Synthesis and Rearrangement of *N*-Organyloxy β-Lactams Derived from a (4+2)/(3+2) Sequential Cycloaddition Reaction Involving Enol Ethers and Nitro Alkenes

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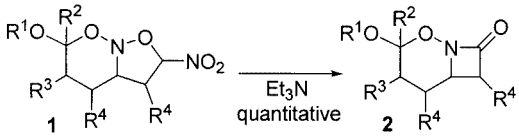
The synthesis of *N*-organyloxy β-lactams **2** by treatment of nitroso acetals **1** with a base is discussed. Based on the formation of a by-product, a mechanism for the rearrangement to *N*-organyloxy β-lactams is proposed. This mechanism is supported by trapping of the intermediate acyl nitro compound **8** with dimethylamine. Furthermore, it was discovered that upon more forcing basic conditions these *N*-organyloxy β-lactams can rearrange further to 3-organyloxy β-lactams. By using a series of structurally diverse *N*-organyloxy β-lactams the generality of this novel rearrangement is demonstrated. A mechanism for the conversion of *N*-organyloxy β-lactams to 3-organyloxy β-lactams is proposed.

Introduction

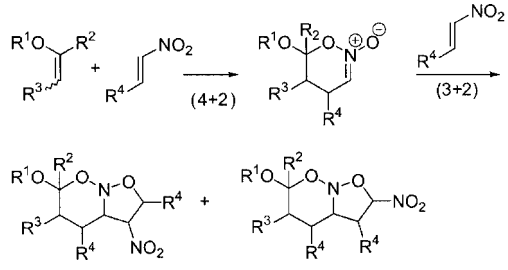
Because of the important role in the treatment of bacterial infections, β-lactams have received much scientific attention. Due to the developed resistance of bacteria against β-lactams antibiotics, the search for novel antibiotics remains a challenging problem.[1] Though organic chemists have succeeded to develop numerous successful synthetic methodologies towards this class of compounds, the discovery of novel synthetic strategies remains an important endeavor.

Recently we reported on a stereoselective route towards bicyclic *N*-organyloxy β-lactams **2** via a base-induced rearrangement of nitroso acetals **1** (Scheme 1).[2]



Scheme 1. Rearrangement to give *N*-organyloxy β-lactams

Key feature of the synthetic methodology was a high pressure promoted (4+2)/(3+2) cycloaddition reaction of an enol ether with two equivalents of a nitro alkene to give a mixture of nitroso acetals (Scheme 2).[3−4]



Scheme 2. Formation of nitroso acetals

During a study to get more insight in the mechanism of *N*-organyloxy β-lactam formation, we have found that under slightly more forcing basic conditions these *N*-organyloxy β-lactams rearrange further to another lactam. In this paper, the result of the mechanistic study towards the formation of *N*-organyloxy β-lactams is presented. Furthermore, the scope and mechanism of the novel base-initiated rearrangement of *N*-organyloxy β-lactams to 3-organyloxy β-lactams will be discussed.

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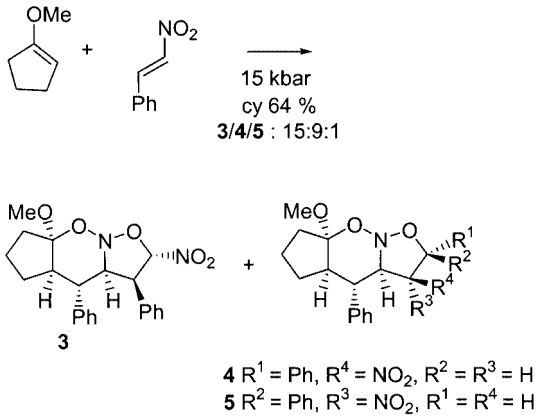
Results and Discussion

Formation of *N*-Organyloxy β-Lactams

As part of a study to investigate the scope of *N*-organyloxy β-lactam formation and as continuation of previous work,[2,3] 1-methoxycyclopent-1-ene was reacted with two equivalents of β-nitrostyrene at 1.5 GPa to give the nitroso acetals **3**, **4** and **5** in a yield of 64% and in a ratio of 15:9:1 respectively (Scheme 3). The stereochemistry of the three isomers was assigned by using 2D-NOESY experiments. The stereochemistry of nitroso acetal **3** was confirmed by using X-ray analysis (Figure 1).[5]



Scheme 3. (4+2)/(3+2) cycloaddition of β-nitrostyrene and 1-methoxycyclopent-1-ene

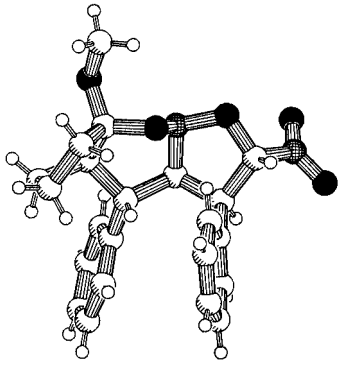
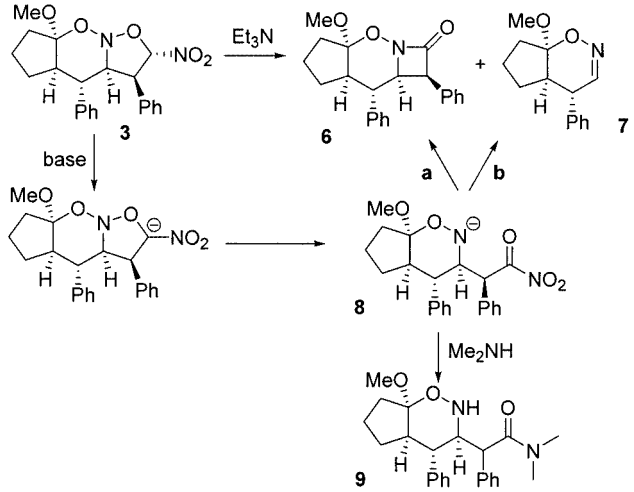


Figure 1. X-ray structure of nitroso acetal **3**[6]

Unexpectedly, nitroso acetal **3** did not give a clean and quantitative conversion into *N*-organyloxy β-lactam **6** upon treatment with triethylamine (Scheme 4). When nitroso acetal **3** was reacted with a stoichiometric amount[7] of triethylamine, *N*-organyloxy β-lactam **6** was initially formed but under the reaction conditions this β-lactam slowly reacted to give two new products. To prevent *N*-organyloxy β-lactam **6** to react further, the reaction was performed at 0 °C for 90 minutes. Interestingly, examination of the reaction mixture indicated that not only lactam **6** was formed but also the oxime *O*-ether **7**. Although a concerted mechanism for *N*-organyloxy β-lactam formation had been proposed previously,[2] this result suggested that the reaction involves nitro acyl anion **8** as intermediate (Scheme 4).[8] After formation of **8** via deprotonation and N−O bond cleavage,[9] intramolecular substitution at the carbonyl group affords *N*-organyloxy β-lactam **6** with loss of a NO_2 anion (pathway a).[10] Otherwise compound **8** reacts via pathway b which involves elimination of 1-nitro-2-phenylethan-1-one and formation of oxime O-ether **7**.[11]

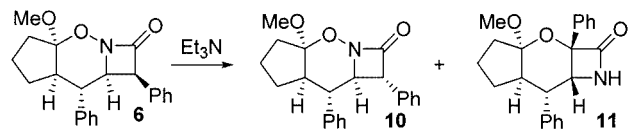


Scheme 4. Formation of *N*-organyloxy β-lactam **6** and trapping of intermediate **8**

It was attempted to support this mechanism by trapping of compound **8** with a nucleophile. Treatment of the nitroso acetal **3** with an excess of dimethylamine at −50 °C for 2 h gave the amide **9** in a yield of 63% (Scheme 4). To exclude the possibility that amide **9** is formed by ring opening of lactam **6** with dimethylamine, compound **6** was reacted under the same conditions. This resulted only in partial epimerization of the starting material.[12]

Rearrangement of *N*-Organyloxy β-Lactams

Next, the base-promoted transformation of *N*-organyloxy β-lactam **6** was investigated in further detail (Scheme 5). A solution of the lactam **6** and 1.0 equivalent of triethylamine in $CDCl_3$ was stirred at room temp. and the reaction was studied with ^1H NMR spectroscopy. After 24 h the conversion was 94% and two new compounds were formed in a ratio of 2:1. After another 24 h the conversion was complete and the ratio of products changed to 1.3:1 and after 4 days this ratio was 1:1.6. At this point the reaction was stopped and epimer **10** and 3-organyloxy β-lactam **11** were isolated from the reaction in a yield of 34% and

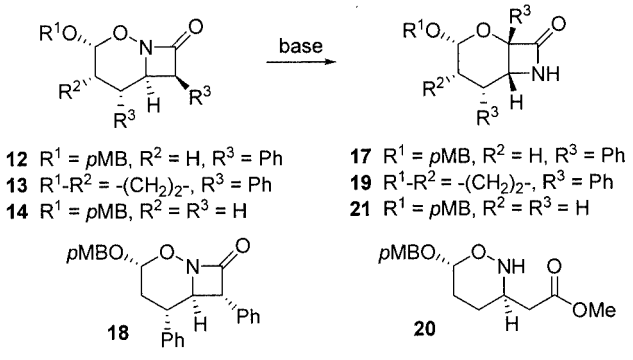


Scheme 5. Base-initiated rearrangement of *N*-organyloxy β-lactam

Table 1. Results of base-induced rearrangement of *N*-organyloxy β-lactams.

Entry	*N*-Organyloxy β-lactam	Conditions[a]	Yield[b]	Product[c]
1	**6**	A	95 %	**11/10**, 1.6:1
2	**12**	A	0	
3	**13**	A	0	
4	**14**	A	0	
5	**12**	B	92 %	**17/18**, 3.3:1
6	**13**	B	91 %	**19**
7	**14**	B	0	
8	**12**	C	78 %	**17**
9	**14**	C	n.d.	**20**
10	**14**	D	53 %	**21**[d]

[a] Conditions A: Et_3N, $CHCl_3$, room temp.. B: Et_3N, reflux C: NaOMe, THF, room temp.. D: LDA, THF, −78 °C. [b] Isolated yield. [c] Product ratio based on ^1H NMR analysis of crude reaction mixture. [d] *p*MBOH was isolated as by-product in 25% yield.



61% respectively (Entry 1, Table 1). The stereochemistry of the rearranged lactam **11** was determined by X-ray crystallography (Figure 2).[5]

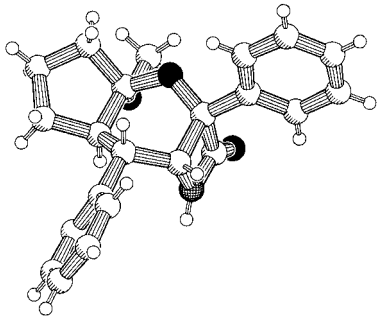
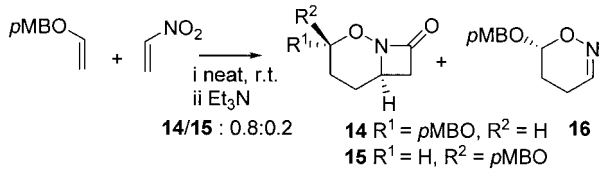


Figure 2. X-ray structure of lactam **11**[6]

To demonstrate the generality and the scope of this rearrangement, it was decided to investigate the lactams **12** and **13** (Table 1).[2] To examine the effect of the acidity of the proton next to the lactam carbonyl, *N*-organyloxy β-lactam **14** was prepared. The lactams **14** and **15** were obtained in a yield of 53% and 13% respectively by reacting *p*-methoxybenzyl vinyl ether with two equivalents of nitroethene followed by treatment with triethylamine. The oxime O-ether **16** was obtained as by-product in 2% (Scheme 6, Figure 3).[13−14]



Scheme 6. Synthesis of *N*-organyloxy β-lactam **14** and **15**

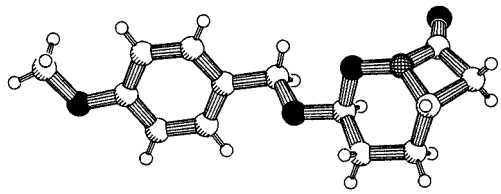


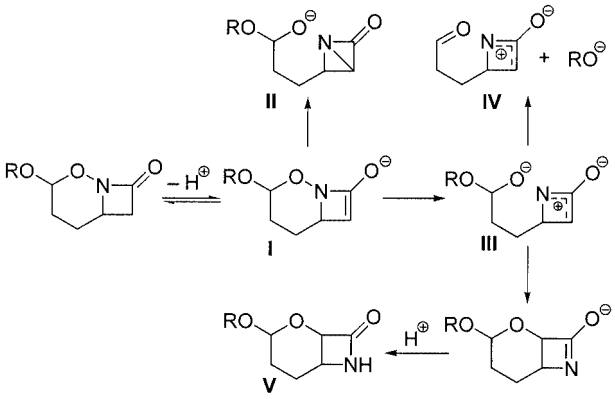
Figure 3. X-ray structure of compound **14**[6]

The rearrangement of the *N*-organyloxy β-lactams **12**−**14** was studied by using a series of different conditions (Table 1). Unexpectedly, the lactams **12**−**14** did not rearrange at room temperature with triethylamine (Entry 2−4). However, when the lactams **12** and **13** were heated at reflux in the presence of triethylamine, rearrangement did occur (Entry 5−6). Whereas the lactam **13** gave a clean and near quantitative yield of the lactam **19**, the lactam **12** gave in good yield both the epimer **18** and the lactam **17**. Lactam **14** did not rearrange under these conditions (Entry 7).

Upon treatment with sodium methoxide, the *N*-organyloxy β-lactam **12** gave the rearranged lactam **17** in 15 minutes in good yield (Entry 8). However, when these conditions were applied to lactam **14**, the main product of the reaction was the ester **20** (Entry 9). It was reasoned that ring opening is caused by the nucleophilicity of sodium methoxide, and that application of a strong non-nucleophilic base should circumvent this problem. To our delight, treatment of lactam **14** with LDA gave the lactam **21** in a yield of 53% (Entry 10). In addition to the desired lactam, *p*-methoxybenzyl alcohol was isolated as by-product in a yield of 25%.

Mechanistic Consideration

To explain the base-induced rearrangement, the mechanism must involve cleavage of the N−O bond (Scheme 7). Since it was observed that the rate of the reaction depends on the base that is employed, it is likely that the rearrangement of the *N*-organyloxy β-lactam starts by deprotonation to give enolate **I**. After deprotonation, cleavage of the N−O bond can occur by formation of intermediate **II**, or via a S_N1'-type pathway to give **III**.[15−16] Since it is unlikely that the highly strained azabicyclobutanone **II** is formed, rearrangement most likely involves the zwitterionic intermediate **III**. After formation of the intermediate **III**, ring closure followed by protonation gives 3-organyloxy β-lactam **V**. Alternatively, intermediate **III** might give an elimination re-



Scheme 7. Proposed mechanism for rearrangement of *N*-organyloxy β-lactam

action yielding an aldehyde **IV**. This is supported by the observation that *p*-methoxybenzyl alcohol was formed as side product in the rearrangement of the *N*-organyloxy β-lactam **14**. Unfortunately, we did not succeed to isolate or detect the formation of an aldehyde **IV**.[17]

Though this mechanism explains the formation of the products, the influence of base, and the lower reactivity of compound **14** compared with **6**, **12**, and **13**, it is still not clear to what extent the reactivity is influenced by structural factors of the *N*-organyloxy β-lactams.

Conclusions

This work has confirmed the general applicability of the (4+2)/(3+2) cycloaddition reaction of enol ethers and nitro alkenes as a means to prepare *N*-organyloxy β-lactams. It has been demonstrated that the rearrangement to these lactams occurs via formation of an acyl nitro intermediate.

Furthermore, it has been discovered that these *N*-organyloxy β-lactams can give another base-induced rearrangement yielding 3-organyloxy β-lactams. It was demonstrated with a series of structurally diverse substrates that this novel rearrangement has a broad scope. The reaction rate strongly correlates with the acidity of proton on the α position of the carbonyl group and therefore depends on the strength of the base that is used. It is believed that the reaction is initiated by enolization, followed by a S_N1' type cleavage of the N−O bond and cyclisation.

Because of the possibility to perform the (4+2)/(3+2) cycloaddition reaction in a highly stereoselective and enantioselective manner,[4] this methodology has opened a new route towards new β-lactam antibiotics.

Experimental Section

General Remarks: ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded with a Bruker AC-300 spectrometer in $CDCl_3$ with tetramethylsilane as internal standard. 2D NMR experiments (NOESY, COSY) were performed with a Bruker AM-400 spectrometer in $CDCl_3$. Chemical shifts are reported in parts per million (ppm) and coupling constants (*J*) are given in Hertz (Hz). Mass spectra were recorded with a VG7070E double-focusing mass spectrometer with EI and CI modes. IR spectra were recorded with a Anadis Thermo Mattson IR300 spectrometer. Elemental analysis were carried out with a Carlo−Erba Instruments CHNSO EA 1108 element analyzer. Thin layer chromatography (TLC) was carried out on Merck precoated silica gel 60 F-254 plates. Spots were visualised with UV or by dipping the TLC plate into a 6.2% aqueous sulfuric acid solution containing ammonium molybdate (42g/L) and ceric ammonium sulfate (3.6g/L) followed by charring. Column chromatography was carried out with Baker silica gel (63−200 mesh) and flash chromatography was carried out with Acros silica gel (0.035−0.070mm). Melting points were determined on a Buchi B-545 melting point apparatus and are uncorrected. High pressure reactions were performed with the equipment described by Aben et al.[18] When necessary, reactions were performed under standard Schlenk conditions. Ethyl acetate and heptane were distilled prior to use. Tetrahydrofuran was dried by distillation from sodium/benzophenone ketyl.

Literature Preparations: The following compounds were prepared according to literature procedures: nitroethene,[19] 1-methoxycyclopent-1-ene,[20] β-nitrostyrene,[21] *p*-methoxybenzyl vinyl ether[3d].

Preparation of Compounds 3, 4, and 5: 1-Methoxycyclopent-1-ene (1.00 g, 10.2 mmol), β-nitrostyrene (3.12 g, 20.9 mmol, 2.05 equiv.) and a spoontip of 5-*tert*-butyl-4-hydroxy-2-methylphenyl sulfide were dissolved in CH_2Cl_2 in a 15-mL Teflon^R tube. The reaction mixture was pressurized at 1.5 GPa and room temperature for 36 h. After depressurizing the reaction, the solvent was evaporated in vacuo. From NMR analysis of the crude reaction mixture it was determined that the reaction gave 81% conversion into a mixture of the compounds **3**, **4**, and **5** in a ratio of 16:9:1. The crude product was purified by column chromatography (EtOAc/heptane, 1:8) after which the nitroso acetals were isolated in a total yield of 64%. Analytical samples were obtained from crystallization from CH_2Cl_2/heptane.

(±)-(2*S*,3*S*,3a*R*,4*S*,4a*R*,7a*R*)-7a-Methoxy-2-nitro-3,4-diphenylperhydrocyclopenta[*e*]isoxazolo[2,3-*b*][1,2]oxazine (3): M.p. (CH_2Cl_2/heptane) 151 °C (dec). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.84−0.97 (m, 1 H), 1.25−1.62 (m, 4 H), 1.94−2.05 (m, 1 H), 2.18 (dd, *J* = 8.7 Hz, 12.9 Hz, 1 H), 2.30−2.39 (m, 1 H), 3.46 (s, 3 H), 3.96 (dd, *J* = 1.2 Hz, 8.1 Hz, 1 H), 4.29 (dd, *J* = 8.1 Hz, 8.7 Hz, 1 H), 6.29 (d, *J* = 1.2 Hz, 1 H), 6.92−6.96 (m, 2 H), 7.22−7.46 (m, 8 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.9, 28.0, 31.2, 44.7, 47.6, 49.6, 56.6, 72.9, 112.8, 113.8, 127.6, 128.6, 128.7, 128.8, 128.9, 129.8, 134.8, 139.2 ppm. HRMS calcd. for $[M]^+$ ($C_{22}H_{24}N_2O_5$): 396.1685 found 396.1692. $C_{22}H_{24}N_2O_5$ (396.5): calcd. C 66.65, H 6.10, N 7.07; found C 66.99, H 5.87, N 7.07.

(±)-(2*R*,3*S*,3a*R*,4*S*,4a*R*,7a*R*)-7a-Methoxy-3-nitro-2,4-diphenylperhydrocyclopenta[*e*]isoxazolo[2,3-*b*][1,2]oxazine (4): M.p. (CH_2Cl_2/heptane) 178 °C (dec). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.11−1.23 (m, 1 H), 1.59−1.78 (m, 4 H), 2.09−2.19 (m, 1 H), 2.39−2.49 (m, 1 H), 2.56 (dd, *J* = 8.0 Hz, 12.6 Hz, 1 H), 3.45 (s, 3 H), 4.38 (dd, *J* = 8.0 Hz, 9.3 Hz, 1 H), 5.17 (dd, *J* = 6.6 Hz, 9.3 Hz, 1 H), 6.41 (d, *J* = 6.6 Hz, 1 H), 7.22−7.39 (m, 10 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.8, 28.1, 30.9, 45.0, 47.0, 49.4, 76.4, 88.0, 94.3, 112.6, 126.5, 127.8, 128.6, 129.0, 129.1, 129.5, 134.7, 139.4 ppm. HRMS: calcd. for $[M]^+$ ($C_{22}H_{24}N_2O_5$): 396.1685 found 396.1678. $C_{22}H_{24}N_2O_5$ (396.5): calcd. C 66.65, H 6.10, N 7.07; found C 66.79, H 5.89, N 7.02.

(±)-(2*S*,3*R*,3a*R*,4*S*,4a*R*,7a*R*)-7a-Methoxy-3-nitro-2,4-diphenylperhydrocyclopenta[*e*]isoxazolo[2,3-*b*][1,2]oxazine (5): M.p. (CH_2Cl_2/

heptane) 125 °C (dec). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.16−1.28 (m, 1 H), 1.58−1.81 (m, 4 H), 2.06−2.19 (m, 1 H), 2.42−2.51 (m, 1 H), 2.79 (dd, *J* = 7.0 Hz, 12.3 Hz, 1 H), 3.45 (s, 3 H), 4.41 (dd, *J* = 7.0 Hz, 8.4 Hz, 1 H), 5.31 (dd, *J* = 7.2 Hz, 8.4 Hz, 1 H), 5.79 (d, *J* = 7.2 Hz, 1 H), 7.16−7.50 (m, 10 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.4, 28.7, 32.2, 47.8, 49.8, 49.9, 78.6, 90.2, 98.5, 113.2, 126.7, 127.8, 128.2, 128.8, 129.06, 129.08, 136.9, 139.2 ppm. HRMS: calcd. for $[M]^+$ ($C_{22}H_{24}N_2O_5$): 396.1685 found 396.1687. $C_{22}H_{24}N_2O_5$ (396.5): calcd. C 66.65, H 6.10, N 7.07; found C 66.25, H 5.93, N 6.84.

Preparation of Compounds 6 and 7: Nitroso acetal **3** (154 mg, 0.388 mmol) was dissolved in chloroform (3 mL). The solution was cooled to 0 °C and dropwise a solution of triethylamine (42 mg, 0.415 mmol) in chloroform (2 mL) was added. After 90 minutes the reaction mixture was quenched with an excess of 1 M ammonium chloride/water and extracted three times with dichloromethane. The combined organic layers were dried (sodium sulfate), filtered, and the solvents evaporated to dryness. The crude product was purified by column chromatography (EtOAc/heptane, 1:8). The starting material was recovered in 7% yield. The lactam **6** (100 mg, 74%) was obtained as an oil. The imine **7** (7.8 mg, 9%) was also obtained as a clear oil. An analytical sample of the lactam **6** was obtained by crystallisation from CH_2Cl_2/heptane which yielded very small white crystals.

(±)-(1*S*,4a*R*,7a*R*,8*S*,8a*R*)-4a-Methoxy-1,8-diphenylperhydroazeto-[1,2-*b*]cyclopenta[*e*][1,2]oxazin-2-one (6): M.p. (CH_2Cl_2/heptane) 99 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.21−1.34 (m, 1 H), 1.51−1.78 (m, 3 H), 1.93−2.14 (m, 3 H), 2.32 (t, *J* = 10.8 Hz, 1 H), 3.44 (s, 3 H), 4.20 (dd, *J* = 5.1 Hz, 10.8 Hz, 1 H), 4.50 (d, *J* = 5.1 Hz, 1 H), 6.47−6.53 (m, 2 H), 6.95−7.27 (m, 8 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.7, 28.5, 31.1, 45.0, 48.4, 50.7, 53.8, 58.1, 113.9, 126.7, 127.5, 127.9, 128.1, 128.2, 129.2, 131.3, 138.7, 166.9 ppm. HRMS calcd. for $[M]^+$ ($C_{22}H_{23}NO_3$): 349.1680 found 349.1672. IR (film): ṽ = 2952, 1774, 1496, 1452, 1328, 1192, 1133, 1084, 871, 751, 699 cm^{-1}. $C_{22}H_{23}NO_3$ (349.4): calcd. C 75.62, H 6.63, N 4.01; found C 75.27, H 6.55, N 3.89.

(±)-(4*S*,4a*R*,7a*R*)-7a-Methoxy-4-phenyl-4,4a,5,6,7,7a-hexahydrocyclopenta[*e*][1,2]oxazine (7): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.47−2.12 (m, 6 H), 2.25 (ddd, *J* = 7.7 Hz, 7.7 Hz, 7.7 Hz, 1 H), 3.06 (dd, *J* = 2.3 Hz, 7.7 Hz, 1 H), 3.56 (s, 3 H), 7.18−7.36 (m, 5 H), 7.77 (d, *J* = 2.3 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.0, 31.3, 34.3, 43.1, 50.8, 51.2, 110.0, 127.1, 128.2, 128.7, 139.9, 161.1 ppm. HRMS calcd. for $[M + H]^+$ ($C_{14}H_{18}NO_2$): 232.1338 found 232.1328. IR (film): ṽ = 2958, 1494, 1452, 1327, 1189, 1144, 1093, 842, 762, 701 cm^{-1}.

(±)-2-[(3*R*,4*S*,4a*R*,7a*R*)-7a-Methoxy-4-phenylperhydrocyclopenta[*e*][1,2]oxazin-3-yl]-*N*,*N*-dimethyl-2-phenylacetamide (9): To a 2 M solution of dimethylamine in tetrahydrofuran (5 mL) was added dropwise at −70 °C a solution of nitroso acetal **3** (70 mg, 0.177 mmol) in dichloromethane (1.5 mL). The reaction mixture was slowly warmed to −50 °C. After 2 h the reaction was quenched with acetic acid (600 μL). The reaction mixture was diluted with 1 M ammonium chloride/water and extracted two times with dichloromethane. The organic layers were dried (sodium sulfate), filtered and the solvents evaporated to dryness. The crude product was purified with column chromatography (EtOAc/heptane, 1:1). The amide **9** (44.1 mg, 63%) was obtained as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.13−1.28 (m, 1 H), 1.39−1.68 (m, 4 H), 1.80−1.93 (m, 1 H), 2.03−2.14 (m, 1 H), 2.37 (dd, *J* = 9.3 Hz, 10.8 Hz, 1 H), 2.62 (s, 3 H), 2.72 (s, 3 H), 3.23 (s, 3 H), 3.77 (d, *J* = 4.8 Hz, 1 H), 3.97 (dd, *J* = 4.8 Hz, 9.3 Hz, 1 H), 6.25 (br. s, 1 H), 7.18−7.34 (m, 10 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.7, 30.6, 32.8, 36.1, 37.5, 46.0, 49.1, 50.0, 51.5, 62.1, 112.1, 126.7, 127.0, 128.2, 128.4, 129.0, 130.0, 136.0, 142.2, 172.3 ppm. HRMS calcd. for $[M]^+$ ($C_{24}H_{30}N_2O_3$): 394.2257 found 394.2261.

Preparation of Compounds 10 and 11: The *N*-organyloxy β-lactam **6** (39.1 mg, 0.112 mmol) was dissolved in chloroform (1.5 mL). Triethylamine (12.6 mg) was added and the reaction mixture was stirred at room temperature. The reaction mixture was monitored by ^{1}H NMR spectroscopy. After 4 days the reaction solvents were evaporated to dryness and the crude product was purified with column chromatography (EtOAc/heptane, 1:2). *N*-Organyloxy β-lactam **10** (13.3 mg, 34%) was obtained as a white solid and lactam **11** (23.7 mg, 61%) was obtained as an oil. Lactam **10** was crystallized from CH_2Cl_2/heptane to give white crystals. The lactam **11** was crystallized from CH_2Cl_2/diisopropyl ether yielding small white crystals.

(±)-(1*R*,4a*R*,7a*R*,8*S*,8a*R*)-4a-Methoxy-1,8-diphenylperhydroazeto-[1,2-*b*]cyclopenta[*e*][1,2]oxazin-2-one (10): M.p. (CH_2Cl_2/heptane) 149 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.36−1.50 (m, 1 H), 1.51−1.65 (m, 1 H), 1.71−1.98 (m, 3 H), 2.01−2.12 (m, 1 H), 2.22 (td, *J* = 7.2 Hz, 10.8 Hz, 1 H), 2.64 (t, *J* = 10.8 Hz, 1 H), 3.86 (dd, *J* = 2.1 Hz, 10.8 Hz, 1 H), 3.98 (d, *J* = 2.1 Hz, 1 H), 6.96−7.03 (m, 2 H), 7.14−7.38 (m, 8 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.4, 30.6, 33.1, 49.6, 49.7, 51.1, 58.1, 62.2, 114.3, 127.0, 127.5, 127.7, 127.8, 128.7, 129.1, 134.1, 138.5, 167.3 ppm. HRMS calcd. for $[M]^+$ ($C_{22}H_{23}NO_3$): 349.1678 found 349.1681. IR (film): ṽ = 2957, 1772, 1496, 1452, 1326, 1192, 1124, 1099, 873, 747, 699 cm^{-1}.

(±)-(2a*S*,3a*R*,6a*R*,7*S*,7a*R*)-3a-Methoxy-2a,7-diphenylperhydrocyclopenta[5,6]pyrano[3,2-*b*]azet-2-one (11): M.p. (CH_2Cl_2/diisopropyl ether) 169 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.22−1.37 (m, 1 H), 1.51−1.75 (m, 2 H), 1.79−1.96 (m, 2 H), 2.18−2.27 (m, 1 H), 2.70−2.84 (m, 2 H), 3.38 (s, 3 H), 3.89 (d, *J* = 2.1 Hz, 1 H), 6.36 (br. s, 1 H), 7.21−7.44 (m, 8 H), 7.55−7.62 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.7, 30.8, 36.2, 42.1, 46.4, 49.6, 61.8, 86.8, 111.8, 125.6, 127.2, 128.0, 128.3, 128.6, 129.0, 136.8, 139.8, 170.5 ppm. HRMS: calcd. for $[M + H]^+$ ($C_{22}H_{24}NO_3$): 350.1756 found 350.1750. IR (film): ṽ = 1759, 1493, 1448, 1329, 1171, 1090, 1011, 756, 735 cm^{-1}. $C_{22}H_{23}NO_3$ (349.4): calcd. C 75.62, H 6.63, N 4.01; found C 75.45, H 6.58, N 3.64.

(±)-(2*R*,4*S*,4a*R*,5*S*)-2-[(4-Methoxybenzyl)oxy]-4,5-diphenylperhydroazeto[1,2-*b*][1,2]oxazin-6-one (12): Preparation according to procedure in ref.[2]. Analytical sample was obtained by crystallization from CH_2Cl_2/hexane. R_f = 0.22 (EtOAc/hexane, 1:4 + 1% Et_3N). M.p. (CH_2Cl_2/hexane) 143 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.96−2.12 (m, 2 H), 2.64−2.72 (m, 1 H), 3.82 (s, 3 H), 3.99 (dd, *J* = 4.8 Hz, 9.9 Hz, 1 H), 4.47 (d, *J* = 4.8 Hz, 1 H), 4.77 (d, *J* = 11.6 Hz, 1 H), 5.00 (d, *J* = 11.6 Hz, 1 H), 5.02 (dd, *J* = 2.4 Hz, 10.8 Hz, 1 H), 6.42−6.49 (m, 2 H), 6.84−6.94 (m, 2 H), 7.02−7.17 (m, 5 H), 7.20−7.35 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 36.2, 41.4, 53.4, 55.3, 59.4, 71.5, 104.1, 113.9, 127.2, 130.0, 131.5, 138.8, 159.6, 163.7 ppm. IR (film): ṽ = 1771, 1614, 1587, 1515, 1454, 1250, 1149, 1035, 702 cm^{-1}. $C_{26}H_{25}NO_4$ (415.5): calcd. C 75.16, H 6.06, N 3.37; found C 75.23, H 6.00, N 3.05.

(±)-(1*S*,4a*S*,7a*S*,8*S*,8a*R*)-1,8-Diphenylperhydroazeto[1,2-*b*]cyclopenta[*e*][1,2]oxazin-2-one (13): Preparation according to procedure in ref.[2]. R_f = 0.30 (EtOAc/hexane, 1:2 + 1% Et_3N). M.p. (EtOAc/hexane) 145 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.63−1.70 (m, 1 H), 2.19−2.52 (m, 2 H), 2.97 (dd, *J* = 4.8 Hz, 10.4 Hz, 1 H), 3.94 (ddd, *J* = 7.5 Hz, 9.2 Hz, 16.5 Hz, 1 H), 4.28 (dt, *J* = 1.6 Hz, 10.2 Hz, 1 H), 4.36 (dd, *J* = 4.8 Hz, 10.4 Hz, 1 H), 4.54 (d, *J* =

4.8 Hz, 1 H), 5.53 (d, *J* = 2.9 Hz, 1 H), 6.67−6.82 (m, 2 H), 6.98−7.26 (m, 8 H) ppm. HRMS calcd. for $[M]^+$ ($C_{20}H_{19}NO_3$): 321.1365 found 321.1365. $C_{20}H_{19}NO_3$ (321.4): calcd. C 74.75, H 5.96, N 4.36; found C 74.75, H 5.81, N 4.39.

Preparation of 14, 15, and 16: A solution of *p*-methoxybenzyl vinyl ether (497 mg, 3.03 mmol) and nitroethene (470 mg, 6.43 mmol) in 1.5 mL chloroform was stirred at room temperature for 17 h. To the reaction mixture was added triethylamine (400 mg, 3.95 mmol) and the reaction mixture was stirred for 35 minutes. The reaction mixture was diluted with dichloromethane and washed with saturated sodium hydrogen carbonate. The aqueous layer was extracted twice with dichloromethane. The combined organic layers were dried (sodium sulfate), filtered, and the solvents evaporated to dryness. The crude product was purified by column chromatography (EtOAc/heptane, 2:5, 1% triethylamine) to obtain lactam **14** (423 mg, 53%) as a white solid, lactam **15** (101 mg, 13%) as an oil, and the oxime O-ether **16** (16.1 mg, 2%) as an oil. An analytical sample of *N*-organyloxy β-lactam **14** was obtained by crystallization from EtOAc/heptane.

(±)-(2*R*,4a*R*)-2-[(4-Methoxybenzyl)oxy]perhydroazeto[1,2-*b*][1,2]-oxazin-6-one (14): M.p. (EtOAc/heptane) 86 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.50−1.65 (m, 1 H), 1.67−1.81 (m, 1 H), 1.88 (dtd, *J* = 1.8 Hz, 3.9 Hz, 13.8 Hz, 1 H), 2.24−2.33 (m, 1 H), 2.34 (dd, *J* = 1.5 Hz, 13.8 Hz, 1 H), 2.94 (dd, *J* = 4.2 Hz, 13.8 Hz, 1 H), 3.59 (dtd, *J* = 1.5 Hz, 4.2 Hz, 10.1 Hz, 1 H), 3.79 (s, 3 H), 4.65 (d, *J* = 11.4 Hz, 1 H), 4.84 (dd, *J* = 1.8 Hz, 9.0 Hz, 1 H), 4.89 (d, *J* = 11.4 Hz, 1 H), 6.83−6.89 (m, 2 H), 7.23−7.31 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.0, 28.5, 40.2, 48.7, 55.3, 71.2, 103.5, 113.8, 128.3, 129.8, 159.2, 164.0 ppm. HRMS calcd. for $[M]^+$ ($C_{14}H_{17}NO_4$): 263.1158 found 263.1159. IR (film): $\tilde{\nu}$ = 2958, 1771, 1613, 1514, 1249, 1158, 1028, 952, 908, 832, 749 cm^{-1}. $C_{14}H_{17}NO_4$ (263.3): calcd. C 63.87, H 6.51, N 5.32; found C 63.78, H 6.50, N 5.29.

(±)-(2*S*,4a*R*)-2-[(4-Methoxybenzyl)oxy]perhydroazeto[1,2-*b*][1,2]-oxazin-6-one (15): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.80−2.00 (m, 4 H), 2.49 (dd, *J* = 1.5 Hz, 13.5 Hz, 1 H), 2.99 (dd, *J* = 4.2 Hz, 13.5 Hz, 1 H), 3.63−3.72 (m, 1 H), 3.79 (s, 3 H), 4.55 (d, *J* = 11.1 Hz, 1 H), 4.92 (pseudo d, *J* = 2.4 Hz, 1 H), 5.00 (d, *J* = 11.1 Hz, 1 H), 6.78−6.89 (m, 2 H), 7.26−7.33 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.0, 26.4, 41.9, 49.7, 55.5, 70.1, 98.7, 113.8, 129.0, 130.3, 159.3, 166.0 ppm. HRMS calcd. for $[M]^+$ ($C_{14}H_{17}NO_4$): 263.1158 found 263.1156.

(±)-6-[(4-Methoxybenzyl)oxy]-5,6-dihydro-4*H*-1,2-oxazine (16): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.87−2.07 (m, 3 H), 2.25−2.40 (m, 1 H), 3.79 (s, 3 H), 4.54 (d, *J* = 11.4 Hz, 1 H), 4.75 (d, *J* = 11.4 Hz, 1 H), 5.14 (bd, *J* = 5.1 Hz, 1 H), 6.83−6.89 (m, 2 H), 7.23−7.29 (m, 2 H), 7.33 (bd, *J* = 1.5 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.9, 22.3, 55.5, 69.2, 94.4, 113.8, 129.7, 150.4, 159.1 ppm. HRMS calcd. for $[M]^+$ ($C_{12}H_{15}NO_3$): 221.1052 found 221.1052.

Preparation of 17 and 18, Conditions b: A solution of the lactam **12** (71 mg, 0.171 mmol) and triethylamine (20.2 mg, 0.200 mmol) in chloroform (1.5 mL) was heated at reflux for 4 days. The reaction was diluted with dichloromethane and the organic layer was washed with 1 M ammonium chloride/water. The aqueous layers were extracted twice with dichloromethane. The combined organic layers were dried (sodium sulfate), filtered, and the solvents evaporated to dryness. The crude products were separated by using column chromatography (EtOAc/heptane, 1:2) to obtain the lactam **17** (49.9 mg, 70%) as a white solid and the epimer **18** (15.5 mg, 22%) as a clear oil.

Preparation of 17, Conditions c: Under argon, a solution of the lactam **12** (48.8 mg, 0.118 mmol) and sodium methoxide (9.5 mg, 0.176 mmol) in dry tetrahydrofuran (1 mL) was stirred at room temperature. After 15 minutes the reaction was quenched with an excess of 1 M ammonium chloride/water. The resulting mixture was extracted three times with dichloromethane. The organic layer was dried (sodium sulfate), filtered and the solvents evaporated to dryness. The crude product was purified by using column chromatography (EtOAc/heptane, 1:2) to give **17** (38.5 mg, 78%).

(±)-(2a*S*,4*R*,6*R*,6a*R*)-4-[(4-Methoxybenzyl)oxy]-2a,6-diphenylperhydropyrano[3,2-*b*]azet-2-one (17): M.p. (CH_2Cl_2/diisopropyl ether) 154 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.25 (dddd, *J* = 0.9 Hz, 4.2 Hz, 7.2 Hz, 14.1 Hz, 1 H), 2.48 (dt, *J* = 6.6 Hz, 14.1 Hz, 1 H), 3.21 (ddd, *J* = 2.7 Hz, 4.2 Hz, 13.8 Hz, 1 H), 3.78 (s, 3 H), 4.03 (dd, *J* = 0.9 Hz, 2.7 Hz, 1 H), 4.52 (d, *J* = 11.4 Hz, 1 H), 4.95 (d, *J* = 11.4 Hz, 1 H), 5.32 (dd, *J* = 6.6 Hz, 7.2 Hz, 1 H), 5.90 (s, 1 H), 6.83−6.88 (m, 2 H), 7.15−7.43 (m, 10 H), 7.56−7.61 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.6, 38.8, 55.5, 62.0, 69.3, 87.0, 97.7, 113.8, 125.5, 127.2, 127.3, 128.5, 128.7, 129.0, 129.6, 130.1, 137.0, 139.8, 159.1, 170.0 ppm. HRMS: calcd. for $[M + H]^+$ ($C_{26}H_{26}NO_4$): 416.1862 found 416.1862. IR (film): $\tilde{\nu}$ = 2941, 1761, 1610, 1506, 1243, 1174, 1104, 1031, 970, 906, 828, 728, 694 cm^{-1}. $C_{26}H_{25}NO_4$ (415.5): calcd. C 75.16, H 6.06, N 3.37; found C 75.01, H 5.91, N 3.08.

(±)-(2*R*,4*S*,4a*R*,5*R*)-2-[(4-Methoxybenzyl)oxy]-4,5-diphenylperhydroazeto[1,2-*b*][1,2]oxazin-6-one (18): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.08 (ddd, *J* = 9.0 Hz, 12.6 Hz, 13.8 Hz, 1 H), 2.18 (ddd, *J* = 1.9 Hz, 4.2 Hz, 13.8 Hz, 1 H), 3.01 (ddd, *J* = 4.2 Hz, 9.6 Hz, 12.6 Hz, 1 H), 3.61 (dd, *J* = 1.2 Hz, 9.6 Hz, 1 H), 3.80 (s, 3 H), 3.93 (d, *J* = 1.2 Hz, 1 H), 4.75 (d, *J* = 11.4 Hz, 1 H), 4.98 (d, *J* = 11.4 Hz, 1 H), 5.10 (dd, *J* = 1.9 Hz, 9.0 Hz, 1 H), 6.86−6.92 (m, 2 H), 7.11−7.45 (m, 12 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 35.4, 46.5, 55.5, 58.9, 63.7, 71.7, 104.0, 114.0, 126.9, 127.2, 127.73, 127.74, 128.3, 128.8, 129.1, 130.1, 133.8, 138.9, 159.5, 163.4 ppm. HRMS calcd. for $[M]^+$ ($C_{26}H_{25}NO_4$): 415.1784 found 415.1789. IR (film): $\tilde{\nu}$ = 2928, 1776, 1513, 1249, 1157, 1034, 811, 737, 699 cm^{-1}.

(±)-(2a*S*,3a*R*,6a*S*,7*S*,7a*R*)-2a,7-Diphenylperhydrofuro[3′,2′:5,6]-pyrano[3,2-*b*]azet-2-one (19): A solution of the nitroso acetal **13** (40.2 mg, 0.125 mmol) and triethylamine (13.2 mg, 0.130 mmol) in chloroform (1 mL) was heated at reflux for 4 days. The reaction solvents were evaporated to dryness and the crude product was purified by column chromatography (EtOAc/heptane, 1:1) to obtain the lactam **19** (36.5 mg, 91%) as a white solid. An analytical sample was obtained by crystallization from CH_2Cl_2/diisopropyl ether. M.p. (CH_2Cl_2/diisopropyl ether) 187 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.74 (dddd, *J* = 3.3 Hz, 7.7 Hz, 10.7 Hz, 12.9 Hz, 1 H), 2.22 (qd, *J* = 8.6 Hz, 12.9 Hz, 1 H), 2.93−3.06 (m, 1 H), 3.40 (dd, *J* = 2.4 Hz, 6.0 Hz, 1 H), 3.61 (dt, *J* = 8.1 Hz, 8.7 Hz, 1 H), 4.11 (dt, *J* = 3.2 Hz, 8.7 Hz, 1 H), 4.28 (dd, *J* = 0.9 Hz, 2.4 Hz, 1 H), 5.82 (d, *J* = 7.8 Hz, 1 H), 7.20−7.39 (m, 8 H), 7.46 (br. s, 1 H), 7.55−7.64 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.1, 38.6, 40.2, 58.1, 66.0, 86.8, 102.4, 125.8, 127.1, 127.5, 128.6, 129.0, 136.5, 139.7, 170.9 ppm. HRMS: calcd. for $[M + H]^+$ ($C_{20}H_{20}NO_3$): 322.1443 found 322.1435. IR (film): $\tilde{\nu}$ = 2937, 1757, 1493, 1446, 1174, 1053, 1035, 906, 724, 698 cm^{-1}. $C_{20}H_{19}NO_3$ (321.4): calcd. C 74.75, H 5.96, N 4.36; found C 74.48, H 5.80, N 4.06.

(±)-Methyl 2-{(3*R*,6*R*)-6-[(4-Methoxybenzyl)oxy]-1,2-oxazinan-3-yl}acetate (20): To a solution of the lactam **14** (48.8 mg, 0.185 mmol) in dry tetrahydrofuran (1 mL) was added sodium methoxide

Table 2. Crystallographic data and parameters for the compounds **3**, **11**, and **14**

Compound	**3**	**11**	**14**
Empirical formula	$C_{22}H_{24}N_2O_5$	$C_{22}H_{23}NO_3$	$C_{14}H_{17}NO_4$
Molecular mass	396.43	349.41	263.29
Temperature (K)	293(2)	293(2)	208(2)
Wavelength (Å)	0.71073	0.71073	0.71073
Crystal system	monoclinic	triclinic	orthorhombic
Space group	$P2_1/c$	$P\bar{1}$	$P2_12_12_1$
Unit cell dimension (Å, °)			
a	21.719(6)	10.939(2)	6.2622(4)
b	9.2550(13)	10.847(6)	13.6803(16)
c	21.821(4)	17.982(6)	15.5130(17)
α	90	83.02(4)	90
β	111.139(19)	76.50(2)	90
γ	90	63.10(2)	90
Volume (Å^3)	4091.2(15)	1849.9(13)	1329.0(2)
Z	8	4	4
Density (calculated, mg/m^3)	1.287	1.255	1.316
μ (mm^{-1})	0.092	0.083	0.097
F(000)	1680	744	560
Crystal size (mm)	0.31 × 0.16 × 0.07	0.40 × 0.36 × 0.14	0.25 × 0.15 × 0.08
θ Range (°)	2.75−25.00	3.11−21.98	3.51−27.52
Reflections collected	7364	4681	17409
Independent reflections [R_{int}]	7164 [0.0592]	4503 [0.1644]	3016 [0.0428]
Refinement method	Full-matrix least-squares on F^2		
Data/restraint/parameters	7164/937/535	4503/824/471	3017/0/240
Goodness-of-fit on F^2	0.971	0.986	1.055
R_1, wR_2 indices [$I > 2\sigma(I)$]	0.1066, 0.1468	0.1211, 0.1242	0.0473, 0.0793
R_1, wR_2 indices (all data)	0.3562, 0.2209	0.4309, 0.1986	0.0760, 0.0863
Largest diff. peak and hole (e·Å^{-3})	0.248 and −0.215	0.249 and −0.245	0.127 and −0.174

(15.3 mg, 0.283 mmol). The reaction mixture was stirred at room temperature for 45 minutes and then quenched with an excess of 1 M ammonium chloride/water. The resulting mixture was extracted three times with dichloromethane. The combined organic layers were dried (sodium sulfate), filtered and the solvents evaporated to dryness. Ester **20** was purified by using column chromatography (EtOAc/heptane, 1:2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.37−1.47 (m, 1 H), 1.55−1.69 (m, 1 H), 1.86−2.04 (m, 2 H), 2.49 (dd, *J* = 5.4 Hz, 15.9 Hz, 1 H), 2.68 (dd, *J* = 8.4 Hz, 15.9 Hz, 1 H), 3.34−3.45 (m, 1 H), 3.69 (s, 3 H), 3.79 (s, 3 H), 4.51 (d, *J* = 11.4 Hz, 1 H), 4.71−4.75 (m, 2 H), 6.78−6.88 (m, 2 H), 7.23−7.29 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.4, 27.1, 36.5, 52.0, 52.7, 55.5, 69.9, 99.0, 113.9, 129.5, 129.7, 159.2, 172.1 ppm. HRMS calcd. for $[M]^+$ ($C_{15}H_{21}NO_5$): 295.1420 found 295.1420. IR (film): $\tilde{\nu}$ = 2950, 1731, 1610, 1515, 1437, 1299, 1256, 1035, 824 cm^{-1}.

(±)-(2a*S*,4*R*,6a*R*)-4-[(4-Methoxybenzyl)oxy]perhydropyrano[3,2-*b*]-azet-2-one (21): Under argon, a solution of the lactam **14** (56.9 mg, 0.216 mmol) in dry tetrahydrofuran (1 mL) was cooled to −78 °C and a solution of LDA (0.4 mL 0.661 M LDA/THF, 0.264 mmol) was added dropwise over a period of 5 minutes. The reaction mixture was stirred for 90 minutes and then quenched with an excess of saturated sodium hydrogen carbonate. The resulting mixture was extracted three times with dichloromethane. The combined organic layers were dried (sodium sulfate), filtered and the solvents evaporated to dryness. The crude products were separated by using column chromatography (EtOAc/heptane, 2:1) to yield *p*-methoxybenzyl alcohol (7.6 mg, 25%) and the lactam **21** (30.4 mg, 53%) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.73−1.98 (m, 4 H), 3.77 (s, 3 H), 3.81−3.86 (m, 1 H), 4.43 (d, *J* = 11.4 Hz, 1 H), 4.73 (dd, *J* = 1.8 Hz, 5.4 Hz, 1 H), 4.85 (d, *J* = 11.4 Hz, 1 H), 4.92 (dd, *J* = 5.7 Hz, 5.7 Hz, 1 H), 6.33 (br. s, 1 H), 6.80−6.87 (m, 2 H), 7.26−7.33 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.2, 23.7, 47.3, 55.5, 69.0, 76.6, 96.8, 113.7, 129.8, 129.9, 159.0, 170.2 ppm. HRMS: calcd. for $[M]^+$ ($C_{14}H_{17}NO_4$): 263.1158 found 263.1155. IR (film): $\tilde{\nu}$ = 2941, 1753, 1610, 1511, 1455, 1364, 1303, 1242, 1178, 1152, 1100, 1070, 1035, 945, 910, 824, 728, 646, 564 cm^{-1}.

Crystal Structure Determinations:[5] Crystals suitable for X-ray diffraction studies were grown by slow evaporation from CH_2Cl_2/heptane for **3**, CH_2Cl_2/diisopropyl ether for **11**, and EtOAc/heptane for **14**. Single crystals were mounted in air on glass fibres. Intensity data were collected at room temperature for **3** and **11** and at −65 °C for **14**. An Enraf−Nonius CAD4 single-crystal diffractometer was used for **3** and **11** (ω-2θ scan mode) and a Nonius KappaCCD diffractometer for **14**, (π and ω scan mode), all using graphite-monochromated Mo-K_α radiation. The structures were solved by the program CRUNCH[22] and were refined with standard methods using SHELXL-97[23] with anisotropic parameters for the non-hydrogen atoms. For **3** and **11** all hydrogens were placed at calculated positions and were refined riding on the parent atoms. For **14** the hydrogens were initially placed at calculated positions and were freely refined subsequently. Crystallographic data and parameters of the refinements are listed in Table 2.

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