Tandem [4 + 2]/[3 + 2] Cycloadditions of Nitroalkenes. 11. The Synthesis of (+)-Crotanecine

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Abstract: (+)-Crotanecine (**1**) is the necine base component of a number of pyrrolizidine alkaloids. This necine subunit is an amino triol bearing a primary allylic alcohol characterized by an all-cis relationship of its stereocenters. The synthesis of (+)-crotanecine has been accomplished in 10 steps and 10.2% overall yield. The key step in the asymmetric synthesis is a Lewis acid-promoted, tandem inter[4 + 2]/intra[3 + 2] cycloaddition between a (fumaroyloxy)nitroalkene **14** and chiral β-silylvinyl ether (−)-**26**. This synthesis serves to illustrate the synthetic versatility of the tandem cycloaddition to incorporate additional functionality.

Introduction and Background

Synthetic efficiency is currently one of the most important challenges in organic chemistry.[1] In recent years the strategic use of tandem reactions has been well recognized as a powerful method for increasing molecular complexity and thereby synthetic utility.[2,3] The tandem [4 + 2]/[3 + 2] cycloadditions of nitroalkenes have been extensively developed in these laboratories for the construction of various polycyclic nitrogen-containing compounds in enantiomerically enriched form.[4] Indeed, this approach has been successfully employed in the synthesis of the two pyrrolizidine alkaloids (−)-hastanecine[5] and (−)-rosmarinecine.[6]

As a part of a continuing program in methodology-driven alkaloid synthesis, we recognized a challenge provided by such molecules as (+)-crotanecine which bear an additional hydroxyl substituent at C(2). The construction of such a molecule by the tandem sequence would require the ability to install this functionality in the correct configuration by the use of a functionalized chiral dienophile. The evolution of a general approach to these compounds and the successful synthesis of (+)-crotanecine are described below.

(+)-Crotanecine is found conjugated to a variety of necic acids in many pyrrolizidine alkaloids found in plants of the *Crotalaria* species. For example, anacrotine (**4**) isolated from the seeds of *C. anagyroids* obtained from Sri Lanka[7,8] or from *C. incana* shrub grown in South Africa[9] afforded senecic acid and a new amino triol named crotanecine. Upon reexamination of leaves and twigs gathered from *C. agatiflora* grown in
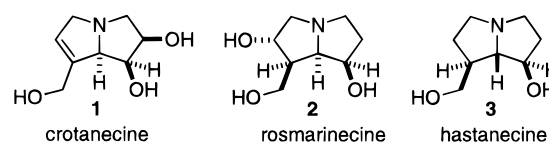

Figure 1. Necine bases that have been prepared with the tandem [4 + 2]/[3 + 2] cycloadditions.

Australia six new alkaloids were isolated, all containing (+)-crotanecine as the base (Figure 2).[10] The structure of anacrotine was unambiguously proven by X-ray crystallographic analysis in 1984, confirming the relative and absolute stereochemistry and the size of the macrolactone.[11] In addition, an X-ray crystal structure of (+)-crotanecine itself has been determined.[12] Thus, the structure of (+)-crotanecine is firmly secured. Until recently,[13] the only ¹H NMR data available for (+)-crotanecine were from the original 60 MHz ¹H NMR spectrum.[7]

(+)-Crotanecine bears a double bond at the C(6)−C(7) position; therefore, all the alkaloids **4**−**11** that contain crotanecine should be hepatotoxic, the most common biological effect of pyrrolizidine alkaloids. However, this has only been demonstrated for anacrotine.[14] In addition to hepatotoxicity, anacrotine displays pneumotoxicity.

There have been only two previous syntheses of (+)-crotanecine[15,16] along with one formal synthesis.[17] They all

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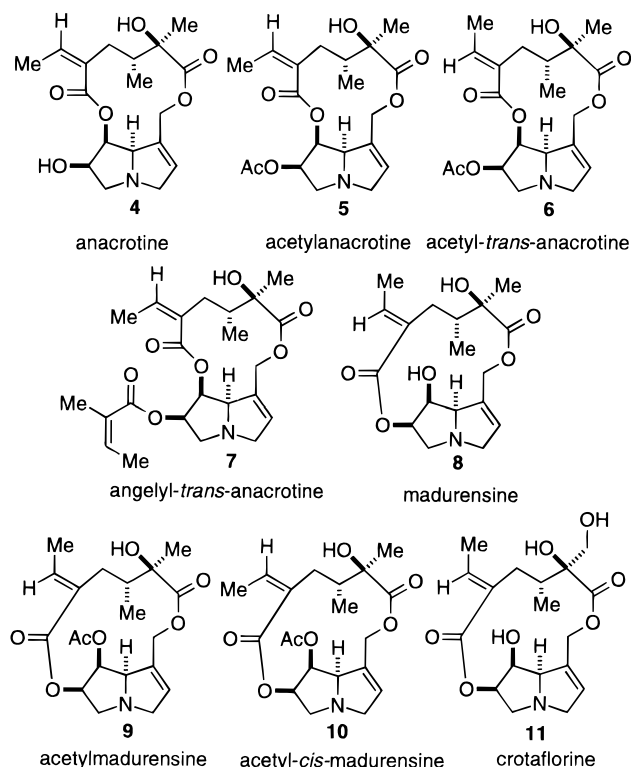
Figure 2. Alkaloids that contain (+)-crotanecine (**1**) as the necine base.

Figure 3. Examples of different necines organized by the classifications of the relationship between C(1), C(7), and C(7a).

Scheme 1

share in common the use of the chiral pool starting material that incorporates one or more of the stereocenters found in (+)-crotanecine.

Synthesis Design[18]

The tandem [4 + 2]/[3 + 2] cycloaddition of nitroalkenes is an extremely flexible method for the synthesis of necines. All of the stereochemical attributes are subject to a high level of predictability and control. Further, the installation of functional groups at key stereocenters can be achieved by appropriate modification of diene and dienophile. Finally, judicious choice of chiral auxiliary and Lewis acid sets the absolute configuration of the molecule as a whole.

The power of this strategy becomes apparent when classifying all the necines on the basis of the relationship among the stereogenic centers at C(1), C(7), and C(7a) (Figure 3). There are 21 structurally unique 7-hydroxymethyl-substituted necines. Ten of those have the all-cis relationship exemplified by (−)-rosmarinecine and could arise from a tandem inter[4 + 2]/*intra*[3 + 2] process. Another seven necines have the all-trans relationship as in (−)-hastanecine and could arise from a tandem inter[4 + 2]/*inter*[3 + 2] process. In addition there are two members which contain a cis/trans relationship, leaving only two necines conceptually not accessible with this method.

(+)-Crotanecine belongs to the family of all-cis-substituted necines. Thus, the retrosynthetic analysis of (+)-crotanecine follows the same logic as was employed for (−)-rosmarinecine;[6] however, it represented a significant synthetic challenge due to the higher level of functionality, namely the C(6)−C(7) olefin
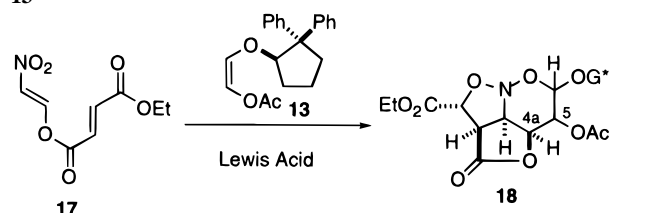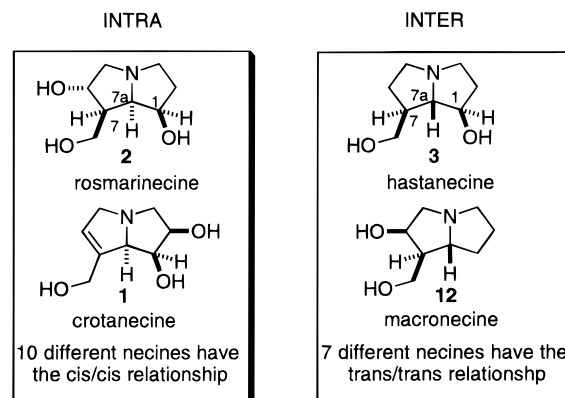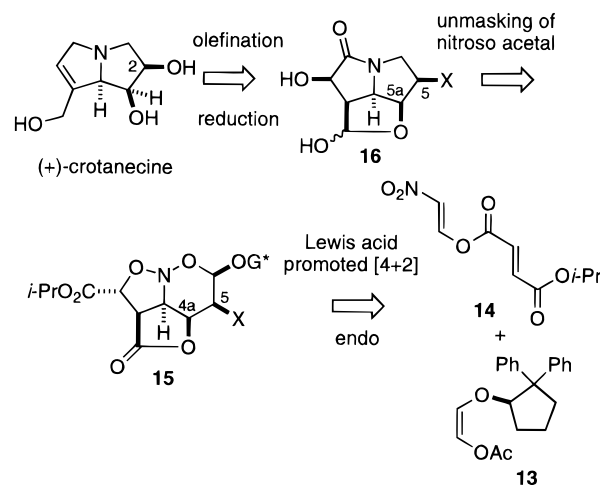
and the C(2) hydroxyl group (Scheme 1). (+)-Crotanecine was envisioned to arise from the α-hydroxy lactam **16**, where X would be an appropriate hydroxyl synthon. The hydroxyl at C(1) then becomes the handle necessary to install the olefin at C(6)−C(7) in (+)-crotanecine. The α-hydroxy lactam **16** would derive from a nitroso acetal **15** after reductive unmasking. The nitroso acetal **15** in turn arises from an inter[4 + 2]/intra[3 + 2] cycloaddition of the nitroalkene **14** and an appropriately substituted propenyl ether. The ideal propenyl ether would be the 2-acetoxyvinyl ether **13**, which was utilized in the tandem intra[4 + 2]/intra[3 + 2] cycloaddition approach to the synthesis of (+)-pretazettine and in the synthesis of 4-hydroxy-substituted pyrrolidines.[19] Since the 2-acetoxyvinyl ether **13** is only easily accessible in the cis configuration, it demands that the cycloaddition with nitroalkene **14** must occur through an endo approach to install the correct relative configuration at C(4a) and C(5) in the resulting nitroso acetal (C(1) and C(2) in (+)-crotanecine). From the outset there were three questions which had to be addressed: (1) would the nitroalkene **14** allow an endo approach of the dienophile in the cycloaddition with **13**, (2) could any Lewis acid other than tin tetrachloride promote the cycloaddition with **13** and thereby alter the inherent exo preference for the approach of the dienophile **13**, and (3) if unsuccessful, could other dienophiles bearing hydroxyl group equivalents be devised and enlisted into service?

Results

First-Generation Approach with 2-Acetoxyvinyl Ether 13.
The nitroalkene **17** was used as a model substrate in cycload-

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Table 1. Survey of Lewis Acids Promoters in Cycloadditions with **13**

entry	Lewis acid	temperature, °C	diastereomer ratio	yield, %
1	SnCl$_4$	−78	13/1/1/1	34
2	Ti(Oi-Pr)$_2$Cl$_2$	−40	1/1/1	32
3	MAPh	−20		0
4	TiCl$_4$	−78	1/1	trace

ditions with **13** due to its simpler preparation. These reactions were promoted by selected Lewis acids used previously in the [4 + 2] cycloaddition with nitroalkenes as heterodienes (Table 1). The initial results were, to some extent, encouraging since a nitroso acetal **18** was isolated from the cycloadditions promoted by Ti(Oi-Pr)$_2$Cl$_2$. Unfortunately, both the yield and the selectivity were poor (entry 2). MAPh was found not to promote this reaction, while tin tetrachloride afforded the cycloadduct with moderate selectivity. In the cycloaddition, all four possible diastereomers were obtained with one dominating in a 13/1/1/1 ratio as determined by ^{1}H NMR analysis. These nitroso acetals were also isolated in poor yield, and changing the amount or addition order of Lewis acid afforded no improvements. By thin layer chromatographic analysis, the vinyl ether was consumed faster by reaction with tin tetrachloride than by cycloaddition. This was confirmed by isolation of a side product derived from chloride addition to the enol ether which was noted previously.[20] For these reasons, and the ambiguity about the relative configuration at C(4a)−C(5), this approach was abandoned and attention redirected to the use of other propenyl ethers bearing a hydroxyl surrogate.

Second-Generation Approach with a 2-Silylvinyl Ether. The need for a hydroxyl surrogate directed attention to the use of substituted silanes as hydroxyl synthons.[21−23] The silyl group has been used on numerous occasions in organic synthesis to modulate the reactivity of functional groups.[24] Therefore the use of a vinylsilane as the dienophile in the tandem [4 + 2]/[3 + 2] cycloaddition was a tempting alternative to the 2-acetoxy-vinyl ether **13**. Indeed, vinylsilanes have previously been used as enol surrogates in the Diels−Alder reaction.[25]

Since both methyl and phenyl propenyl ethers had been employed with great success in the [4 + 2] cycloaddition of nitroalkenes, silyl substitution was not expected to dramatically alter the reactivity of the vinyl ether.[26] Therefore, the approach to (+)-crotanecine using a 2-silylvinyl ether could be outlined

Scheme 2
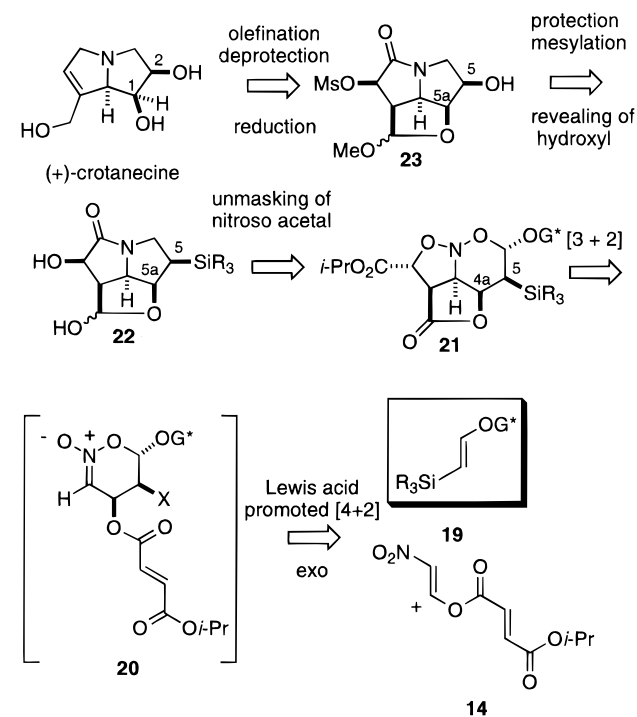
in great detail before the synthesis was undertaken (Scheme 2). (+)-Crotanecine was envisioned to arise from the α-hydroxy lactam **23** where deprotection of the methyl acetal followed by elimination of the mesylate and exhaustive reduction would afford the natural product. The α-hydroxy lactam **23** would arise from **22** by a series of transformations beginning with the differentiation of the two hydroxyl groups. Transformation of the lactol in **22** to a methyl acetal, followed by mesylation and unmasking the silyl group by the Tamao−Fleming protocol[21,22] should produce **23**. The α-hydroxy lactam **22** would arise from nitroso acetal **21** after the two-step unmasking procedure. The nitroso acetal **21** itself is the result of an inter[4 + 2]/intra[3 + 2] cycloaddition of the nitroalkene **14** and a 2-silylvinyl ether. In this instance the isomer of 2-silylvinyl ether **19** was selected, since the nitroalkene **14** had been successfully utilized in the tandem [4 + 2]/[3 + 2] cycloadditions only with MAPh as the Lewis acid promoter. Since MAPh promotes an exo-mode [4 + 2] cycloaddition, a *trans*-2-silylvinyl ether is required to ensure the correct cis relationship at C(4a)−C(5) in the product nitroso acetal (C(1)−C(2) in (+)-crotanecine).

Synthesis of the Desired (*E*)-2-Silylvinyl Ether. The required (*E*)-2-silylvinyl ether **26** was to be prepared by the method of Green[27] from the 2-silylpropynyl ether **25** followed by an LiAlH$_4$ reduction.[28] Attempts to prepare the desired

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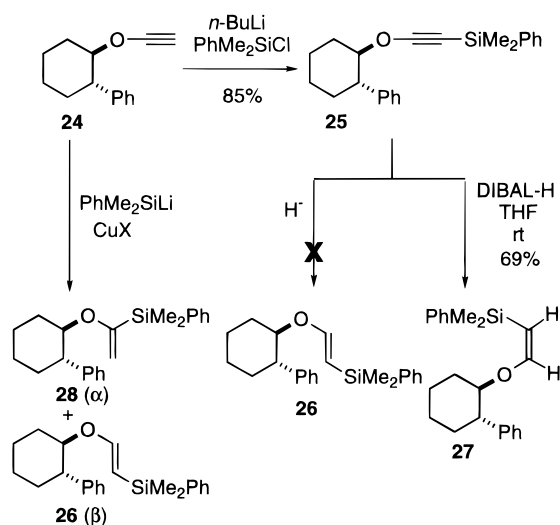
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Scheme 3

Table 2. Temperature Effect in the Silylcupration of **24**

PhMe$_2$SiLi, equiv	CuX	temperature, °C	isomer ratio, α/β	yield, %
2	CuBr·DMS	−78	1/1.9	92
2	CuI	−78	1/2	81
2	CuCN	−78	1/2.2	69
1	CuCN	0	1/2.3	23
2	CuCN	0	0/1	85

silylpropynyl ether in a one-pot reaction, from 2-phenylcyclo-hexanol failed, and only phenylcyclohexenes were isolated. Therefore the acetylenic ether **24** was prepared as described by Porter.[29] The acetylenic ether **24** was then deprotonated with *n*-BuLi at −78 °C, and the resulting lithioalkyne was treated with chlorodimethylphenylsilane to afford the silylated acetylene **25** in 85% yield (Scheme 3). Subjecting the silylpropenyl ether **25** to an LiAlH$_4$ or Red-Al reduction afforded none of the desired product.[30,31] A survey of other aluminum- or chromium-based reducing reagents capable of reducing propenyl com-pounds to (*E*)-alkenes also met with no success.[32−34] The only reagent capable of reducing the propynyl compound was DIBAL-H, which afforded exclusively the (*Z*)-2-silylvinyl ether **27** in 69% yield.[35]

An alternative, the addition of a silyl anion across the acetylenic ether **24**, was next examined. There are several examples of the use of carbocupration of heteroatom (N or O)-substituted alkynes wherein the preferred regiochemistry of addition places the copper β to the heteroatom.[36,37] Fleming has demonstrated the synthetic utility of higher order silyl-cyanocuprates in additions to nonfunctionalized monosubstituted

acetylenes.[38] The silylcuprate adds with excellent regio- and stereoselectivity to afford the vinylsilanes through an exclusive syn addition across the acetylene. Since there was no precedent for the additions of silylcuprates to acetylenic ethers, a survey of copper source and stoichiometry was performed (Table 2). Lithiodimethylphenylsilane was prepared according to the methods of Gilman and Fleming.[38−40] All of the cuprates were prepared by the addition of the silyllithium to the copper reagent in tetrahydrofuran at 0 °C. After being stirred for 20 min, the reaction mixture was cooled to the appropriate temperature. The acetylenic ether **24** was then added as a THF solution, then was stirred for 20 min (−78 °C) or 1.5 h (0 °C) and worked up to afford the vinylsilane. Irrespective of the copper source, the cuprations at −78 °C all afforded the vinylsilane in good yield but in all instances as a mixture of α and β addition products (**28**/**26**) in a ratio of 1/2 favoring the desired (*E*)-vinylsilane **26**. All subsequent reactions were performed with copper cyanide since it is much easier to handle than the other copper salts. At 0 °C, the use of a lower order cuprate afforded no improvements, while the higher order cyanocuprate gave the desired (*E*)-vinylsilane **26** exclusively in 85% yield. This reaction could be scaled up to afford multigram quantities of the vinylsilane (*E*)-**26**. The vinylsilane was stable enough to be purified on both basic alumina and silica gel. However, the residual acid in deuterochloroform could isomerize the vinyl-silane to a mixture of *E* and *Z* isomers. With the desired vinylsilane in hand, attention was directed to establishing its utility as a diene in the tandem cycloaddition sequence.

Optimization of the Tandem [4 + 2]/[3 + 2] with (*E*)-(−)-26. The 2-silylvinyl ether (*E*)-(−)-**26** was subjected to cycloaddition with nitroalkene **14** in the presence of MAPh as the Lewis acid promoter (Scheme 4). This vinyl ether was found to be rather unreactive, affording only a poor yield of the desired nitroso acetal at −78 °C (Table 3, entry 1). Increasing the reaction temperature to 0 °C increased the yield to 54%, but reactions conducted in methylene chloride at this temperature became dark brown and, when quenched, no color change nor gas evolution was observed, indicating the absence of active Lewis acid. A change of solvent to toluene avoided this problem, and the reactions were much cleaner. Further adjustments of stoichiometry and temperature are summarized in Table 3. The optimum reaction conditions for the cycload-dition (entry 10) were found to be the use of 3 equiv of vinyl ether (−)-**26** and 5 equiv of MAPh in toluene at −14 °C. The nitroso acetal (+)-**29** was isolated in 73% yield in greater than a 50/1 diastereomeric ratio of nitroso acetals as judged by ^{1}H NMR analysis. In addition, the chiral vinyl ether (−)-**26** (65%)

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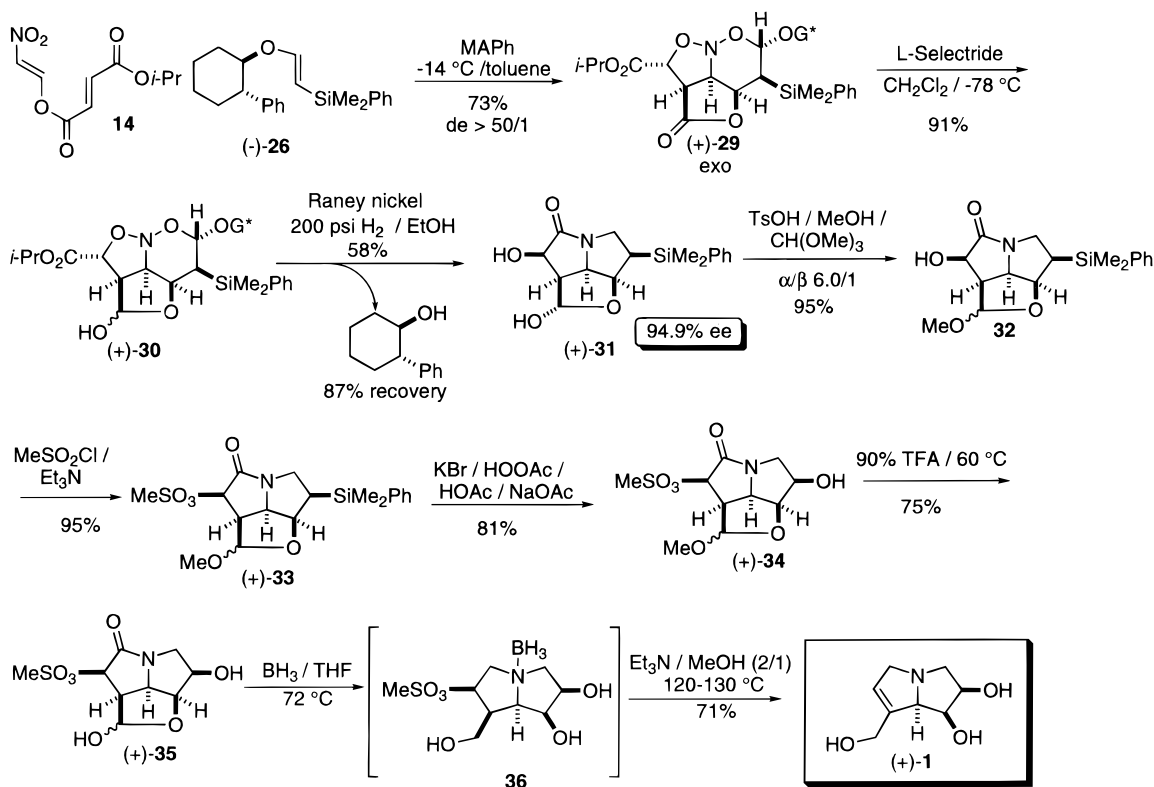
Scheme 4

Table 3. Optimization of Reaction Parameters in the [4 + 2]/[3 + 2] Cycloaddition

entry	(−)-**26**, equiv	MAPh, equiv	temperature, °C	solvent	yield, %
1[a]	3	3	−78	CH₂Cl₂	16
2	3	3	−40	CH₂Cl₂	38
3	3	3	0	toluene	54
4	3	1.2	0	toluene	8
5	3	6	0	toluene	60−79
6	3	8	0	toluene	64
7	1.5	6	0	toluene	44
8	3	6	0	CH₂Cl₂	59
9	3	6	−11	toluene	70
10	3	5	−14	toluene	73

[a] Used ethyl ester nitroalkene **17** as substrate.

and 2,6-diphenylphenol (83%) could be recovered. As in the synthesis of (−)-rosmarinecine the intermediate nitronate was never detected.[6]

To ensure that the full stereostructure of the nitroso acetal (+)-**29** was correctly assigned, an X-ray crystal structure was obtained (Figure 4).[41] The X-ray analysis verifies the relative (and absolute) configuration of the six contiguous stereogenic centers C(2), C(2a), C(7b), C(4a), C(5), and C(6) assuring that the absolute configurations at the critical stereocenters correspond to those in natural (+)-crotanecine. These configurations are uniquely established by an exo-mode [4 + 2] cycloaddition followed by an endo-mode[42] [3 + 2] cycloaddition.

Hydrogenolysis of the Nitroso Acetal (+)-29. As was found in the synthesis of (−)-rosmarinecine,[6] rehybridization of C(3) in (+)-**29** was expected to be necessary to unmask the nitroso acetal to an α-hydroxy lactam. Indeed, that expectation was borne out as nitroso acetal (+)-**29** afforded no identifiable products under hydrogenolysis with Raney nickel. Therefore,
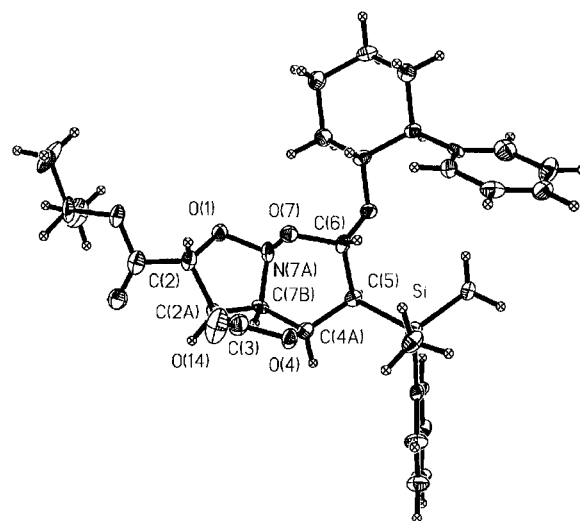
(41) Thorarensen, A.; Swiss, K. A.; Denmark, S. E. *Acta Crystallogr. C* **1996**, *52*, 2558.
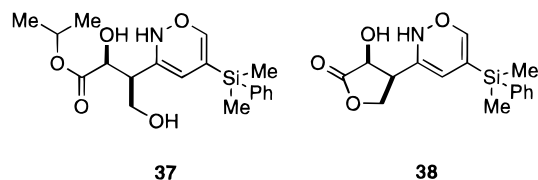(42) Defined with respect to folding of the tether.

Figure 4. X-ray crystal structure of nitroso acetal (+)-**29** (35% ellipsoids).

the lactone (+)-**29** was reduced with L-Selectride (1.2 equiv) to afford the lactol (+)-**30** in 91% yield (Scheme 4).

The second step in the unmasking procedure was hydrogenolysis of the nitroso acetal (+)-**30** with Raney nickel. Subjecting the lactol to hydrogenolysis in MeOH afforded the desired product (−)-**31**; however, it was accompanied by numerous side products which were difficult to remove. The side products were also very unstable and colored rapidly. The identities of two of the roughly eight to nine different side products were assigned as the oxazines **37** and **38** from their spectroscopic data (Figure 5). The hydrogenations in MeOH showed some pressure dependence with the highest yield being obtained at 200 psi (Table 4). A change of the solvent to *i*-PrOH or *n*-PrOH afforded slower reaction and lower yield. The results from reductions in EtOH were comparable to those in MeOH, except that the side products were not as unstable allowing for

Figure 5. Structures of two side products obtained in the hydrogenation.

Table 4. Optimization[a] of Hydrogen Pressure in the Hydrogenolysis of **30**

entry	solvent	pressure, psi	yield, %
1	MeOH	160	36
2	MeOH	200	54
3	MeOH	330	38
4	EtOH	150	64
5	EtOH	200	44–61
6	EtOH	250	62
7	n-PrOH	280	b
8	i-PrOH	200	29

[a] All reactions were run between 24 and 70 h, and most reactions were run for 48 h. [b] Over 50% of the starting material remained after 48 h.
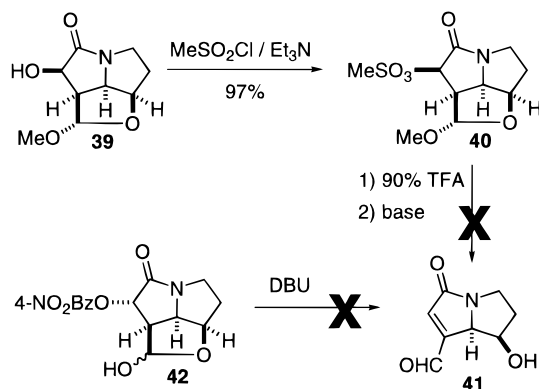
Scheme 5
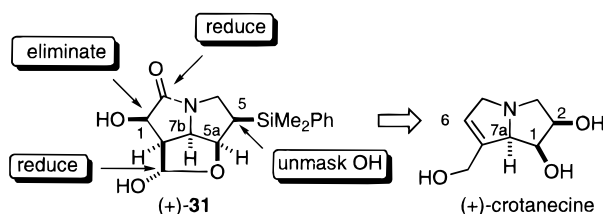
easier purification. The reaction performed in EtOH showed very little pressure dependence over the range surveyed, and all reaction were therefore performed at 200 psi. Under optimal conditions, the α-hydroxy lactam (+)-**31** was isolated in 58% yield and in 94.9% enantiomeric excess as determined by chiral HPLC analysis (Scheme 4). A single recrystallization of this material afforded an 80% recovery of (+)-**31** with >99% enantiomeric excess. In addition, 87% of the chiral auxiliary (−)-(1R,2S)-2-phenylcyclohexanol was recovered.

Unmasking of the Hydroxyl at C(2). The lactam (+)-**31** contains the 1-azabicyclo[3.3.0]octane skeleton of (+)-crotanecine, with the correct relative and absolute configuration at C(5), C(5a), and C(7b) (C(1), C(2), and C(7a) of (+)-crotanecine). To obtain (+)-crotanecine it remained to unmask the hydroxyl group at C(2) (crotanecine numbering) and utilize the hydroxyl group at C(6) to introduce the unsaturation at C(6)−C(7) (Scheme 5). Finally it was necessary to reduce the lactam and the lactol to reveal the pyrrolizidinetriol.

To transform the hydroxyl group at C(1) to a good leaving group, the hydroxyl at C(7) had to be selectively protected. This was readily accomplished in MeOH at room temperature with a catalytic amount of TsOH to afford the protected methyl acetal **32** in excellent yield (95%) as a (6/1) mixture of anomers (¹H NMR analysis) (Scheme 4). The major anomer (+)-**32a** was assigned the α-configuration on the assumption of thermodynamic control. In addition, in the ¹H NMR spectrum, the HC-(7) signal appeared as a singlet at 5.24 ppm, indicating a trans relationship between HC(7) and HC(7a). In the minor β-anomer (−)-**32b** HC(7) appeared as a doublet (J = 6.2 Hz) at 5.12 ppm, now indicating a cis relationship between HC(7) and HC(7a). The anomers were separated and characterized. Interestingly the two compounds have opposite signs of optical rotation; the α-anomer is dextrorotatory while the β-anomer is levorotatory.

Scheme 6

The hydroxyl group at C(1) could be functionalized by treatment of **32** with methanesulfonyl chloride and triethylamine to afford the methanesulfonate (+)-**33** in excellent yield (95%) (Scheme 4). Interestingly the α-anomer (+)-**32a** was mesylated rapidly while the β-anomer (−)-**32b** reacted very slowly. This generally lead to enrichment of the α-anomer during the functionalization of **32**. The difference in the reactivity of the two anomers is easily understood on the basis of steric repulsion where the C(2) hydroxyl in the β-anomer is blocked with both the silyl and methoxy groups inside the concave face of the tricyclic core. The mesylate (+)-**33** was extremely stable and could be distilled at 250 °C to obtain an analytical sample.

Unmasking of the silyl group to the desired hydroxyl group was accomplished by the bromination−desilylation−hydroxylation procedure of Fleming.[43] Mixing the silane (+)-**33** with potassium bromide and sodium acetate in acetic acid followed by the addition of peracetic acid afforded (+)-**34** in 81% yield as a white, crystalline compound (Scheme 4). Since the product was extremely water-soluble, an aqueous workup was avoided. Therefore, most of the excess peracetic acid was quenched by stirring with a catalytic amount of 5% Pd/C for 30 min. The crude product was then purified by silica gel chromatography. *Caution! Under circumstances when the excess peracetic acid had not been properly quenched a very* **exothermic reaction** *took place when the residue was applied to silica gel.* To obtain the optimum yield, it was important that the reaction remained below room temperature during the addition and the destruction of excess peracetic acid so the mixture was cooled in an ice bath during these events. This cooling of the reaction mixture is to minimize hydrolysis of the methyl acetal to a lactol, which is not compatible with these reaction conditions.

Installation of the Double Bond at C(6)−C(7). The simple operations of elimination and reduction of lactam (+)-**34** were necessary to complete the synthesis. Since lactam **39** was readily available from the synthesis of (−)-rosmarinecine, it served ideally as a model system to probe the installation of the C(6)−C(7) double bond.[6] Treatment of **39** with methanesulfonyl chloride and triethylamine afforded the mesylate **40** in 97% yield (Scheme 6). Hydrolysis of the methyl acetal in 90% TFA at room temperature afforded the lactol which was subsequently treated with several bases (DBU, NaOAc, and K₂CO₃). In all instances the reaction mixture turned black after the addition of the base. Monitoring the reactions by ¹H NMR spectroscopy showed the disappearance of the lactol, but no other products could be detected. To probe if this failure was due to the leaving group, the 4-nitrobenzoate **42** (from the synthesis of (−)-rosmarinecine) was treated with DBU and the

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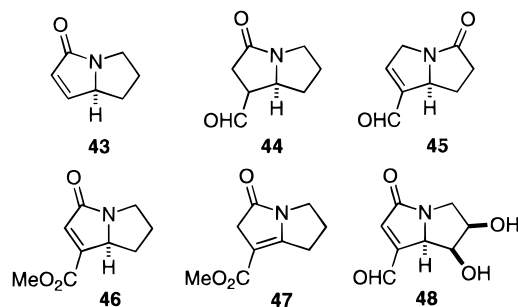
Figure 6. Various ring structures related to the desired compound **48**.

same phenomenon was observed. These results were rather puzzling, and alternative methods were sought for the construction of the olefin. A common method for creating unsaturation at C(6)−C(7) in necines is a selenation at C(7) followed by oxidative elimination.[44] However, the inability to obtain the desired C(6) selenide thwarted this solution as well.[45]

Frustrated by the difficulty of this seemingly trivial operation, we turned to the literature for guidance. Collected in Figure 6 is a group of unsaturated pyrrolizidines, the formation of which provided useful insights. For example, installation of the double bond had been accomplished without any difficulties through a mesylation−elimination sequence to produce **43**, and the ring system in **43** is stable with that degree of unsaturation.[46] The aldehyde lactam in **44** is a stable entity.[47] All the required functionalities are incorporated into **45**, which is also a stable entity.[48] Compounds of the structure **46** are unstable and rearrange readily to **47**, indicating that the target compound **48** may not be stable either.[49]

From this analysis it appeared that all three functional groups (olefin, lactam, and aldehyde) may not exist simultaneously in the same ring system. Therefore, we opted to remove the carbonyl groups sequentially and then install the double bond to obtain the generic structure **43**.

There are several examples of the reduction of a lactam in the presence of a mesylate,[50] but to carry out the desired reduction of both carbonyl groups, it was first necessary to deprotect the methyl acetal (+)-**34** to the corresponding lactol.

Treatment of the methyl acetal in 90% TFA for 20 h afforded only 17% yield of the desired product **35** and 69% recovery of the methyl acetal. To optimize the hydrolysis of the methyl acetal, a series of reactions were performed in deuteriotrifluoroacetic acid (TFA-d_1) diluted to the appropriate concentration with D_2O and then monitored by ^1H NMR spectroscopy. All of the reactions showed first-order kinetics and the linear correlation was of sufficient quality for the purpose of optimization. The reaction performed at room temperature had a half-life ($t_{1/2}$) of 37 h. Employing 95% TFA had a marginal effect ($t_{1/2}$ 35 h), and increasing the temperature to 40 °C led to a $t_{1/2}$ of 22.7 h. These long reaction times were rather unsatisfactory. Fortunately, further increase in temperature to 60 °C led to a more tolerable reaction time with a $t_{1/2}$ of 5.1 h. Under optimal reaction conditions the hydrolysis was performed at 60 °C for 24 h. The TFA was then azeotropically removed with benzene, and the residue was purified on silica gel to afford the lactol (+)-**35** in 75% yield (Scheme 4).[51]

Treating (+)-**35** with large excess of borane (40 equiv) in THF at reflux reduced both the lactam and the lactol, to afford the amino triol **36** (Scheme 4). The reaction was cooled to room temperature and concentrated in vacuo, and the residue was then dissolved in MeOH and evaporated to dryness repeatedly. For analytical purposes the amino triol could be purified by silica gel chromatography in 75% yield. The pyrrolizidinetriol was of similar polarity to the starting lactam−lactol (+)-**35** by TLC, suggesting that the nitrogen had been temporarily complexed. It is well-known that borane forms stables adduct with amines, and indeed, the ^{11}B NMR spectrum showed the presence of a characteristic resonance for an ate complex at −7.95 ppm.[52] The hydrogens attached to borane could not be confidently identified in the ^1H NMR spectrum nor were there any additional signals in the ^{13}C NMR spectrum. However, the IR spectrum, where B−H stretches at 2373 and 2337 cm^{-1} were observed, allowed the structure to be tentatively assigned as a trihydridoborane−pyrrolizidine complex **36**.[53] Heating a solution of this compound in triethylamine afforded (+)-crotanecine. Due to solubility problems it was necessary to perform the reaction in a mixture of MeOH/Et$_3$N (2/1); more lipophilic alcohols such as *i*-PrOH and *t*-BuOH were not as effective. In addition, it was necessary to heat the reaction to 120−130 °C for 5 h to ensure complete consumption of the borane adduct **36**. Under optimal conditions the reaction was performed in a sealed tube which was degassed under Ar prior to heating. The product was purified by silica gel chromatography to afford (+)-crotanecine in 71% yield over the two steps for the reduction−elimination sequence (Scheme 4).

Purification and Identification of (+)-Crotanecine. The purification of (+)-crotanecine presented severe difficulties. It appeared that the side products generated in the solvolysis promoted the decomposition of (+)-crotanecine, thereby complicating the purification. After silica gel chromatography an analytically pure sample of (+)-crotanecine was obtained by recrystallization from EtOH/Et$_2$O which had the same physical properties (mp 193−197 °C, $[\alpha]^{21}_D$ +38.7 (EtOH, *c* = 0.52)

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Table 5.   Chemical Shifts of (+)-Crotanecine and the Hydrochloride Salt (**49**)

¹H NMR			¹³C NMR		
49,[b] ppm (integral)	(+)-**1**,[a] ppm (integral)	(+)-**1**,[b] ppm (integral)	**49**,[b] ppm	(+)-**1**,[a] ppm	(+)-**1**,[b] ppm
5.76 (1H)	5.77 (1H)	5.70 (1H)	139.81	139.5	140.27
4.86 (1H)	4.90 (1H)	4.19−4.15 (4H)	121.21	121.4	125.27
4.43 (1H)	4.45 (1H)	4.03 (1H)	77.59	77.3	76.12
4.37−4.19 (4H)	4.39−4.23 (4H)	3.85 (1H)	73.38	73.2	74.77
3.94 (1H)	3.92 (1H)	3.41−3.37 (1H)	70.91	71.0	72.33
3.80 (1H)	3.84 (1H)	3.23 (1H)	64.11	63.7	64.20
3.13 (1H)	3.12 (1H)	2.60 (1H)	59.21	59.2	59.88
			57.32	57.1	59.30

[a] From ref 13. [b] This work.

(lit.[9] mp 192 °C, [α]$^{20}_D$ +39.2 (EtOH, $c = 1.3$))[54]) as the material obtained by hydrolysis of anacrotine (74%) (mp 192−195 °C, [α]$^{21}_D$ +35.0 (EtOH, $c = 0.644$)). In addition the spectroscopic profiles (¹H NMR, ¹³C NMR, IR, and MS) of the synthetic and natural (+)-crotanecine were nearly identical. Another authentic sample of natural (+)-crotanecine was obtained from Australia, and the ¹H and ¹³C NMR spectra of this sample matched the spectra of synthetic (+)-crotanecine and the natural sample from anacrotine (see Supporting Information).

(+)-Crotanecine displays the most dramatic chemical shift variances in the ¹H NMR spectrum of the three alkaloids that have been prepared using the tandem [4 + 2]/[3 + 2] methodology. The ¹H NMR chemical shifts are very sensitive to traces of salts or hydrates of crotanecine. To demonstrate this, the hydrochloride salt **49** was prepared by dissolving (±)-crotanecine in saturated HCl in MeOH. The chemical shifts for **49** represent one extreme in the ¹H NMR spectrum, while those for pure (+)-crotanecine were on the other (Table 5). Various samples of (+)-crotanecine prepared during the course of this synthetic effort displayed signals throughout this range. The hydrogens that showed the most dramatic shifts in the ¹H NMR spectrum were HC(7a) (4.19−4.15 ppm (**1**), 4.86 (**49**)) and HC(3) (2.60 ppm (**1**), 3.13 ppm (**49**)). To obtain a consistent spectroscopic profile, the compounds were loaded on to a silica gel column in MeOH/Et₃N (1/2), and the column was eluted with CHCl₃/MeOH (4/1) followed by CHCl₃/MeOH/NH₄OH (10/5/1) to remove the (+)-crotanecine. The only other high-field ¹H NMR spectrum reported of (+)-crotanecine[13] must contain a high proportion of protonated material, since the reported data deviate only slightly from the ¹H NMR spectrum of the hydrochloride salt of (+)-crotanecine.[55] In addition, the differences between the reported ¹³C NMR spectrum of (+)-crotanecine[13] and the hydrochloride salt of (+)-crotanecine are minuscule, but both are very different from the ¹³C NMR spectrum of authentic (+)-crotanecine.

Discussion

Silylcupration. Although silylcupration has been an important synthetic transformation in organic synthesis, there are no reports of the addition of silyl cuprates to acetylenic ethers.[37] The composition of the various silylcopper reagents has been explored in a series of elegant spectroscopic studies.[56] Using copper(I) cyanide as the copper source, two distinctly different non-interconverting cuprates, (PhMe₂Si)CuCNLi and (PhMe₂-Si)₂CuCNLi₂, can be formed depending upon the stoichiometry

of mixing. In addition, the cyanide, in neither case, exists as free LiCN in solution. The lower order cuprate has been demonstrated to have low selectivity in addition to monosubstituted acetylenes, as was observed for **24**.

The temperature dependence of the regioisomeric addition products obtained in the silylcupration of **24** is puzzling. Two explanations are proposed: (1) the β-bound copper species (*i*) (Scheme 8) would undergo elimination at higher temperatures to regenerate the alkoxide along with the silylacetylene as a byproduct, or (2) the reaction is readily reversible and exclusive isolation of the β-addition product at higher temperature represents the thermodynamic ratio between the α- and the β-bound vinylcopper species. If elimination of the β-vinylcopper species occurred at higher temperature, only 66% of the yield from the low-temperature reaction (2/1 mixture) would be expected. Therefore, the first scenario can be ruled out on the basis of the similar yield obtained in the two reactions (−78 °C (69%), 0 °C (85%)).

Thermodynamic control of the reaction selectivity at 0 °C is more likely. The mechanistic hypothesis can therefore be put forward that the higher order silylcuprate adds in a syn fashion across the acetylenic ether in a rapidly reversible reaction (Scheme 7). The kinetic preference for addition is therefore the same as that observed in carbocupration of acetylene ethers, but in this instance, the reversible nature of the higher order cyanosilylcuprate allows the isolation of **26** exclusively. Notably, Fleming has observed that the higher order cyanosilyl-cuprate adds reversibly to allenes.[57] A similar observation has been documented for the addition of higher order cyanostannylcuprates to acetylenic ethers, where in the presence of an internal trap (MeOH), the α-addition product was isolated exclusively.[58]

[4 + 2] Cycloaddition. The mechanism of the [4 + 2] cycloaddition is considered to be a stepwise process in which the first carbon−carbon bond forming reaction is irreversible.[59] Since the excess vinyl ether (−)-**26** recovered from the reaction was exclusively of the trans configuration, the irreversibility of this process is further substantiated.[28b,60] The stereochemical outcome of the tandem process is established in the [4 + 2] cycloaddition by the creation of the C(4) stereocenter. That stereocenter then controls the formation of the other stereocenters as a consequence of the subsequent [3 + 2] process wherein the tether folds only in an endo orientation.

The critical stereochemical issues in the [4 + 2] cycloaddition promoted with MAPh and the new vinyl ether (−)-**26** are (1)

(54) Reference 9 has the only reported data of analytically pure (+)-crotanecine; in other publications, the [α]$_D$ of synthetic or natural crotanecine ranges from +25° [13] to +44° [15] and the mp ranges from 188[16] to 202 °C.[7]

(55) Similar observation have been made by Dr. Russell J. Molyneux (U.S. Department of Agriculture, Albany, CA) (private communications).

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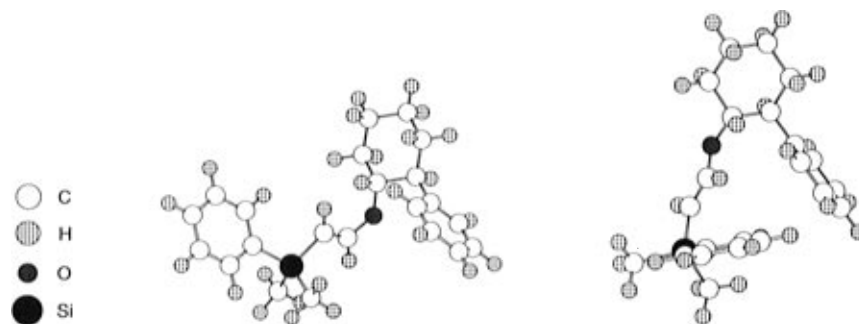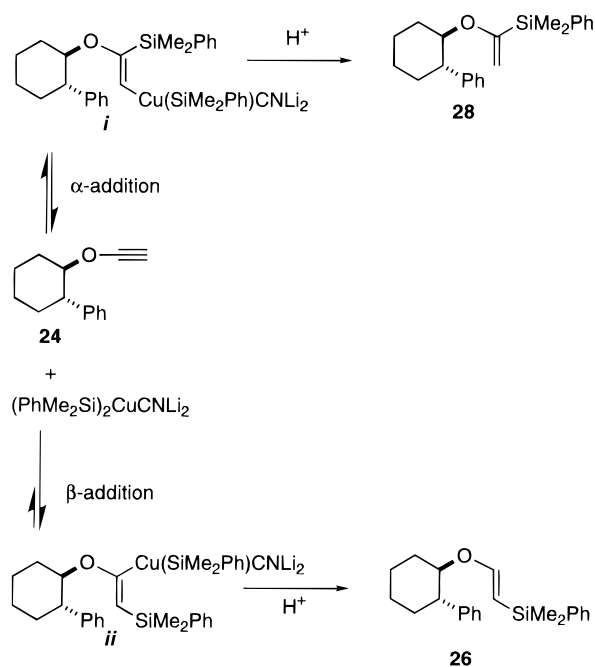
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Figure 7. Two distinct s-cis and s-trans conformations of vinyl ether (−)-**26** located by MOPAC calculations with PM3.

Scheme 7

Figure 8. Proposed approach of the dienophile (−)-**26** in the [4 + 2] cycloaddition to **14** promoted by MAPh.

the reactive conformation of the vinyl ether, (2) the facial selectivity of the vinyl ether, and (3) the orientation (exo/endo) of the dienophile with respect to heterodiene.

MOPAC calculations of the vinyl ether (−)-**26** using the PM3 Hamiltonian located two distinct conformations of the vinyl ether (Figure 7). The lowest in energy was an s-cis conformation; 1.63 kcal higher was an s-trans conformation. In the s-cis conformation, the *si* face of the vinyl ether is shielded by the phenyl ring of the auxiliary, while in the s-trans conformation, the *re* face of the vinyl ether is shielded.[61]

The X-ray crystal structure of the product nitroso acetal (+)-**29** provided clear answers to some of the issues mentioned above. The cis relationship of HC(4a) and HC(5) is uniquely established by an exo-mode orientation of the dienophile with respect to the heterodiene in the [4 + 2] cycloaddition. In addition, since the absolute configuration of the auxiliary (1*R*,2*S*)-2-phenylcyclohexanol is known, the configurations of HC(4a) and HC(5) can both be assigned as *S*. To obtain the 4a*S* configuration, the vinyl ether (−)-**26** must approach the *si* face of the nitroalkene **14**.[62] Furthermore, to obtain the 5*S* configuration, the nitroalkene **14** has to approach the *si* face of the vinyl ether. To obtain the observed selectivity, which is the best recorded so far from an exo-mode cycloaddition of a 2-substituted vinyl ether, the auxiliary has to be very efficient

in shielding the *re* face of the dienophile. In formulating a transition structure for this cycloaddition it should be remembered that any differences due to small steric or electronic preferences between the two ground state conformations can be overcome when challenged with the demands of the transition structure leading to product. Only the s-trans conformation of the vinyl ether exposes the reactive face of the vinyl ether in the cycloaddition. Therefore, the preferred mode of reaction of (−)-**26** in the [4 + 2] cycloaddition promoted by MAPh is via the exo mode where the dienophile prefers an s-trans conformation, thus exposing the *si* face for approach to the *si* face of the nitroalkene as depicted in Figure 8.

Mechanistic Implications of the Hydrogenolysis. The hydrogenolysis of the nitroso acetal is the pivotal operation for the construction of the 1-azabicyclo[3.3.0]octane ring system in all of the necine syntheses which employ the tandem [4 + 2]/[3 + 2] cycloaddition. These reactions have required extensive optimization compared to the high yielding hydrogenolyses in simpler model systems. In an earlier report, a detailed discussion was presented for the individual steps in this process,[5] and indeed, the isolation of the intermediates **37** and **38** supports the notion of preferential cleavage of the five-membered ring.[63] Scheme 8 depicts additional problems which could arise if the initial N−O cleavage occurs in the six-membered ring. In this scenario, the rate of cleavage of the second N−O bond in *i* leading to *ii* must be faster than both the elimination and lactamization which form the oxazines **37** and **38**. It is apparent that, in this reaction, the rate of elimination to the oxazines has to be comparable to the rate of second N−O bond cleavage. Furthermore, breakdown of the

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(61) The *si* and *re* faces of the vinyl ether are defined with respect to the oxygen.

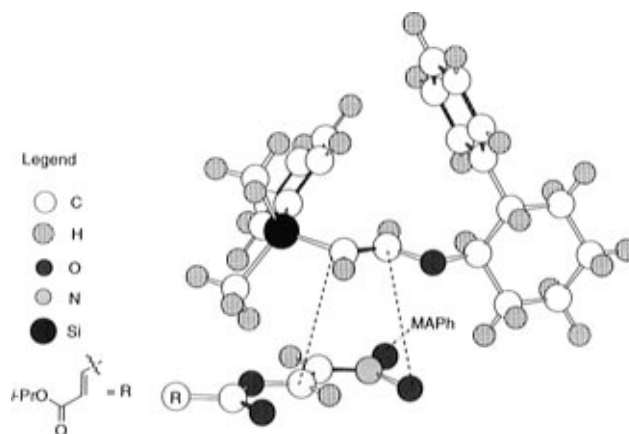(62) The *si* and *re* faces of the nitroalkene are defined with respect to the nitrogen.

(63) An intermediate resulting from the cleavage of the five-membered ring has been observed for nitroso acetal derived from the tandem inter[4 + 2]/inter[3 + 2] cycloaddition sequence employing nickel−aluminum alloy/sodium hydroxide. Schnute, M. E. Ph.D. Thesis, University of Illinois, Urbana, 1995, p 139.

Scheme 8
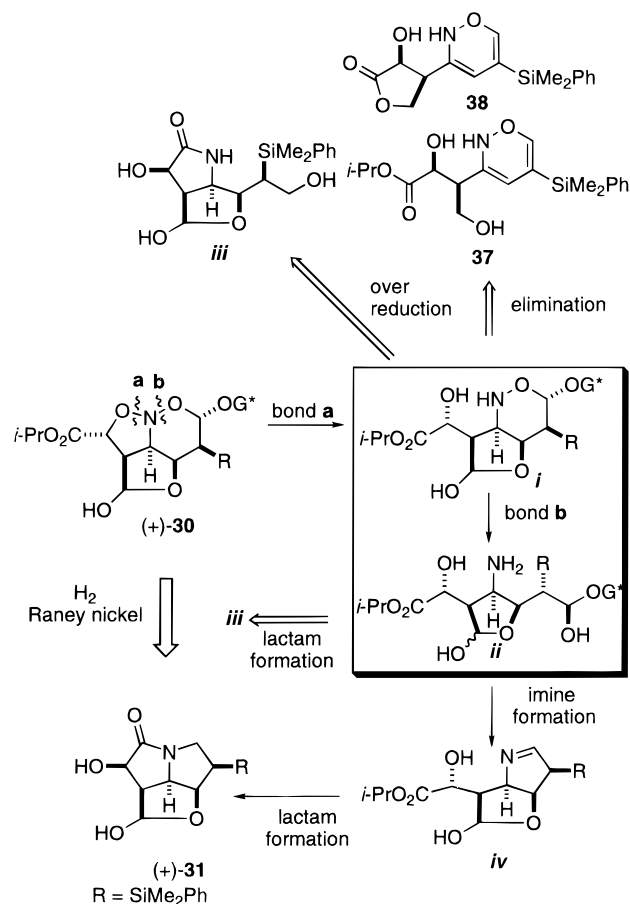
Scheme 9
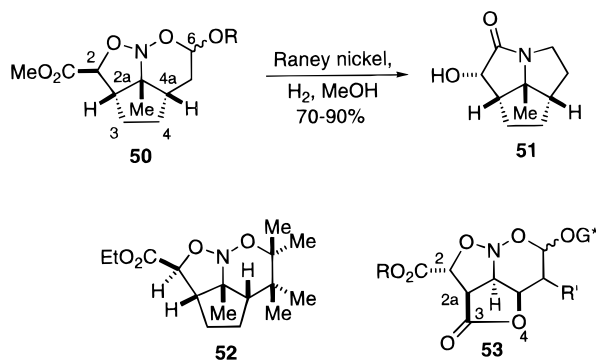
hemiacetal in *ii* and imine formation to *iv* has to be faster than lactamization and overreduction affording *iii* for the overall transformation to be successful.

The hydrogenolysis of the nitroso acetal with the general structure **50** affords a high yield (70−90%) of the final product under very simple reaction conditions (Raney nickel/1 atm H₂/ MeOH) (Scheme 9).[4] In this scenario, the rate of both N−O bond cleavages and imine formation must be faster than possible side reactions. How do the structural differences between the simplified, all-carbon nitroso acetals and the lactone-containing nitroso acetal **53** influence their behavior toward reduction? The X-ray crystal structure of (+)-**29** allows the comparison of these two different systems and further comparison to a simpler analogue of a similar ring structure **52**.[64] In both of these structures the tetrahydro-1,2-oxazine ring exists in a twist-boat conformation. A structural attribute of (+)-**29** which critically

(64) Denmark, S. E.; Moon, Y.-C.; Senanayake, C. B. W. *J. Am. Chem. Soc.* **1990**, *112*, 311.

differentiates its reactivity from **52** is the contraction of the five-membered ring lactone in (+)-**29** compared to the carbocycle found in **52**. The bonds O−C(4a), O−C(3), and C(3)−C(2a) are 0.08, 0.18, and 0.03 Å shorter than the corresponding C−C bonds in **52**. Taken together with the sp² hybridization of C(3), these changes increase the strain in this ring and may slow the rate of the second N−O bond cleavage and subsequent imine formation, thereby allowing possible side reactions to intervene with (+)-**29** compared to **52**.

For the continued success of the tandem [4 + 2]/[3 + 2] cycloaddition method, a thorough understanding of this apparently simple reaction is necessary. In addition it would be desirable to find an easily handled catalyst, which could be accurately metered and would be homogeneous under the reaction conditions to avoid many of the problems that have been encountered.

Conclusion

The (*E*)-2-silylvinyl ether (−)-**26** has afforded the best selectivity of any substituted dienophile explored so far in the exo-mode [4 + 2] cycloaddition promoted by MAPh. Using this reaction the synthesis of (+)-crotanecine was completed in 10 steps and 10.2% overall yield. This constitutes the second example of the fused-mode [4 + 2]/[3 + 2] cycloaddition in necine base synthesis. It demonstrates that, with this method, the basic ring system can be functionalized by the employment of substituted vinyl ethers as dienophiles. In addition, unsaturation can be introduced at the C(6)−C(7) position, a common functionality many necines share. The extension of this methodology to the synthesis of more structurally challenging pyrrolizidine alkaloids is under active investigation.

Experimental Section

General Experimental Procedures. See Supporting Information.

rel-(1*R*,2*S*)-*trans*-2-Phenyl-1-[[2-(dimethylphenylsilyl)ethynyl]-oxy]cyclohexane (25). A solution of the acetylenic ether **24** (1.040 g, 5.19 mmol) in THF (30 mL) was cooled to −74 °C followed by a dropwise addition of *n*-BuLi (1.51 M, 3.61 mL, 5.45 mmol, 1.05 equiv). The resulting solution was stirred for 20 min, chlorodimethylphenyl-silane (0.91 mL, 5.45 mmol, 1.05 equiv) was added, and the reaction mixture was stirred for 1 h at −74 °C, then warmed to 0 °C and stirred for 1 h. The reaction mixture was diluted with pentane (300 mL), washed with NaHCO₃ (1 × 100 mL) and brine (1 × 100 mL), dried with Na₂SO₄ and filtered. The organic extract was concentrated in vacuo, and the crude product was purified by chromatography on basic alumina II (pentane/MTBE, (1/0, 18/1, 9/1)) to afford 1.484 g (85%) of silane **25**. An analytical sample was obtained by high-vacuum, bulb-to-bulb distillation. **25**: bp 120−125 °C (3.2 × 10⁻⁵ mmHg); ¹H NMR (400 MHz, CDCl₃) 7.60−7.58 (m, 2H), 7.36−7.23 (m, 8H), 4.19 (dt, J_d = 4.5, J_t = 10.8, 1H), 2.77 (ddd, *J* = 3.8, 10.6, 12.3, 1H), 2.46−2.42 (m, 1H), 1.97−1.92 (m, 2H), 1.79−1.29 (m, 5H), 0.32 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) 142.15, 138.64, 133.58, 128.91, 128.40, 127.59, 127.53, 126.71, 109.11, 90.16, 49.01, 33.75, 30.88, 25.41, 24.65, 24.62, −0.05; IR (neat) 2170 (s); MS (70 eV) 334 (M⁺, 0.72); TLC R_f = 0.46 (hexane/EtOAc, 19/1). Anal. Calcd for C₂₂H₂₆OSi (334.53): C, 78.98%; H, 7.83%. Found: C, 78.98%; H, 7.85%.

rel-(1*R*,2*S*)-*trans*-2-Phenyl-1-[[(*Z*)-2-(dimethylphenylsilyl)ethenyl]-oxy]cyclohexane (27). To a solution of propenyl ether **25** (0.530 g, 1.58 mmol) in THF (12 mL) at room temperature (**rt**) was added a solution of diisobutylaluminum hydride (2.18 M in THF, 2.18 mL, 4.75 mmol, 3.0 equiv). The resulting mixture was stirred for 2 h then was cooled to 0 °C and quenched with water. The mixture was poured into CH₂Cl₂ (100 mL) and was washed with water (2 × 50 mL). The aqueous layer was back-extracted with MTBE (50 mL), and the combined organic extracts were dried (Na₂SO₄), filtered, and concentrated in vacuo. The residue was purified by chromatography on basic alumina activity II (pentane/MTBE, (1/0, 4/1, 1/1)) to afford 368 mg (69%) of **27**. An analytical sample was prepared by high-vacuum, bulb-

to-bulb distillation. **27**: bp 100−110 °C (4 × 10⁻⁵ mmHg); ¹H NMR (400 MHz, C₆D₆) 7.61−7.59 (m, 2H), 7.27−7.07 (m, 8H), 6.27 (d, *J* = 8.3, 1H), 4.17 (d, *J* = 8.3, 1H), 3.35 (dt, *J*ₐ = 4.4, *J*ₜ = 10.5, 1H), 2.39 (ddd, *J* = 3.4, 10.1, 12.2, 1H), 1.85−1.81 (m, 1H), 1.66−1.62 (m, 1H), 1.51−1.48 (m, 1H), 1.41−1.39 (m, 1H), 1.24−1.16 (m, 2H), 1.02−0.93 (m, 2H), 0.43 (s, 3H), 0.40 (s, 3H); ¹³C NMR (100 MHz, C₆D₆) 158.95, 143.80, 140.66, 134.19, 128.73, 128.50, 128.09, 127.83, 127.56, 126.61, 96.50, 84.63, 50.72, 33.70, 33.32, 25.81, 24.90, −0.83, −1.07; IR (neat) 2857 (m), 1605 (s), 1494 (w); MS (70 eV) 336 (M⁺, 3). Anal. Calcd for C₂₂H₂₈OSi (336.54): C, 78.51%; H, 8.38%. Found: C, 78.67%; H, 8.44%.

(1*R*,2*S*)-*trans*-2-Phenyl-1-[[(*E*)-2-(dimethylphenylsilyl)ethenyl]oxy]cyclohexane ((−)-26). In a 1-L three-necked, round-bottomed flask was placed CuCN (5.80 g, 64.8 mmol, 2.0 equiv) and THF (350 mL). The white suspension was cooled to −10 °C followed by the addition of a solution of lithiodimethylphenylsilane (0.90 M, 144 mL, 129.6 mmol, 4.0 equiv). The resulting black solution was stirred for 30 min. A solution of (−)-**24** (6.48 g, 32.4 mmol) in THF (60 mL) was added to the cuprate over 15 min, and the reaction mixture was then stirred at 0 °C. After 1.5 h, the mixture was poured into water (0.7 L) and the biphase was extracted with MTBE (3 × 0.3 L). The combined organic extracts were filtered through Celite and rewashed with brine (2 × 0.25 L). The organic layer was dried (Na₂SO₄), filtered, and concentrated in vacuo. The crude product was purified by chromatography on basic alumina II (pentane/MTBE, (1/0, 19/1, 9/1)), and the mixed fractions were repurified by basic alumina II (pentane/MTBE, (1/0, 19/1, 9/1)) to afford 9.24 g (85%) of vinyl ether (−)-**26**. An analytical sample was obtained by high-vacuum, bulb-to-bulb distillation. (−)-**26**: bp 130 °C (4 × 10⁻⁵ mmHg); ¹H NMR (400 MHz, CDCl₃) 7.39−7.36 (m, 2H), 7.32−7.26 (m, 5H), 7.21−7.19 (m, 3H), 5.90 (d, *J* = 14.6, 1 H), 4.46 (d, *J* = 14.6, 1H), 3.91−3.85 (m, 1H), 2.64 (ddd, *J* = 3.7, 10.0, 12.4, 1H), 2.20−2.16 (m, 1H), 1.93−1.85 (m, 2H), 1.79 (m, 1H), 1.59−1.45 (m, 2H), 1.43−1.31 (m, 2H), 0.14 (s, 3H), 0.14 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) 156.98, 143.45, 139.69, 133.79, 128.61, 128.28, 127.87, 127.50, 126.35, 93.63, 82.53, 50.78, 33.70, 32.57, 25.81, 24.90, −1.85, −1.90; IR (neat) 2935 (s), 1613 (s), 1494 (w); MS (70 eV) 336 (M⁺, 3); [α]²³_D −11.6 (CHCl₃, *c* = 1.06); TLC *R_f* = 0.47 (hexane/EtOAc, 19/1). Anal. Calcd for C₂₂H₂₈OSi (336.54): C, 78.51%; H, 8.38%. Found: C, 78.47%; H, 8.38%.

(2*R*,2a*S*,4a*S*,5*S*,6*S*,7b*R*)-6-[[(1*R*,2*S*)-*trans*-2-Phenylcyclohexyl]oxy]-3-oxooctahydro-5-(dimethylphenylsilyl)-1,4,7-trioxa-7a-azabicyclopent[*cd*]indenecarboxylic Acid 1-Methylethyl Ester ((+)-29). To a solution of 2,6-diphenylphenol (9.26 g, 37.6 mmol, 10.0 equiv) in toluene (80 mL) was added trimethylaluminum (2.0 M in toluene, 9.40 mL, 18.8 mmol, 5.0 equiv). Gas evolution was observed, and the resulting light yellow solution was stirred at rt for 30 min.

To a solution of **14** (0.862 g, 3.76 mmol) and vinyl ether (−)-**26** (3.80 g, 11.29 mmol, 3.0 equiv) in toluene (33 mL) at −30 °C was added the MAPh solution prepared above slowly over 12 min keeping the internal temperature below −16 °C. During the addition the solution changed color from deep, dark brown to light brown. The brown solution was stirred for additional 3.7 h and then was quenched with MeOH (1.5 mL), poured into CH₂Cl₂ (1 L), and washed with water (2 × 0.5 L). The aqueous phases were back-extracted with MTBE (2 × 0.5 L), and the ether extracts were washed with brine (2 × 0.3 L). The combined organic extracts were dried (Na₂SO₄), filtered through Celite, and concentrated in vacuo. The crude product was purified by silica gel (330 g) column chromatography eluting with hexane/EtOAc (1/0, 9/1, 6/1, 4/1, 1/1, 0/1). The first fractions contained 2,6-diphenylphenol (and some vinyl ether), which was recrystallized from hexane (300 mL) to afford 7.70 g (83%) of recovered 2,6-diphenylphenol. The mother liquor was concentrated in vacuo, and the residue was purified on basic alumina activity II (pentane/MTBE, (1/0, 19/1, 9/1)) to afford 2.49 g (65%) of recovered vinyl ether (−)-**26**. Later fractions from the silica gel chromatography were repurified by silica gel chromatography (hexane/EtOAc, (12/1, 9/1, 6/1, 1/1)) to afford a combined yield of 1.556 g (73%) of (+)-**29** as a white foam, the composition of which was determined by ¹H NMR to be a >50/1 (exo/endo, at 500 MHz) mixture of diastereomers **29**. An analytical sample and a X-ray suitable crystals were obtained by recrystallization from MeOH. (+)-**29**: mp (sealed tube) 201−203 °C dec (MeOH); ¹H NMR (400 MHz,

CDCl₃) 7.41−7.15 (m, 10H), 5.23 (d, *J* = 3.6, 1H), 5.07 (septet, *J* = 6.3, 1H), 4.72 (d, *J* = 7.6, 1H), 4.42 (dd, *J* = 1.5, 6.6, 1H), 4.25 (dd, *J* = 6.6, 8.3, 1H), 4.02−3.96 (m, 1H), 3.72 (dd, *J* = 3.5, 8.5, 1H), 2.63−2.57 (m, 1H), 2.48−2.46 (m, 1H), 1.86−1.81 (m, 2H), 1.72−1.69 (m, 1H), 1.54−1.34 (m, 5H), 1.29 (d, *J* = 5.8, 6H), −0.10 (s, 3H), −0.17 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) 173.86, 167.14, 144.89, 135.95, 133.93, 129.46, 128.66, 127.93, 127.76, 126.36, 101.46, 84.86, 79.78, 77.16, 75.17, 70.47, 51.25, 49.27, 36.16, 34.41, 28.98, 25.87, 25.18, 21.58, 21.55, −3.63, −5.53; IR (KBr) 1782 (s), 1745 (s); MS (FAB) 566 (M⁺ + H, 5); [α]²³_D + 53.9° (CHCl₃, *c* = 0.83); TLC *R_f* = 0.20 (hexane/EtOAc, 4/1). Anal. Calc for C₃₁H₃₉NO₇Si (565.73): C, 65.81%; H, 6.94%; N, 2.47%. Found: C, 66.05%; H, 7.05%; N, 2.47%.

(2*R*,2a*S*,4a*S*,5*S*,6*S*,7b*R*)-6-[[(1*R*,2*S*)-*trans*-2-Phenylcyclohexyl]oxy]-3-hydroxyoctahydro-5-(dimethylphenylsilyl)-1,4,7-trioxa-7a-azabicyclopent[*cd*]indenecarboxylic Acid 1-Methylethyl Ester ((+)-30). To a solution of (+)-**29** (1.555 g, 2.74 mmol) in CH₂Cl₂ (60 mL) at −74 °C was added dropwise a solution of lithium tris(*sec*-butyl)borohydride (1.09 M in THF, 3.01 mL, 3.29 mmol, 1.2 equiv). The resulting solution was stirred for 70 min and was then quenched with a solution of aqueous phosphate buffer (pH 6.9)/glycerol (1/1, 15 mL). The mixture was immediately poured into CH₂Cl₂ (300 mL), then washed with water (1 × 100 mL) and brine (2 × 100 mL), and back-extracted with CH₂Cl₂ (1 × 100 mL). The combined organic extracts were dried (Na₂SO₄), filtered, and concentrated in vacuo. The crude product was purified by silica gel column chromatography eluting with hexane/EtOAc (4/1, 2/1, 1/1) to afford 1.42 g (91%) of (+)-**30** as a white foam, the composition of (+)-**30** was determined by ¹H NMR of the anomeric proton HC(3) to be (3a)/(3b) 16.3/1. An analytical sample was prepared by recrystallization from hexane/EtOAc. (+)-**30**: mp (sealed tube) 133−136 °C dec (hexane/EtOAc); ¹H NMR (400 MHz, CDCl₃) 7.39−7.15 (m, 10H), 5.45 (d, *J* = 2.0, 0.9H), 5.30 (dd, *J* = 6.8, 12.9, 0.1H), 5.18 (d, *J* = 3.4, 0.1H), 5.10 septet, *J* = 6.3, 1H), 4.93 (d, *J* = 7.1, 0.9H), 4.72 (d, *J* = 7.1, 1H), 4.32 (d, *J* = 12.9, 0.1H), 4.25−4.18 (m, 2H), 4.04−3.96 (m, 1H), 3.39 (ddd, *J* = 3.4, 6.8, 8.5, 0.1H), 3.13 (t, *J* = 7.6, 0.9H), 2.61−2.49 (m, 2H), 2.19 (d, *J* = 2.7, 0.9H), 1.83−1.78 (m, 2H), 1.69−1.66 (m, 1H), 1.52−1.30 (m, 4H), 1.28 (d, *J* = 6.1, 6H), 1.15 (dd, *J* = 1.6, 7.2, 1H), −0.08 (s, 0.3H), −0.12 (s, 2.7H), −0.19 (s, 0.3H), −0.22 (s, 2.7H); ¹³C NMR (100 MHz, CDCl₃) 168.34, 145.23, 136.82, 134.05, 129.11, 128.53, 127.72, 127.53, 126.16, 101.32, 101.11, 84.04, 79.13, 78.41, 75.72, 69.64, 58.61, 51.31, 36.21, 34.48, 27.98, 25.94, 25.23, 21.63, −3.54, −4.80; IR (KBr) 3543 (m), 1732 (s); MS (FAB) 606 (M⁺ + K, 3); [α]²³_D +56.6° (CHCl₃, *c* = 1.09); TLC *R_f* = 0.13 (hexane/EtOAc, 4/1). Anal. Calcd for C₃₁H₄₁NO₇Si (567.75): C, 65.58%; H, 7.27%; N, 2.46%. Found: C, 65.62%; H, 7.44%; N, 2.38%.

(1*R*,5a*S*,5*R*,7a*R*,7b*R*)-1,7-Dihydroxy-6-oxa-5-(dimethylphenylsilyl)octahydro-2*H*-cyclopenta[*gh*]pyrrolizin-2-one ((+)-31), (2*S*,3*S*)-2,4-Dihydroxy-3-[5-(dimethylphenylsilyl)-2*H*-1,2-oxazine]butanoic Acid 1-Methylethyl Ester (37), (2*S*,3*S*)-2-Hydroxy-3-[5-(dimethylphenylsilyl)-2*H*-1,2-oxazinyl]butyrolactone (38). To a solution of (+)-**30** (910 mg, 1.60 mmol) in EtOH (150 mL) was added a catalytic amount of EtOH-washed (300 mL) W-2 Raney nickel. The suspension was stirred at rt in a 300-mL flask inside a steel autoclave for 48 h under a 200 psi atmosphere of H₂. The catalyst was filtered off through Celite, washed with methanol (200 mL), and then concentrated in vacuo. The residue was separated by silica gel column chromatography eluting with hexane/EtOAc (4/1, 2/1, 1/1, 1/2, 0/1, then CHCl₃/MeOH 9/1, 6/1) into four fractions. The first fraction contained 245 mg (87%) of recovered (1*R*,2*S*)-*trans*-2-phenylcyclohexanol. The second fraction contained 9 mg of the lactone oxazine **38**, and the third fractions contained 47 mg of the isopropyloxazine **37**. The oxazines were very unstable, and multiple purifications were required to isolate them in a somewhat pure state. The fourth fraction contained 296 mg (58%) of (+)-**31** as a white amorphous solid. The enantiomeric purity of (+)-**31** was determined by chiral HPLC to be 94.9% ee. An analytical sample of (+)-**31** was obtained by recrystallization from EtOAc/hexane. (+)-**31**: mp (sealed tube) 125−135 °C dec (hexane/EtOAc); ¹H NMR (400 MHz, CDCl₃) 7.44−7.41 (m, 2H), 7.27−7.24 (m, 3H), 5.65 (d, *J* = 2.4, 1H), 4.73 (dd, *J* = 3.1, 3.8, 1H), 4.60 (d, *J* = 8.0, 1H), 4.03 (dd, *J* = 3.0, 5.4, 1H), 3.75 (dd, *J* = 8.6, 11.6, 1H), 3.44 (s, 1H, OH), 3.09−3.02 (m, 2H), 2.80 (s, 1H), 1.75 (ddd, *J* = 4.1, 8.5, 10.8, 1H),

0.29 (s, 3H), 0.23 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) 177.27, 137.86, 133.56, 129.24, 127.88, 98.81, 84.48, 71.83, 67.91, 51.80, 45.30, 30.39, -3.34, -3.41; IR (KBr) 3543 (w), 1732 (s); MS (CI, CH$_4$) 348 (14), 320 (M$^+$ + H, 31); [α]^{25}$_D$ $-116.5°$ (CHCl$_3$, c = 0.60); TLC R_f = 0.36 (CHCl$_3$/MeOH, 9/1); HPLC (Column Daicel, Chiralpak AD amylose tris(3,5-dimethylphenylcarbamate) (25 cm × 4.6 mm); method hexane/ EtOH, 90/10, 0.9 mL/min) t_R (1S,5aR,5R,7aS,7bR) 18.1 min (97.4%), t_R (1R,5aS,5S,7aR,7bS) 27.2 min (2.5%). Anal. Calcd for C$_{16}$H$_{21}$NO$_4$- Si (319.42): C, 60.16%; H, 6.62%; N, 4.38%. Found: C, 59.99%; H, 6.77%; N, 4.30%. **37**: ^{1}H NMR (400 MHz, CDCl$_3$) 9.04 (s, 1H), 7.55$-$ 7.28 (m, 5H), 6.74 (t, J = 1.8, 1H), 6.02 (t, J = 1.9, 1H), 4.95 (septet, J = 6.2, 1H), 4.59 (d, J = 2.7, 1H), 3.98 (d, J = 6.3, 2H), 3.42 (dt, J_d = 2.8, J_t = 6.4, 2H), 1.20 (d, J = 6.4, 3H), 1.09 (d, J = 6.1 3H), 0.42 (s, 3H), 0.42 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) 173.07, 140.05, 133.84, 128.57, 128.28, 127.49, 124.87, 114.26, 113.31, 71.66, 70.06, 64.17, 43.38, 21.63, -1.51, -1.58; IR (CDCl$_3$) 3608 (w), 3520 (w), 1725 (s); MS (70 eV) 378 (M$^+$ + H, 2); HRMS calcd for (C$_{19}$H$_{28}$- NO$_5$Si) 378.172095, found 378.173677. **38**: ^{1}H NMR (400 MHz, CDCl$_3$) 8.67 (s, 1H), 7.56$-$7.53 (m, 2H), 7.36$-$7.32 (m, 3H), 6.83 (dd, J = 1.5, 2.2, 1H), 6.03 (m, 1H), 4.66 (dd, J = 8.2, 8.9, 1H), 4.39 (d, J = 10.9, 1H), 4.34 (dd, J = 9.0, 11.0, 1H), 3.71 (dddd, J = 0.7, 8.1, 11.0, 11.0, 1H), 0.46 (s, 6H); MS (70 eV) 318 (M$^+$ + H, 1).

(1R,5aS,5R,7R,7aR,7bR) and (1R,5aS,5R,7S,7aR,7bR)-1-Hydroxy-7-methoxy-6-oxa-5-(dimethylphenylsilyl)octahydro-2H-cyclopenta-[gh]pyrrolizin-2-one (32). To a solution of (+)-**31** (0.445 g, 1.39 mmol) and p-toluenesulfonic acid (0.072 g, 0.422 mmol, 0.30 equiv) in MeOH (85 mL) was added trimethyl orthoformate (3.3 mL). The resulting solution was stirred at rt for 13 h and was quenched with poly(vinylpyridine) (0.089 g). The suspension was filtered, and the filtrate was concentrated in vacuo. The resulting crude product was purified by basic alumina (activity II) column chromatography eluting with CHCl$_3$/MeOH (1/1, 6/1, 4/1, 2/1) to afford 0.439 g (95%) of **32** (mixture of methyl acetal anomer) as a light brown oil. The composition of **32** was determined by ^{1}H NMR to be an 6.0/1 mixture of 7α/ 7β anomers. For analytical purposes the anomers were separated by silica gel chromatography eluting with hexane/EtOAc (2/1, 1/1, 1/2, 1/4, 0/1, then CHCl$_3$/MeOH 4/1) followed by high-vacuum bulb-to-bulb distillation. (+)-**32a**: (7α) bp 195 °C (5 × 10^{-5} mmHg); ^{1}H NMR (400 MHz, CDCl$_3$) 7.56$-$7.54 (m, 2H), 7.37$-$7.39 (m, 3H), 5.24 (s, 1H), 4.70 (d, J = 8.3, 1H), 4.58 (t, J = 3.5, 1H), 4.08 (dd, J = 2.9, 5.4, 1H), 3.88 (dd, J = 8.4, 11.6, 1H), 3.51 (s, 1H), 3.28 (s, 3H), 3.21$-$ 3.15 (m, 1H), 3.10 (dd, J = 5.4, 8.3, 1H), 1.83 (ddd, J = 4.1, 8.3, 10.6, 1H), 0.41 (s, 3H), 0.36 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) 177.62, 137.86, 133.59, 129.19, 127.79, 105.12, 84.01, 71.65, 67.59, 54.60, 51.01, 45.26, 30.25, -3.32, -3.47; IR (CHCl$_3$) 3528 (w), 1702 (s); MS (CI, CH$_4$) 362 (17), 334 (M$^+$ + H, 33); [α]^{25}$_D$ $+172.2°$ (CHCl$_3$, c = 0.73); TLC R_f = 0.56 (CHCl$_3$/MeOH, 9/1), R_f = 0.33 (EtOAc). Anal. Calcd for C$_{17}$H$_{23}$NO$_4$Si (333.45): C, 61.23%; H, 6.95%; N, 4.20%. Found: C, 61.07%; H, 7.07%; N, 4.18%. (−)-**32b**: (7β) bp 195 °C (3 × 10^{-5} mmHg); ^{1}H NMR (400 MHz, CDCl$_3$) 7.55$-$7.52 (m, 2H), 7.37$-$7.34 (m, 3H), 5.12 (d, J = 6.2, 1H), 4.73 (dd, J = 6.1, 11.3, 1H), 4.61 (t, J = 3.7, 1H), 3.99 (dd, J = 3.8, 4.8, 1H), 3.93 (d, J = 11.7, 1H), 3.71 (t, J = 10.8, 1H), 3.39$-$3.31 (m, 1H), 3.34 (s, 3H), 3.29$-$3.25 (m, 1H), 1.81 (dt, J_d = 3.8, J_t = 10.2, 1H), 0.43 (s, 3H), 0.39 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) 177.22, 137.42, 133.57, 129.32, 127.91, 108.85, 85.27, 75.24, 66.61, 57.33, 49.37, 45.98, 33.40, -3.43, -3.46; IR (CHCl$_3$) 1713 (s); MS (CI, CH$_4$) 363 (10), 362 (39), 334 (M$^+$ + H, 17); [α]^{23}$_D$ $-21.0°$ (CHCl$_3$, c = 0.32); TLC R_f = 0.59 (CHCl$_3$/MeOH, 9/1), R_f = 0.14 (EtOAc). Anal. Calcd for C$_{17}$H$_{23}$- NO$_4$Si (333.45): C, 61.23%; H, 6.95%; N, 4.20%. Found: C, 61.38%; H, 7.01%; N, 4.32%.

(1R,5aS,5R,7aR,7bR)-5-(Dimethylphenylsilyl)-1-(methane-sulfonyloxy)-7-methoxy-6-oxooctahydro-2H-cyclopenta[gh]pyrrolizin-2-one ((+)-33). To a solution of methyl acetal **32** (433 mg, 1.29 mmol) in CH$_2$Cl$_2$ (36 mL) was added methanesulfonyl chloride (0.20 mL, 2.59 mmol, 2.0 equiv) and triethylamine (0.36 mL, 2.59 mmol, 2.0 equiv) at rt. The resulting solution was stirred for 1.5 h and then was diluted with CH$_2$Cl$_2$ (100 mL) and washed with saturated aqueous CuSO$_4$ solution (50 mL) and brine (50 mL). The aqueous layers were back-extracted with CH$_2$Cl$_2$ (50 mL), and the combined organic extracts were dried (Na$_2$SO$_4$), filtered, and concentrated in vacuo. The crude product was purified by silica gel chromatography eluting with hexane/EtOAc

(4/1, 2/1, 1/1, 1/2, 0/1) to afford 505 mg (95%) of (+)-**33** as a 11/1 mixture of methyl anomers as determined by ^{1}H NMR. An analytical sample was prepared by high-vacuum, bulb-to-bulb distillation. (+)-**33**: bp 250 °C (4.8 × 10^{-5} mmHg); ^{1}H NMR (400 MHz, CDCl$_3$) 7.55$-$ 7.53 (m, 2H), 7.38$-$7.34 (m, 3H), 5.56 (d, J = 8.5, 1H), 5.16 (s, 1H), 4.61 (t, J = 3.5, 1H), 4.10 (dd, J = 3.0, 5.6, 1H), 4.88 (dd, J = 8.4, 11.6, 1H), 3.32 (s, 3H), 3.28 (s, 3H), 3.24$-$3.18 (m, 2H), 1.85 (ddd, J = 4.1, 8.2, 10.6, 1H), 0.42 (s, 3H), 0.37 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) 170.85, 137.50, 133.56, 129.32, 127.86, 105.21, 84.30, 78.11, 67.17, 54.64, 50.12, 45.74, 39.98, 30.10, -3.31, -3.50; IR (CHCl$_3$) 1721 (s); MS (CI, CH$_4$) 414 (11), 413 (25), 412 (M$^+$ + H, 100); [α]^{25}$_D$ $+134.1°$ (CHCl$_3$, c = 0.57); TLC R_f = 0.77 (CHCl$_3$/MeOH, 9/1). Anal. Calcd for C$_{18}$H$_{25}$NO$_6$SiS (411.54): C, 52.53%; H, 6.12%; N, 3.40%. Found: C, 52.38%; H, 6.16%; N, 3.30%.

(1R,5aS,5R,7aR,7bR)-5-Hydroxy-1-(methanesulfonyloxy)-7-meth-oxy-6-oxaoctahydro-2H-cyclopenta[gh]pyrrolizin-2-one ((+)-34). A solution of (+)-**33** (0.501 g, 1.217 mmol), potassium bromide (0.173 g, 1.46 mmol, 1.2 equiv), and sodium acetate (1.23 g, 15.0 mmol, 12.4 equiv) in acetic acid (2.9 mL) was cooled to 0 °C. Peracetic acid (8.9 mL, 36% v/v) was added dropwise at a rate to maintain the reaction temperature below rt (ca. 20 min). Gas evolution was observed during the addition of the peracetic acid. The resulting solution was stirred at rt for 3 h then was cooled to 0 °C. The reaction mixture was quenched by adding a catalytic amount of 5% Pd/C, and the resulting black suspension was stirred at 0 °C for 30 min and then was directly purified by silica gel chromatography eluting with CHCl$_3$/MeOH (1/0, 19/1, 9/1). (Note: *extreme care should be taken handling the peracetic acid residue during the silica gel chromatography, since a violent exothermic reaction can take place if the reaction is not quenched properly*.) The crude product was repurified by silica gel chromatography eluting with CHCl$_3$/MeOH (1/0, 19/1, 9/1) to afford 291 mg (81%) of (+)-**34**. An analytical sample was obtained by recrystallization from acetone/Et$_2$O/pentane. (+)-**34**: mp (sealed tube) 145 °C dec (acetone/Et$_2$O/pentane); ^{1}H NMR (400 MHz, CD$_3$OD) 5.72 (d, J = 8.0, 1H), 5.24 (s, 1H), 4.66 (dt, J_d = 4.0, J_t = 7.3, 1H), 4.44 (dd, J = 2.8, 4.0, 1H), 4.36 (dd, J = 2.7, 5.3, 1H), 3.43 (d, J = 7.6, 2H), 3.36 (s, 3H), 3.27 (s, 3H), 3.28$-$3.23 (m, 1H); ^{13}C NMR (100 MHz, CD$_3$OD) 172.84, 107.48, 83.34, 78.25, 73.35, 67.00, 55.53, 52.75, 50.63, 39.00; IR (KBr) 1692 (s); MS (CI, CH$_4$) 294 (M$^+$ + H, 24); [α]^{23}$_D$ $+93.9°$ (MeOH, c = 0.46); TLC R_f = 0.39 (CHCl$_3$/MeOH, 9/1). Anal. Calcd for C$_{10}$H$_{15}$NO$_7$S (293.29): C, 40.95%; H, 5.15%; N, 4.77%. Found: C, 40.76%; H, 5.21%; N, 4.94%.

(1R,5aS,5R,7S,7aR,7bR)-5-Dihydroxy-1-(methanesulfonyloxy)-6-oxaoctahydro-2H-cyclopenta[gh]pyrrolizin-2-one ((+)-35). A solution of (+)-**34** (0.304 g, 1.036 mmol) in 90% aqueous trifluoroacetic acid (TFA) (25 mL) was stirred at 60 °C for 24 h. The solution was then repeatedly diluted with benzene (3 × 30 mL) and concentrated in vacuo. The crude product was then purified by silica gel column chromatography eluting with hexane/EtOAc (2/1, 1/1, then acetone) and repurified by silica gel chromatography eluting with hexane/EtOAc (2/1, 1/1, then CHCl$_3$/MeOH 9/1, then acetone) to afford 0.218 g (75%) of (+)-**35**. (+)-**35**: mp 101$-$106 °C (EtO$_2$/MeOH); ^{1}H NMR (400 MHz, CD$_3$OD) 5.73 (d, J = 7.8, 1H), 5.66 (s, 1H), 4.64 (ddd, J = 4.3, 6.6, 7.7, 1H), 4.57 (dd, J = 3.0, 4.2, 1H), 4.37 (dd, J = 2.9, 5.4, 1H). 3.43$-$3.40 (m, 2H), 3.27 (s, 3H), 3.22 (ddd, J = 1.2, 7.8, 5.3, 1H); ^{13}C NMR (100 MHz, CD$_3$OD) 172.90, 100.74, 83.03, 78.62, 73.35, 67.20, 53.49, 50.71, 38.99; IR (KBr) 3450 (s, br), 1715 (s); MS (CI, CH$_4$) 280 (M$^+$ + H, 12); HRMS calcd for (C$_9$H$_{14}$NO$_7$S) 280.049 099, found 280.048 001; [α]^{23}$_D$ $+67.5°$ (MeOH, c = 0.58); TLC R_f = 0.19 (CHCl$_3$/ MeOH, 9/1).

(1S,2R,6R,7S,7aR)-7-(Hydroxymethyl)-6-(methanesulfonyloxy)-4-(trihydridoboryl)hexahydro-1H-pyrrolizine-1,2-diol (36). To a solution of lactol (+)-**35** (20 mg, 0.0716 mmol) in THF (20 mL) was added BH$_3$ (1.0 M in THF, 2.86 mL, 2.86 mmol, 40 equiv). Gas evolution was observed, and the resulting solution was heated to 72 °C (external 80 °C) for 4 h, whence a white precipitate formed. The mixture was cooled to rt and concentrated in vacuo. The residual oil was redissolved in MeOH (2 × 10 mL) and concentrated in vacuo to afford 23 mg of **36**. The crude product was purified by silica gel chromatography eluting with CHCl$_3$/MeOH (1/0, 19/1, 9/1, 6/1, 4/1) to give 15.2 mg (75%) of **36**. **36**: ^{1}H NMR (400 MHz, CD$_3$OD) 5.31 (ddd, J = 4.4, 6.9, 7.8, 1H), 4.39 (ddd, J = 3.7, 7.8, 9.7, 1H), 4.12$-$

4.08 (m, 2H), 3.96 (dd, J = 6.9, 11.0, 1H), 3.75 (dd, J = 6.8, 12.4, 1H), 3.70 (dd, J = 3.6, 9.4, 1H), 3.57−3.53 (m, 1.5H, HC(5 and THF), 3.46 (dd, J = 7.8, 10.8, 1H), 3.22−3.10 (m, 2H), 3.09 (s, 3H), 1.59−1.28 (m, br, 4H, (BH$_3$ and THF)); ^{13}C NMR (100 MHz, CD$_3$OD) 81.27, 78.27, 73.48, 73.15, 72.15, 67.74, 62.79 (CH$_2$/THF), 58.20, 45.61, 37.81, 30.14 (CH$_2$/THF)); ^{11}B NMR (96 MHz, CD$_3$OD) −7.95; IR (KBr) 3435 (m, br), 2373 (m), 2337 (m); MS (70 eV) 359 (1), 358 (4), 357 (2), 273 (2), 272 (1), 185 (M$^+$ − MeSO$_3$H, 1); TLC R_f = 0.20 (CH$_3$Cl/MeOH, 9/1).

Synthetic (+)-Crotanecine (1). To a solution of lactol (+)-**35** (178 mg, 0.637 mmol) in THF (130 mL) was added BH$_3$ (1.0 M in THF, 25.5 mL, 25.5 mmol, 40 equiv). Gas evolution was observed, and the resulting solution was heated to 72 °C (external 80 °C) for 4 h, during which a white precipitate formed. The mixture was cooled to rt and concentrated in vacuo. The residual oil was redissolved in MeOH (2 × 50 mL) and concentrated in vacuo to afford 200 mg of **36**. The triol was dissolved in MeOH (28 mL) and transferred into a Carius tube, and Et$_3$N (57 mL) was added. The mixture was degassed by two freeze/thaw cycles with argon. The clear, colorless reaction solution was then heated at 120−130 °C for 5 h (whence the solution turned brown), then was cooled to rt and concentrated in vacuo to ca. 3 mL. The crude product was then purified by chromatography on silica gel (CHCl$_3$/MeOH, 4/1, then CHCl$_3$/MeOH/NH$_4$OH, 10/5/1) to afford 77.1 mg (70.7%) of (+)-**1** as a light brown solid. An analytical sample was obtained by recrystallization from EtOH/Et$_2$O. (+)-**1**: mp 193−197 °C (EtOH/Et$_2$O); ^{1}H NMR (500 MHz, CD$_3$OD) 5.70 (d, J = 1.5, 1H), 4.19−4.15 (m, 4H), 4.03 (t, J = 3.7, 1H), 3.85 (dt, J_d = 15.0, J_t = 1.8, 1H), 3.41−3.37 (m, 1H), 3.23 (dd, J = 6.9, 8.7, 1H), 2.60 (t, J = 9.5, 1H); ^{13}C NMR (125 MHz, CD$_3$OD) 140.27, 125.27, 76.12, 74.77, 72.33, 64.20, 59.88, 59.30; IR (KBr) 3325 (s), 3277 (s), 3269 (s), 3261 (s), 3248 (s); MS (70 eV) 171 (M$^+$, 30); $[\alpha]^{21}_D$ + 38.7° (EtOH, c = 0.52); TLC R_f = 0.20 (CHCl$_3$/MeOH/NH$_4$OH, 10/5/1). Anal. Calcd for C$_8$H$_{13}$NO$_3$ (171.19): C, 56.12%; H, 7.65%; N, 8.18%. Found: C, 55.84%; H, 7.52%; N, 7.95%.

Natural (+)-Crotanecine (1). A solution of anacrotine (**4**) (0.052 g, 0.147 mmol) and NaOH (40.0 mg, 1.0 mmol, 6.7 equiv) in water (1.1 mL) was heated at reflux for 2.5 h. The resulting yellow solution was cooled to rt, diluted with EtOH, and concentrated in vacuo. The crude product was purified by silica gel chromatography (the column was prepared with a large Celite plug (one-half the height of the silica gel) at the bottom) eluting with (CHCl$_3$/MeOH/NH$_4$OH, 10/5/1) to give 18.9 mg of a yellow solid. The product was further purified by chromatography on silica gel (prepared as above, the compound was loaded on the column in 2/1 Et$_3$N/MeOH) eluting with (CHCl$_3$/MeOH, 4/1, followed by CHCl$_3$/MeOH/NH$_4$OH, 10/5/1) to give 18.5 mg (74%) of (+)-**1** as an off white solid (+)-**1**: mp 192−195 °C; ^{1}H NMR (500 MHz, CD$_3$OD) 5.70 (d, J = 1.4, 1H), 4.20−4.16 (m, 4H), 4.05 (t, J = 3.6, 1H), 3.88 (dt, J_d = 14.6, J_t = 1.8, 1H), 3.44−3.40 (m, 1H), 3.26 (dd, J = 6.7, 8.7, 1H), 2.63 (t, J = 9.6, 1H); ^{13}C NMR (125 MHz, CD$_3$OD) 140.24, 125.06, 76.20, 74.70, 72.26, 64.19, 59.84, 59.19; IR (KBr) 3326 (s), 3270 (m), 3265 (m), 3256 (m), 3105 (w); MS (70 eV) 171 (M$^+$, 34); $[\alpha]^{21}_D$ + 35.0° (EtOH, c = 0.64); TLC R_f = 0.20 (CHCl$_3$/MeOH/NH$_4$OH 10/5/1).

Supporting Information Available: Complete listing of ^{1}H NMR and ^{13}C NMR data with assignments, infrared absorbances, and mass spectrum fragments of all compounds, general experimental procedures and preparation and spectroscopic data for compounds **18**, **40**, and **49** along with ^{1}H NMR, ^{13}C NMR, IR, and MS spectra of natural and synthetic (+)-crotanecine, and a ^{1}H NMR comparison of (+)-crotanecine and the hydrochloride salt (33 pages). See any current masthead page for ordering or Internet access instructions.

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