Total Synthesis of (+)-Aloperine. Use of a Nitrogen-Bound Silicon Tether in an Intramolecular Diels−Alder Reaction

Arthur D. Brosius, Larry E. Overman,* and Lothar Schwink

Contribution from the Department of Chemistry, University of California, 516 Rowland Hall, Irvine, California 92697-2025

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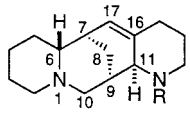
Abstract: Enantioselective total syntheses of aloperine (**1**), *N*-methylaloperine (**2**), and *N*-allylaloperine (**3**) are reported. The central element of the synthetic strategy is an intramolecular Diels−Alder reaction in which the cycloaddends are tethered by a *N*-silylamine linkage. The total synthesis of **1** proceeds from commercially available 3-hydroxypiperidine hydrochloride (**54**) and (*R*)-pipecolinic acid (**35**) by way of nine isolated and purified intermediates. The synthesis is sufficiently efficient that gram quantities of (+)-aloperine (**1**) can be readily prepared. Early exploratory studies also introduced a convenient method for tethering cycloaddition partners with a sulfonamide unit to realize the intramolecular Diels−Alder cycloaddition of a vinylsulfonamide: **45** → **46**.

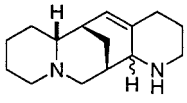
Introduction

Aloperine (**1**) is the parent member of a small family of C_{15} lupinine alkaloids that includes the *N*-methyl (**2**) and *N*-allyl (**3**) derivatives. Aloperine was first isolated in 1935 from the seeds and leaves of *Sophora alopecuroides* L.,[2] a shrub that is indigenous to northwestern China and southern Russia, and later from *Leptorhabdos parviflor* Benth.[3] These plants have long been used in the treatment of inflammation in traditional Chinese medicine.[4] Recent investigations of the isolated alkaloid have revealed its ability not only to inhibit inflammatory and allergic responses in rats[5] but also to inhibit experimental heart arrhythmias in rats, rabbits, and guinea pigs,[6] to effect contraction of isolated guinea pig ileum,[7] and to elicit additional immunological effects.[8]

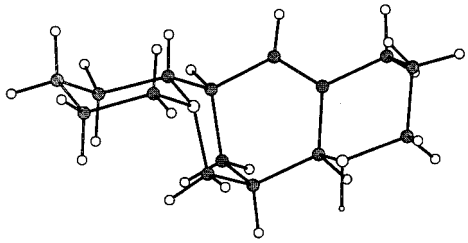
Structural studies of aloperine and its derivatives did not appear until 1975, at which time a bridged tetracyclic skeleton was correctly proposed on the basis of chemical degradation, low-field NMR, and mass spectrometric data.[9] However, the relative orientation of the hydrogen atoms at C6 and C11, and



1 aloperine; R = H
2 R = Me
3 R = $CH_2CH{=}CH_2$



4 α-C11- H
5 β-C11- H



X-ray model of aloperine

their stereochemistries with respect to the methano bridge C8 were not established at that time. Recently, we elucidated the relative and absolute stereochemistry of aloperine on the basis of single-crystal X-ray analyses of both the free alkaloid and its dihydrochloride monohydrate salt.[10,11,] These analyses revealed that natural aloperine possesses the 6*R*,7*R*,9*R*,11*S* stereochemistry, as shown.

Prior to the X-ray studies, we had initiated a program to synthesize the four possible diastereomers of aloperine to elucidate the relative stereochemistry of the natural product. Our early efforts resulted in the syntheses of two stereoisomers of natural aloperine, **4** and **5**.[11] After the X-ray studies, our synthetic efforts were directed toward natural aloperine (**1**) and its derivatives. Unlike our syntheses of **4** and **5**, which featured an iodide-terminated *N*-acyliminium ion-alkene cyclization, the central transformation in the approaches to aloperine (**1**) discussed below is a Diels−Alder cycloaddition. Herein we present a complete account of these recent investigations, which culminated in the first total syntheses of (+)-aloperine (**1**), (+)-*N*-methylaloperine (**2**), and (+)-*N*-allylaloperine (**3**).[12]

(1) Current address: Department of Chemistry and Chemical Biology, Harvard University, 12 Oxford Street, Cambridge, MA 02138.

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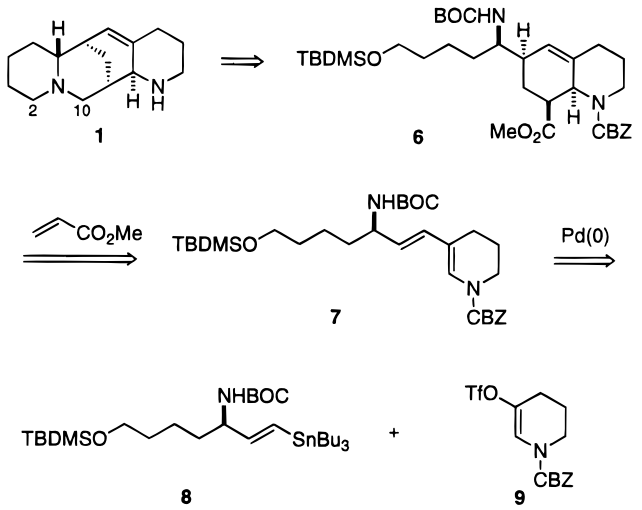
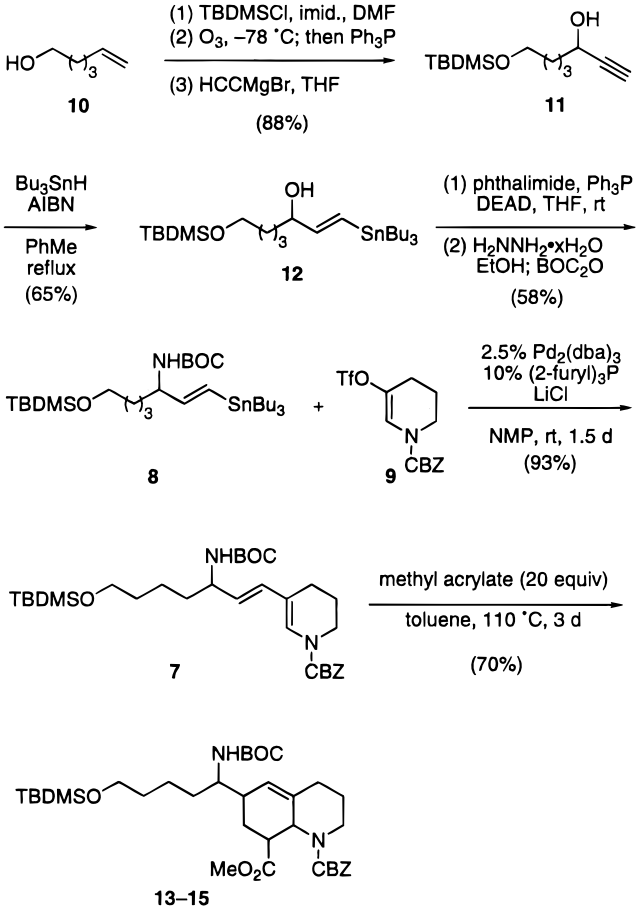
Scheme 1



Scheme 2



Results and Discussion

Intermolecular Diels−Alder Approaches to Aloperine. Our initial synthetic plan called for simplification of the tetracycle by retrosynthetic cleavage of the N−C2 and N−C10 bonds, revealing an appropriately functionalized Diels−Alder product **6** (Scheme 1). Bicycle **6** could arise from a [4 + 2]-cycloaddition reaction between chiral diene **7** and methyl acrylate. The diene, in turn, could be constructed by the palladium-mediated cross-coupling of stannane **8** and triflate **9**.

The proposed Diels−Alder reaction of 1-*N*-acylamino-1,3-diene **7** with methyl acrylate would generate three new stereocenters under the control of the diene's allylic stereocenter. In theory, eight isomers are possible from such a reaction, yet we expected that isomer **6**, which is the product of an *ortho*-, *endo*-, and *lk (like)*-[13] selective cycloaddition, would predominate on the basis of several precedents. First, bimolecular [4 + 2]-cycloaddition reactions of 1-*N*-acylamino-1,3-dienes have been well-studied,[14] and typically proceed with high regioselectivity to form "ortho" products. Second, acrylate dienophiles exhibit moderate to high dienophile facial selectivity in bimolecular reactions with 1-*N*-acylamino-1,3-dienes to form *endo* products.[14] The third and most problematic issue was how an allylic stereogenic center bearing a nitrogen substituent would influence diene facial selectivity. Several examples in the literature indicate that 1,3-dienes bearing allylic heteroatom substituents undergo cycloadditions with acrylate or maleate derivatives in a *lk* fashion.[15−17] Of particular relevance to the case at hand was a recent report by Crisp and Gebauer, who demonstrated that dienes with allylic *N*-acylamino substituents react with maleic anhydride to give largely *lk*-diene facial isomers.[17b]

The synthesis of racemic diene **7** (Scheme 2) began with commercially available 5-hexen-1-ol (**10**). Treatment of **10** with *tert*-butyldimethylsilyl chloride (TBDMSCl) and subsequent ozonolysis gave an intermediate aldehyde, which was treated with ethynylmagnesium bromide to furnish propargylic alcohol **11** in 88% yield. Treatment of **11** with tributyltin hydride and catalytic AIBN gave 65% of (*E*)-stannane **12** and 21% of the corresponding *Z*-isomer; these stereoisomers were readily separable by chromatography. Mitsunobu displacement[18] of alcohol **12** with phthalimide, followed by hydrazinolysis and *tert*-butoxycarbonyl (BOC) protection of the resulting primary amine delivered amino stannane **8** in 58% yield. Finally, palladium-mediated Stille coupling[19] of **8** with the known triflate **9**[20] provided **7** in 93% yield.

In the key cycloaddition step, diene **7** was allowed to react with a large excess of methyl acrylate at 110 °C in a sealed tube. Two major cycloadducts **13** and **14**, formed in an approximate ratio of 1.4:1, and one minor cycloadduct **15** were isolated in a combined yield of 70% (Scheme 2). Small amounts of the major adduct **13** could be obtained in pure form by

(12) For an impressive total synthesis by the Valenta group of (±)-ormosamine and three congeneric C_{20} *Ormosia* alkaloids, which bear considerable structural similarity to **1**−**3**, see: (a) Liu, H.-J.; Sato, Y.; Valenta, Z.; Wilson, J. S.; Yu, T. T.-J. *Can. J. Chem.* **1976**, *54*, 97. (b) Liu, H. J.; Valenta, Z.; Yu, T. T. J. *J. Chem. Soc., Chem. Commun.* **1970**, 1116. (c) Liu, H. J.; Valenta, Z.; Wilson, J. S.; Yu, T. T. J. *Can. J. Chem.* **1969**, *47*, 509.

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(16) Allylic silane: Fleming, I.; Sarkar, A. K.; Doyle, M. J.; Raithby, P. R. *J. Chem. Soc., Perkin Trans. 1* **1989**, 2023.

(17) Allylic amines: (a) Kozikowski, A. P.; Jung, S. H.; Springer, J. P. *J. Chem. Soc., Chem. Commun.* **1988**, 167. (b) Crisp, G. T.; Gebauer, M. G. *J. Org. Chem.* **1996**, *61*, 8425.

(18) Mitsunobu, O.; Wada, M.; Sano, T. *J. Am. Chem. Soc.* **1972**, *94*, 679.

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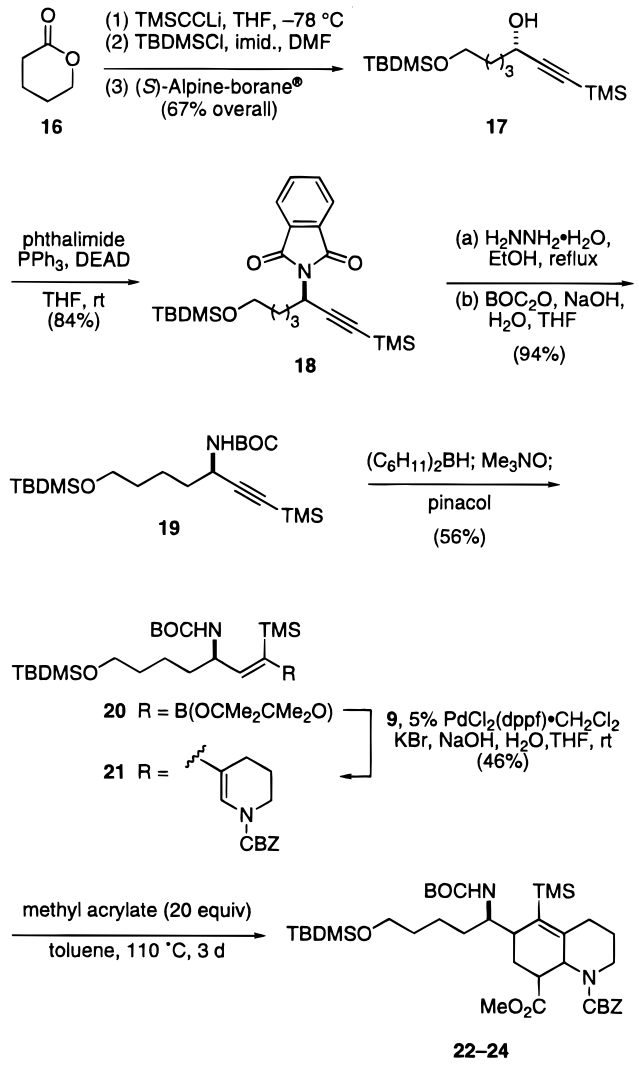
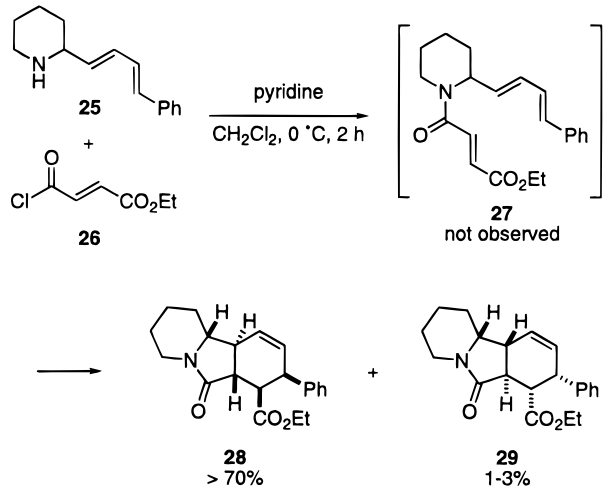
Scheme 3



repeated chromatographic purification. However, the presence of two carbamate functional groups, which give rise to multiple rotational isomers on the NMR time scale, prevented straightforward stereochemical analysis by NMR.[21]

In an effort to increase selectivity for the *lk* Diels−Alder product, a new diene was designed. Placing a large substituent at the diene carbon β to the allylic stereocenter should enhance the level of selectivity imparted by the *N*-acylamino substituent by virtue of enhanced allylic interactions.[22] Diene **21**, which incorporates a trimethylsilyl group in this position, was prepared from δ-valerolactone (**16**) as summarized in Scheme 3. Valerolactone was initially condensed with 1 equiv of lithium trimethylsilylacetylide, and the liberated hydroxyl was subsequently protected as a *tert*-butyldimethylsilyl (TBDMS) ether. The resulting propargylic ketone was reduced with Alpine-borane, furnishing enantioenriched alcohol **17** (93% ee by Mosher ester analysis[23]) in 67% yield for the three steps. By using the sequence employed previously, **17** was converted to carbamate **19** in high overall yield. Hydroboration of silyl alkyne **19** with dicyclohexylborane, selective oxidation of the sp^3 C−B bonds, and transesterification with pinacol afforded the intermediate pinacolboronate **20** in moderate yield. This intermediate was then coupled under Suzuki conditions[24] with triflate **9** to provide diene **21** in 25% overall yield from **17**.

Scheme 4



Diene **21** was tested for its reactivity with various dienophiles, including methyl acrylate, acrolein, acryloyl chloride, and the corresponding oxazolidinone.[25] Of these, only methyl acrylate reacted. Cycloaddition of **21** with excess methyl acrylate at 110 °C for 3 days furnished three products, together with considerable recovered diene. By comparison of NMR spectra with those of cycloadducts **13**−**15**, the products were surmised to be cycloadducts: two major **22** and **23** (ratio ~2:1) and one minor **24**. Attempts to promote the reaction of the more acid stable *tert*-butyldiphenylsilyl analogue of **21** with Lewis acids were also unsuccessful; no cycloaddition products were observed under these conditions. Since an improvement in stereoselection was not realized with diene **21**, no attempt was made to determine the stereochemistry of the major cycloadducts. Instead, our efforts were directed toward an alternative, intramolecular Diels−Alder strategy.

Intramolecular Diels−Alder Approaches to Aloperine. Background and Synthesis Plan. In 1973 Gschwend reported that intramolecular cycloaddition of triene **27**, constructed in situ from diene **25** and acid chloride **26**, furnished tricycle **28** in good yield (Scheme 4).[26] Tethering the cycloaddends resulted in complete control of regioselectivity and dienophile facial selectivity and good modulation of diene facial selectivity. An intramolecular Diels−Alder cycloaddition strategy for preparing aloperine (**1**), which is based on the Gschwend precedent, is enunciated in Scheme 5. By a series of straightforward transformations, aloperine can be disconnected to reveal **30**, where PG denotes a nitrogen protecting group. Tricycle **30** would arise from tetracycle **31** after excision of a tethering functionality Y. The intramolecular Diels−Alder substrate **32** would, in turn, be constructed from diene **33** and an acrylate fragment **34** containing the tether Y attached to a leaving group X.

The discussion that follows outlines the evolution of an efficient enantioselective synthesis of aloperine, along the lines outlined in Scheme 5. As will become apparent, the central issue

(21) To probe the stereochemistry of the major cycloadduct **13**, it was converted in four steps to the aloperine skeleton by sequential treatment with: (a) TBAF (b) MsCl (c) TFA, then $(i\text{-Pr})_2$NEt, 80 °C (d) $LiAlH_4$. The ^{1}H NMR spectrum of the product of these transformations was clearly different from the ^{1}H NMR spectrum of authentic *N*-methylaloperine.

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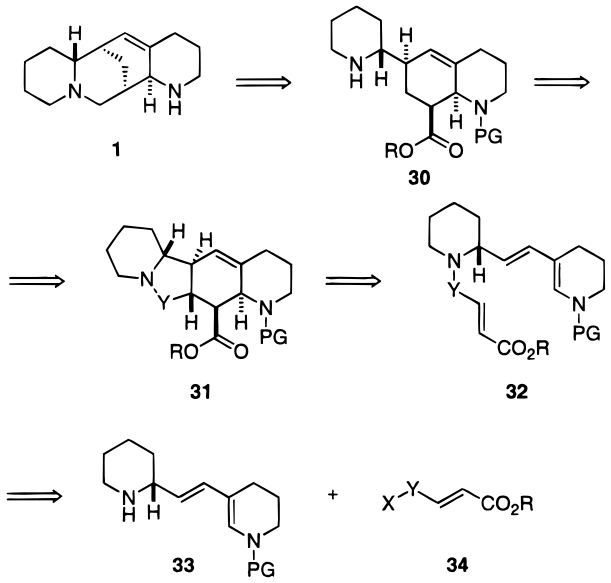
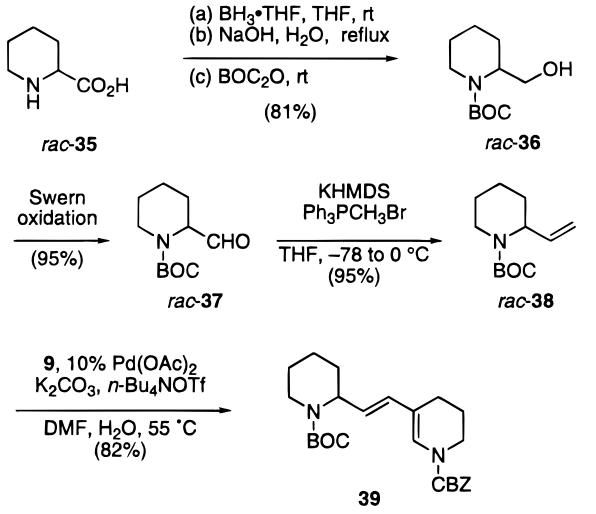
Scheme 5



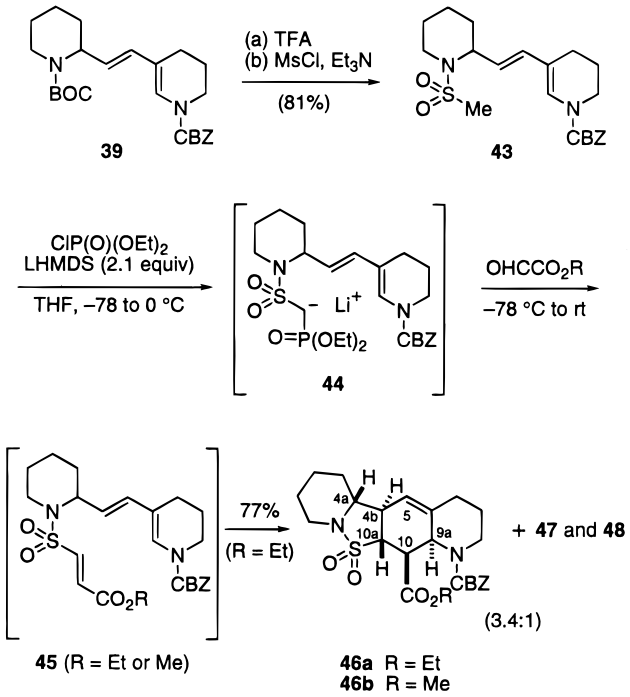
Scheme 6



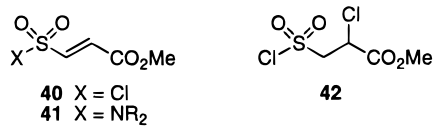
was finding a suitable tethering group. Three potentially disposable tethers for the intramolecular Diels−Alder reaction were evaluated: the sulfonyl group (Y = SO_2), the carbonyl group (Y = CO), and a dimethylsilyl group (Y = $SiMe_2$). Although selective cycloaddition could be achieved with all three, the synthesis was significantly simplified by use of the silyl tether. Before discussing the final optimal strategy, we will briefly relate our experience with sulfonyl and carbonyl tethers.

Initial Investigations of Sulfonyl- and Carbonyl-Tethered Intramolecular Diels−Alder Approaches. Our initial investigations employed diene **39** having the dienamine and piperidine nitrogens protected with benzyloxycarbonyl (CBZ) and BOC groups, respectively. This intermediate was prepared in racemic fashion from racemic pipecolinic acid (*rac*-**35**) as outlined in Scheme 6. Pipecolinic acid was reduced with borane, the resulting amino alcohol was *N*-protected,[27] and *rac*-**36** was oxidized by the Swern procedure[28] to provide known aldehyde *rac*-**37**,[29] in 77% overall yield. Wittig methylenation of *rac*-**37** furnished alkene *rac*-**38**, which underwent Heck coupling with vinyl triflate **9** under conditions recently described by Crisp and Gebauer[30] to furnish racemic diene **39** in 60% overall yield from pipecolinic acid. ^1H and ^{13}C NMR spectra of **39** showed no detectable contamination by the corresponding *Z*-stereoisomer.

Scheme 7



The SO_2 group was the first tether we examined due to its electron-withdrawing capability, a property that was expected to facilitate the cycloaddition reaction, and the potential that this unit could be removed from the cycloadducts under reductive conditions.[31] Although sulfonyl halides such as **40** are unknown, the related sulfonyl chloride **42** has been prepared and shown to produce sulfonamide **41** (R_2 = PhMe) in moderate yield upon reaction with *N*-methylaniline.[32] Upon exposure of **42** to 1 equiv of piperidine at room temperature, we found that the desired sulfonamide **41** [$R_2 = (CH_2)_5$] was accompanied by significant amounts of a product containing two piperidine units (the second incorporated by 1,4-addition). When **42** was allowed to react with the free amine derived from deprotection of **39** with TFA, a number of products were formed, none of which appeared to be the desired triene or corresponding cycloadducts.



Unable to utilize **42** as precursor to the sulfonyl-tethered cycloaddends, we chose to employ a Horner−Wadsworth−Emmons reaction to construct the requisite intermediate. As illustrated in Scheme 7, diene **39** was first converted to the corresponding methanesulfonamide **43** in 81% yield. Lithium salt **44** was then generated by treatment of **43** with 2.1 equiv of lithium hexamethyldisilazane (LHMDS) in the presence of

(27) Hart, D. J.; Wu, W.-L.; Kozikowski, A. P. *J. Am. Chem. Soc.* **1995**, *117*, 9369.

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(32) Behringer, H.; Zillikens, P. *Liebigs Ann. Chem.* **1951**, *574*, 140.

diethyl chlorophosphate. Although this anion could be quenched with water and the resulting α-sulfonamidophosphonate isolated, it proved more efficient to treat **44** in situ with ethyl (or methyl) glyoxylate. This two-step sequence directly generated three cycloadducts **46**−**48**. The major products, **46** and **47**, were formed in a ∼3.4:1 ratio (as determined by ^{1}H NMR analysis of the crude reaction mixture at 100 °C), while the third minor cycloadduct **48** (<5%) was detected only during chromatographic purification. The presumed triene intermediate **45** was not detected.[33]

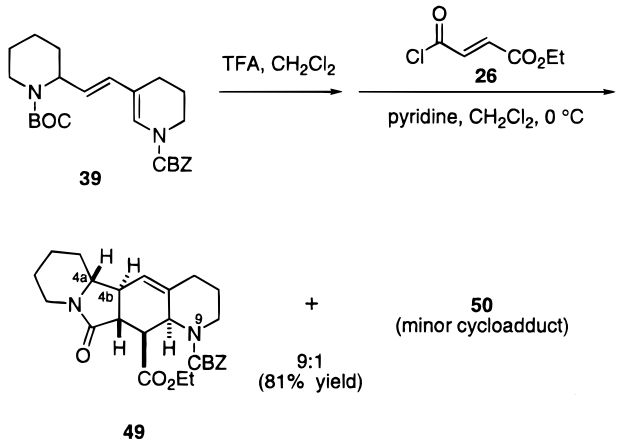
Characterization of the major cycloadduct was accomplished with the methyl congener **46b**, which could be isolated in pure form by preparative HPLC. High temperature (100 °C) ^{1}H−^{1}H COSY and NOE experiments showed that this product possessed the relative stereochemistry depicted in Scheme 7. Of particular importance to the stereochemical assignment is H4a, which was coupled to H4b with a coupling constant of 10.2 Hz, consistent with a *trans* diaxial relationship of these hydrogens. A smaller value for this coupling constant would have been expected if the *ul*-diene facial isomer had predominated. Also, when H10a is irradiated, an NOE enhancement of H4a is observed; however, no NOE enhancements H10, H4b, or H9a could be detected, further verifying that only H4a is on the same face of the skeleton as H10a, as would be expected for the *lk*-isomer **46b**.

Having found conditions that delivered predominantly the desired cycloadduct, we proceeded to examine removing the SO_2 tether. The mixture of cycloadducts **46**−**48** was treated with a number of reducing agents, including sodium bis(2-methoxyethoxy)aluminum hydride, Raney-Ni, Na/hexamethylphosphoramide (HMPA)/*t*-BuOH,[34] Na/NH_3/*t*-BuOH, and Li/NH_3/*t*-BuOH. Most reductants did not cleave either the N−S or C−S bonds. Sodium or lithium metal in refluxing ammonia afforded a product that lacked the SO_2 group (mass spectrometric analysis); however, this product was invariably only a minor component of a complex reaction mixture.

Due to our lack of success with removal of the sulfonyl tether, we briefly investigated the carbonyl group as a tethering entity (Scheme 8). Diene **39** was first selectively deprotected to reveal the corresponding piperidine free base, which was not purified but instead treated directly with a slight excess of acid chloride **26** and pyridine at 0 °C. The presumed intermediate triene was again not observed, since cycloaddition occurred rapidly at 0 °C to afford a 9:1 mixture of cycloadducts **49** and **50** in 81% yield. Unfortunately, these isomers were inseparable by silica gel chromatography. Nevertheless, we were able to determine the stereochemistry of major cycloadduct **49** by high temperature (100 °C) ^{1}H NMR and ^{1}H−^{1}H COSY experiments using the cycloadduct mixture. Once again, H4a exhibited diagnostic coupling to H4b with a large value of ∼10.8 Hz, consistent with a *trans* relationship of these hydrogens. Thus, **49** possesses the same relative stereochemistry as Gschwend's tricycle **28** (Scheme 4) and sulfonyltetracycle **46** (Scheme 7).

Although several strategies were briefly investigated for conversion of the **49**/**50** cycloadduct mixture, and related cycloadducts having *p*-toluenesulfonyl protection of N9, to the aloperine skeleton, it soon became apparent that this conversion

Scheme 8



would be protracted.[35] Thus we turned to the ultimately successful strategy employing dimethylsilyl as the tethering group.

Silyl-Tethered Intramolecular Diels−**Alder Cycloaddition Approach. Efficient Enantioselective Total Synthesis of Aloperine and Congeners.** The utility of disposable silyl tethers, most commonly involving an O−Si linkage, for controlling diastereoselectivity in intramolecular transformations has been amply documented[36] since the pioneering early studies in this area by Stork and Nishiyama.[37] Potential advantages of a silicon tether in an aloperine synthesis would be the ease with which the N−Si bond could be cleaved after the cycloaddition and considerable precedent that scission of the C−Si bond could be accomplished by a Tamao oxidation[38]−Barton deoxygenation[39] sequence. The diminished electron-withdrawing ability of a dimethylsilyl group, relative to that of sulfonyl or carbonyl tethers, was a potential concern, since it could necessitate the use of higher temperatures to promote the cycloaddition step, thereby potentially diminishing cycloaddition stereoselectivity. As we soon show, this concern was unfounded; the silicon tether proved remarkably successful in terms of both cycloaddition stereoselectivity and ease of removal.[40]

The dienophilic coupling fragment **53** was prepared from methyl (*E*)-*β*-iodoacrylate (**51**)[41] by initial condensation with the cuprate reagent derived from lithiodimethylphenylsilane,[42] to furnish *β*-silyl acrylate **52** (eq 1).[43] Protodesilylation[44] of this

(33) Optimal conditions for this two-step condensation reaction were discovered utilizing piperidine methanesulfonamide as a model. Under conditions otherwise identical to those employed with sulfonamide **43**, condensation of 1-(methanesulfonyl)piperidine with methyl glyoxylate yielded 3-(piperidine-1-sulfonyl)-acrylic acid methyl ester with an *E*:*Z* selectivity of 15:1.

(34) Cuvigny, T.; Larchevêque, M. *J. Organomet. Chem.* **1974**, *64*, 315.

(35) Brosius, A. D., Ph.D. Dissertation, University of California, Irvine, 1998.

(36) For recent reviews on the use of silicon as a temporary (or disposable) tether for intramolecular transformations, see: (a) Gauthier, D. R., Jr.; Zandi, K. S.; Shea, K. J. *Tetrahedron* **1998**, *54*, 2289. (b) Fensterbank, L.; Malacria, M.; Sieburth, S. M. *Synthesis* **1997**, 813. (c) Bols, M.; Skrydstrup, T. *Chem. Rev.* **1995**, *95*, 1253.

(37) (a) Stork, G.; Kahn, M. *J. Am. Chem. Soc.* **1985**, *107*, 500. (b) Nishiyama, H.; Kitajima, T.; Matsumoto, M.; Itoh, K. *J. Org. Chem.* **1984**, *49*, 2298.

(38) (a) Tamao, K.; Ishida, N.; Tanaka, T.; Kumada, M. *Organometallics* **1983**, *2*, 1694. (b) Fleming, I. *Chemtracts: Org. Chem.* **1996**, *9*, 1. (c) Jones, G. R.; Landais, Y. *Tetrahedron* **1996**, *52*, 7599.

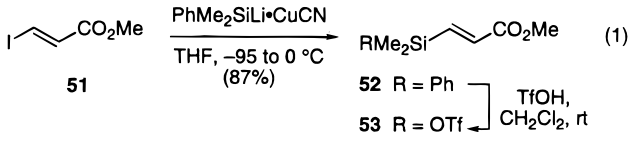
(39) (a) Barton, D. H. R.; Dorchak, J.; Jaszberenyi, J. C. *Tetrahedron* **1992**, *48*, 7435. (b) Barton, D. H. R.; Blundell, P.; Dorchak, J.; Jang, D. O.; Jaszberenyi, J. C. *Tetrahedron* **1991**, *47*, 8969. (c) Barton, D. H. R.; Jaszberenyi, J. C. *Tetrahedron Lett.* **1989**, *30*, 2619.

(40) For the use of N−Si-linked intermediates in other intramolecular transformations, see, inter alia: (a) Bismara, C.; Di Fabio, R.; Donati, D.; Rossi, T.; Thomas, R. J. *Tetrahedron Lett.* **1995**, *36*, 4283. (b) Tamao, K.; Nakagawa, Y.; Ito, Y. *J. Am. Chem. Soc.* **1992**, *114*, 218. (c) Murakami, M.; Suginome, M.; Fujimoto, K.; Nakamura, H.; Anderson, P. G.; Ito, Y. *J. Am. Chem. Soc.* **1993**, *115*, 6487.

(41) (a) Carpita, D.; Neri, D.; Rossi, R. *Gazz. Chim. Ital.* **1987**, *117*, 481. (b) Oda, H.; Kobayashi, T.; Kosugi, M.; Migita, T. *Tetrahedron* **1995**, *51*, 695.

(42) Fleming, I.; Newton, T. W.; Roessler, F. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2527.

(43) Alvisi, D.; Blart, E.; Bonini, B. F.; Mazzanti, G.; Ricci, A.; Zani, P. *J. Org. Chem.* **1996**, *61*, 7139.



intermediate with trifluoromethanesulfonic acid (TfOH) generated the labile silyltriflate intermediate **53** which was used without purification.[45]

For the diene component we chose **58** having the dienamine nitrogen protected with a *p*-toluenesulfonyl (Ts) group (Scheme 9). Although a dienesulfonamide would be expected to be a less reactive cycloaddend than a dienecarbamate, if cycloaddition was successful, this mode of protecting N9 was expected to simplify conversion of the cycloadduct to aloperine.

Diene sulfonamide **57** was accessed from 3-hydroxypiperidine hydrochloride (**54**) and 2-vinylpiperidine (*R*)-**38**. The latter intermediate (97.2% ee)[46] is available in 73% overall yield from commercially available (*R*)-pipecolinic acid by the sequence we employed previously to prepare the corresponding racemate (Scheme 6). Commercially available **54** was first selectively tosylated on nitrogen by reaction with tosyl chloride (1.07 equiv) and excess triethylamine in CH_2Cl_2 at 0 °C, and this crude intermediate was oxidized with Jones reagent to give ketone **55** in 89% overall yield. The thermodynamic lithium enolate of **55**, generated by treatment of **55** with 0.95 equiv of LHMDS and subsequent equilibration at 0 °C for 1 h, was trapped with *N*-phenyltriflimide to provide enol triflate **56** in 40% yield. The yield of **56** could not be improved despite considerable effort.[47] Some of the key observations made during these investigations are summarized in Table 1. Enol triflation of **55** with triflic anhydride and 2,6-di-*tert*-butyl-4-methylpyridine proceeded efficiently under forcing conditions (refluxing 1,2-dichloroethane) to give a 1:1 mixture of regioisomeric enol triflates **56** and **59**. Kinetic enolization with excess LHMDS also proceed efficiently to give predominantly (ds = 6:1) enol triflate **59** (entry 2). Under thermodynamic conditions, **56** predominated to the extent of 6−7:1; however, enolate equilibration at 0 °C was accompanied by considerable decomposition (entries 3 and 4). That decomposition was not reduced when the equilibration was carried out at a lower concentration (entry 4) suggests that the lithium enolate precursor of **56** undergoes competitive unimolecular elimination of *p*-toluenesulfinic acid at 0 °C. Attempts to increase the rate of enolate equilibration (entries 5 and 6) did not improve the yield of **56**.[48]

Heck coupling[30] of triflate **56** with (*R*)-**38** (97.2% ee) provided diene **57** in 83% yield on a multigram scale (Scheme 9). However, deprotection of **57** ($[\alpha]^{23}_{405}$ +82.5) with TFA in CH_2Cl_2 at room temperature unexpectedly yielded racemic diene **58**, presumably because of the acid-promoted formation of the

Scheme 9

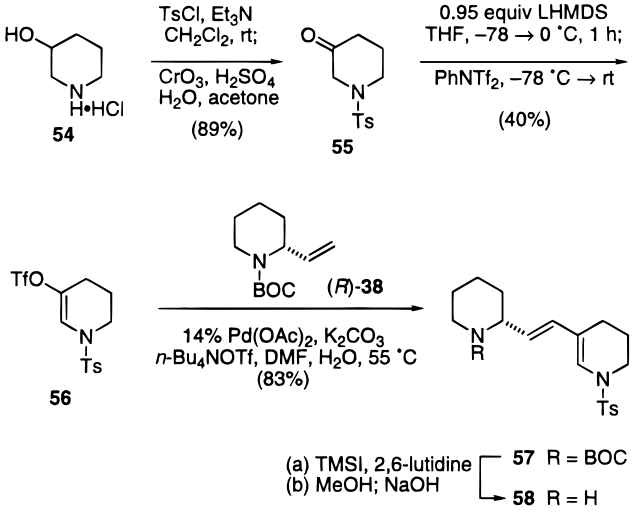
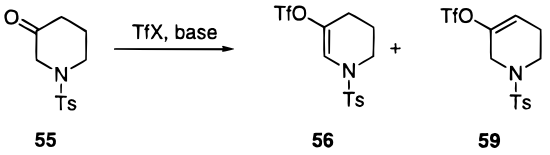


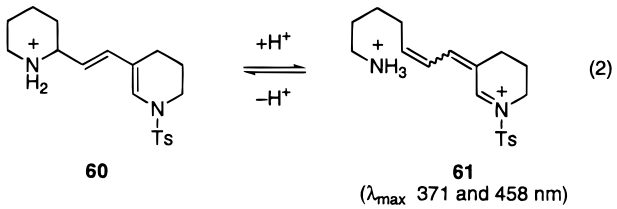
Table 1. Enoltriflation of Piperidinone **55**



entry	base	equiv	mol/L	X	56:59	yield, %[a]
1[b]	DTBMPc	2.20	0.13	OTf	1:1	80
2[d]	LHMDS	1.05	0.20	N(Tf)Ph	1:6	85
3[d]	LHMDS	0.90	0.20	N(Tf)Ph	7:1	34−40
4[d]	LHMDS	0.90	0.05	N(Tf)Ph	6:1	e
5[d]	LHMDS	0.95	0.20	N(Tf)Ph	5:1f	36
6[d]	KHMDDS	1.00	0.10	N(Tf)Ph	1:12	∼30

[a] Combined isolated yield of **56** and **59**. [b] At reflux in 1,2-dichloroethane. [c] 2,6-di-*tert*-Butyl-4-methylpyridine. [d] In THF, −78 °C → 0 °C; TfX was added after re-cooling to −78 °C. [e] Triflate **56** was isolated in 20% yield. [f] HMPA was used as an additive.

ring-opened, conjugated *N*-tosyliminium ion **61** (eq 2).[49]



Consistent with this explanation, samples of **58** in CH_2Cl_2 containing excess TFA were yellow and showed new λ_{max} at 371 and 458 nm in the UV/visible spectra. Fortunately, racemization could be prevented by cleaving the BOC group under nonacidic conditions by initial reaction of **57** with trimethylsilyl iodide (TMSI) in the presence of excess 2,6-lutidine, followed by solvolysis of the silyl carbamate in methanol to provide **58**, after basification. Reprotection (BOC_2O) of **58** generated in this way furnished (*R*)-**57** with no erosion of enantiopurity ($[\alpha]^{23}_{405}$ +83.1).

We were delighted to find that when **57** was deprotected by sequential reaction with TMSI/2,6-lutidine and methanol and **58** then was coupled with silyl triflate **53**, a 5:1 mixture of tetracyclic Diels−Alder products **63** and **64** was produced

(44) Coppi, L.; Ricci, A.; Taddei, M. *Tetrahedron Lett.* **1987**, *28*, 965.

(45) For the first use of a silyl-tethered propenoate in a Diels−Alder reaction see: Stork, G.; Chan, T. Y.; Breault, G. A. *J. Am. Chem. Soc.* **1992**, *114*, 7578. For another synthesis of related silyl chlorides, see: Denmark, S. E., Hurd, A. R., Sacha, H. J. *J. Org. Chem.* **1997**, *62*, 1668.

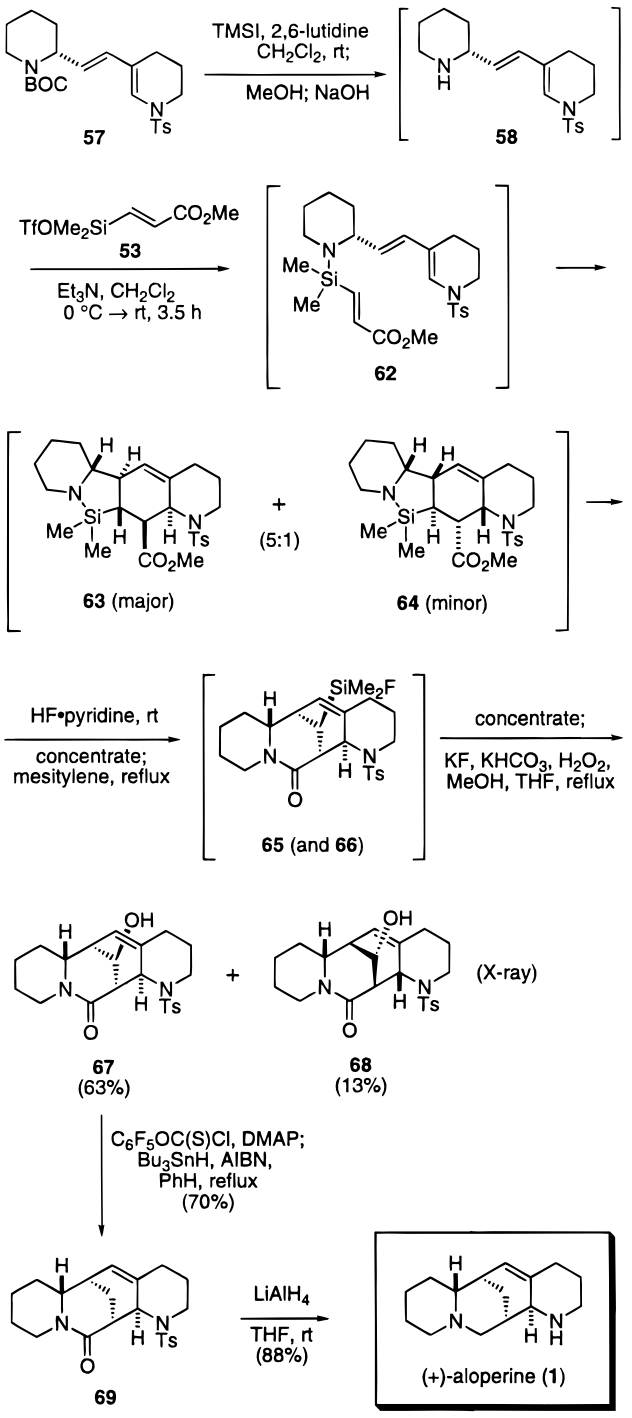
(46) The enantiopurity of (*R*)-**38** was determined after its conversion to the corresponding tosyl derivative [(a) TFA/CH_2Cl_2 (b) TsCl, Et_3N] and HPLC analysis of this sulfonamide (Chiralcel AS-II, 9:1 *n*-hexane−*i*-PrOH).

(47) The 1-benzyloxycarbonyl analogue **9** is reported to be available in high yield from the corresponding ketone.[20] In our hands, the formation of **9** was also low-yielding (35−40%).[35]

(48) Bromination of **55** (NBS, AIBN in refluxing CCl_4) gave the 2-bromoderivative, which upon reduction with activated zinc and TMSCl provided the $\Delta^{2,3}$ enoxysilane in moderate yield. Reaction of this intermediate with MeLi in ether−THF at 0 °C to generate the corrresponding lithium enolate and trapping with *N*-phenyltriflimide gave **56** in 70% yield. The efficiency of this latter conversion establishes that the lithium enolate precursor of **56** is stable for 50 min at 0 °C in ether−THF.

(49) Craig, D.; McCague, R.; Potter, G. A.; Williams, M. R. V. *Synlett* **1998**, 58.

Scheme 10



directly[50] (Scheme 10). These adducts were unstable toward aqueous workup, which prevented their isolation and full characterization. When the **63**/**64** mixture was exposed to water, hydrolysis of the N−Si bond occurred to generate compounds of general formula RSiOSiR (mass spectral analysis), where R is a cycloadduct fragment.[51] However, the crude Diels−Alder product could be treated directly with anhydrous HF·pyridine, which cleaved the N−Si bond and placed a fluoride substituent on silicon, thus activating the C−Si bond toward subsequent oxidative cleavage.[52] After a solvent change to mesitylene, the mixture of tricyclic silyl fluorides was heated to 165 °C to induce intramolecular lactamization. The resulting tetracycles **65** and **66**, which were also somewhat unstable toward aqueous workup, could nonetheless be partially characterized by ^{1}H NMR, ^{19}F NMR, and mass spectrometric analysis. Finally, after another solvent exchange, Tamao−Fleming oxidation[38] delivered tetracyclic alcohols **67** and **68** as the first isolated and fully characterized intermediates of this multistep, one-pot sequence. Despite the large number of operations that had been performed, the ^{1}H NMR spectrum of the crude reaction product after workup was remarkably clean, showing only two products in an approximate 5:1 ratio. After separation by chromatography, pure **67** and **68** were isolated in 63 and 13% overall yields, respectively, from (*R*)-**57**. The structure and stereochemistry of the major product **67** was confirmed by its conversion to (+)-aloperine (**1**), while the stereochemistry of the minor isomer **68** was secured by single-crystal X-ray analysis.[53] Three-dimensional models of **67** and **68** are shown in Figure 1. As in the sulfonyl- and carbonyl-tethered cycloaddition reactions we had studied earlier and the related cycloadditions reported by Gschwend,[26] the dimethylsilyl tether promoted preferential formation of the *lk*-diene facial cycloadduct, with the minor cycloadduct arising from the *ul* cycloaddition pathway (Figure 2).

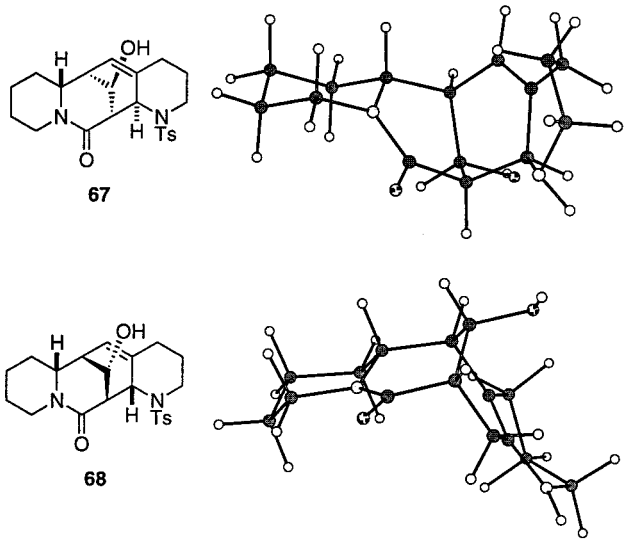


Figure 1. Molecular mechanics models of **67** and **68**. The *p*-toluenesulfonyl group is not shown.

The synthesis of natural aloperine was completed in two additional steps. First, deoxygenation of **67** was effected under Barton's conditions by esterification with pentafluorophenyl chlorothionoformate and subsequent treatment with Bu_3SnH/AIBN, providing **69** in 70% yield.[39] Second, and rather surprisingly, both the lactam carbonyl and the tosyl protecting group were cleanly removed with $LiAlH_4$ at room temperature to give (+)-**1** in 88% yield. Synthetic **1** was indistinguishable from natural aloperine by ^{1}H NMR, ^{13}C NMR, IR, and TLC comparisons. The specific optical rotation of synthetic **1** at the sodium D line (+83.0) also agreed well with that of the natural material (+85.1),[2e] and is consistent with the 97% enantiopurity of (*R*)-**38**.

(50) Intramolecularity was critical to the success of the cycloaddition, since reaction of β-silyl acrylate **52** with **58** failed to yield cycloaddition products at temperatures as high as 165 °C.

(51) Attempts to oxidize the C−Si bond in these disiloxanes failed.

(52) We also attempted a one-step cleavage of the N−Si and C−Si bonds by reaction with CsF or TAS-F in DMF at elevated temperature. Such a transformation is precendented with oxasilacyclopentanes: Hale, M. R., Hoveyda, A. H. *J. Org. Chem.* **1992**, *57*, 1643.

(53) The authors have deposited atomic coordinates for **68** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 23 Union Road, Cambridge, CB2 1EZ, UK.

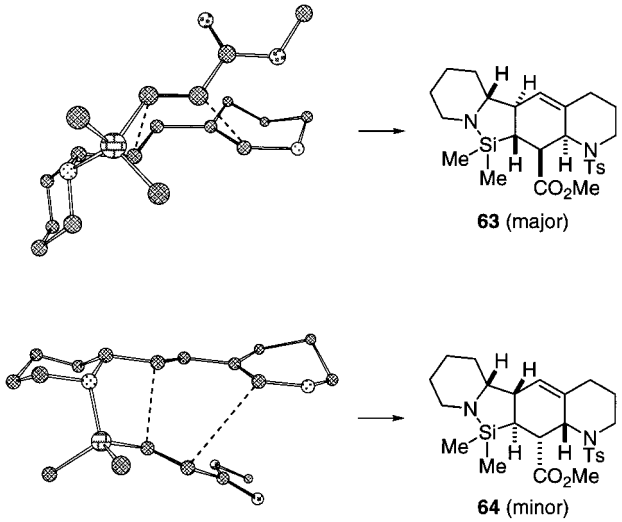
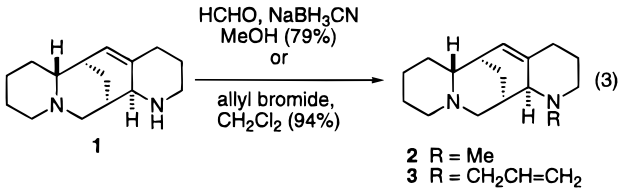


Figure 2. Models of the *lk* and *ul* transition states that lead to cycloadducts **63** and **64**. The *p*-toluenesulfonyl group is not shown.

Synthetic aloperine was also methylated and allylated, furnishing (+)-*N*-methylaloperine (**2**) and (+)-*N*-allylaloperine (**3**), in 79% and 94% yields, respectively. These simple conversions completed enantioselective total syntheses of all members of the aloperine family of natural products (eq 3).



Conclusion

The first total syntheses of aloperine (**1**) and congeners **2** and **3** were accomplished in an enantioselective fashion. The synthesis of **1** is notably concise and proceeds from commercially available 3-hydroxypiperidine hydrochloride (**54**) and (*R*)-pipecolinic acid (**35**) in a convergent fashion by way of a total of nine isolated and purified intermediates. The synthesis is sufficiently efficient, 24% overall yield from (*R*)-(+)-pipecolinic acid, that 1.4 g of (+)-aloperine (**1**) could be prepared from 4 g of this starting material. The defining step in the synthesis is an intramolecular Diels−Alder reaction of cycloaddends joined by an *N*-silylamine linkage: **62** → **63**. To our knowledge, this is the first use of a *N*−Si bond as a readily introduced and easily removable temporary tether for intramolecular Diels−Alder cycloaddition reactions.[40]

Our early exploratory studies also introduced a convenient method for tethering cycloaddition partners with a sulfonamide unit to trigger a rare intramolecular Diels−Alder cycloaddition of a vinylsulfonamide: **45** → **46**.

Experimental Section[54]

(2*R*)-2-Vinylpiperidine-1-carboxylic Acid *tert*-Butyl Ester [(*R*)-38]. Potassium bis(trimethylsilyl)amide (0.5 M in toluene, 49.0 mL, 24.5 mmol) was added over 10 min to a cold (0 °C), stirred suspension of dry methyltriphenylphosphonium bromide (9.47 g, 26.5 mmol) and THF (80 mL). The bright yellow mixture was stirred at 0 °C for 45 min and then cooled to −78 °C, whereupon a solution of aldehyde (*R*)-**37**[55] (4.33 g, 20.3 mmol) and THF (15 mL) was added via cannula. The resulting solution was maintained at 0 °C for 1.5 h and then partitioned between saturated aqueous NH_4Cl (200 mL) and Et_2O (250 mL). The layers were separated, the aqueous layer was extracted with Et_2O (2 × 250 mL), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated to remove all volatiles. The residue was purified on silica gel (9:1 petroleum ether−Et_2O), affording 4.07 g (95%) of (*R*)-**38** as a clear oil: $[\alpha]^{23}_D$ +35.3, $[\alpha]^{23}_{577}$ +36.8, $[\alpha]^{23}_{546}$ +42.3, $[\alpha]^{23}_{435}$ +77.2, $[\alpha]^{23}_{405}$ +93.4 (c = 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.72 (ddd, J = 17.4, 10.6, 4.2 Hz, 1H), 5.14 (dddd, J = 10.6, 1.4, 1.4, 0.7 Hz, 1H), 5.01 (dddd, J = 17.4, 1.4, 1.4, 0.6 Hz, 1H), 4.75 (br s, 1H), 3.92 (br d, J = 13.2 Hz, 1H), 2.80 (dt, J = 12.9, 2.8 Hz, 1H), 1.74−1.69 (m, 1H), 1.68−1.61 (m, 1H), 1.58−1.53 (m, 2H), 1.49−1.30 (m, 2H), 1.42 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.3, 136.8, 115.4, 79.2, 52.4, 39.6, 28.9, 28.4, 25.5, 19.4; IR (film) 3083, 2977, 1694, 1406, 1185 cm^{-1}; HRMS (FAB) m/z 155.0939 (MH − *t*-Bu, 155.0946 calcd for $C_8H_{13}NO_2$). Anal. Calcd for $C_{12}H_{21}NO_2$: C, 68.21; H, 10.02; N, 6.63. Found: C, 67.92; H, 10.04; N, 6.44. The enantiomeric purity was determined by the procedure described in ref 46.

1-(*p*-Toluenesulfonyl)-piperidin-3-one (55). Solid *p*-toluenesulfonyl chloride (10.2 g, 53.5 mmol) was added in portions to a cold (0 °C), rapidly stirred suspension of 3-hydroxypiperidine hydrochloride (**54**) (6.88 g, 50.0 mmol), triethylamine (20.9 mL, 150 mmol), and CH_2Cl_2 (200 mL). The cooling bath was removed and the mixture was stirred at room temperature for 3 h and then poured into H_2O (200 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 75 mL). The combined organic layers were washed with 1 N HCl (150 mL), the aqueous layer re-extracted with CH_2Cl_2 (2 × 50 mL), and the combined organic layers were then dried (K_2CO_3), filtered, and concentrated, affording 1-(*p*-toluenesulfonyl)-piperidin-3-ol as a light yellow solid: mp 104−105 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64−7.63 (m, 2H), 7.33−7.31 (m, 2H), 3.86−3.84 (m, 1H), 3.32−3.20 (m, 1H), 3.12−3.09 (m, 1H), 2.79−2.75 (m, 1H), 2.69−2.67 (m, 1H), 2.43 (s, 3H), 2.12 (br s, 1H), 1.84−1.80 (m, 1H), 1.76−1.72 (m, 1H), 1.63−1.59 (m, 1H), 1.39−1.35 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.6, 133.1, 129.7, 127.6, 65.7, 52.5, 46.2, 31.6, 21.8, 21.5; IR (film) 3510, 2943, 2855, 1597, 1449, 1339, 1165, 750 cm^{-1}; HRMS (CI−isobutane) m/z 255.0926 (M, 255.0929 calcd for $C_{12}H_{17}NO_3S$). Anal. Calcd for $C_{12}H_{17}NO_3S$: C, 56.45; H, 6.71; N, 5.49. Found: C, 56.54; H, 6.78; N, 5.52.

Jones' reagent (2.7 M, 20 mL, 55 mmol) was added to a cold (0 °C) solution of this crude alcohol and acetone (200 mL). The resulting mixture was stirred rapidly at room temperature for 2 h, and then *i*-PrOH (3 mL) was added. The mixture was filtered through a plug of glass wool, the filtercake was washed with acetone, and the filtrate was concentrated to an approximate volume of 70 mL. The residue was partitioned between saturated aqueous $NaHCO_3$ (150 mL), Et_2O (200 mL), and EtOAc (200 mL), the layers were separated, and the organic layer was washed with H_2O (100 mL) and saturated aqueous NaCl (100 mL). The combined aqueous layers were extracted with Et_2O (2 × 100 mL), and the combined organic extracts were dried (K_2CO_3), filtered, and concentrated. This afforded 11.3 g (89%) of ketone **55** as a colorless solid which was judged to be >95% pure by ^{1}H NMR and was used without further purification.

(54) The procedure we employed to purify THF, CH_2Cl_2, and toluene has been described: Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518. Triethylamine, pyridine, and diisopropylethylamine were distilled from CaH_2 at atmospheric pressure. Other general experimental details have been described: Deng, W.; Overman, L. E. *J. Am. Chem. Soc.* **1994**, *116*, 11241.

(55) An improved preparation of this known compound is described in the Supporting Information.

Analytically pure material could be obtained by precipitation from CH_2Cl_2, petroleum ether, and Et_2O (1:2:1): mp 99−100 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66−7.64 (m, 2H), 7.34 (d, J = 8.1 Hz, 2H), 3.58 (s, 2H), 3.27 (t, J = 5.8 Hz, 2H), 2.43 (s, 3H), 2.35 (t, J = 6.9 Hz, 2H), 2.03−1.98 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.6, 144.2, 132.5, 129.9, 127.7, 55.7, 44.5, 37.9, 22.7, 21.5; IR ($CHCl_3$) 2958, 1729, 1355, 1166 cm^{-1}; HRMS (CI−isobutane) *m*/*z* 253.0771 (M, 253.0773 calcd for $C_{12}H_{15}NO_3S$). Anal. Calcd for $C_{12}H_{15}NO_3S$: C, 56.90; H, 5.97; N, 5.53. Found: C, 56.94; H, 5.98; N, 5.46.

Trifluoromethanesulfonic Acid 1-(*p*-Toluenesulfonyl)-1,4,5,6-tetrahydro-pyridin-3-yl Ester (56). Lithium bis(trimethylsilyl)amide (1.0 M in THF, 11.3 mL, 11.3 mmol) was added to a cold (−78 °C) solution of ketone **55** (3.00 g, 11.8 mmol) and THF (59 mL). The solution was maintained at −78 °C for 5 min, warmed to 0 °C, and then maintained for 1.0 h. The resulting light-orange solution was recooled to −78 °C, and a solution of *N*-phenyltrifluoromethanesulfonimide (5.50 g, 15.4 mmol) and THF (20 mL) was added rapidly. The mixture was warmed to 0 °C, maintained for 45 min, allowed to come to room temperature, and then maintained for an additional 6 h. The reaction mixture was then partitioned between saturated aqueous $NaHCO_3$ (300 mL) and Et_2O (500 mL), the layers were separated, and the aqueous layer was extracted with Et_2O (2 × 500 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. The residue was purified on silica gel (3:1 benzene-hexanes), affording 1.84 g (40%) of the unstable, regioisomerically pure triflate **56** which was contaminated by a small amount of an unidentified byproduct (<5% by ^{1}H NMR): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, J = 8.3 Hz, 2H), 7.34 (d, J = 8.1 Hz, 2H), 7.04 (s, 1H), 3.32−3.30 (m, 2H), 2.44 (s, 3H), 2.30 (dt, J = 6.3, 1.2 Hz, 2H), 1.77−1.72 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.6, 135.8, 133.9, 130.0, 127.2, 121.8, 119.7, 117.2, 42.9, 24.9, 21.6, 20.0; IR (film) 3102, 2931, 2867, 1418, 1357 cm^{-1}; HRMS (CI−NH_3) *m*/*z* 386.0339 (MH, 386.0343 calcd for $C_{13}H_{15}F_3NO_5S_2$). Anal. Calcd for $C_{13}H_{14}F_3NO_5S_2$: C, 40.52; H, 3.66; N, 3.63. Found: C, 40.64; H, 3.73; N, 3.65.

(2*R*)-2-{(1*E*)-2-[1-(*p*-Toluenesulfonyl)-1,4,5,6-tetrahydro-pyridin-3-yl]-vinyl}-piperidine-1-carboxylic acid *tert*-butyl Ester ((*R*)-57). A round-bottomed flask equipped with a stir bar and rubber septum was charged with alkene (*R*)-**38** (2.76 g, 13.1 mmol), triflate **56** (5.81 g, 15.0 mmol), tetrabutylammonium trifluoromethanesulfonate (6.52 g, 16.6 mmol), K_2CO_3 (5.75 g, 41.6 mmol), H_2O (1.50 mL, 83.2 mmol), and DMF (22 mL).[30] The mixture was degassed at 0.5 mm for ∼1 min and then purged with argon. This evacuation/purge cycle was repeated several times until bubbling from the mixture had nearly subsided. Palladium(II) acetate (374 mg, 1.67 mmol) was added and the evacuation/purge cycle was repeated several more times. The resulting mixture was heated at 55 °C with rapid stirring for 14 h and then partitioned between Et_2O (150 mL) and saturated aqueous NH_4Cl (50 mL). The layers were separated, the organic layer was washed with H_2O (50 mL) and saturated aqueous NaCl (50 mL), and the combined aqueous layers were extracted with Et_2O (2 × 100 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. The residue was purified on silica gel (2:1 petroleum ether−Et_2O), affording 4.84 g (83%) of diene (*R*)-**57** as a viscous oil: $[\alpha]^{23}_D$ +39.6, $[\alpha]^{23}_{577}$ +40.6, $[\alpha]^{23}_{546}$ +46.5, $[\alpha]^{23}_{435}$ +87.0, $[\alpha]^{23}_{405}$ +108.6 (c = 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, J = 8.3 Hz, 2H), 7.29 (d, J = 8.4 Hz, 2H), 6.70 (s, 1H), 5.95 (d, J = 15.3 Hz, 1H), 5.38 (dd, J = 15.8, 5.0 Hz, 1H), 4.82 (br s, 1H), 3.92 (d, J = 13.3 Hz, 1H), 3.36−3.33 (m, 2H), 2.79 (td, J = 12.9, 2.6 Hz, 1H), 2.41 (s, 3H), 2.03 (t, J = 6.2 Hz, 2H), 1.73−1.66 (m, 4H), 1.58−1.48 (m, 2H), 1.46 (s, 9H), 1.44−1.32 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.3, 143.7, 134.9, 130.9, 129.8, 126.9, 125.0, 123.9, 118.5, 79.3, 52.0, 43.7, 39.7, 29.5, 28.4, 25.5, 21.5, 21.0, 20.6, 19.5; IR (film) 3073, 2934, 2861, 1682, 1652, 1416, 1360, 1265, 1162 cm^{-1}; HRMS (FAB) *m*/*z* 469.2131 (M + Na, 469.2137 calcd for $C_{24}N_{34}N_2NaO_4S$). Anal. Calcd for $C_{24}H_{34}N_2O_4S$: C, 64.55; H, 7.67; N, 6.27. Found: C, 64.44; H, 7.77; N, 6.16.

(6*R*,7*R*,13*R*,14*R*,15*S*)-14-Hydroxy-1-(*p*-toluenesulfonyl)-tetradecahydro-6,13-methano-dipyrido[1,2-a;3′,2′-e]azocin-12-one (67) and (6*S*,7*R*,13*S*,14*S*,15*R*)-14-Hydroxy-1-(*p*-toluenesulfonyl)-tetradecahydro-6,13-methano-dipyrido[1,2-a;3′,2′-e]azocin-12-one (68). Iodotrimethylsilane (2.9 mL, 20 mmol) was added to a solution of diene (*R*)-**57** (3.60 g, 8.06 mmol), 2,6-lutidine (3.8 mL, 32 mmol) and CH_2Cl_2 (20 mL) at room temperature. After 10 min, MeOH (7 mL) was added dropwise, and the mixture was maintained for an additional 15 min and then was concentrated. The residue was partitioned between CH_2Cl_2 (100 mL) and 1 N NaOH (50 mL), the layers were separated, and the aqueous layer was extracted further with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were dried (K_2CO_3−$MgSO_4$), filtered, and concentrated, affording the crude secondary amine **58** as a nearly colorless oil, which was dried by azeotropic removal of H_2O with benzene (3 × 25 mL).

In a separate flask, triflic acid (1.8 mL, 20 mmol) was added to a solution of silylacrylate **52** (3.33 g, 15.1 mmol) and CH_2Cl_2 (16 mL) at room temperature. The resulting solution was maintained for 2 h and then cooled to 0 °C. Triethylamine (4.1 mL, 30.2 mmol) was added, the resulting solution was maintained at 0 °C for 10 min, and then a solution of the secondary amine **58** and CH_2Cl_2 (10 mL) was added to this solution of crude silyltriflate **53**. The cooling bath was removed, and the solution was maintained for 3 h to provide a mixture of cycloadducts **63** and **64**. Diagnostic characterization data:^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84 and 5.82 (s, 1H total), 4.54 and 4.52 (s, 1H total), 3.66 and 3.65 (s, 3H total).

Pyridine·HF (0.84 mL) was added at room temperature to this mixture of crude cycloadducts, and the resulting solution was maintained for an additional 2 h. The reaction was concentrated in vacuo (20 mm), and the brown residue was suspended in mesitylene (50 mL) and heated at reflux for 3.5 h. Volatile materials were then removed by distillation (100 °C oil bath, 20 mm), affording a 4.5:1 mixture of tetracyclic silyl fluorides **65** and **66**. Diagnostic characterization data: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98−7.95 (m, 2H), 7.34−7.32 (m, 2H), 5.66−5.64 (m, 1H), 4.81−4.77 (m, 1H), 4.68 (br s, 1H), 3.55 and 3.53 (app q, J = 8.0 Hz, 1H), 0.29 (d, J = 8.0 Hz, 3H), 0.29 (d, J = 8.0 Hz, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ 162.8 (octet, J = 7.9 Hz); HRMS (CI−isobutane) *m*/*z* 477.2053 (MH, 477.2043 calcd for $C_{24}H_{34}N_2O_3FSSi$).

Hydrogen peroxide (30% aqueous, 13.5 mL, 120 mmol) was added to a suspension of this mixture of **65** and **66**, $KHCO_3$ (2.25 g, 22.5 mmol), KF (3.04 g, 52.3 mmol), MeOH (50 mL), and THF (50 mL). The resulting mixture was heated at reflux for 1.5 h and allowed to cool to room temperature. Then a solution of saturated aqueous $NaHSO_3$ (100 mL) was added. The mixture was stirred for 0.5 h, and the organic solvents were removed by distillation under reduced pressure. The resulting suspension was extracted with CH_2Cl_2 (3 × 200 mL). The combined organic layers were dried (K_2CO_3−$MgSO_4$), filtered, and concentrated, affording an oil which was purified on silica gel (EtOAc), furnishing 2.11 g (63%) of tetracyclic alcohol **67** as a colorless solid: mp 228 °C; $[\alpha]^{23}_D$ +129, $[\alpha]^{23}_{577}$ +133,

$[\alpha]^{23}_{546}$ +152, $[\alpha]^{23}_{435}$ +263, $[\alpha]^{23}_{405}$ +318 (c = 0.27, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 5.49 (br s, 1H), 5.02 (br s, 1H), 4.76 (br d, J = 11.6 Hz, 1H), 4.39 (br s, 1H), 3.58 (dd, J = 15.2, 7.2 Hz, 1H), 3.50 (br s, 1H), 3.14 (br d, J = 10.8 Hz, 1H), 3.06−3.09 (m, 1H), 2.80−2.72 (m, 1H), 2.41 (s, 3H), 2.41−2.35 (m, 2H), 2.08−2.04 (m, 1H), 1.92−1.46 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 143.0, 137.7, 135.5, 129.5, 127.6, 122.2, 64.7, 61.4, 54.4, 47.9, 43.6, 41.0, 40.3, 32.8, 27.1, 25.4, 25.3, 23.6, 21.5; IR (film) 3380, 2939, 2860, 1623, 1444, 1340, 1157, 732 cm^{-1}; HRMS (CI−isobutane) m/z 417.1845 (MH, 417.1848 calcd for $C_{22}H_{29}N_2O_4S$). Anal. Calcd for $C_{22}H_{28}N_2O_4S$: C, 63.44; H, 6.78; N, 6.73. Found: C, 63.26; H, 6.74; N, 6.66.

Also isolated was 0.45 g (13%) of the diastereomeric tetracyclic alcohol **68** as a colorless solid: mp 197 °C; $[\alpha]^{23}_D$ −141, $[\alpha]^{23}_{577}$ −148, $[\alpha]^{23}_{546}$ −172, $[\alpha]^{23}_{435}$ −291, $[\alpha]^{23}_{405}$ −353 (c = 0.38, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (d, J = 8.2 Hz, 2H), 7.28 (d, J = 8.2 Hz, 2H), 5.49 (br s, 1H), 5.02 (br s, 1H), 4.96 (br s, 1H), 4.64 (br d, J = 12.2 Hz, 1H), 4.20 (br s, 1H), 3.58 (dd, J = 15.2, 8.0 Hz, 1H), 3.32−3.30 (m, 1H), 3.20 (br s, 1H), 3.09−3.07 (m, 1H), 2.77−2.74 (m, 1H), 2.53 (br s, 1H), 2.44−2.40 (m, 1H), 2.39 (s, 3H), 2.10 (dd, J = 13.0, 9.8 Hz, 1H), 1.91−1.79 (m, 3H), 1.70−1.64 (m, 2H), 1.42−1.37 (m, 3H), 1.18−1.13 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.6, 143.1, 137.7, 136.7, 129.5, 127.7, 119.8, 67.8, 59.6, 55.2, 48.2, 42.1, 41.1, 39.7, 30.2, 27.6, 25.2, 24.3, 24.1, 21.5; IR (film) 3380, 3054, 2940, 2858, 1629, 1442, 1339, 1158, 737 cm^{-1}; HRMS (CI−isobutane) m/z 417.1839 (MH, 417.1848 calcd for $C_{22}H_{29}N_2O_4S$). Anal. Calcd for $C_{22}H_{28}N_2O_4S$: C, 63.44; H, 6.78; N, 6.73. Found: C, 63.38; H, 6.72; N, 6.69. Single crystals suitable for X-ray analysis were obtained by recrystallization from ethyl acetate.

(6*R*,7*R*,13*S*,15*S*)-1-(*p*-Toluenesulfonyl)-tetradecahydro-6,13-methano-dipyrido[1,2-a;3′,2′-e]azocin-12-one (69). By following the procedures of Barton,[39] pentafluorophenyl chlorothionoformate (4.26 g, 16.2 mmol) was added to a solution of tetracyclic alcohol **67** (3.75 g, 9.00 mmol), DMAP (2.20 g, 18.0 mmol), pyridine (2.14 g, 27.0 mmol), and CH_2Cl_2 (30 mL) at room temperature. The resulting solution was maintained for 0.5 h, H_2O (5 mL) was added, and the mixture was stirred for 10 min and then partitioned between 0.5 N HCl (80 mL) and CH_2Cl_2 (150 mL). The layers were separated, and the aqueous layer was extracted further with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were washed with 0.5 N HCl (50 mL), and the aqueous layer was then re-extracted with CH_2Cl_2 (2 × 50 mL). This procedure was repeated once more. The combined organic extracts were dried (K_2CO_3−$MgSO_4$), filtered, and concentrated, affording the crude thiocarbonate as an oil.

To a solution of the crude thiocarbonate from above, AIBN (386 mg, 2.35 mmol), and benzene (90 mL) was added tributyltin hydride (7.3 mL, 27.0 mmol). The reaction flask was evacuated (20 mm) and refilled with N_2. This procedure was repeated once more, and then the solution was heated at reflux for 1 h. The reaction mixture was then concentrated, and the residue was purified on silica gel (2:1 EtOAc−Petroleum ether), affording 2.35 g (70%) of **69** as a colorless solid: mp 157−158 °C; $[\alpha]^{23}_D$ +127, $[\alpha]^{23}_{577}$ +131, $[\alpha]^{23}_{546}$ +151, $[\alpha]^{23}_{435}$ +257, $[\alpha]^{23}_{405}$ +308 (c = 0.55, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, J = 8.1 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 5.59 (br s, 1H), 4.78−4.76 (m, 2H), 3.42 (dd, J = 15.3, 7.0 Hz, 1H), 3.10 (d, J = 10.2 Hz, 1H), 2.80−2.78 (m, 1H), 2.76−2.69 (m, 1H), 2.39 (s, 3H), 2.33 (td, J = 12.8, 2.1 Hz, 1H), 2.19−1.84 (m, 7H), 1.62−1.39 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.5, 143.0, 137.7, 135.9, 129.4, 127.9, 125.5, 62.1, 58.1, 43.7, 41.1, 40.6, 33.6, 32.5, 27.4, 25.5, 25.3, 24.4, 23.9, 21.5; IR (film) 2942, 1634, 1443, 1345, 1156, 749 cm^{-1}; HRMS (CI−isobutane) m/z 401.1897 (MH, 401.1899 calcd for $C_{22}H_{29}N_2O_3S$). Anal. Calcd for $C_{22}H_{28}N_2O_3S$: C, 65.97; H, 7.05; N, 6.99. Found: C, 65.74; H, 7.02; N, 6.90.

(+)-Aloperine (1). Solid $LiAlH_4$ (60 mg) was added to a solution of **69** (124 mg, 0.31 mmol) and THF (3 mL) at room temperature, and the resulting suspension was stirred for 18 h. Et_2O (20 mL) was then added, followed by the dropwise addition of water (3 drops) and 10 N NaOH (3 drops). After the gas evolution had ceased, the mixture was filtered and the filtrate concentrated to afford (+)-aloperine (58 mg, 81%) which was >95% pure by NMR analysis. A larger scale reduction of **69** (2.80 g, 7.00 mmol), affording (+)-aloperine (1.40 g, 88%) required repeated additions of fresh $LiAlH_4$ (3 × 1.5 g) to complete the reaction. Pure (+)-aloperine (**1**) was obtained as large, colorless prisms by chromatography on silica gel (90:9:1 CH_2Cl_2−MeOH−TFA), followed by liberation of the free base from the formed bis(hydrotrifluoroacetate) (CH_2Cl_2 extraction from 1 N NaOH), and finally recrystallization from petroleum ether: mp 70−70.5 °C; $[\alpha]^{23}_D$ +83.0, $[\alpha]^{23}_{577}$ +86.0, $[\alpha]^{23}_{546}$ +97.9, $[\alpha]^{23}_{435}$ +170, $[\alpha]^{23}_{405}$ +206 (c = 1.05, EtOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.43 (d, J = 6.1 Hz, 1H), 3.15 (d, J = 6.2 Hz, 1H), 3.12−3.09 (m, 1H), 2.90 (dd, J = 11.8, 5.0 Hz, 1H), 2.77−2.74 (m, 1H), 2.65 (td, J = 12.9, 2.3 Hz, 1H), 2.55 (td, J = 13.0, 2.5 Hz, 1H), 2.47 (dd, J = 11.7, 3.4 Hz, 1H), 2.31−2.25 (m, 2H), 2.11−2.06 (m, 2H), 1.85−1.30 (m, 8H), 1.20 (d, J = 13.4 Hz, 1H), 1.11 (dd, J = 13.0, 1.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.2, 124.8, 61.1, 58.5, 55.1, 48.5, 46.8, 35.5, 33.2, 32.9, 29.6, 26.4, 25.8, 25.6, 21.1; IR (film) 3278, 2923, 2851, 1651, 1454, 1105, 842 cm^{-1}; HRMS (CI−isobutane) m/z 232.1940 (M, 232.1939 calcd for $C_{15}H_{24}N_2$). Anal. Calcd for $C_{15}H_{24}N_2$: C, 77.53; H, 10.41; N, 12.06. Found: C, 77.60; H, 10.36; N, 12.01.

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Supporting Information Available: Experimental procedures and characterization data for (+)-*N*-methylaloperine (**2**) and (+)-*N*-allylaloperine (**3**); new compounds reported in Schemes 2, 3, 6, 7 and 8; compounds (*R*)-**37** and **52**; and copies of 500 MHz ^{1}H NMR and 125 MHz ^{13}C NMR spectra of synthetic (+)-aloperine (18 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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