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Synthesis of Alkaloid Analogues from β-Amino Alcohols by β-Fragmentation of Primary Alkoxyl Radicals

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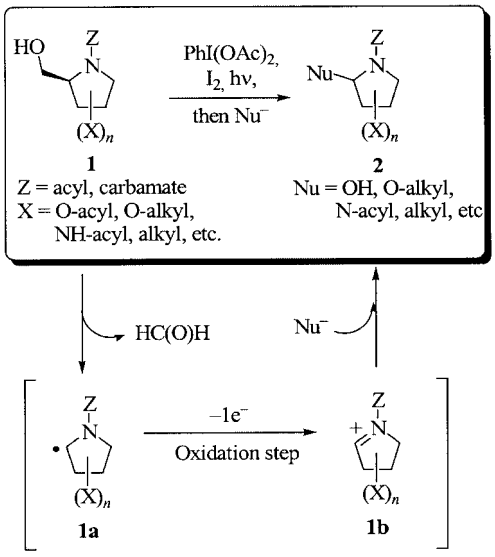
The fragmentation of primary alkoxyl radicals is usually a minor process with respect to hydrogen abstraction and other competing reactions. However, when β-amino alcohols were used as substrates, the scission proceeded in good to excellent yields and no side reactions were observed. The fragmentation can be coupled with an allylation or alkylation reaction, to give alkaloid analogues and functionalized nitrogen heterocycles.

Introduction

The β-fragmentation of alkoxyl radicals is useful methodology to obtain a wide range of compounds such as olefins, halogenated compounds, medium- and large-sized rings, and heterocycles.[1,2] The β-scission was the key step in the synthesis of bioactive natural products such as (–)-CP-263,114[3a,3b] the cytotoxic chondriamides A and C,[3c] and the antifungals deoxyvernolepin[3d,3e] and preussin.[3f] The substrates for the scission step were alcohols or hemiacetals, which generated alkoxyl radicals on treatment with reagents[1] such as (diacetoxyiodo)benzene (DIB) and iodine, HgO–iodine, or LTA. When tertiary alkoxyl radicals were formed, the β-fragmentation was the major or the exclusive pathway. However, the fragmentation of primary alkoxyl radicals usually proceeded in low yields, and processes such as intramolecular hydrogen abstraction (IHA)[4] or addition to double bonds[5] predominated.

We reasoned that the scission of primary alkoxyl radicals could be synthetically useful with substrates where the *C*-radicals resulting from fragmentation were stabilized by adjacent functionalities, such as oxygen[6] or nitrogen atoms.[7] Moreover, if the *C*-radicals could be readily transformed into other intermediates, the fragmentation would be further favored. Hence, we decided to explore the fragmentation of β-amino alcohol derivatives **1** (Scheme 1) on treatment with DIB and iodine.



Scheme 1. Fragmentation of primary alkoxyl radicals derived from β-amino alcohols.

Many β-amino alcohols **1** are commercial products or are readily prepared therefrom. Moreover, functionalized amino alcohols with different stereochemistries can be obtained from carbohydrates and other chiral compounds. The β-fragmentation of substrates **1** (Scheme 1) would generate *C*-radical **1a** stabilized by the nitrogen atom. Under the reaction conditions, intermediate **1a** would presumably be oxidized to acyliminium ion intermediate **1b**,[8] which could be trapped by nucleophiles to afford a variety of 2-substituted heterocycles **2**,[9] which can be found in alkaloids,[10] chiral auxiliaries,[10b,10c] and synthetic drugs.[10d]

It must be noted that competing intramolecular hydrogen abstraction (IHA) reactions could take place. In effect, in intermediate **1c** (Scheme 2) the distance between 5-H_a and

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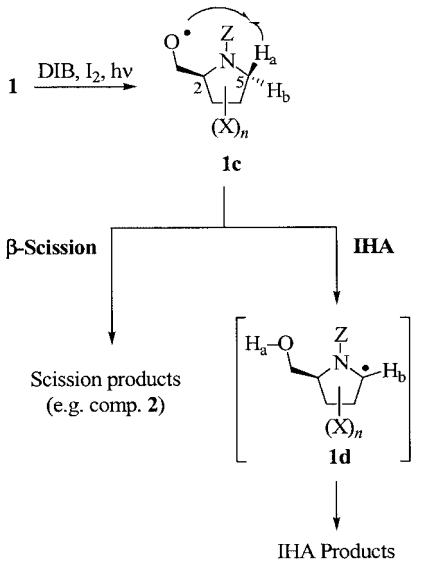
the alkoxyl radical (2.3–2.8 Å) is optimal for IHA, and resulting radical **1d** would also be stabilized by a nitrogen atom. The extent of IHA or other side reactions will determine whether the β-scission is a synthetically useful process.



Scheme 2. Fragmentation of primary alkoxyl radicals versus intramolecular hydrogen abstraction in β-hydroxy amino derivatives.

Results and Discussion

The synthesis of three substrates for the β-fragmentation reaction was carried out from commercial 2-(hydroxymethyl)pyrrolidine (**3**; Scheme 3). Thus, standard acylation[11] or sulfonylation of compound **3** afforded β-amino alcohol derivatives **4**–**6** in excellent yields.

To our satisfaction, when substrates **4**–**6** were treated with DIB and iodine at room temperature (Table 1, Entries 1–3), fragmentation products **7**–**9**[8f,12] (Scheme 3) were obtained in good yields, and no products derived from IHA were isolated. These results suggested that the scission was much faster than intramolecular H-abstraction. Since the fragmentation is a reversible reaction, a rapid and irreversible oxidation of the *C*-radical to acyliminium ions **4a**–**6a** was also presumed. The acyliminium ion was trapped by water during the work up.

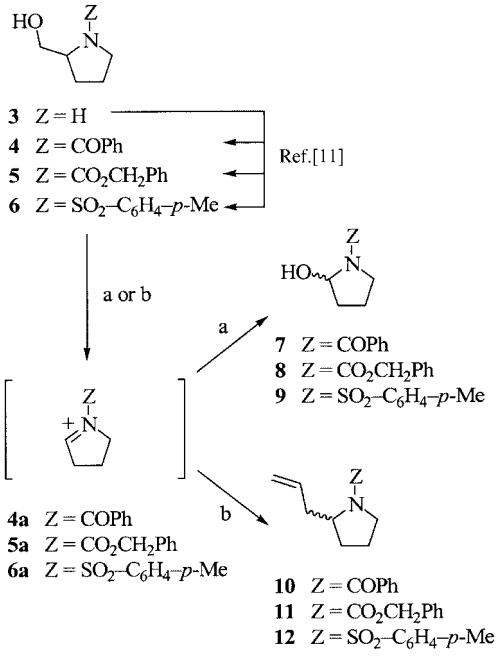
Table 1. One-pot β-scission of primary alkoxyl radicals–oxidation–nucleophilic addition.

Entry	Substrate	Nucleophile	Products (yield [%])[a]	Global yield [%][b]
1	**4**	H_2O	**7** (66)	66
2	**5**	H_2O	**8** (67)	67
3	**6**	H_2O	**9** (64)	64
4	**4**	allylTMS	**7** (4), **10** (91)	95
5	**5**	allylTMS	**8** (10), **11** (76)	86
6	**6**	allylTMS	**9** (5), **12** (86)	91

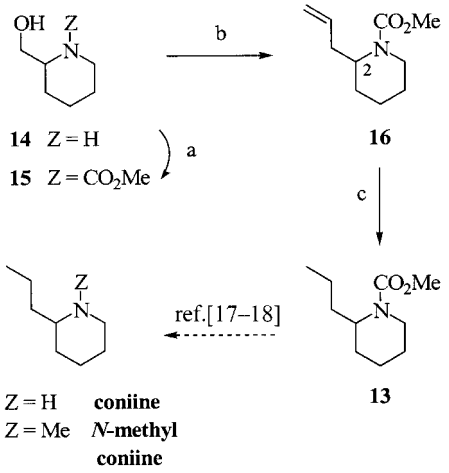
[a] Conditions: See Scheme 4 and Experimental Section. [b] Yields are given for products purified by chromatography on silica gel.

The addition of carbon nucleophiles to the acyliminium intermediate was subsequently studied. Substrates **4**–**6** were treated with DIB–iodine for 2.5 h, the reaction mixture was cooled to 0 °C, and allyltrimethylsilane and $BF_3{\cdot}OEt_2$ were added (Table 1, Entries 4–6) to afford desired allylpyrrolidines **10**–**12**[12,13] in good to excellent yields.

The application of the fragmentation–allylation reaction to the synthesis of natural products is illustrated with the preparation of coniine methyl carbamate (**13**) (Scheme 4). (±)-Coniine and (±)-*N*-methyl coniine are the active components of hemlock poison.[14]



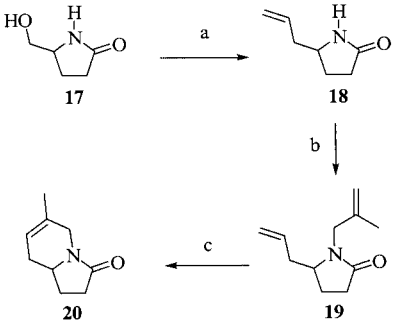
Scheme 3. β-Fragmentation of primary alkoxyl radicals and addition of nucleophiles. Reagents and conditions: (a) DIB, I_2, *hv*, CH_2Cl_2, 26 °C, then H_2O; (b) DIB, I_2, *hv*, CH_2Cl_2, 26 °C; then 0 °C, $BF_3{\cdot}OEt_2$, allylTMS, CH_2Cl_2. For product yields, see Table 1.



Scheme 4. Scission–allylation reaction in the synthesis of (±)-coniine and (±)-*n*-methyl coniine. Reagents and conditions: (a) MeOC(O)Cl, $NaHCO_3$ (aq.), THF, 96%; (b) DIB, I_2, *hv*, CH_2Cl_2, 26 °C, then 0 °C, $BF_3{\cdot}OEt_2$, allylTMS, 52%; (c) H_2, Pd/C, EtOAc, 90%.

(±)-(Hydroxymethyl)piperidine (**14**) was then transformed into *N*-methyl carbamate **15**, which was treated under the fragmentation–allylation conditions to yield volatile allyl derivative **16**[15] in 52% yield. Reduction of the double bond afforded (±)-coniine methyl carbamate (**13**)[16] in excellent yield. This product can be transformed into coniine by hydrolysis of the methyl carbamate,[17] and into *N*-methyl coniine by reduction of the protecting group with $LiAlH_4$.[17,18]

Another application of this methodology to the synthesis of natural product analogues is shown in Scheme 5. The preparation of indolizidine alkaloid analogues has been undertaken by many groups because several of these alkaloids are potent glycosidase inhibitors that present biological activities that range from hypoglucemic to antiviral or cytotoxic activities.[19]

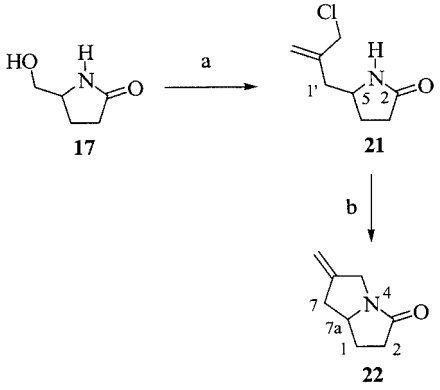


Scheme 5. Synthesis of the indolizidine alkaloid core. Reagents and conditions: (a) DIB, I_2, CH_2Cl_2, *hv*, then $BF_3{\cdot}OEt_2$, allylTMS, 85%; (b) NaH, THF, 0 °C, $CH_3C(=CH_2)CH_2Br$, 64%; (c) Grubbs' catalyst (2nd generation), CH_2Cl_2, 95%.

The starting material, commercial (±)-pyroglutamol (**17**; Scheme 5), was treated under the fragmentation–allylation conditions to afford allylpyrrolidone **18**[8f] in 85% yield. Potential side products derived from a nitrogen radical were not isolated. Presumably, the formation of a nitrogen radical was slow compared to the fragmentation and subsequent formation of an acyliminium ion. Allylpyrrolidone **18** was then *N*-allylated and diene **19**[20] underwent a metathesis reaction[21] to give indolizidine core **20**,[20] in overall good yield.

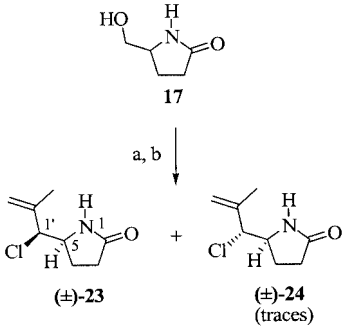
Other interesting alkaloids have a pyrrolizidine core[22–24] (Scheme 6). Some of them are hepatotoxic to animals;[23a] hence, they are used by plants or insects as deterrents against predators.[23b–23d] Other pyrrolizidines (e.g. the alexines) are powerful glycosidase inhibitors[24] that display antiviral and retroviral activities.

The formation of the pyrrolizidine core in just two steps was achieved by using a fragmentation–allylation reaction as the key step (Scheme 6). Thus, pyroglutamol **17** was transformed into allyl derivative **21** with the use of 2-(chloromethyl)-3-(trimethylsilyl)propene as the nucleophile. An intramolecular alkylation reaction[25] was then used to generate pyrrolizidine core **22** in good yield.



Scheme 6. Synthesis of the pyrrolizidine alkaloid core. Reagents and conditions: (a) DIB, I_2, CH_2Cl_2, *hv*, then 0 °C, $BF_3{\cdot}OEt_2$, $CH_2=C(CH_2Cl)–CH_2TMS$, 70%; (b) NaH, DMF, 0 °C, 73%.

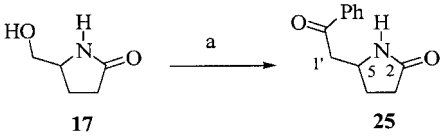
Interestingly, when the scission–allylation reaction was repeated with an old batch of the allyl reagent, followed by treatment with sodium hydride, cyclization product **22** was not formed (Scheme 7). Instead, chloroallyl derivative **23** was isolated, together with a residual amount of diastereomer **24**. Their stereochemistry is tentatively proposed, by comparison with similar compounds described in the literature.[26]



Scheme 7. Reagents and conditions: (a) DIB, I_2, CH_2Cl_2, *hv*, then 0 °C, $BF_3{\cdot}OEt_2$, $Cl–CH=C(CH_3)–CH_2TMS$; (b) NaH, DMF, 0 °C; **23** (32% for the two steps) and **24** (traces).

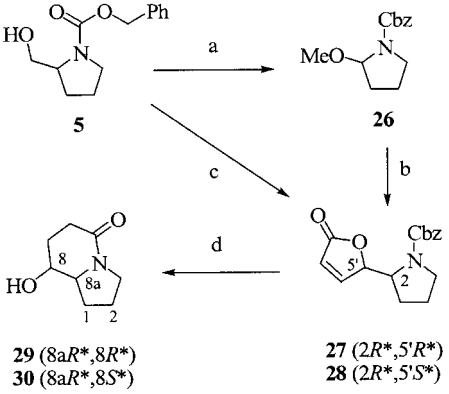
The formation of **23** could be due to isomerization of the allyl reagent before its use,[27] from 2-(chloromethyl)-3-(trimethylsilyl)propene to 1-chloro-2-methyl-3-trimethylsilylpropene. The generation of compound **23** is interesting, since the replacement of the chloro group by different nucleophiles could lead to a variety of 5-substituted pyrrolidinones.

A tandem scission–alkylation reaction was also developed by using silyl enol ethers as nucleophiles. When (±)-pyroglutamol (**17**; Scheme 8) was treated under fragmentation conditions followed by the addition of phenyl(trimethylsilyloxy)ethene and boron trifluoride, phenyl ketone **25** was formed in 73% yield. This ketone is an analogue of the alkaloid (±)-sedamine.[28]



Scheme 8. Tandem fragmentation–addition of silyl enol ethers. Reagents and conditions: (a) DIB, I_2, CH_2Cl_2, *hv*, then 0 °C, $BF_3{\cdot}OEt_2$, CH_2=C(OTMS)–Ph, 73%.

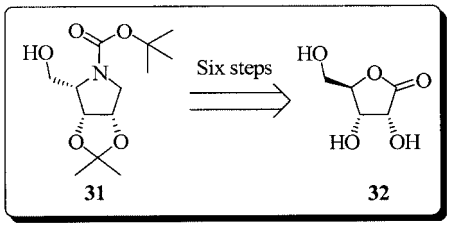
Another interesting application of this methodology is the formation of a hydroxylated indolizidine core, which can be found in glycosidase inhibitors. Hence, the fragmentation of prolinol derivative **5** (Scheme 9), followed by addition of methanol, afforded 2-methoxy pyrrolidine (±)-**26**.[29] This product was treated with boron trifluoride and (trimethylsilyloxy)furan to generate compounds **27** and **28**,[30] which are analogues of the norpandamarilactonine alkaloids.[31]

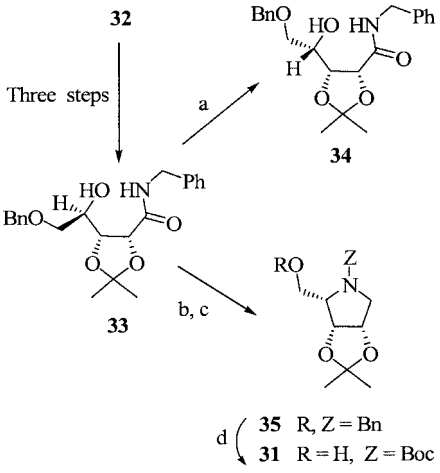


Scheme 9. Synthesis of indolizidine alkaloid analogues **29** and **30**.Reagents and conditions: (a) DIB, I_2, CH_2Cl_2, *hv*, then MeOH, 78%; (b) $BF_3{\cdot}OEt_2$, 2-(trimethylsilyloxy)furan, 0 °C, CH_2Cl_2, 74%, **27/28** (10:1); (c) DIB, I_2, CH_2Cl_2, *hv*, then 0 °C, $BF_3{\cdot}OEt_2$, 2-(trimethylsilyloxy)furan, 66%, **27/28** (6:1); (d) **27/28** (10:1), H_2, 10% $Pd(OH)_2$, MeOH, MeONa (cat), room temp., 91%, **29/30** (8:1).

The alkylation reaction proceeded in good yields and with good diastereoselectivity (**27/28**, *dr* 10:1). The one-pot transformation of prolinol **17** into compounds **27/28** was then carried out, and took place in 66% yield and good diastereomeric ratio (**27/28**, 6:1). The mixture of **27/28** can be transformed into the hydroxylated indolizidine core in one step, by the sequential reduction of the double bond, hydrogenolysis of the benzyl carbamate, and formation of the lactam. Thus, (8a*R**,8*R**)-indolizidine **29**[32] and (8a*R**,8*S**)-epimer **30** were obtained in excellent yield and good diastereoselectivity (**29/30**, 8:1).

The previous examples show the versatility of the fragmentation–alkylation process. Moreover, since many β-amino alcohols can be readily prepared from sugars and other chiral compounds, their scission–alkylation could afford a wide range of functionalized, chiral nitrogen heterocycles. For instance, fragmentation substrate **31** (Scheme 10) was prepared from commercially available ribonolactone (**32**) in six steps.[33]



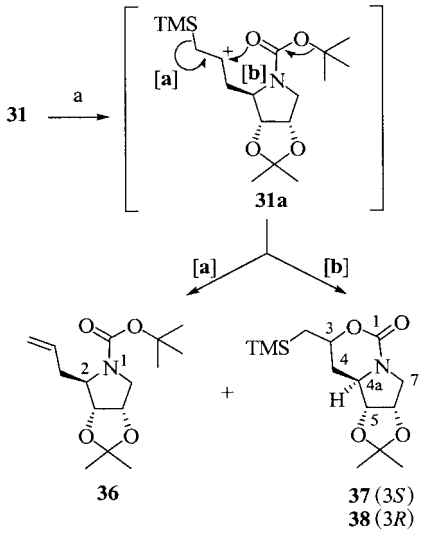


Scheme 10. Synthesis of functionalized pyrrolidines from the chiral pool. Reagents and conditions: (a) DIAD, PPh_3, dioxane, 80 °C, 72%; (b) $LiAlH_4$, Et_2O, reflux, 84%; (c) DIAD, PPh_3, dioxane, 80 °C, 66%; (d) H_2, Pd/C, MeOH, $(t BuO_2C)_2O$, 26 °C, 94%.

Lactone **32** was transformed into its isopropylidene acetal,[34] the 5-hydroxy group was protected as its benzyl ether,[35] and finally the lactone was opened by treatment with benzylamine to afford compound **33**. Amide **33** was subjected to Mitsunobu conditions in order to obtain a lactam, but the expected cyclization did not take place and the 5-epimer of compound **33** was obtained instead. The formation of 5-epimer **34** could be explained by formation of a 5-oxyphosphonium group, which is displaced by nucleophilic attack from the amide oxygen. An intermediate imidoate is formed, which finally undergoes hydrolysis to give observed product **34**. A similar reaction has been recently reported, which was applied to obtain furanolactones of different series.[36] In order to avoid this isomerization, amide **33** was reduced to an amine, and the latter underwent Mitsunobu cyclization to *N*-benzylpyrrolidine **35**. The benzyl protecting groups were then removed by hydrogenolysis and the amine was protected in situ as its *tert*-butyl carbamate to afford product **31** in excellent yield.

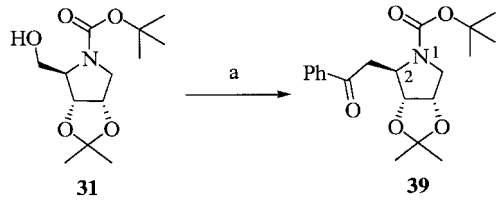
By using chiral β-hydroxy amine **31** as the substrate, the fragmentation–addition reaction of nucleophiles was studied. A scission–allylation reaction was carried out first (Scheme 11), which generated intermediate **31a** by addition of the allylsilane from the less hindered face of the acyliminium ion. Intermediate **31a** underwent loss of the TMS group (Route a) to afford **36**, or nucleophilic addition of

the carbamate oxygen followed by loss of the *tert*-butyl group[37] (Route b) to give cyclic carbamates **37** and **38**. The alkylation reaction proceeded with excellent stereoselectivity, and no (2*S*) or (4a*S*) products could be detected.[38]



Scheme 11. Stereoselective fragmentation–allylation of compound **31**. Reagents and conditions: (a) DIB, I_2, CH_2Cl_2, *hv*, then 0 °C, $BF_3{\cdot}OEt_2$, allylTMS, **36** (41%), **37** (23%), **38** (22%).

When phenyl(trimethylsilyloxy)ethene was used as a nucleophile, the fragmentation–alkylation reaction (Scheme 12) took place in good yield to afford (2*R*)-phenyl ketone **39** (99% *de*).[39] No H-abstraction or oxidation products were isolated.



Scheme 12. Stereoselective fragmentation–alkylation. Reagents and conditions: (a) DIB, I_2, CH_2Cl_2, *hv*, then 0 °C, $BF_3{\cdot}OEt_2$, CH_2=C(OTMS)Ph, **39** (64%, 99% *de*).

Conclusions

The fragmentation of primary alkoxyl radicals has been scarcely used in synthesis since other competing processes (such as H-abstraction) usually predominate. However, when β-amino alcohols were used as substrates, the scission took place in good to excellent yields. Tandem scission–allylation, or –alkylation reactions were subsequently developed. This one-pot methodology was applied to the synthesis of alkaloid analogues and functionalized, chiral nitrogen heterocycles.

Experimental Section

General Remarks: Commercially available reagents and solvents were analytical grade or were purified by standard procedures prior to use.[40] All reactions involving air- or moisture-sensitive materials were carried out under a nitrogen atmosphere. The spray reagents for TLC analysis were 0.5% vanillin in H_2SO_4/EtOH (4:1) or 0.25% ninhydrin in ethanol. Merck silica gel 60 PF (0.063–0.2 mm) was used for chromatography. Melting points were determined with a hot-stage apparatus. IR spectra were recorded with a Perkin-Elmer 1600/FTIR spectrometer. NMR chemical shift values are reported relative to TMS as an internal standard, unless otherwise stated. For some compounds, a mixture of two rotamers was observed at room temperature, which caused broadening or splitting of the NMR signals. The rate of rotamer interconversion usually increased on heating, and in many cases only one rotamer could be detected at 70 °C. When the NMR resolution improved significantly on heating, the spectra at 70 °C are described.

Preparation of 2-Hydroxy Pyrrolidines 7–9. General Procedure: 2-(Hydroxymethyl)pyrrolidines **4**–**6** (1 mmol) in dry dichloromethane (15 mL) were treated with DIB (2.5 mmol) and iodine (1 mmol) and stirred at room temperature under a nitrogen atmosphere for 2.5 h. After that time, the mixture was poured into aqueous $NaHCO_3$/10% $Na_2S_2O_3$ and extracted with CH_2Cl_2. Purification by column chromatography on silica gel (hexanes/EtOAc) afforded 1-benzoyl-2-pyrrolidinol (**7**)[8f] (66%), benzyl 2-hydroxy-1-pyrrolidinecarboxylate (**8**)[8f] (67%), and 1-tolylsulfonyl-2-pyrrolidinol (**9**)[12] (64%), respectively.

Standard Procedure for the Fragmentation–Allylation or Fragmentation–Alkylation Reaction: 2-(Hydroxymethyl)pyrrolidine (1 mmol) in dry dichloromethane (15 mL) was treated with DIB (2.5 mmol) and iodine (1 mmol) and stirred at room temperature under a nitrogen atmosphere for 2.5 h. After that time, the mixture was cooled to 0 °C and $BF_3{\cdot}OEt_2$ (2 equiv.) and excess nucleophile (5 equiv.; allylsilane or silyl enol ether) were added. The reaction was allowed to reach 26 °C and stirred for 4 h, and the mixture was then poured into aqueous $NaHCO_3$/10% $Na_2S_2O_3$ and extracted with CH_2Cl_2. The products were purified by column chromatography on silica gel (hexanes/EtOAc).

2-Allyl-1-benzoylpyrrolidine (10):[13a] Compound **4** was treated under the standard fragmentation–allylation conditions to afford after column chromatography (hexanes/EtOAc, 90:10), pyrrolidinol **7** (4%) and 2-allyl-1-benzoylpyrrolidine **10** (91%).

Benzyl 2-Allyl-1-pyrrolidinecarboxylate (11):[13b] Compound **5** was treated under the standard fragmentation–allylation conditions to afford after column chromatography (hexanes/EtOAc, 90:10) benzyl 2-hydroxy-1-pyrrolidinecarboxylate (**8**) (10%) and benzyl 2-allyl-1-pyrrolidinecarboxylate (**11**) (76%).

2-Allyl-1-(tolylsulfonyl)pyrrolidine (12):[12] Compound **6** was treated under the standard fragmentation–allylation conditions to afford after column chromatography (hexanes/EtOAc, 90:10) *N*-tolylsulfonyl-2-pyrrolidinol **9** (5%) and 2-allyl-*N*-(tolylsulfonyl)-pyrrolidine **12** (86%).

Methyl 2-Allyl-1-piperidinecarboxylate (16):[15] Compound **15** was treated under the standard fragmentation–allylation conditions, but with the use of iodine (0.5 equiv.), to afford after column chromatography (hexanes/EtOAc, 90:10) 2-allylpiperidine **16** (52%).

Methyl 2-Propyl-1-piperidinecarboxylate (13):[16] To a solution of allyl derivative **16** (20 mg) in EtOAc (10 mL) was added 10% Pd/C (50 mg), and the solution was stirred at 26 °C under a hydrogen

atmosphere (1 atm) for 18 h. The reaction mixture was filtered through a celite column which was eluted with EtOAc. The organic layer was evaporated under vacuum to yield product **13** (18 mg, 90%).

5-Allyl-2-pyrrolidinone (18):[8f] Compound **17** was treated under the standard fragmentation–allylation conditions to afford after column chromatography (hexanes/EtOAc, 90:10) product**18** (85%).

5-Allyl-1-(2-methyl-2-propenyl)-2-pyrrolidinone (19):[20] To a solution of allylpyrrolidinone **18** (200 mg, 1.6 mmol) in dry DMF (5 mL) at 0 °C, was added sodium hydride (60% dispersion in mineral oil, 160 mg, 3.2 mmol). The reaction mixture was stirred at 0 °C for 1 h and then $ClCH_2C(Me)=CH_2$ (240 μL, 2.4 mmol) was added dropwise. After stirring at 0 °C for 30 min, the reaction mixture was allowed to reach room temperature (26 °C) and stirred for another 16 h. The mixture was then cooled to 0 °C and methanol (1 mL) was added dropwise to destroy excess sodium hydride. Afterwards, the reaction mixture was poured into a saturated sodium hydrogen carbonate solution and extracted with diethyl ether. The organic layer was washed with brine, dried on sodium sulfate, and the solvents evaporated under vacuum. The residue was purified by column chromatography on silica gel (hexanes/EtOAc, 95:5) to afford product **19** (192 mg, 64%).

6-Methyl-1,5,8,8a-tetrahydro-3(2*H*)-indolizinone (20):[20] To a solution of compound **19** (110 mg, 0.6 mmol) in dry dichloromethane (20 mL) was added a catalytic amount (10 mg) of Grubbs' catalyst 2nd generation {benzylidene[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(tricyclohexylphosphane)ruthenium}, and the solution was heated at reflux for 3 h. The reaction mixture was then cooled to room temperature, poured into a saturated aqueous $NaHCO_3$ solution, and extracted with dichloromethane. The organic layer was dried and evaporated as usual, and the residue was purified by column chromatography on silica gel (hexanes/EtOAc, 95:5) to afford indolizinone **20** (88 mg, 95%).

5-[(2-Chloromethyl)-2-propenyl]-2-pyrrolidinone (21): To a solution of pyroglutamol (**17**, 57.5 mg, 0.5 mmol) in dry CH_3CN (7 mL) under a nitrogen atmosphere was added I_2 (63.5 mg, 0.25 mmol) and DIB (322 mg, 1.0 mmol), and the resulting mixture was stirred at 25 °C, under irradiation with visible light (80 W tungsten-filament lamp) for 3 h. The reaction mixture was cooled to 0 °C; afterwards 2-chloromethyl-3-trimethylsilyl-1-propene (272 μL, 244 mg, 1.5 mmol) and $BF_3{\cdot}OEt_2$ (127 μL, 141.9 mg, 1.0 mmol) were added dropwise. The mixture was allowed to reach room temperature and stirred for 3 h. The mixture was then poured into a solution of $Na_2S_2O_3$ (10% aq.)/$NaHCO_3$ (saturated aq.) and extracted with CH_2Cl_2. The organic layers were dried (Na_2SO_4) and the solvents evaporated under vacuum. Silica gel chromatography (hexanes/EtOAc, 70:30) gave compound **21** (36.5 mg, 70%). Compound **21** was previously reported,[25] but its physical and spectroscopic data were not described. Crystalline solid. M.p. 60–62 °C (from EtOAc/*n*-hexane). IR (film): $\tilde{\nu}$ = 3431, 3087, 1694, 1260, 925 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.75 (m, 1 H, 4-H_a), 2.26–2.44 (m, 5 H, 3-H_2 + 4-H_b + CH_2C=), 3.89 (dddd, J = 6.5, 6.6, 6.7, 6.9 Hz, 1 H, 5-H), 4.01 (d, J = 11.8 Hz, 1 H, C$H_a$$H_b$Cl), 4.04 (d, J = 11.6 Hz, 1 H, $CH_a$$H_b$Cl), 5.03 (s, 1 H, =C$H_a$$H_b$), 5.25 (s, 1 H, =$CH_a$$H_b$), 6.37 (br. b., 1 H, NH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 27.1 (CH_2, C-4), 30.1 (CH_2, C-3), 40.6 (CH_2, C-1′), 48.0 (CH_2, CH_2Cl), 52.2 (CH, C-5), 117.6 (CH_2, $=CH_2$), 141.4 (C, =C), 178.0 (C, C-2) ppm. MS (EI, 70 eV): *m*/*z* (%) = 176/174 (3.8/11.8) $[M + H]^+$, 138 (13) $[M - Cl]^+$, 84 (100) $[M - ClCH_2C(=CH_2)CH_2]^+$. HRMS (EI, 70 eV): calcd. for $C_8H_{13}{}^{37}ClNO/C_8H_{13}{}^{35}ClNO$ 176.0656/174.0686; found 176.0651/174.0694; calcd. for C_4H_6NO 84.0449; found 84.0451. $C_8H_{12}ClNO$ (173.64): calcd. C 55.34, H 6.97, N 8.07; found C 55.66, H 7.05, N 7.82.

6-Methylenehexahydro-3*H*-pyrrolizin-3-one (22): Compound **21** (25 mg, 0.14 mmol) in dry THF (2 mL) was cooled to 0 °C and treated with 60% NaH (15 mg, 2.5 mmol). The solution was stirred overnight at room temperature, then poured into H_2O, and extracted with EtOAc. Column chromatography as usual gave product **22** (14 mg, 73%). Compound **22** was previously reported,[25] but its physical and spectroscopic data were not described. Colorless oil. IR (film): $\tilde{\nu}$ = 3085, 1681, 1236, 897 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.77 (dddd, J = 2.6, 2.9, 10.0, 10.3 Hz, 1 H, 1-H_a), 2.15 (m, 1 H, 7-H_a), 2.36 (dddd, J = 2.3, 6.9, 9.3, 12.8 Hz, 1 H, 1-H_b), 2.43 (ddd, J = 2.3, 9.7, 16.7 Hz, 1 H, 2-H_a), 2.68 (m, 2 H, 2-H_b + 7-H_b), 3.58 (ddd, J = 1.7, 1.9, 15.9 Hz, 1 H, 5-H_a), 3.99 (dddd, J = 6.5, 6.9, 6.8, 10.0 Hz, 1 H, 7a-H), 4.22 (br. d, J = 15.9 Hz, 1 H, 5-H_b), 4.99 (m, 1 H, =C$H_a$$H_b$), 5.04 (m, 1 H, =$CH_a$$H_b$) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 27.1 (CH_2, C-1), 34.1 (CH_2, C-2), 40.2 (CH_2, C-7), 46.1 (CH_2, C-5), 61.2 (CH, C-7a), 108.2 (CH_2, =CH_2), 147.2 (C, C-6), 174.3 (C, C-3) ppm. MS (EI, 70 eV): *m*/*z* (%) = 137 (99) $[M]^+$, 82 (100) $[M - COCH_2CH_2]^+$. HRMS (EI, 70 eV): calcd. for $C_8H_{11}NO$ 137.0842; found 137.0835; calcd. for C_5H_8N 82.0419; found 82.0421. $C_8H_{11}NO$ (137.18): calcd. C 70.04, H 8.08, N 10.21; found C 70.01, H 8.03, N 10.41.

(5*S,1′*R**)-5-(1-Chloro-2-methyl-2-propenyl)-2-pyrrolidinone (23) and (5*S**,1′*S**)-5-(1-Chloro-2-methyl-2-propenyl)-2-pyrrolidinone (24):** Fragmentation–allylation as described to obtain product **21**, but using 1-chloro-2-methyl-3-trimethylsilyl-1-propene as the nucleophile. The crude reaction product was treated with NaH in DMF as described to obtain product **22**. Usual purification afforded product **23** (32% for both steps) and traces of diastereomer **24**. Compound **23**: Crystalline solid. M.p. 115–117 °C (from EtOAc/*n*-hexane). IR (film): $\tilde{\nu}$ = 3430, 3088, 1700, 1260, 917 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.78 (m, 1 H, 4-H_a), 1.80 (s, 3 H, 2′-CH_3), 2.17 (m, 1 H, 4-H_b), 2.33–2.45 (m, 2 H, 3-H_2), 3.92 (ddd, J = 7.5, 7.9, 8.4 Hz, 1 H, 5-H), 4.20 (d, J = 9.3 Hz, 1 H, 1′-H), 5.05 (s, 1 H, =C$H_a$$H_b$), 5.11 (s, 1 H, =$CH_a$$H_b$), 6.04 (br. s, 1 H, NH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 17.5 (CH_3, 2′-CH_3), 24.5 (CH_2, C-4), 30.1 (CH_2, C-3), 57.5 (CH, C-5), 70.7 (CH, C-1′), 117.3 (CH_2, $=CH_2$), 140.6 (C, C-2′), 177.0 (C, C-2) ppm. MS (EI, 70 eV): *m*/*z* (%) = 176/174 (2.7/8.2) $[M + H]^+$, 138 (15) $[M - Cl]^+$, 84 (100) $[M - CH(Cl)C(Me)=CH_2]^+$. HRMS (EI, 70 eV): calcd. for $C_8H_{13}{}^{37}ClNO/C_8H_{13}{}^{35}ClNO$ 174.0656/174.0686; found 174.0650/174.0692; calcd. for C_4H_6NO 84.0449; found 84.0447. $C_8H_{12}ClNO$ (173.64): calcd. C 55.34, H 6.97, N 8.07; found C 55.69, H 7.16, N 7.66. Compound **24**: Minor diastereomer **24** could not be purified from its mixture with major diastereomer **23**. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.82 (s, 3 H, 2′-CH_3), 2.03 (m, 1 H, 4-H_a), 2.15 (m, 1 H, 4-H_b), 2.31–2.45 (m, 2 H, 3-H_2), 3.90 (m, 1 H, 5-H), 4.12 (d, J = 8.8 Hz, 1 H, 1′-H), 5.05 (s, 1 H, =C$H_a$$H_b$), 5.09 (s, 1 H, =$CH_a$$H_b$), 6.18 (br. s, 1 H, NH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 17.5 (CH_3, 2′-CH_3), 25.1 (CH_2, C-4), 29.8 (CH_2, C-3), 56.6 (CH, C-5), 68.4 (CH, C-1′), 117.3 (CH_2, $=CH_2$), 141.2 (C, C-2′), 177.9 (C, C-2) ppm.

5-(2-Oxo-2-phenylethyl)-2-pyrrolidinone (25): The general fragmentation–alkylation procedure with the use of 1-phenyl-1-(trimethylsilyloxy)ethene as the nucleophile, afforded compound **25** (73%). Crystalline solid. M.p. 125–127.5 °C (from EtOAc/*n*-pentane). IR ($CHCl_3$): $\tilde{\nu}$ = 3432, 1697, 1682 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.80 (m, 1 H, 4-H_a), 2.40 (m, 3 H, 3-H_2 + 4-H_b), 3.11 (dd, J = 8.9, 17.8 Hz, 1 H, 1′-H_a), 3.27 (dd, J = 4.0, 17.8 Hz, 1 H, 1′-H_b), 4.20 (m, 1 H, 5-H), 6.53 (br. s., 1 H, NH), 7.45 (dd, J = 7.7, 7.7 Hz, 2 H, arom.), 7.57 (dd, J = 7.3, 7.4 Hz, 1 H, arom.), 7.91 (d, J =

7.7 Hz, 2 H, arom.) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 26.8 (CH_2, C-4), 29.5 (CH_2, C-3), 45.2 (CH_2, C-1′), 50.0 (CH, C-5), 127.8 (2 × CH, arom.), 128.6 (2 × CH, arom.), 133.5 (CH, arom.), 136.1 (C, arom.), 177.8 [C, C(O)N], 198.2 (C, CO) ppm. MS (EI, 70 eV): *m*/*z* (%) = 203 (31) $[M]^+$, 175 (26) $[M - CO]^+$, 105 (100) [PhCO], 84 (90) $[M - CH_2COPh]^+$. HRMS (EI, 70 eV): calcd. for $C_{12}H_{13}NO_2$ 203.0946; found 203.0907; calcd. for C_7H_5O 105.0340; found 105.0341. $C_{12}H_{13}NO_2$ (203.24): calcd. C 70.90, H 6.45, N 6.89; found C 70.79, H 6.60, N 6.82.

Benzyl 2-Methoxy-1-pyrrolidinecarboxylate (26):[29] 2-(Hydroxymethyl)pyrrolidine **5** (250 mg, 1.06 mmol) in CH_2Cl_2 (7 mL) was treated with I_2 (135 mg, 0.53 mmol) and DIB (685 mg, 2.13 mmol), and stirred under irradiation with visible light for 3 h. Dry MeOH (0.5 mL) was then added, and the solution was stirred for other 30 min. Work up and purification, as previously described, afforded product **26** (193 mg, 78%).

(2*R,5′*R**)- (27)**[30a] **and (2*R**,5′*S**)-Benzyl 2-(5-Oxo-2,5-dihydro-2-furanyl)-1-pyrrolidinecarboxylate (28):**[30a] *Method A:* To a solution of compound **26** (43.8 mg, 0.2 mmol) in dry CH_2Cl_2 (4 mL) at 0 °C under N_2 was added 2-(trimethylsilyloxy)furan (168 μL, 156 mg, 1 mmol), and $BF_3{\cdot}OEt_2$ (51 μL, 56 mg, 0.4 mmol) was then injected dropwise. The solution was stirred at room temperature for 1 h, poured into a saturated aqueous $NaHCO_3$ solution, and extracted with CH_2Cl_2. Usual drying, evaporation, and chromatography afforded products **27** and **28** (40.2 mg, 74%) as a diastereoisomeric mixture [**27** (*threo*)/**28** (*erythro*), 10:1]. *Method B:* 2-(Hydroxymethyl)pyrrolidine (**5**) underwent the standard fragmentation–alkylation procedure with the use of 2-(trimethylsilyloxy)furan as the nucleophile to give products **27** and **28** (66%) as a diastereoisomeric mixture (**27**/**28**, 6:1).

(8a*R,8*R**)- (29)**[32a] **and (8a*R**,8*S**)-8-Hydroxyhexahydro-5-(1*H*)-indolizinone (30):**[32b] To a solution of diastereomers **27**/**28** (10:1) (40 mg, 0.15 mmol) in MeOH (3 mL) was added $Pd(OH)_2$/C (20 mg) and a catalytic amount of MeONa (5 mg), and the resulting mixture was stirred at room temperature under a hydrogen atmosphere (1 atm) overnight. The suspension was filtered through a silica gel–celite (1:1) path and the organic layers were concentrated under vacuum to yield products **29** and **30** (21 mg, 91%; *dr* 8:1).

Tandem Fragmentation–Allylation of Compound 31: The reaction was carried out according to the standard procedure to afford *tert*-butyl (2*R*,3*R*,4*S*)-2-allyl-3,4-*O*-isopropylidene-1-pyrrolidinecarboxylate (**36**) (41%), (3*S*,4a*R*,5*R*,6*S*)-5,6-dioxy-3-[(trimethylsilyl)methyl]hexahydropyrrolo[1,2-*c*][1,3]oxazin-1-one (**37**) (23%), and (3*R*,4a*R*,5*R*,6*S*)-5,6-dioxy-3-[(trimethylsilyl)methyl]hexahydropyrrolo[1,2-*c*][1,3]oxazin-1-one (**38**) (22%) (global yield 86%). Compound **36**: Two rotamers at 26 °C (1:1), one rotamer at 70 °C. Oil. $[\alpha]_D$ = –64 (*c* 0.64, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 1687, 1409 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, 26 °C): δ = 1.29 [s, 3 H, C(Me)CH_3], 1.44 [s, 3 H, C(Me)CH_3], 1.45 [s, 9 H, OC(CH_3)$_3$], 2.20/2.33 (m/m, 2 H, 1′-H_2), 3.33 (dd, *J* = 5.2, 13.0 Hz, 1 H, 5-H_a), 3.75/3.86 (d, *J* = 12.9 Hz/d, *J* = 13.0 Hz, 1 H, 5-H_b), 4.02/4.15 (dd, *J* = 5.8, 6.4 Hz/m, 1 H, 2-H); 4.45 (d, *J* = 5.9 Hz, 1 H, 3-H), 4.67 (m, 1 H, 4-H), 5.09 (d, *J* = 11.1 Hz, 1 H, 3′-H_a), 5.10 (d, *J* = 16.3 Hz, 1 H, 3′-H_b), 5.75 (m, 1 H, 2′-H) ppm. ^{1}H NMR (500 MHz, $CDCl_3$, 70 °C): δ = 1.30 [s, 3 H, C(Me)CH_3], 1.46 [s, 3 H, C(Me)CH_3], 1.47 [s, 9 H, OC(CH_3)$_3$], 2.21 (ddd, *J* = 7.7, 7.7, 15.1 Hz, 1 H, 1′-H_a), 2.31 (m, 1 H, 1′-H_b), 3.33 (dd, *J* = 5.2, 13.0 Hz, 1 H, 5-H_a), 3.81 (d, *J* = 13.0 Hz, 1 H, 5-H_b), 4.10 (m, 1 H, 2-H), 4.45 (d, *J* = 5.9 Hz, 1 H, 3-H), 4.66 (dd, *J* = 5.4, 5.5 Hz, 1 H, 4-H), 5.09 (dd, *J* = 1.5, 9.3 Hz, 1 H, 3′-H_a), 5.11 (dd, *J* = 1.0, 18.3 Hz, 1 H, 3′-H_b), 5.76 (dddd, *J* = 7.0, 7.1, 10.4, 17.2 Hz, 1 H, 2′-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 26 °C): δ = 25.0 [CH_3, C(Me)*C*H_3], 26.9 [CH_3, C(Me)*C*H_3], 28.4 [3 × CH_3, OC(CH_3)$_3$], 36.0/35.3 (CH_2, C-1′), 51.4/52.0 (CH_2, C-5), 62.6/63.1 (CH, C-2), 78.6/79.3 (CH, C-4), 79.7 [C, OC(CH_3)$_3$], 83.2/84.0 (CH, C-3), 111.6 [C, O*C*(Me)$_3$], 118.2 (CH_2, C-3′), 133.8 (CH, C-2′), 154.3 (C, CO) ppm. MS (EI, 70 eV): *m*/*z* (%) = 268 (4) $[M - Me]^+$, 242 (7) $[M - CH_2CH{=}CH_2]^+$, 186 (22) $[M + H - CH_2CH{=}CH_2 - CMe_3]^+$, 142 (100) $[M + H - CH_2CH{=}CH_2 - CO_2CMe_3]^+$. HRMS (EI, 70 eV): calcd. for $C_{14}H_{22}NO_4$ 268.1549; found 268.1592; calcd. for $C_7H_{12}NO_2$ 142.0868; found 142.0872. $C_{15}H_{25}NO_4$ (283.37): calcd. C 63.58, H 8.89, N 4.94; found C 63.60, H 8.86, N 4.78. Compound **37**: White crystals. M.p. 101.5–103.5 °C (from EtOAc/*n*-pentane), $[\alpha]_D$ = +62 (*c* 0.25, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 1686, 1441, 1376 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.08 [s, 9 H, Si(CH_3)$_3$], 0.94 (dd, *J* = 7.7, 14.5 Hz, 1 H, TMSCH_aH$_b$), 1.17 (dd, *J* = 6.8, 14.5 Hz, 1 H, TMSCH$_a$$H_b$), 1.34 [s, 3 H, C(Me)C$H_3$], 1.40 (ddd, *J* = 11.4, 11.5, 13.4 Hz, 1 H, 4-H_a), 1.53 [s, 3 H, C(Me)CH_3], 2.31 (ddd, *J* = 2.0, 4.6, 13.5 Hz, 1 H, 4-H_b), 3.46 (dd, *J* = 2.3, 13.3 Hz, 1 H, 7-H_a), 3.51 (ddd, *J* = 5.1, 6.4, 11.5 Hz, 1 H, 4a-H), 4.18 (dd, *J* = 6.4, 13.2 Hz, 1 H, 7-H_b), 4.24 (dd, *J* = 6.3, 6.3 Hz, 1 H, 5-H), 4.36 (dddd, *J* = 1.9, 6.8, 7.0, 12.8 Hz, 1 H, 3-H), 4.75 (ddd, *J* = 2.5, 6.3, 6.3 Hz, 1 H, 6-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = –0.9 [3 × CH_3, Si(CH_3)$_3$], 24.4 (CH_2, TMSCH_2), 25.5 [CH_3, C(Me)*C*H_3], 27.7 [CH_3, C(Me)*C*H_3], 34.7 (CH_2, C-4), 50.3 (CH_2, C-7), 60.9 (CH, C-4a), 76.0 (CH, C-3), 77.6 (CH, C-6), 84.4 (CH, C-5), 113.8 [C, *C*(Me)$_2$], 152.2 (C, C-1) ppm. MS (EI, 70 eV): *m*/*z* (%) = 299 (1) $[M]^+$, 284 (31) $[M - Me]^+$, 258 (46) $[M + H - CMe_2]^+$, 214 (65) $[M + H - CMe_2 - CO_2]^+$, 142 (37) $[M - CO_2 - TMSCH_2 - CH{=}CH_2]^+$, 73 (100) [TMS]. HRMS (EI, 70 eV): calcd. for $C_{14}H_{25}NO_4Si$ 299.1552; found 299.1577; calcd. for C_3H_9Si 73.0473; found 73.0459. $C_{14}H_{25}NO_4Si$ (299.44): calcd. C 56.16, H 8.42, N 4.68; found C 56.08, H 8.77, N 4.68. Compound **38**: Oil. $[\alpha]_D$ = +8 (*c* 0.17, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 1683, 1441 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.09 [s, 9 H, Si(CH_3)$_3$], 0.88 (dd, *J* = 7.0, 14.5 Hz, 1 H, TMSCH_aH$_b$), 1.21 (dd, *J* = 8.8, 14.6 Hz, 1 H, TMSCH$_a$$H_b$), 1.36 [s, 3 H, C(Me)C$H_3$], 1.55 [s, 3 H, C(Me)C$H_3$], 1.81 (ddd, *J* = 4.7, 11.2, 13.4 Hz, 1 H, 4-H_a), 2.15 (ddd, *J* = 2.2, 4.9, 13.5 Hz, 1 H, 4-H_b), 3.49 (dd, *J* = 2.2, 13.2 Hz, 1 H, 7-H_a), 3.58 (ddd, *J* = 5.5, 5.7, 11.0 Hz, 1 H, 4a-H), 4.21 (dd, *J* = 6.4, 13.3 Hz, 1 H, 7-H_b), 4.28 (dd, *J* = 6.4, 6.4 Hz, 1 H, 5-H), 4.61 (m, 1 H, 3-H), 4.75 (ddd, *J* = 2.3, 6.2, 6.2 Hz, 1 H, 6-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = –1.1 [3 × CH_3, Si(CH_3)$_3$], 22.5 (CH_2, TMSCH_2), 25.5 [CH_3, C(Me)*C*H_3], 27.7 [CH_3, C(Me)*C*H_3], 31.8 (CH_2, C-4), 50.4 (CH_2, C-7), 57.1 (CH, C-4a), 74.8 (CH, C-3), 77.4 (CH, C-6), 84.6 (CH, C-5), 113.9 [C, *C*(Me)$_2$], 151.6 (C, C-1) ppm. MS (EI, 70 eV): *m*/*z* (%) = 284 (16) $[M - Me]^+$, 258 (26) $[M + H - CMe_2]^+$, 214 (41) $[M + H - CMe_2 - CO_2]^+$, 142 (49) $[M - CO_2 - TMSCH_2CH{=}CH_2]^+$, 73 (100) [TMS]. HRMS (EI, 70 eV): calcd. for $C_{13}H_{22}NO_4Si$ 284.1318; found 284.1297; calcd. for C_3H_9Si 73.0474; found 73.0471. $C_{14}H_{25}NO_4Si$ (299.44): calcd. C 56.16, H 8.42, N 4.68; found: C 56.11, H 8.48, N 4.77.

Tandem Fragmentation–Alkylation of Compound 31: The reaction was carried out according to the standard procedure to afford *tert*-butyl (2*R*,3*R*,4*S*)-2-(2-oxo-2-phenylethyl)-3,4-*O*-isopropylidene-1-pyrrolidinecarboxylate (**39**) (64%, 99% *de*). Two rotamers at 26 °C (1:1), one rotamer at 70 °C. Colorless crystals. M.p. 103.5–105.5 °C (from EtOAc/*n*-pentane). $[\alpha]_D$ = –16 (*c* 0.24, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 1686, 1597, 1406 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, 26 °C): δ = 1.30 [s, 3 H, C(Me)CH_3], 1.41/1.42 [s/s, 9 H, OC(CH_3)$_3$], 1.45 [s, 3 H, C(Me)CH_3], 3.18 (m, 1 H, CH_aH$_b$COPh), 3.29/3.44 (dd, *J* = 3.4, 16.6 Hz/dd, *J* = 7.3, 16.9 Hz, 1 H, CH$_a$$H_b$COPh), 3.45/3.50 (dd, *J* = 5.2, 12.9 Hz/dd, *J* = 5.2, 12.6 Hz, 1 H, 5-H_a), 3.71/3.91 (d, *J* = 12.6 Hz/d, *J* = 12.9 Hz, 1 H, 5-H_b), 4.43 (m, 1 H, 2-H), 4.61/

4.70 (d, J = 5.9 Hz/d, J = 6.0 Hz, 1 H, 3-H), 4.82/4.87 (dd, J = 5.4, 5.4 Hz/dd, J = 5.5, 5.4 Hz, 1 H, 4-H), 7.44/7.46 (dd, J = 7.6, 7.7 Hz/dd, J = 7.6, 7.6 Hz, 2 H, arom.), 7.55/7.57 (dd, J = 5.6, 7.4 Hz/dd, J = 6.6, 7.4 Hz, 1 H, arom.), 7.94/7.96 (d, J = 7.0 Hz/d, J = 7.2 Hz, 2 H, arom.) ppm. ^{1}H NMR (500 MHz, $CDCl_3$, 70 °C): δ = 1.30 [s, 3 H, C(Me)CH_3], 1.42 [s, 9 H, OC(CH_3)$_3$], 1.44 [s, 3 H, C(Me)-CH_3], 3.21 (m, 1 H, CH_aH$_b$COPh), 3.35 (m, 1 H, 5-H$_a$), 3.46 (m, 1 H, CH$_a$$H_b$COPh), 3.78 (m, 1 H, 5-H$_b$), 4.43 (dd, J = 5.7, 6.1 Hz, 1 H, 2-H), 4.68 (m, 1 H, 3-H), 4.83 (dd, J = 5.3, 5.3 Hz, 1 H, 4-H), 7.44 (dd, J = 7.8, 7.7 Hz, 2 H, arom.), 7.54 (dd, J = 7.4, 7.4 Hz, 1 H, arom.), 7.95 (d, J = 7.6 Hz, 2 H, arom.) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 26 °C): δ = 24.8 [CH_3, C(Me)CH_3], 26.9 [CH_3, C(Me)CH_3], 28.3 [3 × CH_3, OC(CH_3)$_3$], 39.4/40.1 (CH_2, C-1′), 51.7/52.8 (CH_2, C-5), 60.9 (CH, C-2), 78.8/79.6 (CH, C-4), 79.8/80.1 [C, OC(Me)$_3$], 83.9/84.7 (CH, C-3), 111.6 [C, C(Me)$_2$], 128.2 (2 × CH, arom.), 128.6/128.7 (2 × CH, arom.), 133.3/133.5 (CH, arom.), 136.6 (C, arom.), 153.8/154.1 [C, C(O)N], 197.6/198.6 (C, CO) ppm. MS (EI, 70 eV): m/z (%) = 361 (3) [M]$^+$, 288 (8) [M – OCMe$_3$]$^+$, 261 (10) [M – CO$_2$CMe$_3$]$^+$, 186 (100) [M – CH$_2$COPh – CMe$_3$]$^+$, 105 (64) [COPh], 57 (79) [CMe$_3$]. HRMS (EI, 70 eV): calcd. for $C_{20}H_{27}NO_5$ 361.1889; found 361.1914; calcd. for $C_8H_{12}NO_4$ 186.0766; found 186.0771. $C_{20}H_{27}NO_5$ (361.44): calcd. C 66.46, H 7.53, N 3.88; found C 66.26, H 7.92, N 3.67.

Supporting Information (see footnote on the first page of this article): The synthesis of substrates **4**–**6**, **15**, **31**, **33**–**35**, and **40**–**42**, and the spectroscopic data for the new or partially described products (**4**, **6**, **15**, **31**, **33**–**35**, and **42**). The ^{1}H- and ^{13}C NMR spectra for fragmentation substrate **31** and its precursors **33**–**35** and **42**. The ^{1}H- and ^{13}C NMR spectra for the following fragmentation products or compounds derived therefrom: products **21**–**23**, **25**, **29**/**30**, and **36**–**39**. This material is available on the WWW under http://www.eurjoc.org or from the author.

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[38] The assigned stereochemistries were supported by NOESY experiments. Compound **40**: Spatial correlations were observed for 2-H (δ_H 4.10)/Me_b (δ_H 1.46), and for 3-H (δ_H 4.45)/Me_a (δ_H 1.30)/4-H (δ_H 4.66); Compound **41**: Spatial correlations were observed for: 3-H (δ_H 4.36)/4a-H (δ_H 3.51) and 4-H_a (δ_H 1.40)/5-H (δ_H 4.24); Compound **42**: Spatial correlations were observed for: CH_2TMS (δ_H 1.21 and 0.88)/4a-H (δ_H 3.58), for 4a-H (δ_H 3.58)/Me_b (δ_H 1.55), and for 6-H (δ_H 4.75)/Me_a (δ_H 1.36) [δ_H in ppm].
[39] The assigned stereochemistry for compound **43** was also supported by NOESY experiments. Spatial correlations were observed for 2-H (δ_H 4.43) and Me_b (δ_H 1.45), for C$H_a$$H_b$COPh ($\delta_H$ 3.18)/3-H (δ_H 4.70), for 3-H (δ_H 4.70)/Me_a (δ_H 1.30)/4-H (δ_H 4.82), and for 4-H (δ_H 4.82)/CH_aH_bCOPh (δ_H 3.44) [δ_H in ppm].
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