ChemPubSoc Europe

DOI: 10.1002/ejoc.201701771

EurJOC European Journal of Organic Chemistry

Full Paper

Spiro-Fused Heterocycles

SPECIAL ISSUE

Domino Thermal Rearrangement/[4+2] Addition Reactions of an *exo*-Methylene Spirocyclopropane Isoxazolidine

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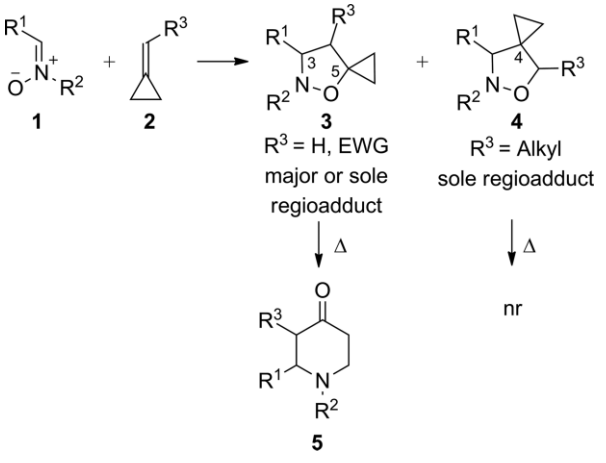
Abstract: A 4-methylene-5-spirocyclopropane isoxazolidine was prepared with complete regioselectivity through the 1,3-dipolar cycloaddition reaction of a pyrroline *N*-oxide with a cyclopropylidene acetate, followed by reduction and elimination. Thermal rearrangement of the isoxazolidine gives an indolizidinone that retains the exocyclic methylene moiety. The *exo*-methylene substituent confers a particular reactivity to this heterocycle; it can undergo thermal hetero-Diels–Alder cycloadditions and ene reactions with different reaction partners.

Introduction

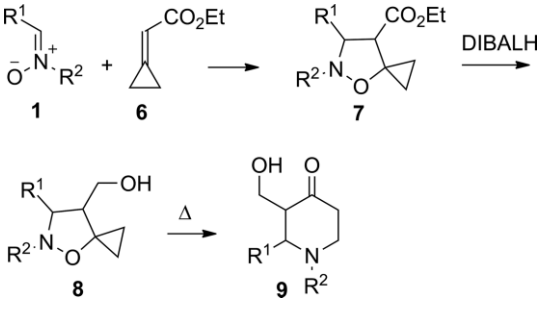
During our studies on the chemistry of 5-spirocyclopropane isoxazolidines, we have been confronted by limitations arising from the method used to access these compounds, i.e., the 1,3-dipolar cycloaddition of nitrones to methylenecyclopropanes (MCPs). The method is quite general, and can be used to form many structurally diverse 5-spirocyclopropane isoxazolidines **3** as major or sole products when the parent MCP **2** (R^3 = H) or MCPs bearing an EWG (electron-withdrawing group) at the exocyclic position **2** (R^3 = EWG) are used as dipolarophiles. However, when alkylidenecyclopropanes **2** (R^3 = Alk) are used in the reaction with nitrones, the only cycloadducts obtained are 4-spirocyclopropane isoxazolidines **4** (Scheme 1).[1] This inverted regioselectivity has its origin in unfavorable steric interactions in the transition state of the cycloaddition leading to a 5-spirocyclopropane isoxazolidine when a substituent on the alkylidenecyclopropane approaches the carbon of the nitrone group.

4-Spirocyclopropane isoxazolidines **4**, of course, cannot undergo the well-known Brandi–Guarna rearrangement to tetrahydropyridones, which represents a straightforward entry to polycyclic heterocycles and natural products.[2]

Recently, a practical way to overcome this limitation has been found. First, a nitrone undergoes a highly regioselective cycloaddition reaction with a cyclopropylidene acetate **6** to give 5-spirocyclopropane isoxazolidines **7**. This is followed by a chemoselective reduction of the ester group to a hydroxymethylene group (Scheme 2).[3] Through subsequent exploitation of the hydroxymethylene group, this approach could become a general method for the production of 3-substituted tetrahydropyridones **9**, which were unavailable by our previous approach.



Scheme 1. Regioselectivity of the 1,3-dipolar cycloaddition of nitrones **1** with *exo*-substituted methylenecyclopropanes **2**. nr = no reaction.



Scheme 2. Approach to 3-hydroxymethyl-piperidin-4-ones through nitrone 1,3-dipolar cycloaddition and thermal rearrangement of 5-spirocyclopropane isoxazolidines. DIBALH = diisobutylaluminium hydride.

In this paper, we present another example related to this strategy, involving the formal elimination of H_2O from 4-

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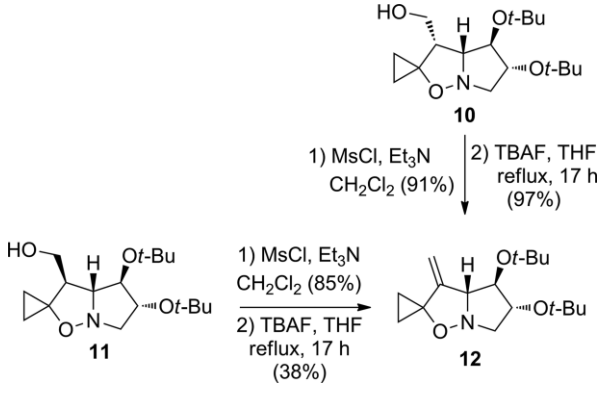
hydroxymethylene 5-spirocyclopropane isoxazolidine **8** to give the corresponding 4-*exo*-methylene isoxazolidine. This then rearranges into the 3-*exo*-methylene-4-tetrahydropyridone in the presence of dienophiles or enophiles to produce [4+2] cycloadducts or ene-reaction products.

Results and Discussion

Diastereomeric hydroxymethylene isoxazolidines **10** and **11** were recently obtained during our studies on the synthesis of derivatives of (–)-lentiginosine. This 1,2-dihydroxyindolizidine alkaloid shows interesting proapoptotic activity and has a low cytotoxicity.[3] Compounds **10** and **11** were obtained in a 3.5:1 ratio after reduction of the respective carboxylate precursors, which, in turn, were obtained by a 1,3-dipolar cycloaddition reaction of 3,4-bis(*tert*-butoxy)pyrroline *N*-oxide with cyclopropylidene acetate **6**.

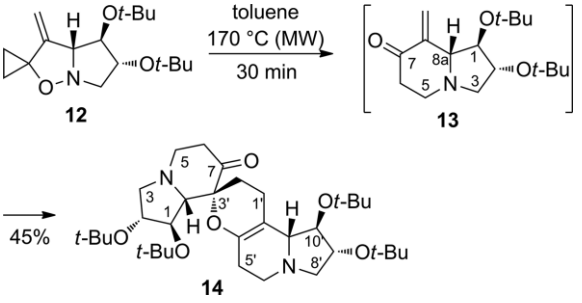
When we attempted to transform **10** and **11** into the corresponding fluoro derivatives by deoxyfluorination, we found that treatment of the mesylate derivatives of **10** and **11** with tetrabutylammonium fluoride (TBAF) resulted in a smooth elimination to give *exo*-methylene isoxazolidine **12** (Scheme 3).[4] Other attempts to induce elimination of the mesylate to produce **12** using bases such as DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) and DIPEA (diisopropylethylamine) were not as efficient.



Scheme 3. Synthesis of *exo*-methylene isoxazolidine **12**.

exo-Methylene isoxazolidine **12**, made available by the simple method described here, could be used to extend the Brandi–Guarna rearrangement to the synthesis of 8-substituted indolizidinones. Indeed, the double-bond might undergo several selective transformations to give derivatives that are unavailable by the direct 1,3-dipolar cycloaddition strategy (see above).

Nevertheless, isoxazolidine **12** could undergo the thermal rearrangement on its own to give an 8-methylene-7-indolizidinone. To test this possibility, compound **12** was heated in toluene in a sealed tube in a microwave (MW) apparatus at 170 °C for 30 min (Scheme 4). ^{1}H NMR spectroscopic analysis of the crude reaction mixture indicated the formation of indolizidinone **13** as the major product, along with a minor dimeric product. The NMR spectrum of **13** is characterized by the presence of methylene protons at δ = 6.10 and 5.54 ppm (pseudo t, J = 1.8 Hz). However, *exo*-methylene derivative **13** could not be isolated because it slowly dimerizes in solution, even at low temperature. The dimerization of **13** is faster at high temperature and/or in the condensed phase. After concentration of the thermal rearrangement reaction mixture and purification by chromatography, dimer **14** was isolated in 45 % yield as a single isomer. Dimer **14** is formed as the result of a [4+2] cycloaddition of the oxadiene moiety of one molecule with the *exo*-methylene bond of a second molecule of **13**.[5]



Scheme 4. Thermal rearrangement of **12** followed by dimerization of **13**.

The structure of **14** was assigned by ESI-MS and NMR spectroscopic analysis, including ^{1}H and ^{13}C NMR, COSY, HMQC, and HMBC analysis. The NMR spectra of **14** clearly show the signal patterns of the bicyclic and tricyclic fragments. For example, the indolizidin-7-one system is characterized by the resonances of the bridgehead hydrogen atom 8a-H at δ = 2.41 ppm (d, J = 5.1 Hz) and the carbonyl C-7 at δ = 206.9 ppm; representative of the octahydro-1*H*-pyrano[2,3-*g*]indolizine part are the broad singlet at δ = 3.26 ppm of 10a′-H, and the signals of the double-bond carbons C-4a′ and C-10b′ at δ = 144.5 and 102.0 ppm, respectively. The configuration of the spiro center 3′-C is tentatively assigned as *R* based on the idea that an *endo* approach[5] of the methylene and the heterodiene moieties from the less hindered α face of **13** in the hetero-Diels–Alder reaction would probably be favored, i.e., opposite to the bridgehead hydrogen 8a-H and the vicinal 1-O*t*Bu group. The regioselectivity observed is consistent with literature data for analogous cycloadditions.[5,6]

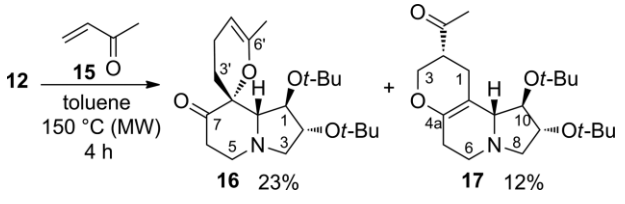
The fact that the diene in **13** is electron-deficient makes the ease of formation of [4+2] cycloaddition product **14** surprising. Nevertheless, it opens the way to another application of **13**, and to the synthesis of new complex indolizidines.

The scope of the reaction was checked using other dienophiles. To try to minimize the dimerization process, the cycloaddition reaction was run by adding an excess of the dienophile to the solution of **12** just before the thermal rearrangement to generate indolizidinone **13** in situ; this makes the reaction a domino thermal rearrangement/[4+2] cycloaddition process.

The first dienophiles studied, due to the electron-deficient nature of the diene, were electron-rich alkenes, including 2,3-dihydrofuran, *cis*-stilbene, and β-pinene. Unexpectedly, none of these underwent cycloaddition with **13**, and only dimer **14** was recovered after heating at 150 °C for 1–2 h in the microwave.

The use of methyl vinyl ketone (MVK; **15**) as dienophile led to cycloadducts **16** and **17** in a ca. 2:1 ratio, along with traces

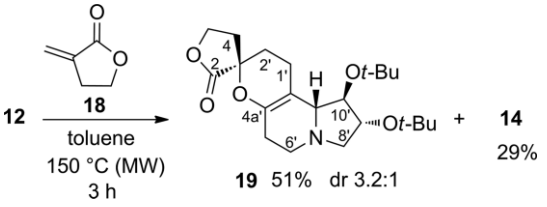
of two isomers that were not isolated and characterized (Scheme 5). A very large excess of the dienophile was necessary (20 equiv.), because with a lower excess (10 equiv.), dimer **14** was still the major product. Adducts **16** and **17** partially decompose on silica gel, and were recovered in moderate yields after chromatography. Spiro-fused isoxazolidinone **16** is formed by a [4+2] cycloaddition reaction between MVK as a heterodiene and the *exo*-methylene moiety of **13**. Analogously to **14**, the NMR spectra of **16** are characterized by the resonances of the bridgehead hydrogen 8a-H at δ = 2.43 ppm (d, J = 5.3 Hz) and the carbonyl C-7 at δ = 206.7 ppm. In addition, the narrow multiplet at δ = 1.8 ppm with an integration of three protons is consistent with the presence of an allylic coupling between 6′-CH_3 and 5′-H. Compound **17** is formed by a cycloaddition reaction between the exocyclic enone moiety of **13** and the alkene component of MVK. Also in this case, the NMR spectroscopic data are very similar to those for the corresponding octahydro-1*H*-pyrano[2,3-*g*]indolizine fragment of **14**. In particular, the bridgehead hydrogen 10a-H resonates as a broad singlet at δ = 3.26 ppm, and the olefinic carbons C-4a and C-10b at δ = 144.5 and 104.2 ppm, respectively. The absolute configurations of the new stereogenic centers in **16** and **17** were only tentatively assigned. For **16**, this was done based on the idea of preferential attack of diene **15** onto **13** on the face opposite the proximal *tert*-butoxy group. For **17**, the configuration was assigned based on the idea of a preferential *endo* approach of dienophile **15**.



Scheme 5. Domino thermal rearrangement of **12** and cycloaddition with MVK.

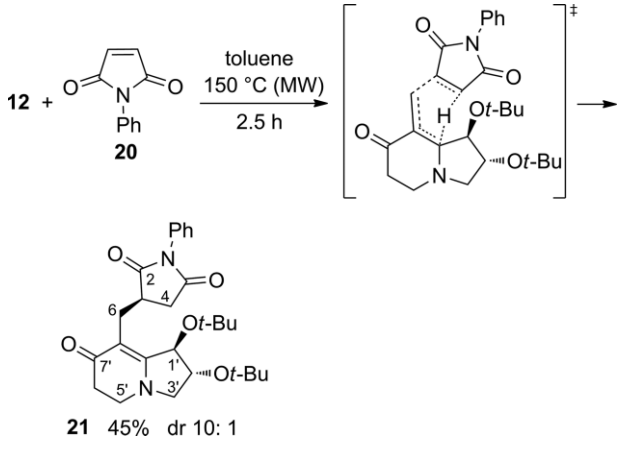
The [4+2] cycloaddition of **13** with 3-methylene-butyrolactone (**18**) took place smoothly to give spiro-cycloadduct **19** in 51 % yield as a mixture of two diastereoisomers in a 3.2:1 ratio, along with a minor amount of dimer **14** (Scheme 6). The formation of the two diastereoisomers can now be explained by the lower bulkiness of **18**, which can approach each of the two diastereotopic faces of heterodiene **13**. The two isomers were easily separable by chromatography on silica gel. Just as for the previous examples, the NMR spectroscopic data are consistent with the reported structures (major and minor isomers **19a** and **19b**: 10a′-H: δ = 3.2–3.3 ppm, C-4a′: δ = 143 ppm, and C-10b′: δ = 103 ppm). *exo*-Methylene lactone **18** reacts exclusively as a dienophile with **13**. This result represents further evidence for the preference of heterodiene **13** to react with electron-deficient dienophiles, even more so if they are 1,1-disubstituted. Analogously to the previous examples, the major isomer is probably derived from an *endo* approach of the CO_2R group of **18** to the less hindered α face of diene **13**.

As a final example, the reactive *N*-phenylmaleimide (**20**) was subjected to the domino thermal rearrangement/[4+2] cycloaddition process. Surprisingly, instead of a cycloaddition



Scheme 6. Domino thermal rearrangement of **12** and cycloaddition with lactone **18**.

product, the product of an intermolecular ene reaction **21** was isolated in 45 % yield as a 10:1 mixture of two inseparable diastereomers (Scheme 7). Thus, in this case, **20** preferentially reacts as an enophile rather than as a dienophile, and extracts the allylic tertiary hydrogen 8a-H of **13**. The NMR spectroscopic data of **21** are consistent with the reported structure: for example, in contrast to the previous adducts, the bridgehead hydrogen is missing, and the C-7′ resonance at δ = 191.2 ppm attests the presence of a conjugated carbonyl moiety. The stereochemical assignment of the new stereogenic center C-3 in the major isomer is only tentatively based on considerations of transition-state trajectories, which assume a preferential attack of the enophile from the face opposite the proximal *tert*-butoxy group, as in the previous cases.



Scheme 7. Domino thermal rearrangement of **12** and ene reaction with maleimide **20**.

The enophile reactivity of maleimide **20** has a few precedents in the literature,[7] even if the migrating atom is usually not a tertiary hydrogen but an allylic or benzylic one. The origin of this different reactivity is not clear. It cannot even be excluded that a primary strained [4+2] cycloadduct undergoes a ring-opening rearrangement under the reaction conditions, but to establish the reaction mechanism further investigations are necessary.

Conclusions

We have demonstrated that 4-methylene-5-spirocyclopropane isoxazolidines can be easily prepared by a four-step sequence involving a nitrone 1,3-dipolar cycloaddition with cyclopropylidene acetate, a chemoselective reduction of the ester moiety, mesylation, and elimination. The thermal rearrangement

product of the *exo*-methylene isoxazolidine features an exocyclic enone moiety that can undergo [4+2]-cycloaddition processes as both the diene and the dienophile component. This dualistic reactivity can be used to prepare highly decorated spiro-fused heterocycles with high stereoselectivity, either through dimerization or by reaction with different dienes or dienophiles. In addition, the reaction with *N*-phenyl maleimide highlights a third and quite unexpected reactivity of the *exo*-methylene moiety as an ene component. Despite the only moderate overall yield of the reported domino process of thermal rearrangement and [4+2] addition, its potential as a new method for the synthesis of complex heterocycles has been demonstrated. The intriguing multifaceted reactivity of *exo*-methylene indolizidinones should generate interest in this structure, and encourage further studies on similar compounds.

Experimental Section

General Remarks: Reactions requiring anhydrous conditions were carried out under a nitrogen atmosphere, and solvents were dried appropriately before use. Microwave-assisted reactions were carried out in a CEM Discover™ single-mode microwave reactor with an IR temperature sensor. Chromatographic purifications were carried out on silica gel 60 (0.040–0.063 mm, 230–400 mesh ASTM, Merck) using the flash technique. R_f values refer to TLC analysis on 0.25 mm silica gel plates. Melting points (m.p.) were determined with a Thiele Electrothermal apparatus. Polarimetric measurements were carried out with a JASCO DIP-370 polarimeter. NMR spectra were measured with Varian Mercury (^{1}H, 400 MHz, ^{13}C, 100 MHz) and Varian Inova (^{1}H, 400 MHz, ^{13}C, 100 MHz) nuclear magnetic resonance spectrometers. ^{1}H and ^{13}C NMR spectroscopic data are reported in δ (ppm), and spectra were calibrated using $CDCl_3$ signals (δ = 7.26 and 77.0 ppm). Peak assignments were made on the basis of ^{1}H,^{1}H COSY, HSQC, and HMBC experiments. IR spectra were recorded with a Perkin–Elmer Spectrum BX FTIR System spectrophotometer. Elemental analyses were carried out with a Perkin–Elmer 2400 analyzer. MS (ESI) spectra were recorded with an LCQ Fleet ion-trap mass spectrometer with a Surveyor Plus LC System (Thermo Scientific) operating in positive (ESI$^+$) and negative (ESI$^-$) ion mode, with direct infusion of sample solutions in methanol. Accurate-mass spectra were recorded with an LTQ Orbitrap high-resolution mass spectrometer (Thermo, San Jose, CA, USA), equipped with a conventional ESI source.

(3a′*R*,4′*R*,5′*R*)-4′,5′-Di-*tert*-butoxy-3′-methylenetetrahydro-3′*H*-spiro[cyclopropane-1,2′-pyrrolo[1,2-*b*]isoxazole] (12)

Procedure A: Freshly distilled MsCl (0.150 mL, 1.94 mmol) was added dropwise to a solution of alcohol **10**[3] (509 mg, 1.62 mmol) and distilled Et_3N (0.316 mL, 2.27 mmol) in anhydrous CH_2Cl_2 (2.3 mL) at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred for 1.5 h in an ice bath, and then it was diluted with CH_2Cl_2 (10 mL) and H_2O (10 mL). The two layers were separated, and the aqueous solution was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (EtOAc/petroleum ether, 1.5:1) to give {(3′*S*,3a′*R*,4′*R*,5′*R*)-4′,5′-di-*tert*-butoxytetrahydro-3′*H*-spiro[cyclopropane-1,2′-pyrrolo[1,2-*b*]isoxazol]-3′-yl}methyl methanesulfonate (576 mg, 91 %) as a colorless oil. R_f = 0.33 (EtOAc/petroleum ether, 1.5:1). $[\alpha]_D^{27}$ = –80.2 (*c* = 0.94, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.65 (dd, *J* = 9.9, 7.1 Hz, 1 H, C*H*HO), 4.36 (dd, *J* = 9.9, 7.1 Hz, 1 H, C*H*HO), 4.06 (pseudo t, *J* = 2.3 Hz, 1 H, 4′-H), 3.99–3.94 (m, 2 H, 3a′-H, 5′-H), 3.48 (dd, *J* = 12.6, 5.4 Hz, 1 H, 6′-Ha), 3.07 (br. dd, *J* = 12.6, 4.5 Hz, 1 H, 6′-Hb), 3.05 (s, 3 H, SCH_3), 2.80 (pseudo dt, *J* = 9.0, 7.1 Hz, 1 H, 3′-H), 1.20 [s, 9 H, C(CH_3)$_3$], 1.19 [s, 9 H, C(CH_3)$_3$], 1.06–0.86 (m, 3 H, *c*Pr), 0.56 (ddd, *J* = 10.1, 7.2, 5.1 Hz, 1 H, *c*Pr) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 78.5 (d, C-5′), 77.3 (d, C-4′), 75.3 (d, C-3a′), 74.4 [s, *C*(CH_3)$_3$], 74.3 [s, *C*(CH_3)$_3$], 69.1 (t, *C*H_2O), 64.3 (s, C-2′), 61.6 (t, C-6′), 45.7 (d, C-3′), 37.4 (q, SCH_3), 28.4 [q, 3 C, C(CH_3)$_3$], 28.3 [q, 3 C, C(CH_3)$_3$], 9.7 (t, *c*Pr), 7.7 (t, *c*Pr) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 2978, 2936, 2872, 1391, 1366, 1342, 1180, 1073 cm^{-1}. MS (ESI): *m*/*z* = 392 [M + H]$^+$, 414 [M + Na]$^+$. $C_{18}H_{33}NO_6S$ (391.52): calcd. C 55.22, H 8.50, N 3.58; found C 55.18, H 8.17, N 3.26.

A mixture of the mesylate (170 mg, 0.434 mmol) and TBAF (1 M in THF; 1.3 mL, 1.3 mmol) in anhydrous THF (10.9 mL) was heated at reflux for 17 h under a nitrogen atmosphere. After this time, the solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel (petroleum ether/EtOAc, 4:1) to give **12** (125 mg, 97 %) as a white solid. R_f = 0.4 (petroleum ether/EtOAc, 3:1). M.p. 56.7–57.6 °C. $[\alpha]_D^{25}$ = –87.2 (*c* = 0.58, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.93–4.90 (m, 1 H, =C*H*H), 4.61–4.58 (m, 1 H, =C*H*H), 4.12–4.07 (m, 1 H, 3a′-H), 4.03–3.94 (m, 2 H, 4′-H, 5′-H), 3.40 (dd, *J* = 10.1, 6.2 Hz, 1 H, 6′-Ha), 2.99 (pseudo t, *J* = 9.5 Hz, 1 H, 6′-Hb), 1.23 [s, 9 H, C(CH_3)$_3$], 1.16 [s, 9 H, C(CH_3)$_3$], 1.25–1.09 (m, 2 H, *c*Pr), 0.91–0.75 (m, 2 H, *c*Pr) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 153.8 (s, C-3′), 100.0 (t, =CH_2), 81.8 (d, C-4′), 77.6 (d, C-5′), 75.0 (d, C-3a′), 74.3 [s, *C*(CH_3)$_3$], 73.9 [s, *C*(CH_3)$_3$], 63.5 (s, C-2′), 58.7 (t, C-6′), 28.8 [q, 3 C, C(CH_3)$_3$], 28.5 [q, 3 C, C(CH_3)$_3$], 17.9 (t, *c*Pr), 11.6 (t, *c*Pr) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 2979, 2935, 2902, 1814, 1793, 1472, 1382, 1190, 1097 cm^{-1}. MS (ESI): *m*/*z* = 296 [M + H]$^+$, 318 [M + Na]$^+$. $C_{17}H_{29}NO_3$ (295.42): calcd. C 69.12, H 9.89, N 4.74; found C 69.45, H 9.50, N 4.37.

Procedure B: Freshly distilled MsCl (0.018 mL, 0.233 mmol) was added dropwise to a solution of alcohol **11**[3] (61 mg, 0.195 mmol) and distilled Et_3N (0.038 mL, 0.273 mmol) in anhydrous CH_2Cl_2 (0.278 mL) at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred for 2 h in an ice bath, and then it was diluted with CH_2Cl_2 (5 mL) and H_2O (5 mL). The two layers were separated, and the aqueous solution was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was filtered through a short pad of silica gel (Et_2O) to give {(3′*R*,3a′*R*,4′*R*,5′*R*)-4′,5′-di-*tert*-butoxytetrahydro-3′*H*-spiro[cyclopropane-1,2′-pyrrolo[1,2-*b*]isoxazol]-3′-yl}methyl methanesulfonate (65 mg, 85 %) as a colorless viscous oil. R_f = 0.33 (Et_2O). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.29 (A part of an ABX system, *J* = 9.8, 7.1 Hz, 1 H, C*H*HO), 4.20 (B part of an ABX system, *J* = 9.8, 7.5 Hz, 1 H, C*H*HO), 3.98 (pseudo t, *J* = 5.3 Hz, 1 H, 4′-H), 3.87 (pseudo dt, *J* = 7.8, 5.8 Hz, 5′-H), 3.51 (dd, *J* = 10.7, 5.9 Hz, 1 H, 6′-Ha), 3.41 (dd, *J* = 4.8, 3.2 Hz, 3a′-H), 3.17 (dd, *J* = 10.7, 8.1 Hz, 1 H, 6′-Hb), 3.01 (s, 3 H, SCH_3), 2.72 (pseudo dt, *J* = 3.2, 7.2 Hz, 1 H, 3′-H), 1.21 [s, 9 H, C(CH_3)$_3$], 1.17 [s, 9 H, C(CH_3)$_3$], 1.13–1.00 (m, 3 H, *c*Pr), 0.91–0.76 (m, 3 H, *c*Pr) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 80.3 (d, C-4′), 75.5 (d, C-5′), 74.2 [s, *C*(CH_3)$_3$], 74.0 [s, *C*(CH_3)$_3$], 73.5 (d, C-3a′), 70.1 (t, *C*H_2O), 63.1 (s, C-2′), 59.6 (t, C-6′), 50.1 (d, C-3′), 37.4 (q, SCH_3), 29.0 [q, 3 C, C(CH_3)$_3$], 28.5 [q, 3 C, C(CH_3)$_3$], 13.6 (t, *c*Pr), 1.7 (t, *c*Pr) ppm.

A mixture of the mesylate (60 mg, 0.153 mmol) and TBAF (1 M in THF; 0.46 mL, 0.46 mmol) in anhydrous THF (3.8 mL) was heated at reflux for 2.5 h under a nitrogen atmosphere. The solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel (petroleum ether/EtOAc, 4:1) to give **12** (17 mg, 38 %) along with the 3-fluoromethyl derivative (3′*S*,3a′*R*,4′*R*,5′*R*)-4′,5′-di-*tert*-butoxy-3′-(fluoromethyl)tetrahydro-3′*H*-spiro-[cyclopropane-1,2′-pyrrolo[1,2-*b*]isoxazole][3] (13 mg, 27 %).

(1*R*,2*R*,3′*R*,8a*S*,9′*R*,10′*R*,10a′*R*)-1,2,9′,10′-Tetra-*tert*-butoxy-1′,2,2′,3,5,5′,6,6′,8′,9′,10′,10a′-dodecahydro-1*H*-spiro[indolizine-8,3′-pyrano[2,3-*g*]indolizin]-7(8a*H*)-one (14): *exo*-Methylene isoxazolidine **12** (29 mg, 0.099 mmol) was dissolved in toluene (4.6 mL), and the resulting solution was heated in a microwave reactor (300 W, 170 °C) for 20 min. After this time, part of the solvent was evaporated. The concentrated solution was heated in the microwave reactor (300 W, 100 °C) for 1 h, and then the solvent was completely evaporated under reduced pressure. The residue was purified by chromatography on silica gel (Et_2O/MeOH, 15:1) to give dimer **14** (13 mg, 45 %) as a pale yellow oil. R_f = 0.29 (Et_2O/MeOH, 15:1). $[\alpha]_D^{23}$ = –68.7 (*c* = 0.31, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.00 (d, *J* = 5.1 Hz, 1 H, 1-H), 3.96 (ddd, *J* = 6.7, 5.0, 2.5 Hz, 1 H, 9′-H), 3.89 (pseudo t, *J* = 2.8 Hz, 1 H, 10′-H), 3.79 (d, *J* = 4.9 Hz, 1 H, 2-H), 3.26 (br. s, 1 H, 10a′-H), 3.18 (dd, *J* = 10.0, 6.7 Hz, 1 H, 5-Ha), 3.07 (dd, *J* = 10.0, 6.7 Hz, 1 H, 8′-Ha), 3.04–2.94 (m, 3 H, 6′-H, 3-Ha), 2.81 (ddd, *J* = 13.6, 12.5, 7.4 Hz, 1 H, 6-Ha), 2.67 (dd, *J* = 10.0, 5.0 Hz, 1 H, 8′-Hb), 2.60 (dd, *J* = 9.7, 4.9 Hz, 1 H, 3-Hb), 2.52–2.44 (m, 1 H, 1′-Ha), 2.41 (d, *J* = 5.1 Hz, 1 H, 8a-H), 2.42–2.33 (m, 1 H, 5-Hb), 2.32–2.20 (m, 2 H, 5′-Ha, 6-Hb), 2.19–1.95 (m, 3 H, 1′-Hb, 2′-Ha, 5′-Hb), 1.65–1.52 (m, 1 H, 2′-Hb), 1.204 [s, 9 H, $C(CH_3)_3$], 1.201 [s, 9 H, $C(CH_3)_3$], 1.19 [s, 9 H, $C(CH_3)_3$], 1.15 [s, 9 H, $C(CH_3)_3$] ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 206.9 (s, C-7), 144.5 (s, C-4a′), 102.0 (s, C-10b′), 84.2 (s, C-3′), 81.6 (d, C-10′), 79.8 (d, C-1), 79.7 (d, C-9′), 79.4 (d, C-2), 76.5 (d, C-8a), 74.4 [s, *C*$(CH_3)_3$], 74.0 [s, *C*$(CH_3)_3$], 73.6 [s, *C*$(CH_3)_3$], 73.2 [s, *C*$(CH_3)_3$], 66.3 (d, C-10a′), 59.9 (t, C-3), 57.2 (t, C-8′), 50.7 (t, C-5), 45.8 (t, C-6′), 37.6 (t, C-6), 29.1 [q, 3 C, C(*C*$H_3)_3$], 28.9 [q, 3 C, C(*C*$H_3)_3$], 28.8 [q, 6 C, 2 C(*C*$H_3)_3$], 24.2 (t, C-2′), 22.8 (t, C-5′), 18.4 (t, C-1′) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 2977, 2934, 2870, 2803, 1723, 1684, 1469, 1390, 1366, 1191, 1070 cm^{-1}. MS (ESI): *m*/*z* = 591 [M + H]$^+$, 613 [M + Na]$^+$, 1181 [2M + H]$^+$, 1203 [2M + Na]$^+$. $C_{34}H_{58}N_2O_6$ (590.83): calcd. C 69.12, H 9.89, N 4.74; found C 68.80, H 9.70.

(1*R*,2*R*,8a*S*)-1,2-Di-*tert*-butoxy-6′-methyl-2,3,3′,4′,5,6-hexahydro-1*H*-spiro[indolizine-8,2′-pyran]-7(8a*H*)-one (16) and 1-[(9*R*,10*R*,10a*R*)-9,10-di-*tert*-butoxy-2,3,5,6,8,9,10,10a-octahydro-1*H*-pyrano[2,3-*g*]indolizin-2-yl]ethanone (17): *exo*-Methylene isoxazolidine **12** (45 mg, 0.153 mmol) was dissolved in toluene (2.5 mL), and methyl vinyl ketone (**15**; 0.254 mL, 3.06 mmol) was added. The reaction mixture was heated in a microwave reactor (300 W, 150 °C) for 4 h, then the mixture was concentrated under reduced pressure. The residue was purified by chromatography on silica gel (petroleum ether/Et_2O, 5:1, followed by Et_2O, and then Et_2O/MeOH, 50:1) to give products **16** (13 mg, 23 %) and **17** (7 mg, 12 %), both as pale yellow oils.

Data for 16: R_f = 0.32 (CH_2Cl_2/MeOH, 25:1). $[\alpha]_D^{25}$ = – 64.3 (*c* = 0.94, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.45–4.40 (m, 1 H, 5′-H), 4.05–4.01 (m, 1 H, 1-H), 3.80 (d, *J* = 4.9 Hz, 1 H, 2-H), 3.17 (ddd, *J* = 10.6, 7.3, 1.4 Hz, 1 H, 5-Ha), 2.99 (br. d, *J* = 9.7 Hz, 1 H, 3-Ha), 2.81 (ddd, *J* = 13.8, 12.3, 7.3 Hz, 1 H, 6-Ha), 2.60 (dd, *J* = 9.7, 4.9 Hz, 1 H, 3-Hb), 2.49–2.43 (m, 1 H, 3′-Ha), 2.43 (d, *J* = 5.3 Hz, 1 H, 8a-H), 2.38 (ddd, *J* = 12.3, 10.6, 3.4 Hz, 1 H, 5-Hb), 2.25 (ddd, *J* = 13.8, 3.4, 1.4 Hz, 1 H, 6-Hb), 2.01–1.89 (m, 2 H, 3′-Hb, 4′-Ha), 1.81–1.79 (m, 3 H, 2′-CH_3), 1.75–1.62 (m, 1 H, 4′-Hb), 1.21 [s, 9 H, $C(CH_3)_3$], 1.20 [s, 9 H, $C(CH_3)_3$] ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 206.7 (s, C-7), 150.0 (s, C-6′), 94.4 (d, C-5′), 85.1 (s, C-8), 79.9 (d, C-1), 79.4 (d, C-2), 76.6 (d, C-8a), 74.4 [s, *C*$(CH_3)_3$], 73.6 [s, *C*$(CH_3)_3$], 60.0 (t, C-3), 50.8 (t, C-5), 37.7 (t, C-6), 29.1 [q, 3 C, C(*C*$H_3)_3$], 28.9 [q, 3 C, C(*C*$H_3)_3$], 23.9 (t, C-3′), 19.9 (q, 2′-*C*H_3), 17.5 (t, C-4′) ppm. HRMS (ESI$^+$): calcd. for $C_{21}H_{36}NO_4$ [M + H]$^+$ 366.26389; found 366.26390.

Data for 17: R_f = 0.15 (CH_2Cl_2/MeOH, 25:1). $[\alpha]_D^{25}$ = – 54.2 (*c* = 0.64, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.14 (dd, *J* = 10.6, 2.5 Hz, 1 H, 3-H), 3.95 (ddd, *J* = 6.3, 4.3, 2.0 Hz, 1 H, 9-H), 3.87 (pseudo t, *J* = 2.5 Hz, 1 H, 10-H), 3.26 (br. s, 1 H, 10a-H), 3.15–3.08 (m, 1 H, 8-Ha), 3.07 (ddd, *J* = 13.2, 5.9, 1.7 Hz, 1 H, 6-Ha), 2.92 (ddd, *J* = 13.2, 10.7, 5.0 Hz, 1 H, 6-Hb), 2.73 (dd, *J* = 10.0, 4.3 Hz, 1 H, 8-Hb), 2.38–2.19 (m, 2 H, 1-Ha, 5-Ha), 2.25 (s, 3 H, CH_3CO), 2.16–2.09 (m, 1 H, 2-Ha), 1.95–1.85 (m, 2 H, 1-Hb, 5-Hb), 1.76 (pseudo ddt, *J* = 13.2, 5.7, 10.5 Hz, 1 H, 2-Hb), 1.22 [s, 9 H, $C(CH_3)_3$], 1.15 [s, 9 H, $C(CH_3)_3$] ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 209.1 (s, C=O), 144.5 (s, C-4a), 104.2 (s, C-10b), 81.1 (d, C-10), 79.8 (d, C-3), 79.3 (d, C-9), 74.2 [s, *C*$(CH_3)_3$], 73.4 [s, *C*$(CH_3)_3$], 67.7 (d, C-10a), 57.1 (t, C-8), 45.4 (t, C-6), 28.9 [q, 3 C, C(*C*$H_3)_3$], 28.8 [q, 3 C, C(*C*$H_3)_3$], 25.9 (q, *C*H_3CO), 24.9 (t, C-2), 22.5 (t, C-5), 21.8 (t, C-1) ppm. HRMS (ESI$^+$): calcd. for $C_{21}H_{36}NO_4$ [M + H]$^+$ 366.26389; found 366.26389.

(3*R*,9′*R*,10′*R*,10a′*R*)- and (3*S*,9′*R*,10′*R*,10a′*R*)-9′,10′-Di-*tert*-butoxy-1′,2′,4,5,5′,6′,8′,9′,10′,10a′-decahydro-2*H*-spiro[furan-3,3′-pyrano[2,3-*g*]indolizin]-2-one (19): *exo*-Methylene isoxazolidine **12** (21 mg, 0.071 mmol) was dissolved in toluene (0.7 mL), and α-methylene-γ-butyrolactone (0.03 mL, 0.347 mmol) was added. The reaction mixture was heated in a microwave reactor (300 W, 150 °C) for 3 h, then the mixture was concentrated under reduced pressure. The residue was purified by chromatography on silica gel (Et_2O/MeOH, initially 50:1, then 40:1, 20:1, and 5:1) to give product **19a** (10.7 mg, 39 %) as a white solid, **19b** (3.4 mg, 12 %) as a pale yellow oil, and dimer **14** (6.0 mg, 29 %).

Data for 19a: R_f = 0.32 (Et_2O/MeOH, 25:1). M.p. 49–51 °C (Et_2O). $[\alpha]_D^{24}$ = –64.2 (*c* = 0.72, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.40 (pseudo dt, *J* = 9.1, 7.2 Hz, 1 H, 5-Ha), 4.29 (ddd, *J* = 9.1, 7.8, 5.0 Hz, 1 H, 5-Hb), 3.96–3.91 (m, 1 H, 9′-H), 3.85–3.83 (m, 1 H, 10′-H), 3.32 (br. s, 1 H, 10a′-H), 3.17 (dd, *J* = 10.0, 6.6 Hz, 1 H, 8′-Ha), 3.03 (ddd, *J* = 13.6, 6.5, 1.3 Hz, 1 H, 6′-Ha), 2.95 (ddd, *J* = 13.6, 11.2, 4.9 Hz, 1 H, 6′-Hb), 2.63 (dd, *J* = 10.0, 3.8 Hz, 1 H, 8′-Hb), 2.44 (ddd, *J* = 13.4, 7.3, 5.0 Hz, 1 H, 4-Ha), 2.31–1.93 (m, 5 H, 1′-Ha, 2′-H, 4-Hb, 5′-Ha), 1.87–1.75 (m, 2 H, 1′-Hb, 5′-Hb), 1.23 [s, 9 H, $C(CH_3)_3$], 1.12 [s, 9 H, $C(CH_3)_3$] ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 175.2 (s, C-2), 143.8 (s, C-4a′), 103.4 (s, C-10b′), 80.4 (d, C-10′), 79.2 (d, C-9′), 76.2 (s, C-3), 74.2 [s, *C*$(CH_3)_3$], 73.2 [s, *C*$(CH_3)_3$], 67.8 (d, C-10a′), 65.5 (t, C-5), 57.1 (t, C-8′), 44.8 (t, C-6′), 33.4 (t, C-4), 28.8 [q, 3 C, C(*C*$H_3)_3$], 28.7 [q, 3 C, C(*C*$H_3)_3$], 26.7 (t, C-1′), 21.6 (t, C-5′), 19.0 (t, C-2′) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 2977, 2933, 2867, 1783, 1688, 1390, 1365, 1193, 1065, 1024 cm^{-1}. MS (ESI): *m*/*z* = 394.33 [M + H]$^+$. $C_{22}H_{35}NO_5$ (393.52): calcd. C 67.15, H 8.96, N 3.56; found C 66.84, H 8.62, N 3.31.

Data for 19b: R_f = 0.31 (Et_2O/MeOH, 5:1). $[\alpha]_D^{22}$ = –6.5 (*c* = 0.53, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.42 (ddd, *J* = 9.0, 7.4, 6.6 Hz, 1 H, 5-Ha), 4.28 (ddd, *J* = 9.0, 7.6, 5.7 Hz, 1 H, 5-Hb), 3.99–3.94 (m, 2 H, 9′-H, 10′-H), 3.24–3.19 (m, 1 H, 10a′-H), 3.16–3.06 (m, 2 H, 6′-Ha, 8′-Ha), 2.84 (ddd, *J* = 12.5, 7.5, 5.4 Hz, 1 H, 6′-Hb), 2.78 (dd, *J* = 11.1, 3.7 Hz, 1 H, 8′-Hb), 2.56–2.46 (m, 1 H, 2′-Ha), 2.42 (ddd, *J* = 13.3, 7.4, 5.7 Hz, 1 H, 4-Ha), 2.32–2.18 (m, 1 H, 5′-Ha), 2.19 (ddd, *J* = 13.3, 7.6, 6.6 Hz, 1 H, 4-Ha), 2.15–2.06 (m, 1 H, 1′-Ha), 1.99–1.88 (m, 2 H, 2′-Hb, 5′-Hb), 1.84 (pseudo dt, *J* = 13.2, 5.7 Hz, 1 H, 1′-Hb), 1.24 [s, 9 H, $C(CH_3)_3$], 1.17 [s, 9 H, $C(CH_3)_3$] ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 174.7 (s, C-2), 143.4 (s, C-4a′), 103.9 (s, C-10b′), 82.7 (d, C-10′), 80.1 (d, C-9′), 75.6 (s, C-3), 74.4 [s, *C*$(CH_3)_3$], 73.4 [s, *C*$(CH_3)_3$], 66.4 (d, C-10a′), 65.0 (t, C-5), 58.4 (t, C-8′), 46.8 (t, C-6′), 35.0 (t, C-4), 29.1 [q, 3 C, C(*C*$H_3)_3$], 29.0 [q, 3 C, C(*C*$H_3)_3$], 26.7 (t, C-1′), 24.6 (t, C-5′), 18.8 (t, C-2′) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 2977, 2931, 2867, 1781, 1699, 1390, 1366, 1191, 1173, 1070, 1026 cm^{-1}. MS (ESI): *m*/*z* = 394.33 [M + H]$^+$, 416.55 [M + Na]$^+$.

3-{[(1*R*,2*R*)-1,2-Di-*tert*-butoxy-7-oxo-1,2,3,5,6,7-hexahydroindolizin-8-yl]methyl}-1-phenylpyrrolidine-2,5-dione (21): *exo*-Methylene isoxazolidine **12** (50 mg, 0.169 mmol) was dissolved in toluene (1.7 mL), and *N*-phenylmaleimide (**20**, 88 mg, 0.508 mmol) was added. The reaction mixture was heated in a microwave reactor

(300 W, 150 °C) for 2.5 h, and then it was concentrated under reduced pressure. The residue was purified by chromatography on silica gel (Et_2O/MeOH, 15:1) to give **21** (36 mg, 45 %) as a yellow solid.

Data for 21 (10:1 mixture of epimers): R_f = 0.31 (Et_2O/MeOH, 15:1). M.p. 75–77 °C (Et_2O). $[\alpha]_D^{23}$ = –33.2 (c = 0.70, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): major isomer, δ = 7.48–7.42 (m, 2 H, H_{Ph}), 7.38–7.28 (m, 3 H, H_{Ph}), 4.68 (d, J = 1.8 Hz, 1 H, 1′-H), 4.10 (pseudo dt, J = 4.6, 2.0 Hz, 1 H, 2′-H), 3.75 (dd, J = 10.2, 4.6 Hz, 1 H, 3′-Ha), 3.51–3.35 (m, 2 H, 5′-H), 3.31 (pseudo tt, J = 9.0, 5.2 Hz, 1 H, 3-H), 3.11 (dd, J = 10.2, 2.2 Hz, 1 H, 3′-Hb), 3.01 (dd, J = 18.7, 4.9 Hz, 1 H, 4-Ha), 2.88 (dd, J = 14.1, 5.6 Hz, 1 H, 6-Ha), 2.78 (dd, J = 18.7, 9.3 Hz, 1 H, 4-Hb), 2.71 (dd, J = 14.1, 8.7 Hz, 1 H, 6-Hb), 2.60–2.48 (m, 2 H, 6′-H), 1.34 [s, 9 H, $C(CH_3)_3$], 1.22 [s, 9 H, $C(CH_3)_3$]; minor isomer, discernible signals, δ = 4.63 (d, J = 2.2 Hz, 1 H, 1′-H), 4.14–4.11 (m, 1 H, 2′-H), 3.71 (dd, J = 10.2, 4.8 Hz, 1 H, 3′-Ha), 3.09 (dd, J = 10.2, 2.7 Hz, 1 H, 3′-Hb), 2.77 (dd, J = 18.8, 9.4 Hz, 1 H, 4-Hb), 1.33 [s, 9 H, $C(CH_3)_3$], 1.23 [s, 9 H, $C(CH_3)_3$] ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): major isomer, δ = 191.2 (s, C-7′), 179.1 and 176.5 (s, C-2 and C-5), 164.9 (s, C-8a′), 132.2 (s, C_{Ph}), 128.9 (d, 2 C, CH_{Ph}), 128.2 (d, CH_{Ph}), 126.5 (d, 2 C, CH_{Ph}), 101.9 (s, C-8′), 80.2 (d, C-1′), 76.2 [s, $C(CH_3)_3$], 74.5 [s, $C(CH_3)_3$], 74.0 (d, C-2′), 59.6 (t, C-3′), 45.4 (t, C-5′), 40.7 (d, C-3), 35.1 (t, C-6′), 33.7 (t, C-4), 29.1 [q, 3 C, $C(CH_3)_3$], 28.7 [q, 3 C, $C(CH_3)_3$], 26.0 (t, C-6) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 2979, 2936, 1709, 1584, 1384, 1184 cm^{-1}. MS (ESI): m/z = 491.42 $[M + Na]^+$, 959.08 $[2M + Na]^+$. $C_{27}H_{36}N_2O_6$ (468.59): calcd. C 69.21, H 7.74, N 5.98; found C 68.88, H 7.35, N 5.80.

Acknowledgments

The authors thank the Italian Ministry of Education, University, and Research [Ministero dell'Università e della Ricerca (MIUR)-Rome] for financial support (PRIN20109Z2XRJ). The Consorzio Interuniversitario Nazionale per le Metodologie e Processi Innovativi di Sintesi (CINMPIS) is acknowledged for partial financial support of a fellowship for C. V.

Keywords: Cycloaddition · Dimerization · Ene reaction · Heterocycles · Small ring systems

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[4] Compound **11** reacted somewhat differently from diastereomer **10**. In fact, besides *exo*-methylene isoxazolidine **12**, which was obtained in lower yield, some fluorinated compound was isolated in 27 % yield. A mixture of the two diastereomers **10** and **11** could be submitted to the mesylation and elimination sequence to yield *exo*-methylene isoxazolidine **13**.

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Received: December 21, 2017