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Selective Ring Contraction of 5-Spirocyclopropane Isoxazolidines Mediated by Acids

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Thermolysis of 3,4-cis ring-fused 5-spirocyclopropane isoxazolidines **16**, **18**−**21**, **33**, **34**, **38a**, and **61**, in the presence of a protic acid at 70−110 °C, yielded 3,4-cis ring-fused azetidin-2-ones **22**−**26**, **41**, **42**, **46**, and **62** with concomitant extrusion of ethylene, in good yields. So far, the collected evidences strongly support a mechanism started by a homolytic cleavage of the protonated N−O bond for the rearrangement of 5-spirocyclopropane isoxazolidines to *β*-lactams. Some different competitive pathways can then follow depending on the stability or the stereoelectronic properties of cationic diradical intermediates. The two-step process, intramolecular 1,3-dipolar cycloaddition/thermal rearrangement under acidic conditions, represents a general synthesis of a new class of 3,4-cis-fused bicyclic azetidin-2-ones starting from easily available compounds such as amino acids, hydroxy acids, and dicarbonyl or amino alcohol derivatives.

Introduction

5-Spirocyclopropane isoxazolidines **1** can be easily synthesized by 1,3-dipolar cycloaddition of nitrones and methylenecyclopropane derivatives[1] and are characterized by a unique reactivity caused by the presence of the strained three-membered ring spiro-fused on the adjacent position of the weak N−O bond. Isoxazolidines **1** undergo a thermally induced ring expansion to tetrahydropyridin-4-ones **4** through a homolytic cleavage of the N−O bond, followed by the opening of the cyclopropane ring and formation of the relatively more stable oxoethyl diradical **3**. The intermediate **3** can then evolve to **4** by radical ring closure (Scheme 1).[2,3]

The temperature necessary to trigger the rearrangement in solution phase usually ranges from 110 to 180 °C, except for *N*-aryl-substituted 5-spirocyclopropane isoxazolidines which undergo the N−O cleavage also at room temperature.[4] The two-step process 1,3-dipolar cycloaddition/thermal rearrangement has been successfully applied to the synthesis of several selectively

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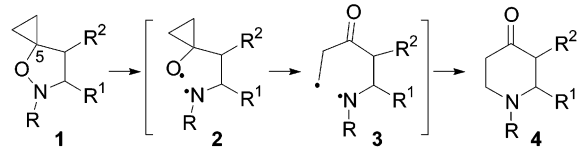

substituted piperidines including indolizidine and quinolizidine alkaloids.[1a,5]

We report here a new specific behavior of 5-spirocyclopropane isoxazolidines **1**. In particular, cycloadducts **1** can be selectively converted into *β*-lactam derivatives through ring contraction and concomitant extrusion of ethylene by heating at 70−110 °C in the presence of a protic acid.[6]

Results and Discussion

Recently, new tri- and tetracyclic spirocyclopropane isoxazolidines **8** were prepared starting from the 1-vinylcyclopropyl tosylate (**5**), which underwent Pd^0-catalyzed nucleophilic substitution of α-amino and α-hydroxy

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(1) (a) Brandi, A.; Garro, S.; Guarna, A.; Goti, A.; Cordero, F.; De Sarlo, F. *J. Org. Chem.* **1988**, *53*, 2430−2434. (b) For a review, see: Goti, A.; Cordero, F. M.; Brandi, A. *Top. Curr. Chem.* **1996**, *178*, 1−97.

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

(3) For a theoretical study of the rearrangement mechanism, see: Ochoa, E.; Mann, M.; Sperling, D.; Fabian, J. *Eur. J. Org. Chem.* **2001**, 4223−4231.

(4) (a) Cordero, F. M.; Goti, A.; De Sarlo, F.; Guarna, A.; Brandi, A. *Tetrahedron* **1989**, *45*, 5917−5924. (b) Cordero, F. M.; Barile, I.; De Sarlo, F.; Brandi, A. *Tetrahedron Lett.* **1999**, *40*, 6657−6660.

(5) (a) Cordero, F. M.; Brandi, A.; Querci, C.; Goti, A.; De Sarlo, F.; Guarna, A. *J. Org. Chem.* **1990**, *55*, 1762−1767. (b) Brandi, A.; Dürüst, Y.; Cordero, F. M.; De Sarlo, F. *J. Org. Chem.* **1992**, *57*, 5666−5670. (c) Cordero, F. M.; Anichini, B.; Goti A.; Brandi, A. *Tetrahedron* **1993**, *49*, 9867−9876. (d) Cordero, F. M.; Cicchi, S.; Goti, A.; Brandi, A. *Tetrahedron Lett.* **1994**, *35*, 949-952. (e) Brandi, A.; Cicchi, S.; Cordero, F. M.; Frignoli, R.; Goti, A.; Picasso, S.; Vogel, P. *J. Org. Chem.* **1995**, *60*, 6806−6812. (f) Cordero, F. M.; Brandi A. *Tetrahedron Lett.* **1995**, *36*, 1343−1346. (g) Machetti, F.; Cordero, F. M.; De Sarlo, F.; Guarna, A.; Brandi, A. *Tetrahedron Lett.* **1996**, *37*, 4205−4208.

(6) For preliminary communications, see: (a) Cordero,F. M.; Pisaneschi, F.; Goti, A.; Ollivier, J.; Salaün, J.; Brandi, A. *J. Am. Chem. Soc.* **2000**, *122*, 8075−8076. (b) Paschetta, V.; Cordero, F. M.; Paugam, R.; Ollivier, J.; Brandi, A.; Salaün, J. *Synlett* **2001**, 1233−1236.

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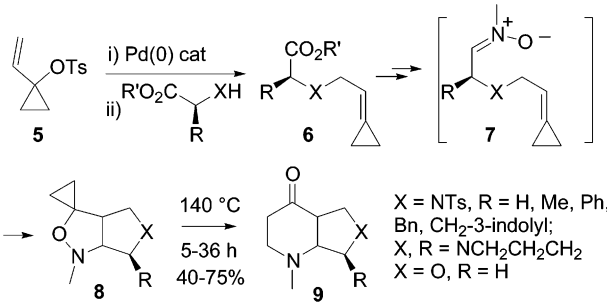


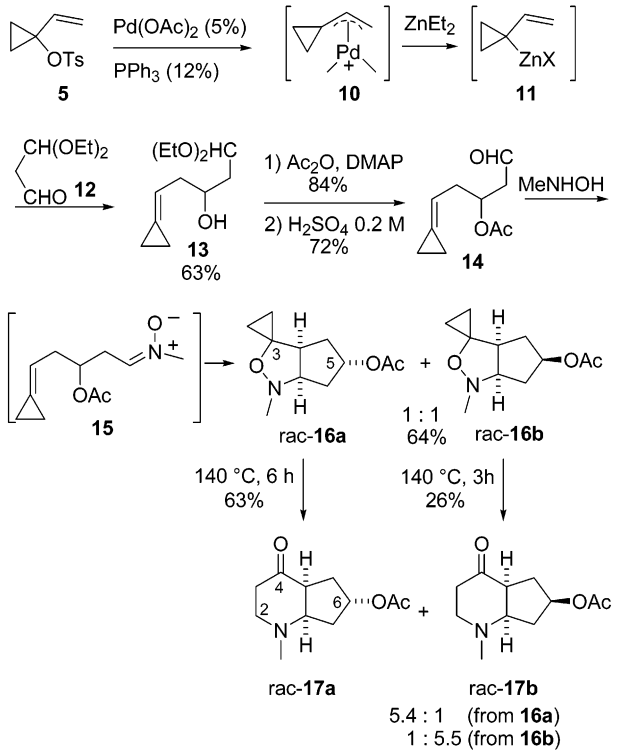
acid derivatives to afford exclusively alkylidenecyclopropanes **6**. The esters **6** were easily converted into the corresponding nitrones **7** which spontaneously evolved to **8** (Scheme 2).[7]

Alternatively, the treatment of **5** with diethylzinc, in the presence of a catalytic amount of Pd^0, afforded the zinc complex **11**,[8] which underwent selective electrophilic addition of aldehyde **12** to give alkylidenecyclopropane **13**. This process represents a nice example of "umpolung of reactivity"[9] for the synthesis of alkylidenecyclopropanes. After acetylation and hydrolysis of the acetal moiety, aldehyde **14** was treated with *N*-methylhydroxylamine to generate the alkylidenecyclopropane nitrone **15,** which underwent intramolecular cycloaddition to give an equimolecular mixture of diastereomers *exo*-**16a** and *endo*-**16b** (Scheme 3).[6b] As in the previous examples,[7] the presence of the short three-atom chain between the two reacting sites affected the cycloaddition mode by disfavoring the formation of bridged regioisomeric cycloadducts.

The assignment of the relative configuration of adducts *exo*-**16a** and *endo*-**16b** was based on the ^{1}H NMR resonances of 5-H. In particular, 5-H in *exo*-**16a** (δ = 5.28 ppm, quintet, J = 4.7 Hz) has a downfield chemical shift with respect to the corresponding proton in *endo*-**16b** (δ = 4.97 ppm, quintet, J = 6.5 Hz) in accord with the more congested endo position. The structural assignment was confirmed by the analysis of the NOESY spectrum of *endo*-**16b** which exhibited a correlation between 5-H (δ = 4.97 ppm) and the hydrogen atoms of the bridge 3a-H (δ = 2.87−2.75 ppm) and 6a-H (δ = 3.59−3.55 ppm).

The adducts *exo*-**8**, *exo*-**16a**, and *endo*-**16b** rearranged into the corresponding pyridones by simple heating in refluxing xylenes (Schemes 2 and 3). In particular, each adduct *exo*-**8**[7] gave the *exo*-**9** as a unique product. On the contrary, both isoxazolidines *exo*-**16a** and *endo*-**16b** were converted into a mixture of two diastereomeric pyridones *exo*-**17a** and *endo*-**17b** in a 5.4:1 ratio (63%) and a 1:5.5 ratio (26%), respectively. The epimerization at C-6 likely occurred during the rearrangement process as the isolated *exo*-**17a** and *endo*-**17b** did not interconvert under the rearrangement reaction conditions. In contrast to unsubstituted octahydro-1-methyl-4*H*-cyclopenta[*b*]pyridin-4-one[5f] and some octahydro-1*H*-pyrrolo[3,4-*b*]pyridin-4-ones,[10] pyridones **17** do not seem to isomerize to the corresponding trans-fused compounds.

SCHEME 3



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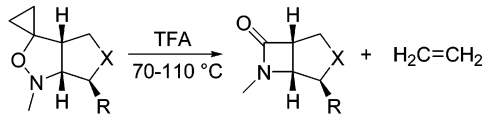


	X	R		Yield (%)
18	NTs	*i*-Pr	**22**	63
19	NTs	CH_2-3-indolyl	**23**	57
20	$NCH_2CH_2CH_2$		**24**	47
rac-**21**	O	H	rac-**25**	60
rac-**16a,b**	CHOAc	H	rac-**26a,b**	63-92

The thermal behavior of 5-spirocyclopropane isoxazolidines, after protonation, was completely different.[6] The enantiopure compounds *exo*-**18**−**20** and the racemic **21** in the presence of trifluoroacetic acid (TFA) underwent a clean reaction at 70−110 °C to afford 6-azabicyclo[3.2.0]-heptan-7-ones **22**−**25** with conservation of the relative and absolute configuration (Scheme 4).[6] Under the same conditions, both *exo*-**16a** and *endo*-**16b** were converted into a diastereomeric mixture of *exo*-**26a** and *endo*-**26b** in a 1.6:1 ratio (96%) and a 1:2 ratio (82%), respectively.[11] Analogously to the products of the rearrangement in neutral conditions, such as *exo*-**17a** and *endo*-**17b**, both the isolated β-lactams *exo*-**26a** and *endo*-**26b** were stable under the reaction conditions. An explanation of this epimerization of acetates is not available at the moment.

(7) (a) Estieu, K.; Paugam, R.; Ollivier, J.; Salaün, J.; Cordero, F. M.; Goti, A.; Brandi, A. *J. Org. Chem.* **1997**, *62*, 8276−8277. (b) Ferrara, M.; Cordero, F. M.; Goti, A.; Brandi, A.; Estieu, K.; Paugam, R.; Ollivier, J.; Salaün, J. *Eur. J. Org. Chem.* **1999**, 2725−2739.

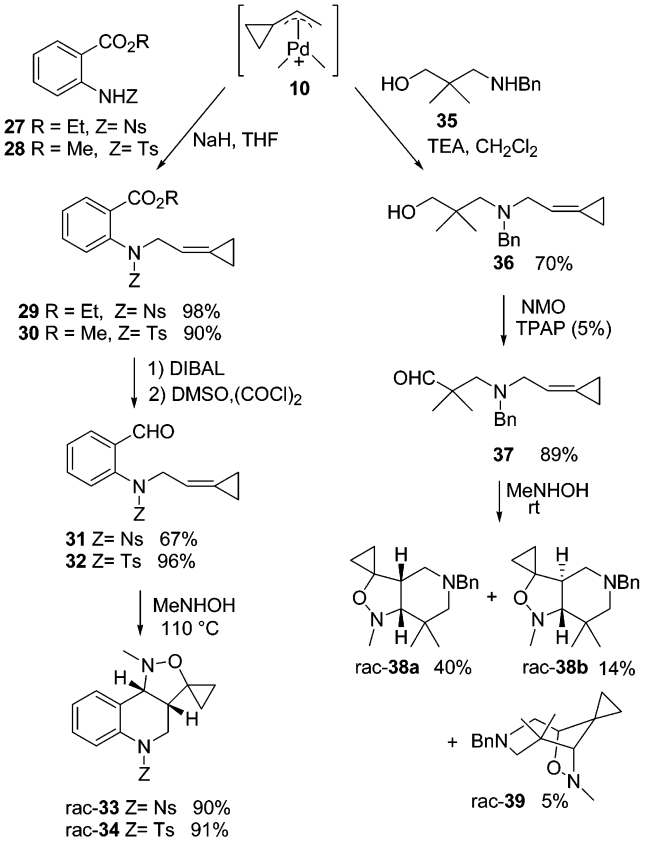
(8) Ollivier, J.; Girard, N.; Salaün, J. *Synlett* **1999**, 1539−1542.

(9) Seebach, D. *Angew. Chem.* **1979**, *91*, 259−278; *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 239.

(10) Pisaneschi, F.; Cordero, F. M.; Goti, A.; Paugam, R.; Ollivier, J.; Brandi, A.; Salaün, J. *Tetrahedron*: *Asymmetry* **2000**, *11*, 897−909.

(11) An equimolecular mixture of *exo*-**16a** and *endo*-**16b** was converted in equimolecular amounts of *exo*- and *endo*-β-lactams in only 63% yield under the same reaction conditions (TFA, CH_3CN, reflux temperature, 15 min).

SCHEME 5



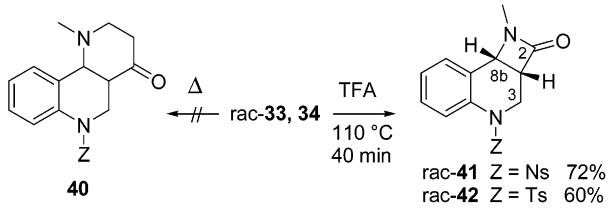
Compounds *exo*-**22**, *exo*-**23**, *rac*-**25**, *exo*-**26a**, and *endo*-**26b** could be easily purified and were obtained in fair yield after chromatography on silica gel. Unfortunately, the tricylic lactam *exo*-**24** could be only partially purified by treatment with Dowex 50WX8-200 ion-exchange resin or by reversed-phase HPLC, although its structure could be fully determined by spectroscopical means. β-Lactams **22**−**25** and **26a**,**b** were characterized by distinctive spectral data such as IR stretching (ν_{CO} = 1740−1756 cm^{-1}) and ^{13}C NMR resonances (δ_{CO} = 170.7−165.4 ppm). Furthermore, the values of the coupling constants between vicinal C−H were consistent with the depicted stereochemistry (**22**, **23**, **25**, **26**: H_1-H_5 J = 3.5−4.0 Hz; **22**, **23**: H_4-H_5 J = 0 Hz; **24**: H_{2a}-H_{6a} J = 3.9 Hz and H_{2a}-H_{2b} J = 0 Hz). The optical purity of **22** and **23** was ascertained by ^1H NMR analysis in the presence of increasing amount of Eu(hfc)$_3$.

Finally, the exact structure of the C_2 fragment, eliminated in the acid-induced reorganization of 5-spirocyclopropane isoxazolidines, was unequivocally established by analyzing the ^1H NMR spectra of the CD_3CN solution of protonated **18**−**21** after heating at 70 °C. In particular, the presence of the intense singlet at 5.41 ppm, besides the β-lactam **22**−**25** signal set, was a clear evidence of ethylene formation during the reaction.

The same strategy previously used to prepare the spirofused isoxazolidines **18**−**21** was applied to the syntheses of their superior homologues **33**, **34**, and **38a**,**b**, starting from the anthranilic acid derivatives **27** [Z = 2-nitrobenzenesulfonyl (Ns)], **28** [Z = Tosyl (Ts)], and the amino alcohol **35**, respectively (Scheme 5).

The Pd^0-catalyzed nucleophilic substitution of **5** occurred either with **27**, **28**, or **35** with complete regioselectivity and in good yields (64−98%). In the last case, the use of a tertiary amine as a base allowed to carry out the reaction in the presence of the unprotected hydroxyl group. The alkylidenecyclopropanes **29**, **30**, and **36** were converted into the corresponding aldehydes **31**, **32**, and **37** and then treated with *N*-methylhydroxylamine to generate the nitrone moiety, which underwent the intramolecular 1,3-dipolar cycloaddition. The cis-fused cycloadducts **33** and **34** were obtained at 110 °C in high yields (90−91%) and with complete control of regio- and stereochemistry. The nitrone derived from **37** reacted at room temperature and produced a mixture of adducts **38a**,**b** and the bridged-regioisomer **39** in 8:3:1 ratio and 59% overall yield (Scheme 5). Major compound **38a** was assigned the cis ring fusion on the basis of the bridged hydrogen coupling constant value (J_{H-H} = 4.6 Hz compared to J_{H-H} = 11.4 for **38b**). The higher selectivity showed by the aromatic compounds can be ascribed to the lower flexibility inferred by the aromatic ring to the four-atom chain linking the two reactive sites.

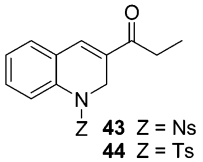
SCHEME 6



The thermal behavior of 5-spirocyclopropane isoxazolidines **33**, **34**, and **38a**,**b** was studied either in neutral and acidic conditions.

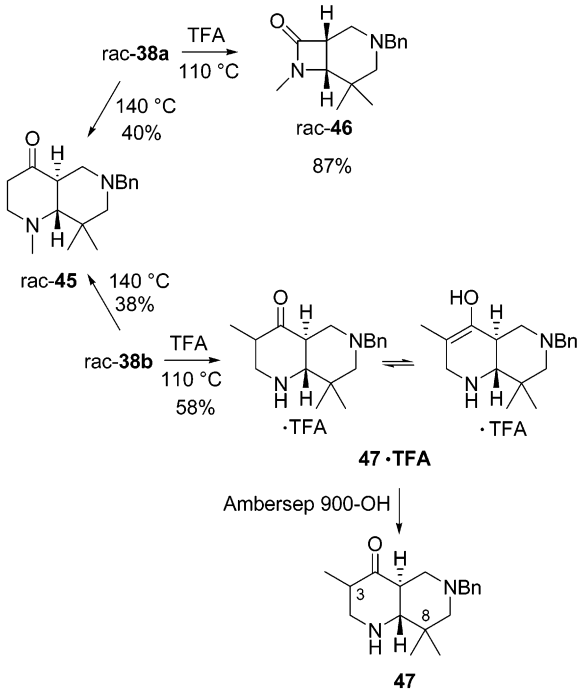
The adducts **33** and **34** failed to give pyridones **40** by heating (Scheme 6) up to 120 °C where they proved to be stable, but decomposed at higher temperatures. On the contrary, the cis- and trans-fused isoxazolidines **38a** and **38b** underwent the usual rearrangement by heating in refluxing xylenes, and both afforded the thermodynamically more stable trans-fused bicyclic ketone **45** in 40 and 38% yield, respectively (Scheme 7).

A rather different behavior was observed in acidic conditions. The tetracyclic isoxazolidines **33** and **34** underwent a clean reaction at 110 °C in the presence of a small excess of TFA. Under these conditions, the cis-fused β-lactams **41** and **42** were obtained in good yields (60−72%) by ring contraction and loss of ethylene (Scheme 6). The same reaction occurred by heating **33** and **34** in toluene in the presence of *p*-toluenesulfonic acid (TsOH) or in refluxing ethanol with HCl or on treating directly the aldehydes **31** and **32** with MeNHOH·HCl in refluxing ethanol in absence of triethylamine. It has to be stressed that all these reactions had to be carried out in strictly anhydrous conditions; otherwise, a 2:1 mixture of β-lactams **41**, **42** and ethyl ketones **43**, **44** were obtained when traces of H_2O were present.



The structures of **41** and **42** were unambiguously established as for **22**−**25** and **26a**,**b** from spectroscopic

SCHEME 7

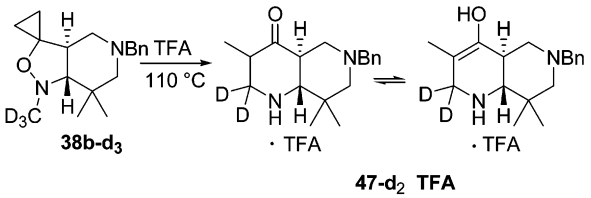


data. Especially diagnostic were IR stretching ν_{CO} (1750 and 1752 cm^{-1} for **41** and for **42**, respectively), ^{13}C NMR resonances δ_{CO} (166.2 and 166.9 ppm for **41** and for **42**, respectively), and ^1H NMR resonances of H_{8b} (δ = 4.45 ppm, d, J = 5.1 Hz for **41** and δ = 4.29 ppm, d, J = 5.1 Hz for **42**).

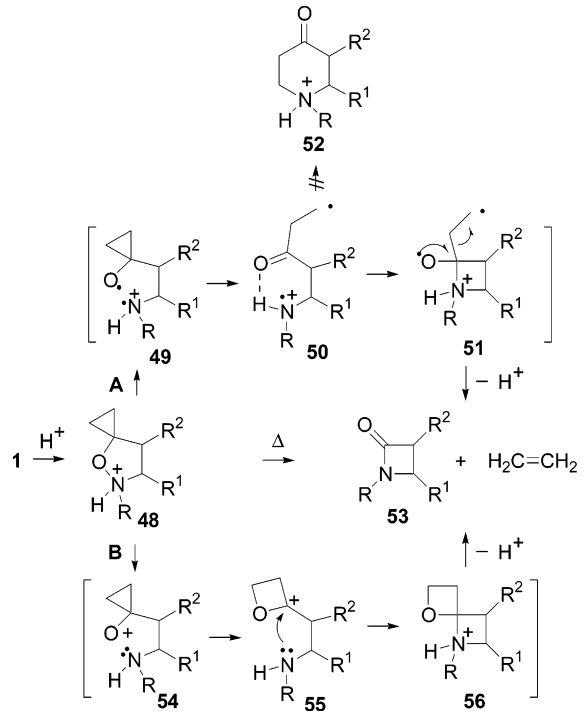
The two isomeric cis- and trans-fused isoxazolidines **38a** and **38b** showed a different thermal behavior in the presence of TFA. In particular, the cis isomer **38a** was converted into the corresponding β-lactam **46** in high yields (87%) (**46**: δ_{CO} = 168.3 ppm; ν_{CO} = 1754 cm^{-1}), while the isomer **38b** failed to give the more strained trans-fused bicyclic azetidin-2-one and underwent a different rearrangement to a new ketone to which the structure of 1,6-naphthyridinone **47** was assigned (Scheme 7). The bicyclic ketone **47** is clearly a structural isomer of **45**, the rearrangement product in neutral conditions, with a methyl group shifted from N-1 (in **45**) to C-3 (in **47**). Compound **47** was recovered as a TFA salt after chromatography on silica gel, and the ^1H NMR spectrum showed the α-carbonyl protons of **47·TFA** were lacking probably for a rapid keto−enolic exchange under the acidic conditions. The free ketone **47** could be obtained by treatment with a basic ion-exchange resin. The synthesis of the trideuteriomethyl derivative **38b-d$_3$**[12] allowed us to establish that the *N*-methyl group of **38b** becomes the 2-methylene in **47** (Scheme 8). In fact, the ^1H NMR spectra of **47·TFA** and **47-d$_2$·TFA** were analogous except for the resonances corresponding to the two H atoms on C-2 (δ: 3.07 ppm, br s) which were not present in the spectrum of the deuterated compound. The new and unexpected behavior of the protonated trans-fused bicyclic 5-spirocyclopropane isoxazolidine **38b** provided a significant piece of information for the elucidation of the mechanism of β-lactam formation (see below).

(12) **38b-d$_3$** was obtained starting from aldehyde **37** and CD_3NHOH and following the same procedure used for the synthesis of **38b**.

SCHEME 8



SCHEME 9



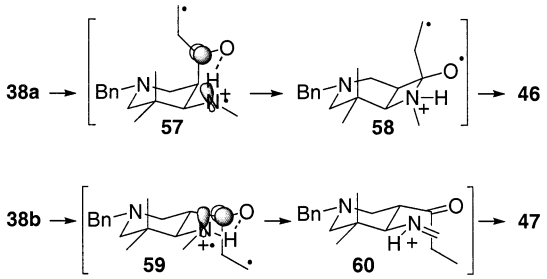
In a preliminary attempt to rationalize the mechanism of β-lactam formation from 5-spirocyclopropane isoxazolidines **1**, the possible involvement of piperidin-4-ones **4**, as reaction intermediates, was examined and discarded when proved that they are stable under the acidic rearrangement conditions.

The protonation of the isoxazolidine nitrogen atom, unequivocally demonstrated by the significant downfield shift of signals in the ^1H NMR spectra of adducts **1** in the presence of protic acids, must be the initial step of the formation of β-lactams **53**. The protonated isoxazolidine **48**, then, undergoes a thermally induced cleavage of the weak protonated N−O bond that might occur either in a homo- (Scheme 9, path A) or in a heterolytic (Scheme 9, path B) mode.

In the first hypothesis,[13] the diradical cation **49** could evolve to the relatively more stable ionic diradical **50**, in analogy to the process in neutral condition. The lack of any trace of tetrahydropyridones in acidic conditions could be explained by the formation of a strong intramolecular hydrogen bond in **50** that should prevent the radical ring closure to piperidone **52**. At the same time,

(13) This hypothesis recalls the first step of the Hoffman Loffler Freitag reaction that is the thermal induced homolysis of N−X bond in the presence of strong protic acid, where X is a chlorine or bromine atom: (a) Corey, E. J.; Hertler, W. R. *J. Am. Chem. Soc.* **1960**, *82*, 1657−1668. (b) Wolff, M. E. *Chem. Rev.* **1963**, *63*, 55−64. (c) Stella, L. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 337−350.

SCHEME 10



the hydrogen bond might keep the nitrogen and C=O group close enough and with the correct orbital overlapping required for the closure of a four-membered ring with formation of a N−CO bond. Finally, the *β*-lactam **53** could be formed from **51** by radical fragmentation and deprotonation (path A).

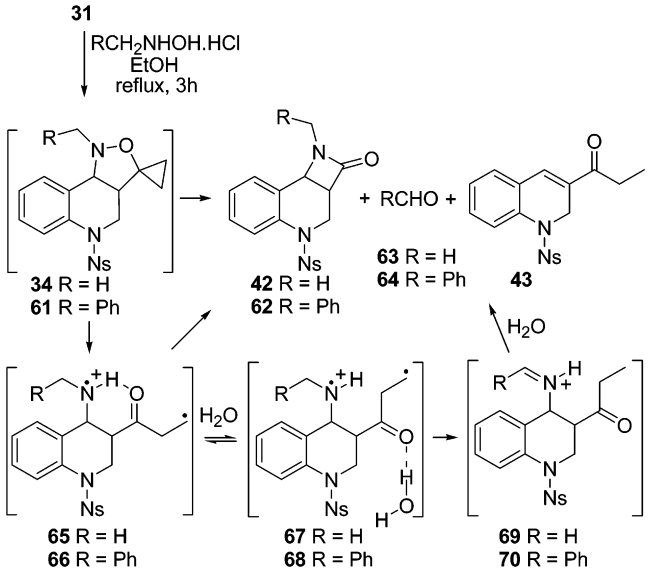
In the second hypothesis, the heterolysis of the N−O bond could be assisted by the concomitant C3−C4 ring expansion of a cyclopropyloxonium ion in analogy with the cyclopropylcarbinyl cation behavior. The formed oxetane cation **55** might be intramolecularly trapped by nitrogen to form a highly strained oxaazaspiroheptane **56**. This strained intermediate could evolve to **53** and ethylene through a formal retro Paternò−Buchi reaction and deprotonation (path B).

The different behaviors of the cis- and trans-fused isoxazolidines **38a** and **38b** appear to be in accord with the illustrated diradical pathway. In the cis-intermediate **57**, the relative orientation of the orbitals is suitable for the attack of the radical nitrogen to the carbonyl as shown diagrammatically in Scheme 10. In the trans-intermediate **59**, there is an unfavorable stereoelectronic orientation for the overlapping of nitrogen and C=O orbitals. This fact should cause a relatively longer lifetime for the diradical cation **59** which undergoes different reaction pathways. The diradical **59**, via intra- or intermolecular H-shift, could give rise to the iminium ion **60** which is exactly the expected precursor of ketone **47** via an intramolecular Mannich reaction (Scheme 10).

The formation of an iminium intermediate can also explain the formation of ethyl ketones **43** and **44** in the presence of traces of H_2O. Hydrogen bonding with molecules of H_2O destabilizes the intramolecular hydrogen bond in the intermediates **65** and **66** hampering the four-membered ring closure (Scheme 11). Therefore, the diradical cations **67** and **68** could evolve to the iminium ions **69** and **70**, respectively, analogues of **60**. The *β*-iminium ketones **69** and **70** preferentially undergo either elimination to **43**, or hydrolysis to aldehydes **63** and **64** and the corresponding amine, which successively produces **43** by a retro-Michael addition. A confirmation of this hypothesis came by treating the aldehyde **31** with a slight excess of *N*-benzylhydroxylamine chlorhydrate in absolute ethanol (ca. 99.8%) (Scheme 11). After 3 h at the reflux temperature the reaction mixture consisted of the *β*-lactam **62**, the ethyl ketone **43**, benzaldehyde (**64**), and a small amount of *N*-benzyl-*C*-phenyl nitrone derived from the condensation of benzaldehyde with the excess of hydroxylamine.

Finally, more support for the proposed homolytic mechanism derived from the study of the rearrangement of the spirocyclopropane isoxazolidines **71**. At room

SCHEME 11



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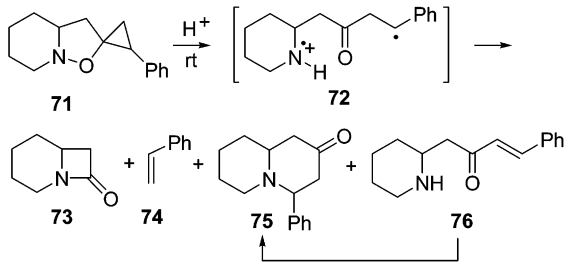

temperature and in the presence of TsOH, the mixture of isoxazolidines **71** provided a complex mixture of the *β*-lactam **73**,[14] styrene (**74**), the *cis*- and *trans*-quinolizidinones **75**[15] (trans/cis ratio 2:1), and the enone **76**[16] which slowly underwent intramolecular cyclization to **75** (Scheme 12).

The formation of all the observed products can be rationalized starting from the common diradical intermediate **72** which could evolve to the *β*-lactam **73** and styrene (**74**) through ring closure and fragmentation (Scheme 9, path A), but the relatively more stable benzyl radical could also undergo an 1,5-hydrogen shift to give, after deprotonation, the conjugated enone **76**.

Conclusion

A novel chemoselective reaction of 5-spirocyclopropane isoxazolidines has been reported. These compounds can selectively undergo ring contraction to *β*-lactams, with concurrent extrusion of ethylene, or ring expansion to tetrahydropyridones, depending on the preliminary treatment with or without a protic acid.

The two-step process 1,3-dipolar cycloaddition/acidic thermal rearrangement represents a useful strategy to

(14) Brunwin, D. M.; Lowe, G.; Parker, J. *J. Chem. Soc. C* **1971**, 3756−3762.

(15) The diastereomeric mixture of 5-spirocyclopropane isoxazolidines **71** was converted into the *cis*- and *trans*-quinolizidinones **76** in 28% and 52% isolated yield, respectively, by heating at 110 °C under neutral conditions.

(16) Quick, J.; Meltz, C. *J. Org. Chem*. **1979**, *44*, 573−578.

synthesize new classes of 3,4-cis-fused bicyclic azetidin-2-ones, starting from easily available alkylidenecyclopropanes obtained from α-amino or α-hydroxy acids, 1,3-dicarbonyl, β-amino alcohol, and acid derivatives.

Two different hypotheses have been formulated to rationalize the formation of β-lactam and ethylene, but the formation of transient cation diradical intermediates from the homolytic cleavage of the protonated N−O bond was shown to be consistent with the observed behavior of 5-spirocyclopropane isoxazolidines under acidic conditions.

Experimental Section

General Remarks. All the reactions requiring anhydrous conditions were carried out under nitrogen or argon, and the solvents were appropriately dried before use. NMR spectra were recorded in $CDCl_3$ (except were indicated), and the data are reported in δ (ppm) from TMS. Multiplicity of the ^{13}C NMR was determined by means of APT experiments. In mass spectra, relative percentages are shown in brackets. R_f values refer to TLC on 0.25 mm silica gel plates and were measured (except were indicated) using the same eluant employed in the purification of the corresponding compounds.

5-Cyclopropylidene-1,1-diethoxy-3-pentanol (13). A mixture of $Pd(OAc)_2$ (11.2 mg, 5% mol) and PPh_3 (31.4 mg, 12% mol) was degassed under reduced pressure for 1 h. Then THF (5 mL) was added under Ar, and the solution was stirred for 5 min. A solution of **5** (286 mg, 1.2 mmol) in THF (5 mL) was added, and when the solution had turned green, a solution of aldehyde **12** (146.2 mg, 1 mmol) in THF (5 mL) was added. After the mixture was stirred for 5 min, diethylzinc (224 mg, 2 mmol) was added and the mixture was stirred at rt for 3 h. The mixture was quenched with a 6 M solution of NH_4Cl/NH_4OH (2 mL) and filtered through Celite and Na_2SO_4. The solvent was removed under reduced pressure, and the crude **13** was purified by chromatography on silica gel (CH_2Cl_2/diethyl ether 9:1) to obtain **13** as a colorless oil (135 mg, 63%).

13: R_f = 0.38; ^1H NMR (250 MHz) δ 5.70 (m, 1H), 4.65 (t, J = 5.7 Hz, 1H), 3.38 (m, 1H), 3.67−3.42 (m, 4H), 3.13 (d, J = 2.4 Hz, 1H), 2.30 (m, 2H), 1.74−1.68 (m, 2H), 1.15 (t, J = 7.1 Hz, 6H), 0.98 (m, 4H); ^{13}C NMR (66 MHz) δ 124.2 (s), 114.0 (d), 102.0 (d), 68.1 (d), 62.0 (t), 61.2 (t), 39.6 (t), 15.2 (q), 15.1 (q), 2.5 (t), 1.6 (t); MS (EI) m/z 213 (0.08), 101 (68), 75 (37), 73 (90), 45 (100).

3-(Acetyloxy)-5-cyclopropylidenepentanal (14). (1) Acetylation of the Hydroxyl Group. Acetic anhydride (55 μL, 0.59 mmol) was added dropwise at 0 °C to a solution of the alcohol **13** (1.76 g, 8.2 mmol) and DMAP (53 mg, 0.43 mmol) in diethyl ether (2 mL). The solution was stirred at rt for 1.5 h. The resulting mixture was concentrated under reduced pressure, diluted with hexane, filtered through a sintered glass funnel, and concentrated. After purification of the crude mixture by chromatography on silica gel (pentane/diethyl ether 8:2), the acetyl derivative was obtained as a colorless oil (1.77 g, 84%).

3-(Acetyloxy)-5-cyclopropylidene-1,1-diethoxypentane: R_f = 0.43; ^1H NMR (200 MHz) δ 5.70 (tp, J = 7.1, 2.1 Hz, 1H), 5.08 (quintet, J = 6.2 Hz, 1H), 4.54 (t, J = 5.9 Hz, 1H), 3.60 (m, 2H), 3.48 (m, 2H), 2.44 (t, J = 6.4 Hz, 2H), 2.01 (s, 3H), 1.86 (t, J = 6.0 Hz, 2H), 1.18 (t, J = 7.1 Hz, 6H), 1.03 (m, 4H); ^{13}C NMR (66 MHz) δ 170.4 (s), 125.0 (s), 112.8 (d), 100.3 (d), 70.9 (d), 61.7 (t), 61.0 (t), 37.8 (t), 36.8 (t), 21.2 (q), 15.3 (q), 15.2 (q), 2.7 (t), 1.8 (t); IR ($CDCl_3$) ν 2977, 2930, 1739 cm^{-1}; MS (EI) m/z 213 (0.1), 103 (55), 96 (15), 79 (13), 75 (29), 43 (100); MS (CI with NH_3) m/z 274 (1, MNH_4^+), 211 (100).

(2) Deprotection of the Aldehyde. A 0.2 M aqueous solution of H_2SO_4 (100 mL) was added to a solution of the acetal (1.77 g, 6.9 mmol) in THF (80 mL) at rt. The mixture was stirred for 7 h, and then diethyl ether (80 mL) was added. The two phases were separated, and the organic layer was washed sequentially with a saturated solution of $NaHCO_3$ and a saturated solution of NaCl. The resulting crude product was purified by chromatography on silica gel (pentane/diethyl ether 75:25). Aldehyde **14** was obtained as a colorless oil (905 mg, 72%).

14: R_f = 0.25; ^1H NMR (200 MHz) δ 9.73 (t, J = 2.2 Hz, 1H), 5.70 (tp, J = 7.1, 2.1 Hz, 1H), 5.39 (quintet, J = 6.2 Hz, 1H), 2.64 (dd, J = 6.2, 2.2 Hz, 2H), 2.55−2.43 (m, 2H), 2.01 (s, 3H), 1.13−0.98 (m, 4H); ^{13}C NMR (66 MHz) δ 199.5 (d), 170.3 (s), 126.4 (s), 112.0 (d), 68.9 (d), 47.4 (t), 36.4 (t), 21.1 (q), 2.8 (t), 1.9 (t); IR ($CDCl_3$) ν 2981, 1734 cm^{-1}; MS (CI with NH_3) m/z 200 (71, MNH_4^+), 183 (100, MH^+), 182 (34, M^+), 140 (60), 123 (92).

(3a*R,5*R**,6a*S**)- and (3a*R**,5*S**,6a*S**)-1,3a,4,5,6,6a-Hexahydro-1-methylspiro[3*H*-cyclopent[*c*]isoxazole-3,1′-cyclopropan]-5-yl Acetate (16a and 16b).** *N*-Methylhydroxylamine hydrochloride (468 mg, 5.6 mmol) and pyridine (453 μL, 5.6 mmol) were added to a solution of the aldehyde **14** (850 mg, 4.7 mmol) in diethyl ether (235 mL) at rt. The mixture was stirred at rt overnight, and the salts were eliminated by filtration through a short pad of Celite. The solvent was removed under reduced pressure, and the crude mixture (**16a**/**16b** = 1:1) was separated by chromatography on silica gel (pentane/diethyl ether 25:75) to obtain **16a** as a colorless oil (379 mg, 32%) and **16b** as a colorless oil (379 mg, 32%).

16a: R_f = 0.25; ^1H NMR (400 MHz) δ 5.28 (quintet, J = 4.8 Hz, 1H), 3.74 (br d, J = 6.7 Hz, 1H), 3.04 (q, J = 8.2 Hz, 1H), 2.78 (s, 3H), 2.07 (br s, 2H), 2.01 (s, 3H), 2.00−1.94 (m, 1H), 1.89−1.83 (m, 1H), 1.04 (ddd, J = 11.5, 6.0, 1.6 Hz, 1H), 0.88 (quintet, J = 6.3 Hz, 1H), 0.76 (quintet, J = 5.2 Hz, 1H), 0.63 (dt, J = 10.5, 6.3 Hz, 1H); ^{13}C NMR (66 MHz) δ 170.4 (s), 76.5 (d), 73.2 (d), 66.6 (s), 48.4 (d), 45.4 (q), 38.2 (t), 36.3 (t), 21.1 (q), 14.4 (t), 4.7 (t); IR ($CDCl_3$) ν 2960, 1736 cm^{-1}; MS (EI) m/z 211 (5, M^+), 94 (28), 66 (100), 43 (73); HRMS found 211.1212, $C_{11}H_{17}NO_3$ required 211.1208.

16b: R_f = 0.14 (pentane/diethyl ether 25:75); ^1H NMR (400 MHz) δ 4.94 (quintet, J = 7.3 Hz, 1H), 3.57 (br d, J = 6.9 Hz, 1H), 2.85 (t, J = 6.5 Hz, 1H), 2.77 (s, 3H), 2.39−2.32 (m, 1H), 2.16 (quintet, J = 6.9 Hz, 1H), 2.04 (s, 3H), 1.89−1.77 (m, 2H), 1.04 (quintet, J = 5.6 Hz, 1H), 0.94−0.84 (m, 1H), 0.79−074 (m, 1H), 0.62 (dt, J = 10.5, 6.1 Hz, 1H); ^{13}C NMR (50 MHz) δ 171.0 (s), 74.3 (d), 72.3 (d), 66.7 (s), 48.0 (d), 45.6 (q), 37.5 (t), 35.7 (t), 21.1 (q), 15.1 (t), 4.9 (t); IR ($CDCl_3$) ν 2955, 1736 cm^{-1}; MS (EI) m/z 211 (10, M^+), 94 (28), 66 (100), 57 (11), 43 (93); HRMS found 211.1201, $C_{11}H_{17}NO_3$ required 211.1208.

(4a*R,6*R**,7a*S**)- and (4a*R**,6*S**,7a*S**)-6-(Acetyloxy)-octahydro-1-methyl-4*H*-cyclopenta[*b*]pyridin-4-ones (17a and 17b).** A solution of the adduct **16a** (51 mg, 0.24 mmol) in xylenes (30 mL) was refluxed for 6 h. After being cooled at rt, the solution was passed through a short pad of silica gel, eluting first with petroleum ether to remove the high boiling solvent and then with MeOH to recover the product. The solvent was removed under reduced pressure to give a mixture of **17a** and **17b** in a 5.4:1 ratio. The crude residue was purified by chromatography on silica gel (MeOH/diethyl ether 1:9) to obtain **17a** as a colorless oil (27 mg, 53%) and **17b** as a colorless oil (5 mg, 10%).

Starting from **16b** (50 mg, 0.24 mmol) and following the same procedure, a mixture of the two diastereomers **17a** and **17b** (ratio 1:5.5) was obtained in 26% overall yield.

17a: R_f = 0.35; ^1H NMR (400 MHz) δ 5.24 (t, J = 5.8 Hz, 1H), 3.15 (q, J = 7.2 Hz, 1H), 2.97−2.92 (m, 1H), 2.91 (quintet, J = 8.4 Hz, 1H), 2.75−2.59 (m, 2H), 2.50−2.41 (m, 2H), 2.34 (s, 3H), 2.03 (s, 3H), 1.98−1.87 (m, 3H); ^{13}C NMR (66 MHz) δ 210.2 (s), 170.4 (s), 74.4 (d), 66.6 (d), 52.9 (t), 49.7 (d), 43.4 (q), 39.2 (t), 37.4 (t), 33.0 (t), 21.2 (q); IR ($CDCl_3$) ν 2952, 2841, 1736 cm^{-1}; MS (EI) m/z 211 (15, M^+), 152 (48), 124 (44), 110 (60), 96 (12), 82 (20), 68 (12), 42 (100); HRMS found 234.11025, $C_{11}H_{17}NNaO_3$ required 234.11061.

17b: R_f = 0.35; ^1H NMR (400 MHz) δ 5.08 (quintet, J = 6.2 Hz, 1H), 3.11 (q, J = 7.1 Hz, 1H), 3.00−2.93 (m, 1H), 2.79−

2.61 (m, 3H), 2.49 (ddt, J = 16.2, 1.0, 5.0 Hz, 1H), 2.38 (s, 3H), 2.35 (dt, J = 1.1, 6.8 Hz, 1H), 2.23 (quintet, J = 6.8 Hz, 1H), 2.16−2.08 (m, 1H), 2.04 (s, 3H), 1.69 (quintet, J = 6.7 Hz, 1H); ^{13}C NMR (66 MHz) δ 210.9 (s), 170.9 (s), 73.4 (d), 65.7 (d), 51.8 (t), 49.5 (d), 43.4 (q), 39.4 (t), 35.0 (t), 32.0 (t), 29.7 (q); IR ($CDCl_3$) ν 2926, 1721, 1467, 1362, 1253, 1048 cm^{-1}; MS (EI) m/z 211 (5, M^+), 151 (100), 134 (16), 124 (58), 108 (23), 85 (32), 82 (64); HRMS found 234.11002, $C_{11}H_{17}NNaO_3$ required 234.11061.

(1*R,3*R**,5*S**)- and- (1*R**,3*S**,5*S**)-3-(Acetyloxy)-6-methyl-6-azabicyclo[3.2.0]heptan-7-one (26a and 26b).** TFA (15 μL, 0.2 mmol) was added dropwise to a solution of pure **16a** (21 mg, 0.1 mmol) in CH_3CN (2.5 mL). The mixture was refluxed for 15 min, and after cooling to rt, the solvent was removed at reduced pressure to give a 1.6:1 mixture of **26a** and **26b**. The two diastereomers were separated by chromatography on silica gel (MeOH/diethyl ether 1: 9) to obtain **26a** as a yellow oil (10 mg, 56%) and **26b** as a yellow oil (6.6 mg, 36%).

Starting from **16b** (20 mg, 0.09 mmol) and following the same procedure a ca. 1:2 mixture of **26a** and **26b** was obtained (**26a**: 5 mg, **26b**: 9 mg; 82% overall yield).

Starting from a 1:1 mixture of **16a** and **16b** and following the same procedure a 1:1 mixture of **26a** and **26b** was obtained in 63% overall yield.

26a: R_f = 0.53; ^{1}H NMR (400 MHz) δ 5.16 (tt, J = 9.9, 3.3 Hz, 1H), 3.98 (t, J = 4.5 Hz, 1H), 3.57 (dd, J = 8.8, 4.0 Hz, 1H), 2.76 (s, 3H), 2.52 (t, J = 6.7 Hz, 1H), 2.47 (t, J = 5.3 Hz, 1H), 2.06 (s, 3H), 1.62 (ddd, J = 13.3, 10.0, 8.8 Hz, 1H), 1.43 (ddd, J = 14.3, 9.5, 4.8 Hz, 1H); ^{13}C NMR (66 MHz) δ 170.4 (s; C-7), 168.7 (s; *C*OCH_3), 73.2 (d; C-3), 56.3, 52.3 (d; C-1, C-5), 31.8, 29.8 (t; C-2, C-4), 26.3 (q; NCH_3), 21.0 (q; $COCH_3$); IR ($CDCl_3$) ν 2961, 1742 cm^{-1}; MS (EI) m/z 183 (0.4, M^+), 125 (2), 66 (75), 43 (100); MS (CI with NH_3) m/z 201 (35, MNH_4^+), 184 (MH^+); HRMS found 206.0793, $C_9H_{13}NNaO_3$ required 206.07931.

26b: R_f = 0.32; ^{1}H NMR (400 MHz) δ 5.39 (t, J = 4.9 Hz, 1H), 4.08 (t, J = 3.8 Hz, 1H), 3.59 (dd, J = 8.4, 3.2 Hz, 1H), 2.73 (s, 3H), 2.30 (d, J = 15.1 Hz, 1H), 2.25 (dd, J = 15.7, 1.6 Hz, 1H), 2.02 (s, 3H), 1.84 (ddd, J = 15.1, 8.4, 5.0 Hz, 1H), 1.70 (dt, J = 15.7, 5.1 Hz, 1H); ^{13}C NMR (50 MHz) δ 170.7 (s), 170.1 (s), 76.9 (d), 58.5 (d), 54.5 (d), 31.9 (d), 31.7 (t), 26.4 (q), 21.1 (q); IR ($CDCl_3$) ν 3689, 2958, 1740, 1676, 1601, 1395, 1250 cm^{-1}; MS (EI) m/z 184 (0.4, MH^+), 125 (2), 66 (75), 43 (100); MS (CI with NH_3) m/z = 184 (6, MH^+), 122 (19), 93 (18), 65 (100); HRMS found 206.07928, $C_9H_{13}NNaO_3$ required 206.07931.

Ethyl 2-[(2-Cyclopropylideneethyl)-[(2-nitrophenyl)-sulfonyl)]amino]benzoate (29). A mixture of $Pd(dba)_2$ (134 mg, 0.23 mmol) and dppe (111 mg, 0.28 mmol) was degassed under vacuum for 1 h and then treated with a solution of 1-tosyloxy-1-vinylcyclopropane (**5**) (928 mg, 3.9 mmol) in THF (10 mL) under N_2. After 10 min the mixture, which had turned green, was added to a mixture of the amino ester **27** (1.5 g, 4.3 mmol) and NaH (93.6 mg, 5.8 mmol) in THF (20 mL). The reaction mixture was stirred at rt overnight and filtered through a short pad of Celite, and then the solvent was removed under reduced pressure. The crude residue was purified by chromatography on silica gel (CH_2Cl_2/petroleum ether 9:1) to obtain **29** as a white waxy solid (1.76 g, 98%).

29: R_f = 0.42 (CH_2Cl_2); ^{1}H NMR (200 MHz) δ 7.89 (dd, J = 6.1, 3.4 Hz, 1H), 7.70−7.50 (m, 4H), 7.47−7.38 (m, 2H), 7.07 (dd, J = 5.9, 3.4 Hz, 1H), 5.96 (tp, J = 7.3, 2.0 Hz, 1H), 4.85−4.35 (m, 2H), 4.19 (q, J = 7.2 Hz, 2H), 1.33 (t, J = 7.2 Hz, 3H), 1.04−0.50 (m, 4H); ^{13}C NMR (50 MHz) δ 165.8 (s), 147.9 (s), 136.6 (s), 133.3 (d), 132.6 (d), 132.4 (s), 131.9 (d), 131.5 (d), 131.2 (d), 131.1 (d), 128.7 (s), 128.6 (d), 123.6 (d), 112.8 (d), 61.3 (t), 53.9 (t), 13.9 (q), 2.5 (t), 1.3 (t); IR ($CDCl_3$) ν 2987, 2935, 1713, 1544, 1365, 1255, 1164, 1125 cm^{-1}; MS (EI) m/z 350 (2), 230 (32), 184 (100). Anal. Calcd for $C_{20}H_{20}N_2O_6S$ (416.45): C, 57.68; H, 4.84; N, 6.73. Found: C, 57.65; H, 5.24; N, 6.43.

Methyl 2-[(2-Cyclopropylideneethyl)[(4-methylphenyl)-sulfonyl]amino]benzoate (30). The same procedure was followed, starting from **28**, to obtain **30** as a yellow solid in 90% yield.

30: R_f = 0.22 (CH_2Cl_2); mp 71−72 °C; ^{1}H NMR (200 MHz) δ 7.87−7.79 (m, 1H), 7.54 (d, J = 8.3 Hz, 2H), 7.40−7.32 (m, 2H), 7.25 (d, J = 8.3 Hz, 2H), 6.94−6.87 (m, 1H), 5.88 (tp, J = 6.9, 1.9 Hz, 1H), 4.39 (d, J = 6.9 Hz, 2H), 3.82 (s, 3H), 2.42 (s, 3H), 1.03−0.90 (m, 2H), 0.80−0.68 (m, 2H); ^{13}C NMR (50 MHz) δ 166.4 (s), 142.9 (s), 137.9 (s), 136.8 (s), 132.6 (s), 131.5 (d), 130.9 (d), 130.6 (d), 129.2 (d, 2C), 127.8 (d), 127.4 (s), 127.3 (d, 2C), 112.8 (d), 53.0 (t), 52.1 (q), 21.5 (q), 2.7 (t), 1.5 (t); IR ($CDCl_3$) ν 3061, 2986, 2954, 1722, 1596, 1433, 1341, 1297, 1255, 1155 cm^{-1}; MS (EI) m/z 340 (1), 318 (4), 216 (70), 184 (100), 156 (13), 132 (27), 91 (67), 77 (20), 65 (14); MS (CI with NH_3) m/z 372 (90, MH^+). Anal. Calcd for $C_{20}H_{21}NO_4S$ (371.45): C, 64.67; H, 5.70; N, 3.77. Found: C, 64.37; H, 5.85; N, 3.76.

***N*-(2-Cyclopropylideneethyl)-*N*-(2-formylphenyl)-2-nitrobenzenesulfonamide (31). (1) Reduction of the Ester Group to Alcohol.** A 1 m solution of DIBALH in CH_2Cl_2 (9.2 mL, 9.2 mmol) was added dropwise to solution of ester **29** (1.28 g, 3.1 mmol) in CH_2Cl_2 (16 mL) at −30 °C. The mixture was stirred for 2 h at low temperature, and then it was allowed to reach rt and treated first with methanol and then with a saturated solution of sodium and potassium tartrate. The two phases were separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4. Evaporation of the solvent gave the crude alcohol (983.9 mg, 86%) as a yellow oil, which was used in the next step without further purification.

***N*-(2-Cyclopropylideneethyl)-*N*-[2-(hydroxymethyl)-phenyl]-2-nitrobenzenesulfonamide:** R_f = 0.18 (petroleum ether/diethyl ether 1:2); ^{1}H NMR (200 MHz) δ 7.74−7.48 (m, 5H), 7.35 (dt, J = 1.2, 7.5 Hz, 1H), 7.13 (dt, J = 1.9, 8.1 Hz, 1H), 6.78 (dd, J = 8.0, 1.1 Hz, 1H), 5.81 (tp, J = 7.3, 2.0 Hz, 1H), 4.85−4.63 (m, 2H), 4.51−4.40 (m, 1H), 4.31−4.20 (m, 1H), 2.75−2.62 (m, 1H), 1.17−0.66 (m, 3H), 0.52−0.38 (m, 1H); ^{13}C NMR (75 MHz) δ 148.2 (s), 142.3 (s), 135.5 (s), 133.8 (d), 132.1 (d), 131.8 (s), 131.1 (d), 130.8 (d), 130.1 (s), 129.6 (d), 129.5 (d), 128.4 (d), 123.9 (d), 111.5 (d), 60.8 (t), 54.9 (t), 2.8 (t), 1.4 (t); IR ($CDCl_3$) ν 3550, 3063, 2960, 2926, 1543, 1364, 1160 cm^{-1}; MS (EI) m/z 374 (0.1, M^+), 291 (4), 277 (7), 188 (57), 186 (44), 170 (100), 158 (52), 91 (28).

(2) Swern Oxidation. A solution of DMSO (0.6 mL) in CH_2Cl_2 (2 mL) was added to a solution of oxalyl chloride (320 μL) in CH_2Cl_2 (8 mL) at −78 °C, and then a solution of the crude alcohol (983.9 mg, 3.07 mmol) in CH_2Cl_2 (2 mL) was added dropwise to the mixture. After the mixture was stirred at −60 °C for 20 min, TEA (2.1 mL) was added, and then the mixture was allowed to reach rt and poured into an equal volume of water. The aqueous phase was extracted twice with CH_2Cl_2. The collected organic phases were dried over Na_2SO_4 and concentrated to give the crude aldehyde **31**. After purification by chromatography on silica gel (petroleum ether/diethyl ether 1:3), **31** was obtained as a yellow solid (980 mg, 81%).

31: R_f = 0.53; mp 140−142 °C; ^{1}H NMR (200 MHz) δ 10.14 (s, 1H), 7.95−7.90 (m, 1H), 7.72−7.68 (m, 2H), 7.58−7.47 (m, 4H), 7.27−7.12 (m, 1H), 5.89 (tp, J = 7.3, 1.9 Hz, 1H), 4.85−4.65 (m, 1H), 4.60−4.32 (m, 1H), 1.00−0.80 (m, 2H), 0.40−0.80 (m, 2H); ^{13}C NMR (50 MHz) δ 189.7 (d), 147.9 (s), 140.0 (s), 135.6 (s), 134.4 (d), 134.0 (d), 131.8 (d), 131.7 (s), 131.3 (d), 131.1 (s), 131.0 (d), 129.3 (d), 128.4 (d), 124.0 (d), 111.3 (d), 55.2 (t), 2.9 (t), 1.5 (t); IR (KBr) ν 3089, 2979, 2916, 1689, 1597, 1545, 1369, 1356, 1171, 773 cm^{-1}; MS (EI) m/z 372 (0.7, M^+), 319 (2), 186 (100) 168 (9), 158 (12), 143 (12), 77 (15); HRMS found 372.0774, $C_{18}H_{16}N_2O_5S$ requires 372.0779.

***N*-(2-Cyclopropylideneethyl)-*N*-(2-formylphenyl)-4-methylbenzenesulfonamide (32).** The same procedure was followed starting from **30** to obtain **32** as a colorless solid in 96% yield.

***N*-(2-Cyclopropylideneethyl)-*N*-[2-(hydroxymethyl)-phenyl]-4-methylbenzenesulfonamide:** yellow solid; R_f =

0.18 (petroleum ether/diethyl ether 1:1); ^{1}H NMR (250 MHz) δ 7.58 (d, J = 8.2 Hz, 2H), 7.55 (dd, J = 7.3, 1.6 Hz, 1H), 7.32 (td, J = 7.4, 1.2 Hz, 1H), 7.32 (d, J = 8.2 Hz, 2H), 7.11 (td, J = 7.6, 1.6 Hz, 1H), 6.46 (dd, J = 8.1, 1.2 Hz, 1H), 5.70 (m, 1H), 4.98 (dd, J = 11.9, 2.7 Hz, 1H), 4.62 (dd, J = 13.2; 5.8 Hz, 1H), 4.48 (t, J = 11.0 Hz, 1H), 3.90 (dd, J = 13.1; 8.4 Hz, 1H), 3.06 (dd, J = 9.9, 3.6 Hz, 1H), 2.47 (s, 3H), 1.04−0.76 (m, 3H), 0.58−0.44 (m, 1H); ^{13}C NMR (62.5 MHz) δ 143.8 (s), 142.3 (s), 137.1 (s), 134.8 (s), 130.6 (d), 129.5 (d, 2C), 128.9 (s), 128.8 (d), 128.0 (d), 127.9 (d, 2C), 127.5 (d), 111.4 (d), 61.1 (t), 53.5 (t), 21.5 (q), 2.6 (t), 1.3 (t); MS (EI) m/z = 290 (6), 188 (46), 186 (10), 170 (62), 158 (23), 130 (22), 118 (45), 106 (27), 91 (100), 77 (31), 65 (27); MS (CI with NH_3) m/z 344 (100, MH^+).

32: R_f = 0.40 (petroleum ether/diethyl ether 1:2); mp 90−91 °C; ^{1}H NMR (250 MHz) δ 10.38 (s, 1H), 7.98−7.90 (m, 1H), 7.51 (d, J = 8.2 Hz, 2H), 7.45−7.35 (m, 2H), 7.29 (d, J = 8.2 Hz, 2H), 6.78−6.69 (m, 1H), 5.73 (tp, J = 7.1, 1.9 Hz, 1H), 4.68 (br s, $w^1/_2$h = 29.0 Hz, 1H), 4.02 (br s, $w^1/_2$h = 25.3 Hz; 1H), 2.44 (s, 3H), 1.05−0.71 (m, 3H), 0.70−0.49 (m, 1H); ^{13}C NMR (62.5 MHz) δ 190.2 (d), 144.0 (s), 141.6 (s), 136.0 (s), 134.6 (s), 133.8 (d), 129.7 (s), 129.6 (d, 2C), 128.4 (d), 128.0 (d), 127.9 (d), 127.8 (d, 2C), 111.4 (d), 53.0 (t), 21.5 (q), 2.7 (t), 1.5 (t); IR ($CDCl_3$) ν 3065, 2995, 2925, 2775, 1687, 1590, 1343, 1155 cm^{-1}; MS (EI) m/z 341 (0.6, M^+), 186 (100), 158 (10), 143 (14), 91 (73), 77 (25); HRMS found 341.1063, $C_{19}H_{19}NO_3S$ requires 341.1085.

(3′a*R,9′b*R**)-3′a,4′,5′,9′b-Tetrahydro-1′-methyl-5′-[(2-nitrophenyl)sulfonyl]-spiro[cyclopropane-1,3′(1*H*)-isoxazolo[4,3-*c*]quinoline] (33).** TEA (55.6 μL, 0.4 mmol) was added to a mixture of aldehyde **31** (100 mg, 0.27 mmol) and *N*-methylhydroxylamine hydrochloride (33.7 mg, 0.4 mmol) in toluene (2 mL) cooled to 0 °C. The mixture was refluxed for 15 min, diluted with diethyl ether, dried over Na_2SO_4, and filtered. The solvent was removed, and the crude mixture was chromatographed on silica gel (CH_2Cl_2, then CH_2Cl_2/AcOEt 1:9) to give the isoxazolidine **33** as a yellow solid (97.3 mg, 90%).

33: R_f = 0.07 (CH_2Cl_2); mp 169−172 °C; ^{1}H NMR (500 MHz, 280 K) δ 7.76−7.71 (m, 2H), 7.68 (dd, J = 8.0, 1.2 Hz, 1H), 7.61 (dt, J = 1.3, 7.7 Hz, 1H), 7.51−7.46 (m, 2H), 7.32−7.25 (m, 2H), 4.23 (dd, J = 14.0, 5.9 Hz, 1H), 3.80 (d, J = 7.5 Hz, 1H), 3.49 (t, J = 13.3 Hz, 1H), 2.98 (s, 3H), 2.82 (dt, J = 11.6, 6.6 Hz, 1H), 1.07−1.02 (m, 1H), 0.94−0.84 (m, 2H), 0.81−0.75 (m, 1H); ^{13}C NMR (50 MHz) δ = 147.8 (s), 136.1 (s), 134.0 (d), 133.0 (s), 131.7 (d), 130.1 (d), 129.9 (d), 129.1 (s), 128.2 (d), 126.2 (d), 124.2 (d), 123.9 (d), 66.7 (d), 64.4 (s), 46.8 (t), 46.2 (q), 44.4 (d), 12.4 (t), 4.1 (t); IR($CDCl_3$) ν 3040, 3005, 2957, 2879, 1598, 1484, 1450, 1347, 1158, 1078 cm^{-1}; MS (EI) m/z 401(2, M^+), 344 (1), 215 (55), 186 (9), 159 (22), 130 (100); HRMS found 401.1041, $C_{19}H_{19}N_3O_5S$ requires 401.1045.

(3′a*R,9′b*R**)-3′a,4′,5′,9′b-Tetrahydro-1′-methyl-5′-[(4-methylphenyl)sulfonyl]spiro[cyclopropane-1,3′(1*H*)-isoxazolo[4,3-*c*]quinoline] (34).** The synthesis of **34** was performed from **32** following the same procedure. Product **34** was obtained as a yellow solid in 91% yield.

34: R_f = 0.39 (petroleum ether/ethyl acetate 2:1); mp 132−135 °C; ^{1}H NMR (500 MHz, 280 K) δ 7.64 (d, J = 7.5 Hz, 1H), 7.55 (d, J = 8.1 Hz, 2H), 7.40 (d, J = 7.6 Hz, 1H), 7.30 (dt, J = 1.4, 7.7 Hz, 1H), 7.25 (d, J = 8.1 Hz, 2H), 7.22 (dt, J = 1.2, 7.5 Hz, 1H), 4.19 (dd, J = 13.9, 5.9 Hz, 1H), 3.52 (d, J = 7.5 Hz, 1H), 3.40 (t J = 12.9 Hz, 1H), 2.87 (s, 3H), 2.54 (dt, J = 12.5, 6.3 Hz, 1H), 2.39 (s, 3H), 1.05−1.00 (m, 1H), 0.91−0.86 (m, 1H), 0.80−0.75 (m, 1H), 0.71−0.75 (m, 1H); ^{13}C NMR (50 MHz) δ 143.8 (s), 137.0 (s), 136.7 (s), 129.6 (d, 3C), 128.6 (s), 128.0 (d), 127.0 (d, 2C), 125.6 (d), 124.3 (d), 66.5 (d), 64.2 (s), 46.4 (t), 46.0 (q), 43.7 (d), 21.4 (q), 12.3 (t), 3.9 (t); IR ($CDCl_3$) ν 3070, 3037, 3004, 2927, 2861, 1599, 1484, 1447, 1348, cm^{-1}; MS (EI) m/z 370 (2, M^+), 215 (36), 159 (24) 130 (100), 91 (66). HRMS found 393.12477, $C_{20}H_{22}N_2NaO_3S$ requires 393.124885.

Synthesis of *β*-Lactams 22, 23, 41, and 42. General Procedure. TFA (freshly distilled over P_2O_5) (1.2−2 equiv) was added to a solution of isoxazolidine **18**, **19**, **33**, or **34** (0.2 mmol) in toluene (5 mL). The mixture was heated to reflux for 45−60 min, stirred at rt in the presence of K_2CO_3 overnight, and filtered. The solvent was removed under reduced pressure, and the crude product was purified by chromatography on silica gel.

(1*R*,4*S*,5*R*)-6-Methyl-4-(1-methylethyl)-3-[(4-methylphenyl)sulfonyl)-3,6-diazabicyclo[3.2.0]heptan-7-one (22): colorless solid; 63% yield; R_f = 0.14 (ethyl acetate/petroleum ether 2:1); mp 162−163 °C; $[\alpha]^{22}_D$ = 74.4 (c = 0.215, CH_3OH); ^{1}H NMR (200 MHz) δ 7.72 (d, J = 8.0 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 4.04 (d, J = 12.4 Hz, 1H), 3.83 (d, J = 3.7 Hz, 1H), 3.61 (d, J = 6.6 Hz, 1H), 3.50 (dd, J = 7.0, 3.7 Hz, 1H), 3.39 (dd, J = 12.4, 7.0 Hz, 1H), 2.43 (s, 3H), 2.24 (s, 3H), 1.89 (octet, J = 6.7 Hz, 1H), 1.02 (d, J = 7.0 Hz, 3H), 1.00 (d, J = 6.6 Hz, 3H); ^{13}C NMR (50 MHz) δ 165.4 (s), 143.3 (s), 136.7 (s), 129.6 (d, 2C), 127.0 (d, 2C), 63.9 (d), 60.6 (d), 55.3 (d), 46.2 (t), 31.0 (d), 26.4 (q), 21.5 (q), 19.3 (q), 18.7 (q); IR ($CDCl_3$) ν 3034, 2967, 2877, 1756, 1341, 1151 cm^{-1}; MS (EI) m/z = 322 (3, M^+), 279 (64), 222 (14), 155 (100), 91 (41). Anal. Calcd for $C_{16}H_{22}N_2O_3S$ (322.42): C, 59.60; H, 6.88; N, 8.69. Found: C, 59.60; H, 6.83; N, 9.00.

(1*R*,4*S*,5*R*)-4-(1*H*-Indol-3-ylmethyl)-6-methyl-3-[(4-methylphenyl)sulfonyl]-3,6-diazabicyclo[3.2.0]heptan-7-one (23): pale yellow glass; 57% yield; R_f = 0.31 (ethyl acetate); $[\alpha]^{23}_D$ = 35.0 (c = 0.575, CH_3OH); ^{1}H NMR (200 MHz) δ 8.15 (br s, 1H), 7.78−7.69 (m, 3H), 7.43−7.36 (m, 1H), 7.34−7.14 (m, 4H), 7.08 (d, J = 2.2 Hz, 1H), 4.15 (dd, J = 9.9, 4.0 Hz, 1H), 3.99 (d, J = 12.1 Hz, 1H), 3.88 (d, J = 3.7 Hz, 1H), 3.43 (dd, J = 6.6, 3.7 Hz, 1H), 3.31 (dd, J = 12.1, 6.6 Hz, 1H), 3.24 (dd, J = 14.3, 4.0 Hz, 1H), 2.92 (dd, J = 14.3, 9.9 Hz, 1H), 2.40 (s, 3H), 2.09 (s, 3H); ^{13}C NMR (50 MHz) δ 165.8 (s), 143.3 (s), 137.0 (s), 136.3 (s), 129.7 (d, 2C), 127.3 (s), 126.9 (d, 2C), 122.7 (d), 122.4 (d), 120.0 (d), 118.7 (d), 111.3 (d), 110.8 (s), 61.8 (d), 58.4 (d), 54.8 (d), 45.3 (t), 28.2 (t), 26.3 (q), 21.5 (q); IR ($CDCl_3$) ν 3479, 3041, 2925, 1753, 1341, 1152 cm^{-1}; MS (EI) m/z 409 (10, M^+), 279 (19), 254 (8), 222 (3), 130 (100), 91 (19); HRMS found 409.1459, $C_{22}H_{23}N_3O_3S$ requires 409.1460.

(2a*R,8b*R**)-2a,3,4,8b-Tetrahydro-1-methyl-4-[(2-nitrophenyl)sulfonyl]azeto[3,2-*c*]quinolin-2(1*H*)-one] (41):** colorless solid; 72% yield; R_f = 0.18 (CH_2Cl_2/AcOEt 1:1); mp 206−209 °C; ^{1}H NMR (200 MHz) δ 8.21−8.14 (m, 1H), 7.80−7.63 (m, 4H), 7.58 (d, J = 8.1 Hz, 1H), 7.42−7.23 (m, 2H), 4.56 (dd, J = 14.6, 1.8 Hz, 1H), 4.45 (d, J = 5.1 Hz, 1H), 3.70 (br dd, J = 5.1, 4.4 Hz, 1H), 3.50 (dd, J = 14.6, 4.4 Hz, 1H), 2.44 (s, 3H); ^{13}C NMR (50 MHz) δ 166.2 (s), 138.6 (s), 134.1 (d), 133.6 (s), 132.3 (d), 132.1 (d), 130.6 (d), 129.8 (d), 126.1 (d), 125.8 (s, 2C), 125.0 (d), 124.5 (d), 54.3 (d), 52.8 (d), 45.3 (t), 26.4 (q); IR ($CDCl_3$) ν 3078, 3029, 2930, 1750, 1603, 1542, 1486, 1361, 1166 cm^{-1}; MS (EI) m/z 373 (13, M^+), 299 (19), 277 (17), 215 (2), 186 (4), 130 (100), 77 (56). Anal. Calcd for $C_{17}H_{15}N_3O_5S$ (373.38): C, 54.69; H, 4.05; N, 11.25. Found: C, 55.01; H, 3.97; N, 10.86.

(2a*R,8b*R**)-2a,3,4,8b-Tetrahydro-1-methyl-4-[(4-methylphenyl)sulfonyl)]azeto[3,2-*c*]quinolin-2(1*H*)-one] (42):** pale yellow solid; 60% yield; R_f = 0.43 (petroleum ether/diethyl ether 1:1); mp 108−112 °C; ^{1}H NMR (300 MHz) δ 7.93 (d, J = 8.0 Hz, 1H), 7.63 (d, J = 8.1 Hz, 2H), 7.42−7.34 (m, 1H), 7.22−7.18 (m, 4H), 4.76 (dd, J = 14.3, 2.2 Hz, 1H), 4.29 (d, J = 5.1 Hz, 1H), 3.56 (dt, J = 2.0, 4.8 Hz, 1H), 3.47 (dd, J = 14.3, 4.7 Hz, 1H), 2.36 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (75 MHz) δ 166.9 (s), 143.6 (s), 138.2 (s), 136.5 (s), 130.4 (d), 129.6 (d), 129.3 (d, 2C), 127.8 (d, 2C), 126.3 (s), 125.5 (d), 124.4 (d), 54.4 (d), 52.6 (d), 44.6 (t), 26.1 (q), 21.5 (q); IR (KBr) ν 3071, 2949, 1752, 1596, 1335, 1157, 1078 cm^{-1}; MS (EI) m/z 342 (2, M^+), 277 (7), 187 (2), 130 (71), 91 (26), 84 (100); HRMS found 365.09356, $C_{18}H_{18}N_2NaO_3S$ requires 365.09358.

1-[1(2-Nitrobenzensulfonyl)-1,2-dihydroquinolin-3-yl]-propan-1-one (43) and 41. A mixture of aldehyde **31** (80 mg, 0.21 mmol) and *N*-methylhydroxylamine hydrochloride (26.9 mg, 0.32 mmol) in absolute ethanol (1 mL) was refluxed for 3 h. The ethanol was removed at reduced pressure, CH_2Cl_2 was added, and the solution was stirred over Na_2CO_3. After

filtration and concentration, the crude 2:1 mixture of **41** and **43** was separated by chromatography on silica gel (CH_2Cl_2/AcOEt 1:1) to obtain **41** (45.1 mg, 62%) as a pale yellow solid and **43** (21.9 mg, 28%) as a yellow solid.

43: R_f = 0.37 (CH_2Cl_2); mp 114−116 °C; ^{1}H NMR (200 MHz) δ 7.72−7.58 (m, 3H), 7.51−7.41 (m, 3H), 7.37−7.22 (m, 2H), 7.08 (br s, 1H), 4.72 (br s, 2H), 2.56 (q, J = 7.3 Hz, 2H), 1.06 (t, J = 7.3 Hz, 3H); ^{13}C NMR (50 MHz) δ 198.3 (s), 135.6 (s), 134.1 (s, 2C), 133.9 (d), 132.6 (d), 131.7 (s), 131.1 (d), 131.0 (d, 2C), 129.0 (d), 128.3 (s), 127.4 (d), 126.4 (d), 123.7 (d), 44.3 (t), 30.3 (t), 8.2 (q); IR ($CDCl_3$) ν 3075, 2981, 2929, 2857, 1662, 1543, 1365, 1167 cm^{-1}; MS (EI) m/z 372 (0.5, M$^+$), 355 (2), 260 (1), 232 (1), 204 (3), 186 (100), 156 (58), 130 (56); HRMS found 372.0781, $C_{18}H_{16}N_2O_5S$ requires 372.0779.

(2a*R,8b*R**)-2a,3,4,8b-Tetrahydro-1-benzyl-4-[(2-nitrophenyl)sulfonyl]azeto[3,2-*c*]quinolin-2(1*H*)-one (62).** A mixture of aldehyde **31** (50 mg, 0.13 mmol) and *N*-benzylhydroxylamine hydrochloride (32 mg, 0.20 mmol) in absolute ethanol (1.3 mL) was refluxed for 3 h. The ethanol was removed at reduced pressure, and the ^{1}H NMR of the crude mixture showed the presence of β-lactam **62**, aldehyde **31**, enone **43**, benzaldehyde (**64**), and *C*,*N*-diphenylnitrone in ca. 18.8: 4.4:3.8:1.8:1 molecular ratio. The crude residue was separated by chromatography on silica gel (AcOEt/petroleum ether 3:1) to obtain **62** (40 mg, 74%) as a colorless solid.

62: R_f = 0.17 (petroleum ether/AcOEt 1:1); mp 164−167 °C; ^{1}H NMR (200 MHz) δ 8.25−8.21 (m, 1H), 7.80−7.75 (m, 3H), 7.75−7.73 (m, 1H) 7.72−7.20 (m, 5H), 7.16−7.12 (m, 2H), 7.02−6.97 (m, 1H), 4.61 (dd, J = 14.6, 1.1 Hz, 1H), 4.38−4.30 (m, 2H), 3.68−3.64 (m, 1H), 3.53−3.40 (m, 2H); ^{13}C NMR (50 MHz) δ 165.9 (s), 147.7 (s), 138.7 (s), 135.0 (s), 134.0 (d), 133.7 (s), 132.2 (d), 132.0 (d), 130.7 (d), 129.6 (d), 128.8 (d, 2C), 128.4 (d, 2C), 127.8 (d), 126.0 (d), 124.8 (d), 124.4 (d), 54.1 (d), 50.6 (d), 45.6 (t), 44.2 (t); IR ($CDCl_3$) ν 3032, 2927, 1753, 1604, 1544, 1489, 1371, 1247, 1173 cm^{-1}; MS (EI) m/z 449 (3, M$^+$), 299 (23), 263 (14), 202 (22), 187 (17), 168 (32), 127 (100), 103 (93), 100 (62), 89 (75), 76 (100), 63 (82). Anal. Calcd for $C_{23}H_{19}N_3O_5S$ (449.48): C, 61.46; H, 4.26; N, 9.35. Found: C, 61.42; H, 4.16; N, 9.18.

(2a*R*,2b*S*,6a*R*)-2-Methyloctahydro-2,5a-diazacyclobuta[*a*]pentalen-1-one (24). TFA (32 μL) was added to a solution of isoxazolidine **20** (41 mg, 0.21 mmol) in toluene (5.2 mL). The reaction flask was dipped in an oil bath at 88 °C, and the mixture was refluxed for 2 min. After the mixture was cooled to rt, the solvent was removed under reduced pressure and the crude product was treated with Dowex 50WX8-200 ion-exchange resin. β-Lactam **24** was obtained as a colorless oil (16.5 mg, 47%).

24: ^{1}H NMR (400 MHz) δ 3.95 (d, J = 3.9 Hz, 1H), 3.70 (dd, J = 3.8, 6.8 Hz, 1H), 3.56 (dd, J = 10.4, 7.0 Hz, 1H), 3.32 (d, J = 10.3 Hz, 1H), 3.06 (dt, J = 12.7, 8.3 Hz, 1H), 2.97 (ddd, J = 12.7, 8.4, 3.7 Hz, 1H), 2.82 (s, 3H), 2.41 (dd, J = 10.7, 6.8 Hz, 1H), 2.12−2.02 (m, 1H), 1.89−1.77 (m, 2H), 1.34 (dt, J = 5.4, 10.7 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 168.0 (s), 63.5 (d), 60.3 (d), 54.9 (d), 51.2 (t), 49.0 (t), 26.1 (q), 24.8 (t), 22.6 (t); IR ($CDCl_3$) ν 2967, 2881, 1743, 1426, 1396, 1199, 1085 cm^{-1}; GC−MS m/z 166 (24, M$^+$), 138 (44), 123 (22), 108 (47), 95 (100), 80 (45), 70 (65), 68 (75), 55 (41), 42 (69).

(1*S,5*R**)-6-Methyl-3-oxa-6-azabicyclo[3.2.0]heptan-7-one (25).** TFA (10 μL, 0.13 mmol) was added to a solution of isoxazolidine **21** (10 mg, 0.064 mmol) in CD_3CN (200 μL) in an NMR tube, and the mixture was heated at 70 °C for 6 min. The NMR spectra of the mixture showed the disappearance of **10** and the appearance of **25** and ethylene. Evaporation of the solvent and purification on a short pad of silica gel (MeOH) afforded β-lactam **25** as a colorless oil (5 mg, 60%).

25: ^{1}H NMR(200 MHz) δ 4.22 (d, J = 9.9 Hz, 1H), 4.12 (dd, J = 3.8, 2.9 Hz, 1H), 4.05 (d, J = 10.8 Hz, 1H), 3.68 (m, 1H), 3.38 (dd, J = 9.9, 5.7 Hz, 1H), 3.25 (dd, J = 10.9, 3.0 Hz, 1H), 2.77 (s, 3H); ^{13}C NMR (50 MHz) δ 167.6 (s), 65.9 (t), 65.8 (t), 58.2 (d), 55.8 (d), 26.6 (q); IR ($CDCl_3$) ν 2969, 2863, 1747, 1671, 1427, 1398, 1209, 1173, 1073 cm^{-1}; MS m/z 127 (10, M$^+$), 105 (18), 91 (41), 84 (46), 69 (100), 57 (81), 55 (94). HRMS: the observed peak corresponds to the M − 1 mass. The compound polymerizes on storage. Found 126.0673, $C_6H_8N_2O_2$ requires 126.0555.

3-[Benzyl(2-cyclopropylideneethyl)amino]-2,2-dimethyl-1-propanol (36). A mixture of $Pd(dba)_2$ (144 mg, 0.25 mmol) and PPh_3 (157 mg, 0.60 mmol) was degassed under vacuum for 1 h. Then, under nitrogen, a solution of 1-tosyloxy-1-vinylcyclopropane **5** (1.19 g, 5 mmol) in CH_2Cl_2 (14 mL) was added. In a different flask, TEA (1.66 mL, 12 mmol) was added to a solution of amino alcohol **35** (1.07 g, 5.5 mmol) in CH_2Cl_2 (7 mL). After 10 min, when the mixture containing **5** and the catalyst had turned orange, the solution of **35** was added to. The mixture was stirred overnight, diluted with diethyl ether, and filtered over Celite. Evaporation of the solvent and chromatography on silica gel (petroleum ether/diethyl ether 3:1) of the residue gave **36** (903 mg, 70%) as a colorless oil.

36: R_f = 0.13; ^{1}H NMR (200 MHz) δ 7.35−7.26 (m, 5H), 5.91 (tp, J = 6.8, 2.0 Hz, 1H), 5.71 (br s, 1H), 3.66 (s, 2H), 3.40 (s, 2H), 3.21 (d, J = 7.0 Hz, 2H), 2.55 (s, 2H), 1.27−0.80 (m, 4H), 0.95 (s, 6H); ^{13}C NMR (50 MHz) δ 138.6 (s), 129.1 (d, 2C), 128.4 (d, 2C), 127.2 (d), 126.5 (s), 114.1 (d), 73.4 (t), 65.2 (t), 60.8 (t), 56.5 (t), 35.6 (s), 24.4 (q, 2C), 2.5 (t), 1.9 (t); GC−MS m/z = 186 (M$^+$, 11), 157 (1), 129 (4), 118 (1), 91 (100), 65 (6); IR ($CDCl_3$) ν 3292, 3064, 3033, 2982, 2873, 1448, 1360, 1100, 1035 cm^{-1}. Anal. Calcd for $C_{17}H_{25}NO$ (259.39): C, 78.72; H, 9.71; N, 5.40. Found: C, 78.56; H, 9.46; N, 5.55.

3-[Benzyl(2-cyclopropylideneethyl)amino]-2,2-dimethylpropanal (37). Activated powdered molecular sieves (4 Å, 500 mg), NMO (337 mg, 2.79 mmol), and TPAP (33 mg, 0.09 mmol) were added, under nitrogen atmosphere, to a solution of **36** (483 mg, 1.86 mmol) in CH_2Cl_2 (3.7 mL). The mixture was stirred at rt for 1 h and then filtered through a short pad of silica gel. Evaporation of the solvent afforded the crude aldehyde **37** (478 mg, 85%) as a colorless oil, which was used in the next step without further purifications.

37: R_f = 0.88 (petroleum ether/diethyl ether 1:1); ^{1}H NMR (200 MHz) δ 9.45 (s, 1H), 7.35−7.20 (m, 5H), 5.84 (tp, J = 6.6, 1.8 Hz, 1H), 3.60 (s, 2H), 3.15 (d, J = 6.9 Hz, 2H), 2.67 (s, 2H), 1.20−0.75 (m, 4H), 1.05 (s, 6H).

(3′a*R,7′a*R**)-Octahydro-1′,7′,7′-trimethyl-5′-(phenylmethyl)spiro[cyclopropane-1,3′-isoxazolo[4,3-*c*]pyridine] (38a), (3′a*R**,7′a*S**)-Octahydro-1′,7′,7′-trimethyl-5′-(phenylmethyl)spiro[cyclopropane-1,3′-isoxazolo[4,3-*c*]-pyridine] (38b), and 5′,5′,7′-Trimethyl-3′-(phenylmethyl)-spiro[cyclopropane-1,9′-[8]oxa[3,7]diazabicyclo[4.2.1]-nonane (39).** *N*-Methylhydroxylamine hydrochloride (324 mg, 2.89 mmol) and TEA (0.54 mL, 3.89 mmol) were added to a solution of the aldehyde **37** (665 mg, 2.59 mmol) in toluene (18.5 mL) at 0 °C. After being stirred overnight at rt, the mixture was diluted with an equivalent volume of diethyl ether, treated with Na_2SO_4, and filtered. The solvent was removed under reduced pressure, and the crude mixture was separated by chromatography on silica gel (petroleum ether/AcOEt 6:1) to obtain **38a** (300 mg, 40%) as a pale yellow oil, **38b** (105 mg, 14%) as a white solid, and **39** (40 mg, 5%) as a colorless oil.

38a: R_f = 0.22; ^{1}H NMR (500 MHz) δ 7.34−7.23 (m, 5H), 3.54 (A part of an AB system, J = 13.4 Hz, 1H), 3.45 (B part of an AB system, J = 13.4 Hz, 1H), 2.83 (s, 3H), 2.78 (dd, J = 9.3, 4.4 Hz, 1H), 2.75 (d, J = 4.6 Hz, 1H), 2.34−2.26 (m, 2H), 2.20 (AB syst., J = 11.3 Hz, 1H), 2.17 (AB syst, J = 11.3 Hz, 1H), 1.12 (s, 3H), 0.90 (s, 3H), 0.86−0.77 (m, 2H), 0.60−0.50 (m, 2H); ^{13}C NMR (50 MHz) δ 139.1 (s), 128.5 (d, 2C), 127.9 (d, 2C), 126.6 (d), 75.5 (d), 63.7 (s), 62.8 (t), 60.4 (t), 53.2 (t), 50.0 (d), 45.8 (q), 33.5 (s), 27.6 (q), 25.5 (q), 12.5 (t), 2.4 (t); MS (70 eV) m/z 230 (4), 200 (2), 186 (3), 174 (8), 91 (100); IR ($CDCl_3$) ν 2961, 2815, 2786, 1452, 1361, 1251, 1165, 1122, 1036 cm^{-1}. Anal. Calcd for $C_{18}H_{26}N_2O$ (286.41): C, 75.48; H, 9.15; N, 9.78. Found: C, 75.25; H, 8.88; N, 9.82.

38b: R_f = 0.11; ^{1}H NMR (200 MHz) δ 7.37−7.24 (m, 5H), 3.59 (A part of an AB system, J = 13.5 Hz, 1H), 3.51 (B part

of an AB system, J = 13.5 Hz, 1H), 2.94 (td, J = 11.2, 3.7 Hz, 1H), 2.82 (s, 3H), 2.66 (ddd, J = 9.9, 3.7, 1.5 Hz, 1H), 2.46 (dd, J = 11.5, 1.4 Hz, 1H), 2.24 (d, J = 11.4 Hz, 1H), 1.78 (t, J = 10.6 Hz, 1H), 1.77 (d, J = 11.4 Hz, 1H), 1.16 (s, 3H), 0.93 (s, 3H), 0.95−0.83 (m, 1H), 0.64−0.45 (m, 3H); ^{13}C NMR (50 MHz) δ 138.6 (s), 128.3 (d, 2C), 128.1 (d, 2C), 126.8 (d), 81.4 (d) 65.3 (s), 62.5 (t), 62.1 (t), 53.8 (t), 48.9 (d), 43.9 (q), 34.2 (s), 27.4 (q), 19.2 (q), 8.6 (t), 4.4 (t); MS (70 eV) m/z 287 (3, M^+), 272 (4), 235 (3), 230 (6), 200 (7), 195 (6), 174 (17), 120 (16), 91 (100), 84 (43); IR ($CDCl_3$) ν 2970, 2933, 2811, 1599, 1453, 1366, 1244, 1108, 1058 cm^{-1}; HRMS found 287.21221, $C_{18}H_{27}N_2O$ required 287.21234.

39: R_f = 0.35; ^{1}H NMR (500 MHz) δ 7.38−7.20 (m, 5H), 3.81 (d, J = 4.0 Hz, 1H), 3.63 (A part of an AB system, J = 13.1 Hz, 1H), 3.57 (B part of an AB system, J = 13.1 Hz, 1H), 2.88 (s, 3H), 2.84 (AB syst, J = 13.1 Hz, 1H), 2.56 (dd, J = 12.9, 3.2, Hz, 1H), 2.28 (d, J = 13.2 Hz, 1H), 2.15 (AB syst, J = 13.1 Hz, 1H), 2.10 (s, 1H), 1.22−1.09 (m, 1H), 1.06 (s, 3H), 0.89 (s, 3H), 0.67−0.63 (m, 3H); ^{13}C NMR (50 MHz) δ 140.1 (s), 128.9 (d, 2C), 128.0 (d, 2C), 126.8 (d), 84.7 (d), 79.3 (d), 64.5 (t), 61.9 (t), 59.0 (t), 47.9 (q), 39.0 (s), 26.8 (s), 26.4 (q), 25.6 (q), 16.2 (t), 2.0 (t); GC−MS m/z 174 (3), 133 (5), 120 (5), 112 (6), 98 (5), 91 (100), 77 (5); IR ($CDCl_3$) ν 3737, 3034, 2985, 2955, 2812, 1599, 1451, 1359, 1177, 1134, 1100 cm^{-1}. Anal. Calcd for $C_{18}H_{26}N_2O$ (286.41): C, 75.48; H, 9.15; N, 9.78. Found: C, 74.93; H, 9.19; N, 10.00.

(3′a*R,7′a*S**)-Octahydro-7′,7′-dimethyl-1′-(methyl-d_3)-5′-(phenylmethyl)-spiro[cyclopropane-1,3′-isoxazolo[4,3-*c*]pyridine] (38b-d$_3$).** The same procedure was followed for the synthesis of the deuterated derivative **38b-d$_3$**, starting from **37** and *N*-(methyl-d_3)-hydroxylamine acetate.

38b-d$_3$: R_f = 0.11 (petroleum ether/AcOEt 6:1); ^{1}H NMR (200 MHz) δ 7.37−7.24 (m, 5H), 3.59 (A part of an AB system, J = 13.6 Hz, 1H), 3.51 (B part of an AB system, J = 13.5 Hz, 1H), 2.94 (td, J = 11.2, 3.7 Hz, 1H), 2.66 (ddd, J = 9.9, 3.7, 1.5 Hz, 1H) 2.46 (dd,, J = 11.5, 1.4 Hz, 1H) 2.24 (d, J = 11.4 Hz, 1H), 1.78 (t, J = 10.6 Hz, 1H), 1.77 (d, J = 11.4 Hz, 1H), 1.16 (s, 3H), 0.93 (s, 3H), 0.95−0.83 (m, 1H), 0.64−0.45 (m, 3H).

(4a*R,8a*R**)-Octahydro-1,8,8-trimethyl-6-(methylphenyl)[1,6]naphthyridin-4(1*H*)-one (45).** A solution of cycloadduct **38a** (69 mg, 0.24 mmol) in xylenes (4 mL) was refluxed for 5 h. After the solution was cooled to rt, the solvent was eliminated by filtration on silica gel eluting in turn with petroleum ether and with ethyl acetate. Purification by chromatography on silica gel (petroleum ether/AcOEt 1:1) afforded the ketone **45** (25 mg, 40%) as a colorless oil.

Under the same conditions, adduct **38b** (55 mg, 0.19 mmol) afforded the ketone **45** (21 mg, 38%).

45: R_f = 0.34; ^{1}H NMR (200 MHz) δ 7.18−7.12 (m, 5H), 3.48−3.32 (m, 1H), 3.55 (A part of an AB system, J = 13.5 Hz, 1H), 3.20 (B part of an AB system, J = 13.5 Hz, 1H), 3.18 (ddd, J = 11.5, 3.5, 2.4 Hz, 1H), 3.00−2.78 (m, 2H), 2.60 (ddd, J = 17.6, 9.5, 4.8 Hz, 1H), 2.47 (s, 3H), 2.42 (dd, J = 11.5, 2.5 Hz, 1H), 2.28 (dt, J = 17.6, 4.8 Hz, 1H), 1.98 (d, J = 11.1 Hz, 1H), 1.96 (dd, J = 11.6, 10.6 Hz, 1H) 1.70 (d, J = 11.7 Hz, 1H), 1.16 (s, 3H), 0.94 (s, 3H); ^{13}C NMR (50 MHz) δ 211.6 (q), 138.8 (s), 128.6 (d, 2C), 128.1 (d, 2C), 126.8 (d), 72.8 (d), 66.4 (t), 62.6 (t), 53.5 (t), 51.5 (t), 47.0 (q), 44.8 (d), 37.1 (s), 36.6 (t), 27.2 (q), 19.2 (q); GC−MS m/z 286 (3), 174 (12), 162 (11), 120 (19), 91 (100); IR ($CDCl_3$) ν 3031, 2953, 2805, 1707, 1452, 1361 cm^{-1}. Anal. Calcd for $C_{18}H_{26}N_2O$: C, 75.48; H, 9.15; N, 9.78. Found: C, 75.28; H, 8.77; N, 9.80.

(1*R,6*R**)-5,5,7-Trimethyl-3-(methylphenyl)-3,7-diazabicyclo[4.2.0]octan-8-one (46).** TFA (31 μL, 0.40 mmol) was added to a solution of the adduct **38a** (59 mg, 0.20 mmol) in toluene (5 mL) at rt. The mixture was refluxed for 2 h. Evaporation of the solvent and purification of the crude product by chromatography on silica gel (CH_2Cl_2/MeOH 30:1) gave **46** (47 mg, 87%) as a colorless oil.

46: R_f = 0.31; ^{1}H NMR (200 MHz) δ 7.54−7.37 (m, 5H), 4.37 (A part of an AB system, J = 12.4 Hz, 1H) 4.24 (B part of an AB system, J = 12.8 Hz, 1H), 3.74−3.57 (m, 1H), 3.57−3.44 (m, 2H), 3.40−3.24 (m, 1H), 3.32 (A part of an AB system, J = 12.6 Hz, 1H), 2.95 (s, 3H), 2.86 (B part of an AB system, J = 12.6 Hz, 1H), 1.19 (s, 3H), 1.10 (s, 3H); ^{13}C NMR (50 MHz) δ 168.3 (s), 131.1 (d, 2C), 130.1 (d), 129.3 (d, 2C), 128.5 (s), 62.5 (t), 58.4 (q), 54.8 (t), 44.9 (d), 41.5 (t), 34.2 (s), 30.3 (d), 25.4 (q), 24.0 (q); MS (70 eV) m/z 258 (1, M^+), 174 (16), 167 (8), 139 (15), 124 (81), 120 (35), 91 (100), 69 (30); IR ($CDCl_3$) ν 2975, 2931, 1754, 1663, 1420, 1189 cm^{-1}; HRMS found 281.16295, $C_{16}H_{22}N_2NaO$ required 281.16298.

(4a*R,8a*R**)-Octahydro-3,8,8-trimethyl-6-(methylphenyl)[1,6]naphthyridin-4(1*H*)-one (47).** TFA (18 μL, 0.24 mmol) was added to a solution of **38b** (33 mg, 0.12 mmol) in toluene (3 mL) at rt and under nitrogen atmosphere The mixture was refluxed for 2 h 45 min. Evaporation of the solvent and purification by chromatography on silica gel (MeOH + 1% NH_3) gave the 1,6-naphthyridine **47·TFA** (18 mg, 58%) as TFA salt. After treatment with Ambersep 900 OH ion-exchange resin and purification by chromatography on silica gel (petroleum ether/ethyl acetate + 1% TEA 1:1), the ketone **47** (13 mg, 40%) was obtained as a colorless oil.

47·TFA: ^{1}H NMR (400 MHz, CD_3CN) δ 7.54−7.47 (m, 5H), 4.81 (d, J = 12.0 Hz, 1H), 4.37 (A part of an AB system, J = 12.8 Hz, 1H), 4.16 (B part of an AB system, J = 12.8 Hz, 1H), 3.86 (dm, J = 9.3 Hz, 1H), 3.75 (tm, J = 10.5 Hz, 1H), 3.17 (br t, J = 112.2 Hz, 1H), 3.07 (br s, 2H), 3.02−2.95 (m, 2H), 1.51 (s, 3H), 1.21 (s, 3H), 0.95 (s, 3H).

47: R_f = 0.37 (AcOEt); ^{1}H NMR (500 MHz, CD_3OD) δ 7.48−7.32 (m, 5H), 3.68 (A part of an AB system, J = 13.2 H, 1H), 3.54 (B part of an AB system, J = 13.2 Hz, 1H), 3.52 (dd, J = 12.3, 6.3 Hz, 1H), 3.18 (ddd, J = 12.0, 3.5, 2.3 Hz, 1H), 2.78−2.46 (m, 2H), 2.59 (t, J = 12.0 Hz, 1H), 2.58 (dd, J = 11.4, 2.2 Hz, 1H), 2.35 (d, J = 11.3 Hz, 1H), 2.13 (t, J = 11.6 Hz, 1H), 1.86 (d, J = 11.3 Hz, 1 H), 1.24 (s, 3H), 1.08 (s, 3H) 1.06 (d, J = 6.7 Hz, 3H); ^{13}C NMR (50 MHz, CD_3OD) δ 212.9 (s), 139.8 (s), 129.9 (d, 2C), 129.1 (d, 2C), 128.0 (d), 71.6 (d), 67.3 (t), 63.9 (t), 55.7 (t), 54.1 (t), 52.0 (d), 46.8 (d), 35.9 (s), 26.8 (q), 19.9 (q), 11.4 (q); MS m/z 195 (7), 166 (19), 152 (11), 134 (40), 106 (14), 91 (100), 84 (49); IR ($CDCl_3$) ν 3031, 2953, 2805, 1707, 1452, 1361 cm^{-1}; HRMS found 287.21236, $C_{18}H_{27}N_2O$ required 287.21234.

(4a*R,8a*R**)-1,2,4a,5,6,7,8,8a-Octahydro-3,8,8-trimethyl-6-(methylphenyl)[1,6]naphthyridin-4-ol-*2,2-d*$_2$ Trifluoroacetate (47-d$_2$·TFA).** The same procedure was followed for the synthesis of the deuterated derivative **47-d$_2$·TFA**, starting from **38b-d$_3$**.

47-d$_2$·TFA: ^{1}H NMR (600 MHz, CD_3CN) δ 7.54−7.47 (m, 5H), 4.77 (d, J = 12.1 Hz, 1H), 4.30 (A part of an AB system, J = 13.2 Hz, 1H), 4.13 (B part of an AB system, J = 13.2 Hz, 1H), 3.77 (ddd, J = 12.0, 4.3, 2.4 Hz, 1H), 3.63 (dt, J = 12.0, 4.3 Hz, 1H), 3.07 (t, J = 12.0 Hz, 1H), 3.00 (dd, J = 12.4, 2.4 Hz, 1H), 2.89 (d, J = 12.4 Hz, 1H), 1.30 (s, 3H), 1.20 (s, 3H), 0.94 (s, 3H).

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