Total Synthesis of (±)-Tazettine

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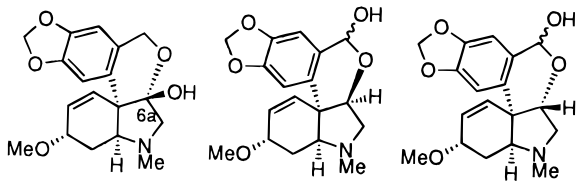
Abstract: The total synthesis of (±)-tazettine (**1**) has been achieved in 16 steps from commercially available piperonyl alcohol in 11% overall yield. The crucial quaternary center was assembled by a novel [4+1] cycloaddition between dimethoxycarbene and *β*-aryl vinyl isocyanate (**4**). Samarium diiodide conditions were employed to reduce the enamide unsaturation in the [2]benzopyrano[3,4-*c*]hydroindole intermediate **19** to compound **20** exhibiting a *cis*-AB ring fusion.

Introduction

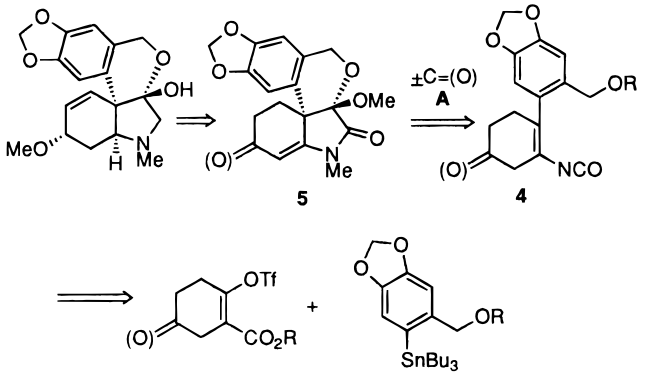
The *Amaryllidaceae* alkaloids have long been a rich source of structural diversity that continues to challenge the capabilities of contemporary organic synthesis.[1] The [2]benzopyrano[3,4-*c*]hydroindole derived members of this family, as exemplified by tazettine (**1**), pretazettine (**2**), and 6a-epipretazettine (**3**), are an intriguing group of natural products, and the anticancer activity exhibited, in particular, by pretazettine has recently stimulated considerable interest in these compounds.[2] Tazettine also exhibits mild activity against certain tumor cell lines.[2d] While tazettine was one of the earliest known members of this class of compounds, it appears now to be only an artifact of a facile base-mediated Cannizzaro-like rearrangement of pretazettine.[3] Indeed, a reinvestigation of the alkaloids of *Aprekelia formosissima* and *Ismene calithina*[4a,b] as well as other species[4c,d] under conditions designed to suppress the pretazettine to tazettine conversion revealed that little, if any, of the latter material was present in the extracts.



A noteworthy structural feature common to all of these species is the sterically congested quaternary carbon center located at the hydroindolone bridgehead, which represents a major challenge to any total synthesis endeavor, and a number of creative strategies have emerged over the years to address this problem.[5] Total syntheses of members of this group of alkaloids have been reported by Hendrickson,[6] Tsuda,[7] Danishefsky,[8] White,[9] Martin,[10] and Overman,[11] as have a number of important approaches into the characteristic core ring system.[12]

Scheme 1 outlines the basic tenets of our synthesis strategy into the [2]benzopyrano[3,4-*c*]hydroindole system of tazettine. Recognizing that carbon 6a is at the carbonyl oxidation level,

Scheme 1



‡ To whom inquiries regarding X-ray determinations should be directed.

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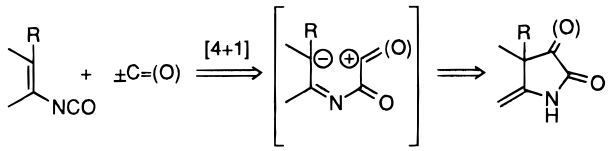
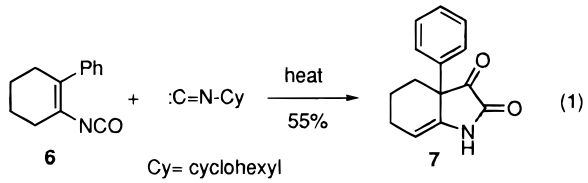
Scheme 2



the key bond construction becomes an insertion of a carbonyl 1,1-dipole equivalent (**A**) between the reactive termini of an appropriately functionalized β-aryl vinyl isocyanate **4**. This operation simultaneously assembles the hydroindolone substructure and creates the critical quaternary center at the incipient ring fusion position in intermediate **5**. The vinyl isocyanate substrate would in turn be derived from the combination of a substituted aryl unit with an appropriately functionalized A-ring building block via a palladium(0)-mediated cross-coupling process.

The propensity to react as a 1,4-dipolar equivalent makes the vinyl isocyanate function particularly versatile for nitrogen heterocycle construction, and 1,2-dipole reagents such as enamines, ester enolates, and benzyne have been previously combined with these species to produce a range of substituted pyridine products at various oxidation levels.[13] More recently, alkyl and aryl isocyanides have been shown to be useful carbonyl 1,1-dipole equivalents in reactions with vinyl isocyanates to produce highly functionalized hydroindolone products.[14] Formally this transformation represents a net [4+1] cycloaddition process, and as such, was regarded as ideally suited for assembling the hydroindole substructure of tazettine and related alkaloids wherein position 6a was at the carbonyl oxidation level or could be easily derived from a carbonyl group. The putative pathway followed by this reaction involves an initial addition of the nucleophilic isocyanide to the carbonyl carbon of the isocyanate function to produce a dipolar intermediate that undergoes cyclization and tautomerization to give the observed product (Scheme 2).



(1)

The suitability of this overall strategy for constructing tazettine and related alkaloids, however, was critically dependent on how effectively the [4+1] cycloaddition protocol could creat carbon−carbon bonds at sterically congested sites. The *intramolecular* nature of the second bond forming event depicted in Scheme 2 was reason for optimism in this regard, but it was considered prudent to examine appropriate model systems prior to embarking on the actual total synthesis route. To that end, a model study relevant to [2]benzopyrano[3,4-*c*]hydroindole ring construction revealed that β-phenylvinyl isocyanate **6** provided hydroindolone **7** in quite reasonable yield when treated with excess cyclohexyl isocyanide at elevated temperatures (eq 1), thus setting the stage for further development of the process as the key ring assembly event in a synthesis of tazettine.

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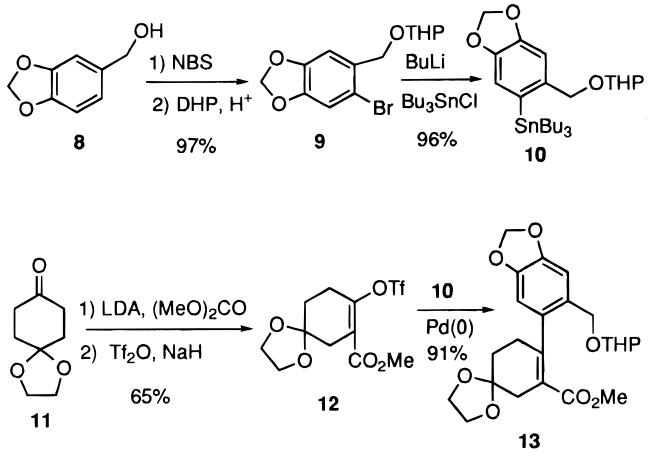
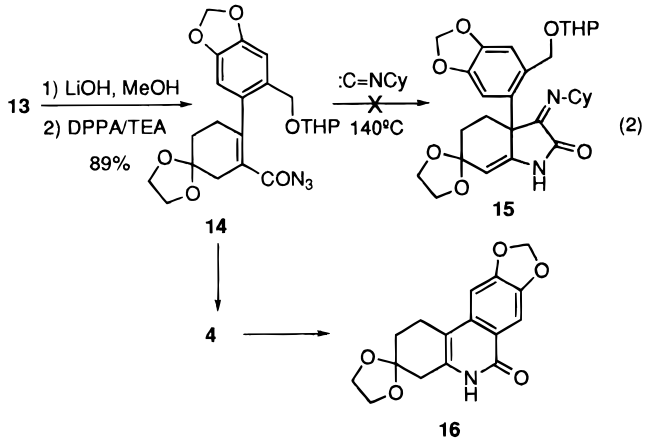
Scheme 3



Results and Discussion

Synthesis of the [2]Benzopyrano[3,4-*c*]hydroindole Core Structure of Tazettine. Encouraged by the success of the model study described in eq 1, the synthesis of tazettine was initiated with the assembly of the key AC ring fragment **13**[15] (Scheme 3). Thus, conversion of commercially available piperonyl alcohol **8** into the known bromide **9**[16] proceeded in virtually quantitative yield, and subsequent metal−bromide exchange followed by routine stannylation of the resultant aryllithium intermediate afforded the arylstannane **10** in excellent yield. The corresponding A-ring building block was prepared by carbomethoxylation[17] of commercial **11** followed by conversion into the vinyl triflate **12**.[18] Stille cross coupling of **10** and **12**[19] under optimized conditions afforded the α,β-unsaturated ester **13** in 91% yield, thus providing the substrate upon which the crucial [4+1] cycloaddition step would be attempted.



(2)

Routine processing of the ester in compound **13** into the requisite acyl azide **14** was accomplished by saponification to the carboxylic acid with LiOH followed by treatment with diphenylphosphorazidate (DPPA) in the presence of triethylamine (TEA).[20] Heating this moderately labile material in the

(15) The ring designations orignally suggested by Wildman[4] are employed in this paper.

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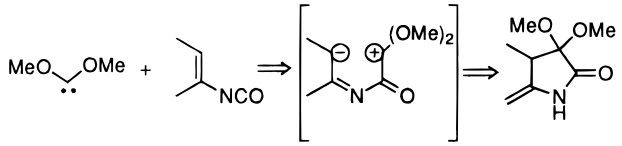
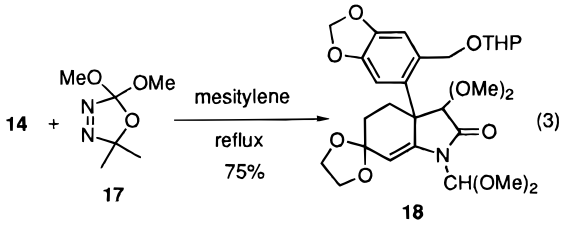


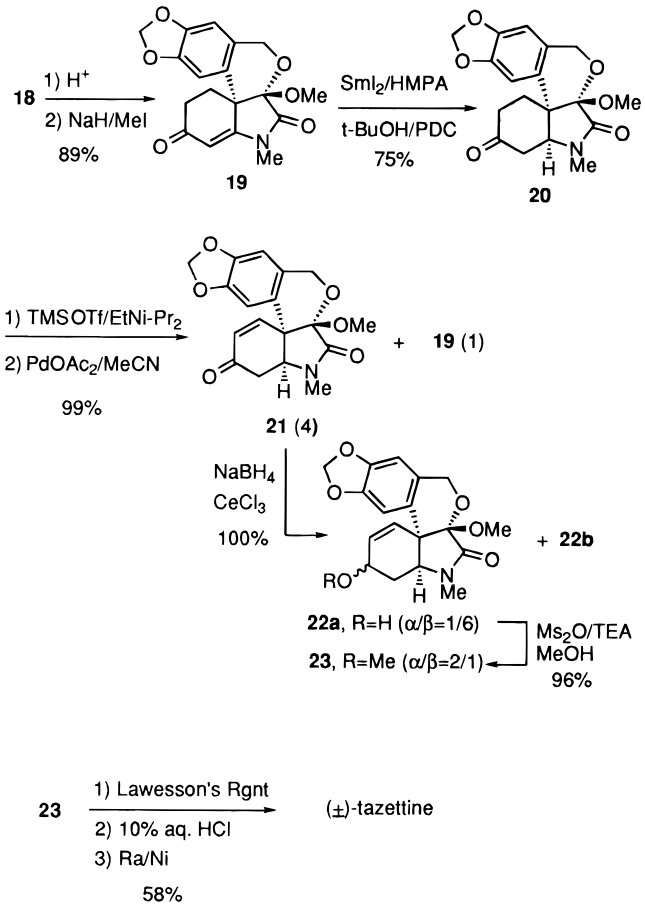
Figure 1. Reaction of dimethoxycarbene with a vinyl isocyanate.

presence of excess cyclohexyl isocyanide in refluxing xylenes under conditions identical to those use for the preparation of **7** (eq 1) failed to deliver *any* of the desired hydroindolone **15**.



Control experiments confirmed that isocyanate **4** was in fact being produced, but it proved resistant to further reaction with the isocyanide reaction partner, even under the most forcing conditions. A wide range of reaction conditions and isocyanide partners were examined in this context, but to no avail. Indeed the major product of the reaction in this case was the benzo-[*c*]quinolone **16** presumably arising from an electrocyclic closure of the β-arylvinyl isocyanate followed by loss of the CH_2OTHP side chain.[21] The very different behavior of the ostensibly similar isocyanates **6** and **4** was initially quite puzzling; however, there is circumstantial evidence suggesting that angular aryl groups possessing ortho substituents in this type of system may be substantially more sterically hindered than those without comparable substituents.[22] On the basis of this analysis, it was reasoned that a sterically less demanding and more reactive carbonyl 1,1-dipole equivalent would be more likely to deliver the desired [4+1] adduct. Consequently, so-called nucleophilic carbenes,[23] and in particular dimethoxycarbene,[24] were considered as candidate 1,1-dipole equivalents for use in the [4+1] cycloaddition process in this environment. It was presumed that dimethoxycarbene would initially add to the carbonyl carbon of the isocyanate in a fashion analogous to the presumed pathway followed by isocyanides. Subsequent cyclization of the resultant dipolar intermediate would ensue to afford a functionalized indolone product as before (Figure 1). While these intriguing reactive intermediates have been the subject of considerable investigation from a more theoretical perspective, it has been only recently that synthetic applications for these species have been considered.[23−25] In light of the current

Scheme 4



paucity of useful 1,1-dipole equivalents, these species could emerge as important additions to the synthetic arsenal if they can be shown to react in a productive fashion.[25]

In the event, heating acyl azide **14** in the presence of an excess of the readily available Warkentin oxadiazoline **17**[26] in refluxing mesitylene afforded the key hydroindolone **18** as a 2:1 carbene/isocyanate adduct in 75% yield. This material is the result of a reaction pathway that presumably involves initial [4+1] cycloaddition of dimethoxycarbene across the vinyl isocyanate followed by a second, very rapid insertion into the N−H bond of the enamide emerging from the first step. This 2:1 addition reaction channel has been shown to be typical of these transformations in most circumstances.[25] With compound **18**, the entire carbon skeleton of tazettine was in hand and all that remained was a set of functional group manipulations that were presumed at the time to be routine.

Conversion of 18 into (±)-Tazettine. Among the transformations needed to convert **18** into the target molecule was the reduction of the enamide unsaturation that was formed during the [4+1] cycloaddition event. Achieving this objective proved to be an unexpected challenge. Treatment of **18** with aqueous acid removed the amide nitrogen substituent as well as effecting cyclization of the benzyl alcohol onto the indolone moiety to provide the fully formed [2]benzopyrano[3,4-*c*]hydroindole ring system. This material was then simultaneously methylated at the enamide nitrogen and at the cyclic hemiacetal oxygen to afford **19** in excellent overall yield. The stage was then set for

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reduction of the enamide double bond to the requisite cis-fused hydroindolone found in the target molecule. Numerous methods for effecting this transformation were examined at this juncture of the synthesis. These included several reduction conditions known to furnish saturated amides from enamides, such as catalytic hydrogenation,[27] triethylsilane/TFA,[28] $Me_3O^+BF_4^-$/$NaBH_4$,[29] $(Ph_3P)_3RhCl/Et_3SiH$,[30] as well as numerous others.[31] In each instance either recovered starting material or ill-defined mixtures of products were obtained. Finally, after considerable investigation the interesting reducing system (SmI_2/HMPA/*t*-BuOH), developed by Molander and McKie for entirely different purposes,[32] proved to bring about the desired transformation in serviceable yields. Thus exposure of **19** to these conditions followed by an oxidative workup with PDC delivered ketolactam **20** in 75% yield based on recovered starting material. Single-crystal X-ray analysis of **20** confirmed the presence of the requisite cis-ring fusion.[33] To the best of our knowledge this transformation represents the first example of enamide saturation with samarium as the reductant.

At this point our attention turned to the final functional group interchanges required to complete the synthesis. Thus, treatment of compound **20** with trimethylsilyl triflate and Hünig's base followed by Saegusa-Ito oxidation[34] afforded a 99% yield of an inseparable 4:1 mixture of the desired enone **21** along with the regioisomeric enamide **19**. Several other bases were explored in this reaction in an effort to improve regioselectivity. The results of this study are compiled in Table 1. The reversal of regioselectivity with di-*tert*-butylpyridine is noteworthy and is presumably due to steric factors. While dicyclohexylethylamine provided a more attractive ratio of enones, the chemical yield of this transformation was unacceptably low. Consequently, the Hünig's base conditions were selected for moving forward in the synthesis.

The next objective was to incorporate the α-oriented methoxy group required at C-3 of the target. Thus, Luche 1,2-reduction[35] of the mixture of enones **21**/**19** afforded **22a** as a 1:6 (α/*β*) mixture of allylic alcohol epimers in the $\Delta^{1,2}$ series along with **22b** (derived from reduction of **19**) in the $\Delta^{4,4a}$ series. This material could be easily separated from alcohols **22a** and oxidized back to enamide **19** and recycled through the sequence, if desired. Finally, in an operation that is reminiscent of a similar process in Danishefsky's tazettine synthesis,[8] alcohols **22a** were treated with Ms_2O/NEt_3 followed by immediate solvolysis in methanol at room temperature to provide a 96% yield of an easily separable 2:1 mixture of the desired α-methoxy derivative **23** and the corresponding *β*-species. The fact that the epimer ratio for the starting material and product is not of the same magnitude (although it is reversed) is interesting and may be reflective of the involvement of an S_N1 process.

The ultimate success of the final conversion of **23** into tazettine was critically dependent on the timing of the remaining three steps. It had been observed by Ikeda and co-workers during their early work on the structure of tazettine that hydrolysis of the O-methyl acetal derivative of tazettine did not effectively regenerate the natural product.[36] Therefore, it appeared that the projected hydrolysis would have to be performed on the lactam **23** itself or on some derivative thereof. In the event, this overall objective was best accomplished by first converting the lactam **23** into the corresponding thiolactam, which was then treated with 10% aqueous HCl to produce the desired hemiacetal. It is interesting to note that the hydrolysis of this acetal failed when attempted on lactam **23** itself. At this point, routine Raney nickel desulfurization of the thiolactam then followed to afford (±)-tazettine in 58% yield for the three steps.[37] The 500 MHz ^{1}H NMR, TLC mobility, and IR of this synthetic (±)-tazettine, mp 177−9 °C (EtOAc/Hexanes) [lit.[8] mp 175−6 °C (acetone); lit.[11] mp 173−5 °C (benzene)] were identical with an authentic sample of tazettine kindly provided by the Drug Synthesis and Chemistry Branch, Developmental Therapeutics Program of the National Cancer Institute.

Table 1. Effect of Base on the Ratio of Compounds **21** and **19**

base	**21**	**19**	yield (%)
Et_3N	2	1	84
$(i\text{-}Pr)_2NEt$	4	1	99
di-*tert*-butylpyridine	1	2.6	78
$(Cy)_2NEt$	6	1	32

Conclusion

Application of a [4+1] cycloaddition between a *β*-aryl vinyl isocyanate and dimethoxycarbene permits the rapid assembly of the [2]benzopyrano[3,4-*c*]hydroindole core structure of the *Amaryllidaceae* alkaloid, (±)-tazettine. A key reduction of the enamide arising from the cycloaddition step followed by straightforward functional group manipulation provided the racemic target molecule in 16 steps from commercial piperonyl alcohol in 11% overall yield.

Experimental Section[38]

2-Bromo-4,5-methylenedioxybenzyl 1-Tetrahydropyranyl Ether (9). 3,4-Methylenedioxybenzyl alcohol (**8**) (19.55 g, 129 mmol) was dissolved in dichloromethane (200 mL), and the solution was cooled in an ice/water bath. *N*-Bromosuccinimide (22.9 g, 129 mmol) was added over a period of 20 min, and the mixture was stirred for an additional 2 h at 5 °C. At this time, 10% aqueous sodium sulfite solution (100 mL) was added and the resultant mixture was stirred for 5 min. The organic layer was separated and the water layer was extracted with dichloromethane (2 × 100 mL). The combined organic layers were dried over anhydrous sodium sulfate, and solvent evaporation under reduced pressure yielded 6-bromopiperonyl alcohol (29.7 g, 100%), which was used for the next step without further purification: IR (NaCl) ν 3250, 2908, 1034 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.64 (s, 2H), 5.98 (s, 2H), 6.97 (s, 1H), 7.00 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 64.9, 101.9, 109.1, 112.7, 112.9, 133.3, 147.6, 147.8.

2-Bromo-4,5-methylenedioxybenzyl alcohol (29.7 g, 128 mmol) was dissolved in dichloromethane (200 mL) and pyridinium *p*-toluenesulfonate (35 mg, 0.14 mmol) and dihydropyran (11.0 g, 130 mmol) were added at room temperature. The reaction mixture was allowed to stir overnight, then water (100 mL) was added and the organic layer was separated. The water layer was extracted with dichloromethane (100 mL), and the combined organic layers were dried over anhydrous sodium sulfate. Filtration followed by solvent evaporation at reduced

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(37) If too large an excess of Ra−Ni is employed, reduction of the A ring alkene begins to occur.

(38) General experimental details have been recently described.[39]

pressure yielded the product. Purification via silica gel chromatography (hexanes/EtOAc, 95:5) afforded 39.0 g (97%) of 2-bromo-4,5-methylenedioxybenzyl 1-tetrahydropyranyl ether: IR (NaCl) ν 2941, 1035 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.46−1.81 (m, 6H), 3.49 (m, 1H), 3.84 (m, 1H), 4.41 (d, J = 13 Hz, 1H), 4.64 (d, J = 13 Hz, 1H), 4.66 (s, 1H), 5.88 (s, 2H), 6.91 (s, 1H), 6.93 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.4, 25.5, 30.6, 62.2, 68.5, 98.3, 101.8, 109.3, 112.6, 113.2, 131.1, 147.5, 147.7; mass spectrum (EI), *m*/*e* (rel intensity) 316 (M^+, 21), 215 (99), 213 (100); HRMS, calcd for $C_{13}H_{15}BrO_4$ 316.0134, found 316.0132.

2-Tri-*n*-butylstannyl-4,5-methylenedioxybenzyl 1-Tetrahydropyranyl Ether (10). 2-Bromo-4,5-methylenedioxybenzyl 1-tetrahydropyranyl ether (**9**) (24 g, 76.2 mmol) was placed in a 2 L round-bottom flask, THF (750 mL) was added, and the solution was cooled to −78 °C. *n*-Butyllithium (2.5 M in hexane, 31 mL, 77.5 mmol) was then added and the resultant solution was stirred for 45 min at −78 °C. At this time, tri-*n*-butyltin chloride (21 mL, 77.4 mmol) was added and the resultant mixture was allowed to stir for an additional 1 h. The reaction mixture was then quenched at −78 °C with saturated aqueous ammonium chloride solution (500 mL) and water (250 mL). The organic layer was then separated and the water layer was extracted with dichloromethane (2 × 250 mL). The combined organic layers were dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure after filtration. Silica gel chromatography was done first with hexanes as eluent to remove excess tri-*n*-butyltin chloride and then with hexanes/EtOAc (19:1). (**Note:** Chromatography should be performed as fast as possible otherwise yields will be lower because of product decomposition on the silica gel solid support.) This afforded 38.5 g (96%) of the product: IR (NaCl) ν 2950, 1037 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, J = 7.2 Hz, 9H), 1.08 (t, J = 8.1 Hz, 6H), 1.28−1.58 (m, 18 H), 3.56 (m, 1H), 3.93 (m, 1H), 4.35 (d, J = 11.4 Hz, 1H), 4.68 (d, J = 11.4 Hz, 1H), 4.70 (s, 1H), 5.93 (s, 2H), 6.92 (s, 1H), 7.01 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.6, 13.7, 19.5, 25.6, 27.5, 29.2, 30.7, 65.2, 71.00, 97.7, 100.7, 109.6, 115.4, 133.8, 138.8, 146.9, 148.2; mass spectrum (EI), *m*/*e* (rel intensity) 469 (2), 385 (17), 329 (8), 236 (14), 135 (100); HRMS, calcd for $C_{25}H_{42}O_4Sn$ 526.2104 − C_4H_9 = 469.1400, found 469.1408.

2-Carbomethoxy-4,4-ethylenedioxy-1-trifluoromethanesulfonate-1-cyclohexene (12). A flame-dried flask was charged with sodium hydride (60% oil dispersion, 1.9 g, 47.5 mmol) and ethyl ether (600 mL). (**Note:** Higher concentrations produced lower yields.) The resulting solution was cooled to 0 °C and 2-carbomethoxycyclohexa-1,4-dione-4-ethylene acetal[17] (8.5 g, 39.7 mmol) in dichloromethane (20 mL) was added. The reaction mixture was allowed to stir for 75 min at 0 °C and trifluoromethanesulfonate anhydride (6.7 mL, 39.7 mmol) was then added all at once. The resultant reaction mixture became viscous, so the ice bath was removed, and stirring was continued for an additional 20 min. The reaction mixture was then quenched with saturated aqueous ammonium chloride solution (100 mL). The organic layer was separated and the water layer was extracted with dichloromethane (2 × 75 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and solvent was removed under reduced pressure to afford the crude product. Silica gel chromatography (hexanes/EtOAc, 95:5) afforded 12.8 g (93%) of the product: IR (NaCl) ν 2957, 1731, 1365 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.80 (t, J = 6.3 Hz, 2H), 2.55 (m, 4H), 3.69 (s, 3H), 3.90 (d, J = 4.2 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.7, 30.9, 35.8, 52.3, 64.9, 105.7, 112.1, 116.3, 120.4, 124.8, 151.5, 164.3.

1-(4′,5′-Methylenedioxy-2′-tetrahydropyranyloxymethyl)phenyl-2-carbomethoxy-4,4-ethylenedioxy-1-cyclohexene (13). A 25 mL, oven-dried flask fitted with a condenser was charged with 2-carbomethoxy-4,4-ethylenedioxy-1-trifluoromethanesulfonate-1-cyclohexene (**12**) (1.0 g, 2.9 mmol), 2-tri-*n*-butylstannyl-4,5-methylenedioxybenzyl 1-tetrahydropyranyl ether (**10**) (1.7 g, 3.2 mmol), tris(dibenzylideneacetone)dipalladium(0) (0.055 g, 0.06 mmol), potassium carbonate (0.55 g, 3.9 mmol), copper(I) iodide (0.065 g, 0.348 mmol), triphenylphosphine (0.125 g, 0.476 mmol), and *N*-methylpyrrolidinone (NMP, 4 mL). The resultant reaction mixture was stirred for 10 min at room temperature and then heated for an additional 22 to 40 h in a sand bath at 82 °C. Water (50 mL) and ethyl acetate (50 mL) were added and the organic layer was separated. The separated organic layer was stirred with potassium fluoride (2.4 g) and water (30 mL) for 1 h. The heterogeneous mixture was filtered and the organic layer was separated. The organic layer was then dried over anhydrous sodium sulfate, filtered, and the solvent was removed under reduced pressure. Silica gel chromatography (hexanes/EtOAc, 4:1) afforded 1.13 g (91% yield) of the coupled product: IR (NaCl) ν 2950, 1724, 1034 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.52−1.83 (m, 8H), 2.51−2.63 (m, 4H), 3.45 (s, 3H), 3.83−4.29 (m, 7H), 4.42−4.56 (m, 1H), 4.63 (s, 1H), 5.91 (s, 1H), 6.48 (s, 1H), 6.90 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.4, 25.6, 30.6, 31.0, 33.9, 36.3, 51.4, 62.0, 64.6, 66.7, 97.8, 101.1, 107.2, 109.2, 125.2, 127.8, 135.9, 146.6, 146.9, 147.6, 167.1; mass spectrum (EI), *m*/*e* (rel intensity) 432 (16), 347 (18), 330 (32), 316 (17), 287 (19), 244 (33), 185 (24), 115 (15), 99 (31), 84 (100); HRMS, calcd for $C_{23}H_{28}O_8$ 432.1784, found 432.1788.

1-(4′,5′-Methylenedioxy-2′-tetrahydropyranyloxymethyl)phenyl-2-(azidocarbonyl)-4,4-ethylenedioxy-1-cyclohexene (14). Compound **13** (1.7 g, 4.0 mmol) was dissolved in methanol (14 mL) and water (7 mL) in a 100 mL flask fitted with a condenser. Lithium hydroxide monohydrate (0.6 g, 13.6 mmol) was then added at room temperature. The reaction mixture was refluxed overnight and then cooled to room temperature. Water (300 mL) was added and the resultant mixture was extracted with ethyl acetate (150 mL). The water layer was acidified with 5% aqueous hydrochloric acid solution (100 mL) and extracted with ethyl acetate (3 × 150 mL). The last three organic layers were combined and dried over anhydrous sodium sulfate, filtered, and the solvent was removed under reduced pressure. Silica gel chromatography ($CHCl_3$/MeOH, 9:1) afforded 1.6 g (97%) of the acid as a white foam which solidified under high vacuum: mp 65 °C; IR (NaCl) ν 3147, 2922, 1698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.47−1.83 (m, 16H), 2.45−2.55 (m, 8H), 3.49−3.54 (m, 2H), 3.80−3.84 (m, 2H), 3.99 (m, 8H), 4.22 (d, J = 11 Hz, 1H), 4.26 (d, J = 10.5 Hz, 1H), 4.53 (d, J = 12 Hz, 1H), 4.56 (d, J = 11 Hz, 1H), 4.68 (m, 1H), 4.75 (m, 1H), 5.94 (m, 4H), 6.52 (s, 1H), 6.54 (s, 1H), 6.83 (s, 1H), 6.84 (s, 1H), 9.72 (bs, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.8, 19.3, 25.2, 25.3, 30.1, 30.2, 31.0, 31.1, 33.1, 33.6, 36.2, 36.3, 61.8, 62.3, 64.5, 64.6, 67.3, 67.8, 98.2, 98.5, 101.2, 101.3, 107.0, 107.8, 108.1, 110.0, 110.2, 126.7, 127.0, 127.7, 135.3, 135.4, 144.5, 146.1, 147.0, 147.1, 147.5, 147.8, 169.7, 170.0; mass spectrum (EI), *m*/*e* (rel intensity) 418 (13), 316 (69), 230 (97), 85 (100), 55 (61); HRMS, calcd for $C_{22}H_{26}O_8$ 418.1628, found 418.1634. Anal. Calcd for $C_{22}H_{26}O_8$: C, 63.15; H, 6.26. Found: C, 62.90; H, 6.38.

In a 25 mL flask, benzene (5 mL) and triethylamine (1.2 mL, 8.6 mmol) were added to the acid (3.0 g, 7.2 mmol). The solution was cooled to 0 °C and diphenylphosphorazidate (DPPA, 1.64 mL, 8.6 mmol) was added. The reaction mixture was allowed to stir for an additional 35 min at 0 °C. Then the reaction mixture was poured onto a plug of silica gel and chromatographed (hexanes/EtOAc, 1:4) as fast as possible (slow chromatography resulted in lower yields). The solvent was removed under reduced pressure to afford 2.9 g (92%) of the acyl azide product: IR (NaCl) ν 2941, 2250, 1503 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.49−1.84 (m, 8H), 2.39 (bs, 2H), 2.47 (bs, 2H), 3.50−3.54 (m, 1H), 3.87 (t, 1H), 4.00 (s, 4H), 4.24−4.27 (m, 1H), 4.53 (t, 1H), 4.66 (bs, 1H), 5.95 (s, 2H), 6.55 (s, 1H), 6.95 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.3, 25.4, 29.5, 30.5, 31.3, 40.6, 61.8, 64.6, 66.5, 96.1, 97.8, 98.2, 101.1, 107.3, 108.3, 109.5, 123.3, 128.8, 129.5, 147.1; mass spectrum (EI), *m*/*e* (rel intensity) 415 (6), 331 (4), 313 (25), 288 (5), 227 (76), 187 (4), 115 (5), 99 (21), 85 (100); HRMS, calcd for $C_{22}H_{25}N_3O_7$ 443.1692 − N_2 = 415.1631, found 415.1626.

3a,4,5,6-Tetrahydro-6,6-(ethylenedioxy)-3,3-dimethoxy-1-(dimethoxymethyl)-3a-{[4′,5′-(methylenedioxy)-2′-(tetrahydropyranyloxymethyl)]phenyl}indol-2-one (18). To the acyl azide (14) (3.8 g, 8.6 mmol) in mesitylene (43 mL) was added dimethoxy-Δ^3-1,3,4-oxadiazoline (**17**) (3.4 g, 21.4 mmol). After 3 h at reflux, the reaction was cooled to room temperature and the solvent removed under high vacuum. Workup with water/ethyl acetate and flash chromatography (hexanes/EtOAc, 4:1) afforded the product (3.6 g, 75%) as an inseparable mixture of diastereoisomers: mp = 68−69 °C (hexanes/EtOAc); IR (NaCl) ν 2940, 1731, 1671 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.47−1.85 (m, 10 H), 2.32−2.42 (m, 2H), 3.08 (s, 1.5H), 3.09 (s, 1.5H), 3.39 (s, 1.5H), 3.39 (s, 1.5H), 3.45 (s, 1.5H), 3.45 (s, 1.5H), 3.55 (s, 1.5H), 3.55 (s, 1.5H), 3.80−4.20 (m, 6H), 4.56 (dd, J

= 11.5, 62 Hz, 1H), 4.64 (m, 1H), 4.77 (m, 1H), 4.90 (dd, J = 12, 118.5 Hz, 1H), 5.73 (d, J = 2 Hz, 0.5H), 5.74 (d, J = 1 Hz, 0.5H), 5.90 (m, 2H), 5.94 (s, 0.5H), 5.95 (s, 0.5H), 6.88 (s, 0.5H), 6.89 (s, 0.5H), 6.98 (s, 0.5H), 6.99 (s, 0.5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.4, 25.5, 25.5, 27.2, 27.4, 30.5, 30.7, 30.7, 30.8, 52.4, 52.5, 54.2, 54.2, 54.9, 55.3, 55.3, 56.0, 56.0, 62.3, 64.1, 64.7, 66.0, 67.9, 68.0, 97.7, 97.9, 101.2, 102.9, 103.1, 106.6, 108.2, 108.4, 110.3, 110.4, 111.72, 112.03, 129.5, 129.7, 133.2, 133.4, 142.3, 142.4, 146.6, 146.8, 146.9, 168.0, 168.2; mass spectrum (EI), *m*/*e* (rel intensity) 386 (9), 288 (16), 99 (22), 75 (100); HRMS, calcd for $C_{28}H_{37}NO_{11}$ 563.2366 − $C_3H_6O_2$ = 489.1999, found 489.1994. Anal. Calcd for $C_{28}H_{37}NO_{11}$: C, 59.67; H, 6.62; N, 2.49. Found: C, 60.78; H, 6.54; N, 2.73.

(6a*β*,12bα)-1,2-Dihydro-6a-methoxy-5-methyl-3-oxo-8*H*-[1,3]dioxolo[6,7][2]benzopyrano[3,4-*c*]indol-6(5*H*)-one (19). The indolone **18** (2.7 g, 4.8 mmol) was refluxed overnight in a solution of acetone (30 mL) and 10% aqueous hydrochloric acid solution (20 mL). The reaction mixture was then cooled to room temperature and diluted with water and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and the solvent was removed under reduced pressure. Purification by column chromatography (silica gel, hexanes/EtOAc, 1:1 then EtOAc) afforded a dione (1.5 g, 100%) as a white solid that was poorly soluble in most organic solvents: mp 273 °C ($CHCl_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.6, 32.8, 48.9, 64.6, 96.6, 101.5, 106.7, 107.3, 107.9, 126.1, 130.5, 147.1, 147.3, 159.2, 173.2, 198.3; mass spectrum (EI), *m*/*e* (rel intensity) 315 (70), 242 (100); HRMS, calcd for $C_{16}H_{13}NO_6$ 315.0743, found 315.0739.

To sodium hydride (60% oil dispersion, 0.46 g, 11.6 mmol) was added, at room temperature, the dione prepared above (1.5 g, 4.8 mmol) in DMF (20 mL). The mixture was stirred for 1 h at which point it became very thick. Iodomethane (0.73 mL, 11.6 mmol) was then added and the solution was stirred for 4 h. The solution was poured onto water and extracted several times with $CHCl_3$. The combined organic layers were dried over anhydrous magnesium sulfate and filtered and the solvent was removed under reduced pressure. Flash chromatography (silica gel, hexanes/EtOAc, 2:1) afforded the product (1.5 g, 89%) as a white solid: mp 248−9 °C (EtOAc); IR (NaCl) ν 2940, 1748, 1623 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.68 (ddd, J = 2, 5.5, 13.5 Hz, 1H), 2.32 (m, 1H), 2.44 (m, 1H), 2.85 (dt, J = 5, 13.5 Hz, 1H), 3.03 (s, 3H), 3.56 (s, 3H), 4.62 (d, J = 13.5 Hz, 1H), 4.84 (d, J = 13.5 Hz, 1H), 5.81 (s, 1H), 5.95 (d, J = 1.5 Hz, 1H), 5.96 (d, J = 1.5 Hz, 1H), 6.74 (s, 1H), 6.79 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.6, 26.9, 33.3, 48.9, 52.0, 64.6, 98.2, 101.5, 105.8, 106.6, 107.3, 126.5, 130.7, 147.1, 147.3, 161.0, 168.9, 196.9; mass spectrum (EI), *m*/*e* (rel intensity) 343 (41), 256 (100); HRMS, calcd for $C_{18}H_{17}NO_6$ 343.1056, found 343.1053. Anal. Calcd for $C_{18}H_{17}NO_6$: C, 62.97; H, 4.99; N, 4.08. Found: C, 63.05; H, 5.05; N, 4.05.

(4aα,6a*β*,12bα)-1,2,4,4a-Tetrahydro-6a-methoxy-5-methyl-3-oxo-8*H*-[1,3]dioxolo[6,7][2]benzopyrano[3,4-*c*]indol-6(5*H*)-one (20). A flame-dried flask, filled with argon, was charged with samarium(II) iodide (0.1 M solution in THF, 35 mL, 3.5 mmol) and freshly distilled hexamethylphosphoramide (HMPA, 3.5 mL, 20.4 mmol). The mixture was degassed by bubbling argon for 30 min, at which point the color changed from dark blue to dark purple. Compound **19** (0.2 g, 0.6 mmol) and freshly distilled *tert*-butyl alcohol (0.11 mL, 1.16 mmol) were dissolved in THF (20 mL) and added dropwise over 10 min to this purple solution. After the resulting mixture was stirred overnight, the color had changed from purple to brown/light purple. The reaction was quenched by adding Rochelle's salt with 10% aqueous potassium carbonate solution and stirring for an additional 2 h. The organic layer was separated and the aqueous layer was extracted several times with ethyl acetate. The combined organic layers were washed with brine solution, dried over anhydrous magnesium sulfate, and filtered. The solvent was removed under reduced pressure to afford the crude product in HMPA, which was diluted in methylene chloride (5 mL). Pyridinium dichromate (PDC, 1.1 g, 2.9 mmol) was added to oxidize any overreduced compounds. The resulting solution was stirred for 4 h and then filtered through Celite. The solvent was evaporated under reduced pressure to afford the crude product in HMPA. The latter could be removed under high vacuum by gently warming. Purification via radial chromatography (ether/hexanes, 4:1) afforded the starting material (55 mg, 28%) and the product (109 mg, 75% based on the recovered starting material) as a white solid: mp 218 °C ($CHCl_3$/ether); IR (NaCl) ν 2946, 1700, 1034 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.01 (m, 1H), 2.38−2.52 (m, 2H), 2.60 (dt, J = 5, 14.5 Hz, 1H), 2.75 (s, 3H), 2.83 (dd, J = 5.5, 16 Hz, 1H), 2.96 (dd, J = 4, 16 Hz, 1H), 3.76 (s, 3H), 3.88 (dd, J = 4, 5.5 Hz, 1H), 4.61 (d, J = 14.5 Hz, 1H), 4.73 (d, J = 14.5 Hz, 1H), 5.95 (s, 1H), 6.51 (s, 1H), 6.80 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.6, 29.9, 37.0, 41.5, 43.1, 51.5, 62.3, 62.9, 98.0, 101.3, 104.4, 106.1, 127.1, 131.4, 146.5, 147.6, 168.6, 209.3; mass spectrum (EI), *m*/*e* (rel intensity) 345 (81), 256 (100), 115 (58); HRMS, calcd for $C_{18}H_{19}NO_6$ 345.1212, found 345.1221. Anal. Calcd for $C_{18}H_{19}NO_6$: C, 62.60; H, 5.55; N, 4.06. Found: C, 61.96; H, 5.59; N, 3.99.

(4aα,6a*β*,12bα)-4,4a-Dihydro-6a-methoxy-5-methyl-3-oxo-8*H*-[1,3]dioxolo[6,7][2]benzopyrano[3,4-*c*]indol-6(5*H*)-one (21). To ketone **20** (0.19 g, 0.54 mmol) and *N*,*N*-diisopropylethylamine (1.9 mL, 10.7 mmol) in methylene chloride (15 mL) was added trimethylsilyl trifluoromethanesulfonate (1.0 mL, 5.4 mmol). The reaction mixture was allowed to stir for 2 h. Cold pentane was slowly added, followed by cold saturated aqueous sodium bicarbonate solution. The organic layer was separated and the aqueous layer was extracted several times with cold pentane. The combined organic layers were dried over anhydrous sodium sulfate and filtered. The solvent was removed under reduced pressure to afford the crude silyl enol ether, which was immediately dissolved in acetonitrile (15 mL). After the addition of palladium(II) acetate (0.16 mg, 0.7 mmol), the orange solution was stirred overnight. The resulting black mixture was concentrated under reduced pressure and the residue was directly purified by flash chromatography (hexanes/EtOAc, 2:1). This afforded an inseparable 4:1 mixture of the product and **19** (181 mg, 99%): IR (NaCl) ν 2946, 1721, 1707, 1686, 1482 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.78 (s, 3H), 2.81 (d, J = 4 Hz, 1H), 2.86 (d, J = 4.5 Hz, 1H), 3.84 (s, 3H), 3.90 (m, 1H), 4.76 (d, J = 15 Hz, 1H), 4.82 (d, J = 15.5 Hz, 1H), 5.95 (d, 2H), 6.26 (d, J = 10.5 Hz, 1H), 6.58 (s, 1H), 6.64 (s, 1H), 6.70 (dd, J = 2, 10.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.0, 35.7, 47.0, 51.5, 60.7, 62.6, 97.7, 101.4, 104.8, 108.3, 122.4, 125.6, 129.8, 147.2, 147.4, 147.6, 168.3, 194.7; mass spectrum (EI), *m*/*e* (rel intensity) 343 (63), 226 (100), 42 (70); HRMS, calcd for $C_{18}H_{17}NO_6$ 343.1056, found 343.1062. Anal. Calcd for $C_{18}H_{17}NO_6$: C, 62.97; H, 4.99; N, 4.08. Found: C, 62.69; H, 5.09; N, 4.04.

(3α,4aα,6a*β*,12bα)-3,4,4a,5-Tetrahydro-6a-methoxy-5-methyl-8*H*-[1,3]dioxolo[6,7][2]benzopyrano[3,4-*c*]indol-6-one (23). To the mixture of enones **19** and **21** in methanol (10 mL) was added successively, at 0 °C, cerium(III) chloride heptahydrate (61.8 mg, 0.17 mmol) and sodium borohydride (13 mg, 0.34 mmol). The reaction mixture was stirred for 30 min and water was added. The aqueous layer was extracted with ethyl acetate and the combined organic layers were dried over anhydrous magnesium sulfate and filtered. The solvent was removed under reduced pressure to afford a 6:1 mixture of alcohols, **22a** along with **22b**.

The crude mixture was dissolved in tetrahydrofuran (5 mL) with triethylamine (0.16 mL, 1.1 mmol) and methanesulfonic anhydride (97 mg, 0.5 mmol). The solution was stirred for 30 min at which point dry methanol (5 mL) was added, and the reaction mixture was allowed to stand overnight. Workup with water/ethyl acetate afforded a 2:1 mixture of the desired product and its 3β isomer. Radial chromatography (hexanes/EtOAc, 4:1) afforded the stereochemically homogeneous product **23** (25.5 mg, 64%) as an oil: IR (NaCl) ν 2941, 1700, 1032 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.05 (m, 1H), 2.19 (m, 1H), 2.84 (s, 3H), 3.46 (s, 3H), 3.65 (dd, J = 3, 6.5 Hz, 1H), 3.75 (s, 3H), 3.80 (m, 1H), 4.74 (s, 2H), 5.61 (d, J = 10.5 Hz, 1H), 5.91 (d, 2H), 6.13 (dd, J = 3, 10 Hz, 1H), 6.47 (s, 1H), 6.82 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.3, 27.7, 45.7, 51.4, 56.3, 60.3, 63.1, 71.0, 98.4, 101.1, 103.7, 109.1, 125.7, 127.0, 128.2, 129.4, 146.9, 169.0; mass spectrum (EI), *m*/*e* (rel intensity) 359 (100), 328 (69), 242 (77), 227 (71), 210 (69); HRMS, calcd for $C_{19}H_{21}NO_6$ 359.1369, found 359.1373.

(±)-Tazettine. Compound **23** (73.6 mg, 0.2 mmol) and Lawesson's reagent[40] (0.8 g, 2 mmol) were refluxed in toluene for 1 h. The solution was then cooled to room temperature and water was added. The aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and

the solvent was removed under reduced pressure. Purification via flash chromatography (pentane/acetone, 10:1) afforded the corresponding thioamide (63.1 mg, 82%) as an oil: IR (NaCl) ν 2933, 1031 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.96 (m, 1H), 2.32 (dt, J = 4.2, 13.2 Hz, 1H), 3.17 (s, 3H), 3.47 (s, 3H), 3.74 (s, 3H), 3.90 (dd, J = 4.5, 8.1 Hz, 1H), 3.97 (dd, J = 4.5, 10.8 Hz, 1H), 4.76 (d, J = 15.3 Hz, 1H), 5.17 (d, J = 15 Hz, 1H), 5.75 (d, J = 9.6 Hz, 1H), 5.90 (s, 2H), 6.17 (dd, J = 4.5, 9.9 Hz, 1H), 6.41 (s, 1H), 6.77 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.6, 34.0, 48.0, 51.7, 56.4, 64.8, 67.6, 71.2, 99.3, 101.1, 103.3, 103.7, 108.7, 125.9, 126.7, 128.5, 132.0, 147.0, 147.1.

The thioamide was dissolved in acetone (5 mL) and 10% aqueous hydrochloric acid solution (5 mL). The mixture was refluxed overnight and then cooled to room temperature. Workup with water and chloroform afforded the crude tazettine-6-thione (55.7 mg, 92%). The latter was dissolved in ethanol and Raney nickel (50% slurry in water, 42 drops) was added portionwise over a 4 h period (too fast of an addition or a large excess of Raney nickel would promote overreduction of the alkene). The Raney nickel was then filtered off and the ethanol was removed under reduced pressure. Flash chromatography (hexanes/EtOAc, 1:2) afforded (±)-tazettine (38.9 mg, 77% from tazettine-6-thione): mp 177−9 °C (EtOAc/hexanes); IR (NaCl) ν 3339, 2929, 1030 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.63 (m, 1H), 2.23 (m, 1H), 2.41 (s, 3H), 2.68 (d, J = 10.5 Hz, 1H), 2.87 (bs, 1H), 3.31 (d, J = 10.5 Hz, 1H), 3.46 (s, 3H), 4.12 (m, 1H), 4.63 (d, J = 15 Hz, 1H), 4.96 (d, J = 15 Hz, 1H), 5.61 (d, J = 10.5 Hz, 1H), 5.90 (s, 2H), 6.14 (d, J = 10 Hz, 1H), 6.49 (s, 1H), 6.85 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.6 (CH_2), 42.0 (CH_3), 49.9 (C), 56.1 (CH_3), 62.0 (CH_2), 65.4 (CH_2), 70.0 (CH), 72.8 (CH), 100.9 (CH_2), 102.0 (C), 104.0 (CH), 109.3 (CH), 125.5 (C), 127.9 (C), 128.6 (CH), 130.6 (CH), 146.4 (C), 146.6 (C); 500 MHz ^1H NMR and TLC mobility of synthetic (±)-tazettine were in all respects identical with those of an authentic sample of (+)-tazettine kindly provided by the Drug Synthesis & Chemistry Branch, Developmental Therapeutics Program, Division of Cancer Treatment, National Cancer Institute.

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