffold.

2. Summary of Results. A brief summary of the rate and enantioselectivity data is necessary to facilitate the following discussion. The kinetic results are summarized in bar graph format in Figure 10. In general:

- Catalysts that bear an oxygen substituent at C(1) are more active than catalysts without.
- The configuration of the oxygen functional group does not influence the catalyst activity.
- Ethers are more active than the corresponding alcohols.
- Strong electron-withdrawing groups (e.g., $R^4 = (3,5\text{-}CF_3)_2\text{-}C_6H_3$) on nitrogen decrease catalyst activity.
- Less dependence on the nitrogen substituent was observed when R^2 was aromatic (Ph, mesityl, 1-naphthyl).
- The catalytic activities of the unfunctionalized ring systems are not as high as tetraethylammonium but better than cetyltrimethylammonium in activity.

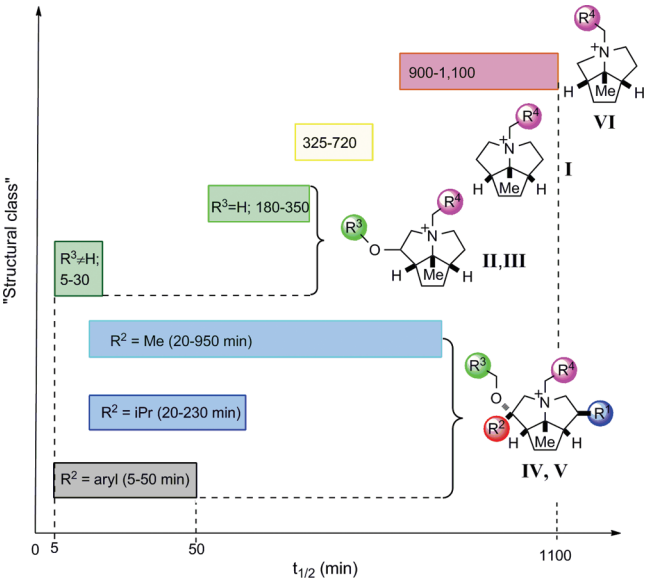

Figure 10. Structural clustering of kinetic data.

Given the large volume of data presented herein, a concise statistical summary provides a good indication of which data is the most interesting and worthy of detailed analysis. The relative contribution of the groups to the variation in the observed data is estimated by examining the standard deviation as a function of each group (R^1−R^4).[82] That is, the larger the deviation in the observed rate (or selectivity) as a function of group positional substitution, the greater the relationship of that substituent (R^2−R^4) to the observed effect (rate or selectivity, Figure 11). Therefore, the variation approximates the sensitivity of the rate and selectivity to a structural change at the indicated substituent. Both catalyst activity and rate are influenced the most by the groups R^2 and R^4, with the greatest dependence on R^4. Also, in both cases, the R^3 group has the least influence. The R^1 group was not sufficiently varied for interpretation by this analysis.

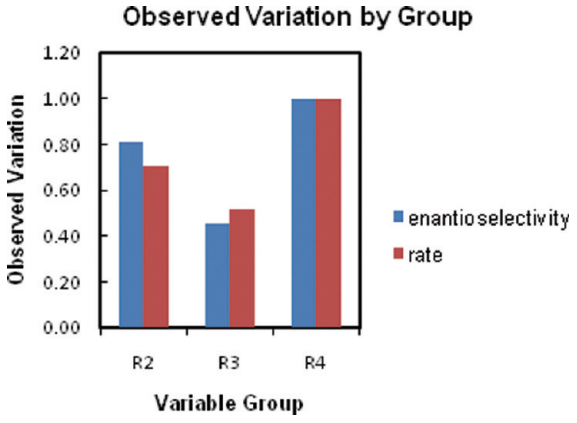

Figure 11. Variation in rate and selectivity as a function of positional group substitution.

3. Catalyst Activity. *3.1. Effect of an Oxygen Substituent.* The presence of an oxygen at C(1) is a natural consequence of the tandem cycloaddition utilized to construct the scaffolds. Indeed, a β-oxygen substituent is a common structural motif employed in many asymmetric quaternary ammonium phase-transfer

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catalysts including the cinchona alkaloids.[83] Inclusion of an oxygen substituent β to the ammonium center strongly affects the catalytic activity (compare libraries **I** and **II**), which has previously been reported for other catalyst systems.[84,85] A more quantitative treatment of β-oxygen stubstitution is presented in the accompanying paper (DOI 10.1021/jo2005457), but a qualitative analysis, as follows, is required to analyze the differences in catalyst activity in this data set.

Introduction of an oxygen atom two carbons removed from the ammonium center results in two related electronic effects: (1) it influences the direction of the dipole and (2) it modulates the magnitude of positive electrostatic potential interaction (δ^+). The electrostatic potential maps of the oxygenated and unoxygenated catalyst scaffolds are compared in Figure 12. In the C_s symmetric ammonium salts (library **I**), the charge distribution is equally dispersed between the two convex faces. In contrast, inclusion of an alkoxy group two carbons removed from the ammonium nitrogen results in a considerable polarization of the positive potential toward the face to which it is attached (library **II**, methoxy is included for simplicity). In library **II** type ammonium ions the two convex faces are differentiated electronically, placing a greater positive potential on the left face. Similarly, the dipole vector in the library **I** type ammonium ions bisects the R^4 substituent but is rotated ~60° clockwise in the library **II** ammonium ions projecting the positive end toward the left convex face of the ammonium ion.

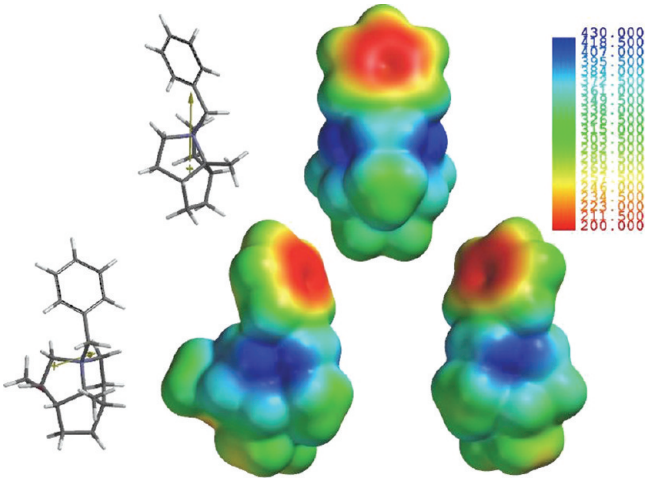


Figure 12. Electrostatic potential (ESP) maps (M06−2X/6-31G(d)) of scaffolds for Library **I** (unoxygenated) and Library **II** (oxygenated) where C(6)−C(7) and N(3)−C(9) dihedrals are constrained to 0° in the geometry optimization to exclude bias of a specific twist conformer (Figure 11). For computational simplification, a methyl group is used at R^3. The directions of the dipoles are illustrated. ESPs are mapped onto electron density isosurfaces (0.002 electrons/au^3). Legend is in units of kJ/mol. The difference in the maximum electrostatic potential energies of the left and right faces of the oxygenated scaffold is 3.0 kcal/mol and 0 kcal/mol for the unoxygenated scaffold (C_s symmetric).

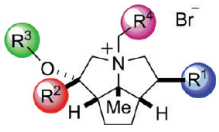
This analysis is consistent with a stronger electrostatic interaction with the left convex face than the right, which in turn, is consistent with the experimentally observed fact that the R^2 substituent has a large effect on the observed rate and selectivity. Since both rate and selectivity are highly dependent on the R^2 group and little to no selectivity is observed when R^1 = H, our data seems most consistent with a selective "docking" of the enolate to the left convex face of the ammonium. That is, the oxygen serves to increase the positive potential on the left convex face and the R^1 group acts to sterically shield the right convex face of the ammonium ion.

3.2. Accessibility of the Ammonium Ion. The catalytic activity of PTC alkylation processes has been correlated with the accessibility of the ammonium nitrogen (in terms of q), where an optimum accessibility is found.[49] The observation of a maximum catalyst activity as a function of ammonium accessibility has two similar explanations. In the first, the accessibility of the ammonium nitrogen is related to the rate of exchange of anions, a kinetic phenomenon.[47] In the second, the accessibility of the ammonium nitrogen is related to the ability of the catalyst to decrease the interfacial tension and thereby facilitate enolate transfer, a thermodynamic phenomenon.[46,86]

The data collected herein are largely consistent with these proposals, with the added complexity that the magnitude of the exposed positive potential (δ^+) should be considered as well. On the basis of the analysis above, the accessibility of the positive potential (δ^+, left convex face) should be correlated with the steric bulk of the R^2 substituent. The sensitivity of the catalytic activity to the R^2 substituent discussed above (Figure 11) advocates a strong dependence of the overall catalyst activity on the nitrogen accessibility (steric nature of R^2).

The dependence of the catalytic activity on the size of the R^2 substituent and electron-withdrawing ability of the R^4 substituent is summarized tabularly in Table 7 (MR = molar refractivity).[87] The dependence is weak when the electronic character of R^4 is neutral or electron rich (R^4 = C_6H_5, 4-$MeOC_6H_4$) but strong when R^4 is strongly electron-withdrawing (3,5-$(CF_3)_2C_6H_3$). In these catalysts, an increase in the size of the R^2 substituent (Me to *i*-Pr to *t*-Bu, to Ph) leads to a significant rate enhancement, which is somewhat attenuated for larger aromatic groups (mesityl or naphthyl). This disparity may be rationalized by ammonium accessibility, such that catalysts with R^2 = Ph have an optimum accessibility.

Table 7. Half-lives (min) of Selected Catalysts with R^1 = Me, R^3 = Ph, and Variable R^2 and R^4.



		R^4		
R^2	MR[a]	C_6H_5	3,5-$(CF_3)_2C_6H_3$	4-$(MeO)C_6H_4$
Me	6.88	21	900	18
i-Pr	16.08	132	122	174
t-Bu	20.85		96	
phenyl	25.28	11	10	18
mesityl	42.97	12	62	12
1-naphthyl	42.45	14	29	11

[a] MR = molar refractivity of the R^2 substituent calculated by Chemdraw.

Rationalizing the effect of the R^2 substituent in terms of steric bulk makes intuitive sense because placing groups in this position modulates the relative accessibility of the positive potential at the two convex faces. However, other explanations are possible. For example, if the major structural perturbation of replacing a branched aliphatic group with an aromatic group is the introduction of a π-surface then the increase in catalyst activity could be caused by an affinity of catalyst for substrate (through $\pi-\pi$ interactions). In this scenario, a shift in the equilibrium between catalyst$^+$X$^-$ (Br$^-$ or HO$^-$) and catalyst$^+$enolate$^-$ ion pair toward the enolate complex would be the origin of the net increase in observed catalyst activity.

Most consistent with the above analysis of charge polarization, the 3,5-$(CF_3)_2C_6H_3$ group must impart sufficient charge polarization to amplify the effect of the variable R^2 group. Interpretation of these observations in the context of a transfer rate limiting regime has led to the conclusion that an optimum ammonium accessibility, or charge exposure is likely. In other words, a greater charge exposure will increase the ammonium ions association with the anionic hydroxide surface. However, if the exposed $\delta+$ area or charge density is too great, then the catalyst will not dissociate away from the interface as readily.

3.3. Summary of Catalyst Activity Discussion. Three important elements can be inferred from the discussion of rate:

(1) The observed increase in catalyst activity upon the inclusion of an oxygen substituent is attributed to the increase in the rate of ion pair formation and/or a decrease in interfacial tension

(2) The observed decrease in catalyst activity upon the inclusion of the 3,5-$(CF_3)_2C_6H_3$ group at R^4 for small groups at R^2 (H, Me, *i*-Pr) is attributed to a diminished tendency of the ion-pair to transport from the interface to the organic phase for alkylation due to greater charge density at the ammonium center.

(3) The observed increase in catalyst activity upon the inclusion of aryl groups at R^2 with R^4= 3,5-$(CF_3)_2C_6H_3$ is attributed to an enhanced ability of the ion-pair to transport from the interface into the organic phase for alkylation because of an optimum surface exposure of the ammonium ion (kinetic) or a change in enolate binding equilibrium (thermodynamic).

4. Enantioselectivity. The intermolecular forces that have been proposed to contribute to enantioselectivity in APTC reactions include (1) ROH$\cdots^-$O$-$CR$=$CR$_2$ hydrogen bonding,[20a,c] (2) R$_3$N$^+-$CHR$-$H$\cdots^-$O$-$CR$=$CR$_2$ (α-CH hydrogen bonding),[51b] and (3) $\pi-\pi$ interactions.[20a,c] The most selective catalysts in this study do not contain OH hydrogen-bond-donating sites; therefore, intermolecular force (1) can be eliminated as a stereocontrolling element. The results here support the operation of interactions (2) and potentially (3).

The unique structural features of the catalyst scaffold include the intrinsic shielding of two of the four faces of the imaginary tetrahedron encompassing the nitrogen and the capacity to differentiate the two remaining exposed faces (cf. Figure 12). The second feature arises from the modular nature of the cycloaddition-based construction, which allows both exposed front faces to be differentiated electronically (β-oxygenation) and sterically (relative steric bulk of R^1 and R^2). Although those factors that control the topicity of the enolate reactivity are difficult to predict, the factors that dictate the relative binding strengths of the enolate to each of the tetrahedral faces are more easily controlled and predicted. Initially, these factors were the primary focus for the design and construction of the libraries.

The observed enantioselectivities are largely dependent on the substituents that influence the binding of the anion to the face of the hypothetical tetrahedron around the ammonium ion with the largest concentration of positive potential (R^2 and R^4, Figure 12). The observation that the enantioselectivity is greatest for catalysts that bear strongly electron withdrawing groups on the nitrogen is consistent with the need for one or both of the following potential interactions: (1) α-CH-hydrogen bonding or (2) a tighter ion pair resulting from increased Coulombic interaction. Additionally, a π-surface is necessary at the R^2 substituent, presumably to engage in π-stacking interactions with the phenyl rings of the reacting enolate. Moreover, the presence of an alkyl group at R^1 is necessary to decrease the accessibility of the right-hand face of the pyrrolizidine moiety because in its absence, the enantioselectivity is poor. This observation suggests that binding to the right-hand face leads to lower selectivity because of the pseudoenantiotopic local chirality. The aforementioned interactions seem to operate in concert as the absence of one of the interactions leads to significantly diminished enantioselectivities.

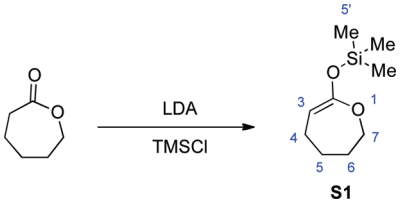
CONCLUSIONS

A synthetic strategy for the synthesis of diverse libraries of quaternary ammonium ions has been developed. The key feature of the synthetic strategy was to divide the preparative work into two distinct stages: (1) scaffold preparation and (2) diversity-oriented parallel synthesis. In this way, a total of 160 structurally diverse quaternary ammonium ions were prepared that share a common scaffold constructed by a tandem inter [4 + 2]/intra [3 + 2] cycloaddition of a nitroalkene. A method was developed for the collection of kinetic data of a biphasic reaction that is applicable over a wide range of catalyst activities (half-lives ranging from days to minutes). The range of data collected covers many orders of magnitude and therefore is well suited for analysis by the application of quantitative structure−activity relationships. Inclusion of an oxygen atom in the vicinity of the quaternary ammonium ion affects the catalytic activity. The catalyst enantioselectivity is strongly dependent on the substituent attached to the same carbon as the oxygen atom. These observations were rationalized in terms of a selective polarization of the positive potential on one of the faces of the tetrahedral ammonium over the other. The inclusion of a 3,5-substituted aromatic substituent on nitrogen proved crucial for catalyst enantioselectivity. With strongly electron-withdrawing 3,5-trifluoromethyl groups, the previously observed dependencies on rate were amplified. The proposed dependencies of rate on the ammonium accessibility are consistent with the data reported herein with the added complexity that the magnitude of the "ammonium charge" or charge density should be considered as well. Quantitative models have been developed to describe both the reactivity and selectivity trends discussed herein and constitute the focus of the following paper (DOI 10.1021/jo2005457).

EXPERIMENTAL SECTION

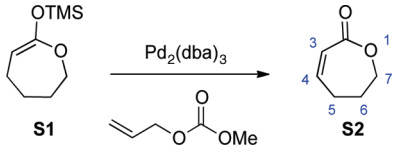
For general experimental details and literature preparations, see the Supporting Information.

I. Preparative Studies: Tandem Cycloaddition Precursors and Scaffolds.

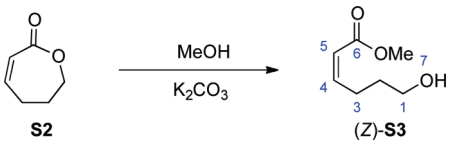


*A. Scale up of Alcohol (Z)-**6***

*Preparation of Trimethyl(4,5,6,7-tetrahydrooxepin-2-yloxy)silane (**S1**).* A jacketed 500 mL, three-necked, liquid addition flask fitted with a nitrogen inlet adaptor and two rubber septa was fitted to a 1-L, two-necked, round-bottomed flask fitted with a magnetic stir bar, a rubber septum, and an internal temperature probe (through rubber septum). To the addition flask were added diisopropylamine (36.5 mL, 209 mmol, 1.3 equiv) and THF (300 mL). The resulting solution was cooled to −78 °C (bath temperature) by addition of an acetone/$CO_{2(s)}$ bath to the jacket reservoir. Then, *n*-butyllithium (2.56 M in hexanes, 81.8 mL, 1.3 equiv) was added dropwise over 20 min. To the 1-L, two-necked flask were added ε-caprolactone (18.4 g, 161 mmol), THF (150 mL), and trimethylsilyl chloride (26.5 mL, 209 mmol, 1.3 equiv) via syringe. The reaction vessel was brought to <−80 °C by immersion in a hexanes/N_2 bath. The freshly generated solution of LDA (above) was added dropwise at a rate that maintained an internal temperature <−75 °C (ca. 1 h). The resulting turbid solution was allowed to warm to −25 °C and was then concentrated by rotary evaporation (15 mmHg, 20−25 °C). The resulting mixture was triturated with pentane (∼100 mL) and filtered (Celite). The filtrate was again concentrated by rotary evaporation (15 mmHg, 20−25 °C). Purification by distillation (0.5 mmHg, 43 °C) afforded ketene acetal **S1** (24.8 g, 83%) as a clear colorless oil. The data collected were consistent with those previously reported.[88] Data for **S1**: bp 58−60 °C (2−3 mmHg); ^{1}H NMR (500 MHz, $CDCl_3$) 4.12 (t, *J* = 5.9, 1 H, HC(3)), 3.99 (dd, *J* = 5.4, 5.6, 2 H, $H_2C(7)$), 2.02 (dd, *J* = 5.9, 11.6, 2 H, $H_2C(4)$) 1.83 (ddd, *J* = 5.7, 10.7, 11.5, 2 H, $H_2C(6)$), 1.65−1.59 (m, 2 H, $H_2C(5)$), 0.22 (s, 9 H, $H_3C(5')$); ^{13}C NMR (126 MHz, $CDCl_3$) 160.0 (C(2)), 83.1 (C(3)), 71.5 (C(7)), 31.3 (C(4)), 26.2 (C(6)), 23.3 (C(5)), 0.16 (C(5′)) IR (neat, NaCl plate) 2931 (s), 2837 (m), 1682 (s), 1455 (m), 1355 (m); MS (ESI, Q-tof) 187 (21) [M + 1], 171 (38), 147 (14), 132 (12), 129 (13), 117 (30), 75 (100), 69 (32), 55 (23), 54 (23); TLC R_f 0.77 (hexanes/Et_2O, 4:1) [UV, $KMnO_4$].

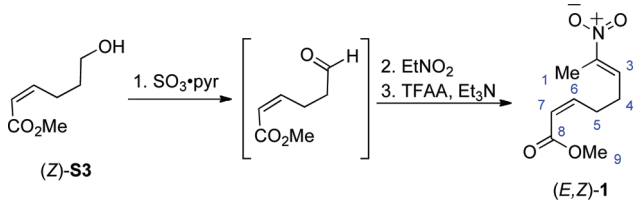


*Preparation of 6,7-Dihydro-5H-oxepin-2-one (**S2**).* To a 1.0-L, one-necked, round-bottomed flask fitted with a reflux condenser, a magnetic stir bar, and a nitrogen inlet adapter, fitted with a rubber septum, were added sequentially palladium(0)bisdibenzylideneacetone (309 mg, 0.537 mmol, 0.01 equiv), allyl methyl carbonate (12.2 mL, 107 mmol, 2.0 equiv), and acetonitrile (268 mL). Silyl ketene acetal **S2** (1.0 g, 21.5 mmol) was then added via syringe. The resulting solution was placed in an oil bath preheated to 40 °C and allowed to stir. After being stirred for 30 min at 40 °C, the reaction mixture was removed from the oil bath and allowed to cool to room temperature. The solution was concentrated to approximately one-quarter of the total volume (∼70 mL). This solution was passed through a plug of silica gel (20 mm × 5 cm) using hexanes/Et_2O (1:4, 3 × 50 mL). The filtrate was concentrated by rotary evaporation (15 mmHg, 20−25 °C) to afford 5.13 g (97%) of **S2** as a pale-yellow oil. This material was carried on to the next step without further purification. The data collected were consistent with those previously reported.[89] Data for **S2**: bp 70 °C (0.1 mmHg); ^{1}H NMR (500 MHz, $CDCl_3$) 6.41 (td, *J* = 4.4, 12.1, 1 H, HC(4)), 5.98 (d, *J* = 12.4, 1 H, HC(3)),4.28 (m, 2 H, $H_2C(7)$), 2.50 (dd, *J* = 5.4, 10.2, 2 H, $H_2C(5)$), 2.12 (td, *J* = 6.6, 12.9, 2 H, $H_2C(6)$); ^{13}C NMR (126 MHz, $CDCl_3$) 169.2 (C(2)), 144.0 (C(4)), 121.9 (C(3)), 67.3 (C(7)), 30.1 (C(5)), 27.0 (C(6)); TLC R_f 0.20 (pentane/MTBE, 1:1) [$KMNO_4$].



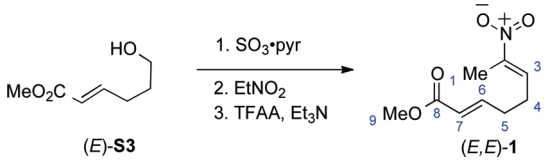
dx.doi.org/10.1021/jo2005445 |*J. Org. Chem.* 2011, 76, 4260–4336

*Preparation of (Z)-Methyl 6-Hydroxy-2-hexenoate ((Z)-**S3**).* To a 100 mL, one-necked, round-bottomed flask fitted with a rubber septum, a large a magnetic stir bar, and a nitrogen inlet adaptor was added ester **S2** (4.5 g, 40.1 mmol) via syringe. Methanol (80 mL) was then added followed by potassium carbonate (554 mg, 4 mmol, 0.1 equiv). The suspension was stirred vigorously for 20 min, during which time the solution gradually became opaque. The resulting suspension was poured into a 500 mL separatory funnel containing water (100 mL) and diluted with dichloromethane (100 mL). The layers were separated, and the aqueous layer was extracted with dichloromethane (5 × 50 mL). The combined organic extracts were dried ($MgSO_4$), filtered (cotton plug), and concentrated via rotary evaporation (15 mmHg, 20−25 °C). The resulting clear oil was filtered through a small plug of silica gel (1.8 cm ×2 cm) with 25 mL of EtOAc to remove any remaining base impurities. Concentration of the resulting solution yielded 5.19 g (89%) of geometrically pure (Z)-**S3** as determined by ^{1}H NMR analysis. The data collected were consistent with those previously reported.[90] Data for (*Z*)-**S3**: ^{1}H NMR (500 MHz, $CDCl_3$) 6.24 (td, *J* = 8.3, 11.5, 1 H, HC(4)), 5.87 (td, *J* = 1.4, 11.5, 1 H, HC(5)), 3.72 (s, 3 H, $H_3C(7)$), 3.61 (t, *J* = 5.9, 2 H, $H_2C(1)$), 2.74 (dt, *J* = 1.4, 8.2, 2 H, $H_2C(C(3))$, 1.73 (td, *J* = 8.3, 11.5, 1 H, $H_2C(2)$); ^{13}C NMR (126 MHz, $CDCl_3$) 167.5 (C(6)), 149.8 (C(4)), 120.2 (C(5)), 61.1 (C(1)), 51.3 (C(7)), 31.2 (C(2)), 25.1 (C(3)); IR (neat) 3423 (br), 2950 (m), 2870 (m), 2343 (w), 2361 (w), 1723 (s), 1645 (m), 1439 (s), 1408 (m), 1202 (s), 1173 (s); MS (ESI, Q-tof) 167 (100), 145 (35), 127 (15); TLC R_f 0.22 (hexanes/EtOAc, 4:1) [UV, $KMnO_4$].

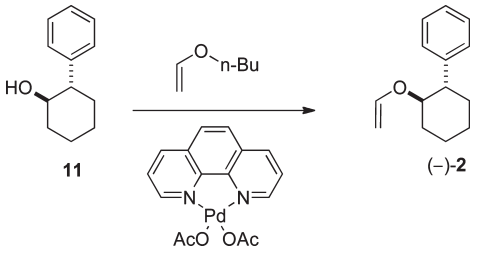


B. Preparation of Nitroalkenes and Chiral Vinyl Ethers

*1. **Nitroalkene Preparations.** Preparation of Methyl (2Z,6E)-7-Nitro-2,6-octadienoate ((E,Z)-**1**).* To a 500 mL, two-necked, round-bottomed flask fitted with a rubber septum and a nitrogen inlet adaptor was added alcohol (*Z*)-**S3** (3.0 g, 20.8 mmol) along with CH_2Cl_2 and DMSO (100 mL each). Triethylamine (17.4 mL, 125 mmol, 6.0 equiv) was added, and the flask was immersed in an ice/NaCl(s) bath. Once the internal temperature reached −5 °C, SO_3·pyridine complex was added in a single portion (5.5 g, 31 mmol, 1.5 equiv). After 2 h at <0 °C, an additional portion of SO_3·pyridine complex (5.5 g, 31 mmol, 1.5 equiv) was added. After another 2 h, the reaction was quenched by pouring into a 500 mL separatory funnel containing 100 mL of satd aq NH_4Cl. The organic phase was diluted with another 100 mL of CH_2Cl_2 and rinsed with NH_4Cl (3 × 50 mL) followed by $CuSO_4$ (1 × 50 mL), brine (100 mL), and H_2O (100 mL). The combined organic extracts were dried ($MgSO_4$), filtered over a silica gel plug (3 × 1 cm), and concentrated to afford 2.98 g (89%) of crude intermediate aldehyde as a light yellow oil. The aldehyde was carried on directly to nitroalkene (*E,Z*)-**1** without further purification as previously described. The data collected were consistent with those previously reported.[90] Data for (*E,Z*)-**1**: ^{1}H NMR (500 MHz, $CDCl_3$) 7.10 (t, *J* = 7.8, 1 H, HC(3)), 6.19 (dd, *J* = 8.2, 10.9, 1 H, HC(6)), 5.85 (d, *J* = 11.4, 1 H, HC(7)), 3.70 (s, 3 H, $H_3C(9)$), 2.84 (dq, *J* = 1.6, 7.6, 2 H, $H_2C(4)$), 2.38 (m, 2 H, $H_2C(5)$), 2.16 (s, 3 H, $H_3C(1)$); ^{13}C NMR (126 MHz, $CDCl_3$) 166.4 (C(8)), 147.1 (C(2)), 134.6 (C(6)), 121.1 (C(3)), 51.2 (C(7)), 27.3 (C(9, 1)), 12.5 (C(4,5)); IR (neat) 3054 (w), 2987 (w), 2954 (w), 2254 (m), 1719 (s), 1650 (m), 1521 (s), 1440 (m); MS (EI, 70 eV) 197 (5), 182 (12), 168 (25), 150 (42), 149 (45), 93 (100), 91; TLC R_f 0.57 (hexanes/EtOAc, 4:1) [UV, $KMnO_4$].



*Preparation of Methyl (2E,6E)-7-Nitro-2,6-octadienoate ((E,E)-**1**).* To a 1-L, three-necked, round-bottomed flask fitted with two rubber septa and a nitrogen inlet adaptor and an internal temperature probe (through a septum) was added alcohol (*E,E*)-**S3** (21 g, 147 mmol) along with CH_2Cl_2 and DMSO (147 mL each). Triethylamine (12 mL, 874 mmol, 6.0 equiv) was added, and the flask was immersed in a ice/NaCl(s) bath. Once the internal temperature reached −5 °C, SO_3·pyridine complex was added in a single portion (29.4 g, 184 mmol, 1.25 equiv). After 2 h at <0 °C, an additional portion of SO_3·pyridine complex (29.4 g, 184 mmol, 1.25 equiv) was added. After another 2 h, the reaction was quenched by pouring into a 1-L separatory funnel containing 200 mL of satd aq NH_4Cl. The organic phase was diluted with 150 mL of Et_2O and rinsed with NH_4Cl (3 × 100 mL) followed by $CuSO_4$ (2 × 100 mL), brine (100 mL) and satd aq $NaHCO_3$ (100 mL). The combined organic extracts were dried ($MgSO_4$), filtered over a silica gel plug (3 × 1 cm), and concentrated to afford the crude aldehyde as a light yellow oil. The aldehyde was carried on directly to the nitroalkene without further purification as previously described to give 22.9 g (80%) of nitroalkene (*E,E*)-**1** as a light-yellow oil. The data collected were consistent with those previously reported.[90] Data for (*E,E*)-**1**: ^{1}H NMR (500 MHz, $CDCl_3$) 7.14 (t, *J* = 7.7, 1 H, HC(6)), 6.19 (td, *J* = 11.4, *J* = 7.6, 1 H, HC(3)), 5.85 (d, *J* = 11.9, 1 H,HC(2)), 3.70 (s, 3 H, $H_3C(9)$), 2.85 (m, 2 H), 2.38 (m, 2 H), 2.16 (s, 3 H, $H_3C(8)$); ^{13}C NMR (126 MHz, $CDCl_3$) 166.5 (C(8)), 148.4 (C(2)), 146.2 (C(6)), 133.9 (C(3)), 122.5 (C(7)), 51.6 (C(9)), 26.5 (C(4)), 22.4 (C(5)), 12.6 (C(1)); IR (neat) 2992 (w), 2953 (w), 2843 (w), 2255 (m), 1721 (s), 1662 (m), 1523 (s), 1438 (m), 1391 (m), 1334 (s), 1284 (m), 1213 (m), 1173 (m), 1042 (w), 971 (w), 906 (s); TLC R_f 0.6 (hexanes/EtOAc, 4:1) [UV, $KMnO_4$].



*2. **Preparation of Chiral Vinyl Ether 2.** Preparation of (1R,2S)-2-Phenylcyclohexyloxyethene (**2**).* To a 250 mL, one-necked, round-bottomed flask fitted with a drying tube containing calcium chloride with a reflux condenser attached open to air and a magnetic stir bar were added sequentially *n*-butyl vinyl ether (110 mL, 851 mmol, 30 equiv), alcohol (1*R*,2*S*)-2-phenylcyclohexanol[91] (5.0 g, 28.4 mmol), and palladium(II) acetate−1,10-phenanthroline (115 mg, 0.284 mmol, 0.01 equiv). The flask was immersed in an oil bath and heated to 65 °C over 4 h. After being stirred for 3 days, the reaction mixture was allowed to cool to room temperature and concentrated to 1/2 of the total volume (~50 mL) by rotary evaporation (15 mmHg, 20−25 °C). The resulting solution was filtered over a plug of silica gel (40 mm × 4 cm), rinsed with hexanes/EtOAc/Et_3N (49:49:2, 3 × 30 mL), and concentrated by rotary evaporation (15 mmHg,

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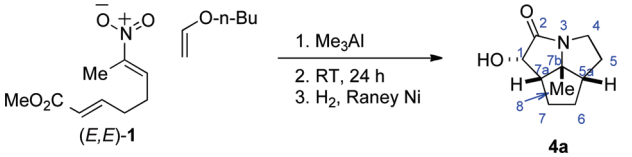
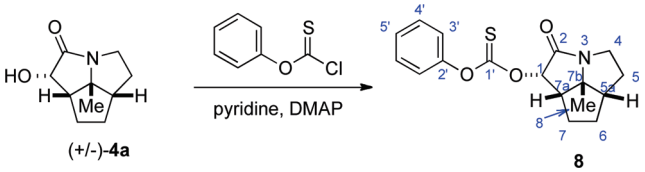
20−25 °C). The resulting pale yellow oil was purified by silica gel column chromatography (4 cm ×10 cm, gradient elution, hexanes/EtOAc/Et_3N, 49:0:1, 48:1:1, 47:2:1, 44:5:1, 250 mL each) to afford 4.3 g (74%) of **2** as a colorless oil along with 1.2 g of recovered (1*R*,2*S*)-2-phenylcyclohexanol. The data collected were consistent with those previously reported.[90] Data for **2**: bp 85 °C (0.1 mmHg); ^{1}H NMR (500 MHz, $CDCl_3$) 7.31−7.16 (m, 5 H,), 6.05 (dd, *J* = 14.1, 6.5, 1 H, HC(1′)), 4.11 (dd, *J* = 14.0, 1.1, 1 H, HC(2′)), 3.84 (dt, *J* = 10.3, 4.5, 1 H, HC(1)), 3.77 (dd, *J* = 6.6, 1.1, 1 H, HC(2′)), 2.65 (dt, *J* = 11.8, 3.5, 1 H, HC(2)), 2.25−2.20 (m, 1 H), 1.94−1.86 (m, 2 H), 1.78−1.74 (m, 1 H), 1.58−1.34 (m, 4 H); ^{13}C NMR (126 MHz, $CDCl_3$) 151.1 (C(1′)), 143.7 (C(7)), 128.2 (C(9)), 127.6 (C(8)), 126.2 (C(10)), 87.4 (C(2′)), 81.8 (C(1)), 50.3 (C(2)), 34.1 (C(6)), 32.1 (C(3)), 25.9 (C(4)), 24.8 (C(5)); IR (neat) 3031 (w), 2936 (s), 2859 (m), 1632 (s), 1559 (w), 1495 (w), 1449 (m), 1356 (w), 1183 (s), 1119 (m), 1076 (s), 818 (s); MS (EI, 70 eV) 202 (100), 160 (3), 159 (28), 158 (11), 91 (100), 81 (17), 67 (8), 55 (6); TLC R_f 0.90 (hexanes/Et_2O, 9:1) [I_2].

C. Scaffold Preparation by Tandem Cycloaddition of Nitroalkenes

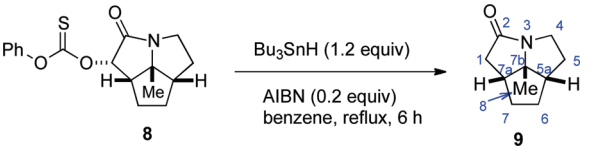
1. Preparation of Scaffold for Library ***I***.



*Preparation of rel-(1S,3S,5aS,7aS,7bR)-Octahydro-1-hydroxy-7b-methyl-2H-cyclopenta[gh]pyrrolizin-2-one ((±)-**4a**).* To a 50 mL, three-necked, round-bottom flask fitted with two rubber septa, a magnetic stir bar, a nitrogen inlet adaptor, and an internal temperature probe was added nitroalkene (*E*,*E*)-**1** (1.0 g, 5 mmol) followed by CH_2Cl_2 (20 mL). The internal temperature was brought to −60 °C by immersion in acetone/$CO_{2(s)}$ bath. Then a Me_3Al was added (6.3 mL of a 2 M solution in toluene, 12.5 mmol, 2.5 equiv) via syringe followed by *n*-butyl vinyl ether (1.25 mL, 12.6 mmol, 2.5 equiv). The resulting bright yellow solution solution was allowed to stir at for 6 h, during which time the yellow color gradually faded. The reaction was quenched by the cautious addition of silica gel (ca. 2 g) via a long stem funnel until no bubbling was observed. The mixture was then poured into a funnel containing more silica gel (∼3 g, prewetted with EtOAc) and rinsed with ethyl acetate (200 mL). The resulting clear solution was dried ($MgSO_4$) to remove any adventitious water, filtered, and concentrated by rotary evaporation (15 mmHg, 20−25 °C) to give a clear viscous oil. The intermediate nitronate was diluted with 50 mL of toluene and transferred to a 100 mL round-bottomed flask. The flask was fitted with a nitrogen inlet adaptor, and $NaHCO_3$ was added (420 mg, 5 mmol, 1.0 equiv) along with a stir bar. The suspension was allowed to stir at room temperature for 7 h, filtered, and concentrated by rotary evaporation (15 mmHg, 20−25 °C). The resulting mixture of nitroso acetals was diluted in EtOAc/MeOH (9/1, 25 mL) and added to a test tube (6 cm ×14 cm) containing a spatula tip (∼100 mg) of Raney Ni (previously washed with H_2O, MeOH, and EtOAc, 2 × 15 mL each) along with a magnetic stir bar. The tube was placed in a steel autoclave, which was then pressurized with H_2 (350 psi) and allowed allowed to stir for 2 days. After 2 days, the autoclave was *carefully* vented in a fume hood and the solution was filtered through a plug of Celite (5 cm ×5 cm) with EtOAc (200 mL). The resulting clear filtrate was concentrated by rotary evaporation (15 mmHg, 20−25 °C) and purified by silica gel column chromatography (2 cm ×6 cm, CH_2Cl_2/EtOAc, 19:1, 10:1, 1:1, 100 mL each) to afford 778 mg (86%) of the racemic α-hydroxy lactam **4a** as a white powder. The data collected were consistent with those previously reported.[90] Data for **4a**: mp 108−115 °C; ^{1}H NMR (500 MHz, $CDCl_3$) 4.67 (d (br), *J* = 7.2, 1 H, HC(2)), 3.91 (ddd, *J* = 3.8, *J* = 8.5, *J* = 12.1, 1 H, HC(8)), 2.94 (ddd, *J* = 7.9, *J* = 8.1, *J* = 11.9, 1 H, HC(8)), 2.71−2.66 (m, 1 H, HO), 2.64 (dd, J = 7.5, J = 14.9, 1 H, HC(7a)), 2.28 (ddd, *J* = 4.9, *J* = 7.5, *J* = 12.5, 1 H, HC(5a)), 2.13 (ddd, *J* = 3.8, *J* = 8.0, *J* = 11.9, 1 H, HC(5)), 1.80 (m, 1 H, HC(5)), 1.72 (m, 2 H, HC(7), HC(5a)), 1.50 (m, 1 H, HC(7)), 1.33 (s, 3 H, H_3C(8)), 1.27 (ddd, 1 H, *J* = 5.7, *J* = 10.6, 10.6, HC(6)); ^{13}C NMR (126 MHz, $CDCl_3$) 176.4 (C(2)), 75.5 (C(7b)), 72.8 (C(1)), 51.0 (C(7a)), 49.1 (C(5a)), 42.0 (C(4)), 31.4 (C(6)), 30.9 (C(7)), 24.8 (C(5)), 22.8 (C(8)); IR (NaCl plate) 3283 (s, br), 2961 (s), 2860 (s), 1697 (s), 1677 (s), 1653 (s); MS (ESI, Q-tof) 182 (13), 181 (99), 167 (11), 166 (100), 163 (10), 162 (15), 138 (56), 111 (17), 110 (16), 107 (26), 96 (27), 82 (33), 81 (26), 67 (21), 56 (29), 55 (37), 53 (18); TLC R_f 0.20 (hexane/EtOAc, 4:1) [I_2, $KMnO_4$].



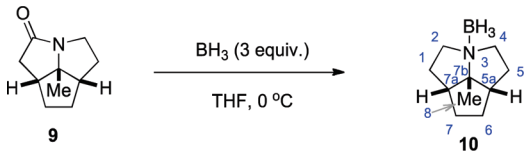
*Preparation of (1S,3S,5aS,7aS,7bR)-Octahydro-1-oxo[(phenoxy-thiocarbonyl)oxy]-7b-methyl-2H-cyclopenta[gh]pyrrolizin-2-one ((±)-**8**).* To a 50 mL, single-necked, round-bottomed flask fitted with a nitrogen inlet, a rubber septum, and a magnetic stir bar was added racemic α-hydroxy lactam **4a** (215 mg, 1.2 mmol) followed by dimethylaminopyridine (72 mg, 0.59 mmol, 0.5 equiv) and CH_2Cl_2 (17 mL). Lastly, pyridine (202 μL, 2.4 mmol, 2.0 equiv) was added followed by phenylchlorothionoformate (330 μL, 2.4 mmol, 2 equiv), both via syringe. The resulting light-yellow solution was stirred for 4 h at room temperature, during which time it gradually became darker. The solution was concentrated by rotary evaporation (15 mmHg, 20−25 °C), and the residue was purified by silica gel column chromatography (2 cm ×10 cm, hexane/EtOAc, 4:1). Hot filtration followed by recrystallization hexanes/CH_2Cl_2 (25:1, ∼20 mL) afforded 294 mg (78%) of **8** as colorless rhomboids. Data for **8**: mp 100−101 °C; ^{1}H NMR (500 MHz, $CDCl_3$) 7.42 (m, (second order), 2 H, HC(4′)), 7.30 (dt (second order), *J* = 1.2, 7.2, 1 H, HC(5′)), 7.14 (m, 2 H, HC(3′)), 6.12 (dd, *J* = 1.0, 7.3, 1 H, HC(1)), 4.02 (ddd, *J* = 3.8, 8.6, 12.2, 1 H, HC(4)), 3.01 (m, 2 H, HC(4), HC(7a)), 2.34 (m, 1 H, HC(5a)), 2.18 (et, *J* = 3.8, 8.1, 8.1, 11.9, 1 H, HC(7)), 1.86 (ddd, *J* = 7.6, 7.6, 12.8, 1 H, HC(7 or 6)), 1.78 (m, 2 H, HC(5), HC(6)), 1.59 (et, *J* = 4.8, 8.2, 8.2, 13.0, 1 H, HC(5)), 1.39 (s, 3 H, H_3C(8)), 1.37 (d, *J* = 5.7, 1 H, HC(6)); ^{13}C NMR (126 MHz, $CDCl_3$) 194.5 (C(1′)), 169.8 (C(1)), 153.4 (C(2′)), 129.5 (C(4′)), 126.6 (C(5′)), 121.8 (C(3′)), 82.6 (C(2)), 75.6 (C(9)), 49.5 (C(3)), 48.7 (C(6)), 42.5 (C(8)), 31.4 (C(7)), 30.9 (C(4)), 25.7 (C(5)), 23.2, (C(10)); IR (CH_2Cl_2, film) 2966 (w), 2252(m), 1706 (s), 1490 (m), 1278 (s), 1208 (s); TLC R_f 0.78 (hexanes/EtOAc, 1:1) [UV, $KMnO_4$]; HRMS $C_{17}H_{19}O_3NS$ (317.10857) calcd 317.10857, found 317.10814. Anal. Calcd for $C_{17}H_{19}O_3NS$ (317.11): C, 64.33; H, 6.03; N, 4.41. Found: C, 64.44; H, 6.00; N, 4.50.



*Preparation of (3S,5aS,7aR,7bR)-Octahydro-7b-methyl-2H-cyclopenta[gh]pyrrolizin-2-one ((±)-**9**).*

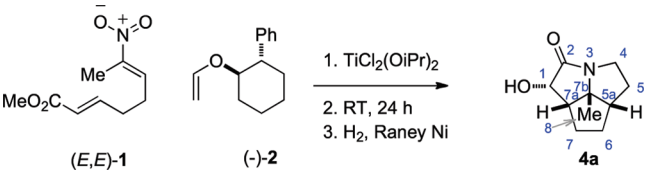
Thionocarbonate **8** (140 mg, 0.59 mmol) in benzene (40 mL) was added to a one-necked, round-bottomed flask via syringe

which was fitted with a reflux condenser and a magnetic stir bar. Atop the reflux condenser was fitted a nitrogen inlet adaptor and a rubber septum. The round-bottomed flask was immersed in a preheated (100 °C) oil bath and allowed to come to reflux (~20 min). During this time, tributyltin hydride (1.08 mL, 0.77 mmol, 1.3 equiv) and AIBN (206 μL, 0.12 mmol, 0.2 equiv) were added to a separate 25 mL, one-necked, conical flask along with 15 mL of benzene and a magnetic stir bar. Once the round-bottomed flask reached reflux, the tributyltin hydride AIBN solution was transferred dropwise via cannula over 3.5 h, maintaining a consistent gentle reflux. The resulting solution was allowed to reflux for an additional 2 h and then cooled to room temperature. Potassium fluoride (3.0 g, 51.6 mmol) was added to the resulting light-yellow solution, and the resulting mixture was allowed to stir for an additional 3 h. The suspension was filtered (cotton plug), and the filtrate was concentrated by rotary evaporation (15 mmHg, 20−25 °C). The residue was purified by silica gel column chromatography (3 cm ×10 cm, hexane/EtOAc, 1:0, 9:1, 4:2, 7:3, 3:2 1:1, 50 mL each) with a plug of KF to afford 82.1 mg (83%) of lactam **9** as a colorless oil. Data for **9**: bp 80 °C (0.1 mmHg); ^{1}H NMR (500 MHz, $CDCl_3$) 3.88 (ddd, J = 3.6, 8.6, 12.0, 1 H, HC(4)), 2.94 (dd, J = 8.0, 16.6, 2 H, HC(1), HC(4)), 2.28 (dd, J = 7.8, 13.9, 1 H, HC(5a)), 2.15 (m, 3 H, HC(7a), HC(1), HC(7 or 6)), 1.94 (ddd, J = 7.2, 7.2, 20.6, 1 H, HC(5)), 1.76 (ddd, J = 6.8, 13.5, 13.6, 1 H, HC(7)), 1.62 (m, 2 H, HC(5), HC(7 or 6)), 1.42 (m, 1 H, HC(7 or 6)), 1.30 (s, 3 H, H_3C(8)); ^{13}C NMR (126 MHz, $CDCl_3$) 176.6 (C(2)), 79.1 (C(7b)), 48.5 (C(7a)), 44.1 (C(5a)), 42.2 (C(4)), 40.3 (C(1)), 33.3 (C(5)), 32.2 (C(6)), 31.3 (C(7)), 23.0 (C(8)); IR (neat) 3019 (s), 2957 (m), 2865 (w), 2400 (m), 1676 (m), 1521 (m), 1400 (w), 1215 (s); MS (ESI, Q-tof) 167 (M^+ + 1, 12), 166 (M^+, 100); mol formula $C_{10}H_{15}NO$ (165.23); HRMS $C_{10}H_{15}NO$ (165.1232) calcd 166.1232, found 166.1231; TLC R_f 0.17 (hexanes/EtOAc, 1:1) [$KMnO_4$].



*Preparation of (5aS,7aR)-Octahydro-7b-methylcyclopenta[gh]-pyrrolizine·Borane (**10**).* To a 100 mL, one-necked, round-bottomed flask fitted with a rubber septum and a nitrogen inlet adaptor were added lactam **15** (1.09 g, 6.6 mmol) and THF (60 mL). The flask was cooled to 0 °C in an ice bath, and BH_3·THF complex (3.0 equiv, 1.0 M solution, 7.0 mL) was added dropwise over 10 min (bubbling observed). The cooling bath was removed, and the resulting clear solution was stirred for 8 h. The reaction was quenched by the addition of 30 mL of MeOH, and the reaction was concentrated by rotary evaporation (15 mmHg, 20−25 °C). The resulting thick, glassy oil was purified by silica gel column chromatography (2 cm ×12 cm, hexanes/EtOAc, 10:1, 5:1, 3:1, 200 mL each) to afford 794 mg (80%) of borane complex **10** as a white wax. Data for **10**: ^{1}H NMR (500 MHz, $CDCl_3$) 3.27 (ddd, J = 7.0, 7.0, 11.9, 2 H, HC(2 and 4)), 3.14 (m, 2 H, HC(2 and 4)), 2.30 (m, 2 H, HC(5a), HC(7a)), 2.14 (ddd, J = 6.9, 6.9, 15.2, 2 H, HC(1), HC(5)), 1.86 (m, 2 H, CH_2), 1.56 (ddd, J = 9.8, 9.8, 10.3, 3 H, CH_2), 1.47 (s, 3 H, HC(8)), 1.26 (m, J = 6.6, 13.7, 2 H, CH_2), (0.8−2.5, br, 3 H, (H_3B)[92]); ^{13}C NMR (126 MHz, $CDCl_3$) 87.3 (C(7b)), 62.5 (C(2)), 52.2 (C(5a)), 31.9 (C(1)), 28.5 (C(8)), 24.9 (C(6)); IR (NaCl plates, thin film) (m), 3020 (s)2971 (w), 292 (w), 2400 (m), 2361 (m), 2326 (m), 1517 (m), 1475 (w), 1425 (w), 1361 (w), 1215 (s), 929 (m), 756 (s), 669 (s); MS (ESI, Q-tof) 165 (M^+, 10), 164 (83), 163 (19), 153 (13), 152 (100); mol formula $C_{10}H_{20}BN$ (165.08); HRMS $C_{10}H_{19}BN$ (164.1611) calcd 164.1611, found 164.1611; TLC R_f 0.54 (CH_2Cl_2/hexanes, 3:1) [I_2, CAM].

*2. Preparation of the Scaffold for Library **II**.*

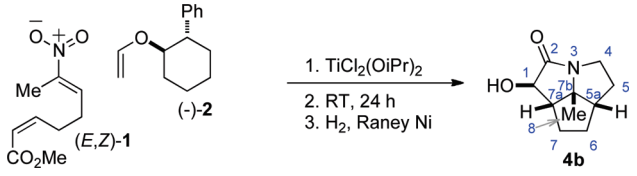


*Preparation of (1S,3S,5aS,7aS,7bR)-Octahydro-1-hydroxy-7b-methyl-2H-cyclopenta[gh]pyrrolizin-2-one (**4a**).* To a 250 mL, three-necked, round-bottom flask fitted with two rubber septa, a magnetic stir bar, a nitrogen inlet adaptor, and an internal temperature probe were added nitroalkene (*E,E*)-**1** (3.68 g, 18.45 mmol) and chiral vinyl ether 2 (5.6 g, 28 mmol, 1.5 equiv) via syringe. The flask was then evacuated using high vacuum (~0.1 mmHg) for 30 min and then was backfilled with N_2 and charged with CH_2Cl_2 (110 mL). The internal temperature was set to −85 °C (hexanes/N_2 bath). This yellow solution was sirred for 15 min, and then freshly prepared $TiCl_2$(O-*i*-Pr)$_2$ solution[93] (1.2 M in CH_2Cl_2, 3.0 equiv) was added dropwise via syringe at a rate that the internal temperature did not rise above −70 °C (ca. 15 min). After addition of the Lewis acid, the cooling bath was replaced with an acetone/$CO_{2(s)}$ bath, and the resulting bright yellow solution was stirred for another 5 h while an internal temperature ≤−75 °C was maintained. Throughout the reaction, the yellow color gradually faded and a white precipitate formed. After 5 h, the reaction was quenched with triethylamine (6.1 equiv, 1.0 M in MeOH) via syringe while an internal temperature of less than −40 °C was maintained. The cooling bath was then removed, and the reaction mixture was allowed to warm to 0 °C (ca. 15 min). The resulting white suspension was then diluted with ethyl acetate (100 mL) and poured into a 1 L separatory funnel containing satd aq NH_4Cl (250 mL) and *tert*-butyl methyl ether (100 mL). The layers were separated, and the organic phase was washed with satd aq NH_4Cl (2 × 50 mL), brine (1 × 100 mL), and satd aq $NaHCO_3$ (1 × 150 mL). The aqueous layers were combined and back-extracted with *tert*-butylmethyl ether (3 × 100 mL). The combined organic layers were dried over $NaHCO_3/MgSO_4$ (1/1), filtered (cotton plug), and concentrated by rotary evaporation (15 mmHg, 20−25 °C). The resulting residue was filtered through a pad of silica gel (3 × 3 cm), eluting with ethyl acetate (100 mL) to remove any remaining amine impurities. The resulting clear solution was concentrated (15 mmHg, 20−25 °C) to a pale-yellow residual oil in a 1 L, one-necked, round-bottom flask. *tert*-Butylmethyl ether (200 mL) was added followed by $NaHCO_3$ (1.5 g, 1.0 equiv) and a large a magnetic stir bar. The flask was fitted with an a nitrogen inlet adaptor, evacuated, backfilled with N_2, and allowed to stir at room temperature for 12 h. The suspension was stirred at room temperature for 12 h and then filtered through Celite (3 × 3 cm) and concentrated by rotary evaporation (15 mmHg, 20−25 °C). The resulting mixture of nitroso acetals was diluted in EtOAc/MeOH (9/1, 25 mL) and added to a test tube (6 cm ×14 cm) containing a spatula tip (~200 mg) of Raney Ni (previously washed with H_2O, MeOH, and EtOAc, 2 × 15 mL each) along with a magnetic stir bar. The tube was placed in a steel autoclave, which was then pressurized with H_2 (350 psi) and set on a stir-plate. After being stirred for 2 days at room temperature, the autoclave was *carefully* vented in a fume hood and the solution was through a plug of Celite (5 cm ×5 cm) with EtOAc (200 mL). The resulting clear solution was concentrated by rotary evaporation (15 mmHg, 20−25 °C) and purified by silica gel column chromatography (30 mm × 8 mm) (CH_2Cl_2/EtOAc, 19:1, 10:1, 1:1, 200 mL each) to afford 2.76 g (76%, three steps) of α-hydroxy lactam **4a** as a white powder. The spectroscopic data are in accord with those previously reported.[62c,91] Data for **4a**: mp 110−114 °C (hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) 4.69 (d, J = 7.2, 1 H, HC(1)), 3.93 (ddd, J = 12.0, 8.5, 3.6, 1 H, HC(4)), 2.99−2.93 (m, 1 H, HC(4)), 2.70−2.64 (m, J = 7.4, 2 H, HOC(1), HC(7)), 2.33−2.27 (m, 1 H, HC(5a)), 2.18−2.12 (m, 1 H, HC(5)), 1.85−1.70 (m, 3 H, HC(6), H_2C(7)), 1.56−1.42 (m, 1 H, HC(5)), 1.35 (s, 3 H, H_3C(10)), 1.33−1.27 (m, 1 H, HC(6)); ^{13}C NMR (126 MHz,

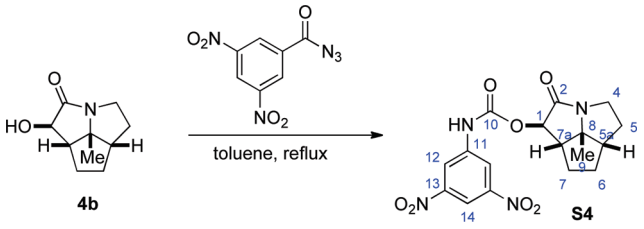
$CDCl_3$) 176.6 (C(1)), 75.7 (C(9)), 72.9 (C(2)), 51.2 (C(3)), 49.3 (C(6)), 42.2 (C(8)), 31.6 (C(7)), 31.1 (C(5)), 24.9 (C(4)), 23.0 (C(10)); IR ($CDCl_3$, film) 3390 (s), 2961 (s), 2860 (m), 1705 (s), 1325 (s); MS (ESI, Qtof) 182 (100), 102 (14); $[\alpha]^{24}_D$ −35.2 (c = 1.07, CH_2Cl_2) (lit. (99:1) = −36.9 (c = 1.00, CH_2Cl_2));[90] TLC R_f 0.20 (hexane/EtOAc, 4:1) [I_2, $KMnO_4$].

*Preparation of (1S,3R,5aS,7aS,7bR)-Octahydro-1-hydroxy-7b-methyl-2H-cyclopenta[gh]pyrrolizin·Borane (**11a**).* To a 50 mL, two-necked, round-bottomed flask fitted with a rubber septum, a nitrogen inlet adaptor, a magnetic stir bar, and an internal temperature probe (inserted through a rubber septum) were added lactam **4a** (181 mg, 1.0 mmol) and THF (1 mL). The flask was cooled to 0 °C in an ice bath, and BH_3·THF complex (5.0 equiv, 1.0 M solution, 5 mL) was added dropwise over 10 min (bubbling observed). The cooling bath was removed, and the resulting clear solution was stirred for 2 h. The reaction was quenched by the addition of 20 mL of MeOH and the mixture was concentrated by rotary evaporation (15 mmHg, 20−25 °C). This process was repeated three more times to afford the crude product as a white solid. Purification by silica gel column chromatography ((2 cm ×7 cm), hexanes/EtOAc, 95:5, 85:15, 3:1, 150 mL each) afforded ∼185 mg of **11a**. Recrystallization from hexanes/MTBE (5:1) afforded 175 mg (96%) of the borane complex **11a** as white needles. Data for **11a**: mp 164−165 °C (MTBE/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) 4.75 (dd, J = 8.1, 15.3, 1 H, HC(1)), 3.44 (dd, J = 6.5, 10.9, 1 H, HC(2)), 3.28 (ddd, J = 2.5, 6.7, 12.1, 1 H, HC(4)), 3.16 (dt, J = 6.6, 11.7, 1 H, HC(4)), 3.03 (m, 1 H, HC(2)), 2.39 (m, 2 H HC(5a), HC(7a)), 2.07−2.00 (m, 1 H, HC(7)), 1.99−1.90 (m, 1 H, HC(6)), 1.89−1.73 (m, 2 H, HC(6), HC(5)), 1.74−1.58 (M, 2 H, HC(7), HC(5)), 2.10−1.25 (s, broad, 3 H, H_3B), 1.48 (s, 3 H, H_3C(8)); ^{13}C NMR (126 MHz, $CDCl_3$) 87.8 (C(7b)), 69.4 (C(1)), 66.0 (C(2)), 63.1 (C(4)), 55.1 (C(7a)), 53.1 (C(5a)), 32.1 (C(5)), 28.0 (C(7)), 26.4 (C(6)), 25.2 (C(8)); IR (NaCl plate, film) 3018 (m), 2969 (m), 2872 (w), 2367 (m), 2363 (m), 2333 (m), 2276 (w), 1215 (s); MS (ESI, Q-tof) 180 (42), 167 (21), 152 (100), 96 (59); $[\alpha]^{24}_D$ −1.74 (c = 1.0, CH_2Cl_2); TLC R_f 0.33 (hexanes/EtOAc, 3:1) [I_2]. Anal. Calcd for $C_{10}H_{20}BNO$ (181.08): C, 66.33; H, 11.13; N, 7.73. Found: C, 66.05; H, 10.95; N, 7.52.

*3. Preparation of Scaffold for Library **III**.*



*Preparation of (1R,3S,5aS,7aS,7bR)-Octahydro-1-hydroxy-7b-methyl-2H-cyclopenta[gh]pyrrolizin-2-one (**4b**).* To a 250 mL, three-necked, round-bottomed flask fitted with two rubber septa, a magnetic stir bar, a nitrogen inlet adaptor, and an internal temperature probe were added nitroalkene (*E*,*Z*)-**1** (2.0 g, 10.0 mmol) and chiral vinyl ether **2** (3.1 g, 15.1 mmol, 1.5 equiv) via syringe. The resulting yellow oil was then evacuated using high vacuum (∼0.1 mmHg) for 30 min. The flask was backfilled with N_2 and charged with CH_2Cl_2 (60 mL). The solution was cooled to −85 °C by immersion in a hexanes/N_2 bath. This cooled yellow solution was sirred for 15 min, and then freshly prepared $TiCl_2$(O-*i*-Pr)$_2$ solution (1.2 M in CH_2Cl_2, 3.0 equiv) was added dropwise via syringe while an internal temperature <−70 °C was maintained (ca. 15 min). After addition of the Lewis acid, the cooling bath was replaced with an acetone/$CO_{2(s)}$ bath, and the resulting bright yellow solution was stirred for another 5 h while an internal temperature ≤−72 °C was maintained. During the course of the reaction, the yellow color gradually faded and a white precipitate formed. After 5 h, the reaction was quenched with triethylamine (6.1 equiv, 1 M in MeOH) via syringe while an internal temperature <−40 °C. The cooling bath was then removed and the reaction mixture was allowed to warm to 0 °C (ca. 15 min). The resulting white suspension was then diluted with ethyl acetate (50 mL) and poured in a 500 mL separatory funnel containing a biphasic mixture of satd aq NH_4Cl and MTBE (100 mL each). The biphasic solution was separated and the organic extract was extracted with satd aq NH_4Cl solution (2 × 50 mL), H_2O (2 × 50 mL) and brine (2 × 50 mL). The combined aqueous layers were back extracted with MTBE (3 × 75 mL). The combined organic layers were dried over $NaHCO_3$/$MgSO_4$ (1/1), filtered (cotton plug), and concentrated by rotary evaporation (15 mmHg, 20−25 °C). The resulting residue was filtered through a pad of silica gel (3 × 3 cm), eluting with ethyl acetate (100 mL) to remove any remaining amine impurities. The resulting clear solution was concentrated by rotary evaporation (15 mmHg, 20−25 °C) to a pale-yellow residual oil in a 1-L one-necked, round-bottomed flask. Hexanes (200 mL) was added followed by $NaHCO_3$ (4.22 g, 50.0 mmol, 5.0 equiv) and a large a magnetic stir bar. The flask was fitted with a nitrogen inlet adaptor evacuated and backfilled with N_2 and immersed in a preheated 40 °C oil bath. The suspension was stirred at 40 °C (bath temperature) for 30 h and then filtered through Celite (3 × 3 cm) and concentrated by rotary evaporation (15 mmHg, 20−25 °C). The resulting mixture of nitroso acetals was diluted in EtOAc/MeOH (9:1, 25 mL) and added to a test tube (6 cm ×14 cm) containing a spatula tip (∼200 mg) of Raney Ni (previously washed with H_2O, MeOH, and EtOAc, 2 × 15 mL each) along with a magnetic stir bar. The tube was placed in a steel autoclave, which was then pressurized with H_2 (350 psi). After 2 days, the autoclave was *carefully* vented in a fume hood, and the solution was filtered through a plug of Celite (5 cm ×5 cm) with EtOAc (200 mL). The resulting clear filtrate was concentrated by rotary evaporation (15 mmHg, 20−25 °C) and purified by silica gel column chromatography (2 cm ×8 cm, CH_2Cl_2/EtOAc, 19:1, 10:1, 1:1, 100 mL each). Recrystallization from hot hexanes/EtOAc (10:1, ∼50 mL) afforded 1.15 g (63%, 3 steps) of analytically pure α-hydroxy lactam **4b** as colorless needles. Data for **4b**: mp 112−117 °C; ^{1}H NMR (500 MHz, $CDCl_3$) 4.68 (dd, J = 1.2, 7.3, 1 H, HC(1)), 3.90 (ddd, J = 3.7, 8.5, 12.0, 1 H, HC(4)), 3.05 (br, 1 H, HOC(1)), 2.93 (ddd, J = 1.2, 8.1, 12.0, 1 H, HC(4)), 2.63 (q, J = 7.3, 1 H, HC(7a)), 2.25 (m, 1 H, HC(5a)), 2.12 (m, 1 H, HC(5)), 1.79 (m, 1 H, HC(6)), 1.72 (m, 2 H, H_2C(7)), 1.49 (m, 1 H, HC(5)), 1.32 (s, 3 H, H_3C(8)), 1.27 (m, 1 H, HC(6)); ^{13}C NMR (126 MHz, $CDCl_3$) 176.2 (C(1)), 75.8 (C(9)), 73.0 (C(2)), 51.2 (C(3)), 49.3 (C(6)), 42.2 (C(8)), 31.5 (C(4)), 31.1 (C(7)), 24.8 (C(8)), 23.0 (C(10)); IR (KBr plate) 3302 (s, br), 2952 (s), 2864 (s), 1700 (s), 1653 (s); MS (ESI, Q-tof) 181 (100), 166 (91), 38 (53), 107 (26), 82 (28), 55 (35); TLC R_f 0.33 (EtOAc/CH_2Cl_2, 1:3) [I_2, $KMnO_4$]; $[\alpha]^{24}_D$ +50.6 (c = 1.03, CH_2Cl_2). Anal. Calcd for $C_{10}H_{15}NO_2$ (181.23): C, 66.27; H, 8.34; N, 7.65. Found: C, 65.97; H, 8.32; N, 7.65.



*Preparation of (1R,3R,5aS,7aS,7bR)-Octahydro-1-[N-(3,5-Dinitrophenyl)carbamoxy]-7b-methyl-2H-cyclopenta[gh]pyrrolizin-2-one (**S4**).* A 25 mL round-bottomed flask (A) was fitted with a reflux condenser,

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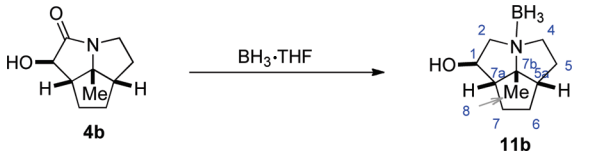
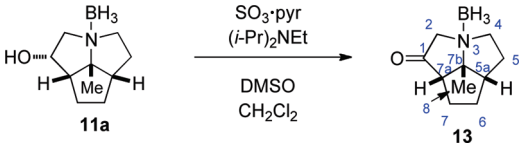
a nitrogen inlet adaptor, a rubber rubber septum, and a magnetic stir bar. The apparatus was opened, and 3,5-dinitrobenzoylazide (25 mg, 0.105 mmol, 1.2 equiv) was added as a solid. The apparatus was evacuated and backfilled with N_2 three times and toluene (5.0 mL) was added. The clear solution was immersed in a preheated (115 °C) oil bath and stirred at reflux for 30 min. In a separate, two-neck, 5 mL conical flask (B) fitted with a triangular a magnetic stir bar, rubber septum, and a nitrogen inlet adaptor the starting alcohol was added (17.2 mg, 0.087 mmol) followed by toluene (1.0 mL). The resulting solution (B) was transferred to flask (A) via cannula. The resulting light yellow solution was heated to reflux for 2 h and then allowed to cool to room temperature. The reaction mixture was concentrated in vacuo, and the crude product was purified by column chromatography (hexane/EtOAc (3/1, 1/1)) to afford 36 mg (75%) of enantioenriched (**S4**) as a white solid. The sample was compared to racemate as previously described.[90,93] Data for **S4**: ^{1}H NMR (500 MHz, $CDCl_3$) 9.65 (s, 1 H, HN) 8.71 (d, J = 2.0, 2 H), 8.67 (dd, J = 2.0, 2.0, 1 H), 5.03 (s, 1 H), 3.93 (ddd, 1 H, J = 3.9, 8.7, 12.6), 3.09 (m, 1 H), 2.40 (dd, J = 4.8, 9.0, 1 H,), 2.28 (m, 2 H), 2.13 (m, 1 H), 1.87 (m, 2 H), 1.71 (m, 2 H), 1.43 (s, 3 H), 1.28 (m, 5 H), 0.85 (dd, J = 11.2, 13.1, 1 H); ^{13}C NMR (126 MHz, *d*7-DMF) 170.7 (C(2)), 152.9 (C(10)), 148.8 (C(11)), 141.8 (C(13)), 117.6 (C(14)), 111.8 (C(12)), 82.4 (C(7b)), 48.4 (C(1)), 50.1 (C(7a)), 48.1 (C(5a)), 41.9 (C(4)), 31.3 (C(6)), 30.9 (C(7)), 23.0 (C(9)); MS (EI, 70 eV) 405(82), 390(100), 374(12), 187(24), 91(25), 75(40); TLC R_f 0.32 (hexanes/EtOAc, 3:1) [I_2]; CSF-SFC: t_R = 11.27 min (96%) and 15.73 (4%) (Chiralpak AD, 125 bar, 40 °C, 15% MeOH in CO_2, 3.0 mL/min, 220 nm).



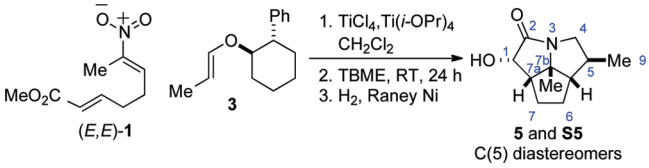
*Preparation of (1R,3R,5aS,7aS,7bR)-Octahydro-1-hydroxy-7b-methyl-2H-cyclopenta[gh]pyrrolizine·Borane (**11b**).* To a 100 mL, single-necked, round-bottomed flask fitted with a rubber septum, a magnetic stir bar, and a nitrogen inlet adaptor were added lactam **4b** (170 mg, 0.866 mmol) and THF (60 mL). The flask was cooled in an ice bath, and BH_3·THF complex (30 equiv, 1.0 M solution, 9.0 mL) was added dropwise over 10 min (bubbling observed). The cooling bath was removed, and the clear solution was stirred for 8 h. The reaction was quenched by the addition of 30 mL of MeOH, and the mixture was concentrated by rotary evaporation (15 mmHg, 20−25 °C). The resulting white solid was redissolved in 15 mL of MeOH (15 mL) and again concentrated by rotary evaporation (15 mmHg, 20−25 °C). Purification by silica gel column chromatography ((2 cm ×7 cm), hexanes/EtOAc, 1:0, 10:1, 8:1, 5:1, 3:1, 100 mL each) afforded 130.2 mg (77%) of borane complex **11b** as a white solid. Data for **11b**: mp 88−91 °C; ^{1}H NMR (500 MHz, $CDCl_3$) 3.89, (br, 1 H, HC(1)), 3.54, (d, J = 8.7, 1 H, HO(C(1)), 3.33, (ddd, J = 12.7, 2.9, 1.3, 1 H, HC(2), 3.30, (dd, J = 12.6, 5.22, 1 H, HC(4)), 3.19−3.10, (m, 2 H HC(7a), HC(5a)), 2.32−2.25, (m, 2 H, HC(2), HC(4)), 2.02−1.90, (m, 2 H, HC(6), HC(7)), 1.83−1.75, (m, 1 H, HC(6)), 1.55−1.45, (m, 3 H, HC(5), HC(6), HC(7)), 1.51, (s, 3 H H_3C(8)), 0.8−2.5, (br, 3 H, (H_3B)); ^{13}C NMR (126 MHz, $CDCl_3$) 87.5, (C(1)) 75.2, (C(7b)) 68.4, (C(2)) 64.1, (C(4)) 60.9, (C(7a)) 53.0, (C(5a)) 31.5, (C(5)) 30.7, (C(6)) 28.0, (C(7)) 25.2, (C(8)); IR (NaCl plate, film) 3053 (m), 2986 (m), 2871 (w), 2386 (m), 2306 (m), 2253 (m), 1421 (w), 1382 (w), 1265 (s); MS (ESI, Q-tof) 180 (100); TLC R_f 0.33 (hexanes/EtOAc, 3:1) [I_2]. Anal. Calcd for $C_{10}H_{20}BNO$ (181.08): C, 66.33; H, 11.13; N, 7.73. Found: C, 66.32; H, 10.90; N, 7.66.

*4. Preparation of Scaffold for Library **IV**.*



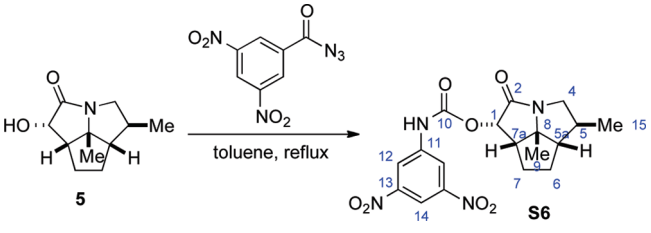
*Preparation of (3R,5aS,7aS,7bR)-Octahydro-7b-methyl-2H-cyclopenta[gh]pyrrolizin-1-one·Borane (**13**).* To a 100 mL, three-necked, round-bottomed flask fitted with a nitrogen inlet adapter, a magnetic stir bar, and an internal temperature probe were added **11a** (500 mg, 2.76 mmol), CH_2Cl_2 (11.5 mL), and DMSO (2.3 mL). The resulting solution was cooled to −12 °C in an ice/salt bath. To this solution was added diisopropylethylamine (2.41 mL, 13.8 mmol, 5.0 equiv) followed by a solution of SO_3·pyridine complex (1.32 g, 8.28 mmol, 3.0 equiv) in DMSO (4.6 mL) at rate such that the internal temperature remained <−5 °C (∼5 min). After the solution was stirred for an additional 20 min at −10 °C, the cooling bath was removed, and the solution was allowed to warm to room temperature (∼10 min) and then cooled to 0 °C by reimmersion in the ice/salt bath. The solution was diluted with Et_2O (10 mL) and quenched with H_2O (10 mL). This mixture was poured into a 250 mL separatory funnel, and the layers were separated. The aqueous extract was washed with Et_2O (2 × 25 mL). The organic extracts were washed with satd aq $CuSO_4$ solution (2 × 25 mL), satd aq $NaHCO_3$ solution (1 × 25 mL), and brine (25 mL) and the combined organic extracts dried over $MgSO_4$, filtered through Celite (20 mm × 5 cm), and rinsed with TBME (3 × 10 mL). The filtrate was concentrated by rotary evaporation (15 mmHg, 20−25 °C) to afford 498 mg (99%) of **13** as a white solid without further purification. Data for **13**: ^{1}H NMR (500 MHz, $CDCl_3$) 3.89 (d, J = 17.6, 1 H, HC(2)), 3.55 (ddd, J = 7.6, 7.6, 12.2, 1 H, HC(4)), 3.48 (d, J = 17.6, 1 H, HC(2)), 3.16 (ddd, J = 6.5, 1 H, HC(4)), 2.63−2.57 (m, 2 H, HC(7a), HC(5a)), 2.40 (J = 6.0, 7.4, 9.4, 13.6, 1 H, HC(5)), 2.16−2.03 (m, 3 H, HC(7), HC(7)), 1.65 (s, 3 H, H_3C(8)), 1.65−1.58 (m, 2 H, HC(5)), 1.48−1.41 (m, 1 H, HC(6)), 0.8−2.5 (br, 3 H, (H_3B)^3); ^{13}C NMR (126 MHz, $CDCl_3$) 212.1 (C(1)), 86.5 (C(7b)), 70.0 (C(2)), 64.9 (C(4)), 58.4 (C(7a)), 51.8 (C(5a)), 35.1 (C(6)), 32.3 (C(7)), 29.9 (C(5)), 24.4 (C(8)); IR (NaCl plate, thin film) 2964 (s), 2865 (w), 2381 (s), 2333 (s), 2273 (s), 1755 (s), 1468 (m), 1419 (w), 1383 (m), 1195 (s), 1164 (s), 1071 (m), 913 (s), 732 (s); MS (EI, 70 eV) 179 (12), 178 (100), 165 (28), 150 (24), 137 (48), 121 (15), 108 (16), 95 (27); mol formula $C_{10}H_{18}BNO$ (179.07); HRMS $C_{10}H_{17}ONB^+$ (178.1403) calcd 178.1403, found 178.1406; TLC R_f 0.35 (hexanes/EtOAc, 3:2) [I_2, CAM].

*5. Preparation of Scaffold for Library V (via **20** and **21**).*

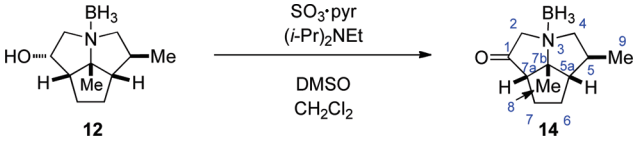


*Preparation of (1S,3S,5S,5aS,7aS,7bR)-Octahydro-1-hydroxy-5-methyl-7b-methyl-2H-cyclopenta[gh]pyrrolizin-2-one ((+)-**5**).* To a 100 mL, three-necked, round-bottomed flask fitted with two rubber septa, a magnetic stir bar, a nitrogen inlet adaptor, and an internal temperature probe were added nitroalkene (*E,E*)-**1** (1.0 g, 5.02 mmol) and chiral propenyl ether **3** (1.63 g, 7.53 mmol, 1.5 equiv) via syringe. The resulting yellow oil was then evacuated under high vacuum (∼0.1 mmHg) for 30 min. The flask was backfilled with N_2 and charged with CH_2Cl_2 (22 mL). The solution was cooled to −85 °C (internal temperature) using hexanes/N_2 bath. This yellow solution was sirred for 15 min, and then freshly prepared $TiCl_2$(O-*i*-Pr)$_2$ solution (1.2 M in CH_2Cl_2, 12.6 mL, 15.1 mmol, 3.0 equiv) was added dropwise via syringe while an internal temperature ≤−70 °C was maintained (ca. 15 min).

After addition of the Lewis acid, the cooling bath was replaced with an acetone/$CO_{2(s)}$ bath, and the resulting bright yellow solution was stirred for another 5 h while an internal temperature ≤ −75 °C was maintained. During the course of the reaction, the yellow color gradually faded and a white precipitate formed. After 5 h, the reaction was quenched with triethylamine (30.6 mL, 6.1 equiv, 1 M in MeOH) via syringe while an internal temperature of <−40 °C was maintained. The cooling bath was then removed, and the reaction mixture was allowed to warm to 0 °C (ca. 15 min). The resulting white suspension was then diluted with ethyl acetate (50 mL) and poured onto a biphasic mixture of satd aq NH_4Cl and ethyl acetate (75 mL) in a 500 mL separatory funnel. The aqueous extract was washed with ethyl acetate (3 × 75 mL). The organic extracts were washed with satd aq NH_4Cl solution (2 × 50 mL), H_2O (2 × 50 mL), and brine (2 × 50 mL). The combined organic extracts were dried over $NaHCO_3/MgSO_4$ (1/1), filtered (cotton plug), and concentrated by rotary evaporation (15 mmHg, 20−25 °C). The resulting residue was filtered through a pad of silica gel (3 × 3 cm), eluting with ethyl acetate (100 mL) to remove any remaining amine impurities. The resulting clear solution was concentrated by rotary evaporation (15 mmHg, 20−25 °C) to a pale-yellow residual oil in a 1 L, one-necked, round-bottomed flask. TBME (100 mL) was added followed by $NaHCO_3$ (5 g, 50.0 mmol, 10.0 equiv). The flask was equipped with a nitrogen inlet adaptor and a magnetic stir bar and then evacuated and backfilled with N_2 (3×). The suspension was stirred at room temperature for 12 h, filtered through Celite (3 × 3 cm, cotton plug), and concentrated by rotary evaporation (15 mmHg, 20−25 °C). The resulting mixture of nitroso acetals was diluted in EtOAc/MeOH (9:1, 25 mL) and added to a test tube (6 cm ×14 cm) containing a spatula tip (~200 mg) of Raney Ni (previously washed with H_2O, MeOH, and EtOAc, 2 × 15 mL each) along with a magnetic stir bar. The tube was placed in a steel autoclave, which was then pressurized with H_2 (350 psi). After 2 days, the autoclave was *carefully* vented in a fume hood and the solution was filtered through a plug of Celite (5 cm ×5 cm, cotton plug) with EtOAc (100 mL). The resulting clear solution was concentrated by rotary evaporation (15 mmHg, 20−25 °C) and purified by silica gel column chromatography (2 cm × 8 cm, hexanes/EtOAc, 9:1, 4:1, 7:3, 2:3, 1:4, 100 mL each) affording 870 mg (89%) of a mixture of epimeric α-hydroxy lactams **5** and **S5** as a white solid (11:1 by ^{1}H NMR analysis). Data for **5**: ^{1}H NMR (500 MHz, $CDCl_3$) 4.63 (dd, *J* = 6.8, 1.5, 1 H, HC(4)), 4.05 (dd, *J* = 11.8, 7.4, 1 H, HC(4)), 2.73 (br, s, 1 H, OH), 2.59−2.46 (m, 2 H), 1.86−1.73 (m, 3 H), 1.67−1.55 (m, 1 H), 1.53−1.40 (m, 2 H), 1.34 (s, 3 H, $H_3C(8)$), 1.07 (d, *J* = 6.7, 3 H, $H_3C(9)$); ^{13}C NMR (126 MHz, $CDCl_3$) 176.0 (C(2)), 75.4 (C(7b)), 72.4 (C(1)), 58.1 (C(5a)), 51.9 (C(7a)), 50.5 (C(4)), 42.1 (C(5)), 30.8 (C(6)), 25.2 (C(7)), 24.8 (C(9)), 17.5 (C(8)); IR (NaCl plate, film) 3338 (br), 2959 (s), 2870 (s), 1685 (s), 1462 (m), 1412 (m), 1334 (m), 1269 (w), 1223 (s), 1142 (m), 1115 (w), 1097 (w), 1044 (w), 964 (w), 880 (w); MS (ESI, Q-tof) 195.1 (67), 180.1 (100), 167.1 (12), 152.1 (56), 138.1 (14), 111 (43), 96.1 (15), 81.1 (24); TLC R_f 0.20 (hexanes/EtOAc, 1:1) [I_2]. Anal. Calcd for $C_{11}H_{17}NO_2$ (195.26): C, 67.66; H, 8.78; N, 7.17. Found: C, 67.41; H, 9.05; N, 7.19.



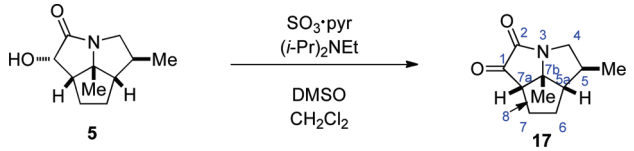
*Preparation of (1R,3R,5R,5aS,7aS,7bR)-Octahydro-1-[N-(3,5-Dinitrophenyl)carbamoxy]-7b-methyl-2H-cyclopenta[gh]pyrrolizin-2-one (**S6**).* A 25 mL round-bottomed flask (A) was fitted with a reflux condenser, a nitrogen inlet adaptor, a rubber rubber septum, and a magnetic stir bar. The apparatus was opened, and 3,5-dinitrobenzoyl azide (25 mg, 0.11 mmol, 1.1 equiv) was added as a solid. The apparatus was evacuated and backfilled with N_2 three times, and toluene (4.8 mL) was added. The clear solution was immersed in a preheated (115 °C) oil bath and stirred at reflux for 30 min. In a separate, two-neck, 5 mL conical flask (B) fitted with a triangular a magnetic stir bar, rubber septum, and a nitrogen inlet adaptor was added the starting alcohol (18.9 mg, 0.096 mmol) followed by toluene (1.0 mL). The resulting solution (B) was transferred to flask A via cannula. The resulting light yellow solution was heated to reflux for 2 h and then allowed to cool to room temperature. The reaction mixture was concentrated in vacuo, and the crude product was purified by column chromatography (hexane/EtOAc (3/1, 1/1)) to afford 38 mg (98%) of enantioenriched **S6** as a white solid. The sample was compared to racemate as previously described.[90] Data for **S6**: ^{1}H NMR (500 MHz, $CDCl_3$) 9.90 (s, 1 H, NH), 8.61 (s, 1 H, HC(14)), 8.56 (s, 2 H, HC(12)), 5.89 (d, *J* = 6.7, 1 H, HC(1)), 4.12 (dd, *J* = 7.4, 11.9, 1 H, HC(4)), 2.71 (dd, *J* = 9.5, 14.1, 1 H), 2.69 (dd, *J* = 10.7, 23.5, 1 H), 1.96 (dd, *J* = 7.0, 7.0, 1 H), 1.93−1.81 (m, 2 H), 1.63−1.50 (m, 3 H), 1.46 (s, 3 H, $H_3C(9)$), 1.14 (d, *J* = 6.7, 3 H, $H_3C(15)$); ^{13}C NMR (126 MHz, $CDCl_3$) 220.6, 171.5, 152.6, 148.8, 141.2, 118.3, 118.2, 112.6, 75.9, 75.0, 58.3, 50.9, 42.7, 31.3, 26.3, 24.3, 17.7; TLC R_f 0.34 (hexanes/EtOAc, 3:1) [I_2]; CSF-HPLC t_R = 7.98 min (1%) and 9.88 (99%) (Chiralpak AD, 125 bar, 40 °C, 15% MeOH in CO_2, 3.0 mL/min, 220 nm).



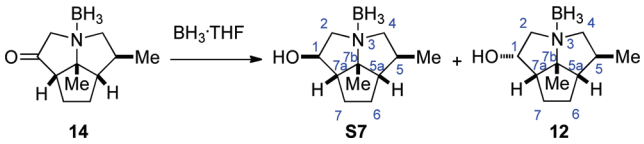
*Preparation of (3R,5aS,7aS,7bR)-Octahydro-5-methyl-7b-methyl-2H-cyclopenta[gh]pyrrolizin-1-one (**14**).* To a 50 mL, three-necked, round-bottomed flask fitted with a nitrogen inlet adapter, a magnetic stir bar, and an internal temperature probe were added **12** (505 mg, 2.59 mmol), CH_2Cl_2 (10.8 mL), and DMSO (2.2 mL). The resulting solution was cooled to −12 °C in an ice/NaCl bath. To this solution was added diisopropylethylamine (2.25 mL, 12.9 mmol, 5.0 equiv) followed by the dropwise addition of a solution of SO_3·pyridine complex (1.24 g, 7.76 mmol, 3 equiv) in DMSO (4.3 mL) while an internal temperature <−5 °C was maintained. After the mixture was stirred for 20 min at −10 °C, the cooling bath was removed and the mixture was allowed to warm to room temperature. This mixture was poured into a 250 mL separatory funnel, and the layers were separated. The aqueous extract was washed with Et_2O (2 × 25 mL). The organic extracts were washed with satd aq $CuSO_4$ solution (2 × 25 mL), satd aq $NaHCO_3$ solution (1 × 25 mL), and brine (25 mL), and the combined organic extracts were dried over $MgSO_4$, filtered through Celite (20 mm × 5 cm, cotton plug), and rinsed with TBME (3 × 10 mL). The filtrate is concentrated in vacuo (15 mmHg, 20−25 °C) to afford 498 mg (99%) of **14** as a white solid. Data for **14**: ^{1}H NMR (500 MHz, $CDCl_3$) 3.98 (d, *J* = 18.1, 1 H, HC(2)), 3.49 (d, *J* = 18.1, 1 H, HC(2)), 3.39 (dd, *J* = 6.4, 12.8, 1 H, HC(4)), 3.23 (dd, *J* = 12.4, 12.4, 1 H, HC(4)), 2.59 (d, *J* = 8.1, 1 H, HC(7a)), 2.28−2.23 (m, 1 H, HC(7)), 2.15−2.07 (m, 2 H, HC(6), HC(5a)), 2.09−1.96 (m, 2 H, HC(7), HC(5)), 1.66 (s, 3 H, $H_3C(8)$), 1.46−1.38 (m, 1 H, HC(6)), 1.10 (d, *J* = 6.5, 3 H, $H_3C(9)$), 0.8−2.5 (br, 3 H, $(H_3B)^3$); ^{13}C NMR (126 MHz, $CDCl_3$) 212.4 (C(1)), 87.3 (C(7b)), 72.0 (C(4)), 70.3 (C(2)), 60.9 (C(5a)), 57.9 (C(7a)), 38.1 (C(5)), 32.54 (C(7 or 6)), 32.45 (C(7 or 6)), 24.8 (C(8)), 17.5 (C(9)); IR (NaCl plate, film) 2965 (s), 2964(s), 2963 (s), 2962 (m), 1757 (s), 1457 (w), 1383 (w), 1215 (s), 1163 (s), 745 (s); MS (EI, 70 eV) 192 (100), 180 (50), 166 (32), 151 (71), 149 (67), 136 (32), 123 (19), 95 (44), 81 (100); mol formula $C_{11}H_{20}BNO$ (193.09); HRMS

$C_{11}H_{19}BNO^+$ (192.1560) calcd 192.1560, found 192.1560; TLC R_f 0.45 (CH_2Cl_2/Et_2O, 19:1) [I_2, CAM].

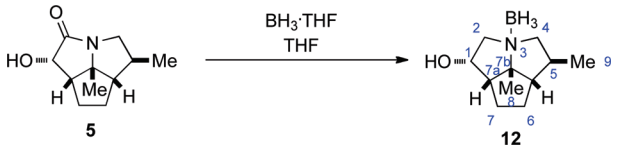
*Preparation of Scaffold for Library V via (α-Keto Lactam **17**).*



*Preparation of (3R,5S,5aS,7aS,7bR)-Octahydro-5-methyl-7b-methyl-2H-cyclopenta[gh]pyrrolizin-1,2-one (**17**).* To a 50 mL, three-necked, round-bottomed flask fitted with a nitrogen inlet adapter, a magnetic stir bar, and an internal temperature probe were added **5** (491 mg, 2.51 mmol), CH_2Cl_2 (10.5 mL), and DMSO (2.1 mL). The resulting solution was cooled to −12 °C in an ice/salt bath. To this solution was added diisopropylethylamine (2.2 mL, 12.6 mmol, 5.0 equiv) followed by the dropwise addition of a solution of SO_3·pyridine complex (1.2 g, 7.54 mmol, 3.0 equiv) in DMSO (5.2 mL) while an internal temperature <−5 °C was maintained. After being stirred for 20 min at −10 °C, the mixture was allowed to warm to room temperature. The mixture was then cooled to 0 °C and diluted with CH_2Cl_2 (25 mL) and H_2O (25 mL). This mixture was poured into a 250 mL separatory funnel, and the layers were separated. The aqueous extract was washed with CH_2Cl_2 (2 × 25 mL). The organic extracts were washed with satd aq $CuSO_4$ solution (2 × 25 mL), satd aq $NaHCO_3$ solution (1 × 25 mL), and brine (25 mL) and the combined organic extracts dried over $MgSO_4$, filtered (cotton plug), and rinsed with TBME (3 × 10 mL). The resulting pale-yellow oil was purified by silica gel column chromatography (10 mm × 10 cm column, gradient elution, hexanes/EtOAc, 3:1, 1:1, 1:3, 1:9, 100 mL each) followed by recrystallization (hexanes/TBME, 1:1, 25 mL) to afford 485 mg (82%) of 17 as white needles and as a single diastereomer. Data for **17**: mp 83−84 °C (MTBE/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) 4.36 (ddd, J = 1.2, 7.7, 12.3, 1 H, HC(4)), 2.98 (dd, J = 7.8, 12.0, 1 H, HC(4)), 2.71 (dd, J = 5.6, 9.0, 1 H, HC(7a)), 2.13−2.04 (m, 1 H, HC(7)), 2.06−1.97 (m, 3 H, HC(6), HC(5a), HC(5)), 1.77−1.70 (m, 1 H, HC(7)), 1.45 (s, 3 H, H_3C(8)), 1.40−1.32 (m, 1 H, HC(6)), 1.20 (d, J = 5.9, 3 H, H_3C(9)), 0.8−2.5 (br, 3 H, $(H_3B)^{92}$) ; ^{13}C NMR (126 MHz, $CDCl_3$) 203.6 (C(1)), 160.4 (C(2)), 74.4 (C(7b)), 57.0 (C(5a)), 55.8 (C(7a)), 51.9 (C(4)), 41.0 (C(5)), 32.8 (C(6)), 30.7 (C(7)), 25.1 (C(8)), 19.8 (C(9)); IR (NaCl plate, film) 3496 (w), 3404 (w), 2961 (s), 2873 (s), 1760 (s), 1713 (s), 1462 (s), 1401 (s), 1332 (w), 1226 (s), 1180 (s), 1084 (m), 678 (w); MS (EI, 70 eV) 193 (26), 165 (26), 150 (32), 122 (6), 107 (11), 93 (5), 81 (100); TLC R_f 0.35 (hexanes/EtOAc, 3:1) [I_2]. Anal. Calcd for $C_{11}H_{15}N$ (193.24): C, 68.37; H, 7.82; N, 7.25. Found: C, 68.57; H, 8.02; N, 7.31.

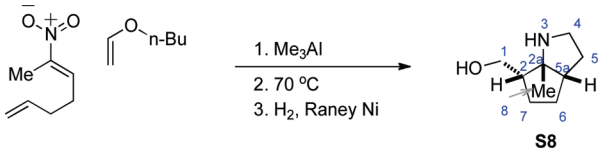


*Preparation of (1R,3R,5S,5aS,7aS,7bR)-Octahydro-1-hydroxy-5-methyl-7b-methyl-2H-cyclopenta[gh]pyrrolizine·Borane (**12**) and (1S,3R,5S,5aS,7aS,7bR)-Octahydro-1-hydroxy-5-methyl-7b-methyl-2H-cyclopenta[gh]pyrrolizine·Borane (**S7**).* To a 25 mL, two-necked, round-bottomed flask equipped with a nitrogen adapter, a rubber septum, and a magnetic stir bar were added sequentially **14** (63 mg, 0.326 mmol), THF (1.6 mL, 0.2 M), and BH_3·HF complex (1.6 mL, 1.0 M solution, 5.0 equiv) dropwise over 5 min during which time gas evolution was observed. After the mixture was stirred for 2 h at room temperature, the reaction was quenched with methanol (5 mL), and the resulting solution was concentrated by rotary evaporation (15 mmHg, 20−25 °C) to afford crude **S7** as a mixture of diastereomers (5/9, ^{1}H NMR). The crude mixture was purified by silica gel column chromatography (1.8 cm × 8 cm column, gradient elution, CH_2Cl_2/ether, 99:1, 49:1, 24:1, 47:3, 9:1, 25 mL each) to afford 22 mg (35%) of **S7** as a white solid. Data for **S7**: ^{1}H NMR (500 MHz, $CDCl_3$) 3.88 (dd, J = 4.4, 10.6, 1 H, HC(1)), 3.74 (d, J = 10.8, 1 H, OH)), 3.56 (d, J = 12.7, 1 H, HC(2)), 3.37 (dd, J = 4.4, 12.7, 1 H, HC(2)), 3.24 (dd, J = 5.2, 12.7, 1 H, HC(4)), 2.85 (dd, J = 12.2, 12.2, 1 H, HC(4)), 2.39 (dd, J = 9.1, 9.1, 1 H, HC(7a)), 2.11−2.04 (m, 1 H, HC(7)), 1.91−1.84 (m, 2 H, HC(5a), HC(5)), 1.77−1.68 (m, 1 H, HC(6)), 1.66−1.63 (m, 1 H, HC(6)), 1.60 (s, 3 H, H_3C(8)), 1.41−1.32 (m, 1 H, HC(7)), 1.01 (d, J = 5.8, 3 H, H_3C(9)), 0.8−2.5 (br, 3 H, $(H_3B)^{92}$); ^{13}C NMR (126 MHz, $CDCl_3$) 88.5 (C(7b)), 76.0 (C(1)), 71.1 (C(4)), 69.2 (C(2)), 62.1 (C(5a)), 61.4 (C(7a)), 34.8 (C(5)), 31.2 (C(7)), 29.6 (C(6)), 26.0 (C(8)), 16.5 (C(9)); IR ($CDCl_3$) 3492 (s), 2964 (s), 2922 (s), 2869 (s), 2369 (s), 2318 (s), 2270 (s), 1454 (s), 1412 (m), 1381 (m), 1348 (m), 1250 (m), 1186 (s), 1160 (m) 1121 (m), 1048 (s), 1023 (m), 996 (m), 973 (m), 925 (m), 869 (m), 844 (w), 818 (w), 802 (w); MS (EI, 70 eV) 194.2 (78), 181 (24), 166 (100), 150 (3), 138 (12), 124 (10), 110 (44), 96 (11), 84 (14); mol formula $C_{11}H_{22}BNO$ (195.11); HRMS $C_{11}H_{21}BNO$ (194.1716) calcd 194.1716, found 194.1720; TLC R_f 0.61 (CH_2Cl_2/ether, 9:1) [I_2].



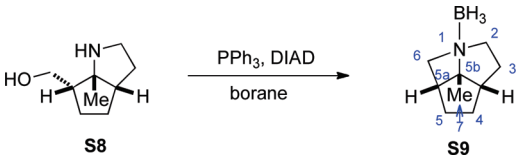
*Preparation of (1S,3S,5S,5aS,7aS,7bR)-Octahydro-1-hydroxy-5-methyl-7b-methyl-2H-cyclopenta[gh]pyrrolizine·Borane (**12**).* To a 250 mL round-bottomed flask equipped with a nitrogen inlet adapter, a rubber septum, and a magnetic stir bar were added sequentially **5** (931 mg, 4.77 mmol), THF (23.9 mL, 0.2 M), and BH_3·THF complex (23.9 mL, 1.0 M solution, 10.0 equiv) dropwise over 5 min during which time gas evolution was observed. After the mixture was stirred for 4 h at room temperature, the reaction was quenched with methanol (40 mL), and the resulting mixture was concentrated by rotary evaporation (15 mmHg, 20−25 °C). The resulting colorless oil was purified by silica gel column chromatography (2 cm × 15 cm column, gradient elution, CH_2Cl_2/ether, 99:1, 49:1, 24:1, 47:3, 9:1, 100 mL each) to afford 875 mg (94%) of **12** as a white solid. Data for **12**: mp 86.5−87.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) 4.81 (ddd, J = 7.2, 7.2, 10.5, 1 H, HC(1)), 3.46 (dd, J = 6.6, 10.3, 1 H, HC(2)), 3.17 (dd, J = 6.2, 12.5, 1 H, HC(4)), 3.02 (dd, J = 10.5, 10.5, 1 H, HC(2)), 2.82 (dd, J = 12.5, 12.5, 1 H, HC(4)), 2.34 (dd, J = 8.2, 17.0, 1 H, HC(7a)), 2.11−2.01 (m, 1 H, HC(5)), 1.94−1.85 (m, 2 H, HC(7), HC(5a)), 1.81−1.76 (m, 1 H, HC(6)), 1.76−1.67 (m, 2 H, HC(7), HC(6)), 1.56 (br, s, 1 H, OH), 1.50 (s, 3 H, H_3C(8)), 1.03 (d, J = 6.4, 3 H, H_3C(9)), 0.8−2.5 (br, 3 H, $(H_3B)^{92}$); ^{13}C NMR (126 MHz, $CDCl_3$) 88.1 (C(7b)), 70.0 (C(4)), 68.8 (C(1)), 65.7 (C(2)), 62.0 (C(5a)), 55.1 (C(7a)), 34.6 (C(5)), 29.7 (C(7)), 26.4 (C(6)), 25.7 (C(8)), 16.4 (C(9)); IR ($CHCl_3$ film) 3447 (br), 2962 (s), 2963 (s), 2964 (s), 2965 (m), 2378 (s), 2377 (s), 2375 (s), 1474 (m), 1457 (m), 1381 (w), 1214(s), 1166 (s), 1118 (m), 1088 (m), 141 (w), 1010 (w), 995 (w), 946 (w), 755 (s); MS (EI, 70 eV) 194 ([M^+-1],8), 181 (16), 166 (100), 110 (60), 96 (12), 82 (8); TLC R_f 0.36 (CH_2Cl_2/ether, 9:1) [I_2]; $[\alpha]^{24}_D$ −11.14 (c = 1.0, $CHCl_3$). Anal. Calcd for $C_{11}H_{22}BNO$ (195.1095): C, 67.71; H, 11.37; N, 7.18. Found: C, 67.8; H, 11.31; N, 7.06.

*6. Preparation of Scaffold for Library **VI**.*



*Preparation of rel-(2S,2aR,5aS)-6-[6a-Methylperhydrocyclopenta[b]pyrrole]methanol (**S8**).* To a 500 mL, three-necked, round-bottomed flask fitted with a nitrogen inlet adaptor, a magnetic stir bar, a rubber septum, and an internal temperature probe were added *n*-butyl vinyl ether (1.4 mL, 10.5 mmol, 2.5 equiv), CH_2Cl_2 (100 mL), and trimethylaluminum (10.5 mL, 10.5 mmol, 2.5 equiv, 1.0 M). The resulting clear solution was allowed to stir for 10 min as the vessel was cooled to −77 °C by submersion in an *i*-PrOH/$CO_{2(s)}$ bath. Nitroalkene (590 mg, 4.2 mmol) was dissolved in CH_2Cl_2 (100 mL) and was transferred to the trimethylaluminum solution by cannulation while an internal temperature <−70 °C was maintained (ca. 45 min). The resulting orange solution was allowed to stir for an additional 3 h during which time the color gradually faded. The mixture was quenched by the slow, cautious addition of silica gel via a long stem addition funnel until no bubbling was observed (∼2 g). The mixture filtered through more silica gel (∼1 g, prewetted with EtOAc) and rinsed with ethyl acetate (80 mL). The resulting clear filtrate was dried ($MgSO_4$), filtered, and concentrated by rotary evaporation (15 mmHg, 20−25 °C) to yield 3.8 g (98%) of the intermediate nitronates as as a clear oil.

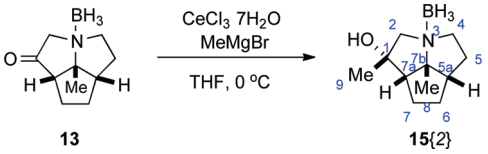
The clear oil was transferred to a 250 mL, single-necked, round-bottomed flask with benzene (150 mL). The flask was fitted with a reflux condenser, a nitrogen inlet adaptor, and a magnetic stir bar and immersed in a preheated (85 °C) oil bath. After 12 h, the starting material was consumed (TLC), and the light-yellow solution was allowed to cool to room temperature. The solvent was removed by rotary evaporation (15 mmHg, 20−25 °C) to give the intermediate nitrosoacetals as a viscous, light-yellow oil. The crude nitroso acetals were dissolved in methanol in methanol (20 mL) and transferred to a test tube (3 × 14 cm) containing Raney nickel (∼50 mg, previously washed with H_2O, MeOH, and EtOAc, 2 × 10 mL each) and a magnetic stir bar. The test tube was placed in a steel autoclave which was then pressured with H_2 (300 psi) and placed on a stir plate. The reaction was stirred under H_2 for 28 h and was then filtered through a pad of Celite, washing with 150 mL of methanol. The filtrate was concentrated by rotary evaporation (15 mmHg, 20−25 °C) and purified by silica gel column chromatography (2 cm ×5 cm, gradient elution: CH_2Cl_2/MeOH/NH_4OH, 20:1:0.01, 10:2:.01, 150 mL each) to afford 456 mg (70%, three steps) of amino alcohol **S8** as a white solid. Data for **S8**: mp 154−160 °C; ^{1}H NMR (500 MHz, $CDCl_3$) 3.95 (dd, *J* = 11.3, 2.0, 1.0, 1 H, HC(1)), 3.67 (dd, *J* = 11.5, 3.9, 1 H, HC(4)), 2.96 (p, *J* = 5.60, 1 H, HC(4)), 2.84−2.79 (m, 1 H, HC(4)), 2.21 (tt, 1 H), 1.96−1.80 (m, 2 H, HC(5), HC(6)), 1.79−1.71 (m, 1 H, HC(5)), 1.62−1.51 3 H, HC(6), H_2C(7)) 1.45−1.40 (m, 1 H, HC(5a)), 1.29, (s, 3 H, H_3C(8)); ^{13}C NMR (126 MHz, $CDCl_3$) 72.4 (C(2a)), 62.1 (C(1)), 50.7 (C(5a)), 50.4(C(2)), 47.8 (C(4)), 34.8 (C(5)), 30.7 (C(6)), 27.9 (C(7)), 27.6 (C(8)); IR (NaCl plate) 329 (s, br), 2949 (s), 2858 (s), 1692 (m), 1682 (m), 1633.6 (m), 1455 (m); MS (EI, 70 eV) 155 (8), 97 (10), 96(100), 83 (19), 82(32), 42 (9), 36 (20); GC (method 1) t_R 5.96 min; TLC R_f 0.26 (CH_2Cl_2/CH_3OH,/NH_4OH, 20:3:0.1) [I_2, $KMnO_4$].



*Preparation of rel-(1S,3aS,5aR,5bR)-1-Boranyl-5b-methylcyclopenta[ef]azoniabicyclo[3.2.0]heptane (**S9**).* To a 100 mL, three-necked, round-bottomed flask fitted with a nitrogen inlet adaptor, two rubber septa, an internal temperature probe, and a magnetic stir bar was added amino alcohol **S8** (420 mg, 2.71 mmol) as a solution in THF (25 mL). To this solution was added triphenylphosphine (0.711 g, 2.71 mmol, 1.0 equiv). The resulting slightly cloudy solution was allowed room temperature until all of the phosphine was dissolved (15 min) and was then brought to −1 °C by use of a salt/ice bath. Diisopropyl azodicarboxylate (DIAD, 0.53 mL, 2.71 mmol, 1.0 equiv) was then added dropwise over 5 min while an internal temperature of ≤3 °C was maintained. During the addition of the first three-fifths of DIAD, the orange color quickly dissipated but persisted during the addition of the last two-fifths. The reaction was allowed to stir for an additional 25 min during which time it gradually turned from orange to a very light-yellow. At this point, the reaction was judged to be complete (TLC) and was quenched by the addition of BH_3·THF solution (1.0 M THF, 13.6 mL, 13.6 mmol) over 10 min while an internal temperature of ≤5 °C was maintained. The reaction was allowed to stir for an additional 30 min, and the remaining borane was quenched by *carefully* pouring the mixture into a 250 mL separatory funnel containing H_2O (50 mL), which bubbled vigorously. The milky white mixture was extracted with dichloromethane (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered (cotton plug), and concentrated by rotary evaporation (15 mmHg, 20−25 °C). Purification of **S9** by silica gel chromatography (3 cm ×16 cm, gradient elution, hexanes/EtOAc, 93:7, 90:10, 85:15) afforded 329 mg of **S9** as a white solid which was then sublimed (70 °C, cold water, 0.2 mmHg) to afford 324.0 mg (79%) of analytically pure **S9** as a white, waxy solid. Data for **S9**: mp 154−156 °C; ^{1}H NMR (500 MHz, $CDCl_3$) 3.90 (t, *J* = 10.25, 1 H, HC(1)), 3.19−3.14 (m, 1 H, HC(7)), 3.06−3.02 (m, 1 H, HC(7)), 2.93 (dd, *J* = 6.1, 1 H, HC(1)), 2.50−2.46 (m, 2 H, HC(2), HC(5)), 2.10−1.60 (m, 9 H, HC(1)), 1.50 (s, 3 H, HC(9)), 0.8−2.5 (br, 3 H, $(H_3B)^3$); ^{13}C NMR (126 MHz, $CDCl_3$) 87.0 (C(8)), 64.3 (C(1)), 63.9 (C(7)), 51.7 (C(2)), 36.9 (C(5)), 31.3 (C(3)), 31.1 (C(6)), 29.4 (C(4)), 19.9 (C(9)); IR (KBr plate) 2962 (s), 2968 (s), 2358 (s), 2260 (s), 1772 (w), 1734 (w), 1716 (w), 1699 (w), 1683 (w), 1652 (w), 1635 (w), 1558 (m), 1521 (m), 1540 (m), 1474 (m), 1456 (s), 1376 (s), 1167 (s); MS (EI, 70 ev) 137 (2), 149 (22), 150 (100), 151 (53), 152 (5); TLC R_f 0.31 (hexane/EtOAc, 4:1) [CAM]. Anal. Calcd for $C_9H_{18}BN$ (151.06): C, 71.56; H, 12.08; N, 9.27. Found: C, 71.37; H, 12.08; N, 9.22.

II. Parallel Syntheses: Library Intermediates and Quaternary Ammonium Bromides. *A. Variable Group R^2: Organometal Ketone Additions*

*1. Cerium-Mediated Additions to Keto Amine **13**.*



*Preparation of (1S,3S,5aS,7aS,7bR)-Octahydro-1-hydroxy-1-methyl-7b-methyl-2Hcyclopenta[gh]pyrrolizine·Borane (**15**{2}).* To a 25 mL, two-necked, round-bottomed flask equipped with a nitrogen inlet adapter, a rubber septum, and a magnetic stir bar was added $CeCl_3$·7 H_2O (559 mg, 1.50 mmol, 1.5 equiv). The flask was immersed in a preheated oil bath (140 °C) under vacuum (<0.1 mmHg) for 2 h. The flask was backfilled with nitrogen, allowed to cool to room temperature, and then immersed in an ice bath. To the solid was added THF (4.0 mL) via syringe, and the resulting milky, heterogeneous mixture was allowed to stir vigorously at room temperature for 2 h. The mixture was then sonicated and stirred intermittently for 15 min intervals over a 2 h time period. The flask was then immersed in an ice bath, and methylmagnesium bromide (2.7 M, 556 μL, 1.5 mmol, 1.5 equiv) was added via syringe. The ice bath was removed, and the solution

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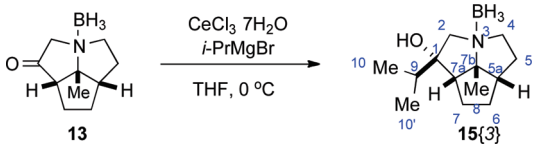
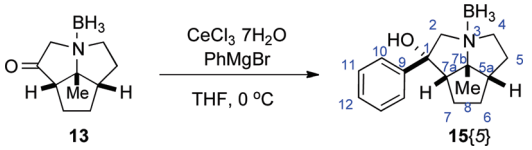
was stirred at room temperature for 1.5 h. The flask was immersed in an ice bath, and ketone **13** (179 mg, 1.0 mmol) was added as a solution in THF (1.0 mL) via syringe. After the mxiture was stirred for 30 min while immersed in an ice bath, the reaction was quenched with satd aq NH_4Cl solution (5.0 mL). The biphasic mixture was poured into a 125 mL separatory funnel containing satd aq NH_4Cl solution (20 mL) and Et_2O (20 mL). The layers were separated, and the aqueous extract was washed with Et_2O (2 × 25 mL). The organic extracts were washed with satd aq $NaHCO_3$ (1 × 25 mL) and brine (1 × 25 mL), and the combined organic extracts were dried over $MgSO_4$, filtered (cotton plug), and concentrated by rotary evaporation (15 mmHg, 20−25 °C). The resulting pale-yellow oil was purified by silica gel column chromatography (2 cm × 8 cm, gradient elution, CH_2Cl_2/EtOAc, 1:0, 99:1, 49:1, 19:1, 50 mL each) to afford **15**{2} (134 mg, 68%) as a white solid. Data for **15**{2}: ^{1}H NMR (500 MHz, $CDCl_3$) 3.88 (ddd, J = 6.3, 10.6, 10.3, 1 H, HC(4)), 3.37 (d, J = 13.4, 1 H, HC(2)), 3.33 (d, J = 13.6, 1 H, HC(2)), 3.31−3.27 (m, 1 H, HC(4)), 2.35−2.34 (m, 1 H, HC(5a)), HC(5)), 2.16−2.13 (m, 1 H, HC(7a)), 1.96−1.89 (m, 2 H, HC(7), HC(6)), 1.80−1.68 (m, 2 H, HC(7), HC(6)), 1.54−1.49 (m, 1 H, HC(5)), 1.50 (s, 3 H, H_3C(8), 1.41 (s, 3 H, H_3C(9)), 0.8−2.5 (br, 3 H, $(H_3B)^{93}$); ^{13}C NMR (126 MHz, $CDCl_3$) 89.2 (C(7b)), 78.1 (C(1)), 74.7 (C(2)), 63.7 (C(7a)), 63.6 (C(4)), 52.2 (C(5a)), 34.6 (C(6)), 30.5 (C(8 or 9)), 29.6 (C(5)), 27.3 (C(7)), 25.8 (C(8 or 9)); IR (thin film) 3503 (s), 2383 (s), 2329 (s), 2277 (s), 1301 (m), 1258 (m), 1178 (m), 1124 (w), 1070 (m), 1018 (w), 953 (w), 850 (w); MS (EI, 70 eV) 194.2 (93), 181 (34), 166 (50), 138 (6), 110 (57), 96 (100), 81 (18); mol formula $C_{11}H_{22}BNO$ (195.18); HRMS $C_{11}H_{21}BNO^+$ (194.1716) calcd 194.1716, found 194.1714; TLC R_f 0.25 (CH_2Cl_2/EtOAc, 19:1) [I_2, CAM].

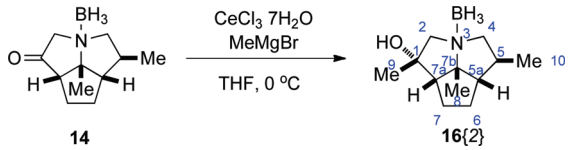


*Preparation of (1S,3S,5aS,7aS,7bR)-Octahydro-1-hydroxy-1-isopropyl-7b-methyl-2H-cyclopenta[gh]pyrrolizine·Borane (**15**{3}).* To a 25 mL, two-necked, round-bottomed flask equipped with a nitrogen inlet adapter, a rubber septum, and a magnetic stir bar was added $CeCl_3 \cdot 7H_2O$ (559 mg, 1.50 mmol, 1.5 equiv). The flask was immersed in a preheated oil bath (140 °C) and stirred under vacuum (<0.1 mmHg) for 2 h. The flask was backfilled with nitrogen, allowed to cool to room temperature, and then immersed in an ice bath. To the solid was added THF (4.0 mL), and the resulting milky, heterogeneous mixture was allowed to stir vigorously at room temperature for 2 h. The mixture was then sonicated and stirred intermittently for 15 min intervals over a 2 h time period. The flask was then immersed in an ice bath, and isopropylmagnesium chloride (1.9 M, 811 μL, 1.5 mmol, 1.5 equiv) was added via syringe. The ice bath was removed, and the solution was stirred at room temperature for 1.5 h. The flask was immersed in an ice bath, and ketone **13** (179 mg, 1.0 mmol) was added as a solution in THF (1.0 mL) via syringe. After the mixture was stirred for 30 min while immersed in an ice bath, the reaction was quenched with satd aq NH_4Cl solution (5.0 mL). The biphasic mixture was poured into a 125 mL separatory funnel containing satd aq NH_4Cl solution (20 mL) and Et_2O (20 mL). The layers were separated, and the aqueous extract was washed with Et_2O (2 × 25 mL). The organic extracts were washed with satd aq $NaHCO_3$ (1 × 25 mL) and brine (1 × 25 mL), and the combined organic extracts were dried over $MgSO_4$, filtered (cotton plug), and concentrated by rotary evaporation (15 mmHg, 20−25 °C). The resulting pale-yellow oil was purified by silica gel column chromatography (1.8 cm × 8 cm, gradient elution, CH_2Cl_2/EtOAc, 1:0, 99:1, 49:1, 19:1, 50 mL each) to afford **15**{3} (89 mg, 40%) as a white solid. Data for **15**{3}: ^{1}H NMR (500 MHz, $CDCl_3$) 3.98 (ddd, J = 6.6, 11.1, 11.5, 1 H, HC(4)), 3.39 (d, J = 13.8, 1 H, HC(2)), 3.35 (d, J = 9.0, 1 H, HC(2)), 3.34−3.31 (m, 1 H, HC(4)), 2.46−2.43 (m, 2 H, HC(5a), HC(5)), 2.20−2.17 (m, 1 H, HC(7a)), 2.00−1.90 (m, 2 H, HC(7), HC(6)), 1.80 (m, 1 H, HC(6)), 1.74−1.67 (m, 1 H, HC(7)), 1.67−1.60 (m, 1 H, HC(9)), 1.53−1.49 (m, 1 H, HC(5)), 1.48 (s, 3 H, H_3C(8)), 1.40 (br, s, 1 H, OH), 0.91 (d, J = 2.4, 3 H, H_3C(10), 0.90 (d, J = 2.5, 3 H, H_3C(10′)), 0.8−2.5 (br, 3 H, $(H_3B)^3$); ^{13}C NMR (126 MHz, $CDCl_3$) 89.0 (C(7b), 82.4 (C(1)), 74.2 (C(2)), 63.2 (C(4)), 62.5 (C(7a)), 51.4 (C(5a)), 39.7 (C(9)), 35.5 (C(6)), 30.0 (C(5)), 27.9 (C(7)), 25.5 (C(8)), 16.9 (C(10)), 16.7 (C(10)); IR (thin film) 3433 (s), 2411 (m), 2319 (s), 2270 (s), 1309 (w), 1280 (S), 1162 (m), 1070 (w), 988 (m), 975 (w), 849 (w), 703 (w); MS (ESI, Q-tof) 222 (89), 209 (50), 194 (34), 178 (18), 166 (16), 124 (21), 110 (65), 96 (100), 81 (20); $C_{13}H_{26}BNO$ (223.16); HRMS $C_{13}H_{25}BNO$ (222.2029) calcd 222.2029, found 222.2030; TLC R_f 0.40 (hexanes/EtOAc, 4:1) [I_2, CAM].



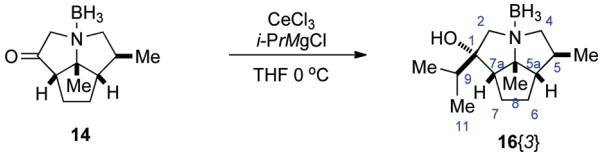
*Preparation of (1S,3S,5aS,7aS,7bR)-Octahydro-1-hydroxy-1-phenyl-7b-methyl-2H-cyclopenta[gh]pyrrolizine·Borane (**15**{5}).* To a 25 mL, two-necked, round-bottomed flask equipped with a nitrogen inlet adapter, a rubber septum, and a magnetic stir bar was added $CeCl_3 \cdot 7H_2O$ (559 mg, 1.50 mmol, 1.5 equiv). The flask was immersed in a preheated oil bath (140 °C) and stirred under vacuum (<0.1 mmHg) for 2 h. The flask was backfilled with N_2, allowed to cool to room temperature, and then immersed in an ice bath. To the solid was added THF (4.0 mL), and the resulting milky, heterogeneous mixture was allowed to stir vigorously at room temperature for 2 h. The mixture was then sonicated and stirred intermittently for 15-min intervals over a 2 h time period. The flask was then immersed in an ice bath, and phenylmagnesium bromide (3.0 M, 500 μL, 1.5 mmol, 1.5 equiv) was added. The ice bath was removed, and the solution was stirred at room temperature for 1.5 h. The flask was immersed in an ice bath, and ketone **13** (179 mg, 1.0 mmol) was added as a solution in THF (1.0 mL) via syringe. After the mixture was stirred for 30 min while immersed in an ice bath, the reaction was quenched with satd aq NH_4Cl solution (5.0 mL). The biphasic mixture was poured into a 125 mL separatory funnel containing satd aq NH_4Cl solution (20 mL) and Et_2O (20 mL). The layers were separated, and the aqueous extract was washed with Et_2O (2 × 25 mL). The organic extracts were washed with satd aq $NaHCO_3$ (1 × 25 mL) and brine (1 × 25 mL), and the combined organic extracts were dried over $MgSO_4$, filtered (cotton plug), and concentrated by rotary evaporation (15 mmHg, 20−25 °C). The resulting pale-yellow oil was purified by silica gel column chromatography (1.8 cm ×8 cm, gradient elution, CH_2Cl_2/EtOAc, 1:0, 99:1, 49:1, 19:1, 50 mL each) to afford **15**{5} (131 mg, 51%) as a white solid. Data for **15**{5}: ^{1}H NMR (500 MHz, $CDCl_3$) 7.42−7.36 (m, 4 H, HC(10), HC(11)), 7.33−7.28 (m, 1 H, HC(12)), 4.28−4.20 (m, 1 H, HC(4)), 3.81 (d, J = 13.9, 1 H, HC(2)), 3.68 (d, J = 13.9, 1 H, HC(2)), 3.45−3.40 (m, 1 H, HC(4)), 2.75 (dd, J = 3.0, 8.3, 1 H, HC(7a)), 2.45−2.36 (m, 2 H, HC(5a), HC(5)), 2.12−2.02 (m, 2 H, HC(7), HC(6)), 1.94−1.78 (m, 3 H, HC(7), HC(6), OH), 1.63−1.58 (m, 1 H, HC(5)), 1.58 (s, 3 H, H_3C(8)), 0.8−2.5 (br, 3 H, $(H_3B)^{92}$); ^{13}C NMR (126 MHz, $CDCl_3$) 145.1 (C(9)), 129.0 (C(10 or 11)), 128.0 (C(10 or 11)), 124.9 (C(12)), 89.2 (C(7b)), 82.1 (C(1)), 74.9 (C(2)), 64.3 (C(7a)), 63.3 (C(4)), 52.2 (C(5a)), 35.2 (C(6)), 29.7 (C(5)), 27.3 (C(7)), 25.9 (C(8)); IR (thin film) 3433 (s), 2411 (m), 2319 (s), 2270 (s), 1309 (w), 1280 (S), 1162 (m), 1070 (w), 988 (m), 975 (w), 849 (w), 703 (w); MS (EI, 70 eV) 254.2 (62), 243.2 ([M^+], 66), 228 (20), 210 (10), 178 (8),

158 (48), 149 (15), 138 (11), 123 (46), 110 (100); mol formula $C_{16}H_{24}BNO$; 257.18; HRMS $C_{16}H_{21}NO$ (243.1623) calcd 243.16232, found 243.16251; TLC R_f 0.20 (CH_2Cl_2/EtOAc, 19:1) [I_2, CAM].

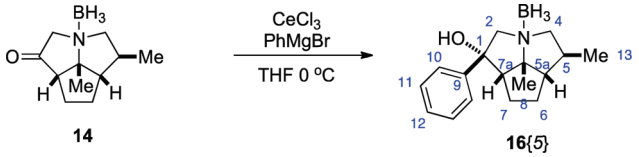


Cerium-Mediated Additions to Keto Amine ***14***

Cerium-Mediated Additions to ***14****. Preparation of (1S,3S,5S,-5aS,7aS,7bR)-Octahydro-1-hydroxy-1-methyl-5-methyl-7b-methyl-2H-cyclopenta[gh]pyrrolizine·Borane (****16****{2}).* To a 100 mL, two-necked, round-bottomed flask equipped with a nitrogen inlet adapter, a rubber septum, and a magnetic stir bar was added $CeCl_3 \cdot 7H_2O$ (2.30 g, 8.70 mmol, 1.5 equiv). The flask was immersed in a preheated oil bath (140 °C) and stirred under vacuum (~0.1 mmHg). After 2 h, the flask was backfilled with nitrogen, allowed to cool to room temperature, and then immersed in an ice bath. To the solid was added THF (25 mL), and the resulting milky, heterogeneous mixture was allowed to stir vigorously at room temperature for 2 h. The mixture was then sonicated and stirred intermittently for 15 min intervals over a 2 h time period. The flask was then immersed in an ice bath, and methylmagnesium bromide (3.0 M, 3.0 mL, 1.50 mmol, 1.5 equiv) was added . The ice bath was removed, and the solution was stirred at room temperature for 1.5 h. The flask was immersed in an ice bath, and ketone **14** (1.12 g, 5.80 mmol) was added as a solution in THF (4.0 mL). After the mixture was stirred for 30 min while immersed in an ice bath, the reaction was quenched with satd aq NH_4Cl solution (20 mL). The biphasic mixture was poured into a 250 mL separatory funnel containing satd aq NH_4Cl solution (30 mL) and Et_2O (40 mL). The layers were separated, and the aqueous extract was washed with Et_2O (2 × 50 mL). The organic extracts were washed with satd aq $NaHCO_3$ (1 × 50 mL) and brine (1 × 50 mL), and the combined organic extracts were dried over $MgSO_4$, filtered (cotton plug), and concentrated by rotary evaporation (15 mmHg, 20−25 °C). The resulting pale-yellow oil was purified by silica gel column chromatography (2 cm ×12 cm, gradient elution, CH_2Cl_2/ether, 1:0, 99:1, 49:1, 24:1, 9:1, 4:1, 100 mL each) to afford **16**{2} (1.1 g, 87%) as a white solid. Data for **16**{2}: mp 84−85 °C (MTBE/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) 3.43 (d, J = 12.0, 1 H, HC(2)), 3.28 (dd, J = 6.8, 12.6, 1 H, HC(4)), 3.25 (d, J = 12.3, 1 H, HC(2)), 2.97 (dd, J = 12.2, 12.2, 1 H, HC(4)), 2.13 (et, J = 4.8, 8.1, 9.6, 12.7, 1 H, HC(5)), 2.06 (ddd, J = 8.2, 8.2, 7.8, 1 H, HC(7a)), 2.02−1.96 (m, 1 H, HC(7)), 1.85 (dd, J = 7.0, 7.0, 1 H, HC(5a)), 1.83−1.70 (m, 3 H, HC(7), HC(6), HC(6)), 1.61 (s, 3 H,H_3C(9)), 1.52 (s, 3 H, H_3C(8)), 1.38 (d, J = 4.7, 1 H, OH), 0.99 (d, J = 6.5, 3 H, H3C(10)), 0.8−2.5 (br, 3 H, $(H_3B)^{92}$); ^{13}C NMR (126 MHz, $CDCl_3$) 88.9 (C(7b)), 75.5 (C(1)), 74.9 (C(2)), 73.4 (C(4)), 61.9 (C(7a)), 61.8 (C(5a)), 34.0 (C(5)), 31.0 (C(9)), 29.7 (C(6)), 27.1 (C(7)), 26.0 (C(8)), 16.5 (C(10)); IR ($CHCl_3$) 3969 (br), 2962 (s), 2870 (s), 2380 (s), 2331 (s), 2276 (s), 1459 (s), 1381 (s), 1340 (m), 1180 (s), 1134 (s), 1064 (s), 1049 (w), 1019 (w), 960 (s), 871 (w), 826 (m); MS (EI, 70 eV) 208 (4), 195 (16), 180 (48), 124 (28), 110 (100), 96 (16), 81 (8); mol formula $C_{12}H_{24}BNO$ (209.14); HRMS $C_{12}H_{23}BNO$ (208.1873) calcd 208.1873, found 208.1875; TLC R_f 0.33 (CH_2Cl_2/Et_2O, 19:1) [I_2, CAM].



*Preparation of (1S,3S,5S,5aS,7aS,7bR)-Octahydro-1-hydroxy-1-isopropyl-5-methyl-7b-methyl-2H-cyclopenta[gh]pyrrolizine·Borane (****16****{3}).* To a 100 mL, two-necked, round-bottomed flask equipped with a nitrogen inlet adapter, a rubber septum, and a magnetic stir bar was added $CeCl_3 \cdot 7H_2O$ (2.90 g, 7.77 mmol, 1.5 equiv). The flask was immersed in a preheated oil bath (140 °C) and stirred under vacuum (~0.1 mmHg). After 2 h, the flask was backfilled with nitrogen, allowed to cool to room temperature, and then immersed in an ice bath. To the solid was added THF (22 mL), and the resulting milky, heterogeneous mixture was allowed to stir vigorously at room temperature for 2 h. The mixture was then sonicated and stirred intermittently for 15 min intervals over a 2 h time period. The flask was then immersed in an ice bath, and isopropylmagnesium chloride (1.8 M, 4.3 mL, 1.50 mmol, 1.5 equiv) was added via syringe. The ice bath was removed, and the solution was stirred at room temperature for 1.5 h. The flask was immersed in an ice bath, and ketone 14 (1.0 g, 5.18 mmol) was added as a solution in THF (4.0 mL). After the mixture was stirred for 30 min while immersed in an ice bath, the reaction was quenched with satd aq NH_4Cl solution (20 mL). The biphasic mixture was poured into a 250 mL separatory funnel containing satd aq NH_4Cl solution (30 mL) and Et_2O (40 mL). The layers were separated, and the aqueous extract was washed with Et_2O (2 × 50 mL). The organic extracts were washed with satd aq $NaHCO_3$ (1 × 50 mL) and brine (1 × 50 mL), and the combined organic extracts were dried over $MgSO_4$, filtered (cotton plug), and concentrated by rotary evaporation (15 mmHg, 20−25 °C). The resulting pale-yellow oil was purified by silica gel column chromatography (2 cm × 10 cm, gradient elution, CH_2Cl_2/ether, 1:0, 99:1, 49:1, 24:1, 47:3, 9:1, 17:3, 100 mL each) to afford **16**{3} (931 mg, 79%) as a pale yellow oil. Data for **16**{3}: ^{1}H NMR (500 MHz, $CDCl_3$) 3.60 (d, J = 13.5, 1 H, HC(2)), 3.51 (dd, J = 7.9, 12.2, 1 H, HC(4)), 3.31 (d, J = 13.5, 1 H, HC(2)), 3.16 (dd, J = 10.7, 12.1, 1 H, HC(4)), 2.42−2.32 (m, 1 H, HC(5)), 2.18 (dd, J = 7.0, 9.1, 1 H, HC(7a)), 2.09−1.98 (m, 1 H, HC(7)), 1.89−1.83 (m, 3 H, HC(6), HC(6), HC(5a)), 1.82−1.69 (m, 2 H, HC(7), HC(9)), 1.49 (s, 3 H, H_3C(8)), 1.37 (br, s, 1 H, OH), 0.99 (d, J = 6.6, 3 H, H_3C(12)), 0.91 (d, J = 6.8, 3 H, H_3C(10)), 0.87 (d, J = 6.9, 3 H, H_3C(11)), 0.8−2.5 (br, 3 H, $(H_3B)^{92}$); ^{13}C NMR (126 MHz, $CDCl_3$) 89.4 (C(7b)), 80.2 (C(1)), 77.1 (C(2)), 74.1 (C(4)), 60.9 (C(7a)), 60.0 (C(5a)), 38.3 (C(9)), 34.5 (C(5)), 31.3 (C(6)), 25.4 (C(7)), 25.3 (C(8)), 17.6 (C(12)), 17.0 (C(10)), 16.8 (C(11)); IR ($CHCl_3$) 3507 (br), 2964 (s), 2866 (m), 2380 (s), 2326 (s), 2268 (s), 1465 (m), 1171 (m), 1000 (w); MS (EI, 70 eV) 236 (18), 234 (24), 223 (23), 208 (30), 192 (7), 180 (15), 124 (36), 110 (100), 96 (12), 81 (10); mol formula $C_{14}H_{28}BNO$ (237.19); HRMS $C_{14}H_{27}BNO$ (236.2186) calcd 236.2186, found 236.2183; TLC R_f 0.40 (CH_2Cl_2/ether, 19:1) [I_2, CAM].



*Preparation of (1S,3S,5S,5aS,7aS,7bR)-Octahydro-1-hydroxy-1-phenyl-5-methyl-7b-methyl-2H-cyclopenta[gh]pyrrolizine·Borane (****16****{5}).* To a 50 mL, two-necked, round-bottomed flask equipped with a nitrogen inlet adapter, a rubber septum, and a magnetic stir bar was added $CeCl_3 \cdot 7H_2O$ (1.74 g, 4.66 mmol, 1.5 equiv). The flask was immersed in a preheated oil bath (140 °C) and stirred under vacuum (~0.1 mmHg). After 2 h, the flask was backfilled with nitrogen, allowed to cool to room temperature, and then immersed in an ice bath. To the solid was added THF (14 mL), and the resulting milky, heterogeneous mixture was allowed to stir vigorously at room temperature for 2 h. The mixture was then sonicated and stirred intermittently for 15 min intervals over a 2 h time period. The flask was then immersed in an ice bat,h and phenylmagnesium bromide (2.9 M, 1.6 mL, 1.50 mmol, 1.5 equiv) was added via syringe. The ice bath was removed, and the solution

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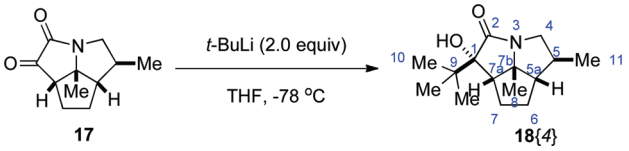
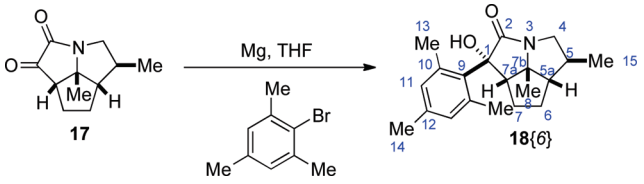
was stirred at room temperature for 1.5 h. The flask was immersed in an ice bath, and ketone **14** (600 mg, 3.11 mmol) was added as a solution in THF (2.0 mL) via syringe. After the mixture was stirred for 30 min while immersed in an ice bath, the reaction was quenched with satd aq NH_4Cl solution (15 mL). The biphasic mixture was poured into a 250 mL separatory funnel containing satd aq NH_4Cl solution (30 mL) and Et_2O (40 mL). The layers were separated, and the aqueous extract was washed with Et_2O (2 × 50 mL). The organic extracts were washed with satd aq $NaHCO_3$ (1 × 50 mL) and brine (1 × 50 mL), and the combined organic extracts were dried over $MgSO_4$, filtered (cotton plug), and concentrated by rotary evaporation (15 mmHg, 20−25 °C). The resulting pale-yellow oil was purified by silica gel column chromatography (1.8 cm × 10 cm, gradient elution, hexanes/TBME, 9:1, 4:1, 7:3, 1:1, 1:4, 50 mL each) to afford **16**{*5*} (828 mg, 98%) as a white solid. Data for **16**{*5*}: mp 81.5−82 °C (MTBE/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) 7.37 (d, *J* = 4.3, 1 H, HC(10), HC(11)), 7.31 (m, 1 H, HC(12)), 4.10 (d, *J* = 13.7, 1 H, HC(2)), 3.70 (d, *J* = 13.6, 1 H, HC(2)), 3.68 (dd, *J* = 8.3, 12.0, 1 H, HC(4)), 3.29 (dd, *J* = 10.8, 12.1, 1 H, HC(4)), 2.75 (dd, *J* = 6.1, 9.3, 1 H, HC(7a)), 2.64−2.55 (m, 1 H, HC(5)), 2.34−2.37 (m, 1 H, HC(5a)), 1.99−1.93 (m, 3 H, H_2C(7), HC(6)), 1.93−1.83 (m, 1 H, HC(6)), 1.80 (br, s, 1 H, OH), 1.55 (s, 3 H, H_3C(8)), 1.02 (d, *J* = 6.6, 3 H, H_3C(13)), 0.8−2.5 (br, 3 H, $(H_3B)^{92}$); ^{13}C NMR (126 MHz, $CDCl_3$) 146.0 (C(9)), 128.9 (C(11)), 128.0 (C(12)), 125.1 (C(10)), 89.6 (C(7b), 79.3 (C(1)), 78.8 (C(2)), 74.5 (C(4)), 62.6 (C(5a)), 59.8 (C(7a)), 34.7 (C(5)), 31.5 (C(7)), 25.1 (C(8)), 24.1 (C(6)), 17.7 (C(13)); IR ($CHCl_3$ film) 3475 (br), 2960 (s), 2871 (s), 2377 (s), 2327 (s), 2271 (s), 1494 (w), 1447 (m), 1266 (w), 1172 (s), 1131 (m), 1067 (w), 1004 (m), 954 (w), 876 (w), 700 (s); MS (EI, 70 eV) 268.2 (24), 257.2 (23), 242.1 (11), 224.1 (3), 192.1 (4), 178.1 (4), 158 (14), 137.1 (11), 124.1 (26), 110.1 (100); mol formula $C_{17}H_{26}BNO$ (271.21); HRMS $C_{17}H_{23}NO$ (257.1780) calcd 257.1780, found 257.1775; TLC R_f 0.58 (hexanes/TBME, 1:1) [I_2, CAM].

*3. Grignard Additions to Keto Amide **17**.*

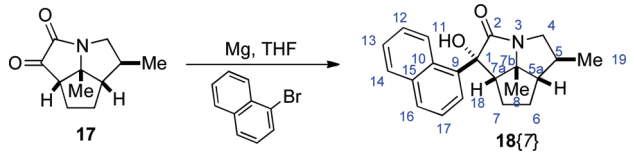


*Preparation of (1R,3S,5S,5aS,7aS,7bR)-Octahydro-1-hydroxy-1-(tert-butyl)-5-methyl-7b-methyl-2H-cyclopenta[gh]pyrrolizin-2-one (**18**{4}).* To a 25 mL, two-necked, round-bottomed flask equipped with a nitrogen inlet adapter, a rubber septum, and a magnetic stir bar was added **17** (100 mg, 0.518 mmol) followed by THF (5.0 mL). The flask was immersed in an acetone/$CO_{2(s)}$ bath and stirred for 20 min. Then, *t*-BuLi (1.6 M, 648 μL, 2.0 equiv) was added dropwise over 5 min via syringe. After the mixture was stirred for 10 min, the acetone/$CO_{2(s)}$ bath was replaced with an ice bath and the reaction was stirred for 1 h. The reaction was quenched by the dropwise addition of satd aq NH_4Cl solution (15 mL) and further diluted with Et_2O (10 mL). The biphasic mixture was poured into a 125 mL separatory funnel containing satd aq NH_4Cl solution (10 mL) and Et_2O (30 mL). The layers were separated, and the aqueous extract was washed with Et_2O (2 × 25 mL). The organic extracts were washed with H_2O (1 × 25 mL) and brine (1 × 25 mL), and the combined organic extracts were dried over Na_2SO_4, filtered (cotton plug), and concentrated by rotary evaporation (15 mmHg, 20−25 °C). The resulting pale-yellow oil was purified by silica gel column chromatography (1.8 cm × 6 cm, gradient elution, hexanes/TBME, 17:3, 5:1, 3:1, 3:1, 3:2, 25 mL each) to afford 18{*4*} (43 mg, 33%) as a white solid. Data for **18**{*4*}: ^{1}H NMR (500 MHz, $CDCl_3$) 4.30 (dd, *J* = 8.6, 12.2, 1 H, HC(4)), 2.63 (dd, *J* = 7.3, 12.2, 1 H, HC(4)), 2.55 (s, 1 H, HC(OH)), 2.38 (d, *J* =8.0, 1 H, HC(7a)), 2.07 (dd, *J* = 5.3, 12.7, 1 H, HC(7)), 1.99 (dd, *J* = 7.3, 15.3, 1 H, HC(5)), 1.86 (ddd, *J* = 6.4, 6.4, 12.8, 1 H, HC(6)), 1.78 (ddd, *J* = 2.1, 7.4, 9.8, 1 H, HC(5a)), 1.64−1.56 (m, 1 H, HC(7)), 1.40 (s, 3 H, H_3C(8)), 1.11 (d, *J* = 7.1, 3 H, H_3C(11)), 1.09−1.02 (m, 1 H, HC(6)), 0.97 (s, 9 H, H_3C(10)), 0.8−2.5 (br, 3 H, $(H_3B)^{93}$); ^{13}C NMR (126 MHz, $CDCl_3$) 179.3 (C(2)), 83.2 (C(1 or 7b)), 76.6 (C(1 or 7b)), 59.3 (C(5a)), 51.4 (C(4)), 49.6 (C(7a)), 37.8 (C(5)), 37.3 (C(10)), 33.9 (C(6)), 29.8 (C(7)), 25.0 (C(11)), 23.9 (C(8)), 21.3 (C(9)); IR ($CDCl_3$, film) 3404 (br), 2958 (s), 2865 (s), 2248 (w), 1678 (s), 1464 (m), 1395 (m), 1365 (m), 1340 (m), 1230 (w), 1181 (w), 1147 (w), 1115 (w), 1087 (w), 1057 (w), 1015 (w), 994 (w), 910 (w), 766 (w); MS (EI, 70 eV) 251.2 (1), 236.2 (1.8), 218 (1.9), 195.1 (100), 166.1 (2.7), 152.1 (3.1), 140.1 (2.8), 110.1 (8.7); mol formula $C_{15}H_{25}NO_2$ (251.36); HRMS $C_{15}H_{25}NO_2$ (251.1885) calcd 251.1885, found 251.1883; TLC R_f 0.25 (hexanes/TBME, 3:1) [I_2].

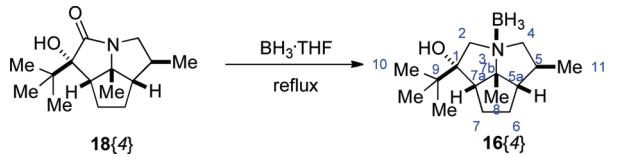


*Preparation of (1S,3S,5S,5aS,7aS,7bR)-Octahydro-1-hydroxy-1-(2,4,6-trimethylphenyl)-5-methyl-7b-methyl-2H-cyclopenta[gh]-pyrrolizine·Borane (**18**{6}).* To a 25 mL, two-necked, round-bottomed flask equipped with a nitrogen inlet adapter, a rubber septum, and a magnetic stir bar was added **17** (100 mg, 0.517 mmol) followed by THF (2.7 mL). The flask was immersed in an ice bath, and mesitylmagnesium bromide (0.39 M, 2.0 mL, 1.5 equiv) was added dropwise via syringe. After the mixture was stirred for 10 min, the cooling bath was removed, and the solution was stirred at room temperature for 20 min. The reaction flask was immersed in an ice bath, and the reaction was quenched with satd aq NH_4Cl solution (15 mL). The biphasic mixture was poured into a 125 mL separatory funnel containing satd aq NH_4Cl solution (10 mL) and Et_2O (30 mL). The layers were separated, and the aqueous extract was washed with Et_2O (2 × 25 mL). The organic extracts were washed with H_2O (1 × 25 mL) and brine (1 × 25 mL), and the combined organic extracts were dried over $MgSO_4$, filtered (cotton plug), and concentrated by rotary evaporation (15 mmHg, 20−25 °C). The resulting pale-yellow oil was purified by silica gel column chromatography (1.8 cm × 8 cm, gradient elution, hexanes/EtOAc, 9:1, 4:1, 7:3, 1:1, 25 mL each) to afford 18{*6*} (157 mg, 97%) as a white solid. Data for **18**{*6*}: mp 101−102 °C (hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) 6.92 (s, 1 H, HC(11)), 6.68 (s, 1 H, HC(11)), 4.17 (dd, *J* = 7.3, 11.7, 1 H, HC(4)), 3.47 (s, 1 H, OH), 2.65 (dd, *J* = 7.6, 10.1, 1 H, HC(4)), 2.64 (dd, *J* = 10.4, 11.6, 1 H, HC(5)), 2.48 (s, 3 H, H_3C(8, 13, or 14), 2.41 (s, 3 H, H_3C(8, 13, or 14)), 2.22 (s, 3 H, H_3C(8, 13, or 14)), 1.98−1.92 (m, 1 H, HC(7)), 1.84−1.79 (m, 1 H, HC(7a)), 1.78−1.66 (m, 3 H, HC(7), HC(6), HC(5a)), 1.55−1.48 (m, 1 H, HC(6)), 1.09 (d, *J* = 6.7, 3 H, H_3C(15)), 1.08 (s, 3 H, H_3C(8, 13, or 14)), 0.8−2.5 (br, 3 H, $(H_3B)^{92}$); ^{13}C NMR (126 MHz, $CDCl_3$) 179.1 (C(2)), 139.4 (C(9)), 138.3 (C(10 or 12)), 136.6 (C(10 or 12)), 133.9 (C(10 or 12)), 131.9 (C(11)), 130.8 (C(11)), 82.3 (C(1)), 75.3 (C(7b)), 60.2 (C(5)), 58.9 (C(7a)), 50.9 (C(4)), 41.7 (C(5a)), 29.9 (C(6)), 27.1 (C(7)), 23.8 (C(8, 13 or 14)), 22.3 (C(8, 13, or 14)), 21.2 (C(8, 13, or 14)), 20.7 (C(8, 13, or 14)), 17.7 (C(15)); IR (NaCl plate, film) 3404 (br), 3000 (s), 2959 (s), 2922 (s), 2870 (s), 1693 (s), 1610 (m), 1560 (w), 1460 (s), 1407 (s), 1379 (m), 1351 (m), 1280 (w), 1232 (m), 1120 (m), 1072 (m), 1035 (m), 978 (w), 851 (m); MS (EI, 70 eV) 313 (10), 295 (84), 285 (4), 280 (6), 270 (3), 252 (5), 147 (100), 138 (10), 124 (21), 119 (29), 110 (90); mol formula $C_{20}H_{27}NO_2$ (313.43); HRMS $C_{20}H_{27}NO_2$ (313.2042) calcd 313.2042, found 313.2045; TLC R_f 0.32 (hexanes/EtOAc, 3:1) [I_2, CAM].

dx.doi.org/10.1021/jo2005445 |*J. Org. Chem.* 2011, 76, 4260–4336

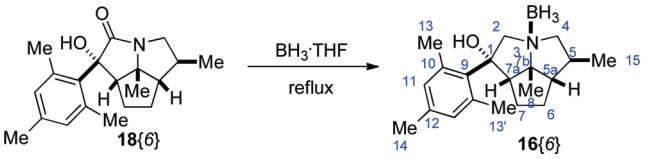


*Preparation of (1R,3S,5S,5aS,7aS,7bR)-Octahydro-1-hydroxy-1-[1]naphthyl-5-methyl-7b-methyl-2H-cyclopenta[gh]pyrrolizin-2-one (**18**{7}).* To a 25 mL, two-necked, round-bottomed flask equipped with a nitrogen inlet adapter, a rubber septum, and a magnetic stir bar was added **17** (100 mg, 0.517 mmol) followed by THF (2.7 mL). The flask was immersed in an ice bath, and 1-naphthylmagnesium bromide (0.4 M, 2.0 mL, 1.5 equiv) was added dropwise via syringe. After being stirred for 10 min, the cooling bath was removed, and the reaction was stirred at room temperature for 20 min. The biphasic mixture was poured into a 125 mL separatory funnel containing satd aq NH_4Cl solution (10 mL) and Et_2O (30 mL). The layers were separated, and the aqueous extract was washed with Et_2O (2 × 25 mL). The organic extracts were washed with H_2O (1 × 25 mL) and brine (1 × 25 mL), and the combined organic extracts were dried over $MgSO_4$, filtered (cotton plug), and concentrated by rotary evaporation (15 mmHg, 20−25 °C). The resulting pale-yellow oil was purified by silica gel column chromatography (1.8 cm ×8 cm, gradient elution, hexanes/EtOAc, 9:1, 4:1, 7:3, 1:1, 25 mL each) to afford 18{7} (157 mg, 95%) as a white solid. Data for **18**{7}: mp 150−151 °C (hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) 8.43 (d, J = 8.4, 1 H, HC(11)), 7.87 (d, J = 7.9, 1 H, HC(14)), 7.78 (d, J = 7.9, 1 H, HC(16)), 7.56−7.48 (m, 2 H, HC(12), HC(13)), 7.34−7.28 (m, 2 H, HC(17), HC(18)), 4.27 (dd, J = 6.8, 11.5, 1 H, HC(4)), 3.44 (br, s, 1 H, OH), 2.96 (dd, J = 7.6, 10.1, 1 H, HC(7a)), 2.69 (dd, J = 10.0, 11.5, 1 H, HC(4)), 2.21−2.14 (m, 1 H, HC(7)), 2.00−1.92 (m, 1 H, HC(7)), 1.83−1.73 (m, 3 H, HC(6), HC(5a), HC(5)), 1.60−1.55 (m, 1 H, HC(6)), 1.11 (d, J = 6.4, 3 H, H_3C(19)), 0.87 (s, 3 H, H_3C(8)), 0.8−2.5 (br, 3 H, $(H_3B)^{93}$); ^{13}C NMR (126 MHz, $CDCl_3$) 177.2 (C(2)), 138.9 (C(9)), 135.0 (C(15)), 131.1 (C(10)), 129.3 (C(16)), 129.1 (C(14)), 126.6 (C(11)), 126.0 (C(12 or 13)), 125.7 (C(12 or 13)), 124.7 (C(17 or 18)), 124.7 (C(17 or 18)), 84.1 (C(1 or 7b)), 75.9 (C(1 or 7b)), 58.9 (C(5a)), 57.9 (C(7a)), 51.2 (C(4)), 41.9 (C(5)), 30.0 (C(6)), 27.0 (C(7)), 24.4 (C(8)), 17.7 (C(19)); IR (NaCl plate, film) 3386 (s), 3050 (w), 3007 (m), 2959 (s), 2871 (s), 1693 (s), 1596 (w), 1509 (m), 1461 (s), 1411 (s), 1352 (m), 1376 (m), 1330 (m), 1280 (m), 1230 (s), 1213 (m), 1174 (w), 1131 (s), 1074 (s), 1030 (w), 967 (w), 915 (w), 862 (w), 802 (s); MS (EI, 70 eV) 321 (19), 293 (6), 183 (9), 165 (13), 155 (68), 127 (46), 110 (100); mol formula $C_{21}H_{23}NO_2$ (321.41); HRMS $C_{21}H_{23}NO_2$ (321.1729) calcd 321.1729, found 321.1732; TLC R_f 0.28 (hexanes/EtOAc, 3:1) [I_2, CAM].

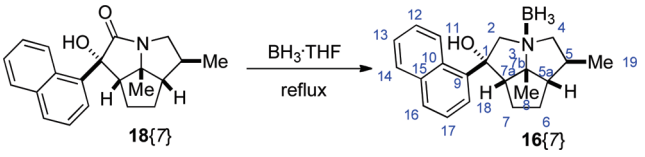


*4. Borane Reduction of Hydroxy Amides **19**.*

*Preparation of (1R,3S,5S,5aS,7aS,7bR)-Octahydro-1-hydroxy-1-tert-butyl-5-methyl-7b-methyl-2H-cyclopenta[gh]pyrrolizine·Borane (**16**{4}).* To a 25 mL, single-necked, round-bottomed flask equipped with a nitrogen inlet adapter, a rubber septum, a reflux condenser, and a magnetic stir bar were added sequentially **18**{4} (29 mg, 0.115 mmol), THF (200 μL), and BH_3·THF complex (3.3 mL, 1.0 M solution, 20 equiv). The reaction flask was immersed in an oil bath and heated to reflux (70 °C). After being stirred for 12 h at reflux, the solution was allowed to reach room temperature and then quenched by dropwise addition of methanol (10 mL) and concentrated by rotary evaporation (15 mmHg, 20−25 °C). The resulting colorless oil was purified by silica gel column chromatography (1.8 cm × 8 cm column, gradient elution, hexanes/TBME, 19:1, 9:1, 3:1, 3:2, 25 mL each) to afford 27 mg (93%) of **16**{4} as a white solid. Data for **16**{4}: ^{1}H NMR (500 MHz, $CDCl_3$) 3.80 (d, J = 13.9, 1 H, HC(2)), 3.63 (dd, J =8.5, 12.0, 1 H, HC(4)), 3.23 (d, J = 13.8, 1 H, HC(2)), 3.23−3.18 (m, 1 H, HC(4)), 2.48−2.40 (m, 1 H, HC(7a)), 2.41 (dd, J = 6.8, 9.2, 1 H, HC(5)), 2.09−1.99 (m, 1 H, HC(7)), 1.91−1.84 (m, 3 H, H_2C(6), HC(5a)), 1.72−1.63 (m, 1 H, HC(7)), 1.62 (br, s, 1 H, HO), 1.46 (s, 3 H, H_3C(8)), 0.99 (d, J = 6.6, 3 H, H_3C(9)), 0.92 (s, 3 H, H_3C(11)), 0.8−2.5 (br, 3 H, $(H_3B)^{93}$); ^{13}C NMR (126 MHz, $CDCl_3$) 89.7 (C(1 or 7b)), 83.0 (C(1 or 7b)), 75.7 (C(2)), 74.6 (C(4)), 59.6 (C(5a)), 56.5 (C(7a)), 37.5 (C(10)), 35.0 (C(5)), 32.1 (C(6)), 25.5 (C(10)), 25.4 (C(7)), 24.7 (C(8)), 18.1 (C(11)); IR ($CDCl_3$ film) 3503 (s), 2961 (s), 2872 (s), 2376 (s), 2327 (s), 2271 (s), 1465 (m), 1400 (w), 1378 (m), 1335 (w), 1267 (w), 1174 (m), 1140 (m), 1091 (w), 1057 (w), 1002 (w), 980 (w), 958 (w), 940 (w), 910 (s), 882 (w), 841 (w), 733 (s), 649 (w); MS (ESI, Q-tof) 422.2 (10), 344.2 (25), 318.2 (40), 308.2 (100); mol formula $C_{15}H_{30}BNO$ (251.22); HRMS $C_{15}H_{27}NO$: (237.2093) calcd 237.2093, found 237.2091; TLC R_f 0.27 (hexanes/TBME, 3:1) [I_2, CAM].



*Preparation of (1R,3S,5S,5aS,7aS,7bR)-Octahydro-1-hydroxy-1-mesityl-5-methyl-7b-methyl-2H-cyclopenta[gh]pyrrolizine·Borane (**16**{6}).* To a 25 mL round-bottomed flask equipped with a nitrogen inlet adapter, a rubber septum, a reflux condenser, and a magnetic stir bar were added sequentially **18**{6} (50 mg, 0.160 mmol), THF (200 μL), and BH_3·THF complex (3.2 mL, 1.0 M solution, 20 equiv). The reaction flask was immersed in an oil bath and heated to reflux (70 °C). After being stirred for 12 h at reflux, the solution was allowed to reach room temperature and then was quenched with methanol (5 mL) and concentrated by rotary evaporation (15 mmHg, 20−25 °C). The resulting colorless oil was purified by silica gel column chromatography (1.8 cm × 8 cm column, gradient elution, hexanes/TBME, 19:1, 9:1, 4:1, 3:1,25 mL each) to afford 36 mg (72%) of **16**{6} as a white solid. Data for 16{6}: mp 131−132 °C (MTBE/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) 6.81 (s, 2 H, HC(11)), 4.09 (d, J = 14.1, 1 H, HC(9)), 4.02 (d, J = 14.1, 1 H, HC(9)), 3.72 (dd, J = 8.2, 12.1, 1 H, HC(4)), 3.29 (dd, J = 9.9, 12.0, 1 H, HC(4)), 3.10 (dd, J = 6.0, 8.5, 1 H, HC(7a)), 2.62−2.52 (m, 1 H, HC(5)), 2.52 (s, 6 H, H_3C(13), H_3C(13)), 2.40−2.31 (m, 1 H, HC(7)), 2.22 (s, 3 H, H_3C(14)), 2.06−1.98 (m, 1 H, HC(7)), 1.99−1.93 (m, 3 H, H_2C(6), HC(5a)), 1.51 (s, 3 H, H_3C(8)), 1.04 (d, J = 6.7, 3 H, H_3C(14)), 0.8−2.5 (br, 3 H, $(H_3B)^{93}$); ^{13}C NMR (126 MHz, $CDCl_3$) 139.1 (C(12)), 136.9 (C(9)), 136.4 (C(10)), 132.5 (C(11)), 88.4 (C(7b)), 82.4 (C(1)), 79.9 (C(2)), 75.1 (C(4)), 62.5 (C(7a)), 60.6 (C(5a)), 35.4 (C(5)), 31.8 (C(6)), 27.0 (C(7)), 25.6 (C(8)), 25.1 (C(13 or 14)), 20.4 (C(13 or 14)), 18.2 (C(15)); IR (thin film) 3508 (s), 2383 (s), 2319 (s), 2274 (s), 1606 (m), 1378 (s), 1309 (w), 1287 (w), 1187 (s), 1128 (w), 1071 (m), 1034 (m), 943 (m), 860 (w), 734 (w); MS (ESI, Q-tof) 314.2 (12), 300.2 (30), 296.2 (100), 268.2 (25); mol formula $C_{20}H_{32}BNO$ (313.29); HRMS $C_{20}H_{30}NO$ (300.2327) calcd 300.2327, found 300.2332; TLC R_f 0.33 (hexanes/TBME, 9:1) [I_2, CAM].



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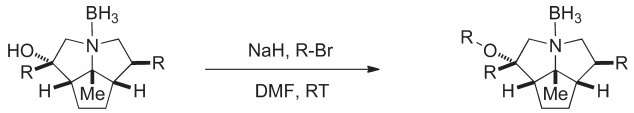
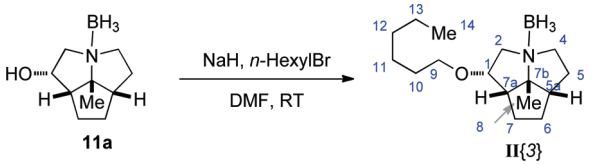
*Preparation of (1R,3S,5S,5aS,7aS,7bR)-Octahydro-1-hydroxy-1-[1]-naphthyl-5-methyl-7b-methyl-2H-cyclopenta[gh]pyrrolizine·Borane (**16**{7}).* To a 25 mL, round-bottomed flask equipped with a nitrogen inlet adapter, a rubber septum, a reflux condenser, and a magnetic stir bar were added sequentially 18{7} (50 mg, 0.156 mmol), THF (200 μL), and BH_3·THF complex (3.1 mL, 1.0 M solution, 20 equiv). The reaction flask was immersed in an oil bath and heated to reflux (70 °C). After being stirred for 12 h at reflux, the solution was allowed to reach room temperature and then quenched with methanol (5 mL) and concentrated by rotary evaporation (15 mmHg, 20−25 °C). The resulting colorless oil was purified by silica gel column chromatography (1.8 cm × 8 cm column, gradient elution, hexanes/TBME, 19:1, 9:1, 3:1, 3:2, 25 mL each) to afford 42 mg (85%) of **16**{7} as a white solid. Data for **16**{7}: mp 151−153 °C (MTBE/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) 8.44 (d, *J* = 8.5, 1 H, HC(11)), 7.87 (d, *J* = 7.9, 1 H, HC(14)), 7.81 (d, *J* = 8.2, 1 H, HC(16)), 7.67 (d, *J* = 7.3, 1 H, HC(18)), 7.55−7.47 (m, 2 H, HC(12), HC(17)), 7.40 (dd, *J* = 7.8, 7.8, 1 H, HC(13)), 4.23 (d, *J* = 13.4, 1 H, HC(2)), 4.04 (d, *J* = 13.5, 1 H, HC(2)), 3.66 (dd, *J* = 7.5, 12.2, 1 H, HC(4)), 3.25−3.19 (m, 2 H, HC(7a), HC(4)), 2.60−2.50 (m, 1 H, HC(5)), 2.40−2.32 (m, 1 H, HC(7)), 2.22 (br, s, 1 H, OH), 2.10−2.01 (m, 1 H, HC(7)), 2.00−1.93 (m, 3 H, H_2C(6), HC(5a)), 1.54 (s, 3 H, H_3C(8)), 1.05 (d, *J* = 6.5, 3 H, H_3C(19)), 0.8−2.5 (br, 3 H, (H_3B)[93]); ^{13}C NMR (126 MHz, $CDCl_3$) 139.2 (C(9)), 135.3 (C(15)), 131.2 (C(10)), 130.0 (C(16)), 129.6 (C(14)), 126.4 (C(11)), 126.3 (C(12 or 17)), 125.9 (C(12 or 17)), 124.8 (C(13)), 124.2 (C(18)), 88.1 (C(7b)), 80.9 (C(1)), 76.5 (C(2)), 74.6 (C(4)), 61.3 (C(5a)), 60.4 (C(7a)), 34.8 (C(5)), 31.0 (C(6)), 26.8 (C(7)), 25.7 (C(8)), 17.5 (C(19)); IR (thin film) 3475 (m), 2383 (s), 2332 (s), 2269 (s), 1596 (w), 1444 (w), 1309 (w), 1202 (w), 1163 (m), 1134 (m), 1067 (w), 1040 (w), 1000 (w), 933 (w), 872 (w), 808 (m), 782 (s); MS (ESI, Q-tof) 422.2 (10), 344.2 (25), 318.2 (40), 308.2 (100); mol formula $C_{21}H_{28}BNO$ (321.26); HRMS $C_{21}H_{26}NO$, (308.2014) calcd 308.2014, found 308.2011; TLC R_f 0.39 (hexanes/TBME, 3:1) [I_2, CAM].

B. Variable Group R[3]: Williamson Ether Synthesis.



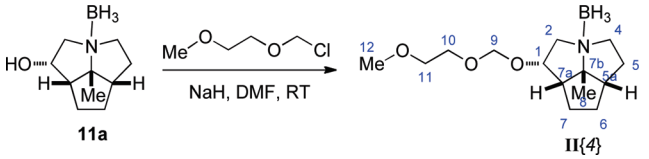
*1. General Procedure (**I**) for the Preparation of Library Intermediates.* To a two-necked, 25 mL, round-bottomed flask equipped with a nitrogen inlet adapter, a rubber septum, and a magnetic stir bar were added sequentially alcohol X (X mg, 0.X mmol) and DMF (2.74 mL, ~0.35 M). The flask was then immersed in an ice/NaCl bath for 15 min. Sodium hydride (xx mg, 0.xx mmol, 1.2 equiv) was weighed into a vial in a glovebox and then transferred to the flask in one portion (bubbling was observed). The resulting solution was allowed to stir for 15 min, and then alkyl bromide (X μL, 0.X mmol, 1.2 equiv) was added via syringe in a single portion. The resulting cloudy mixture was stirred for 2 h, then quenched by pouring onto onto ice−water (20 mL). This mixture was transferred to a 125 mL separatory funnel where an additional 20 mL of water was added and the aqueous phase was extracted with dichloromethane (3 × 20 mL). The organic extracts were washed with water (2 × 20 mL), and brine (2x 20 mL), then the combinded organic extracts were dried ($MgSO_4$). The floculant suspension was filtered through a small pad of Celite (1 cm × 2 cm) and concentrated by rotary evaporation (15 mmHg, 20−25 °C) to afford a thick oil. Purification by silica gel chromatography (1.8 cm ×8 cm column, gradient elution, hexanes/EtOAc, 1:9, 1:3, 1:1) afforded X mg (XX%) of ether X{*x*}.

*2. Preparation of Amino·Borane Intermediates **II**{2−5}. Preparation of (1S,3S,5aS,7aS,7bR)-Octahydro-1-benzyloxy-7b-methyl-2H-cyclopenta[gh]pyrrolizine·Borane (**II**{2}).* Following general procedure I, to a two-necked, 25 mL, round-bottomed flask equipped with a nitrogen inlet adapter, a rubber septum, and a magnetic stir bar were added sequentially alcohol **11a** (54.3 mg, 0.30 mmol), dimethylformamide (3.0 mL, ~0.1 M), then sodium hydride (9.1 mg, 0.36 mmol, 1.2 equiv) at 0 °C. After 15 min, benzyl bromide (42.8 μL, 0.36 mmol, 1.2 equiv) was added via syringe. The solution was stirred for 2 h and then quenched onto ice−water (20 mL). Extraction and purification by silica gel column chromatography as described in general procedure I afforded 65.1 mg (78%) of benzyl ether **II**{2} as a clear, viscous oil. Data for **II**{2}: ^{1}H NMR (500 MHz, $CDCl_3$) 7.41−7.23 (m, 5 H, HC(11), HC(12), HC(13)), 4.52−4.45 (m, 3 H, H_2C(9), HC(1)), 3.48 (dd, *J* = 6.3, 10.9, 1 H, HC(2)), 3.30−3.25 (m, 1 H, HC(4)), 3.20−3.15 (m, 1 H, HC(4)), 3.14−3.01 (m, 1 H, HC(4)), 2.46 (dd, *J* = 7.8, 15.8, 1 H, HC(7a)), 2.40 (dd, *J* = 6.5, 15.1, 1 H, HC(5a)), 2.36−2.34 (m, 1 H, HC(7a)), 2.19−2.17 (m, 1 H, HC(7)), 2.07−1.99 (m, 1 H, HC(6)), 1.88−1.75 (m, 2 H, HC(6), HC(5)), 1.69 (m, 1 H, HC(7), HC(5)), 1.50 (s, 3 H, H_3C(8)), 0.8−2.5 (br, 3 H, (H_3B)[92]); ^{13}C NMR (126 MHz, $CDCl_3$) 137.9 (C(10)), 128.5 (C(12)), 127.8 (C(13)), 127.5 (C(11)), 87.7 (C(7b)), 76.6 (C(1)), 72.2 (C(9)), 64.3 (C(2)), 63.1 (C(4)), 53.6 (C(7a)), 53.1 (C(5a)), 32.1 (C(5)), 28.0 (C(6)), 26.6 (C(7)), 25.3 (C(8)); IR ($CDCl_3$, film) 3014 (m), 2698 (m), 2929 (m), 2858 (m), 2362 (m), 2326 (m), 2276 (m), 241 (w), 1480 (m), 1453 (m), 1380 (w), 115 (s); MS (EI, 70 eV) 270 (15), 242 (22), 166 (100), 151 (33), 91 (70); mol formula $C_{17}H_{26}BNO$ (271.21); HRMS $C_{17}H_{25}NOB$ (270.2029) calcd 270.2029, found 270.2029; TLC R_f 0.39 (EtOAc/hexanes, 1:3) [I_2, CAM].

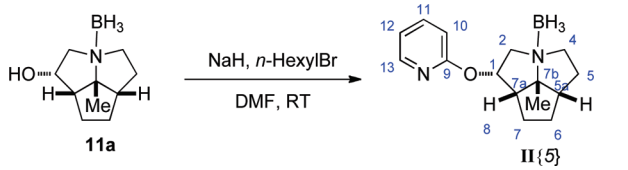


*Preparation of (1S,3S,5aS,7aS,7bR)-Octahydro-1-hexyloxy-7b-methyl-2H-cyclopenta[gh] pyrrolizine·Borane (**II**{3}).* Following general procedure I, to a two-necked, 25 mL, round-bottomed flask equipped with a nitrogen inlet adapter, a rubber septum, and a magnetic stir bar were added sequentially alcohol **11a** (54.3 mg, 0.30 mmol), dimethylformamide (3.0 mL, ~0.1 M), then sodium hydride (9.1 mg, 0.36 mmol, 1.2 equiv) at 0 °C. After 15 min, 1-bromohexane (51 μL, 0.36 mmol, 1.2 equiv) was added via syringe. The solution was stirred for 2 h, and then more sodium hydride was added (4.5 mg, 0.18 mmol, 0.6 equiv) followed by more 1-bromohexane (25 μL, 0.18 mmol, 0.6 equiv). After another 2 h, the process was repeated a third time, sequentially adding NaH (2.3 mg, 0.09 mmol, 0.3 equiv) and then 1-bromohexane (12 μL, 0.09 mmol, 0.3 equiv). After another 2 h, the reaction was quenched onto ice−water (20 mL). Extraction and purification by silica gel column chromatography as described in general procedure I afforded 58 mg (73%) of *n*-hexyl ether **II**{3} as a clear, viscous oil. Data for **II**{3}: ^{1}H NMR (500 MHz, $CDCl_3$) 4.30 (dd, *J* = 7.8, 15.4, 1 H, C(1)), 3.44 (dd, *J* = 6.4, 10.9, 1 H, HC(2)), 3.39 (dt, *J* = 2.3, 6.6, 2 H, HC(9)), 3.26 (ddd, *J* = 2.7, 6.7, 11.9, 1 H, HC(4)), 3.15 (dt, *J* = 6.6, 11.7, 1 H, HC(4)), 3.03 (dd, *J* = 8.9, 11.5, 1 H, HC(2)), 2.45−2.35 (m, 1 H, HC(6 or 7)), 2.05−1.98 (m, 1 H, HC(7a)), 1.97−1.89 (m, 1 H, HC(5a)), 1.85−1.76 (m, 1 H, HC(6 or 7)), 1.56−1.50 (m, 4 H, $(CH_2)_2$), 1.48 (s, 3 H, H_3C(8)), 1.34−1.25 (m, 8 H, $(CH_2)_4$), 0.88 (t, *J* = 6.9, 3 H, H_3C(14)), 0.8−2.5 (br, 3 H, (H_3B)[92]); ^{13}C NMR (126 MHz, $CDCl_3$) 87.6 (C(7b)), 76.6 (C(1)), 70.2 (C(2)), 64.2 (C(7a)), 63.1 (C(4)), 53.6 (C(9)), 53.1 (C(5a)), 32.0 (C(6)), 31.6 (C(10)), 29.8 (C(11)), 27.9 (C(5)), 26.4 (C(7)), 25.8 (C(12 or 13)), 25.3 (C(8)), 22.5 (C(12 or 13)), 13.9 (C(14)); IR (NaCl plate, film) 2935 (m), 2933 (m), 2858 (m),

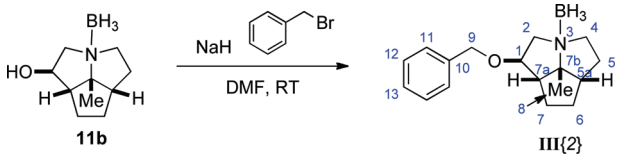
2379 (m), 2340 (m), 2283 (m), 1163 (m); MS (ESI, Q-tof) 264 (25), 251 (15), 236 (100), 180 (21), 166 (64), 150 (22), 110 (25), 96 (69), 84 (29), 55 (19); mol formula $C_{16}H_{32}BNO$ (265.24); HRMS $C_{16}H_{31}BNO$ (264.2499) calcd 264.2499, found 264.2499; TLC R_f 0.62 (hexanes/EtOAc, 3:1) [I_2, CAM].



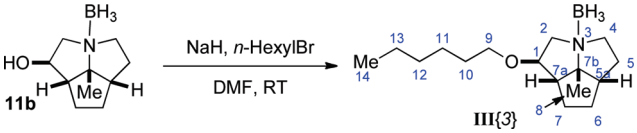
*Preparation of (1S,3S,5aS,7aS,7bR)-Octahydro-1-(methoxyethoxymethoxy)-7b-methyl-2H-cyclopenta[gh]pyrrolizine·Borane (**II**{4}).* Following general procedure I, to a two-necked, 25 mL, round-bottomed flask equipped with a nitrogen inlet adapter, a rubber septum, and a magnetic stir bar were added sequentially alcohol **11a** (54.3 mg, 0.30 mmol), dimethylformamide (3.0 mL, ~0.1 M), and then sodium hydride (9.1 mg, 0.36 mmol, 1.2 equiv) at 0 °C. After 15 min, *freshly distilled* methoxyethoxymethyl chloride was added (57 μL, 0.50 mmol, 1.7 equiv) via syringe. The solution was stirred for 2 h and then quenched onto ice−water (20 mL). Extraction and purification by silica gel column chromatography as described in general procedure I afforded 70.3 mg (87%) of ether **II**{4} as a clear, viscous oil. Data for **II**{4}: ^{1}H NMR (500 MHz, $CDCl_3$) 4.70 (m, 2 H, $H_2C(9)$), 4.57 (dd, J = 8.1, = 15.5, 1 H, HC(1)), 3.68 (ddt, J = 5.1, 10.9, 16.2, 2 H, $H_2C(10)$), 3.55 (ddd, J = 1.5, 3.9, 5.4, 2 H, HC(11)), 3.50 (dd, J = 6.5, 11.1, 1 H, HC(2)), 3.40 (s, 3 H, HC(12)), 3.26 (ddd, J = 2.7, 6.8, J = 12.3, 1 H, HC(4)), 3.16 (m, 1 H, HC(4)), 3.08 (m, 1 H, HC(2)), 2.44 (dd, J = 8.1, 16.1, 2 H, HC(7a), HC(5a)), 2.39 (m, 2 H, HC(7), HC(6)), 2.03 (m, 1 H, HC(6)), 1.93 (m, 1 H, HC(5)), 1.81 (m, 1 H, HC(7)), 1.75 (m, 1 H, HC(5)), 1.66 (m, 3 H, HC(8)), 0.8−2.5 (br, 3 H, (H_3B)[92]); ^{13}C NMR (126 MHz, $CDCl_3$) 95.3 (C(9)), 87.4 (C(7b)), 74.9 (C(1)), 71.7 (C(10)), 67.4 (C(11)), 64.5 (C(2)), 63.1 (C(4)), 59.1 (C(12)), 53.9 (C(7a)), 53.1 (C(5a)), 31.9 (C(5)), 28.0 (C(7)), 26.9 (C(6)), 25.1 (C(8)); IR ($CDCl_3$, film) 3019 (m), 2399 (w), 1734 (w), 1700 (w), 1653 (m), 1215 (s), 758 (s), 669 (m); MS (ESI, Q-tof) 268 (41), 240 (65), 224 (47), 196 (67), 166 (96), 150 (64), 149 (88), 96 (93), 89 (87), 59 (100); mol formula $C_{14}H_{28}BNO_3$ (269.10); HRMS $C_{14}H_{27}BNO_3$ (268.2084) calcd 268.2084, found 268.2084; TLC R_f 0.18 (hexanes/TBME, 9:1 [I_2, CAM].



*Preparation of (1S,3S,5aS,7aS,7bR)-Octahydro-1-(2-pyridyloxy)-7b-methyl-2H-cyclopenta[gh]pyrrolizine·Borane (**II**{5}).* Following general procedure I, to a two-necked, 25 mL, round-bottomed flask equipped with a nitrogen inlet adapter, a rubber septum, and a magnetic stir bar were added sequentially alcohol **11a** (54 mg, 0.3 mmol), dimethylformamide (3.0 mL, ~0.1 M), and then sodium hydride (9.1 mg, 0.36 mmol, 1.2 equiv) at 0 °C. After 15 min, 2-fluoropyridine (26 μL, 0.36 mmol, 1.2 equiv) was added via syringe. The solution was stirred for 2 h then quenched onto ice−water (20 mL). Extraction and purification by silica gel column chromatography as described in general procedure I afforded 73 mg (95%) of ether **II**{5} as a clear, viscous oil. Data for **II**{5}: ^{1}H NMR (500 MHz, $CDCl_3$) 8.14 (dd, J = 1.7, 5.0, 1 H, HC(13)), 7.56 (m, 1 H, HC(11)), 6.88 (dd, J = 5.2, 6.4, 1 H, HC(12)), 6.70 (d, J = 8.3, 1 H, HC(10)), 5.69 (dd, J = 7.8, 14.9, 1 H, HC(1)), 3.73 (dd, J = 6.8, 11.7, 1 H, HC(2)), 3.41 (ddd, J = 4.5, 6.8, 11.6, 1 H, HC(4)), 3.29 (m, 2 H, HC(2), HC(4)), 2.81 (q, J = 7.7, 1 H, HC(5a)), 2.44 (m, 1 H, HC(7a)), 2.16 (et, J = 4.5, 6.9, 8.9, 13.4, 1 H, HC(6)), 1.89 (m, 3 H, HC(7), HC(6), HC(5)), 1.70 (ddt, J = 5.4, 8.8, 10.5, 2 H, HC(7), HC(5)), 1.56 (s, 3 H, HC(8)), 0.8−2.5 (br, 3 H, (H_3B)[92]); ^{13}C NMR (126 MHz, $CDCl_3$) 162.6 (C(9)), 147.0 (C(13)), 138.7 (C(11)), 117.1 (C(12)), 110.8 (C(10)), 88.0 (C(7b)), 72.9 (C(1)), 65.0 (C(2)), 63.4 (C(4)), 54.0 (C(7a)), 52.8 (C(5a)), 33.1 (C(5)), 28.5 (C(6)), 27.3 (C(7)), 25.1 (C(8)); IR ($CDCl_3$, film) 3149 (w), 2971 (w), 2382 (w), 2253 (s), 1793 (w), 1470 (m), 1433 (w), 1382 (m), 1096 (m); MS (EI, 70 eV) 257 (21), 149 (100), 134 (39), 120 (15), 108 (17), 96 (19), 78 (13), 55 (18); mol formula $C_{15}H_{23}BN_2O$ (258.17); HRMS $C_{15}H_{21}N_2O$ (245.1654) calcd 245.1654, found 245.1649; TLC R_f 0.20 (hexanse/TBMS, 93/7) [I_2, CAM].



*3. Preparation of Amino·Borane Intermediates **III**{2−5}. Preparation of (1R,3S,5aS,7aS,7bR)-Octahydro-1-benzyloxy-7b-methyl-2H-cyclopenta[gh]pyrrolizine·Borane (**III**{2}).* Following general procedure I, a two-necked, 25 mL, round-bottomed flask equipped with a nitrogen inlet adapter, a rubber septum, and a magnetic stir bar were added sequentially alcohol **11b** (25 mg, 0.14 mmol), dimethylformamide (1.5 mL, ~0.1 M), then sodium hydride (4 mg, 0.17 mmol, 1.2 equiv) at 0 °C. After 15 min, benzyl bromide (20 μL, 0.17 mmol, 1.2 equiv) was added via syringe. The solution was stirred for 2 h then quenched onto ice−water (20 mL). Extraction and purification by silica gel column chromatography as described in general procedure I afforded 35 mg (95%) of benzyl ether **III**{2} as a clear, viscous oil. Data for **III**{2}: ^{1}H NMR (500 MHz, $CDCl_3$) 7.33 (m, 5 H, HC(11), HC(12), HC(13)), 4.50 (dd, 2 H, J = 3.4, 11.7, $H_2C(9)$), 3.88 (ddd, 1 H, J = 5.9, 5.9, 8.3, HC(1)), 3.46 (dd, 1 H, J = 6.1, 12.8, HC(2)), 3.40 (m, 1 H, HC(4)), 3.35 (dd, 1 H, J = 8.5, 12.7, HC(2)), 2.99 (ddd, 1 H, J = 6.6, 10.3, 10.3, HC(4)), 2.37−2.27 (m, 2 H, HC(7a)), HC(6)), 1.98−1.676 (m, 3 H, HC(7), HC(6)), HC(5)), 1.56 (s, 3 H, $H_3C(8)$), 1.55−1.40 (m, 3 H, HC(7)), HC(6), HC(5)), 0.8−2.5 (br, 3 H, (H_3B)[3]); ^{13}C NMR (126 MHz, $CDCl_3$) 137.6 (C(10)), 128.5 (C(12)), 127.9 (C(13)), 127.6 (C(11)), 86.8 (C(7b)), 80.0 (C(1)), 72.0 (C(9)), 66.6 (C(2)), 64.2 (C(4)), 58.9 (C(7a)), 51.3 (C(5a)), 33.2 (C(5)), 31.0 (C(7)), 29.1 (C(6)), 24.8 (C(8)); IR ($CDCl_3$, film) 3019 (s), 2971 (m), 2858 (w), 2400 (m), 2361 (w), 269 (w), 1602 (w), 1524 (m), 1475 (w), 1421 (m), 1215 (s), 928 (m), 756 (s), 669 (s); MS (ESI, Q-tof); mol formula $C_{17}H_{26}BNO$ (271.21); HRMS $C_{17}H_{24}NO$ (258.1858) calcd 258.1858, found 258.1864; TLC R_f 0.45 (hexanes/EtOAc).



*Preparation of (1R,3S,5aS,7aS,7bR)-Octahydro-1-hexyloxy-7b-methyl-2H-cyclopenta[gh]pyrrolizine·Borane (**III**{3}).* Following general procedure I, to a two-necked, 25 mL, round-bottomed flask equipped with a nitrogen inlet adapter, a rubber septum, and a magnetic stir bar were added sequentially alcohol **11b** (40 mg, 0.20 mmol), dimethylformamide (2 mL, ~0.1 M), and then sodium hydride (15 mg, 0.6 mmol, 3.0 equiv) at 0 °C. After 15 min, 1-bromohexane (84 μL, 0.6 mmol, 3.0 equiv) was added via syringe. The solution was stirred for 2 h and then quenched onto ice−water (20 mL). Extraction and

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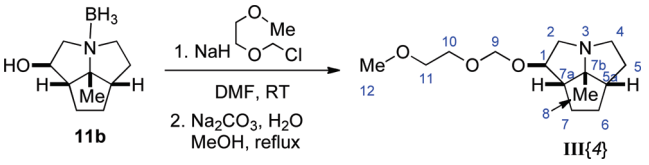
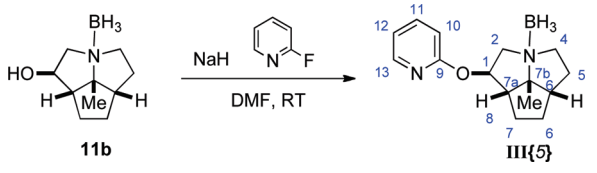
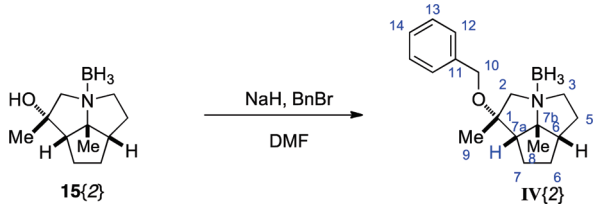
purification by silica gel column chromatography as described in general procedure I afforded 40 mg (84%) of *n*-hexylyl ether **III**{*3*} as a clear, viscous oil. Data for **III**{*3*}: ^{1}H NMR (500 MHz, $CDCl_3$) 3.76 (td, *J* = 6.0, 8.9, 1 H, HC(1)), 3.47 (dd, *J* = 6.1, 12.7, 1 H, HC(2)), 3.43−3.34 (m, 3 H, HC(4), $H_2C(9)$), 3.23 (dd, *J* = 8.9, 12.7, 1 H, HC(4)), 3.01 (m, 1 H, HC(2)), 2.36−2.27 (m, 2 H, HC(6), HC(7)), 2.23 (dd, *J* = 6.0, 11.8, 1 H, HC(7a)), 2.01−1.86 (m, 2 H, HC(5a), HC(5)), 1.77−1.71 (m, 2 H, (CH_2)), 1.54 (s, 3 H, HC(8)), 1.28 (m, 9 H, (CH_2)), 0.88 (t, 3 H, *J* = 7.0, HC(14)), 0.8−2.5 (br, 3 H, $(H_3B)^3$); ^{13}C NMR (126 MHz, $CDCl_3$) 86.7 (C(7b)), 80.4 (C(1)), 70.4 (C(2)), 66.8 (C(7a)), 64.1 (C(4)), 58.9 (C(9)), 51.2 (C(5a)), 33.2 (C(6)), 31.6 (C(10)), 31.1 (C(11)), 29.8 (C(5)), 29.1 (C(7)), 25.7 (C(12 or 13)), 24.8 (C(8)), 22.5 (C(12 or 13)), 14.0 (C(14)); IR ($CDCl_3$, film) 2964 (m), 2950 (s), 2930 (s), 2858 (m), 2361 (s), 2341 (s), 262 (m), 1654 (w), 1631 (w), 1475 (w), 1457 (w), 1378 (w), 1365 (w), 163 (w), 1126 (w), 1092 (w); MS (ESI, Q-tof) 264 (83), 252 (100), 179 (12); mol formula $C_{16}H_{32}BNO$ 265.24; HRMS $C_{16}H_{31}BNO$ (264.2499) calcd 264.2499, found 264.2487; TLC R_f 0.67 (hexanes/EtOAc, 3:1) [I_2].



*Preparation of (1R,3S,5aS,7aS,7bR)-Octahydro-1-(methoxyethoxymethoxy)-7b-methyl-2H-cyclopenta[gh]pyrrolizine·Borane (**III**{4}).* Following general procedure I, to a two-necked, 25 mL, round-bottomed flask equipped with a nitrogen inlet adapter, a rubber septum, and a magnetic stir bar were added sequentially alcohol **11b** (200 mg, 1.1 mmol), dimethylformamide (3.6 mL, ∼0.3 M), and then sodium hydride (32 mg, 1.32 mmol, 1.2 equiv) at 0 °C. After 15 min, methoxyethoxylmethyl chloride (151 μL, 1.32 mmol, 1.2 equiv) was added via syringe. The solution was stirred for 2 h and then quenched onto ice−water (20 mL). Extraction and purification by silica gel column chromatography as described in general procedure I afforded 127 mg (43%) of methoxyethoxymethyl ether **III**{*4*} as a clear, viscous oil. Data for **III**{*4*}: ^{1}H NMR (500 MHz, $CDCl_3$) 4.81 (m, 2 H, HC(9), HC(1)), 4.73 (ddd, *J* = 7.1, 7.1, 7.1, 1 H, HC(9)), 3.98 (m, 1 H, HC(2)), 3.71 (m, 2 H, $H_2C(10)$), 3.56 (dd, *J* = 3.7, 5.6, 1 H, $H_2C(11)$), 3.39 (s, 3 H, HC(12)), 3.03 (m, 2 H, HC(7a), HC(5a)), 2.96 (m, 1 H, HC(4)), 2.70 (ddd, 1 H, *J* = 6.2, 11.1, 11.0, HC(2)), 2.12 (m, 2 H, HC(4), HC(5)), 1.83 (m, 3 H, HC(5), HC(6), HC(7)), 1.51 (m, 1 H, HC(6)), 1.40 (m, 1 H, HC(7)), 1.31 (s, 3 H, HC(8)); ^{13}C NMR (126 MHz, $CDCl_3$) 94.3 (C(11)), 92.1 (C(11)), 90.7 (C(11)), 82.5 (C(9)), 82.0 (C(9)), 71.7 (C(2)), 67.4 (C(12)), 66.8 (C(13)), 59.0 (C(1)), 57.7 (C(14)), 56.6 (C(8)), 53.5 (C(3)), 51.5 (C(6)), 31.4 (C(7)), 30.6 (C(5)), 30.4 (C(4)), 27.6 (C(10)); IR (NaCl plate, film) 2932 (s), 2879 (m), 2366 (s), 2331 (s), 2276 (m), 1653 (w), 1478 (m), 1452 (m), 1379 (m), 1162 (s), 1121 (s), 1097 (s), 1051 (s), 989 (m), 934 (w), 849 (m), 796 (w), 668 (w); MS (ESI, Q-tof) 256 (100), 257 (16); mol formula $C_{14}H_{25}NO_3$ 255.18; HRMS $C_{14}H_{26}NO_3$ (256.1913) calcd 256.1913, found 256.1903; TLC R_f 0.35 (CH_2Cl_2/MeOH, 9/1) [I_2].



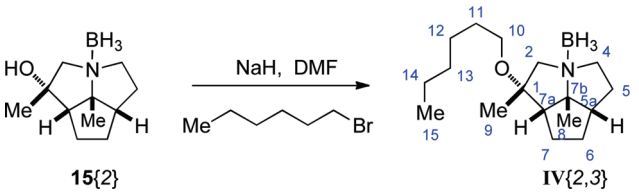
*Preparation of (1R,3S,5aS,7aS,7bR)-Octahydro-1-(2-pyridyloxy)-7b-methyl-2H-cyclopenta[gh]pyrrolizine·Borane (**III**{5}).* Following general procedure I, to a two-necked, 25 mL, round-bottomed flask equipped with a nitrogen inlet adapter, a rubber septum, and a magnetic stir bar were added sequentially alcohol **11b** (25 mg, 0.14 mmol), dimethylformamide (1.5 mL, ∼0.1 M), and then sodium hydride (4 mg, 0.17 mmol, 1.2 equiv) at 0 °C. After 15 min, 2-fluoropyridine (7.4 μL, 0.17 mmol, 1.2 equiv) was added via syringe. The solution was stirred for 2 h and then quenched onto ice−water (20 mL). Extraction and purification by silica gel column chromatography as described in general procedure I afforded 33 mg (93%) of 2-pyridyl ether **III**{*5*} as a clear, viscous oil. Data for **III**{*5*}: ^{1}H NMR (500 MHz, $CDCl_3$) 8.09 (ddd, *J* = 0.6, 1.9, 5.0, 1 H, HC(13)), 7.56 (ddd, *J* = 2.0, 7.1, 8.4, 1 H, HC(11)), 6.86 (ddd, *J* = 0.8, 5.1, 7.0, 1 H, HC(12)), 6.74 (d, *J* = 8.3, 1 H, HC(10)), 5.27 (ddd, *J* = 5.9, 7.5, 7.3, 1 H, HC(1)), 3.80 (dd, *J* = 6.2, 13.0, 1 H, C(2)), 3.47 (ddd, *J* = 4.2, 7.3, 11.4, 1 H, HC(4)), 3.38 (dd, *J* = 7.7, 12.9, 1 H, HC(2)), 3.22 (ddd, *J* = 6.7, 3.7, 10.7, 1 H, HC(4)), 2.49 (dd, *J* = 5.3, 12.6, 1 H, HC(7a)), 2.40−2.29 (m, 1 H, HC(5a), HC(5 or 6)), 2.04−1.85 (m, 1 H, HC(5 or 6), HC(7))), 1.69−1.51 (m, 3 H, HC(6), HC(7), HC(5)), 1.61 (s, 3 H, $H_3C(8)$), 0.8−2.5 (br, 3 H, $(H_3B)^3$); ^{13}C NMR (126 MHz, $CDCl_3$) 162.8 (C(9)), 146.6 (C(13)), 138.7 (C(11)), 117.1 (C(12)), 111.5 (C(10)), 86.6 (C(7b)), 75.9 (C(1)), 66.9 (C(2)), 64.6 (C(4)), 58.3 (C(7a)), 51.6 (C(5a)), 33.1 (C(5)), 30.9 (C(6)), 29.2 (C(7)), 24.8 (C(8)); IR (NaCl plate, film) 2953 (s), 2864 (m), 2374 (m), 2330 (m), 2277 (m), 1598 (s), 1570 (s), 1470 (s), 1433 (s), 1371 (m), 1307 m), 1272 (s), 1252 (m), 1163 (m), 142 (w), 1097 (w), 1049 (w), 1014 (w); MS (ESI, Q-tof) 257 (8), 255 (16), 246 (25), 245 (100), 162 (12), 150 (31); mol formula $C_{15}H_{23}BN_2O$ (258.17); HRMS $C_{15}H_{24}BN_2O$ 257.1825 calcd 257.1825, found 257.1815; TLC R_f 0.55 (hexanes/EtOAc, 3:1) [I_2].



*4. Preparation of Amino·Borane Intermediates **IV**{2−5,2−3}. Preparation of (1S,3S,5aS,7aS,7bR)-Octahydro-1-benzyloxy-1-methyl-7b-methyl-2H-cyclopenta[gh]pyrrolizine·Borane (**IV**{2,2}).* Following general procedure I, to a two-necked, 10 mL, round-bottomed flask equipped with a nitrogen inlet adapter, rubber septum, and a magnetic stir bar were added sequentially alcohol 15{*2*} (49 mg, 0.250 mmol), dimethylformamide (2.5 mL, ∼0.1 M), and then sodium hydride (9.0 mg, 0.375 mmol, 1.2 equiv) at 0 °C. After 15 min, benzyl bromide (60 μL, 0.500 mmol, 1.2 equiv) was added via syringe. The solution was stirred for 2 h and then quenched onto ice−water (10 mL). Extraction and purification by silica gel column chromatography as described in general procedure I afforded 64 mg (89%) of benzyl ether **IV**{*2,2*} as a clear, viscous oil. Data for **IV**{*2,2*}: ^{1}H NMR (500 MHz, $CDCl_3$) 7.37−7.26 (m, 5 H, HC(12), HC(13), HC(14)), 4.40 (s, 2 H, $H_2C(10)$), 3.64 (dd, *J* = 6.7, 10.3, 1 H, HC(4)), 3.56 (d, *J* = 13.5, 1 H, HC(2)), 3.25 (dd, *J* = 4.5, 11.0, 1 H, HC(4)), 3.24 (d, *J* = 13.4, 1 H, HC(2)), 2.39−2.33 (m, 1 H, HC(5a)), 2.29−2.22 (m, 2 H, HC(7a), HC(5)), 2.22−2.13 (m, 1 H, HC(7)), 1.86−1.78 (m, 1 H, HC(6)), 1.77−1.69 (m, 2 H, HC(7), HC(6)), 1.49 (s, 3 H, $H_3C(8$ or 9)), 1.47 (s, 3 H, $H_3C(8$ or 9)), 1.47−1.43 (m, 1 H, HC(5)), 0.8−2.5 (br, 3 H, $(H_3B)^{92}$); ^{13}C NMR (126 MHz, $CDCl_3$) 139.0 (C(11)), 129.0 (C(12, 13, or 14)), 128.0 (C(12, 13, or 14)), 127.0 (C(12, 13, or 14)), 88.7 (C(7b)), 81.8 (C(1)), 70.8 (C(2)), 65.3 (C(10)), 64.4 (C(7a)), 64.0 (C(4)), 52.1 (C(5a)), 34.3 (C(6)), 29.5 (C(5)), 27.3 (C(7)), 25.6 (C(8 or 9)), 25.5 (C(8 or 9)); IR (NaCl plate, film) 2966 (s), 2858 (m), 2375 (s), 2326 (s), 2279 (s), 1454 (m), 1382 (m), 1172 (s), 1087 (m), 1028 (m), 933 (w) 905 (w), 855 (w), 754 (s) (696 (m); MS (EI, 70 eV) 284 (5), 271 (1), 256 (2), 180 (100), 165 (28), 149 (3), 138 (2), 122 (4), 109 (8); mol formula

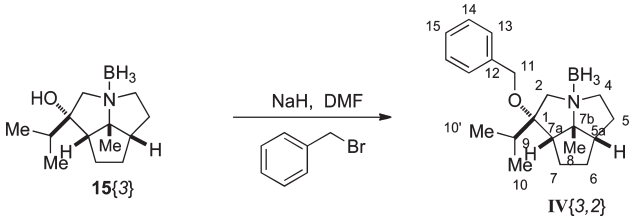
dx.doi.org/10.1021/jo2005445 |*J. Org. Chem.* 2011, 76, 4260–4336

$C_{18}H_{28}BNO$ (285.23); HRMS $C_{18}H_{27}BNO$ (284.2186) calcd 284.2186, found 284.2184; TLC R_f 0.23 (hexanes/TBME, 9:1) [I_2, CAM].



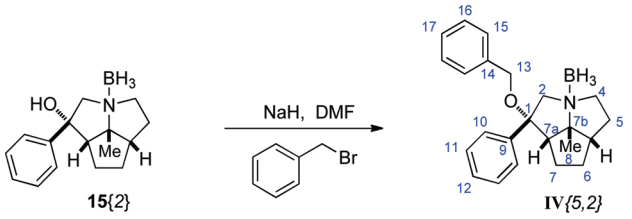
15{2} **IV**{2,3}

*Preparation of (1S,3S,5aS,7aS,7bR)-Octahydro-1-hexyloxy-1-methyl-7b-methyl-2H-cyclopenta[gh]pyrrolizine·Borane (**IV**{2,3}).* To a one-necked, round-bottomed flask equipped with a nitrogen inlet adapter, rubber septum, and a magnetic stir bar were added sequentially **15**{2} (49 mg, 0.250 mmol), dimethylformamide (2.5 mL, 0.1 M), and sodium hydride (6 mg, 0.250 mmol). After being stirred for 15 min, 1-bromohexane (41 μL, 0.250 mmol) was added. After the mixture was stirred for 2 h, NaH (6 mg, 0.250 mmol) was added. After an addition 15 min of stirring, 1-bromohexane (41 μL, 0.250 mmol) was added. After the resulting mixture was stirred for 2 h, NaH (6 mg, 0.250 mmol) was added, followed by 1-bromohexane (41 μL, 0.250 mmol) after an additional 15 min of stirring. After 2 h, the reaction was quenched with water (10 mL) at 0 °C. Extraction and purification by silica gel column chromatography as described in general procedure I afforded 47 mg (69%) of hexyl ether **IV**{2,3} as a clear, viscous oil. Data for **IV**{2,3}: ^{1}H NMR (500 MHz, $CDCl_3$) 3.64 (ddd, J = 6.5, 10.2, 10.0, 1 H, HC(4)), 3.48 (d, J = 13.4, 1 H, HC(2)), 3.29 (ddd, J = 1.6, 6.6, 6.6, 2 H, H_2C(10)), 3.28 (m, 1 H, HC(4)), 3.14 (d, J = 13.4, 1 H, HC(2)), 2.33 (m, 1 H, HC(5a)), 2.25 (m, 1 H, HC(5)), 2.15 (dd, J = 6.3, 8.1, 1 H, HC(7a)), 2.07 (ddd, J = 6.2, 6.2, 13.1, 1 H, HC(7)), 1.85 (dddd, J = 7.3, 7.3, 7.2, 12.6, 1 H, HC(6)), 1.77−1.71 (m, 1 H, HC(6)), 1.71−1.64 (m, 1 H, HC(6)),1.54−1.49 (m, 3 H, HC(5), H_2C(11)) 1.49 (s, 3 H, H_3C(8)), 1.35 (s, 3 H, H_3C(9)), 1.35−1.25 (m, 6 H, H_2C(12), H_2C(13), H_2C(14)), 0.88 (dd, J = 6.9, 6.9, 3 H, H_3(15)), 0.8−2.5 (br, 3 H, $(H_3B)^{92}$); ^{13}C NMR (126 MHz, $CDCl_3$) 88.6 (C(7b)), 81.1 (C(1)), 70.3 (C(2)), 64.6 (C(7a)), 63.7 (C(4)), 62.9 (C(10)), 52.1 (C(5a)), 34.5 (C(6)), 31.8 (C(13)), 30.3 (C(11)), 29.6 (C(5)), 27.0 (C(7)), 26.1 (C(12 or 14)), 25.7 (C(8)), 25.1 (C(9)), 22.7 (C(12 or 14)), 14.2 (C(15)); IR (NaCl plate, film) 2931 (s), 2865 (s), 2376 (s), 2326 (s), 2279 (s), 1456 (s), 1378 (s), 1301 (m), 1172 (s), 1086 (s), 1021 (m), 965 (w), 924 (w), 851 (w), 756 (s); MS (EI, 70 eV) 278 (13), 265 (6), 250 (16), 194 (10), 180 (100), 165 (38), 150 (6), 138 (10), 123 (13), 110 (41); mol formula $C_{17}H_{34}BNO$ (279.27); HRMS $C_{17}H_{33}BNO$ (278.2655) calcd 278.2655, found 278.2656; TLC R_f 0.35 (hexanes/TBME, 9:1) [I_2, CAM].



15{3} **IV**{3,2}

*Preparation of (1S,3S,5aS,7aS,7bR)-Octahydro-1-benzyloxy-1-isopropyl-7b-methyl-2H-cyclopenta[gh]pyrrolizine·Borane (**IV**{3,2}).* Following general procedure I, to a two-necked, 10 mL, round-bottomed flask equipped with a nitrogen inlet adapter, rubber septum, and a magnetic stir bar were added sequentially alcohol **15**{3} (30 mg, 0.134 mmol), dimethylformamide (1.3 mL, ~0.1 M), and then sodium hydride (4.8 mg, 0.202 mmol, 1.5 equiv) at 0 °C. After 15 min, benzyl bromide (24 μL, 0.202 mmol, 1.5 equiv) was added via syringe. The solution was stirred for 2 h and then quenched onto ice−water (10 mL). Extraction and purification by silica gel column chromatography as described in general procedure I afforded 39 mg (92%) of benzyl ether **IV**{3,2} as a clear, viscous oil. Data for **IV**{3,2}: ^{1}H NMR (500 MHz, $CDCl_3$) 7.37−7.33 (m, 4 H, HC(13), HC(14)), 7.31−7.27 (m, 1 H, HC(15)), 4.49 (d, J = 11.3, 1 H, HC(11)), 4.42 (d, J = 11.3, 1 H, HC(11)), 3.84−3.77 (m, 1 H, HC(4)), 3.63 (d, J = 14.5, 1 H, HC(2)), 3.39 (d, J = 14.5, 1 H, HC(1)), 3.29 (dd, J = 8.5, 8.5, 1 H, HC(4)), 2.41−2.32 (m, 3 H, HC(7a), HC(5a), HC(5)), 2.27−2.20 (m, 1 H, HC(6)), 2.22−2.16 (m, 1 H, HC(9)), 1.96−1.88 (m, 1 H, HC(7)), 1.78−1.66 (m, 2 H, HC(7), HC(6)), 1.49 (s, 3 H, H_3C(8)), 1.44−1.40 (m, 1 H, HC(5)), 1.00 (d, J = 6.8, 3 H, H_3C(10)), 0.96 (d, J = 6.8, 3 H, H_3C(10′)), 0.8−2.5 (br, 3 H, $(H_3B)^{92}$); ^{13}C NMR (126 MHz, $CDCl_3$) 138.5 (C(12)), 128.7 (C(13)), 127.6 (C(15)), 127.1 (C(14)), 88.6 (C(1)), 87.5 (C(7b)), 65.1 (C(11)), 64.1 (C(2)), 63.1 (C(4)), 58.4 (C(7a)), 51.5 (C(5a)), 35.9 (C(7)), 30.6 (C(9)), 30.4 (C(5)), 28.3 (C(6)), 25.1 (C(8)), 18.4 (C(10)), 17.6 (C(11)); IR ($CHCl_3$) 3071 (w), 3028 (w), 2964 (s), 2379 (s), 2326 (s), 2278 (s), 2234 (w), 1957 (w), 1876 (w), 1812 (w), 1727 (w), 1599 (w), 1496 (m), 1468 (m), 1454 (s), 1379 (s), 1330 (w), 1264 (m), 1168 (s), 1085 (s), 1063 (s), 1028 (m), 970 (w), 912 (s), 850 (w), 794 (w), 734 (s), 697 (s); MS (EI, 70 eV) 312 (41), 299 (4), 268 (6), 256 (8), 220 (5), 208 (100), 193 (27), 164 (8), 149 (16), 126 (24); mol formula $C_{20}H_{32}BNO$ (313.29); HRMS $C_{20}H_{31}BNO$ (312.2499) calcd 312.2499, found 312.2497; TLC R_f 0.25 (hexanes/TBME, 4:1) [I_2, CAM].



15{2} **IV**{5,2}

*Preparation of (1R,3S,5aS,7aS,7bR)-Octahydro-1-benzyloxy-1-phenyl-7b-methyl-2H-cyclopenta[gh]pyrrolizine·Borane (**IV**{5,2}).* Following general procedure I, to a two-necked, 10 mL, round-bottomed flask equipped with a nitrogen inlet adapter, rubber septum, and a magnetic stir bar were added sequentially alcohol **15**{5,2} (60 mg, 0.233 mmol), dimethylformamide (2.3 mL, ~0.1 M), and then sodium hydride (8.4 mg, 0.350 mmol, 1.5 equiv) at 0 °C. After 15 min, benzyl bromide (42 μL, 0.350 mmol, 1.5 equiv) was added via syringe. The solution was stirred for 2 h and then quenched onto ice−water (10 mL). Extraction and purification by silica gel column chromatography as described in general procedure I afforded 80 mg (98%) of benzyl ether **IV**{5,2} as a clear, viscous oil. Data for **IV**{5,2}: ^{1}H NMR (500 MHz, $CDCl_3$) 7.41−7.36 (m, 4 H), 7.34−7.30 (m, 3 H), 7.30−7.23 (m, 3 H), 4.32 (d, J = 11.5, 1 H, HC(2)), 4.01 (ddd, J = 14.3, 14.3, 14.2, 2 H, HC(13)), 3.98 (d, J = 11.9, 1 H, HC(2)), 4.00−3.95 (m, 1 H, HC(4)), 3.46−3.42 (m, 1 H, HC(4)), 2.68 (dd, J = 3.9, 8.3, 1 H, HC(7a)), 2.58−2.53 (m, 1 H, HC(7)), 2.44−2.46 (m, 2 H, HC(5a), HC(5)), 2.05−2.01 (m, 1 H, HC(6)), 1.94−1.83 (m, 2 H, HC(7), HC(6)), 1.57 (dd, 7.9, 10.5, 1 H, HC(5)), 1.51 (s, 3 H, H_3C(8)), 0.8−2.5 (br, 3 H, $(H_3B)^{92}$); ^{13}C NMR (126 MHz, $CDCl_3$) 142.2 (C(9)), 138.1 (C(14)), 128.9, 128.5, 128.1, 127.5, 127.0, 126.0, 88.6 (C(7b)), 85.9 (C(1)), 66.1 (C(2)), 65.6 (C(13)), 65.4 (C(4)), 62.7 (C(7a), 52.0 (C(5a)), 35.5 (C(6)), 29.9 (C(5)), 27.2 (C(7)), 25.7 (C(8)); IR ($CHCl_3$) 3064 (w), 3031 (w), 2965 (s), 2869 (m), 2376 (s), 2332 (s), 2277 (s), 2243 (m), 1497 (m), 1448 (m), 1379 (w), 1177 (s), 1132 (w), 1088 (m), 1059 (s), 1027 (w), 911 (s), 849 (w), 732 (s), 699 (s); MS (EI, 70 eV) 333.2 (1), 332.2 (1), 318.2 (1), 242.1 (100), 227.1 (9), 105 (32); mol formula $C_{23}H_{30}BNO$ (347.30); HRMS $C_{23}H_{27}NO$,

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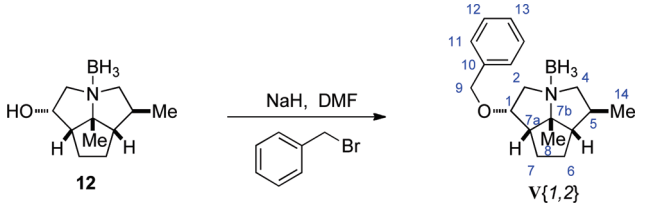
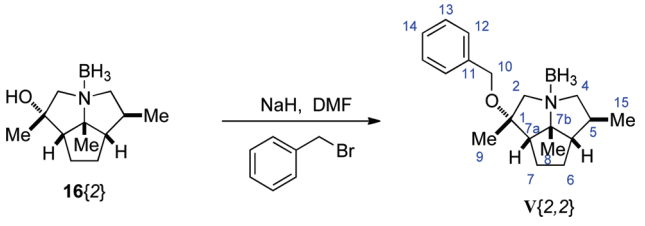
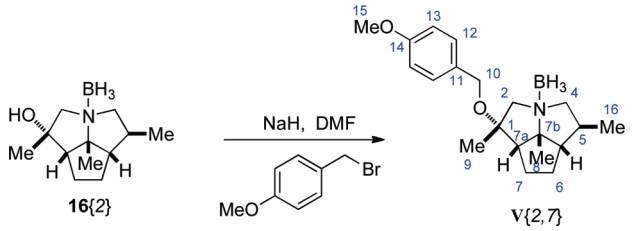
(333.2093) calcd 333.20927, found 333.20927; TLC R_f 0.28 (hexanes/TBME, 9:1) [I_2, CAM].



5. Preparation of Amino·Borane Intermediates ***V****{2−7, 2−7}. Preparation of (1S,3S,5S,5aS,7aS,7bR)-Octahydro-1-benzyloxy-5-methyl-7b-methyl-2H-cyclopenta[gh]pyrrolizine·Borane (****V****{1,2}).* Following general procedure I, to a two-necked, 10 mL, round-bottomed flask equipped with a nitrogen inlet adapter, rubber septum, and a magnetic stir bar were added sequentially alcohol **12** (30 mg, 0.154 mmol), dimethylformamide (1.5 mL, ∼0.1 M), and then sodium hydride (5.5 mg, 0.231 mmol, 1.2 equiv) at 0 °C. After 15 min, benzyl bromide (27 μL, 0.231 mmol, 1.2 equiv) was added via syringe. The solution was stirred for 2 h and then quenched onto ice−water (10 mL). Extraction and purification by silica gel column chromatography as described in general procedure I afforded 40 mg (91%) of benzyl ether V{*1,2*} as a clear, viscous oil. Data for **V**{*1,2*}: ^{1}H NMR (500 MHz, $CDCl_3$) 7.33 (m, 5 H, HC(11), HC(12), HC(13)), 4.53 (ddd, *J* = 6.6, 6.6, 10.7, 1 H, HC(1)), 4.51 (d, *J* = 11.7, 1 H, HC(1)), 4.45 (d, *J* = 11.4, 1 H, HC(9)), 3.51 (dd, *J* = 6.5, 10.4, 1 H, HC(2)), 3.16 (dd, *J* = 6.1, 12.5, 1 H, HC(4)), 3.06 (dd, *J* = 10.6, 10.6, 1 H, HC(2)), 2.82 (dd, *J* = 12.5, 12.5, 1 H, HC(4)), 2.42 (dd, *J* = 8.0, 17.0, 1 H, HC(7a)), 2.09−2.00 (m, 1 H, HC(5)), 2.00−1.92 (m, 1 H, HC(7)), 1.89−1.85 (m, 1 H, HC(5a)), 1.82−1.76 (m, 1 H, HC(7)), 1.75−1.70 (m, 2 H, H_2C(6)), 1.51 (s, 1 H, H_3C(8)), 1.02 (d, *J* = 6.4, 3 H, H_3C(14)), 0.8−2.5 (br, 3 H, $(H_3B)^3$); ^{13}C NMR (126 MHz, $CDCl_3$) 138.1 (C(10)), 128.6 (C(13)), 128.0 (C(12)), 127.8 (C(11)), 88.1 (C(7b)), 76.0 (C(1)), 72.0 (C(9)), 70.0 (C(4)), 64.3 (C(2)), 62.0 (C(5a)), 53.3 (C(7a)), 34.6 (C(5)), 29.6 (C(6)), 26.7 (C(7)), 25.9 (C(8)), 16.4 (C(16)); IR (NaCl plate, film) 3064 (w), 3021 (w), 2960 (s), 2922 (s), 2872 (s), 2379 (s), 2326 (s), 2276 (s), 2234 (w), 1654 (w), 1497 (w), 1472 (m), 1456 (s), 1380 (m), 1364 (s), 1326 (w), 1305 (w), 1234 (w), 1186 (s), 1167 (s), 1142 (s), 1124 (s), 1054 (m), 1018 (w), 991 (m), 956 (w), 913 (s), 844 (w), 810 (w), 698 (s); MS (EI, eV) 284 (18), 256 (19), 228 (5), 180 (100), 165 (31), 110 (30), 91 (71), 84 (13); mol formula $C_{18}H_{28}BNO$ (285.23); HRMS $C_{18}H_{27}BNO$, (284.2186) calcd 284.21858, found 284.21909; TLC R_f 0.25 (hexanes/TBME, 9:1) [I_2, CAM].

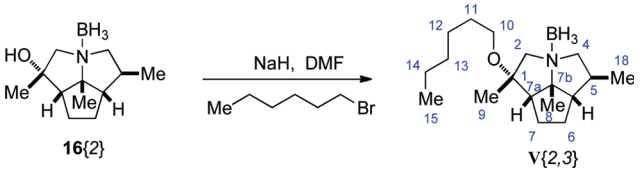


*Preparation of (1S,3S,5S,5aS,7aS,7bR)-Octahydro-1-benzyloxy-1-methyl-5-methyl-7b-methyl-2H-cyclopenta[gh]pyrrolizine·Borane (****V****{2,2}).* Following general procedure I, to a two-necked, 10 mL, round-bottomed flask equipped with a nitrogen inlet adapter, rubber septum, and a magnetic stir bar were added sequentially alcohol **16**{*2*} (42 mg, 0.200 mmol), dimethylformamide (2.0 mL, ∼0.1 M), and then sodium hydride (7.2 mg, 0.300 mmol, 1.5 equiv) at 0 °C. After 15 min, benzyl bromide (48 μL, 0.4 mmol, 2.0 equiv) was added via syringe. The solution was stirred for 2 h and then quenched onto ice−water (10 mL). Extraction and purification by silica gel column chromatography as described in general procedure I afforded 58 mg (97%) of benzyl ether **V**{*2,2*} as a clear, viscous oil. Data for **V**{*2,2*}: ^{1}H NMR (500 MHz, $CDCl_3$) 7.36−7.27 (m, 5 H, HC(12), HC(13), HC(14)), 4.43 (d, *J* = 11.1, 1 H, HC(10)), 4.35 (d, *J* = 11.1, 1 H, HC(10)), 3.50 (d, *J* = 11.6, 1 H, HC(2)), 3.35 (d, *J* = 11.6, 1 H, HC(2)), 3.23 (dd, *J* = 6.3, 12.5, 1 H, HC(4)), 2.96 (dd, *J* = 12.4, 12.4, 1 H, HC(4)), 2.21−2.12 (m, 2 H, HC(7a), HC(7)), 2.10−2.01 (m, 1 H, HC(5)), 1.88−1.83 (m, 2 H, HC(5a), HC(7)), 1.78−1.74 (m, 1 H, HC(6)), 1.75 (s, 3 H, H_3C(9)), 1.71−1.64 (m, 1 H, HC(6)), 1.57 (s, 3 H, H_3C(8)), 0.99 (d, *J* = 6.4, 3 H, H_3C(15)), 0.8−2.5 (br, 3 H, $(H_3B)^{92}$); ^{13}C NMR (126 MHz, $CDCl_3$) 138.7 (C(11)), 128.5 (C(13)), 127.6 (C(12)), 127.2 (C(14)), 88.7 (C(7b)), 79.9 (C(1)), 73.5 (C(4)), 73.3 (C(2)), 65.8 (C(10)), 62.1 (C(5a)), 61.3 (C(7a)), 33.5 (C(5)), 29.0 (C(6)), 27.3 (C(7)), 26.3 (C(8)), 25.9 (C(9)), 16.0 (C(15)); IR ($CHCl_3$) 2961 (s), 2398 (s), 2282 (s), 1497 (w), 1457 (s), 1384 (m), 1152 (s), 1063 (m), 1028 (m), 956 (w), 697 (m); MS (EI, 70 eV) 298 (4), 270 (4), 194 (100), 179 (20), 110 (28), 91 (28); mol formula $C_{19}H_{30}BNO$ (299.26); HRMS $C_{19}H_{29}BNO$ (298.2342) calcd 298.2342, found 298.2341; TLC R_f 0.30 (hexanes/TBME, 9:1) [I_2, CAM].

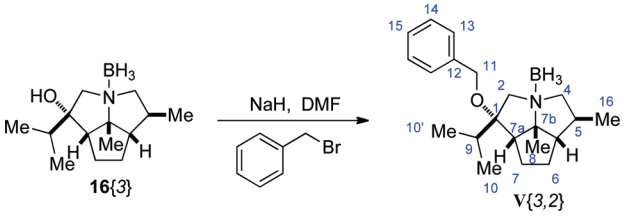


*Preparation of (1S,3S,5S,5aS,7aS,7bR)-Octahydro-1-(4-methoxybenzyloxy)-1-methyl-5-methyl-7b-methyl-2H-cyclopenta[gh]pyrrolizine·Borane (****V****{2,7}).* Following general procedure I, to a two-necked, 10 mL, round-bottomed flask equipped with a nitrogen inlet adapter, rubber septum, and a magnetic stir bar were added sequentially alcohol **16**{*2*} (42 mg, 0.200 mmol), dimethylformamide (2.0 mL, ∼0.1 M), then sodium hydride (7.2 mg, 0.300 mmol, 1.5 equiv) at 0 °C. After 15 min, 4-methoxybenzyl bromide (32 μL, 0.220 mmol, 1.1 equiv) was added via syringe. The solution was stirred for 2 h and then quenched onto ice−water (10 mL). Extraction and purification by silica gel column chromatography as described in general procedure I afforded 58 mg (86%) of 4-methoxybenzyl ether **V**{*2,7*} as a clear, viscous oil. Data for **V**{*2,7*}: ^{1}H NMR (500 MHz, $CDCl_3$) 7.23 (d, *J* = 8.6, 2 H, HC(13)), 6.87 (d, *J* = 8.7, 2 H, HC(12)), 4.35 (d, *J* = 10.6, 1 H, HC(10)), 4.26 (d, *J* = 10.6, 1 H, HC(10)), 3.80 (s, 1 H, H_3C(13)), 3.48 (d, *J* = 11.6, 1 H, HC(2)), 3.32 (d, *J* = 11.6, 1 H, HC(2)), 3.21 (dd, *J* = 6.3, 12.4, 1 H, HC(4)), 2.95 (dd, *J* = 12.4, 12.4, 1 H, HC(4)), 2.19−2.10 (m, 2 H, HC(7a), HC(7)), 2.08−2.00 (m, 1 H, HC(5)), 1.90−1.82 (m, 2 H, HC(7), HC(5a)), 1.77−1.74 (m, 1 H, HC(6)), 1.74 (s, 3 H, H_3C(9)), 1.70−1.62 (m, 1 H, HC(6)), 1.56 (s, 3 H, H_3C(8)), 0.98 (d, *J* = 6.4, 3 H, H_3C(16)), 0.8−2.5 (br, 3 H, $(H_3B)^{92}$); ^{13}C NMR (126 MHz, $CDCl_3$) 159.2 (C(14)), 130.7 (C(11)), 128.9 (C(13)), 113.9 (C(12)), 88.7 (C(7b)), 79.8 (C(1)), 73.5 (C(4)), 73.3 (C(2)), 65.5 (C(10)), 62.1 (C(5a)), 61.2 (C(7a)), 55.4 (C(15)), 33.4 (C(5)), 29.0 (C(6)), 27.3 (C(7)), 26.3 (C(8)), 25.9 (C(9)), 16.0 (C(16)); IR (NaCl plate, film) 2958 (s), 2929 (s), 2835 (s), 2396 (s), 2330 (s), 2282 (s), 1612 (s), 1586 (w), 1514 (s), 1457 (s), 1384 (s), 1349 (w), 1337 (w), 1302 (m), 1249 (s), 1166 (s), 1152 (s), 1108 (w), 1092 (m), 1064 (s), 1036 (s), 956 (m), 910 (w), 873 (w), 823(s); MS (EI, 70 eV) 328 (8), 194 (100), 179 (49), 164 (3), 151 (3), 121 (52), 110 (34); mol formula $C_{20}H_{32}BNO_2$ (329.28); HRMS $C_{20}H_{31}BNO_2$ (328.2448) calcd 328.2448, found 328.2448; TLC R_f 0.28 (hexanes/TBME, 9:1) [I_2, CAM].

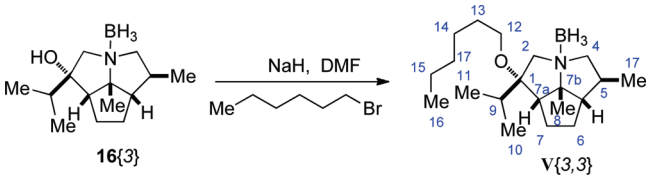
*Preparation of (1S,3S,5S,5aS,7aS,7bR)-Octahydro-1-hexyloxy-1-methyl-5-methyl-7b-methyl-2H-cyclopenta[gh]pyrrolizine·Borane (****V****{2,3}).* To a one-necked, round-bottomed flask equipped with a nitrogen inlet adapter, rubber septum, and a magnetic stir bar were added sequentially



16{2} (40 mg, 0.191 mmol), dimethylformamide (1.9 mL, 0.1 M), and sodium hydride (5 mg, 0.191 mmol). After the mixture was stirred for 15 min, 1-iodohexane (28 μL, 0.191 mmol) was added. After the mixture was stirred for 2 h, NaH (5 mg, 0.191 mmol) was added, followed by 1-iodohexane (28 μL, 0.191 mmol) after 15 min of stirring. After the mixture was stirred for 2 h, NaH (5 mg, 0.191 mmol) was added, followed by 1-iodohexane (28 μL, 0.191 mmol) after 15 min of stirring. After 2 h, the reaction was quenched with water (10 mL) at 0 °C. Extraction and purification by silica gel column chromatography as described in general procedure I afforded 31 mg (55%) of hexyl ether **V**{2,3} as a clear, viscous oil. Data for **V**{2,3}: ^{1}H NMR (500 MHz, $CDCl_3$) 3.40 (d, J = 11.7, 1 H, HC(2)), 3.25 (m, 4 H, HC(10), HC(2), HC(4)), 2.95 (dd, J = 12.4, 12.4, 1 H, HC(4)), 2.11−2.02 (m, 3 H, HC(7a), HC(7), HC(5)), 1.81 (dd, J = 6.4, 9.8, 1 H, HC(5a)), 1.73 (m, 2 H, HC(7), HC(6)), 1.69−1.62 (m, 1 H, HC(6)), 1.59 (s, 1 H, H_3C(9)), 1.52 (s, 3 H, H_3C(8)), 1.52−1.46 (m, 2 H, HC(11)), 1.33−1.22 (m, 6 H, HC(12), HC(13), HC(14)), 0.98 (d, J = 6.4, 3 H, H_3C(16)), 0.88 (dd, J = 6.9, 6.9, 3 H, H_3C(15)), 0.8−2.5 (br, 3 H, $(H_3B)^{92}$); ^{13}C NMR (126 MHz, $CDCl_3$) 88.65 (C(9)), 79.08 (C(2)), 73.55 (C(1 or 12)), 73.36 (C(1 or 12)), 63.69 (C(8)), 62.05 (C(3)), 61.47 (C(6)), 33.56 (C(7)), 31.85 (C(14, 15 or 16), 30.37 (C(13)), 29.11 (C(5)), 26.89 (C(4)), 26.24 (C(10)), 26.05 (C(14, 15, or 16)), 25.63 (C(11)), 22.74 (C(14, 15, or 16)), 16.12 (C(18)), 14.19 (C(17)); IR ($CDCl_3$, film) 2957 (s), 2931 (s), 2872 (s), 2396 (s), 2284 (s), 2241 (w), 1730 (w), 1459 (s), 1381 (m), 1348 (w), 1184 (s), 1168 (s), 1149 (s), 1064 (m), 913 (s); MS (ESI, 70 eV) 292 (51), 279 (7), 264 (20), 250 (5), 222 (3), 208 (13), 194 (100), 184 (30), 179 (41), 164 (8), 137 (6), 124 (22), 110 (67); mol formula $C_{18}H_{36}BNO$ (293.30); HRMS $C_{18}H_{35}BNO$ (292.2812) calcd 292.28118, found 292.28154; TLC R_f 0.35 (hexanes/TBME, 9:1) [I_2, CAM].

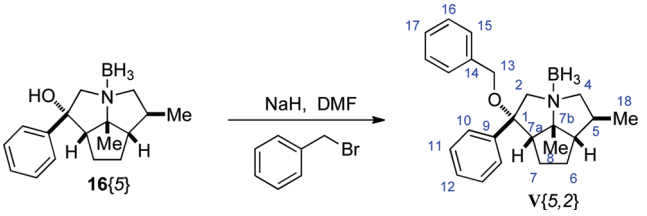


*Preparation of (1S,3S,5S,5aS,7aS,7bR)-Octahydro-1-benzyloxy-1-isopropyl-5-methyl-7b-methyl-2H-cyclopenta[gh]pyrrolizine·Borane (**V**{3,2}).* Following general procedure I, to a two-necked, 10 mL, round-bottomed flask equipped with a nitrogen inlet adapter, rubber septum, and a magnetic stir bar were added sequentially alcohol **16**{3} (59 mg, 0.250 mmol), dimethylformamide (2.5 mL, ~0.1 M), and then sodium hydride (9.0 mg, 0.375 mmol, 2.0 equiv) at 0 °C. After 15 min, benzyl bromide (60 μL, 0.500 mmol, 2.0 equiv) was added via syringe. The solution was stirred for 2 h and then quenched onto ice−water (10 mL). Extraction and purification by silica gel column chromatography as described in general procedure I afforded 80 mg (98%) of benzyl ether **V**{3,2} as a clear, viscous oil. Data for **V**{3,2}: ^{1}H NMR (500 MHz, $CDCl_3$) 7.37−7.28 (m, 5 H, HC(13), HC(14), HC(15)), 4.51 (d, J = 11.1, 1 H, HC(11)), 4.38 (d, J = 11.1, 1 H, HC(11)), 3.63 (d, J = 14.3, 1 H, HC(2)), 3.60 (d, J = 14.3, 1 H, HC(2)), 3.36 (dd, J = 8.3, 12.1, 1 H, HC(4)), 3.14 (dd, J = 10.3, 12.1, 1 H, HC(4)), 2.45−2.38 (m, 1 H, HC(7)), 2.37 (dd, J = 7.7,16.4, 1 H, HC(7a)), 2.29−2.21 (m, 1 H, HC(5)), 2.21−2.13 (m, 1 H, HC(9)), 1.84−1.77 (m, 3 H, H_2C(6), HC(5a)), 1.67−1.61 (m, 1 H, HC(7)), 1.48 (s, 3 H, H_3C(8)), 0.99 (d, J = 6.8, 1 H, H_3C(10)), 0.93 (d, J = 6.8, 3 H, H_3C(10′)), 0.84 (d, J = 6.7, 3 H, H_3C(16)), 0.8−2.5 (br, 3 H, $(H_3B)^{92}$); ^{13}C NMR (126 MHz, $CDCl_3$) 138.3 (C(12)), 128.6 (C(13) or C(15)), 127.6 (C(14)), 127.3 (C(13) or C(15)), 88.8 (C(7b) or C(1)), 85.1 (C(7b) or C(1)), 74.0 (C(4)), 69.4 (C(2)), 64.8 (C(11)), 59.6 (C(5a)), 57.1 (C(7a)), 34.7 (C(5)), 31.6 (C(6)), 30.3 (C(9)), 24.8 (C(7)), 24.7 (C(8)), 18.2 (C(10)), 17.7 (C(10′)), 17.6 (C(16)); IR ($CDCl_3$, film) 2962 (s), 2922 (s), 2870 (s), 2374 (s), 2327 (s), 2272 (s), 1497 (w), 1454 (s), 1379 (m), 1170 (s), 1147 (m), 1131 (m), 1057 (m), 1027 (m), 868 (w), 697 (m); MS (EI, 70 eV) 326 (6), 234 (6), 270 (11), 222 (s), 207 (21); mol formula $C_{21}H_{34}BNO$ (327.31); HRMS $C_{21}H_{33}BNO$ (326.2655) calcd 326.2655, found 326.2652; TLC R_f 0.24 (hexanes/TBME, 9:1) [I_2].

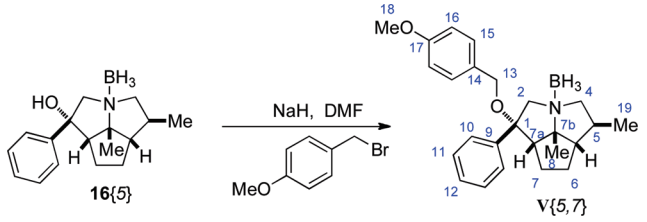


*Preparation of (1S,3S,5S,5aS,7aS,7bR)-Octahydro-1-hexyloxy-1-isopropyl-5-methyl-7b-methyl-2H-cyclopenta[gh]pyrrolizine·Borane (**V**{3,3}).* To a one-necked, round-bottomed flask equipped with a nitrogen inlet adapter, rubber septum, and a magnetic stir bar were added sequentially **16**{3} (59 mg, 0.250 mmol), dimethylformamide (2.5 mL, 0.1 M), and sodium hydride (6 mg, 0.250 mmol). After the mixture was stirred for 15 min, 1-bromohexane (35 μL, 0.250 mmol) was added. After 2 h of stirring, NaH (6 mg, 0.250 mmol) was added, followed 1-bromohexane (35 μL, 0.250 mmol) after an additional 15 min of stirring. After the mixture was stirred for 2 h, NaH (6 mg, 0.250 mmol) was added, followed by 1-bromohexane (35 μL, 0.250 mmol) after 15 min of stirring. After 2 h, the reaction was quenched with water (10 mL) at 0 °C. Extraction and purification by silica gel column chromatography as described in general procedure I afforded 37 mg (44%) of hexyl ether **V**{3,3} as a clear, viscous oil. Data for **V**{3,3}: ^{1}H NMR (500 MHz, $CDCl_3$) 3.51 (d, J = 14.2, 1 H, HC(2)), 3.45 (d, J = 14.2, 1 H, HC(2)), 3.40−3.26 (m, 3 H, HC(4), H_2C(14), 3.18 (dd, J = 10.5, 12.0, 1 H, HC(4)), 2.42−2.32 (m, 2 H, HC(7), HC(5)), 2.27 (dd, J = 7.0, 9.3, 1 H, HC(7a)), 2.01 (hept, J = 6.8, 1 H, HC(9)), 1.87−1.77 (m, 3 H, H_2C(6), HC(5a)), 1.60−1.51 (m, 3 H, HC(7), H_2C(13)), 1.45 (s, 3 H, H_3C(8)), 1.38−1.32 (m, 2 H, H_2C(14)), 1.36−1.25 (m, 4 H, H_2C(15), H_2C(16)), 0.96 (d, J = 6.7, 3 H, H_3C(10)), 0.91 (d, J = 6.8, 3 H, H_3C(10)), 0.89 (dd, J = 6.9, 6.9, 3 H, H_3C(11)), 0.82 (d, J = 6.8, 3 H, H_3C(17)), 0.8−2.5 (br, 3 H, $(H_3B)^{92}$); ^{13}C NMR (126 MHz, $CDCl_3$) 88.7 (C(1) or C(7b)), 84.1 (C(1) or C(7b)), 74.2 (C(4)), 69.3 (C(2)), 62.1 (C(12)), 59.6 (C(5a)), 57.0 (C(7a)), 34.7 (C(5)), 31.9 (C(15)), 31.6 (C(6)), 30.2 (C(13)), 29.9 (C(9)), 26.2 (C(14)), 24.6 (C(8)), 24.4 (C(7)), 22.7 (C(16)), 18.2 (C(10) or C(11)), 17.6 (C(10) or C(11) or C(17)), 17.6 (C(10) or C(11) or C(17)), 14.2 (C(16)); IR ($CDCl_3$, film) 2957 (s), 2230 (s), 2870 (s), 2376 (s), 2327 (s), 2273 (s), 1457 (s), 1378 (s), 1270 (w), 1170 (s), 1147 (m), 1084 (s); MS (EI, 70 eV) 320 (25), 318 (50), 307 (7), 292 (6), 278 (9), 276 (10), 264 (49), 236 (9), 222 (100), 207 (47), 192 (19), 180 (17), 164 (13), 137 (7), 124 (30), 110 (77); mol formula $C_{20}H_{40}BNO$ (321.35); HRMS $C_{20}H_{39}BNO$ (320.3125) calcd 320.3125, found 320.3125; TLC R_f 0.34 (hexanes/TBME, 9:1) [I_2]

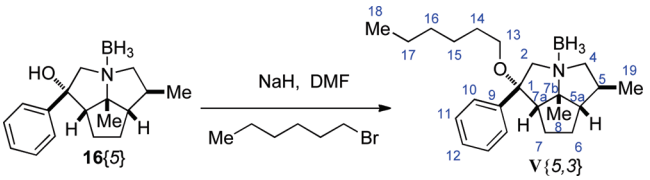
*Preparation of (1R,3S,5S,5aS,7aS,7bR)-Octahydro-1-benzyloxy-1-phenyl-5-methyl-7b-methyl-2H-cyclopenta[gh]pyrrolizine·Borane (**V**{5,2}).* Following general procedure I, to a two-necked, 10 mL, round-bottomed flask equipped with a nitrogen inlet adapter, rubber septum, and a magnetic stir bar were added sequentially alcohol **16**{5}(68 mg, 0.250 mmol), dimethylformamide (2.5 mL, ~0.1 M), and then sodium



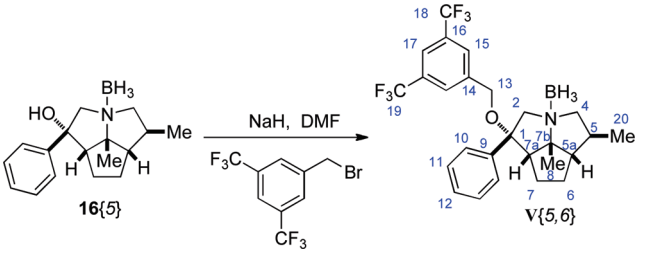
hydride (9.0 mg, 0.375 mmol, 2.0 equiv) at 0 °C. After 15 min, benzyl bromide (60 μL, 0.500 mmol, 2.0 equiv) was added via syringe. The solution was stirred for 2 h and then quenched onto ice−water (10 mL). Extraction and purification by silica gel column chromatography as described in general procedure I afforded 80 mg (89%) of benzyl ether **V**{*5,2*} as a clear, viscous oil. Data for **V**{*5,2*}: ^{1}H NMR (500 MHz, $CDCl_3$) 7.39 (m, 4 H), 7.33 (m, 3 H), 7.28 (d, *J* = 7.1, 1 H), 7.21 (d, *J* = 6.8, 2 H), 4.17 (d, *J* = 11.3, 1 H, HC(13)), 4.14 (d, *J* = 13.8, 1 H, HC(2)), 3.97 (d, *J* = 11.1, 1 H, HC(13)), 3.96 (d, *J* = 13.5, 1 H, HC(2)), 3.46 (dd, *J* = 7.9, 12.3, 1 H, HC(4)), 3.21 (dd, *J* = 11.2, 12.2, 1 H, HC(4)), 2.79 (dd, *J* = 8.0, 8.0, 1 H, HC(7a)), 2.73−2.63 (m, 1 H, HC(7)), 2.52−2.42 (m, 1 H, HC(5)), 1.97−1.88 (m, 4 H, HC(7), H_2C(6), HC(5a)), 1.52 (s, 3 H, H_3C(8)), 0.96 (d, *J* = 6.6, 3 H, H_3C(18)), 0.8−2.5 (br, 3 H, $(H_3B)^{92}$); ^{13}C NMR (126 MHz, $CDCl_3$) 141.8 (C(9) or C(14)), 138.0 (C(9) or C(14)), (128.7, 128.5, 128.1, 127.6, 127.4, 126.4) (C(10), C(11), C(12), C(15), C(16), C(17)), 88.8 (C(1) or C(7b)), 83.4 (C(1) or C(7b)), 73.6 (C(4)), 70.6 (C(2)), 66.3 (C(13)), 62.2 (C(7a)), 60.3 (C(5a)), 34.4 (C(5)), 30.9 (C(6)), 25.0 (C(8)), 24.2 (C(7)), 17.3 (C(18)); IR (NaCl plate, film) 2960 (s), 2329 (s), 1497 (m), 1172 (s), 1136 (w), 1058 (s), 931 (w), 700 (s); MS (EI, 70 eV) 358.2 (3), 256.1 (100), 241.1 (11), 105 (35); mol formula $C_{24}H_{32}BNO$ (361.33); HRMS $C_{24}H_{29}BNO$ (358.2342) calcd 358.2342, found 358.2336; TLC R_f 0.25 (hexanes/TBME, 9:1) [I_2].



*Preparation of (1R,3S,5S,5aS,7aS,7bR)-Octahydro-1-(4-methoxybenzyloxy)-1-phenyl-5-methyl-7b-methyl-2H-cyclopenta[gh]pyrrolizine·Borane (**V**{5,7}).* Following general procedure I, to a two-necked, 10 mL, round-bottomed flask equipped with a nitrogen inlet adapter, rubber septum, and a magnetic stir bar were added sequentially alcohol **16**{*5*} (68 mg, 0.250 mmol), dimethylformamide (2.5 mL, ∼0.1 M), and then sodium hydride (9.0 mg, 0.375 mmol, 2.0 equiv) at 0 °C. After 15 min, 4-methoxybenzyl bromide (40 μL, 0.275 mmol, 1.1 equiv) was added via syringe. The solution was stirred for 2 h and then quenched onto ice−water (10 mL). Extraction and purification by silica gel column chromatography as described in general procedure I afforded 89 mg (91%) of 4-methoxybenzyl ether **V**{*5,7*} as a clear, viscous oil. Data for **V**{*5,7*}: ^{1}H NMR (500 MHz, $CDCl_3$) 7.39 (m, 4 H, HC(10), HC(11)), 7.33 (m, 1 H, HC(12)), 7.11 (d, *J* = 8.7, 2 H, HC(15)), 6.84 (d, *J* = 8.7, 2 H, HC(16)), 4.12 (d, *J* = 13.4, 1 H, HC(13)), 4.09 (d, *J* = 10.7, 1 H, HC(2)), 3.94 (d, *J* = 13.4, 1 H, HC(13)), 3.89 (d, *J* = 10.6, 1 H, HC(2)), 3.79 (s, 3 H, H_3C(18)), 3.45 (dd, *J* = 7.9, 12.3, 1 H, HC(4)), 3.20 (dd, *J* = 11.2, 12.1, 1 H, HC(4)), 2.77 (dd, *J* = 7.9, 7.9, 1 H, HC(7a)), 2.70−2.61 (m, 1 H, HC(7)), 2.50−2.40 (m, 1 H, HC(5)), 1.96−1.83 (m, 4 H, HC(7), H_2C(6), HC(5a)), 1.51 (s, 3 H, H_3C(8)), 0.96 (d, *J* = 6.6, 3 H, H_3C(19)); ^{13}C NMR (126 MHz, $CDCl_3$) 159.2 (C(19)), 141.9 (C(11)), 130.1 (C(16)), 129.0 (C(17)), 128.7 (C(12) or C(11)), 128.1 (C(12)), 126.5 (C(10) or C(11)), 113.9 (C(16)), 88.8 (C(1) or C(7b)), 83.2 (C(1) or C(7b)), 73.6 (C(4)), 70.6 (C(13)), 66.0 (C(2)), 62.0 (C(7a)), 60.3 (C(5a)), 55.4 (C(18)), 34.4 (C(5)), 30.8 (C(6)), 25.0 (C(8)), 24.1 (C(7)), 17.3 (C(19)), 0.8−2.5 (br, 3 H, $(H_3B)^{92}$); IR ($CDCl_3$, film) 2957 (s), 2922 (s), 2869 (s), 2369 (s), 2329 (s), 2274 (s), 1613 (s), 1585 (w), 1514 (s), 1457 (s), 1379 (m), 1301 (m), 1249 (s), 1173 (s), 1136 (m), 1116 (w), 1033 (s), 823 (m), 756 (s), 700 (s); MS (EI, 70 eV) 388.2 (1), 256.2 (100), 241.2 (17), 105 (38); mol formula $C_{25}H_{34}BNO_2$ (391.35); HRMS $C_{25}H_{31}BNO_2$ (388.2448) calcd 388.2448, found 388.2444; TLC R_f 0.22 (hexanes/TBME, 9:1) [I_2].



*Preparation of (1R,3S,5S,5aS,7aS,7bR)-Octahydro-1-hexyloxy-1-phenyl-5-methyl-7b-methyl-2H-cyclopenta[gh]pyrrolizine·Borane (**V**{5,3}).* To a one-necked, round-bottomed flask equipped with a nitrogen inlet adapter, rubber septum, and a magnetic stir bar were added sequentially **16**{*5*} (64 mg, 0.236 mmol), dimethylformamide (2.4 mL, 0.1 M), and sodium hydride (6 mg, 0.250 mmol). After the mixture was stirred for 15 min, 1-bromohexane (33 μL, 0.236 mmol) was added, followed by addition of NaH (6 mg, 0.250 mmol) after 2 h of stirring. After the mixture was stirred for 15 min, 1-bromohexane (33 μL, 0.236 mmol) was added, followed by addition of NaH (6 mg, 0.250 mmol) after 2 h of stirring. After the mixture was stirred 15 min, 1-bromohexane (33 μL, 0.236 mmol) was added. After 2 h, the reaction was quenched with water (10 mL) at 0 °C. Extraction and purification by silica gel column chromatography as described in general procedure I afforded 63 mg (75%) of hexyl ether **V**{*5,3*} as a clear, viscous oil. Data for **V**{*5,3*}: ^{1}H NMR (500 MHz, $CDCl_3$) 7.33 (dd, *J* = 7.3, 7.3, 2 H, HC(10)), 7.29−7.24 (m, 3 H, HC(11), HC(12)), 4.03 (d, *J* = 13.6, 1 H, HC(2)), 3.85 (d, *J* = 13.6, 1 H, HC(2)), 3.45 (dd, *J* = 8.1, 12.2, 1 H, HC(4)), 3.24 (dd, *J* = 11.1, 12.0, 1 H, HC(4)), 3.13 (ddd, *J* = 6.4, 6.4, 8.9, 1 H, HC(13)), 2.82 (ddd, *J* = 6.5, 6.5, 8.9, 1 H, HC(13)), 2.70−2.61 (m, 2 H, HC(7a), HC(7)), 2.59−2.50 (m, 1 H, HC(5)), 1.90 (m, 4 H, HC(7), H_2C(6), HC(5a)), 1.47 (s, 3 H, H_3C(8)), 1.47−1.41 (m, 2 H, H_2C(14)), 1.32−1.20 (m, 4 H, H_2C(15), H_2C(16)), 1.23−1.15 (m, 2 H, H_2C(17)), 1.00 (d, *J* = 6.6, 3 H, H_3C(19)), 0.86 (t, *J* = 7.2, 3 H, H_3C(18)), 0.8−2.5 (br, 3 H, $(H_3B)^{92}$); ^{13}C NMR (126 MHz, $CDCl_3$) 142.3 (C(9)), 128.5 (C(10)), 127.8 (C(11)), 126.3 (C(12)), 88.8 (C(7b) or C(1)), 82.4 (C(7b) or C(1)), 73.8 (C(4)), 70.2 (C(2)), 63.8 (C(13)), 63.2 (C(7a)), 56.0 (C(5a)), 34.5 (C(5)), 31.7 (C(7b)), 31.1 (C(6)), 29.9 (C(14)), 26.1 (C(16)), 24.9 (C(8)), 23.4 (C(7)), 22.7 (C(15)), 17.4 (C(18)), 14.1 (C(19)); IR (NaCl plate, film) 2950 (s), 2929 (s), 2869 (s), 2377 (s), 2329 (s), 2274 (s), 1457 (s), 1337 (m), 1379 (m), 1173 (s), 1137 (m), 1092 (m), 1064 (m), 924 (w), 868 (w), 751 (w), 700 (s); MS (EI, 70 eV) 352.2 (3), 341.2 (6), 326.2 (4), 270.1 (4), 256.1 (100), 241.1 (29), 110.1 (24); mol formula $C_{23}H_{38}BNO$ (355.36); HRMS $C_{23}H_{35}NO$ (341.2719) calcd 341.2719, found 341.2722; TLC R_f 0.35 (hexanes/TBME, 9:1) [I_2].



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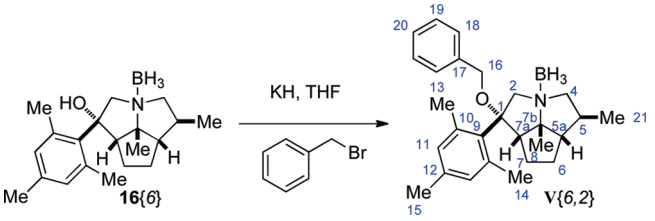
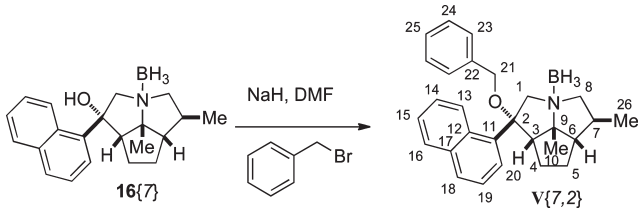
*Preparation of (1R,3S,5S,5aS,7aS,7bR)-Octahydro-1-(3,5-bistrifluoromethyl-benzyloxy)-1-phenyl-5-methyl-7b-methyl-2H-cyclopenta[gh]pyrrolizine·Borane (**V**{5,6}).* To a two-necked, 25 mL, round-bottomed flask equipped with a nitrogen inlet adapter, rubber septum, and a magnetic stir bar were added sequentially alcohol **16**{5} (105 mg, 0.287 mmol), THF (2.0 mL, 0.1 M), and then potassium hydride (19 mg, 0.474 mmol, 1.22 equiv). The flask was immersed in an ice/NaCl cooling bath. To the resulting mixture was added 3,5-bis-(trifluoromethyl)benzyl bromide dropwise, via syringe, as a solution in THF (2.0 mL). The bath was removed, and the reaction was allowed to reach room temperature. After being stirred for 2 h at room temperature, the flask was immersed in an ice bath and the reaction was quenched with satd aq ammonium chloride (5.0 mL). Extraction and purification by silica gel column chromatography as described in general procedure I afforded 146 mg (76%) of 3,5-bis(trifluomethyl)benzyl ether **V**{5,6} as a clear, viscous oil. Data for **V**{5,6}: ^{1}H NMR (500 MHz, $CDCl_3$) 7.75 (s, 1 H, HC(17)), 7.60 (s, 2 H, HC(15)), 7.39−7.38 (m, 4 H, HC(10), HC(11)), 7.36−7.31 (m, 1 H, HC(12)), 4.24 (d, J = 12.4, 1 H, HC(13)), 4.16 (d, J = 13.2, 1 H, HC(2)), 4.07 (d, J = 12.4, 1 H, HC(13)), 3.93 (d, J = 13.2, 1 H, HC(2)), 3.42 (dd, J = 7.7, J = 12.4, 1 H, HC(4)), 3.21 (dd, J = 11.8, J = 11.8, 1 H, HC(4)), 2.91 (dd, J = 8.4, J = 8.4, 1 H, HC(7a)), 2.64−2.55 (m, 1 H, HC(7)), 2.45−2.35 (m, 1 H, HC(5)), 2.03−2.87 (m, 4 H, HC(7), H_2C(6), HC(5a)), 1.53 (s, 3 H, H_3C(8)), 1.00 (d, J = 6.5, 3 H, H_3C(20)), 0.8−2.5 (br, 3 H, $(H_3B)^{92}$); ^{13}C NMR (126 MHz, $CDCl_3$) 140.9 (C(9 or 14)), 140.8 (C(9 or 14)), 130.2 (q, J = 33.2, C(19)), 127.1 (C(10)), 127.1 (C(11)), 127.1 (C(12), 126.7 (C(15)), 121.5 (hept, J = 3.8, C(17)), 88.9 (C(7b)), 84.1 (C(1)), 73.4 (C(4)), 71.2 (C(2)), 65.1 (C(13)), 60.6 (C(7a or 5a)), 60.6 (C(7a or 5a)), 34.5 (C(5)), 30.7 (C(6)), 25.1 (C(7)), 25.0 (C(8)), 17.0 (C(20)); IR ($CDCl_3$, film) 3063 (w), 2962 (s), 2931 (s), 2874 (s), 2376 (s), 2331 (s), 2277 (s), 2243 (s), 1808 (w), 1624 (m), 1497 (m), 1461 (s), 1448 (s), 1366 (s), 1279 (s), 1174 (s), 1134 (s), 1091 (s), 1016 (m), 994 (m), 957 (w), 911 (s), 844 (s), 812 (w), 704 (s); MS (ESI, Q-tof) 494.2 (75), 484.2 (100); mol formula $C_{26}H_{30}BF_6NO$ (497.32); HRMS $C_{26}H_{28}NOF_6$, (484.2075) calcd 484.2075, found 484.2064; TLC R_f 0.38 (hexanes/TBME, 9:1) [I_2].



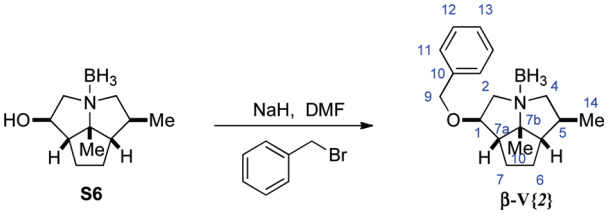
*Preparation of (1R,3S,5S,5aS,7aS,7bR)-Octahydro-1-benzyloxy-1-(2,4,6-trimethylphenyl)-5-methyl-7b-methyl-2H-cyclopenta[gh]pyrrolizine·Borane (**V**{6,2}).* Following general procedure I, to a two-necked, 10 mL, round-bottomed flask equipped with a nitrogen inlet adapter, rubber septum, and a magnetic stir bar were added sequentially alcohol **16**{6} (31 mg, 0.099 mmol), dimethylformamide (1.0 mL, ∼0.1 M), and then sodium hydride (3.6 mg, 0.148 mmol, 1.5 equiv) at 0 °C. After 15 min, benzyl bromide (18 μL, 0.148 mmol, 1.5 equiv) was added via syringe. The solution was stirred for 2 h and then quenched onto ice−water (10 mL). Extraction and purification by silica gel column chromatography as described in general procedure I afforded 39 mg (98%) of benzyl ether **V**{6,2} as a clear, viscous oil. Data for **V**{6,2}: ^{1}H NMR (500 MHz, $CDCl_3$) 7.32 (dd, J = 7.2, 7.2, 1 H, HC(19)), 7.29−7.25 (m, 1 H, HC(20)), 7.23 (d, J = 7.2, 1 H, HC(18)), 6.86 (s, 2 H, HC(11)) 4.28 (d, J = 11.1, 1 H, HC(16)), 4.25 (d, J = 14.1, 1 H, HC(2)), 4.17 (d, J = 11.0, 1 H, HC(16)), 4.07 (d, J = 13.8, 1 H, HC(2)), 3.94 (dd, J = 9.3, 11.6, 1 H, HC(4)), 3.25 (dd, J = 6.9, 11.8, 1 H, HC(4)), 2.99 (dd, J = 9.1, 9.1, 1 H, HC(7a)), 2.54 (s, 3 H, H_3C(13)) 2.52 (s, 3 H, H_3C(14)), 2.25 (s, 3 H, H_3C(15)), 2.26−2.19 (m, 1 H, HC(5)), 2.15−2.09 (m, 1 H, HC(7)), 2.01−1.98 (m, 1 H, HC(5a)), 1.90−1.84 (m, 2 H, H_2C(6), 1.41 (s, 3 H, H_3C(8)), 1.13 (d, J = 6.9, 3 H, H_3C(21)), 0.8−2.5 (br, 3 H, $(H_3B)^{92}$); ^{13}C NMR (126 MHz, $CDCl_3$) 138.4, 138.0, 137.0, 137.0, 132.3, 132.1, 128.5, 127.6, 127.3, 87.5 (C(1 or 7b)), 87.4 (C(1 or 7b)), 74.6 (C(4)), 71.8 (C(2)), 66.9 (C(16)), 64.4 (C(7a)), 59.5 (C(5a)), 36.2 (C(5)), 33.0 (C(6)), 28.5 (C(15)), 25.6 (C(8)), 25.0 (C(13 or 14)), 24.6 (C(13 or 14)), 20.5 (C(7)), 19.9 (C(21)); IR ($CDCl_3$, film) 3028 (w), 2950 (s), 2930 (s), 2865 (s), 2376 (s), 2330 (s), 2277 (m), 2241 (m), 1610(m), 1454 (s), 1379 (m), 1348 (w), 1277 (w), 1173 (s), 1086 (s), 1063 (s), 1028 (s), 993 (w), 911 (s), 872 (w); MS (EI, 70 eV) 400.3 (1), 389.2 (2), 298.2 (100), 281.2 (4), 147.1 (47), 124.1 (26); mol formula $C_{27}H_{38}BNO$ (403.41); HRMS $C_{27}H_{35}NO$, 389.2719) calcd 389.2719, found 389.2719; TLC R_f 0.25 (hexanes/TBME, 9:1) [I_2].



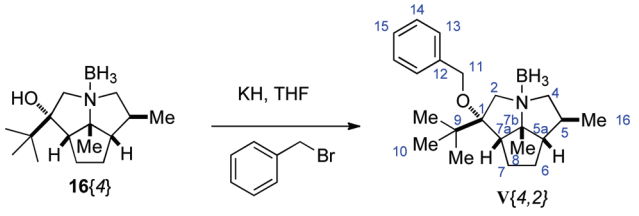
*Preparation of (1R,3S,5S,5aS,7aS,7bR)-Octahydro-1-benzyloxy-1-(1-naphthyl)-5-methyl-7b-methyl-2H-cyclopenta[gh]pyrrolizine·Borane **V**{7,2}.* Following general procedure I, to a two-necked, 10 mL, round-bottomed flask equipped with a nitrogen inlet adapter, rubber septum, and a magnetic stir bar were added sequentially alcohol **16**{7} (38 mg, 0.118 mmol), dimethylformamide (1.2 mL, ∼0.1 M), and then sodium hydride (4.3 mg, 0.177 mmol, 1.5 equiv) at 0 °C. After 15 min, benzyl bromide (21 μL, 0.177 mmol, 1.5 equiv) was added via syringe. The solution was stirred for 2 h and then quenched onto ice−water (10 mL). Extraction and purification by silica gel column chromatography as described in general procedure I afforded 45 mg (93%) of benzyl ether **V**{7,2} as a clear, viscous oil. Data for **V**{7,2}: ^{1}H NMR (500 MHz, $CDCl_3$) 8.58 (d, J = 8.0, 0.6 H), 8.53−8.50 (m, 1 H), 7.95−7.85 (m, 4 H), 7.54−7.48 (m, 4 H), 7.31−7.25 (m, 4 H), 7.16−7.13 (m, 3 H), 4.71 (d, J = 13.5, 0.6 H), 4.47 (d, J = 11.4, 1 H), 4.21 (d, J = 11.1, 0.6 H), 4.05−3.98 (m, 1.6 H), 3.91−3.84 (m, 1.6 H), 3.78 (d, J = 10.5, 1 H), 3.73 (dd, J = 8.2, 11.8, 0.6 H), 3.60 (dd, J = 9.3, 9.3, 1 H), 3.30 (dd, J = 11.2, 11.2, 0.6 H), 3.25 (dd, J = 6.2, 12.5, 1 H), 3.04−2.95 (m, 0.6 H), 2.89 (dd, J = 12.5, 12.5, 1 H), 2.79 (dd, J = 8.7, 8.7, 0.6 H), 2.59−2.50 (m, 1 H), 2.45−2.37 (m, 0.6 H), 2.26−2.11 (m, 3 H), 2.03−1.80 (m, 5H), 1.72 (s, 3 H), 1.35 (s, 1.8 H), 1.09 (d, J = 6.5, 1.8 H), 1.06 (d, J = 6.3, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) 138.13, 138.08, 136.6, 136.0, 135.1, 134.8, 131.4, 130.3, 129.8, 129.6, 129.2, 128.4, 128.0, 127.7, 127.6, 126.4, 126.3, 126.2, 126.0, 125.9, 125.8, 125.78, 126.76, 125.7, 124.6, 124.3, 88.8, 86.9, 85.3, 85.0, 73.5, 72.8, 72.4, 70.6, 67.2, 66.8, 64.1, 63.4, 60.3, 54.8, 34.5, 33.7, 31.1, 28.7, 28.6, 27.7, 25.0, 25.3, 17.8, 16.1; IR ($CDCl_3$, film) 3050 (w), 2959 (s), 2929 (s), 2870 (m), 2397 (s), 2326 (s), 2279 (m), 2242 (m), 1602 (w), 1509 (w), 1498 (w), 1455 (s), 1380 (s), 1336 (w), 1287 (w), 1241 (w), 1173 (s), 1142 (m), 1113 (m), 1059 (s), 1026 (m), 959 (w), 911 (s), 865 (w), 804 (s), 780 (s), 733 (s), 699 (s), 648 (m); MS (EI, 70 eV) 426.2 (9), 408.2 (5), 398.2 (64), 382.2 (8), 306.1 (100), 290.1 (94), 270.1 (8), 155.0 (11); mol formula $C_{28}H_{34}BNO$ (411.3867); HRMS $C_{28}H_{35}BNO$ (412.2812) calcd 412.2812, found 412.2640; TLC R_f 0.40 (hexanes/TBME, 4:1) [I_2, CAM].

*Preparation of (1R,3S,5S,5aS,7aS,7bR)-Octahydro-1-benzyloxy-5-methyl-7b-methyl-2H-cyclopenta[gh]pyrrolizine·Borane (β-**V**{2}).* Following general procedure I, to a two-necked, 10 mL, round-bottomed flask equipped with a nitrogen inlet adapter, rubber septum,

dx.doi.org/10.1021/jo2005445 |J. Org. Chem. 2011, 76, 4260–4336

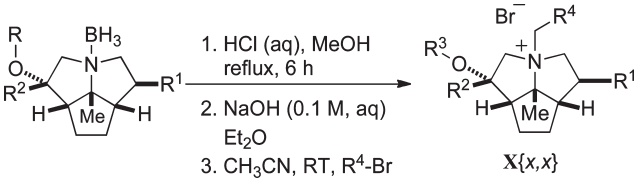


and a magnetic stir bar were added sequentially alcohol **S6** (22 mg, 0.113 mmol), dimethylformamide (1.1 mL, ~0.1 M), and then sodium hydride (4 mg, 0.17 mmol, 1.5 equiv) at 0 °C. After 15 min, benzyl bromide (20 μL, 0.17 mmol, 1.5 equiv) was added via syringe. The solution was stirred for 2 h and then quenched onto ice−water (10 mL). Extraction and purification by silica gel column chromatography as described in general procedure I afforded 28 mg (88%) of benzyl ether β-**V**{2} as a clear, viscous oil. Data for β-**V**{2}: ^{1}H NMR (500 MHz, $CDCl_3$) 7.35 (m, 4 H, HC(11), HC(12)), 7.28 (m, 1 H, HC(13)), 4.63 (d, J = 11.7, 1 H, HC(9)), 4.38 (d, J = 11.7, 1 H, HC(9)), 3.79−3.75 (m, 2 H, HC(2), HC(1)), 3.26−3.21 (m, 2 H, HC(2), HC(4)), 3.04 (dd, J = 12.2, 12.2, 1 H, HC(4)), 2.40 (dd, J = 7.9, 7.9, 1 H, HC(7a)), 2.07−2.01 (m, 1 H, HC(7)), 1.86−1.81 (m, 2 H, HC(5a), HC(5)), 1.81−1.73 (m, 1 H, HC(6)), 1.71−1.66 (m, 1 H, HC(6)), 1.60 (s, 3 H, H_3C(8)), 1.60−1.52 (m, 1 H, HC(7)), 1.00 (d, J = 5.9, 3 H, H_3C(14)), 0.8−2.5 (br, 3 H, $(H_3B)^{92}$); ^{13}C NMR (126 MHz, $CDCl_3$) 138.1 (C(10)), 128.5 (C(12)), 127.8 (C(13)), 127.7 (C(11)), 88.0 (C(7b)), 81.8 (C(1)), 73.0 (C(4)), 70.8 (C(9)), 67.7 (C(2)), 60.9 (C(5a)), 58.2 (C(7a)), 35.4 (C(5)), 30.6 (C(7)), 29.7 (C(6)), 25.0 (C(8)), 16.6 (C(14)); IR ($CDCl_3$, film) 2956 (s), 2915 (s), 2872 (s), 2383 (s), 2328 (s), 2262 (s), 1496 (w), 1455 (s), 1379 (m), 1316 (w), 1273 (w), 1234 (w), 1177 (s), 1106 (m), 1067 (m), 1014 (w), 913 (m), 862 (w), 798 (w); MS (ESI, Q-tof) 284.2 (70), 272.2 (100), 192.2 (35), 141 (12); mol formula $C_{18}H_{28}BNO$ 285.23; HRMS $C_{18}H_{26}NO$, (272.2014) calcd 272.2014, found 272.2008; TLC R_f 0.24 (hexanes/TBME, 9:1) [I_2].

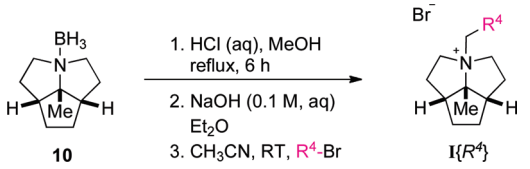


*Preparation of (1R,3S,5S,5aS,7aS,7bR)-Octahydro-1-benzyloxy-1-tert-butyl-5-methyl-7b-methyl-2H-cyclopenta[gh]pyrrolizine·Borane (**V**{4,2}).* Following general procedure I, to a two-necked, 10 mL, round-bottomed flask equipped with a nitrogen inlet adapter, rubber septum, and a magnetic stir bar were added sequentially alcohol **16**{4} (25 mg, 0.100 mmol), tetrahydrofuran (1.0 mL, ~0.1 M), and then potassium hydride (6 mg, 0.149 mmol, 1.5 equiv) at 0 °C. After 15 min, benzyl bromide (26 μL, 0.149 mmol, 1.5 equiv) was added via syringe. The solution was stirred for 2 h and then quenched onto ice−water (10 mL). Extraction and purification by silica gel column chromatography as described in general procedure I afforded 33 mg (97%) of benzyl ether **V**{4,2} as a clear, viscous oil. Data for **V**{4,2}: ^{1}H NMR (500 MHz, $CDCl_3$) 7.38−7.33 (m, 4 H, HC(13), HC(14)), 7.30−7.27 (m, 1 H, HC(15)), 4.83 (d, J = 11.2, 1 H, HC(2)), 4.56 (d, J = 11.2, 1 H, HC(2)), 3.81 (d, J = 15.2, 1 H, HC(11)), 3.77 (d, J = 15.1, 1 H, HC(11)), 3.32 (dd, J = 8.0, 12.4, 1 H, HC(4)), 3.15 (dd, J = 11.2, 12.0, 1 H, HC(4)), 2.59 (dd, J = 6.9, 9.6, 1 H, HC(7a)), 2.57−2.48 (m, 1 H, HC(7)), 2.09−2.01 (m, 1 H, HC(5)), 1.80−1.72 (m, 3 H, H_2C(6), HC(5a)), 1.65−1.59 (m, 1 H, HC(7)), 1.48 (s, 3 H, H_3C(8)), 1.00 (s, 9 H, H_3C(10)), 0.72 (d, J = 6.6, 3 H, H_3C(16)), 0.8−2.5 (br, 3 H, $(H_3B)^{92}$); ^{13}C NMR (126 MHz, $CDCl_3$) 138.5 (C(12)), 128.6 (C(14)), 127.6 (C(15)), 127.2 (C(13)), 88.7 (C(1 or 7b)), 86.8 (C(1 or 7b)), 74.0 (C(4)), 68.6 (C(2)), 68.5 (C(11)), 59.7 (C(5a)), 59.5 (C(7a)), 39.2 (C(9)), 34.3 (C(5)), 31.4 (C(6)), 27.6 (C(10)), 24.6 (C(7)), 24.4 (C(8)), 16.9 (C(16)); IR ($CDCl_3$, film) 2960 (s), 2871 (s), 2382 (s), 2328 (s), 2274 (s), 1728 (w), 1604 (w), 1497 (w), 1455 (s), 1401 (w), 1378 (m), 1318 (w), 1285 (w), 1235 (w), 1175 (s), 1133 (m), 1092 (s), 1061 (m), 1028 (m), 1007 (w), 977 (w), 955 (w), 926 (m), 913 (m), 869 (w), 735 (s), 698 (s); MS (EI, 70 eV) 338.2 (13), 270.1 (12), 236.2 (100), 221.2 (3.9), 204.1 (3), 178.1 (10), 164.1 (3), 138.1 (3), 124.1 (4), 110.1 (10.2); mol formula $C_{22}H_{36}BNO$ (341.34); HRMS $C_{22}H_{33}NO^+$ (327.2562) calcd 327.2562, found 327.2556; TLC R_f 0.28 (hexanes/TBME, 9:1) [I_2].

C. Variable Group R^4: Deborylation and N-Quaternization.



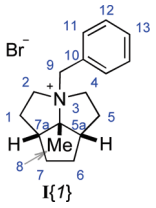
1. Parallel Synthesis Steps II−III: General Procedure II. A solution of borane adduct X (XX mg, XX mmol) in CH_3OH (0.03 M) was transferred to a 250 mL, round-bottomed, flask fitted with a reflux condenser, a magnetic stir bar, and a nitrogen inlet adapter with a rubber septum. Lastly, 1.0 M aq HCl solution (x.x mL, 5.0 equiv) was added via syringe. The resulting clear solution was immersed in an oil bath (preheated, 60 °C) and stirred for 12 h. The mixture was allowed to cool to room temperature and was concentrated by rotary evaporation (15 mmHg, 20−25 °C), whereupon a 0.1 M aq NaOH solution (xx. x mL, 6.0 equiv) was added. The resulting solution was tested to ensure basicity by pH paper (typically pH ~11−14). The basic solution was extracted with Et_2O (3 × 100 mL), and the combined extracts were dried (K_2CO_3). The resulting floculant suspension was filtered (cotton plug), and concentrated by rotary evaporation (15 mmHg, 20−25 °C) to furnish the crude intermediate amine as a pale-yellow oil. The amine was dissolved in acetonitrile (0.2 M) and distributed among five 20 mL test tubes fitted in a Büchi SynCore reactor (Figure X) which were then evacuated and backfilled with N_2. An alkyl bromide (x.x mL, x.x mmol, 1.2 equiv) was added to each test tube via syringe (the solid bromides were added as solids), and the reactor was set to agitate at 200 rpm. After 12 h, the individual reaction mixtures were concentrated by rotary evaporation (15 mmHg, 20−25 °C). Each salt was purified by silica gel plug filtration (1.8 cm ×5 cm, CH_2Cl_2/EtOAc, 1:1 (50 mL), then CH_2Cl_2/methanol 49:1, 24:1, 9:1 (50 mL each) afforded the product ammonium salts as a clear, sticky residues. The residues were triturated with Et_2O (~10 mL) in a 20 mL scintillation vial to free-flowing solids which were then concentrated by rotary evaporation (15 mmHg, 20−25 °C). The resulting solids were dried under vacuum (0.1 mmHg, 20−25 °C) for 12 h to afford the final quaternary ammonium bromides X{x} as free-flowing powers.



*2. Preparation of Quaternary Ammonium Bromides **I**{1−6}.* Following general procedure II, amino borane **10** (785 mg, 4.8 mmol) was added to a 250 mL, round-bottomed flask as a solution in 150 mL of MeOH (~0.03 M). The flask was fitted with a reflux condenser, a magnetic stir bar, and a nitrogen inlet adapter. Lastly, 1.0 M aq HCl solution (24 mL, 5.0 equiv) was added via syringe. The resulting solution was heated and then concentrated by rotary evaporation (15 mmHg,

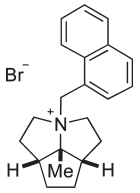
dx.doi.org/10.1021/jo2005445 |J. Org. Chem. 2011, 76, 4260–4336

20−25 °C) as described in general procedure II. The resulting free amine was dissolved in acetonitrile and was distributed among six test tubes that were subsequently charged with benzyl bromide (tube 1, 114 μL, 0.96 mmol, 1.2 equiv), 1-bromomethylnaphthalene (tube 2, 212 mg, 0.96 mmol, 1.2 equiv), 2-bromomethylnaphthalene (tube 3, 212 mg, 0.96 mmol, 1.2 equiv), 9-bromomethylanthracene (tube 4, 260 mg, 0.96 mmol, 1.2 equiv), 3,5-(bistrifluoromethyl)benzyl bromide (tube 5, 176 μL, 0.96 mmol, 1.2 equiv), and 1-bromohexane (tube 6, 140 μL, 0.96 mmol, 1.2 equiv). After being agitated for 12 h, the reaction mixtures were worked up and the products isolated and purified as described in general procedure II.



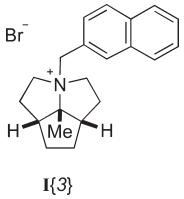
I{*1*}

*Preparation of rel-(5aS,7aR)-3-Benzyloctahydrocyclopenta[gh]-pyrrolizinium Bromide (**I**{1}).* Data for **I**{*1*}: yield 223 mg (84%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 7.74 (m, 2 H), 7.42 (m, 3 H), 4.82 (s, 2 H), 4.36 (m, 2 H), 3.13 (m, 2 H), 2.80 (t, *J* = 8.5, 2 H), 2.50 (qd, *J* = 7.2, 14.6, 2 H,), 2.05−1.96 (m, 2 H) 2.01 (s, 3 H), 1.79 (dt, *J* = 6.3, 13.0, 2 H), 1.70 (m, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) 134.6, 132.4, 132.1, 131.2, 99.7, 62.2, 61.5, 53.4, 33.1, 29.3, 23.6; MS (ESI, Q-tof) 242 (100); mol formula $C_{17}H_{24}BrN$ (322.28); HRMS $C_{17}H_{24}N$ (242.1909) calcd 242.1909, found 242.1906; TLC R_f 0.21 (CH_2Cl_2/MeOH, 9:1) [I_2].



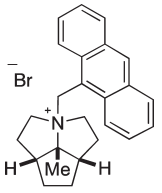
I{*2*}

*Preparation of rel-(5aS,7aR)-3-(1-Naphthylmethyl)octahydrocyclo-penta[gh]pyrrolizinium Bromide (**I**{2}).* Data for **I**{*2*}: yield 267 mg (90%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 8.34 (d, *J* = 7.2, 1 H), 8.11 (d, *J* = 8.6, 1 H), 7.91 (dd, *J* = 3.8, 8.1, 2 H), 7.64 (t, *J* = 7.7, 1 H), 7.53 (dd, *J* = 7.4, 17.9, 2 H), 5.29 (s, 2 H), 4.38 (m, 2 H), 3.08 (m, 2 H), 2.91 (m, 2 H), 2.58 (dt, *J* = 7.3, 14.6, 2 H), 2.22 (s, 3 H), 2.03 (m, 2 H), 1.77 (dt, *J* = 6.3, 12.6, 2 H), 1.69 (td, *J* = 7.9, 11.4, 2 H); MS (ESI, Q-tof) 293 (24), 292 (100); mol formula $C_{21}H_{26}BrN$ (372.34); HRMS $C_{21}H_{26}N$ (292.2065) calcd 292.2065, found 292.2056; TLC R_f 0.27 (CH_2Cl_2/MeOH, 9:1) [I_2].



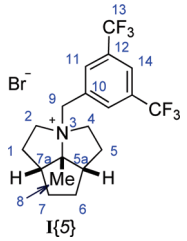
I{*3*}

*Preparation of rel-(5aS,7aR)-3-(2-Naphthylmethyl)octahydrocyclo-penta[gh]pyrrolizinium Bromide (**I**{3}).* Data for **I**{*3*}: yield 243 mg (82%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 8.19 (s, 1 H), 7.87 (m, 1 H), 7.75 (td, *J* = 5.4, 11.5, 3 H,), 7.49 (m, 2 H), 5.05 (s, 2 H), 4.39 (td, *J* = 6.5, 12.7, 2 H), 3.09 (m, 2 H), 2.82 (s, 2 H), 2.58 (dt, *J* = 7.1, 14.6, 2 H), 2.08 (s, 3 H), 2.00 (m, 2 H), 1.76 (dt, *J* = 6.0, 12.6, 2 H), 1.68 (m, 2 H); MS (ESI, Q-tof) 293 (22), 292 (100); mol formula $C_{21}H_{26}BrN$ (372.34); HRMS $C_{21}H_{26}N^+$ (292.2065) calcd 292.2065, found 292.2055; TLC R_f 0.26 (CH_2Cl_2/MeOH, 9:1) [I_2].



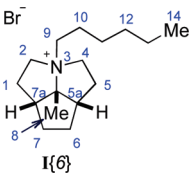
I{*4*}

*Preparation of rel-(5aS,7aR)-3-(9-Anthrylmethyl)octahydrocyclo-penta[gh]pyrrolizinium Bromide (**I**{4}).* Data for **I**{*4*}: yield 265 mg (77%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 8.68 (d, 2 H, *J* = 9.0), 8.47 (s, 1 H), 7.96 (d, 2 H, *J* = 7.7), 7.68 (m, 2 H), 7.48 (t, 2 H, *J* = 7.1), 5.72 (s, 2 H), 4.00 (m, 2 H), 3.01 (s, 2 H), 2.75 (m, 2 H), 2.64 (dt, 2 H, *J* = 7.3, *J* = 14.6), 2.40 (s, 3 H), 1.99 (m, 2 H), 1.66 (m, 6H); MS (ESI, Q-tof) 343.2 (27), 342 (98), 192 (13), 191 (100); mol formula $C_{25}H_{28}BrN$ (422.40); HRMS $C_{25}H_{28}N^+$ (342.222) calcd 342.2222, found 342.2216; TLC R_f 0.31 (CH_2Cl_2/MeOH, 9:1) [I_2].



I{*5*}

*Preparation of rel-(5aS,7aR)-3-(3,5-Bistrifluoromethylbenzyl)-octahydrocyclopenta[gh]pyrrolizinium Bromide (**I**{5}).* Data for **I**{*5*}: yield 120 mg (86%), free-flowing white powder;[93] ^{1}H NMR (500 MHz, $CDCl_3$) 8.40 (s, 2 H), 7.94 (s, 1 H), 5.31 (s, 2 H), 4.27 (ddd, *J* = 6.7, 12.3, 18.3, 2 H,), 3.11 (ddd, *J* = 6.4, 12.0, 12.0, 2 H,), 2.81 (s (broad), 1 H), 2.61 (ddd, *J* = 6.7, 13.9, 14.1, 2 H), 2.07 (s, 3 H, $H_3C(10)$), 2.02 (dd, *J* = 7.6, 12.8, 2 H), 1.83 (dd, *J* = 6.3, 13.3, 2 H), 1.71 (dd, *J* = 8.5, 16.7, 2 H,); MS (ESI, Q-tof) 379 (23), 378 (100); mol formula $C_{19}H_{22}BrF_6N$ (458.28); HRMS $C_{19}H_{22}F_6N^+$ (378.1656) calcd 378.1656, found 378.1659; TLC R_f 0.30 (CH_2Cl_2/MeOH, 9:1) [I_2].

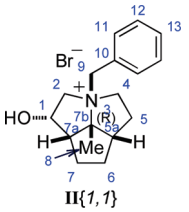


I{*6*}

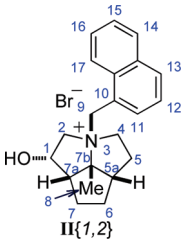
*Preparation of rel-(5aS,7aR)-3-Hexyloctahydrocyclopenta[gh]-pyrrolizinium Bromide (**I**{6}).* Data for **I**{*6*}: yield 180 mg (72%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 3.95 (td, *J* = 7.1, *J* = 12.4, 2 H), 3.83 (m, 2 H), 3.38 (m, 2 H), 2.63 (m, 2 H), 2.33 (qd, *J* = 7.2, *J* = 14.8, 2 H), 1.96 (m, 4 H), 1.81 (m, 4 H), 1.73 (s, 3 H), 1.44 (m, 2 H), 1.33 (m, 4 H), 0.89 (t, *J* = 7.0, 3 H); MS (ESI, Q-tof) 237 (26), 236 (100); mol formula $C_{16}H_{30}BrN$ (316.32); HRMS $C_{16}H_{30}N^+$

(236.2378) calcd 236.2378, found 236.2370; TLC R_f 0.35 (CH_2Cl_2/MeOH, 9:1) [I_2].

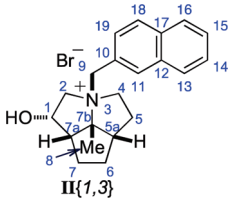
3. Preparation of Quaternary Ammonium Bromides ***II****{1−5,1−6}*. Following general procedure II, amino borane **11a** (488.9 mg, 2.7 mmol) was added to a 250 mL, round-bottomed flask as a solution in 150 mL of MeOH (∼0.03 M). The flask was fitted with a reflux condenser, a magnetic stir bar, and a nitrogen inlet adapter. Lastly, 1.0 M aq HCl solution (24 mL, 5.0 equiv) was added via syringe. The resulting solution was heated and then concentrated by rotary evaporation (15 mmHg, 20−25 °C) as described in general procedure II. The resulting free amine was dissolved in acetonitrile and was distributed among six test tubes that were subsequently charged with benzyl bromide (tube 1, 108 μL, 0.9 mmol, 2.0 equiv), 1-bromomethylnaphthalene (tube 2, 199 mg, 0.9 mmol, 2.0 equiv), 2-bromomethylnaphthalene (tube 3, 199 mg, 0.9 mmol, 2.0 equiv), 9-bromomethylanthracene (tube 4, 244 mg, 0.9 mmol, 2.0 equiv), 3,5-(bistrifluoromethyl)benzyl bromide (tube 5, 93 μL, 0.9 mmol, 2.0 equiv), and 1-bromohexane (tube 6, 130 μL, 0.9 mmol, 2.0 equiv). After being agitated for 12 h, the reaction mixtures were worked up and the products isolated and purified as described in general procedure II.



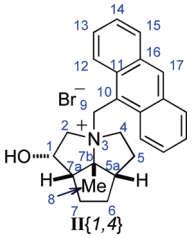
*Preparation of rel-(1S,3R,5aS,7aS,7bR)-Octahydro-1-hydroxy-3-benzyl-7b-methylcyclopenta[gh]pyrrolizinium Bromide (****II****{1,1}).* Data for **II**{*1,1*}: yield 109 mg (72%), free-flowing white powder; ^{1}H NMR (500 MHz, CD_3OD) 7.54 (m, 1 H), 4.72 (dd, *J* = 6.0, 13.6, 1 H), 4.47 (q, *J* = 12.8, 2 H), 3.85 (dd, *J* = 5.9, 12.7, 1 H), 3.74 (m, 2 H), 3.22 (dd, *J* = 5.9, 12.7, 1 H), 2.72 (ddd, *J* = 6.4, 11.2, 13.1, 1 H), 2.43 (dt, *J* = 7.4, 14.9, 1 H), 2.16 (m, 1 H), 2.05 (m, 1 H), 1.88 (m, 4 H), 1.77 (s, 3 H, Me); MS (ESI, Q-tof) 259 (27), 258 (100), 221 (40), 187 (49); mol formula $C_{17}H_{24}BrNO$ (338.28); HRMS $C_{17}H_{24}NO$ (258.1858) calcd 258.1858, found 258.1862; TLC R_f 0.08 (CH_2Cl_2/MeOH, 9:1) [I_2].



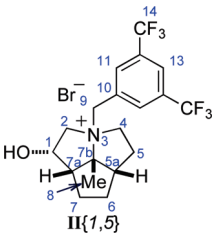
*Preparation of rel-(1S,3R,5aS,7aS,7bR)-Octahydro-1-hydroxy-3-(1-naphthylmethyl)-7b-methylcyclopenta[gh]pyrrolizinium Bromide (****II****{1,2}).* Data for **II**{*1,2*}: yield 103 mg (59%), free-flowing white powder; ^{1}H NMR (500 MHz, CD_3OD) 8.30 (d, *J* = 8.6, 1 H), 8.11 (d, *J* = 8.3, 1 H), 8.04 (d, *J* = 7.8, 1 H), 7.86 (s, 1 H), 7.73 (s, 1 H), 7.63 (dd, *J* = 8.6, *J* = 8.0, 2 H), 5.00 (s, 1 H), 4.86 (m, 1 H), 3.81 (dd, *J* = 5.9, 12.7, 1 H), 3.73 (t, 1 H, *J* = 6.8), 3.18 (s, 1 H), 2.81 (m, 2 H), 2.52 (dt, *J* = 6.8, 14.8, 1 H), 2.10 (m, 2 H), 1.92 (s, 3 H), 1.87 (m, 3 H); MS (ESI, Q-tof) 309 (2), 308 (100), 221(32), 187 (47); mol formula $C_{21}H_{26}$-BrNO (388.34); HRMS $C_{21}H_{26}NO$ (308.2014) calcd 308.2014, found 308.2026; TLC R_f 0.10 (CH_2Cl_2/MeOH, 9:1) [I_2].



*Preparation of rel-(1S,3R,5aS,7aS,7bR)-Octahydro-1-hydroxy-3-(2-naphthylmethyl)-7b-methylcyclopenta[gh]pyrrolizinium Bromide (****II****{1,3}).* Data for **II**{*1,3*}: yield 96 mg (56%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 8.12 (s, 1 H), 8.04 (s, 1 H), 8.02 (s, 1 H), 7.97 (m, 2 H), 7.62 (m, 3 H), 4.78 (s, 1 H), 4.64 (s, 1 H), 3.95 (s, 1 H), 3.81 (m, 2 H), 3.26 (dd, *J* = 6.1, 12.7, 1 H), 2.76 (ddd, *J* = 6.7, 10.9, 13.1, 2 H), 2.48 (s, 1 H), 2.12 (s, 1 H), 1.90 (m, 3 H), 1.82 (s, 3 H); MS (ESI, Q-tof) 309 (26), 308 (100), 221 (32), 187 (63); mol formula $C_{21}H_{26}BrNO$ (388.34); HRMS $C_{21}H_{26}NO$ (308.2014) calcd 308.2014, found 308.2017; TLC R_f 0.09 (CH_2Cl_2/MeOH, 9:1) [I_2].



*Preparation of rel-(1S,3R,5aS,7aS,7bR)-Octahydro-1-hydroxyl-3-(9-anthrylmethyl)cyclopenta[gh]pyrrolizinium Bromide (****II****{1,4}).* Data for **II**{*1,4*}: yield 107 mg (54%), free-flowing yellow powder; ^{1}H NMR (500 MHz, CD_3OD) 7.41 (s, 1 H), 7.13 (d, *J* = 9.0, 2 H), 6.80 (dd, *J* = 4.3, 8.4, 2 H), 6.34 (m, 2 H), 6.21 (dd, *J* = 6.8, 14.7, 2 H), 2.35 (m, 2 H), 1.87 (m, 1 H), 1.46 (m, 2 H), 1.39 (dd, *J* = 6.9, 12.8, 1 H), 1.07 (ddd, *J* = 7.1, 14.6, 14.5, 1 H), 0.72 (s, 3 H), 0.65 (m, 2 H), 0.40 (m, 3 H); MS (ESI, Q-tof) 360 (8), 359 (30), 358 (100), 192 (19), 191 (99); mol formula $C_{25}H_{28}BrNO$ (438.40); HRMS $C_{25}H_{28}NO$: (358.2171) calcd 358.2171, found 358.2184; TLC R_f 0.12 (CH_2Cl_2/MeOH, 9:1) [I_2].



*Preparation of rel-(1S,3R,5aS,7aR,7bR)-Octahydro-1-hydroxyl-3-(3,5-bistrifluoromethylbenzyl)cyclopenta[gh]pyrrolizinium Bromide (****II****{1,5}).* Data for **II**{*1,5*}: yield 125 mg (59%), free-flowing white powder; ^{1}H NMR (500 MHz, CD_3OD) 8.25 (s, 2 H), 8.24 (s, 1 H), 4.76 (dd, *J* = 5.8, 13.5, 1 H), 4.68 (q, *J* = 13.0, 2 H,), 3.84 (m, 1 H),

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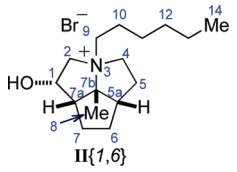
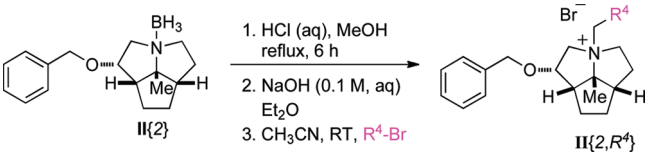
3.73 (td, J = 6.8, 13.3, 1 H), 2.77 (m, 1 H), 2.49 (dt, J = 7.0, 14.4, 1 H), 2.18 (m, 1 H), 2.09 (td, J = 5.7, 12.8, 1 H), 1.93 (m, 1 H), 1.80 (s, 3 H); MS (ESI, Q-tof) 340 (17), 339 (83), 25 (31), 219 (68), 212 (100); mol formula $C_{19}H_{22}BrF_6NO$ (474.28); HRMS $C_{19}H_{22}F_6NO^+$ (394.1606) calcd 394.1606, found 394.1606; TLC R_f 0.13 (CH_2Cl_2/MeOH, 9:1) [I_2].



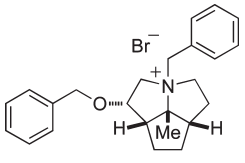
II{*1,6*}

*Preparation of rel-(1S,3R,5aS,7aR,7bR)-Octahydro-1-hydroxyl-3-hexylcyclopenta[gh]pyrrolizinium Bromide (**II**{1,6}).* Data for **II**{*1,6*}: yield 89 mg (59%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 4.55 (q, J = 5.9, 1 H), 4.02 (dt, J = 12.1, 6.78, 1 H), 3.70 (dd, J = 5.9, 12.6, 1 H), 3.58 (td, J = 7.1, 12.1, 1 H), 3.53 (dd, J = 5.7, 12.7, 1 H), 3.21 (m, 1 H) 2.60 (m, 2 H), 2.27 (tdd, 1 H, J = 6.8, 8.6, 14.0), 2.14 (ddd, J = 5.8, 10.4, 19.7, 1 H), 1.90 (m, 6 H), 1.59 (s, 3 H), 1.40 (m, 6H), 0.94 (t, J = 7.0, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) 98.0, 68.4, 67.3, 61.4, 58.4, 56.1, 51.1, 33.5, 31.3, 28.6, 26.5, 26.3, 25.5, 23.5, 22.4, 13.9; MS (ESI, Q-tof) 253 (20), 252 (100), 221 (24), 187 (71); mol formula $C_{16}H_{30}BrNO$ (332.32); HRMS $C_{16}H_{30}NO^+$ (252.2327) calcd 252.2327, found 252.2332; TLC R_f 0.19 (CH_2Cl_2/MeOH, 9:1) [I_2].



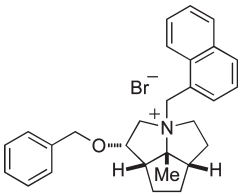
II{*2*} **II**{*2,R*^{4}}

*Preparation of Quaternary Ammonium Bromides **II**{2,1−6}.* Following general procedure II, amino borane **II**{*2*} (888 mg, 3.3 mmol) was added to a 250 mL, round-bottomed flask as a solution in 150 mL of MeOH (~0.03 M). The flask was fitted with a reflux condenser, a magnetic stir bar, and a nitrogen inlet adapter. Lastly, 1.0 M aq HCl solution (24 mL, 5.0 equiv) was added via syringe. The resulting solution was heated and then concentrated by rotary evaporation (15 mmHg, 20−25 °C) as described in general procedure II. The resulting free amine was dissolved in acetonitrile and was distributed among six test tubes that were subsequently charged with benzyl bromide (tube 1, 78 μL, 0.66 mmol, 1.2 equiv), 1-bromomethylnaphthalene (tube 2, 145 mg, 0.66 mmol, 1.2 equiv), 2-bromomethylnaphthalene (tube 3, 145 mg, 0.66 mmol, 1.2 equiv), 9-bromomethylanthracene (tube 4, 178 mg, 0.66 mmol, 1.2 equiv), 3,5-(bistrifluoromethyl)benzyl bromide (tube 5, 120 μL, 0.66 mmol, 1.2 equiv), and 1-bromohexane (tube 6, 92 μL, 0.66 mmol, 1.2 equiv). After being agitated for 12 h, the reaction mixtures were worked up and the products isolated and purified as described in general procedure II.



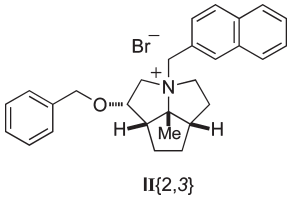
II{*2,1*}

*Preparation of rel-(1S,3R,5aS,7aS,7bR)-Octahydro-1-benzyloxy-3-benzyl-7b-methylcyclopenta[gh]pyrrolizinium Bromide (**II**{2,1}).* Data for **II**{*2,1*}: yield 205 mg (88%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 7.68 (m, 2 H), 7.43 (m, 3 H), 7.32 (m, 3 H), 7.25 (d, J = 6.3, 2 H), 5.01 (d, J = 12.5, 1 H), 4.93 (dd, J = 5.7, 12.9, 1 H), 4.63 (dd, J = 7.2, 9.8, 1 H), 4.50 (m, 3 H), 4.02 (m, 1 H), 3.61 (ddd, J = 6.4, 9.3, 12.1, 1 H), 3.17 (dd, J = 3.9, 12.7, 1 H), 3.05 (dd, J = 6.9, 14.2, 1 H), 2.76 (m, 1 H), 2.45 (dt, J = 8.6, 15.2, 1 H), 2.17 (s, 3 H), 2.10 (m, 5 H), 1.84 (m, 1 H); MS (ESI) 348 (100); mol formula $C_{24}H_{30}BrNO$ (428.41); HRMS $C_{24}H_{30}NO^+$ (348.2327) calcd 348.2327, found 348.2322; TLC R_f 0.23 (CH_2Cl_2/MeOH, 9:1) [I_2].



II{*2,2*}

*Preparation of rel-(1S,3R,5aS,7aS,7bR)-Octahydro-1-benzyloxy-3-(1-napthylmethyl)-7b-methylcyclopenta[gh]pyrrolizinium Bromide (**II**{2,2}).* Data for **II**{*2,2*}: yield 253 mg (97%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 8.23 (d, J = 7.1, 1 H), 8.20 (d, J = 8.5, 1 H), 7.83 (d, J = 8.2, 1 H), 7.79 (d, J = 8.1, 1 H), 7.59 (t, J = 7.7, 1 H), 7.49 (t, J = 7.5, 1 H), 7.36 (t, J = 7.6, 1 H), 7.30−7.27 (m, 4 H, J = 1.8, 5.7), 7.17 (dd, J = 1.7, 7.5, 1 H), 5.33 (d, J = 13.1, 1 H) 5.23 (d, J = 13.0, 1 H), 4.85 (dd, J = 5.4, 12.5, 1 H), 4.70 (m, 1 H), 4.45 (d, J = 11.6, 1 H), 4.39 (d, J = 11.6, 1 H), 3.90 (td, J = 5.9, 11.7, 1 H), 3.54 (ddd, J = 6.5, 9.5, 11.9, 1 H), 3.13 (m, 2 H), 2.90 (s, 1 H), 2.63 (dt, J = 8.6, 15.5, 1 H), 2.26 (s, 3 H), 2.07 (m, 2 H), 1.88−1.72 (m, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) 136.9, 133.6, 133.6, 133.0, 130.8, 129.1, 128.5, 128.0, 127.6, 127.5, 126.0, 125.3, 125.2, 123.1, 98.9, 72.8, 63.6, 60.3, 56.4, 54.9, 50.7, 33.4, 28.7, 26.2, 23.9; MS ESI 398 (100); mol formula $C_{28}H_{32}BrNO$, (478.46); HRMS $C_{28}H_{32}NO^+$ (398.2484) calcd 398.2484, found 398.2480; TLC R_f 0.32 (CH_2Cl_2/MeOH, 1:9) [I_2].

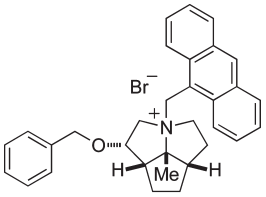


II{*2,3*}

*Preparation of rel-(1S,3R,5aS,7aS,7bR)-Octahydro-1-benzyloxy-3-(2-napthylmethyl)-7b-methylcyclopenta[gh]pyrrolizinium Bromide (**II**{2,3}).* Data for **II**{2,3}: yield 261 mg (100%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 8.16 (s, 1 H), 7.90−7.87 (m, 1 H), 7.72 (m, 3 H), 7.50 (m, 2 H), 7.30−7.21 (m, 3 H) 7.22−7.20 (m, 2 H), 5.22 (d, J = 12.5, 1 H), 4.96 (dd, J = 5.8, 12.8, 1 H), 4.79 (dd, J = 12.6, 24.6, 1 H), 4.68 (s(broad), 1 H,), 4.45 (s, 2 H), 4.05−4.01 (m, 1 H), 3.63−3.57 (m, 1 H), 3.19 (dd, J = 3.8, 12.7, 1 H), 3.06 (t, J = 6.7, 1 H), 2.80 (s(broad), 1 H), 2.54 (m(broad), 1 H), 2.12 (s, 3 H), 2.04 (m, 1 H); mol formula $C_{28}H_{32}BrNO$ (478.46); HRMS $C_{28}H_{32}NO^+$, (398.2484) calcd 398.2484, found 398.2475; TLC R_f 0.28 (CH_2Cl_2/MeOH, 9:1) [I_2].

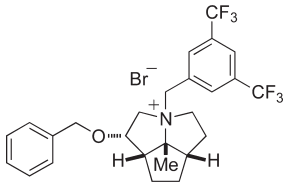
*Preparation of rel-(1S,3R,5aS,7aS,7bR)-Octahydro-1-benzyloxy-3-(9-anthrylmethyl)-7b-methylcyclopenta[gh]pyrrolizinium Bromide (**II**{2,4}).* Data for **II**{*2,4*}: yield 186 mg (64%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 8.88 (d, J = 9.1, 1 H), 8.51

dx.doi.org/10.1021/jo2005445 |J. Org. Chem. 2011, 76, 4260–4336



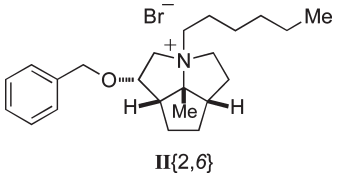
II{2,4}

(d, J = 9.5, 2 H), 8.00 (d, J = 8.3, 2 H), 7.75 (m, 1 H), 7.66 (m, 1 H), 7.50 (m, 2 H), 7.24−7.21 (m, 3 H), 7.12−7.10 (m, 2 H), 5.77 (d, J = 14.1, 1 H), 5.61 (d, J = 14.1, 1 H), 4.85 (dd, J = 5.4, 13.2, 1 H), 4.52 (dd, J = 4.7, 11.9, 1 H), 4.42 (d, J = 11.6, 1 H), 4.31 (d, J = 11.5, 1 H), 3.81 (td, J = 6.3, 12.5, 1 H), 3.35 (dd, J = 7.8, 14.5, 1 H), 3.30−3.24 (m, 1 H), 3.02 (m, 1 H), 2.74 (dd, J = 4.7, 12.6, 1 H), 2.61 (dt, J = 8.3, 15.4, 2 H), 2.46 (s, 1 H), 2.05 (m, 2 H), 1.90−1.61 (m, 4 H), 1.33−1.25 (m, 2 H); MS (ESI, Q-tof) 449 (49), 448 (100), 354 (37), 191 (54); mol formula $C_{32}H_{34}BrNO$ (528.52); HRMS $C_{32}H_{34}NO^+$ (448.2640) calcd 448.2640, found 448.2628; TLC R_f 0.35 (CH_2Cl_2/MeOH, 9:1) [I_2].



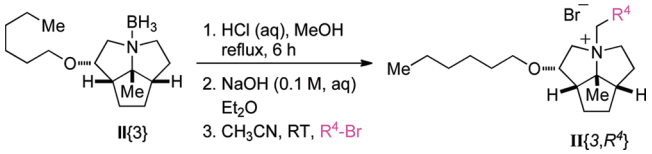
II{2,5}

*Preparation of rel-(1S,3R,5aS,7aS,7bR)-Octahydro-1-benzyloxy-3-(3,5-trifluoromethylbenzyl)-7b-methylcyclopenta[gh]pyrrolizinium Bromide (**II**{2,5}).* Data for **II**{2,5}: yield 20 mg (64%), free-flowing white powder;[93] ^{1}H NMR (500 MHz, $CDCl_3$) 8.34 (s, 2 H), 7.95 (s, 1 H), 7.31 (m, 3 H), 7.24 (m, 2 H), 5.56 (d, J = 12.7, 1 H), 4.99 (dd, J = 5.7, 12.6, 1 H), 4.90 (d, J = 12.7, 1 H), 4.64−4.61 (m(so), 1 H), 4.52 (d, J = 11.6, 1 H), 4.48 (d, J = 11.6, 1 H), 3.83−3.78 (m(so), 1 H), 3.71−3.65 (m(so), 1 H), 3.10 (dd, J = 3.2, 12.7, 1 H), 3.02 (dd, J = 7.5, 12.8, 1 H), 2.81−2.75 (m(br), 1 H), 2.56 (td, J = 8.1, 15.1, 1 H), 2.18−2.05 (m, 2 H), 2.09 (s, 3 H), 1.91−1.82 (m, 3 H); MS (ESI, Q-tof) 485 (33), 484 (100), 399 (14), 398 (49); mol formula $C_{26}H_{28}BrF_6NO$ (564.40); HRMS $C_{26}H_{28}F_6NO^+$ (484.2075) calcd 484.2075, found 484.2063; TLC R_f 0.21 (CH_2Cl_2/MeOH, 9:1) [I_2].



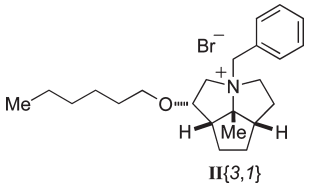
II{2,6}

*Preparation of rel-(1S,3R,5aS,7aS,7bS)-Octahydro-1-benzyloxy-3-hexyl-7b-methylcyclopenta[gh]pyrrolizinium Bromide (**II**{2,6}).* Data for **II**{2,6}: yield 99 mg (43%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 7.33 (m, 5 H), 4.59 (dd, 1 H, J = 6.1, 17.1), 4.54 (s, 1 H), 4.45 (dd, 1 H, J = 6.9, 13.4), 3.84 (td, 1 H, J = 6.1, 12.3), 3.62 (m, 1 H), 3.30 (td, 1 H, J = 6.0, 17.9), 3.04 (m, 1 H), 2.60 (dd, 1 H, J = 7.4, 15.0), 2.52 (dd, 1 H, J = 6.3, 12.6), 2.32 (td, 1 H, J = 6.8, 20.5), 2.03 (dt, 1 H, J = 6.0, 13.3), 1.87 (m, 5 H), 1.74 (s, 3 H), 1.33 (dd, 2 H, J = 5.0, 9.3), 0.89 (t, 3 H, J = 7.0); MS (ESI, Q-tof) 343 (32), 342 (100), 259 (21), 258 (92); mol formula $C_{23}H_{36}BrNO$ (422.44); HRMS $C_{23}H_{36}NO^+$ (342.2797) calcd 342.2797, found 342.2797; TLC R_f 0.38 (CH_2Cl_2/MeOH, 9:1) [I_2].



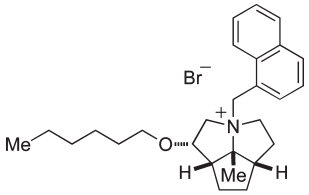
II{3} **II**{3,R^4}

*Preparation of Quaternary Ammonium Bromides: **II**{3,1−6}.* Following general procedure II, amino borane **II**{3} (441.6 mg, 1.68 mmol) was added to a 250 mL, round-bottomed flask as a solution in 150 mL of MeOH (~0.03 M). The flask was fitted with a reflux condenser, a magnetic stir bar, and a nitrogen inlet adapter. Lastly, 1.0 M aq HCl solution (24 mL, 5.0 equiv) was added via syringe. The resulting solution was heated and then concentrated by rotary evaporation (15 mmHg, 20−25 °C) as described in general procedure II. The resulting free amine was dissolved in acetonitrile and was distributed among six test tubes that were subsequently charged with benzyl bromide (tube 1, 40 μL, 0.33 mmol, 1.2 equiv), 1-bromomethylnaphthalene (tube 2, 73 mg, 0.33 mmol, 1.2 equiv), 2-bromomethylnaphthalene (tube 3, 73 mg, 0.33 mmol, 1.2 equiv), 9-bromomethylanthracene (tube 4, 90 mg, 0.33 mmol, 1.2 equiv), 3,5-(bistrifluoromethyl)benzyl bromide (tube 5, 61 μL, 0.33 mmol, 1.2 equiv), and 1-bromohexane (tube 6, 78 μL, 0.56 mmol, 2.0 equiv). After being agitated for 12 h, the reaction mixtures were worked up and the products isolated and purified as described in general procedure II.



II{3,1}

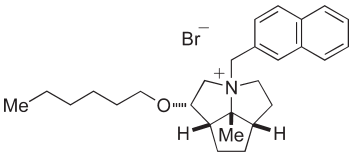
*Preparation of rel-(1S,3R,5aS,7aS,7bR)-Octahydro-1-hexyloxy-3-benzylcyclopenta[gh]pyrrolizinium Bromide (**II**{3,1}).* Data for **II**{3,1}: yield 96 mg (83%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 7.73 (dd, J = 2.2, 7.1, 2 H), 7.45 (d, J = 4.7, 3 H), 5.05 (d, J = 12.5, 2 H), 4.42 (m, 2 H), 3.97 (m, 1 H), 3.66 (dd, J = 5.6, 7.4, 1 H), 3.37 (m, 2 H), 3.18 (d, J = 12.8, 1 H), 3.06 (s, 1 H), 2.73 (s, 1 H), 2.49−2.40 (m, 1 H,), 2.05 (s, 1 H), 1.81 (m, 3 H), 1.48 (s, 1 H), 1.26 (m, 6H), 0.85 (t, J = 6.9, 3 H); MS (ESI, Q-tof) 342.2 (100), 343.3 (28), 336.3 (10); mol formula $C_{23}H_{36}BrNO$ (422.44); HRMS $C_{23}H_{36}NO$ (342.2797) calcd 342.2797, found 342.2786; TLC R_f 0.32 (CH_2Cl_2/MeOH, 9:1) [I_2].



II{3,2}

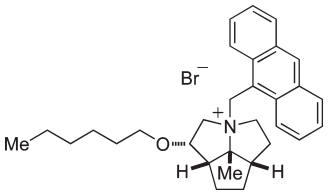
*Preparation of rel-(1S,3R,5aS,7aS,7bR)-Octahydro-1-hexyloxy-3-[1]naphthylmethylcyclopenta[gh]pyrrolizinium Bromide (**II**{3,2}).* Data for **II**{3,2}: yield 109 mg (84%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 8.31 (d, J = 7.2, 1 H), 8.20 (d, J = 8.6, 1 H), 7.88 (t, J = 7.8, 2 H), 7.65 (t, J = 7.3, 1 H), 7.54 (t, J = 7.5, 1 H), 7.46 (t, J = 7.3, 1 H), 5.35 (d, J = 13.1, 1 H), 5.18 (d, J = 13.1, 1 H), 4.99

(dd, J = 5.4, 12.7, 1 H), 4.50 (m, 1 H), 3.88 (m, 1 H), 3.61 (dt, J = 6.3, 11.3, 1 H), 3.35 (t, J = 6.5, 2 H), 3.14 (m, 2 H), 2.88 (m, 1 H), 2.65 (m, 1 H), 2.26 (s, 3 H), 2.06 (ddd, J = 6.5, 13.0, 19.3, 2 H), 1.80 (m, 3 H), 1.44 (p, J = 6.6, 2 H), 1.23 (m, 6 H), 0.84 (t, J = 6.9, 3 H); MS (ESI, Q-tof) 394 (8), 393 (40), 392 (100); mol formula $C_{27}H_{38}BrNO$ (472.50); HRMS $C_{27}H_{38}NO$ (392.2953) calcd 392.2953, found 392.2957; TLC R_f 0.35 (CH_2Cl_2/MeOH, 9:1) [I_2].



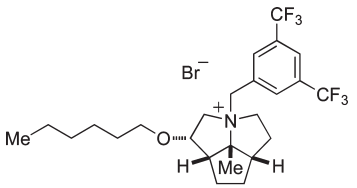
II{*3,3*}

*Preparation of rel-(1S,3R,5aS,7aS,7bR)-Octahydro-1-hexyloxy-3-[2]naphthylmethylcyclopenta[gh]pyrrolizinium Bromide (**II**{3,3}).* Data for **II**{*3,3*}: yield 98 mg (75%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 8.18 (s, 1 H), 7.89 (dd, J = 4.0, 5.3, 1 H), 7.75 (d, J = 10.2, 3 H), 7.51 (td, J = 3.1, 5.2, 2 H), 5.22 (d, J = 12.5, 1 H), 5.03 (dd, J = 5.6, 12.7, 1 H), 4.70 (d, J = 12.5, 1 H), 4.44 (m, 1 H), 3.98 (m, 1 H), 3.63 (dt, J = 6.1, 11.1, 1 H), 3.33 (m, 2 H), 3.19 (dd, J = 3.0, 12.8, 1 H), 3.05 (dd, J = 7.6, 12.7, 1 H), 2.77 (dd, J = 7.5, 11.1, 1 H), 2.56 (m, 1 H), 2.10 (s, 3 H), 2.05 (dd, J = 5.0, 11.0, 2 H), 1.81 (m, 3 H), 1.44 (m, 2 H), 1.22 (m, 8 H), 0.82 (t, J = 6.8, 3 H); MS (ESI, Q-tof) 394 (6), 393 (34), 392 (100), 324 (10), 309 (4), 252 (19), 196 (8); mol formula $C_{27}H_{38}BrNO$ (472.50); HRMS $C_{27}H_{38}NO$ (392.2953) calcd 392.2953, found 392.2936; TLC R_f 0.37 (CH_2Cl_2/MeOH, 9:1) [I_2].



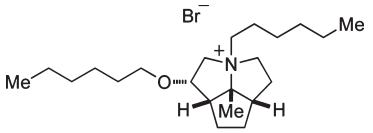
II{*3,4*}

*Preparation of rel-(1S,3R,5aS,7aS,7bR)-Octahydro-1-hexyloxy-3-[9]anthrylmethylcyclopenta[gh]pyrrolizinium Bromide (**II**{3,4}).* Data for **II**{*3,4*}: yield 133 mg (92%), free-flowing yellow powder; ^{1}H NMR (500 MHz, $CDCl_3$) 8.65 (d, J = 7.8, 1 H), 8.43 (t, J = 7.4, 1 H), 8.21 (dd, J = 1.3, 7.7, 1 H), 8.16 (dd, J = 1.3, 7.7, 1 H), 7.78 (m, 2 H), 7.59 (m, 2 H), 4.53 (dd, J = 5.6, 13.2, 1 H), 4.26 (d, J = 13.8, 2 H), 4.19 (m, 1 H), 3.43 (d, J = 6.25, 7 H), 3.01 (m, 2 H), 2.61 (m, 1 H), 2.34 (dd, J = 7.2, 13.8, 1 H), 1.88 (m, 6 H), 1.65 (s, 3 H), 1.27 (m, 13 H), 0.93 (t, J = 6.9, 3 H); MS (ESI, Q-tof) 442 (83), 336 (100), 252 (75); mol formula $C_{31}H_{40}BrNO$ (522.56); HRMS $C_{31}H_{40}NO$ (442.3110) calcd 442.3110, found 442.3098; TLC R_f 0.35 (CH_2Cl_2/MeOH, 9:1) [I_2].



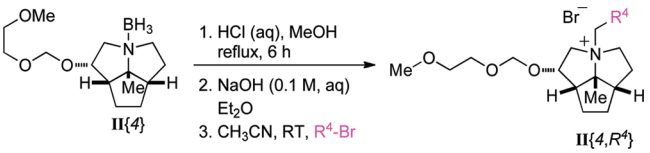
II{*3,5*}

*Preparation of rel-(1S,3R,5aS,7aS,7bR)-Octahydro-1-hexyloxy-3-(3,5-bistrifluoromethylbenzyl)cyclopenta[gh]pyrrolizinium Bromide (**II**{3,5}).* Data for **II**{*3,5*}: yield 137 mg (88%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 8.38 (s, 2 H), 7.94 (s, 1 H), 5.58 (d, J = 12.6, 1 H), 4.98 (m, 2 H), 4.42 (dd, J = 5.4, 7.1, 1 H), 3.78 (m, 1 H), 3.67 (m, 1 H), 3.38 (dtd, J = 6.6, 9.1, 15.8, 2 H), 3.12 (d, J = 12.5, 1 H), 2.99 (s, 1 H), 2.76 (s, 1 H), 2.60 (m, 1 H), 2.07 (s, 5 H), 1.83 (m, 3 H), 1.49 (m, 2 H), 1.25 (m, 7 H), 0.85 (t, J = 6.9, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) 133.3, 133.0,132.3(q), 123.9, 122.7 (q), 99.7, 71.3, 64.5, 60.4, 58.2, 55.2, 50.5, 33.5, 31.4, 29.4, 28.5, 25.9, 25.6, 23.3, 22.4, 13.8; MS (ESI, Q-tof) 479 (29), 478 (100); mol formula $C_{25}H_{34}BrF_6NO$ (558.44); HRMS $C_{25}H_{34}F_6NO$ (478.2545) calcd 478.2545, found 478.2539; TLC R_f 0.32 (CH_2Cl_2/MeOH, 9:1) [I_2].



II{*3,6*}

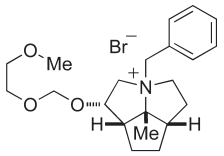
*Preparation of rel-(1S,3S,5aS,7aS,7bR)-Octahydro-1-hexyloxy-3-hexylcyclopenta[gh]pyrrolizinium Bromide (**II**{3,6}).* Data for **II**{*3,6*}: yield 104 mg (91%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 4.62 (dd, J = 5.6, 12.8, 1 H), 4.30 (m, 1 H), 3.98 (ddd, J = 6.7, 9.3, 11.8, 1 H), 3.81 (ddd, J = 5.2, 6.7, 11.9, 1 H), 3.66 (dt, J = 4.6, 12.2, 1 H), 3.55 (dd, J = 3.3, 12.9, 1 H), 3.50 (td, J = 6.4, 9.1, 1 H), 3.40 (td, J = 6.6, 9.1, 1 H), 3.22 (dt, J = 4.3, 12.3, 1 H), 2.99 (dd, J = 7.8, 12.9, 1 H), 2.61 (m, 1 H), 2.27 (td, J = 8.1, 15.5, 1 H), 2.06 (m, 2 H), 1.84 (s, 3 H), 1.76 (m, 4 H), 1.54 (m, 3 H), 1.30 (m, 12 H), 0.89 (dt, 6 H, J = 3.1, 6.9); MS (ESI, Q-tof) 337 (30), 336 (100); mol formula $C_{22}H_{42}BrNO$ (416.48); HRMS $C_{22}H_{42}NO$ (336.3266) calcd 336.3266, found 336.3269; TLC R_f 0.42 (CH_2Cl_2/MeOH, 9:1) [I_2].



II{*4*} **II**{*4,R*^{4}}

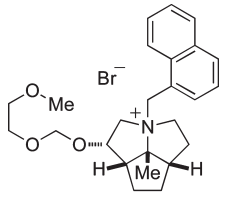
*4. Preparation of Quaternary Ammonium Bromides **II**{4,1−6}.* Following general procedure II, amino borane **II**{*4*} (432 mg, 1.68 mmol) was added to a 250 mL, round-bottomed flask as a solution in 150 mL of MeOH (~0.03 M). The flask was fitted with a reflux condenser, a magnetic stir bar, and a nitrogen inlet adapter. Lastly, 1.0 M aq HCl solution (24 mL, 5.0 equiv) was added via syringe. The resulting solution was heated and then concentrated by rotary evaporation (15 mmHg, 20−25 °C) as described in general procedure II. The resulting free amine was dissolved in acetonitrile and was distributed among six test tubes that were subsequently charged with benzyl bromide (tube 1, 40.8 μL, 0.34 mmol, 1.2 equiv), 1-bromomethylnaphthalene (tube 2, 75 mg, 0.34 mmol, 1.2 equiv), 2-bromomethylnaphthalene (tube 3, 75 mg, 0.34 mmol, 1.2 equiv), 9-bromomethylanthracene (tube 4, 92 mg, 0.34 mmol, 1.2 equiv), 3,5-(bistrifluoromethyl)benzyl bromide (tube 5, 62 μL, 0.34 mmol, 1.2 equiv), and 1-bromohexane (tube 6, 80 μL, 0.56 mmol, 2.0 equiv). After being agitated for 12 h, the reaction mixtures were worked up and the products isolated and purified as described in general procedure II.

*Preparation of rel-(1S,3R,5aS,7aS,7bR)-Octahydro-1-methoxyethoxymethoxy-3-benzylcyclopenta[gh]pyrrolizinium Bromide (**II**{4,1}).* Data for **II**{*4,1*}: yield 91 mg (76%), free-flowing white powder; ^{1}H



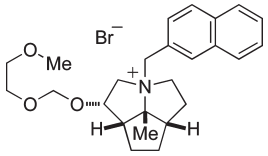
II{*4,1*}

NMR (500 MHz, $CDCl_3$) 7.75 (m, 2 H), 7.43 (dd, *J* = 1.8, 5.1, 3 H), 4.85 (d, *J* = 12.4, 1 H), 4.75 (m, 2 H), 4.70 (s, 2 H), 4.26 (ddd, *J* = 6.6, 12.2, 1 H), 3.63−3.56 (m, 2 H), 3.50 (dd, *J* = 6.8, 6.2, 12.7, 1 H), 3.45 (t, *J* = 4.6, 2 H), 3.24 (s, 3 H), 3.19 (dd, *J* = 5.0, 12.5, 1 H), 2.96 (dd, *J* = 7.8, 14.1, 1 H), 2.85−2.80 (m, 1 H), 2.48 (ddd, *J* = 7.6, *J* = 14.6, 14.7, 1 H), 2.04 (s, 3 H), 2.04−1.96 (m, 2 H) 1.87−1.73 (m, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) 133.0, 130.1, 129.6, 129.1, 97.7, 96.0, 74.9, 71.5, 67.7, 63.2, 60.4, 60.2, 58.9, 54.6, 51.0, 33.0, 28.0, 26.4, 23.4; MS (ESI, Q-tof) 347 (28), 346 (100), 192 (13), 174 (37), 133 (18); mol formula $C_{21}H_{32}BrNO_3$ (426.39); HRMS $C_{21}H_{32}NO_3$ (346.2382) calcd 346.2382, found 346.2372; TLC R_f 0.26 (CH_2Cl_2/MeOH, 9:1) [I_2].



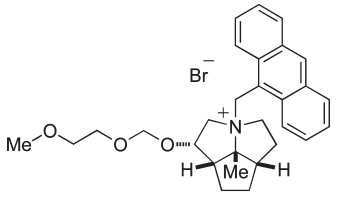
II{*4,2*}

*Preparation of rel-(1S,3R,5aS,7aS,7bR)-Octahydro-1-methoxyethoxymethoxy-3-(1-naphthylmethyl)cyclopenta[gh]pyrrolizinium Bromide (**II**{4,2}).* Data for **II**{*4,2*}: yield 110 mg (82%), free-flowing white powder; ^1H NMR (500 MHz, $CDCl_3$) 8.32 (d, *J* = 7.1, 1 H), 8.18 (d, *J* = 8.6, 1 H), 7.88 (d, *J* = 8.2, 2 H), 7.64 (dd, *J* = 7.2, 7.2, 1 H), 7.53 (dd, *J* = 7.5, 7.5, 2 H) 7.48 (dd, J = 7.7, 7.7, 2 H) 5.32 (d, *J* = 13.1, 1 H) 5.23 (d, *J* = 13.1, 1 H) 4.82 (dd, *J* = 5.9, 13.7, 1 H), 4.68−4.63 (m, 3 H) 4.31 (ddd, *J* = 6.6, 12.3, 12.36, 1 H), 3.53 (m, 2 H), 3.49−3.43 (m, 1 H), 3.37 (dd, *J* = 4.1, 8.8, 2 H), 3.16 (s, 3 H), 3.14 (dd, *J* = 5.9, 12.8, 1 H), 3.05 (t, *J* = 7.8, 14.2, 1 H), 2.99−2.95 (m, 1 H), 2.62−2.55 (m, 1 H), 2.25 (s, 3 H), 2.05−1.95 (m, 2 H), 1.90−1.71 (m, 3 H); MS (ESI, Q-tof) 397 (32), 396 178 (100), 179 (18); mol formula $C_{25}H_{34}NO_3Br$ (476.45); HRMS $C_{25}H_{34}NO_3$ (396.2539) calcd 396.2539, found 396.2535; TLC R_f 0.26 (CH_2Cl_2/MeOH, 9:1) [I_2].



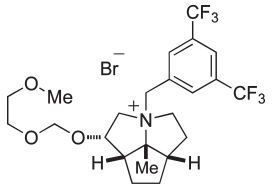
II{*4,3*}

*Preparation of rel-(1S,3R,5aS,7aS,7bR)-Octahydro-1-methoxyethoxymethoxy-3-(2-naphthylmethyl)cyclopenta[gh]pyrrolizinium Bromide (**II**{4,3}).* Data for **II**{*4,3*}: yield 126 mg (94%), free-flowing white powder; ^1H NMR (500 MHz, $CDCl_3$) 8.20 (s, 1 H), 7.91−7.89 (m, 1 H), 7.79 (s (broad), 2 H), 7.78−7.76 (m, 1 H), 7.52−50 (m, 2 H), 5.05 (d, *J* = 12.5, 1 H), 4.96 (d, *J* = 12.5, 1 H), 4.85 (dd, *J* = 5.9, 12.7, 1 H), 4.74 (dd, *J* = 5.5, 13.3, 1 H), 4.69 (q, *J* = 6.8, 2 H), 4.31 (ddd, J = 6.3, 12.0, 12.7, 1 H), 3.56 (dd, *J* = 4.1, 8.4, 2 H), 3.53−3.48 (m, 1 H), 3.38 (dd, *J* = 4.5, 4.6, 2 H), 3.20 (dd, *J* = 5.1, 12.7, 1 H), 3.09 (s, 3 H), 3.01 (dd, *J* = 7.9, 14.1, 1 H), 2.89−2.84 (m, 1 H), 2.55 (ddd, *J* = 7.6, 14.3, 14.6, 1 H), 2.12 (s, 3 H), 2.05−1.98 (m, 2 H), 1.87−1.74 (m, 3 H); MS (ESI, Q-tof) 397 (35), 396 (100), 179 (12); mol formula $C_{25}H_{34}NO_3Br$ (476.45); HRMS $C_{25}H_{34}NO_3$ (396.2539) calcd 396.2539, found 396.2532; TLC R_f 0.30 (CH_2Cl_2/MeOH, 9:1) [I_2].



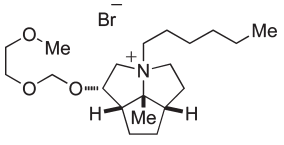
II{*4,4*}

*Preparation of rel-(1S,3R,5aS,7aS,7bR)-Octahydro-1-methoxyethoxymethyl-3-(9-anthrylmethyl)cyclopenta[gh]pyrrolizinium Bromide (**II**{4,4}).* Data for **II**{*4,4*}: yield 134 mg (90%), free-flowing white powder; ^1H NMR (500 MHz, $CDCl_3$) 8.73 (d, *J* = 9.0, 2 H), 8.53 (s, 1 H), 8.44 (m, 1 H), 8.00 (dd, *J* = 3.8, 8.2, 2 H), 7.74 (m, 2 H), 7.50 (q, 3 H), 5.71 (q, *J* = 14.3, 2 H), 4.94 (td, *J* = 6.2, 14.1, 1 H), 4.74 (dd, *J* = 7.0, 16.1, 1 H), 4.57 (dd, *J* = 6.7, 18.6, 2 H), 4.23 (dd, *J* = 5.9, 12.8, 1 H), 4.11 (m, 1 H), 3.87 (td, *J* = 6.0, 12.1, 1 H), 3.67 (m, 1 H), 3.54 (t, *J* = 4.5, 1 H), 3.44 (m, 2 H), 3.39 (s, 1 H), 3.28 (m, 2 H), 3.16 (m, 1 H), 3.09 (s, 1 H), 2.76 (dd, *J* = 6.5, 12.8, 1 H), 2.54 (m, 1 H), 2.44 (s, 3 H), 2.34 (m, 1 H), 1.90 (m, 5 H), 1.74 (s, 3 H); MS (ESI, Q-tof) 447 (40), 446 (100), 256 (40), 191 (46); mol formula $C_{29}H_{36}BrNO_3$ (526.50); HRMS $C_{29}H_{36}NO_3$ (446.2695) calcd 446.2695, found 446.2686; TLC R_f 0.34 (CH_2Cl_2/MeOH, 9:1) [I_2].



II{*4,5*}

*Preparation of rel-(1S,3R,5aS,7aS,7bR)-Octahydro-1-methoxyethoxymethyl-3-(3,5-trifluoromethylbenzyl)cyclopenta[gh]pyrrolizinium Bromide (**II**{4,5}).* Data for **II**{*4,5*}: yield 120 mg (76%), free-flowing white powder; ^1H NMR (500 MHz, $CDCl_3$) 8.42 (s, 2 H), 7.94 (s, 1 H), 5.32 (s, 2 H), 4.77 (dd, *J* = 5.8, 13.7, 1 H), 4.73 (d, *J* = 6.8, 1 H), 4.70 (d, *J* = 6.8, 1 H), 4.65 (dd, *J* = 5.8, 12.6, 1 H), 4.22 (td, *J* = 6.9, 12.2, 1 H), 3.63−3.54 (m, 2 H), 3.47 (dd, *J* = 5.8, 12.4, 1 H), 3.48−3.39 (m, 2 H), 3.17 (dd, *J* = 5.7, 12.7, 1 H), 3.14 (s, 3 H), 2.94 (dd, *J* = 7.8, 14.3, 1 H), 2.84 (ddd, *J* = 6.0, 12.4, 13.4, 1 H), 2.56 (ddd, *J* = 7.1, 14.7, 15.1, 1 H), 2.08 (s, 3 H), 2.06−1.97 (m, 2 H), 1.88−1.73 (m, 3 H); MS (ESI, Q-tof) 483 (30), 482 (100), 174 (25), 133 (28); mol formula $C_{23}H_{30}BrF_6NO_3$ (562.38); HRMS $C_{23}H_{30}F_6NO_3^+$ (482.2130) calcd 482.2130, found 482.2119; TLC R_f 0.27 (CH_2Cl_2/MeOH, 9:1) [I_2].



II{*4,6*}

*Preparation of rel-(1S,3S,5aS,7aS,7bR)-Octahydro-1-methoxyethoxymethoxy-3-hexylcyclopenta[gh]pyrrolizinium Bromide (**II**{4,6}).* Data for **II**{*4,6*}: yield 92 mg (77%), free-flowing white

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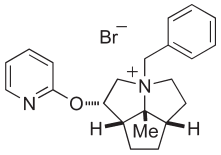
powder; ^{1}H NMR (500 MHz, $CDCl_3$) 4.77 (d, J = 7.0, 2 H), 4.73 (d, J = 7.0, 2 H), 4.52 (dd, J = 5.3, 12.9, 1 H), 4.45 (dd, J = 5.8, 12.8, 1 H), 3.95 (t, J = 6.2, 1 H), 3.77−3.67 (m, 2 H), 3.58−3.47 (m, 3 H), 3.42−3.56 (m, 1 H), 3.37 (s, 3 H), 2.93 (dd, J = 7.6, 13.9, 1 H), 2.69 (ddd, J = 7.1, 12.6, 12.8, 1 H), 2.32 (ddd, J = 7.1, 13.9, 14.1, 1 H), 2.09−1.85 (m, 3 H), 1.83 (s, 3 H), 1.81−1.74 (m, 4 H), 1.50−1.39 (m, (broad), 1 H), 1.35−1.32 (m, 3 H), 0.89 (t, J = 7.0, 3 H); MS (ESI, Q-tof) 341 (31), 340 (100), 133 (24); mol formula $C_{20}H_{38}BrNO_3$ (420.42); HRMS $C_{20}H_{38}NO_3^+$ (340.2852) calcd 340.2852, found 340.2845; TLC R_f 0.36 (CH_2Cl_2/MeOH, 9:1) [I_2].

II{5} **II**{5,R^4}

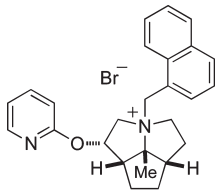
Preparation of Quaternary Ammonium Bromides ***II****{5,1−6}*. Following general procedure II, amino borane **II**{5} (960 mg, 3.72 mmol) was added to a 250 mL, round-bottomed flask as a solution in 150 mL of MeOH (~0.03 M). The flask was fitted with a reflux condenser, a magnetic stir bar, and a nitrogen inlet adapter. Lastly, 1.0 M aq HCl solution (24 mL, 5.0 equiv) was added via syringe. The resulting solution was heated and then concentrated by rotary evaporation (15 mmHg, 20−25 °C) as described in general procedure II. The resulting free amine was dissolved in acetonitrile and was distributed among six test tubes that were subsequently charged with benzyl bromide (tube 1, 100 μL, 0.75 mmol, 1.2 equiv), 1-bromomethylnaphthalene (tube 2, 166 mg, 0.75 mmol, 1.2 equiv), 2-bromomethylnaphthalene (tube 3, 166 mg, 0.75 mmol, 1.2 equiv), 9-bromomethylanthracene (tube 4, 203 mg, 0.75 mmol, 1.2 equiv), 3,5-(bistrifluoromethyl)benzyl bromide (tube 5, 62 μL, 0.34 mmol, 1.2 equiv),[93] and 1-bromohexane (tube 6, 110 μL, 0.75 mmol, 1.2 equiv). After being agitated for 12 h, the reaction mixtures were worked up and the products isolated and purified as described in general procedure II.



II{5,1}

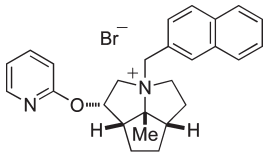
*Preparation of rel-(1S,3R,5aS,7aS,7bR)-Octahydro-1-(2-pyridyl)-3-benzylcyclopenta[gh]pyrrolizinium Bromide (****II****{5,1)*. Data for **II**{5,1}: yield 240 mg (92%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 8.15 (d, J = 4.7, 1 H), 7.85 (dd, J = 2.9, 6.6, 1 H), 7.62−7.58 (m, 1 H), 7.47−7.43 (m(br), 3 H), 6.95 (t, J = 6.0, 1 H), 6.71 (d, J = 8.3, 1 H), 5.87 (dd, J = 6.3, 14.3, 1 H), 5.05 (d, J = 12.4, 1 H), 4.95 (dd, J = 6.2, 12.9, 1 H), 4.79 (d, J = 12.4, 1 H), 4.58−4.52 (m, (so), 1 H), 3.44 (dt, J = 7.2, 12.5, 1 H), 3.24 (dd, J = 6.3, 12.9, 1 H), 3.14 (q, J = 7.7, 1 H), 2.98 (m, (broad), 1 H), 2.63−2.55 (m, 1 H), 2.15 (s, 3 H, H_3C(10)), 2.08−1.99 (m, (broad), 2 H), 1.90−1.78 (m, (broad), 3 H); MS (ESI, Q-tof) 336.2 (30), 335.2 (100), 264 (23), 263 (99), 185.0 (56); mol formula $C_{22}H_{27}BrN_2O$ (415.37); HRMS $C_{22}H_{27}N_2O^+$ (335.2123) calcd 335.2123, found 335.2121; TLC R_f 0.24 (CH_2Cl_2/MeOH, 9:1) [I_2].

*Preparation of rel-(1S,3R,5aS,7aS,7bR)-Octahydro-1-(2-pyridyloxy)-3-(1-napthylmethyl)cyclopenta[gh]pyrrolizinium Bromide (****II****{5,2})*. Data for **II**{5,2}: yield 274 mg (94%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 8.42 (d, 1 H, J = 7.1), 8.26 (d, 1 H, J = 8.6), 8.09 (dd, 1 H, J = 1.3, 4.9), 7.90 (t, 1 H, J = 7.6), 7.65 (t, 1 H, J = 7.5), 7.57−7.51



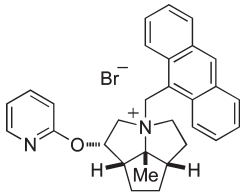
II{5,2}

(m, 3 H), 6.92 (dd, 1 H, J = 5.4, 6.7), 6.62 (d, 1 H, J = 8.4), 6.04 (dd, 1 H, J = 6.1, 14.1), 5.44 (d, 1 H, J = 13.0), 5.30 (d, 1 H, J = 13.1), 4.98 (dd, 1 H, J = 6.2, 13.0), 4.50 (m, (broad), 1 H), 3.26 (dd, 2 H, J = 5.9, 13.0), 3.11 (m, (broad), 1 H), 2.72−2.64 (m, 1 H), 2.35 (s, 3 H, (H_3C(C10)), 2.10−1.99 (m, 2 H), 1.90−1.77 (m, 3 H); MS (ESI, Q-tof) 386 (35), 385 (100), 264 (22), 263 (90), 185.0 (47); mol formula $C_{26}H_{29}BrN_2O$, 465.43; HRMS $C_{26}H_{29}N_2O^+$ (385.2280) calcd 385.2280, found 385.2276; TLC R_f 0.30 (CH_2Cl_2/MeOH, 9:1) [I_2].



II{5,3}

*Preparation of rel-(1S,3R,5aS,7aS,7bR)-Octahydro-1-(2-pyridyl)-3-[2]naphthylmethylcyclopenta[gh]pyrrolizinium Bromide (****II****{5,3})*. Data for **II**{5,3}: yield 251 mg (87%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 8.29 (s, 1 H), 8.18 (d, J = 4.3, 1 H), 7.91 (d, J = 7.5, 2 H), 7.80 (m, 2 H), 7.58 (t, J = 7.7, 1 H), 7.52 (d, J = 4.2, 2 H), 6.94 (t, J = 6.1, 1 H), 6.69 (d, J = 8.2, 1 H), 5.91 (dd, J = 6.3, 14.2, 1 H), 5.25 (d, J = 12.5, 1 H), 5.01 (dd, J = 6.1, 12.8, 1 H), 4.96 (d, J = 12.5, 1 H), 4.63 (s, 1 H), 3.44 (dt, J = 6.3, 12.0, 1 H), 3.22 (dd, J = 6.3, 12.8, 1 H), 3.16 (q, J = 7.9, 1 H), 3.03 (s (broad), 1 H), 2.69−2.59 (m, 1 H), 2.22 (s, 3 H), 2.10−2.00 (m, 2 H), 1.92−1.77 (m, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) 161.7, 146.9, 139.1, 133.5, 133.3, 132.7, 129.1, 128.8, 128.4, 127.5, 127.3, 126.7, 126.6, 118.0, 110.7, 98.0, 71.5, 62.4, 60.6, 60.5, 54.3, 51.0, 33.0, 28.3, 26.9, 23.6; MS (ESI, Q-tof) 386.2 (34), 385.2 (100), 263.1 (50), 185 (31) 133 (29); mol formula $C_{26}H_{29}BrN_2O$ (465.43); HRMS $C_{26}H_{29}N_2O^+$ (385.2280) calcd 385.2280, found 385.2276; TLC R_f 0.27 (CH_2Cl_2/MeOH, 9:1) [I_2].

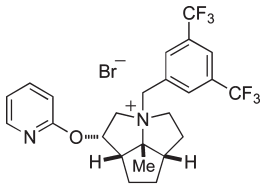


II{5,4}

*Preparation of rel-(1S,3R,5aS,7aS,7bR)-Octahydro-1-(2-pyridyl)-3-[9]anthrylmethylcyclopenta[gh]pyrrolizinium Bromide (****II****{5,4})*. Data for **II**{5,4}: yield 250 mg (78%), free-flowing pale-yellow powder; ^{1}H NMR (500 MHz, $CDCl_3$) 8.88 (d, J = 9.0, 1 H), 8.72 (d, J = 9.0, 1 H), 8.55 (s, 1 H), 8.01 (m,3 H), 7.77 (t, J = 7.5, 1 H), 7.71 (t, J = 7.7, 1 H), 7.54−7.49 (m, 3 H), 6.87 (dd, J = 5.1, 7.1, 1 H), 6.55 (d, J = 8.3, 1 H), 6.05 (dd, J = 6.2, 14.5, 1 H), 5.99 (d, J = 14.2, 1 H), 5.74 (d, J = 14.2, 1 H), 4.51 (dd, J = 6.4, 3.1, 1 H), 4.29 (dt, J = 7.3, 2.2, 1 H), 3.41 (dd, J = 7.8, 15.3, 1 H), 3.31 (m, (broad), 1 H), 3.24 (dt, J = 7.0, 12.2, 1 H), 2.93 (dd, J = 6.0, 13.1, 1 H), 2.78 (dt, J = 7.1, 14.4, 1 H), 2.54 (s, 3 H), 2.09−190 (m, 3 H), 1.82−1.66 (m, 3 H); MS (ESI, Q-tof) 436 (41),

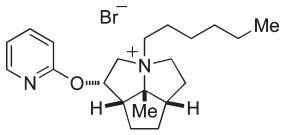
dx.doi.org/10.1021/jo2005445 |*J. Org. Chem.* 2011, 76, 4260–4336

435.2 (100), 236 (41), 191 (70); mol formula $C_{30}H_{31}BrN_2O$ (515.48); HRMS $C_{30}H_{31}N_2O^+$ (435.2436) calcd 435.2436, found 435.2434; TLC R_f 0.31 (CH_2Cl_2/MeOH, 9:1) [I_2].



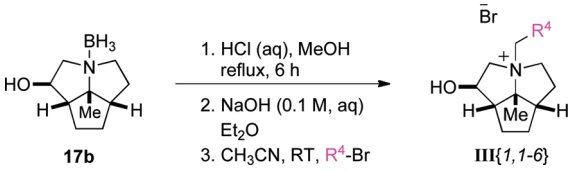
II{*5,5*}

*Preparation of rel-(1S,3R,5aS,7aS,7bR)-Octahydro-1-(2-pyridyl)-3-(3,5-trifluoromethylbenzyl)cyclopenta[gh]pyrrolizinium Bromide (**II**{5,5}).* Data for **II**{*5,5*}: yield 45 mg (63%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 8.57 (s, 2 H), 8.18 (d, J = 4.5, 1 H), 7.99 (s, 1 H), 7.63 (m, 1 H), 6.99 (dd, J = 5.4, 6.8, 1 H), 6.74 (d, J = 8.2, 1 H), 5.84 (dd, J = 7.9, 14.3, 1 H), 5.77 (d, J = 12.7, 1 H), 4.94−4.83 (m, (broad), 2 H), 4.74 (dd, J = 6.0, 12.6, 1 H), 3.30 (m, 1 H), 3.12−3.03 (m, (second order), 3 H), 2.64−2.56 (m, 1 H), 2.23 (s, 3 H), 2.16−1.98 (m, 3 H), 1.90−1.81 (m, 2 H); MS (ESI, Q-tof) 472.2 [M^++1] (31), 471.2 [M^++1] (100); mol formula $C_{24}H_{25}BrF_6N_2O$ (551.36); HRMS $C_{24}H_{25}F_6N_2O^+$ (471.1871) calcd 471.1871, found 471.1862; TLC R_f 0.21 (CH_2Cl_2/MeOH, 9:1) [I_2].



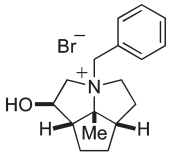
II{*5,6*}

*Preparation of rel-(1S,3S,5aS,7aS,7bR)-Octahydro-1-(2-pyridyl)-3-hexylcyclopenta[gh]pyrrolizinium Bromide (**II**{5,6}).* Data for **II**{*5,6*}: yield 70 mg (27%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 8.16 (ddd, J = 0.8, 2.0, 5.1, 1 H), 7.85 (dd, J = 3.0, 6.5, 2 H), 7.60 (ddd, J = 2.0, 7.2, 8.3, 1 H), 7.45 (m, 3 H), 6.95 (ddd, J = 0.9, 5.1, 7.1, 1 H), 6.70 (d, J = 8.3, 1 H), 5.87 (dd, J = 6.3, 14.3, 1 H), 5.05 (d, J = 12.4, 1 H), 4.96 (dd, J = 6.2, 12.9, 1 H), 4.77 (d, J = 12.4, 1 H), 4.61 (dt, J = 7.1, 12.1, 1 H), 3.44 (ddd, J = 6.5, 6.3, 12.2, 1 H), 3.23 (dd, J = 6.4, 12.9, 1 H), 3.14 (q, J = 7.7, 1 H), 3.02−2.97 (m, 1 H), 2.58 (dt, J = 6.9, 14.6, 1 H), 2.16 (s, 3 H), 2.08−2.00 (m, 2 H,), 1.91−178 (m, 3 H), 1.33−1.20 (m, (second order), 1 H), 0.88 (t, J = 7.1, 3 H); MS (ESI, Q-tof) 329 (100); mol formula $C_{21}H_{33}BrN_2O$ (409.40); HRMS $C_{21}H_{33}N_2O^+$ (329.2593) calcd 329.2593, found 329.2580; TLC *Rf* 0.38 (CH_2Cl_2/MeOH, 9:1) [I_2].



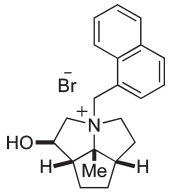
III{*1,1-6*}

*5. Preparation of Quaternary Ammonium Bromides **III**{1−5,1−6}.* Following general procedure II, amino borane **11b** (50 mg, 0.28 mmol) was added to a 50 mL round-bottomed flask as a solution in 9.5 mL of MeOH (0.03 M). The flask was fitted with a reflux condenser, a magnetic stir bar, and a nitrogen inlet adapter. Lastly, 1.0 N aq HCl solution (1.5, 5.0 equiv) was added via syringe. The resulting solution was heated and then concentrated by rotary evaporation (15 mmHg, 20−25 °C) as described in general procedure II. The resulting free amine was dissolved in acetonitrile and was distributed among six test tubes that were subsequently charged with benzyl bromide (tube 1, 39 mg, 0.33 mmol, 1.1 equiv), 1-bromomethylnaphthalene (tube 2, 67 mg, 0.3 mmol, 1.2 equiv), 2-bromomethylnaphthalene (tube 3, 73 mg, 0.33 mmol, 1.1 equiv), 9-bromomethylanthracene (tube 4, 49 mg, 0.18 mmol, 1.2 equiv), 3,5-bis(trifluoromethyl)benzyl bromide (tube 5, 63.7 μL, 0.18 mmol, 1.2 equiv), and 1-bromohexane (tube 6, 36 μL, 0.25 mmol, 1.2 equiv). After being agitated for 12 h, the reaction mixtures were worked up and the products isolated and purified as described in general procedure II.



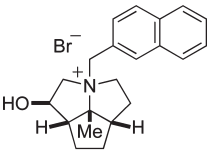
III{*1,1*}

*Preparation of rel-(1R,3R,5aS,7aS,7bR)-Octahydro-1-hydroxy-3-benzyl-7b-methylcyclopenta[gh]pyrrolizinium Bromide (**III**{1,1}).* Data for **III**{*1,1*}: yield 64 mg (69%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 7.61 (m, 2 H), 7.52 (m, 3 H), 4.98 (d, J = 12.2, 1 H), 4.56 (d, J = 12.2, 1 H), 4.25 (d, J = 3.1, 1 H), 3.84 (dd, J = 1.6, 13.7, 1 H), 3.74 (m, 2 H), 3.38 (dd, J = 6.4, 11.5, 1 H), 2.71 (dd, J = 8.5, 17.1, 1 H), 2.59 (t, J = 8.8, 1 H), 2.24 (m, 1 H), 2.13 (m, 1 H), 1.90 (m, 2 H), 1.85 (s, 3 H), 1.78 (ddd, J = 4.7, 12.9, 16.9, 2 H), 1.62 (ddd, J = 4.8, 9.4, 12.1, 1 H); MS (ESI, Q-tof) 259 (21), 258 (100), 166 (13); mol formula $C_{17}H_{24}BrNO$ (338.28); HRMS $C_{17}H_{24}NO^+$ (258.1858) calcd 258.1858, found 258.1855; TLC R_f 0.09 (CH_2Cl_2/MeOH, 9:1) [I_2].



III{*1,2*}

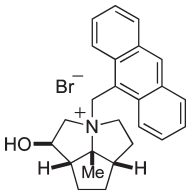
*Preparation of rel-(1R,3R,5aS,7aS,7bR)-Octahydro-1-hydroxy-3-(1-naphthyl)-7b-methylcyclopenta[gh]pyrrolizinium Bromide (**III**{1,2}).* Data for **III**{*1,2*}: yield 88 mg (82%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 8.72 (d, J = 8.6, 1 H), 8.09 (d, J = 8.3, 1 H), 8.00 (d, J = 8.0, 1 H), 7.94 (d, J = 7.2, 1 H), 7.67 (ddd, J = 1.3, 6.8, 8.5, 1 H), 7.61 (td, J = 7.2, 10.3, 2 H), 5.57 (d, J = 12.9, 1 H), 5.01 (d, J = 12.9, 1 H), 4.30 (s, 1 H), 3.98 (d, J = 13.6, 1 H), 3.92 (dd, J = 6.2, 12.1, 1 H), 3.20 (dd, J = 6.0, 11.6, 1 H), 2.77 (dd, J = 8.7, 16.5, 1 H), 2.66 (t, J = 9.1, 1 H), 2.23 (m, 1 H), 2.14 (td, J = 6.8, 13.6, 1 H), 2.00 (s, 3 H), 1.93 (m, 1 H), 1.69 (m, 3 H); MS (ESI, Q-tof) 310 (4), 309 (32), 308 (100); mol formula $C_{21}H_{26}BrNO$ (388.34); HRMS $C_{21}H_{26}NO^+$ (308.2014) calcd 308.2014, found 308.2033; TLC R_f 0.10 (CH_2Cl_2/MeOH, 9:1) [I_2].



III{*1,3*}

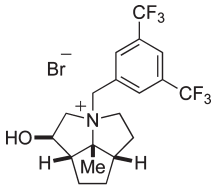
*Preparation of rel-(1R,3R,5aS,7aS,7bR)-Octahydro-1-hydroxy-3-(2-naphthyl)-7b-methylcyclopenta[gh]pyrrolizinium Bromide (**III**{1,3}).* Data for **III**{*1,3*}: yield 98 mg (84%), free-flowing white

powder; ^{1}H NMR (500 MHz, $CDCl_3$) 8.37 (s, 1 H), 8.07 (d, J = 7.3, 1 H), 7.88 (d, J = 8.4, 1 H), 7.83 (d, J = 7.2, 1 H), 7.67 (dd, J = 1.6, 8.4, 1 H), 7.52 (m, 3 H), 5.99 (d, J = 3.3, 1 H), 5.31 (d, J = 12.1, 1 H), 4.61 (d, J = 12.0, 1 H), 4.54 (s, 1 H), 4.30 (d, J = 13.3, 1 H), 3.83 (ddd, J = 6.2, 12.3, 12.4, 1 H), 3.30 (dd, J = 6.3, 11.6, 1 H), 3.15 (d, J = 11.7, 1 H), 2.89 (dd, J = 9.1, 9.1, 1 H), 2.74 (dd, J = 8.9, 16.3, 1 H), 2.28 (dd, J = 6.7, 13.9, 1 H), 2.16 (m, 1 H), 1.93 (s, 3 H), 1.76 (m, 5 H); MS (ESI, Q-tof) 310 (5), 309 (23), 308 (100); mol formula $C_{21}H_{26}BrNO$ (388.34); HRMS $C_{21}H_{26}NO^+$ (308.2014) calcd 308.2014, found 308.2024; TLC R_f 0.10 (CH_2Cl_2/MeOH, 9:1) [I_2].



III{*1,4*}

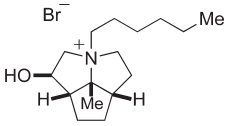
*Preparation of rel-(1R,3R,5aS,7aS,7bR)-Octahydro-1-hydroxy-3-(9-anthracenylmethyl)-7b-methylcyclopenta[gh]pyrrolizinium Bromide (**III**{1,4}).* Data for **III**{*1,4*}: yield 33 mg (51%), free-flowing yellow powder; ^{1}H NMR (500 MHz, $CDCl_3$) 9.10 (d, J = 9.1, 1 H), 8.62 (s, 1 H), 8.22 (s, 1 H), 8.07 (dd, J = 8.4, 27.8, 2 H), 7.86 (m, 1 H), 7.68 (m, 1 H), 7.55 (td, J = 8.0, 11.4, 2 H), 6.38 (d, J = 13.9, 1 H), 5.62 (d, J = 14.0, 1 H), 4.62 (s, 1 H), 4.43 (d, J = 13.2, 1 H), 3.67 (dt, J = 6.2, 12.3, 1 H), 3.34 (t, J = 9.3, 1 H), 2.94 (dd, J = 3.0, 13.1, 1 H), 2.76 (dd, J = 8.8, 16.1, 1 H), 2.47 (dd, J = 5.7, 12.1, 1 H), 2.26 (s, 3 H), 2.08 (dd, J = 7.3, 14.0, 1 H), 1.90 (tt, J = 6.9, 13.5, 1 H), 1.74 (dd, J = 6.4, 13.4, 1 H), 1.51 (m, 5 H); ^{13}C NMR (126 MHz, $CDCl_3$) 134.4, 134.3, 133.2, 131.0, 130.8, 128.9, 126.5, 126.3, 125.0, 121.9, 100.4, 75.5, 64.3, 63.3, 62.3, 56.0, 53.6, 30.9, 29.8, 28.0, 24.8; MS (ESI, Q-tof) 359 (11), 358 (36), 306 (27), 305 (83), 191 (43), 168 (10); mol formula $C_{25}H_{28}BrNO$ (438.40); HRMS $C_{25}H_{28}NO^+$ (358.2171) calcd 358.2171, found 358.2156; TLC R_f 0.13 (CH_2Cl_2/MeOH, 9:1) [I_2].



III{*1,5*}

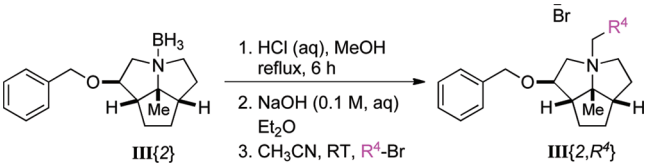
*Preparation of rel-(1R,3R,5aS,7aS,7bR)-Octahydro-1-hydroxy-3-(3,5-bistrifluoromethylbenzyl)-7b-methylcyclopenta[gh]pyrrolizinium Bromide (**III**{1,5}).* Data for **III**{*1,5*}: ^{1}H NMR (500 MHz, $CDCl_3$) 8.24 (s, 2 H), 8.21 (s, 1 H), 5.20 (d, 1 H, J = 12.6), 4.75 (d, 1 H, J = 12.7), 4.29 (dd, 1 H, J = 2.2, 8.8), 3.85 (ddd, 1 H, J = 6.4, 12.3, 12.2), 3.63 (dd, 1H, J = 1.8, 13.9), 3.44 (m, 3 H), 2.74 (dd, 1 H, J = 9.2, 17.0), 2.62 (dd, 1 H, J = 8.7, 8.7), 2.29 (m, 1 H), 2.15 (m, 1 H), 1.96 (m, 2 H), 1.88 (s, 3 H), 1.75 (m, 3 H); MS (ESI, Q-tof) 394 (100); mol formula $C_{19}H_{22}BrF_6NO$ (474.2785); HRMS $C_{19}H_{22}F_6NO^+$ (394.1606) calcd 394.1606, found 394.1595; TLC R_f 0.16 (CH_2Cl_2/MeOH, 9:1) [I_2].

*Preparation of rel-(1R,3R,5aS,7aS,7bR)-Octahydro-1-hydroxy-3-hexyl-7b-methylcyclopenta[gh]pyrrolizinium Bromide (**III**{1,6}).* Data for **III**{*1,6*}: yield 54 mg (79%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 5.66 (d, J = 8.9, 1 H), 5.41 (d, J = 9.1, 1 H), 4.28 (s, 1 H), 4.22 (s, 1 H), 4.15 (d, J = 13.1, 1 H), 3.91 (dd, J = 6.6, 11.6, 1 H), 3.75 (m, 6 H), 3.55 (d, J = 12.9, 2 H), 2.71 (dd, J = 8.4, 16.6, 1 H), 2.58



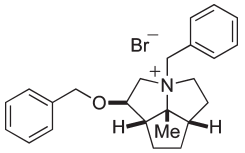
III{*1,6*}

(m, 2 H), 2.47 (t, J = 9.4, 1 H), 2.15 (m, 5 H), 1.81 (m, 10 H), 1.74 (s, 3 H), 1.62 (m, 3 H), 1.40 (m, 10 H), 0.94 (t, J = 6.5, 3 H); MS (ESI, Q-tof) 252 (100); mol formula $C_{16}H_{30}BrNO$ (332.32); HRMS $C_{16}H_{30}NO^+$ (252.2327) calcd 252.2327, found 252.2327; TLC R_f 0.13 (CH_2Cl_2/MeOH, 9:1) [I_2].



III{*2*} **III**{*2,R*^{4}}

*Preparation of Quaternary Ammonium Bromides **III**{2,1−6}.* Following general procedure II, amino borane **X** (324 mg, 1.2 mmol) was added to a 100 mL round-bottomed flask as a solution in 42 mL of MeOH (0.03 M). The flask was fitted with a reflux condenser, a magnetic stir bar, and a nitrogen inlet adapter. Lastly, 1.0 N aq HCl solution (6.0, 5.0 equiv) was added via syringe. The resulting solution was heated and then concentrated by rotary evaporation (15 mmHg, 20−25 °C) as described in general procedure II. The resulting free amine was dissolved in acetonitrile and was distributed among six test tubes that were subsequently charged with benzyl bromide (tube 1, 30 μL, 0.24 mmol, 1.2 equiv), 1-bromomethylnaphthalene (tube 2, 82 mg, 0.37 mmol, 1.2 equiv), 2-bromomethylnaphthalene (tube 3, 66 mg, 0.3 mmol, 1.2 equiv), 3,5-bis(trifluoromethyl)benzyl bromide[93] (tube 4, 31 mg, 0.104 mmol, 1.2 equiv), 9-bromomethylanthracene (tube 5, 60 mg, 0.24 mmol, 1.2 equiv), and 1-bromohexane (tube 6, 31 μL, 0.24 mmol, 1.2 equiv). After being agitated for 12 h, the reaction mixtures were worked up and the products isolated and purified as described in general procedure II.



III{*2,1*}

*Preparation of rel-(1R,3R,5aS,7aS,7bR)-Octahydro-1-benzyloxy-3-benzyl-7b-methylcyclopenta[gh]pyrrolizinium Bromide (**III**{2,1}).* Data for **III**{*2,1*}: yield 61 mg (71%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 7.64 (dd, 2 H, J = 1.6, 7.6) 7.41 (m, 8), 5.14 (d, 1 H, J = 12.0), 4.87 (ddd, 1 H, J = 6.4, 12.4, 12.8), 4.72 (d, 3 H, J = 11.7) 4.65 (d, 1 H, J = 12.0), 4.61 (d, 1 H, J = 11.7) 4.08 (d, 1 H, J = 3.0), 4.01 (dd, 2 H, J = 1.8, 14.0), 3.48 (dd, 1 H, J = 2.3, 13.9), 3.29 (dd, 1 H, J = 6.4, 11.5), 3.06 (dd, 1 H, J = 8.6, 14.9), 2.71 (dd, 1 H, J = 9.0, 9.0), 2.39 (ddd, 1 H, J = 6.7, 6.7, 13.7), 2.15−2.10 (m, 1 H), 2.04 (s, 3 H), 1.89−1.80 (m, 3 H), 1.75−1.67 (m, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) 136.6, 133.1, 130.3, 129.6, 129.2, 128.8, 128.4, 127.6, 97.8, 81.8, 71.8, 63.3, 63.2, 61.4, 56.5, 52.1, 30.1, 29.4, 27.2, 24.2; MS (ESI, Q-tof) 348 (100), 349 (31); mol formula $C_{24}H_{30}BrNO$ (428.40); HRMS $C_{24}H_{30}NO^+$ (348. 2327) calcd 348.2327, found 348.2312; TLC R_f 0.25 (CH_2Cl_2/MeOH, 9:1) [I_2].

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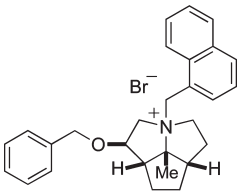
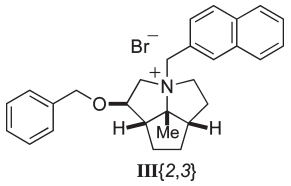


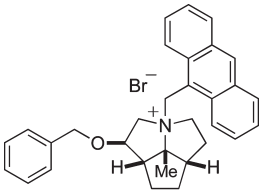
III{2,2}

*Preparation of rel-(1R,3R,5aS,7aS,7bR)-Octahydro-1-benzyloxy-3-(1-naphthylmethyl)-7b-methylcyclopenta[gh]pyrrolizinium Bromide (**III**{2,2}).* Data for **III**{2,2}: yield 117 mg (81%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 8.51 (d, J = 8.6, 1 H), 8.26 (d, J = 7.2, 1 H), 7.95 (d, J = 8.3, 1 H), 7.88 (d, J = 8.2, 1 H), 7.64 (dd, J = 1.7, 7.7, 1 H), 7.55 (dd, J = 7.3, 8.1, 1 H), 7.49 (m, 1 H), 7.46 (d, J = 4.4, 3 H), 7.44−7.34 (m, 3 H), 5.39 (d, J = 12.8, 1 H), 5.32 (d, J = 12.6, 1 H), 5.10 (m, 1 H), 4.87 (d, J = 11.5, 1 H), 4.60 (d, J = 10.9, 1 H), 4.12 (d, J = 4.4, 1 H), 4.03 (dd, J = 2.0, 13.4, 1 H), 3.42 (dd, J = 3.6, 13.5, 1 H), 3.31−3.21 (m, 1 H), 3.17 (dd, J = 6.5, 11.3, 1 H), 2.82 (dd, J = 9.8, 9.8, 1 H), 2.41−2.35 (m, 1 H), 2.23 (s, 3 H), 2.17−2.09 (m, 1 H), 1.91−1.61 (m, 2 H); MS (ESI, Q-tof) 399 (),398 (100), 258 (40); mol formula $C_{28}H_{32}$BrNO (478.46); HRMS $C_{28}H_{32}NO^+$ (398.2484) calcd 398.2484, found 398.2476; TLC R_f 0.2 (CH_2Cl_2/MeOH, 9:1) [I_2].



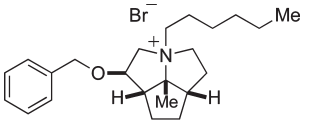
III{2,3}

*Preparation of rel-(1R,3R,5aS,7aS,7bR)-Octahydro-1-benzyloxy-3-(2-naphthylmethyl)-7b-methylcyclopenta[gh]pyrrolizinium Bromide (**III**{2,3}).* Data for **III**{2,3}: yield 93 mg (79%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 8.11 (s, 1 H), 7.88 (dd, J = 8.0, 16.5, 3 H,), 7.74 (dd, J = 1.7, 8.4, 1 H), 7.59−7.54 (m, 2 H), 7.38 (ddd, J = 11.2, 18.2, 27.0, 6 H), 5.33 (d, J = 11.8, 1 H), 5.02 (ddd, J = 6.3, 12.3, 12.3, 1 H), 4.83−4.77 (m, 3 H), 4.65 (d, J = 11.7, 1 H), 4.45 (d, J = 11.7, 1 H), 4.13−4.00 (m, 3 H), 3.74 (dddd, J = 6.2, 6.2, 12.2, 12.2, 1 H), 3.40−3.33 (m, 2 H), 3.18−3.10 (m, 2 H), 2.98 (ddd, J = 3.6, 6.9, 12.6, 1 H), 2.75 (dd, J = 9.3, 9.3, 1 H), 2.5−2.51 (m, 1 H), 2.48−2.42 (m, 1 H), 2.36-.29 (m, 1 H), 2.17−2.11 (m, 1 H), 2.10 (s, 3 H), 2.06−2.01 (m, 1 H), 1.91−1.83 (m, 2 H), 1.78−1.63 (m, 3 H); MS (ESI, Q-tof) 399 (39), 398 (100), 258 (49); mol formula $C_{28}H_{32}$BrNO (478.46); HRMS $C_{28}H_{32}NO^+$ (398.2484) calcd 398.2484, found 398.2473; TLC R_f 0.27 (CH_2Cl_2/MeOH, 9:1) [I_2].



III{2,4}

*Preparation of rel-(1R,3R,5aS,7aS,7bR)-Octahydro-1-benzyloxy-3-(9-anthracenylmethyl)-7b-methylcyclopenta[gh]pyrrolizinium Bromide (**III**{2,4}).* Data for **III**{2,4}: yield 32 mg (29%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 9.10 (d, J = 9.1, 1 H), 8.62 (s, 1 H), 8.21 (d, J = 8.9, 1 H), 8.10 (d, J = 8.4, 2 H), 8.04 (d, J = 8.5, 2 H), 7.86 (m, 1 H), 7.68 (dd,J = 7.2, 7.2, 1 H), 7.55 (dd, J = 8.0, 18.3, 2 H), 6.38 (d, J = 13.9, 1 H), 5.62 (d, J = 14.0, 1 H), 4.62 (s, 1 H), 4.43 (d, J = 13.2, 1 H), 3.67 (ddd, J = 6.2, 12.3, 12.3, 1 H), 3.34 (dd, J = 9.3, 9.3, 1 H), 2.94 (dd, J = 3.0, 13.1, 1 H), 2.76 (dd, J = 8.8, 16.1, 1 H), 2.47 (dd, J = 5.7, 12.1, 1 H), 2.30−2.27 (m, 1 H), 2.26 (s, 3 H), 2.08 (dd, J = 7.0, 13.4, 1 H), 1.90 (dddd, J = 6.9, 6.9, 13.5, 13.5, 1 H), 1.74 (dd, J = 6.4, 13.4, 1 H), 1.58−1.44 (m, 3 H); MS (ESI, Q-tof) 449 (41), 448 (100), 256 (20), 191 (60); mol formula $C_{32}H_{34}$BrNO (528.52); HRMS $C_{32}H_{34}NO^+$ (448.2640) calcd 448.2640, found 448.2633; TLC R_f 0.31 (CH_2Cl_2/MeOH, 9:1) [I_2].



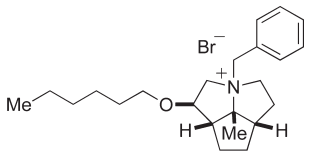
III{2,6}

*Preparation of rel-(1R,3R,5aS,7aS,7bR)-Octahydro-1-benzyloxy-3-hexyl-7b-methylcyclopenta[gh]pyrrolizinium Bromide (**III**{2,6}).* Data for **III**{2,6}: yield 64 mg (76%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 7.36 (ddd, J = 4.4, 8.5, 12.6, 2 H), 7.27 (s, 1 H), 4.58 (s, 1 H), 4.49 (d, J = 11.7, 2 H), 4.22 (m, 2 H), 4.12 (m, 1 H), 3.99 (d, J = 14.3, 1 H), 3.54 (m, 2 H), 3.29 (m, 1 H), 2.71 (dd, J = 9.4, 13.6, 1 H), 2.57 (dd, J = 7.5, 7.5, 1 H), 2.22 (m, 2 H), 2.09 (dd, J = 6.0, 16.5, 1 H), 1.81 (m, 4 H), 1.70 (s, 3 H), 1.26 (s, 1 H), 0.87 (dd, J = 5.1, 5.1, 3 H); MS (ESI, Q-tof); mol formula $C_{23}H_{36}$BrNO (422.44); HRMS $C_{23}H_{36}NO^+$ (342.2791) calcd 342.2797, found 342.2782; TLC R_f 0.31 (CH_2Cl_2/MeOH, 9:1) [I_2].

III{3} **III**{3,R^4}

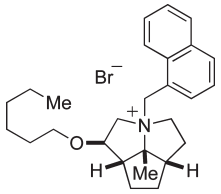
*Preparation of Quaternary Ammonium Bromides **III**{3,1−6}.* Following general procedure II, amino borane **III**{3} (560 mg, 2.22 mmol) was added to a 100 mL round-bottomed flask as a solution in 50 mL of MeOH (0.03 M). The flask was fitted with a reflux condenser, a magnetic stir bar, and a nitrogen inlet adapter. Lastly, 1.0 N aq HCl solution (12.0, 5.0 equiv) was added via syringe. The resulting solution was heated and then concentrated by rotary evaporation (15 mmHg, 20−25 °C) as described in general procedure II. The resulting free amine was dissolved in acetonitrile and was distributed among six test tubes that were subsequently charged with benzyl bromide (tube 1, 53 μL, 0.44 mmol, 1.2 equiv), 1-bromomethylnaphthalene (tube 2, 69 mg, 0.37 mmol, 1.2 equiv), 2-bromomethylnaphthalene (tube 3, 66 mg, 0.3 mmol, 1.2 equiv), 3,5-bis(trifluoromethyl)benzyl bromide (tube 4, 44 μL, 0.24 mmol, 1.2 equiv), 9-bromomethylanthracene (tube 5, 65 mg, 0.24 mmol, 1.2 equiv), and 1-bromohexane (tube 6, 62 μL, 0.44 mmol, 1.2 equiv). After being agitated for 12 h, the reaction mixtures were worked up and the products isolated and purified as described in general procedure II.

*Preparation of rel-(1R,3R,5aS,7aS,7bR)-Octahydro-1-hexyloxy-3-benzyl-7b-methylcyclopenta[gh]pyrrolizinium Bromide (**III**{3,1}).* Data for **III**{3,1}: yield 145 mg (93%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 7.69 (dd, J = 1.9, 7.0, 2 H), 7.45 (m, 3 H), 5.16 (d, J = 11.9, 1 H), 4.90 (m, 1 H), 4.62 (d, J = 11.9, 1 H), 3.94 (dd, J = 8.3, 22.7, 1 H), 3.62 (td, J = 6.7, 8.8, 1 H), 3.47 (td, J = 6.3, 8.9, 1 H), 3.39 (d, J = 13.9, 1 H), 3.25 (dd, J = 6.5, 11.5, 1 H), 3.07 (dd, J = 8.6, 15.4, 1 H), 2.64 (t, J = 9.2, 1 H), 2.40 (m, 1 H), 2.13 (m, 1 H), 2.03 (s, 3 H), 1.82 (m, 3 H), 1.67 (m, 3 H), 1.34 (m, 7 H), 0.91 (t, J = 7.1, 3 H);



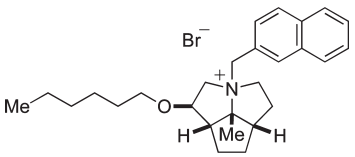
III{3,1}

MS (ESI, Q-tof) 393 (12), 343 (28), 342 (100), 336 (8); mol formula $C_{23}H_{36}BrNO$ (422.44); HRMS $C_{23}H_{36}NO^+$ (342.2797) calcd 342.2797, found 342.2782; TLC R_f 0.28 (CH_2Cl_2/MeOH, 9:1) [I_2].



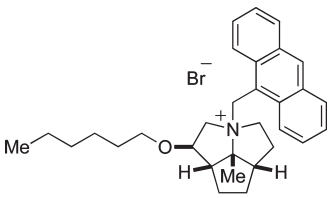
III{3,2}

*Preparation of rel-(1R,3R,5aS,7aS,7bR)-Octahydro-1-hexyloxy-3-(1-naphthylmethyl)-7b-methylcyclopenta[gh]pyrrolizinium Bromide (**III**{3,2}).* Data for **III**{3,2}: yield 117 mg (81%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 8.70 (d, *J* = 8.5, 1 H), 8.30 (d, *J* = 7.2, 1 H), 7.98 (d, *J* = 8.2, 1 H), 7.92 (d, *J* = 7.6, 1 H), 7.58 (ddd, *J* = 6.2, 13.2, 24.1, 3 H), 5.40 (d, *J* = 12.6, 1 H), 5.32 (d, *J* = 12.6, 1 H), 5.07 (dt, *J* = 6.2, 12.7, 1 H), 4.04 (dd, *J* = 1.8, 13.9, 1 H), 3.96 (d, *J* = 3.3, 1 H), 3.76 (td, *J* = 6.8, 8.8, 1 H), 3.51 (m, 1 H), 3.35 (ddd, *J* = 4.2, 12.9, 24.2, 3 H), 3.23 (m, 2 H), 3.14 (dd, *J* = 6.2, 11.5, 1 H), 2.72 (t, *J* = 9.5, 1 H), 2.39 (m, 1 H), 2.20 (s, 3 H), 2.10 (td, *J* = 7.4, 17.8, 2 H), 1.78 (ddd, *J* = 15.8, 24.6, 37.5, 5 H), 1.56 (s, 1 H), 1.29 (m, 7 H), 0.92 (t, *J* = 7.1, 3 H); MS (ESI, Q-tof) 394 (8), 393 (34), 392 (100), 336 (13); mol formula $C_{27}H_{38}BrNO$ (472.50); HRMS $C_{27}H_{38}NO^+$ (392.2953) calcd 392.2953, found 392.2951; TLC R_f 0.31 (CH_2Cl_2/MeOH, 9:1) [I_2].



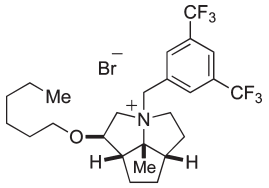
III{3,3}

*Preparation of rel-(1R,3R,5aS,7aS,7bR)-Octahydro-1-hexyloxy-3-(2-naphthylmethyl)-7b-methylcyclopenta[gh]pyrrolizinium Bromide (**III**{3,3}).* Data for **III**{3,3}: yield 93 mg (79%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 8.17 (s, 1 H), 7.91 (d, *J* = 8.6, 2 H), 7.88 (d, (broad), J = 7.3, 1 H), 7.78 (dd, 1 H, *J* = 1.6, 8.4), 7.59−7.54 (m, 2 H), 5.37 (d, *J* = 11.9, 1 H), 5.09 (dt, *J* = 6.3, 12.4, 12.4, 1 H), 4.78 (d, *J* = 11.9, 1 H), 4.04 (dd, *J* = 1.7, 13.8, 1 H), 3.94 (d, *J* = 2.8, 1 H), 3.67 (ddd, *J* = 6.6, 8.9, 9.1, 1 H), 3.52 (ddd, *J* = 6.3, 8.9, 12.7, 1 H), 3.34 (dd, *J* = 2.1, 14.0, 1 H), 3.28 (dd, *J* = 6.5, 11.4, 1 H), 3.12 (dd, *J* = 9.2, 16.1, 1 H), 2.67 (t, *J* = 9.2, 1 H), 2.42 (ddd, *J* = 7.2, 13.8, 13.8, 1 H), 2.14 (dd, *J* = 6.7, 13.4, 1 H), 2.09 (s, 3 H), 1.91−1.61 (m, 7 H), 1.52−1.46 (m, 2 H), 1.40−1.37 (m, 6 H), 0.93 (t, *J* = 7.1, 3 H); MS (ESI, Q-tof) 393 (31), 392 (100); mol formula $C_{27}H_{38}BrNO$ (472.50); HRMS $C_{27}H_{38}NO^+$ (392.2953) calcd 392.2953, found 392.2950; TLC R_f 0.30 (CH_2Cl_2/MeOH, 9:1) [I_2].



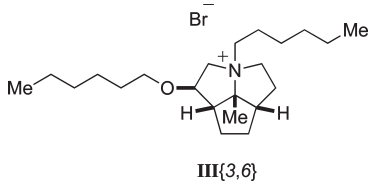
III{3,4}

*Preparation of rel-(1R,3R,5aS,7aS,7bR)-Octahydro-1-hexyloxy-3-(9-anthracenylmethyl)-7b-methylcyclopenta[gh]pyrrolizinium Bromide (**III**{3,4}).* Data for **III**{3,4}: yield 76 mg (73%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 8.85 (d, *J* = 8.5, 1 H), 8.66 (m, 1 H), 8.08 (d, *J* = 8.2, 2 H), 7.81 (t, *J* = 6.9, 1 H), 7.55 (m, 3 H), 5.87 (d, *J* = 13.7, 1 H), 5.71 (d, *J* = 13.7, 1 H), 4.22 (d, *J* = 14.1, 1 H), 4.13 (d, *J* = 3.3, 1 H), 4.07 (dt, *J* = 6.3, 12.3, 1 H), 3.84 (m, 1 H), 3.80 (td, *J* = 6.8, 8.9, 2 H), 3.59 (td, *J* = 6.4, 9.0, 1 H), 3.14 (m, 1 H), 2.76 (t, *J* = 9.3, 1 H), 2.62 (dd, *J* = 5.9, 11.7, 1 H), 2.23 (s, 1 H), 2.06 (m, 4 H), 1.83 (m, 5 H), 1.42 (m, 6 H), 0.92 (t, *J* = 7.1, 3 H); MS (ESI, Q-tof) 442 (100); mol formula $C_{31}H_{40}BrNO$ (522.56); HRMS $C_{31}H_{40}NO^+$ (442.3110) calcd 442.3110, found 442.3110; TLC R_f 0.35 (CH_2Cl_2/MeOH, 9:1) [I_2].



III{3,5}

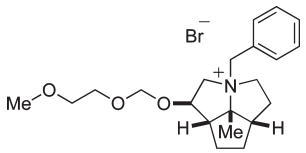
*Preparation of rel-(1R,3R,5aS,7aS,7bR)-Octahydro-1-hexyloxy-3-(3,5-bistrifluoromethylbenzyl)-7b-methylcyclopenta[gh]pyrrolizinium Bromide (**III**{3,5}).* Data for **III**{3,5}: yield 97 mg (87%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 8.30 (s, 2 H), 7.98 (s, 1 H), 5.87 (d, *J* = 12.2, 1 H), 5.27 (ddd, *J* = 6.3, 12.1, 12.3, 1 H), 4.73 (d, *J* = 12.2, 1 H), 3.96 (d, *J* = 3.2, 1 H), 3.68 (m, 2 H), 3.46 (m, 2 H), 3.24 (dd, *J* = 6.6, 11.1, 1 H), 3.06 (dd, *J* = 8.7, 15.8, 1 H), 2.69 (dd, *J* = 9.1, 9.1, 1 H), 2.45 (m, 1 H), 2.16 (m, 1 H), 2.11 (s, 3 H), 1.86 (m, 4 H), 1.67 (m, 3 H), 1.42 (dd, *J* = 7.3, 14.8, 2 H), 1.33 (m, 4 H), 0.90 (t, 3 H, *J* = 7.1); MS (ESI, Q-tof) 479 (26), 478 (100); mol formula $C_{25}H_{34}BrF_6NO$ (558.44); HRMS $C_{25}H_{34}F_6NO^+$ (478.2545) calcd 478.2545, found 478.2541; TLC R_f 0.29 (CH_2Cl_2/MeOH, 9:1) [I_2].



III{3,6}

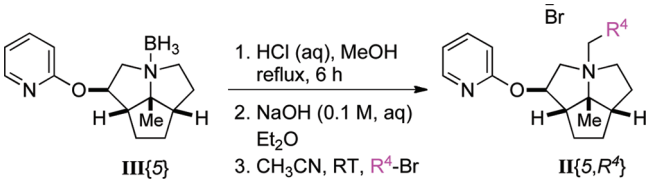
*Preparation of rel-(1R,3R,5aS,7aS,7bR)-Octahydro-1-hexyloxy-3-hexyl-7b-methylcyclopenta[gh]pyrrolizinium Bromide (**III**{3,6}).* Data for **III**{3,6}: yield 115 mg (94%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 4.16 (td, *J* = 5.0, 9.7, 1 H), 3.92 (d, *J* = 12.2, 2 H), 3.45 (m, 6 H), 2.72 (dt, *J* = 5.9, 9.7, 1 H), 2.50 (t, *J* = 7.7, 1 H), 2.29 (td, *J* = 7.4, 14.9, 1 H), 2.08 (m, 2 H), 1.81 (m, 6 H), 1.70 (s, 3 H), 1.52 (m, 7 H), 1.28 (ddd, *J* = 5.9, 11.0, 25.6, 13 H), 0.89 (t, *J* = 5.7, 6 H); MS (ESI, Q-tof) 337 (28), 336 100); mol formula $C_{22}H_{42}BrNO$ (416.48); HRMS $C_{22}H_{42}NO^+$ (336.3266) calcd 336.3266, found 336.3256; TLC R_f 0.42 (CH_2Cl_2/MeOH, 9:1) [I_2].

*Preparation of rel-(1R,3R,5aS,7aS,7bR)-Octahydro-1-hexyloxy-3-hexyl-7b-methylcyclopenta[gh]pyrrolizinium Bromide (**III**{4,1}).* Data for **III**{4,1}: ^{1}H NMR (500 MHz, $CDCl_3$) 7.70 (m, 2 H) 5.24 (d, 1 H, *J* = 12.2) 7.45 (m, 3H) 5.15 (d, 1 H, *J* =



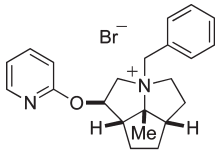
III{4,1}

6.3, 11.7) 4.88 (m, 2 H) 4.58 (dd, 1 H, J = 5.6, 13.1) 4.30 (dd, 1 H, J = 4.0, 8.0) 3.77 (m, 2 H) 3.58 (ddd, 2 H, J = 2.9, 6.1, 8.4) 3.38 (m, 3 H) 3.24 (ddd, 1 H, J = 7.1, 12.8, 12.5) 3.07 (m, 1 H) 2.67 (m, 1 H) 2.39 (m, 1 H) 2.15 (m, 1 H) 2.04 (d, 3 H, J = 15.5) 1.77 (m, 5 H) 4.00 (S, 1 H); MS (ESI, Q-tof) 346 (100); mol formula $C_{21}H_{32}BrNO_3$ (426.39); HRMS $C_{21}H_{32}NO_3$ (346.2382) calcd 346.2382, found 346.2372; TLC R_f 0.26 (CH_2Cl_2/MeOH, 9:1) [I_2].



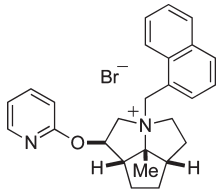
III{5} II{5,R4}

Preparation of Quaternary Ammonium Bromides ***III****{5,1−6}*. Following general procedure II, amino borane **III**{*5*} (252 mg, 96 mmol) was added to a 100 mL round-bottomed flask as a solution in 33 mL of MeOH (0.03 M). The flask was fitted with a reflux condenser, a magnetic stir bar, and a nitrogen inlet adapter. Lastly, 1.0 N aq HCl solution (4.8, 5.0 equiv) was added via syringe. The resulting solution was heated and then concentrated by rotary evaporation (15 mmHg, 20−25 °C) as described in general Procedure II. The resulting free amine was dissolved in acetonitrile and was distributed among six test tubes that were subsequently charged with benzyl bromide (tube 1, 22 μL, 0.18 mmol, 1.1 equiv), 1-bromomethylnaphthalene (tube 2, 44 mg, 0.2 mmol, 1.1 equiv), 2-bromomethylnaphthalene (tube 3, 58 mg, 0.26 mmol, 1.1 equiv), 3,5-bis(trifluoromethyl)benzyl bromide (44 μL, 0.24 mmol, 1.2 equiv), 9-bromomethylanthracene (tube 5, 65 mg, 0.24 mmol, 1.2 equiv), and 1-bromohexane (tube 6, 34 μL, 0.24 mmol, 1.2 equiv). After being agitated for 12 h, the reaction mixtures were worked up and the products isolated and purified as described in general procedure II.



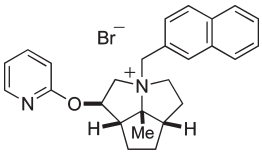
III{5,1}

*Preparation of rel-(1R,3R,5aS,7aS,7bR)-Octahydro-1-(2-pyridyloxy)-3-benzyl-7b-methylcyclopenta[gh]pyrrolizinium Bromide (****III****{5,1}).* Data for **III**{*5,1*}: yield 50 mg (73%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 8.19 (d, J = 3.7, 1 H), 7.77−7.74 (m, 1 H), 7.48 (d, J = 7.3, 2 H), 7.41 (dd, J = 7.3, 7.3, 1 H), 7.34 (dd, J = 7.1, 7.1, 2 H), 7.06 (dd, J = 5.1, 6.9, 1 H), 6.94 (d, J = 8.2, 1 H), 5.47 (s, 1 H), 5.43 (d, J = 12.2, 1 H), 5.18 (s, 1 H), 4.55 (d, J = 11.5, 1 H), 4.25 (d, J = 14.0, 1 H), 3.38 (d, J = 13.9, 1 H), 3.22 (d, J = 30.4, 2 H), 2.78 (dd, J = 8.8, 8.8, 1 H), 2.50 (s, 1 H), 2.30 (ddd, J = 7.1, 7.1, 13.9, 1 H), 2.14 (s, 3 H), 1.95−1.70 (m, 4 H); MS (ESI, Q-tof) 336 (28), 335 (100); mol formula $C_{22}H_{27}BrN_2O$ (415.37); HRMS $C_{22}H_{27}N_2O^+$: (335.2123) calcd 335.2123, found 335.2114; TLC R_f 0.23 (CH_2Cl_2/MeOH, 9:1) [I_2].



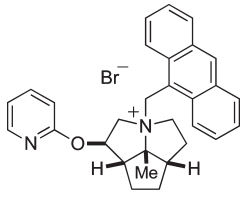
III{5,2}

*Preparation of rel-(1R,3R,5aS,7aS,7bR)-Octahydro-1-(2-pyridyloxy)-3-(1-naphthylmethyl)-7b-methylcyclopenta[gh]pyrrolizinium Bromide (****III****{5,2}).* Data for **III**{*5,2*}: yield 69 mg (74%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 8.50 (d, J = 8.7, 1 H), 8.24 (d, J = 7.2, 1 H), 8.16 (dd, J = 1.5, 4.8, 1 H), 7.92 (d, J = 8.2, 1 H), 7.86 (d, J = 8.1, 1 H), 7.79 (ddd, J = 2.0, 8.4, 8.4, 1 H), 7.50−7.47 (m, 1 H), 7.43 (dd, J = 7.5, 7.5, 1 H), 7.28−7.24 (m, 1 H), 7.05 (dd, J = 8.1, 14.2, 2 H), 5.58 (dd, J = 8.2, 15.4, 2 H), 5.29 (d, J = 12.7, 1 H), 5.17 (ddd, J = 6.2, 12.2, 12.3, 1 H), 4.17 (s, 1 H), 3.61 (s, 1 H), 3.51 (dd, J = 3.7, 14.6, 1 H), 3.26 (d, J = 3.5, 1 H), 3.15 (dd, J = 6.1, 11.3, 1 H), 2.78 (dd, J = 7.8, 7.8, 1 H), 2.40 (ddd, J = 7.5, 14.0, 13.4, 1 H), 2.32−2.24 (m, 1 H), 2.22 (s, 3 H), 1.96−1.71 (m, 5 H), 1.34 (dd, J = 2.0, 5.5, 1 H), 1.23 (ddd, J = 1.6, 7.1, 7.1, 1 H); MS (ESI, Q-tof) 385 (100); mol formula $C_{26}H_{29}BrN_2O$ (465.43); HRMS $C_{26}H_{29}N_2O^+$ (385.2280) calcd 385.2280, found 385.2275; TLC R_f 0.26 (CH_2Cl_2/MeOH, 9:1) [I_2].



III{5,3}

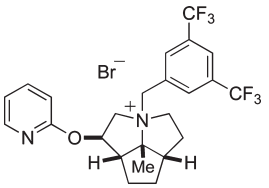
*Preparation of rel-(1R,3R,5aS,7aS,7bR)-Octahydro-1-(2-pyridyloxy)-3-(2-naphthylmethyl)-7b-methylcyclopenta[gh]pyrrolizinium Bromide (****III****{5,3}).* Data for **III**{*5,3*}: yield 103 mg (91%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 8.22 (dd, J = 1.5, 4.8, 1 H), 7.83 (m, 3 H), 7.69 (dd, J = 1.5, 8.5, 1 H), 7.61 (s, 1 H), 7.52 (m, 3 H), 7.16 (dd, J = 5.1 7.1, 1 H), 7.05 (d, J = 8.0, 1 H), 5.64 (d, J = 12.0, 1 H), 5.46 (s, 1 H), 5.36 (ddd, J = 6.4, 12.3, 12.2, 1 H) 4.66 (d, J = 12.1, 1 H), 4.35 (dd, J = 1.7, 14.4, 1 H), 3.32 (dd, J = 2.7, 14.2, 1 H), 3.24 (ddd, J = 7.2, 7.2, 14.4, 2 H), 2.83 (dd, J = 9.0, 9.0, 1 H), 2.54−2.48 (m, 1 H), 2.31 (ddd, J = 7.6, 7.6, 14.9, 1 H), 2.22 (s, 3 H), 1.96−1.66 (m, 4 H); MS (ESI, Q-tof) 385 (100); mol formula $C_{26}H_{29}BrN_2O$ (465.43); HRMS $C_{26}H_{29}N_2O^+$: (385.2280) calcd 385.2280, found 385.2276; TLC R_f 0.21 (CH_2Cl_2/MeOH, 9:1) [I_2].



III{5,4}

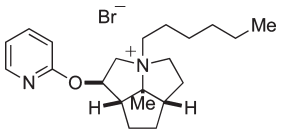
*Preparation of rel-(1R,3R,5aS,7aS,7bR)-Octahydro-1-(2-pyridyloxy)-3-(9-anthracenylmethyl)-7b-methylcyclopenta[gh]pyrrolizinium Bromide (****III****{5,4}).* Data for **III**{*5,4*}: yield 68 mg (66%), free-flowing yellow powder; ^{1}H NMR (500 MHz, $CDCl_3$) Rotamer *S* 8.99 (d, J = 9.3, 1 H), 8.66 (s, 1 H), 8.61 (d, J = 9.0, 1 H), 8.22 (d, J = 4.0, 1 H), 8.09 (d, J = 8.6, 2 H), 7.92 (m, 1 H), 7.84 (m, 1 H), 7.62 (m, 1 H), 7.44 (dd, J = 7.1,

7.1, 1 H), 7.15 (m, 2 H), 6.01 (d, J = 13.8, 1 H), 5.96 (d, J = 13.8, 1 H), 5.68 (d, J = 3.2, 1 H), 4.39 (m, 2 H), 3.62 (dd, J = 4.2, 14.5, 1 H), 3.40 (m, 1 H), 2.91 (dd, J = 8.2, 8.2, 1 H), 2.72 (dd, J = 6.0, 12.1, 1 H), 2.40 (m, 2 H), 1.93 (m, 2 H), 1.89 (s, 3 H), 1.83 (m, 1 H); MS (ESI, Q-tof) 436 (32), 435 (100); mol formula $C_{30}H_{31}BrN_2O$ (515.48); HRMS $C_{30}H_{31}N_2O^+$ (435.2436) calcd 435.2436, found 435.2426; TLC R_f 0.23 (CH_2Cl_2/MeOH, 9:1) [I_2].



III{*5,5*}

*Preparation of rel-(1R,3R,5aS,7aS,7bR)-Octahydro-1-(2-pyridyloxy)-3-(3,5-bistrifluoromethylbenzyl)-7b-methylcyclopenta[gh]pyrrolizinium Bromide (**III**{5,5}).* Data for **III**{*5,5*}: yield 97 mg (88%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 8.18 (d, J = 4.9, 1 H), 7.98 (s, 2 H), 7.90 (s, 1 H), 7.79 (dd, J = 6.8, 6.8, 1 H), 7.11 (dd, J = 4.4, 6.9, 1 H), 6.96 (d, J = 8.2, 1 H), 6.11 (d, J = 12.3, 1 H), 5.52−5.43 (m, 2 H), 4.56 (d, J = 12.3, 1 H), 4.08 (dd, J = 6.7, 12.6, 1 H), 3.5−3.42 (m, 1 H), 3.17 (dd, J = 6.6, 10.7, 2 H), 2.85 (dd, J = 8.6, 8.6, 1 H), 2.51 (s, 1 H), 2.32 (dd, J = 5.5, 11.8, 1 H), 2.25 (s, 3 H), 1.98−1.77 (m, 4 H); MS (ESI, Q-tof) 471 (100), 472 (30); mol formula $C_{24}H_{25}BrF_6N_2O$ (551.36); HRMS $C_{24}H_{25}F_6N_2O^+$: (471.1871) calcd 471.1871, found 471.1865; TLC R_f 0.20 (CH_2Cl_2/MeOH, 9:1) [I_2].

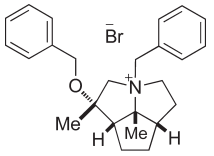


III{*5,6*}

*Preparation of rel-(1R,3R,5aS,7aS,7bR)-Octahydro-1-(2-pyridyloxy)-3-hexyl-7b-methylcyclopenta[gh]pyrrolizinium Bromide (**III**{5,6}).* Data for **III**{*5,6*}: yield 44 mg (54%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 8.14 (ddd, J = 0.6, 1.9, 5.0, 1 H), 7.65 (ddd, J = 2.0, 7.2, 8.3, 1 H), 6.98 (ddd, J = 0.8, 5.0, 7.1, 1 H), 6.73 (d, J = 8.3, 1 H), 5.44 (d, J = 3.0, 1 H), 4.17−3.99 (m, 4 H), 3.71 (ddd, J = 4.9, 11.7, 11.5, 1 H), 3.48 (dt, J = 3.9, 12.2, 1 H), 2.93−2.88 (m, 1 H), 2.67 (t, J = 8.0, 1 H), 2.42 (ddd, J = 7.3, 14.4, 14.4, 1 H), 2.28−2.20 (m, 1 H), 2.10−2.01 (m, 1 H), 1.95−1.85 (m, 4 H), 1.84 (s, 3 H), 1. 49 −1.43(m, 1 H), 1.26−1.17 (m, 5 H), 0.83 (t, J = 6.9, 3 H); MS (ESI, Qtof) 329 (100), 330 (29); mol formula $C_{21}H_{33}BrN_2O$ (409.40); HRMS $C_{21}H_{33}N_2O^+$: (329.2593) calcd 329.2593, found 329.2580; TLC R_f 0.33 (CH_2Cl_2/MeOH, 9:1) [I_2].

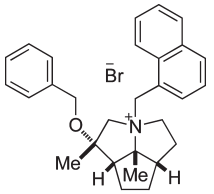
IV{*2,2*} **IV**{*2,2,R*^{4}}

*6. Preparation of Quaternary Ammonium Bromides **IV**{2−7, 1−7,1−11}. Preparation of Quaternary Ammonium Bromides **IV**{2,2,R^4}.* Following general procedure II, amino borane **V**{*2,2*} (210 mg, 0.74 mmol) was added to a 250 mL, round-bottomed flask as a solution in 150 mL of MeOH (~0.03 M). The flask was fitted with a reflux condenser, a magnetic stir bar, and a nitrogen inlet adapter. Lastly, 1.0 M aq HCl solution (24 mL, 5.0 equiv) was added via syringe. The resulting solution was heated and then concentrated by rotary evaporation (15 mmHg, 20−25 °C) as described in general procedure II. The resulting free amine was dissolved in acetonitrile and was distributed among six test tubes that were subsequently charged with benzyl bromide (tube 1, 23 mg, 0.30 mmol, 1.2 equiv), 1-bromomethylnaphthalene (tube 2, 80 mg, 0.3 mmol, 1.2 equiv), and 2-bromomethylnaphthalene (tube 3, 80 mg, 0.3 mmol, 1.2 equiv). After being agitated for 12 h, the reaction mixtures were worked up and the products isolated and purified as described in general procedure II.



IV{*2,2,1*}

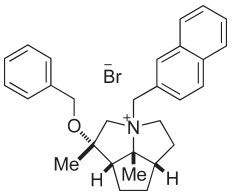
*Preparation of rel-(1S,3R,5aS,7aS,7bR)-Octahydro-1-benzyloxy-1-methyl-3-benzyl-7b-methylcyclopenta[gh]pyrrolizinium Bromide (**IV**{2,2,1}).* Data for **IV**{*2,2,1*}: yield 63 mg (57%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 7.78−7.75 (m, 2 H), 7.48−7.42 (m, 3 H), 7.31−7.24 (m, 3 H), 7.18 (d, J = 7.1, 2 H), 5.38 (d, J = 12.4, 1 H), 5.34 (d, J = 13.0, 1 H), 4.45 (d, J = 11.4, 1 H), 4.26−4.21 (m, 2 H), 3.86−3.78 (m, 1 H), 3.72 (dd, J = 6.8, 12.2, 1 H), 3.44 (d, J = 13.1, 1 H), 2.83−2.79 (m, 1 H), 2.68 (dd, J = 6.4, 13.5, 1 H), 2.49−2.40 (m, 1 H), 2.27−2.20 (m, 1 H), 2.12 (s, 3 H), 2.12−2.04 (m, 1 H), 1.91−1.80 (m, 1 H), 1.80−1.75 (m, 1 H), 1.75 (s, 3 H); MS (ESI, Q-tof) 362.2 (100); mol formula $C_{25}H_{32}BrNO$, (442.43); HRMS $C_{25}H_{32}NO^+$ (362.2484) calcd 362.2484, found 362.2479; TLC R_f 0.22 (CH_2Cl_2/MeOH, 9:1) [I_2].



IV{*2,2,2*}

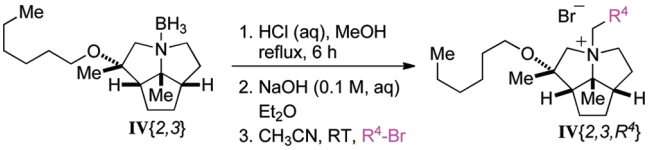
*Preparation of rel-(1S,3R,5aS,7aS,7bR)-Octahydro-1-benzyloxy-1-methyl-3-(1-naphthylmethyl)-7b-methylcyclopenta[gh]pyrrolizinium Bromide (**IV**{2,2,2}).* Data for **IV**{*2,2,2*}: yield 71 mg (58%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 8.44−8.35 (m, 1 H), 8.17−8.10 (m, 1 H), 7.88−7.74 (m, 2 H), 7.59 (t, J = 7.2, 1 H), 7.53−7.47 (m, 1 H), 7.34 (s, 1 H), 7.25−7.16 (m, 3 H), 7.12−7.07 (m, 2 H), 5.60−5.42 (m, 2 H), 5.17−4.97 (m, 1 H), 4.41 (d, J = 11.4, 1 H), 4.13 (d, J = 11.6, 1 H), 3.83−3.73 (m, 1 H), 3.51−3.44 (m, 1 H), 3.36−3.28 (m, 1 H), 2.93−3.67 (m, 3 H), 2.33 (s, 3 H), 2.26−2.18 (m, 1 H), 2.11 (s, 1 H), 1.91−1.71 (m, 3 H), 1.75 (s, 3 H); MS (ESI, Q-tof) 412.3 (100); mol formula $C_{29}H_{34}BrNO$ (492.49); HRMS $C_{29}H_{34}NO^+$ (412.2640) calcd 412.2640, found 412.2636; TLC R_f 0.25 (CH_2Cl_2/MeOH, 9:1) [I_2].

*Preparation of rel-(1S,3R,5aS,7aS,7bR)-Octahydro-1-benzyloxy-1-methyl-3-(2-naphthylmethyl)-7b-methylcyclopenta[gh]pyrrolizinium Bromide (**IV**{2,2,3}).* Data for **IV**{*2,2,3*}: yield 64 mg (53%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 8.21 (s, 1 H),



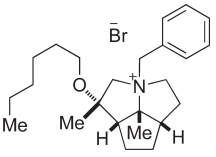
IV{2,2,3}

7.94−7.88 (m, 1 H), 7.83−7.74 (m, 3 H), 7.56−7.48 (m, 2 H), 7.28−7.17 (m, 3 H), 7.13 (d, J = 7.4, 2 H), 5.56−5.34 (m, 2 H), 4.45−4.40 (m, 1 H), 4.42 (d, J = 11.0, 1 H), 4.17 (d, J = 11.4, 1 H), 3.85−3.70 (m, 2 H), 3.47 (d, J = 13.0, 1 H), 2.88−2.69 (m, 2 H), 2.64−2.50 (m, 1 H), 2.28−2.17 (m, 1 H), 2.19 (s, 3 H), 2.12−2.04 (m, 1 H), 1.91−1.73 (m, 3 H), 1.75 (s, 3 H); MS (ESI, Q-tof) 412.3 (100); mol formula $C_{29}H_{34}BrNO$ (492.49); HRMS $C_{29}H_{34}NO^+$ (412.2640) calcd 412.2640, found 412.2631; TLC R_f 0.25 (CH_2Cl_2/MeOH, 9:1) [I_2].



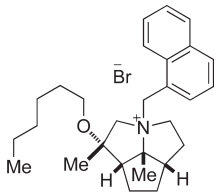
IV{2,3} IV{2,3,R4}

Preparation of Quaternary Ammonium Bromides ***IV***{2,3,1−3}. Following general procedure II, amino borane **IV**{2,3} (103 mg, 0.37 mmol) was added to a 50 mL round-bottomed flask as a solution in 12 mL of MeOH (0.03 M). The flask was fitted with a reflux condenser, a magnetic stir bar, and a nitrogen inlet adapter. Lastly, 1.0 N aq HCl solution (3.68 mL, 5.0 equiv) was added via syringe. The resulting solution was heated and then concentrated by rotary evaporation (15 mmHg, 20−25 °C) as described in general Procedure II. The resulting free amine was dissolved in acetonitrile and was distributed among six test tubes that were subsequently charged with benzyl bromide (tube 1, 82 mg, 0.478 mmol, 4.0 equiv), 1-bromomethylnaphthalene (tube 2, 79 mg, 0.358 mmol, 3.0 equiv), and 2-bromomethylnaphthalene (tube 3, 79 mg, 0.358 mmol, 3.0 equiv). After being agitated for 12 h, the reaction mixtures were worked up and the products isolated and purified as described in general procedure II.



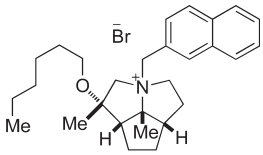
IV{2,3,1}

*Preparation of rel-(1S,3R,5aS,7aS,7bR)-Octahydro-1-hexyloxy-1-methyl-3-benzyl-7b-methylcyclopenta[gh]pyrrolizinium Bromide (****IV****{2,3,1}).* Data for **IV**{2,3,1}: yield 41 mg (51%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 7.79−7.73 (m, 2 H), 7.48−7.42 (m, 3 H), 5.35 (d, J = 12.3, 1 H), 5.17 (d, J = 13.0, 1 H), 4.27−4.18 (m, 1 H), 3.84 (ddd, J = 6.0, 12.1, 12.1, 1 H), 3.79−3.73 (m, 1 H), 3.32 (d, J = 12.9, 2 H), 3.30 (dd, J = 6.9, 15.2, 1 H), 3.11 (dd, J = 6.4, 15.1, 1 H), 2.76−2.70 (m, 1 H), 2.66 (dd, J = 7.2, 14.7, 1 H), 2.53−2.42 (m, 1 H), 2.19−2.00 (m, 2 H), 2.09 (s, 3 H), 1.86−1.72 (m, 3 H), 1.60 (s, 3 H), 1.47−1.38 (m, 2 H), 1.30−1.15 (m, 6H), 0.84 (t, J = 6.9, 3 H); MS (ESI, Q-tof) 356.3 (100); mol formula $C_{24}H_{38}BrNO$ (436.47); HRMS $C_{24}H_{38}NO^+$ (356.2953) calcd 356.2953, found 356.2951; TLC R_f 0.32 (CH_2Cl_2/MeOH, 9:1) [I_2].



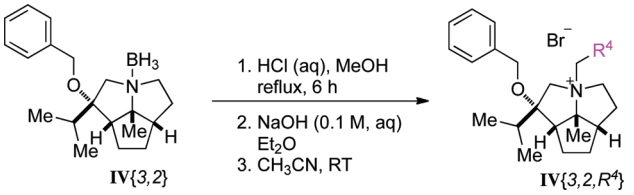
IV{2,3,2}

*Preparation of rel-(1S,3R,5aS,7aS,7bR)-Octahydro-1-hexyloxy-1-methyl-3-(1-naphthylmethyl)-7b-methylcyclopenta[gh]pyrrolizinium Bromide (****IV****{2,3,2}).* Data for **IV**{2,3,2}: yield 45 mg (51%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 8.42−8.36 (m, 1 H), 8.16−8.10 (m, 1 H), 7.85 (d, J = 7.7, 1 H), 7.82−7.76 (m, 1 H), 7.61 (dd, J = 7.6, 7.6, 1 H), 7.51 (dd, J = 7.5, 7.5, 1 H), 7.41−7.33 (m, 1 H), 5.53 (d, J = 12.5, 1 H), 5.31 (d, J = 12.9, 1 H), 5.06 (d, J = 12.6, 1 H), 3.84−3.75 (m, 1 H), 3.35 (d, J = 12.9, 2 H), 3.25 (dd, J = 7.1, 15.2, 1 H), 2.99 (dd, J = 6.3, 15.0, 1 H), 2.84−2.69 (m, 3 H), 2.30 (s, 3 H), 2.15−2.05 (m, 2 H), 1.83−1.74 (m, 3 H), 1.60 (s, 3 H), 1.38−1.25 (m, 2 H), 1.22−1.09 (m, 6H), 0.79 (t, J = 7.0, 3 H); MS (ESI, Q-tof) 406.3 (100); mol formula $C_{28}H_{40}BrNO$ (486.53); HRMS $C_{28}H_{40}NO^+$: (406.3110) calcd 406.3110, found 406.3099; TLC R_f 0.35 (CH_2Cl_2/MeOH, 9:1) [I_2].



IV{2,3,3}

*Preparation of rel-(1S,3R,5aS,7aS,7bR)-Octahydro-1-hexyloxy-1-methyl-3-(2-naphthylmethyl)-7b-methylcyclopenta[gh]pyrrolizinium Bromide (****IV****{2,3,3}).* Data for **IV**{2,3,3}: yield 51 mg (57%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 8.21 (s, 1 H), 7.94−7.89 (m, 1 H), 7.83−7.74 (m, 3 H), 7.56−7.48 (m, 2 H), 5.53−5.46 (m, 1 H), 5.27−5.17 (m, 1 H), 4.55−4.39 (m, 1 H), 3.87−3.73 (m, 2 H), 3.35 (d, J = 12.9, 1 H), 3.26 (dd, J = 7.2, 13.6, 1 H), 3.04 (dd, 1 H, J = 6.9, 13.3), 2.78−2.67 (m, 2 H), 2.65−2.54 (m, 1 H), 2.18−2.02 (m, 2 H), 2.16 (s, 3 H), 1.88−1.72 (m, 3 H), 1.60 (s, 3 H), 1.45−1.29 (m, 2 H), 1.24−1.11 (m, 6H), 0.80 (t, J = 6.8, 3 H); MS (ESI, Q-tof) 406.3 (100); mol formula $C_{28}H_{40}BrNO$ (486.53); HRMS $C_{28}H_{40}NO^+$ (406.3110) calcd 406.3110, found 406.3109; TLC R_f 0.35 (CH_2Cl_2/MeOH, 9:1) [I_2].



IV{3,2} IV{3,2,R4}

Preparation of Quaternary Ammonium Bromides ***IV***{3,2,R4}. Following general procedure II, amino borane **IV**{3,2} (533 mg, 1.68 mmol) was added to a 50 mL round-bottomed flask as a solution in 56 mL of MeOH (0.03 M). The flask was fitted with a reflux condenser, a magnetic stir bar, and a nitrogen inlet adapter. Lastly, 1.0 N aq HCl solution (8.4 mL, 5.0 equiv) was added via syringe. The resulting solution was heated and then concentrated by rotary evaporation (15 mmHg, 20−25 °C) as described in general Procedure II. The resulting free amine was dissolved in acetonitrile and was distributed among four test

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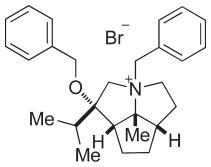
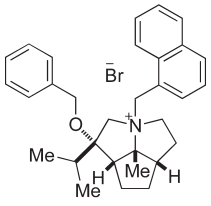
tubes that were subsequently charged with benzyl bromide (tube 1, 87 mg, 0.509 mmol, 1.2 equiv), 1-bromomethylnaphthalene (tube 2, 116 mg, 0.509 mmol, 1.2 equiv), 2-bromomethylnaphthalene (tube 3, 116 mg, 0.509 mmol, 1.2 equiv), and 3,5-bis(trifluoromethyl)benzyl bromide (tube 4, 156 mg, 0.509 mmol, 1.2 equiv). After being agitated for 12 h, the reaction mixtures were worked up and the products isolated and purified as described in general procedure II.



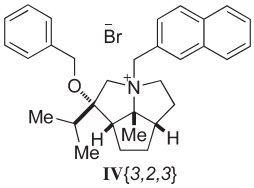
IV{*3,2,1*}

*Preparation of rel-(1R,3R,5aS,7aS,7bR)-Octahydro-1-benzyloxy-1-isopropyl-3-benzyl-7b-methylcyclopenta[gh]pyrrolizinium Bromide (**IV**{3,2,1}).* Data for **IV**{3,2,1}: yield 235 mg (99%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 7.82−7.77 (dd, J = 2.2, 7.2, 2 H), 7.44−7.37 (s, 3 H), 7.30−7.21 (m, 3 H), 7.19−7.15 (m, 2 H), 5.50 (d, J = 12.5, 1 H), 4.77 (d, J = 13.4, 1 H), 4.62−4.53 (m, 1 H), 4.46 (d, J = 11.3, 1 H), 4.21 (d, J = 11.3, 1 H), 3.91−3.82 (m, 1 H), 3.72 (d, J = 13.5, 1 H), 3.49 (dd, J = 7.2, 12.3, 1 H), 2.83−2.76 (m, 1 H), 2.73 (dd, J = 8.2, 8.2, 1 H), 2.67−2.56 (m, 1 H), 2.42−2.32 (m, 1 H), 2.31−2.21 (m, 1 H), 2.09−1.99 (m, 1 H), 1.96 (s, 3 H), 1.86−1.76 (m, 2 H), 1.69−1.59 (m, 1 H), 1.28 (d, J = 6.8, 3 H), 1.05 (d, J = 6.8, 3 H); MS (ESI, Q-tof) 390.3 (100); mol formula $C_{27}H_{36}BrNO$ (470.48); HRMS $C_{27}H_{36}NO^+$ (390.2797) calcd 390.2797, found 390.2789; TLC R_f 0.21 (CH_2Cl_2/MeOH, 9:1) [I_2].



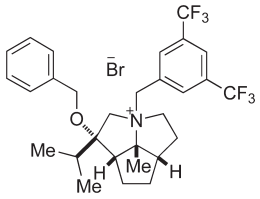
IV{*3,2,2*}

*Preparation of rel-(1R,3R,5aS,7aS,7bR)-Octahydro-1-benzyloxy-1-isopropyl-3-(1-naphthylmethyl)-7b-methylcyclopenta[gh]pyrrolizinium Bromide (**IV**{3,2,2}).* Data for **IV**{3,2, 2}: yield 194 mg (74%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 8.35 (s, 1 H), 8.24 (s, 1 H), 7.66 (s, 1 H), 7.53 (dd, J = 7.9, 7.9, 1 H), 7.45−7.40 (m, 2 H), 7.18−7.13 (m, 3 H), 7.02 (d, J = 5.9, 2 H), 6.99−6.89 (m, 1 H), 5.62−5.49 (m, 2 H), 4.82 (d, J = 13.8, 1 H), 4.37 (d, J = 11.2, 1 H), 4.00 (d, J = 11.3, 1 H), 3.76−3.67 (m, 1 H), 3.54 (d, J = 13.9, 1 H), 3.26−3.16 (m, 1 H), 3.03−2.94 (m, 2 H), 2.78 (dd, J = 7.3, 7.3, 1 H), 2.39−2.16 (m, 2 H), 2.30 (s, 3 H), 2.11−2.02 (m, 1 H), 1.85−1.75 (m, 2 H), 1.63−1.55 (m, 1 H), 1.35 (d, J = 6.8, 3 H), 1.04 (d, J = 6.8, 3 H); MS (ESI, Q-tof) 440.3 (100); mol formula $C_{31}H_{38}BrNO$ (520.54); HRMS $C_{31}H_{38}NO^+$ (440.2953) calcd 440.2953, found 440.2960; TLC R_f 0.25 (CH_2Cl_2/MeOH, 9:1) [I_2].



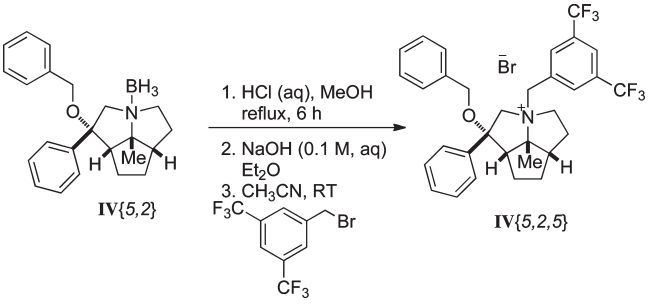
IV{*3,2,3*}

*Preparation of rel-(1R,3R,5aS,7aS,7bR)-Octahydro-1-benzyloxy-1-isopropyl-3-(2-naphthylmethyl)-7b-methylcyclopenta[gh]pyrrolizinium Bromide (**IV**{3,2,3}).* Data for **IV**{3,2,3}: yield 195 mg (75%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 8.22 (s, 1 H), 7.86−7.81 (m, 1 H), 7.74 (d, J = 8.3, 1 H), 7.64−7.55 (m, 2 H), 7.45−7.42 (m, 2 H), 7.20−7.14 (m, 3 H), 7.11−7.08 (m, 2 H), 5.62 (d, J = 12.8, 1 H), 4.92−4.82 (m, 1 H), 4.83 (d, J = 13.4, 1 H), 4.41 (d, J = 11.3, 1 H), 4.11 (d, J = 11.2, 1 H), 3.87−3.78 (m, 1 H), 3.69 (d, J = 13.4, 1 H), 3.49−3.41 (m, 1 H), 2.95−2.89 (m, 1 H), 2.82−2.71 (m, 2 H), 2.37 (hept, J = 6.9, 1 H), 2.29−2.21 (m, 1 H), 2.10−2.02 (m, 1 H), 2.07 (s, 3 H), 1.86−1.75 (m, 2 H), 1.68−1.60 (m, 1 H), 1.33 (d, J = 6.8, 3 H), 1.03 (d, J = 6.7, 3 H); MS (ESI, Q-tof) 440.3 (100); mol formula $C_{31}H_{38}BrNO$ (520.54); HRMS $C_{31}H_{38}NO^+$ (440.2953) calcd 440.2953, found 440.2960; TLC R_f 0.25 (CH_2Cl_2/MeOH, 9:1) [I_2].



IV{*3,2,5*}

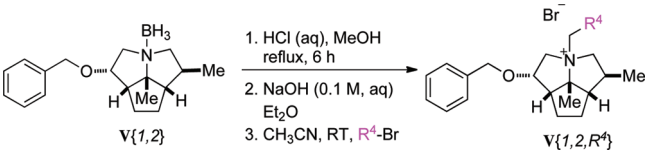
*Preparation of rel-(1R,3R,5aS,7aS,7bR)-Octahydro-1-benzyloxy-1-isopropyl-3-(3,5-trifluoromethyl benzyl)-7b-methylcyclopenta[gh]pyrrolizinium Bromide (**IV**{3,2,5}).* Data for **IV**{3,2,5}: yield 199 mg (66%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 8.32 (s, 2 H), 7.83 (s, 1 H), 7.25−7.19 (m, 3 H), 7.15−7.10 (m, 2 H), 5.88 (d, J = 12.7, 1 H), 5.17−5.09 (m, 1 H), 4.88 (d, J = 13.2, 1 H), 4.47 (d, J = 11.5, 1 H), 4.16 (d, J = 11.5, 1 H), 3.94−3.85 (m, 1 H), 3.47 (d, J = 13.1, 1 H), 3.02−2.93 (m, 2 H), 2.80−2.70 (m, 2 H), 2.38 (hept, J = 6.7, 1 H), 2.31−2.22 (m, 1 H), 2.12−1.99 (m, 1 H), 2.04 (s, 3 H), 1.91−1.77 (m, 2 H), 1.74−1.65 (m, 1 H), 1.31 (d, J = 6.7, 3 H), 1.02 (d, J = 6.7, 3 H); MS (ESI, Q-tof) 526.3 (100); mol formula $C_{29}H_{34}BrF_6NO$ (606.48); HRMS $C_{29}H_{34}NOF_6^+$ (526.2545) calcd 526.2545, found 526.2549; TLC R_f 0.30 (CH_2Cl_2/MeOH, 9:1) [I_2].



IV{*5,2*} **IV**{*5,2,5*}

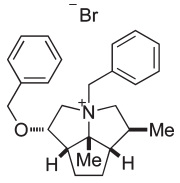
*Preparation of rel-(1R,3R,5aS,7aS,7bR)-Octahydro-1-benzyloxy-1-phenyl-3-(3,5-trifluoromethylbenzyl)-7b-methylcyclopenta[gh]pyrrolizinium Bromide (**IV**{5,2,5}).* Following general procedure II, benzyl ether **IV**{*5,2*} (69 mg, 0.268 mmol) was added to a 50 mL round-bottomed flask as a solution in 8.9 mL of MeOH (0.03 M). The flask was fitted with a reflux condenser, a magnetic stir bar, and a nitrogen inlet adapter. Lastly, 1.0 N aq HCl solution (1.3 mL, 5.0 equiv) was added via syringe. The resulting solution was heated and then concentrated by rotary evaporation (15 mmHg, 20−25 °C) as described in general Procedure II. The resulting free amine (30 mg, 0.09 mmol) was dissolved in acetonitrile along with 3,5-bis(trifluoromethyl)benzyl bromide (33 mg, 0.108 mmol, 2.0 equiv) and was allowed to react for 12 h. Purification of described in general procedure II afforded 44 mg (75%) of the quaternary ammonium ion **IV**{*5,2,5*} as a free-flowing white

power. Data for **IV**{*5,2,5*}: yield 44 mg (75%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 8.12 (s, 1 H), 7.93 (s, 1 H), 7.76 (d, *J* = 7.5, 1 H), 7.64 (dd, *J* = 7.6, 7.6, 1 H), 7.55 (dd, *J* = 7.3, 7.3, 1 H), 7.30−7.24 (m, 1 H), 7.12 (dd, *J* = 2.1, 7.5, 1 H), 5.59 (d, *J* = 12.5, 1 H), 4.80 (s, 1 H), 4.59 (d, *J* = 13.0, 1 H), 4.37 (d, *J* = 11.6, 1 H), 4.07 (d, *J* = 11.0, 1 H), 3.91 (d, *J* = 11.0, 1 H), 3.62 (d, *J* = 13.1, 1 H), 3.44−3.39 (m, 1 H), 3.32 (dd, *J* = 8.1, 8.1, 1 H), 3.15−3.08 (m, 1 H), 2.61−2.45 (m, 1 H), 2.26 (s, 3 H), 2.16−2.03 (m, 1 H), 2.01−1.95 (m, 1 H), 1.87 (ddd, *J* = 7.8, 14.5, 14.3, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) 139.1, 136.7, 133.4, 132.53 (q, *J* = 34.3),132.5, 130.0, 129.8, 128.7, 128.2, 127.4, 126.7, 124.2, 122.8 (q *J* = 273),99.6, 84.5, 66.8, 64.5, 61.4, 59.3, 58.9, 52.0, 32.1, 28.1, 26.7, 24.0; MS (ESI, Q-tof) 560.2 (100); mol formula $C_{32}H_{32}BrF_6NO$ (640.50); HRMS $C_{32}H_{32}F_6NO^+$ (560.2388) calcd 560.2388, found 560.2388; TLC R_f 0.32 (CH_2Cl_2/MeOH, 9:1) [I_2].



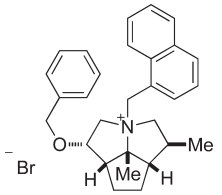
V{*1,2*} **V**{*1,2,R*^{4}}

7. Preparation of Quaternary Ammonium Bromides ***V****-*{*1−7,1−7,1−11*}. *Preparation of Quaternary Ammonium Bromides* ***V***{*1,2,R*^{4}}. Following general procedure II, amino borane **V**{*1,2*} (533 mg, 1.68 mmol) was added to a 100 mL round-bottomed flask as a solution in 37 mL of MeOH (0.03 M). The flask was fitted with a reflux condenser, a magnetic stir bar, and a nitrogen inlet adapter. Lastly, 1.0 N aq HCl solution (5.5 mL, 5.0 equiv) was added via syringe. The resulting solution was heated and then concentrated by rotary evaporation (15 mmHg, 20−25 °C) as described in general Procedure II. The resulting free amine was dissolved in acetonitrile and was distributed among seven test tubes that were subsequently charged with benzyl bromide (tube 1, 40 mg, 0.235 mmol, 1.5 equiv), 1-bromomethylnaphthalene (tube 2, 42 mg, 0.188 mmol, 1.2 equiv), 2-bromomethylnaphthalene (tube 3, 42 mg, 0.188 mmol, 1.2 equiv), 3,5-bis(trifluoromethyl)benzyl bromide (tube 4, 58 mg, 0.188 mmol, 1.2 equiv), 3,5-bis(*tert*-butyl)benzyl bromide (tube 5, 54 mg, 0.188 mmol, 1.2 equiv), 4-methoxybenzyl bromide (tube 6, 38 mg, 0.188 mmol, 1.2 equiv), and 1-bromohexane (tube 7, 129 mg, 0.785 mmol, 5.0 equiv). After being agitated for 12 h, the reaction mixtures were worked up and the products isolated and purified as described in general procedure II.

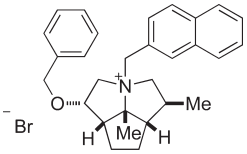


V{*1,2,1*}

*Preparation of rel-(1S,3R,5S,5aS,7aS,7bR)-Octahydro-1-benzyloxy-3-benzyl-5-methyl-7b-methylcyclopenta[gh]pyrrolizinium Bromide (****V****{1,2,1}).* Data for **V**{*1,2,1*}: yield 63 mg (90%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 7.64 (d, *J* = 6.7, 2 H), 7.43−7.31 (m, 8H), 5.14 (d, *J* = 12.3, 1 H), 4.99−4.93 (dd, *J* = 6.9, 17.2, 1 H), 4.65 (d, *J* = 12.3, 1 H), 4.63 (d, *J* = 11.7, 1 H), 4.57 (d, *J* = 11.7, 1 H), 4.37 (dd, *J* = 11.9, 11.9, 1 H), 3.87 (dd, *J* = 6.2, 12.5, 1 H), 3.10 (dd, *J* = 6.1, 11.5, 1 H), 2.88−2.82 (m, 2 H), 2.45−2.40 (s, 1 H), 2.15−2.06 (m, 1 H), 2.06−1.95 (m, 1 H), 2.04 (s, 3 H), 1.93−1.78 (m, 3 H), 1.20 (d, *J* = 6.4, 3 H); MS (ESI, Q-tof) 362.2 (100); mol formula $C_{25}H_{32}$-BrNO (442.43); HRMS $C_{25}H_{32}NO^+$ (362.2484) calcd 362.2484, found 362.2484; TLC R_f 0.20 (CH_2Cl_2/MeOH, 9:1) [I_2].

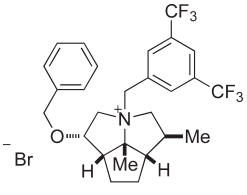


*Preparation of rel-(1S,3R,5S,5aS,7aS,7bR)-Octahydro-1-benzyloxy-3-(1-naphthylmethyl)-5-methyl-7b-methylcyclopenta[gh]pyrrolizinium Bromide (****V****{1,2,2}).* Data for **V**{*1,2,2*}: yield 77 mg (99%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 8.25−8.16 (m, 2 H), 7.85−7.73 (m, 2 H), 7.53−7.47 (m, 1 H), 7.49 (dd, *J* = 7.6, 14.6, 1 H), 7.40−7.26 (m, 7H), 5.54 (d, *J* = 13.0, 1 H), 5.25 (d, *J* = 13.0, 1 H), 5.17−5.08 (m, 1 H), 4.72 (dd, *J* = 11.9, 11.9, 1 H), 4.64 (d, *J* = 11.8, 1 H), 4.49 (d, *J* = 11.8, 1 H), 3.56 (dd, *J* = 6.1, 12.4, 1 H), 3.06 (dd, *J* = 5.9, 11.3, 1 H), 2.91 (dd, *J* = 8.4, 16.9, 1 H), 2.74 (t, *J* = 11.8, 11.8, 1 H), 2.59−2.53 (m, 1 H), 2.31 (s, 3 H), 2.04−1.75 (m, 5 H), 1.59 (s, 3 H), 1.21 (d, *J* = 6.3, 3 H) MS (ESI, Q-tof) 412.3 (100); mol formula $C_{29}H_{34}BrNO$ (492.49); HRMS $C_{29}H_{34}NO^+$ (412.2640) calcd 412.2640, found 412.2633; TLC R_f 0.23 (CH_2Cl_2/MeOH, 9:1) [I_2].



V{*1,2,3*}

*Preparation of rel-(1S,3R,5S,5aS,7aS,7bR)-Octahydro-1-benzyloxy-3-(2-naphthylmethyl)-5-methyl-7b-methylcyclopenta[gh]pyrrolizinium Bromide (****V****{1,2,3}).* Data for **V**{*1,2,3*}: yield 65 mg (84%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 8.15 (s, 1 H), 7.91−7.82 (m, 1 H), 7.73−7.62 (m, 3 H), 7.52−7.44 (m, 2 H), 7.39−7.28 (m, 5 H), 5.33 (d, *J* = 12.3, 1 H), 5.10 (dd, *J* = 6.9, 17.2, 1 H), 4.93 (d, *J* = 12.4, 1 H), 4.65 (d, *J* = 14.1, 1 H), 4.62 (d, *J* = 14.1, 1 H), 4.42 (dd, *J* = 11.9, 11.9, 1 H), 3.94 (dd, *J* = 6.2, 12.4, 1 H), 3.11 (dd, *J* = 6.0, 11.4, 1 H), 2.89 (dd, *J* = 8.5, 16.9, 1 H), 2.83 (dd, *J* = 11.4, 11.4, 1 H), 2.47−2.41 (m, 1 H), 2.15−1.94 (m, 2 H), 2.13 (s, 3 H), 1.92−1.74 (m, 3 H), 1.20 (d, *J* = 6.4, 3 H); MS (ESI, Q-tof) 412.3 (100); mol formula $C_{29}H_{34}BrNO$ (492.49); HRMS $C_{29}H_{34}NO^+$ (412.2640) calcd 412.2640, found 412.2625; TLC R_f 0.24 (CH_2Cl_2/MeOH, 9:1) [I_2].



V{*1,2,5*}

*Preparation of rel-(1S,3R,5S,5aS,7aS,7bR)-Octahydro-1-benzyloxy-3-(3,5-trifluoromethylbenzyl)-5-methyl-7b-methylcyclopenta-[gh]pyrrolizinium Bromide (****V****{1,2,5}).* Data for **V**{*1,2,5*}: yield 84 mg (98%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 8.40 (s, 2 H), 7.90 (s, 1 H), 7.38−7.27 (m, 5 H), 5.58 (d, *J* = 12.4, 1 H), 5.32−5.24 (m, 1 H), 5.13−5.04 (m, 1 H), 4.61 (d, *J* = 11.6, 1 H), 4.58 (d, *J* = 11.6, 1 H), 4.44 (dd, *J* = 11.6, 11.6, 1 H), 3.83 (dd, *J* = 6.1, 12.5, 1 H), 3.06−3.00 (m, 1 H), 2.95−2.84 (m, 2 H), 2.42−2.36 (m, 1 H), 2.26−2.15 (m, 1 H), 2.00−1.97 (m, H), 2.09 (s, 3 H), 1.89−1.79 (m, 3 H), 1.19 (d, *J* = 6.2, 3 H); MS (ESI, Q-tof) 498.2 (100); mol formula

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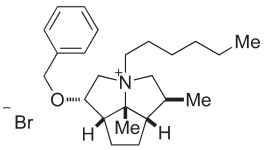
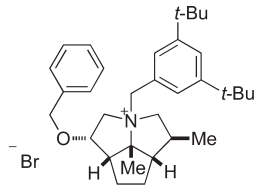
$C_{27}H_{30}BrF_6NO$ (578.43); HRMS $C_{27}H_{30}F_6NO^+$ (498.2232) calcd 498.2232, found 498.2222; TLC R_f 0.28 (CH_2Cl_2/MeOH, 9:1) [I_2].



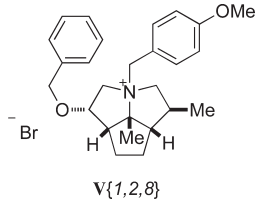
V{*1,2,6*}

*Preparation of rel-(1S,3S,5S,5aS,7aS,7bR)-Octahydro-1-benzyloxy-3-hexyl-5-methyl-7b-methylcyclopenta[gh]pyrrolizinium Bromide (**V**{1,2,6}).* Data for V{*1,2,6*}: yield 65 mg (95%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 7.40−7.30 (m, 5 H), 4.63 (dd, *J* = 7.9, 14.6, 1 H), 4.60 (d, *J* = 11.5, 1 H), 4.57 (d, *J* = 11.5, 1 H), 4.11 (dd, *J* = 6.2, 12.5, 1 H), 3.71−3.58 (m, 3 H), 3.49 (ddd, *J* = 4.4, 4.4, 12.2, 1 H), 3.31 (dd, *J* = 8.9, 12.5, 1 H), 2.84−2.78 (m, 1 H), 2.37−2.20 (m, 2 H), 2.17 (s, 2 H), 2.13−2.02 (m, 1 H), 1.92−1.81 (m, 3 H), 1.84 (s, 3 H), 1.80−1.64 (m, 2 H), 1.51−1.40 (m, 2 H), 1.36−1.27 (m, 4 H), 1.16 (d, *J* = 6.3, 3 H), 0.89 (t, *J* = 7.1, 3 H); MS (ESI, Q-tof) 356.3 (100); mol formula $C_{24}H_{38}BrNO$ (436.47); HRMS $C_{24}H_{38}NO^+$ (356.2953) calcd 356.2953, found 356.2947; TLC R_f 0.25 (CH_2Cl_2/MeOH, 9:1) [I_2].



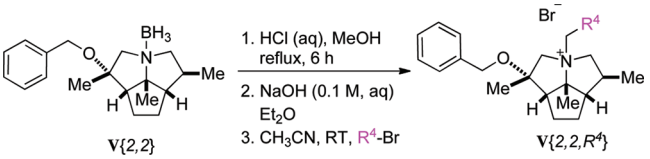
V{*1,2,7*}

*Preparation of rel-(1S,3R,5S,5aS,7aS,7bR)-Octahydro-1-benzyloxy-3-(3,5-tert-butyl-benzyl)-5-methyl-7b-methylcyclopenta[gh]pyrrolizinium Bromide (**V**{1,2,7}).* Data for V{*1,2,7*}: yield 84 mg (96%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 7.52−7.48 (m, 3 H), 7.40−7.28 (m, 5 H), 5.08 (d, *J* = 12.4, 1 H), 4.83 (dd, *J* = 6.9, 16.8, 1 H), 4.62 (d, *J* = 11.9, 1 H), 4.54 (d, *J* = 11.9, 1 H) 4.52 (d, *J* = 11.9, 1 H), 4.42 (dd, *J* = 11.7, 11.7, 1 H), 4.17 (dd, *J* = 6.2, 12.5, 1 H), 3.19 (dd, *J* = 6.2, 11.6, 1 H), 3.00 (dd, *J* = 11.2, 11.2, 1 H), 2.90 (dd, *J* = 8.2, 16.4, 1 H), 2.50−2.45 (m, 1 H), 2.22−2.12 (m, 1 H), 2.12−1.99 (m, 1 H), 2.10 (s, 3 H), 1.95−1.80 (m, 3 H), 1.34 (s, 18H), 1.24 (d, *J* = 6.5, 3 H); MS (ESI, Q-tof) 474.4 (100); mol formula $C_{33}H_{48}BrNO$ (554.64); HRMS $C_{33}H_{48}NO^+$ (474.3736) calcd 474.3736, found 474.3723; TLC R_f 0.32 (CH_2Cl_2/MeOH, 9:1) [I_2].



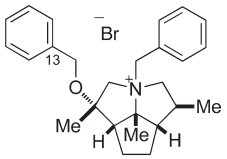
V{*1,2,8*}

*Preparation of rel-(1S,3R,5S,5aS,7aS,7bR)-Octahydro-1-benzyloxy-3-(4-methoxy-benzyl)-5-methyl-7b-methylcyclopenta[gh]pyrrolizinium Bromide (**V**{1,2,8}).* Data for V{*1,2,8*}: yield 77 mg (99%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 7.56 (d, *J* = 8.6, 2 H), 7.40−7.31 (m, 5 H), 6.85 (d, *J* = 8.4, 2 H), 5.07 (d, *J* = 12.4, 1 H), 5.00−4.90 (m, 1 H), 4.65−4.52 (m, 3 H), 4.31 (dd, *J* = 11.9, 1 H), 3.90−3.82 (m, 1 H), 3.80 (s, 3 H), 3.07 (dd, *J* = 6.5, 11.2, 1 H), 2.83 (dd, *J* = 8.03, 15.8, 2 H), 2.44−2.38 (m, 1 H), 2.14−2.05 (m, 1 H), 2.05−1.93 (m, 1 H), 2.03 (s, 3 H), 1.91−1.76 (m, 3 H), 1.20 (d, *J* = 6.4, 3 H); MS (ESI, Q-tof) 392.3 (100); mol formula $C_{26}H_{34}BrNO_2$ (472.46); HRMS $C_{26}H_{34}NO_2^+$ (392.2590) calcd 392.2590, found 392.2578; TLC R_f 0.18 (CH_2Cl_2/MeOH, 9:1) [I_2].



V{*2,2*} V{*2,2,R*^{4}}

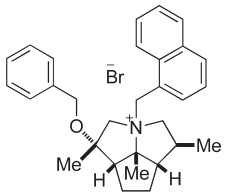
*Preparation of Quaternary Ammonium Bromides **V**{2,2,R^4}.* Following general procedure II, amino borane V{*2,2*} (397 mg, 1.33 mmol) was added to a 100 mL round-bottomed flask as a solution in 44 mL of MeOH (0.03 M). The flask was fitted with a reflux condenser, a magnetic stir bar, and a nitrogen inlet adapter. Lastly, 1.0 N aq HCl solution (6.6 mL, 5.0 equiv) was added via syringe. The resulting solution was heated and then concentrated by rotary evaporation (15 mmHg, 20−25 °C) as described in general Procedure II. The resulting free amine was dissolved in acetonitrile and was distributed among seven test tubes that were subsequently charged with benzyl bromide (tube 1, 48 mg, 0.279 mmol, 1.2 equiv), 1-bromomethylnaphthalene (tube 2, 50 mg, 0.279 mmol, 1.2 equiv), 2-bromomethylnaphthalene (tube 3, 50 mg, 0.279 mmol, 1.2 equiv), 3,5-bis(trifluoromethyl)benzyl bromide (tube 4, 70 mg, 0.279 mmol, 1.2 equiv), 3,5-bis(*tert*-butyl)benzyl bromide (tube 5, 64 mg, 0.279 mmol, 1.2 equiv), 4-methoxybenzyl bromide (tube 6, 70 mg, 0.279 mmol, 1.2 equiv), and 1-bromohexane (tube 7, 70 mg, 0.279 mmol, 1.2 equiv). After being agitated for 12 h, the reaction mixtures were worked up and the products isolated and purified as described in general procedure II.



V{*2,2,1*}

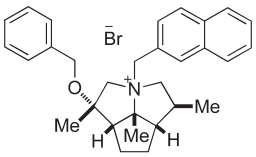
*Preparation of rel-(1S,3R,5S,5aS,7aS,7bR)-Octahydro-1-benzyloxy-1-methyl-3-benzyl-5-methyl-7b-methylcyclopenta[gh]pyrrolizinium Bromide (**V**{2,2,1}).* Data for V{*2,2,1*}: yield 79 mg (74%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 7.80−7.77 (m, 2 H), 7.51−7.43 (m, 3 H), 7.38−7.29 (m, 3 H), 7.24 (d, *J* = 6.7, 2 H), 5.20 (d, *J* = 12.2, 1 H), 4.86 (d, *J* = 12.2, 1 H), 4.51 (d, *J* = 13.5, 1 H), 4.49 (d, *J* = 11.1, 11.1, 1 H), 4.41 (d, *J* = 11.0, 1 H), 4.37 (d, *J* = 11.0, 1 H), 3.24 (d, *J* = 13.3, 1 H), 3.18 (dd, *J* = 6.7, 11.7, 1 H), 2.71 (dd, *J* = 8.4, 8.4, 1 H), 2.59−2.52 (m, 1 H), 2.39−2.19 (m, 2 H), 2.16 (s, 3 H), 1.96 (m, 1 H), 1.89 (m, 2 H), 1.84 (s, 3 H), 1.20 (d, *J* = 6.6, 3 H); MS (ESI, Q-tof) 376.3 (100); mol formula $C_{26}H_{34}BrNO$ (456.46); HRMS $C_{26}H_{34}NO^+$ (376.2640) calcd 376.2640, found 376.2638; TLC R_f 0.22 (CH_2Cl_2/MeOH, 9:1) [I_2].

*Preparation of rel-(1S,3R,5S,5aS,7aS,7bR)-Octahydro-1-benzyloxy-1-methyl-3-(1-naphthylmethyl)-5-methyl-7b-methylcyclopenta[gh]-pyrrolizinium Bromide (**V**{2,2,2}).* Data for V{*2,2,2*}: yield 91 mg (77%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 8.42 (d, *J* = 8.6, 1 H), 8.30 (d, *J* = 7.1, 1 H), 7.92−7.87 (m, 2 H), 7.66 (dd, *J* = 7.6, 7.6, 1 H), 7.52 (m, 2 H), 7.30−7.21 (m, 3 H), 7.18−7.12 (m, 2 H), 5.53 (d, *J* = 12.9, 1 H), 5.43 (d, *J* = 12.9, 1 H), 4.61 (d, *J* = 13.2, 1 H), 4.44 (dd, *J* = 11.7, 11.7, 1 H), 4.38 (d, *J* = 11.1, 1 H), 4.29



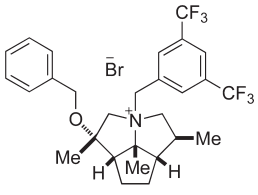
V{2,2,2}

(d, J = 11.1, 1 H), 3.24 (d, J = 13.3, 1 H), 2.98 (dd, J = 6.8, 11.6, 1 H), 2.78 (dd, J = 8.3, 8.3, 1 H), 2.62 (d, J = 9.5, 1 H), 2.36−2.20 (m, 2 H),2.31 (s, 3 H), 1.98−1.83 (m, 3 H), 1.92 (s, 3 H), 1.10 (d, J = 6.5, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) 137.4, 134.2, 134.0, 132.7, 131.4, 129.2, 128.5, 127.9, 127.6, 127.2, 126.1, 125.4, 125.3, 124.2, 100.3, 79.7, 72.0, 70.0, 65.9, 61.4, 60.3, 59.1, 34.2, 29.2, 25.1, 24.7, 24.7, 15.5; MS (ESI, Q-tof) 426.3 (100); mol formula $C_{30}H_{36}BrNO$ (506.52); HRMS $C_{30}H_{36}NO^+$ (426.2797) calcd 426.2797, found 426.2801; TLC R_f 0.24 (CH_2Cl_2/MeOH, 9:1) [I_2].



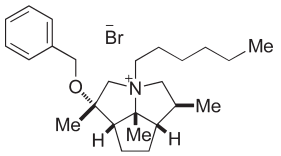
V{2,2,3}

*Preparation of rel-(1S,3R,5S,5aS,7aS,7bR)-Octahydro-1-benzyloxy-1-methyl-3-(2-naphthylmethyl)-5-methyl-7b-methylcyclopenta[gh]pyrrolizinium Bromide (**V**{2,2,3}).* Data for V{2,2,3}: yield 96 mg (81%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 8.27 (s, 1 H), 7.95 (d, J = 8.3, 1 H), 7.86−7.82 (m, 3 H), 7.57−7.52 (m, 2 H), 7.31−7.22 (m, 3 H), 7.21−7.18 (m, 2 H), 5.32 (d, J = 12.2, 1 H), 5.07 (d, J = 12.3, 1 H), 4.60 (d, J = 13.2, 1 H), 4.54 (dd, J = 11.4, 1 H), 4.40 (d, J = 11.0, 1 H), 4.34 (d, J = 11.0, 1 H), 3.23 (d, J = 13.2, 1 H), 3.19 (dd, J = 7.2, 12.0, 1 H), 2.73 (dd, J = 8.3, 8.3, 1 H), 2.59−2.52 (m, 1 H), 2.36−2.27 (m, 1 H), 2.27−2.15 (m, 1 H), 2.2 (s, 3 H), 1.98−1.90 (m, 1 H), 1.90−1.85 (m, 2 H), 1.87 (s, 3 H), 1.19 (d, J = 6.5, 3 H); MS (ESI, Q-tof) 426.3 (100); mol formula $C_{30}H_{36}BrNO$ (506.52); HRMS $C_{30}H_{36}NO^+$ (426.2797) calcd 426.2797, found 426.2806; TLC R_f 0.25 (CH_2Cl_2/MeOH, 9:1) [I_2].



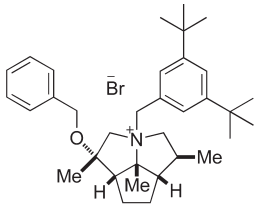
V{2,2,5}

*Preparation of rel-(1S,3R,5S,5aS,7aS,7bR)-Octahydro-1-benzyloxy-1-methyl-3-(3,5-trifluoromethylbenzyl)-5-methyl-7b-methylcyclopenta-[gh]pyrrolizinium Bromide (**V**{2,2,5}).* Data for **V**{2,2,5}: yield 98 mg (71%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 8.40 (s, 2 H), 7.98 (s, 1 H), 7.34−7.27 (m, 3 H), 7.23−7.18 (m, 2 H), 5.43 (d, J = 12.5, 1 H), 5.37 (d, J = 12.5, 1 H), 4.55 (d, J = 13.1, 1 H), 4.44 (d, J = 11.1, 1 H), 4.38 (d, J = 11.1, 1 H), 4.36 (dd, J = 10.6, 10.6, 1 H), 3.24 (d, J = 13.1, 1 H), 3.11 (dd, J = 6.1, 11.3, 1 H), 2.76 (dd, J = 8.0, 8.0, 1 H), 2.51−2.41 (m, 2 H), 2.32−2.23 (m, 1 H), 2.16 (s, 3 H), 1.99−1.87 (m, 3 H), 1.82 (s, 3 H), 1.16 (d, J = 6.2, 3 H); MS (ESI, Q-tof) 512.2 (100); mol formula $C_{28}H_{32}BrF_6NO$ (592.45); HRMS $C_{28}H_{32}NOF_6^+$ (512.2388) calcd 512.2388, found 512.2395; TLC R_f 0.30 (CH_2Cl_2/MeOH, 9:1) [I_2].



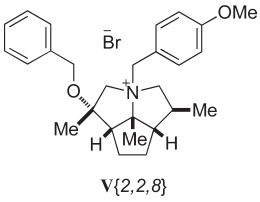
V{2,2,6}

*Preparation of rel-(1S,3S,5S,5aS,7aS,7bR)-Octahydro-1-benzyloxy-1-methyl-3-hexyl-5-methyl-7b-methylcyclopenta[gh]pyrrolizinium Bromide (**V**{2,2,6}).* Data for V{2,2,6}: yield 30 mg (28%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 7.33 (m, 5 H), 4.47 (d, J = 11.1, 1 H), 4.37 (d, J = 11.0, 1 H), 3.41 (dd, J = 6.9, 6.9, 2 H), 3.01 (d, J = 8.9, 1 H), 2.92 (d, J = 8.9, 1 H), 2.82 (dd, J = 6.0, 12.2, 1 H), 2.49 (dd, J = 11.8, 11.8, 1 H), 2.07−2.00 (m, 2 H), 1.94−1.81 (m, 5 H), 1.72−1.63 (m, 3 H), 1.46−1.40 (m, 3 H), 1.36−1.34 (m, 8H), 0.97 (d, J = 6.5, 3 H), 0.90 (t, J = 7.0, 3 H); MS (ESI, Q-tof) 370.3 (100); mol formula $C_{25}H_{40}BrNO$ (450.50); HRMS $C_{25}H_{40}NO^+$ (370.3110) calcd 370.3110, found 370.3109; TLC R_f 0.40 (CH_2Cl_2/MeOH, 9:1) [I_2].



V{2,2,7}

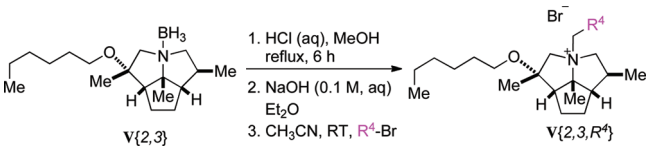
*Preparation of rel-(1S,3R,5S,5aS,7aS,7bR)-Octahydro-1-benzyloxy-1-methyl-3-(3,5-tert-butylbenzyl)-5-methyl-7b-methylcyclopenta[gh]pyrrolizinium Bromide (**V**{2,2,7}).* Data for **V**{2,2,7}: yield 109 mg (82%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 7.57 (d, J = 1.7, 2 H), 7.50 (s, 1 H), 7.34−7.27 (m, 3 H), 7.24−7.22 (m, 2 H), 5.22 (d, J = 12.3, 1 H), 4.74 (d, J = 12.3, 1 H), 4.58 (dd, J = 11.2, 11.2, 1 H), 4.47 (d, J = 13.2, 1 H), 4.41 (s, 2 H), 3.22 (d, J = 11.9, 1 H), 3.21 (d, J = 12.8, 1 H), 2.65 (dd, J = 8.6, 8.6, 1 H), 2.61−2.56 (m, 1 H), 2.32−2.18 (m, 2 H), 2.16 (s, 3 H), 2.00−1.92 (m, 1 H), 1.90−1.86 (m, 2 H), 1.84 (s, 3 H), 1.35 (s, 18H), 1.23 (d, J = 6.6, 3 H); MS (ESI, Q-tof) 488.4 (100); mol formula $C_{34}H_{50}BrNO$ (568.67); HRMS $C_{34}H_{50}NO^+$ (488.3892) calcd 488.3892, found 488.3893; TLC R_f 0.33 (CH_2Cl_2/MeOH, 9:1) [I_2].



V{2,2,8}

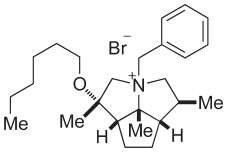
*Preparation of rel-(1S,3R,5S,5aS,7aS,7bR)-Octahydro-1-benzyloxy-1-methyl-3-(4-methoxybenzyl)-5-methyl-7b-methylcyclopenta[gh]pyrrolizinium Bromide (**V**{2,2,8}).* Data for **V**{2,2,8}: yield 88 mg (77%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 7.71 (d, J = 8.7, 2 H), 7.34−7.28 (m, 3 H), 7.22 (d, J = 6.7, 2 H), 6.94 (d, J = 8.4, 2 H), 5.11 (d, J = 12.3, 1 H), 4.78 (d, J = 12.4, 1 H), 4.48−4.40 (m, 2 H), 4.41 (d, J = 11.0, 1 H), 4.37 (d, J = 11.0, 1 H), 3.82 (s, 3 H), 3.20 (d, J = 13.3, 1 H), 3.14 (dd, J = 6.7, 11.7, 1 H), 2.67 (dd, J = 8.4, 8.4, 1 H), 2.55−2.48 (m, 1 H), 2.33−2.17 (m, 2 H), 2.11 (s, 3 H), 1.97−1.89 (m, 1 H), 1.88−1.83 (m, 2 H), 1.81 (s, 3 H), 1.17 (d, J = 6.5, 3 H); MS (ESI, Q-tof) 406.3 (100); mol formula $C_{27}H_{36}BrNO_2$ (486.48);

HRMS $C_{27}H_{36}NO_2^+$ (406.2746) calcd 406.2746, found 406.2748; TLC R_f 0.20 (CH_2Cl_2/MeOH, 9:1) [I_2].



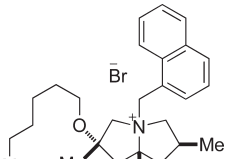
V{2,3} V{2,3,R^4}

Preparation of Quaternary Ammonium Bromides ***V***{*2,3,R*^{4}}. Following general procedure II, amino borane **V**{*2,3*} (397 mg, 1.35 mmol) was added to a 100 mL round-bottomed flask as a solution in 45 mL of MeOH (0.03 M). The flask was fitted with a reflux condenser, a magnetic stir bar, and a nitrogen inlet adapter. Lastly, 1.0 N aq HCl solution (6.8 mL, 5.0 equiv) was added via syringe. The resulting solution was heated and then concentrated by rotary evaporation (15 mmHg, 20−25 °C) as described in general Procedure II. The resulting free amine was dissolved in acetonitrile and was distributed among seven test tubes that were subsequently charged with benzyl bromide (tube 1, 38 mg, 0.220 mmol, 1.2 equiv), 1-bromomethylnaphthalene (tube 2, 48 mg, 0.220 mmol, 1.2 equiv), 2-bromomethylnaphthalene (tube 3, 48 mg, 0.220 mmol, 1.2 equiv), 3,5-bis(trifluoromethyl)benzyl bromide (tube 4, 67 mg, 0.220 mmol, 1.2 equiv), 3,5-bis(*tert*-butyl)benzyl bromide (tube 5, 62 mg, 0.220 mmol, 1.2 equiv), 4-methoxybenzyl bromide (tube 6, 44 mg, 0.220 mmol, 1.2 equiv), and 1-bromohexane (tube 7, 90 mg, 0.549 mmol, 3.0 equiv). After being agitated for 12 h, the reaction mixtures were worked up and the products isolated and purified as described in general procedure II.



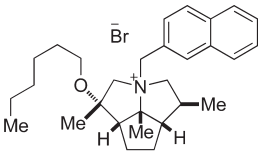
V{*2,3,1*}

*Preparation of rel-(1S,3R,5S,5aS,7aS,7bR)-Octahydro-1-hexyloxy-1-methyl-3-benzyl-5-methyl-7b-methylcyclopenta[gh]pyrrolizinium Bromide (****V****{2,3,1}).* Data for **V**{*2,3,1*}: yield 76 mg (92%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 7.80−7.76 (m, 2 H), 7.47−7.42 (m, 3 H), 5.17 (d, *J* = 12.2, 1 H), 4.80 (d, *J* = 12.2, 1 H), 4.49 (dd, *J* = 11.3, 11.3, 1 H), 4.40 (d, *J* = 13.2, 1 H), 3.26 (t, *J* = 6.6, 2 H), 3.18 (dd, *J* = 6.6, 11.6, 1 H), 3.13 (d, *J* = 13.2, 1 H), 2.58 (t, *J* = 8.1, 8.1, 1 H), 2.55−2.51 (m, 1 H), 2.40−2.30 (m, 1 H), 2.21−2.08 (m, 1 H), 2.11 (s, 3 H), 1.90−1.81 (m, 3 H), 1.68 (s, 3 H), 1.49−1.42 (m, 2 H), 1.32−1.19 (m, 6H), 0.86 (t, *J* = 6.9, 3 H); MS (ESI, Q-tof) 370.3 (100); mol formula $C_{25}H_{40}BrNO$ (450.50); HRMS $C_{25}H_{40}NO^+$: (370.3110) calcd 370.3110, found 370.3101; TLC R_f 0.28 (CH_2Cl_2/MeOH, 9:1) [I_2].



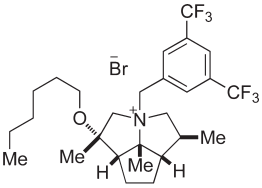
V{*2,3,2*}

*Preparation of rel-(1S,3R,5S,5aS,7aS,7bR)-Octahydro-1-hexyloxy-1-methyl-3-(1-naphthylmethyl)-5-methyl-7b-methylcyclopenta[gh]pyrrolizinium Bromide (****V****{2,3,2}).* Data for **V**{2,3,2}: yield 90 mg (98%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 8.37 (d, *J* = 8.6, 1 H), 8.34 (d, *J* = 6.4, 1 H), 7.93 (dd, *J* = 8.2, 14.1, 1 H), 7.67 (dd, *J* = 7.7, 7.7, 1 H), 7.55 (dd, *J* = 6.4, 14.3, 2 H), 5.51 (d, *J* = 12.9, 1 H), 5.40 (d, *J* = 12.9, 1 H), 4.58 (d, *J* = 13.2, 1 H), 4.45 (dd, *J* = 11.6, 11.6, 1 H), 3.30−3.21 (m, 1 H), 3.20−3.14 (m, 2 H), 3.02 (dd, *J* = 6.8, 11.7, 1 H), 2.70 (dd, *J* = 8.1, 8.1, 1 H), 2.64−2.58 (m, 1 H), 2.42−2.30 (m, 1 H), 2.27 (s, 3 H), 2.25−2.12 (m, 1 H), 1.93−1.79 (m, 3 H), 1.76 (s, 3 H), 1.44−1.34 (m, 2 H), 1.27−1.12 (m, 9H), 0.83 (t, *J* = 6.8, 3 H); MS (ESI, Q-tof) 420.3 (100); mol formula $C_{29}H_{42}BrNO$ (500.55); HRMS $C_{29}H_{42}NO^+$ (420.3266) calcd 420.3266, found 420.3265; TLC R_f 0.30 (CH_2Cl_2/MeOH, 9:1) [I_2].



V{*2,3,3*}

*Preparation of rel-(1S,3R,5S,5aS,7aS,7bR)-Octahydro-1-hexyloxy-1-methyl-3-(2-naphthylmethyl)-5-methyl-7b-methylcyclopenta[gh]pyrrolizinium Bromide (****V****{2,3,3}).* Data for **V**{2,3,3}: yield 82 mg (90%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 8.26 (s, 1 H), 7.96 (d, *J* = 7.3, 1 H), 7.91−7.83 (m, 3 H), 7.59−7.52 (m, 2 H), 5.29 (d, *J* = 12.3, 1 H), 5.02 (d, *J* = 12.3, 1 H), 4.55 (dd, *J* = 11.5, 11.5, 1 H), 4.52 (d, *J* = 13.3, 1 H), 3.29−3.18 (m, 3 H), 3.15 (d, *J* = 13.2, 1 H), 2.66−2.60 (m, 1 H), 2.56−2.53 (m, 1 H), 2.42−2.33 (m, 1 H), 2.21−2.12 (m, 1 H), 2.17 (s, 3 H), 1.91−1.82 (m, 3 H), 1.72 (s, 3 H), 1.48−1.40 (m, 2 H), 1.30−1.17 (m, 9H), 0.84 (t, *J* = 6.9, 3 H); MS (ESI, Q-tof) 420.3 (100); mol formula $C_{29}H_{42}BrNO$ (500.55); HRMS $C_{29}H_{42}NO^+$ (420.3266) calcd 420.3266, found 420.3271; TLC R_f 0.31 (CH_2Cl_2/MeOH, 9:1) [I_2].

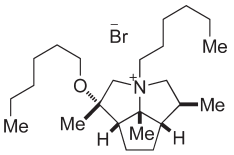


V{*2,3,5*}

*Preparation of rel-(1S,3R,5S,5aS,7aS,7bR)-Octahydro-1-hexyloxy-1-methyl-3-(3,5-trifluoromethylbenzyl)-5-methyl-7b-methylcyclopenta-[gh]pyrrolizinium Bromide (****V****{2,3,5}).* Data for **V**{2,3,5}: yield 101 mg (95%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 8.26 (s, 1 H), 7.96 (d, *J* = 7.3, 1 H), 7.91−7.83 (m, 3 H), 7.59−7.52 (m, 2 H), 5.29 (d, *J* = 12.3, 1 H), 5.02 (d, *J* = 12.3, 1 H), 4.55 (dd, *J* = 11.5, 11.5, 1 H), 4.52 (d, *J* = 13.3, 1 H), 3.29−3.18 (m, 3 H), 3.15 (d, *J* = 13.2, 1 H), 2.66−2.60 (m, 1 H), 2.56−2.53 (m, 1 H), 2.42−2.33 (m, 1 H), 2.21−2.12 (m, 1 H), 2.17 (s, 3 H), 1.91−1.82 (m, 3 H), 1.72 (s, 3 H), 1.48−1.40 (m, 2 H), 1.30−1.17 (m, 9H), 0.84 (t, *J* = 6.9, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) 133.4, 133.3, 132.4 (q, *J* = 34), 124.2, 122.9 (q, *J* = 273), 100.4, 79.0, 72.2, 71.1, 63.5, 61.94, 61.87, 58.8, 34.9, 31.66, 30.1, 29.68, 26.0, 23.9, 23.7, 23.5, 22.6, 15.6, 14.1; MS (ESI, Q-tof) 506.3 (100); mol formula $C_{27}H_{38}BrF_6NO$ (586.49); HRMS $C_{27}H_{38}NOF_6^+$ (506.2858) calcd 506.2858, found 506.2859; TLC R_f 0.39 (CH_2Cl_2/MeOH, 9:1) [I_2].

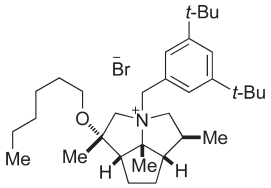
*Preparation of rel-(1S,3S,5S,5aS,7aS,7bR)-Octahydro-1-hexyloxy-1-methyl-3-hexyl-5-methyl-7b-methylcyclopenta[gh]pyrrolizinium Bromide (****V****{2,3,6}).* Data for **V**{2,3,6}: yield 36 mg (44%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 4.31 (d,

dx.doi.org/10.1021/jo2005445 |*J. Org. Chem.* 2011, 76, 4260–4336



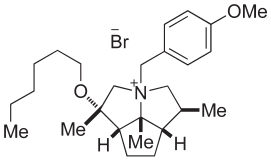
V{2,3,6}

J = 13.1, 1 H), 3.80 (ddd, J = 5.7, 11.4, 11.4, 1 H), 3.73−3.61 (m, 4 H), 3.55 (ddd, J = 5.0, 11.7, 11.7, 1 H), 3.36 (t, J = 6.7, 2 H), 2.65−2.50 (m, 2 H), 2.33−2.15 (m, 2 H), 1.96−1.74 (m, 5 H), 1.88 (s, 3 H), 1.62−1.41 (m, 5 H), 1.52 (s, 3 H), 1.38−1.24 (m, 7H), 1.13 (d, J = 6.7, 3 H), 0.91−0.87 (m, 6H); MS (ESI, Q-tof) 364.4 (100); mol formula $C_{24}H_{46}BrNO$ (444.53); HRMS $C_{24}H_{46}NO^+$ (364.3579) calcd 364.3579, found 364.357; TLC R_f 0.42 (CH_2Cl_2/MeOH, 9:1) [I_2].



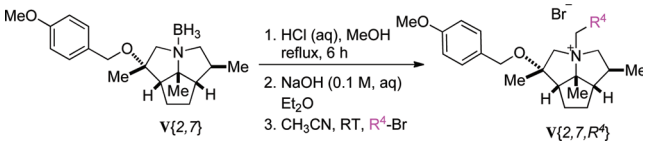
V{2,3,7}

*Preparation of rel-(1S,3R,5S,5aS,7aS,7bR)-Octahydro-1-hexyloxy-1-methyl-3-(3,5-tert-butylbenzyl)-5-methyl-7b-methylcyclopenta-[gh]pyrrolizinium Bromide (**V**{2,3,7}).* Data for **V**{2,3,7}: yield 101 mg (99%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 7.55 (d, J = 1.7, 2 H), 7.49 (s, 1 H), 5.21 (d, J = 12.3, 1 H), 4.68 (d, J = 12.3, 1 H), 4.59 (dd, J = 11.3, 11.3, 1 H), 4.33 (d, J = 13.1, 1 H), 3.27 (t, J = 6.7, 2 H), 3.22 (dd, J = 6.5, 11.6, 1 H), 3.10 (d, J = 13.2, 1 H), 2.60−2.55 (m, 1 H), 2.53 (dd, J = 8.6, 1 H), 2.31−2.22 (m, 1 H), 2.17−2.08 (m, 1 H), 2.12 (s, 3 H), 1.90−1.80 (m, 3 H), 1.70 (s, 3 H), 1.52−1.44 (m, 2 H), 1.35 (s, 18H), 1.31−1.20 (m, 6H), 1.26 (d, J = 6.5, 3 H), 0.86 (t, J = 6.9, 3 H); MS (ESI, Q-tof) 482.4 (100); mol formula $C_{33}H_{56}BrNO$ (562.71); HRMS $C_{33}H_{56}NO^+$: (482.4362) calcd 482.4362, found 482.4358; TLC R_f 0.41 (CH_2Cl_2/MeOH, 9:1) [I_2].



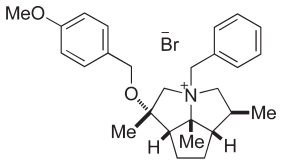
V{2,3,8}

*Preparation of rel-(1S,3R,5S,5aS,7aS,7bR)-Octahydro-1-hexyloxy-1-methyl-3-(4-methoxybenzyl)-5-methyl-7b-methylcyclopenta[gh]-pyrrolizinium Bromide (**V**{2,3,8}).* Data for **V**{2,3,8}: yield 85 mg (98%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 7.70 (d, J = 8.7, 2 H), 6.94 (d, J = 8.7, 2 H), 5.09 (d, J = 12.4, 1 H), 4.73 (d, J = 12.4, 1 H), 4.44 (dd, J = 11.4, 11.4, 1 H), 4.36 (d, J = 13.2, 1 H), 3.82 (s, 3 H), 3.26 (t, J = 6.6, 2 H), 3.16 (dd, J = 6.6, 11.7, 1 H), 3.11 (d, J = 13.2, 1 H), 2.56 (dd, J = 8.1, 8.1, 1 H), 2.54−2.49 (m, 1 H), 2.38−2.29 (m, 1 H), 2.19−2.09 (m, 1 H), 2.08 (s, 3 H), 1.88−1.81 (m, 3 H), 1.66 (s, 3 H), 1.51−1.40 (m, 2 H), 1.33−1.19 (m, 9H), 0.86 (t, J = 6.9, 3 H); MS (ESI, Q-tof) 400.3 (100); mol formula $C_{26}H_{42}BrNO_2$ (480.52); HRMS $C_{26}H_{42}NO_2^+$ (400.3216) calcd 400.3216, found 400.3212; TLC R_f 0.23 (CH_2Cl_2/MeOH, 9:1) [I_2].



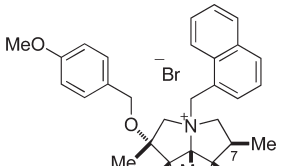
V{2,7} V{2,7,R⁴}

*Preparation of Quaternary Ammonium Bromides **V**{2,7,R^4}.* Following general procedure II, amino borane **V**{2,7} (163 mg, 0.495 mmol) was added to a 50 mL round-bottomed flask as a solution in 17 mL of MeOH (0.03 M). The flask was fitted with a reflux condenser, a magnetic stir bar, and a nitrogen inlet adapter. Lastly, 1.0 N aq HCl solution (2.5 mL, 5.0 equiv) was added via syringe. The resulting solution was heated and then concentrated by rotary evaporation (15 mmHg, 20−25 °C) as described in general Procedure II. The resulting free amine was dissolved in acetonitrile and was distributed among five test tubes that were subsequently charged with benzyl bromide (tube 1, 14 mg, 0.08 mmol, 1.2 equiv), 1-bromomethylnaphthalene (tube 2, 17 mg, 0.08 mmol, 1.2 equiv), 2-bromomethylnaphthalene (tube 3, 17 mg, 0.08 mmol, 1.2 equiv), 3,5-bis(trifluoromethyl)benzyl bromide (tube 4, 25 mg, 0.08 mmol, 1.2 equiv), and 3,5-bis(*tert*-butyl)benzyl bromide (tube 5, 23 mg, 0.08 mmol, 1.2 equiv). After being agitated for 12 h, the reaction mixtures were worked up and the products isolated and purified as described in general procedure II.



V{2,7,1}

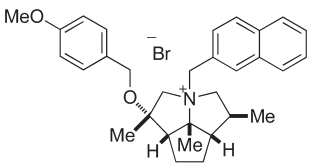
*Preparation of rel-(1S,3R,5S,5aS,7aS,7bR)-Octahydro-1-(4-methoxybenzyloxy)-1-methyl-3-benzyl-5-methyl-7b-methylcyclopenta[gh]-pyrrolizinium Bromide (**V**{2,7,1}).* Data for **V**{2,7,1}: yield 25 mg (76%) free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 7.79−7.76 (m, 2 H), 7.47-.7.44 (m, 3 H), 7.14 (d, J = 8.6, 2 H), 6.84 (d, J = 8.6, 2 H), 5.19 (d, J = 12.3, 1 H), 4.79 (d, J = 12.2, 1 H), 4.49 (dd, J = 11.5, 11.5,1 H), 4.34 (d, J = 10.6, 1 H), 4.31 (d, J = 10.6, 1 H), 3.78 (s, 3 H), 3.18 (d, J = 13.4, 1 H), 3.15 (dd, J = 7.5, 12.4, 1 H), 2.66 (dd, J = 8.5, 8.5, 1 H), 2.56−2.52 (m, 1 H), 2.32−2.18 (m, 2 H), 2.14 (s, 3 H), 1.98−1.91 (m, 1 H), 1.88−1.84 (m, 2 H), 1.82 (s, 3 H), 1.19 (d, J = 6.5, 3 H); MS (ESI, Q-tof) 406.3 (100); mol formula $C_{27}H_{36}BrNO_2$ (486.48); HRMS $C_{27}H_{36}NO_2^+$ (406.2746) calcd 406.2746, found 406.2749; TLC R_f 0.21 (CH_2Cl_2/MeOH, 9:1) [I_2].



V{2,7,2}

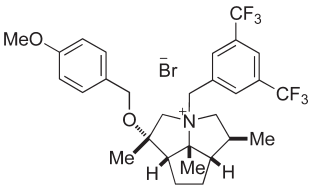
*Preparation of rel-(1S,3R,5S,5aS,7aS,7bR)-Octahydro-1-(4-methoxybenzyloxy)-1-methyl-3-(1-naphthylmethyl)-5-methyl-7b-methyl-cyclopenta[gh]pyrrolizinium Bromide (**V**{2,7,2}).* Data for **V**{2,7,2}: yield 30 mg (85%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 8.39 (d, J = 8.6, 1 H), 8.32 (d, J = 6.5, 1 H), 7.97−7.86 (m, 2 H), 7.67 (dd, J = 7.1, 7.1, 2 H), 7.57−7.51 (m, 2 H), 7.08 (d, J = 8.7, 2 H), 6.77 (d, J = 8.8, 2 H), 5.54 (d, J = 12.9, 1 H), 5.39 (d, J = 12.9, 1 H), 4.56 (d, J = 13.3, 1 H), 4.46 (dd, J = 11.7, 11.7, 1 H), 4.31 (d, J = 10.6, 1 H), 4.23

(d, J = 10.6, 1 H), 3.75 (s, 3 H), 3.20 (d, J = 13.3, 1 H), 2.97 (dd, J = 6.8, 11.7, 1 H), 2.76 (dd, J = 8.5, 8.5, 1 H), 2.65−2.60 (m, 1 H), 2.32−2.19 (m, 2 H), 2.30 (s, 3 H), 1.98−1.84 (m, 3 H), 1.91 (s, 3 H), 1.11 (d, J = 6.5, 3 H); MS (ESI, Q-tof) 456.3; mol formula $C_{31}H_{38}BrNO_2$ (536.54); HRMS $C_{31}H_{38}NO_2^+$ (456.2903) calcd 456.2903, found 456.2906; TLC R_f 0.25 (CH_2Cl_2/MeOH, 9:1) [I_2].



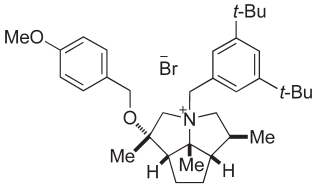
V{2,7,3}

*Preparation of rel-(1S,3R,5S,5aS,7aS,7bR)-Octahydro-1-(4-methoxybenzyloxy)-1-methyl-3-(2-naphthylmethyl)-5-methyl-7b-methylcyclopenta[gh]pyrrolizinium Bromide (**V**{2,7,3}).* Data for **V**{2,7,3}: yield 30 mg (85%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 8.26 (s, 1 H), 7.96 (d, J = 8.4, 1 H), 7.91−7.80 (m, 3 H), 7.60−7.51 (m, 2 H), 7.12 (d, J = 8.6, 2 H), 6.80 (d, J = 8.6, 2 H), 5.32 (d, J = 12.3, 1 H), 5.03 (d, J = 12.3, 1 H), 4.60−4.50 (m, 2 H), 4.33 (d, J = 10.6, 1 H), 4.29 (d, J = 10.6, 1 H), 3.74 (s, 3 H), 3.21−3.13 (m, 2 H), 2.71 (dd, J = 8.4, 8.4, 1 H), 2.58−2.53 (m, 1 H), 2.36−2.15 (m, 2 H), 2.19 (s, 3 H), 1.98−1.90 (m, 1 H), 1.90−1.83 (m, 2 H), 1.86 (s, 3 H), 1.20 (d, J = 6.5, 3 H); MS (ESI, Q-tof) 456.3 (100); mol formula $C_{31}H_{38}BrNO_2$ (536.54); HRMS ($C_{31}H_{38}NO_2^+$ (456.2903) calcd 456.2903, found 456.2900; TLC R_f 0.24 (CH_2Cl_2/MeOH, 9:1) [I_2].



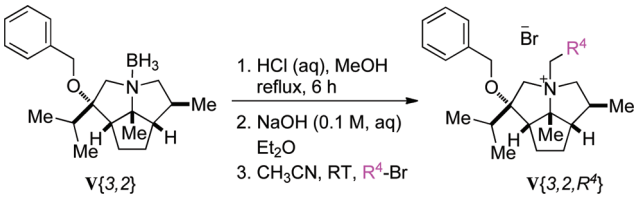
V{2,7,5}

*Preparation of rel-(1S,3R,5S,5aS,7aS,7bR)-Octahydro-1-(4-methoxybenzyloxy)-1-methyl-3-(3,5-trifluoromethylbenzyl)-5-methyl-7b-methylcyclopenta[gh]pyrrolizinium Bromide (**V**{2,7,5}).* Data for **V**{2,7,5}: yield 33 mg (80%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 8.40 (s, 2 H), 7.97 (s, 1 H), 7.13 (d, J = 8.6, 2 H), 6.82 (d, J = 8.6, 2 H), 5.37 (d, J = 12.5, 1 H), 5.37 (d, J = 12.5, 1 H), 4.37 (d, J = 10.9, 1 H), 4.37 (dd, J = 7.2, 10.9, 1 H), 4.31 (d, J = 10.7, 1 H), 3.77 (s, 3 H), 3.21 (d, J = 13.1, 1 H), 3.09 (dd, J = 6.2, 11.3, 1 H), 2.74 (dd, J = 8.0, 8.0, 1 H), 2.53−2.38 (m, 2 H), 2.30−2.21 (m, 1 H), 2.15 (s, 3 H), 1.98−1.85 (m, 3 H), 1.81 (s, 3 H), 1.15 (d, J = 6.2, 3 H); MS (ESI, Q-tof) 542.3 (100); mol formula $C_{29}H_{34}BrF_6NO_2$ (622.48); HRMS $C_{29}H_{34}F_6NO_2^+$ (542.2494) calcd 542.2494, found 542.2488; TLC R_f 0.28 (CH_2Cl_2/MeOH, 9:1) [I_2].



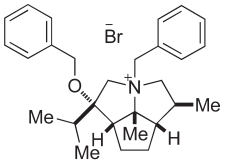
V{2,7,7}

*Preparation of rel-(1S,3R,5S,5aS,7aS,7bR)-Octahydro-1-(4-methoxybenzyloxy)-1-methyl-3-(3,5-tert-butylbenzyl)-5-methyl-7b-methylcyclopenta[gh]pyrrolizinium Bromide (**V**{2,7,7}).* Data for **V**{2,7,7}: yield 33 mg (82%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 7.57 (d, J = 1.7, 2 H), 7.50 (dd, J = 1.7, 1.7, 1 H), 7.16 (d, J = 8.7, 2 H), 6.85 (d, J = 8.8, 2 H), 5.22 (d, J = 12.3, 1 H), 4.71 (d, J = 12.3, 1 H), 4.59 (dd, J = 11.3, 1 H), 4.43 (d, J = 13.2, 1 H), 4.33 (s, 2 H), 3.79 (s, 3 H), 3.25−3.08 (m, 2 H), 2.63 (dd, J = 8.7, 8.7, 1 H), 2.61−2.56 (m, 1 H), 2.30−2.12 (m, 2 H), 2.16 (s, 3 H), 2.00−1.92 (m, 1 H), 1.90−1.84 (m, 2 H), 1.83 (s, 3 H), 1.35 (s, 18H), 1.23 (d, J = 6.6, 3 H); MS (ESI, Q-tof) 518.4 (100); mol formula $C_{35}H_{52}BrNO$ (598.70); HRMS $C_{35}H_{52}NO_2^+$ (518.3998) calcd 518.3998, found 518.3997; TLC R_f 0.31 (CH_2Cl_2/MeOH, 9:1) [I_2].



V{3,2} V{3,2,R^4}

*Preparation of Quaternary Ammonium Bromides **V**{3,2,R^4}.* Following general procedure II, amino borane **V**{3,2} (456 mg, 1.39 mmol) was added to a 100 mL round-bottomed flask as a solution in 50 mL of MeOH (0.03 M). The flask was fitted with a reflux condenser, a magnetic stir bar, and a nitrogen inlet adapter. Lastly, 1.0 N aq HCl solution (7.0 mL, 5.0 equiv) was added via syringe. The resulting solution was heated and then concentrated by rotary evaporation (15 mmHg, 20−25 °C) as described in general procedure II. The resulting free amine was dissolved in acetonitrile and was distributed among seven test tubes that were subsequently charged with benzyl bromide (tube 1, 40 mg, 0.230 mmol, 1.2 equiv), 1-bromomethylnaphthalene (tube 2, 51 mg, 0.230 mmol, 1.2 equiv), 2-bromomethylnaphthalene (tube 3, 51 mg, 0.230 mmol, 1.2 equiv), 3,5-bis(trifluoromethyl)benzyl bromide (tube 4, 71 mg, 0.230 mmol, 1.2 equiv), 3,5-bis(*tert*-butyl)benzyl bromide (tube 5, 65 mg, 0.230 mmol, 1.2 equiv), 4-methoxybenzyl bromide (tube 6, 66 mg, 0.230 mmol, 1.2 equiv), and 1-bromohexane (tube 7, 95 mg, 0.573 mmol, 3.0 equiv). After being agitated for 12 h, the reaction mixtures were worked up and the products isolated and purified as described in general procedure II.



V{3,2,1}

*Preparation of rel-(1S,3R,5S,5aS,7aS,7bR)-Octahydro-1-benzyloxy-1-isopropyl-3-benzyl-5-methyl-7b-methylcyclopenta[gh]pyrrolizinium Bromide (**V**{3,2,1}).* Data for **V**{3,2,1}: yield 91 mg (98%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 7.90−7.85 (m, 2 H), 7.45 (d, J = 5.3, 3 H), 7.32−7.25 (m, 3 H), 7.20−7.16 (m, 2 H), 5.35 (d, J = 12.1, 1 H), 4.83 (d, J = 12.0, 1 H), 4.77 (d, J = 13.7, 1 H), 4.53 (d, J = 11.0, 1 H), 4.18 (d, J = 11.0, 1 H), 3.83 (dd, J = 9.6, 12.2, 1 H), 3.70 (d, J = 13.7, 1 H), 3.19 (dd, J = 9.9, 9.9, 1 H), 2.77 (dd, J = 8.0, 8.0, 1 H), 2.53−2.33 (m, 4 H), 2.00 (s, 3 H), 1.96−1.86 (m, 2 H), 1.81−1.74 (m, 1 H), 1.23 (d, J = 6.8, 3 H), 1.01 (d, J = 6.5, 6 H); MS (ESI, Q-tof) 404.3 (100); mol formula $C_{28}H_{38}BrNO$ (484.51); HRMS $C_{28}H_{38}NO^+$ (404.2953) calcd 404.2953, found 404.2955; TLC R_f 0.23 (CH_2Cl_2/MeOH, 9:1) [I_2].

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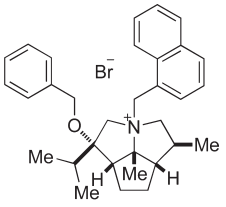
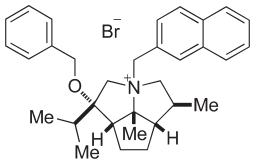


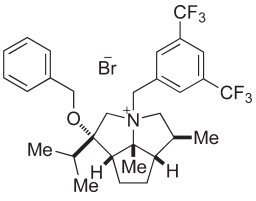
V{3,2,2}

*Preparation of rel-(1S,3R,5S,5aS,7aS,7bR)-Octahydro-1-benzyloxy-1-isopropyl-3-(1-naphthylmethyl)-5-methyl-7b-methylcyclopenta[gh]pyrrolizinium Bromide (**V**{3,2,2}).* Data for **V**{3,2,2}: yield 95 mg (93%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 8.37−8.30 (m, 2 H), 7.83 (d, *J* = 7.9, 1 H), 7.79 (d, *J* = 7.7, 1 H), 7.60 (t, *J* = 7.6, 1 H), 7.49 (t, *J* = 7.4, 1 H), 7.45−7.36 (m, 1 H), 7.24−7.18 (m, 3 H), 7.11−7.06 (m, 2 H), 5.73 (d, *J* = 12.8, 1 H), 5.61 (d, *J* = 12.7, 1 H), 4.90 (d, *J* = 13.6, 1 H), 4.45 (d, *J* = 10.9, 1 H), 4.01 (d, *J* = 10.9, 1 H), 3.90 (dd, *J* = 11.4, 11.4, 1 H), 3.66 (d, *J* = 13.6, 1 H), 2.89 (dd, *J* = 8.5, 11.9, 1 H), 2.81 (dd, *J* = 6.6, 9.7, 1 H), 2.60−2.55 (m, 1 H), 2.54−2.43 (m, 2 H), 2.35−2.26 (m, 1 H), 2.19 (s, 3 H), 2.02−1.85 (m, 2 H), 1.80−1.70 (m, 1 H), 1.24 (d, *J* = 6.8, 3 H), 0.94 (d, *J* = 6.8, 3 H), 0.88 (d, *J* = 6.5, 3 H); MS (ESI, Q-tof) 454.3 (100); mol formula $C_{32}H_{40}BrNO$ (534.57); HRMS $C_{32}H_{40}NO^+$ (454.3110) calcd 454.3110, found 454.3105; TLC R_f 0.25 (CH_2Cl_2/MeOH, 9:1) [I_2].



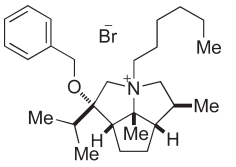
V{3,2,3}

*Preparation of rel-(1S,3R,5S,5aS,7aS,7bR)-Octahydro-1-benzyloxy-1-isopropyl-3-(2-naphthylmethyl)-5-methyl-7b-methylcyclopenta[gh]pyrrolizinium Bromide (**V**{3,2,3}).* Data for **V**{3,2,3}: yield 94 mg (92%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 8.35 (s, 1 H), 7.97−7.92 (m, 1 H), 7.90 (dd, *J* = 1.7, 8.5, 1 H), 7.81−7.77 (m, 2 H), 7.55−7.48 (m, 2 H), 7.24−7.19 (m, 3 H), 7.14−7.10 (m, 2 H), 5.49 (d, *J* = 12.1, 1 H), 5.07 (d, *J* = 12.1, 1 H), 4.82 (d, *J* = 13.7, 1 H), 4.48 (d, *J* = 11.0, 1 H), 4.10 (d, *J* = 10.9, 1 H), 3.91 (dd, *J* = 9.7, 12.1, 1 H), 3.71 (d, *J* = 13.6, 1 H), 3.18 (dd, *J* = 7.1, 12.3, 1 H), 2.78 (dd, *J* = 6.9, 9.5, 1 H), 2.54−2.33 (m, 4 H), 2.05 (s, 3 H), 1.97−1.87 (m, 2 H), 1.81−1.72 (d, *J* = 4.0, 1 H), 1.26 (d, *J* = 6.8, 3 H), 1.04 (d, *J* = 6.2, 3 H), 1.00 (d, *J* = 6.8, 3 H); MS (ESI, Q-tof) 454.3 (100); mol formula $C_{32}H_{40}BrNO$ (534.57); HRMS $C_{32}H_{40}NO^+$ (454.3110) calcd 454.3110, found 454.3104; TLC R_f 0.27 (CH_2Cl_2/MeOH, 9:1) [I_2].



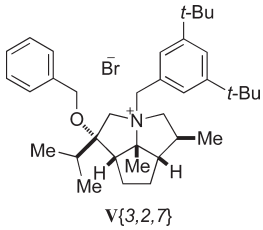
V{3,2,5}

*Preparation of rel-(1S,3R,5S,5aS,7aS,7bR)-Octahydro-1-benzyloxy-1-isopropyl-3-(3,5-trifluoromethylbenzyl)-5-methyl-7b-methylcyclopenta[gh]pyrrolizinium Bromide (**V**{3,2,5}).* Data for **V**{3,2,5}: yield 110 mg (93%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 8.48 (s, 2 H), 7.96 (s, 1 H), 7.31−7.23 (m, 2 H), 7.20−7.12 (m, 2 H), 5.84 (d, *J* = 12.3, 1 H), 5.25−5.18 (m, 1 H), 4.88 (d, *J* = 13.3, 1 H), 4.56 (d, *J* = 11.2, 1 H), 4.18 (d, *J* = 11.2, 1 H), 3.61 (t, *J* = 11.9, 2 H), 3.57 (dd, *J* = 11.9, 11.9, 1 H), 3.15−3.09 (m, 1 H), 2.77 (dd, *J* = 8.3, 8.3, 1 H), 2.60−2.49 (m, 1 H), 2.49−2.32 (m, 3 H), 2.03 (s, 3 H), 1.96−1.89 (m, 2 H), 1.82−1,74 (m, 1 H), 1.25 (d, *J* = 6.7, 3 H), 1.04 (d, *J* = 6.6, 3 H), 0.99 (d, *J* = 6.8, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) 136.9, 133.38, 133.36, 133.2, 132.2 (q, *J* = 33.7), 128.8, 128.2, 127.4, 123.9, 123.0 (q, *J* = 273), 99.0, 84.2, 71.6, 68.9, 65.6, 63.0, 57.5, 57.1, 35.0, 31.9, 31.8, 31.0, 23.5, 22.9, 18.7, 18.6, 18.0, 16.3; MS (ESI, Q-tof) 540.3 (100); mol formula $C_{30}H_{36}BrF_6NO$ (620.51); HRMS $C_{30}H_{36}F_6NO^+$ (540.2701) calcd 540.2701, found 540.2692; TLC R_f 0.31 (CH_2Cl_2/MeOH, 9:1) [I_2].



V{3,2,6}

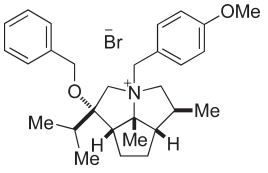
*Preparation of rel-(1S,3S,5S,5aS,7aS,7bR)-Octahydro-1-benzyloxy-1-isopropyl-3-hexyl-5-methyl-7b-methylcyclopenta[gh]pyrrolizinium Bromide (**V**{3,2,6}).* Data for **V**{3,2,6}: yield 66 mg (73%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 7.44 (d, *J* = 7.1, 2 H), 7.36 (t, *J* = 7.3, 2 H), 7.31 (t, *J* = 7.3, 1 H), 4.64 (dt, *J* = 10.8, 20.1, 2 H), 4.16 (d, *J* = 14.0, 1 H), 3.97 (ddd, *J* = 5.0, 12.0, 12.0, 1 H), 3.88 (dd, *J* = 8.4, 12.3, 1 H), 3.25−3.16 (m, 2 H), 2.60 (dd, *J* = 6.7, 9.6, 1 H), 2.57−2.56 (m, 2 H), 2.39−2.31 (m, 1 H), 2.13−2.00 (m, 2 H), 1.94−1.84 (m, 2 H), 1.77−1.66 (m, 2 H), 1.66 (s, 3 H), 1.57−1.51 (m, 1 H), 1.43−1.30 (m, 5 H), 1.11 (d, *J* = 6.7, 3 H), 0.96 (d, *J* = 6.8, 3 H), 0.89 (t, *J* = 6.9, 3 H), 0.83 (d, *J* = 6.6, 3 H); MS (ESI, Q-tof) 398.3 (100); mol formula $C_{27}H_{44}BrNO$ (478.55); HRMS $C_{27}H_{44}NO^+$ (398.3423) calcd 398.3423, found 398.3417; TLC R_f 0.39 (CH_2Cl_2/MeOH, 9:1) [I_2].



V{3,2,7}

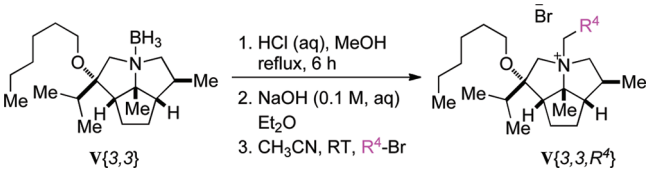
*Preparation of rel-(1S,3R,5S,5aS,7aS,7bR)-Octahydro-1-benzyloxy-1-isopropyl-3-(3,5-tert-butylbenzyl)-5-methyl-7b-methylcyclopenta[gh]pyrrolizinium Bromide (**V**{3,2,7}).* Data for **V**{3,2,7}: yield 115 mg (99%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 7.67 (d, *J* = 1.7, 2 H), 7.51 (s, 1 H), 7.32−7.24 (m, 3 H), 7.21−7.17 (m, 2 H), 5.41 (d, *J* = 12.2, 1 H), 4.92 (d, *J* = 13.7, 1 H), 4.59 (d, *J* = 12.2, 1 H), 4.54 (d, *J* = 11.1, 1 H), 4.24 (d, *J* = 11.1, 1 H), 3.78 (dd, *J* = 8.2, 12.4, 1 H), 3.68 (d, *J* = 13.7, 1 H), 3.37 (dd, *J* = 8.1, 12.6, 1 H), 2.79 (dd, *J* = 8.2, 8.2, 1 H), 2.47−2.31 (m, 4 H), 2.04 (s, 3 H), 2.00−1.88 (m, 2 H), 1.87−1.79 (m, 1 H), 1.37 (s, 18H), 1.22 (d, *J* = 6.8, 3 H), 1.07 (t, *J* = 6.7, 6 H); MS (ESI, Q-tof) 516.4 (100); mol formula $C_{36}H_{54}BrNO$ (596.72); HRMS $C_{36}H_{54}NO^+$: (516.4205) calcd 516.4205, found 516.4190; TLC R_f 0.35 (CH_2Cl_2/MeOH, 9:1) [I_2].

*Preparation of rel-(1S,3R,5S,5aS,7aS,7bR)-Octahydro-1-benzyloxy-1-isopropyl-3-(4-methoxybenzyl)-5-methyl-7b-methylcyclopenta[gh]-pyrrolizinium Bromide (**V**{3,2,8}).* Data for **V**{3,2,8}: yield 93 mg (94%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 7.80 (d, *J* = 8.7, 2 H), 7.34−7.25 (m, 3 H), 7.21−7.17 (m, 2 H), 6.96 (d, *J* = 8.6, 2 H), 5.27 (d, *J* = 12.3, 1 H), 4.72 (d, *J* = 13.6, 2 H), 4.53 (d, *J* = 10.9,



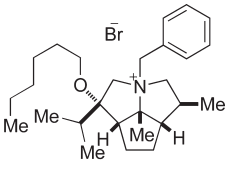
V{3,2,8}

1 H), 4.19 (d, J = 10.9, 1 H), 3.84 (s, 3 H), 3.80 (dd, J = 9.5, 12.3, 1 H), 3.69 (d, J = 13.7, 1 H), 3.22 (dd, J =7.9, 12.1, 1 H), 2.76 (dd, J = 7.0, 9.2, 1 H), 2.53−2.41 (m, 2 H), 2.41−2.34 (m, 2 H), 1.98 (s, 3 H), 1.95−1.87 (m, 2 H), 1.82−1.73 (m, 1 H), 1.23 (d, J = 6.8, 3 H), 1.02 (d, J = 6.9, 3 H), 1.01 (d, J = 6.7, 3 H); MS (ESI, Q-tof) 434.3 (100); mol formula $C_{29}H_{40}BrNO_2$ (514.54); HRMS $C_{29}H_{40}NO_2^+$ (434.3059) calcd 434.3059, found434.3055; TLC R_f 0.20 (CH_2Cl_2/MeOH, 9:1) [I_2].



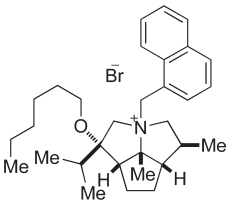
V{3,3} V{3,3,R^4}

Preparation of Quaternary Ammonium Bromides ***V***{3,3,R^4}. Following General Procedure II, amino borane **V**{3,3} (245 mg, 0.762 mmol) was added to a 100 mL round-bottomed flask as a solution in 23 mL of MeOH (0.03 M). The flask was fitted with a reflux condenser, a magnetic stir bar, and a nitrogen inlet adapter. Lastly, 1.0 N aq HCl solution (3.5 mL, 5.0 equiv) was added via syringe. The resulting solution was heated and then concentrated by rotary evaporation (15 mmHg, 20−25 °C) as described in general Procedure II. The resulting free amine was dissolved in acetonitrile and was distributed among seven test tubes that were subsequently charged with benzyl bromide (tube 1, 20 mg, 0.115 mmol, 1.2 equiv), 1-bromomethylnaphthalene (tube 2, 25 mg, 0.115 mmol, 1.2 equiv), 2-bromomethylnaphthalene (tube 3, 25 mg, 0.115 mmol, 1.2 equiv), 3,5-bis(trifluoromethyl)benzyl bromide (tube 4, 35 mg, 0.115 mmol, 1.2 equiv), 3,5-bis(*tert*-butyl)benzyl bromide (tube 5, 32 mg, 0.115 mmol, 1.2 equiv), 4-methoxybenzyl bromide (tube 6, 23 mg, 0.115 mmol, 1.2 equiv), and 1-bromohexane (tube 7, 48 mg, 0.288 mmol, 3.0 equiv). After being agitated for 12 h, the reaction mixtures were worked up and the products isolated and purified as described in general procedure II.



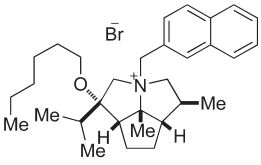
V{3,3,1}

*Preparation of rel-(1S,3R,5S,5aS,7aS,7bR)-Octahydro-1-hexyloxy-1-isopropyl-3-benzyl-5-methyl-7b-methylcyclopenta[gh]pyrrolizinium Bromide (****V****{3,3,1}).* Data for **V**{3,3,*1*}: yield 46 mg (99%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 7.90−7.82 (m, 2 H), 7.47−7.41 (m, 3 H), 5.17 (d, J = 12.1, 1 H), 5.00−4.94 (m, 1 H), 4.54 (d, J = 13.6, 1 H), 4.00 (dd, J = 11.1, 11.1, 1 h), m, 2 H), 2.56−2.46 (m, 1 H), 2.44−2.34 (m, 1 H), 2.24−2.16 (m, 1 H), 2.00−1.91 (m, 2 H), 1.96 (s, 3 H), 1.77−1.67 (m, 1 H), 1.64−1.56 (m, 3 H), 1.48−1.40 (m, 2 H), 1.34−1.17 (m, 3 H), 1.20 (d, J = 6.6, 3 H), 1.14 (d, J = 6.8, 3 H), 0.90 (d, J = 6.8, 3 H), 0.85 (dd, J = 6.0, 7.0, 3 H); MS (ESI, Q-tof) 398 (100); mol formula $C_{27}H_{44}BrNO$ (478.55); HRMS $C_{27}H_{44}NO^+$ (398.3423) calcd 398.3423, found 398.3416; TLC R_f 0.25 (CH_2Cl_2/MeOH, 9:1) [I_2].



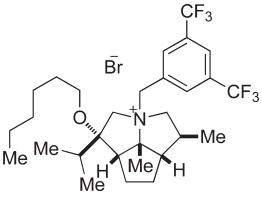
V{3,3,2}

*Preparation of rel-(1S,3R,5S,5aS,7aS,7bR)-Octahydro-1-hexyloxy-1-isopropyl-3-(1-naphthylmethyl)-5-methyl-7b-methylcyclopenta-[gh]pyrrolizinium Bromide (****V****{3,3,2}).* Data for **V**{3,3,2}: yield 50 mg (99%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 8.37 (d, J = 7.2, 1 H), 8.27 (d, J = 8.5, 1 H), 7.87 (t, J = 8.5, 2 H), 7.62 (t, J = 7.7, 1 H), 7.54−7.44 (m, 2 H), 5.67 (d, J = 12.9, 1 H), 5.63 (d, J = 12.9, 1 H), 4.72 (d, J = 13.6, 1 H), 4.09 (dd, J = 11.5, 11.5, 1 H), 3.50 (d, J = 13.5, 1 H), 3.26 (dd, J = 6.9, 15.4, 1 H), 3.02 (dd, J = 8.1, 12.0, 1 H), 2.94 (dd, J = 6.1, 14.9, 1 H), 2.74 (dd, J = 6.5, 9.7, 1 H), 2.72−2.60 (m, 2 H), 2.45 (m, 2 H), 2.48−2.39 (m, 1 H), 2.18−2.08 (m, 1 H), 2.15 (s, 3 H), 2.00−1.94 (m, 2 H), 1.75−1.65 (m, 1 H), 1.44−1.30 (m, 2 H), 1.27−1.14 (m, 6H), 1.16 (d, J = 6.7, 3 H), 1.10 (d, J = 6.4, 3 H), 0.84 (d, J = 6.8, 3 H), 0.81 (t, J = 6.9, 3 H); MS (ESI, Q-tof) 448.3 (100); mol formula $C_{31}H_{46}BrNO$ (528.61); HRMS $C_{31}H_{46}NO^+$ (448.3579) calcd 448.3579, found 448.3573; TLC R_f 0.28 (CH_2Cl_2/MeOH, 9:1) [I_2].



V{3,3,3}

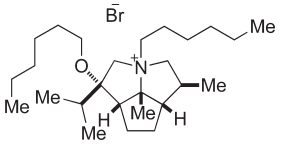
*Preparation of rel-(1S,3R,5S,5aS,7aS,7bR)-Octahydro-1-hexyl-oxy-1-isopropyl-3-(2-naphthylmethyl)-5-methyl-7b-methylcyclopenta-[gh]pyrrolizinium Bromide (****V****{3,3,3}).* Data for **V**{3,3,3}: yield 46 mg (91%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 8.34 (s, 1 H), 7.95−7.92 (m, 1 H), 7.90 (dd, J = 1.7, 8.5, 1 H), 7.80−7.75 (m, 2 H), 7.55−7.48 (m, 2 H), 5.36 (d, J = 12.1, 1 H), 5.20 (d, J = 12.0, 1 H), 4.62 (d, J = 13.5, 1 H), 4.11−4.06 (dd, J = 10.8, 10.8, 1 H), 3.55 (d, J = 13.5, 1 H), 3.30 (dd, J = 6.9, 15.4, 1 H), 3.20 (dd, J = 8.0, 12.0, 1 H), 3.00 (dd, J = 6.3, 14.8, 1 H), 2.72−2.61 (m, 1 H), 2.70 (dd, J = 7.0, 9.7, 1 H), 2.60−2.56 (m, 1 H), 2.44−2.33 (m, 1 H), 2.25−2.15 (m, 1 H), 2.02 (s, 3 H), 1.97−1.91 (m, 2 H), 1.76−1.66 (m, 1 H), 1.44−1.32 (m, 2 H), 1.27−1.14 (m, 6H), 1.22 (d, J = 6.7, 3 H), 1.18 (d, J = 6.7, 3 H), 0.89 (d, J = 6.8, 3 H), 0.81 (t, J = 7.0, 3 H); MS (ESI, Q-tof) 448.4 (100); mol formula $C_{31}H_{46}BrNO$ (528.61); HRMS $C_{31}H_{46}NO^+$ (448.3579) calcd 448.3579, found 448.3577; TLC R_f 0.29 (CH_2Cl_2/MeOH, 9:1) [I_2].



V{3,3,5}

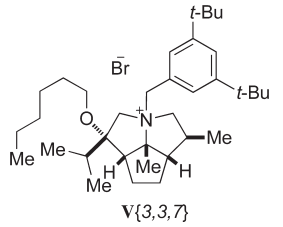
*Preparation of rel-(1S,3R,5S,5aS,7aS,7bR)-Octahydro-1-hexyloxy-1-isopropyl-3-(3,5-trifluoromethyl-benzyl)-5-methyl-7b-methyl-cyclopenta[gh]pyrrolizinium Bromide (****V****{3,3,5}).* Data for **V**{3,3,*5*}: yield

59 mg (99%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 8.49 (s, 2 H), 7.94 (s, 1 H), 5.70 (d, J = 12.2, 1 H), 5.37 (d, J = 12.3, 1 H), 4.70 (d, J = 13.2, 1 H), 3.83 (dd, J = 11.0, 11.0, 1 H), 3.44 (d, J = 13.1, 1 H), 3.36 (dd, J = 6.9, 15.3, 1 H), 3.26 (dd, J = 7.9, 11.9, 1 H), 3.08 (dd, J = 6.3, 14.7, 1 H), 2.75−2.66 (m, 2 H), 2.58−2.53 (m, 1 H), 2.45−2.34 (m, 1 H), 2.23−2.16 (m, 1 H), 2.01 (s, 3 H), 1.98−1.92 (m, 2 H), 1.76−1.68 (m, 1 H), 1.51−1.38 (m, 2 H), 1.36−1.18 (m, 6 H), 1.21 (s, 3 H, J = 6.1), 1.16 (d, J = 6.8, 3 H), 0.88 (d, J = 6.8, 3 H), 0.85 (t, J = 6.9, 3 H); MS (ESI, Q-tof) 534.3 (100); mol formula $C_{29}H_{42}BrF_6NO$ (614.54); HRMS $C_{29}H_{42}F_6NO^+$ (534.3171) calcd 534.3171, found 534.3167; TLC R_f 0.32 (CH_2Cl_2/MeOH, 9:1) [I_2].



V{3,3,6}

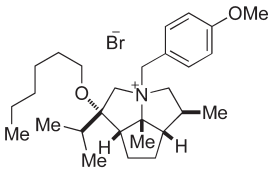
*Preparation of rel-(1S,3S,5S,5aS,7aS,7bR)-Octahydro-1-hexyloxy-1-isopropyl-3-hexyl-5-methyl-7b-methyl-cyclopenta[gh]pyrrolizinium Bromide (**V**{3,3,6}).* Data for **V**{3,3,6}: yield 43 mg (98%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 4.25 (d, J = 13.8, 1 H), 4.07 (d, J = 13.8, 1 H), 4.00−3.82 (m, 2 H), 3.56−3.33 (m, 6H), 2.81−2.70 (m, 1 H), 2.55 (dd, J = 6.6, 9.6, 1 H), 2.49−2.40 (m, 1 H), 2.21−2.12 (m, 3 H), 2.04−1.84 (m, 4 H), 1.81−1.64 (m, 2 H), 1.69 (s, 3 H), 1.64−1.48 (m, 4 H), 1.48−1.20 (m, 6H), 1.09 (d, J = 6.7, 3 H), 1.05 (d, J = 6.7, 3 H), 0.91−0.87 (m, 6H), 0.85 (d, J = 6.8, 3 H); MS (ESI, Q-tof) 392.4 (100); mol formula $C_{26}H_{50}BrNO$ (472.58); HRMS $C_{26}H_{50}NO^+$ (392.3892) calcd 392.3892, found 392.3882; TLC R_f 0.40 (CH_2Cl_2/MeOH, 9:1) [I_2].



V{3,3,7}

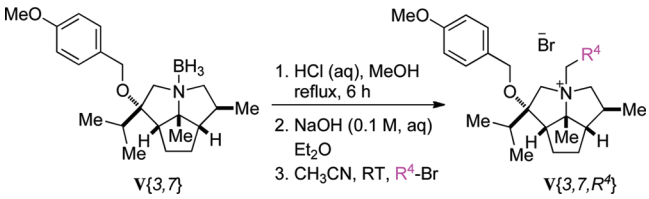
*Preparation of rel-(1S,3R,5S,5aS,7aS,7bR)-Octahydro-1-hexyloxy-1-isopropyl-3-(3,5-tert-butylbenzyl)-5-methyl-7b-methylcyclopenta[gh]pyrrolizinium Bromide (**V**{3,3,7}).* Data for **V**{3,3,7}: yield 56 mg (99%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 7.65 (d, J = 1.5, 2 H), 7.49 (s, 1 H), 5.25 (d, J = 12.2, 1 H), 4.71 (t, J = 12.8, 2 H), 3.96 (dd, J = 8.8, 12.3, 1 H), 3.54 (d, J = 13.6, 1 H), 3.42 (dd, J = 8.1, 12.3, 1 H), 3.39−3.33 (m, 1 H), 3.15 (dd, J = 6.0, 14.5, 1 H), 2.70 (dd, J = 7.0, 9.0, 1 H), 2.60−2.50 (m, 1 H), 2.47−2.40 (m, 1 H), 2.40−2.32 (m, 1 H), 2.29−2.20 (m, 1 H), 2.01 (s, 3 H), 1.99−1.92 (m, 2 H), 1.81−1.73 (m, 1 H), 1.49−1.42 (m, 2 H), 1.38−1.20 (m, 6H), 1.36 (s, 18H), 1.22 (d, J = 6.8, 3 H), 1.14 (d, J = 6.8, 3 H), 0.97 (d, J = 6.8, 3 H), 0.85 (t, J = 6.8, 3 H); MS (ESI, Q-tof) 510.5 (100); mol formula $C_{35}H_{60}BrNO$ (590.76); HRMS $C_{35}H_{60}NO^+$ (510.4675) calcd 510.4675, found 510.4674; TLC R_f 0.35 (CH_2Cl_2/MeOH, 9:1) [I_2].

*Preparation of rel-(1S,3R,5S,5aS,7aS,7bR)-Octahydro-1-hexyloxy-1-isopropyl-3-(4-methoxy-benzyl)-5-methyl-7b-methylcyclopenta[gh]-pyrrolizinium Bromide (**V**{3,3,8}).* Data for **V**{3,3,8}: yield 48 mg (98%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 7.78 (d, J = 8.7, 2 H), 6.93 (d, J = 8.6, 2 H), 5.10 (d, J = 12.0, 1 H), 4.92−4.86 (m, 1 H), 4.48 (d, J = 13.6, 1 H), 3.95 (dd, J = 10.4, 10.4, 1 H), 3.82 (s, 3 H), 3.52 (d, J = 13.6, 1 H), 3.34 (dd, J = 6.8, 15.3, 1 H), 3.26−3.20



V{3,3,8}

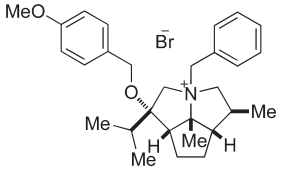
(m, 1 H), 3.09 (dd, J = 6.2, 14.7, 1 H), 2.72−2.57 (m, 2 H), 2.51−2.46 (m, 1 H), 2.45−2.33 (m, 1 H), 2.24−2.13 (m, 1 H), 1.97−1.91 (m, 2 H), 1.95 (s, 3 H), 1.75−1.67 (m, 1 H), 1.48−1.41 (m, 2 H), 1.33−1.18 (m, 6H), 1.19 (d, J = 6.0, 3 H), 1.14 (d, J = 6.8, 3 H), 0.90 (d, J = 6.8, 3 H), 0.85 (t, J = 6.9, 3 H); MS (ESI, Q-tof) 428.4 (100); mol formula $C_{28}H_{46}BrNO_2$ (508.57); HRMS $C_{28}H_{46}NO_2^+$: (428.3529) calcd 428.3529, found 428.3529; TLC R_f 0.21 (CH_2Cl_2/MeOH, 9:1) [I_2].



V{3,7}

V{3,7,R4}

*Preparation of Quaternary Ammonium Bromides **V**{3,7,R^4}.* Following general procedure II, amino borane **V**{3,7} (502 mg, 1.40 mmol) was added to a 100 mL round-bottomed flask as a solution in 50 mL of MeOH (0.03 M). The flask was fitted with a reflux condenser, a magnetic stir bar, and a nitrogen inlet adapter. Lastly, 1.0 N aq HCl solution (7.0 mL, 5.0 equiv) was added via syringe. The resulting solution was heated and then concentrated by rotary evaporation (15 mmHg, 20−25 °C) as described in general Procedure II. The resulting free amine was dissolved in acetonitrile and was distributed among six test tubes that were subsequently charged with benzyl bromide (tube 1, 20 mg, 0.116 mmol, 1.2 equiv), 1-bromomethylnaphthalene (tube 2, 26 mg, 0.116 mmol, 1.2 equiv), 2-bromomethylnaphthalene (tube 3, 26 mg, 0.116 mmol, 1.2 equiv), 3,5-bis(trifluoromethyl)benzyl bromide (tube 4, 35 mg, 0.116 mmol, 1.2 equiv), 3,5-bis(*tert*-butyl)benzyl bromide (tube 5, 33 mg, 0.116 mmol, 1.2 equiv), and 4-methoxybenzyl bromide (tube 6, 23 mg, 0.116 mmol, 1.2 equiv). After being agitated for 12 h, the reaction mixtures were worked up and the products isolated and purified as described in general procedure II.



V{3,7,1}

*Preparation of rel-(1S,3R,5S,5aS,7aS,7bR)-Octahydro-1-(4-methoxybenzyloxy)-1-isopropyl-3-benzyl-5-methyl-7b-methylcyclopenta-[gh]pyrrolizinium Bromide (**V**{3,7,1}).* Data for **V**{3,7,1}: yield 38 mg (75%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 7.90−7.82 (m, 2 H), 7.49−7.42 (m, 3 H), 7.08 (d, J = 8.6, 2 H), 6.80 (d, J = 8.6, 2 H), 5.31 (d, J = 12.1, 1 H), 4.83 (d, J = 12.1, 1 H), 4.72 (d, J = 13.7, 1 H), 4.45 (d, J = 10.6, 1 H), 4.11 (d, J = 10.6, 1 H), 3.83 (dd, J = 9.62, 12.0, 1 H), 3.77 (s, 3 H), 3.69 (d, J = 13.6, 1 H), 3.19 (dd, J = 7.9, 12.2, 1 H), 2.74 (dd, J = 6.86, 9.45, 1 H), 2.54−2.30 (m, 4 H), 1.98 (s, 3 H), 1.96−1.84 (m, 2 H), 1.79−1.70 (m, 1 H), 1.22 (d, J = 6.8, 3 H), 1.01 (t, J = 7.1, 6 H); MS (ESI, Q-tof) 434.3 (100); mol formula

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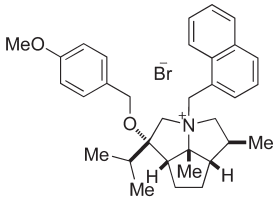
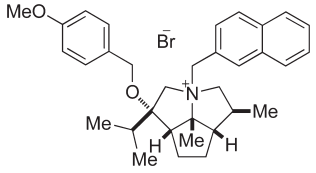
$C_{29}H_{40}BrNO_2$ (514.54); HRMS $C_{29}H_{40}NO_2^+$ (434.3059) calcd 434.3059, found 434.3058; TLC R_f 0.22 (CH_2Cl_2/MeOH, 9:1) [I_2].



V{3,7,2}

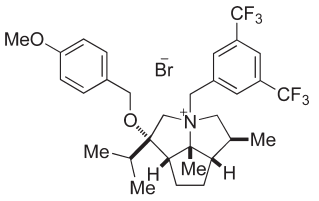
*Preparation of rel-(1S,3R,5S,5aS,7aS,7bR)-Octahydro-1-(4-methoxybenzyloxy)-1-isopropyl-3-(1-naphthylmethyl)-5-methyl-7b-methylcyclopenta[gh]pyrrolizinium Bromide (**V**{3,7,2}).* Data for **V**{3,7,2}: yield 42 mg (77%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 8.38 (d, J = 7.2, 1 H), 8.26 (d, J = 8.6, 1 H), 7.88 (t, J = 7.34, 2 H), 7.62 (t, J = 7.2, 1 H), 7.56−7.46 (m, 2 H), 7.00 (d, J = 8.6, 2 H), 6.74 (d, J = 8.6, 2 H), 5.73 (d, J = 12.8, 1 H), 5.58 (d, J = 12.8, 1 H), 4.87 (d, J = 13.7, 1 H), 4.38 (d, J = 10.6, 1 H), 3.96 (d, J = 10.9, 1 H), 3.96−3.92 (m, 1 H), 3.73 (s, 3 H), 3.67 (d, J = 13.6, 1 H), 2.93 (dd, J = 7.5, 12.2, 1 H), 2.80 (dd, J = 6.5, 9.8, 1 H), 2.57−2.40 (m, 3 H), 2.35−2.26 (m, 1 H), 2.16 (s, 3 H), 2.00−1.87 (m, 2 H), 1.79−1.68 (m, 1 H), 1.23 (d, J = 6.8, 3 H), 0.94 (d, J = 6.8, 3 H), 0.90 (d, J = 6.0, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) 159.4, 133.9, 133.4, 132.8, 130.8, 129.3, 129.0, 128.9, 127.5, 126.0, 125.50, 125.48, 124.2, 114.1, 95.5, 83.9, 72.4, 69.1, 64.7, 61.7, 57.3, 57.1, 55.4, 34.7, 31.1, 31.0, 23.8, 23.1, 18.9, 18.0, 16.6; MS (ESI, Q-tof) 484.3 (100); mol formula $C_{33}H_{42}BrNO_2$ (564.60); HRMS $C_{33}H_{42}NO_2^+$ (484.3216) calcd 484.3216, found 484.3215; TLC R_f 0.25 (CH_2Cl_2/MeOH, 9:1) [I_2].



V{3,7,3}

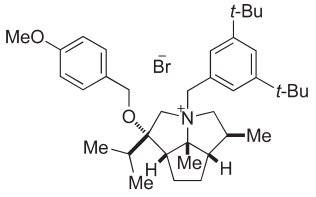
*Preparation of rel-(1S,3R,5S,5aS,7aS,7bR)-Octahydro-1-(4-methoxybenzyloxy)-1-isopropyl-3-(2-naphthylmethyl)-5-methyl-7b-methylcyclopenta[gh]pyrrolizinium Bromide (**V**{3,7,3}).* Data for **V**{3,7,3}: yield 38 mg (69%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 8.35 (s, 1 H), 7.96 (d, J = 8.3, 1 H), 7.91 (dd, J = 1.7, 8.3, 1 H), 7.85−7.81 (m, 2 H), 7.56−7.45 (m, 2 H), 7.03 (d, J = 8.6, 2 H), 6.73 (d, J = 8.7, 2 H), 5.47 (d, J = 12.1, 1 H), 5.07 (d, J = 12.2, 1 H), 4.79 (d, J = 13.7, 1 H), 4.41 (d, J = 10.6, 1 H), 4.04 (d, J = 10.6, 1 H), 3.90 (dd, J = 9.2, 12.1, 1 H), 3.71 (s, 3 H), 3.16 (dd, J = 7.1, 12.6, 1 H), 2.76 (dd, J = 6.9, 9.4, 1 H), 2.52−2.33 (m, 5 H), 2.04 (s, 3 H), 1.96−1.85 (m, 2 H), 1.78−1.69 (m, 1 H), 1.25 (d, J = 6.8, 3 H), 1.05 (d, J = 6.1, 3 H), 0.99 (d, J = 6.8, 3 H); MS (ESI, Q-tof) 484.3 (100); mol formula $C_{33}H_{42}BrNO_2$ (564.60); HRMS $C_{33}H_{42}NO_2^+$ (484.3216) calcd 484.3216, found 484.3221; TLC R_f 0.26 (CH_2Cl_2/MeOH, 9:1) [I_2].

*Preparation of rel-(1S,3R,5S,5aS,7aS,7bR)-Octahydro-1-(4-methoxybenzyloxy)-1-isopropyl-3-(3,5-trifluoromethlybenzyl)-5-methyl-7b-methylcyclopenta[gh]pyrrolizinium Bromide (**V**{3,7,5}).* Data for **V**{3,7,5}: yield 52 mg (82%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 8.48 (s, 2 H), 7.96 (s, 1 H), 7.07 (d, J = 8.6, 2 H), 6.79 (d, J = 8.6, 2 H), 5.81 (d, J = 12.4, 1 H), 5.27−5.20 (m, 1 H), 4.84 (d, J = 13.2, 1 H), 4.48 (d, J = 10.8, 1 H), 4.12 (d, J = 10.8, 1 H), 3.76 (s, 3 H), 3.62 (dd, J = 9.5, 11.9, 1 h), 3.57 (d, J = 13.4, 1 H) 3.14 (dd, J = 7.51, 11.0, 1 H), 2.75 (dd, J = 8.3, 8.3, 1 H), 2.60−2.48 (m, 1 H), 2.48−2.31 (m, 3 H), 2.02 (s, 3 H), 1.95−1.87 (m, 2 H), 1.80−1.71 (m, 1 H), 1.23



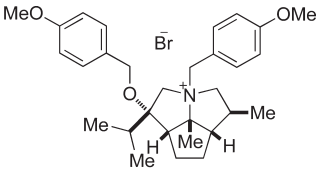
V{3,7,5}

(d, J = 6.7, 3 H), 1.05 (d, J = 6.7, 3 H), 0.99 (d, J = 6.8, 3 H); MS (ESI, Q-tof) 570.3 (100); mol formula $C_{31}H_{38}BrF_6NO_2$ (650.53); HRMS $C_{31}H_{38}F_6NO_2^+$ (570.2807) calcd 570.2807, found 570.2805; TLC R_f 0.31 (CH_2Cl_2/MeOH, 9:1) [I_2].



V{3,7,7}

*Preparation of rel-(1S,3R,5S,5aS,7aS,7bR)-Octahydro-1-(4-methoxybenzyloxy)-1-isopropyl-3-(3,5-tert-butylbenzyl)-5-methyl-7b-methylcyclopenta[gh]pyrrolizinium Bromide (**V**{3,7,7}).* Data for **V**{3,7,7}: yield 47 mg (78%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 7.67 (d, J = 1.7, 2 H), 7.51 (s, 1 H), 7.11 (d, J = 8.6, 2 H), 6.82 (d, J = 8.7, 2 H), 5.37 (d, J = 12.2, 1 H), 4.87 (d, J = 13.7, 1 H), 4.61 (d, J = 12.2, 1 H), 4.46 (d, J = 10.6, 1 H), 4.17 (d, J = 10.6, 1 H), 3.80 (dd, J = 8.21, 12.5, 1 H), 3.78 (s, 3 H), 3.68 (d, J = 13.7, 1 H), 3.40 (dd, J = 8.0, 12.5, 1 H), 2.77 (dd, J = 7.54, 8.9, 1 H), 2.45−2.31 (m, 4 H), 2.03 (s, 3 H), 1.99−1.86 (m, 2 H), 1.85−1.76 (m, 1 H), 1.37 (s, 18H), 1.21 (d, J = 6.8, 3 H), 1.07 (d, J = 6.8, 6 H); MS (ESI, Q-tof) 546.4 (100); mol formula $C_{37}H_{56}BrNO_2$ (626.75); HRMS $C_{37}H_{56}NO_2^+$ (546.4311) calcd 546.4311, found 546.4317; TLC R_f 0.33 (CH_2Cl_2/MeOH, 9:1) [I_2].



V{3,7,8}

*Preparation of rel-(1S,3R,5S,5aS,7aS,7bR)-Octahydro-1-(4-methoxybenzyloxy)-1-isopropyl-3-(4-methoxybenzyl)-5-methyl-7b-methylcyclopenta[gh]pyrrolizinium Bromide (**V**{3,7,8}).* Data for **V**{3,7,8}: yield 35 mg (66%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 7.79 (d, J = 8.7, 2 H), 7.10 (d, J = 8.6, 2 H), 6.95 (d, J = 8.6, 2 H), 6.81 (d, J = 8.7, 2 H), 5.23 (d, J = 12.2, 1 H), 4.75 (d, J = 12.4, 1 H), 4.66 (d, J = 13.7, 1 H), 4.45 (d, J = 10.6, 1 H), 4.12 (d, J = 10.6, 1 H), 3.84 (s, 3 H), 3.83−3.73 (m, 1 H), 3.77 (s, 3 H), 3.67 (d, J = 13.7, 1 H), 3.20 (dd, J = 8.1, 12.2, 1 H), 2.73 (dd, J = 6.8, 9.5, 1 H), 2.52−2.28 (m, 4 H), 1.96 (s, 3 H), 1.94−1.85 (m, 2 H), 1.75 (s, 1 H), 1.21 (d, J = 6.7, 3 H), 1.04−0.99 (m, 6H); MS (ESI, Q-tof) 464.3 (100); mol formula $C_{30}H_{42}BrNO_3$ (544.56); HRMS $C_{30}H_{42}NO_3^+$ (464.3165) calcd 464.3165, found 464.3170; TLC R_f 0.19 (CH_2Cl_2/MeOH, 9:1) [I_2].

*Preparation of Quaternary Ammonium Bromides **V**{4,2,R^4}.* Following general procedure II, amino borane **V**{4,2} (102 mg, 0.300 mmol) was added to a 25 mL round-bottomed flask as a solution in 0 mL of MeOH (0.03 M). The flask was fitted with a reflux condenser, a magnetic stir bar, and a nitrogen inlet adapter. Lastly, 1.0 N aq HCl

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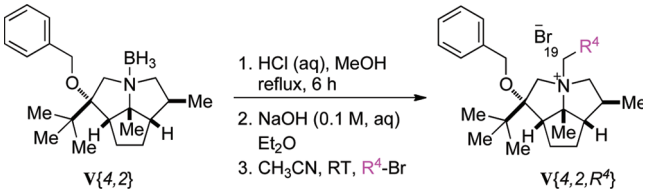
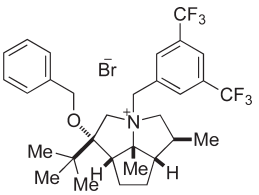
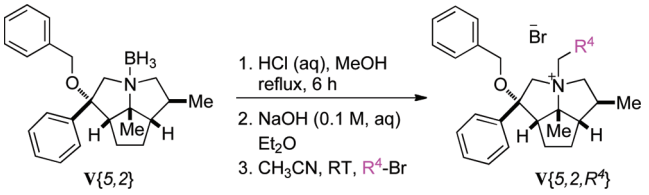


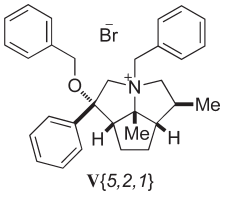
solution (1.5, 5.0 equiv) was added via syringe. The resulting solution was heated and then concentrated by rotary evaporation (15 mmHg, 20−25 °C) as described in general procedure II. The resulting free amine was dissolved in acetonitrile and was transferred to a test tube that were subsequently charged with 3,5-bis(trifluoromethyl)-benzyl bromide (tube 1, 281 mg, 0.915 mmol, 5.0 equiv). After being agitated for 12 h, the reaction mixtures were worked up and the products isolated and purified as described in general procedure II.



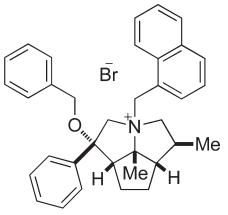
*Preparation of rel-(1R,3R,5S,5aS,7aS,7bR)-Octahydro-1-benzyl-oxy-1-tert-butyl-3-(3,5-trifluoromethylbenzyl)-5-methyl-7b-methyl-cyclopenta[gh]pyrrolizinium Bromide (**V**{4,2,5}).* Data for **V**{4,2,5}: yield 108 mg (93%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 8.53 (s, 2 H), 7.97 (s, 1 H), 7.31 (m, 3 H), 7.22−7.19 (m, 2 H), 5.71 (d, *J* = 12.3, 1 H), 5.60 (d, *J* = 12.3, 1 H), 4.80 (d, *J* = 10.8, 1 H), 4.67 (d, *J* = 13.8, 1 H), 4.24 (d, *J* = 10.8, 1 H), 3.84 (dd, *J* = 11.2, 1 H), 3.74 (d, *J* = 13.7, 1 H), 3.12 (dd, 1 H, *J* = 7.9, 11.9, 1 H), 2.97 (dd, *J* = 6.8, 9.5, 1 H), 2.54−2.47 (m, 2 H), 2.36−2.26 (m, 1 H), 2.00 (s, 3 H), 1.92−1.83 (m, 2 H), 1.79−1.72 (m, 1 H), 1.17 (s, 9 H), 0.88 (d, *J* = 6.7, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) 136.8, 133.4, 133.2, 132.3 (q, *J* = 33.7), 128.8, 128.3, 127.3, 124.0, 122.9 (q, *J* = 273), 98.8, 85.8, 72.0, 68.8, 67.5, 63.6, 58.4, 57.2, 39.4, 34.8, 30.8, 28.0, 23.5, 23.1, 15.7; MS (ESI, Q-tof) 554.2 (100); mol formula $C_{31}H_{38}BrF_6NO$ (634.53); HRMS $C_{31}H_{38}F_6NO^+$ 554.2858 calcd 554.2858, found 554.2866; TLC R_f 0.30 (CH_2Cl_2/MeOH, 9:1) [I_2].



*Preparation of Quaternary Ammonium Bromides **V**{5,2,R^4}.* Following general procedure II, amino borane **V**{5,2} (597 mg, 1.65 mmol) was added to a 100 mL round-bottomed flask as a solution in 50 mL of MeOH (0.03 M). The flask was fitted with a reflux condenser, a magnetic stir bar, and a nitrogen inlet adapter. Lastly, 1.0 N aq HCl solution (7.5, 5.0 equiv) was added via syringe. The resulting solution was heated and then concentrated by rotary evaporation (15 mmHg, 20−25 °C) as described in general Procedure II. The resulting free amine was dissolved in acetonitrile and was distributed among eight test tubes that were subsequently charged with benzyl bromide (tube 1, 44 mg, 0.259 mmol, 1.2 equiv), 1-bromomethylnaphthalene (tube 2, 58 mg, 0.259 mmol, 1.2 equiv), 2-bromomethylnaphthalene (tube 3, 58 mg, 0.259 mmol, 1.2 equiv), 3,5-bis(trifluoromethyl)benzyl bromide (tube 4, 80 mg, 0.259 mmol, 1.2 equiv), 3,5-bis(*tert*-butyl)benzyl bromide (tube 5, 80 mg, 0.259 mmol, 1.2 equiv), 4-methoxybenzyl bromide (tube 6, 52 mg, 0.259 mmol, 1.2 equiv), 4-trifluoromethylbenzyl bromide (tube 7, 20 mg, 0.085 mmol, 1.2 equiv), and 4-cyanobenzyl bromide (tube 8, 17 mg, 0.085 mmol, 1.2 equiv). After being agitated for 12 h, the reaction mixtures were worked up and the products isolated and purified as described in general procedure II.

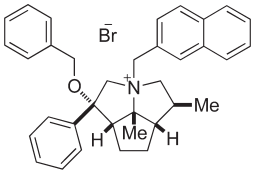


*Preparation of rel-(1R,3R,5S,5aS,7aS,7bR)-Octahydro-1-benzyl-oxy-1-phenyl-3-benzyl-5-methyl-7b-methylcyclopenta[gh]pyrroli-zinium Bromide (**V**{5,2,1}).* Data for **V**{5,2,1}: yield 107 mg (95%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 7.77 (d, *J* = 8.2, 2 H), 7.67 (t, *J* = 7.5, 2 H), 7.57 (t, *J* = 7.3, 2 H), 7.42 (d, *J* = 7.8, 2 H), 7.40−7.31 (m, 3 H), 7.31−7.24 (m, 2 H), 7.12 (d, *J* = 6.8, 2 H), 5.25 (d, *J* = 12.0, 1 H), 5.03 (dd, *J* = 11.9, 11.9, 1 H), 4.30 (d, *J* = 13.1, 1 H), 3.99 (d, *J* = 10.6, 1 H), 3.82 (d, *J* = 10.7, 1 H), 3.53 (d, *J* = 13.0, 1 H), 3.45 (dd, *J* = 9.3, 9.3, 1 H), 3.36 (d, *J* = 12.1, 1 H), 2.98 (dd, *J* = 6.0, 11.4, 1 H), 2.85 (dd, *J* = 5.72, 9.75, 1 H), 2.49−2.39 (m, 1 H), 2.29 (s, 3 H), 2.27−2.15 (m, 2 H), 1.98−1.91(m, 2 H), 1.30 (d, *J* = 6.3, 3 H); MS (ESI, Q-tof) 438.3 (100); mol formula $C_{31}H_{36}BrNO$ (518.53); HRMS $C_{31}H_{36}NO^+$ (438.2797) calcd 438.2797, found 438.2784; TLC R_f 0.21 (CH_2Cl_2/MeOH, 9:1) [I_2].



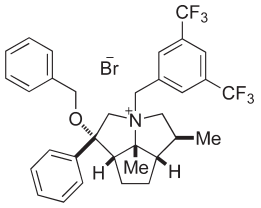
*Preparation of rel-(1R,3R,5S,5aS,7aS,7bR)-Octahydro-1-benzyl-oxy-1-phenyl-3-(1-naphthylmethyl)-5-methyl-7b-methylcyclo-penta[gh]pyrrolizinium Bromide (**V**{5,2,2}).* Data for **V**{5,2,2}: yield 113 mg (92%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 7.91 (dd, *J* = 8.4, 14.2, 2 H), 7.85 (t, *J* = 8.3, 2 H), 7.74 (d, *J* = 7.7, 2 H), 7.67 (t, *J* = 7.7, 2 H), 7.58 (d, *J* = 7.4, 1 H), 7.57−7.53 (m, 2 H), 7.51 (d, *J* = 7.2, 1 H), 7.47 (dd, *J* = 5.7, 13.6, 2 H), 7.32−7.23 (m, 1 H), 7.10 (dd, *J* = 2.0, 7.4, 2 H), 5.55 (d, *J* = 12.8, 1 H), 4.74 (d, *J* = 11.9, 1 H), 4.69 (d, *J* = 13.9, 1 H), 4.53 (d, *J* = 12.8, 1 H), 3.98 (d, *J* = 11.0, 1 H), 3.91 (d, *J* = 11.0, 1 H), 3.62 (d, *J* = 13.3, 1 H), 3.39 (dd, *J* = 9.1, 9.1, 1 H), 3.04 (d, *J* = 10.4, 1 H), 2.90 (dd, *J* = 6.4, 11.5, 1 H), 2.55 (dd, *J* = 11.2, 21.0, 1 H), 2.46 (s, 3 H), 2.37−2.27 (m, 1 H), 2.16 (d, *J* = 9.0, 1 H), 2.02−1.95 (m, 2 H), 1.22 (d, *J* = 6.4, 3 H); MS (ESI, Q-tof) 488.3 (100); mol formula $C_{35}H_{38}BrNO$ (568.59); HRMS $C_{35}H_{38}NO^+$ (488.2953) calcd 488.2953, found 488.2956; TLC R_f 0.24 (CH_2Cl_2/MeOH, 9:1) [I_2].

*Preparation of rel-(1R,3R,5S,5aS,7aS,7bR)-Octahydro-1-benzyloxy-1-phenyl-3-(2-naphthylmethyl)-5-methyl-7b-methylcyclopenta-[gh]pyrrolizinium Bromide (**V**{5,2,3}).* Data for **V**{5,2,3}: yield 110 mg (90%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 7.86−7.79 (m, 5 H), 7.75 (t, *J* = 7.7, 2 H), 7.68−7.60 (m, 3 H), 7.57−7.50 (m, 2 H), 7.31−7.25 (m, 3 H), 7.12 (dd, *J* = 1.9, 7.5, 2 H),



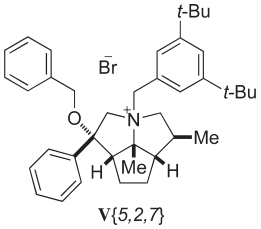
V{*5,2,3*}

5.48 (d, *J* = 12.1, 1 H), 5.18 (dd, *J* = 11.9, 11.9, 1 H), 4.35 (d, *J* = 13.0, 1 H), 4.00 (d, *J* = 10.7, 1 H), 3.84 (d, *J* = 10.7, 1 H), 3.53 (dd, *J* = 12.4, 12.4, 2 H), 3.47 (dd, *J* = 9.2, 9.2, 1 H), 3.06 (dd, *J* = 6.0, 11.3, 1 H), 2.89 (dt, *J* = 2.75, 5.63, 10.2, 1 H), 2.51−2.40 (m, 1 H), 2.35 (s, 3 H), 2.29−2.15 (m, 2 H), 1.99−1.93 (m, 2 H), 1.32 (d, *J* = 6.4, 3 H); MS (ESI, Q-tof) 488.3 (100); mol formula $C_{35}H_{38}BrNO$ (568.59); HRMS $C_{35}H_{38}NO^+$ (488.2953) calcd 488.2953, found 488.2943; TLC R_f 0.25 (CH_2Cl_2/MeOH, 9:1) [I_2].



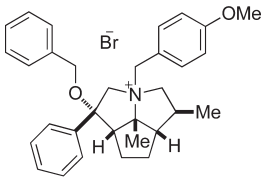
V{*5,2,5*}

*Preparation of rel-(1R,3R,5S,5aS,7aS,7bR)-Octahydro-1-benzyloxy-1-phenyl-3-(3,5-trifluoromethylbenzyl)-5-methyl-7b-methylcyclopenta[gh]pyrrolizinium Bromide (***V**{*5,2,5*}*).* Data for **V**{*5,2,5*}: yield 1 mg (85%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 7.93 (s, 2 H), 7.91 (s, 1 H), 7.76 (d, *J* = 7.42, 2 H), 7.72 (t, *J* = 7.7, 2 H), 7.63 (t, *J* = 7.2, 1 H), 7.33−7.27 (m, 3 H), 7.13 (dd, *J* = 2.1, 7.3, 2 H), 5.96 (d, *J* = 12.3, 1 H), 5.34 (dd, *J* = 11.7, 11.7, 1 H), 4.01 (d, *J* = 10.6, 1 H), 3.98 (d, *J* = 13.1, 1 H), 3.84 (d, *J* = 10.6, 1 H), 3.58 (d, *J* = 13.2, 1 H), 3.49 (dd, *J* = 9.4, 9.4, 1 H), 3.39 (d, *J* = 12.4, 1 H), 3.00 (dd, *J* = 6.1, 11.0, 1 H), 2.82 (dd, *J* = 5.8, 10.2, 1 H), 2.51−2.40 (m, 1 H), 2.35 (s, 3 H), 2.31−2.18 (m, 2 H), 2.04−1.92 (m, 2 H), 1.32 (d, *J* = 6.3, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) 139.0, 136.6, 133.2, 132.5 (q, *J* = 34); 132.0, 130.7, 130.3, 128.6, 128.2, 127.7, 127.4, 124.3, 125.8 (q, *J* = 273),100.8, 83.4, 68.8, 67.7, 67.1, 60.8, 59.5, 53.1, 34.2, 28.0, 27.3, 24.2, 14.8;MS (ESI, Q-tof) 574.3 (100); mol formula $C_{33}H_{34}BrF_6NO$ (654.52); HRMS $C_{33}H_{34}NOF_6^+$: (574.2545) calcd 574.2545, found 574.2541; TLC R_f 0.28 (CH_2Cl_2/MeOH, 9:1) [I_2].



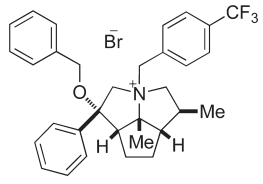
V{*5,2,7*}

*Preparation of rel-(1R,3R,5S,5aS,7aS,7bR)-Octahydro-1-benzyloxy-1-phenyl-3-(3,5-tert-butylbenzyl)-5-methyl-7b-methylcyclopenta[gh]pyrrolizinium Bromide (***V**{*5,2,7*}*).* Data for **V**{*5,2,7*}: yield 113 mg (83%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 7.78 (d, *J* = 7.4, 2 H), 7.68 (t, *J* = 7.7, 2 H), 7.58 (t, *J* = 7.4, 1 H), 7.40 (s, 1 H), 7.33−7.28 (m, 5 H), 7.18−7.13 (m, 2 H), 5.17 (d, *J* = 11.8, 1 H), 5.10 (dd, *J* = 11.9, 11.9, 1 H), 4.35 (d, *J* = 13.1, 1 H), 4.01 (d, *J* = 10.6, 1 H), 3.80 (d, *J* = 10.6, 1 H), 3.54 (d, *J* = 13.1, 1 H), 3.49 (dd, *J* = 9.4, 9.4, 1 H), 3.25 (d, *J* = 12.0, 1 H), 2.92 (dd, *J* = 5.9, 11.4, 1 H), 2.90−2.85 (m, 1 H), 2.49−2.39 (m, 1 H), 2.30 (s, 3 H), 2.25−2.15 (m, 2 H), 1.98−1.92 (m, 2 H), 1.31 (s, 18H), 1.30 (d, *J* = 6.5, 3 H); MS (ESI, Q-tof) 550.4 (100); mol formula $C_{39}H_{52}BrNO$ (630.74); HRMS $C_{39}H_{52}NO^+$ (550.4049) calcd 550.4049, found 550.4048; TLC R_f 0.31 (CH_2Cl_2/MeOH, 9:1) [I_2].



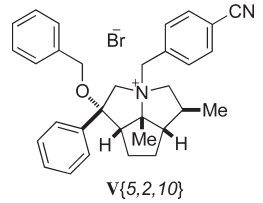
V{*5,2,8*}

*Preparation of rel-(1R,3R,5S,5aS,7aS,7bR)-Octahydro-1-benzyloxy-1-phenyl-3-(4-methoxybenzyl)-5-methyl-7b-methylcyclopenta[gh]pyrrolizinium Bromide (***V**{*5,2,8*}*).* Data for **V**{*5,2,8*}: yield 105 mg (89%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 7.76 (d, *J* = 7.5, 2 H), 7.67 (t, *J* = 7.7, 2 H), 7.57 (t, *J* = 7.4, 1 H), 7.36 (d, *J* = 8.7, 2 H), 7.32−7.23 (m, 3 H), 7.16−7.10 (m, 2 H), 6.84 (d, *J* = 8.7, 2 H), 5.17 (d, *J* = 12.1, 1 H), 4.98 (t, *J* = 11.9, 1 H), 4.28 (d, *J* = 13.0, 1 H), 3.99 (d, *J* = 10.7, 1 H), 3.82 (d, *J* = 10.6, 1 H), 3.78 (s, 3 H), 3.52 (d, *J* = 13.1, 1 H), 3.44 (dd, *J* = 9.3, 9.3, 1 H), 3.31 (d, *J* = 12.2, 1 H), 2.96 (dd, *J* = 6.0, 11.4, 1 H), 2.84 (dd, *J* = 5.71, 10.1, 1 H), 2.50−2.38 (m, 1 H), 2.26 (s, 3 H), 2.25−2.15 (m, 2 H), 1.98−1.89 (m, 2 H), 1.29 (d, *J* = 6.4, 1 H); MS (ESI, Q-tof) 468.3 (100); mol formula $C_{32}H_{38}BrNO_2$ (548.55); HRMS $C_{32}H_{38}NO_2^+$ (468.2903) calcd 468.2903, found 468.2901; TLC R_f 0.20 (CH_2Cl_2/MeOH, 9:1) [I_2].



V{*5,2,9*}

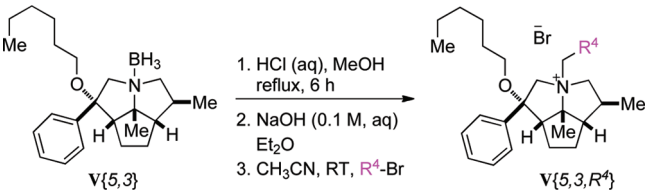
*Preparation of rel-(1R,3R,5S,5aS,7aS,7bR)-Octahydro-1-benzyloxy-1-phenyl-3-(4-trifluoromethylbenzyl)-5-methyl-7b-methylcyclopenta[gh]pyrrolizinium Bromide (***V**{*5,2,9*}*).* Data for **V**{*5,2,9*}: yield 35 mg (89%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 7.77 (m, 2 H), 7.69 (dd, *J* = 7.8, 7.8, 2 H), 7.64−7.57 (m, 5 H) 7.30 (m, 3 H), 7.13 (m, 2 H), 5.50 (d, *J* = 12.1, 1 H), 5.12 (dd, *J* = 11.8, 11.8, 1 H), 4.21 (d, *J* = 13.1, 1 H), 4.01 (d, *J* = 10.7, 1 H), 3.84 (d, *J* = 10.7, 1 H), 3.57 (d, *J* = 13.1, 1 1 H), 3.45 (dd, *J* = 9.3, 9.3, 1 H), 3.44 (d, *J* = 12.2, 1 H), 2.97 (dd, *J* = 6.1, 11.3, 1 H), 2.82 (dd, *J* = 5.9, 10.1, 1 H), 2.46 (m, 1 H), 2.31 (s, 3 H), 2.25 (m, 2 H), 1.96 (m, 2 H), 1.30 (d, *J* = 6.4, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) 139.1, 136.8, 133.7, 133.4, 132.6, 132.3, 130.5, 130.2, 128.7, 128.3, 127.7, 127.5, 126.10, 126.07, 122.7, 100.1, 83.4, 69.6, 67.8, 67.1, 60.8, 60.5, 54.3, 34.3, 28.4, 26.9, 24.3, 15.0; MS (ESI, Q-tof) 506.3 (100); mol formula $C_{32}H_{35}BrF_3NO$ (586.53); HRMS $C_{32}H_{35}F_3NO^+$ (506.2671) calcd 506.2671, found 506.2670; TLC R_f 0.25 (CH_2Cl_2/MeOH, 9:1) [I_2].



V{*5,2,10*}

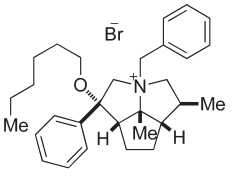
*Preparation of rel-(1R,3R,5S,5aS,7aS,7bR)-Octahydro-1-benzyloxy-1-phenyl-3-(4-cyanobenzyl)-5-methyl-7b-methylcyclopenta[gh]pyrrolizinium Bromide (***V**{*5,2,10*}*).* Data for **V**{*5,2,10*}: yield 35 mg

(95%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 7.77 (d, J = 7.4, 2 H), 7.71−7.63 (m, 6H), 7.60 (dd, J = 7.3, 7.3, 1 H), 7.31−7.26 (m, 3 H), 7.13−7.10 (m, 2 H), 5.54 (d, J = 12.0, 1 H), 5.13 (dd, J = 11.8, 11.8, 1 H), 4.16 (d, J = 13.2, 1 H), 4.01 (d, J = 10.6, 1 H), 3.83 (d, J = 10.6, 1 H), 3.58 (d, J = 13.1, 1 H), 3.48−3.40 (m, 2 H), 2.94 (dd, J = 6.1, 11.2, 1 H), 2.80 (dd, J = 5.8, 10.0, 1 H), 2.50−2.40 (m, 1 H), 2.30 (s, 3 H), 2.30−2.17 (m, 2 H), 2.00−1.92 (m, 2 H), 1.29 (d, J = 6.3, 1 H); MS (ESI, Q-tof) 463.3 (100); mol formula $C_{32}H_{35}BrN_2O$ (543.54); HRMS $C_{32}H_{35}N_2O^+$ (463.2749) calcd 463.2749, found 463.2742; TLC R_f 0.19 (CH_2Cl_2/MeOH, 9:1) [I_2].



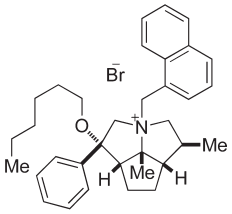
V{5,3} V{5,3,R^4}

Preparation of Quaternary Ammonium Bromides ***V****{5,3,R^4}*. Following general procedure II, amino borane **V**{*5,3*} (403 mg, 1.13 mmol) was added to a 100 mL round-bottomed flask as a solution in 43 mL of MeOH (0.03 M). The flask was fitted with a reflux condenser, a magnetic stir bar, and a nitrogen inlet adapter. Lastly, 1.0 N aq HCl solution (6.9, 5.0 equiv) was added via syringe. The resulting solution was heated and then concentrated by rotary evaporation (15 mmHg, 20−25 °C) as described in general Procedure II. The resulting free amine was dissolved in acetonitrile and was distributed among six test tubes that were subsequently charged with benzyl bromide (tube 1, 37 mg, 0.215 mmol, 1.2 equiv), 1-bromomethylnaphthalene (tube 2, 48 mg, 0.215 mmol, 1.2 equiv), 2-bromomethylnaphthalene (tube 3, 48 mg, 0.215 mmol, 1.2 equiv), 3,5-bis(trifluoromethyl)benzyl bromide (tube 4, 66 mg, 0.215 mmol, 1.2 equiv), 3,5-bis(*tert*-butyl)benzyl bromide (tube 5, 61 mg, 0.215 mmol, 1.2 equiv), and 4-methoxybenzyl bromide (tube 6, (43 mg, 0.215 mmol, 1.2 equiv). After being agitated for 12 h, the reaction mixtures were worked up and the products isolated and purified as described in general procedure II.



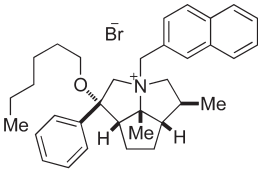
V{5,3,1}

*Preparation of rel-(1R,3R,5S,5aS,7aS,7bR)-Octahydro-1-hexyloxy-1-phenyl-3-benzyl-5-methyl-7b-methylcyclopenta[gh]pyrrolizinium Bromide (****V****{5,3,1}).* Data for **V**{*5,3,1*}: yield 82 mg (89%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 7.65 (t, J = 8.1, 2 H), 7.62 (d, J = 8.07, 2 H), 7.53 (t, J = 7.2, 1 H), 7.41 (d, J = 6.61, 2 H), 7.39−7.31 (m, 3 H), 5.22 (d, J = 12.0, 1 H), 5.02 (dd, J = 11.9, 11.9, 1 H), 4.21 (d, J = 13.0, 1 H), 3.44 (d, J = 13.2, 1 H), 3.34 (d, J = 12.0, 1 H), 3.31 (dd, J = 9.28, 9.28, 1 H), 2.98 (dd, J = 6.1, 11.4, 1 H), 2.90 (ddd, J = 6.4, 8.8, 8.8, 1 H), 2.83 (dd, J = 6.0, 10.1, 1 H), 2.74 (ddd, J = 6.7, 8.8, 8.8, 1 H), 2.40−2.30 (m, 1 H), 2.28−2.19 (m, 1 H), 2.25 (s, 3 H), 2.12−2.03 (m, 1 H), 1.98−1.84 (m, 2 H), 1.41−1.34 (m, 2 H), 1.31 (d, J = 6.4, 3 H), 1.27−1.10 (m, 6H), 0.84 (t, J = 7.2, 3 H); MS (ESI, Q-tof) 432.3 (100); mol formula $C_{30}H_{42}BrNO$ (512.56); HRMS $C_{30}H_{42}NO^+$ (432.3266) calcd 432.3266, found 432.3263; TLC R_f 0.25 (CH_2Cl_2/MeOH, 9:1) [I_2].



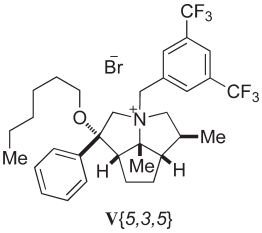
V{5,3,2}

*Preparation of rel-(1R,3R,5S,5aS,7aS,7bR)-Octahydro-1-hexyloxy-1-phenyl-3-(1-naphthylmethyl)-5-methyl-7b-methylcyclopenta[gh]pyrrolizinium Bromide (****V****{5,3,2}).* Data for **V**{*5,3,2*}: yield 94 mg (93%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 7.93−7.87 (m, 3 H), 7.85 (d, J = 8.1, 1 H), 7.62−7.59 (m, 4 H), 7.58−7.44 (m, 4 H), 5.54 (d, J = 12.8, 1 H), 4.71 (dd, J = 11.8, 11.8, 1 H), 4.63 (d, J = 13.3, 1 H), 4.57 (d, J = 12.8, 1 H), 3.54 (d, J = 13.2, 1 H), 3.26 (dd, J = 8.9, 8.9, 1 H), 3.01 (dd, J = 5.5, 10.1, 1 H), 2.93 (dd, J = 6.5, 11.5, 1 H), 2.87−2.87 (m, 2 H), 2.56−2.46 (m, 1 H), 2.43−2.33(m, 1 H), 2.09−2.01 (m, 1 H), 2.01−1.91 (m, 2 H), 1.36 (dd, J = 6.9, 14.0, 2 H), 1.26 (d, J = 6.4, 2 H), 1.24−1.07 (m, 8H), 0.82 (t, J = 7.2, 3 H); MS (ESI, Q-tof) 482.3 (100); mol formula $C_{34}H_{44}BrNO$ (562.62); HRMS $C_{34}H_{44}NO^+$ (482.3423) calcd 482.3423, found 482.3428; TLC R_f 0.28 (CH_2Cl_2/MeOH, 9:1) [I_2].



V{5,3,3}

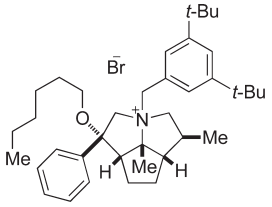
*Preparation of rel-(1R,3R,5S,5aS,7aS,7bR)-Octahydro-1-hexyloxy-1-phenyl-3-(2-naphthylmethyl)-5-methyl-7b-methylcyclopenta[gh]-pyrrolizinium Bromide (****V****{5,3,3}).* Data for **V**{*5,3,3*}: yield 103 mg (99%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 7.85−7.79 (m, 3 H), 7.73−7.66 (m, 4 H), 7.65−7.57 (m, 3 H), 7.56−7.50 (m, 2 H), 5.44 (d, J = 12.1, 1 H), 5.14 (dd, J = 11.9, 11.9, 1 H), 4.27 (d, J = 13.0, 1 H), 3.53 (d, J = 12.1, 1 H), 3.43 (d, J = 13.0, 1 H), 3.34 (dd, J = 9.3, 9.3, 1 H), 3.06 (dd, J = 6.1, 11.3, 1 H), 2.91 (ddd, J = 6.38, 8.90, 8.90, 1 H), 2.87 (dd, J = 5.8, 10.2, 1 H), 2.75 (dd, J = 6.7, 15.5, 1 H), 2.44−2.19 (m, 2 H), 2.30 (s, 3 H), 2.13−2.05 (m, 1 H), 1.97−1.87 (m, 2 H), 1.40− 1.34 (m, 2 H), 1.33 (d, J = 6.4, 3 H), 1.28−1.09 (m, 7H), 0.83 (t, J = 7.2, 3 H); MS (ESI, Q-tof) 482.3 (100); mol formula $C_{34}H_{44}BrNO$ (562.62); HRMS $C_{34}H_{44}NO^+$ (482.3423) calcd 482.3423, found 482.3423; TLC R_f 0.29 (CH_2Cl_2/MeOH, 9:1) [I_2].



V{5,3,5}

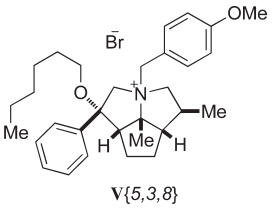
*Preparation of rel-(1R,3R,5S,5aS,7aS,7bR)-Octahydro-1-hexyloxy-1-phenyl-3-(3,5-trifluoromethyl-benzyl)-5-methyl-7b-methylcyclopenta-[gh]pyrrolizinium Bromide (****V****{5,3,5}).* Data for **V**{*5,3,5*}: yield 104 mg (90%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 7.90 (s, 2 H), 7.69−7.63 (m, 4 H), 7.61−7.56 (m, 1 H), 5.92 (d, J = 12.3, 1 H), 5.32 (dd, J = 11.6, 11.6, 1 H), 3.88 (d, J = 13.1, 1 H), 3.49 (d, J = 13.1, 1 H), 3.39−3.32 (m, 2 H), 3.00 (dd, J = 6.0, 11.0, 1 H), 2.91 (dd, J = 6.5, 15.2, 1 H), 2.79 (dd, J = 6.19, 10.1, 1 H), 2.75

(dd, J = 6.67, 15.4, 1 H), 2.43−2.20 (m, 2 H), 2.30 (s, 3 H), 2.15−2.09 (m, 1 H), 2.00−1.89 (m, 2 H), 1.42−1.35 (m, 2 H), 1.33 (d, J = 6.3, 3 H), 1.28−1.12 (m, 6H), 0.84 (t, J = 7.2, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) 139.4, 133.3, 132.5 (q, J = 34.2), 132.1, 130.4, 130.1, 127.3, 124.3, 125.8 (q, J = 273), 100.8, 82.8, 68.9. 67.8, 64.8, 60.9, 59.5, 53.2, 34.2, 31.6, 29.6, 28.0, 27.2, 25.7, 24.3, 22.6, 14.8, 14.1; MS (ESI, Q-tof) 568.3 (100); mol formula $C_{32}H_{40}BrF_6NO$ (648.56); HRMS $C_{32}H_{40}NOF_6^+$ (568.3014) calcd 568.3014, found 568.3007; TLC R_f 0.39 (CH_2Cl_2/MeOH, 9:1) [I_2].



V{*5,3,7*}

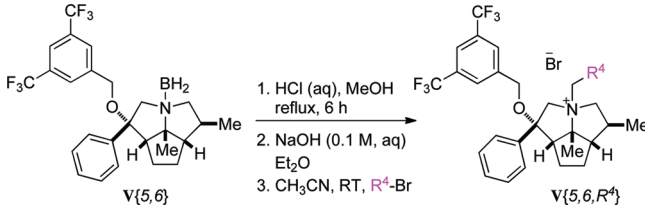
*Preparation of rel-(1R,3R,5S,5aS,7aS,7bR)-Octahydro-1-hexyloxy-1-phenyl-3-(3,5-tert-butylbenzyl)-5-methyl-7b-methylcyclopenta[gh]-pyrrolizinium Bromide (**V**{5,3,7}).* Data for **V**{*5,3,7*}: yield 105 mg (93%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 7.67 (d, J = 7.3, 2 H), 7.62 (t, J = 7.7, 2 H), 7.52 (t, J = 7.2, 1 H), 7.40 (s, 1 H), 7.30 (s, 2 H), 5.16 (d, J = 11.9, 1 H), 5.08 (dd, J = 11.9, 11.9, 1 H), 4.26 (d, J = 12.9, 1 H), 3.44 (d, J = 12.9, 1 H), 3.34 (dd, J = 9.3, 9.3, 1 H), 3.22 (d, J = 12.0, 1 H), 2.95−2.87 (m, 2 H), 2.84 (dd, J = 5.8, 9.9, 1 H), 2.73 (dd, J = 6.8, 15.5, 1 H), 2.39−2.29 (m, 1 H), 2.26 (s, 3 H), 2.23−2.15 (m, 1 H), 2.12−2.05 (m, 1 H), 1.96−1.86 (m, 2 H), 1.42−1.35 (m, 2 H), 1.35−1.11 (m, 27H), 0.84 (t, J = 7.2, 3 H); MS (ESI, Q-tof) 544.5 (100); mol formula $C_{38}H_{58}BrNO$ (624.78); HRMS $C_{38}H_{58}NO^+$ (544.4518) calcd 544.4518, found 544.4509; TLC R_f 0.41 (CH_2Cl_2/MeOH, 9:1) [I_2].



V{*5,3,8*}

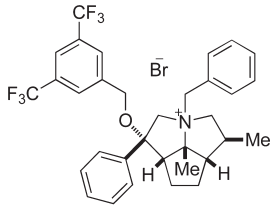
*Preparation of rel-(1R,3R,5S,5aS,7aS,7bR)-Octahydro-1-hexyloxy-1-phenyl-3-(4-methoxybenzyl)-5-methyl-7b-methylcyclopenta[gh]-pyrrolizinium Bromide (**V**{5,3,8}).* Data for **V**{*5,3,8*}: yield 87 mg (90%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 7.67−7.59 (m, 4 H), 7.52 (t, J = 7.1, 1 H), 7.35 (d, J = 8.7, 2 H), 6.84 (d, J = 8.8, 2 H), 5.13 (d, J = 12.2, 1 H), 4.94 (dd, J = 11.9, 11.9, 1 H), 4.19 (d, J = 12.8, 1 H), 3.78 (s, 4 H), 3.42 (d, J = 13.2, 1 H), 3.33−3.26 (m, 2 H), 2.96 (dd, J = 6.0, 11.4, 1 H), 2.90 (ddd, J = 6.3, 8.7, 8.7, 1 H), 2.81 (dd, J = 6.0, 10.2, 1 H), 2.73 (dd, J = 6.7, 15.4, 1 H), 2.42−2.29 (m, 1 H), 2.28−2.16 (m, 1 H), 2.22 (s, 3 H), 2.10−2.03 (m, 1 H), 1.98−1.85 (m, 2 H), 1.40−1.34 (m, 2 H), 1.30 (d, J = 6.4, 3 H), 1.27−1.10 (m, 6H), 0.84 (t, J = 7.2, 3 H); MS (ESI, Q-tof) 462.3 (100); mol formula $C_{31}H_{44}BrNO_2$ (542.59); HRMS $C_{31}H_{44}NO_2^+$ (462.3372) calcd 462.3372, found 462.3372; TLC R_f 0.25 (CH_2Cl_2/MeOH, 9:1) [I_2].

*Preparation of Quaternary Ammonium Bromides **V**{5,6,R^4}.* Following general procedure II, amino borane **V**{*5,6*} (80 mg, 0.161 mmol) was added to a 100 mL round-bottomed flask as a solution in 5.4 mL of MeOH (0.03 M). The flask was fitted with a reflux condenser, a magnetic stir bar, and a nitrogen inlet adapter. Lastly, 1.0 N aq HCl solution (0.8, 5.0 equiv) was added via syringe. The resulting solution was heated and then concentrated by rotary evaporation (15 mmHg,



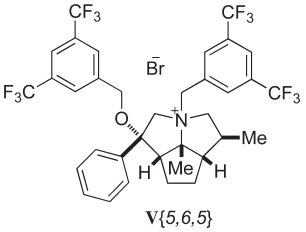
V{*5,6*} **V**{*5,6,R^4*}

20−25 °C) as described in general Procedure II. The resulting free amine was dissolved in acetonitrile and was distributed among three test tubes that were subsequently charged with benzyl bromide (tube 1, 8 mg, 0.048 mmol, 1.2 equiv), 3,5-bis(*tert*-butyl)benzyl bromide (tube 2, 15 mg, 0.048 mmol, 1.2 equiv), and 4-methoxybenzyl bromide (tube 3, 10 mg, 0.048 mmol, 1.2 equiv). After being agitated for 12 h, the reaction mixtures were worked up and the products isolated and purified as described in general procedure II.



V{*5,6,1*}

*Preparation of rel-(1R,3R,5S,5aS,7aS,7bR)-Octahydro-1-(3,5-trifluoro-methylbenzyloxy)-1-phenyl-3-benzyl-5-methyl-7b-methylcyclopenta-[gh]pyrrolizinium Bromide (**V**{5,6,1}).* Data for **V**{*5,6,1*}: yield 21 mg (79%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 7.79−7.75 (m, 2 H), 7.75 (s, 1 H), 7.69 (t, J = 7.8, 2 H), 7.60 (t, J = 7.3, 1 H), 7.54 (s, 2 H), 7.44−7.33 (m, 5 H), 5.31 (d, J = 12.1, 1 H), 5.13 (dd, J = 11.9, 11.9, 1 H), 4.34 (d, J = 13.0, 1 H), 4.16 (d, J = 12.0, 1 H), 3.95 (d, J = 12.0, 1 H), 3.59 (d, J = 13.1, 1 H), 3.49 (dd, J = 9.4, 9.4, 1 H), 3.30 (d, J = 12.1, 1 H), 3.04 (dd, J = 6.0, 11.4, 1 H), 2.90 (dd, J = 5.9, 10.3, 1 H), 2.45−2.20 (m, 2 H), 2.31 (s, 3 H), 2.20−2.10 (m, 1 H), 2.02−1.92 (m, 2 H), 1.33 (d, J = 6.4, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) 139.5, 138.2, 133.1, 131.9 (q, J = 33.5), 130.9, 130.5, 130.2, 129.3, 129.1, 127.6, 127.1, 123.2 (q, J = 273), 121.9, 99.5, 83.9, 69.3, 67.0, 65.4, 61.5, 60.7, 52.8, 34.0, 28.1, 27.5, 24.2, 14.7; MS (ESI, Q-tof) 574.3 (100); mol formula $C_{33}H_{34}BrF_6NO$ (654.52); HRMS $C_{33}H_{34}NOF_6^+$ (574.2545) calcd574.2545, found 574.2549; TLC R_f 0.28 (CH_2Cl_2/MeOH, 9:1) [I_2].



V{*5,6,5*}

*Preparation of rel-(1R,3R,5S,5aS,7aS,7bR)-Octahydro-1-(3,5-trifluoro-methylbenzyloxy)-1-phenyl-3-(3,5-trifluoromethylbenzyl)-5-methyl-7b-methylcyclopenta[gh]pyrrolizinium Bromide (**V**{5,6,5}).* Data for **V**{*5,6,5*}: yield 21 mg (66%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 7.93 (s, 1 H), 7.89 (s, 2 H), 7.79 (s, 1 H), 7.76−7.70 (m, 3 H), 7.70−7.63 (m, 2 H), 7.55 (s, 2 H), 6.00 (d, J = 12.3, 1 H), 5.41 (dd, J = 11.7, 11.7, 1 H), 4.16 (d, J = 11.9, 1 H), 4.02 (d, J = 13.0, 1 H), 3.96 (d, J = 12.0, 1 H), 3.65 (d, J = 13.1, 1 H), 3.52 (dd, J = 9.3, 9.3, 1 H), 3.34 (d, J = 12.4, 1 H), 3.09 (dd, J = 11.0, 6.0, 1 H), 2.86 (dd,

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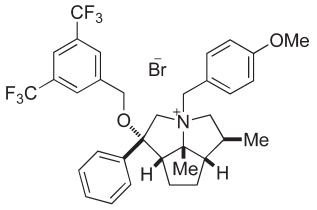
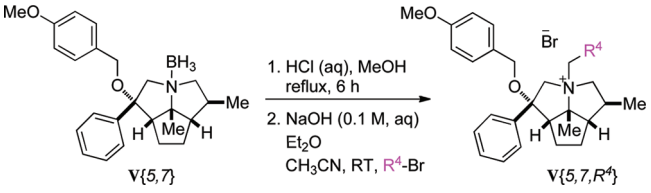
J = 5.8, 10.1, 1 H), 2.45−2.26 (m, 2 H), 2.36 (s, 3 H), 2.24−2.15 (m, 1 H), 2.07−1.93 (m, 2 H), 1.35 (d, J = 6.3, 3 H); MS (ESI, Q-tof) 710.2 (100); mol formula $C_{35}H_{32}BrF_{12}NO$ (790.52); HRMS $C_{35}H_{32}NOF_{12}^{+}$ (710.2292) calcd 710.2292, found 710.2285; TLC R_f 0.35 (CH_2Cl_2/MeOH, 9:1) [I_2].



V{*5,6,8*}

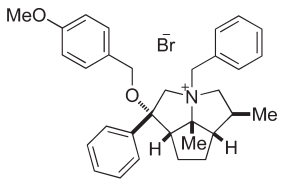
*Preparation of rel-(1R,3R,5S,5aS,7aS,7bR)-Octahydro-1-(3,5-trifluoromethylbenzyloxy)-1-phenyl-3-(4-methoxybenzyl)-5-methyl-7b-methylcyclopenta[gh]pyrrolizinium Bromide (**V**{5,6,8}).* Data for **V**{*5,6,8*}: yield 22 mg (82%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 7.80−7.72 (m, 3 H), 7.76 (t, J = 7.8, 2 H), 7.59 (t, J = 7.3, 1 H), 7.54 (s, 2 H), 7.35 (d, J = 8.7, 2 H), 6.86 (d, J = 8.8, 2 H), 5.22 (d, J = 12.1, 1 H), 5.06 (dd, J = 12.0, 12.0, 1 H), 4.33 (d, J = 13.1, 1 H), 4.16 (d, J = 12.0, 1 H), 3.95 (d, J = 12.0, 1 H), 3.79 (s, 3 H), 3.56 (d, J = 13.1, 1 H), 3.48 (dd, J = 9.3, 9.3, 1 H), 3.25 (d, J = 12.2, 1 H), 3.02 (dd, J = 6.0, 11.5, 1 H), 2.88 (dd, J = 5.6, 10.3, 1 H), 2.43−2.31 (m, 1 H), 2.31−2.18 (m, 2 H), 2.28 (s, 3 H), 2.18−2.10 (s, 1 H), 2.01−1.91 (m, 2 H), 1.32 (d, J = 6.3, 3 H); MS (ESI, Q-tof) 604.3 (100); mol formula $C_{34}H_{36}BrF_6NO_2$ (684.55); HRMS $C_{34}H_{36}NO_2F_6^{+}$ (604.2650) calcd 604.2650, found 604.2649; TLC R_f 0.29 (CH_2Cl_2/MeOH, 9:1) [I_2].



V{*5,7*} **V**{*5,7,R*^{4}}

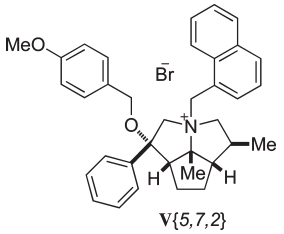
*Preparation of Quaternary Ammonium Bromides **V**{5,7,R^4}.* Following general procedure II, amino borane **V**{*5,7*} (606 mg, 1.55 mmol) was added to a 100 mL round-bottomed flask as a solution in 47 mL of MeOH (0.03 M). The flask was fitted with a reflux condenser, a magnetic stir bar, and a nitrogen inlet adapter. Lastly, 1.0 N aq HCl solution (7.0, 5.0 equiv) was added via syringe. The resulting solution was heated and then concentrated by rotary evaporation (15 mmHg, 20−25 °C) as described in general procedure II. The resulting free amine was dissolved in acetonitrile and was distributed among five test tubes that were subsequently charged with benzyl bromide (tube 1, 34 mg, 0.199 mmol, 1.2 equiv), 1-bromomethylnaphthalene (tube 2, 45 mg, 0.199 mmol, 1.2 equiv), 2-bromomethylnaphthalene (tube 3, 45 mg, 0.199 mmol, 1.2 equiv), 3,5-bis(trifluoromethyl)benzyl bromide (tube 4, 62 mg, 0.199 mmol, 1.2 equiv), and 3,5-bis(*tert*-butyl)benzyl bromide (tube 5, 57 mg, 0.199 mmol, 1.2 equiv). After being agitated for 12 h, the reaction mixtures were worked up and the products isolated and purified as described in general procedure II.

*Preparation of rel-(1R,3R,5S,5aS,7aS,7bR)-Octahydro-1-(4-methoxybenzyloxy)-1-phenyl-3-benzyl-5-methyl-7b-methylcyclopenta[gh]-pyrrolizinium Bromide (**V**{5,7,1}).* Data for **V**{*5,7,1*}: yield 89 mg (98%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 7.77 (d, J = 7.3, 2 H), 7.68 (t, J = 7.7, 2 H), 7.57 (t, J = 7.3, 1 H), 7.45−7.40 (m, 2 H), 7.39−7.31 (m, 3 H), 7.04 (d, J = 8.7, 2 H), 6.81 (d, J = 8.7, 2 H), 5.24 (d, J = 12.2, 1 H), 5.02 (dd, J = 11.9, 11.9, 1 H), 4.27 (d, J = 13.2, 1 H),



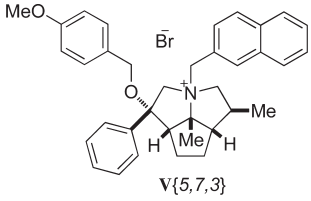
V{*5,7,1*}

3.92 (d, J = 10.2, 1 H), 3.77 (s, 3 H), 3.70 (d, J = 10.2, 1 H), 3.50 (d, J = 13.1, 1 H), 3.44 (dd, J = 9.0, 9.0, 1 H) 3.35 (d, J = 12.1, 1 H), 2.96 (dd, J = 6.1, 11.5, 1 H), 2.85 (dd, J = 5.5, 9.9, 1 H), 2.49−2.39 (m, 1 H), 2.29 (s, 3 H), 2.25−2.11 (m, 2 H), 1.99−1.89 (m, 2 H), 1.29 (t, J = 7.1, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) 159.5, 139.2, 133.0, 130.3, 129.9, 129.3, 129.2, 129.1, 128.9, 127.5, 114.0, 99.3, 83.2, 69.2, 67.3, 66.6, 61.5, 60.6, 55.4, 53.5, 34.0, 28.1, 27.2, 24.1, 14.8; MS (ESI, Q-tof) 468.3 (100); mol formula $C_{32}H_{38}BrNO_2$ (548.55); HRMS $C_{32}H_{38}NO_2^{+}$ (468.2903) calcd 468.2903, found 468.2899; TLC R_f 0.21 (CH_2Cl_2/MeOH, 9:1) [I_2].



V{*5,7,2*}

*Preparation of rel-(1R,3R,5S,5aS,7aS,7bR)-Octahydro-1-(4-methoxybenzyloxy)-1-phenyl-3-(1-naphthylmethyl)-5-methyl-7b-methylcyclopenta[gh]pyrrolizinium Bromide (**V**{5,7,2}).* Data for **V**{*5,7,2*}: yield 95 mg (95%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 7.94 (d, J = 8.7, 1 H), 7.89 (d, J = 8.3, 1 H), 7.86−7.82 (m, 2 H), 7.74 (d, J = 7.4, 2 H), 7.67 (t, J = 7.7, 2 H), 7.59−7.54 (m, 2 H), 7.52−7.43 (m, 2 H), 7.02 (d, J = 8.7, 2 H), 6.78 (d, J = 8.7, 2 H), 5.54 (d, J = 12.8, 1 H), 4.73−4.64 (m, 2 H), 4.52 (d, J = 12.8, 1 H), 3.91 (d, J = 10.9, 1 H), 3.83 (d, J = 10.9, 1 H), 3.75 (s, 3 H), 3.59 (d, J = 13.3, 1 H), 3.38 (dd, J = 9.1, 9.1, 1 H), 3.02 (d, J = 10.9, 1 H), 2.87 (dd, J = 6.2, 11.6, 1 H), 2.61−2.50 (m, 1 H), 2.45 (s, 3 H), 2.35−2.26 (m, 1 H), 2.20−2.11 (m, 1 H), 1.98 (d, J = 10.1, 3 H), 1.22 (d, J = 6.4, 3 H); MS (ESI, Q-tof) 518.3 (100); mol formula $C_{36}H_{40}BrNO_2$ (598.61); HRMS $C_{36}H_{40}NO_2^{+}$ (518.3059) calcd 518.3059, found 518.3065; TLC R_f 0.25 (CH_2Cl_2/MeOH, 9:1) [I_2].



V{*5,7,3*}

*Preparation of rel-(1R,3R,5S,5aS,7aS,7bR)-Octahydro-1-(4-methoxybenzyloxy)-1-phenyl-3-(2-naphthylmethyl)-5-methyl-7b-methylcyclopenta[gh]pyrrolizinium Bromide (**V**{5,7,3}).* Data for **V**{*5,7,3*}: yield 92 mg (92%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 7.86−7.78 (m, 5 H), 7.75 (t, J = 7.7, 3 H), 7.69−7.57 (m, 3 H), 7.56−7.48 (m, 2 H), 7.03 (d, J = 8.7, 2 H), 6.80 (d, J = 8.7, 2 H), 5.46 (d, J = 11.9, 1 H), 5.15 (dd, J = 11.9, 11.9, 1 H), 4.33 (d, J = 12.8, 1 H), 3.93 (d, J = 10.2, 1 H), 3.77 (d, J = 10.3, 1 H), 3.76 (s, 3 H), 3.54 (d, J = 12.1, 1 H), 3.51−3.43 (m, 2 H), 3.03 (dd, J = 6.0, 11.3, 1 H), 2.91−2.86 (m, 1 H), 2.51−2.40 (m, 1 H), 2.34 (s, 3 H), 2.27−2.17 (m, 2 H), 1.99−1.93 (m, 2 H), 1.31 (d, J = 6.3, 3 H); MS (ESI, Q-tof) 518.3 (100); mol

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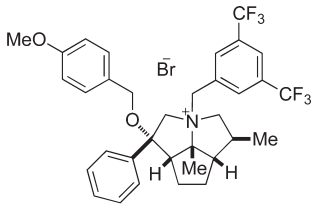
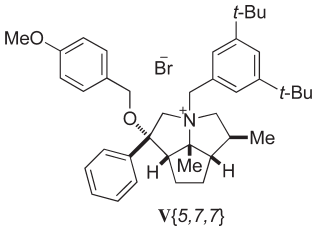
formula $C_{36}H_{40}BrNO_2$ (598.61); HRMS $C_{36}H_{40}NO_2^+$ (518.3059) calcd 518.3059, found 518.3071; TLC R_f 0.26 (CH_2Cl_2/MeOH, 9:1) [I_2].



V{*5,7,5*}

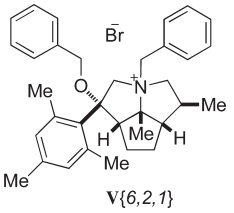
*Preparation of rel-(1R,3R,5S,5aS,7aS,7bR)-Octahydro-1-(4-methoxybenzyloxy)-1-phenyl-3-(3,5-trifluoromethylbenzyl)-5-methyl-7b-methylcyclopenta[gh]pyrrolizinium Bromide (**V**{5,7,5}).* Data for **V**{*5,7,5*}: yield 97 mg (85%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 7.92 (s, 2 H), 7.91 (s, 1 H), 7.81−7.68 (m, 4 H), 7.63 (t, *J* = 7.1, 1 H), 7.04 (d, *J* = 8.7, 2 H), 6.82 (d, *J* = 8.7, 2 H), 5.94 (d, *J* = 12.3, 1 H), 5.32 (dd, *J* = 11.6, 11.6, 1 H), 3.94 (d, *J* = 10.3, 2 H), 3.78 (s, 3 H), 3.55 (d, *J* = 13.0, 1 H), 3.48 (dd *J* = 9.4, 9.4, 1 H), 3.36 (d, *J* = 11.4, 1 H), 2.98 (dd, *J* = 5.7, 10.5, 1 H), 2.84−2.78 (m, 1 H), 2.52−2.38 (s, 1 H), 2.34 (s, 3 H), 2.25 (s, 2 H), 2.03−1.93 (m, 2 H), 1.31 (d, *J* = 6.3, 3 H); MS (ESI, Q-tof) 604.3 (100); mol formula $C_{34}H_{36}BrF_6NO_2$ (684.55); HRMS $C_{34}H_{36}NO_2F_6^+$ (604.2650) calcd 604.2650, found 604.2635; TLC R_f 0.29 (CH_2Cl_2/MeOH, 9:1) [I_2].



V{*5,7,7*}

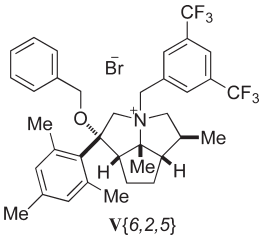
*Preparation of rel-(1R,3R,5S,5aS,7aS,7bR)-Octahydro-1-(4-methoxybenzyloxy)-1-phenyl-3-(3,5-tert-butylbenzyl)-5-methyl-7b-methylcyclopenta[gh]pyrrolizinium Bromide (**V**{5,7,7}).* Data for **V**{*5,7,7*}: yield 103 mg (94%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 7.78 (d, *J* = 7.5, 2 H), 7.68 (t, 2 H, *J* = 7.7), 7.57 (t, *J* = 7.4, 1 H), 7.40 (t, *J* = 1.6, 1 H), 7.33 (d, *J* = 1.4, 2 H), 7.07 (d, *J* = 8.6, 2 H), 6.83 (d, *J* = 8.7, 2 H), 5.17 (d, *J* = 11.7, 1 H), 5.09 (dd, *J* = 12.0, 12.0, 1 H), 4.33 (d, *J* = 13.0, 1 H), 3.95 (d, *J* = 10.2, 1 H), 3.78 (s, 3 H), 3.73 (d, *J* = 10.2, 1 H), 3.51 (d, *J* = 13.6, 1 H), 3.48 (dd, *J* = 9.4, 9.4 1 H), 3.24 (d, *J* = 12.0, 1 H), 2.92−2.84 (m, 2 H), 2.51−2.38 (m, 1 H), 2.30 (s, 3 H), 2.27−2.12 (m, 2 H), 1.98−1.92 (d, *J* = 6.4, 2 H), 1.31 (s, 18H), 1.29 (d, *J* = 6.3, 3 H); MS (ESI, Q-tof) 580.4 (100); mol formula $C_{40}H_{54}BrNO_2$ (660.77); HRMS ($C_{40}H_{54}NO_2^+$ (580.4155) calcd 580.4155, found 580.4160; TLC R_f 0.31 (CH_2Cl_2/MeOH, 9:1) [I_2].

*Preparation of Quaternary Ammonium Bromides **V**{6,2,R^4}.* Following general procedure II, amino borane **V**{*6,2*} (110 mg, 0.273 mmol) was added to a 100 mL round-bottomed flask as a solution in 9.1 mL of MeOH (0.03 M). The flask was fitted with a reflux condenser, a magnetic stir bar, and a nitrogen inlet adapter. Lastly, 1.0 N aq HCl solution (1.4, 5.0 equiv) was added via syringe. The resulting solution was heated and then concentrated by rotary evaporation (15 mmHg, 20−25 °C) as described in general Procedure II. The resulting free amine was dissolved in acetonitrile and was distributed among three test tubes that were subsequently charged with benzyl bromide (tube 1, 13 mg, 0.073 mmol, 1.2 equiv), 3,5-bis(trifluoromethyl)benzyl bromide (tube 2, (94 mg, 0.915 mmol, 5.0 equiv), and 4-methoxybenzyl bromide (tube 3, 15 mg, 0.073 mmol, 1.2 equiv). After being agitated for 12 h, the reaction mixtures were worked up and the products isolated and purified as described in general procedure II.



V{*6,2,1*}

*Preparation of rel-(1R,3R,5S,5aS,7aS,7bR)-Octahydro-1-benzyloxy-1-(2,4,6-methylphenyl)-3-benzyl-5-methyl-7b-methylcyclopenta[gh]pyrrolizinium Bromide (**V**{6,2,1}).* Data for **V**{*6,2,1*}: yield 25 mg (74%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 7.57−7.43 (m, 2 H), 7.44−7.38 (m, 3 H), 7.32−7.27 (m, 3 H), 7.20−7.14 (m, 3 H), 6.98 (s, 1 H), 5.25 (d, *J* = 12.0, 1 H), 4.94 (dd, *J* = 11.6, 11.6, 1 H), 4.38 (d, *J* = 13.2, 1 H), 4.22 (d, *J* = 10.3, 1 H), 4.13−4.07 (m, 2 H), 3.58 (d, *J* = 13.2, 1 H), 3.37 (d, *J* = 12.0, 1 H), 3.11 (dd, *J* = 6.3, 11.4, 1 H), 2.83 (dd, *J* = 5.9, 9.3, 1 H), 2.74 (s, 3 H), 2.52 (s, 3 H), 2.51−2.42 (m, 1 H), 2.34 (s, 3 H), 2.26−2.17 (m, 2 H), 2.16 (s, 3 H), 1.94−1.83 (m, 2 H), 1.30 (d, *J* = 6.4, 3 H); MS (ESI, Q-tof) 480.3 (100); mol formula $C_{34}H_{42}BrNO$ (560.61); HRMS $C_{34}H_{42}NO^+$ (480.3266) calcd 480.3266, found 480.3260; TLC R_f 0.26 (CH_2Cl_2/MeOH, 9:1) [I_2].

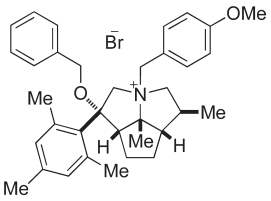


V{*6,2,5*}

*Preparation of rel-(1R,3R,5S,5aS,7aS,7bR)-Octahydro-1-benzyloxy-1-(2,4,6-trimethylphenyl)-3-(3,5-trifluoromethylbenzyl)-5-methyl-7b-methylcyclopenta[gh]pyrrolizinium Bromide (**V**{6,2,5}).* Data for **V**{*6,2,5*}: yield 22 mg (65%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 8.11 (s, 2 H), 7.94 (s, 1 H), 7.34−7.29 (m, 3 H), 7.20−7.16 (m, 3 H), 7.02 (s, 1 H), 5.82 (d, *J* = 12.2, 1 H), 5.22 (dd, *J* = 11.5, 11.5, 1 H), 4.25 (d, *J* = 10.3, 1 H), 4.25−4.15 (m, 2 H), 4.13 (d, *J* = 10.2, 1 H), 3.57 (d, *J* = 13.1, 1 H), 3.30 (d, *J* = 12.3, 1 H), 3.07 (dd, *J* = 6.2, 11.0, 1 H), 2.81−2.75 (m, 1 H), 2.76 (s, 3 H), 2.45 (s, 3 H), 2.52−2.42 (m, 1 H), 2.35 (s, 3 H), 2.24 (s, 3 H), 2.28−2.20 (m, 2 H), 1.90−1.84 (m, 2 H), 1.31 (d, *J* = 6.4, 3 H); MS (ESI, Q-tof) 616.3 (100); mol formula $C_{36}H_{40}BrF_6NO$ (696.60); HRMS $C_{36}H_{40}F_6NO^+$ (616.3014) calcd 616.3014, found 616.3024; TLC R_f 0.30 (CH_2Cl_2/MeOH, 9:1) [I_2].

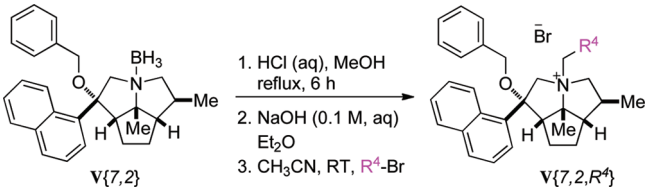
*Preparation of rel-(1R,3R,5S,5aS,7aS,7bR)-Octahydro-1-benzyloxy-1-(2,4,6-methylphenyl)-3-(4-methoxybenzyl)-5-methyl-7b-methylcyclopenta[gh]pyrrolizinium Bromide (**V**{6,2,8}).* Data for **V**{*6,2,8*}: yield 28 mg (78%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 7.47 (d, *J* = 8.7, 2 H), 7.33−7.27 (m, 3 H), 7.19−7.16 (m, 2 H),

dx.doi.org/10.1021/jo2005445 |*J. Org. Chem.* 2011, 76, 4260–4336



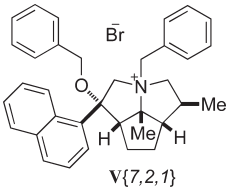
V{6,2,8}

7.13 (s, 1 H), 6.97 (s, 1 H), 6.90 (d, J = 8.7, 2 H), 5.16 (d, J = 12.2, 1 H), 4.90 (dd, J = 11.6, 11.6, 1 H), 4.37 (d, J = 12.9, 1 H), 4.22 (d, J = 10.3, 1 H), 4.11 (dd, J = 9.3, 9.3, 1 H), 4.09 (d, J = 11.3, 1 H), 3.81 (s, 3 H), 3.55 (d, J = 13.2, 1 H), 3.31 (d, J = 12.2, 1 H), 3.08 (dd, J = 6.4, 11.5, 1 H), 2.81 (dd, J = 6.0, 9.4, 1 H), 2.73 (s, 3 H), 2.51 (s, 3 H), 2.50–2.42 (m, 1 H), 2.34 (s, 3 H), 2.24–2.16 (m, 2 H), 2.14 (s, 3 H), 1.93–1.81 (m, 2 H), 1.29 (d, J = 6.4, 3 H); MS (ESI, Q-tof) 510.3 (100); mol formula $C_{35}H_{44}BrNO_2$ (590.63); HRMS $C_{35}H_{44}NO_2^+$ (510.3372) calcd 510.3372, found 510.3382; TLC R_f 0.25 (CH_2Cl_2/MeOH, 9:1) [I_2].



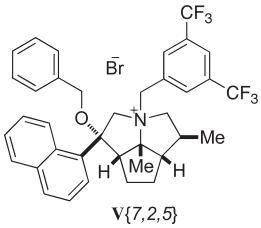
V{7,2} V{7,2,R^4}

Preparation of Quaternary Ammonium Bromides ***V***{7,2,R^4}. Following general procedure II, amino borane **V**{7,2} (258 mg, 0.627 mmol) was added to a 50 mL round-bottomed flask as a solution in 21 mL of MeOH (0.03 M). The flask was fitted with a reflux condenser, a magnetic stir bar, and a nitrogen inlet adapter. Lastly, 1.0 N aq HCl solution (3.1, 5.0 equiv) was added via syringe. The resulting solution was heated and then concentrated by rotary evaporation (15 mmHg, 20–25 °C) as described in general procedure II. The resulting free amine was dissolved in acetonitrile and was distributed among five test tubes that were subsequently charged with benzyl bromide (tube 1, 25 mg, 0.149 mmol, 1.2 equiv), 3,5-bis(trifluoromethyl)benzyl bromide (tube 2, 46 mg, 0.149 mmol, 1.2 equiv), 4-methoxybenzyl bromide (tube 3, 30 mg, 0.149 mmol, 1.2 equiv), 4-cyanobenzyl bromide (tube 4, 29 mg, 0.149 mmol, 1.2 equiv), and 4-trifluoromethylbenzyl bromide (tube 5, 36 mg, 0.149 mmol, 1.2 equiv). After being agitated for 12 h, the reaction mixtures were worked up and the products isolated and purified as described in general procedure II.



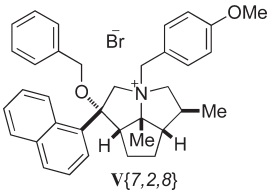
V{7,2,1}

*Preparation of rel-(1R,3R,5S,5aS,7aS,7bR)-Octahydro-1-benzyloxy-1-(1-naphthyl)-3-benzyl-5-methyl-7b-methylcyclopenta[gh]pyrrolizinium Bromide (****V****{7,2,1}).* Data for **V**{7,2,1}: yield 70 mg (97%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 8.52 (d, J = 8.7, 1 H), 8.13–8.08 (m, 2 H), 8.03 (d, J = 7.2, 1 H), 7.74 (dd, J = 7.4, 7.4, 1 H), 7.68–7.64 (m, 2 H), 7.29–7.26 (m, 3 H), 7.16 (dd, J = 7.5, 7.5, 1 H), 7.11–7.08 (m, 2 H), 6.92 (dd, J = 7.8, 7.8, 2 H), 6.37 (d, J = 7.4, 1 H), 5.17 (d, J = 12.0, 1 H), 5.08 (dd, J = 12.0, 12.0, 1 H), 4.65 (d, J = 13.0, 1 H), 4.12 (d, J = 10.4, 1 H), 3.90 (d, J = 10.4, 1 H), 3.83 (dd, J = 9.5, 9.5, 1 H), 3.55 (d, J = 13.1, 1 H), 2.94 (dd, J = 5.9, 11.4, 1 H), 2.90–2.86 (m, 1 H), 2.76 (d, J = 12.0, 1 H), 2.59–2.50 (m, 1 H), 2.35 (s, 3 H), 2.30–2.17 (m, 2 H), 1.99–1.95 (m, 2 H), 1.31 (d, J = 6.3, 3 H); MS (ESI, Q-tof) 488.3 (100); mol formula $C_{35}H_{38}BrNO$ (568.59); HRMS $C_{35}H_{38}NO^+$ (488.2953) calcd 488.2953, found 488.2958; TLC R_f 0.27 (CH_2Cl_2/MeOH, 9:1) [I_2].



V{7,2,5}

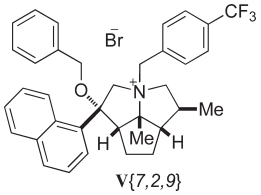
*Preparation of rel-(1R,3R,5S,5aS,7aS,7bR)-Octahydro-1-benzyloxy-1-(1-naphthyl)-3-(3,5-trifluoromethylbenzyl)-5-methyl-7b-methylcyclopenta[gh]pyrrolizinium Bromide (****V****{7,2,5}).* Data for **V**{7,2,5}: yield 40 mg (45%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 8.50 (d, J = 8.7, 1 H), 8.04–8.02 (m, 2 H), 8.04 (d, J = 7.3, 1 H), 7.77–7.73 (m, 2 H), 7.71–7.63 (m, 2 H), 7.32 (s, 2 H), 7.29–7.27 (m, 3 H), 7.11–7.06 (m, 2 H), 5.66 (d, J = 12.1, 1 H), 5.28 (dd, J = 11.8, 11.8, 1 H), 4.57 (d, J = 12.8, 1 H), 4.09 (d, J = 10.3, 1 H), 3.87 (dd, J = 9.5, 9.5, 1 H), 3.82 (d, J = 10.3, 1 H), 3.70 (d, J = 13.1, 1 H), 2.94 (d, J = 12.2, 1 H), 2.90–2.82 (m, 2 H), 2.62–2.53 (m, 1 H), 2.46 (s, 3 H), 2.33–2.20 (m, 2 H), 2.03–1.96 (m, 2 H), 1.32 (d, J = 6.3, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) 136.5, 135.3, 133.1, 132.8, 132.5, 132.4 (q, J = 34.0), 131.5, 130.4, 130.0, 128.9, 128.6, 128.3, 128.1, 127.9, 126.3, 124.9, 124.2, 124.1, 122.4 (q, J = 274), 99.0, 84.6, 68.4, 67.5, 65.6, 61.4, 59.8, 53.8, 34.0, 28.4, 27.6, 25.0, 14.7 ; MS(ESI, Q-tof) 624.3 (100); mol formula $C_{37}H_{36}BrF_6NO$ (704.5823); HRMS $C_{37}H_{36}F_6NO^+$ (624.2701) calcd 624.2701, found 624.2696; TLC R_f 0.35 (CH_2Cl_2/MeOH, 9:1) [I_2].



V{7,2,8}

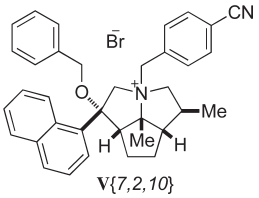
*Preparation of rel-(1R,3R,5S,5aS,7aS,7bR)-Octahydro-1-benzyloxy-1-(1-naphthyl)-3-(4-methoxybenzyl)-5-methyl-7b-methylcyclopenta[gh]pyrrolizinium Bromide (****V****{7,2,8}).* Data for **V**{7,2,8}: yield 62 mg (82%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 8.52 (d, J = 8.7, 1 H), 8.12–8.07 (m, 2 H), 8.02 (d, J = 7.4, 1 H), 7.74 (dd, J = 7.5, 7.5, 1 H), 7.67–7.63 (m, 2 H), 7.30–7.26 (m, 3 H), 7.12–7.09 (m, 2 H), 6.43 (d, J = 8.7, 2 H), 6.29 (d, J = 7.5, 1 H), 5.08 (d, J = 12.1, 1 H), 5.00 (dd, J = 12.0, 12.0, 1 H), 4.64 (d, J = 13.1, 1 H), 4.12 (d, J = 10.3, 1 H), 3.89 (d, J = 10.3, 1 H), 3.82 (dd, J = 9.4, 9.4, 1 H), 3.67 (s, 3 H), 3.53 (d, J = 13.2, 1 H), 2.91 (dd, J = 5.9, 11.4, 1 H), 2.90–2.84 (m, 2 H), 2.70 (d, J = 12.1, 1 H), 2.60–2.50 (m, 1 H), 2.32 (s, 3 H), 2.30–2.15 (m, 2 H), 1.98–1.94 (m, 2 H), 1.30 (d, J = 6.3, 3 H); MS (ESI, Q-tof) 518.3 (100); mol formula $C_{36}H_{40}BrNO_2$ (598.61); HRMS $C_{36}H_{40}NO_2^+$ (518.3059) calcd 518.3059, found 518.3065; TLC R_f 0.28 (CH_2Cl_2/MeOH, 9:1) [I_2].

*Preparation of rel-(1R,3R,5S,5aS,7aS,7bR)-Octahydro-1-benzyloxy-1-(1-naphthyl)-3-(4-trifluoromethylbenzyl)-5-methyl-7b-methylcyclopenta[gh]pyrrolizinium Bromide (****V****{7,2,9}).* Data for **V**{7,2,9}: yield 59 mg (74%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 8.52 (d, J = 8.7, 1 H), 8.15–8.10 (m, 2 H), 8.04 (d, J = 7.4, 1 H), 7.79 (dd, J = 7.5, 7.5, 1 H), 7.71–7.66 (m, 2 H), 7.30–7.25 (m, 3 H), 7.18 (d, J = 8.2, 2 H), 7.12–7.09 (m, 2 H), 6.55 (d, J = 7.7, 2 H), 5.39 (d, J = 12.0, 1 H), 5.18 (dd, J = 11.9, 11.9,



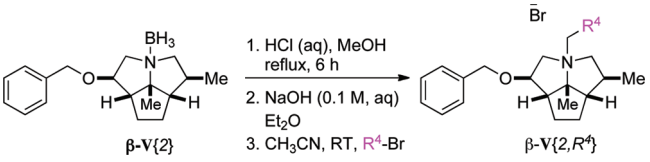
V{7,2,9}

1 H), 4.55 (d, J = 13.1, 1 H), 4.14 (d, J = 10.3, 1 H), 3.92 (d, J = 10.3, 1 H), 3.84 (dd, J = 9.3, J = 9.3, 1 H), 3.59 (d, J = 13.1, 1 H), 2.90 (dd, J = 5.9, 11.2, 1 H), 2.87−2.83 (m, 1 H), 2.75 (d, J = 12.0, 1 H), 2.60−2.50 (m, 1 H), 2.36 (s, 3 H), 2.32−2.19 (m, 2 H), 2.01−1.95 (m, 2 H), 1.30 (d, J = 6.3, 3 H); MS (ESI, Q-tof) 556.3; mol formula $C_{36}H_{37}BrF_3NO$ (636.58); HRMS $C_{36}H_{37}F_3NO^+$ (556.2827) calcd 556.2827, found 586.2837; TLC R_f 0.30 (CH_2Cl_2/MeOH, 9:1) [I_2].



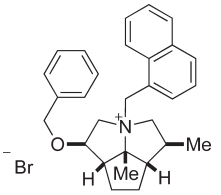
V{7,2,10}

*Preparation of rel-(1R,3R,5S,5aS,7aS,7bR)-Octahydro-1-benzyloxy-1-(1-naphthyl)-3-(4-cyanobenzyl)-5-methyl-7b-methylcyclopenta[gh]pyrrolizinium Bromide (**V**{7,2,10}).* Data for **V**{7,2,10}: yield 57 mg (76%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 8.50 (d, J = 8.6, 1 H), 8.16−8.11 (m, 2 H), 8.04 (d, J = 7.3, 1 H), 7.79 (dd, J = 7.6, 7.6, 1 H), 7.71−7.66 (m, 2 H), 7.31−7.25 (m, 3 H), 7.22 (d, J = 8.5, 2 H), 7.11−7.08 (m, 2 H), 6.54 (d, J = 7.9, 2 H), 5.47 (d, J = 12.4, 1 H), 5.22 (dd, J = 11.7, 11.7, 1 H), 4.48 (d, J = 13.1, 1 H), 4.14 (d, J = 10.3, 1 H), 3.92 (d, J = 10.3, 1 H), 3.84 (dd, J = 9.5, 9.5, 1 H), 3.59 (d, J = 13.1, 1 H), 2.89 (dd, J = 5.9, 11.3, 1 H), 2.85−2.81 (m, 1 H), 2.73 (d, J = 11.9, 1 H), 2.59−2.51 (m, 1 H), 2.35 (s, 3 H), 2.33−2.19 (m, 2 H), 2.02−1.96 (m, 2 H), 1.30 (d, J = 6.3, 3 H); MS (ESI, Q-tof) 513.3 (100); mol formula $C_{36}H_{37}BrN_2O$ (593.60); HRMS $C_{36}H_{37}N_2O^+$ (513.2906) calcd 513.2906, found 513.2899; TLC R_f 0.26 (CH_2Cl_2/MeOH, 9:1) [I_2].



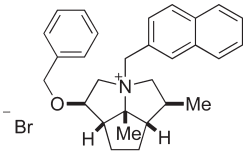
β-V{2} β-V{2,R^4}

*Preparation of Quaternary Ammonium Bromides β-**V**{1,2,R^4}.* Following general procedure II, amino borane β-**V**{2} (164 mg, 0.589 mmol) was added to a 100 mL round-bottomed flask as a solution in 19 mL of MeOH (0.03 M). The flask was fitted with a reflux condenser, a magnetic stir bar, and a nitrogen inlet adapter. Lastly, 1.0 N aq HCl solution (2.9, 5.0 equiv) was added via syringe. The resulting solution was heated and then concentrated by rotary evaporation (15 mmHg, 20−25 °C) as described in general procedure II. The resulting free amine was dissolved in acetonitrile and was distributed among seven test tubes that were subsequently charged with 1-bromomethylnaphthalene (tube 1, 22 mg, 0.104 mmol, 1.2 equiv), 2-bromomethylnaphthalene (tube 3, 22 mg, 0.104 mmol, 1.2 equiv), 3,5-bis(trifluoromethyl)benzyl bromide (tube 4, 31 mg, 0.104 mmol, 1.2 equiv), 3,5-bis(*tert*-butyl)-benzyl bromide (tube 5, 29 mg, 0.104 mmol, 1.2 equiv), 4-methoxybenzyl bromide (tube 6, 31 mg, 0.104 mmol, 1.2 equiv), and 1-bromohexane (tube 7, 68 mg, 0.435 mmol, 5.0 equiv). After being agitated for 12 h, the reaction mixtures were worked up and the products isolated and purified as described in general procedure II.



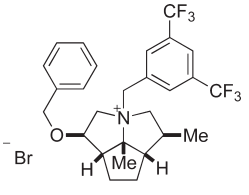
β-V{1,2,2}

*Preparation of rel-(1R,3R,5S,5aS,7aS,7bR)-Octahydro-1-benzyloxy-3-(1-naphthylmethyl)-5-methyl-7b-methylcyclopenta[gh]pyrrolizinium Bromide (β-**V**{1,2,2}).* Data for β-V{1,2,2}: yield 42 mg (98%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 8.48 (d, J = 8.6, 1 H), 8.30 (d, J = 7.2, 1 H), 7.94 (d, J = 8.2, 1 H), 7.87 (d, J = 8.2, 1 H), 7.56 (dd, J = 7.3, 7.3, 1 H), 7.50−7.45 (m, 5 H), 7.43−7.37 (m, 1 H), 7.32 (dd, J = 7.8, 7.8, 1 H), 4.87 (d, J = 12.6, 1 H), 4.59 (d, J = 12.6, 1 H), 4.75 (dd, J = 11.9, 11.9, 1 H), 4.92−4.52 (m, 3 H), 4.12 (d, J = 3.4, 1 H), 4.03 (d, J = 14.1, 1 H), 3.52 (d, J = 11.3, 1 H), 3.18 (dd, J = 5.8, 11.3, 1 H), 2.82 (dd, J = 9.5, 9.5, 1 H), 2.69 (dd, J = 5.9, 10.3, 1 H), 2.24 (s, 3 H), 2.19−2.10 (m, 2 H), 1.90−1.77 (m, 2 H), 1.73−1.63 (m, 1 H), 1.25 (d, J = 6.3, 3 H); MS (ESI, Q-tof) 412.3 (100); mol formula $C_{29}H_{34}BrNO$ (492.49); HRMS $C_{29}H_{34}NO^+$ (412.2640) calcd 412.2640, found 412.2632; TLC R_f 0.25 (CH_2Cl_2/MeOH, 9:1) [I_2].



β-V{1,2,3}

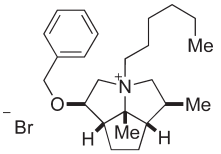
*Preparation of rel-(1R,3R,5S,5aS,7aS,7bR)-Octahydro-1-benzyloxy-3-(2-naphthylmethyl)-5-methyl-7b-methylcyclopenta[gh]pyrrolizinium Bromide (β-**V**{1,2,3}).* Data for β-V{1,2,3}: yield 39 mg (91%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 8.09 (s, 1 H), 7.90−7.84 (m, 3 H), 7.73 (dd, J = 1.7, 8.4, 1 H), 7.59−7.51 (m, 2 H), 7.48−7.34 (m, 5 H), 5.39 (d, J = 11.9, 1 H), 4.79 (d, J = 11.8, 1 H), 4.77 (d, J = 11.7, 1 H), 4.71 (dd, J = 11.9, 11.9, 1 H), 4.64 (d, J = 11.7, 1 H), 4.14−4.08 (m, 2 H), 3.53 (d, J = 11.1, 1 H), 3.32 (dd, J = 6.0, 11.3, 1 H), 2.74 (dd, J = 9.2, 9.2, 1 H), 2.59 (dd, J = 5.9, 9.9, 1 H), 2.24−2.07 (m, 2 H), 2.10 (s, 3 H), 1.89−1.77 (m, 2 H), 1.73−1.61 (m, 1 H), 1.26 (d, J = 6.3, 3 H); MS (ESI, Q-tof) 412.3 (100); mol formula $C_{29}H_{34}BrNO$ (492.49); HRMS $C_{29}H_{34}NO^+$ (412.2640) calcd 412.2640, found 412.2639; TLC R_f 0.26 (CH_2Cl_2/MeOH, 9:1) [I_2].



β-V{1,2,5}

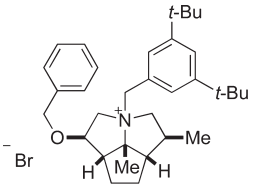
*Preparation of rel-(1R,3R,5S,5aS,7aS,7bR)-Octahydro-1-benzyloxy-3-(3,5-bistrifluoromethylbenzyl)-5-methyl-7b-methylcyclopenta-[gh]pyrrolizinium Bromide (β-**V**{1,2,5}).* Data for β-V{1,2,5}: yield 45 mg

(89%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 8.20 (s, 2 H), 7.94 (s, 1 H), 7.46−7.31 (m, 5 H), 5.84 (d, *J* = 12.1, 1 H), 4.96 (dd, *J* = 11.7, 11.7, 1 H), 4.75 (d, *J* = 11.3, 1 H), 4.69 (d, *J* = 12.1, 1 H), 4.54 (d, *J* = 11.3, 1 H), 4.13 (s, 1 H), 3.68 (dd, *J* = 14.1, 24.4, 2 H), 3.23 (dd, *J* = 6.0, 11.0, 1 H), 2.76 (dd, *J* = 9.5, 9.5, 1 H), 2.57−2.48 (m, 1 H), 2.31−2.22 (m, 1 H), 2.19−2.09 (m, 1 H), 2.11 (s, 3 H), 1.91−1.78 (m, 2 H), 1.75−1.65 (m, 1 H), 1.24 (d, *J* = 6.3, 3 H); MS (ESI, Q-tof) 498.2 (100); mol formula $C_{27}H_{30}BrF_6NO$ (578.43); HRMS $C_{27}H_{30}F_6NO^+$ (498.2232) calcd 498.2232, found 498.2214; TLC R_f 0.29 (CH_2Cl_2/MeOH, 9:1) [I_2].



β-V{*1,2,6*}

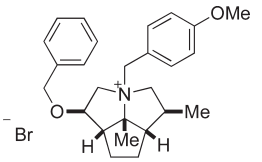
*Preparation of rel-(1R,3R,5S,5aS,7aS,7bR)-Octahydro-1-benzyloxy-3-hexyl-5-methyl-7b-methylcyclopenta[gh]pyrrolizinium Bromide β-**V**{1,2,6}*. Data for β-V{*1,2,6*}: yield 33 mg (87%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 7.38−7.31 (m, 3 H), 7.27−7.24 (m, 2 H), 4.56 (d, *J* = 11.7, 1 H), 4.48 (d, *J* = 11.7, 1 H), 4.39 (d, *J* = 13.3, 1 H), 4.25 (dd, *J* = 6.1, 11.1, 1 H), 4.12 (s, 1 H), 4.03 (d, *J* = 12.7, 1 H), 3.57−3.50 (m, 1 H), 3.31−3.22 (m, 1 H), 3.05 (dd, *J* = 11.9, 11.9, 1 H), 2.59−2.48 (m, 2 H), 2.17−2.05 (m, 2 H), 1.91−1.70 (m, 5 H), 1.68 (s, 3 H), 1.38 (s, 1 H), 1.32−1.20 (m, 5 H), 1.15 (d, *J* = 6.3, 3 H), 0.86 (t, *J* = 6.8, 3 H); MS (ESI, Q-tof) 356.3 (100); mol formula $C_{24}H_{38}BrNO$ (436.47); HRMS $C_{24}H_{38}NO^+$ (356.2953) calcd 356.2953, found 356.2944; TLC R_f 0.37 (CH_2Cl_2/MeOH, 9/1) [I_2].



β-V{*1,2,7*}

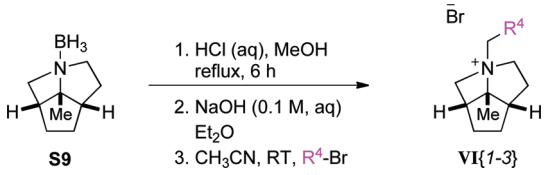
*Preparation of rel-(1R,3R,5S,5aS,7aS,7bR)-Octahydro-1-benzyloxy-3-(3,5-tert-butylbenzyl)-5-methyl-7b-methylcyclopenta[gh]pyrrolizinium Bromide (β-**V**{1,2,7}).* Data for β-V{*1,2,7*}: yield 42 mg (87%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 7.50−7.48 (m, 1 H), 7.41−7.31 (m, 5 H), 7.29 (d, *J* = 1.7, 2 H), 4.71 (d, *J* = 11.3, 1 H), 4.58 (d, *J* = 11.3, 1 H), 4.68 (s, 2 H), 4.23 (s, 1 H), 4.18 (d, *J* = 14.1, 1 H), 4.04 (d, *J* = 14.1, 1 H), 3.82 (dd, *J* = 11.8, 11.8, 1 H), 3.44 (dd, *J* = 5.9, 11.1, 1 H), 2.73 (dd, *J* = 9.6, 9.6, 1 H), 2.70−2.61 (m, 1 H), 2.35 (dd, *J* = 6.5, 10.1, 1 H), 2.16−2.08 (m, 2 H), 1.96−1.90 (m, 1 H), 1.93 (s, 3 H), 1.84−1.75 (m, 1 H), 1.29 (s, 18H), 1.20 (d, *J* = 6.3, 3 H); MS (ESI, Q-tof) 474.4 (100); mol formula $C_{33}H_{48}BrNO$ (554.64); HRMS $C_{33}H_{48}NO^+$ (474.3736) calcd 474.3736, found 474.3723; TLC R_f 0.30 (CH_2Cl_2/MeOH, 9:1) [I_2].

*Preparation of rel-(1R,3R,5S,5aS,7aS,7bR)-Octahydro-1-benzyloxy-3-(4-methoxybenzyl)-5-methyl-7b-methylcyclopenta[gh]pyrrolizinium Bromide (**β-V**{1,2,8}).* Data for β-V{*1,2,8*}: yield 39 mg (92%), free-flowing white powder; ^{1}H NMR (500 MHz, $CDCl_3$) 7.54 (d, *J* = 8.7, 2 H), 7.44−7.32 (m, 5 H), 6.93 (d, *J* = 8.7, 2 H), 5.07 (d, *J* = 12.0, 1 H), 4.70 (d, *J* = 11.7, 1 H), 4.59 (d, *J* = 11.7, 1 H), 4.58 (d, *J* = 12.1, 1 H), 4.41 (dd, *J* = 11.9, 11.9, 1 H), 4.09 (d, *J* = 3.0, 1 H), 4.02 (d, *J* = 14.0, 1 H), 3.82 (s, 3 H), 3.60 (d, *J* = 11.7, 1 H), 3.25 (dd, *J* = 6.0, 11.3, 1 H), 2.68 (dd, *J* = 9.1, 9.1, 1 H), 2.50 (dd, *J* = 5.8, 10.0, 1 H), 2.27−2.19

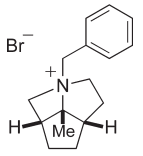


β-V{*1,2,8*}

(m, 1 H), 2.16−2.07 (m, 1 H), 2.01 (s, 3 H), 1.88−1.65 (m, 3 H), 1.22 (d, *J* = 6.3, 3 H); MS (ESI, Q-tof) 392.3 (100); mol formula $C_{26}H_{34}BrNO_2$ (472.46); HRMS $C_{26}H_{34}NO_2^+$ (392.2590) calcd 392.2590, found 392.2582; TLC R_f 0.19 (CH_2Cl_2/MeOH, 9:1) [I_2].



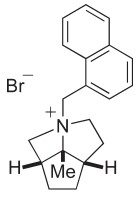
*Preparation of Quaternary Ammonium Bromides **VI**{1−3}*. Following general procedure II, amino borane **S9** (453 mg, 3.0 mmol) was added to a 100 mL round-bottomed flask as a solution in 100 mL of MeOH (0.03 M). The flask was fitted with a reflux condenser, a magnetic stir bar, and a nitrogen inlet adapter. Lastly, 1.0 N aq HCl solution (15 mL, 5.0 equiv) was added via syringe. The resulting solution was heated and then concentrated by rotary evaporation (15 mmHg, 20−25 °C) as described in general Procedure II. The resulting free amine was dissolved in acetonitrile and was distributed among three test tubes that were subsequently charged with benzyl bromide (tube 1, 142 μL, 1.2 mmol, 1.2 equiv), 1-bromomethylnaphthalene (tube 2, 308 mg, 1.4 mmol, 1.2 equiv), and 9-bromomethylanthracene (tube 4, 179.5 mg, 0.662 mmol, 1.0 equiv). After being agitated for 12 h, the reaction mixtures were worked up and the products isolated and purified as described in general procedure II.



VI{*1*}

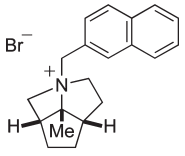
*Preparation of rel-(1S,3aS,5aR,5bR)-1-Benzyl-5b-methylcyclopenta[ef]azoniabicyclo[3.2.0]heptane Bromide (**VI**{1}).* Data for **VI**-{*1*}: yield 33 mg (87%), free-flowing white powder; mp 222−223 °C (CH_3CN/Et_2O, decomposition); ^{1}H NMR (500 MHz, $CDCl_3$) 7.78 (d, *J* = 8.2, 2 H, HC(12)), 7.323−7.244 (m, 1 H, HC(13), 1 H, HC(14)), 5.31 (d, *J* = 12.1 1 H, HC(10)), 5.09 (t, *J* = 12.0 1 H, HC(1)), 4.72 (d, *J* = 12.1, 1 H, HC(10)), 4.18 (dt, *J* = 12.1, 4.77, 1 H, HC(7)), 3.31−3.29 (m, 1 H, HC(2)), 3.07 (dd, *J* = 6.3, 12.0 1 H, HC(1)), 3.00 (dd, 1 H, HC(6)), 3.08−2.86 (m, 2 H, HC(5), HC(7)), 2.40 (p, *J* = 7.05, 1 H, HC(3)), 2.03−1.94 (m, 2 H, HC(3), HC(4)), 1.923 (s, 3 H, H_3C(9)), 1.90−1.72 (m, 2 H, HC(4), HC(6)); MS (ESI, Q-tof) 230 (2), 229 (17), 228 (100) 134 (5), 91 (9); TLC R_f 0.12 (CH_2Cl_2/MeOH, 9:1) [I_2]; mol formula $C_{16}H_{22}BrN$ (308.26). Anal. Calcd for $C_{16}H_{22}N^+$ (228.17): C, 62.34; H, 7.19; N, 25.90. Found: C, 62.01; H, 6.79; N, 26.01.

*Preparation of rel-(1S,3aS,5aR,5bR)-1-(1-Naphthylmethyl)-5b-methylcyclopenta[ef]-azoniabicyclo[3.2.0]heptane Bromide **VI**{2}.* Data for **VI**{*2*}: yield 217 mg (52%), free-flowing white powder; mp 182−183 °C (CH_3CN/Et_2O, decomposition); ^{1}H NMR (500 MHz,



VI{*2*}

$CDCl_3$) 8.47 (d, *J* = 8.8, 1 H, HC(19)), 8.13 (d, *J* = 7.1, 1 H, HC(13)), 7.80 (d, *J* = 8.1, 1 H, HC(12)), 7.61 (t *J* = 7.7, 1 H, HC(14)), 7.48 (t *J* = 7.4, 1 H, HC(18)), 7.38 (t *J* = 7.7, 1 H, HC(17)), 5.70 (d, *J* = 13.2, 1 H, HC(10)), 5.31 (d, *J* = 13.2, 1 H, HC(10)), 5.18 (t *J* = 11.1, 1 H, HC(1)), 4.21 (dt *J* = 11.84, 7.08, 1 H, HC(7)), 3.421−3.364 (m, 1 H, HC(2)), 3.07 (dd, *J* = 11.8, 5.29, 1 H, HC(1)), 3.03−2.97 (m, 1 H, HC(5)), 2.90 (dd, 11.71, 6.6 1 H, HC(7)), 2.41 (p, 7.3 1 H, HC(6)), 2.1 196 s, 3 H, HC(9)), 2.18−2.0 (m, 1 H, HC(6)), 1.8−1.95 (m, 5 H, HC(3, 6)), HC(4)), HC(6)); ^{13}C NMR(126 MHz, $CDCl_3$) 133.8, 132.2, 132.1, 130.8, 129.0, 127.6, 126.2, 125.3, 124.9, 123.8, 96.9, 62.8, 62.3, 55.5, 50.5, 35.5, 30.5, 29.6, 28.1, 19.5; MS (ESI, Q-tof) 279 (10), 278 (100); mol formula $C_{20}H_{24}BrN$ 358.31; HRMS $C_{20}H_{24}N^+$ (278.1909) calcd (278.1909), found 278.1904; TLC R_f 0.15 (CH_2Cl_2/MeOH, 9:1) [I_2].



VI{*3*}

Preparation of rel-(1S,3aS,5aR,5bR)-1-(2-Naphthylmethyl)-5b-methylcyclopenta[ef]azoniabicyclo[3.2.0]heptane Bromide ***VI****-*{*3*}. Data for **VI**{*3*}: ^1H NMR (500 M, $CHCl_3$) 8.30 (s, 1 H), 7.77 (m, 4 H), 7.46 (m, 2 H), 5.56 (d, 1 H, *J* = 12.2), 5.19 (t, 1 H, *J* = 10.9), 4.97 (d, 1 H, *J* = 12.2), 4.22 (dt, 1 H, *J* = 7.6, *J* = 11.9), 3.38 (td, 1 H, *J* = 4.7, *J* = 13.3), 3.03 (m, 2 H), 2.94 (dd, 1 H, *J* = 8.0, *J* = 13.1), 2.46 (td, 1 H, *J* = 7.5, *J* = 14.8), 2.12 (m, 1 H), 2.05 (s, 3 H), 1.84 (m, 4 H); MS (ESI, Q-tof) 279.2 (32), 278.2 (100), 149.0(8); mol formula $C_{20}H_{24}NBr$ 358.32; HRMS ($C_{20}H_{24}N^+$, 278.1909) calcd 278.1909, found 278.1917; TLC R_f 0.17 (CH_2Cl_2/MeOH, 9/1) [I_2].

■ ASSOCIATED CONTENT

Supporting Information. All of the kinetic runs for each catalyst, enantioselectivity determination and stirring rate experiments, and copies of ^1H and ^{13}C NMR spectra of all intermediates and selected catalysts. This material is available free of charge via the Internet at http://pubs.acs.org.

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(79) For the details of the synthesis, see the Supporting Information.

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