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Synthesis of Enantiopure Indolizinones by Cascade Ring Enlargements of 4′-Chlorospiro[cyclopropane-1,5′-isoxazolidines]

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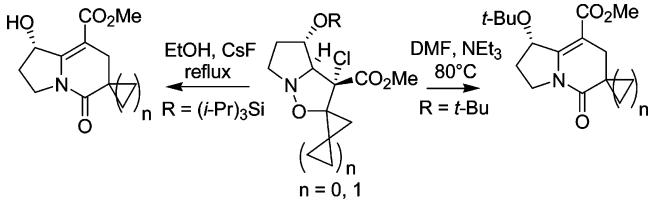

2-Chloro-2-cyclopropylideneacetates (**1**-Me and **1**-Et) and their spiropentane analogues **2** cycloadd enantiopure five-membered cyclic nitrones to give the corresponding adducts (quantitatively, four examples), which undergo cascade ring enlargements to yield indolizinone derivatives (53−70%, four examples). The ring enlargement process is triggered by the abstraction of a bridgehead proton induced by a base and can be suppressed by the presence of a bulky substituent nearby, such as a (triisopropylsilyl)-oxy group.

Introduction

The various transformations of spiro[cyclopropane-1,5′-isoxazolidines] have turned out to be a valuable asset for organic synthesis.[1,2] These compounds, which are easily obtained through 1,3-dipolar cycloadditions of various functionalized nitrones to alkylidenecyclopropanes,[3] feature the reactivity of the highly strained cyclopropane ring.[4,5] The formation and the reactivity of spiro[cyclopropane-1,5-isoxazolidines] can be tuned by the substituents present on the alkylidenecyclopropanes and on the nitrone reactants as well as by the reaction conditions applied. Whereas their thermal rearrangement to produce tetrahydropyridones has found wide application in the synthesis of natural compounds or nonnatural analogues,[1] only recently has the use of acidic conditions or the catalysis by Pd(II) salts revealed the possibility to also produce β-lactams[6] and dihydropyridones,[7] respectively. Another novel reaction mode has previously been reported for the cycloadducts **4** obtained from nitrones **3** and methyl 2-chloro-2-cyclopropylideneacetates **1** and **2**.[8−10] This reactivity depended largely on the substrate and

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[§] For this author this is to be counted as Part 123 in the series Cyclopropyl Building Blocks for Organic Synthesis. Part 122: Zanobini, A.; Brandi, A.; de Meijere, A. *Eur. J. Org. Chem.* **2006**, in press. Part 121: Kurahashi, T.; de Meijere, A. *Angew. Chem.* **2005**, *114*, 8093−8096; *Angew. Chem., Int. Ed.* **2005**, *44*, 7881−7884.

(1) Brandi, A.; Cicchi, S.; Cordero, F. M.; Goti, A. *Chem. Rev.* **2003**, *103*, 1213−1270.

(2) Goti, A.; Cordero, F. M.; Brandi, A. *Top. Curr. Chem.* **1996**, *178*, 1−97.

(3) Brandi, A.; Cordero, F. M.; De Sarlo, F.; Goti, A.; Guarna, A. *Synlett* **1993**, 1−8.

(4) *Houben-Weyl, Methods of Organic Chemistry, Carbocyclic Three-Membered Ring Compounds*; de Meijere, A., Ed.; Thieme: Stuttgart, 1997; Vol. E17A−C.

(5) Kulinkovich, O. G. *Chem. Rev.* **2003**, *103*, 2597−2632.

(6) (a) Cordero, F. M.; Pisaneschi, F.; Goti, A.; Ollivier, J.; Salaün, J.; Brandi, A. *J. Am. Chem. Soc.* **2000**, 122, 8075−8076. (b) Cordero, F. M.; Pisaneschi, F.; Salvati, M.; Paschetta, V.; Ollivier, J.; Salaün, J.; Brandi, A. *J. Org. Chem.* **2003**, *68*, 3271−3280. (c) Zanobini, A.; Gensini, M.; Magull, J.; Vidoviæ, D.; Kozhushkov, S. I.; Brandi, A.; de Meijere, A. *Eur. J. Org. Chem.* **2004**, 4158−4166. (d) Cordero, F. M.; Salvati, M.; Pisaneschi, F.; Brandi, A. *Eur. J. Org. Chem.* **2004**, 2205−2213. (e) Zanobini, A.; Brandi, A.; de Meijere, A. *Eur. J. Org. Chem.* **2006**, in press.

(7) (a) Cicchi, S.; Revuelta, J.; Zanobini, A.; Betti, M.; Brandi, A. *Synlett* 2003, 2305−2308. (b) Revuelta, J.; Cicchi, S.; Brandi, A. *J. Org, Chem.* **2005**, *70*, 5636−5642.

(8) Zorn, C.; Goti, A.; Brandi, A.; Johnsen, K.; Kozhushkov, S. I.; de Meijere, A. *Chem. Commun.* **1998**, 903−904.

(9) Zorn, C.; Goti, A.; Brandi, A.; Johnsen, K.; Noltemeyer, M.; Kozhushkov, S. I.; de Meijere, A. *J. Org. Chem.* **1999**, *64*, 755−763.

(10) For the general reactivity of 2-chloro-2-cyclopropylideneacetate and its spiropentane analogue, see: (a) Tamm, M.; Thutewohl, M.; Ricker, C. B.; Bes, M. T.; de Meijere, A. *Eur. J. Org. Chem.* **1999**, 2017−2024. (b) de Meijere, A.; Ernst, K.; Zuck, B.; Brandl, M.; Kozhushkov, S. I.;

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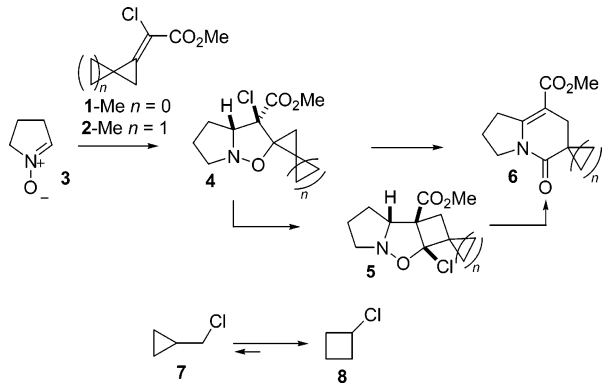
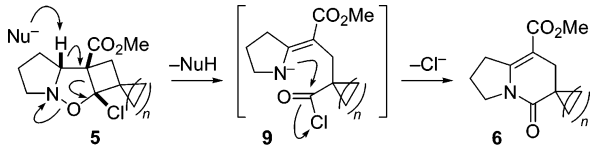
SCHEME 1



SCHEME 2



varied greatly with the nature of the substituents on the isoxazolidine. The most promising result was the observed rearrangement of the adducts **4** into the corresponding indolizinone derivatives **6** (Scheme 1).

This transformation was rationalized considering the nature of compound **4**, which features a cyclopropylmethyl chloride moiety and equilibrates with a cyclobutyl chloride substructure as present in **5**. This equilibration is well-known for the parent compounds **7** and **8** as well as simple derivatives (Scheme 1),[11] and in the current case of **4** ($n = 0$) it implies the formation of the strained methyl 2a-chlorohexahydrocyclobuta[*d*]pyrrolo[1,2-*b*]isoxazole-7b(1*H*)-carboxylate **5** ($n = 0$), which finally undergoes a further ring enlargement with loss of HCl to give the five-membered annelated lactam **6** ($n = 0$). Compounds **5** ($n = 0$, 1) turned out to be rather labile, consistent with their being chloro-hemiacetals; however, they were sufficiently stable to be spectroscopically characterized. Their uncommon structure was also confirmed by an X-ray analysis of a crystalline stable analogue.[9] The mechanistic hypothesis for the transformation of **5** to **6** called for an abstraction of the bridgehead proton followed by opening of both the cyclobutane and the isoxazolidine ring with subsequent closure to give a six-membered lactam moiety by attack of the pyrrolidine nitrogen in the intermediate **9** on the acyl chloride function (Scheme 2).

As this overall two-step process appeared to be very convenient for the synthesis of functionalized indolizinones **6**, we engaged ourselves in synthesizing a number of enantiopure functionally substituted indolizinones by employing optically pure five-membered cyclic nitrones **10**[12] and **11**.[13] This new study was also intended to add significant new insights into the mechanism of this unusual rearrangement and especially to disclose the role of the base in accelerating the second step of the overall transformation.

Results and Discussion

The cycloaddition of nitrone **10** to the 2-chlorocyclopropylidene acetate **1**-Me proceeded at ambient temperature within 6 d with 100% conversion to afford a mixture of the diastereoisomeric cycloadducts **12a** and **12b** in a ratio of 6:1.

Compounds **12a** and **12b** and their relative configurations were identified as arising from an *endo* and an *exo* approach, respectively, with respect to the methoxycarbonyl group of the dipolarophile **1** to the nitrone **10**. The structures were assigned on the basis of the ^{1}H NMR spectra of the two adducts showing the same signal patterns for the H3a′ (a singlet) and the H4′ proton (a doublet, $J = 6.6$ Hz, for **12a**, and $J = 5.1$ Hz for **12b**), differing only in the shift to lower fields (∼0.4 ppm) of the H3a′ signal of the minor isomer. This downfield shift of the signal for the 3a′ proton facing the CO_2Me group, as in **12b**, is in line with previous results.[9] These data suggest the same relative configuration of the C4′ and C3a′ stereogenic centers, and indicate an *S* absolute configuration for C3′ in **12a**.

Compounds **12a** and **12b** subsequently rearranged into the corresponding tricyclic derivatives **14a,b** as evidenced by an NMR spectrum of the crude reaction mixture. The transformation reached completion upon stirring the cycloadducts **12** in CH_2Cl_2 at ambient temperature for several days but could be more conveniently brought about in refluxing 1,2-dichloroethane in the presence of neutral Al_2O_3 (complete transformation in 12 h). However, only the major isomer **14a** proved to be stable enough to be isolated by flash chromatography and be completely characterized. The structure of compound **14a** was assigned on the basis of 1D and 2D NMR spectra and was in line with the stereochemistry of an S_N2-like mechanism for the three-membered ring enlargement. In this process the migrating C−C bond replaces the chloride with inversion of configuration at the reacting center. The attack of the chloride at the cyclobutyl cation center then occurs only from the side of the methoxycarbonyl group leading to a *cis* junction of the cyclobutane and the isoxazolidine ring. This initial structural assignment was confirmed by an X-ray crystal structure analysis (see Supporting Information).

The behavior of the enantiomerically pure nitrone cycloadducts **12** was comparable to that of the racemic model compounds **4** ($n = 0$), but the final transformation to afford the expected indolizinone derivative presented several differences (vide infra).

The cycloaddition of nitrone **10** to the 2-chlorospiropentylideneacetate **2**-Me led directly to a mixture of the two diastereomeric rearrangement products, **17a** and **17b** in a ratio of 7:1. Apparently, the initial cycloadducts **16** are less stable than **12a,b**, probably as a result of the enhanced strain in their spiropentane moiety. The primary cycloadducts **16** were only evidenced as transient products according to ^{1}H NMR spectra recorded for the reaction mixture before the cycloaddition was complete. The cyclobutane moiety in compounds **17a,b** was easily assigned by comparison of the NMR data with those of **5** ($n = 1$) and **14a,b**, and the relative configurations of **17a** and **17b** were tentatively assigned by analogy with those of **14a,b**. Like compounds **12a,b** and **14b**, the tetracyclic products **17a,b** proved to be unstable upon attempted separation and therefore could

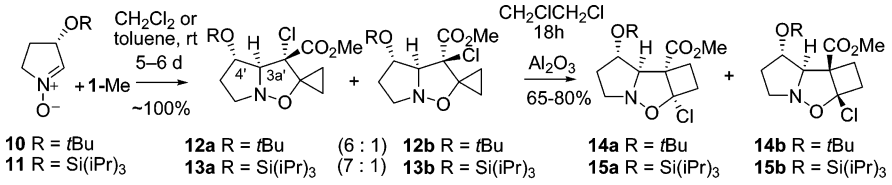
Tamm, M.; Yufit, D. S.; Howard, J. A. K.; Labahn, T. *Eur. J. Org. Chem.* **1999**, 3105−3115. (c) Nötzel, M. W.; Tamm, M.; Labahn, T.; Noltemeyer, M.; Es-Sayed, M.; de Meijere, A. *J. Org. Chem.* **2000**, 3850−3852. (d) Nötzel, M. W.; Labahn, T.; Es-Sayed, M.; de Meijere, A. *Eur. J. Org. Chem.* **2001**, 3025−3030. (e) Nötzel, M. W.; Rauch, K.; Labahn, T.; de Meijere, A. *Org. Lett.* **2002**, *4*, 839−841.

(11) (a) Klunder, A. J. H.; Zwanenburg, B. in *Houben-Weyl*; de Meijere, A., Ed.; Thieme: Stuttgart, 1997; Vol. E17C, pp 2419−2437. (b) Renk, E.; Roberts, J. D. *J. Am. Chem. Soc.* **1961**, *83*, 878−881.

(12) Cicchi, S.; Goti, A.; Brandi, A. *J. Org. Chem.* **1995**, *60*, 4743−4748.

(13) Goti, A.; Cacciarini, M.; Cardona, F.; Brandi, A. *Tetrahedron Lett.* **1999**, *40*, 2853−2856.

SCHEME 3



SCHEME 4. Proposed Mechanism for the Ring Enlargement in Compound 12a

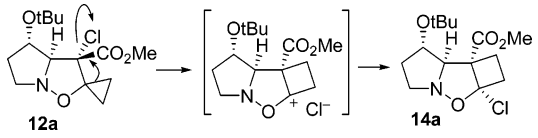
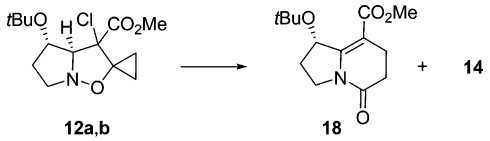


TABLE 1. Optimization of Conditions for the Rearrangement of Cycloadducts 12a,b to the Indolizinone 18



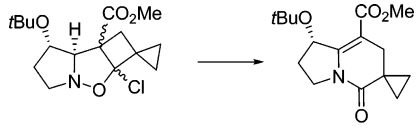
entry	solvent	base (equiv)	temp (°C)	time (h)	yield (%)	**18**:**14**
1	DMSO		100	4	*a*	
2	DMSO	Py (2)	100	4	30	1:3
3	DMSO	NEt_3 (2)	100	4	45	1:3
4	DMF	NEt_3 (2)	80	4	60	1:3
5	DMF	NEt_3 (2)	80	12	30	1:0
6	DMF	NEt_3 (2+2[b])	80	96	70	1:0

[a] Complete decomposition. [b] An additional 2 equiv was added after 48 h.

not be purified, yet each isomer in the mixture was spectroscopically characterized.

Although compounds **4** (n = 0, 1) without the additional alkoxy substituent, upon heating in DMSO at 100 °C, were cleanly transformed into the corresponding indolizinones **6** (Scheme 1),[8] the cycloadducts **12a,b** under these conditions underwent decomposition only (Table 1, entry 1), and the same happened with the cyclobutane derivative **14a** under the same conditions. Since the final rearrangement was supposed to be triggered by the abstraction of the bridgehead proton by a nucleophile, the more severe steric encumbrance caused by the large *tert*-butoxy group in **12a,b** and **14a** could hamper this process. Therefore, a base was added in order to facilitate the rearrangement. The first result, employing 2 equiv of pyridine (Table 1, entry 2), was encouraging, since the final product **18** could be observed, albeit in a mixture with the cyclobutane intermediate **14** as the major compound. This situation was partially improved using Et_3N (Table 1, entry 3). By switching the solvent from DMSO to DMF,[15] a small increase of the yield was observed (Table 1, entry 4). Extending the reaction time in the presence of 4 equiv of Et_3N base was detrimental (Table 1, entry 5), whereas heating the solution of **12a,b** with 2 equiv of NEt_3 for 2 days and adding another 2 equiv with additional heating for 2 days afforded the indolizinone in 70% yield (Table 1, entry 6). Although the isolated cyclobutane derivative **14a** also underwent clean rearrangement to **18** under these conditions, the overall yield of **18** was better when the primary cycloadducts **12a,b** were directly subjected to the optimized basic conditions.

TABLE 2. Optimization of the Conditions for the Rearrangement of 17a,b to the Spirocyclopropanated Indolizinone 19



entry	solvent	base (equiv)	temp (°C)	time (h)	yield (%)
1	DMSO		100	6	18
2	DMSO	NEt_3 (2)	100	4	45
3	DMF	NEt_3 (2)	80	4	60
4	DMF	NEt_3 (4)	80	12	25
5	DMF	NEt_3 (2 + 2[a])	80	96	80

[a] 2 equiv of NEt_3 was added after 2 d.

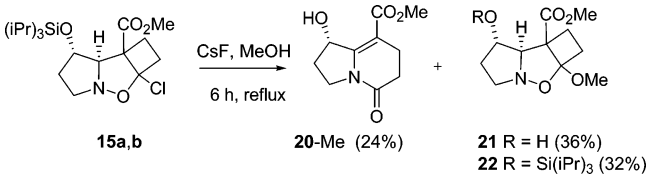
Compounds **17a,b** presented the same trends (Table 2) upon variation of the reaction conditions and afforded compound **19** in an optimized yield of 80% after 4 days of heating in DMF at 80 °C with addition of 2 equiv of NEt_3 after 2 days (Table 2, entry 5).

The cycloaddition of the enantiopure nitrone **11** with a (triisopropylsilyl)oxy group, which is even bulkier than the *tert*-butoxy substituent in **10**, onto **1**-Me nevertheless proceeded cleanly affording the adducts **13a,b** with quantitative conversion. Subsequent treatment with Al_2O_3 in refluxing 1,2-dichloroethane gave the cyclobutane derivatives **15a,b** (65%), which proved to be unstable toward flash chromatography just like **12a,b**. Treatment of both adducts **13a,b** and derivatives **15a,b** with triethylamine under the best conditions found for the rearrangement of **12** did not yield the expected silyloxyindolizinone derivative but left **15a,b** almost unchanged. On the other hand, more forcing conditions led to decomposition only. As expected, the very bulky triisopropylsilyl-protecting group hampers the final rearrangement, which is the best evidence that abstraction of the bridgehead proton by a base is the crucial initiating step.

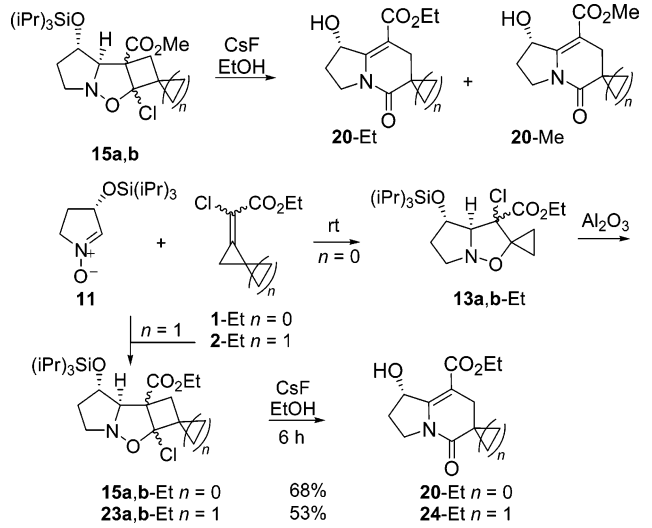
(14) The X-ray CIF file for this structure has been deposited at the Cambridge Crystallographic Data Center: deposition number CCDC 292383. Copies of the data can be obtained, free of charge, from CCDC, 12 Union Road, Cambridge, CB2 1EZ UK (e-mail: deposit@ccdc.cam.ac.uk; Internet: //www.ccdc.cam.ac.uk).

(15) This change in the reaction solvent was suggested by the characteristic stink of dimethyl sulfide revealed with DMSO, indicating that the solvent participated to some extent in the reaction.

SCHEME 5



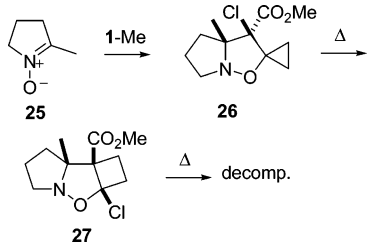
SCHEME 6



In the absence of any added base, the isoxazolidine nitrogen may act as a basic center. This bridgehead nitrogen is very unlikely to reach the bridgehead proton in another molecule when a very bulky substituent is positioned on the adjacent carbon, and even added NEt_3 apparently is not able to reach it, when the substituent is a (triisopropylsilyl)oxy group. However, upon heating **15a,b** in methanol under reflux in the presence of cesium fluoride, a mixture of compounds was obtained from which the expected desilylated lactam **20** could be isolated in poor yield (24%) along with the unrearranged products **21** (36%) and **22** (32%), from substitution of the chlorine atom in **15** by methanol with or without protiodesilylation.

Because of the poorer leaving group ability of the methoxy group, compounds **21** and **22** are far less prone than the chlorides **15a,b** to undergo the ring-enlarging rearrangement. Upon heating **15a,b** in the less nucleophilic ethanol in the presence of cesium fluoride, the desilylated indolizinone derivative **20**-Me along with the corresponding ethyl ester **20**-Et resulting from transesterification of either **15a,b** or **20**-Me was obtained in good yield (70%). Since this transesterification could neither be suppressed nor brought to completion, the 1,3-dipolar cycloaddition of **11** was carried out with ethyl 2-chloro-2-cyclopropylideneacetate (**1**-Et), and the products **13a,b**-Et after conversion to the cyclobutane derivatives **15a,b**-Et were heated in ethanol in the presence of cesium fluoride. This furnished the oxoindolizinecarboxylic acid ethyl ester **20**-Et in 68% yield (Scheme 6). It is interesting to note that this rearrangement to **20**-Et proceeds cleanly only with the cyclobutane derivatives **15a,b**-Me and **15a,b**-Et; the primary cycloadducts **13a,b**-Me and **13a,b**-Et under the same conditions underwent decomposition only. The same procedure was applied to compounds **23a,b**-Et, derived from the cycloaddition of nitrone **11** to ethyl 2-chloro-2-spiropentylideneacetate **2**-Et to give the expected spiro[cyclopropane-1,5′-indolizinone] **24**-Et (Scheme 6).

SCHEME 7



The inertness of **13a,b** and **15a,b** to NEt_3 suggests that the rearrangement to **20** takes place only after protiodesilylation. To test whether fluoride in ethanol would be a strong enough small base to initiate the rearrangement to the indolizinone before the removal of the triisopropylsilyl group, the *tert*-butoxy derivatives **14a,b** were also subjected to the same reaction conditions and yet were recovered unchanged. This result confirmed that the removal of the protecting group from **15a,b** triggered the final rearrangement.

The presence of the bridgehead proton in the cyclobutane-annelated isoxazolidines **14a,b** and **15a,b** is essential for their transformation to indolizinones, as was further corroborated by the observation that compound **27**, obtained by cycloaddition of nitrone **25** to **1**-Me, upon heating in DMSO at 100 °C for 4 h failed to give any stable rearrangement product. Further heating of **27** under the same conditions led to decomposition. Hence, the presence of the bridgehead methyl group prevents any further enlargement of the cyclobutane ring.

In conclusion, the data obtained for this series of substrates are in line with the proposed mechanism in which the abstraction of the bridgehead proton in heterocyclic compounds of type **14** induces a cascade reorganization of bonds. It is particularly interesting that the change from a *tert*-butyloxy to a trialkylsilyloxy group at the position adjacent to the bridgehead proton influences the reactivity significantly. The overall process provides a useful access to functionalized indolizinone derivatives, also in enantiopure form, compounds that can find applications as rigid dipeptide mimetics,[16] or by using polyhydroxylated five-membered cyclic nitrones, sugar mimetics.[17]

Experimental Section

Ethyl Chloro(cyclopropylidene)acetate (1-Et). A solution of the acrylate **1**-Me[18] (1.23 g, 8.61 mmol) and titanium tetraisoproxide (1.63 g, 5.68 mmol) in anhydrous EtOH (43 mL) was heated under reflux under a nitrogen atmosphere for 12 h. The mixture was cooled to room temperature, and HCl (1 M) was added (60 mL). The resulting solution was extracted with Et_2O (3 × 150 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated to yield 750 mg of the crude product. Flash column chromatography (SiO_2, Et_2O/petroleum ether, 1:10) afforded compound **1**-Et (617 mg, 45%) as a colorless oil. $R_f = 0.4$. ^1H NMR: δ 4.27 (q, $J = 4.2$ Hz, 2H), 1.75−1.65 (m, 2H), 1.48−1.39 (m, 2H), 1.67 (t, $J = 4.2$

(16) Millet, R.; Domarkas, J.; Rombaux, P.; Rigo, B.; Houssin, R.; Henichart, J.-P. *Tetrahedron Lett.* **2002**, *43*, 5087−5088.

(17) (a) Cicchi, S.; Höld, I.; Brandi, A. *J. Org. Chem.* **1993**, *58*, 5274−5275. (b) Cicchi, S.; Corsi, M.; Brandi, M.; Goti, A. *J. Org. Chem.* **2002**, *67*, 1678−1681. (c) Cardona, F.; Faggi, E.; Liguori, F.; Cacciarini, M.; Goti, A. *Tetrahedron Lett.* **2003**, *44*, 2315−2318. (d) Toyao, A.; Tamura, O.; Takagi, H.; Ishibashi, H. *Synlett* **2003**, 35−38. (e) Chevrier, C.; LeNouen, D.; Neuburger, M.; Defoin, A.; Tarnus, C. *Tetrahedron Lett.* **2004**, *45*, 5363−5366. (f) Holzapfel, C. W.; Crous, R. *Heterocycles* **1998**, *48*, 1337−1342.

(18) Liese, T.; Seyed-Mahdavi, F.; de Meijere, A. *Org. Synth.* **1990**, *69*, 148−153.

Hz, 3H). ^{13}C NMR: 162.0 (s), 138.5 (s), 115.0 (s), 62.2 (t), 14.3 (q), 9.9 (t), 5.6 (t). Anal. Calcd for $C_7H_9ClO_2$: C, 52.35; H, 5.65. Found: C, 52.45; H, 5.41.

Ethyl 2-(*E*/*Z*)-Chloro(spiropent-1-ylidene)acetate (2-Et). An equimolar mixture of (*E*)- and (*Z*)-**2**-Me[19] (8.49 g, 49.24 mmol) was transformed into a 1:1 mixture of **2**-Et by the same procedure as employed for **1**-Et. Flash column chromatography (Et_2O/petroleum ether, 1:20) afforded the mixture of (*E*)- and (*Z*)-**2**-Et (6.87 g, 71%) as a colorless oil. R_f = 0.5. ^{1}H NMR: δ 4.30 (q, J = 7.0 Hz, 2H), 4.17 (q, J = 7.2 Hz, 2H), 1.98 (s, 1H), 1.78 (s, 2H), 1.42−1.25 (m, 14H). ^{13}C NMR: 162.2 (s), 161.9 (s), 146.3 (s), 144.9 (s), 110.7 (s), 110.4 (s), 61.8 (t, 2C), 17.4 (s), 15.5 (t), 14.4 (q), 14.3 (s), 14.2 (q), 11.8 (t), 10.8 (t), 10.4 (t). Anal. Calcd for $C_9H_{11}ClO_2$: C, 57.92; H, 5.94. Found: C, 57.85; H, 5.77.

Methyl (3′*S*,3a′*S*,4′*S*)-4′-*tert*-Butoxy-3′-chlorotetrahydro-3′*H*-spiro[cyclopropane-1,2′ pyrrolo[1,2-*b*]isoxazole-3′-carboxylate (12a) and Methyl (3′*R*,3a′*S*,4′*S*)-4′-*tert*-Butoxy-3′-chlorotetrahydro-3′*H*-spiro[cyclopropane-1,2′pyrrolo[1,2-*b*]isoxazole-3′-carboxylate (12b). A solution of the nitrone **10** (123 mg, 0.55 mmol) and the acrylate **1**-Me (90 mg, 0.61 mmol) in CH_2Cl_2 (1.1 mL) was stirred at room temperature for 6 d. The solution was concentrated to give a mixture (203 mg, quantitative yield) of crude **12a** and **12b** (6:1), which proved to be unstable to chromatography on silica gel and Al_2O_3. **12a.** ^{1}H NMR: δ 4.09 (s, 1H), 4.05 (d, J = 6.6 Hz, 1H), 3.77 (s, 3H), 3.42−3.15 (m, 2H), 2.18−1.96 (m, 1H), 1.81−1.59 (m, 1H), 1.11 (s, 9H), 0.94−0.76 (m, 4H). ^{13}C NMR: δ 166.7 (s), 86.7 (d), 80.9 (s), 74.9 (s), 74.3 (d), 69.2 (s), 55.9 (t), 53.2 (q), 34.8 (t), 28.7 (q), 13.5 (t), 9.8 (t). **12b.** ^{1}H NMR: δ 4.56 (s, 1H), 4.38 (d, J = 5.1 Hz, 1H), 3.73 (s, 3H), 1.81−1.59 (m, 1H), 1.47−1.32 (m, 1H), 1.11 (s, 9H), 0.94−0.76 (m, 4H). ^{13}C NMR: δ 166.8 (s), 80.4 (s), 76.9 (s), 75.8 (d), 69.8 (s), 55.3 (t), 53.6 (q), 34.5 (t), 28.6 (q), 14.6 (t), 9.2 (t). **12a,b.** MS (EI): *m*/*z* 303 (3), 211 (4), 84 (11), 68 (5), 59 (12), 57 (100), 55 (11). **12a,b.** IR ($CDCl_3$): 2978, 2245, 1745, 1437, 1391, 1365, 1257, 1191, 1065 cm^{-1}.

Methyl (3′*S*,3a′*S*,4′*S*)-4′-Triisopropylsilyloxy-3′-chlorotetrahydro-3′*H*-spiro[cyclopropane-1,2′-pyrrolo[1,2-*b*]isoxazole]-3′-carboxylate (13a) and Methyl (3′*R*,3a′*S*,4′*S*)-4′-Triisopropylsilyloxy-3′-chlorotetrahydro-3′*H*-spiro[cyclopropane-1,2′-pyrrolo[1,2-*b*]isoxazole]-3′-carboxylate (13b). A solution of the nitrone **11** (301 mg, 1.17 mmol) and the acrylate **1**-Me (205 mg, 1.4 mmol) in toluene (2.3 mL) was stirred at room temperature for 5 d. The solution was concentrated to yield 470 mg (quantitative yield) of a mixture of **13a** and **13b** (7:1), which proved to be unstable to chromatography. **13a.** ^{1}H NMR: δ 4.40 (d, J = 5.0 Hz, 1H), 4.20 (s, 1H), 3.79 (s, 3H), 3.44−3.24 (m, 2H), 2.12−2.03 (m, 1H), 1.81−1.72 (m, 1H), 1.15−1.22 (m, 4H), 1.05−0.95 (m, 21H).^{13}C NMR: δ 167.0 (s), 88.7 (d), 82.0 (s), 76.5 (d), 69.0 (s), 55.9 (t), 53.1 (q), 35.5 (t), 17.7 (q), 12.4 (d), 12.1 (t), 10.1 (t). **13b.** ^{1}H NMR: δ 4.75 (d, J = 5 Hz, 1H), 4.64 (s, 1H), 3.77 (s, 3H), 3.43−3.30 (m, 2H), 2.12−2.03 (m, 1H),1.81−1.72 (m, 1H), 1.15−1.22 (m, 4H), 1.05−0.95 (m, 21H). ^{13}C NMR: δ 168.0 (s), 88.3 (d), 82.2 (s), 76.4 (d), 69.2 (s), 54.2 (t), 53.0 (0), 35.1 (t), 17.7 (q), 12.3 (d), 12.1 (t), 9.6 (t). **13a,b.** MS (EI) *m*/*z* 405 (8), 403 (25), 375 (44), 367 (65), 257 (30), 202 (60), 84 (100). **13a,b.** IR ($CDCl_3$) 2980, 1740, 1425 cm^{-1}.

Ethyl (3′*S*,3a′*S*,4′*S*)-4′-Triisopropylsilanoxy-3′-chlorotetrahydro-3′*H*-spiro[cyclopropane-1,2′-pyrrolo[1,2-*b*]isoxazole-3′-carboxylate (13a-Et) and Ethyl (3′*R*,3a′*S*,4′*S*)-4′-Triisopropylsilanoxy-3′-chlorotetrahydro-3′*H*-spiro[cyclopropane-1,2′-pyrrolo[1,2-*b*]isoxazole-3′-carboxylate (13b-Et). A solution of the nitrone **11** (301 mg, 1.17 mmol) and the acrylate **1**-Et (224 mg, 1.4 mmol) in toluene (2.3 mL) was stirred at room temperature for 5 d. The solution was concentrated to yield 490 mg (quantitative yield) of a mixture of **13a**-Et and **13b**-Et (5:1), which proved to be unstable to chromatography. **13a-Et.** ^{1}H NMR: δ 4.40 (d, J = 5 Hz, 1H), 4.20 (s, 1H), 4.37−4.16 (m, 2H), 3.44−3.24 (m, 2H), 2.12−2.03 (m, 1H), 1.81−1.72 (dd, J = 10.8, 5.0 Hz, 1H), 1.17 (t, J = 7 Hz, 3H), 1.18−1.05 (m, 21H), 1.00−0.95 (m, 4H). ^{13}C NMR: δ 166.5 (s), 89.1 (d), 82.1 (s), 75.4 (d), 69.1 (s), 62.5 (t), 55.6 (t), 35.4 (t), 18.0 (q), 17.7 (q), 12.2 (d), 12.1 (t), 10.5 (t). **13b-Et.** ^{1}H NMR: δ 4.77 (d, J = 5.0 Hz, 1H), 4.66 (s, 1H), 4.37−4.16 (m, 2H), 3.44−3.24 (m, 2H), 2.12−2.03 (m, 1H), 1.81−1.72 (m, 1H), 1.17 (m, 3H), 1.18−1.05 (m, 21H), 1.05−0.95 (m, 4H). ^{13}C NMR: δ 166.0 (s), 88.9 (d), 81.5 (s), 75.2 (d), 69.2 (s), 62.6 (t), 54.9 (t), 35.1 (t), 17.7 (q), 14.8 (q), 12.3 (d), 12.1 (t), 8.7 (t). **13a,b-Et.** MS (EI) *m*/*z* 417 (3), 329 (6), 314 (8), 294 (3), 245 (3), 207 (4), 149 (15), 86 (72), 84 (100), 55 (73). **13a,b-Et.** IR ($CDCl_3$) 2980, 2940, 1720, 1680, 1430 cm^{-1}.

(3′*S*,6′*R*,7′*R*,8′*S*)-Methyl 8-*tert*-Butoxyspiro[cycloproane-1-4′-(3′-chloro-1′-aza-2′-oxatricyclo[5.3.0.0^{3,6}]decane-6′-carboxylate] (17a) and (3′*R*,6′*S*,7′*R*,8′*S*)-Methyl 8-*tert*-Butoxyspiro[cycloproane-1-4′-(3′-chloro-1′-aza-2′-oxatricyclo[5.3.0.0^{3,6}]decane-6′-carboxylate] (17b). A solution of the nitrone **10** (160 mg, 1.02 mmol) and the (*Z*)-diastereomer of **2**-Me (211 mg, 1.22 mmol) in CH_2Cl_2 (2 mL) was stirred at room temperature for 6 d. The solution was concentrated, and the residue (340 mg) was purified by FCC on Al_2O_3 (activity II, pH 7) to furnish a mixture of **17a** and **17b** (6:1) as a yellow oil (269 mg, 80% yield). R_f = 0.75 (AcOEt/petroleum ether, 1:4). **17a.** ^{1}H NMR: δ 4.39 (d, J = 2.0 Hz, 1H), 4.02 (dd, J = 6.2, 2.0 Hz, 1H), 3.84 (s, 3H), 3.60−3.50 (m, 1H), 3.33 (ddd, J = 14.0, 6.2, 5.8 Hz, 1H), 2.82 (AB system, part A), 2.27 (AB system, part B), 2.33−2.23 (m, 1H), 1.87−1.79 (m, 1H), 1.11 (s, 9H), 1.05−0.99 (m, 1H), 0.87−0.79 (m, 2H), 0.56−0.50 (m, 1H). ^{13}C NMR: δ 169.2 (s), 106.9 (s), 80.55 (d), 73.3 (d), 69.3 (s), 57.7 (s), 54.9 (q), 52.8 (t), 34.5 (t), 28.3 (q), 27.4 (t), 12.2 (t), 7.5 (t). **17b.** ^{1}H NMR: δ 4.60 (s, 1H), 4.06 (d, J = 4.3 Hz, 1H), 3.94−3.91 (m, 1H), 3.78 (s, 3H), 3.70−3.64 (m, 1H), 2.74 (AB system, part A), 2.46 (AB system, part B), 2.00−1.88 (m, 1H), 1.69 (dd, J = 13.3, 4.2 Hz, 1H), 1.11 (s, 9H), 0.73−0.67 (m, 2H), 0.58−0.48 (m, 2H). ^{13}C NMR: δ 161.9 (s), 101.6 (s), 79.8 (d), 73.7 (d), 68.0 (s), 56.8 (s), 54.5 (q), 50.6 (t), 30.7 (t), 28.8 (q), 14.3 (t), 12.0 (t), 9.6 (t). **17a,b.** MS (EI) *m*/*z* 329 (21), 314 (35), 294 (45), 266 (18), 240 (31), 169 (25), 157 (63), 86 (40), 84 (70), 55 (100). **17a,b.** IR ($CDCl_3$) 2933, 2880, 1735, 1725, 1435 cm^{-1}. Anal. Calcd for $C_{16}H_{24}ClNO_4$: C, 58.27; H, 7.33; N, 4.25. Found: C, 58.45; H, 7.41; N, 4.18.

(3′*S*,6′*R*,7′*R*,8′*S*)-Ethyl 8′-(Triisopropylsilyloxy)-spiro[cycloproane-1-4′-(3′-chloro-1′-aza-2′-oxatricyclo[5.3.0.0^{3,6}]decane-6′-carboxylate] (23a-Et) and (3′*R*,6′*S*,7′*R*,8′*S*)-Ethyl 8′-(Triisopropylsilyloxy)-spiro[cycloproane-1-4′-(3′-chloro-1′-aza-2′-oxatricyclo[5.3.0.0^{3,6}]decane-6′-carboxylate] (23b-Et). A solution of the nitrone **11** (301 mg, 1.17 mmol) and the ethyl acrylate **2**-Et (211 mg, 1.22 mmol) in CH_2Cl_2 (2 mL) was stirred at room temperature for 6 d. The solution was concentrated, and the residue (510 mg) purified by FCC on Al_2O_3 (activity II, pH 7) to yield a mixture of **23a**-Et and **23b**-Et as an orange oil (441 mg, 85%). R_f = 0.8 (AcOEt/petroleum ether, 1:5). **23a-Et.** ^{1}H NMR: δ 4.48 (s, 1H), 4.35 (m, 1H), 4.24 (q, J = 7.2 Hz, 2H), 3.67−3.52 (dt, J = 14.6, 6.5 Hz, 1H), 3.48−3.25 (dd, J = 14.6, 6.5 Hz, 1H), 2.73 (AB system, part A), 2.43−2.20 (m, 2H), 2.15 (AB system, part B), 1.29 (t, J = 7.2 Hz, 3H), 1.00 (m, 21H), 0.86−0.73 (m, 2H), 0.72−0.61 (m, 1H), 0.53−0.45 (m, 1H). ^{13}C NMR: δ 174.5 (s), 111.9 (s), 81.6 (d), 75.2 (d), 62.2 (t), 55.6 (s), 55.0 (t), 44.6 (t), 36.2 (t), 28.4 (s), 17.9 (q), 14.3 (q), 12.0 (d), 10.4 (t), 7.4 (t). MS (EI) *m*/*z* 212 (8), 194 (8), 157 (22), 131 (20), 115 (21), 84 (32), 75 (100), 61 (61). IR ($CDCl_3$) 2894, 1734, 1445 cm^{-1}. HRMS: 444.23314. Selected data for **23b-Et.** ^{1}H NMR: δ 4.46 (s, 1H), 4.24 (q, J = 7.2 Hz, 2H), 2.85 (AB system, part A) 2.40 (AB system, part B), 1.29 (t, J = 7.2 Hz, 3H).

Methyl 3′-Chloro-3a′-methyltetrahydro-3*H*′-spiro[cyclopropane-1,2′-pyrrolo[1,2-*b*]isoxazole]-3′-carboxylate (26). A solution of the nitrone **25** (260 mg, 2.63 mmol) and the acrylate **1**-Me (460 mg, 3.15 mmol) in toluene (5 mL) was heated at 80 °C in a sealed

(19) (a) Wessjohann, L.; Giller, K.; Zuck, B.; Skattebøl, L.; de Meijere, A. *J. Org. Chem.* **1993**, *58*, 6442−6450. (b) de Meijere, A.; Ernst, K.; Zuck, B.; Brandl, M.; Kozhushkov, S. I.; Tamm, M.; Yufit, D. S.; Howard, J. A. K.; Labahn, T. *Eur. J. Org. Chem.* **1999**, *3105*, 5−3115.

vial for 20 h. The solution was concentrated and the residue (660 mg) purified by FCC on Al_2O_3 (activity II, pH 7) to yield **26** as a yellow oil (470 mg, 73% yield). $R_f = 0.22$ (Et_2O/petroleum ether, 1:1). ^{1}H NMR: δ 3.74 (s, 3H), 3.32−3.21 (m, 2H), 2.02−1.83 (m, 4H), 1.49 (s, 3H), 1.30−1.00 (m, 4H). ^{13}C NMR: δ 166.3 (s), 81.3 (s), 79.2 (s), 68.4 (s), 56.0 (t), 52.7 (q), 36.7 (t), 24.7 (t), 22.9 (q), 16.1 (t), 8.43 (t). MS (EI) *m*/*z* 245 (10), 230 (3), 209 (3), 182 (17), 154 (50), 146 (15), 122 (39), 84 (50), 83 (30), 55 (100); IR ($CDCl_3$) 2980, 2840, 1740, 1440 cm^{-1}. Anal. Calcd for $C_{11}H_{16}ClNO_3$: C, 53.77; H, 6.56; N, 5.70. Found: C, 53.84; H, 6.76; N, 5.63.

General Procedure for the Cyclopropane to Cyclobutane Ring Enlargement. To a well-stirred solution of the cycloadduct (1 mmol) in 1,2-dichloroethane (20 mL) was added Al_2O_3 (3.5 g/mmol), and the suspension was heated at 80 °C for 18 h. The mixture was then filtered through a short pad of Celite, and the solution was concentrated to afford the corresponding cyclobutane derivatives.

Methyl (2a*S*,7*S*,7a*R*,7b*R*)-7-*tert*-Butoxy-2a-chlorohexahydrocyclobuta[*d*]pyrrolo[1,2-*b*]isoxazole-7b-(1*H*)-carboxylate (14a). The crude product (310 mg) obtained from **10** and **1**-Me was purified by flash column chromatography on silica gel to yield **14a** as a colorless oil (243 mg, 80%). $R_f = 0.45$ (AcOEt/petroleum ether, 1:4). $[\alpha]^{20}_D = +13.9$ (CH_2Cl_2, *c* 0.7). ^{1}H NMR: δ 4.39 (s, 1H), 3.92 (d, $J = 5.8$ Hz, 1H), 3.85 (s, 3H), 3.55 (dd, $J = 14.4$, 6.6 Hz, 1H), 3.31 (ddd, $J = 14.4$, 12.4, 5.8 Hz, 1H), 2.76−2.62 (m, 2H), 2.49−2.40 (m, 1H), 2.17 (tt, $J = 12.4$, 6.6 Hz, 1H), 1.95−1.86 (m, 1H), 1.83 (dd, $J = 13.2$, 5.8 Hz, 1H), 1.11 (s, 9H). ^{13}C NMR: δ 169.4 (s), 102.1 (s), 80.6 (d), 74.0 (s), 73.7 (d), 66.4 (s), 55.3 (t), 53.1 (q), 35.1 (d), 33.5 (d), 28.4 (q), 22.8 (t). MS (EI) *m*/*z* 303 (1.80), 246.15 (10), 170 (31), 88 (8), 86 (38), 84 (87), 59 (19), 57 (100), 55 (19), 53 (11), 51 (23). IR ($CDCl_3$) 2977, 2260, 2239, 1732 cm^{-1}. Anal. Calcd for $C_{14}H_{22}ClNO_4$: C, 55.35; H, 7.30; N, 4.30. Found: C, 55.78; H, 7.09; N, 4.47.

Methyl (2a*S*,7*S*,7a*R*,7b*R*)-7-Triisopropylsilyloxy-2a-chlorohexahydrocyclobuta[*d*]pyrrolo[1,2-*b*]isoxazole-7b-(1*H*)-carboxylate (15a). The crude product (410 mg) obtained from **11** and **1**-Me was purified by FCC on Al_2O_3 (activity II, pH 7) to yield **15a** (containing some of the diastereoisomer **15b**) as a yellow oil (262 mg, 65% yield). $R_f = 0.60$ (AcOEt/petroleum ether, 1:10). ^{1}H NMR: δ 4.45 (s, 1H), 4.20 (d, $J = 4.8$ Hz, 1H), 3.82 (s, 3H), 3.55 (dt, $J = 14.2$, 6.6 Hz, 1H), 3.33 (dt, $J = 7.2$, 3.2 Hz, 1H), 2.74−2.56 (m, 2H), 2.46−2.36 (m, 1H), 2.23−2.01 (m, 1H), 1.92−1.72 (m, 2H), 1.13−0.89 (m, 21H). ^{13}C NMR: δ 169.1 (s), 101.1 (s), 89.0 (d), 76.5 (d), 55.9 (q), 53.1 (t), 34.5 (t), 26.0 (t), 21.4 (t), 17.9 (d), 12.4 (q). MS (EI) *m*/*z* 405 (5), 403 (15), 375 (20), 367 (30), 257 (20), 202 (70), 154 (60), 84 (100). IR ($CDCl_3$) 2970, 2935, 1735, 1715, 1440 cm^{-1}. Anal. Calcd for $C_{19}H_{34}ClNO_4Si$: C, 56.48; H, 8.48; N, 3.47. Found: C, 56.78; H, 8.29; N, 3.58.

Ethyl (2a*S*,7*S*,7a*R*,7b*R*)-7-Triisopropylsilyloxy-2a-chlorohexahydrocyclobuta[*d*]pyrrolo[1,2-*b*]isoxazole-7b-(1*H*)-carboxylate (15a-Et). The crude product (400 mg) obtained from **11** and **1**-Et was purified by FCC on Al_2O_3 (activity II, pH 7) to yield **15a**-Et (containing some of the diastereoisomer **15b**) as a yellow oil (309 mg, 78% yield). $R_f = 0.50$ (AcOEt/petroleum ether, 1:10). ^{1}H NMR: δ 4.45 (s, 1H), 4.28 (q, $J = 7.0$ Hz, 1H), 4.27 (q, $J = 7.0$ Hz, 1H), 4.19 (d, $J = 5.0$ Hz, 1H), 3.56 (dd, $J = 14.4$, 6.8 Hz, 1H), 3.33 (ddd, $J = 14.0$, 12.8, 5.8 Hz, 1H), 2.73−2.58 (m, 2H), 2.43−2.37 (m, 1H), 2.14 (ddt, $J = 12.8$, 6.8, 5.0 Hz, 1H), 1.86 (dd, $J = 12.8$, 5.4 Hz, 1H), 1.81−1.73 (m, 1H), 1.31 (t, $J = 7.0$ Hz, 3H), 1.12−0.91 (m, 21H). ^{13}C NMR: δ 168.5 (s), 100.5 (s), 81.4 (d), 75.0 (s), 71.5 (d), 62.2 (t), 54.8 (t), 36.2 (t), 33.3 (t), 22.9 (t), 18.0 (q), 14.0 (q), 12.0 (d). MS (EI) *m*/*z* 417 (3), 329 (6), 314 (8), 294 (3), 245 (3), 207 (4), 149 (15), 86 (72), 84 (100), 55 (73). IR ($CDCl_3$) 2980, 2940, 1720, 1680, 1430 cm^{-1}. HRMS 418.21749.

Methyl 2a-Chloro-7a-methylhexahydrocyclobuta[*d*]pyrrolo-[1,2-*b*]isoxazole-7b(1*H*)-carboxylate (27). The crude product (243 mg) obtained from **26** and **1**-Me was purified by FCC on Al_2O_3 (activity II, pH 7) to yield **27** as a yellow oil (95 mg, 39% yield). $R_f = 0.55$ (AcOEt/petroleum ether, 1:10). ^{1}H NMR: δ 3.74 (s, 3H), 3.64−3.45 (m, 2H), 2.50−2.00 (m, 4H), 1.80−1.51 (m, 4H), 1.53 (s, 3H). ^{13}C NMR: δ 169.1 (s), 101.1 (s), 72.5 (s), 56.0 (s), 53.1 (t), 50.5 (q), 34.5 (t), 26.0 (t), 25.4 (t), 22.0 (t), 20.2 (q). MS (EI) *m*/*z* 245 (10), 230 (3), 209 (3), 182 (17), 154 (50), 146 (15), 122 (39), 84 (50), 83 (30), 55 (100). IR ($CDCl_3$) 2929, 2857, 1710 cm^{-1}. Anal. Calcd for $C_{11}H_{16}ClNO_3$: C, 53.77; H, 6.56; N, 5.70. Found: C, 53.78; H, 6.29; N, 5.82.

Synthesis of Indolizine Derivatives. Methyl (1*S*)-1-*tert*-Butoxy-5-oxo-1,2,3,5,6,7-hexahydroindolizine-8-carboxylate (18). A solution of cycloadducts **12a** and **12b** (267 mg, 1 mmol) and Et_3N (202 mg, 2 mmol) in DMF (3 mL) was heated in a sealed vial at 80 °C for 2 d. After this time, another 2 equiv of Et_3N was added, and the solution was heated for another 2 d. The solution was diluted with water (20 mL) and extracted with diethyl ether (3 × 20 mL). The organic phase was dried over Na_2SO_4, concentrated, and the residue (250 mg) was purified by flash column chromatography to yield **18** as a yellow oil (186 mg, 70%). $R_f = 0.25$ (AcOEt/petroleum ether, 1:4); $[\alpha]^{20}_D = +17.0$ (CH_2Cl_2, *c* 0.4). ^{1}H NMR: δ 5.47 (d, $J = 4.3$ Hz, 1H), 3.94−3.72 (m, 1H), 3.74 (s, 3H), 3.74−3.54 (m, 1H), 2.84−2.65 (m, 1H), 2.60−2.43 (m, 3H), 2.11−1.96 (m, 1H), 1.72−1.69 (m, 1H), 1.25 (s, 9H). ^{13}C NMR: δ 168.9 (s), 166.0 (s), 152.2 (s), 102.2 (s), 74.6 (s), 70.7 (d), 51.3 (q), 43.4 (t), 31.3 (t), 30.4 (t), 28.9 (q), 21.4 (t). MS (EI) *m*/*z* 267 (4), 194 (11), 178 (33), 168 (12), 151 (19), 134 (8), 124 (8), 151 (19), 134 (8), 124 (8), 106 (18), 104 (12), 92 (29), 86 (23), 84 (42), 80 (14), 79 (10), 69 (10), 59 (29), 58 (10), 57 (100), 51 (17). IR ($CDCl_3$) 2979, 2249, 1673, 1654, 1438 cm^{-1}. Anal. Calcd for $C_{14}H_{21}NO_4$: C, 62.90; H, 7.92; N, 5.24. Found: C, 62.71; H, 7.64; N, 5.05.

Methyl (1*S*)-Hydroxy-5-oxo-1,2,3,5,6,7-hexahydroindolizine-8-carboxylate (20-Me), Methyl 8′-Hydroxy-spiro[cyclopropane-1-4′-(3′-chloro-1′-aza-2′-oxatricyclo[5.3.0.0^{3,6}]decane-6′-carboxylate] (21), and 8′-(Triisopropylsilyloxy)-spiro[cyclopropane-1-4′-(3′-methoxy-1′-aza-2′-oxatricyclo[5.3.0.0^{3,6}]decane-6′-carboxylate] (22). CsF (302 mg, 2 mmol) was added to a solution of the cycloadducts **15a** and **15b** (404 mg, 1 mmol) in MeOH (14 mL), and the mixture was heated under reflux under a nitrogen atmosphere for 6 h. The solution was concentrated, and the residue (720 mg) purified by flash column chromatography to yield **20**-Me (50 mg, 24%), **21** (87 mg, 36%), and **22** (129 mg, 32%). **20-Me.** $R_f = 0.31$ (AcOEt/petroleum ether, 1:1). $[\alpha]^D_{20} = +37.3$ (CH_2Cl_2, *c* 0.4). ^{1}H NMR: δ 5.21 (dd, $J = 7.3$, 4.7 Hz, 1H), 4.65 (bs, 1H), 3.94−3.62 (m, 2H), 3.74 (s, 3H), 2.71−2.59 (m, 2H), 2.56−2.44 (m, 2H), 2.28 (td, $J = 14.2$, 5.9 Hz, 1H), 2.19−1.95 (m, 1H). ^{13}C NMR: δ 169.5 (s), 167.9 (s), 153.7 (s), 101.0 (s), 72.1 (d), 52.9 (q), 46.3 (t), 31.2 (t), 30.5 (t), 21.5 (t). MS (EI) *m*/*z* 211 (70), 196 (65), 180 (80), 163 (40), 135 (100), 106 (40), 84 (47). IR ($CDCl_3$) 2900, 2840, 1685, 1640 cm^{-1}. Anal. Calcd for $C_{10}H_{13}NO_4$: C, 56.86; H, 6.20; N, 6.63. Found: C, 56.93; H, 6.32; N, 6.52. **21.** $R_f = 0.68$ (AcOEt/petroleum ether, 1:1). ^{1}H NMR: δ 4.23 (s, 1H), 4.13 (d, $J = 4.2$ Hz, 1H), 3.80 (s, 3H), 3.77−3.17 (m, 2H), 3.14 (s, 3H), 2.46−2.37 (dt, $J = 7.0$, 1.8 Hz, 1H), 2.17−2.13 (m, 5H). ^{13}C NMR: δ 167.1 (s), 94.1 (s), 80.0 (d), 75.0 (d), 60.0 (q), 55.3 (q), 57.5 (s), 53.1 (t), 32.2 (t), 25.1 (t), 20.0 (t). MS (EI) *m*/*z* 226 (5), 195 (30), 149 (50), 131 (80), 103 (70), 84 (100), 75 (92). **22.** $R_f = 0.11$ (AcOEt/petroleum ether, 1:1). ^{1}H NMR: δ 4.19 (s, 1H), 4.10 (d, $J = 4.2$ Hz, 1H), 3.80 (s, 3H), 3.77−3.67 (m, 2H), 3.14 (s, 3H), 2.41 (dt, $J = 7.0$, 1.8 Hz, 1H), 2.17−2.13 (m, 5H), 1.05 (m, 21H). ^{13}C NMR: δ 168.4 (s), 94.5 (s), 90.3 (d), 75.9 (d), 60.7 (q), 58.9 (s), 56.4 (q), 52.5 (t), 35.1 (t), 26.4 (t), 25.2 (t), 17.5 (d), 12.5 (q). MS (EI) *m*/*z* 398 (3), 367 (40), 356 (12), 300 (9), 272 (4), 209 (10), 168 (15), 149 (30), 142 (28), 84 (100).

Ethyl (1*S*)-Hydroxy-5-oxo-1,2,3,5,6,7-hexahydroindolizine-8-carboxylate (20-Et). CsF (302 mg, 2 mmol) was added to a solution of **15a,b**-Et (417 mg, 1 mmol) in EtOH (14 mL), and the mixture was heated under reflux under a nitrogen atmosphere for 6 h. The solution was concentrated, and the residue (730 mg) was purified by flash column chromatography to yield **20**-Et (146 mg, 68%). $R_f = 0.25$ (AcOEt/petroleum ether, 1:1). $[\alpha]^D_{20} = +13.2$ (CH_2Cl_2, *c* 0.7). ^{1}H NMR: δ 5.21 (dd, $J = 7.3$, 4.7 Hz, 1H), 4.70 (bs, 1H),

4.23 (q, J = 7.0 Hz, 2H), 3.87 (dt, J = 11.8, 5.7 Hz, 1H), 3.65−3.62 (m, 1H), 2.72−2.64 (m, 2H), 2.57−2.48 (m, 2H), 2.37−2.19 (m, 1H), 2.00−2.16 (m, 1H), 1.31 (t, J = 7.0 Hz, 3H). ^{13}C NMR: δ 169.0 (s), 168.0 (s), 156.0 (s), 101.8 (s), 72.0 (d), 60.9 (t), 44.3 (t), 30.5 (t), 29.3 (t), 21.2 (t), 14.3 (q). MS (EI) *m*/*z* 196 (7), 180 (26), 168 (36), 152 (24), 106 (44), 84 (47). IR ($CDCl_3$) 2900, 2830, 1680, 1640 cm^{-1}. Anal. Calcd for $C_{11}H_{15}NO_4$: C, 58.64; H, 6.72; N, 6.22. Found: C, 58.74; H, 6.80; N, 6.25.

Methyl (1′*S*)-1′-*tert*-Butoxy-5′-oxo-1′-2′-3′-7′-tetrahydrospiro-[cyclopropane-1,6′-indolizine]-8′-carboxylate (19). Compound **17ab** (160 mg, 0.48 mmol) was transformed into **19** using the procedure described above for the synthesis of **18**. Flash column chromatography (AcOEt/petroleum ether, 1:4) afforded compound **19** (83 mg, 70% yield) as a yellow oil. R_f = 0.30 (AcOEt/petroleum ether, 1:4). $[\alpha]^{D}_{20}$ = + 24.3 (CH_2Cl_2, *c* 1.0). ^{1}H NMR: δ 5.50 (d, J = Hz, 1H), 3.90−3.57 (m, 2H), 3.71 (s, 3H), 2.83 (system AB, part, A, 1H), 2.03 (system AB, part B, 1H), 2.15−1.73 (m, 2H), 1.25 (s, 9H), 1.96−0.62 (m, 4H). ^{13}C NMR: δ 169.0 (s); 168.0 (s), 156.0 (s), 101.8 (s), 79.0 (d), 72.0 (s), 60.9 (q), 44.3 (t), 30.5 (t), 29.3 (t); 21.2 (t); 14.3 (t). MS *m*/*z* (EI) 265 (2); 250 (25); 221 (30); 205 (32); 148 (54); 120 (20); 96 (30); 85 (65); 83 (100); 69 (38); 55 (54). IR ($CDCl_3$) 2955−2932; 2855; 1707; 1652 cm^{-1}. Anal. Calcd for $C_{16}H_{23}NO_4$: C, 65.51; H, 7.90; N, 4.77. Found: C, 65.63; H, 7.83; N, 4.56.

Ethyl 1′S-1′-Hydroxy-5′-oxo-1′-2′-3′-7′-tetrahydrospiro[cyclopropane-1,6′-indolizine]-8′-carboxylate (24-Et). Compound **23a,b**-Et (230 mg, 0.51 mmol) was transformed into **24**-Et using the procedure described above for the synthesis of **20**-Et. Flash column chromatography (AcOEt/petroleum ether, 1:2) afforded compound **24**-Et (70 mg, 53%) as a yellow oil. R_f = 0.21 (AcOEt/petroleum ether, 1:2). $[\alpha]^{D}_{20}$ = +35.8 (CH_2Cl_2, *c* 0.6). ^{1}H NMR: δ 5.24 (dd, J = 7.2, 5.0 Hz, 1H); 4.72 (bs, 1H); 4.20 (q, J = 6.8 Hz, 2H); 3.94−3.78 (m, 1H); 3.74−3.62 (m, 1H); 2.55 (system AB, 2H); 2.38−2.20 (m, 1H); 2.18−2.00 (m, 1H); 1.28 (t, J = 6.8 Hz, 3H); 1.04 (m, 1H); 0.86 (m, 1H); 0.73 (q, J = 2.9 Hz, 2H). ^{13}C NMR: δ 171.9 (s); 167.9 (s); 155.7 (s); 99.8 (s); 72.2 (d); 60.8 (t); 44.8 (t); 31.0 (t); 29.5 (t); 19.7 (s); 17.3 (t); 16.5 (t); 14.3 (t). MS (EI) *m*/*z* 251 (24); 232 (26); 204 (44); 178 (74); 166 (63); 161 (65); 65 (100). IR ($CDCl_3$) 2925; 2853; 1707−1640 cm^{-1}. Anal. Calcd for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.57. Found: C, 62.33; H, 7.09; N, 4.20.

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Supporting Information Available: General experimental details; copies of ^{1}H and ^{13}C NMR spectra for compounds **12a,b**, **14a**, **18**, **20**-Et, and **24**-Et, and the data of the X-ray analysis of **14a**, including CIF file. This material is available free of charge via the Internet at http://pubs.acs.org.

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