Tandem [4 + 2]/[3 + 2] Cycloadditions with Nitroethylene

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The simplest nitroalkene, nitroethylene, undergoes Lewis acid-promoted [4 + 2] cycloaddition with chiral vinyl ethers to afford cyclic nitronates with high diastereoselectivity. The resulting cyclic nitronates react with electron deficient alkenes to effect a face selective [3 + 2] cycloaddition. The origin of stereocontrol in the [3 + 2] cycloaddition is due to the single ring substituent, a remote acetal center. The scope and limitations of the use of nitroethylene as a 4π component in Lewis acid-promoted cycloadditions are documented and discussed. Additionally, concise syntheses of the pyrrolizidine alkaloids (+)-macronecine and (+)-petasinecine are presented.

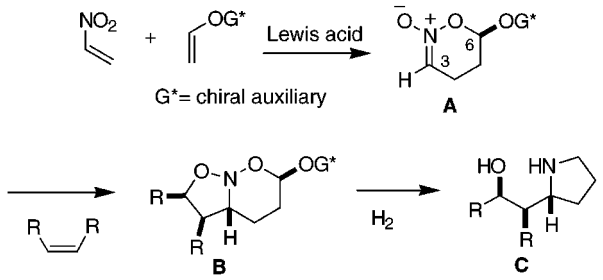
Introduction

The scope and sythetic utility of the asymmetric, tandem [4 + 2]/[3 + 2] cycloaddition of nitroalkenes have been extensively documented in reports from these laboratories.[1,2] While a variety of substituted nitroalkenes have been employed in this sequence (2-monosubstituted and 2,2-disubstituted 1-nitroalkenes, and 2-substituted 2-nitroalkenes),[3−5] the very reactive nitroethylene[6] had never been investigated. Since we have envisioned the syntheses of several complex alkaloids devoid of substitution at the nitroalkene carbons, we chose to systematically investigate the utility of nitroethylene in Lewis acid-promoted tandem cycloadditions.

Lewis acid-promoted [4 + 2] cycloaddition between nitroethylene and a chiral vinyl ether would create cyclic nitronate **A** possessing a single stereogenic center at the configurationally labile C(6) acetal carbon, Scheme 1. Previous studies have shown that C(3)-unsubstituted nitronates are both less stable and more reactive in [3 + 2] cycloadditions than the substituted analogues.[1,7] Thus, it was not clear whether compounds **A** would be isolable. Moreover, the stereochemical course of the [3 + 2] cycloaddition would be controlled by the remote substituent at C(6). From our studies in the spiro-mode tandem cycloaddition[5] we anticipated that a fair degree of selectivity in the creation of three new stereocenters in nitroso acetal **B** could be realized. Reduction would afford a pyrrolidine-containing product in which the stereodirecting acetal center had been removed.

Nitroethylene has been used as a 2π component in [4 + 2] cycloadditions and as a powerful Michael acceptor,[8]

Scheme 1



but its use as a 4π component in cycloadditions has not been documented. The closest analogy might be the recently reported addition of silyl ketene acetals to nitroethylene with an aluminum-based Lewis acid to provide Michael addition products.[9] We report, herein, that nitroethylene engages in diastereoselective, Lewis acid-promoted [4 + 2] cycloadditions with chiral vinyl ethers and that the resulting nitronates undergo selective [3 + 2] cycloadditions with electron deficient alkenes.

Results

To establish the potential for nitroethyleneas a 4π component in tandem cycloadditions, it was necessary to find reaction conditions suitable for [4 + 2] cycloaddition with vinyl ethers which allowed for the isolation of the (expectedly) reactive nitronates. The addition of a solution of nitroethylene[10] (1 equiv) to a cold (−78 °C) solution of MAPh[11] (2 equiv) and chiral vinyl ether (1 equiv) in toluene proved to afford the best results.[12] The reactions were effectively spontaneous at −78 °C, as judged by the formation and rapid dissipation of the red, Lewis acid−nitroalkene complex. The nitronates were surprisingly stable and could be isolated after an aqueous workup,

(1) Denmark, S. E.; Thorarensen, A. *Chem. Rev.* **1996**, *96*, 137.
(2) (a) Denmark, S. E.; Senanayake, C. B. W.; Ho, G.-D. *Tetrahedron* **1990**, *46*, 4857. (b) Denmark, S. E.; Schnute, M. E. *J. Org. Chem.* **1991**, *56*, 6738. (c) Denmark, S. E.; Schnute, M. E.; Senanayake, C. B. W. *J. Org. Chem.* **1993**, *58*, 1859. (d) Denmark, S. E.; Schnute, M. E.; Marcin, L. R.; Thorarensen, A. *J. Org. Chem.* **1995**, *60*, 3205. (e) Denmark, S. E.; Thorarensen, A. *J. Org. Chem.* **1996**, *61*, 6727.
(3) Denmark, S. E.; Kesler, B. S.; Moon, Y.-C. *J. Org. Chem.* **1992**, *57*, 4912.
(4) (a) Denmark, S. E.; Marcin, L. R. *J. Org. Chem.* **1993**, *58*, 3857. (b) Denmark, S. E.; Schnute, M. E. *J. Org. Chem.* **1994**, *59*, 4576. (c) Denmark, S. E.; Marcin, L. R. *J. Org. Chem.* **1995**, *60*, 3221.
(5) Denmark, S. E.; Middleton, D. S *J. Org. Chem.* **1998**, *63*, 1604.
(6) Buckley, G. D.; Scaife, C. W. *J. Chem. Soc.* **1947**, 1471.
(7) Chlenov, I. E.; Morozova, N. S.; Khudak, V. I.; Tartakovskii, V. A. *Izv. Akad. Nauk. SSSR, Ser. Chem.* **1970**, 2641 (English translation, *Bull. Acad. Sci., SSSR* **1970**, 2492).
(8) Ranganathan, D.; Rao, C. B.; Ranganathan, S.; Mehrotra, A. K.; Iyengar, R. *J. Org. Chem.* **1980**, *45*, 1185−1189 and references therein.
(9) Tucker, J. A.; Clayton, T. L.; Mordas, D. M. *J. Org. Chem.* **1997**, *62*, 4370.
(10) Nitroethylene is easily prepared by the dehydration of nitroethanol with phthallic anhydride (see ref 6), and despite reports concerning its instability, it can be stored as a neat oil at −20 °C for several months without loss in purity.
(11) Methylaluminum bis(2,6-diphenylphenoxide). Nonoshita, X.; Banno, H.; Maruoka, K.; Yamomoto, H. *J. Am. Chem. Soc.* **1990**, *112*, 316.
(12) Trimethylaluminum also promoted the cycloaddition but was not diastereoselective.

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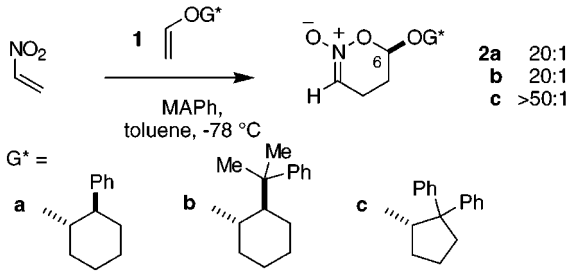
Scheme 2



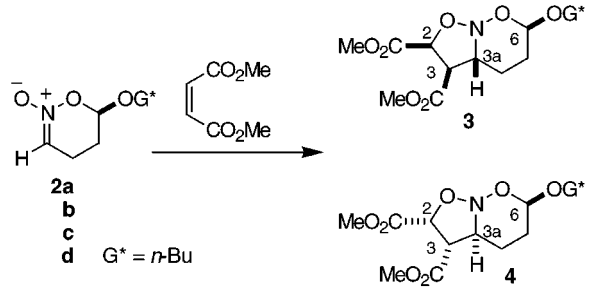
but could not withstand chromatographic purification (silica gel or alumina).[13]

Several chiral vinyl ethers were surveyed to optimize the diastereoselectivity of the [4 + 2] process. Cycloadditions with vinyl ethers **1a**[2c] and **1b**[2e] provided nitronates **2a** and **2b** as a 20/1 ratio of diastereomers at C(6) in both cases, whereas vinyl ether **1c**[2d] afforded the nitronate **2c** as a single diastereomer, as judged by ^{1}H NMR analysis, Scheme 2. The major nitronates **2a**−**c** were assigned the *R* configuration at the acetal center on the basis of previous studies using the (+)-(1*S*) enantiomer of these vinyl ethers and MAPh.[2]

The crude nitronates were reactive 1,3-dipoles and could be trapped with electron deficient dipolarophiles (cis and trans disubstituted and monosubstituted activated alkenes). Reaction of **2** with dimethyl maleate at room temperature afforded nitroso acetals **3** and **4** in good yield as a mixture of diastereomers. The two major diastereomers were both assigned as C(3)/C(3a) trans isomers on the basis of the known exo preference for dimethyl maleate in [3 + 2] cycloadditions with nitronates Scheme 3.[14] The major diastereomer **3** arises from an approach *distal* the C(6) alkoxy substituent and the minor diastereomer **4** *proximal* to the C(6) alkoxy substituent. The facial selectivity was approximately 6/1 for nitroso acetals **3a** and **3b** and improved slightly to 8.3/1 for nitroso acetal **3c**, Scheme 3. Dipolar cycloaddition with **2c** was more selective, as only two of eight possible diastereomers were detected. This is a reflection of the complete stereocontrol in the [4 + 2] cycloaddition with vinyl ether **1c**. Dipolar cycloaddition of **2a**−**d** with dimethyl maleate shows very little stereoselectivity dependence on the size of alkoxy substituent. In fact, the facial selectivty was 7/1 for nitroso acetal **3d**, derived from butyl vinyl ether, indicating that the size of the alkoxy substituent has little influence in this process.

Dipolar cycloadditions with dimethyl fumarate were next examined to ascertain the stereocontrol with trans dipolarophiles, Scheme 4. The product analyses in these reactions are complicated by the lack of exo/endo selectivity with dimethyl fumarate.[15] Both major diastereomers (**5** and **6**) were assigned as arising from approach *distal*

Scheme 3



nitronate	no. of diastereomers[a]	**3**/**4**	yield, %
2a	6	6/1	86
2b	4	6/1	84
2c	2	8.3/1	89
2d	2	7/1	

[a] Determined by ^{1}H NMR analysis.

to the C(6) alkoxy substituent.[16] Nitroso acetal **5** bears an α C(2) carbomethoxy group and nitroso acetal **6** has a *β* C(2) carbomethoxy group. These assignments were confirmed by conversion to pyrrolizidine alkaloids of known structure (*vide infra*). The facial preference of the nitronate in the reaction with a trans disubstituted alkene was determined on the assumption that *all* the minor diastereomers arise from approach *proximal* to the C(6) alkoxy substituent. Again, tandem cycloadditions using nitronates **2a** and **2b** produced a number of diastereomers. However, the facial selectivity is still 11/1 for nitronate **2a** and 7/1 for nitronate **2b**. The analysis is clearer for reactions which employed nitronate **2c**. When the C(2) carbomethoxy substituent is oriented endo (**5c**), the facial selectivity is 8/1. Likewise, when the C(2) substituent is oriented exo (**6c**), the facial selectivity is 6/1.

Methyl acrylate also reacted with nitronate **2c** to provide nitroso acetal **7c** in 81% yield with 7.5/1/1 ratio of diastereomers, Scheme 5. The major product has been assigned as arising from an exo, distal approach to the C(6) alkoxy group and the two minor nitroso acetals as endo, distal and exo, proximal.[17] The endo, proximal product is either not seen or obscured in the analysis. Therefore, the facial selectivity for this monosubstituted alkene is 8.5/1.

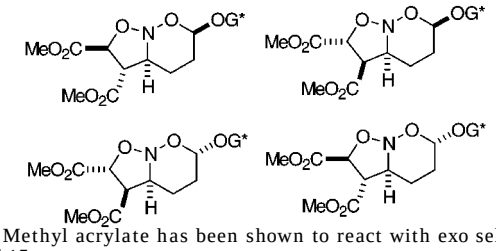
Hydrogenolysis of Nitroso Acetals and Conversion to Pyrrolizidine Alkaloids. Nitroso acetals **3c**−

(13) Thermal [4 + 2] cycloaddition with nitroethylene is also possible. Nitroethylene reacted with butyl vinyl ether at room temperature with approximate reaction half-lives of 3 h in $CDCl_3$ and 24 h in toluene-d_8. However, the product nitronates are immediately consumed by a [3 + 2] cycloaddition with unreacted nitroethylene and the reactions stop at 50% conversion of vinyl ether. The undesired [3 + 2] cycloaddition of nitronates was also problematic in the Lewis-acid-promoted [4 + 2] cycloadditions. It was critical to use no more than a single equivalent of nitroethylene, as upon quench (Me_2NH/MeOH or KOH/MeOH) excess nitroethylene would undergo [3 + 2] cycloaddition prior to or at least competitive with its destruction.

(14) Denmark, S. E.; Thorarensen, A. *J. Org. Chem.* **1994**, *60*, 5672.

(15) In reactions with a nitronate system which is highly facially selective, dimethyl fumarate was poorly endo/exo selective (1/1). Denmark, S. E.; Herbert B.; Seierstad, M. J., unpublished results.

(16) The probable structures of the other four diastereomers are shown below. All nitroso acetals have the same relative configuration of the chiral auxiliary (OG*).

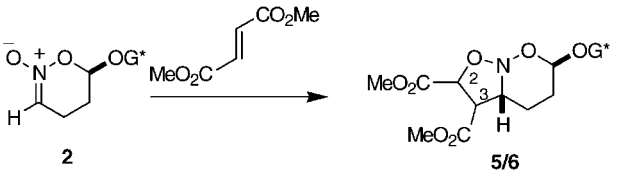


(17) Methyl acrylate has been shown to react with exo selectivity. See ref 15.

(18) The enantiomeric excess was determined by chiral-stationary-phase, supercritical-fluid chromatography (SFC) (Chiralcel OD, 150 bar, 5% MeOH, 2 mL/min, 220 nm).

(19) The enantiomeric excess was determined by chiral-stationary-phase, supercritical-fluid chromatography (SFC) (Chiralcel AD, 150 bar, 20% MeOH, 3 mL/min, 220 nm). The mother liquor contained a mixture of (+)-**10** and an unidentified hydroxy lactam, indicating that the other nitroso acetal diastereomer present in (+)-**6c** was of a different enantiomeric family.

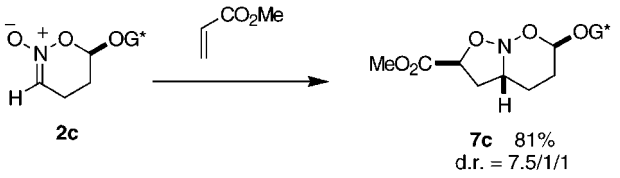
Scheme 4



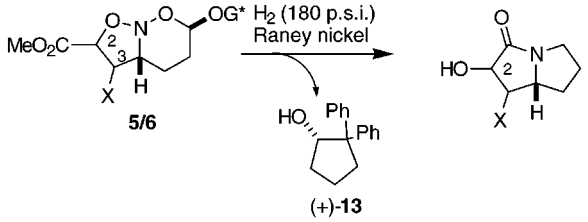
nitronate	**5**/**6**/diastereomers[a]	products	C(2)	C(3)	yield[b]
2a	57/54/5/2/2/1	**5a**	α	*β*	33%
		6a	*β*	α	35%
2b	39/33/4/2/2/1	**5b**	α	*β*	30%
		6b	*β*	α	24%
2c	8/6/1/1	**5c**	α	*β*	40%
		6c	*β*	α	34%

[a] dr determined by crude ^{1}H NMR analysis. [b] Yield of isolated material.

Scheme 5



Scheme 6



nitroso acetal	yield[a]	product	C(2)	X	ee[b]	**13**
3c	46%	**8**	α	*β*-CO_2Me		96%
(−)-**5c**	53%	(+)-**9**	*β*	*β*-CO_2Me	99%	96%
(+)-**6c**	55%	(+)-**10**	α	α-CO_2Me	99%	94%
7c	58%	**11**[20]	*β*	H		98%

[a] Yield of isolated material. [b] ee determined by CSP SFC.

7c were reduced with H_2 (180 psi) over Raney nickel in modest yields (46−68%) and with high recovery of the chiral alcohol **13** (94−98%), Scheme 6. Since the assignment of the two fumarate-derived nitroso acetals (−)-**5** and (+)-**6** was not possible, a two-step conversion to known pyrrolizidine alkaloids was required for structural correlation. A single diastereomer of nitroso acetal (−)-**5c** was reduced to afford hydroxy lactam (+)-**9** in 53% yield (>99% ee).[18] Nitroso acetal (+)-**6c** (d.r. = 6/1) was reduced and after a single recrystallization afforded hydroxy lactam (+)-**10** in 55% yield (>99% ee).[19]

The hydroxy lactams (+)-**9** and (+)-**10** were converted to the known pyrrolizidine alkaloids (+)-macronecine and (+)-petasinecine, Scheme 7. Hydroxy lactam (+)-**9** was treated with $LiAlH_4$ in THF for 3.5 h to afford, after silica gel chromatography and recrystallization, (+)-macronecine in 76% yield.[21] Likewise, hydroxy lactam (+)-**10** was reduced with $LiAlH_4$ to afford, after silica gel chromatography and recrystallization, the unnatural, dextrorotatory enantiomer of petasinecine in 80% yield.[22]

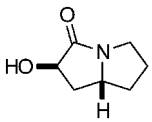
Discussion

[4 + 2] Cycloadditions with Nitroethylene. There are two factors which influence the stereochemical outcome of the [4 + 2] cycloaddition: (1) the endo/exo approach of the dienophile and (2) the accessible face of the vinyl ether. Although it is impossible to determine if the nitronate derived from nitroethylene and (+)-**1c** arises from an exo or endo approach of the vinyl ether, an exo approach of the vinyl ether in MAPh-promoted reactions with other nitroalkenes is preferred.[2] Additionally, it is well documented that (+)-(1*S*)-**1c** exposes the re face of the vinyl ether for cycloaddition to produce nitronates with the *R* configuration at the acetal center C(6). The improved diastereoselectivity in exo-mode cycloadditions using **1c** versus **1a** and **1b** has been noted previously.[2d]

Given the propensity for nucleophile-promoted polymerization of nitroethylene,[6,8] and the documented Michael-type transfer of trialkylaluminums to nitroalkenes,[23] it is noteworthy that the admixing of aluminum Lewis acids (MAPh or trimethylaluminum), vinyl ethers, and nitroethylene produces nitronates with high efficiency, as judged by the conversion to nitroso acetals (yields typically 68−89%). Additionally, it is not surprising that the compatibility of nitroethylene and Lewis acids has only recently been demonstrated,[9] because nitroethylene itself is usually sufficiently reactive for most synthetic purposes.

The [3 + 2] Cycloaddition. The facial selectivity in the [3 + 2] cycloaddition with C(6) monosubstituted nitronates (**2**) is dependent upon the configuration of the C(6) substituent and the reactive conformation of the cyclic nitronate. Since the configuration is assigned by analogy with previous systems (vide supra), discussion of the reactive conformation is relevant. The fact that the size of the C(6) alkoxy substituent has no effect on the selectivity in reactions producing nitroso acetals **3a**−**d** suggests that in the transition structure the bulk of the alkoxy group is oriented away from the nitronate ring, but the mere presence of an alkoxy group in these reactions with cis dipolarophiles is sufficient for selectivity. Nonbonded steric interactions should be expected to become more severe when a trans dipolarophile is employed and selectivities would be expected to increase.[5] Yet, all dipolarophiles in this study whether monosubstituted, cis disubstituted, or trans disubstituted produce nitroso acetals with a facial selectivity in the range of

(20) Hydroxy lactam **12** was isolated in 10% yield and is derived from nitroso acetal **7c′** which is the endo addition product of methyl acrylate to nitronate **2c**.



12

(21) The physical and spectral properties of synthetic material matched those reported for the natural (+)-macronecine: mp = 128−129 °C, $[\alpha]^{23}_D$ = +42.7° (EtOH, *c* = 0.96); lit. mp = 129 °C, $[\alpha]^{23}_D$ = +49.3° (EtOH, *c* = 0.50). (a) Danilova, A.; Utkin, L.; Massagetov, P. *J. Gen. Chem. USSR.* **1955**, *25*, 797. (b) Ito, H.; Ikeuchi, Y.; Taguchi, T.; Hanazawa, Y.; Shiro, M. *J. Am. Chem. Soc.* **1994**, *116*, 5469.

(22) The physical and spectral properties of synthetic material matched those reported for the natural (−)-petasinecine except for the sign of the optical rotation: mp = 133−134 °C, $[\alpha]^{23}_D$ = +24.8° (EtOH, *c* = 0.25); lit. mp = 132−134 °C, $[\alpha]^{23}_D$ = −20.0° (EtOH, *c* = 0.25). (a) Yamada, K.; Tatematsu, H.; Unno, R.; Hirata, Y.; Hirono, I. *Tetrahedron Lett.* **1978**, 4543. (b) Mulzer, J.; Shanyoor, M. *Tetrahedron Lett.* **1993**, *34*, 6545.

(23) Pecunioso, A.; Menicagli, R. *J. Org. Chem.* **1988**, *53*, 45.

Scheme 7

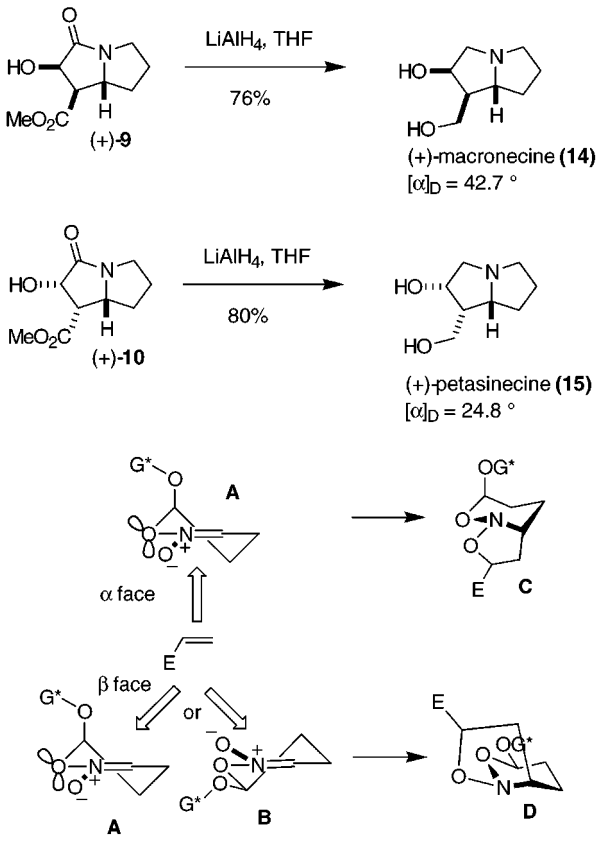


Figure 1. Preferred approach of dipolarophile to nitronate **2**.

6−8/1. The directing ability of any alkoxy group and the insensitivity to steric constraints is suggestive of an electronic controlling element.

There are two likely reactive conformations of the nitronate in the [3 + 2] cycloaddition: a twist-chair with an axially disposed alkoxy group (**A**) and with an equatorially alkoxy group (**B**), Figure 1. The α-face approach to nitronate **A** would lead directly to a favorable chair conformation of the major product **C**. Additionally, this pathway may also benefit from a kinetic anomeric effect.[24] The minor diastereomer **D** may arise from either an *β*-face approach to nitronate **A**, which must then undergo a ring flip to **D**,[25] or react directly through nitronate conformer **B**.

In addition to confirming structural assignments, the enantioselective, four-step syntheses of (+)-macronecine and (+)-petasinecine in 16% and 15% yields, respectively, represent the shortest synthesis of these compounds on record.

Conclusion

Nitroethylene readily engages in Lewis acid-promoted [4 + 2] cycloadditions with chiral vinyl ethers with high chemical efficiency and diastereoselectivity. Despite the lack of proximate stereodirecting groups, nitroethylene-derived cyclic nitronates undergo selective [3 + 2] cycloadditions with external dipolarophiles. Natural product syntheses using either a tethered dipolarophile[26] or a more complex external dipolarophile are currently under consideration.

Experimental Section

General Experimental. See Supporting Information for details.

General Procedure I: Tandem [4 + 2]/[3 + 2] Cycloadditions with Nitroethylene. (2*S,3a*R**,3*S**,6*R**)-Hexahydro-6-[(1*S**)-2,2-diphenylcyclopentyloxy]isoxazolo[2,3-*b*][1,2]oxazine-2,3-dicarboxylic Acid Dimethyl Ester (3c).** Trimethylaluminum (4.00 mL, 8.00 mmol, 2 equiv) was added rapidly to a solution of 2,6-diphenylphenol (3.94 g, 16.0 mmol, 4 equiv) in 80 mL of toluene at rt. The resulting clear, yellow solution was allowed to stir for 30 min and then was added to a solution of chiral ether **1c** (1.05 g, 4.00 mmol) in 20 mL of toluene at −78 °C (5 min). The resulting solution was stirred at −78 °C for 10 min before a 0.83 M solution of nitroethylene in toluene (4.90 mL, 4.07 mmol, 1.02 equiv) was added dropwise (10 min). During the addition a brown complex developed and rapidly faded. After the addition was completed, the mixture was stirred at −78 °C for 10 min and then was quenched with H_2O (10 mL) and allowed to warm to room temperature. The resulting mixture was partitioned between CH_2Cl_2 (200 mL) and H_2O (200 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 200 mL), the combined organic extracts were washed with brine (100 mL), and the brine wash was back extracted with CH_2Cl_2 (100 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated to approximately 50 mL. The solution was diluted with toluene (50 mL) and concentrated again to approximately 50 mL. An aliquot was removed and concentrated under high vacuum to afford a crude oil which was shown by ^{1}H NMR analysis to be a 20/1 mixture of diastereomeric nitronates. Dimethyl maleate (1.00 mL, 8.00 mmol, 2.0 equiv) was added neat, and the solution was stirred at rt for 17 h. Concentration of the solution under vaccum afforded a pale-yellow oil, which was purified by silica gel chromatography (hexane/EtOAc; 6/1, 4/1, 2/1) to afford 3.93 g of 2,6-diphenylphenol, 0.510 g of dimethyl maleate, and 1.708 g (89%) of nitroso acetal **3c** as a 8.25/1 mixture of diastereomers. Recrystallization from MeOH afforded 1.465 g (77%) of **3c** as a 10/1 mixture of diastereomers. Data for **3c**: mp 139−140 °C (MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08−7.28 (m, 10 H), 5.19 (d, J = 10.1, 1 H), 4.75 (t, J = 4.4, 1H), 4.50 (br s, 1 H), 3.91−3.96 (m, 1 H), 3.72−3.77 (m, 1 H), 3.74 (s, 3 H), 3.69 (s, 3 H), 2.59 (dt, J = 12.3, 9.1, 1H), 2.32−2.42 (m, 1 H), 2.16−2.30 (m, 3 H), 1.76−1.90 (m, 1 H), 1.62−1.70 (m, 1 H), 1.36−1.48 (m, 2 H), 1.09−1.16 (m, 1 H); ^{13}C NMR (125.6 MHz, $CDCl_3$) δ 170.15, 168.73, 146.83, 145.60, 128.62, 128.13, 127.51, 127.09, 125.84, 125.49, 101.85, 85.07, 82.02, 69.92, 59.99, 52.58, 52.55, 49.06, 35.24, 31.20, 22.39, 20.49, 18.79; IR (KBr) 1762 (s), 1730 (s); MS (CI, CH_4) 482 (M^+ + 1); TLC, R_f = 0.37 (hexane/EtOAc, 2/1). Anal. Calcd for $C_{27}H_{31}NO_7$ (481.54): C, 67.35; H, 6.49; N, 2.91. Found: C, 67.14; H, 6.52: N, 2.77.

(2*R*,3a*R*,3*S*,6*R*)-Hexahydro-6-[(1*S)-2,2-diphenylcyclopentyloxy]isoxazolo[2,3-*b*][1,2]oxazine-2,3-dicarboxylic Acid Dimethyl Ester ((−)-5c) and (2*S*,3a*R*,3*R*,6*R*)-Hexahydro-6-[(1*S**)-2,2-diphenylcyclopentyloxy]isoxazolo[2,3-*b*][1,2]oxazine-2,3-dicarboxylic Acid Dimethyl Ester ((+)-6c).** Following General Procedure I with the following quantity of reagents and reaction times: MAPh (15.00 mmol, 2.5 equiv), (+)-**1c** (1.59 g, 6.00 mmol), nitroethylene (438 mg, 6.00 mmol, 1.0 equiv) at −78 °C for 15 min,

(24) A kinetic anomeric effect has been used to rationalize stereoselective [3 + 2] cycloadditions of nitrones (Vasella, A. *Helv. Chim. Acta* **1977**, *60*, 1273. Petrizilka, M.; Felix, D.; Eschenmoser, A. *Helv. Chim. Acta* **1973**, *56*, 2950) and nitronates (Denmark, S. E.; Dappen, M. S.; Cramer, C. J. *J. Am. Chem. Soc.* **1986**, *108*, 1306. Denmark, S. E.; Cramer, C. J.; Sternberg, J. A. *Helv. Chim. Acta* **1986**, *69*, 1971).

(25) The ground state conformation of the minor diastereomers in all tandem cycloadditions has an equatorially disposed C(6) alkoxy substituent, as determined by NMR analysis.

(26) (a) Denmark, S. E.; Stolle, A.; Dixon, J. A.; Guagnano, V. *J. Am. Chem. Soc.* **1995**, *117*, 2100. (b) Denmark, S. E.; Guagnano, V.; Dixon, J. A.; Stolle, A. *J. Org. Chem.* **1997**, *62*, 4610. (c) Denmark, S. E.; Dixon, J. A. *J. Org. Chem.* **1997**, *62*, 7086.

dimethyl fumarate (1.08 g, 7.50 mmol, 1.25 equiv) at rt for 16 h. The crude product was purified by silica gel chromatography (hexane/EtOAc; 6/1, 4/1, 2/1) to afford 6.44 g of 2,6-diphenylphenol, 1.160 g (40%) of nitroso acetal (−)-**5c** as a white foam (single diastereomer), and 0.980 g (34%) of nitroso acetal (+)-**6c** as a white foam (**6c**/**6c′** = 6/1). Data for (−)-**5c**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08−7.24 (m, 10 H), 5.21 (d, J = 6.1, 1 H), 4.80 (dd, J = 5.6, 2.7, 1H), 4.47 (m, 1 H), 3.93 (dd, J = 10.0, 6.1, 1 H), 3.86 (s, 3 H), 3.80 (s, 3 H), 3.70 (m, 1 H), 2.64 (td, J = 12.3, 9.2, 1H), 2.41 (tt, J = 13.6, 4.9, 1 H), 2.17−2.32 (m, 3 H), 1.78−1.92 (m, 2 H), 1.42−1.55 (m, 2 H), 1.03−1.06 (m, 1 H); ^{13}C NMR (125.6 MHz, $CDCl_3$) δ 171.52, 170.84, 146.88, 145.54, 128.66, 128.11, 127.51, 127.15, 125.84, 125.52, 101.64, 84.84, 83.44, 71.26, 59.98, 52.91, 52.82, 47.82, 35.35, 31.33, 21.95, 20.43, 18.49; IR (KBr) 1739 (s); MS (CI, CH_4) 482 (M^+ + 1); $[\alpha]^{23}_D$ = -21.1° (EtOH, c = 1.00), TLC R_f = 0.32 (hexane/EtOAc, 2/1). Anal. Calcd for $C_{27}H_{31}NO_7$ (481.54): C, 67.35; H, 6.49; N, 2.91. Found: C, 67.12; H, 6.49: N, 2.81. Data for (+)-**6c**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08−7.29 (m, 10 H), 5.62 (d, J = 6.8, 1 H), 4.79 (dd, J = 5.9, 2.2, 1H), 4.57 (t, J = 4.6, 1 H), 3.97 (td, J = 10.3, 5.9, 1 H), 3.84 (s, 3 H), 3.78 (s, 3 H), 3.56 (dd, J = 10.4, 7.0, 1 H), 2.64 (td, J = 12.5, 9.2, 1H), 2.09−2.33 (m, 4 H), 1.83−1.91 (m, 1 H), 1.67−1.74 (m, 1 H), 1.39−1.48 (m, 1 H), 1.07−1.19 (m, 2 H); ^{13}C NMR (125.6 MHz, $CDCl_3$) δ 170.63, 169.54, 146.70, 145.59, 128.5, 128.14, 127.53, 127.06, 125.85, 125.46, 101.68, 85.40, 81.92, 68.80, 60.06, 52.83, 52.61, 49.62, 35.21, 31.46, 23.49, 20.47, 18.80; IR (KBr) 1747 (s), 1722 (s), 1711 (s); MS (CI, CH_4) 482 (M^+ + 1); $[\alpha]^{23}_D$ = +68.6° (CH_2Cl_2, c = 0.95), TLC R_f = 0.31 (hexane/EtOAc, 2/1). Anal. Calcd for $C_{27}H_{31}NO_7$ (481.54): C, 67.35; H, 6.49; N, 2.91. Found: C, 67.22; H, 6.52: N, 2.81.

(2*S,3a*R**,6*R**)-Hexahydro-6-[(1*S**)-2,2-diphenylcyclopentyloxy]isoxazolo[2,3-*b*][1,2]oxazine-2-carboxylic Acid Methyl Ester (7c).** Following the General Procedure I with the following quantity of reagents and reaction times: MAPh (8.00 mmol, 2.0 equiv), **1c** (1.06 g, 4.00 mmol), nitroethylene (295 mg, 4.01 mmol, 1.0 equiv) at −78 °C for 10 min, methyl acrylate (0.720 mL, 8.00 mmol, 2.0 equiv) at rt for 20 h. The crude product was purified by silica gel chromatography (hexane/EtOAc; 8/1, 6/1, 4/1, 2/1) to afford 3.92 g of 2,6-diphenylphenol and 1.371 g (81%) of nitroso acetal **7c** as a 7.5/1/1 mixture of diastereomers. Data for **7c**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.03−7.15 (m, 10 H), 5.00 (dd, J = 10.5, 3.5 1 H), 4.75 (t, J = 4.4, 1H), 4.48 (m, 1 H), 3.76 (s, 3 H), 3.66 (m, 1 H), 2.59 (td, J = 12.3, 9.0, 1H), 2.50 (td, J = 11.3, 10.8, 1H), 2.30−2.37 (m, 1 H), 2.19−2.28 (m, 4 H), 1.81−1.87 (m, 1 H), 1.53−1.59 (m, 1 H), 1.38−1.46 (m, 2 H), 1.07−1.12 (m, 1 H); ^{13}C NMR (125.6 MHz, $CDCl_3$) δ 171.06, 146.94, 145.70, 128.66, 128.11, 127.48, 127.12, 125.81, 125.43, 101.84, 84.93, 80.79, 66.65, 59.99, 52.49, 35.29, 31.84, 31.29, 22.41, 20.49, 19.35; IR (KBr) 1758 (s); MS (CI, CH_4) 424 (M^+ + 1); TLC, R_f = 0.32 (hexane/EtOAc, 2/1). Anal. Calcd for $C_{25}H_{29}NO_5$ (423.51): C, 70.90; H, 6.90; N, 3.31. Found: C, 71.10; H, 7.17; N, 3.32.

General Procedure II: Hydrogenolysis of Nitroso Acetals. [1*S,2*S**,7a*R**]-Hexahydro-2-hydroxy-3-oxo-1*H*-pyrrolizine-1-carboxylic Acid Methyl Ester (8).** A suspension of a catalytic amount of Raney nickel W-2 (washed 5 × 75 mL MeOH) and nitroso acetal **3c** (730 mg, 1.45 mmol) in 72 mL of MeOH was pressurized with H_2 to 180 psi in a steel autoclave. The mixture was stirred at rt for 45 h. The reaction vessel was carefully vented, and the suspension was filtered through Celite (4 cm pad). The Celite pad was rinsed with 500 mL of MeOH, and the filtrate was concentrated. The resulting pale yellow oil was purified by silica gel chromatography (hexane/EtOAc; 4/1; CH_2Cl_2/ MeOH; 19/1) to afford 334 mg (98%) of white, crystalline 2,2-diphenylcyclopentanol (**13**) and crude hydroxy lactam **8**, which was recrystallized (EtOAc/hexane) to provide 133 mg (46%) of **8** as a white crystalline solid. Data for **8**: mp 136−137 °C (EtOAc/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.88 (d, J = 9.8, 1 H), 4.25 (br s, 1 H), 3.90 (td, J = 9.7, 6.0, 1 H,), 3.81 (s, 3 H), 3.62 (dt, J = 11.5, 8.1, 1 H), 3.15 (m, 1 H), 2.91 (dd, J = 9.8, 8.3), 2.20−2.30 (m, 1 H), 2.11−2.20 (m, 1 H), 2.00−2.11 (m, 1 H), 1.51−1.59 (m, 1 H); ^{13}C NMR (125.6 MHz, $CDCl_3$) δ 172.32, 171.60, 75.70, 59.23, 56.03, 52.52, 41.59, 31.48, 25.86; IR (KBr) 1726 (s), 1686 (s); MS (CI, CH_4) 200 (M^+ + 1); TLC R_f = 0.28 (CH_2Cl_2/MeOH, 19/1). Anal. Calcd for $C_9H_{13}NO_4$ (199.21): C, 54.26; H, 6.58; N, 7.03. Found: C, 54.30; H, 6.68; N, 6.96.

[1*R*,2*R*,7a*R*]-Hexahydro-2-hydroxy-3-oxo-1*H*-pyrrolizine-1-carboxylic Acid Methyl Ester ((+)-9). Following General Procedure II with the following quantity of reagents and reaction times: nitroso acetal (−)-**5c** (1.00 g, 2.08 mmol) in 80 mL of MeOH, 48 h, 180 psi H_2. The crude product was purified by silica gel chromatography (hexane/ EtOAc; 4/1; CH_2Cl_2/MeOH; 19/1) to afford 466 mg (94%) of white, crystalline 2,2-diphenylcyclopentanol (**13**) and hydroxy lactam (+)-**9**, which was recrystallized (EtOAc) to afford 219 mg (53%) of (+)-**9** as a white, crystalline solid. Hydroxy lactam (+)-**9** was determined to be greater than 99% ee by chiral stationary phase supercritical fluid chromatography (Chiralcel OD, 150 bar, 5% MeOH, 2 mL/min, 220 nm). Data for (+)-**9**: mp 191−192 °C (EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.65 (dd, J = 6.2, 3.8, 1 H), 4.45 (ddd, J = 9.8, 7.8, 5.9, 1 H), 4.00 (d, J = 3.7, 1 H), 3.83 (s, 3 H), 3.53 (dt, J = 12.0, 8.3, 1 H), 3.23 (ddd, J = 12.2, 9.0, 3.4, 1 H), 2.97 (dd, J = 7.7, 6.2, 1 H), 2.15−2.29 (m, 3 H), 1.36−1.75 (m, 1 H); ^{13}C NMR (125.6 MHz, $CDCl_3$) δ 70.72, 169.65, 76.83, 61.56, 52.32, 52.20, 40.72, 31.04, 27.04; IR (KBr) 1741 (s), 1731 (s), 1713 (s); MS (CI, CH_4) 200 (M^+ + 1); $[\alpha]^{23}_D$ = +120.0° (EtOH, c = 1.00); TLC R_f = 0.20 (CH_2Cl_2/MeOH, 19/1). Anal. Calcd for $C_9H_{13}NO_4$ (199.21):C, 54.26; H, 6.58; N, 7.03. Found: C, 54.38; H, 6.67; N, 7.04.

[1*S*,2*S*,7a*R*]-Hexahydro-2-hydroxy-3-oxo-1*H*-pyrrolizine-1-carboxylic Acid Methyl Ester ((+)-10). Following General Procedure II with the following quantity of reagents and reaction times: nitroso acetal (+)-**6c** (880 mg, 1.84 mmol) (d.r. = 6/1) in 80 mL of MeOH, 48 h, 180 psi H_2. The crude product was purified by silica gel chromatography (hexane/ EtOAc; 4/1, 0/1; CH_2Cl_2/ MeOH; 19/1) to afford 420 mg (96%) of white, crystalline 2,2-diphenylcyclopentanol (**13**) and 237 mg of hydroxy lactam (+)-**10**, which was recrystallized (EtOAc) to afford 201 mg (55%) of (+)-**10** as a white, crystalline solid. An analytical sample of hydroxy lactam (+)-**10**, obtained by sublimation (100 °C, 0.1 mmHg), which was determined to be greater than 99% ee by chiral stationary phase supercritical fluid chromatography (Chiralcel AD, 150 bar, 20% MeOH, 3 mL/min, 220 nM). Data for (+)-**10**: sublimation point 100 °C (0.1 mmHg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.80 (br d, J = 6.6, 1 H), 4.08 (dt, J = 8.8, 6.4, 1 H), 3.76 (s, 3 H), 3.70 (t, J = 6.4, 1 H), 3.65 (dt, J = 11.2, 7.1, 1 H), 3.15−3.19 (m, 2 H), 2.01−2.14 (m, 3 H), 1.51−1.59 (m, 1 H); ^{13}C NMR (125.6 MHz, $CDCl_3$) δ 172.52, 170.21, 73.97, 57.82, 51.82, 51.43, 41.99, 27.00, 25.67; IR (KBr) 1734 (s), 1684 (s); MS (CI, CH_4) 200 (M^+ + 1); $[\alpha]^{23}_D$ = +50.0° (EtOH, c = 0.95); TLC R_f = 0.27 (CH_2Cl_2/MeOH, 19/1). Anal. Calcd for $C_9H_{13}NO_4$ (199.21): C, 54.26; H, 6.58; N, 7.03. Found: C, 54.12; H, 6.61; N, 6.95.

[2*S,7a*R**]-Hexahydro-2-hydroxy-3*H*-pyrrolizin-3-one (11) and [2*R**,7a*R**]-Hexahydro-2-hydroxy-3*H*-pyrrolizin-3-one (12).** Following General Procedure II with the following quantity of reagents and reaction times: nitroso acetal **7c** (630 mg, 1.49 mmol, d.r. = 7.5/1/1) in 72 mL of MeOH, 48 h, 180 psi H_2. The crude product was purified by silica gel chromatography (hexane/EtOAc; 4/1; CH_2Cl_2/ MeOH; 19/1) to afford 348 mg (98%) of white, crystalline 2,2-diphenylcyclopentanol (**13**) and 146 mg (70%) of a mixture of **11**/**12** (6/1). The diastereomeric hydroxy lactams were separated on preparative HPLC (silica gel, EtOAc, 10 mL/min) to afford 123 mg (58%) of hydroxy lactam **11** as a white solid and 21.3 mg (10%) of hydroxy lactam **12** as a 9/1 mixture of **12**/**11**. Data for **11**: mp 111−112 °C (EtOAc/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.59 (t, J = 9.0, 1 H), 3.71 (tt, J = 9.0, 5.9, 1 H), 3.60 (dt, J = 11.5, 7.8, 1 H), 3.10 (ddd, J = 11.7, 9.3, 3.0, 1 H), 2.82 (br s, 1 H), 2.79 (ddd, J = 12.1, 7.6, 5.9, 1 H), 1.99−2.16 (m, 3 H), 1.63 (ddd, J = 12.1, 10.6, 9.0, 1 H), 1.40 (m, 1 H); ^{13}C NMR (125.6 MHz, $CDCl_3$) δ 174.80, 73.57, 57.04, 41.15, 38.23, 32.16, 26.03; IR (KBr) 1672 (s); MS (CI, CH_4) 142 (M^+ + 1); TLC R_f = 0.31 (CH_2Cl_2/MeOH, 19/1). Anal. Calcd for $C_7H_{11}NO_2$ (141.17): C, 59.56; H, 7.85; N, 9.92. Found: C, 59.58; H, 7.90: N, 9.97. Data for **12**: mp 109−113 °C (EtOAc/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.43 (dd, J = 7.2, 1.8, 1 H), 4.04

(m, 1 H), 3.51 (dt, J = 11.7, 8.0, 1 H), 3.15 (ddd, J = 12.3, 9.3, 3.7, 1 H), 2.53 (br s, 1 H), 2.27 (ddd, J = 13.9, 6.6, 2.0, 1 H), 2.02−2.20 (m, 3 H), 1.93−2.00 (m, 1 H), 1.21−1.28 (m, 1 H); ^{13}C NMR (125.6 MHz, $CDCl_3$) δ 174.19, 75.61, 60.63, 40.65, 35.44, 31.89, 26.97; IR (KBr) 1692 (s); MS (CI, CH_4) 142 (M^+ + 1); TLC R_f = 0.22 (CH_2Cl_2/MeOH, 19/1). Anal. Calcd for $C_7H_{11}NO_2$ (141.17): C, 59.56; H, 7.85; N, 9.92. Found: C, 59.72; H, 7.69; N, 9.87.

[1*S*,2*R*,7a*R*]-Hexahydro-2-hydroxy-1*H*-pyrrolizine-1-methanol, (+)-macronecine ((+)-14). A suspension of hydroxy lactam (+)-**9** (116 mg, 0.582 mmol) in 8 mL of THF was added dropwise to a cold (0 °C) suspension of $LiAlH_4$ (145 mg, 3.63 mmol, 6.2 equiv) in 3 mL of THF. The gray suspension was then heated to reflux for 3.5 h. After the solution was cooled to rt, the reaction was quenched with H_2O (0.15 mL), 10% NaOH (0.15 mL), and H_2O (0.30 mL) and was stirred for 1 h. The light gray suspension was filtered through a sintered glass filter, and the filter cake was rinsed with 50 mL of MeOH. The filtrate was concentrated to a white solid, which was purified by silica gel chromatography on a column which had a 10 mm × 40 mm plug of Celite under the silica gel (MeOH/CH_2Cl_2/NH_4OH; 5/10/1). Recrystallization from acetone afforded 69.8 mg (76%) of (+)-macronecine as a highly crystalline, white solid. Data for (+)-**14**: mp 128−129 °C (acetone), lit.[21a] mp = 129 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.49 (t, J = 3.7,1 H), 4.03 (br s, 2 H), 3.82−3.88 (m, 2 H), 3.51−3.57 (m, 1 H), 3.17 (d, J = 11.0, 1 H), 2.95 (td, J = 10.6, 6.5, 1 H), 2.67 (dd, J = 11.0, 3.4, 1 H), 257 (m, 1 H), 1.95 (dq, J = 12.2, 7.2, 1 H), 1.76−1.86 (m, 3 H), 1.52 (dq, J = 12.2, 6.0, 1 H); ^{13}C NMR (125.6 MHz, $CDCl_3$) δ 75.33, 64.00, 62.94, 60.56, 54.97, 52.51, 31.20 25.40; IR (KBr) 3322 (s), 2951 (s); MS (70 ev) 157 (M^+); $[\alpha]^{23}_D$ = +42.7° (EtOH, c = 0.96), lit.[21a] $[\alpha]^{23}_D$ = +49.3° (EtOH, c = 0.50); TLC R_f = 0.13 (CH_2Cl_2/MeOH/NH_4-OH, 10/5/1). Anal. Calcd for $C_8H_{15}NO_2$ (157.21): C, 61.16; H, 6.62; N, 8.91. Found: C, 60.93; H, 9.39; N, 8.88.

[1*R*,2*S*,7a*R*]-Hexahydro-2-hydroxy-1*H*-pyrrolizine-1-methanol, (+)-Petasinecine ((+)-15). A suspension of hydroxy lactam (+)-**10** (140 mg, 0.703 mmol) in 8 mL of THF was added dropwise to a cold (0 °C) suspension of $LiAlH_4$ (175 mg, 4.38 mmol, 6.2 equiv) in 3 mL of THF. The gray suspension was then heated to reflux for 3.5 h. After the solution was cooled to rt, the reaction was quenched with H_2O (0.175 mL), 10% NaOH (0.175 mL), and H_2O (0.35 mL) and was stirred for 1 h. The light gray suspension was filtered through a sintered glass filter, the filter cake was rinsed with 50 mL of MeOH, and the filtrate was concentrated to a white solid. The crude product was purified by silica gel chromatography on a column which had a 10 mm × 40 mm plug of Celite under the silica gel (MeOH/CH_2Cl_2/NH_4OH; 5/10/1). Recrystallization from acetone afforded 88.6 mg (80%) of (+)-petasinecine as white needles. Data for (+)-**15**: mp 132−133 °C (acetone), lit.[22a] mp = 132−134 °C; ^{1}H NMR (500 MHz, CD_3-OD) δ; ^{13}C NMR (125.6 MHz, CD_3OD) δ 4.30 (dt, J = 4.4, 1.25, 1 H), 3.92 (dd, J = 10.8, 7.3, 1 H), 3.76 (dd, J = 10.8, 7.3, 1 H), 3.59 (m, 1 H), 3.21 (ddd, J = 9.5, 7.0, 2.5, 1 H), 3.13 (dd, J = 12.7, 3.9, 1 H), 2.91 (dt, J = 9.9, 5.7, 1 H), 2.83 (dd, J = 12.7, 1.2, 1 H), 2.31 (m, 1 H,), 1.96−2.04 (m, 2 H), 1.67−1.79 (m, 2 H); ^{13}C NMR (125.6 MHz, CD_3OD) δ 74.54, 67.83, 63.47 59.80, 57.81, 49.73, 28.65, 27.90; IR (KBr) 3289 (br s); MS (70 ev) 157 (M^{+}); $[\alpha]^{23}_D$ = +24.8° (EtOH, c = 0.25), lit.[22a] $[\alpha]^{23}_D$ = −20.0° (EtOH, c = 0.25); TLC R_f = 0.13 (CH_2Cl_2/MeOH/NH_4OH, 10/5/1). Anal. Calcd for $C_8H_{15}NO_2$ (157.21): C, 61.16; H, 6.62; N, 8.91. Found: C, 60.93; H, 9.39; N, 8.88.

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Supporting Information Available: General experimental, a full list of IR absorbances, MS fragments, ^{1}H NMR, and ^{13}C NMR listings with assignments for compounds **3c**, **5c**−**7c**, **8**−**12**, **14** and **15**, and full experimental details and characterization data for compounds **3a**, **5a**, **6a**, **3b**, **5b**, and **6b** (19 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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