Straightforward Access to Enantiomerically Pure, Highly Functionalized Pyrrolizidines by Cycloaddition of Maleic Acid Esters to Pyrroline *N*-Oxides Derived from Tartaric, Malic and Aspartic Acids − Synthesis of (−)-Hastanecine, 7-*epi*-Croalbinecine and (−)-Croalbinecine

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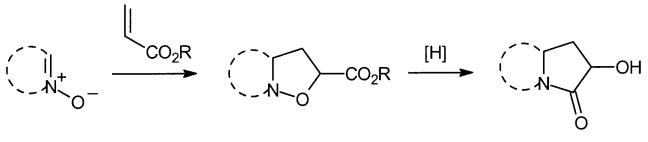
The cycloaddition reactions of dimethyl maleate to three functionalized enantiopure pyrroline *N*-oxides and one related racemic nitrone are reported. The study of the diastereoselectivity in the cycloaddition has been carried out by ample variation of the substituents at both the dipole and dipolarophile counterparts. The major cycloadducts, derived from the preferred *exo-anti* transition states and formed with 62–90% diastereoselectivity, have been subjected to $Mo(CO)_6$-induced reductive ring-opening to afford directly highly functionalized enantiopure pyrrolizinone derivatives, valuable as synthetic intermediates. Applications of this strategy to a straightforward formal synthesis of (–)-hastanecine and to the total synthesis of the novel 7-*epi*-croalbinecine and of (–)-croalbinecine are reported.

Introduction

Nitrones constitute powerful tools for the construction of aza heterocycles, based on their reactivity either as 1,3-dipoles in cycloadditions towards alkenes[1] or as electrophilic acceptors in alkylations by organometallic derivatives.[2] The former reactions give rise to isoxazolidine adducts which may in turn be elaborated in a variety of ways, usually originated by isoxazolidine ring-opening at the weak N−O bond. One of such useful transformations consists of the formation of γ-lactams by hydrogenolysis of isoxazolidines bearing an ester functionality at the 5-position. A nucleophilic attack on the ester carbonyl by the amino group generated in the reaction followed by spontaneous ring-closure results in a lactam ring (Scheme 1).[3] When the starting nitrone is a pyrroline *N*-oxide, the pyrrolizidine nucleus can be accessed directly by this strategy.



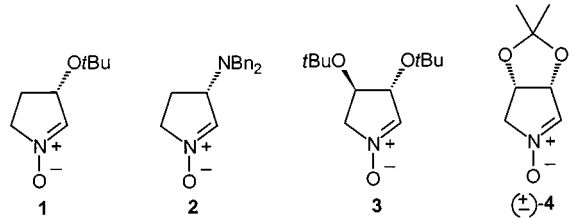
Scheme 1. General strategy for the synthesis of γ-lactams from nitrones

In this paper we report the straightforward synthesis of highly functionalized enantiomerically pure pyrrolizidines based on the application of this strategy to enantiopure pyrroline *N*-oxides. Applications of this procedure to a short synthesis of the necine base (−)-hastanecine[4] and of natural product analogues, i.e. 7-*epi*-croalbinecine and (−)-croalbinecine are also reported.

Results and Discussion

Synthesis of Nitrones and Cycloaddition Reactions

Enantiomerically pure nitrones **1**−**3** (Scheme 2),[5] readily obtained from inexpensive starting materials from the chiral pool, namely L-malic, L-aspartic and D-tartaric acid, respectively, were used in this study. The racemic protected *cis*-dihydroxy-substituted nitrone **4**, which was synthesized (Scheme 3) according to a modification of the procedure reported by Wightman and co-workers,[6] was also employed. The *meso*-dimesylate **7**, prepared from L-arabinose (**5**) (or its enantiomer) as previously reported,[6] was converted into the nitrone **4** according to the route developed by us[5] via the cyclic hydroxylamine **8**, which proved advantageous in terms of overall yields and number of steps.



Scheme 2. Nitrones employed in the study

The cycloaddition reactions of dimethyl maleate (**9**) to nitrones **1**−**4** occurred smoothly at room temperature in benzene to afford mixtures of two to three diastereomeric cycloadducts in good yields (Scheme 4). Structural assignment to all the adducts has been based unequivocally on

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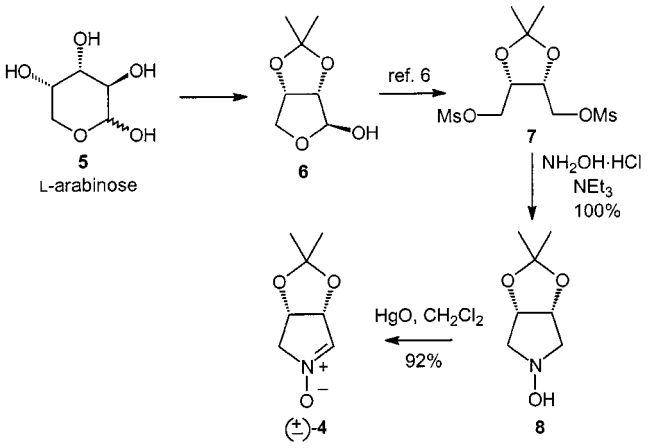
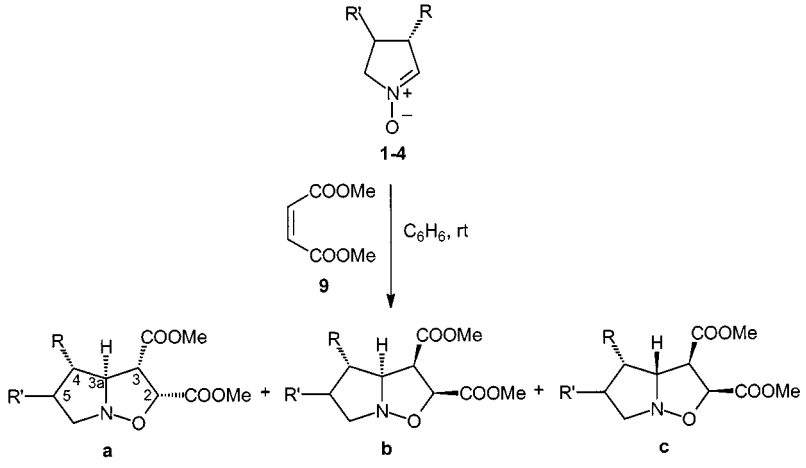


Scheme 3. Synthesis of the racemic nitrone **4**

the values of vicinal coupling constants 3-H,3a-H and 3a-H,4-H (with $J_{cis} > 7$ Hz and $J_{trans} < 7$ Hz) and on 2D-NOESY spectra, as exemplified in Figure 1 and Figure 2 for adducts **10**, as well as by comparison with previous analogous results.[5a,7] Upon chromatographic separation, the major adducts **10**−**13a** were isolated and identified in each case as the products derived from the least sterically hindered *exo-anti* approaches (Scheme 5), where *anti* refers to the position of the C-3 substituent on the nitrone relative to the direction of the approaching dipolarophile.[5a,7] The minor products derived from *endo-anti* and *exo-syn* approaches, with the relative amount depending on the different steric requirements furnished by the nitrone. As a matter of fact, nitrones with bulkier substituents, such as **2** and **4**, gave no *syn* adduct **c**, while the *trans*-substituted nitrone **3** gave a higher stereoselectivity in favor of the *exo-anti* adduct **a** and only small amounts of the *endo* adduct **b**, since the *tert*-butoxy group at C-4 hindered the approach of maleate from its side in an *endo* fashion. No trace of the fourth possible cycloadduct was detected in any case, demonstrating that the most encumbered *endo-syn* approach requires a substantially higher energy.[5a,7]

Attempts to improve the selectivity in the cycloaddition of malic acid derived nitrones (e.g. nitrone **1**) by increasing the steric demand of either the nitrone, with the use of the triisopropylsilyl-protected nitrone **18** synthesized from diethyl malate according to Scheme 6,[8] or of the dipolarophile substituents, with the use of diisopropyl ester **19**, met with very limited success (Scheme 7). These results are consistent with the opinion that nitrone cycloadditions occur through early transition states,[9] with reactants not close enough to make the steric requirements more crucial. Even less successful was the attempt to catalyze the reaction of **1** and **9** with Lewis acids [$TiCl_4$, $TiCl_2(OiPr)_2$, ZnI_2].[1g] Remarkably, however, the cycloadducts **21a**−**c** and **23a**−**c** derived from diisopropyl maleate were more readily separated than their methyl analogues by a single flash column chromatography employing a petroleum ether/ethyl acetate mixture with an increasing gradient to the more polar solvent. In this way, all the three adducts were obtained pure, com-



R	R'	Nitrone	Reaction time (d)	Adducts (Ratio)	Yield (%)
O*t*Bu	H	**1**	3	**10a** + **10b** + **10c** (5 : 1 : 1)	89
NBn_2	H	**2**	3 (at 40 °C)	**11a** + **11 b** (4 : 1)	63
O*t*Bu	O*t*Bu	**3**	3	**12a** + **12b** + **12c** (13 : 1 : 1.4)	94
$OC(CH_3)_2O$		**4**	1	**13a** + **13b** (1.6 : 1)	85

Scheme 4. Cycloaddition reactions of nitrones **1**−**4** with dimethyl maleate (**9**)

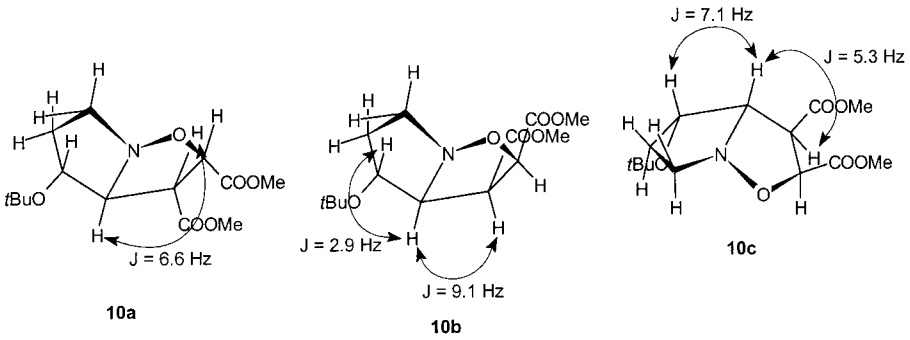


Figure 1. Relevant coupling constant values assessing the relative stereochemistry for cycloadducts **10a−c**

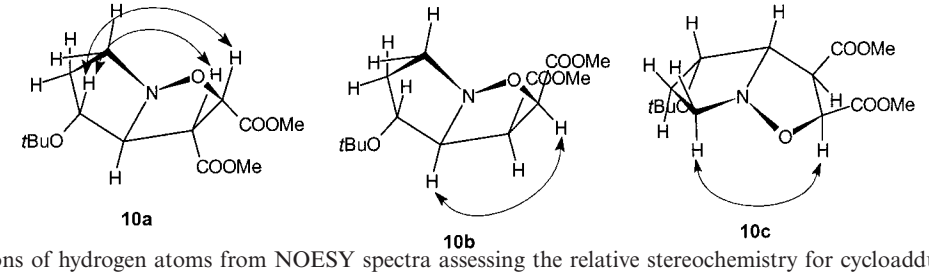
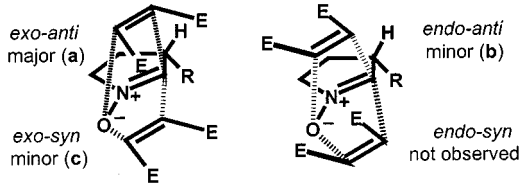


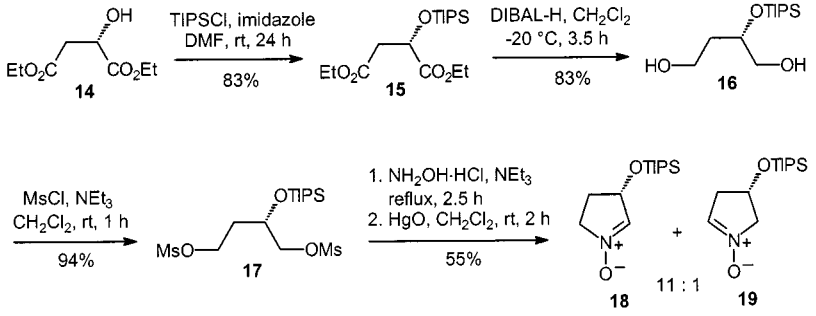
Figure 2. Correlations of hydrogen atoms from NOESY spectra assessing the relative stereochemistry for cycloadducts **10a−c**



Scheme 5. Possible approaches for cycloaddition of dimethyl maleate (**9**) to nitrones **1−4**

Synthesis of 7-*epi*-Croalbinecine and (−)-Croalbinecine

The ready access to highly functionalized, enantiomerically pure pyrrolizidines outlined by this strategy, together with the high predictability of the stereochemical outcome, suggested the employment of the method for the synthesis of hydroxylated pyrrolizidine alkaloids and their congeners. For example, the pyrrolizidinone **24** has been readily converted into the trihydroxypyrrolizidine **31** (7-*epi*-croalbinec-



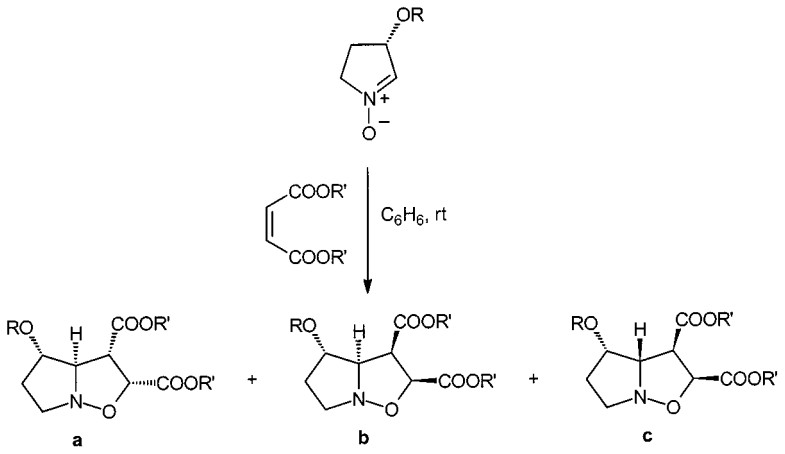
Scheme 6. Synthesis of the silyl-protected nitrone **18**

pletely separated from each other, with an almost quantitative overall yield.

Reductive Ring-Opening of Pyrroloisoxazolidines

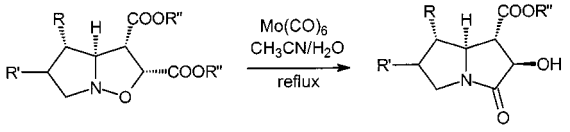
In order to access the pyrrolizidine nucleus, the major adducts **10−13a** and **23a** and the *syn* adduct **10c** were subjected to the isoxazolidine reductive ring-opening. The method chosen for this transformation, developed in our group, consists of heating the isoxazolidine at reflux in an aqueous acetonitrile solution in the presence of $Mo(CO)_6$.[10] The resulting pyrrolizidinones **24−29** have been recovered in good yields (Scheme 8), providing the standing of the reaction mixture over silica gel overnight for an efficient removal of the metal from the products.[11]

ine), a previously unknown diastereoisomer of the naturally occurring croalbinecine and rosmarinecine,[12] by a simple reduction followed by final deprotection (Scheme 9). The analogous process carried out on pyrrolizidinone **29** derived from the minor adduct **10c** afforded (−)-croalbinecine (**33**), the enantiomer of the natural alkaloid necine base.[13] The spectral data of **33** were consistent with those reported for the isolated natural (+)-croalbinecine,[13] even though its measured optical rotation was somewhat lower in absolute value {$[\alpha]_D^{22} = -36.5$ ($c = 0.52$, EtOH) vs. $[\alpha]_D^{25} = +45.7$ ($c = 0.0024$, EtOH)[13b]}. However, racemization has been ruled out by derivatization of the precursor **29** as its Mosher's ester [with (*R*)configuration], which showed the presence of only one set of signals by ^{1}H NMR analysis.[14]

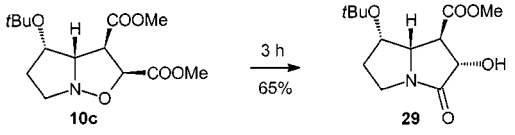


R	Nitrone	R'	Maleate	Reaction time (d)	Adducts (Ratio)	Yield (%)
*t*Bu	**1**	*i*Pr	**20**	2	**21a** + **21b** + **21c** (5 : 1 : 1)	97
TIPS	**18**	Me	**9**	3	**22a** + **22b** + **22c** (5.5 : 1.4 : 1)	100
TIPS	**18**	*i*Pr	**20**	5	**23a** + **23b** + **23c** (6 : 1.6 : 1)	91

Scheme 7. Cycloaddition of nitrone **1** with diisopropyl maleate (**20**) and cycloadditions of nitrone **18**



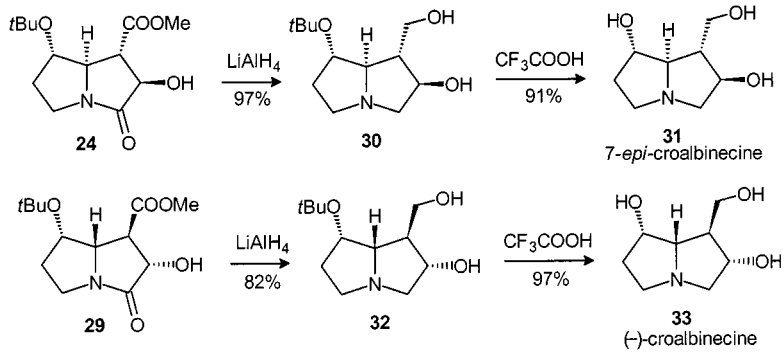
R	R'	R"	Isoxazolidine	Reaction time (h)	Product	Yield (%)
O*t*Bu	H	Me	**10a**	3	**24**	82
NBn_2	H	Me	**11a**	2.5	**25**	84
O*t*Bu	O*t*Bu	Me	**12a**	3.5	**26**	65
$OC(CH_3)_2O$		Me	**13a**	2	**27**	77
OTIPS	H	*i*Pr	**23a**	18	**28**	85



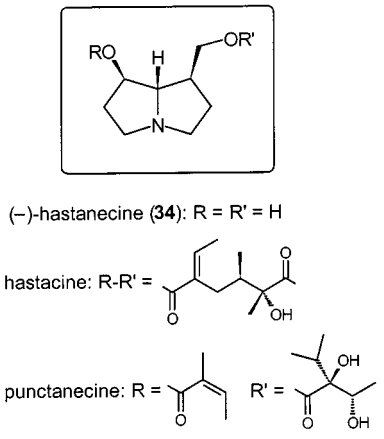
Scheme 8. Hexacarbonylmolybdenum-induced reductive ring-opening of pyrroloisoxazolidines **10**−**13a** and **10c**

Synthesis of (−)-Hastanecine

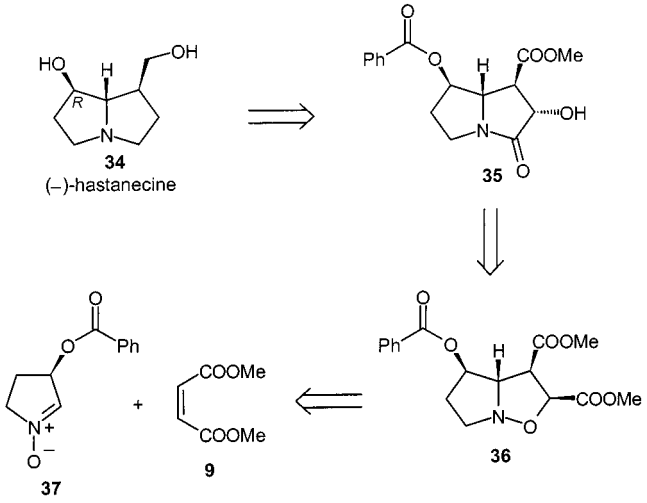
(−)-Hastanecine (**34**), the necine base of several alkaloids (Scheme 10),[12] has been chosen as the first target among pyrrolizidine natural products. Hydrolysis of hastacine, isolated in 1945 from *Cacalia hastata* and successively from *Cacalia robusta*,[15] furnished for the first time (−)-hastanecine. More recently, it has also been recognized as the necine base of the alkaloid punctanecine, isolated from *Liatris punctata*.[16] Its structural and stereochemical assignment was secured by the first enantioselective synthesis of its enantiomer achieved by Culvenor and co-workers in 1968.[17] Successively, several syntheses of hastanecine have been targeted and reported as a probe for new methodologies.[18] One of the most recent,[18g] achieved by Denmark with the use of his [4+2]/[3+2] tandem cycloaddition strategy, considered the pyrrolizidinone **35** (Scheme 11) as an advanced intermediate, from which the target alkaloid **34** was obtained by radical deoxygenation of the corresponding thiocarbonate followed by $LiAlH_4$ reduction. We envisaged that the same intermediate **35** might be easily accessed by the use of the strategy outlined above starting from an appropriate nitrone **37**, according to the retrosynthesis in Scheme 11. The relative stereochemistry at the three stereogenic centers should be derived from the major *exo-anti* adduct. However, the absolute configuration of (−)-hastanecine required D-malic acid as the chiral starting material, which is commercially available but with a lower optical purity[19] and about 30 times as expensive as its enantiomer. This would constitute a major drawback in offering a general access to pyrrolizidine alkaloid necine bases, considering that almost all of them possess the (*R*) absolute configuration (derived from D-malic acid) at C-7.[12] We reasoned that use of L-malic acid might still be considered if an inversion of configuration were to be carried out during the synthesis of nitrone **37**. Since a benzoyl group was the protecting group to be introduced, the Mitsunobu reaction with the use of benzoic acid as nucleophile appeared to be the most appropriate way to simultaneously introduce the protecting group and invert the absolute configuration.[20] Furthermore, introduction of the benzoyloxy group prior to nitrone formation by oxidation of the parent hydroxylamine



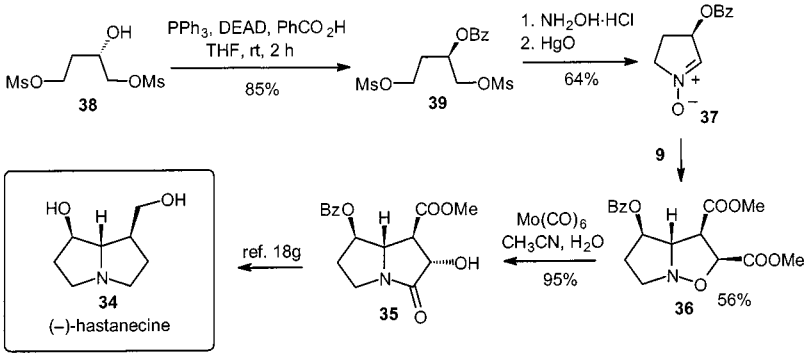
Scheme 9. Synthesis of 7-*epi*-croalbinecine and (−)-croalbinecine by reduction of pyrrolizidinones and deprotection



Scheme 10. Pyrrolizidine alkaloids constituted by the necine base (−)-hastanecine



Scheme 11. Retrosynthetic scheme for the synthesis of (−)-hastanecine (**34**) from nitrone **37**



Scheme 12. Synthesis of (−)-hastanecine (**34**)

would drive the regioselectivity of the oxidation completely towards the desired nitrone.[5b]

The Mitsunobu reaction was then carried out on the hydroxy mesylate **38** (Scheme 12), prepared according to our previous report.[5b] Although rare examples of Mitsunobu reactions on compounds containing sulfonate moieties have been reported,[21] it has been demonstrated that mesylate groups tolerate the reaction conditions.[21d] The benzoyloxy dimesylate **39** was thus obtained in good yield; the resulting complete inversion of configuration was proved by comparison of its specific optical rotation with that of the enantiomeric compound.[5b] The usual two-step cyclization/oxidation procedure furnished the required nitrone **37** exclusively, as already reported for the enantiomer.[5b] Cycloaddition of nitrone **37** to dimethyl maleate, analogously to **1**, afforded a mixture of three adducts in a 4.5:1:1 ratio, from which the major *exo-anti* isoxazolidine **36** was isolated in 56% yield, thus establishing the correct *trans-trans* relative stereochemistry as required for (−)-hastanecine. Reductive ring-opening/lactamization to the key intermediate **35** was achieved by the use of $Mo(CO)_6$, completing the formal synthesis of (−)-hastanecine in **12** steps and 8.7% overall

yield from L-malic acid.[4][18g] The optical rotation of the synthesized compound confirmed its complete enantiomeric integrity.[17,18]

Conclusion

A cycloaddition-based strategy to the straightforward synthesis of highly functionalized enantiomerically pure pyrrolizidines has been described and applied to a formal synthesis of the necine base (−)-hastanecine and the total synthesis of 7-*epi*-croalbinecine and of (−)-croalbinecine. The strategy appears to warrant broad application to the synthesis of stereochemically differentiated natural necine bases and their analogues, and provides a good prediction of the stereochemical outcome. Further work to widen the scope of this process is currently underway.

Experimental Section

General Remarks: All operations were carried out under inert gas and with anhydrous solvents where required. R_f values refer to TLC on 0.25-mm silica gel plates (Merck F_{254}) with the same eluent used for separation of the compound by flash column chromatography. − Melting points (m.p.) are uncorrected. − Optical rotation measurements were carried out with a Jasco DIP-370 polarimeter. − ^{1}H and ^{13}C NMR spectra (in $CDCl_3$ solution, unless otherwise stated) were recorded at 200 MHz and 50.3 MHz, respectively, with a Varian Gemini spectrometer or at 500 MHz (^{1}H) with a Bruker DRX 500 spectrometer; the chemical shifts for ^{1}H and ^{13}C NMR spectra are given in ppm from TMS. − IR spectra were recorded with a Perkin−Elmer 881 spectrophotometer. − Mass spectra (EI, 70 eV) were recorded with a QMD 1000 Carlo Erba instrument by GC or direct inlet. − Elemental analyses were carried out with a Perkin−Elmer 240 C or with a Perkin−Elmer 2400 instrument.

Syntheses of Nitrones: Nitrones **1**,[5a] **2**,[5b] and **3**[5c] were synthesized as reported in the literature.

***cis*-1-Hydroxy-3,4-isopropylidenedioxypyrrolidine (8):** A solution of the dimesylate **7**[6] (5.0 g, 15.7 mmol) and NH_2OHHCl (4.36 g, 62.8 mmol) in triethylamine (52 mL) was heated at reflux for 3.5 h. After evaporation of the solvent under reduced pressure, the residue was washed with ether (4−5 times). Removal of the ether from the extract afforded analytically pure **8** (2.5 g, 15.7 mmol, 100%) as a colorless solid. − M.p. 155−156 °C. − ^{1}H NMR: δ = 6.90 (br. s, 1 H, OH), 4.68 (m, 2 H, 3-H, 4-H), 3.44 (d, *J* = 11.4 Hz, 2 H, 2-H, 5-H), 2.68 (br. d, *J* = 11.4 Hz, 2 H, 2-H, 5-H), 1.44 (s, 3 H, Me), 1.27 (s, 3 H, Me). − ^{13}C NMR: δ = 110.2 (s, O*C*Me$_2$O), 76.6 (d, 2 C, C-3, C-4), 62.6 (t, 2 C, C-2, C-5), 25.8 (q, Me), 23.7 (q, Me). − IR ($CDCl_3$): $\tilde{\nu}$ = 3580 (O-H), 3209, 3107, 1206 (C−O−C) cm^{-1}. − MS; *m*/*z* (%): 159 (25) [M]$^+$, 144 (51), 101 (35), 84 (100), 59 (85). − $C_7H_{13}NO_3$ (159.2): calcd. C 52.82, H 8.23, N 8.80; found C 52.63, H 8.34, N 8.45.

(±)-3,4-Isopropylidenedioxypyrroline 1-Oxide (4): Yellow HgO (4.76 g, 22 mmol) was added portionwise to an ice-cooled solution of the hydroxypyrrolidine **8** (1.76 g, 11 mmol) in CH_2Cl_2 (22 mL) and the mixture was stirred for 2 h at room temp. Filtration through Celite, evaporation of the solvent and purification on silica gel (eluent dichloromethane/methanol, 10:1) afforded pure nitrone (±)-**4**[6] (1.52 g, 9.68 mmol, 88%) as a colorless solid. − R_f = 0.15. − M.p. 101−102 °C (diisopropyl ether). − ^{1}H NMR: δ = 6.84 (q, *J* = 1.5 Hz, 1 H, 2-H), 5.26 (d, *J* = 6.2 Hz, 1 H, 3-H), 4.87 (ddd, *J* = 6.2, 5.1, 1.5 Hz, 1 H, 4-H), 4.11 (ddd, *J* = 15.0, 5.1, 2.0 Hz, 1 H, 5-H), 3.98 (dq, *J* = 15.0, 1.5 Hz, 1 H, 5-H), 1.41 (s, 3 H, Me), 1.33 (s, 3 H, Me). − ^{13}C NMR: δ = 132.6 (d, C-2), 112.1 (s, O*C*-Me$_2$O), 79.8 (d, C-3), 73.6 (d, C-4), 67.9 (t, C-5), 27.1 (q, Me), 25.6 (q, Me). − IR ($CDCl_3$): $\tilde{\nu}$ = 3103, 1580 cm^{-1}. − MS; *m*/*z* (%): 157 (15) [M]$^+$, 142 (38), 82 (100). − $C_7H_{11}NO_3$ (157.2): calcd. C 53.49, H 7.05, N 8.91; found C 53.38, H 7.19, N 8.68.

Diethyl (2*S*)-Triisopropylsilyloxymalate (15): TIPSCl (3.64 g, 18.88 mmol) was added portionwise at 0 °C to a solution of L-diethyl malate (**14**) (3.0 g, 15.77 mmol) and imidazole (1.12 g, 16.45 mmol) in dry DMF (20 mL) and the mixture was stirred at room temp. for 24 h. The resulting reaction mixture was added to H_2O and extracted with diethyl ether. The organic layer was dried with Na_2SO_4 and concentrated. The crude product was purified on silica gel (eluent petroleum ether/ethyl acetate, 12:1) to give **15** (4.54 g, 13.09 mmol, 83%) as a colorless oil. − R_f = 0.42. − $[\alpha]_D^{29}$ = −28.7 (*c* = 1.01, $CHCl_3$). − ^{1}H NMR: δ = 4.73 (t, *J* = 6.1 Hz, 1 H, 2-H), 4.21 (q, *J* = 7.0 Hz, 2 H, OCH_2), 4.14 (q, *J* = 7.0 Hz, 2 H, OCH_2), 2.82−2.74 (m, 2 H, 3-H$_2$), 1.29 (t, *J* = 7.0 Hz, 3 H, OCH_2CH_3), 1.26 (t, *J* = 7.0 Hz, 3 H, OCH_2CH_3), 1.20−1.00 (m, 21 H, Si*i*Pr$_3$). − ^{13}C NMR: δ = 172.4 (s, C=O), 170.3 (s, C=O), 69.4 (d, C-2), 61.0 (t, OCH_2), 60.7 (t, OCH_2), 40.8 (t, C-3), 17.8 [q, 6 C, Si(CH*Me*$_2$)$_3$], 14.0 (q, 2 C, OCH_2CH_3), 12.2 [d, 3 C, Si(*C*HMe$_2$)$_3$]. − IR ($CHCl_3$): $\tilde{\nu}$ = 1731 (C=O), 1167 cm^{-1}. − MS; *m*/*z* (%): 347 (2) [M]$^+$, 304 (100), 273 (24), 229 (44), 157 (56), 145 (80), 131 (77), 117 (60), 103 (53), 75 (76), 59 (95). − $C_{17}H_{34}O_5Si$ (346.5): calcd. C 58.92, H 9.89; found C 59.20, H 10.21.

(2*S*)-2-Triisopropylsilyloxy-1,4-butanediol (16): A solution of DIBAL-H in CH_2Cl_2 (1 M, 18 mL) was added dropwise to a cooled (−50 °C) solution of **15** (1.04 g, 3.0 mmol) in dry CH_2Cl_2 (15 mL). The mixture was stirred at −20 °C for 3 h, then allowed to warm to room temp. MeOH was added, followed by sodium tartrate. The resulting suspension was filtered through Celite and then extracted several times with CH_2Cl_2. The organic layer was dried with Na_2SO_4 and concentrated. The crude mixture was purified on silica gel (eluent petroleum ether/ethyl acetate, 1:2) to give **16** (0.654 g, 2.49 mmol, 83%) as a colorless solid. − R_f = 0.48. − M.p. 39−41 °C. − $[\alpha]_D^{24}$ = +7.7 (*c* = 0.35, $CHCl_3$). − ^{1}H NMR: δ = 4.10 (m, 1 H, 2-H), 3.90−3.58 (m, 4 H, 1-H$_2$, 4-H$_2$), 2.50 (br, 2 H, OH), 1.95−1.84 (m, 2 H, 3-H$_2$), 1.20−1.00 (m, 21 H, Si*i*Pr$_3$). − ^{13}C NMR: δ = 70.7 (d, C-2), 65.9 (t, C-1), 58.6 (t, C-4), 37.2 (t, C-3), 18.6 (q, 6 C, Si(CH*Me*$_2$)$_3$), 12.3 (d, 3 C, Si(*C*HMe$_2$)$_3$). − IR ($CHCl_3$): $\tilde{\nu}$ = 3692, 3616, 3448, 1463, 1090 cm^{-1}. − MS; *m*/*z* (%): 231 (2) [M − CH_2OH]$^+$, 201 (9), 173 (13), 103 (33), 83 (38), 71 (100). − $C_{13}H_{30}O_3Si$ (262.5): calcd. C 59.49, H 11.52; found C 59.63, H 11.81.

(2*S*)-2-Triisopropylsilyloxy-1,4-bis(methansulfonyloxy)butane (17): MsCl (0.5 mL, 6.48 mmol) was added dropwise to an ice-cooled solution of **16** (0.39 g, 1.49 mmol) and TEA (1.25 mL, 8.94 mmol) in dry CH_2Cl_2 (2 mL) under nitrogen. The solution was stirred at room temp. for 30 min; ice was then added, and the organic phase was washed with an acetate buffer solution and with saturated Na_2CO_3. The organic phase was dried with Na_2SO_4 and concentrated to give a crude product, which was purified on silica gel (eluent petroleum ether/ethyl acetate, 2:1) to give **17** (0.586 g, 1.4 mmol, 94%) as a yellow oil. − R_f = 0.31. − $[\alpha]_D^{29}$ = −6.4 (*c* = 0.80, $CHCl_3$). − ^{1}H NMR: δ = 4.47−4.05 (m, 5 H, 1-H, 2-H$_2$, 4-H$_2$), 3.01 (s, 3 H, SO_2CH_3), 2.99 (s, 3 H, SO_2CH_3), 2.12−1.95 (q, *J* = 5.9 Hz, 2 H, 3-H$_2$), 1.11−0.97 (m, 21 H, Si*i*Pr$_3$). − ^{13}C NMR: δ = 71.2 (t, C-1), 67.1 (d, C-2), 65.5 (t, C-4), 37.4 (q, 2 C, 2 × SO_2CH_3), 33.6 (t, C-3), 17.9 [q, 6 C, Si(CH*Me*$_2$)$_3$], 12.3 [d, 3 C,

Si(*C*HMe$_2$)$_3$]. − IR ($CHCl_3$): $\tilde{\nu}$ = 3013, 1463, 1360, 1170, 1137 cm^{-1}. − MS; *m*/*z* (%): 375 (0.3) [M − *i*Pr]$^+$, 209 (100), 71 (51). − $C_{15}H_{34}O_7S_2Si$ (418.6): calcd. C 43.04, H 8.19; found C 42.75, H 8.13.

(3*S*)-3-Triisopropylsilyloxy-1-pyrroline 1-Oxide (18) and (4*S*)-4-Triisopropylsilyloxy-1-pyrroline 1-Oxide (19): A suspension of **17** (208 mg, 0.5 mmol) and hydroxylamine hydrochloride (160 mg, 2.29 mmol) in dry TEA (5.5 mL) was heated at reflux for 2.5 h under nitrogen. TEA was then evaporated, and the solid residue was washed repeatedly with diethyl ether. The ethereal extracts were concentrated to give the crude cyclic hydroxylamine, which showed low stability and was used immediately for the subsequent oxidation step. Yellow HgO (218 mg, 1.0 mmol) was added to the cooled solution (0 °C) of the *N*-hydroxypyrrolidine in dry CH_2Cl_2 (5 mL). The mixture was allowed to stir vigorously at room temp. for 2 h and was then filtered through Celite. Concentration and purification afforded a 11:1 mixture (by integration of the ^{1}H NMR spectrum of the crude product) of regioisomeric nitrones **18** and **19**. Purification on silica gel (eluent methanol/ethyl acetate, 1:10) afforded pure nitrones **18** (64 mg, 0.25 mmol, 50%) and **19** (5 mg, 0.02 mmol, 4%) as oily compounds.

18: R_f = 0.41. − $[\alpha]_D^{20}$ = −35.2 (*c* = 0.31, CH_2Cl_2). − ^{1}H NMR: δ = 6.90 (q, *J* = 1.8 Hz, 1 H, 2-H), 5.10 (d, *J* = 5.3 Hz, 1 H, 3-H), 4.22−4.05 (m, 1 H, 5-H), 3.90−3.75 (m, 1 H, 5-H), 2.70−2.45 (m, 1 H, 4-H), 2.20−2.00 (m, 1 H, 4-H), 1.20−0.90 (m, 21 H, Si*i*Pr$_3$). − ^{13}C NMR: δ = 136.0 (d, C-2), 72.3 (d, C-3), 61.2 (t, C-5), 31.2 (t, C-4), 17.8 [q, 6 C, Si(CH*Me$_2$*)$_3$], 11.9 [d, 3 C, Si(*C*HMe$_2$)$_3$]. − IR ($CDCl_3$): $\tilde{\nu}$ = 2950, 1584, 1461, 1187 cm^{-1}. − MS; *m*/*z* (%): 257 (8) [M]$^+$, 213 (34), 103 (61), 77 (100), 75 (48). − $C_{13}H_{27}NO_2Si$ (257.4): calcd. C 60.65, H 10.57, N 5.44; found C 60.35, H 10.39, N 5.32.

19: R_f = 0.13. − $[\alpha]_D^{23}$ = +5.4 (*c* = 0.86, $CHCl_3$). − ^{1}H NMR: δ = 6.91 (br. s, 1 H, 2-H), 4.75−4.67 (m, 1 H, 4-H), 4.12 (ddd, *J* = 14.3, 6.2, 1.5 Hz, 1 H, 5-H), 3.83 (d, *J* = 14.3 Hz, 1 H, 5-H), 3.08 (dd, *J* = 19.0, 5.5 Hz, 1 H, 3-H), 2.65 (d, *J* = 19.0 Hz, 1 H, 3-H), 1.22−0.88 (m, 21 H, Si*i*Pr$_3$). − ^{13}C NMR: δ = 133.8 (d, C-2), 70.7 (t, C-5), 66.5 (d, C-4), 40.2 (t, C-3), 17.7 [q, 6 C, Si(CH*Me$_2$*)$_3$], 11.8 [d, 3 C, Si(*C*HMe$_2$)$_3$]. − IR ($CDCl_3$): $\tilde{\nu}$ = 2948, 1595, 1461, 1156 cm^{-1}. − MS; *m*/*z* (%): 257 (7) [M]$^+$, 213 (29), 129 (29), 103 (44), 101 (76), 77 (100), 75 (48). − $C_{13}H_{27}NO_2Si$ (257.4): calcd. C 60.65, H 10.57, N 5.44; found C 60.35, H 10.64, N 5.61.

(2*R*)-2-Benzoyloxy-1,4-bis(methanesulfonyloxy)butane (39): To a solution of dimesylate **38**[5b] (2.0 g, 7.62 mmol) in dry THF (50 mL) were added PPh_3 (6.02 g, 22.87 mmol) and benzoic acid (2.79 g, 22.87 mmol), then DEAD (3.6 mL, 22.87 mmol) dropwise at 0 °C. The mixture was stirred for 2 h at room temp., then concentrated, diluted with CH_2Cl_2, washed with 1 M NaOH and 1 M HCl and dried with Na_2SO_4. Purification of the crude mixture by flash column chromatography (eluent CH_2Cl_2/MeOH, 25:1) afforded **39** (2.37 g, 6.47 mmol, 85%) as a solid product, whose spectral data are identical with those reported for its enantiomer.[5b] − R_f = 0.43. − M.p. 68−69 °C (diisopropyl ether). − $[\alpha]_D^{21}$ = +31.1 (*c* = 0.98, $CHCl_3$). − $C_{13}H_{18}O_8S_2$ (366.4): calcd. C 42.62, H 4.95; found C 42.68, H 5.07.

(3*R*)-3-Benzoyloxy-1-pyrroline 1-Oxide (37): A suspension of **39** (2.30 g, 6.28 mmol) and hydroxylamine hydrochloride (1.73 g, 25.0 mmol) in triethylamine (48 mL) was heated at reflux for 2 h. Triethylamine was distilled and the resulting solid mass was washed thoroughly 5 times with diethyl ether. The ethereal extracts were then concentrated to give the crude hydroxylamine (1.93 g), which was directly oxidized without purification. Dichloromethane (44 mL) was added to the crude hydroxylamine. The solution was cooled in ice, then yellow HgO (1.93 g, 23.2 mmol) was added and the suspension was stirred at room temp. for 4 h. The reaction mixture was filtered through Celite and concentrated. Purification of the crude mixture on silica gel (eluent AcOEt/MeOH, 20:1) afforded **37** (829 mg, 4.04 mmol, 64%) as a solid product, whose spectral data are identical with those reported for its enantiomer.[5b] − R_f = 0.22. − M.p. 102−103 °C (diisopropyl ether). − $[\alpha]_D^{21}$ = +148.8 (*c* = 1.10, $CHCl_3$). − $C_{11}H_{11}NO_3$ (205.2): calcd. C 64.38, H 5.40, N 6.83; found C 64.00, H 5.51, N 6.75.

Synthesis of Diisopropyl Maleate (20): A solution of maleic anhydride (1.06 g, 10.8 mmol) in isopropyl alcohol (3.3 mL) was heated at reflux for 1.5 h. Evaporation of the solvent afforded the monoisopropyl ester (1.7 g, 10.8 mmol, 100%), sufficiently pure to be used for the next step. 4-(Dimethylamino)pyridine (132 mg, 1.08 mmol) and isopropyl alcohol (942 μL, 12.3 mmol) in dry CH_2Cl_2 (38 mL) were added to an ice-cooled solution of the monoester. DCC (2.45 g, 11.87 mmol) was then added under nitrogen. The mixture was stirred for 1 h at room temp., then filtered through Celite. Purification of the crude on silica gel (eluent petroleum ether/ethyl acetate, 20:1) afforded the diester **20** (1.39 g, 6.94 mmol, 64%) as an oil. − R_f = 0.20. − ^{1}H NMR: δ = 6.16 (s, 2 H, CH=CH), 5.11 (sept, *J* = 6.3 Hz, 2 H, 2 × C*H*Me$_2$), 1.27 (d, *J* = 6.3 Hz, 12 H, 2 × CH*Me$_2$*). − ^{13}C NMR: δ = 164.7 (s, 2 C, 2 × C=O), 129.8 (d, 2 C, C=C), 68.7 (d, 2 C, 2 × *C*HMe$_2$), 21.5 (q, 4 C, 2 × CH*Me$_2$*). − IR ($CDCl_3$): $\tilde{\nu}$ = 2985, 2941, 2878, 1728, 1638 cm^{-1}.

Cycloadditions of Nitrones to Maleic Acid Esters

Cycloaddition of Nitrone 1 to Dimethyl Maleate (9): A solution of nitrone **1** (1.00 g, 6.37 mmol) and dimethyl maleate (955 mg, 7.64 mmol) in benzene (20 mL) was allowed to react at room temp. for 3 d. Concentration of the reaction mixture gave the crude cycloadducts **10a**, **10b** and **10c** in a 5:1:1 ratio calculated by ^{1}H NMR integration. Purification by flash chromatography (eluent petroleum ether/ethyl acetate, 2:1) afforded a mixture of the adducts **10a** and **10b** (R_f = 0.18, 1.384 g, 4.60 mmol, 72%); successive elution with methanol gave pure **10c** (330 mg, 1.10 mmol, 17%) as a solid. Recrystallization of the mixture of cycloadducts **10a** and **10b** from heptane afforded the major adduct **10a** (957 mg, 50%) as an analytically pure colorless solid.

(2*R*,3*S*,3a*R*,4*S*)-4-*tert*-Butoxy-2,3-bis(methoxycarbonyl)hexahydropyrrolo[1,2-*b*]isoxazole (10a): M.p. 76−77 °C (heptane). − $[\alpha]_D^{25}$ = −88.4 (*c* = 0.95, $CHCl_3$). − ^{1}H NMR: δ = 4.81 (d, *J* = 7.3 Hz, 1 H, 2-H), 4.09 (m, 1 H, 3a-H), 4.01 (m, 1 H, 4-H), 3.80 (s, 3 H, COOMe), 3.75 (s, 3 H, COOMe), 3.42 (m, 1 H, 6-H), 3.39 (m, 1 H, 6-H), 3.35 (dd, *J* = 7.3, 6.6 Hz, 1 H, 3-H), 2.15 (dddd, *J* = 13.0, 10.9, 7.2, 5.6 Hz, 1 H, 5-H), 1.73 (m, 1 H, 5-H), 1.20 (s, 9 H, *t*Bu). − ^{13}C NMR: δ = 170.2 (s, C=O), 170.0 (s, C=O), 77.5, 77.4, 75.7 (d, 3 C, C-2, C-4, C-3a), 74.5 (s, *C*Me$_3$), 56.3 (t, C-6), 55.8 (d, C-3), 53.1 (q, COO*Me*), 52.8 (q, COO*Me*), 33.1 (t, C-5), 28.8 (q, 3 C, C*Me$_3$*). − IR ($CDCl_3$): $\tilde{\nu}$ = 1751 (C=O), 1189 (C−O−C) cm^{-1}. − MS; *m*/*z* (%): 301 (1) [M]$^+$, 244 (5), 84 (40), 57 (100). − $C_{14}H_{23}NO_6$ (301.3): calcd. C 55.80, H 7.69, N 4.65; found C 55.79, H 7.80, N 5.00.

(2*S*,3*R*,3a*R*,4*S*)-4-*tert*-Butoxy-2,3-bis(methoxycarbonyl)hexahydropyrrolo[1,2-*b*]isoxazole (10b): ^{1}H NMR: δ = 4.61 (d, *J* = 7.7 Hz, 1 H, 2-H), 4.06−3.94 (m, 2 H, 4-H, 3-H), 3.85 (dd, *J* = 9.1, 2.9 Hz, 1 H, 3a-H), 3.75 (s, 3 H, COOMe), 3.72 (s, 3 H, COOMe), 3.55 (ddd, *J* = 13.9, 7.3, 2.0 Hz, 1 H, 6-H), 3.20 (ddd, *J* = 13.9, 11.1, 6.8 Hz, 1 H, 6-H), 2.31 (ddt, *J* = 13.6, 11.1, 7.0 Hz, 1 H, 5-H), 1.68 (m, 1 H, 5-H), 1.06 (s, 9 H, *t*Bu). − ^{13}C NMR: δ = 169.6 (s, C=O), 169.0 (s, C=O), 77.6, 77.1 (d, 2 C, C-2, C-4), 74.4 (s, *C*Me$_3$),

74.3 (d, C-3a), 55.2 (t, C-6), 53.3 (d, C-3), 52.7 (q, COO*Me*), 52.4 (q, COO*Me*), 34.5 (t, C-5), 28.9 (q, 3 C, C*Me*$_3$).

(2*S*,3*R*,3a*S*,4*S*)-4-*tert*-Butoxy-2,3-bis(methoxycarbonyl)hexahydropyrrolo[1,2-*b*]isoxazole (10c): M.p. 60−62 °C. − $[\alpha]_D^{22}$ = +72.9 (*c* = 0.44, $CHCl_3$). − ^{1}H NMR: δ = 4.82 (d, *J* = 7.7 Hz, 1 H, 2-H), 4.20 (q, *J* = 6.7 Hz, 1 H, 4-H), 4.09 (dd, *J* = 7.1, 5.3 Hz, 1 H, 3a-H), 3.96 (dd, *J* = 7.7, 5.3 Hz, 1 H, 3-H), 3.76 (s, 3 H, COOMe), 3.71 (s, 3 H, COOMe), 3.30 (dt, *J* = 12.9, 6.4 Hz, 1 H, 6-H), 3.10 (ddd, *J* = 12.9, 8.7, 6.7 Hz, 1 H, 6-H), 1.90 (m, 2 H, 5-H), 1.17 (s, 9 H, *t*Bu). − ^{13}C NMR: δ = 172.4 (s, C=O), 170.2 (s, C=O), 77.8 (d, C-2), 74.2 (s, *C*Me$_3$), 70.8, 69.5 (d, 2 C, C-4, C-3a), 53.7 (d, C-3), 52.4 (q, COO*Me*), 52.2 (q, COO*Me*), 51.1 (t, C-6), 32.6 (t, C-5), 28.1 (q, 3 C, C*Me*$_3$). − IR ($CDCl_3$): ṽ = 1752 (C=O), 1195 (C−O−C) cm^{-1}. − MS; *m*/*z* (%): 301 (1) [M]$^+$, 244 (6), 213 (22), 181 (48), 57 (100). − $C_{14}H_{23}NO_6$ (301.3): calcd. C 55.80, H 7.69, N 4.65; found C 56.00, H 7.84, N 4.63.

Cycloaddition of Nitrone 2 to Dimethyl Maleate (9): A solution of nitrone **2** (151 mg, 0.54 mmol) and dimethyl maleate (93 mg, 0.65 mmol) in benzene (2 mL) was allowed to react at 40 °C for 3 d. Concentration of the reaction mixture gave the crude cycloadducts **11a** and **11b** in a 4:1 ratio calculated by ^{1}H NMR integration. Purification by flash chromatography (eluent petroleum ether/ethyl acetate, 1:1) afforded a mixture of the inseparable adducts **11a** and **11b** (R_f = 0.35, 145 mg, 0.34 mmol, 63%).

(2*R*,3*S*,3a*R*,4*S*)-4-Dibenzylamino-2,3-bis(methoxycarbonyl)hexahydropyrrolo[1,2-*b*]isoxazole (11a): ^{1}H NMR: δ = 7.31−7.15 (m, 10 H, 2 × Ph), 4.68 (d, *J* = 8.3 Hz, 1 H, 2-H), 4.03 (t, *J* = 5.5 Hz, 1 H, 3a-H), 3.70 (s, 3 H, COOMe), 3.69 (s, 3 H, COOMe), 3.59 (AB system, *J* = 14.0 Hz, 4 H, N(C*H*$_2$Ph)$_2$), 3.37−3.32 (m, 1 H, 6-H), 3.31−3.25 (m, 2 H, 3-H, 4-H), 2.97 (dt, *J* = 11.8, 8.1 Hz, 1 H, 6-H), 2.04 (ddt, *J* = 13.4, 8.0, 4.8 Hz, 1 H, 5-H), 1.89 (dq, *J* = 13.4, 7.8 Hz, 1 H, 5-H). − ^{13}C NMR: δ = 169.9 (s, C=O), 169.6 (s, C=O), 139.5 (s, 2 C, Ph), 128.4 (d, 4 C, Ph), 128. 3 (d, 4 C, Ph), 127. 0 (d, 2 C, Ph), 77.4 (d, C-2), 68.8 (d, C-3a), 64.0 (d, C-4), 55.8 (t, C-6), 55.3 (d, C-3), 54.7 (t, 2 C, N(*C*H$_2$Ph)$_2$), 52.5 (q, COO*Me*), 52.4 (q, COO*Me*), 25.4 (t, C-5). − IR (of the mixture, $CDCl_3$): ṽ = 1736 (C=O), 1708 (C=O), 1231 (C−O−C) cm^{-1}. − MS (of the mixture); *m*/*z* (%): 365 (9) [M$^+$ − COOMe], 236 (12), 91 (100).

(2*S*,3*R*,3a*R*,4*S*)-4-Dibenzylamino-2,3-bis(methoxycarbonyl)hexahydropyrrolo[1,2-*b*]isoxazole (11b): ^{1}H NMR: δ = 7.31−7.15 (m, 10 H, 2 × Ph), 4.66 (d, *J* = 8.5 Hz, 1 H, 2-H), 3.92 (t, *J* = 5.5 Hz, 1 H, 3-H), 3.85 (m, 1 H, 3a-H), 3.68 (s, 6 H, 2 × COOMe), 3.62−3.54 (m, 1 H, 4-H), 3.51 (AB system, *J* = 14.3 Hz, 4 H, N(C*H*$_2$Ph)$_2$), 3.47−3.41 (m, 1 H, 6-H), 3.15 (m, 1 H, 6-H), 1.97 (m, 1 H, 5-H), 1.74 (m, 1 H, 5-H). − ^{13}C NMR: δ = 171.0 (s, C=O), 169.9 (s, C=O), 138.9 (s, 2 C, Ph), 128.8 (d, 4 C, Ph), 128. 2 (d, 4 C, Ph), 127. 1 (d, 2 C, Ph), 78.2 (d, C-2), 71.2 (d, C-3a), 61.9 (d, C-4), 55.1 (t, C-6), 54.3 [t, 2 C, N(*C*H$_2$Ph)$_2$] 53.5 (d, C-3), 52.4 (q, COO*Me*), 52.0 (q, COO*Me*), 24.7 (t, *C-5*).

Cycloaddition of Nitrone 3 to Dimethyl Maleate (9): Dimethyl maleate (**9**, 60 μL, 0.48 mmol) in benzene (1 mL) was added to a solution of nitrone **3** (92 mg, 0.40 mmol) in benzene (1.2 mL). The mixture was stirred at room temp. until no more nitrone was detected by TLC (3 d). The crude mixture was then concentrated to give a 13:1:1.4 mixture (by 500 MHz ^{1}H NMR integration) of cycloadducts **12a**, **12b** and **12c**. Purification by column chromatography (eluent petroleum ether/ethyl acetate, 2.5:1) afforded pure **12a** (R_f = 0.22, 115 mg, 0.31 mmol, 77%) as a solid and a fraction containing **12b** and **12c** (R_f = 0.19, 25 mg, 0.07 mmol, 17%). Samples of pure **12c** (R_f = 0.35, 6.5 mg) and **12b** (R_f = 0.30, 2.1 mg) for characterization purposes were obtained by further separation on column chromatography, eluent chloroform/diethyl ether, 6:1.

(2*R*,3*S*,3a*R*,4*R*,5*R*)-4,5-Bis-*tert*-butoxy-2,3-bis(methoxycarbonyl)-hexahydropyrrolo[1,2-*b*]isoxazole (12a): M.p. 106−107 °C. − $[\alpha]_D^{24}$ = −89.6 (*c* = 0.56, $CHCl_3$). − ^{1}H NMR: δ = 4.93 (d, *J* = 7.4 Hz, 1 H, 2-H), 3.97−3.81 (m, 4 H, 3-H, 3a-H, 4-H, 5-H), 3.76 (s, 3 H, COOMe), 3.72 (s, 3 H, COOMe), 3.57 (dd, *J* = 13.5, 4.7 Hz, 1 H, 6-H), 3.09 (dd, *J* = 13.5, 3.1 Hz, 1 H, 6-H), 1.19 (s, 9 H, *t*Bu), 1.17 (s, 9 H, *t*Bu). − ^{13}C NMR: δ = 170.1 (s, C=O), 169.5 (s, C=O), 80.9, 77.9, 77.4 (d, 3 C, C-5, C-2, C-4), 74.3 (s, 2 C, 2 × *C*Me$_3$), 74.0 (d, C-3a), 62.9 (t, C-6), 54.2 (d, C-3), 52.2 (q, COO*Me*), 52.1 (q, COO*Me*), 28.2 (q, 6 C, 2 × C*Me*$_3$). − IR ($CDCl_3$): ṽ = 1746 (C=O), 1190 (C−O−C) cm^{-1}. − MS; *m*/*z* (%): 373 (2) [M]$^+$, 316 (2), 229 (25), 197 (24), 85 (43), 83 (64), 57 (100). − $C_{18}H_{31}NO_7$ (373.4): calcd. C 57.89, H 8.37, N 3.75; found C 57.88, H 8.53, N 4.00.

(2*S*,3*R*,3a*R*,4*R*,5*R*)-4,5-Bis-*tert*-butoxy-2,3-bis(methoxycarbonyl)-hexahydropyrrolo[1,2-*b*]isoxazole (12b): ^{1}H NMR: δ = 4.79−4.76 (m, 1 H, 2-H), 4.01−3.72 (m, 4 H, 3-H, 3a-H, 4-H, 5-H), 3.77 (s, 6 H, 2 × COOMe), 3.48 (dd, *J* = 9.5, 6.2 Hz, 1 H, 6-H), 3.24 (t, *J* = 9.5 Hz, 1 H, 6-H), 1.17 (s, 9 H, *t*Bu), 1.14 (s, 9 H, *t*Bu). − ^{13}C NMR: δ = 170.4 (s, C=O), 168.9 (s, C=O), 79.9, 77.6, 76.8 (d, 3 C, C-5, C-2, C-4), 74.2 (s, *C*Me$_3$), 73.6 (s, *C*Me$_3$), 73.2 (d, C-3a), 59.9 (t, C-6), 52.6 (d, C-3), 52.5 (q, COO*Me*), 52.1 (q, COO*Me*), 28.6 (q, 3 C, C*Me*$_3$), 28.5 (q, 3 C, C*Me*$_3$). − IR ($CDCl_3$): ṽ = 1739 (C=O), 1195 (C−O−C) cm^{-1}. − MS; *m*/*z* (%): 373 (3) [M]$^+$, 260 (3), 114 (21), 86 (63), 84 (100), 57 (99).

(2*S*,3*R*,3a*S*,4*R*,5*R*)-4,5-Bis-*tert*-butoxy-2,3-bis(methoxycarbonyl)-hexahydropyrrolo[1,2-*b*]isoxazole (12c): ^{1}H NMR: δ = 4.81 (d, *J* = 7.7 Hz, 1 H, 2-H), 4.18 (dd, *J* = 7.2, 5.3 Hz, 1 H, 4-H), 4.08−3.96 (m, 3 H, 3-H, 3a-H, 5-H), 3.76 (s, 3 H, COOMe), 3.72 (s, 3 H, COOMe), 3.41 (dd, *J* = 13.9, 5.5 Hz, 1 H, 6-H), 2.92 (dd, *J* = 13.9, 8.4 Hz, 1 H, 6-H), 1.18 (s, 9 H, *t*Bu), 1.17 (s, 9 H, *t*Bu). − ^{13}C NMR: δ = 170.1 (s, C=O), 169.7 (s, C=O), 77.6, 76.5, 75.3 (d, 3 C, C-5, C-2, C-4), 74.6 (s, *C*Me$_3$), 73.8 (s, *C*Me$_3$), 67.1 (d, C-3a), 59.5 (t, C-6), 52.5 (q, COO*Me*), 52.3 (q, COO*Me*), 51.8 (d, C-3), 28.5 (q, 6 C, 2 × C*Me*$_3$). − IR ($CDCl_3$): ṽ = 1741 (C=O), 1188 (C−O−C) cm^{-1}. − MS; *m*/*z* (%): 373 (8) [M]$^+$, 316 (7), 258 (12), 114 (55), 57 (100).

Cycloaddition of Nitrone 4 to Dimethyl Maleate (9): Dimethyl maleate (**9**, 250 μL, 2 mmol) was added to a solution of the racemic nitrone **4** (157 mg, 1 mmol) in benzene (2 mL). The mixture was stirred at room temp. for 1 d. The crude mixture was then concentrated to give a 1.6:1 mixture (by ^{1}H NMR integration) of cycloadducts **13a** and **13b**. Purification by column chromatography (eluent petroleum ether/ethyl acetate, 1:1) afforded the pure adducts **13b** (R_f = 0.45, 100 mg, 0.33 mmol, 33%) as a colorless oil and **13a** (R_f = 0.33, 156 mg, 0.52 mmol, 52%) as a colorless solid.

(2*R,3*S**,3a*R**,4*R**,5*S**)-4,5-Isopropylidenedioxy-2,3-bis(methoxycarbonyl)hexahydropyrrolo[1,2-*b*]isoxazole (13a):** M.p. 107−108 °C (diisopropyl ether). − ^{1}H NMR: δ = 4.93 (dt, *J* = 3.4, 6.0 Hz, 1 H, 5-H), 4.86 (d, *J* = 8.8 Hz, 1 H, 2-H), 4.66 (dd, *J* = 6.4, 1.8 Hz, 1 H, 4-H), 4.17 (dd, *J* = 7.1, 1.8 Hz, 1 H, 3a-H), 3.76 (s, 3 H, COOMe), 3.75 (s, 3 H, COOMe), 3.53 (dd, *J* = 8.8, 7.1 Hz, 1 H, 3-H), 3.47 (dd, *J* = 13.5, 3.4 Hz, 1 H, 6-H), 3.30 (dd, *J* = 13.5, 5.5 Hz, 1 H, 6-H), 1.50 (s, 3 H, Me), 1.31 (s, 3 H, Me). − ^{13}C NMR: δ = 169.2 (s, C=O), 169.1 (s, C=O), 112.8 (s, O*C*Me$_2$O), 83.1, 79.8, 77.5 (d, 3 C, C-5, C-2, C-4), 73.3 (d, C-3a), 61.2 (t, C-6), 53.6 (d, C-3), 52.5 (q, COO*Me*), 52.4 (q, COO*Me*), 26.6 (q, Me), 24.9 (q, Me). − IR ($CHCl_3$): ṽ = 1744 (C=O), 1259 (C−O−C) cm^{-1}. − MS; *m*/*z* (%): 301 (6) [M]$^+$, 286 (9), 198 (11),

142 (57), 124 (81), 113 (70), 82 (100), 59 (52). − $C_{13}H_{19}NO_7$ (301.3): calcd. C 51.82, H 6.36, N 4.65; found C 51.95, H 6.41, N 4.60.

(2*S,3*R**,3a*R**,4*R**,5*S**)-4,5-Isopropylidenedioxy-2,3-bis(methoxycarbonyl)hexahydropyrrolo[1,2-*b*]isoxazole (13b):** ^{1}H NMR: δ = 5.07 (q, *J* = 6.2 Hz, 1 H, 5-H), 4.85 (dd, *J* = 6.6, 3.8 Hz, 1 H, 4-H), 4.65 (d, *J* = 9.1 Hz, 1 H, 2-H), 4.09 (dd, *J* = 9.1, 8.1 Hz, 1 H, 3-H), 3.93 (dd, *J* = 8.1, 3.8 Hz, 1 H, 3a-H), 3.82 (dd, *J* = 14.3, 6.2 Hz, 1 H, 6-H), 3.75 (s, 3 H, COOMe), 3.73 (s, 3 H, COOMe), 3.24 (dd, *J* = 14.3, 4.6 Hz, 1 H, 6-H), 1.49 (s, 3 H, Me), 1.31 (s, 3 H, Me). − ^{13}C NMR: δ = 169.5 (s, 2 C, 2 × C=O), 114.0 (s, O*C*Me$_2$O), 82.3, 81.5, 77.0 (d, 3 C, C-5, C-2, C-4), 73.8 (d, C-3a), 61.2 (t, C-6), 53.3 (d, C-3), 52.5 (q, COO*Me*), 52.4 (q, COO*Me*), 27.2 (q, Me), 24.9 (q, Me). − IR ($CHCl_3$): ṽ = 1742 (C=O), 1174 (C−O−C) cm^{-1}. − MS; *m*/*z* (%): 301 (25) [M]$^+$, 286 (7), 198 (26), 142 (29), 82 (100), 59 (89). − $C_{13}H_{19}NO_7$ (301.3): calcd. C 51.82, H 6.36, N 4.65; found C 52.05, H 6.52, N 4.59.

Cycloaddition of Nitrone 1 to Diisopropyl Maleate (20): A solution of diisopropyl maleate (**20**, 96 mg, 0.48 mmol) in benzene (1 mL) was added to a solution of nitrone **1** (62.8 mg, 0.4 mmol) in benzene (0.1 mL). The mixture was stirred at room temp. for 2 d. The crude mixture was then concentrated to give a 5:1:1 mixture (by 500 MHz ^{1}H NMR integration) of cycloadducts **21a**, **21b**, and **21c**. Purification by column chromatography, eluting with mixtures of increasing polarity, afforded the pure adducts **21a** (eluent petroleum ether/ethyl acetate, 5:1; R_f = 0.18, 94 mg, 0.263 mmol, 66%) as a solid, and **21b** (eluent petroleum ether/ethyl acetate, 4:1; R_f = 0.23, 23 mg, 0.064 mmol, 16%) and **21c** (eluent petroleum ether/ethyl acetate, 3:1; R_f = 0.17, 21 mg, 0.059 mmol, 15%) as oily compounds.

(2*R*,3*S*,3a*R*,4*S*)-4-*tert*-Butoxy-2,3-bis(isopropyloxycarbonyl)hexahydropyrrolo[1,2-*b*]isoxazole (21a): M.p. 101−102 °C. − $[\alpha]_D^{24}$ = −83.5 (*c* = 0.39, $CHCl_3$). − ^{1}H NMR: δ = 5.07 (sept, *J* = 6.3 Hz, 1 H, C*H*Me$_2$), 5.06 (sept, *J* = 6.3 Hz, 1 H, C*H*Me$_2$), 4.68 (d, *J* = 7.4 Hz, 1 H, 2-H), 4.01 (d, *J* = 6.4 Hz, 1 H, 3a-H), 3.98−3.96 (m, 1 H, 4-H), 3.35 (ddd, *J* = 13.4, 10.4, 5.8 Hz, 1 H, 6-H), 3.29 (ddd, *J* = 13.4, 7.3, 3.1 Hz, 1 H, 6-H), 3.23 (dd, *J* = 7.4, 6.4 Hz, 1 H, 3-H), 2.10 (dddd, *J* = 12.9, 10.4, 7.3, 5.6 Hz, 1 H, 5-H), 1.67 (dddd, *J* = 12.9, 5.5, 2.9, 2.6 Hz, 1 H, 5-H), 1.29 (d, *J* = 6.3 Hz, 3 H, CH*Me*$_2$), 1.27 (d, *J* = 6.3 Hz, 3 H, CH*Me*$_2$), 1.26 (d, *J* = 6.3 Hz, 3 H, CH*Me*$_2$), 1.24 (d, *J* = 6.3 Hz, 3 H, CH*Me*$_2$), 1.20 (s, 9 H, *t*Bu). − ^{13}C NMR: δ = 168.6 (s, C=O), 168.4 (s, C=O), 77.3, 76.9, 75.2 (d, 3 C, C-2, C-4, C-3a), 73.9 (s, *C*Me$_3$), 69.2 (d, *C*HMe$_2$), 68.8 (d, *C*HMe$_2$), 55.7 (t, C-6), 55.6 (d, C-3), 32.5 (t, C-5), 28.4 (q, 3 C, C*Me*$_3$), 21.7 (q, CH*Me*$_2$), 21.6 (q, CH*Me*$_2$), 21.6 (q, 2 C, CH*Me*$_2$). − IR ($CDCl_3$): ṽ = 1737 (C=O), 1186 (C−O−C) cm^{-1}. − MS; *m*/*z* (%): 357 (2) [M]$^+$, 300 (15), 214 (17), 128 (37), 85 (69), 83 (100). − $C_{18}H_{31}NO_6$ (357.4): calcd. C 60.48, H 8.74, N 3.92; found C 60.56, H 8.92, N 4.05.

(2*S*,3*R*,3a*R*,4*S*)-4-*tert*-Butoxy-2,3-bis(isopropyloxycarbonyl)hexahydropyrrolo[1,2-*b*]isoxazole (21b): $[\alpha]_D^{21}$ = −15.1 (*c* = 0.61, $CHCl_3$). − ^{1}H NMR: δ = 5.07 (sept, *J* = 6.3 Hz, 1 H, C*H*Me$_2$), 5.02 (sept, *J* = 6.3 Hz, 1 H, C*H*Me$_2$), 4.58 (m, A part of an AXY system, 1 H, 2-H), 4.05 (d, *J* = 5.8 Hz, 1 H, 4-H), 4.00−3.80 (m, XY part of an AXY system, 2 H, 3-H, 3a-H), 3.59 (ddd, *J* = 13.5, 7.1, 1.8 Hz, 1 H, 6-H), 3.21 (ddd, *J* = 13.5, 11.5, 6.0 Hz, 1 H, 6-H), 2.36−2.29 (m, 1 H, 5-H), 1.71−1.66 (m, 1 H, 5-H), 1.30 (d, *J* = 6.3 Hz, 3 H, CH*Me*$_2$), 1.29 (d, *J* = 6.3 Hz, 3 H, CH*Me*$_2$), 1.27 (d, *J* = 6.3 Hz, 3 H, CH*Me*$_2$), 1.24 (d, *J* = 6.3 Hz, 3 H, CH*Me*$_2$), 1.17 (s, 9 H, *t*Bu). − ^{13}C NMR: δ = 169.2 (s, C=O), 167.3 (s, C=O), 77.6, 77.2, 73.8 (d, 3 C, C-4, C-2, C-3a), 74.0 (s, *C*Me$_3$), 69.0 (d, *C*HMe$_2$), 68.9 (d, *C*HMe$_2$), 55.0 (t, C-6), 52.9 (d, C-3), 34.0 (t, C-5), 28.4 (q, 3 C, C*Me*$_3$), 21.8 (q, CH*Me*$_2$), 21.7 (q, CH*Me*$_2$), 21.7 (q, CH*Me*$_2$), 21.6 (q, CH*Me*$_2$). − IR ($CDCl_3$): ṽ = 1727 (C=O), 1195 (C−O−C) cm^{-1}. − MS; *m*/*z* (%): 357 (1) [M]$^+$, 300 (6), 85 (63), 83 (100). − $C_{18}H_{31}NO_6$ (357.4): calcd. C 60.48, H 8.74, N 3.92; found C 60.52, H 9.06, N 4.33.

(2*S*,3*R*,3a*S*,4*S*)-4-*tert*-Butoxy-2,3-bis(isopropyloxycarbonyl)hexahydropyrrolo[1,2-*b*]isoxazole (21c): $[\alpha]_D^{21}$ = +28.3 (*c* = 0.87, $CHCl_3$). − ^{1}H NMR: δ = 5.07 (sept, *J* = 6.3 Hz, 1 H, C*H*Me$_2$), 5.02 (sept, *J* = 6.3 Hz, 1 H, C*H*Me$_2$), 4.75 (d, *J* = 7.7 Hz, 1 H, 2-H), 4.20 (q, *J* = 6.7 Hz, 1 H, 4-H), 4.11 (t, *J* = 6.7 Hz, 1 H, 3a-H), 3.87 (dd, *J* = 7.7, 6.6 Hz, 1 H, 3-H), 3.24 (dt, *J* = 12.7, 6.3 Hz, 1 H, 6-H), 3.10 (ddd, *J* = 12.7, 8.4, 6.7 Hz, 1 H, 6-H), 1.90−1.83 (m, 2 H, 5-H), 1.28 (d, *J* = 6.3 Hz, 3 H, CH*Me*$_2$), 1.26 (d, *J* = 6.3 Hz, 3 H, CH*Me*$_2$), 1.26 (d, *J* = 6.3 Hz, 3 H, CH*Me*$_2$), 1.25 (d, *J* = 6.3 Hz, 3 H, CH*Me*$_2$), 1.18 (s, 9 H, *t*Bu). − ^{13}C NMR: δ = 169.4 (s, C=O), 168.7 (s, C=O), 78.2 (d, C-2), 74.1 (s, *C*Me$_3$), 70.9, 69.5 (d, C-4, C-3a), 69.0 (d, *C*HMe$_2$), 68.5 (d, *C*HMe$_2$), 53.7 (t, C-6), 51.2 (d, C-3), 32.4 (t, C-5), 28.2 (q, 3 C, C*Me*$_3$), 21.8 (q, CH*Me*$_2$), 21.7 (q, CH*Me*$_2$), 21.6 (q, CH*Me*$_2$), 21.6 (q, CH*Me*$_2$). − IR ($CDCl_3$): ṽ = 1732 (C=O), 1195 (C−O−C) cm^{-1}. − MS; *m*/*z* (%): 357 (1) [M]$^+$, 322 (4), 300 (3), 85 (63), 83 (100). − $C_{18}H_{31}NO_6$ (357.4): calcd. C 60.48, H 8.74, N 3.92; found C 60.23, H 8.97, N 4.17.

Cycloaddition of Nitrone 18 to Dimethyl Maleate (9): Dimethyl maleate (**9**, 35 μL, 0.28 mmol) was added to a solution of nitrone **18** (59.8 mg, 0.23 mmol) in benzene (0.7 mL). The mixture was stirred at room temp. until no more nitrone was detected by TLC (3 days). The crude mixture was then concentrated to give a 5.5:1.4:1 mixture (by 500 MHz ^{1}H NMR integration) of cycloadducts **22a**, **22b**, and **22c**. Purification by column chromatography, eluting with mixtures of increasing polarity, afforded the pure cycloadducts **22a** (eluent dichloromethane/ethyl acetate, 20:1; R_f = 0.16, 62 mg, 0.155 mmol, 66%) as a colorless solid, and **22b** (eluent dichloromethane/ethyl acetate, 10:1; R_f = 0.20, 18 mg, 0.044 mmol, 19%) and **22c** (eluent dichloromethane/ethyl acetate, 2:1; R_f = 0.39, 14 mg, 0.035 mmol, 15%) as oily compounds.

(2*R*,3*S*,3a*R*,4*S*)-2,3-Bis(methoxycarbonyl)-4-[(triisopropyl)silyloxy]hexahydropyrrolo[1,2-*b*]isoxazole (22a): M.p. 82−83 °C. − $[\alpha]_D^{20}$ = −63.9 (*c* = 1.00, $CHCl_3$). − ^{1}H NMR: δ = 4.74 (d, *J* = 7.3 Hz, 1 H, 2-H), 4.26 (d, *J* = 4.4 Hz, 1 H, 4-H), 4.10 (d, *J* = 6.6 Hz, 1 H, 3a-H), 3.76 (s, 3 H, COOMe), 3.72 (s, 3 H, COOMe), 3.38 (dd, *J* = 9.1, 3.3 Hz, 2 H, 6-H), 3.19 (t, *J* = 7.0 Hz, 1 H, 3-H), 2.08 (m, 1 H, 5-H), 1.73 (dt, *J* = 12.4, 3.7 Hz, 1 H, 5-H), 1.04 (s, 21 H, Si*i*Pr$_3$). − ^{13}C NMR: δ = 169.5 (s, C=O), 169.0 (s, C=O), 78.2, 77.0, 76.1 (d, 3 C, C-2, C-4, C-3a), 55.6 (t, C-6), 55.1 (d, C-3), 52.5 (q, COO*Me*), 52.2 (q, COO*Me*), 33.2 (t, C-5), 17.9 [q, 6 C, Si(CH*Me*$_2$)$_3$], 12.0 [d, 3 C, Si(*C*HMe$_2$)$_3$]. − IR ($CHCl_3$): ṽ = 1742 (C=O), 1191 (C−O−C) cm^{-1}. − MS; *m*/*z* (%): 401 (4) [M]$^+$, 358 (65) [M$^+$ − *i*Pr], 270 (18), 145 (35), 142 (35), 113 (100), 75 (70), 59 (78). − $C_{19}H_{35}NO_6Si$ (401.6): calcd. C 56.83, H 8.78, N 3.49; found C 56.85, H 9.00, N 3.40.

(2*S*,3*R*,3a*R*,4*S*)-2,3-Bis(methoxycarbonyl)-4-[(triisopropyl)silyloxy]hexahydropyrrolo[1,2-*b*]isoxazole (22b): $[\alpha]_D^{20}$ = +17.6 (*c* = 0.15, $CHCl_3$). − ^{1}H NMR: δ = 4.60 (m, A part of an AXY system, 1 H, 2-H), 4.16 (d, *J* = 4.8 Hz, 1 H, 4-H), 4.10−3.90 (m, XY part of an AXY system, 2 H, 3-H, 3a-H), 3.76 (s, 3 H, COOMe), 3.69 (s, 3 H, COOMe), 3.58 (dd, *J* = 13.7, 6.8 Hz, 1 H, 6-H), 3.25 (dt, *J* = 5.5, 12.4 Hz, 1 H, 6-H), 2.26 (ddt, *J* = 6.7, 4.8, 11.8 Hz, 1 H, 5-H), 1.71 (dd, *J* = 12.8, 5.1 Hz, 1 H, 5-H), 1.04 (s, 21 H, Si*i*Pr$_3$). − ^{13}C NMR: δ = 165.4 (s, 2 C, 2 × C=O), 78.4, 77.4, 75.5 (d, 3

C, C-2, C-4, C-3a), 54.9 (t, C-6), 52.9 (d, C-3), 52.4 (q, COO*Me*), 52.0 (q, COO*Me*), 34.9 (t, C-5), 17.9 [q, 6 C, Si(CH*Me*$_2$)$_3$], 12.1 [d, 3 C, Si(*C*HMe$_2$)$_3$]. − IR ($CDCl_3$): $\tilde{\nu}$ = 1727 (C=O), 1187 (C−O−C) cm^{-1}. − MS; *m*/*z* (%): 401 (1) [M]$^+$, 358 (66) [M$^+$ − *i*Pr], 270 (16), 145 (49), 142 (44), 113 (65), 87 (29), 75 (100), 59 (95). − $C_{19}H_{35}NO_6Si$ (401.6): calcd. C 56.83, H 8.78, N 3.49; found C 56.86, H 8.61, N 3.87.

(2*S*,3*R*,3a*S*,4*S*)-2,3-Bis(methoxycarbonyl)-4-[(triisopropyl)silyloxy]hexahydropyrrolo[1,2-*b*]isoxazole (22c): $[\alpha]_D^{18}$ = +55.5 (*c* = 0.22, $CHCl_3$). − ^{1}H NMR: δ = 4.84 (d, *J* = 7.3 Hz, 1 H, 2-H), 4.51 (q, *J* = 6.2 Hz, 1 H, 4-H), 4.17 (dd, *J* = 6.4, 4.9 Hz, 1 H, 3a-H), 4.01 (dd, *J* = 7.3, 4.8 Hz, 1 H, 3-H), 3.80 (s, 3 H, COOMe), 3.70 (s, 3 H, COOMe), 3.32 (dt, *J* = 12.7, 6.4 Hz, 1 H, 6-H), 3.26 (dt, *J* = 12.7, 7.1 Hz, 1 H, 6-H), 1.97 (q, *J* = 6.6 Hz, 2 H, 5-H), 1.08−1.04 (m, 21 H, Si*iPr*$_3$). − ^{13}C NMR: δ = 170.1 (s, C=O), 169.6 (s, C=O), 77.9, 72.4, 70.3 (d, 3 C, C-2, C-4, C-3a), 53.5 (t, C-6), 52.5 (q, COO*Me*), 52.2 (q, COO*Me*), 50.9 (d, C-3), 33.7 (t, C-5), 17.9 [q, 6 C, Si(CH*Me*$_2$)$_3$], 12.1 [d, 3 C, Si(*C*HMe$_2$)$_3$]. − IR ($CHCl_3$): $\tilde{\nu}$ = 1738 (C=O), 1190 (C−O−C) cm^{-1}. − MS; *m*/*z* (%): 401 (4) [M]$^+$, 358 (65) [M$^+$ − *i*Pr], 270 (18), 145 (35), 142 (35), 113 (100), 75 (70), 59 (78). − $C_{19}H_{35}NO_6Si$ (401.6): calcd. C 56.83, H 8.78, N 3.49; found C 56.70, H 8.55, N 3.76.

Cycloaddition of Nitrone 18 to Diisopropyl Maleate (20): A solution of diisopropyl maleate (**20**, 99 mg, 0.49 mmol) in benzene (1 mL) was added to a solution of nitrone **18** (106 mg, 0.41 mmol) in benzene (0.1 mL). The mixture was stirred at room temp. until no more nitrone was detected by TLC (5 d). The crude mixture was then concentrated to give a 6:1.6:1 mixture (by 500 MHz ^{1}H NMR integration) of cycloadducts **23a**, **23b**, and **23c**. Purification by column chromatography, eluting with mixtures of increasing polarity, afforded the pure cycloadducts **23a** (eluent petroleum ether/ethyl acetate, 11:1; R_f = 0.33, 126 mg, 0.276 mmol, 67%), **23b** (eluent petroleum ether/ethyl acetate, 6:1; R_f = 0.47, 26 mg, 0.057 mmol, 14%) and **23c** (eluent petroleum ether/ethyl acetate, 3:1; R_f = 0.50, 22 mg, 0.049 mmol, 12%) as oily compounds.

(2*R*,3*S*,3a*R*,4*S*)-2,3-Bis(isopropyloxycarbonyl)-4-[(triisopropyl)silyloxy]hexahydropyrrolo[1,2-*b*]isoxazole (23a): $[\alpha]_D^{24}$ = −56.3 (*c* = 0.56, $CHCl_3$). − ^{1}H NMR: δ = 5.07 (sept, *J* = 6.2 Hz, 1 H, C*H*Me$_2$), 5.06 (sept, *J* = 6.2 Hz, 1 H, C*H*Me$_2$), 4.65 (d, *J* = 7.4 Hz, 1 H, 2-H), 4.28 (br. d, *J* = 4.4 Hz, 1 H, 4-H), 4.11 (d, *J* = 6.6 Hz, 1 H, 3a-H), 3.42−3.35 (m, 2 H, 6-H), 3.16 (dd, *J* = 7.4, 6.6 Hz, 1 H, 3-H), 2.17−1.99 (m, 1 H, 5-H), 1.84−1.71 (m, 1 H, 5-H), 1.29 (d, *J* = 6.2 Hz, 3 H, CH*Me*$_2$), 1.27 (d, *J* = 6.2 Hz, 3 H, CH*Me*$_2$), 1.26 (d, *J* = 6.2 Hz, 3 H, CH*Me*$_2$), 1.24 (d, *J* = 6.2 Hz, 3 H, CH*Me*$_2$), 1.06−1.05 (m, 21 H, Si*i*Pr$_3$). − ^{13}C NMR: δ = 168.3 (s, 2 C, 2 × C=O), 78.4, 77.3, 76.4 (d, 3 C, C-2, C-4, C-3a), 69.2 (d, *C*HMe$_2$), 68.8 (d, *C*HMe$_2$), 55.6 (t, C-6), 55.5 (d, C-3), 33.3 (t, C-5), 21.7 (q, CH*Me*$_2$), 21.6 (q, CH*Me*$_2$), 21.6 (q, CH*Me*$_2$), 21.6 (q, CH*Me*$_2$), 18.0 [q, 6 C, Si(CH*Me*$_2$)$_3$], 12.1 [d, 3 C, Si(*C*HMe$_2$)$_3$]. − IR ($CDCl_3$): $\tilde{\nu}$ = 1737 (C=O), 1209 (C−O−C) cm^{-1}. − MS; *m*/*z* (%): 457 (0.2) [M]$^+$, 414 [M$^+$ − *i*Pr], 330 (2), 87 (40), 86 (47), 85 (100), 82 (100). − $C_{23}H_{43}NO_6Si$ (457.7): calcd. C 60.36, H 9.47, N 3.06; found C 60.23, H 9.55, N 3.50.

(2*S*,3*R*,3a*R*,4*S*)-2,3-Bis(isopropyloxycarbonyl)-4-[(triisopropyl)silyloxy]hexahydropyrrolo[1,2-*b*]isoxazole (23b): $[\alpha]_D^{19}$ = −8.0 (*c* = 0.46, $CHCl_3$). − ^{1}H NMR: δ = 5.05 (sept, *J* = 6.2 Hz, 1 H, C*H*Me$_2$), 4.96 (sept, *J* = 6.2 Hz, 1 H, C*H*Me$_2$), 4.52 (d, *J* = 6.3 Hz, 1 H, 2-H), 4.21 (d, *J* = 4.4 Hz, 1 H, 4-H), 3.99 (d, *J* = 10.5 Hz, 1 H, 3a-H), 3.83 (dd, *J* = 10.5, 6.3 Hz, 1 H, 3-H), 3.61 (dd, *J* = 13.2, 6.4 Hz, 1 H, 6-H), 3.25 (dt, *J* = 5.3, 13.2 Hz, 1 H, 6-H), 2.34−2.15 (m, 1 H, 5-H), 1.75−1.63 (m, 1 H, 5-H), 1.26 (d, *J* = 6.2 Hz, 3 H, CH*Me*$_2$), 1.25 (d, *J* = 6.2 Hz, 6 H, CH*Me*$_2$), 1.22 (d, *J* = 6.2 Hz, 3 H, CH*Me*$_2$), 1.06−1.03 (m, 21 H, Si*i*Pr$_3$). − ^{13}C NMR: δ = 169.3 (s, C=O), 166.9 (s, C=O), 78.7, 77.7, 75.3 (d, 3 C, C-2, C-4, C-3a), 69.1 (d, 2 C, 2 × *C*HMe$_2$), 58.4 (t, C-6), 52.8 (d, C-3), 34.9 (t, C-5), 21.8 (q, CH*Me*$_2$), 21.7 (q, CH*Me*$_2$), 21.6 (q, CH*Me*$_2$), 21.5 (q, CH*Me*$_2$), 17.9 [q, 6 C, Si(CH*Me*$_2$)$_3$], 12.0 [d, 3 C, Si(*C*HMe$_2$)$_3$]. − IR ($CDCl_3$): $\tilde{\nu}$ = 1727 (C=O), 1187 (C−O−C) cm^{-1}. − MS; *m*/*z* (%): 457 (2) [M]$^+$, 414 (7) [M$^+$ − *i*Pr], 372 (11), 256 (43), 232 (41), 128 (100) 84 (79), 75 (81), 59 (73). − $C_{23}H_{43}NO_6Si$ (457.7): calcd. C 60.36, H 9.47, N 3.06; found C 60.66, H 9.55, N 3.56.

(2*S*,3*R*,3a*S*,4*S*)-2,3-Bis(isopropyloxycarbonyl)-4-[(triisopropyl)silyloxy]hexahydropyrrolo[1,2-*b*]isoxazole (23c): $[\alpha]_D^{26}$ = +55.0 (*c* = 0.92, $CHCl_3$). − ^{1}H NMR: δ = 5.08 (sept, *J* = 6.2 Hz, 1 H, C*H*Me$_2$), 5.04 (sept, *J* = 6.2 Hz, 1 H, C*H*Me$_2$), 4.73 (d, *J* = 7.0 Hz, 1 H, 2-H), 4.50 (q, *J* = 6.0 Hz, 1 H, 4-H), 4.14 (dd, *J* = 6.2, 4.4 Hz, 1 H, 3a-H), 3.92 (dd, *J* = 7.0, 4.4 Hz, 1 H, 3-H), 3.34−3.07 (m, 2 H, 6-H), 1.99−1.89 (m, 2 H, 5-H), 1.27 (d, *J* = 6.2 Hz, 3 H, CH*Me*$_2$), 1.26 (d, *J* = 6.2 Hz, 3 H, CH*Me*$_2$), 1.22 (d, *J* = 6.2 Hz, 6 H, CH*Me*$_2$), 1.10−1.06 (m, 21 H, Si*i*Pr$_3$). − ^{13}C NMR: δ = 169.4 (s, C=O), 168.3 (s, C=O), 78.1 (d, C-2), 72.3, 70.5 (d, 2 C, C-4, C-3a), 69.0 (d, *C*HMe$_2$), 68.6 (d, *C*HMe$_2$), 53.4 (t, C-6), 50.8 (d, C-3), 33.9 (t, C-5), 21.7 (q, 2 C, CH*Me*$_2$), 21.7 (q, 2 C, CH*Me*$_2$), 18.0 [q, 6 C, Si(CH*Me*$_2$)$_3$], 12.1 [d, 3 C, Si(*C*HMe$_2$)$_3$]. − IR ($CDCl_3$): $\tilde{\nu}$ = 1737 (C=O), 1209 (C−O−C) cm^{-1}. − MS; *m*/*z* (%): 457 (0.3) [M]$^+$, 414 (0.6) [M$^+$ − *i*Pr], 372 (2), 128 (22) 85 (58), 83 (100). − $C_{23}H_{43}NO_6Si$ (457.7): calcd. C 60.36, H 9.47, N 3.06; found C 60.42, H 9.48, N 2.76.

Cycloaddition of Nitrone 37 to Dimethyl Maleate (9): A solution of nitrone **37** (209 mg, 1.02 mmol) and dimethyl maleate (**9**, 159 μL, 1.22 mmol) in benzene (3.3 mL) was stirred at room temp. for 3 d. After concentration, a ^{1}H NMR of the crude mixture showed the presence of the major cycloadduct **36** together with its diastereoisomers deriving from *endo-anti* and *exo-syn* transition states in a 4:1.5:1 ratio. Flash column chromatography (eluent petroleum ether/ethyl acetate, 2:1) gave a ca. 2:1 mixture of the *endo-anti* isomer with the major adduct **36** (R_f = 0.29, 75 mg) and the pure major cycloadduct **36** (R_f = 0.26, 199 mg, 0.57 mmol, 56%) as a colorless solid. Further elution with MeOH gave the *exo-syn* isomer slightly impure with adduct **36** (40 mg).

(2*S*,3*R*,3a*S*,4*R*)-4-Benzoyloxy-2,3-bis(methoxycarbonyl)hexahydropyrrolo[1,2-*b*]isoxazole (36): M.p. 103−104 °C. − $[\alpha]_D^{25}$ = +52.8 (*c* = 1.02, $CHCl_3$). − ^{1}H NMR: δ = 8.08−8.00 (m, 2 H, Ph), 7.62−7.50 (m, 1 H, Ph), 7.50−7.35 (m, 2 H, Ph), 5.31 (dt, *J* = 5.4, 1.4 Hz, 1 H, 4-H), 4.87 (d, *J* = 8.1 Hz, 1 H, 2-H), 4.32 (dd, *J* = 6.2, 1.4 Hz, 1 H, 3a-H), 3.80 (s, 3 H, COOMe), 3.76 (s, 3 H, COOMe), 3.62 (dd, *J* = 8.1, 6.2 Hz, 1 H, 3-H), 3.59−3.33 (m, 2 H, 6-H), 2.53−2.34 (m, 2 H, 5-H). − ^{13}C NMR: δ = 169.3 (s, MeO*C*=O), 168.8 (s, MeO*C*=O), 165.9 (s, Ph*C*=O), 133.3 (d, Ph), 129.6 (d, 2 C, Ph), 129.5 (s, Ph), 128.4 (d, 2 C, Ph), 79.9, 77.3, 73.8 (d, 3 C, C-2, C-4, C-3a), 55.5 (t, C-6), 55.4 (d, C-3), 52.6 (q, COO*Me*), 52.5 (q, COO*Me*), 30.4 (t, C-5). − IR ($CDCl_3$): $\tilde{\nu}$ = 1745 (C=O), 1720 (C=O), 1269 (C−O−C) cm^{-1}. − MS; *m*/*z* (%): 349 (4) [M]$^+$, 227 (28), 105 (93), 85 (85), 71 (91), 57 (100). − $C_{17}H_{19}NO_7$ (349.3): calcd. C 58.45, H 5.48, N 4.01; found C 58.69, H 5.51, N 3.70.

(2*R*,3*S*,3a*S*,4*R*)-4-Benzoyloxy-2,3-bis(methoxycarbonyl)hexahydropyrrolo[1,2-*b*]isoxazole (*endo-anti*): ^{1}H NMR: δ = 8.04−7.98 (m, 2 H, Ph), 7.60−7.54 (m, 1 H, Ph), 7.47−7.41 (m, 2 H, Ph), 5.40 (br. d, *J* = 6.3 Hz, 1 H, 4-H), 4.71 (d, *J* = 7.4 Hz, 1 H, 2-H), 4.16 (t, *J* = 7.5 Hz, 1 H, 3-H), 4.10 (dd, *J* = 7.6, 2.1 Hz, 1 H, 3a-H), 3.80 (s, 3 H, COOMe), 3.78−3.70 (m, 1 H, 6-H), 3.75 (s, 3 H, COOMe), 3.36−3.28 (m, 1 H, 6-H), 2.76−2.66 (m, 1 H, 5-H), 2.05−1.97 (m, 1 H, 5-H).

(2*R*,3*S*,3a*R*,4*R*)-4-Benzoyloxy-2,3-bis(methoxycarbonyl)hexahydropyrrolo[1,2-*b*]isoxazole (*exo-syn*): ^{1}H NMR: δ = 8.04−7.96 (m, 2 H, Ph), 7.62−7.56 (m, 1 H, Ph), 7.51−7.42 (m, 2 H, Ph), 5.57 (q, *J* = 6.0 Hz, 1 H, 4-H), 4.95 (d, *J* = 7.7 Hz, 1 H, 2-H), 4.38 (dd, *J* = 6.3, 4.8 Hz, 1 H, 3a-H), 3.88 (dd, *J* = 7.7, 4.8 Hz, 1 H, 3-H), 3.78 (s, 3 H, COOMe), 3.67 (s, 3 H, COOMe), 3.65−3.18 (m, 2 H, 6-H), 2.22−2.08 (m, 2 H, 5-H). − ^{13}C NMR: δ = 169.5 (s, 2 C, 2 × MeO*C*=O), 165.5 (s, Ph*C*=O), 133.5 (d, Ph), 129.5 (d + s, 3 C, Ph), 128.6 (d, 2 C, Ph), 78.2, 73.7, 69.0 (d, 3 C, C-2, C-4, C-3a), 53.7 (t, C-6), 52.6 (q, COO*Me*), 52.4 (q, COO*Me*), 51.1 (d, C-3), 31.2 (t, C-5).

Hexacarbonylmolybdenum-Induced Reductive Ring-Opening/Ring-Closure of Pyrroloisoxazolidines to 3-Pyrrolizidinones

General Procedure: A mixture of the appropriate isoxazolidine **10**−**13a**, **23a**, **10c**, or **36** and $Mo(CO)_6$ (0.7 equiv.) in CH_3CN (15 mL/mmol isoxazolidine) and H_2O (1 mL/mmol isoxazolidine) was heated at reflux until no more starting isoxazolidine was detectable by TLC (see Scheme 8). The hot mixture was then poured on silica gel (5 g/mmol isoxazolidine) spread onto a Petri dish and left overnight. The silica was then poured into a Gooch containing Celite and washed thoroughly with ethyl acetate. Concentration of the crude mixture followed by purification (recrystallization or flash column chromatography) afforded the pure pyrrolizidinone **24**−**29** or **35**.

Reaction of Isoxazolidine 10a: Adduct **10a** (1.9 g, 6.3 mmol) and $Mo(CO)_6$ (1.164 g, 4.4 mmol) were heated at reflux in CH_3CN (90 mL)/H_2O (6.3 mL) for 3 h. The solid residue obtained after usual workup was crystallized from diisopropyl ether to afford the pure **24** (1.41 g, 5.18 mmol, 82%).

(1*S*,2*R*,7*S*,7a*R*)-7-*tert*-Butoxy-2-hydroxy-1-(methoxycarbonyl)hexahydropyrrolizin-3-one (24): M.p. 102−103 °C. − $[\alpha]_D^{25}$ = +70.9 (*c* = 0.56, $CHCl_3$). − ^{1}H NMR: δ = 4.80 (d, *J* = 9.5 Hz, 1 H, 2-H), 3.92 (q, *J* = 6.2 Hz, 1 H, 7-H), 3.78 (s, 3 H, COOMe), 3.77−3.68 (m, 2 H, 7a-H, 5-H), 3.30−3.14 (m, 1 H, 5-H), 2.87 (dd, *J* = 9.5, 8.4 Hz, 1 H, 1-H), 2.22−2.02 (m, 1 H, 6-H), 2.02−1.84 (m, 1 H, 6-H), 1.18 (s, 9 H, *t*Bu). − ^{13}C NMR: δ =172.7 (s, C=O), 171.5 (s, C=O), 75.4, 75.1 (d, 2 C, C-2, C-7), 74.2 (s, *C*Me$_3$), 64.4 (d, C-7a), 54.4 (d, C-1), 52.3 (q, COO*Me*), 40.8 (t, C-5), 34.4 (t, C-6), 28.2 (q, 3 C, C*Me$_3$*). − IR (CCl_4): $\tilde{\nu}$ = 3357 (br, O−H), 1740 (C=O), 1705 (C=O), 1190 (C−O−C) cm^{-1}. − MS; *m*/*z* (%): 271 (18) [M]$^+$, 215 (71), 197 (80) 126 (86), 110 (88), 82 (72), 57 (100). − $C_{13}H_{21}NO_5$ (271.2): calcd. C 57.55, H 7.80, N 5.16; found C 57.26, H 7.73, N 4.96.

Reaction of Isoxazolidines 11: A 4:1 mixture of adducts **11a** and **11b** (45 mg, 0.106 mmol) and $Mo(CO)_6$ (30 mg, 0.11 mmol) was refluxed in CH_3CN (1.5 mL)/ H_2O (0.1 mL) for 2.5 h. After usual workup of the reaction mixture, elution with MeOH from silica gel gave **25** (28 mg, 0.071 mmol, 84% based on the calculated amount of isoxazolidine **11a**) as a yellowish oil, which contained traces of an inseparable unidentified by-product (detected by ^{1}H NMR).

(1*S*,2*R*,7*S*,7a*R*)-7-Dibenzylamino-2-hydroxy-1-(methoxycarbonyl)-hexahydropyrrolizin-3-one (25): ^{1}H NMR: δ = 7.33−7.24 (m, 10 H, Ph), 4.75 (d, *J* = 9.7 Hz, 1 H, 2-H), 4.09 (t, *J* = 8.2 Hz, 1 H, 7a-H), 3.91 (s, 3 H, COOMe), 3.76 (d, *J* = 13.9 Hz, 2 H, C*H$_2$*Ph), 3.54 (m, 1 H, 5-H), 3.49 (d, *J* = 13.9 Hz, 2 H, C*H$_2$*Ph), 3.25 (m, 1 H, 5-H), 3.10 (q, *J* = 8.5 Hz, 1 H, 7-H), 2.72 (dd, *J* = 9.7, 7.9 Hz, 1 H, 1-H), 2.19−2.03 (m, 2 H, 6-H). − ^{13}C NMR: δ = 172.6 (s, C=O), 172.4 (s, C=O), 139.4 (s, 2 C, Ph), 129.0 (d, 4 C, Ph), 128.9 (d, 4 C, Ph), 127.8 (d, 2 C, Ph), 76.8 (d, C-2), 64.8 (d, C-7a), 59.5 (d, C-7), 55.9 (d, C-1), 55.1 (t, 2 C, N(*C*H$_2$Ph)$_2$), 53.1 (q, COO*Me*), 41.0 (t, C-5), 24.7 (t, C-6).

Reaction of Isoxazolidine 12a: Adduct **12a** (43.3 mg, 0.116 mmol) and $Mo(CO)_6$ (21 mg, 0.081 mmol) were heated at reflux in CH_3CN (1.6 mL)/ H_2O (110 μL) for 3.5 h. After the usual workup, purification of the mixture on silica gel (eluent petroleum ether/ethyl acetate, 2:1) afforded analytically pure **26** (R_f = 0.20, 24.7 mg, 0.072 mmol, 62%) as a colorless solid.

(1*S*,2*R*,6*R*,7*R*,7a*R*)-6,7-Bis(*tert*-butoxy)-2-hydroxy-1-(methoxycarbonyl)hexahydropyrrolizin-3-one (26): M.p. 124−126 °C. − $[\alpha]_D^{21}$ = +4.6 (*c* = 1.00, $CHCl_3$). − ^{1}H NMR: δ = 4.75 (dd, *J* = 9.8, 2.2 Hz, 1 H, 2-H), 3.86 (quint, *J* = 2.0 Hz, 1 H, 6-H), 3.80−3.74 (m, 2 H, 5-H, 7-H), 3.78 (s, 3 H, COOMe), 3.67 (dd, *J* = 9.2, 1.8 Hz, 1 H, 7a-H), 3.40 (br. s, 1 H, OH), 3.16 (ddd, *J* = 12.1, 3.7, 1.5 Hz, 1 H, 5-H), 3.11 (dd, *J* = 9.8, 9.2 Hz, 1 H, 1-H), 1.17 (s, 9 H, *t*Bu), 1.15 (s, 9 H, *t*Bu). − ^{13}C NMR: δ = 175.5 (s, C=O), 171.8 (s, C=O), 79.5, 76.5, 74.0 (d, 3 C, C-7, C-2, C-6), 74.7 (s, *C*Me$_3$), 74.3 (s, *C*Me$_3$), 65.0 (d, C-7a), 54.1 (d, C-1), 52.2 (q, COO*Me*), 50.5 (t, C-5), 28.2 (q, 6 C, 2 × C*Me$_3$*). − IR ($CDCl_3$): $\tilde{\nu}$ = 3359 (br, O−H), 1701 (C=O), 1188 (C−O−C) cm^{-1}. − MS; *m*/*z* (%): 343 (0.4) [M]$^+$, 294 (2), 287 (2), 231 (10), 230 (61), 83 (100), 57 (90). − $C_{17}H_{29}NO_6$ (343.4): calcd. C 59.46, H 8.51, N 4.08; found C 59.90, H 8.80, N 3.84.

Reaction of Isoxazolidine 13a: Adduct **13a** (344 mg, 1 mmol) and $Mo(CO)_6$ (185 mg, 0.7 mmol) were heated at reflux in CH_3CN (15 mL)/H_2O (1 mL) for 2 h. After the usual workup, purification of the mixture on silica gel (eluent petroleum ether/ethyl acetate, 1:2) followed by crystallization from petroleum ether, afforded pure **27** (R_f = 0.20, 210 mg, 0.77 mmol, 77%) as a colorless solid.

(1*S,2*R**,6*S**,7*R**,7a*R**)-2-Hydroxy-1-methoxycarbonyl-6,7-(isopropylidenedioxy)hexahydropyrrolizin-3-one (27):** M.p. 187−189 °C. − ^{1}H NMR: δ = 4.86 (dt, *J* = 3.6, 6.6 Hz, 1 H, 6-H), 4.74 (dd, *J* = 9.5, 1.1 Hz, 1 H, 2-H), 4.49 (dd, *J* = 6.6, 4.6 Hz, 1 H, 7-H), 4.17 (dd, *J* = 12.9, 6.6 Hz, 1 H, 5-H), 3.94 (dd, *J* = 8.6, 4.6 Hz, 1 H, 7a-H), 3.84 (s, 3 H, COOMe), 3.16 (ddd, *J* = 12.9, 3.6, 1.1 Hz, 1 H, 5-H), 2.94 (dd, *J* = 9.5, 8.6 Hz, 1 H, 1-H), 1.55 (s, 3 H, Me), 1.36 (s, 3 H, Me). − ^{13}C NMR: δ = 172.1 (s, C=O), 171.0 (s, C=O), 114.5 (s, O*C*Me$_2$O), 84.1, 79.9 (d, 2 C, C-7, C-2), 74.3 (d, C-6), 63.8 (d, C-7a), 54.1 (d, C-1), 52.7 (q, COO*Me*), 47.5 (t, C-5), 27.3 (q, Me), 25.2 (q, Me). − IR ($CDCl_3$): $\tilde{\nu}$ = 3359 (br, O−H), 1710 (C=O), 1214 (C−O−C) cm^{-1}. − MS; *m*/*z* (%): 271 (3) [M]$^+$, 256 (25), 242 (28), 213 (53), 156 (45), 136 (55), 43 (100). − $C_{12}H_{17}NO_6$ (271.1): calcd. C 53.12, H 6.32, N 5.17; found C 53.40, H 6.34, N 5.17.

Reaction of Isoxazolidine 23a: Adduct **23a** (34.7 mg, 0.076 mmol) and $Mo(CO)_6$ (14 mg, 0.053 mmol) were heated at reflux in CH_3CN (1 mL)/H_2O (76 μL) for 18 h. After the usual workup, purification on silica gel (eluent petroleum ether/ethyl acetate, 2:1) afforded **28** (R_f = 0.14, 25.8 mg, 0.065 mmol, 85%) as an oil.

(1*S*,2*R*,7*S*,7a*R*)-2-Hydroxy-1-isopropyloxycarbonyl-7-[(triisopropyl)silyloxy]hexahydropyrrolizin-3-one (28): $[\alpha]_D^{22}$ = +48.7 (*c* = 1.15, $CHCl_3$). − ^{1}H NMR: δ = 5.08 (sept, *J* = 6.2 Hz, 1 H, C*H*Me$_2$), 4.76 (d, *J* = 9.5 Hz, 1 H, 2-H), 4.23 (q, *J* = 4.8 Hz, 1 H, 7-H), 3.84 (dd, *J* = 8.5, 4.4 Hz, 1 H, 7a-H), 3.78 (dd, *J* = 12.0, 7.4 Hz, 1 H, 5-H), 3.45 (br. s, 1 H, OH), 3.20 (dt, *J* = 12.0, 7.7 Hz, 1 H, 5-H), 2.76 (dd, *J* = 9.5, 8.5 Hz, 1 H, 1-H), 2.09−1.90 (m, 2 H, 6-H), 1.30 (d, *J* = 6.2 Hz, 3 H, CH*Me$_2$*), 1.29 (d, *J* = 6.2 Hz, 3 H, CH*Me$_2$*), 1.22−0.88 [m, 3 H, Si(C*H*Me$_2$)$_3$], 1.05 [s, 18 H, Si(C*HMe$_2$*)$_3$]. − ^{13}C NMR: δ = 173.4 (s, C=O), 170.5 (s, C=O), 76.1 (d, C-2), 75.6 (d, C-7), 69.4 (d, *C*HMe$_2$), 66.4 (d, C-7a), 55.1

(d, C-1), 41.1 (t, C-5), 35.3 (t, C-6), 21.7 (q, CH*Me*$_2$), 21.7 (q, CH*Me*$_2$), 17.9 [q, 3 C, Si(CH*Me*$_2$)$_3$], 17.9 [q, 3 C, Si(CH*Me*$_2$)$_3$], 12.1 [d, 3 C, Si(*C*HMe$_2$)$_3$]. − IR ($CDCl_3$): $\tilde{\nu}$ = 3371 (br, O−H), 1708 (C=O), 1190 (C−O−C) cm^{-1}. − MS; *m*/*z* (%): 313 (25) [M$^+$ − CO_2*i*Pr], 85 (51), 83 (100), 57 (61). − $C_{20}H_{37}NO_5Si$ (399.6): calcd. C 60.11, H 9.33, N 3.51; found C 59.93, H 9.39, N 3.61.

Reaction of Isoxazolidine 10c: Adduct **10c** (547 mg, 1.8 mmol) and $Mo(CO)_6$ (370 mg, 1.4 mmol) were heated at reflux in CH_3CN (30 mL)/H_2O (2 mL) for 3 h. The solid residue obtained after the usual workup was crystallized from heptane to afford pure **29** (316 mg, 1.17 mmol, 65%).

(1*R*,2*S*,7*S*,7a*S*)-7-*tert*-Butoxy-2-hydroxy-1-(methoxycarbonyl)-hexahydropyrrolizin-3-one (29): M.p. 128−129 °C. − $[\alpha]_D^{24}$ = +11.0 (*c* = 0.38, $CHCl_3$). − ^{1}H NMR: δ = 4.77 (dd, *J* = 9.6, 3.5 Hz, 1 H, 2-H), 4.05 (t, *J* = 3.6 Hz, 1 H, 7-H), 3.90 (dd, *J* = 8.1, 3.7 Hz, 1 H, 7a-H), 3.76 (s, 3 H, COOMe), 3.59 (dt, *J* = 8.1, 9.9 Hz, 1 H, 5-H), 3.39 (dd, *J* = 9.6, 8.1 Hz, 1 H, 1-H), 3.14 (t, *J* = 9.9 Hz, 1 H, 5-H), 2.90 (d, *J* = 3.5 Hz, 1 H, OH), 2.15−2.07 (m, 1 H, 6-H), 2.05−1.96 (m, 1 H, 6-H), 1.16 (s, 9 H, *t*Bu). − ^{13}C NMR: δ = 172.4 (s, C=O), 172.0 (s, C=O), 75.3 (d, C-2), 74.4 (s, *C*Me$_3$), 67.7 (d, C-7), 63.0 (d, C-7a), 52.1 (q, COO*Me*), 48.3 (d, C-1), 39.7 (t, C-5), 35.1 (t, C-6), 28.0 (q, 3 C, C*Me*$_3$). − IR (CCl_4): $\tilde{\nu}$ = 3356 (br, O−H), 1721 (C=O), 1192 (C−O−C) cm^{-1}. − MS; *m*/*z* (%): 271 (42) [M]$^+$, 215 (90), 197 (50), 126 (100), 114 (76), 110 (94), 82 (53), 57 (81). − $C_{13}H_{21}NO_5$ (271.2): calcd. C 57.55, H 7.80, N 5.16; found C 57.88, H 7.86, N 5.69.

Reaction of Isoxazolidine 36: Adduct **36** (100 mg, 0.28 mmol) and $Mo(CO)_6$ (53 mg, 0.2 mmol) were heated at reflux in CH_3CN (4 mL)/H_2O (0.3 mL) for 3 h. After usual workup, purification on silica gel (eluent $CHCl_3$/MeOH, 50:1) gave a solid product, which was recrystallized from AcOEt/(*i*Pr)$_2$O to afford pure **35** (85 mg, 0.27 mmol, 95%), intermediate in the synthesis of (−)-hastanecine (**34**). The spectral data of **35** were identical and its optical rotation fully consistent with that previously reported in the literature for the same compound with a 97.7% *ee*.[18g]

(1*R*,2*S*,7*R*,7a*S*)-7-Benzoyloxy-2-hydroxy-1-(methoxycarbonyl)hexahydropyrrolizin-3-one (35): M.p. 143−144 °C (ref. m.p. 142−143.5 °C, 97.7% *ee*).[18g] − $[\alpha]_D^{26}$ = −69.7 (*c* = 1.09, $CHCl_3$) {ref. $[\alpha]_D^{25}$ = −67.8 (*c* = 0.97, CH_3OH)}.[18g] − $C_{16}H_{17}NO_6$ (319.3): calcd. C 60.18, H 5.37, N, 4.39; found C 59.95, H 5.48, N 3.92.

Synthesis of 7-*epi*-Croalbinecine

(1*R*,2*R*,7*S*,7a*R*)-7-*tert*-Butoxy-2-hydroxy-1-(hydroxymethyl)-hexahydro-1*H*-pyrrolizine (30): An ethereal solution of $LiAlH_4$ (1 M, 0.74 mL, 0.74 mmol) was added slowly to a solution of pyrrolizidinone **24** (67 mg, 0.247 mmol) in diethyl ether (2 mL) cooled to 0 °C. The mixture was heated at reflux for 1.5 h and then cooled to 0 °C. A saturated aqueous solution of Na_2SO_4 (260 μL) was added to the stirred mixture. After filtration through Celite and washing with ethyl acetate, the solution was concentrated in vacuo to give the monoprotected pyrrolizidine triol **30** (57 mg, 0.246 mmol, 97%) as a solid. Attempted purification on silica gel caused extensive decomposition of the product which was consequently used directly for the following deprotection step. An analytically pure sample was obtained by recrystallization from diisopropyl ether. − M.p. 101−102 °C. − $[\alpha]_D^{24}$ = +65.0 (*c* = 0.50, $CHCl_3$). − ^{1}H NMR: δ = 4.25 (dt, *J* = 8.6, 6.4 Hz, 1 H, 2-H), 3.94 (q, *J* = 5.5 Hz, 1 H, 7-H), 3.78 (dd, *J* = 10.8, 5.5 Hz, 1 H, C*H*$_2$OH), 3.73 (dd, *J* = 10.8, 5.7 Hz, 1 H, C*H*$_2$OH), 3.28 (dd, *J* = 9.0, 6.0 Hz, 1 H, 3-H), 3.18 (dt, *J* = 10.8, 6.2 Hz, 1 H, 5-H), 3.05 (dd, *J* = 8.2, 5.0 Hz, 1 H, 7a-H), 2.69 (dt, *J* = 10.8, 6.8 Hz, 1 H, 5-H), 2.45 (t, *J* = 9.0 Hz, 1 H, 3-H), 2.12 (dq, *J* = 12.4, 6.1 Hz, 1 H, 6-H), 1.90 (tt, *J* = 8.3, 5.7 Hz, 1 H, 1-H), 2.12 (dq, *J* = 12.4, 6.4 Hz, 1 H, 6-H), 1.20 (s, 9 H, *t*Bu). − ^{13}C NMR: δ = 77.3 (d, C-7), 74.1 (s, *C*Me$_3$), 74.0 (d, C-2), 71.7 (d, C-7a), 62.7 (t, C-3), 61.2 (t, C-5), 53.3 (d, C-1), 53.0 (t, CH$_2$OH), 34.2 (t, C-6), 28.5 (q, 3 C, C*Me*$_3$). − IR ($CDCl_3$): $\tilde{\nu}$ = 3366 (br, O−H) cm^{-1}. − MS; *m*/*z* (%): 229 (6) [M]$^+$, 172 (100), 156 (31), 129 (33), 98 (79). − $C_{12}H_{23}NO_3$ (229.3): calcd. C 62.85, H 10.11, N 6.11; found C 62.69, H 10.21, N 6.03.

(1*R*,2*R*,7*S*,7a*R*)-2,7-Dihydroxy-1-(hydroxymethyl)hexahydro-1*H*-pyrrolizine (7-*epi*-Croalbinecine, 31): Trifluoroacetic acid (1 mL, 13 mmol) was added to pyrrolizidine **30** (66 mg, 0.29 mmol) at 0 °C and the resulting mixture was stirred at room temp. for 3 h. After concentration in vacuo, the crude product was purified by ion exchange chromatography on a column (15 cm × 0.5 cm) filled with Dowex 50WX8. After elution with MeOH (30 mL) and H_2O (10 mL), pure **31** (45 mg, 0.261 mmol, 91%) was collected as a solid by elution with aqueous NH_3 (5%, 30 mL). − M.p. 146−147 °C. − $[\alpha]_D^{23}$ = +49.7 (*c* = 0.42, EtOH). − ^{1}H NMR (D_2O): δ = 4.29 (ddd, *J* = 5.8, 3.3, 2.5 Hz, 1 H, 7-H), 4.07 (dt, *J* = 6.0, 7.9 Hz, 1 H, 2-H), 3.75 (dd, *J* = 11.5, 5.3 Hz, 1 H, C*H*$_2$OH), 3.66 (dd, *J* = 11.5, 6.5 Hz, 1 H, C*H*$_2$OH), 3.23 (dd, *J* = 10.2, 5.9 Hz, 1 H, 3-H), 3.09 (ddd, *J* = 11.5, 9.2, 6.1 Hz, 1 H, 5-H), 3.05 (dd, *J* = 8.1, 2.7 Hz, 1 H, 7a-H), 2.86 (ddd, *J* = 11.5, 7.0, 4.4 Hz, 1 H, 5-H), 2.55 (dd, *J* = 10.2, 8.0 Hz, 1 H, 3-H), 2.25−2.18 (m, 1 H, 6-H), 1.98−1.94 (m, 1 H, 1-H), 1.79−1.74 (m, 1 H, 6-H). − ^{13}C NMR (D_2O): δ = 77.3 (d, C-7), 73.6 (d, C-7a), 73.0 (d, C-2), 61.8 (t, CH$_2$OH), 59.7 (t, C-3), 52.3 (t, C-5), 52.3 (d, C-1), 32.4 (t, C-6). − IR (KBr): $\tilde{\nu}$ = 3436 (O−H), 3235 (br, O−H) cm^{-1}. − MS; *m*/*z* (%): 173 (3) [M]$^+$, 155 (5), 129 (22), 98 (100). − $C_8H_{15}NO_3$ (173.2): calcd. C 55.47, H 8.73, N 8.09; found C 55.57, H 8.83, N 7.66.

Synthesis of (−)−Croalbinecine

(1*S*,2*S*,7*S*,7a*S*)-7-*tert*-Butoxy-2-hydroxy-1-(hydroxymethyl)hexahydro-1*H*-pyrrolizine (32): An ethereal 1 M solution of $LiAlH_4$ (0.74 mL, 0.74 mmol) was added slowly to a solution of pyrrolizidinone **29** (67 mg, 0.247 mmol) in diethyl ether (2 mL) cooled to 0 °C. The mixture was heated at reflux for 1.5 h and then cooled at 0 °C. A saturated aqueous solution of Na_2SO_4 (260 μL) was added to the stirred mixture. After filtration through Celite and washing with ethyl acetate, the solution was concentrated in vacuo to give the monoprotected pyrrolizidine triol **32** (46 mg, 0.203 mmol, 82%) as a solid, which was used directly for the following deprotection step. An analytically pure sample was obtained by recrystallization from diisopropyl ether. − M.p. 137−139 °C. − $[\alpha]_D^{24}$ = −1.0 (*c* = 0.59, $CHCl_3$). − ^{1}H NMR: δ = 4.13−4.10 (m, 2 H, 2-H, 7-H), 3.67 (dd, *J* = 10.5, 6.7 Hz, 1 H, C*H*$_2$OH), 3.61 (dd, *J* = 10.5, 6.7 Hz, 1 H, C*H*$_2$OH), 3.39 (dd, *J* = 5.1, 3.5 Hz, 1 H, 7a-H), 3.29 (dd, *J* = 11.7, 4.9 Hz, 1 H, 3-H), 3.18−3.14 (m, 1 H, 5-H), 2.93 (dt, *J* = 7.0, 9.5 Hz, 1 H, 5-H), 2.73 (dd, *J* = 11.7, 2.8 Hz, 1 H, 3-H), 2.41 (tt, *J* = 6.3, 3.0 Hz, 1 H, 1-H), 2.18−1.91 (m, 2 H, 6-H), 1.26 (s, 9 H, *t*Bu). − ^{13}C NMR: δ = 75.7, 72.3 (d, 2 C, C-2, C-7), 75.1 (s, *C*Me$_3$), 70.8 (d, C-7a), 63.6 (t, CH$_2$OH), 62.7 (t, C-3), 53.5 (t, C-5), 49.6 (d, C-1), 35.4 (t, C-6), 28.3 (q, 3 C, C*Me*$_3$). − IR ($CDCl_3$): $\tilde{\nu}$ = 3373 (br, O−H) cm^{-1}. − MS; *m*/*z* (%): 229 (6) [M]$^+$, 172 (100), 154 (10), 130 (19), 98 (83). − $C_{12}H_{23}NO_3$ (229.3): calcd. C 62.85, H 10.11, N 6.11; found C 62.77, H 10.21, N 6.36.

(1*S*,2*S*,7*S*,7a*S*)-2,7-Dihydroxy-1-(hydroxymethyl)hexahydro-1*H*-pyrrolizine [(−)-croalbinecine, 33]: Trifluoroacetic acid (1 mL, 13 mmol) was added to pyrrolizidine **32** (61 mg, 0.266 mmol) at 0 °C and the resulting mixture was stirred at room temp. for 2.5 h. After concentration in vacuo, the crude product was purified by ion exchange chromatography on a column (15 cm × 0.5 cm) filled

with Dowex 50WX8. After elution with MeOH (40 mL) and H_2O (20 mL), spectroscopically pure **33** (45 mg, 0.261 mmol, 97%) was collected by elution with aqueous NH_3 (5%, 30 mL) as a gummy oil which refused to crystallize. The product **33** was further purified on silica gel (eluent $CHCl_3/CH_3OH$/aq. NH_3, 10:5:1) to give an analytically pure oil (27 mg, 0.156 mmol, 59%). – R_f = 0.19. – $[\alpha]_D^{23}$ = −36.5 (c = 0.52, EtOH). – ^{1}H NMR (D_2O): δ = 4.27 (dt, J = 2.1, 4.2 Hz, 1 H, 7-H), 4.17 (dt, J = 5.9, 8.0 Hz, 1 H, 2-H), 3.73 (dd, J = 11.3, 5.3 Hz, 1 H, CH_2OH), 3.62 (dd, J = 11.3, 6.9 Hz, 1 H, CH_2OH), 3.27−3.22 (m, 2 H, 3-H, 7a-H), 3.10 (ddd, J = 9.9, 7.6, 2.3 Hz, 1 H, 5-H), 2.73 (ddd, J = 11.4, 10.3, 6.1 Hz, 1 H, 5-H), 2.53 (dd, J = 9.7, 8.2 Hz, 1 H, 3-H), 2.32 (dq, J = 5.4, 7.5 Hz, 1 H, 1-H), 2.06−1.93 (m, 2 H, 6-H). – ^{13}C NMR (D_2O): δ = 74.7 (d, C-2), 71.4 (d, C-7), 70.5 (d, C-7a), 62.1 (t, CH_2OH), 60.7 (t, C-3), 52.2 (t, C-5), 46.5 (d, C-1), 35.9 (t, C-6). – MS; m/z (%): 173 (8) $[M]^+$, 155 (7), 129 (30), 98 (100). – $C_8H_{15}NO_3$ (173.2): calcd. C 55.47, H 8.73, N 8.09; found C 55.45, H 8.72, N 8.08.

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