Stereodivergent Approach to Enantiopure Hydroxyindolizidines Through 1,3-Dipolar Cycloaddition of 3-Hydroxypyrroline *N*-Oxide Derivatives

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Keywords: Cycloaddition / Diastereoselectivity / Nitrogen heterocycles / Nitrones / Protecting groups

The (3*S*)-3-alkoxypyrroline *N*-oxides **7** and **27** were easily prepared from L-malic acid and used as starting materials for enantiospecific syntheses of stereodifferentiated polyhydroxyindolizidines. Selection of the appropriate modality (inter- or intramolecular) for 1,3-dipolar cycloaddition of the cyclic nitrone with 5-hydroxypentenoic acid derivatives gave access to either [1,8a]-*trans*- or -*cis*-hydroxyindolizidines **31** and **24**, respectively, through elaboration of the primary cycloadducts. Moreover, the choice of the esterification conditions (Ph_3P/DEAD or DIC/DMAP) used in linking the nitrone and the dipolarophile moieties in the intramolecular approach determined the absolute configuration of the final product, allowing the selective synthesis of both enantiomers, (–)-**24** and (+)-**24**. This strategy required protection of the nitrone functionality to avoid racemization of the unprotected hydroxy nitrone during the introduction of the dipolarophile moiety. Protection/deprotection were achieved by cycloaddition/retro-cycloaddition reactions. The different propensity of some pyrrolo[1,2-*b*]isoxazolidines to undergo retro-cycloaddition with regeneration of the nitrone functionality was investigated both experimentally and by semiempirical and ab initio calculations on model compounds. The relative calculated activation energies were qualitatively in good agreement with the experimental observations. Fumaronitrile was found to be a convenient protecting reagent for the nitrone moiety and could be removed by retro-cycloaddition at lower temperatures than styrene and ethyl acrylate.

Introduction

The 1,3-dipolar cycloaddition of enantiomerically pure nitrones and alkenes is a powerful synthetic device that allows up to three new stereogenic centers to be assembled in a stereospecific manner in a single step.[1] The resulting isoxazolidine cycloadducts can be further elaborated to provide polyfunctionalized compounds with preservation of optical purity.

In recent years we have applied the cycloaddition strategy to the synthesis of several natural and unnatural pyrrolizidines and indolizidines by employing a variety of enantiomerically pure mono- and dialkoxypyrroline *N*-oxides derived from malic acid and tartaric acid, respectively (Figure 1).[2]

The process allows control over the relative and absolute configuration of three (or more) stereocenters in the final product, resulting with high efficiency in highly functionalized compounds. The configuration of the bridgehead carbon atom is dictated by the mode of approach of dipolarophiles towards the nitrone. An attack *anti* to the alkoxy group vicinal to the nitrone moiety produces a *cis* relationship of the OR group and the bridgehead H atom in the final product. The opposite *trans* relationship can only be achieved by a *syn* approach of the reagents, but this approach is usually highly hindered by unfavorable steric interactions between the dipolarophile and the alkoxy substituent (Figure 2). A good to excellent selectivity is in fact observed in favor of the *anti* product.[2]

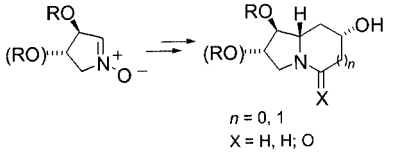

Figure 1. Synthesis of polyhydroxy-indolizidines and -pyrrolizidines

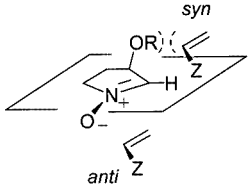

Figure 2. Modes of approach between the cyclic nitrone and alkenes

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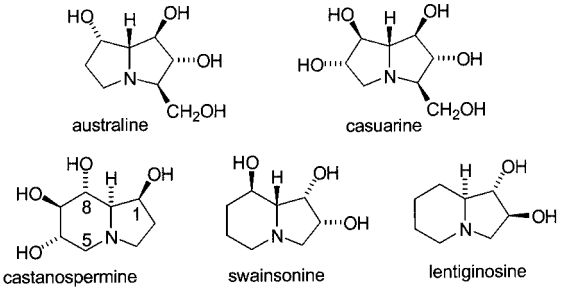
The only possible means to induce a *syn* approach of the reagent, in order to achieve a *trans* (OR, bridgehead H) relationship in the products, relies on forcing the cycloaddition to occur in an intramolecular mode. The success of this alternative approach can expand the usefulness of this strategy in accessing all the broad range of natural and unnatural pyrrolizidines and indolizidines, the most representative of which are shown in Scheme 1.[3]

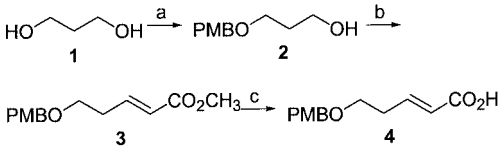


Scheme 1. Some representative natural polyhydroxypyrrolizidines and -indolizidines

In this paper we demonstrate the feasibility of this general strategy applied to the stereocontrolled synthesis of several configurationally differentiated polyhydroxyindolizidines.[4] The dipolarophile chosen for this study contains a carboxylate moiety that plays a double role. It is able to steer the regioselectivity in the intermolecular reaction, and can serve as a removable tether to connect the dipolarophile temporarily to the nitrone for the intramolecular reaction. For this purpose, a new tetrahydropyranyl-protected (THP-protected) nitrone was synthesized, to allow the deprotection of the hydroxy functionality under milder conditions. Moreover, the abilities of three different dipolarophiles − styrene, ethyl acrylate and fumaronitrile − for protection of the nitrone moiety were evaluated both experimentally and computationally.

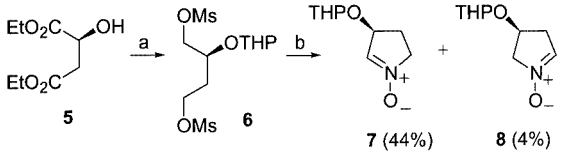
Results and Discussion

The preparation of the previously unknown 5-PMBO-2-pentenoic acid (**4**) (PMB: *p*-methoxybenzyl) was carried out starting from 1,3-propanediol (**1**) through slight modification of published procedures.[5] The monoprotected diol **2**[5a,5b] was subjected to Swern oxidation,[6] followed by Horner−Wadsworth−Emmons olefination to afford the pentenoate **3**[5c,5d] in very good overall yield (Scheme 2). The ester **3** was then hydrolyzed with NaOH to afford the acid **4**, required to connect the dipolarophile with the nitrone.



Scheme 2. (a) *i)* *p*-Anisaldehyde, cat. *p*TsOH, toluene, 110 °C; *ii)* DIBAL, toluene, 0 °C, 91%; (b) *i)* $(COCl)_2$, DMSO, TEA, CH_2Cl_2; *ii)* trimethyl phosphonoacetate, K_2CO_3, H_2O, 98%; (c) *i)* 1 M NaOH, THF; *ii)* HCl, 72%

The novel THP-protected nitrone **7** was prepared on a multigram scale from diethyl (2*S*)-malate in five steps, with only one, final purification and in 44% overall yield. This synthetic methodology had previously been used to make other optically pure pyrroline *N*-oxides,[7] and consists of protection of hydroxy ester **5** with a suitable group, followed in sequence by reduction with $LiAlH_4$, mesylation with methanesulfonyl chloride (MsCl), and cyclization to *N*-hydroxypyrrolidine with NH_2OH in triethylamine (TEA) as solvent. The final oxidation step, carried out with HgO, afforded the THP-protected nitrone **7** and its regioisomer **8** in a 10:1 ratio. As recently reported, use of more environmentally friendly MnO_2 [8] as oxidant afforded the two nitrones **7** and **8** in comparable ratio (each of them as a pair of diastereoisomers), which were easily separated by silica gel chromatography (Scheme 3).

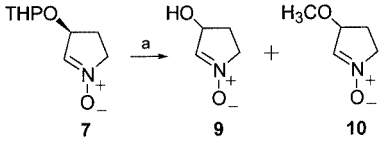


Scheme 3. a: *i)* 2*H*-dihydropyran, Amberlyst 15®, pentane, room temp.; *ii)* $LiAlH_4$, diethyl ether, reflux temperature; *iii)* MsCl, TEA, CH_2Cl_2, 0 °C; b) *i)* NH_2OH HCl, TEA, reflux temperature; *ii)* HgO or MnO_2, CH_2Cl_2, 0 °C → room temp.

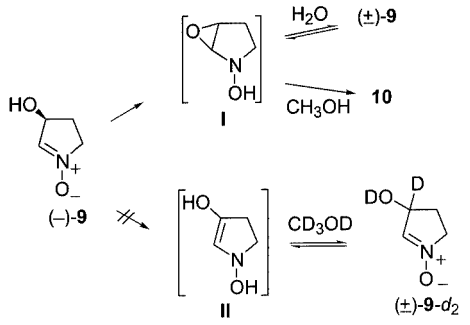
Intramolecular Cycloadditions

To connect the dipolarophile **4** to the cyclic nitrone it was necessary to remove the THP protecting group. Unfortunately, although the THP could be removed under very mild conditions, such as by treatment with an acidic resin (Amberlyst 15®) in methanol at 40 °C, the nitrone **9** turned out to be configurationally unstable and could not be obtained enantiomerically pure.[9] Partial loss of optical activity was also observed during purification of **9** by silica gel chromatography or recrystallization from ethyl acetate.

A thorough analysis of the crude deprotection mixture showed the presence of small amounts of the methylated nitrone **10** (Scheme 4). The racemization process of **9**, as well as the formation of **10**, might be explained by the existence of the transient bicyclic intermediate **I**, which could undergo a nucleophilic attack by H_2O or CH_3OH under the reaction conditions (Scheme 5). On the other hand, the hypothesis that **9** could racemize through the occurrence of fast nitrone/hydroxy enamine tautomerism[10] was discarded, as no H/D exchange of 3-H was observed when the deprotection of **8** was run in CD_3OD (Scheme 5).



Scheme 4. a: Amberlyst 15®, CH_3OH, 40 °C



Scheme 5

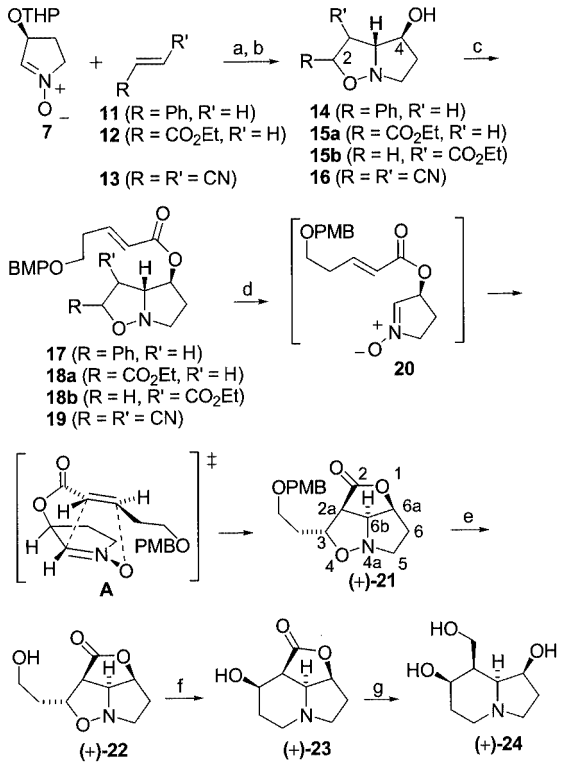
Protection of the nitrone functionality might circumvent the problem of the racemization.[11] The only practical method for nitrone protection available to date consists of the formation of an isoxazolidine, provided that the nitrone functionality can later be restored by retro-cycloaddition. The method was originally reported by Tufariello, who applied it to the synthesis of (±)-cocaine,[11g] and was recently also successfully employed by Holmes for the synthesis of (−)-histrionicotoxine.[11e]

Nitrone **7** was therefore converted into an isoxazolidine before the removal of the THP group. Styrene (**11**),[4][11e] ethyl acrylate (**12**), and fumaronitrile (**13**) were used as dipolarophiles to create the temporary isoxazolidines **14**−**16**. After deprotection, which occurred on the isoxazolidine without any problem, the hydroxy group was connected to the dipolarophile **4**.

The cycloaddition of **7** to **11** took place at 80 °C to give a mixture of two diastereomeric pairs of *anti-exo* and *anti-endo* adducts in a 4:1 ratio and 89% overall yield. The removal of the THP protecting group was achieved with pyridinium *p*-toluenesulfonate (PPTS) in refluxing dry EtOH, and afforded the two diastereomeric isoxazolidines **14** in 89% yield (Scheme 6). The two diastereomeric adducts **14** could easily be separated by chromatography on silica gel and fully characterized, but they were utilized as a mixture in the following synthesis, since both of them afforded the same nitrone intermediate **20** after retro-cycloaddition.

The isoxazolidines **14** were treated with acid **4** in the presence of 1,3-diisopropylcarbodiimide (DIC) and 4-(dimethylamino)pyridine (DMAP) to give the two (4*S*)-esters **17** in 70% yield (Scheme 6). The refluxing temperature of *o*-dichlorobenzene (180 °C)[11e] was necessary to induce the thermal retro-cycloaddition reaction of phenylisoxazolidines **17** to the nitrone **20**, which immediately underwent intramolecular cycloaddition under the reaction conditions. The tricyclic isoxazolidine (+)-**21** was obtained with complete diastereoselectivity, through the *syn*-TS **A**, in 31% yield (Scheme 6).

The efficiencies of ethyl acrylate (**12**) and fumaronitrile (**13**) as protecting dipolarophiles for the nitrone moiety in the process were also evaluated. Ethyl acrylate (**12**) reacted with the nitrone **7** at room temperature to give a mixture of adducts composed, after removal of the THP group, of two pairs of regioisomers, **15a** and **15b**, in a 6:1 ratio (79% overall yield).



Scheme 6. (a) R = Ph, R′ = H: toluene, 80 °C, 10 h, 89%; R = CO_2Et, R′ = H: CH_2Cl_2, room temp., 87%; R = R′ = CN: CH_2Cl_2, room temp., 86%; (b) R = Ph, R′ = H: PPTS, EtOH, reflux, 3 h, 89%; R = CO_2Et, R′ = H and R = H, R′ = CO_2Et: Amberlyst 15, EtOH, reflux, 91%; R = R′ = CN: Amberlyst 15, MeOH, 55 °C, 97%: (c) **4**, DIC, DMAP, CH_2Cl_2 (**17**: 70%; **18**: 94%, **19**: 76%); (d) **17**: *o*-dichlorobenzene, reflux, 14 h, 31%; **18**: *o*-dichlorobenzene, 150 °C, 3 h, 51%; **19**: *o*-xylene, reflux, 1 h, 84%; (e) DDQ, H_2O, CH_2Cl_2, 82%; (f) *i)*: MsCl, TEA, CH_2Cl_2, 0 °C; *ii)*: H_2, Pd/C, MeOH; *iii)*: Ambersep 900® OH, 77%; (g) Red-Al, THF, reflux, 3 h, 78%

The two isoxazolidines **16** were similarly obtained from **7** and fumaronitrile (**13**) in high yields after deprotection (Scheme 6). In this case the removal of THP was achieved with Amberlyst 15 in MeOH at 55 °C and afforded the two diastereoisomers **16** in 97% yield (Scheme 6). When the THP deprotection in the dicyanoisoxazolidines was performed in refluxing EtOH, the formation of small amounts of **13**, **7**, and **9** attested to a promising propensity of the dicyano adducts to undergo thermally induced retro-cycloaddition. The activating effect, exerted on isoxazolidine cycloreversion by electron-withdrawing groups in general and cyano groups in particular, has been already reported, albeit with different nitrones.[11c][11d] In contrast to the reported instability of fumaronitrile cycloadducts even at room temperature,[11d] no retro-cycloaddition was observed by us when the dicyanoisoxazolidines were treated at a temperature below 50 °C, which was of extreme importance for the general application of our process.

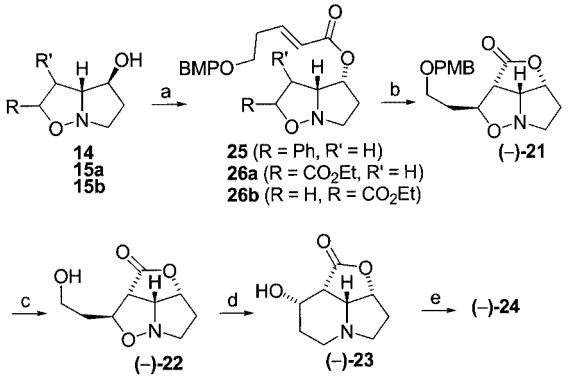
The isoxazolidines **15** and **16** were then acylated as previously (**4**, DIC, DMAP) to give the corresponding esters **18** and **19**, respectively, in good yields (Scheme 6). The esters **18** and **19** underwent the domino retro-cycloaddition/intramolecular cycloaddition process under rather easier condi-

tions than **17** and were completely converted at 145−150 °C after 3 and 1 h, respectively (Scheme 6), to afford (+)-**21** in reasonable to good yields.

Isoxazolidines **19** underwent retro-cycloaddition even at 100 °C, but at that temperature the intramolecular cycloaddition was sluggish and afforded (+)-**21** in very low yields. In contrast, the domino retro-cycloaddition/intramolecular cycloaddition process in refluxing *o*-xylene was fast and (+)-**21** was recovered in high yield (84%) (Scheme 6). The identity of the optical rotatory power in (+)-**21** deriving from the three different isoxazolidines **17**, **18**, and **19** attested to the generality of the process and its ability to induce transformations with complete stereocontrol.

Removal of PMB from (+)-**21** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) afforded the alcohol (+)-**22**, which was subsequently mesylated, and then directly hydrogenated, in the presence of catalytic amounts of Pd/C, to give the indolizidine (+)-**23** (77% yield) through a domino isoxazolidine ring-opening/intramolecular nucleophilic substitution.[12] Reduction of the lactone moiety with Red-Al afforded the final trihydroxyindolizidine (+)-**24** in 78% yield ([α] = +57.8) (Scheme 6).

Its enantiomer (−)-**24** could be synthesized from nitrone **7**, in an enantiodivergent approach, by condensing the same intermediate isoxazolidine alcohols **14**−**15**[4] with pentenoate **4** under Mitsunobu esterification conditions,[13] which cause the inversion of configuration at C-4 (see below). The mixture of adducts **14** was treated with the pentenoate **4** in the presence of diethyl azodicarboxylate (DEAD) and polymer-supported Ph_3P, to give the esters **25** with clean inversion of configuration at C-4 (59% yield) (Scheme 7). Analogously, adducts **15** gave the esters **26** under the classical Mitsunobu reaction conditions (82% yield based on 50% conversion) (Scheme 7).



Scheme 7. (a) **14**: **4**, PPh_3 (polystyrene-supported), DEAD, CH_2Cl_2, 59%; **15**: **4**, PPh_3, DEAD, THF, 82% (50% conversion); (b) **25**: *o*-dichlorobenzene, reflux, 64 h, 62%;. **26**: *o*-dichlorobenzene, 150 °C, 3 h, 74%; (c) TFA, CH_2Cl_2, room temp., 70%; (d) *i)*: MsCl, TEA, CH_2Cl_2, 0 °C; *ii)*: H_2, Pd/C, MeOH; *iii)*: Ambersep 900® OH, 77%; (e) Red-Al, THF, reflux, 3 h, 91%

Unfortunately, any attempt to run the Mitsunobu reaction with **16** as the β-dinitrile moiety proved to be affected under Mitsunobu conditions, affording mainly decomposition products. The use of the Mitsunobu reaction with similar dinitrile compounds is very little addressed in the literature, to the best of our knowledge, and certainly needs further investigation.

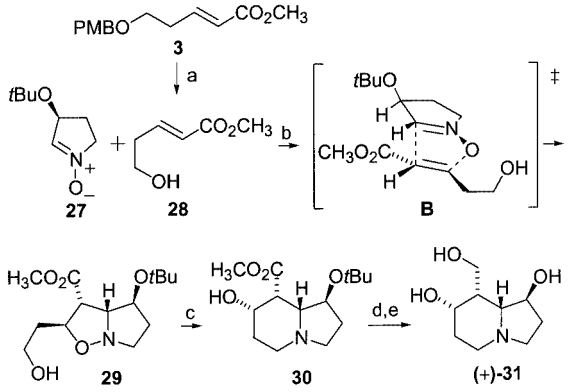
The tricyclic isoxazolidine (−)-**21** (Scheme 7) was obtained from **25** and **26** by heating at 180 °C and 150 °C, respectively, and was converted into (−)-**24** by treatment with trifluoroacetic acid (TFA) to remove the PMB group and mesylation by the same procedure as used to obtain (+)-**24**. The optical rotation of (−)-**24** ([α] = −57.6) proved that the Mitsunobu reaction occurred with complete inversion of configuration in both isoxazolidines **14** and **15**.

Intermolecular Cycloaddition

As previously pointed out, the intermolecular 1,3-dipolar cycloaddition of 3-alkoxy nitrones occurs preferentially with *anti* diastereofacial selectivity to afford the adduct characterized by a *trans* (OR, bridgehead H) relationship. The C-1 epimer of indolizidine (−)-**24** was therefore expected to be easily available from the same starting materials and through the same methodology, just switching from the intra- to the intermolecular mode in the cycloaddition step.

In this case the OH protecting group had to be removed only in the last step. The *tert*-butyl-protected nitrone **27** was therefore used instead of **7**, in order to avoid the formation of diastereomers.

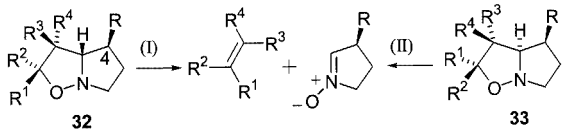
The intermolecular cycloaddition of **27**, obtained from L-malic acid,[7a] with 5-hydroxypentenoate **28**, obtained from **3** by treatment with ceric ammonium nitrate (CAN) (Scheme 8), was carried out at 60 °C and was completely regio- and diastereoselective. As expected,[14] the sole cycloadduct **29**, deriving from an *anti*(O*t*Bu)-*endo*(CO_2CH_3) approach of the two reagents (TS **B**, Scheme 8), was formed. (2*S*,3*R*,3a*S*,4*S*)-Pyrrolo[1,2-*b*]isoxazolidine **29** was sequentially mesylated and hydrogenated on Pd/C to give the indolizidine **30** in 83% overall yield. Reduction of the ester moiety with Red-Al, followed by hydrolysis of the *tert*-butyl ether with TFA, afforded the enantiomerically pure indolizidine (+)-**31**, a diastereoisomer of **24**, in high yields (85%) (Scheme 8).



Scheme 8. (a) CAN, CH_3CN/H_2O or TFA, CH_2Cl_2; 66%; (b) toluene, 60 °C, 1 d, 77%; (c) *i)*: MsCl, TEA, CH_2Cl_2, 0 °C; *ii*: H_2, Pd/C, MeOH; *iii)*: Ambersep 900® OH, 83%; (d) Red-Al, THF, reflux, 89%; (e) *i)*: TFA, H_2O; *ii)*: Ambersep 900® OH, 95%

Computational Data

Semiempirical and ab initio calculations were performed on model cycloreversion reactions I and II of *anti* and *syn* adducts **32** and **33**, respectively, in order to explain the different propensities of pyrrolo[1,2-*b*]isoxazolidines **17**, **18**, **19**, **25**, and **26** to undergo retro-cycloaddition (Scheme 9). All calculations were performed with a Silicon Graphics O2 R10000, by using the Spartan software package (SPARTAN, SGI Version 5.1.1, Wavefunction, Inc., **1991−1998**). The structures of **32**, **33**, and transition states (TSs) were fully optimized at RHF/AM1, PM3, STO3G, and 3-21G* levels in the gas phase. Each TS showed only one imaginary frequency, the corresponding vibration being associated with the nuclear motion along the reaction coordinates.



Scheme 9. Model retro-cycloaddition reactions I and II

The 4-unsubstituted pyrrolo[1,2-*b*]isoxazolidines **32b−32g** showed increasing activation energy (ΔE_a) values in the order CN < CO_2Me < Ph at all the calculation levels (Table 1). The same trend was found for the semiempirical ΔE_a values of the corresponding OMe-*anti* and OMe-*syn* adducts **32h−32m** and **33h−33m**.

Table 1. Calculated activation energies (ΔE_a, kcal/mol)for model reactions I and II

	R	R^1	R^2	R^3	R^4	AM1 ΔE_a[a]	PM3 ΔE_a	STO3G ΔE_a	3-21G* ΔE_a
32a	H	H	H	H	H	60.9	68.0	139.8	65.3
32b	H	H	CN	CN	H	49.2	57.0	119.8	49.5
32c	H	CN	H	H	CN	47.6	56.2	120.0	51.5
32d	H	H	E[b]	H	H	54.1	61.8	132.0	57.8
32e	H	E[b]	H	H	H	54.5	62.5	134.2	61.4
32f	H	H	Ph	H	H	57.0	63.5	134.9	67.8
32g	H	Ph	H	H	H	57.0	64.0	136.2	69.4
32h	OMe	H	CN	CN	H	49.4	56.7		
32i	OMe	CN	H	H	CN	48.3	56.2		
32j	OMe	H	E[b]	H	H	54.5	62.3		
32k	OMe	E[b]	H	H	H	54.9	62.1		
32l	OMe	H	Ph	H	H	57.5	64.6		
32m	OMe	Ph	H	H	H	57.3	64.5		
33h	OMe	H	CN	CN	H	51.0	57.5		
33i	OMe	CN	H	H	CN	48.4	55.8		
33j	OMe	H	E[b]	H	H	55.3	60.3		
33k	OMe	E[b]	H	H	H	55.5	62.4		
33l	OMe	H	Ph	H	H	57.5	63.8		
33m	OMe	Ph	H	H	H	58.4	64.3		

[a] ΔE_a = E(TS) − E(lowest energy conformer of **32** or **33**).[15] [b] E = CO_2Me.

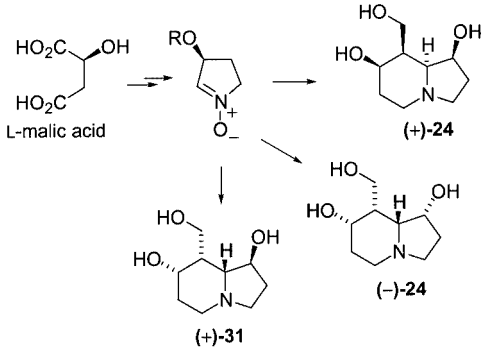
The experimentally determined thermal stability of pyrrolo[1,2-*b*]isoxazolidines was qualitatively well reproduced by both semiempirical and ab initio calculations on the model reactions I and II.

These data support the experimental results, indicating that fumaronitrile (**13**) is in general the most suitable reagent for protection of the nitrone moiety under mild reaction conditions, through a cycloaddition-cycloreversion process. In the cases reported in this study its convenience was partially limited by the lack of stability of the two vicinal nitrile groups under Mitsunobu reaction conditions.

Conclusion

This study has established the high flexibility of application of the cycloaddition approach to enantiomerically pure OR-substituted pyrroline *N*-oxides for the synthesis of substituted polyhydroxyindolizidines.

The two enantiomerically pure hydroxyindolizidines (1*S*,7*R*,8*R*,8*aS*)-**24** and (1*R*,7*S*,8*S*,8a*R*)-**24** were synthesized starting from L-malic acid derivative **7** by an efficient enantiodivergent process, and their diastereoisomer (1*S*,7*S*,8*S*,8a*R*)-**31** was similarly obtained from **27** (Scheme 10). Complete control over the relative configurations of the three new stereocenters was achieved by carrying out the cycloadditions either intra- or intermolecularly. Both the enantiomers (+)-**24** and (−)-**24** could be obtained by proper selection of the esterification mode when assembling the substrate for intramolecular cycloaddition. Analogously, inversion of configuration prior to execution of the intermolecular cycloaddition[2e] might furnish access to the enantiomeric (−)-**31**.



Scheme 10

The performances of three different dipolarophiles − styrene, ethyl acrylate, and fumaronitrile − as protecting reagents for the nitrone moiety were also evaluated. Both experimental and computational studies proved that the dipole could be regenerated from the fumaronitrile cycloadducts more easily and quickly than from the other adducts.

The whole process featured complete stereocontrol over four contiguous stereogenic centers in the final products and appears to be of general application for structurally related 1,3-dipoles and dipolarophiles, which will be the object of further studies in our group.

Experimental Section

General Remarks: All reactions requiring anhydrous conditions were carried out under nitrogen and the solvents were appropriately

dried before use. R_f values refer to TLC on 0.25-mm silica gel plates (Merck F_{254}). Melting points (m.p.) were determined with an RCH Kofler apparatus. Polarimetric measures were performed with a JASCO DIP-370 or a Perkin−Elmer 241 polarimeter. NMR spectra were recorded with Varian Gemini (^{1}H, 200 MHz), VXR 300 (^{1}H, 300 MHz), or Bruker DRX 500 (^{1}H, 500 MHz) instruments, the NMR spectroscopic data are reported in δ (ppm) from TMS at 25 °C. IR spectra were recorded with a Perkin−Elmer 881 spectrophotometer. Mass spectra were recorded with a QMD 1000 Carlo Erba instrument by GC or direct inlet; relative percentages are shown in brackets. Elemental analyses were performed with a Perkin−Elmer 240 C or a Perkin−Elmer 2400 analyzer.

3-(4-Methoxybenzyloxy)-1-propanol (2):[5a][5b] A solution of 1,3-propanediol (**1**, 24 mL, 0.33 mol) and *p*-anisaldehyde (40 mL, 0.33 mol) in toluene (41 mL) was treated with a catalytic amount of *p*-toluenesulfonic acid monohydrate (100 mg) and then heated under reflux in a Dean−Stark apparatus for 11 h. The solvent was evaporated and the resulting crude acetal (64 g, quantitative yield) was directly reduced to propanol **2**.

2-(4-Methoxyphenyl)-1,3-dioxane: R_f = 0.68 (petroleum ether/ethyl acetate, 2:1). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.44−7.40 (m, 2 H, Ar), 6.92−6.87 (m, 2 H, Ar), 5.47 (s, 1 H, 2-H), 4.25 (m, 2 H, 4-H_a, 6-H_a) , 3.99 (m, 2 H, 4-H_b, 6-H_b), 3.80 (s, 3 H, CH_3O), 2.35−2.10 (m, 1 H, 5-H_a), 1.50−1.40 (m, 1 H, 5-H_b) ppm. The crude acetal was dissolved in toluene (100 mL) and the solution was cooled in an ice/salt bath. Diisobutylaluminium hydride (DIBAL, 275 mL, 1.5 M in toluene) was added dropwise at such a rate as to maintain the mixture temperature at 0 °C. The reaction mixture was stirred overnight at room temp., diluted with toluene (80 mL), and cooled in an ice/water bath. Methanol (45 mL) was added dropwise at such a rate as to keep the temperature below 40 °C. Water (40 mL) was then added dropwise and the reaction mixture was stirred at room temp. for 1 h. The white precipitate was filtered through a short pad of Celite and thoroughly washed with toluene. The filtrate was concentrated to give the crude monoprotected propanol **2** (59.2 g, 91%) as a yellow oil, which was used in the next step without further purification.

Compound 2: R_f = 0.50 (petroleum ether/ethyl acetate, 9:1). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.26−7.22 (m, 2 H, Ar), 6.89−6.85 (m, 2 H, Ar), 4.45 (s, 2 H, CH_2Ar), 3.80 (s, 3 H, CH_3O), 3.76 (t, *J* = 5.8 Hz, 2 H, 3-H), 3.63 (t, *J* = 5.5 Hz, 2 H, 1-H), 1.86 (quint, *J* = 5.6 Hz, 2 H, 2-H) ppm.

Methyl (2*E*)-5-(4-Methoxybenzyloxy)-2-pentenoate (3): Swern Oxidation: A solution of DMSO (20.3 mL, 286 mmol) in CH_2Cl_2 (42 mL) was added to a solution of oxalyl chloride (10.6 mL, 122 mmol) in CH_2Cl_2 (125 mL), cooled at −65 °C. After 5 min, a solution of **2** (20.0 g, 102 mmol) in CH_2Cl_2 (83 mL) was added dropwise to the cold mixture over 5 min. After 20 min, NEt_3 (71 mL, 0.510 mol) was added. The mixture was allowed to warm to room temp. and poured into water (125 mL). The organic phase was separated and the aqueous phase was extracted twice with CH_2Cl_2 (2 × 100 mL). The collected organic phases were washed with brine, dried with anhydrous Na_2SO_4, and concentrated to give the crude aldehyde (19.8 g, quantitative yield) as a yellow oil, which was used in the next step without further purification.

3-(4-Methoxybenzyloxy)propionaldehyde: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 9.78 (t, *J* = 1.8 Hz, 1 H, 1-H), 7.30−7.24 (m, 2 H, Ar), 6.98−6.66 (m, 2 H, Ar), 4.47 (s, 2 H, CH_2Ar), 3.82 (s, 3 H, CH_3O), 3.80 (t, *J* = 6.8 Hz, 2 H, 3-H), 2.70 (td, *J* = 6.8, 1.8 Hz, 2 H, 2-H) ppm.

Horner−Wadsworth−Emmons Reaction: Trimethyl phosphonoacetate (1.1 mL, 6.76 mmol) was added to a solution of K_2CO_3 (2.0 g, 13.5 mmol) in water (2 mL), cooled at 0 °C. The reaction mixture was stirred for 15 min, and a solution of the crude aldehyde (1.0 g, 5.2 mmol) in diethyl ether (1.5 mL) was then added. The heterogeneous mixture was stirred overnight at room temp. and then extracted with diethyl ether. The organic phase was dried with anhydrous Na_2SO_4 and concentrated to give the ester **3** (1.28 g, 98%) as a yellow oil, sufficiently pure to be used in the next step without further purification. A sample purified by chromatography on silica gel (eluent: petroleum ether/ethyl acetate, 5:1) afforded analytically pure **3**.

Compound 3: R_f = 0.33 (petroleum ether/ethyl acetate, 5:1). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.28−7.23 (m, 2 H, Ar), 6.99 (dt, *J* = 15.7, 6.8 Hz, 1 H, 3-H), 6.91−6.87 (m, 2 H, Ar), 5.90 (dt, *J* = 15.7, 1.5 Hz, 1 H, 2-H), 4.46 (s, 2 H, CH_2Ar), 3.81 (s, 3 H, CH_3OAr), 3.73 (s, 3 H, CO_2CH_3), 3.56 (t, *J* = 6.6 Hz, 2 H, 5-H), 2.50 (qd, *J* = 6.6, 1.5 Hz, 2 H, 4-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 166.7 (s, C-1), 159.2 (s, Ar), 145.9 (d, C-3), 130.1 (s, Ar), 129.2 (d, 2 C Ar), 122.3 (d, C-2), 113.7 (d, 2 C Ar), 72.6 (t, *C*H_2Ar), 67.8 (t, C-5), 55.1 (q, *C*H_3OAr), 51.3 (q, CO_2CH_3), 32.5 (t, C-4) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3008, 2954, 2862, 1712, 1656, 1610, 1511, 1246, 1171, 1080 cm^{-1}. MS (70 eV, EI): *m*/*z* (%) = 250 (1) [M$^+$], 190 (6), 135 (20), 121 (100), 122 (89), 114 (39). $C_{14}H_{18}O$ (250.29): calcd. C 67.18, H 7.25; found C 67.11, H 7.29.

(2*E*)-5-(4-Methoxybenzyloxy)-2-pentenoic Acid (4): A solution of **3** (12.0 g, 48 mmol) in THF (22.5 mL) was treated with a 1 M aqueous solution of NaOH (72 mL). The resulting mixture was stirred at room temp. for 5 h and diluted with diethyl ether (60 mL). The layers were separated, and the aqueous layer was acidified with 6 M HCl and extracted with CH_2Cl_2 (6 × 90 mL). The combined extracts were dried with Na_2SO_4, filtered, and concentrated. The crude product was washed with diisopropyl ether to give **4** (8.15 g, 72%) as a pure, colorless solid.

Compound 4: R_f = 0.18 (CH_2Cl_2/MeOH, 30:1); m.p. 65−67 °C. ^{1}H NMR (200 MHz $CDCl_3$): δ = 7.29−7.24 (m, 2 H, Ar), 7.09 (dt, *J* = 15.7, 6.8 Hz, 1 H, 3-H), 6.91−6.87 (m, 2 H, Ar), 5.91 (dt, *J* = 15.7, 1.5 Hz, 1 H, 2-H), 4.46 (s, 2 H, CH_2Ar), 3.82 (s, 3 H, CH_3O), 3.58 (t, *J* = 6.4 Hz, 2 H, 5-H), 2.54 (qd, *J* = 6.6, 1.5 Hz, 2 H, 4-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 171.7 (s, C-1), 159.2 (s, Ar), 148.6 (d, C-3), 130.0 (s, Ar), 129.3 (d, 2 C, Ar), 122.2 (d, C-2), 113.8 (d, 2 C, Ar), 72.7 (t, *C*H_2Ar), 67.6 (t, C-5), 55.2 (q, *C*H_3O), 32.6 (t, C-4) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3001, 2940, 2865, 1695, 1512, 1246, 1171, 1086 cm^{-1}. MS (70 eV, EI): *m*/*z* (%) = 236 (5) [M$^+$], 190 (4), 163 (3), 137 (27), 121 (100), 100 (22), 77 (20). $C_{13}H_{16}O_4$ (236.26): calcd. C 66.09, H 6.83; found C 66.15, H 6.99.

(3*S*)-3-[(Tetrahydro-2*H*-pyran-2-yl)oxy]pyrroline 1-Oxide (7): A solution of diethyl (*S*)-malate (**5**, 15.0 g, 79 mmol) and 2*H*-dihydropyran (8.6 mL, 95 mmol) in pentane (22 mL) was added to a suspension of Amberlyst 15® (1.97 g) in pentane (10 mL). The reaction mixture was stirred at room temp. for 1.5 h, filtered through Celite, and concentrated. The mixture of the two diastereoisomeric tetrahydropyranyl ethers was diluted with diethyl ether (80 mL) and added dropwise to a suspension of $LiAlH_4$ (6.84 g, 180 mmol) in diethyl ether (220 mL). The white suspension was vigorously stirred and heated under reflux for 6 h. A saturated aqueous Na_2SO_4 solution (80 mL) was slowly added to the reaction mixture. The suspension was then filtered through Celite, and the salts were washed thoroughly with diethyl ether. The ethereal filtrate was dried with Na_2SO_4, filtered, and concentrated. The crude diols were dissolved in CH_2Cl_2 (85 mL) and NEt_3 (30.6 mL, 221 mmol). Methanesul-

fonyl chloride (MsCl, 14.2 mL, 184 mmol) was added dropwise to the solution at 0 °C, and the mixture was stirred at room temp. for 1 h, cooled to 0 °C, and treated with ice (50 mL) and an aqueous saturated K_2CO_3 solution (50 mL). The two phases were separated and the aqueous phase was extracted with CH_2Cl_2 (50 mL). The collected organic phases were washed with saturated Na_2CO_3 (50 mL) and brine (50 mL), dried with K_2CO_3, and filtered. The solvent was removed to give product **6** as a mixture of two diastereoisomers. A suspension of crude **6** and hydroxylamine hydrochloride (21.0 g, 300 mmol) in NEt_3 (200 mL) was heated at reflux temperature for 5 h. The solvent was then evaporated and the resulting yellow solid was washed thoroughly with diethyl ether. The ethereal extracts were concentrated to give the crude *N*-hydroxypyrrolidine as a mixture of two diastereoisomers. The crude product was dissolved in CH_2Cl_2 (250 mL) and cooled to 0 °C, and yellow mercury oxide (17.8 g, 82 mmol) was added in small portions. The green suspension was stirred at room temp. for 3 h, filtered through Celite, and concentrated. Purification and separation of the two regioisomeric nitrones **7** and **8** (each of them as a mixture of two diastereoisomers) by chromatography on silica gel (eluent: ethyl acetate/MeOH, 10:1) gave **7** (6.46 g, 44% overall yield from the starting diester **5**) as a colorless oil and **8** (678 mg, 4%) as a colorless oil.

Compound 7: Mixture of two diastereoisomers in a 1.3:1 ratio: R_f = 0.20 and 0.13 (ethyl acetate/MeOH, 10:1). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.02−6.98 (m, 1 H, 2-H), 5.00−4.96 (m, 1 H, OC*H*O THP, major isomer), 4.87−4.84 (m, 1 H, OC*H*O THP, minor isomer), 4.75−4.68 (m, 1 H, 3-H), 4.24−4.06 (m, 1 H, 5-H_a), 3.92−3.78 (m, 2 H, 5-H_b, OC*H*HCH_2 THP), 3.57−3.48 (m, 1 H, OCH*H*CH_2 THP), 2.70−2.49 (m, 1 H, 4-H_a), 2.37−2.15 (m, 1 H, 4b-H), 1.91−1.53 (m, 6 H, CH_2 THP) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): major isomer: δ = 132.5 (d, C-2), 97.2 (d, O*C*HO THP), 74.9 (d, C-3), 61.5, 60.4 (t, C-5, O*C*H_2 THP), 29.4 (t, C-4), 27.3, 24.1, 18.3 (t, *C*H_2 THP) ppm; minor isomer: δ = 133.9 (d, C-2), 97.6 (d, O*C*HO THP), 76.1 (d, C-3), 61.2, 59.8 (t, C-5, O*C*H_2 THP), 29.4 (t, C-4), 26.5, 24.1, 18.2 (t, *C*H_2 THP) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 2900, 1590, 1450, 1380, 1280 cm^{-1}. MS (70 eV, EI): *m*/*z* (%) = 185 (2) [M$^+$], 179 (6), 169 (15), 85 (100). $C_9H_{15}O_3$ (185.22): calcd. C 58.36, H 8.16, N 7.56; found C 58.07, H 8.20, N 7.29.

(2*R*,3a*R*,4*S*)- and (2*S*,3a*R*,4*S*)-Hexahydro-2-phenylpyrrolo[1,2-*b*]isoxazol-4-ol (14): A solution of nitrone **7** (2.23 g, 12 mmol) and styrene (**11**, 2.77 mL, 24 mmol) in toluene (12 mL) was heated at 80 °C for 10 h and then concentrated. Purification by chromatography on silica gel (eluent: ethyl acetate/petroleum ether, 2:3) gave a mixture of four diastereoisomeric adducts (2.76 g, 89%), which was diluted with EtOH (60 mL) and treated with pyridinium *p*-toluenesulfonate (PPTS, 3.6 g, 14.4 mmol). The mixture was heated under reflux for 3 h and concentrated under reduced pressure. The crude product was dissolved in MeOH (60 mL), stirred in the presence of Ambersep 900® OH, filtered, and concentrated. The two diastereomeric isoxazolidines **14** (2.19 g, 10.7 mmol, 89% based on **7**) were obtained in a 4:1 ratio as a colorless solid. Separation by flash column chromatography on silica gel (eluent: ethyl acetate) afforded the two isomers **14**. The relative configurations of the two pure compounds **14** were deduced by analysis of NOESY spectra. The *cis* relationship between 2-H (δ = 4.98 ppm) and 4-H (δ = 4.26 ppm) in the major isomer (deriving from an *anti-exo* TS), was confirmed by the presence of a significant cross-peak (Figure 3). No NOE peak was detected between the corresponding 2-H (δ = 5.03 ppm) and 4-H (δ = 4.31 ppm) in the spectrum of the minor isomer (deriving from an *anti-endo* TS), in agreement with the assigned configuration (Figure 3).

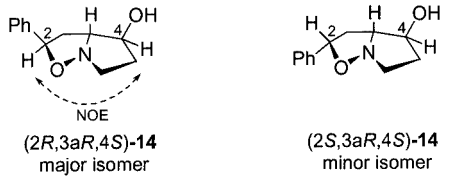


Figure 3. Determination of the configurations of adducts **14** by NOESY

Isomer (2*R*,3a*R*,4*S*)-14: Colorless solid; R_f = 0.16 (ethyl acetate). $[\alpha]_D^{19}$ = −6.9 (*c* = 1.0 in $CHCl_3$); m.p. 118−119 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.40−7.30 (m, 5 H, Ph), 4.98 (dd, *J* = 8.2, 6.8 Hz, 1 H, 2-H), 4.26 (dt, *J* = 5.8, 3.5 Hz, 1 H, 4-H), 3.75 (m, 1 H, 3a-H), 3.59−3.45 (m, 1 H, 6-H_a), 3.40−3.30 (m, 1 H, 6-H_b), 2.50−2.45 (m, 2 H, 3-H), 2.37−2.20 (m, 1 H, 5a-H), 1.88−1.74 (m, 1 H, 5b-H), 1.74 (br. s, 1 H, OH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 139.1 (s, Ph), 128.5 (d, 2 C, Ph), 128.0 (d, Ph), 126.4 (d, 2 C Ph), 79.2, 77.1 (d, C-2, C-4), 74.0 (d, C-3a), 55.7 (t, C-6), 42.6 (t, C-3), 33.8 (t, C-5) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3658, 3323 br, 3071, 2949, 1491, 1445 cm^{-1}. MS (70 eV, EI): *m*/*z* (%) = 205 (7) [M$^+$], 188 (8), 161 (5), 144 (30), 115 (15), 104 (100), 91 (11). $C_{12}H_{15}NO_2$ (205.26): calcd. C 70.22, H 7.37, N 6.82; found C 70.04, H 7.51, N 6.63.

Isomer (2*S*,3a*R*,4*S*)-14: Colorless solid; R_f = 0.27 (ethyl acetate). $[\alpha]_D^{19}$ = +18.3 (*c* = 1.0 in $CHCl_3$); m.p. 161−163 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.42−7.26 (m, 5 H, Ph), 5.03 (dd, *J* = 9.4, 5.8 Hz, 1 H, 2-H), 4.31 (dt, *J* = 5.5, 4.2 Hz, 1 H, 4-H), 3.82 (ddd, *J* = 8.8, 5.5, 1.8 Hz, 1 H, 3a-H), 3.35−3.27 (m, 2 H, 6-H), 2.95 (br. s, 1 H, OH), 2.81 (ddd, *J* = 12.2, 5.8, 1.8 Hz, 1 H, 3-H_a), 2.19 (ddd, *J* = 12.2, 9.4, 8.8 Hz, 1 H, 3-H_b), 2.05−1.94 (m, 2 H, 5-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 139.8 (s, Ph), 128.3 (d, 2 C, Ph), 127.7 (d, Ph), 126.5 (d, 2 C, Ph), 79.3, 71.4 (d, C-2, C-4), 69.5 (d, C-3a), 53.5 (t, C-6), 38.4 (t, C-3), 34.1 (t, C-5) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3624, 3032, 2950, 1490, 1438 cm^{-1}. MS (70 eV, EI): *m*/*z* (%) = 205 (9) [M$^+$], 188 (10), 161 (3), 144 (32), 115 (14), 104 (100), 77 (26). $C_{12}H_{15}NO_2$ (205.26): calcd. C 70.22, H 7.37, N 6.82; found C 70.42, H 7.45, N 6.66.

(3a*R*,4*S*)-Hexahydro-4-hydroxypyrrolo[1,2-*b*]isoxazole-2-carboxylic Acid and Ethyl (3a*R*,4*S*)-Hexahydro-4-hydroxypyrrolo[1,2-*b*]isoxazole-3-carboxylate (15): A solution of nitrone **7** (1.0 g, 5.64 mmol) and ethyl acrylate (**12**, 797 μL, 7.33 mmol) in CH_2Cl_2 (6 mL) was stirred at room temp. for 1 d and then concentrated. Purification of the residue by chromatography on silica gel (eluent: ethyl acetate) gave a mixture of cycloadducts (1.4 g, 87%) that was diluted with EtOH (25 mL) and treated with Amberlyst 15® (300 mg). The mixture was heated at reflux for 1 h, filtered, and concentrated. The crude product was filtered through a small pad of silica gel (eluent: ethyl acetate; then ethyl acetate/MeOH, 1:1) to give a mixture of the two regioisomers **15** (each as a pair of diastereoisomers) (895 mg, 91%, **15a/15b**, 6:1 ratio) that was used in the next step without further purification and separation.

Isomer 15a: Major isomer; colorless oil; R_f = 0.17 (ethyl acetate). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.52 (dd, *J* = 8.4, 4.4 Hz, 1 H, 2-H), 4.28−4.16 (m, 3 H, 4-H, CH_2CH$_3$), 3.68−3.60 (m, 1 H, 3a-H), 3.45−3.35 (m, 2 H, 6-H), 2.87 (ddd, *J* = 12.8, 8.8, 4.4 Hz, 1 H, 3-H_a), 2.34 (ddd, *J* = 12.8, 8.1, 4.8 Hz, 1 H, 3-H_b), 2.33−2.22 (m, 1 H, 5-H_a), 2.00 (br. s, 1 H, OH) 1.80−1.70 (m, 1 H, 5-H_b), 1.30 (t, *J* = 7.1 Hz, 3 H, CH$_2$C*H*$_3$) ppm. ^{13}C NMR (75 MHz,

$CDCl_3$): δ = 171.4 (s, *C*O), 78.3, 75.3 (d, C-2, C-4), 73.7 (d, C-3a), 61.5 (t, *C*H_2CH$_3$), 55.3 (t, C-6), 37.9 (t, C-3), 33.7 (t, C-5), 14.1 (q, CH$_2$*C*H$_3$) ppm. IR ($CDCl_3$): ṽ = 3615, 2945, 1730, 1263, 1205 cm^{-1}. MS (70 eV, EI): *m*/*z* (%) = 201 (4) [M$^+$], 158 (3), 128 (3), 83 (100).

(4*S*)-2,3-Dicyanohexahydropyrrolo[1,2-*b*]isoxazol-4-ol (16): A solution of nitrone **7** (1.0 g, 5.64 mmol) and fumaronitrile (**13**, 570 mg, 7.30 mmol) in CH_2Cl_2 (6 mL) was stirred at room temp. for 1 d and concentrated. The residue was filtered through a small pad of silica gel (eluent: petroleum ether/ethyl acetate, 1:1) to give a mixture of cycloadducts (1.3 g, 86%) that was diluted with MeOH (50 mL) and treated with a catalytic amount of Amberlyst 15®. The mixture was stirred at 55 °C for 1 h, filtered, and concentrated. A mixture of three isomers **16** (919 mg, 97%) was obtained and was used in the next step without further purification and separation.

Compound 16: Major isomer; R_f = 0.40 (petroleum ether/ethyl acetate, 1:1). ^{1}H NMR (200 MHz, CD_3OD): δ = 5.46 (d, *J* = 2.3 Hz, 1 H, 2-H), 4.56−4.49 (m, 1 H, 4-H), 4.49 (dd, *J* = 9.0, 2.2 Hz, 1 H, 3a-H), 3.93 (dd, *J* = 9.0, 2.3 Hz, 1 H, 3-H), 3.54−3.34 (m, 2 H, 6-H), 2.40−2.22 (m, 1 H, 5-H$_a$), 1.94−1.81 (m, 1 H, 5-H$_b$) ppm. ^{13}C NMR (50 MHz, CD_3OD): δ = 117.3 (s, *C*N), 117.2 (s, *C*N), 75.7, 74.9 (d, C-2, C-4), 69.6 (d, C-3a), 55.6 (t, C-6), 43.5 (d, C-3), 34.2 (t, C-5) ppm. IR ($CDCl_3$): ṽ = 3612, 2928, 2252, 1117 cm^{-1}. MS (70 eV, EI): *m*/*z* (%) = 152 (3) [M$^+$ − HCN], 85 (25), 78 (100), 77 (66).

Synthesis of Esters 17, 18, and 19

General Procedure: A solution (0.1 M) of isoxazolidines **14**, **15**, or **16** in CH_2Cl_2 (**14** and **15**) or THF (**16**) was treated with **4** (2.3 equiv.) and 4-(dimethylamino)pyridine (DMAP, 0.25 equiv.), and 1,3-diisopropylcarbodiimide (DIC, 2.5 equiv.) was then added dropwise at room temp. The mixture was stirred for 1 d at room temp., concentrated, and filtered through a short pad of silica gel. The products **17**, **18**, and **19** were obtained as mixtures of isomers and were used in the next step without further purification and separation.

(3a*R*,4*S*)-Hexahydro-2-phenylpyrrolo[1,2-*b*]isoxazol-4-yl (2*E*)-5-(4-Methoxybenzyloxy)-2-pentenoate (17): 70% yield; colorless oil. Major isomer: R_f = 0.27 (diisopropyl ether). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.44−7.25 (m, 7 H, Ar), 7.10−6.86 (m, 3 H, Ar, = C*H*CH$_2$), 5.90 (dt, *J* = 15.7, 1.5 Hz, 1 H, COC*H*=), 5.18−5.03 (m, 2 H, 2-H, 4-H), 4.47 (s, 2 H, C*H*$_2$Ar), 3.83 (s, 3 H, C*H*$_3$O), 3.72−3.41 (m, 3 H, 3a-H, 6-H), 3.58 (t, *J* = 6.4 Hz, 2 H, CH$_2$C*H*$_2$O), 2.77−2.35 (m, 3 H, 3-H, 5-H$_a$), 2.52 (qd, *J* = 6.8, 1.5 Hz, 2 H, C*H*$_2$CH$_2$O), 2.00−1.80 (m, 1 H, 5-H$_b$) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 166.2 (s, *C*O), 159.4 (s, Ar), 146.9 (d, = *C*HCH$_2$), 140.3 (s, Ph), 130.2 (s, Ar), 129.4 (d, 2 C Ar). 128.6 (d, 2 C Ph), 127.9 (d, Ph), 126.2 (d, 2 C Ph), 122.5 (d, CO*C*H=), 113.9 (d, 2 C Ar), 80.0, 79.3 (d, C-2, C-4), 72.8 (t, *C*H$_2$Ar), 72.5 (d, C-3a), 67.9 (t, CH$_2$*C*H$_2$O), 56.2 (t, C-6), 55.4 (q, *C*H$_3$O), 43.1 (t, C-3), 32.8, 30.4 (t, C-5, *C*H$_2$CH$_2$O) ppm.

Ethyl (3a*R*,4*S*)-Hexahydro-4-{[(2*E*)-5-(4-methoxybenzyloxy)-1-oxo-2-pentenyl]oxy}pyrrolo[1,2-*b*]isoxazole-2-carboxylate (18a) and Ethyl (3a*R*,4*S*)-Hexahydro-4-{[(2*E*)-5-(4-methoxybenzyloxy)-1-oxo-2-pentenyl}oxy]pyrrolo[1,2-*b*]isoxazole-3-carboxylate (18b): 94% yield; colorless oil. Major diastereoisomer **18a**: R_f = 0.15 (petroleum ether/ethyl acetate, 2:1). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.30−7.20 (m, 2 H, Ar), 6.96 (dt, *J* = 15.7, 6.8 Hz, 1 H, =C*H*CH$_2$) 6.90−6.81 (m, 2 H, Ar), 5.85 (dt, *J* = 15.7, 1.6 Hz, 1 H, COC*H*=), 5.05−4.95 (m, 1 H, 4-H), 4.54 (dd, *J* = 8.3, 4.1 Hz 1 H, 2-H), 4.44 (s, 2 H, C*H*$_2$Ar), 4.21 (q, *J* = 7.1 Hz, 2 H, C*H*$_2$CH$_3$), 3.79 (s, 3 H, C*H*$_3$O), 3.65−3.43 (m, 1 H, 3a-H), 3.54 (t, *J* = 6.2 Hz, 2 H, CH$_2$C*H*$_2$O), 3.33−3.15 (m, 1 H, 6-H$_a$), 3.03−2.86 (m, 1 H, 6-H$_b$), 2.64−2.28 (m, 3 H, 3-H, 5-H$_a$), 2.48 (qd, *J* = 6.5, 1.5 Hz, 2 H, C*H*$_2$CH$_2$O), 1.93−1.80 (m, 1 H, 5-H$_b$), 1.29 (t, *J* = 7.1 Hz, 3 H, CH$_2$C*H*$_3$) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 171.0 (s, *C*O$_2$Et), 165.7 (s, *C*OCH=), 158.9 (s, Ar), 146.4 (d, =*C*HCH$_2$), 129.8 (s, Ar), 128.9 (d, 2 C Ar), 122.0 (d, CO*C*H=), 113.5 (d, 2 C Ar), 80.5, 75.0 (d, C-2, C-4), 72.4 (t, *C*H$_2$Ar), 71.8 (d, C-3a), 67.5 (t, CH$_2$*C*H$_2$O), 61.1 (t, *C*H$_2$CH$_3$), 55.3 (q, C*H*$_3$O), 55.0 (t, C-6), 37.9 (t, C-3), 32.4, 30.2 (t, C-5, *C*H$_2$CH$_2$O), 13.9 (q, CH$_2$*C*H$_3$) ppm.

(4*S*)-2,3-Dicyanohexahydropyrrolo[1,2-b]isoxazol-4-yl (2*E*)-5-(4-Methoxybenzyloxy)-2-pentenoate (19): 76% yield; colorless oil. Major isomer: R_f = 0.31 (petroleum ether/ethyl acetate, 1:1). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.30−7.23 (m, 2 H, Ar), 7.03 (dt. *J* = 15.6, 6.9 Hz, 1 H, =C*H*CH$_2$), 6.90−6.81 (m, 2 H, Ar), 5.88 (dt, *J* = 15.7, 1.6 Hz, 1 H, COC*H*=), 5.32 (dt, *J* = 7.1, 2.0 Hz, 1 H, 4-H), 5.07 (d, *J* = 1.1 Hz, 1 H, 2-H), 4.45 (s, 2 H, C*H*$_2$Ar), 4.18 (dd, *J* = 9.5, 1.6 Hz, 1 H, 3-H), 4.00 (dd, *J* = 9.5, 2.6 Hz, 1 H, 3a-H), 3.81 (s, 3 H, C*H*$_3$O), 3.72−3.53 (m, 1 H, 6-H$_a$), 3.57 (t, *J* = 6.2 Hz, 2 H, CH$_2$C*H*$_2$O), 3.36 (ddd, *J* = 14.3, 11.7, 6.2 Hz, 1 H, 6-H$_b$), 2.52 (qd, *J* = 6.5, 1.5 Hz, 2 H, C*H*$_2$CH$_2$O), 2.46−2.37 (m, 1 H, 5-H$_a$), 2.08 (ddt, *J* = 14.1, 6.3, 1.8 Hz, 1 H, 5-H$_b$) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 165.6 (s, *C*O), 159.0 (s, Ar), 147.7 (d, =*C*HCH$_2$), 129.9 (s, Ar), 129.1 (d, 2 C Ar), 121.4 (d, CO*C*H=), 115.5 (s, *C*N), 115.3 (s, *C*N), 113.6 (d, 2 C Ar), 77.6 (d,), 72.5 (t, *C*H$_2$Ar), 72.3 (d, C-2 or C-4), 68.3 (d, C-3a), 67.5 (t, CH$_2$*C*H$_2$O), 55.1 (q, *C*H$_3$O), 55.0 (t, C-6), 42.9 (t, C-3), 32.5, 30.5 (t, C-5, *C*H$_2$CH$_2$O).

Synthesis of Esters 25 and 26

General Procedure: A 0.2 M solution of isoxazolidines **14** or **15** (1 equiv.), **4** (1.2 equiv.), and PPh_3 (polystyrene-supported PPh_3 was used with **14**) (3 equiv.) in CH_2Cl_2 (**14**) or in THF (**15**) was cooled at 0 °C, and DEAD (3 equiv.) was added dropwise. The reaction mixture was stirred at 0 °C for 2 h and then at room temp. for 3 d. The polymeric reagent, when present, was filtered off through Celite and the solvent was evaporated. The residue was purified by chromatography on silica gel. The products **25** and **26** were obtained as mixtures of isomers and were used in the next step without further purification and separation.

(3a*R*,4*R*)-Hexahydro-2-phenylpyrrolo[1,2-*b*]isoxazol-4-yl (2*E*)-5-(4-Methoxybenzyloxy)-2-pentenoate (25): 59% yield; colorless oil. Major isomer: R_f = 0.40 (ethyl acetate). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.40−7.21 (m, 7 H, Ar), 7.06 (dt, *J* = 15.8, 6.6 Hz, 1 H, =C*H*CH$_2$), 6.90−6.80 (m, 2 H, Ar), 5.95 (dt, *J* = 15.8, 1.8 Hz, 1 H, COC*H*=), 5.35 (q, *J* = 5.0 Hz, 1 H, 4-H), 5.03 (dd, *J* = 9.1, 6.2 Hz, 1 H, 2-H), 4.50 (s, 2 H, C*H*$_2$Ar), 4.04 (td, *J* = 6.6, 1.8 Hz, 1 H, 3a-H), 3.77 (s, 3 H, C*H*$_3$O), 3.58 (t, *J* = 6.3 Hz, 2 H, CH$_2$C*H*$_2$O), 3.38−3.32 (m, 2 H, 6-H), 2.59−2.50 (m, 3 H, 3-H$_a$, C*H*$_2$CH$_2$O), 2.30−2.20 (m, 3 H, 3-H$_b$, 5-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 165.2 (s, *C*O), 159.0 (s, Ar), 146.8 (d, = *C*HCH$_2$), 139.8 (s, Ph), 133.4 (s, Ar), 129.0 (d, 2 C Ar), 128.3 (d, 2 C Ph), 127.0 (d, Ph), 126.1 (d, 2 C Ph), 122.1 (d, CO*C*H=), 113.6 (d, 2 C Ar), 79.1, 73.9 (d, C-2, C-4), 72.6 (t, *C*H$_2$Ar), 67.8 (d, C-3a), 67.6 (t, CH$_2$*C*H$_2$O), 55.1 (q, *C*H$_3$O), 53.7 (t, C-6), 39.1 (t, C-3), 32.6, 31.2 (t, C-5, *C*H$_2$CH$_2$O) ppm.

(+)-(2a*S*,3*R*,6a*S*,6b*S*)- and (−)-(2a*R*,3*S*,6a*R*,6b*R*)-Hexahydro-3-{2-[(4-methoxyphenyl)methoxy]ethyl}-2*H*-1,4-dioxa-4a-azacyclopenta[*cd*]pentalen-2-one (21)

From 17 and 25: A 0.02 M solution of **17** (75 mg, 0.18 mmol) or **25** (1.046 g, 2.47 mmol) in *o*-dichlorobenzene (9 or 123.5 mL) was

heated at reflux for 14 h or 64 h, respectively. The solution was filtered through silica gel, eluting first with petroleum ether and then with MeOH. The alcohol solution was concentrated and the residue was purified by chromatography on silica gel (eluent: ethyl acetate) to give (+)-**21** (18 mg, 31%) or (−)-**21** (560 mg, 71%), respectively.

From 18 and 26: A 0.02 M solution of **18** (374 mg, 0.89 mmol) or **26** (50 mg, 0.12 mmol) in *o*-dichlorobenzene (44.5 or 6 mL) was heated at 150 °C for 3 h. The solution was filtered through silica gel, eluting first with petroleum ether and then with MeOH. The alcohol solution was concentrated and the residue was purified by chromatography on silica gel (eluent: ethyl acetate) to give (+)-**21** (151 mg, 53%) and (−)-**21** (28 mg, 73%), respectively.

From 19: A solution of **19** (47.3 mg, 0.12 mmol) in *o*-xylene (6 mL) was heated at reflux for 1 h. The solution was filtered through silica gel, eluting first with petroleum ether and then with MeOH. The alcohol solution was concentrated and the residue was purified by chromatography on silica gel (eluent: ethyl acetate) to give (+)-**21** (32.1 mg, 84%).

Compound (+)-21: White solid; R_f = 0.23 (ethyl acetate); m.p. 75−76 °C. $[\alpha]_D^{26}$ = +24.5 (*c* = 0.5 in $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 7.28−7.24 (m, 2 H, Ar), 6.92−6.86 (m, 2 H, Ar), 5.03 (q, *J* = 5.9 Hz, 1 H, 6a-H), 4.64 (dt, *J* = 9.2, 2.6 Hz, 1 H, 3-H), 4.45 (s, 2 H, C*H*$_2$Ar), 4.35 (dd, *J* = 8.6, 6.4 Hz, 1 H, 6b-H), 3.81 (s, 3 H, C*H*$_3$O), 3.61 (dd, *J* = 6.8, 5.3 Hz, 2 H, CH_2CH_2OPMB), 3.46 (dd, *J* = 8.8, 2.6 Hz, 1 H, 2a-H), 3.40−3.31 (m, 1 H, 5-H_a), 3.18−3.09 (m, 1 H, 5-H_b), 2.30−2.21 (m, 2 H, 6-H), 2.13−1.95 (m, 2 H, C*H*$_2$$CH_2$OPMB) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 176.7 (s, *C*O), 159.2 (s, Ar), 130.4 (s, Ar), 129.3 (d, 2 C Ar), 113.8 (d, 2 C Ar), 82.4, 80.9 (d, C-3, C-6a), 72.8 (t, *C*H_2Ar), 70.7 (d, C-6b), 66.2 (t, CH_2*C*H_2OPMB), 55.2 (q, *C*H_3O), 54.9 (d, C-2a), 52.3 (t, C-5), 34.0, 31.9 (t, C-6, *C*$H_2$$CH_2$OPMB) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 2934, 1770, 1510, 1245, 1173, 1085 cm^{-1}. MS (70 eV, EI): *m*/*z* (%) = 319 (0.1) [M^+], 198 (5), 183 (4), 154 (10), 137 (18), 121 (100), 84 (16). $C_{17}H_{21}NO_5$ (319.35): calcd. C 63.94, H 6.63, N 4.39; found C 64.24, H 6.65, N 4.22.

Compound (−)-21: The spectroscopic data are identical to those reported for (+)-**21**, apart from traces of inseparable unidentified impurities.

(+)-(2a*S*,3*R*,6a*S*,6b*S*)-Hexahydro-3-(2-hydroxyethyl)-2*H*-1,4-dioxa-4a-azacyclopenta[*cd*]pentalen-2-one [(+)-22]: DDQ (251 mg, 1.10 mmol) in CH_2Cl_2 (32 mL) was added dropwise to a solution of (+)-**21** (270 mg, 0.85 mmol) in CH_2Cl_2 (180 mL) and water (6 mL), cooled at 0 °C. The mixture was stirred at 0 °C for 3 h, and Na_2SO_4 was added. After the mixture had stirred for 1 h, Na_2SO_4 was filtered off and the solvent was evaporated. The crude product was purified by chromatography on silica gel (eluent: ethyl acetate; then ethyl acetate/MeOH, 1:1) to give the deprotected alcohol (+)-**22** (139 mg, 82%) as a white solid.

Compound (+)-22: White solid; R_f = 0.16 (ethyl acetate/MeOH, 10:1); m.p. 114−116 °C. $[\alpha]_D^{21}$ = +18.1 (*c* = 0.6 in $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 5.07 (dt, *J* = 6.6, 5.0 Hz, 1 H, 6a-H), 4.65 (dt, *J* = 6.2, 2.6 Hz, 1 H, 3-H), 4.42 (dd, *J* = 8.6, 6.2 Hz, 1 H, 6b-H), 3.87−3.69 (m, 2 H, CH_2C*H*$_2$OH), 3.45 (dd, *J* = 8.6, 3.1 Hz, 1 H, 2a-H), 3.44−3.33 (m, 1 H, 5-H_a), 3.19−3.06 (m, 1 H, 5-H_b), 2.06 (br. s, 1 H, OH), 2.34−2.22 (m, 2 H, 6-H), 2.09−1.92 (m, 1 H, C*H*$_2$$CH_2$OH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 176.9 (s, *C*O), 82.6, 82.0 (d, C-3, C-6a), 70.9 (d, C-6b), 59.3 (t, CH_2*C*H_2OH), 54.8 (d, C-2a), 52.0 (t, C-5), 36.6, 31.83 (t, C-6, *C*$H_2$$CH_2$OH) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3629 (br), 2931, 1770, 1357, 1180, 1053 cm^{-1}. MS (70 eV, EI): *m*/*z* (%) = 199 (5) [M^+], 149 (5), 127 (27), 110 (5), 84 (100), 79 (16). $C_9H_{13}NO_4$ (199.21): calcd. C 54.26, H 6.58, N 7.03; found C 54.66, H 6.73, N 7.00.

(−)-(2a*R*,3*S*,6a*R*,6b*R*)-Hexahydro-3-(2-hydroxyethyl)-2*H*-1,4-dioxa-4a-azacyclopenta[*cd*]pentalen-2-one [(−)-22]: A solution of (−)-**21** (575 mg, 1.8 mmol) in TFA/CH_2Cl_2 (10:90, 100 mL) was stirred at room temp. for 45 min, concentrated, diluted with CH_2Cl_2, and treated with Amberlyst A-21®. The mixture was stirred for 30 min, filtered through Celite, and concentrated. Purification of the residue by chromatography on silica gel (eluent: ethyl acetate/MeOH, 10:1) gave the deprotected alcohol (−)-**22** (250 mg, 70%) as a white solid.

Compound (−)-22: The spectroscopic data are identical to those reported for (+)-**22**. $[\alpha]_D^{19}$ = −15.5 (*c* = 0.5, $CHCl_3$). $C_9H_{13}NO_4$ (199.21): calcd. C 54.26, H 6.58, N 7.03; found C 54.29, H 6.62, N 6.84.

(+)-(2a*S*,3*R*,8a*S*,8b*S*)-2a,3,4,5,7,8,8a,8b-Octahydro-3-hydroxy-2*H*-furo[4,3,2-*h*,*i*]indolizin-2-one [(+)-23]: Cold MsCl (45 μL, 0.58 mmol) was added dropwise to a solution of alcohol (+)-**22** (105.4 mg, 0.53 mmol) and NEt_3 (102 μL, 0.79 mmol) in CH_2Cl_2 (distilled from P_2O_5, 1.8 mL) at 0 °C. The mixture was stirred for 1 h at 0 °C, diluted with THF (2 mL), and concentrated. The residue was dissolved in MeOH (9 mL), treated with a catalytic amount of 10% Pd/C, and treated under H_2 (1 atm) for 12 h. The mixture was filtered through a column of Ambersep 900® OH and concentrated. The crude product was purified by chromatography on silica gel (eluent: ethyl acetate/MeOH/NEt_3, 10:1:0.1) to give (+)-**23** (74.3 mg, 77%) as a white solid.

Compound (+)-23: R_f = 0.23 (ethyl acetate/MeOH/NEt_3, 10:1:0.1); m.p. 59−61 °C. $[\alpha]_D^{28}$ = +73.5 (*c* = 0.8 in $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 5.06 (t, *J* = 4.2 Hz, 1 H, 8a-H), 3.97−3.95 (m, 1 H, 3-H), 3.93 (dd, *J* = 6.3, 4.3 Hz, 1 H, 8b-H), 3.13 (dt, *J* = 14.5, 3.2 Hz, 1 H, 5-H_a), 2.97−2.83 (m, 4 H, 2a-H, 5-H_b, 7-H), 2.20 (dd, *J* = 13.6, 4.8 Hz, 1 H, 8-H_a), 2.05−1.97 (m, 1 H, 8b-H), 1.75−1.72 (m, 1 H, 4-H_a), 1.67 (br. s, 1 H, OH), 1.55 (qd, *J* = 12.6, 3.6 Hz, 1 H, 4-H_b) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.1 (s, *C*O), 84.2 (d, C-8a), 68.2 (d, C-3), 60.8 (d, C-8b), 48.3, 45.5 (t, C-5, C-7), 42.7 (d, C-2a), 31.8, 28.2 (t, C-4, C-8) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3493 (br), 2926, 1744, 1342, 1176 cm^{-1}. MS (70 eV, EI): *m*/*z* (%) = 183 (11) [M^+], 120 (33), 112 (13), 95 (100), 84 (30). $C_9H_{13}NO_3$ (183.21): calcd. C 59.00, H 7.15, N 7.65; found C 58.80, H 7.33, N 7.37.

(−)-(2a*R*,3*S*,8a*R*,8b*R*)-2a,3,4,5,7,8,8a,8b-Octahydro-3-hydroxy-2*H*-furo[4,3,2-*h*,*i*]indolizin-2-one [(−)-23]: The tricyclic compound (−)-**22** (104.0 mg, 0.52 mmol) was converted into (−)-**23** (74 mg, 77%) by the same procedure as described for the synthesis of (+)-**23** starting from (+)-**22**.

Compound (−)-23: The spectroscopic data are identical to those reported for (+)-**23**. $[\alpha]_D^{25}$ = −73.3 (*c* = 1.0 in $CHCl_3$). $C_9H_{13}NO_3$ (199.21): calcd. C 59.00, H 7.15, N 7.65; found C 59.04, H 7.03, N 7.98.

(+)-(1*S*,7*R*,8*R*,8a*S*)-8-(Hydroxymethyl)indolizidine-1,7-diol [(+)-24]: Red-Al (0.33 mL, 1.11 mmol) was added dropwise to a solution of (+)-**23** (33.8 mg, 0.18 mmol) in THF (10 mL), and the mixture was heated at reflux for 3 h. The mixture was treated sequentially with H_2O (200 μL), NaOH (2 M, 180 μL), and H_2O (400 μL), diluted with THF, and stirred for 30 min. The solvent was removed at reduced pressure and the crude product was purified by chromatography on silica gel (eluent: $CHCl_3$/MeOH/NH_3, 10:5:1). The indolizidine (+)-**24** (26.7 mg, 78%) was obtained as a colorless oil.

Compound (+)-24: R_f = 0.12 ($CHCl_3$/MeOH/NH_3, 10:5:1). $[\alpha]_D^{23}$ = +57.8 (*c* = 0.7 in MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.30 (ddd, *J* = 6.2, 4.1, 1.7 Hz, 1 H, 1-H), 3.99−3.93 (m, 1 H, C*H*HOH), 3.90 (dd, *J* = 11.0, 3.7 Hz, 2 H, CH*H*OH), 3.82−3.77 (m, 1 H, 7-H), 3.19−3.11 (m, 2 H, 3-H_a, 5-H_a), 2.38−2.18 (m, 5 H, 2-H_a, 3-H_b, 5-H_b, 8-H, 8a-H), 1.90−1.81 (m, 1 H, 2-H_b), 1.75−1.60 (m, 1 H, 6-H) ppm. ^{13}C NMR (50 MHz, CD_3OD): δ = 72.2 (d, C-1), 69.5 (d, C-7), 58.0 (t, *C*H_2OH), 52.7 (t, C-3), 50.8 (t, C-5), 45.3 (d, C-8), 34.0 (t, C-2), 31.3 (t, C-6) ppm. MS (70 eV, EI): *m*/*z* = 187 (0.6) [M^+], 186 (1), 169 (13), 143 (16), 126 (13), 112 (100), 100 (12), 82 (25). $C_9H_{17}NO_3$ (187.24): calcd. C 57.73, H 9.15, N 7.48; found C 57.44, H 9.23, N 7.21.

(−)-(1*R*,7*S*,8*S*,8a*R*) 8-(Hydroxymethyl)indolizidine-1,7-diol [(−)-24]: Indolizidine (−)-**23** (49.7 mg, 0.27 mmol) was reduced to (−)-**24** (46 mg, 91%) by the same procedure as described for the synthesis of (+)-**24** starting from (+)-**23**.

Compound (−)-24: The spectroscopic data are identical to those reported for (+)-**24**. $[\alpha]_D^{29}$ = −57.6 (*c* = 0.8 in MeOH). $C_9H_{17}NO_3$ (187.24): calcd. C 57.73, H 9.15, N 7.48; found C 57.48, H 9.31, N 7.53.

Methyl (2*E*)-5-Hydroxy-2-pentenoate (28)

Method A: $(NH_4)_2Ce(NO_3)_6$ (CAN, 3.34 g, 6.8 mmol) was added to a solution of **3** (762 mg, 3.2 mmol) in CH_3CN/H_2O (9:1). The mixture was stirred at room temp. for 1 h, diluted with CH_2Cl_2 (40 mL), and washed with a saturated aqueous $NaHCO_3$ solution. The two phases were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by chromatography on silica gel (eluent: petroleum ether/ethyl acetate, 1:1) to give **28** (260 mg, 66%) as a yellow oil.

Method B: Compound **3** (700 mg, 2.8 mmol) was dissolved in CH_2Cl_2 (140 mL), and TFA (14 mL) was added dropwise. After 5 min, the mixture was concentrated and the crude product was purified by chromatography on silica gel (eluent: petroleum ether/ethyl acetate, 1:1) to give **28** (238.2 mg, 66%) as a yellow oil.

Compound 28: R_f = 0.28 (petroleum ether/ethyl acetate, 1:1). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.98 (dt, *J* = 15.4, 7.3 Hz, 1 H, 3-H), 5.94 (dt, *J* = 15.7, 1.4 Hz, 1 H, 2-H), 3.78 (t, *J* = 6.4 Hz, 2 H, 5-H), 3.74 (s, 3 H, C*H*$_3$O), 2.48 (dq, *J* = 6.2, 1.4 Hz, 2 H, 4-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 166.9 (s, *C*O), 145.8 (d, C-3), 122.8 (d, C-2), 60.7 (t, C-5), 51.4 (q, *C*H_3O), 35.3 (t, C-4) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3627, 2957, 1714, 1659, 1438, 1275, 1199, 1031 cm^{-1}. MS (70 eV, EI): *m*/*z* (%) = 112 (1) [$M^+ - H_2O$], 100 (64), 99 (26), 81 (7), 68 (100).

Methyl (2*S*,3*R*,3a*R*,4*S*)-4-*tert*-Butoxy-2-(2-hydroxyethyl)-2,3,3a,4,5,6-hexahydropyrrolo[1,2-*b*]isoxazole-3-carboxylate (29): A solution of nitrone **27** (87.9 mg, 0.56 mmol) and alcohol **28** (73.2 mg, 0.56 mmol) in toluene (1.1 mL) was heated at 60 °C for 1 d. The solvent was evaporated at reduced pressure, and the crude adduct was purified by chromatography on silica gel (eluent: petroleum ether/ethyl acetate, 1:1; then ethyl acetate) to give **29** (124.4 mg, 77%) as a colorless oil.

Compound 29: R_f = 0.26 (ethyl acetate). $[\alpha]_D^{21}$ = −28.7 (*c* = 0.9 in $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.39 (ddd, *J* = 8.4, 6.6, 5.1 Hz, 1 H, 2-H), 4.04 (dt, *J* = 7.0, 3.6 Hz, 1 H, 4-H), 3.79−3.69 (m, 3 H, 3a-H, CH_2CH_2OH), 2.73 (s, 3 H, C*H*$_3$O), 3.41 (t, *J* = 8.6 Hz, 1 H, 3-H), 3.36−3.17 (m, 2 H, 6-H), 2.41 (br. s, 1 H, OH), 2.14 (m, 1 H, 5-H_a), 1.90−1.80 (m, 2 H, CH_2CH_2OH), 1.78−1.63 (m, 1 H, 5-H_b), 1.29 (s, 9 H, C*H*$_3$ *t*Bu) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 170.8 (s, *C*O), 77.3, 74.8 (d, C-2, C-4), 73.8 (s, Cq *t*Bu), 73.0 (d, C-3a), 59.5, 55.5 (t, C-6, CH_2CH_2OH), 55.2 (q, *C*H_3O), 51.9 (d, C-3), 35.6, 34.4 (t, C-5, *C*H_2CH_2OH), 28.5 (q, 3 C *C*H_3 *t*Bu) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3600 br, 2973, 1730, 1434, 1363, 1170, 1059 cm^{-1}. MS (70 eV, EI): *m*/*z*: 287 (5) [M^+], 230 (34), 214 (4), 198 (4), 186 (9), 86 (49), 84 (85), 57 (100). $C_{14}H_{25}NO_5$ (287.35): calcd. C 58.52, H 8.77, N 4.87; found C 58.39, H 8.99, N 5.22.

(2*S*,3*R*,3a*R*,4*S*)-1-*tert*-Butoxy-7-hydroxy-8-(methoxycarbonyl)-indolizidine (30): The same procedure as reported for the synthesis of indolizidines **23** was used.

Compound 30: 83% yield; colorless oil; R_f = 0.29 (CH_2Cl_2/MeOH/NH_3, 10:1:0.01). $[\alpha]_D^{28}$ = +39.6 (*c* = 0.7, in $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.32 (td, *J* = 8.3, 3.2 Hz, 1 H, 1-H), 3.76 (s, 3 H, C*H*$_3$O), 3.75−3.69 (m, 1 H, 7-H), 3.19 (t, *J* = 3.7 Hz, 1 H, 8-H), 3.09−3.06 (m, 1 H, 5-H_a), 2.99 (t, *J* = 8.3 Hz, 1 H, 3-H_a), 2.74 (br. s, 1 H, OH), 2.27−2.12 (m, 2 H, 3-H_b, 6-H_a), 2.11−2.04 (m, 3 H, 2-H_a, 6-H_b, 8a-H), 1.85 (m, 1 H, 5-H_b), 1.61−1.57 (m, 1 H, 2-H_b), 1.18 (s, 9 H, C*H*$_3$ *t*Bu) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.2 (s, *C*O), 73.4 (s, *C*q *t*Bu), 72.3 (d, C-1), 71.3 (d, C-8a), 70.7 (d, C-7), 52.8 (t, C-3), 51.3 (q, *C*H_3O), 51.1 (t, C-5), 46.8 (d, C-8), 33.5 (t, C-2), 30.5 (t, C-6), 28.6 (q, 3 C *C*H_3 *t*Bu) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3600, 2975, 1721, 1438, 1364, 1195 cm^{-1}. MS (70 eV, EI): *m*/*z* (%) = 214 (75) [$M^+ - t$Bu], 196 (15), 170 (8), 112 (10), 83 (100), 57 (42). $C_{14}H_{25}NO_4$ (271.36): calcd. C 61.97, H 9.29, N 5.16; found C 61.97, H 9.69, N 5.23.

Synthesis of (1*S*,7*S*,8*S*,8a*R*)-1,7-Dihydroxy-8-(2-hydroxyethyl)indolizidine [(+)-31]

Reduction of the Methoxycarbonyl Functionality: The same procedure as reported for the synthesis of indolizidines **21** was used.

(1*S*,7*S*,8*S*,8a*R*)-1-*tert*-Butoxy-7-hydroxy-8-(2-hydroxyethyl)-indolizidine: 89% yield, yellow solid, R_f = 0.09 (CH_2Cl_2/MeOH, 10:1); m.p. 84−86 °C. $[\alpha]_D^{20}$ = +48.1 (*c* = 0.6, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.24 (td, *J* = 8.0, 3.5, 1 H, 1-H), 4.12−4.04 (m, 2 H, C*H*$_2$OH), 3.87−3.80 (m, 1 H, 7-H), 3.08−2.88 (m, 3 H, 3-H_a, 5-H_a and OH), 2.26−2.01 (m, 7 H, 2-H_a, 3-H_b, 5-H_b, 6-H_a, 8-H, 8a-H and OH), 1.90−1.80 (m, 1 H, 6-H_b), 1.70−1.60 (m, 1 H, 2-H_b) 1.19 (s, 9 H, C*H*$_3$ *t*Bu) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 73.6 (s, Cq *t*Bu), 72.1, 71.8, 71.2 (d, C-1, C-7, C-8a), 59.0 (t, *C*H_2OH), 52.6, 51.2 (t, C-3, C-5), 39.5 (d, C-8), 33.7, 31.5 (d, C-2, C-6), 28.6 (q, 3 C *C*H_3 *t*Bu) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3689, 3600−3100, 2977, 2871, 1446, 1363, 1187 cm^{-1}. MS (70 eV, EI): *m*/*z* (%) = 243 (1.5) [M^+], 196 (2), 187 (25), 186 (100), 168 (45), 138 (29), 112 (73), 100 (28), 84 (41), 57 (77). $C_{13}H_{25}NO_3$ (243.34): calcd. C 64.16, H 10.36, N 5.76; found C 63.96, H 10.14, N 5.83.

Deprotection of *tert*-Butyl Ether: A solution of protected indolizidinetriol (38.5 mg, 0.16 mmol) in trifluoroacetic acid (1 mL) and water (0.1 mL) was stirred at room temp. for 3 h. The TFA was removed at reduce pressure, and the crude product was dissolved in MeOH, filtered through a short column of Ambersep 900 OH, and concentrated to give pure **31** (28 mg, 95%) as a colorless oil.

Compound (+)-31: $[\alpha]_D^{28}$ = +15.1 (*c* = 0.5, in MeOH). ^{1}H NMR (200 MHz, D_2O): δ = 4.29 (td, *J* = 8.2, 3.9 Hz, 1 H, 1-H), 3.87−3.76 (m, 2 H, 7-H and C*H*HOH), 3.65 (dd, *J* = 11.4, 5.2 Hz, 1 H, CH*H*OH), 2.92−2.77 (m, 2 H, 3-H_a, 5-H_a), 2.30−1.98 (m, 5 H, 2-H_a, 3-H_b, 5-H_b, 8-H, 8a-H); 1.73−1.34 (m, 3 H, 2-H_b, 6-H) ppm; (500 MHz, CD_3OD): δ = 4.39 (ddd, *J* = 8.9, 7.6, 4.1 Hz, 1 H, 1-H), 3.99 (dd, *J* = 11.2, 4.8 Hz, 1 H, C*H*HOH), 3.94 (dd, *J* = 11.2, 4.3 Hz, 1 H, CH*H*OH), 3.82−3.76 (m, 1 H, 7-H), 3.02 (ddd, *J* = 11.0, 4.3, 3.9 Hz, 1 H, 5-H_a), 2.95 (td, *J* = 8.6, 1.9, 1 H, 3-

H_a), 2.33−2.07 (m, 5 H, 2-H_a, 3-H_b, 5-H_b, 8-H, 8a-H), 1.83−1.71 (m, 2 H, 2-H_b, 6-H_a), 1.63 (dddd, J = 12.7, 8.6, 4.3, 2.1 Hz, 1 H, 6-H_b) ppm. ^{13}C NMR (50 MHz, D_2O): δ = 72.5, 71.3, 71.2 (d, C-1, C-7, C-8a), 57.8 (t, *C*H_2OH), 52.3, 50.6 (t, C-3, C-5), 42.7 (d, C-8), 32.2, 29.3 (t, C-2, C-6) ppm. MS (70 eV, EI): *m/z* (%) = 187 (3) [M^+], 186 (5), 169 (33), 143 (29), 112 (100), 82 (31). $C_9H_{17}NO_3$ (187.12): calcd. C 57.73, H 9.15, N 7.48; found C 57.69, H 9.25, N 7.30.

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[15] In the case of (methoxycarbonyl)isoxazolidines **32d**, **32e**, **32j**, **32k**, **33j**, and **33k**, the *E*(TS) values of the lowest energy TSs were employed, which showed an *s-cis* conformation of the dipolarophile. TSs of *s-trans* conformation were located from 0.8 to 2 kcal/mol higher in energy. The TS structures were located by the Monte Carlo procedure and then fully optimized at the various calculation levels.

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