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Synthetic Studies toward Halichlorine: Complex Azaspirocycle Formation with Use of an NBS-Promoted Semipinacol Reaction

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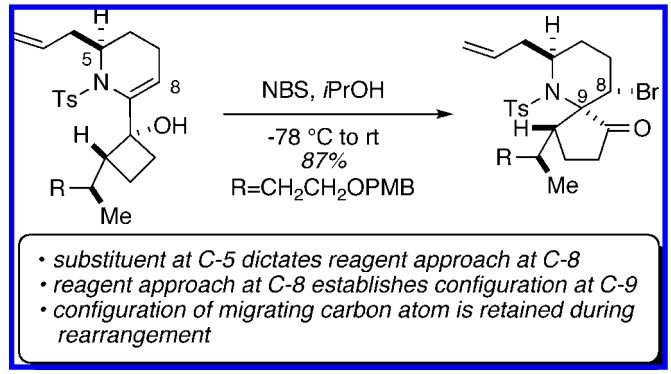

The investigations of a synthetic route incorporating a NBS-promoted semipinacol rearrangement to the 6-azaspiro[4.5]decane fragment within halichlorine (**1**) are presented. A convergent approach was pursued, utilizing two chiral, enantiomerically enriched building blocks, 2-trimethylstannyl piperidene **10** and substituted cyclobutanone **19**. Noteworthy synthetic operations in this study include the following: (a) a highly diastereoselective NBS-promoted semipinacol reaction that established four stereogenic centers in ketone **25** and (b) the use of a *N*-*p*-toluenesulfonyl-2-iodo-2-piperidene as a precursor to a basic organometallic reagent, which was critical to the success of the coupling of fragments **10** and **19**.

Introduction

In 1996, Uemura and co-workers analyzed extracts from the marine sponge *Halichondria okadai* Kadota. From these extracts, they isolated a novel compound, halichlorine (**1**), that was observed to inhibit vascular cell adhesion molecule-1 (VCAM-1) with reasonable efficiency (Figure 1).[1] Two structurally related alkaloids, pinnaic acid and tauropinnaic acid, were discovered later by the Uemura group.[2] The novelty of the structures of these secondary metabolites has inspired a large number of synthetic chemists. That these compounds also possessed interesting biological activity renders them, and their synthetic derivatives, of interest to a broader set of engaged scientists.

As these compounds are appealing targets for the synthetic community, a significant amount of work related to the synthesis

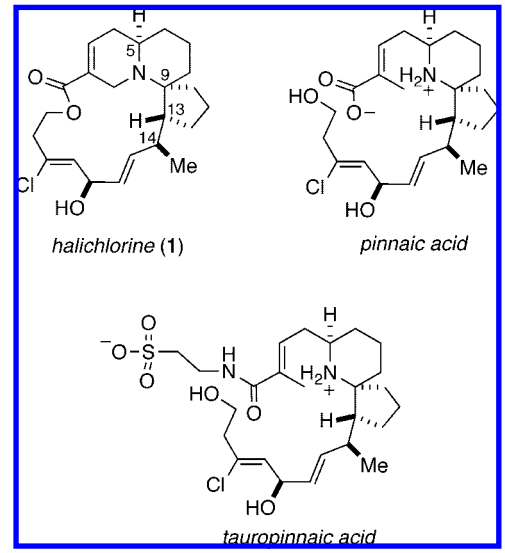

FIGURE 1. Halichlorine, pinnaic acid, and tauropinnaic acid.

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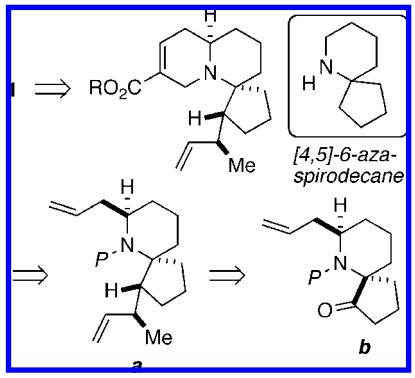
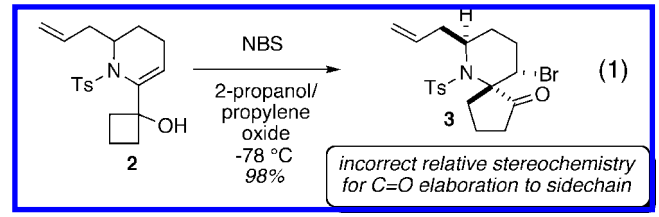


FIGURE 2. An analysis of **1**.

of these compounds has been disclosed since their discovery. This work (up to 2005) has been summarized in an excellent review.[3] The groups of Danishefsky, Heathcock, and Uemura each have reported completed total syntheses of either halichlorine or pinnaic acid.[4] Other groups have completed significant progress to the tricyclic core of halichlorine to construct relay compounds for the formal total syntheses of these natural products.[5] A number of groups have developed new methods for the formation of the [4.5]-6-azaspirodecane ring system within **1**.[6] Our interest in the synthesis of alkaloids that contain spiro-fused ring systems led us to consider **1** as an engaging target for synthesis.[7]

The [4.5]-6-azaspirodecane ring system embedded within **1** served as our inspiration for a possible synthetic route (Figure 2). Our initial analysis centered on the deconstruction of the natural product to a spirocyclic system **a** followed ultimately to an azaspirocyclic ketone represented by **b**. It was envisioned that a compound such as **b** could be generated by using a semipinacol reaction that proceeds through either an azacarbenium ion or an intermediate having azacarbenium ion character. To this end, our research group developed a set of semipinacol processes forming azaspirocyclic ketones.[8,9] One method in the set involved reaction between a *N*-sulfonyl enamide (enesulfonamide) and *N*-bromosuccinimide (NBS) at low temperature. The putative bromonium ion (or bromine−alkene π-complex) intermediate then induced a semipinacol process with simultaneous ring expansion.[8a,b,10] These reactions have the capability of producing azaspirocyclic ketone products in a highly selective manner. As an instructive example, the reaction between cyclobutanol **2** and NBS produced cyclopentanone **3**as a single diastereomer (eq 1). The diastereomer that is produced is important to the halichlorine problem. The relative configurations of the chirality centers in **3** result from (a) the approach of the electrophilic brominating reagent on the opposite face of the 6-allyl substituent of the heterocycle and (b) the *anti*-orientation of the semipinacol process. Consequently, the configuration of the 3° spirocyclic carbon atom in **3** has the alkyl group that migrated in the semipinacol reaction trans to the bromine substituent. In considering the elaboration of the ketone functional group in **3** in a manner to establish the C13−C14 bond of **1**, it is immediately recognizable that compound **3** possesses the *incorrect* relative stereochemical configuration for the successful synthesis of **1**.



This observation led us to devise a new synthetic approach toward **1** (Figure 3). In reconsidering the ring system and its substituents present in **a**, we considered a possible solution that avoided use of the ketone function to establish the C13−C14 bond. Rather, the C13−C14 bond of the target system **a** would be incorporated directly in the semipinacol substrate. It is well-established that, barring unusual geometrical stereoelectronic constraints,[11] more substituted alkyl groups preferentially perform 1,2-shifts, with retention of configuration of the migrating center, to electrophilic atoms.[12] The substrate required for such a semipinacol ring expansion reaction could ultimately derive from a carbonyl addition reaction between an organometallic of structure **c** and a substituted cyclobutanone **d**.

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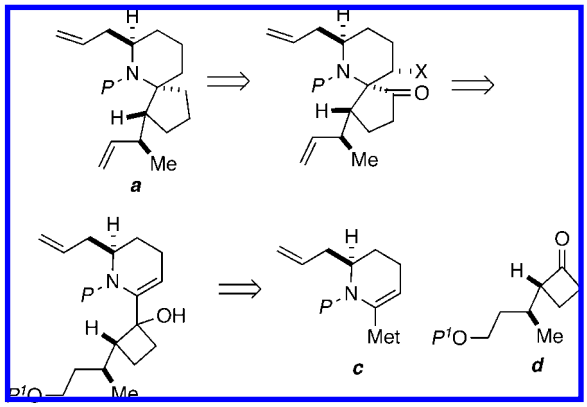
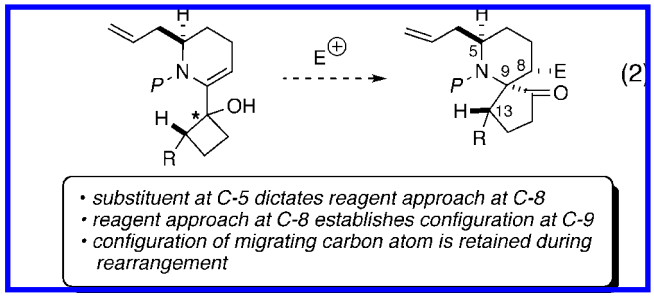


FIGURE 3. A revised analysis of **1**.

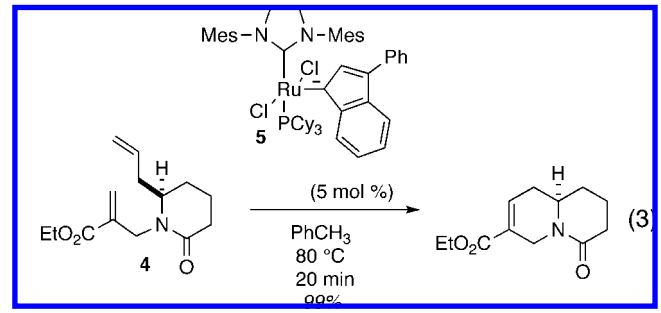
The proposed semipinacol transformation, if successful, would provide a spirocyclic synthetic intermediate with its relative configurations established at C5, C9, C13, and C14 (eq 2). As predicted from our previous work, the electrophile approach to the substrate would occur on the face opposite to that of the allyl substituent. This process would in turn dictate the configuration of the 3° carbon center as the migrating alkyl group would be expected to be delivered *anti* to that electrophile. In this way the configuration at C9 would be established by relayed substrate control from C5. Set correctly in the semipinacol precursor, the configurations at C13 and C14 should be retained throughout the semipinacol process. In terms of the stereochemical outcome, the relative stereochemistry of the 3° carbinol center (starred) should be irrelevant to the proposed transformation. However, one might expect that the behavior of each diastereomeric cyclobutanol will differ in terms of reaction efficiency—whether or not the semipinacol process proceeds at all and/or the rate of each semipinacol reaction 2.



Despite the attraction of using a synthetic route that establishes four stereogenic centers, there are some obvious drawbacks and concerns. These include the following: (a) the necessity to produce both the heterocyclic organometallic **c** and the substituted cyclobutanol **d** individually in enantioenriched form; (b) the efficiency of the proposed carbonyl addition reaction between **c** and **d**; (c) the efficiency and stereofidelity of the proposed semipinacol transformation; and (d) the installation of ultimately superfluous functional groups—the bromine substituent and the carbonyl function—that, having served their synthetic purpose, would require removal before elaboration to **1** was possible. A number of questions arose from this analysis. Would the (presumably axially oriented) allyl substituent induce a high degree of steric strain in the semipinacol transition state? Does the configuration of the carbon that is migrating into a 1,3-diaxial relationship with this allyl substituent have to be retained? Would the formative 1,3 diaxial relationship in the semipinacol reaction transition state introduce too high a reaction barrier? In our view, although this synthetic route contained (a great deal of) recognized risk, we believed these questions dealing with structure and reactivity posed were worth examination. This report describes our investigations of a route to halichlorine that would utilize a semipinacol process as described in eq 2 as a crucial step.

Results and Discussion

Metathesis-Based Formation of the Bicyclic Core and Fragment Synthesis. Very early on in our studies, we had determined to use ring-closing metathesis to form the tricyclic ring system of **1**.[13] We briefly studied this transformation on model substrate **4** (eq 3). As this metathesis-based approach has since been reported by Kibayashi in the literature in a formal total synthesis of **1**,[5c,d] our work on this transformation merits comment only for one specific reason. We prepared ruthenium catalyst **5**, which is surprisingly not previously reported in the literature. The desired transformation was completed in 20 min with use of 5 mol % of **5** at 80 °C. This result compares favorably to other catalyst systems that require 2−24 h to catalyze similar transformations.[14] Satisfied that the metathesis process had a reasonable probability for success, we began the construction of fragments **c** and **d** in earnest.



It was envisioned that an organometallic such as **c** could be derived from transmetalation of an alkenylstannane, as in our previous work.[8a,c] The construction of the necessary alkenylstannane commenced with known chiral alcohol **6**, prepared by

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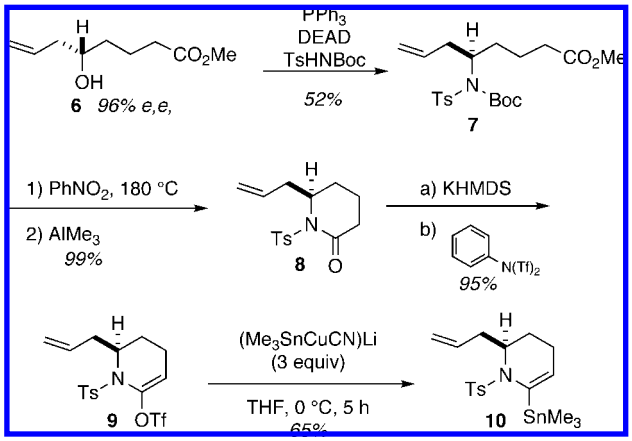
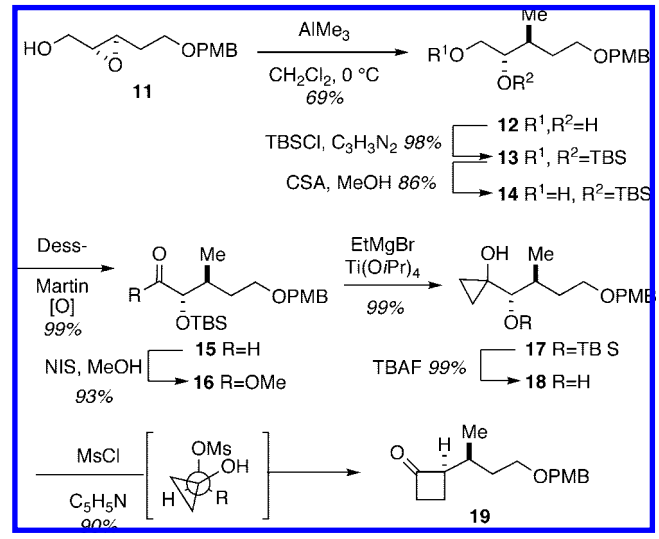
SCHEME 1. Preparation of Alkenylstannane 10.



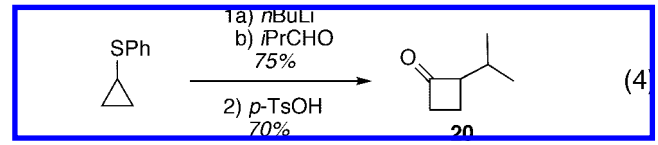
using the method of Brown (Scheme 1).[15] The Mitsonobu reaction of **6** with TsNHBoc proceeded without incident (52% yield).[16] Conversion to lactam **8** was performed by thermal removal of the Boc protecting group followed by $AlMe_3$-promoted lactamization.[17] The lactam was elaborated to its enol triflate by using standard conditions (KHMDS, *N*-phenyltriflimide, 95%). The formation of the alkenylstannane moiety with Pd(0) catalysis with hexamethyldistannane as we had done previously was very low-yielding in this instance.[8a,c,18] Consequently, an alternative method was developed. McMurry had previously shown that lithium dialkylcuprates would undergo coupling with ketone-derived enol triflates.[19] We postulated that a similar process would be possible using the stannylcuprates studied by Piers.[20] In a single example, work in the Piers group had shown that stannylcuprate insertion forming a new C−Sn bond occurred at a triflate placed at the β-position of an α,β-unsaturated enoate. Consequently, the mechanisms of this earlier transformation and our proposed process might differ. The success of our proposed transformation was not assured. In the event, however, the treatment of enol triflate **9** with lithium trimethylstannyl copper(I) cyanide (3 equiv) in THF at 0 °C formed the desired alkenylstannane **10** in 65−73% yields (scale dependent). As alkenylstannanes are necessary components for Stille cross-coupling reactions, this method could prove to be quite useful as an alternative technique for their formation.

A synthetic route reliant on the method of Cha was used for the construction of a chiral-substituted cyclobutanone such as **d** (Scheme 2).[21] This route began by using the known epoxide **11**.[22] Ring-opening of the epoxide was performed with $AlMe_3$ to produce 1,2-diol **12**. Selective oxidation of the 1° hydroxyl group of **12** proved difficult, and so a circuitous route was used. Protection of both hydroxyl groups with TBSCl and imidazole was followed by careful deprotection of the less-hindered silyl ether. Oxidation to methyl ester **16** was performed in a highly efficient manner with use of a two-step procedure (Dess−Martin

SCHEME 2. Synthesis of Functionalized Cyclobutanone 19.



reagent;[23] NIS, K_2CO_3, MeOH, 93% for two steps). This conversion of aldehydes to methyl esters by using the NIS method described by McDonald is recommended.[24] The methyl ester was then subjected to a Kulinkovich cyclopropanation reaction, providing cyclopropanol **17** in essentially quantitative yield.[25] The silyl ether was cleaved, and activation of the resulting 2° alcohol with MsCl in pyridine resulted in smooth ring expansion to produce cyclobutanone **19**. The relative stereochemical configurations within **19** were not rigorously established at this time, but indirect support for the assignments comes from X-ray crystallographic analysis of a compound produced later. Synthetic routes to vinylstannane **10** and cyclobutanone **17** were established. At this stage our challenge was the reaction between these two fragments. As we anticipated that this carbonyl addition reaction might be difficult, an alternative, "sacrificial" substrate for model studies, 2-isopropylcyclobutanone (**20**), was prepared by using literature methods (eq 4).[26]



Carbonyl Addition. The standard procedure that we developed to perform similar carbonyl addition reactions on simpler compounds involved the following: (a) transmetalation of the alkenylstannane with 2.2 equiv of methyllithium in diethyl ether at 0 °C; (b) in some cases, addition of a metal salt for transmetalation (typically 2.6 equiv of $MgBr_2$) at −78 °C; and (c) addition of cyclobutanone (2.7 equiv) in diethyl ether at

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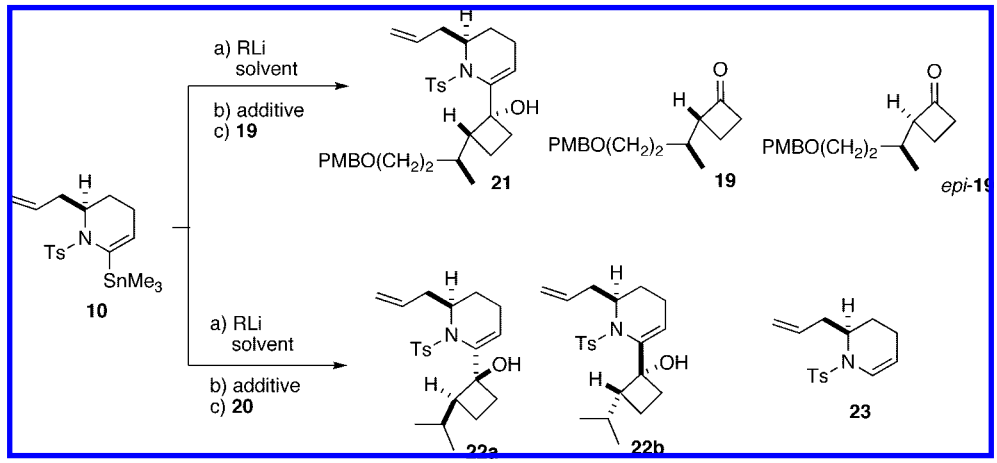
(25) (a) Kulinkovich, O. G.; de Meijere, A. *Chem. Rev.* **2000**, *100*, 2789–2834. (b) Kulinkovich, O. G.; Sviridov, S. V.; Vasilevskii, D. A.; Prityts kaya, T. S. *Zh. Org. Khim.* **1989**, *25*, 2244. (c) Kulinkovich, O. G.; Sviridov, S. V.; Vasilevskii, D. A.; Savchenko, A. I.; Prityts kaya, T. S. *Zh. Org. Khim.* **1991**, *27*, 294. (d) Kulinkovich, O. G.; Sorokin, V. L.; Kel'in, A. V. *Zh. Org. Khim.* **1991**, *29*, 66.
(26) (a) Nordvik, T.; Brinker, U. H. *J. Org. Chem.* **2003**, *68*, 9394–9399. (b) Trost, B. M.; Keeley, D. E.; Arndt, H. C.; Bogdanowicz, M. J. *J. Am. Chem. Soc.* **1977**, *99*, 3088–3100.

SCHEME 3. An Inefficient Carbonyl Addition Reaction



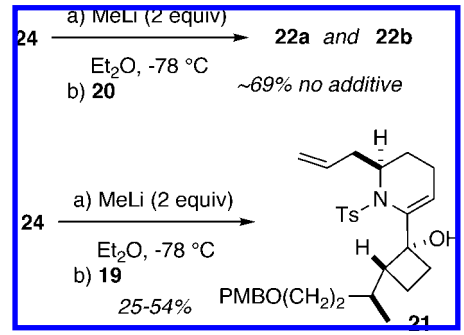
temperatures at or near −100 °C. Clearly, the inherent value within **19** (chiral nonracemic; 14-step construction) compared to cyclobutanone would force a search for experimental parameters that maintained, as best as possible, a 1:1 stoichiometry between **10** and **19**. Trial experiments were carried out with use of 1 equiv of **19** or **20** (Scheme 3).

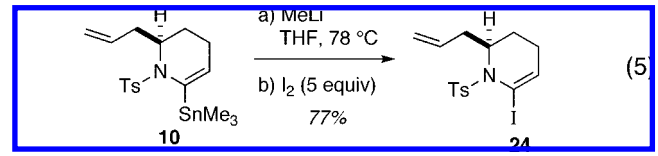
The first experiment that replicated the conditions stated above provided the desired cyclobutanol **21** (25%), unreacted ketone **19** (39%) and its epimer, *epi*-**19** (6%). These compounds were inseparable by chromatography with use of any number of solvent conditions. The presence of ketone **19** in the reaction mixture obviously suggested that a deprotonation-derived reaction path was competitive with the desired carbonyl addition reaction. Similar results for the reaction between **10** and **20** were obtained. As expected, two diastereomeric cyclobutanols **22a** and **22b** were obtained. Both of these diastereomers resulted from carbonyl addition on the less-hindered face of the racemic ketone **20**. A combined yield of 14% for the diastereomeric pair was typical.

Substantial effort to improve this process was expended. Factors that were examined included the following: reaction temperature; the solvent for the tin−lithium exchange process; the solvent for the carbonyl addition process; the effect of (transmetalative) additives such as magnesium bromide, cerium(III) chloride, or ytterbium(III) triflate; and the effect of Lewis acidic additives such as titanium(IV) chloride, boron trifluoride•diethyl etherate among others, reagent stoichiometry, and reagent order of addition. Substantial improvements to this reaction were not made. Significantly, the tin−lithium exchange reaction lacked reproducibility. It was observed that this transmetalation process occurred very rapidly and effectively in THF, but quite poorly and/or irreproducibly in diethyl ether. Unfortunately, the carbonyl addition reaction only proceeded in high yields when diethyl ether was the solvent. Attempts to "titrate" a minimum amount of additive or solvent to the reaction mix in the first step to facilitate the tin−lithium exchange process were unsuccessful. Similarly, attempts to perform a "solvent switch" from THF to diethyl ether between the tin−lithium exchange and the carbonyl addition reaction failed. It appeared that an impasse was reached. Unless a reasonable solution for this carbonyl addition problem was found, the project as a whole would founder.

An alternative to tin−lithium exchange was then considered. As is well-known, alternative conditions for generating organolithium species can involve either deprotonation or halogen-lithium exchange. Deprotonation was not believed to be applicable in this instance as attempts in our laboratory to lithiate compounds similar to **23** with use of *s*-BuLi resulted in reaction on the aromatic ring. We therefore decided to explore halogen−metal exchange. After some experimentation, it was found that tin−lithium exchange of alkenylstannane **10** in THF followed by the addition of iodine (5 equiv) proceeded smoothly to produce the alkenyl iodide **24** (eq 5). Attempts to synthesize **24** by mixing **10** with electrophilic iodine sources were unsuccessful. Unsurprisingly, **24** would decompose within hours on the bench at rt but, somewhat to our surprise, could be stored indefinitely in a foil-wrapped vial in a freezer.

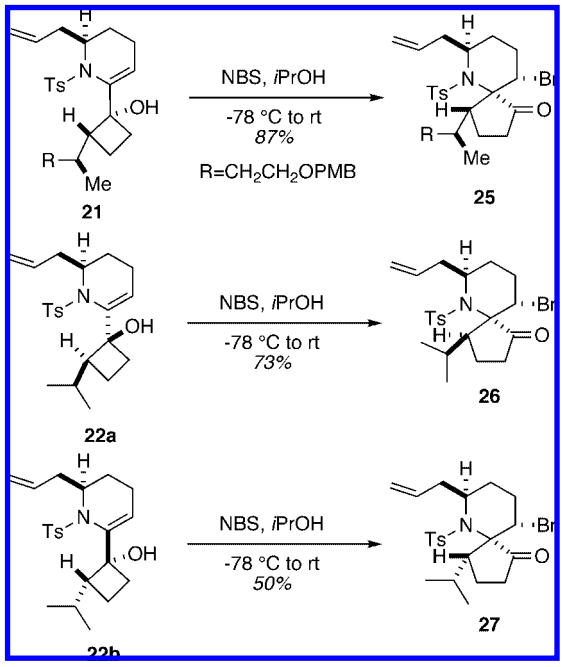
SCHEME 4. Carbonyl Addition Reaction with 24





Treatment of alkenyl iodide **24** with 2 equiv of MeLi in diethyl ether, followed by **20** produced the desired cyclobutanols **22a** and **22b** in ~69% yield (Scheme 4). This procedure was reproducible and gave consistent results for each trial. This procedure was then applied to the more complex cyclobutanone **19**. This procedure did provide sufficient amounts of **21** for further study, but at yields (25−54%) that were disappointing. After reasonably successful trials with **24** and **19** on milligram scale in which **19** was consumed, our reactions at gram-scale did not proceed as well. Consequently at gram scale, the isolated cyclobutanol derivative **21** was contaminated with the chromatographically inseparable ketone **19**. In the end, we were

SCHEME 5. Ring Expansion Reactions of Complex Substrates



forced to treat the mixture of **19** and **21** with lithium triethylborohydride and then separate to acquire **21**.

Ring Expansion. The crucial ring expansion reaction could then be examined (Scheme 5). To our delight, the treatment of cyclobutanol **21** with NBS in *i*-PrOH provided the desired spirocyclic ketone **25** in 87% yield. The presence of the ketone functional group was supported by IR and ^{13}C NMR data (1747 cm^{-1} and 215.5 ppm). Stereochemical assignments were made initially by using NMR methods (Figure 4). The hydrogen on the bromine-substituted carbon in **25** was assigned to be pseudoaxial on the basis of its large coupling constants (δ 4.32, J = 12, 5 Hz). NOESY correlations were used to support stereochemical assignments. Importantly, it was envisoned (assumed) that **25** resided in a boat-type conformation. This assumption was based by analogy with the structurally related compound **3** that has a boat-type conformation in the solid state.[8a] Significant NOE correlations between the protons identified as H_4, H_{10}, and H_{31b} strongly support the assignment that the bromine atom and the ketone attached to the spirocenter are on the same face of the piperidine ring. Eventually, the structure and relative stereochemical assignments were confirmed by using X-ray crystallography of a derivative (vide infra). The reactions of **22a** and **22b** with NBS gave similar results. That these ring expansions worked efficiently as designed was extremely satisfying. In each instance, the more substituted alkyl group underwent preferential migration, with retention of configuration, in an *anti* process, providing a single diastereomeric product. Potential complications due to steric clashing between the allyl substituent and the migrating group during the semipinacol reaction did not appear to be significant.

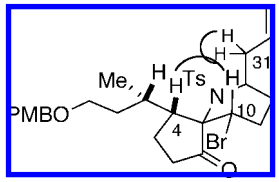
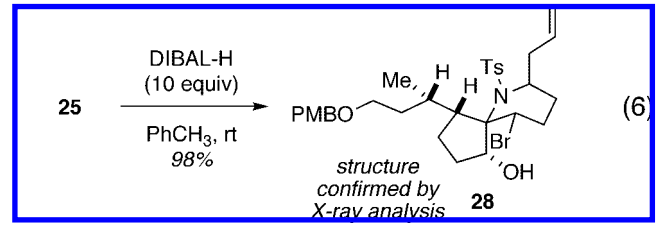


FIGURE 4. NOE experiments supporting assignment of **25**.

Attempts to form crystals of **25** that were amenable to X-ray analysis were unsuccessful. The reaction of **25** with excess DIBAL-H (10 equiv) produced alcohol **28** (eq 6). The NMR spectra of **28** were unusual because the molecule's fluxional behavior in solution led to broad and poorly defined signals. Fortunately, recrystallization of **28** led to the isolation of X-ray quality crystals that provide evidence for the structural constitution of stereochemical assignments of **25**. The solid-state structure confirms that the most-substituted group did migrate in the NBS-promoted ring-expansion reaction. In the reduction reaction, hydride was delivered to the ketone face that is hindered by the bromine atom and not the face blocked by the *p*-tolylsulfonyl group and the C4 side chain.



Obviously, we were delighted by the success of the semipinacol process. This sequence had produced a compound that *might* serve as a viable intermediate for a halichlorine synthesis. Key objectives that would need to be performed include the removal of the *p*-toluenesulfonyl protecting group, the bromine function, and the ketone functional group. Unfortunately, preliminary investigations to achieve these objections produced some unexpected results. For example, the reaction of spirocyclopentanone **25** with Bu_3SnH and AIBN in PhH lead to the formation of a new compound, **29**, whose spectral data clearly established a compound lacking both the bromine and *p*-toluenesulfonyl functionality (Scheme 6). Spectroscopic experiments eventually established its structure. Its formation involves a Dowd−Beckwith rearrangement,[27] followed by explusion of a *p*-toluenesulfonyl group. Proton transfer processes produce the indicated vinylogous amide **29**.

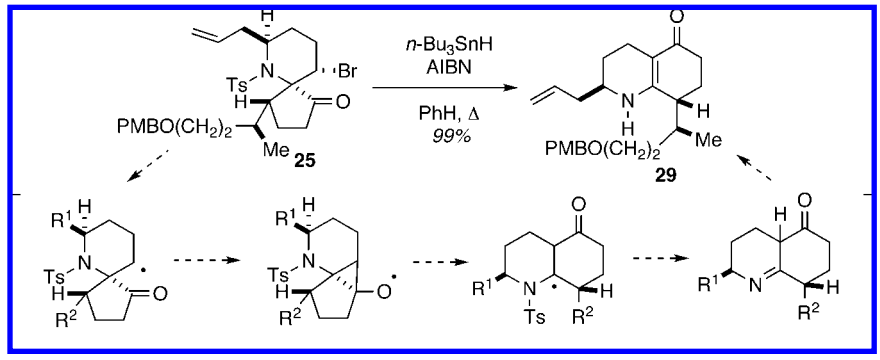
The process outlined in Scheme 6 highlights difficulties often found in our further investigations. The juxtaposition of the functional groups within **25** could not be dealt with in a satisfactory manner. We are currently designing an optimized approach to the spirocyclic core of **1** that will enable (a) the replacement of the *p*-toluenesulfonyl protecting group on nitrogen for a different, more readily removable group, (b) the development of a more efficient synthesis of cyclobutanol **21**, and (c) the possibility of utilizing an alternative electrophile to initiate the semipinacol process.

Concluding Remarks

The synthetic studies in this work uncovered a number of useful observations. The use of a semipinacol reaction to form a highly functionalized azaspirocyclic compound as a single diastereomer proceeded very efficiently as designed. Further noteworthy points included the use of a stannylcuprate reagent for the construction of an alkenylstannane, and the formation and use of an unusual 2-iodoenesulfonamide. The power of the semipinacol process to generate complex structures in a predict-

(27) (a) Dowd, P.; Choi, S. C. *J. Am. Chem. Soc.* **1987**, *109*, 3493–3494. (b) Dowd, P.; Choi, S. C. *J. Am. Chem. Soc.* **1987**, *109*, 6548–6549. (c) Beckwith, A. L. J.; O'Shea, D. N.; Westwood, S. W. *J. Am. Chem. Soc.* **1988**, *110*, 2565–2575.

SCHEME 6. Formation of the Undesired Fused Ring System



able fashion bodes well for its use in the formation of alkaloid ring systems.

Experimental Section

(+)-(2*R*)-2-Allyl-1-(toluene-4-sulfonyl)-6-trimethylstannyl-1,2,3,4-tetrahydropyridine (10). To a stirred solution of 7.60 g of hexamethyldistannane (23.2 mmol, 3 equiv) in 120 mL of THF at −41 °C was added 14.5 mL of methyllithium (23.2 mmol, 3 equiv, 1.6 M in diethyl ether (Aldrich)) and the mixture was warmed to 0 °C for 20 min. After the reaction mixture was cooled to −41 °C, copper(I) cyanide (2.08 g, 23.2 mmol, 3 equiv) was added and the resulting mixture was stirred at −41 °C for 20 min. A solution of 3.29 g of enol triflate **9** (7.73 mmol, 1 equiv) in 60 mL of THF was added and the resulting mixture was stirred at 0 °C for 5 h. An aqueous solution of ammonium chloride−ammonium hydroxide (pH ∼8, 100 mL) was added and the resulting mixture was stirred at rt until the aqueous layer turned blue. Diethyl ether (200 mL) and 200 mL of water were added and the layers were separated. The aqueous layer was extracted with diethyl ether (2 × 200 mL). The combined organic layers were dried over magnesium sulfate then filtered, and solvents were removed under reduced pressure. Purification by column chromatography on silica gel (15% diethyl ether−petroleum ether) gave 2.20 g (65%) of a pale yellow oil.

$[\alpha]^{23.5}_D$ +97.8 (*c* 1.005, $CHCl_3$). IR (NaCl) 2926, 1643, 1598, 1342, 1166 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, J = 8.5 Hz, 2H), 7.24 (d, J = 7.7 Hz, 2H), 5.76 (dddd, J = 16.1, 11.2, 7.3, 6.9 Hz, 1H), 5.26 (t, J = 21 Hz, 1H), 5.01 (br s, 1H), 4.97 (d, J = 6.9 Hz, 1H), 3.94−3.85 (m, 1H), 2.34 (s, 3H), 2.35−2.25 (m, 1H), 2.07 (dt, J = 14.3, 7.3 Hz, 1H), 1.98−1.81 (m, 1H), 1.76−1.57 (m, 1H), 1.41−1.31 (m, 1H), 0.89−0.70 (m, 1H), 0.19 (s, J_{Sn-H} = 27.7 Hz, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.0, 138.9, 136.4, 134.8, 129.5, 127.1, 124.0, 117.1, 53.0, 35.4, 21.9, 21.5, 19.4, −6.1. LRMS for $C_{18}H_{27}NO_2S^{120}Sn$ (ESI^+) *m*/*z* (rel intensity) 464 (M^+ + K, 16.3), 442 (M^+ + Na, 100), 323 (68.9).

(−)-(2*S*,3*S*)-Methyl 5-(4-methoxybenzyloxy)-2-(*tert*-butyldimethylsilyloxy)-3-methylpentanoate (16). A 250-mL foil-wrapped round-bottomed flask was charged with 4.59 g of aldehyde **15** (12.5 mmol, 1 equiv) and 126 mL of methanol. *N*-Iodosuccinimide (7.04 g, 31.3 mmol, 2.5 equiv) and 4.32 g of potassium carbonate (31.3 mmol, 2.5 equiv) were added and the resulting mixture was stirred at rt for 2 d. Water (200 mL) and 9 g of sodium thiosulfate·pentahydrate were added and the resulting mixture was stirred at rt until the solution became colorless (∼10 min). Diethyl ether (400 mL) was added and the layers were separated. The aqueous layer was extracted with diethyl ether (2 × 200 mL). The combined organic layers were dried over magnesium sulfate then filtered, and solvents were removed in vacuo. Purification by column chromatography on silica gel (15% diethyl ether−petroleum ether) gave 4.61 g (93%) of a clear colorless oil.

$[\alpha]^{23.8}_D$ −20.94 (*c* 0.999, $CHCl_3$). IR (thin film) 2954, 1756, 1614, 1515, 1250 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, J = 8.9 Hz, 2H), 6.84 (d, J = 8.9 Hz, 2H), 4.38 (dd, J = 22.3, 11.6 Hz, 2H), 4.05 (d, J = 4.6 Hz, 1H), 3.77 (s, 3H), 3.66 (s, 3H), 3.50−3.38 (m, 2H), 2.10−2.10 (m, 1H), 1.81−1.71 (m, 1H), 1.49−1.38 (m, 1H), 0.92 (s, J = 6.7 Hz, 3H), 0.89 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 159.0, 130.7, 129.1, 113.7, 76.4, 72.3, 67.9, 55.1, 51.4, 34.9, 31.0, 25.7, 18.2, 16.2, −5.1, −5.5. Anal. Calcd for $C_{21}H_{36}O_5Si$: C, 63.60; H, 9.15. Found: C, 63.63; H, 9.38.

(−)-(1*S*,2*S*)-1-[4-(4-Methoxybenzyloxy)-1-(*tert*-butyldimethylsilyloxy)-2-methylbutyl]cyclopropanol (17). To a stirred solution of 4.61 g of ester **16** (11.6 mmol, 1 equiv) and 2.92 mL of 95% chlorotitanium(IV) trisisopropoxide (3.19 g, 11.6 mmol, 1 equiv, (Aldrich)) in tetrahydrofuran at rt was added 19.4 mL of ethylmagnesium bromide (58.1 mmol, 5 equiv, 3 M in diethyl ether (Aldrich)) over 1 h. The resulting solution was stirred at rt for 5 h. Diethyl ether (500 mL) and 100 mL of 1 M aqueous hydrochloric acid were added and the layers were separated. The aqueous layer was extracted with diethyl ether (2−200 mL). The combined organic layers were washed with 200 mL of saturated aqueous sodium bicarbonate and 200 mL of brine. The organic layer was dried over magnesium sulfate then filtered, and solvents were removed in vacuo. Purification by column chromatography on silica gel (25% diethyl ether−petroleum ether) gave 4.59 g (quantitative) of a clear colorless oil.

$[\alpha]^{23.7}_D$ −13.92 (*c* 1.24, $CHCl_3$). IR (thin film) 3440, 2956, 1613, 1587 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.23, J = 8.6 Hz, 2H), 6.85 (d, J = 8.6 Hz, 2H), 4.41 (dd, J = 19.2, 11.6 Hz, 2H), 3.78 (s, 3H), 3.56−3.38 (m, 2H), 2.99 (d, J = 5.4 Hz, 1H), 2.67 (s, 1 H), 2.16−1.91 (m, 2H), 1.45−1.30 (m, 1H), 0.97 (d, J = 6.9 Hz, 3H), 0.90 (s, 9H), 0.66−0.49 (m, 2H), 0.46−0.34 (m, 1 H), 0.07 (s, 3H), 0.05 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 130.7, 129.2, 113.7, 81.0, 72.4, 68.7, 57.6, 55.2, 35.4, 32.0, 26.0, 18.3, 17.1, 13.8, 11.0,−3.7, −4.6. LRMS for $C_{22}H_{38}O_4Si$ (ESI^+) *m*/*z* (rel intensity) 417 (M^+ + Na, 100). Anal. Calcd for $C_{22}H_{38}O_4Si$: C, 66.96; H, 9.71. Found: C, 67.28; H, 9.83.

(+)-(*R*)-2-[(*S*)-4-(4-methoxybenzyloxy)butan-2-yl]cyclobutanone (19). To a stirred solution of 2.89 g of diol **18** (10.3 mmol, 1 equiv) in 100 mL of pyridine at rt was added 8 mL of methanesulfonyl chloride (11.8 g, 10 equiv) dropwise and the resulting solution was stirred at rt for 1 h. The reaction was poured into 100 mL of ice−water. Diethyl ether (200 mL) was added and the layers were separated. The aqueous layer was extracted with diethyl ether (2 × 200 mL). The combined organic layers were washed with 2 M hydrochloric acid (3 × 200 mL), saturated aqueous sodium bicarbonate (200 mL), and 200 mL of brine. The organic layer was dried over magnesium sulfate then filtered, and solvents were removed in vacuo. Purification by column chromatography on silica gel (30% diethyl ether−petroleum ether) gave 2.44 g (90%) of a clear colorless oil.

$[\alpha]^{21.2}_D$ +21.6 (*c* 1.09, $CHCl_3$). IR (thin film) 2959, 1778 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, J = 8.7 Hz, 2H), 6.85 (d, J = 6.8 Hz, 2H), 4.41 (d, J = 11.6 Hz, 1H), 4.37 (d, J = 11.6 Hz, 1H), 3.77 (s, 3H), 3.45 (t, J = 6.4 Hz, 2H), 3.26−3.18 (m, 1H), 2.93 (dddd, J = 17.9, 10.5, 7.2, 2.9 Hz, 1H), 2.79 (dddd, J = 17.8,

9.8, 3.2, 2.7 Hz, 1H), 2.09−1.92 (m, 2H), 1.86 (dddd, J = 12.2, 7.0, 7.0, 2.7 Hz, 1H), 1.79−1.69 (m, 1H), 1.46−1.36 (m, 1H), 0.88 (dd, J = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.7, 159.0, 130.5, 129.1, 113.6, 72.3, 67.6, 65.8, 55.1, 44.1, 34.1, 30.2, 16.5, 13.7. LRMS for $C_{16}H_{22}O_3$ (ESI$^+$) *m/z* (rel intensity): 285 (M^+ + Na, 100). Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.01; H, 8.54.

Allylic Alcohol 21 via Iodide 24. To a stirred solution of 3.25 g of alkenyl iodide **24** (8.07 mmol, 1 equiv) in 57 mL of diethyl ether at −78 °C was added 11.1 mL of methyllithium (16.1 mmol, 2 equiv, 1.46 M in diethyl ether (Aldrich)) and the resulting solution was stirred at −78 °C for 10 min. A solution of 2.12 g of cyclobutanone **19** (8.07 mmol, 1 equiv) in 57 mL of diethyl ether was added and the resulting solution was stirred at −78 °C for 3 h. After the solution was warmed to rt, water (50 mL) was added and the layers were separated. The aqueous layer was extracted with diethyl ether (2 × 50 mL). The combined organic layers were dried over magnesium sulfate then filtered, and solvents were removed in vacuo. Purification by column chromatography on silica gel (30% diethyl ether−petroleum ether) gave 2.35 g of crude product. This material was used in the next step without further purification.

$[\alpha]^{21.8}_D$ +136.0 (*c* 0.48, $CHCl_3$). IR (thin film) 3527, 2952, 1642, 1614, 1515 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J = 8.3 Hz, 2H), 7.25 (d, J = 7.5 Hz, 2H), 7.21 (d, J = 8.6 Hz, 2H), 6.82 (d, J = 8.6 Hz, 2H), 5.86−5.71 (m, 2H), 5.08−4.99 (m, 2H), 4.39 (d, J = 19.0 Hz, 1H), 4.35 (d, J = 19.0 Hz, 1H), 4.11−4.00 (m, 1H), 3.80−3.77 (m, 1H), 3.77 (s, 3H), 3.59−3.36 (m, 2H), 2.51−3.36 (m, 2H), 2.40 (s, 3H), 2.14−1.91 (m, 3H), 1.91−1.72 (m, 3H), 1.52 (dddd, J = 18.7, 6.8, 3.3, 3.3 Hz, 1H), 1.30−1.04 (m, 3H), 0.84 (d, J = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9, 143.7, 141.5, 135.8, 134.7, 131.0, 129.6, 129.1, 127.7, 119.1, 117.3, 113.6, 77.9, 72.3, 68.7, 55.2, 55.1, 49.9, 37.4, 36.4, 34.7, 30.4, 23.0, 21.6, 20.3, 19.0, 16.1. LRMS for $C_{31}H_{41}NO_5S$ (ESI$^+$) *m/z* (rel intensity): 562 (M^+ + Na, 100).

(−)-(2*R*)-2-Allyl-6-iodo-1-(toluene-4-sulfonyl)-1,2,3,4-tetrahydropyridine (24). To a stirred solution of 3.80 g of alkenyl stannane **10** (8.6 mmol, 1 equiv) in 38 mL of THF at −78 °C was added 7.10 mL of methyllithium (10.3 mmol, 1.2 equiv, 1.46 M in diethyl ether (Aldrich)) and the resulting solution was stirred at −78 °C for 10 min. This solution was transferred to another solution of 11.0 g of iodine (43.2 mmol, 5 equiv) in 28 mL of THF at −78 °C. The resulting reaction mixture was stirred at −78 °C for 1 h and warmed to rt over 1 h. A solution of 15.0 g of sodium thiosulfate pentahydrate (60.4 mmol, 1.4 equiv relative to iodine) in 50 mL of water was added and the resulting biphasic mixture was stirred at rt for 10 min. Diethyl ether (100 mL) was added and the layers were separated. The aqueous layer was extracted with diethyl ether (2 × 50 mL). The combined organic layers were dried over magnesium sulfate then filtered, and solvents were removed in vacuo. Column chromatography on silica gel (ran in gradient from 10% up to 20% diethyl ether−petroleum ether) gave 2.67 g (77%) of a yellow solid. The solid was stored in an aluminum foil-wrapped vial in the freezer.

$[\alpha]^{24.0}_D$ −1.81 (*c* 1.03, $CHCl_3$). IR (thin film) 2932, 1692, 1598 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 8.1 Hz, 2H), 7.28 (d, J = 8.1 Hz, 2H), 6.22 (t, J = 3.9 Hz, 1H), 5.55 (dddd, J = 17.0, 9.7, 7.1, 7.1 Hz, 1H), 5.07−4.93 (m, 2H), 4.27 (ddd, J = 9.1, 6.7, 3.6 Hz, 1H), 2.41 (s, 3H), 2.41−2.24 (m, 1H), 2.10−1.80 (m, 3H), 1.67−1.69 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.0, 136.1, 134.3, 129.5, 128.0, 117.8, 81.0, 56.7, 34.8, 24.2, 23.3, 21.6.

(−)-(4*R*,5*S*,7*R*,10*S*)-7-Allyl-10-bromo-4-[(1*S*)-3-(4-methoxybenzyloxy)-1-methylpropyl]-6-(toluene-4-sulfonyl)-6-azaspiro[4.5]decan-1-one (25). To a stirred solution of 41 mg of allylic alcohol **24** (76.0 μmol, 1 equiv) in 2 mL of a 1:1 mixture of propylene oxide and 2-propanol at −78 °C was added 16.2 mg of *N*-bromosuccinimide (91.2 μmol, 1.2 equiv). The resulting mixture was stirred at −78 °C for 2 h and warmed to rt overnight (∼14 h). After concentration in vacuo, purification by column chromatography on silica gel (25% diethyl ether−petroleum ether) gave 41 mg (87%) of a clear colorless oil.

$[\alpha]^{26.3}_D$ −110.4 (*c* 0.78, $CHCl_3$). IR (thin film) 2953, 1747, 1614, 1515 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 8.3 Hz, 2H), 7.27 (d, J = 8.2 Hz, 2H), 7.25 (d, J = 8.9 Hz, 2H), 6.84 (d, J = 8.6 Hz, 2H), 5.54 (dddd, J = 17.1, 10.3, 8.1, 5.7 Hz, 1H), 5.02−4.90 (m, 2H), 4.44 (d, J = 15.5 Hz, 1H), 4.41 (d, J = 15.4 Hz, 1H), 4.32 (dd, J = 12.2, 4.8 Hz, 1H), 3.76 (s, 3 H), 3.67−3.59 (m, 1H), 3.59−3.41 (m, 2H), 2.82−2.70 (m, 2H), 2.58−2.29 (m, 5H), 2.39 (s, 3H), 2.17 (m, 1H), 1.98 (ddd, J = 18.6, 9.3, 4.6 Hz, 1H), 1.88−1.79 (m, 1H), 1.69 (dd, J = 13.1, 6.7 Hz, 1H), 1.61−1.50 (m, 1H), 1.35−1.22 (m, 1H), 1.13 (d, J = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.5, 159.2, 143.5, 136.8, 134.7, 130.6, 129.5, 129.3, 128.8, 117.9, 113.8, 72.9, 71.6, 67.8, 55.2, 53.9, 53.0, 48.3, 43.2, 39.0, 37.6, 27.8, 25.9, 23.8, 21.5, 21.4, 17.0. LRMS for $C_{31}H_{40}{}^{81}BrNO_5S$ (ESI$^+$) *m/z* (rel intensity): 642 (M^+ + Na, 100).

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Supporting Information Available: Experimental procedures and characterization data for compounds **4**−**29**. This material is available free of charge via the Internet at http://pubs.acs.org.

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