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New Highly Strained Multifunctional Heterocycles by Intramolecular Cycloadditions of Nitrones to Bicyclopropylidene Moieties[‡]

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Intramolecular cycloadditions of various nitrone functionalities with different substituents (R = Me, Bn, *t*Bu) at the nitrogen atom tethered to a bicyclopropylidene unit through a two-carbon chain led to *cis*-fused tricyclic isoxazolidines (3-alkyl-3,3a,4,5,5a,6-hexahydrocyclopropa[2,3]cyclopenta[1,2-*c*]isoxazolespiro[1,1′]cyclopropanes) **26** in 42–58 % yield with complete regio- and diastereoselectivity. The thermal rearrangement of the cycloadducts **26** under neutral conditions afforded the corresponding tricyclic tetrahydropyridones **27** (52–53 %). The analogous starting materials with a three-carbon tether, the 4-(bicyclopropyliden-2-yl)butylidenenitrones furnished tricyclic isoxazolidines **28** (54–58 %) and tetrahydropyridones **29** (55–64 %) by subsequent thermal rearrangement. Under acidic conditions (TFA), the cycloadducts **26** and **28** underwent fragmentative rearrangements to afford the tricyclic β-lactams **30** and **32** (50–66 %), respectively, of which the former suffered amide-bond cleavage in situ to provide the corresponding *N*-trifluoroacetyl β-amino acid derivatives **31** (68–71 %).

Introduction

The use of alkylidenecyclopropanes **1** for the synthesis of heterocyclic compounds has widely spread out in recent years mainly because of their unique reactivity due to their high strain and high-lying HOMOs.[1] Because a wide variety of alkylidenecyclopropanes is also easily accessible by various methods,[2] their selective synthetic transformations in domino-type sequential reactions without the use of catalysts and added reagents have become quite popular.[3]

Many syntheses of nitrogen heterocycles by [3+2] dipolar cycloadditions of nitrones[4] to methylenecyclopropane **1** (R^1, R^2 = H) and other alkylidenecyclopropanes **1** (R^1, $R^2 \neq$ H) have been reported.[1] In particular, the intermolecular cycloadditions of nitrones to **1** afford 5- and 4-spirocyclopropane-isoxazolidines **3** and **5**, respectively, with regio- and stereoselectivities varying from moderate to high, depending on the substituents and substitution pattern on the alkene. The facile cleavage of the N–O bond and, specifically, the possibility of transforming the 5-spirocyclopropane-isoxazolidines **3** (isoxazolidine numbering) into tetrahydropyridin-4-ones **7**[5] by thermal rearrangement or into β-lactams **8**[6] by acid-catalyzed fragmentative rearrangement has led to a growing interest in the cycloadditions of methylenecyclopropane **1** (R^1, R^2 = H) and its analogs **1** (R^1, $R^2 \neq$ H) (Scheme 1).

So far, however, only a limited number of intramolecular cycloadditions of cyclopropylidenealkyl-substituted nitrones has been reported in the literature, and all of them concern the methylenecyclopropane derivatives **1**.[6a–b,7] Furthermore, the chain connecting the nitrone functionality and the methylenecyclopropane moiety was always linked through the exomethylene carbon as in **10** (Scheme 2), and no systematic studies have been published for systems in which the chain is connected to the cyclopropane ring as in **13**.[8]

For this purpose, bicyclopropylidene derivatives **14** [R^1–R^2 = $(CH_2)_2$] would be more interesting than methylenecyclopropyl-tethered nitrones **13**, because the latter would yield tricyclic isoxazolidines in which the cyclopropyl group would not be in an appropriate position to participate in any of the interesting transformations depicted in Scheme

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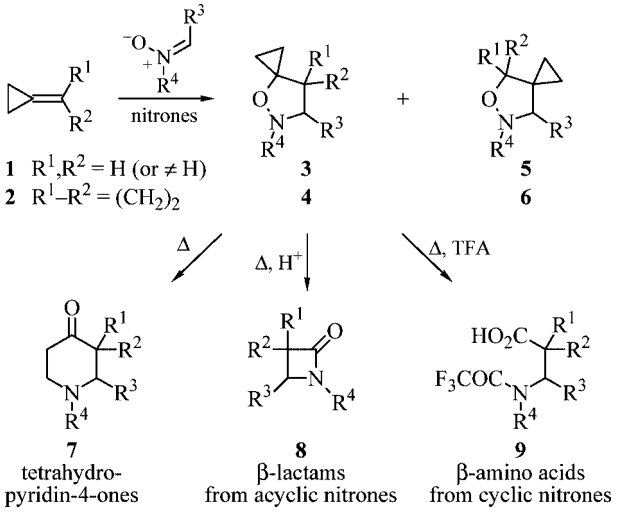
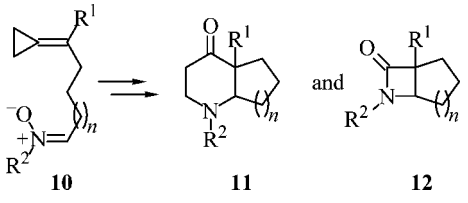
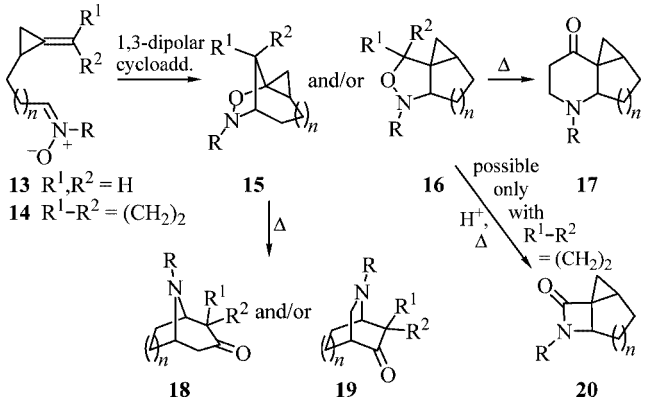


Scheme 1. Known reactivities of alkylidenecyclopropanes **1**, **2** in intermolecular 1,3-dipolar cycloadditions with nitrones and elaboration of adducts by thermal rearrangement and acid-catalyzed fragmentative rearrangement.



Scheme 2. Intramolecular 1,3-dipolar cycloadditions of alkylidenecyclopropyl-substituted nitrones **10**.

1. Compounds with a nitrone functionality tethered to a bicyclopropylidene moiety as **14** might have two ways of undergoing an intramolecular cycloaddition leading to 1,3- or 1,2-annelated tricyclic isoxazolidines **15** and/or **16**, respectively. Both would be prone to undergo thermal or acid-catalyzed fragmentative rearrangements (Scheme 3; for mechanistic aspects, see ref.[5,6] and references cited therein) because they would both contain a spiro- as well as a 1,2-annelated cyclopropane ring, one of which in each of them would necessarily be adjacent to the labile N–O bond.

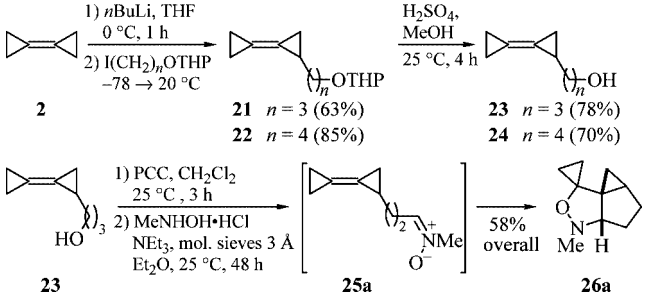


Scheme 3. Possible intramolecular adducts of (bicyclopropylidenyl)alkyl-substituted nitrones **14** and their subsequent thermal or acid-catalyzed fragmentative rearrangements.

Results and Discussion

Because 3-(bicyclopropyliden-2-yl)propan-1-ol **23** and 4-(bicyclopropyliden-2-yl)butan-1-ol **24** are easily accessible by electrophilic substitution of lithiobicyclopropylidene[9–11] with the corresponding ω-iodoalkyl tetrahydropyranyl ethers and acid-catalyzed deprotection,[12] their oxidation to the corresponding aldehydes and further transformations to nitrones should not cause any problem.

Oxidation of **23** was carried with pyridinium chlorochromate (PCC, the use of other oxidizing agents such as TPAP/NMO did not improve the yield), and the aldehyde was not isolated, but directly added to a mixture of *N*-methylhydroxylamine hydrochloride (1.2 equiv.), triethylamine (1.2 equiv.) and molecular sieves (3 Å) in order to generate the desired nitrone **25a**. This, without being isolated, underwent the intramolecular cycloaddition at 25 °C within 48 h to afford, after column chromatography, only the spirocyclopropanated tricyclic isoxazolidine **26a** (for the structural assignment, see below) in 58% overall yield from the alcohol **23** (Scheme 4). The diagnostic signal of the intermediate nitrone **25a** (triplet around δ = 6.70 ppm in the ^{1}H NMR spectrum) was used to monitor the progress of the intramolecular cycloaddition. No signals of other isomers were detected in the ^{1}H NMR spectrum of the crude product, and a careful analysis of the other chromatography fractions also did not disclose the presence of any minor isomer.



Scheme 4. (Bicyclopropyliden-2-yl)alkanols **23** and **24** from bicyclopropylidene (**2**) and transformation of **23** to the nitrone **25a** with subsequent intramolecular cycloaddition to yield **26a**.

It is known that intramolecular cycloadditions of 5-alkenyl-substituted nitrones lead exclusively to *cis*-oxazabicyclo[3.3.0]octanes.[6a,6b,7b–7e,13] The regioselectivity of the cycloaddition, i.e. the exclusive formation of the fused (type **16**) and none of the bridged cycloadduct (type **15**), is also noteworthy. In one case of a 5-cyclopropylidenehexylidene nitrone **10** (n = 1, R^1 = Me, Scheme 2), the 1,3-annelated isomer was found as a minor product;[7a] thus, the reduced flexibility inferred by the additional three-membered ring of the bicyclopropylidene unit – indeed, this additional ring is part of the tether – causes the observed regioselectivity (Figure 1).

According to DFT calculations at the B3LYP/6-31G* level of theory,[14] the *N*-methyl-substituted 1,2-annelated cycloadduct *cis*-**26a** is 11.0 kcal/mol more stable than the *trans* isomer *trans*-**26a** and 23.9 kcal/mol more stable than

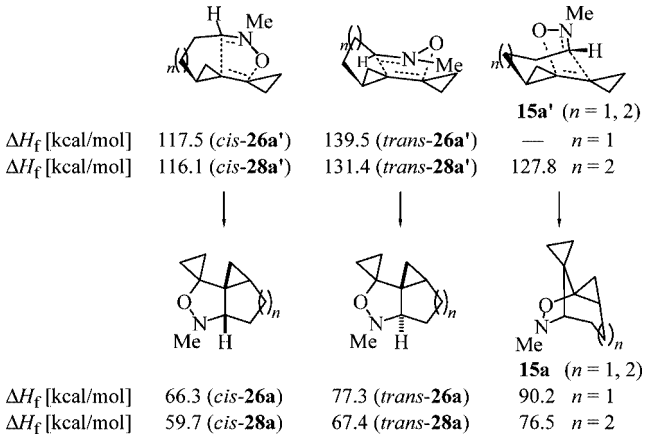


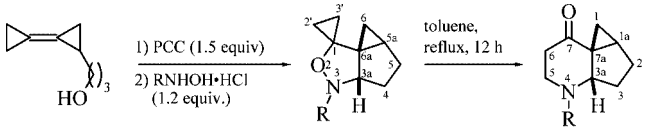
Figure 1. Three conceivable transition structures for the intramolecular 1,3-dipolar cycloadditions of 3-(bicyclopropylidenyl)propylidenenitrones **25a** and calculated (B2LYP/6-31G*) enthalpies of formation.

the 1,3-annelated isomer **15a** (n = 1). Such cycloadditions ought to have product-like transition states, which was confirmed by locating the transition states [except **15a′** (n = 1), see supporting information for structural representations of all calculated compounds and transition states; for supp. inf. see also the footnote on the first page of this article]. Although the transition state **15a′** in the n = 1 series could not be located, taking the results for the n = 2 series into account it is safe to conclude that the *trans*-transition states and the ones leading to the 1,3-annelated products have higher energies than the *cis*-transition states, as already indicated by the significant differences of the enthalpies of formations for the corresponding products (Figure 1). The calculated dihedral angles between the bridgehead proton 3a-H and those of the adjacent methylene group are 29° and 91° for the *cis* isomer *cis*-**26a** as well as 43° and 164° for the *trans* isomer *trans*-**26a**. Accordingly, one should expect to find a doublet with a medium-size coupling constant in the former case (as one angle is nearly 90° and the corresponding coupling constant should be close to zero) and a doublet of doublets (or a triplet) with medium to large J values (according to the dihedral angles of 43° and 164°) in the latter case. Experimentally, a doublet with J = 5.6 Hz is found for proton 3a-H, thus confirming the expected[6a,6b,7b–7e,13] formation of the *cis*-fused isomer *cis*-**26a**.[15]

With other *N*-substituted hydroxylamines (R = Bn, *t*Bu) used in the condensation step, the intramolecular cycloadditions required increased reaction temperatures. While the transformation of the *N*-methylnitrone went to completion in diethyl ether at 25 °C within 48 h, the *N*-benzyl derivative required 36 h in refluxing diethyl ether and the *tert*-butylnitrones 14 h at 65 °C in toluene. Evidently, the size of the N-substituent influences the rate of the cycloaddition (Table 1).

In the case of **26b**, formation of some (*Z*)-benzaldoxime was noted, and this was due to some residual oxidizing agent which reacted with the *N*-benzylhydroxylamine, as an independent experiment confirmed.[16] For this reason, the reaction was also carried out with 1.5 equiv. of *N*-benzylhydroxylamine which improved the yield from 46 to 52%. In the case of **26c** with a *tert*-butyl substituent on the nitrogen, two isomeric cycloadducts were formed in a ratio of 88:12. The relative configuration of the major isomer was confirmed by analogy of its NMR spectra with those of the products **26a**,**b**, and it was rigorously established by an X-ray crystal structure analysis (Figure 2).[17] Whereas the major isomer could be isolated in pure form by chromatography (14% yield), the minor isomer was only obtained as a 1:4.6 mixture (28% yield) with the major one. Therefore, it was not possible to definitely establish whether the minor isomer was the *trans*-fused diastereomer *trans*-**26c** or the bridged isomer of type **15** (n = 2), even though the ^{13}C NMR resonance of the quaternary carbon in the α-position to the oxygen atom (δ =60.2 ppm) better fits the assignment of *trans*-**26c**, because a higher field value would be expected for the bridged system.[7a]

Table 1. Intramolecular 1,3-dipolar cycloadditions of (bicyclopropylidenyl)alkylidenenitrones and thermal rearrangements of the initial products.



23 **26a–c** **27a–c**

R	Reaction conditions[a]	Main adduct	Selectivity [b] Yield [%][c]	Product	Yield [%]	One-pot yield [%][d]
Me	Et_2O, 25 °C, 48 h	**26a**	>95:5 58	**27a**	53	46 (31)
Bn[e]	Et_2O, reflux, 36 h	**26b**	>95:5 52	**27b**	52	24 (27)
*t*Bu	toluene, 65 °C, 14 h	**26c**	88:12 37	**27c**	52	– (19)

[a] Yields for the cycloaddition step. [b] Formation of the *cis*-fused isomer towards the *trans*-fused or the bridged isomers. [c] Based on the alcohol **23**. [d] Yields for the one-pot process, run under the reaction conditions used for the rearrangement step (overall yields in parenthesis as calculated for two steps). [e] 1.5 equiv. of BnNHOH·HCl and NEt_3 were used.

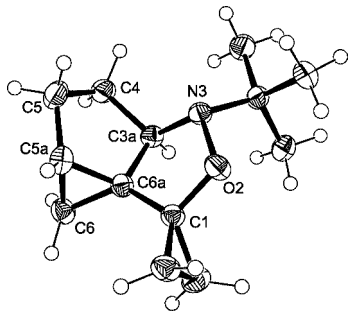


Figure 2. Structure of (3a*R**,5a*S**,6a*S**)-3-*tert*-butyl-3,3a,4,5,5a,6-hexahydrocyclopropa[2,3]cyclopenta[1,2-*c*]isoxazolespiro[1,1′]-cyclopropane (**26c**) in the crystal.[17]

The spirocyclopropanated tricyclic isoxazolidines **26** all underwent the well-known thermal rearrangement with N–O bond cleavage and adjacent cyclopropane ring opening upon heating in refluxing toluene within 12 h to yield the tricyclic piperidinones **27a**–**c** (Table 1). The overall transformation of the alcohol **23** to the piperidinones **27a**–**c** can even be brought about in a one-pot operation. In the case of **27a** (R = Me), the overall yield was thus improved from 31 (for the two step version) to 46%, but in the case of **27b** (R = Bn) the two-step process appears to be slightly better (27 vs. 24%).

The presence of two signals around 40–50 ppm in the ^{13}C NMR spectrum, which correlate with the methylene protons resonating above 2 ppm in the ^{1}H NMR spectrum (g-HSQC), fits well for an N–(CH_2)–(CH_2)–CO sequence, and it is not compatible with the rearrangement products to be expected from bridged cycloadducts of type **15** (Scheme 3). This isolated spin system was enlightened by g-COSY- and g-HMBC NMR experiments. Furthermore, the absence of the typical signals due to the four methylene protons of a spirocyclopropane ring and the presence of the signals of both a cyclopropyl methine and a methylene group clearly indicate that the products are the tricyclic tetrahydropyridones **27a**–**c**.

Analogous results were obtained with the homologous 4-(bicyclopropylidenyl)butylidenenitrones prepared from the 4-(bicyclopropylidenyl)butan-1-ol (**24**). Under the same conditions as used for the preparation of **26a** (ether, 25 °C) or **26b** (refluxing ether), complete conversion to the desired isoxazolidines **28a**,**b** (R = Me, Bn) took far too long, but when the reactions were performed in toluene at 70 °C, the desired products **28a**,**b** could be isolated in good yields (58 and 54%, respectively) after 8 h (Table 2). The rearrangements to the tricyclic piperidinones **29a**,**b** also required higher temperatures and were achieved only by heating in *o*-xylene at 130 °C for 36 h. Prolonged heating in toluene under reflux led only to partial conversion of the isoxazolidines **28a**,**b**, while heating in *o*-xylene under reflux led to complex product mixtures, probably due to partial decomposition of the initial products.

The stereochemical characterization of the tricyclic isoxazolidines **28** was more complicated than that of compounds **26** derived from the lower homologues **25**. As can be inferred from the literature,[13] the substituent R^1 (Scheme 2) plays a critical role in the regiochemical outcome of the cycloaddition reaction. According to DFT calculations at the B3LYP/6-31G* level of theory,[14] the transition state leading to the *cis*-fused *N*-methyl-substituted tricycle would be by 15.3 kcal/mol more favorable than the one leading to the *trans* isomer *trans*-**28a** and still by 11.7 kcal/mol more favorable than the one leading to the 1,3-annelated isomer **15** (*n* = 2) (Figure 1). Indeed, a 2D-NOESY-NMR experiment with compound **28a** clearly identified it as the *cis*-fused isomer.[18] The bridged isomer could be excluded on the basis of the NOE between proton 6a-H and two protons of the spirocyclopropane moiety (Figure 3, left). The spatial proximity of the bridgehead proton 3a-H with one of the cyclopropylmethylene protons 7-H (belonging to the fused cyclopropane moiety) confirms these assignments (Figure 3, right). The assignment of the relative configuration of compound **28b** was based on analogy.

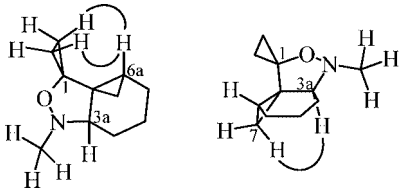
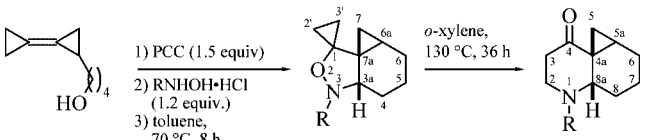


Figure 3. Significant NOEs observed in a 2D-NOESY NMR experiment with the spirocyclopropanated tricyclic isoxazolidine **28a**.

Table 2. Preparation of spirocyclopropanated tricyclic isoxazolidines **28** and tetrahydropyridones **29**.



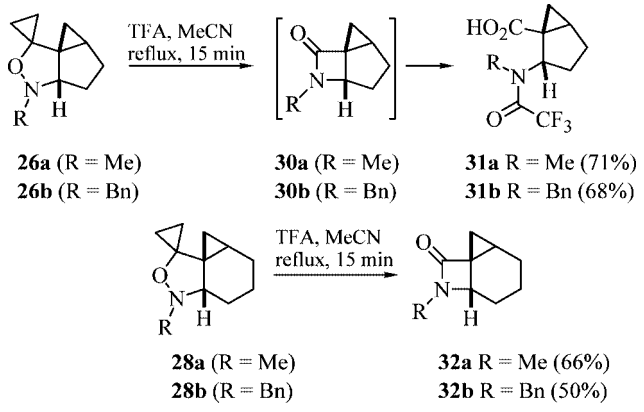
24 **28a**,**b** **29a**,**b**

R	Main adduct	Yield [%][a]	Selectivity[b]	Product	Yield [%][a]
Me	**28a**	58	>95:5	**29a**	55
Bn	**28b**	54[c]	>95:5	**29b**	54

[a] Isolated yield after column chromatography. [b] Formation of the *cis*-fused isomer towards the *trans*-fused and the bridged isomers. [c] 1.5 Equiv. of BnNHOH·HCl and NEt_3 were used.

These results are in accordance with a previous example of an intramolecular cycloaddition of a cyclopropylidenealkyl-substituted nitrone in which two neighboring carbon atoms in the tether are part of a benzene ring and, just like the cyclopropane of the bicyclopropylidene moiety in the current cases create enough rigidity to induce the selectivity for this *cis* junction.[6b]

To further demonstrate the versatility of the cycloadducts **26a**,**b** and **28a**,**b**, they were treated with trifluoroacetic acid (TFA) in refluxing acetonitrile.[6e] Within 15 min the tricyclic cycloadducts **26a**,**b** afforded the *N*-trifluoroacetylated β-amino acids **31a**,**b** in good yields (71 and 68%, respectively). The initially formed β-lactams **30** (Scheme 5) are probably too highly strained and immediately undergo acid-catalyzed ring opening, as it had previously been observed for carbapenam-like systems.[6c,19] The structures of compounds **31a**,**b** were assigned on the basis of the spectroscopic data (see Exp. Sect.). The products were isolated as colorless solids, but in $CDCl_3$ solution they occurred as a 1:1.6 (**31a**) and a 1:1 (**31b**) mixture of rotamers due to the restricted rotation around the amide bond (variable temperature experiments in [D_6]DMSO did not succeed to provide a single set of signals for the molecules). Stoodley et al. noticed analogous phenomena with similar substrates.[19] The acid-catalyzed fragmentative rearrangement of 1-spirocyclopropane-isoxazolidines has been proved to occur without affecting the stereogenic centers of the molecule (for a mechanistic interpretation of this rearrangement, see ref.[6a–6c]), so that the formation of diastereoisomers in the current cases can be excluded.



Scheme 5. Acid-catalyzed fragmentative rearrangement of spirocyclopropanated tricyclic isoxazolidines **26** and **28**.

Under the same conditions, the spirocyclopropanated tricyclic isoxazolidines **28a**,**b** furnished the β-lactams **32a**,**b** in 66 and 50% yield, respectively (Scheme 5). The formation of these products confirms the relative configuration of the starting materials **28a**,**b** as being *cis* configured with respect to the junction between the five- and six-membered rings of these compounds, because *trans*-fused bicyclic isoxazolidines of this type would not afford, for reasons of strain, the corresponding β-lactams upon heating in the presence of TFA.[6b]

Conclusions

Unprecedented intramolecular 1,3-dipolar cycloadditions of nitrones tethered to bicyclopropylidene by a three- or a four-carbon chain provide facile accesses to spirocyclopropanated tricyclic *cis*-fused isoxazolidines which, by thermal rearrangement or acid-catalyzed fragmentative rearrangement yield interesting tricyclic tetrahydropyridones and β-lactams, respectively. The cyclopropane moiety annelated in the α-position of the piperidinone ring of compounds **27a**,**c** and **29a**,**b** makes these molecules very interesting with respect to their potential biological activities. To a certain extent, the ring-annelated azaspiro[2.5]octan-4-one moieties of these new heterooligocycles resemble the toxophoric subunits in the potent antitumor agents CC-1065 as well duocarmycins and analogs.[20,21] The important biological activities of β-lactams[22] and other derivatives of β-amino acids containing cyclopropyl groups[23] also enhances the value of these new intramolecular 1,3-dipolar cycloadditions involving bicyclopropylidene units.

Experimental Section

General Remarks: For the numbering of the reported heterocycles **26**, **27**, **28** and **29** see Table 1 and Table 2. NMR spectra were recorded with Varian Mercury 200 (200 MHz for ^{1}H and 50.3 MHz for ^{13}C NMR), Varian Mercury 300 (300 MHz for ^{1}H and 75.5 MHz for ^{13}C NMR) or INOVA 600 (600 MHz for ^{1}H NMR) instruments for $CDCl_3$ solutions at room temperature unless otherwise specified. Multiplicities of ^{13}C NMR signals were determined by g-HSQC (Heteronuclear Single Quantum Coherence) measurements. The chemical shifts (δ) for ^{1}H and ^{13}C NMR spectra are given in ppm from TMS (δ_{TMS} = 0.00 ppm) using the signals of residual $CHCl_3$ (δ = 7.26 ppm) and $CDCl_3$ (δ = 77.0 ppm) as internal standards. Coupling constants (J) are given in Hertz. Melting points: Büchi 510 capillary melting point apparatus, uncorrected values. IR: Bruker IFS 66 (FT-IR) spectrophotometer, measured for KBr pellets or oils between NaCl plates; the intensities of signals are described as strong (s), medium (m) or weak (w). Flash column chromatography: Merck silica gel, grade 60, 0.040–0.063 mm. TLC: Macherey–Nagel precoated sheets, 0.25 mm Sil G/UV_{254}; R_f values refer to the same eluent used for the chromatographic purifications, unless otherwise specified. Elemental analyses: Mikroanalytisches Laboratorium des Instituts für Organische und Biomolekulare Chemie, Universität Göttingen. MS (EI at 70 eV or DCI with NH_3): Finnigan MAT 95 spectrometer. MS (ESI): Finnigan LCQ. MS (HR-ESI): APEX IV 7T FTICR, Bruker Daltonic spectrometer.

Starting Materials: Bicyclopropylidene (**2**) was prepared in three steps starting from methyl cyclopropanecarboxylate according to the published procedure.[24] The alcohols **23** and **24** were prepared from **2** as described previously,[9] with a full characterization of **23** being reported here for the first time. All reactions requiring anhydrous conditions were carried out under nitrogen in flame-dried glassware, and solvents were appropriately dried before use. Anhydrous tetrahydrofuran (THF) and diethyl ether were obtained by distillation from sodium benzophenone ketyl, dichloromethane (CH_2Cl_2) and acetonitrile from P_2O_5 and triethylamine (NEt_3) from potassium hydroxide. All other chemicals were used as commercially available.

The purification of the isoxazolidines **26** and **28** and the tetrahydropyridones **27**, synthesized in a one-pot fashion from the corresponding alcohol **23**, was achieved by flash column chromatography using at first pure dichloromethane as eluent in order to eliminate the non-polar impurities, then the products were obtained increasing the polarity with methanol up to the eluent specified in each case.

Abbreviations: FCC = flash column chromatography; PCC = pyridinium chlorochromate; TFA = trifluoroacetic acid.

3-(1,1′-Bicyclopropyliden-2-yl)propan-1-ol (23): A few drops of concd. sulfuric acid were added to a methanol (100 mL) solution of the THP-protected alcohol **21** (4.28 g, 19.25 mmol), prepared as reported in the literature.[9] The solution was stirred at 25 °C for 4 h, and then a saturated solution of $NaHCO_3$ (10 mL) was added. The aqueous layer was extracted with Et_2O (4 × 60 mL), and the combined organic phases were dried with $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by FCC (72 g of silica gel, 4 × 18 cm column) eluting with diethyl ether/pentane, 4:5, R_f = 0.32. The desired alcohol **23** (2.07 g, 14.99 mmol, 78%) was obtained as a colorless oil. ^{1}H NMR (300 MHz): δ = 3.70 (t, J = 6.9 Hz, 2 H, 1-H), 1.75–1.64 (m, 2 H, 2-H), 1.58 (dt, J = 13.0, 6.9 Hz, 1 H, 3-H), 1.52–1.44 (m, 2 H, cPr-H and OH), 1.37–1.26 (m, 2 H, cPr-H and 3-H), 1.17–1.12 (m, 4 H, cPr-H), 0.87–0.79 (m, 1 H, cPr-H) ppm. ^{13}C NMR (75.5 MHz): δ = 115.8 (s, 1 C, cPr-C), 109.8 (s, 1 C, cPr-C), 62.6 (t, 1 C, C-1), 32.5 (t, 1 C, C-2), 29.4 (d, 1 C, C-3), 15.6 (d, 1 C, cPr-C), 9.6 (t, 1 C, cPr-C), 2.9 (t, 1 C, cPr-C), 2.7 (t, 1 C, cPr-C) ppm. IR (neat): $\tilde{\nu}$ = 3334 cm^{-1} (s), 3050 (w), 2978 (m), 2934 (m), 2860 (w) and 1060 (s) cm^{-1}. MS (DCI): m/z (rel. int.) = 156 (40) [M + NH_4^+], 139 (100) [M + H^+], 121 (38), 119 (16), 102 (6). $C_9H_{14}O$ (138.21): calcd. C 78.21, H 10.21; found C 78.09, H 9.96.

General Procedure for the Synthesis of Isoxazolidines 26 Starting from the Alcohol 23 (GP 1): A 0.5 M solution of the alcohol **23** (1 equiv.) in anhydrous dichloromethane was added at 25 °C under nitrogen to a suspension of PCC (1.5 equiv.) in anhydrous dichloromethane (1 mL for each mmol of PCC). The mixture was stirred at 25 °C for 3 h, and then diethyl ether (2 mL/mmol) was added. The mixture containing the desired aldehyde was filtered through celite, the dark filter cake was washed with diethyl ether (10 mL/mmol), into a flask containing activated molecular sieves (3 Å) (800 mg/mmol), the respective *N*-substituted hydroxylamine hydrochloride (1.2 equiv.) and triethylamine (1.2 equiv.) in diethyl ether (4.5 mL/mmol) were added. The resulting mixture was stirred (temperature and time are indicated for each case), then filtered through celite and finally the solvents were evaporated. The crude products were purified by FCC.

(3a*R,5a*S**,6a*S**)-3,3a,4,5,5a,6-Hexahydro-3-methylcyclopropa[2,3]cyclopenta[1,2-*c*]isoxazolespiro[1,1′]cyclopropane (26a):** FCC (29 g of silica gel, 3 × 12 cm column) eluting with dichloromethane/methanol, 100:1, of the crude product obtained from alcohol **23** (300 mg, 2.17 mmol) and *N*-methylhydroxylamine hydrochloride (217 mg, 2.60 mmol) according to GP1 (25 °C, 48 h) afforded **26a** (207 mg, 1.25 mmol, 58%) as a colorless oil, R_f = 0.27. ^{1}H NMR (300 MHz): δ = 3.11 (bd, J = 5.6 Hz, 1 H, 3a-H), 2.71 (s, 3 H, NCH_3), 2.26–2.13 (m, 1 H, 5-H^a), 1.78 (bdd, J = 14.3, 9.3 Hz, 1 H, 4-H^a), 1.69 (ddd, J = 10.0, 8.7, 1.9 Hz, 1 H, 5-H^b), 1.51–1.39 (m, 1 H, 4-H^b), 1.18 (dt, J = 8.1, 5.0 Hz, 1 H, 5a-H), 0.97–0.82 (m, 2 H, cPr-H), 0.57–0.43 (m, 3 H, cPr-H and 6-H), 0.22–0.14 (m, 1 H, cPr-H) ppm. ^{13}C NMR (75.5 MHz): δ = 76.3 (d, 1 C, C-3a), 64.0 (s, 1 C, C-1), 44.5 (q, 1 C, NCH_3), 43.8 (s, 1 C, C-6a), 26.6 (t, 2 C, C-4 and C-5), 22.3 (d, 1 C, C-5a), 10.2 (t, 1 C, cPr-C), 8.8 (t, 1 C, C-6), 6.7 (t, 1 C, cPr-C) ppm. IR (neat): $\tilde{\nu}$ = 3077 cm^{-1} (w), 3051 (w), 3028 (w), 2986 (m), 2952 (s), 2865 (s) and 1458 (m) cm^{-1}. MS (EI): m/z (rel. int.) = 165 (17) [M$^+$], 136 (3), 108 (16), 79 (100). $C_{10}H_{15}NO$ (165.23): calcd. C 72.69, H 9.15, N 8.48; found C 72.67, H 8.95, N 8.13.

(3a*R,5a*S**,6a*S**)-3-Benzyl-3,3a,4,5,5a,6-hexahydrocyclopropa[2,3]cyclopenta[1,2-*c*]isoxazolespiro[1,1′]cyclopropane (26b):** FCC (36 g of silica gel, 3 × 15 cm column) eluting with dichloromethane/methanol, 100:1, of the crude product obtained from alcohol **23** (190 mg, 1.37 mmol) and *N*-benzylhydroxylamine hydrochloride (328 mg, 2.05 mmol, 1.5 equiv.) according to GP1 (reflux, 36 h) afforded **26b** (176 mg, 0.72 mmol, 52%) as a colorless oil, R_f = 0.29. ^{1}H NMR (200 MHz): δ = 7.40–7.18 (m, 5 H, Ar-H), 4.12–3.90 (AB system, 2 H, NCH_2Ph), 3.36 (br. s, 1 H, 3a-H), 2.25–2.07 (m, 1 H, 5-H^a), 1.64–1.53 (m, 2 H, 4-H^a and 5-H^b), 1.46–1.31 (m, 1 H, 4-H^b), 1.24 (dt, J = 8.3, 4.9 Hz, 1 H, 5a-H), 0.97–0.79 (m, 2 H, cPr-H), 0.57–0.41 (m, 3 H, cPr-H and 6-H), 0.22–0.13 (m, 1 H, cPr-H) ppm. ^{13}C NMR (50.3 MHz): δ = 137.2 (s, 1 C, Ar-C), 129.3 (d, 2 C, Ar-C), 128.2 (d, 2 C, Ar-C), 127.2 (d, 1 C, Ar-C), 74.0 (d, 1 C, C-3a), 63.8 (s, 1 C, C-1), 62.7 (bt, 1 C, NCH_2Ph), 43.4 (s, 1 C, C-6a), 28.2 (t, 1 C, C-4), 26.8 (t, 1 C, C-5), 22.9 (d, 1 C, C-5a), 10.9 (t, 1 C, cPr-C), 9.1 (t, 1 C, C-6), 5.7 (t, 1 C, cPr-C) ppm. IR (neat): $\tilde{\nu}$ = 3109 cm^{-1} (w), 3061 (w), 3029 (w), 2937 (s), 2864 (s), 1454 (m), 730 (s) and 698 (m) cm^{-1}. MS (EI): m/z (rel. int.) = 241 (6) [M$^+$], 224 (4), 212 (19), 91 (100), 65 (18), 41 (9). $C_{16}H_{19}NO$ (241.33): calcd. C 79.63, H 7.94, N 5.80; found C 79.43, H 7.66, N 5.70.

(3a*R,5a*S**,6a*S**)-3-*tert*-Butyl-3,3a,4,5,5a,6-hexahydrocyclopropa[2,3]cyclopenta[1,2-*c*]isoxazolespiro[1,1′]cyclopropane (26c):** FCC (36 g of silica gel, 3 × 15 cm column) eluting with dichloromethane/methanol, 100:1, of the crude product obtained from alcohol **23** (275 mg, 1.99 mmol) and *N*-*tert*-butylhydroxylamine hydrochloride (300 mg, 2.39 mmol) according to GP1 (65 °C, 14 h, in toluene after solvent evaporation) afforded **26c** (58 mg, 0.28 mmol, 14%) as colorless crystals, R_f = 0.32. M.p. 54–55 °C. ^{1}H NMR (300 MHz): δ = 3.57 (d, J = 5.6 Hz, 1 H, 3a-H), 2.32–2.20 (m, 1 H, 5-H^a), 1.87 (dd, J = 13.7, 9.3 Hz, 1 H, 4-H^a), 1.63 (dd, J = 13.0, 8.7 Hz, 1 H, 5-H^b), 1.56–1.43 (m, 1 H, 4-H^b), 1.37 (dt, J = 8.7, 4.4 Hz, 1 H, 5a-H), 1.12 [s, 9 H, NC$(CH_3)_3$], 0.93 (dt, J = 11.2, 6.4 Hz, 1 H, cPr-H), 0.78 (ddd, J = 11.8, 6.4, 5.0 Hz, 1 H, cPr-H), 0.51 (ddd, J = 10.6, 6.4, 5.0 Hz, 1 H, cPr-H), 0.47–0.37 (m, 2 H, 6-H), 0.21 (dt, J = 10.6, 6.4 Hz, 1 H, cPr-H) ppm. ^{13}C NMR (75.5 MHz): δ = 65.0 (d, 1 C, C-3a), 63.6 (s, 1 C, C-1), 59.0 [s, 1 C, N$C(CH_3)_3$], 43.4 (s, 1 C, C-6a), 31.2 (t, 1 C, C-4), 26.3 (t, 1 C, C-5), 25.9 [q, 3 C, NC$(CH_3)_3$], 23.6 (d, 1 C, C-5a), 12.7 (t, 1 C, cPr-C), 8.3 (t, 1 C, C-6), 4.5 (t, 1 C, cPr-C) ppm. IR (KBr): $\tilde{\nu}$ = 3082 cm^{-1} (w), 3030 (w), 2971 (s), 2927 (s), 2857 (m), 1456 (m), 1360 (s) and 1217 (s) cm^{-1}. MS (EI): m/z (rel. int.) = 207 (100) [M$^+$], 192 (22), 164 (96), 150 (6), 136 (56), 122 (13), 107 (97), 72 (96), 57 (78). $C_{13}H_{21}NO$ (207.31): calcd. C 75.32, H 10.21, N 6.76; found C 75.29, H 10.10, N 6.51.

Minor Isomer *iso*-26c: (116 mg, 0.56 mmol, 28% as a 1:4.6 mixture – calcd. from ^{1}H NMR integrals – of minor isomer ***iso*-26c** and major isomer **26c**, respectively). ^{1}H NMR (300 MHz, detected signals): δ = 3.82 (t, J = 5.6 Hz, 1 H), 2.45–2.35 (m, 1 H), 2.17–1.97 (m, 2 H), 1.88–1.79 (m, 1 H), 1.72–1.62 (m, 2 H), 1.33 [s, 9 H, NC$(CH_3)_3$], 1.23 (dd, J = 5.6, 4.4 Hz, 1 H) ppm. ^{13}C NMR (75.5 MHz, detected signals): δ = 60.2 (d, 1 C), 60.2 (s, 1 C), 53.6 [s, 1 C, N$C(CH_3)_3$], 50.5 (s, 1 C), 37.5 (t, 1 C), 35.0 (t, 1 C), 28.2 [q, 3 C, NC$(CH_3)_3$], 22.9 (t, 1 C), 22.2 (d, 1 C) ppm.

General Procedure for the Transformation of the Isoxazolidines 26 into Tetrahydropyridones 27 (GP 2): A 0.05 M solution of the isoxazolidine **26** in toluene was heated under reflux for 12 h, then the

solvent was evaporated and the crude product was purified by FCC.

(1a*R,3a*S**,7a*R**)-4-Methyl-1,1a,2,3,3a,4,5,6-octahydro-7*H*-cyclopropa[2,3]cyclopenta[1,2-*b*]pyridin-7-one (27a):** FCC (6 g of silica gel, 1 × 10 cm column) eluting with dichloromethane/methanol, 50:1, of the crude product obtained from isoxazolidine **26a** (40 mg, 0.24 mmol) according to GP2 afforded **27a** (21 mg, 0.13 mmol, 53%) as a yellow oil, R_f = 0.15. ^{1}H NMR (300 MHz): δ = 3.13–3.02 (m, 1 H, 5-H^a), 2.69–2.52 (m, 3 H, 3a-H, 5-H^b and 6-H^a), 2.44–2.36 (m, 1 H, 6-H^b), 2.32 (s, 3 H, NCH_3), 2.09–1.88 (m, 2 H, 2-H^a and 3-H^a), 1.84–1.76 (m, 2 H, 1-H^a, 1a-H), 1.68 (dd, J = 12.5, 8.1 Hz, 1 H, 2-H^b), 1.49–1.36 (m, 1 H, 3-H^b), 0.72–0.65 (m, 1 H, 1-H^b) ppm. ^{13}C NMR (75.5 MHz): δ = 207.2 (s, 1 C, C-7), 68.7 (d, 1 C, C-3a), 54.5 (t, 1 C, C-5), 43.8 (q, 1 C, NCH_3), 40.4 (s, 1 C, C-7a), 39.2 (t, 1 C, C-6), 37.2 (d, 1 C, C-1a), 27.7 (t, 1 C, C-3), 25.1 (t, 1 C, C-2), 15.4 (t, 1 C, C-1) ppm. IR (neat): $\tilde{\nu}$ = 3034 cm^{-1} (w), 2952 (s), 2859 (m), 2787 (m), 1693 (s), 1457 (m) and 1382 (m) cm^{-1}. MS (EI): *m*/*z* (rel. int.) = 165 (17) [M$^+$], 150 (38), 136 (100), 124 (91), 108 (34), 79 (27). HRMS (ESI, MeOH + NH_4OAc): found 166.12264, $C_{10}H_{16}NO^+$ [M + H$^+$] requires 166.12264.

(1a*R,3a*S**,7a*R**)-4-Benzyl-1,1a,2,3,3a,4,5,6-octahydro-7*H*-cyclopropa[2,3]cyclopenta[1,2-*b*]pyridin-7-one (27b):** FCC (16 g of silica gel, 2 × 16 cm column) eluting with dichloromethane/methanol, 50:1, of the crude product obtained from isoxazolidine **26b** (181 mg, 0.75 mmol) according to GP2 afforded **27b** (94 mg, 0.39 mmol, 52%) as a yellow oil, R_f = 0.39. ^{1}H NMR (300 MHz): δ = 7.36–7.24 (m, 5 H, Ar-H), 4.08 (d, J = 14.3 Hz, 1 H, NCH_2Ph), 3.14 (d, J = 14.3 Hz, 1 H, NCH_2Ph), 3.10–3.03 (m, 1 H, 5-H^a), 2.96 (d, J = 6.2 Hz, 1 H, 3a-H), 2.57–2.41 (m, 2 H, 5-H^b and 6-H^a), 2.37–2.28 (m, 1 H, 6-H^b), 2.20–2.04 (m, 2 H, 2-H^a and 3-H^a), 1.88–1.68 (m, 3 H, 1-H^a, 1a-H and 2-H^b), 1.61–1.46 (m, 1 H, 3-H^b), 0.77–0.70 (m, 1 H, 1-H^b) ppm. ^{13}C NMR (75.5 MHz): δ = 207.6 (s, 1 C, C-7), 138.7 (s, 1 C, C-Ar), 128.7 (d, 2 C, C-Ar), 128.3 (d, 2 C, C-Ar), 127.0 (d, 1 C, C-Ar), 66.8 (d, 1 C, C-3a), 59.0 (t, 1 C, NCH_2Ph), 50.5 (t, 1 C, C-5), 40.7 (s, 1 C, C-7a), 39.3 (t, 1 C, C-6), 37.3 (d, 1 C, C-1a), 28.3 (t, 1 C, C-3), 25.3 (t, 1 C, C-2), 15.6 (t, 1 C, C-1) ppm. IR (neat): $\tilde{\nu}$ = 3061 cm^{-1} (w), 3028 (w), 2951 (s), 2864 (m), 2801 (s), 1692 (s), 1453 (m), 736 (s) and 699 (s) cm^{-1}. MS (EI): *m*/*z* (rel. int.) = 241 (32) [M$^+$], 224 (10), 212 (27), 200 (9), 91 (100), 65 (12), 41 (6). $C_{16}H_{19}NO$ (241.33): calcd. C 79.63, H 7.94, N 5.80; found C 79.91, H 7.73, N 6.05.

(1a*R,3a*S**,7a*R**)-4-*tert*-Butyl-1,1a,2,3,3a,4,5,6-octahydro-7*H*-cyclopropa[2,3]cyclopenta[1,2-*b*]pyridin-7-one (27c):** FCC (6 g of silica gel, 1 × 10 cm column) eluting with dichloromethane/methanol, 50:1, of the crude product obtained from isoxazolidine **26c** (52 mg, 0.25 mmol) according to GP2 afforded **27c** (27 mg, 0.13 mmol, 52%) as a yellow oil, R_f = 0.14. ^{1}H NMR (300 MHz): δ = 3.57 (t, J = 5.6 Hz, 1 H, 3a-H), 3.24–3.04 (m, 2 H, 6-H or 5-H), 2.48–2.29 (m, 2 H, 6-H or 5-H), 2.15–2.01 (m, 3 H, 1-H^a, 2-H^a and 3-H^a), 1.99–1.91 (m, 1 H, 1a-H), 1.80–1.71 (m, 1 H, 3-H^b), 1.51–1.39 (m, 1 H, 2-H^b), 1.15 [s, 9 H, NC$(CH_3)_3$], 0.79–0.76 (m, 1 H, 1-H^b) ppm. ^{13}C NMR (75.5 MHz): δ = 210.2 (s, 1 C, C-7), 60.4 (d, 1 C, C-3a), 54.7 [s, 1 C, N$C(CH_3)_3$], 42.0 (s, 1 C, C-7a), 40.9 (t, 1 C, C-5 or C-6), 39.2 (d, 1 C, C-1a), 38.7 (t, 1 C, C-5 or C-6), 36.3 (t, 1 C, C-3), 28.6 [q, 3 C, NC(CH_3)$_3$], 27.2 (t, 1 C, C-2), 26.6 (t, 1 C, C-1) ppm. IR (neat): $\tilde{\nu}$ = 3067 cm^{-1} (w), 2968 (s), 2867 (m), 1688 (s), 1462 (m) and 1362 (s) cm^{-1}. MS (EI): *m*/*z* (rel. int.) = 207 (65) [M$^+$], 192 (78), 178 (26), 164 (9), 150 (15), 136 (18), 122 (66), 110 (78), 57 (100). $C_{13}H_{21}NO$ (207.31): calcd. C 75.32, H 10.21, N 6.76; found C 72.25, H 10.11, N 6.89.

General Procedure for the One-Pot Synthesis of Tetrahydropyridones 27 Starting from the Alcohol 23 (GP 3): The crude product obtained according to GP1, the respective aldehyde, molecular sieves (3 Å), the respective *N*-substituted hydroxylamine hydrochloride and triethylamine after evaporation of the solvents, was heated under reflux in toluene (20 mL/mmol) for 12 h. The solvent was evaporated and the crude product was purified by FCC.

(1a*R,3a*S**,7a*R**)-4-Methyl-1,1a,2,3,3a,4,5,6-octahydro-7*H*-cyclopropa[2,3]cyclopenta[1,2-*b*]pyridin-7-one (27a):** FCC (10 g of silica gel, 1 × 18 cm column) eluting with dichloromethane/methanol, 50:1, of the crude product obtained from alcohol **23** (150 mg, 1.09 mmol) and *N*-methylhydroxylamine hydrochloride (109 mg, 1.31 mmol) according to GP3 afforded **27a** (82 mg, 0.50 mmol, 46%) as a yellow oil, R_f = 0.15. The spectroscopic data of the product are identical to those of the compound obtained from the corresponding isoxazolidine **26a** according to GP2.

(1a*R,3a*S**,7a*R**)-4-Benzyl-1,1a,2,3,3a,4,5,6-octahydro-7*H*-cyclopropa[2,3]cyclopenta[1,2-*b*]pyridin-7-one (27b):** FCC (15 g of silica gel, 2 × 15 cm column) eluting with dichloromethane/methanol, 50:1, of the crude product obtained from alcohol **23** (86 mg, 0.62 mmol) and *N*-benzylhydroxylamine hydrochloride (148 mg, 0.93 mmol, 1.5 equiv.) according to GP3 afforded **27b** (36 mg, 0.15 mmol, 24%) as a yellow oil, R_f = 0.39. The spectroscopic data of the product are identical to those of the compound obtained from the corresponding isoxazolidine **26b** according to GP2.

General Procedure for the Synthesis of Isoxazolidines 28 Starting from the Alcohols 24 (GP 4): A 0.5 M solution of the alcohol **24** (1 equiv.) in anhydrous dichloromethane was added at 25 °C under nitrogen to a suspension of PCC (1.5 equiv.) in anhydrous dichloromethane (1 mL for each mmol of PCC), and the mixture was stirred at 25 °C for 3 h, then diethyl ether (2 mL/mmol) was added. The mixture containing the desired aldehyde was filtered through celite, the dark filter cake was washed with diethyl ether (10 mL/mmol), into a flask containing activated molecular sieves (3 Å) (800 mg/mmol), *N*-substituted hydroxylamine hydrochloride (1.2 equiv.) and triethylamine (1.2 equiv.) in diethyl ether (4.5 mL/mmol). The resulting mixture was stirred at 70 °C (after ether evaporation) for 8 h in toluene (20 mL/mmol), then filtered through celite. The solvent was evaporated and the crude product was purified by FCC.

(3a*S,6a*R**,7a*R**)-3a,4,5,6,6a,7-Hexahydro-3*H*-3-methylcyclopropa[*d*][2,1]benzisoxazolespiro[1,1′]cyclopropane (28a):** FCC (18 g of silica gel, 2 × 18 cm column) eluting with dichloromethane/methanol, 100:1, of the crude product obtained from alcohol **24** (220 mg, 1.45 mmol) and *N*-methylhydroxylamine hydrochloride (145 mg, 1.74 mmol) according to GP4 afforded **28a** (151 mg, 0.84 mmol, 58%) as a pale yellow oil, R_f = 0.43. ^{1}H NMR (600 MHz): δ = 2.79 (s, 3 H, NCH_3), 2.71 (dd, J = 9.9, 6.1 Hz, 1 H, 3a-H), 1.76–1.70 (m, 2 H, 4-H^a and 6-H^a), 1.69–1.62 (m, 1 H, 6-H^b), 1.57–1.52 (m, 1 H, 5-H^a), 1.19–1.11 (m, 1 H, 4-H^b), 0.97–0.91 (m, 1 H, 5-H^b), 0.88 (dt, J = 11.4, 6.8 Hz, 1 H, cPr-H), 0.79 (ddd, J = 11.4, 6.8, 5.8 Hz, 1 H, cPr-H), 0.67 (dt, J = 9.4, 5.9 Hz, 1 H, 6a-H), 0.49 (dd, J = 9.4, 5.0 Hz, 1 H, 7-H^a), 0.38 (ddd, J = 10.5, 6.8, 5.8 Hz, 1 H, cPr-H), 0.36–0.34 (m, 1 H, 7-H^b), 0.26 (dt, J = 10.5, 6.8 Hz, 1 H, cPr-H) ppm. ^{1}H NMR (600 MHz, C_6D_6): δ = 2.71 (s, 3 H, NCH_3), 2.55–2.48 (m, 1 H, 3a-H), 1.55–1.51 (m, 1 H, 6-H^a), 1.48 (dt, J = 13.3, 5.3 Hz, 1 H, 6-H^b), 1.46–1.42 (m, 1 H, 4-H^a), 1.27 (m, 1 H, 5-H^a), 1.21–1.13 (m, 1 H, 4-H^b), 0.93–0.87 (m, 2 H, cPr-H), 0.66 (qdd, J = 13.7, 4.7, 2.1 Hz, 1 H, 5-H^b), 0.42 (dt, J = 9.2, 5.3 Hz, 1 H, 6a-H), 0.31 (dd, J = 9.2, 4.9 Hz, 1 H, 7-H^a), 0.28–0.23 (m, 1 H, cPr-H), 0.16–0.13 (m, 1 H, 7-H^b), 0.11–0.03 (m, 1 H, cPr-H) ppm. ^{13}C NMR (75.5 MHz): δ = 70.5 (d, 1 C, C-3a), 65.8 (s, 1 C, C-1), 44.7 (q, 1 C, NCH_3), 30.2 (s, 1 C, C-7a), 27.1 (t, 1 C, C-4), 22.5 (t, 1 C, C-6), 16.7 (t, 1 C, C-5), 14.2 (d,

1 C, C-6a), 12.2 (t, 1 C, C-7), 9.5 (t, 1 C, cPr-C), 6.1 (t, 1 C, cPr-C) ppm. IR (neat): $\tilde{\nu}$ = 3081 cm^{-1} (w), 3057 (w), 2990 (m), 2931 (s), 2855 (s) and 1457 (m) cm^{-1}. MS (EI): *m*/*z* (rel. int.) = 179 (14) [M^+], 150 (13), 123 (23), 94 (71), 79 (100). $C_{11}H_{17}NO$ (179.26): calcd. C 73.70, H 9.56, N 7.81; found C 73.51, H 9.27, N 7.65.

(3a*S,6a*R**,7a*R**)-3-Benzyl-3a,4,5,6,6a,7-hexahydro-3*H*-cyclopropa[*d*][2,1]benzisoxazolespiro[1,1′]cyclopropane (28b):** FCC (18 g of silica gel, 2 × 18 cm column) eluting with dichloromethane/methanol, 100:1, of the crude product obtained from alcohol **24** (135 mg, 0.89 mmol) and *N*-benzylhydroxylamine hydrochloride (223 mg, 1.40 mmol, 1.5 equiv.) according to GP4 afforded **28b** (123 mg, 0.48 mmol, 54%) as a pale yellow oil, R_f = 0.69. ^{1}H NMR (300 MHz): δ = 7.43–7.24 (m, 5 H, Ar-H), 4.20–4.09 (AB system, 2 H, NC*H*$_2$Ph), 2.99 (dd, *J* = 10.3, 5.9 Hz, 1 H, 3a-H), 1.76–1.66 (m, 2 H, 6-H), 1.64–1.47 (m, 2 H, 4-H^a and 5-H^a), 1.28–1.15 (m, 1 H, 4-H^b), 0.97–0.73 (m, 4 H, 5-H^b, 6a-H and cPr-H), 0.46–0.29 (m, 4 H, 7-H and cPr-H) ppm. ^{13}C NMR (75.5 MHz): δ = 137.7 (s, 1 C, C-Ar), 128.9 (d, 2 C, C-Ar), 128.2 (d, 2 C, C-Ar), 127.1 (d, 1 C, C-Ar), 68.3 (d, 1 C, C-3a), 65.9 (s, 1 C, C-1), 62.0 (t, 1 C, N*C*H$_2$Ph), 30.1 (s, 1 C, C-7a), 27.9 (t, 1 C, C-4), 22.6 (t, 1 C, C-6), 16.8 (t, 1 C, C-5), 14.5 (d, 1 C, C-6a), 11.5 (t, 1 C, C-7), 7.7 (t, 2 C, cPr-C) ppm. IR (neat): $\tilde{\nu}$ = 3085 cm^{-1} (w), 3062 (m), 3030 (w), 3000 (w), 2931 (s), 2857 (s), 1454 (m), 755 (s) and 695 (m) cm^{-1}. MS (DCI): *m*/*z* (rel. int.) = 256 (100) [M + H^+], 228 (7). $C_{17}H_{21}NO$ (255.35): calcd. C 79.96, H 8.29, N 5.49; found C 79.66, H 8.08, N 5.71.

General Procedure for the Transformation of Isoxazolidines 28 to Tetrahydropyridones 29 (GP 5): A 0.05 M solution of the isoxazolidine **28** in *o*-xylene was stirred at 130 °C for 36 h, then the solvent was evaporated, and the crude product was purified by FCC.

(4a*R,5a*R**,8a*S**)-1-Methyl-2,3,5,5a,6,7,8,8a-octahydrocyclopropa[*e*]quinolin-4(1*H*)-one (29a):** FCC (6 g of silica gel, 1 × 10 cm column) eluting with dichloromethane/methanol, 50:1, of the crude product obtained from isoxazolidine **28a** (60 mg, 0.33 mmol) according to GP5 afforded **29a** (33 mg, 0.18 mmol, 55%) as a yellow oil, R_f = 0.14. ^{1}H NMR (300 MHz): δ = 3.04 (ddd, *J* = 9.3, 6.2, 3.7 Hz, 1 H, 2-H^a), 2.80–2.58 (m, 2 H, 2-H^b and 3-H^a), 2.51–2.43 (m, 2 H, 3-H^b and 8a-H), 2.44 (s, 3 H, NCH_3), 1.92–1.73 (m, 4 H, 5a-H, 6-H, 8-H^a), 1.61–1.50 (m, 1 H, 7-H^a), 1.41 (dd, *J* = 9.5, 3.7 Hz, 1 H, 5-H^a), 1.20–0.99 (m, 2 H, 7-H^b and 8-H^b), 0.75 (dd, *J* = 7.5, 3.7 Hz, 1 H, 5-H^b) ppm. ^{13}C NMR (75.5 MHz): δ = 209.3 (s, 1 C, C-4), 63.8 (d, 1 C, C-8a), 51.6 (t, 1 C, C-2), 43.6 (q, 1 C, NCH_3), 39.2 (t, 1 C, C-3), 31.8 (s, 1 C, C-4a), 27.8 (t, 1 C, C-8), 27.0 (d, 1 C, C-5a), 24.9 (t, 1 C, C-5), 22.8 (t, 1 C, C-6), 17.0 (t, 1 C, C-7) ppm. IR (neat): $\tilde{\nu}$ = 3070 cm^{-1} (w), 2933 (s), 2856 (m), 2788 (m), 1687 (s) and 1459 (m) cm^{-1}. MS (EI): *m*/*z* (rel. int.) = 179 (21) [M^+], 150 (35), 136 (38), 124 (38), 42 (100). HRMS (ESI, MeOH + NH_4OAc): found 180.13826, $C_{11}H_{18}NO^+$ [M + H^+] requires 180.13829. $C_{11}H_{17}NO$ (179.26): calcd. C 73.70, H 9.56, N 7.81; found C 73.24, H 9.24, N 7.22.

(4a*R,5a*R**,8a*S**)-1-Benzyl-2,3,5,5a,6,7,8,8a-octahydrocyclopropa[*e*]quinolin-4(1*H*)-one (29b):** FCC (11 g of silica gel, 2 × 11 cm column) eluting with dichloromethane/methanol, 50:1, of the crude product obtained from isoxazolidine **28b** (43 mg, 0.17 mmol) according to GP5 afforded **29b** (23 mg, 0.09 mmol, 54%) as a yellow oil, R_f = 0.15. ^{1}H NMR (300 MHz): δ = 7.39–7.22 (m, 5 H, Ar-H), 4.05 (d, *J* = 13.5 Hz, 1 H, NC*H*$_2$Ph), 3.46 (d, *J* = 13.5 Hz, 1 H, NC*H*$_2$Ph), 3.09 (dt, *J* = 12.5, 5.6 Hz, 1 H, 2-H^a), 2.81 (dd, *J* = 10.6, 3.7 Hz, 1 H, 8a-H), 2.65 (ddd, *J* = 12.5, 7.5, 5.6 Hz, 1 H, 2-H^b), 2.45–2.39 (m, 2 H, 3-H), 1.92–1.75 (m, 4 H, 5a-H, 6-H, 8-H^a), 1.67–1.58 (m, 1 H, 7-H^a), 1.56 (dd, *J* = 9.3, 3.7 Hz, 1 H, 5-H^a), 1.32–1.19 (m, 1 H, 8-H^b), 1.12–0.97 (m, 1 H, 7-H^b), 0.73 (dd, *J* = 7.0, 3.7 Hz, 1 H, 5-H^b) ppm. ^{13}C NMR (75.5 MHz): δ = 210.2 (s, 1 C, C-4), 139.1 (s, 1 C, C-Ar), 128.6 (d, 2 C, C-Ar), 128.3 (d, 2 C, C-Ar), 127.0 (d, 1 C, C-Ar), 61.7 (d, 1 C, C-8a), 58.0 (t, 1 C, NCH_2Ph), 45.5 (t, 1 C, C-2), 39.1 (t, 1 C, C-3), 32.1 (s, 1 C, C-4a), 28.0 (d, 1 C, C-5a), 26.6 (t, 1 C, C-8), 24.5 (t, 1 C, C-5), 23.0 (t, 1 C, C-6), 17.7 (t, 1 C, C-7) ppm. IR (neat): $\tilde{\nu}$ = 3084 cm^{-1} (w), 3060 (w), 3025 (w), 2996 (w), 2933 (s), 2856 (m), 2802 (m), 1684 (s), 1452 (m) and 739 (s) and 699 (m) cm^{-1}. MS (EI): *m*/*z* (rel. int.) = 255 (25) [M^+], 226 (13), 123 (23), 91 (100), 77 (8), 65 (6). HRMS (ESI, MeOH/H_2O + HCO_2H): found 256.16965, $C_{17}H_{22}NO^+$ [M + H^+] requires 256.16959. $C_{17}H_{21}NO$ (255.35): calcd. C 79.96, H 8.29, N 5.49; found C 79.90, H 8.38, N 5.07.

General Procedure for the Transformation of Isoxazolidines 26 and 28 to β-Amino Acids 31 and β-Lactams 32 (GP 6): TFA (2 equiv.) was added to a 0.02 M solution of the isoxazolidine **26** or **28** (1 equiv.) in acetonitrile, and the mixture was heated under reflux for 15 min. The solvent was evaporated and the crude product was purified by FCC.

(1*R,2*R**)-2-[Methyl(trifluoroacetyl)amino]bicyclo[3.1.0]hexane-1-carboxylic Acid (31a):** FCC (4 g of silica gel, 1 × 6 cm column) eluting with dichloromethane/methanol/AcOH, 20:1:0.1, of the crude product obtained from isoxazolidine **26a** (46 mg, 0.28 mmol) and TFA (43 μL, 0.56 mmol) according to GP6 afforded **31a** (50 mg, 0.20 mmol, 71%) as a colorless solid (two rotamers in a ratio of 1.6:1), R_f = 0.37, m.p. 131 °C. ^{19}F NMR (282 MHz, Mercury 300): δ = (at 50 °C) –67.6 and –70.0 (each s, 1.15 and 1.85 F, together $NCOCF_3$) ppm. ^{1}H NMR (300 MHz): δ = (at 50 °C) 5.16 and 4.64 (br. s and d, *J* = 6.2 Hz, 0.62 H and 0.38 H, 2-H), 3.01 and 2.91 (each s, 1.85 H and 1.15 H, NCH_3), 2.39 (dt, *J* = 8.1, 5.0 Hz, 1 H, 5-H), 2.19–2.04 (m, 1 H, 4-H^a), 2.00–1.63 (m, 3 H, 3-H and 4-H^b), 1.54–1.42 (m, 1 H, 6-H^a), 0.88–0.83 (m, 1 H, 6-H^b) ppm; the signal of the COOH proton could not be assigned. ^{13}C NMR (75.5 MHz): δ = (at 50 °C) 177.2 and 176.8 (each s, 1 C, CO_2H), 157.1 and 156.9 [each q with *J*(C,F) = 35.5 Hz, 1 C, N*C*OCF$_3$], 116.9 and 116.7 (each q with $J_{C,F}$ = 288.4 Hz, 1 C, NCO*C*F$_3$), 57.5 and ca. 56.8–55.4 (qd, $J_{C,F}$ = 4.1 Hz, and broad signal, 1 C, C-2), 32.0 and 31.7 (each s, 1 C, C-1), 30.6 and 29.5 (each q, 1 C, N*C*H$_3$), 30.2 (d, 1 C, C-5), 30.1 and 29.0 (each t, 1 C, C-3), 26.2 and 25.8 (each t, 1 C, C-4), 19.4 and 19.3 (each t, 1 C, C-6) ppm. IR (KBr): $\tilde{\nu}$ = 3052 cm^{-1} (w), 2998 (w), 2967 (w), 2891 (w), 1684 (s) and 1459 (m) cm^{-1}. MS (EI): *m*/*z* (rel. int.) = 251 (81) [M^+], 206 (59), 154 (82), 146 (42), 136 (42), 124 (50), 79 (100). $C_{10}H_{12}F_3NO_3$ (251.20): calcd. C 47.81, H 4.81, N 5.58; found C 47.98, H 4.61, N 5.76.

(1*R,2*R**)-2-[Benzyl(trifluoroacetyl)amino]bicyclo[3.1.0]hexane-1-carboxylic Acid (31b):** FCC (2 g of silica gel, 1 × 3 cm column) eluting with dichloromethane/methanol/AcOH, 20:1:0.1, of the crude product obtained from isoxazolidine **26b** (32 mg, 0.13 mmol) and TFA (20 μL, 0.26 mmol) according to GP6 afforded **31b** (29 mg, 0.09 mmol, 68%) as a colorless solid (two rotamers in a ratio of 1:1), R_f = 0.46, m.p. 154 °C. ^{19}F NMR (282 MHz, Mercury 300): δ = –67.1 and –68.9 (s and br. s, respectively, each ca. 1.5 F, together $NCOCF_3$) ppm. ^{1}H NMR (300 MHz): δ = 7.39–7.16 (m, 5 H, Ar-H), ≈ 5.12–4.96 (broad signal, 0.5 H), 5.01 (A part of an AB system, 0.5 H, NC*H*$_2$Ph), 4.75 (d, *J* = 6.2 Hz, 0.5 H, 2-H), ≈ 4.62–4.43 (broad signal, 0.5 H), 4.13 (B part of an AB system, 0.5 H, NC*H*$_2$Ph), ≈ 3.73–3.55 (broad signal, 0.5 H), ≈ 2.61–2.44 (broad signal, 0.5 H), 2.41 (dt, *J* = 7.5, 4.9 Hz, 0.5 H, 5-H), 1.89–1.57 (m, 4 H, 3-H and 4-H), 1.53 and 1.47 (each dd, *J* = 8.1, 4.9 Hz and *J* = 8.7, 4.9 Hz, 2 × 0.5 H, respectively, 6-H^a), 0.92–0.86 (m, 0.5 H, 6-H^b), 0.59–0.54 (broad signal, 0.5 H) ppm; the signal of the COOH proton could not be assigned. ^{13}C NMR (75.5 MHz): δ = (one rotamer) 177.4 (s, 1 C, CO_2H), 157.9 (q, $J_{C,F}$ = 35.5 Hz, 1 C, N*C*OCF$_3$), 136.3 (s, 1 C, C-Ar), 128.6 (d, 2 C, C-Ar), 127.3 (d, 1

C, C-Ar), 126.4 (d, 2 C, C-Ar), 116.6 (q, $J_{C,F}$ = 288.7 Hz, 1 C, NCO*C*F_3), 57.9 (qd, $J_{C,F}$ = 4.1 Hz, 1 C, C-2), 46.8 (t, 1 C, N*C*H_2Ph), 31.9 (s, 1 C, C-1), 30.8 (d, 1 C, C-5), 29.0 (t, 1 C, C-3), 25.2 (t, 1 C, C-4), 19.8 (t, 1 C, C-6) ppm; (the signals of the other rotamer are broad and not all of them could be assigned) 178.5 (s, 1 C, CO_2H), 135.4, 128.8, 127.9, 116.9 (q, $J_{C,F}$ = 287.9 Hz, 1 C, NCO*C*F_3), 63.0, 54.7, 33.7, 32.3, 31.8, 26.6, 21.2; the N*C*O*C*F_3 signal and that of one of the aromatic carbon atoms could not be detected probably because of accidental isochronism with the signals of the other rotamer. IR (KBr): $\tilde{\nu}$ = 3066 cm^{-1} (w), 3035 (w), 2998 (w), 2960 (m), 2882 (w), 1695 (s), 1449 (m), 1203 (s), 1132 (s), 754 (m) and 699 (m) cm^{-1}. MS (DCI): *m*/*z* (rel. int.) = 345 (100) [M + NH_4^+], 327 (4) [M^+], 301 (13), 134 (25). $C_{16}H_{16}F_3NO_3$ (327.30): calcd. C 58.71, H 4.93, N 4.28; found C 58.54, H 4.96, N 4.39.

(1*R,3*R**,7*S**)-8-Methyl-8-azatricyclo[5.2.0.0^{1,3}]nonan-9-one (32a):** FCC (4 g of silica gel, 1 × 6 cm column) eluting with dichloromethane/methanol, 50:1, of the crude product obtained from the isoxazolidine **28a** (60 mg, 0.33 mmol) and TFA (51 μL, 0.66 mmol) according to GP6 afforded **32a** (33 mg, 0.22 mmol, 66%) as a colorless oil, R_f = 0.23. ^{1}H NMR (300 MHz): δ = 3.47 (dd, J = 9.0, 5.9 Hz, 1 H, 7-H), 2.87 (s, 3 H, NCH_3), 1.93 (dtd, J = 12.5, 5.9, 2.0 Hz, 1 H, 6-H^a), 1.81–1.65 (m, 2 H, 4-H), 1.65–1.51 (m, 2 H, 3-H and 5-H^a), 1.33 (dd, J = 9.3, 6.2 Hz, 1 H, 2-H^a), 1.11–0.99 (m, 1 H, 6-H^b), 0.94–0.83 (m, 1 H, 5-H^b), 0.79 (t, J = 6.2 Hz, 1 H, 2-H^b) ppm. ^{13}C NMR (75.5 MHz): δ = 172.3 (s, 1 C, C-9), 55.6 (d, 1 C, C-7), 35.0 (s, 1 C, C-1), 27.3 (t and q, 2 C, C-6 and NCH_3), 23.0 (t, 1 C, C-4), 17.8 (t, 1 C, C-5), 14.7 (d, 1 C, C-3), 11.6 (t, 1 C, C-2) ppm. IR (neat): $\tilde{\nu}$ = 3063 cm^{-1} (w), 2991 (w), 2930 (s), 2857 (m), 1750 (s), 1450 (m) and 1382 (m) cm^{-1}. MS (EI): *m*/*z* (rel. int.) = 151 (22) [M^+], 123 (29), 94 (20), 79 (100), 77 (16), 42 (16). $C_9H_{13}NO$ (151.21): calcd. C 71.49, H 8.67, N 9.26; found C 71.27, H 8.65, N 9.09.

(1*R,3*R**,7*S**)-8-Benzyl-8-azatricyclo[5.2.0.0^{1,3}]nonan-9-one (32b):** FCC (2 g of silica gel, 1 × 3 cm column) eluting with dichloromethane/methanol, 50:1, of the crude product obtained from isoxazolidine 28b (50 mg, 0.20 mmol) and TFA (31 μL, 0.40 mmol) according to GP6 afforded **32b** (22 mg, 0.10 mmol, 50%) as a colorless oil, R_f = 0.33. ^{1}H NMR (300 MHz): δ = 7.36–7.24 (m, 5 H), 4.58 (A part of an AB system, 1 H, CH_2Ph), 4.26 (B part of an AB system, 1 H, CH_2Ph), 3.42 (dd, J = 9.4, 6.2 Hz, 1 H, 7-H), 1.77–1.56 (m, 4 H, 6-H^a, 4-H and 3-H), 1.52–1.41 (m, 1 H, 5-H^a), 1.34 (dd, J = 9.0, 5.9 Hz, 1 H, 2-H^a), 0.99–0.87 (m, 1 H, 6-H^b), 0.82–0.67 (m, 1 H, 5-H^b), 0.76 (t, J = 5.9 Hz, 1 H, 2-H^b) ppm. ^{13}C NMR (75.5 MHz): δ = 172.1 (s, 1 C, C-9), 136.4 (s, 1 C, C-Ar), 128.7 (d, 2 C, C-Ar), 128.4 (d, 2 C, C-Ar), 127.5 (d, 1 C, C-Ar), 54.3 (d, 1 C, C-7), 45.3 (t, 1 C, *C*H_2Ph), 34.9 (s, 1 C, C-1), 27.8 (t, 1 C, C-6), 22.9 (t, 1 C, C-4), 17.8 (t, 1 C, C-5), 14.9 (d, 1 C, C-3), 11.8 (t, 1 C, C-2) ppm. IR (neat): $\tilde{\nu}$ = 3064 cm^{-1} (w), 3028 (w), 2930 (s), 2857 (m), 1747 (s), 1453 (m) and 1387 (m) cm^{-1}. MS (EI): *m*/*z* (rel. int.) = 227 (66) [M^+], 199 (22), 136 (16), 94 (19), 91 (86), 79 (100), 77 (16), 65 (13). HRMS (ESI, MeOH/H_2O + HCO_2H): found 228.13828 and 250.12025, $C_{15}H_{18}NO^+$ [M + H^+] requires 228.13829 and $C_{15}H_{17}NONa^+$ [M + Na^+] requires 250.12024. $C_{15}H_{17}NO$ (227.30): calcd. C 79.26, H 7.54, N 6.16; found C 79.24, H 7.60, N 5.70.

Supporting Information (see also the footnote on the first page of this article): Table 1 showing energies obtained from the optimized geometries at the B3LYP/6-31G(d) level of theory. Figure 1 showing optimized structures of the nitrone **25a**, the cycloadducts **26a** and **15a** (*n* = 1), and the corresponding transition states. Figure 2 showing optimized structures of the nitrone **14a**, the cycloadducts **28a** and **15a** (*n* = 2), and the corresponding transition states. A table with atomic coordinates of all calculated structures.

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[15] A 2D-NOESY of **26a** confirmed the *cis* fusion of the five-membered rings as a NOE between the bridgehead proton 3a-H and one belonging to the fused cyclopropane was observed. The experiment was carried out with a Mercury 300 spectrometer (H-300 MHz) using the pulse sequence NOESY (spectral width: 2058 Hz, acquisition time: 0.249 s, mixing time Δ = 1.0 s, relaxation delay: 1.0 s, total acquisition time: 4.20 h). The experiment was run at 25 °C with a 0.4 M sample (33 mg in 0.5 mL) in $CDCl_3$.
[16] A suspension of PCC (65 mg, 0.30 mmol) in 1 mL of anhydrous dichloromethane was filtered through a pad of celite that was washed with 5 mL of diethyl ether. The organic phases were collected in a flask containing activated 3-Å molecular sieves (240 mg), *N*-benzylhydroxylamine hydrochloride (48 mg, 0.30 mmol) and triethylamine (42 μL, 0.30 mmol) under nitrogen. The resulting mixture was stirred at 25 °C for 1 h, then filtered through celite, and finally the solvents were evaporated. The ^{1}H NMR spectrum of the residue showed inter alia the presence of *N*-benzylhydroxylamine and (*Z*)-benzaldoxime in a ca. 1.4:1 ratio (according to the integrals of the signals of methylene protons of *N*-benzylhydroxylamine and of the oxime proton).
[17] CCDC-606887 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
[18] a) 2D-NOESY of **28a** was carried out with an INOVA-600 spectrometer (H-600 MHz) using the pulse sequence NOESY (spectral width: 2155 Hz, acquisition time: 0.150 s, mixing time Δ = 1 s, relaxation delay: 1.4 s, total acquisition time: 3.42 h). The experiment was run at 25 °C with a 0.2 M sample (18 mg in 0.5 mL) in $CDCl_3$; b) 1D NOESY selective irradiation experiments at 25 °C on **28a** were run in C_6D_6 (same instrument, same sample concentration), in which 7-H protons are better separated, and confirmed the 2D-NOESY results. The automatic pulse sequence NOESY 1D was used (spectral width: 9596 Hz, acquisition time: 3.334 s, mixing time Δ = 0.5 s, relaxation delay: 1.0 s, spin off; line broadening: 0.3 Hz for the processing).
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