DOI: 10.1002/ejoc.200700912

3-Spirocyclopropanedihydro- and -tetrahydropyridin-4-ones from Nitrone Cycloadducts of Bicyclopropylidene via 1-(1′-Aminomethylcyclopropyl)-cyclopropanol under Pd^{II} Catalysis[‡]

Julia Revuelta,[a][‡‡] Stefano Cicchi,[a] Armin de Meijere,[b] and Alberto Brandi*[a]

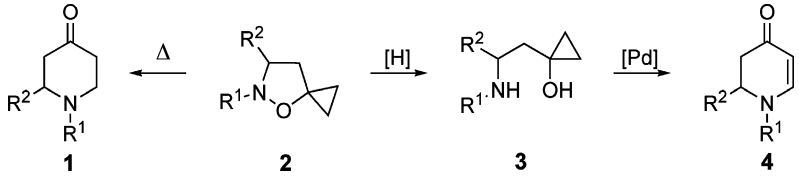
Keywords: Cycloaddition / Cascade reactions / Heterocycles / Palladium / Catalysis / Rearrangement

A series of 3-spirocyclopropanedihydro- and -tetrahydropyrid-4-ones have been synthesized by nitrone cycloaddition to 1,1′-bicyclopropylidene (BCP), chemoselective reduction of the N–O bond of the isoxazolidine ring, and Pd^{II}-catalyzed cascade rearrangement of the β-aminocyclopropanol derivatives into the final products. The new tetrahydropyridone derivatives were also prepared by thermal rearrangement of the isoxazolidines.

Introduction

The release of strain energy associated with the opening of a cyclopropane ring in an organic molecule may lead to multiple transformations, the selectivity of which depends on the nature and pattern of substituents on the cyclopropane ring and on the adjacent positions.[1] The presence of electron-donor substituents on the cyclopropane ring enhances its reactivity and may lead to a high degree of control in the regioselectivity of the ring-opening reaction.[2]

In this context, the transformations of isoxazolidine-5-spirocyclopropanes **2** have recently established themselves as versatile tools in organic synthesis.[3] These compounds can be prepared by the facile assembly of functionalized isoxazolidines through a 1,3-dipolar cycloaddition reaction of nitrones to alkylidenecyclopropanes[4] and feature a highly strained cyclopropane ring that is highly reactive,[1] resulting in a variety of new reactions. The synthesis and reactivity of **2** are tuned by the substituents present on the parent alkylidenecyclopropane and on the nitrone counterparts as well as by the reaction conditions applied. The rearrangement of **2**,[5] which has been extensively studied,[3,4,6] is an example of a useful thermal domino transformation of cyclopropanes, leading to mono- and oligocyclic tetrahydropyridones **1** which have found widespread application in the synthesis of natural and nonnatural compounds. On the other hand, as was found very recently,[7] β-aminocyclopropanols **3**, easily obtained by reduction of **2**,[8] undergo a Pd^{II}-catalyzed rearrangement eventually leading to dihydropyridones **4**. (Scheme 1).



1 **2** **3** **4**

Scheme 1.

The choice of 1,1′-bicyclopropylidene (BCP, **6**)[9] as dipolarophile in these processes appeared particularly interesting to expand the synthetic utility of this methodology. In fact, certain spirocyclopropanated heterocyclic ketones originating from BCP through thermal rearrangement of isoxazolidines **7** have demonstrated an ability to cleave supercoiled DNA in analogy to natural products like illudines and ptaquiloside.[10] In this paper, we report the synthesis of several new spirocyclopropane-annelated azaheterocycles

[‡] Cyclopropyl Building Blocks in Organic Synthesis, 146. Part 145: I. Emme, C. Bruneau, P. H. Dixneuf, A. de Meijere, *Synthesis*, in press. Part 144: I. Nakamura, R. Nagata, T. Nemoto, Y. Yamamoto, A. de Meijere, *Eur. J. Org. Chem.* **2007**, 4479–4482.

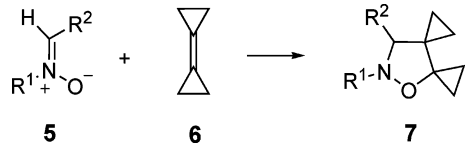
[a] University of Florence, Department of Organic Chemistry "Ugo Schiff" and HeteroBioLab,
Via della Lastruccia 13, 50019 Sesto Fiorentino (FI), Italy
E-mail: alberto.brandi@unifi.it
[b] Institut für Organische und Biomolekulare Chemie der Georg-August-Universität Göttingen,
Tammannstrasse 2, 37077 Göttingen, Germany
E-mail: Armin.deMeijere@chemie.uni-gottingen.de
[‡‡] Current address: Departamento de Química Bioorgánica, Instituto Química Orgánica, CSIC,
Juan de la Cierva, 3, 28006, Madrid, Spain

Supporting information for this article is available on the WWW under http://www.eurjoc.org or from the author.

by a two-step metal-mediated transformation and by thermal rearrangement of isoxazolidine-4,5-dispirocyclopropanes **7**.

Results and Discussion

All isoxazolidine-4,5-dispirocyclopropanes **7** used as starting materials in this work were obtained by 1,3-dipolar cycloaddition of the appropriate nitrone **5** to BCP (Scheme 2). Whereas compounds **13** and **14** have previously been described,[10b] the analogues **15**, **16**, and **17** were newly prepared in excellent yields (Table 1) from **6** and the nitrones **10**,[11] **11**,[12] and **12**[13]. The cycloadditions were carried out at a relatively low temperature (60 °C) with extended reaction times to avoid thermal isomerization of the adducts.



5 **6** **7**

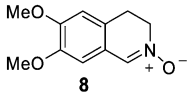
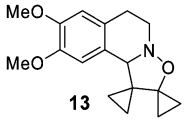
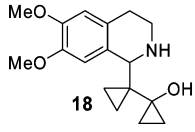
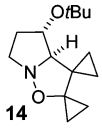
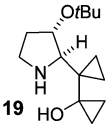
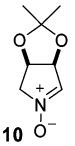
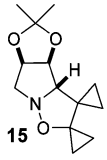
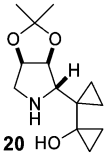
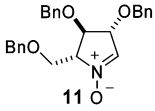
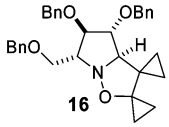
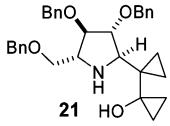
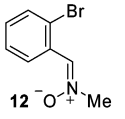
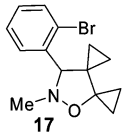
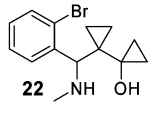
Scheme 2.

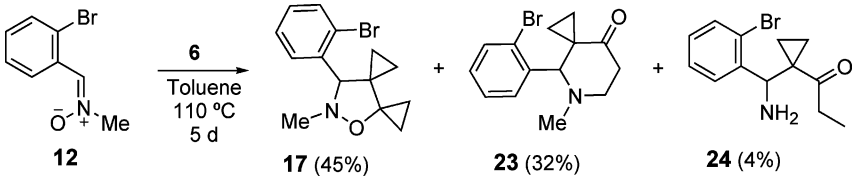
In fact, the reaction shown in entry 5 (Table 1), for example, when carried out at 110 °C was complete within 5 d, but 32 and 4% yields, respectively, of the rearrangement products **23** and **24** were obtained in addition to a 45% yield of the cycloadduct **17** (Scheme 3). The unexpected amine **24** must have been formed in a common side-reaction of the thermal process,[3,4] that is, by a hydrogen shift of the 1,6-diradical intermediate, which here must have occurred through a 1,7 mechanism from the *N*-methyl substituent and the resulting formaldehyde imine subsequently must have undergone hydrolysis during purification.

The structural assignments for the new cycloadducts **15**–**17** were made on the basis of their ^{1}H and ^{13}C NMR spectra which show characteristic peaks for the cyclopropane protons (δ = 0–1 ppm) and carbons (δ = 1–12 ppm).

Reductive opening of the N–O bonds in simple isoxazolidines can be performed with a variety of reagents.[14] How-

Table 1. Cycloaddition of nitrones **8**–**12** to bicyclopropylidene **6** and reduction of cycloadducts with SmI_2.

Entry	Nitrone	React. cond.	Cycloadduct	% Yield	Aminocyclopropanol	% Yield
1	 **8**	ref.[10]	 **13**	32	 **18**	88
2	 **9**	ref.[10]	 **14**	80	 **19**	69
3	 **10**	toluene 60 °C 2 d	 **15**	85	 **20**	70
4	 **11**	toluene 60 °C 2 d	 **16**	90	 **21**	75
5	 **12**	toluene 60 °C 20 d	 **17**	90	 **22**	90



12 **17** (45%) **23** (32%) **24** (4%)

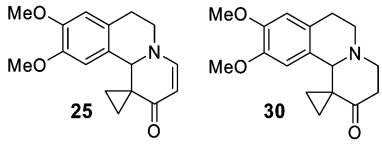
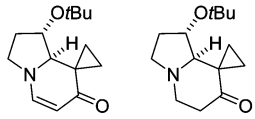
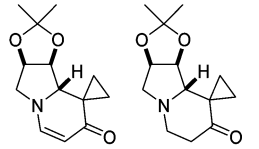
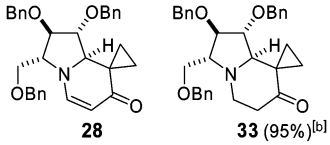
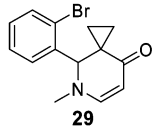
Scheme 3.

ever, with the spirocyclopropane rings present in **18**–**22** it is advantageous to use a reasonably chemoselective reducing agent such as SmI_2.[7b,8] Treatment of isoxazolidines **13**–**17** with an excess of a commercial 0.1 M solution of SmI_2 in THF led to a smooth and efficient conversion into the corresponding γ-(aminoalkyl)cyclopropanols **18**–**22** in good yields (Table 1). In these cases, the Sm^{III} alkoxides[15] formed are rather stable and so it was necessary to work-up the reaction mixture at pH 12 by adding a 1 M solution of NH_3 in MeOH and thus avoid the extraction of such complexes into the organic phase. The integrity of the cyclopropane moiety in the amino alcohols was corroborated by their ^1H and ^{13}C NMR spectra with signals at δ = 0.3–0.8 and 5–14 ppm, respectively.

The amino alcohols **18**–**22** were then subjected to the best reaction conditions previously elaborated for their palladium-catalyzed conversion into tetrahydropyridones,[7b] that is, by treatment with $Pd(OAc)_2$ (10 mol-%), pyridine (2 equiv.), and oxygen at 5 atm pressure in toluene at 80 °C. Only the amino alcohol **22** provided the expected dihydropyridone **29** in excellent yield (90%) (Table 2, entry 5). All the other substrates gave almost 1:1 mixtures of dihydropyridones **25**–**28** and tetrahydropyridones **30**–**33**[10b] which could be separated by flash chromatography in good overall yields (Table 2, entries 1–4).

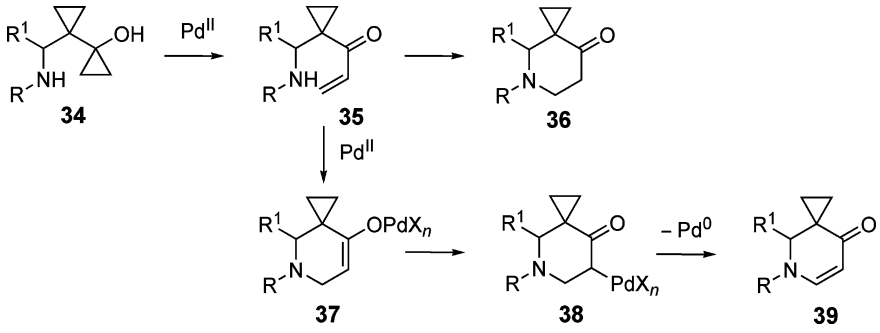
The structural assignments for the new products were made on the basis of their ^1H and ^{13}C NMR spectra. The enaminone moiety in compounds **25**–**29** each display characteristic arrays of signals due to the vinylic protons and carbons. The =CH protons α to the nitrogen resonate downfield (δ = 7.20–7.00 ppm), as do the corresponding carbon nuclei (δ = 152–149 ppm). Conversely, the =CH protons β to the nitrogen resonate at δ = 5.10–5.00 ppm and the corresponding carbon nuclei at δ = 96–100 ppm. On the other hand, compounds **30**–**33** were assigned by comparison of their NMR spectra with those of the known compounds **30** and **31** and on the basis of characteristic signals, for example, for the piperidone carbonyl group (^{13}C NMR: δ = 207.4 and 208.6 ppm for **32** and **33**, respectively) and the cyclopropane moiety. In order to confirm their structures, compounds **32**, **33**, and **23** were also prepared in 65, 95, and 65% yields by thermal rearrangement upon heating 1 M solutions of isoxazolidines **15**, **16**, and **17**, respectively, in xylenes at 125 °C for 12 h.

Table 2. Pd^{II}-mediated rearrangement of γ-(aminoalkyl)cyclopropanols.

Entry	Amino-cyclopropanol	Products (1:1 mixtures)[a]	% Yield
1	**18**	 **25** **30**	87
2	**19**	 **26** **31**	75
3	**20**	 **27** **32** (69%)[b]	92
4	**21**	 **28** **33** (95%)[b]	95
5	**22**	 **29**	90

[a] Ratio determined spectroscopically (^1H NMR) on the crude reaction mixture. [b] Yield obtained upon thermal rearrangement by heating at 125 °C for 12 h.

The formation of mixtures of tetrahydro- and dihydropyridones in the Pd^{II}-catalyzed rearrangement of γ-(aminoalkyl)cyclopropanols **18**–**21** contrasts the results obtained in earlier work[7] and raises questions about the mechanism of the catalytic process proposed previously.[7b] The formation of dihydropyridones was postulated to originate from a palladium–enolate intermediate **37** which would be formed by a Pd^{II}-catalyzed intramolecular Michael-type addition of the amino group to the enone moiety in the intermediate α,β-unsaturated ketone **35**, in



Scheme 4.

turn derived from the Pd^{II}-catalyzed rearrangement of the cyclopropanol moiety in **34**.[16–18] The palladium enolate **37**, after enol/ketone tautomerization to **38**, would then undergo β-dehydropalladation to yield the final product **39** (Scheme 4). The formation of tetrahydropyridones **36** in the cases above, however, does not rule out this mechanism and can be explained by an uncatalyzed intramolecular Michael addition in **35**. The uncatalyzed intramolecular Michael addition might be favored by the 1,1-disubstituted cyclopropane ring in which the enone moiety is proximal to the nitrogen.[19] The exclusive formation of the dihydropyridone **29** must then be due to a difference in the preferred orientation of the two substituents on the cyclopropane ring in the intermediate **35**, when the amino group is not part of a heterocycle as in **18**–**21**, so that cyclization of **35** requires palladium(II) catalysis.

Conclusions

The Pd^{II}-catalyzed rearrangement of γ-(aminoalkyl)cyclopropanols to dihydropyrid-4-one derivatives has been extended to more complex substrates bearing an additional 1,1-disubstituted cyclopropane moiety in the chain. In the presence of a second cyclopropane ring, the rearrangement, except in one case, leads to a mixture of dihydro- and tetrahydropyrid-4-one derivatives, most likely because of competition between a catalyzed and noncatalyzed Michael-type cyclization of the intermediate β-amino-substituted α,β-unsaturated ketone. The overall process, which is carried out at a lower temperature, represents a valuable alternative to the thermal rearrangement, in particular for those compounds sensitive to elevated temperatures. Work is in progress in our laboratory to confirm the mechanism proposed and the role of the palladium species.

Experimental Section

General Remarks: All reactions were carried out under nitrogen or in sealed tubes filled with nitrogen. R_f values refer to TLC on 0.25 mm silica gel plates (Merck F_{254}) obtained by using the same eluent as in the corresponding column chromatography. Melting points were determined with a 510 Büchi apparatus. NMR spectra were recorded with a Varian Gemini (^{1}H, 200 MHz; ^{13}C, 50 MHz), with $CDCl_3$ as solvent; the NMR spectroscopic data are reported in δ (ppm) relative to TMS. The multiplicities of the ^{13}C signals, derived from APT spectra, are reported to support assignments. IR spectra were recorded in $CDCl_3$ solution. Mass spectra were recorded at 70 eV. Compounds **6** and **8**–**14** were prepared according to published procedures.[9–13]

Cycloaddition of Nitrones to BCP. General Procedure: A solution of the respective nitrone (1 mmol) and BCP (1.3 mmol) in toluene (1 mL) was heated in a screw-capped Sovirel tube. After cooling to room temperature, the solvent was removed in vacuo, and the crude material was purified by flash column chromatography on silica gel.

8′,9′-Dimethoxydispiro[cyclopropane-1,1′-(1,5,6,10b-tetrahydro-2*H*-isoxazolo[3,2-*a*]isoquinoline)-2′,1′′-cyclopropane] (13): See ref.[10]

(3′a*R*,4′*S*)-4′-*tert*-Butoxydispiro[cyclopropane-1,2′-(hexahydropyrrolo[1,2-*b*]isoxazole)-3′,1′′-cyclopropane] (14): See ref.[10]

(3′a*S*,4′*S*,5′*R*)-4′,5′-*O*-Isopropylidenedispiro[cyclopropane-1,2′-(hexahydropyrrolo[1,2-*b*]isoxazole)-3′,1′′-cyclopropane] (15): The toluene solution was heated at 60 °C for 2 d. Yellow solid, yield 201 mg, 85%. R_f = 0.36 (AcOEt/light petroleum, 1:4). $[\alpha]_D^{20}$ = +12.0 (c = 0.5, CH_2Cl_2), m.p. 65–67 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.23–0.53 (m, 4 H, *c*Pr-H), 0.68–0.83 (m, 4 H, *c*Pr-H), 1.28 (s, 3 H, Me), 1.45 (s, 3 H, Me), 3.32 (dd, J = 4.4, 1.8 Hz, 1 H, 6-H), 3.40 (dd, J = 4.4, 1.8 Hz, 1 H, 7-H), 3.54–3.65 (m, 1 H, 3a-H), 4.58 (dt, J = 2.2, 6.6 Hz, 1 H, 5-H), 4.85–4.94 (m, 1 H, 4-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 5.7 (t, *c*Pr-C), 6.1 (t, *c*Pr-C), 8.9 (t, *c*Pr-C), 10.0 (t, *c*Pr-C), 25.2 (q, Me), 27.2 (q, Me), 30.0 (s, *c*Pr-C), 62.3 (t, C-6), 66.4 (s, *c*Pr-C), 77.6 (d, C-3a), 80.4 (d, C-5), 84.0 (d, C-4), 112.6 (s, acetonide group) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 2987, 1469, 1383, 1216, 1163, 1095 cm^{-1}. MS: *m*/*z* (%) = 237 (33), 194 (13), 123 (77), 122 (72), 67 (90), 55 (100). $C_{13}H_{19}NO_3$ (237.30): calcd. C 65.80, H 8.07, N 5.90; found C 65.78, H 8.43, N 6.04.

(3′a*S*,4′*S*,5′*S*,6′*S*)-4′,5′-Bis(benzyloxy)-6′-(benzyloxymethyl)dispiro[cyclopropane-1,2′-(hexahydropyrrolo[1,2-*b*]isoxazole)-3′,1′′-cyclopropane] (16): The toluene solution was heated at 60 °C for 2 d. Pale orange oil, yield 447 mg, 90%. R_f = 0.28 (AcOEt/light petroleum, 1:4). $[\alpha]_D^{20}$ = –15.3 (c = 0.95, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.03–0.15 (m, 2 H, *c*Pr-H), 0.56–1.00 (m, 6 H, *c*Pr-H), 3.61 (d, J = 5.0 Hz, 1 H, 6-H), 3.74 (d, J = 1.8 Hz, 1 H, 3a-H), 4.09–4.20 (m, 2 H, 4-H, 5-H), 4.51–4.75 (m, 6 H, CH_2Ph), 7.20–7.45 (m, 15 H, Ar-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 1.2 (t, *c*Pr-C), 3.8 (t, *c*Pr-C), 11.9 (t, 2 C, *c*Pr-C), 30.7 (s, *c*Pr-C), 65.3 (s, *c*Pr-C), 68.5 (d, C-6), 68.9 (t, CH_2Ph), 72.1 (t, CH_2Ph), 72.9 (d, C-3a), 73.4 (t, CH_2Ph), 83.0 (d, C-5), 86.0 (d, C-4), 127.3 (d, Ar-C), 127.5 (d, Ar-C), 127.6 (d, Ar-C), 127.7 (d, 3 C, Ar-C), 127.8 (d, 3 C, Ar-C), 128.1 (d, 4 C, Ar-C), 128.2 (d, 2 C, Ar-C), 137.7 (s, Ar-C), 137.9 (s, Ar-C), 138.1 (s, Ar-C) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3032, 2864, 1454, 1363, 1265, 1208, 1097, 1028 cm^{-1}. MS: *m*/*z* (%) = 497 (2) $[M]^+$, 407 (19), 406 (67), 377 (38), 376 (73), 150 (42), 92 (37), 91 (100). $C_{32}H_{35}NO_4$ (497.63): calcd. C 77.24, H 7.09, N 2.81; found C 77.23, H 7.13, N 2.83.

9-(2-Bromophenyl)-8-methyl-7-oxa-8-azadispiro[2.0.2.3]nonane (17): The toluene solution was heated at 60 °C for 20 d. Colorless solid, yield 264 mg, 90%. R_f = 0.75 (AcOEt/light petroleum, 1:30), m.p. 45–46 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.83–0.94 (m, 4 H, *c*Pr-H), 0.96–1.01 (m, 4 H, *c*Pr-H), 2.86 (s, 3 H, Me), 4.59 (s, 1 H, 9-H), 7.14 (td, J = 7.7, 1.8 Hz, 1 H, Ar-H), 7.36 (t, J = 7.7 Hz, 1 H, Ar-H), 7.51 (d, J = 7.7 Hz, 1 H, Ar-H), 7.78 (dd, J = 7.7, 1.8 Hz, 1 H, Ar-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 6.4 (t, *c*Pr-C), 6.5 (t, *c*Pr-C), 9.6 (t, 2 C, *c*Pr-C), 33.6 (s, *c*Pr-C), 45.2 (q, Me), 68.8 (s, *c*Pr-C), 76.4 (d, 9-C), 124.1 (s, Ar-C), 127.6 (d, Ar-C), 128.9 (d, Ar-C), 130.9 (d, Ar-C), 132.9 (d, Ar-C), 138.6 (s, Ar-C) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3074, 3003, 2876, 1589, 1437, 1029 cm^{-1}. MS: *m*/*z* (%) = 295 (2) $[M + 2]^+$, 293 (2) $[M]^+$, 197 (6), 195 (7), 186 (36), 184 (32), 130 (36), 128 (100). $C_{14}H_{16}BrNO$ (294.19): calcd. C 57.16, H 5.48, N 4.76; found C 57.08, H 5.46, N 4.69.

1-{1-[Amino(2-bromophenyl)methyl]cyclopropyl}propan-1-one (24): This product was obtained as a yellow oil as a byproduct in the cycloaddition of nitrone **12** to **6** in toluene at 110 °C for 5 d, yield 11 mg, 4%. R_f = 0.31 (AcOEt/light petroleum, 1:30). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.38–0.48 (m, 1 H, *c*Pr-H), 0.79–0.90 (m, 1 H *c*Pr-H), 1.06 (t, J = 7.3 Hz, 3 H, Me), 1.14–1.27 (m, 2 H, *c*Pr-H), 2.40 (q, J = 7.3 Hz, 2 H, CH_2), 5.24 (s, 1 H, 1-H), 7.12 (t, J = 8.2 Hz, 1 H, Ar-H), 7.29 (t, J = 8.2 Hz, 1 H, Ar-H), 7.45 (d, J = 8.0 Hz, 1 H, Ar-H), 7.54 (d, J = 8.0 Hz, 1 H, Ar-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 7.9 (t, *c*Pr-C), 8.4 (t, *c*Pr-C), 9.7 (q,

Me), 14.7 (s, *c*Pr-C), 29.8 (t, CH_2), 52.9 (d, C-1), 124.9 (s, Ar-C), 127.4 (d, Ar-C), 127.9 (d, Ar-C), 128.6 (d, Ar-C), 132.6 (d, Ar-C), 150.0 (s, Ar-C), 212.8 (s, C=O) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3400, 3067, 2990, 2879, 1684, 1590, 1466, 1438, 1377, 1024 cm^{-1}. MS: *m*/*z* (%) = 283 (14) $[M + 2]^+$, 281 (14) $[M]^+$, 268 (52), 242 (60), 204 (36), 162 (100). $C_{13}H_{16}BrNO$ (282.17): calcd. C 55.33, H 5.72, N 4.96; found C 55.39, H 5.80, N 4.98.

General Procedure for the Reduction of Isoxazolidines: A commercial 0.1 M THF solution (17.5 mL) of SmI_2 (3.5 equiv.) was added to a 100 mL Schlenk flask charged with the respective isoxazolidine (0.5 mmol) under nitrogen at room temperature. The resulting blue solution was stirred for 2 h. A 1 M solution of NH_3 in MeOH (8.5 mL) was added and the mixture left to stir for 20 min. Finally, water (17 mL) was added and the resulting mixture was brought to pH 8 by addition of a 1 M solution of aqueous NaOH. The mixture was then saturated with Na_2SO_3 and extracted with diethyl ether (3 × 15 mL). The organic phase was dried (Na_2SO_4), filtered, and concentrated to afford the crude product. The crudes were sufficiently pure to be used directly in the next step. Filtration of an aliquot of the crude through a short pad of silica gel afforded the pure products for elemental analysis.

1′-(6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)-1,1′-bicyclopropyl-1-ol (18): Colorless solid, yield 127 mg, 88%. R_f = 0.33 (CH_2Cl_2/MeOH, 14:1), m.p. 148–150 °C. ^1H NMR (200 MHz, $CDCl_3$): δ = 0.02–0.06 (m, 1 H, *c*Pr-H), 0.27–0.16 (m, 2 H, *c*Pr-H), 0.87–0.40 (m, 6 H, *c*Pr-H + 4-H), 2.52–2.65 (m, 1 H, 4-H), 2.80–3.12 (m, 2 H, 3-H, OH), 3.32–3.47 (m, 1 H, 3-H), 3.80 (s, 3 H, Me), 3.85 (s, 3 H, Me), 4.62 (s, 1 H, 1-H), 6.59 (s, 1 H, Ar-H), 6.81 (s, 1 H, Ar-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 8.3 (t, *c*Pr-C), 9.2 (t, *c*Pr-C), 10.3 (t, *c*Pr-C), 14.6 (t, *c*Pr-C), 32.3 (s, *c*Pr-C), 42.4 (t, C-4), 43.8 (t, C-3), 55.9 (q, Me), 56.1 (q, Me), 61.6 (s, *c*Pr-C), 64.1 (d, C-1), 110.4 (d, Ar-C), 111.5 (d, Ar-C), 126.2 (s, Ar-C), 127.6 (s, Ar-C), 146.8 (s, Ar-C), 147.9 (s, Ar-C) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3691, 3154, 2960, 2937, 2903, 2835, 1514, 1465, 1382, 1267, 1246, 1218, 1115, 1096 cm^{-1}. MS: *m*/*z* (%) = 289 (6) $[M]^+$, 288 (11), 192 (100), 91 (8). $C_{17}H_{23}NO_3$ (289.37): calcd. C 70.56, H 8.01, N 4.84; found C 70.75, H 7.84, N 4.68.

1′-[(2*R*,3*S*)-3-*tert*-Butoxypyrrolidin-2-yl]-1,1′-bicyclopropyl-1-ol (19): Yellow oil, yield 83 mg, 69%. R_f = 0.15 (CH_2Cl_2/MeOH, 3:1). $[a]_D^{20}$ = 7.5 (*c* = 0.48, MeOH). ^1H NMR (200 MHz, $CDCl_3$): δ = 0.04–0.16 (m, 2 H, *c*Pr-H), 0.27–0.42 (m, 1 H, *c*Pr-H), 0.43–0.50 (m, 2 H, *c*Pr-H), 0.50–0.64 (m, 1 H, *c*Pr-H), 0.67–0.7 (m, 1 H, *c*Pr-H), 0.78–0.91 (m, 1 H, *c*Pr-H), 1.18 (s, 9 H, *tert*-butyl), 1.72 (ddt, *J* = 9.5, 6.6, 2.9 Hz, 1 H, 4-H), 2.02–2.22 (m, 1 H, 4-H), 2.65 (d, *J* = 4.3 Hz, 1 H, 2-H), 2.95–3.10 (ABX system, 2 H, 5-H), 4.41 (ddd, *J* = 6.6, 4.3, 2.9 Hz, 1 H, 3-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 7.4 (t, *c*Pr-C), 8.0 (t, *c*Pr-C), 11.3 (t, *c*Pr-C), 14.0 (t, *c*Pr-C), 28.9 (q, *tert*-butyl), 29.9 (s, *c*Pr-C), 35.5 (t, C-4), 44.3 (t, C-5), 56.6 (s, *c*Pr-C), 58.9 (d, C-2), 72.8 (s, *tert*-butyl), 74.9 (d, C-3) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3685, 3153, 2900, 1455, 1382, 1262, 1095 cm^{-1}. MS: *m*/*z* (%) = 237 (4), 182 (100), 110 (28). $C_{14}H_{25}NO_2$ (239.35): calcd. C 70.25, H 10.53, N 5.85; found C 70.46, H 10.41, N 6.05.

1′-[(3a*S*,4*S*,6a*R*)-2,2-Dimethyltetrahydro-2*H*,3a*H*-[1,3]dioxolo[4,5-*c*]pyrrol-4-yl]-1,1′-bicyclopropyl-1-ol (20): Yellow oil, yield 93 mg, 70%. R_f = 0.18 (CH_2Cl_2/MeOH, 15:1). $[a]_D^{20}$ = – 10.4 (*c* = 0.70 $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 0.14–0.28 (m, 1 H, *c*Pr-H), 0.28–0.44 (m, 4 H, *c*Pr-H), 0.49–0.62 (m, 1 H, *c*Pr-H), 0.64–0.77 (m, 2 H, *c*Pr-H), 1.29 (s, 3 H, Me), 1.46 (s, 3 H, Me), 2.96–3.22 (m, 2 H, 6-H), 3.58 (s, 1 H, 4-H), 4.17 (d, *J* = 5.8 Hz, 1 H, 3a-H), 4.66 (t, *J* = 5.8 Hz, 1 H, 6a-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 6.7 (t, *c*Pr-C), 8.8 (t, *c*Pr-C), 10.6 (t, *c*Pr-C), 12.3 (t, *c*Pr-C), 22.0 (s, *c*Pr-C), 24.0 (q, Me), 26.4 (q, Me), 52.1 (t, C-6), 60.2 (d, C-4), 68.3 (s, *c*Pr-C), 70.5 (d, C-3a), 82.2 (d, C-6a), 110.0 (s, C-2) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3691, 3154, 2902, 1455, 1382, 1262, 1095 cm^{-1}. MS: *m*/*z* (%) = 239 (4) $[M]^+$, 180 (100), 142 (31) 100 (25). $C_{13}H_{21}NO_3$ (239.15): calcd. C 65.25, H 8.84, N 5.85; found C 65.47, H 8.67, N 5.79.

1′-{(2*R*,3*R*,4*R*,5*R*)-3,4-Bis(benzyloxy)-5-[(benzyloxy)methyl]pyrrolidin-2-yl}-1,1′-bicyclopropyl-1-ol (21): Pale yellow oil, yield 187 mg, 75%. R_f = 0.35 (CH_2Cl_2/MeOH, 3:1). $[a]_D^{20}$ = 7.3 (*c* = 0.5, CH_2Cl_2). ^1H NMR (200 MHz, $CDCl_3$): δ = 0.45–0.71 (m, 4 H, *c*Pr-H), 0.74–1.09 (m, 4 H, *c*Pr-H), 2.95 (d, *J* = 7.3 Hz, 1 H, 2-H), 3.50–3.59 (m, 1 H, 5-H), 3.92 (t, *J* = 4.3 Hz, 1 H, 4-H), 4.40 (dd, *J* = 7.3, 4.3 Hz, 1 H, 3-H), 4.50 (AB system, 2 H, CH_2Ph), 4.57 (AB system, 2 H, CH_2Ph), 4.52–4.59 (m, 2 H, 1-H), 4.61 (AB system, 2 H, CH_2Ph), 7.15–7.47 (m, 15 H, Ar-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 7.3 (t, *c*Pr-C), 8.6 (t, *c*Pr-C), 9.5 (t, *c*Pr-C), 13.2 (t, *c*Pr-C), 29.8 (s, *c*Pr-C), 58.3 (d, C-2), 59.8 (d, C-5), 61.0 (s, *c*Pr-C), 71.7 (t, C-1), 71.9 (t, CH_2Ph), 72.8 (t, CH_2Ph), 73.2 (t, CH_2Ph), 84.1 (d, C-4), 84.8 (d, C-3), 127.3 (d, Ar-C), 127.5 (d, Ar-C), 128.0 (d, Ar-C), 128.1 (d, Ar-C), 137.4 (s, 2 C, Ar-C), 137.6 (s, Ar-C) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3691, 3154, 2902, 1455, 1382, 1262, 1095 cm^{-1}. MS: *m*/*z* (%) = 499 (2) $[M]^+$, 408 (5), 378 (12), 91 (100). $C_{32}H_{37}NO_4$ (499.60): calcd. C 76.92, H 7.46, N 2.80; found C 76.53, H 7.64, N 2.65.

1′-[(2-Bromophenyl)(methylamino)methyl]-1,1′-bicyclopropyl-1-ol (22): Colorless solid, yield 133 mg, 90%. R_f = 0.25 (CH_2Cl_2/MeOH, 10:1), m.p. 119–121 °C. ^1H NMR (200 MHz, $CDCl_3$): δ = 0.18–0.33 (m, 2 H, *c*Pr-H), 0.37–0.64 (m, 2 H, *c*Pr-H), 0.67–0.83 (m, 4 H, *c*Pr-H), 2.35 (s, 3 H, Me), 3.63 (s, 2 H, NH_2), 4.58 (s, 1 H, C-1), 7.08–7.19 (m, 2 H, Ar-H), 7.21–7.38 (m, 1 H, Ar-H), 7.56 (m, 1 H, Ar-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 5.1 (t, *c*Pr-C), 9.6 (t, *c*Pr-C), 12.1 (t, *c*Pr-C), 12.3 (t, *c*Pr-C), 26.8 (s, *c*Pr-C), 34.1 (q, Me), 61.3 (s, *c*Pr-C), 68.2 (d, C-1), 126.2 (s, Ar-C), 127.0 (d, Ar-C), 127.3 (d, Ar-C), 128.7 (d, Ar-C), 133.0 (d, Ar-C), 136.9 (s, Ar-C) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3690, 3150, 3087, 2961, 1468, 1439, 1383, 1261, 1237, 1097, 1025 cm^{-1}. MS: *m*/*z* (%) = 297 (5) $[M + 2]^+$, 295 (5) $[M]^+$, 200 (59), 198 (61), 192 (21), 185 (67), 167 (15), 160 (56), 129 (100). $C_{14}H_{18}BrNO$ (296.21): calcd. C 56.77, H 6.13, N 4.73; found C 56.54, H 6.10, N 4.52.

General Procedure for the Preparation of Dihydropyridones: A suspension of the respective β-aminocyclopropanol (0.5 mmol), $Pd(OAc)_2$ (0.05 mmol), and pyridine (1 mmol) in toluene (5 mL) was stirred at 80 °C for 3 h in a steel reactor under a pressure of O_2 (5 atm). The suspension was then filtered and concentrated, and the residue was purified by flash column chromatography.

9′,10′-Dimethoxyspiro[cyclopropane-1,1′-(1,6,7,11b-tetrahydro-2*H*-pyrido[2,1-*a*]isoquinolin)]-2′-one (25): Yellow oil, yield 57 mg, 40%. R_f = 0.33 (AcOEt/MeOH, 2:1). ^1H NMR (200 MHz, $CDCl_3$): δ = 0.16–0.52 (m, 1 H, *c*Pr-H), 0.65–1.01 (m, 2 H, *c*Pr-H), 1.32–1.48 (m, 1 H, *c*Pr-H), 2.74 (dt, *J* = 15.3, 2.9 Hz, 1 H, 7-H), 3.02 (ddd, *J* = 15.3, 10.6, 5.1 Hz, 1 H, 7-H), 3.48 (td, *J* = 9.5, 3.6 Hz, 1 H, 6-H), 3.64 (ddd, *J* = 9.5, 5.1, 2.9 Hz, 1 H, 6-H), 3.86 (s, 6 H, 2Me), 4.74 (s, 1 H, 11b-H), 5.12 (d, *J* = 7.3 Hz, 1 H, 3-H), 6.63 (s, 1 H, Ar-H), 6.68 (s, 1 H, Ar-H), 7.18 (d, *J* = 7.3 Hz, 1 H, 4-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 9.4 (t, *c*Pr-C), 9.8 (t, *c*Pr-C), 28.5 (s, *c*Pr-C), 30.0 (t, C-7), 49.7 (t, C-6), 55.6 (q, Me), 55.8 (q, Me), 60.3 (d, C-11b), 98.4 (d, C-3), 110.8 (d, Ar-C), 111.1 (d, Ar-C), 123.4 (s, Ar-C), 127.8 (s, Ar-C), 146.8 (s, Ar-C), 147.8 (s, Ar-C), 151.8 (d, C-4), 193.1 (s, C=O) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3050, 2980, 2850, 1695, 1620, 1590, 1580, 1430, 1210 cm^{-1}. HRMS: calcd. for $C_{17}H_{20}NO_3^+$: 286.1443; found 286.1442. The reaction mixture afforded also compound **30**: yield 68 mg, 47%.[10b]

(1′*S*,8a′*R*)-1′-*tert*-Butoxyspiro[cyclopropane-1,8′-(2,3,8,8a-tetrahydroindolizin)]-7′(1′*H*)-one (26): Yellow oil, yield 41 mg, 35%. R_f = 0.20 (AcOEt). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.54–1.01 (m, 4 H, *c*Pr-H), 1.19 (s, 9 H, *tert*-butyl), 1.32–1.68 (m, 1 H, 2-H), 1.72–1.95 (m, 1 H, 2-H), 2.01–2.48 (m, 2 H, 2-H, 3-H), 3.61 (m, 1 H, 3-H), 3.86 (s, 1 H, 8a-H), 5.03 (d, J = 7.3 Hz, 1 H, 6-H), 7.06 (d, J = 7.3 Hz, 1 H, 5-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 11.4 (t, *c*Pr-C), 16.3 (t, *c*Pr-C), 28.7 (q, 3 C, *tert*-butyl), 31.5 (s, *c*Pr-C), 33.4 (t, C-2), 52.9 (t, C-3), 69.3 (d, C-8a), 73.5 (d, C-1), 74.0 (s, *tert*-butyl), 98.3 (d, C-6), 151.8 (d, C-5), 193.0 (s, C=O) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3010, 2978, 2812, 1684, 1336 cm^{-1}. MS: *m*/*z* (%) = 235 (2) $[M]^+$, 178 (100). $C_{14}H_{21}NO_2$ (235.39): calcd. C 71.46, H 8.99, N 5.95; found C 71.58, H 8.67, N 5.73. The reaction mixture afforded also compound **31**: yield 47 mg, 40%.[10b]

(3a′*R*,9a′*S*,9b′*S*)-2′,2′-Dimethylspiro[cyclopropane-1,9′-(3a,9,9a,9b-tetrahydro[1,3]dioxolo[4,5-*a*]indolizin)-8(4*H*)-one (27): Yellow oil, yield 54 mg, 45%. R_f = 0.45 (CH_2Cl_2/MeOH, 15:1). $[\alpha]_D^{20}$ = –57.2 (c = 0.85, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.65–0.90 (m, 2 H, *c*Pr-H), 0.92–1.06 (m, 1 H, *c*Pr-H), 1.09–1.27 (m, 1 H, *c*Pr-H), 1.32 (s, 3 H), 1.51 (s, 3 H), 3.57 (dd, J = 11.7, 2.9 Hz, 1 H, 4-H), 3.85 (dd, J = 11.7, 5.8 Hz, 1 H, 4-H), 3.97 (d, J = 6.6 Hz, 1 H, 9a-H), 4.21 (t, J = 6.6 Hz, 1 H, 9b-H), 4.79 (ddd, J = 6.6, 5.8, 2.9 Hz, 1 H, 3a-H), 5.07 (d, J = 7.3 Hz, 1 H, 7-H), 7.01 (d, J = 7.3 Hz, 1 H, 6-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 8.9 (t, *c*Pr-C), 13.0 (t, *c*Pr-C), 25.5 (q, Me), 25.7 (s, *c*Pr-C), 27.6 (q, Me), 54.7 (t, C-4), 66.1 (d, C-9a), 78.3 (d, C-3a), 79.7 (d, C-9b), 100.2 (d, C-7), 114.0 (s, acetonide group), 149.3 (d, C-6), 192.8 (s, C=O) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3018, 2987, 1693, 1629, 1584, 1460, 1384 cm^{-1}. HRMS: calcd. for $C_{13}H_{18}NO_3^+$: 236.1281; found 236.1282. The reaction mixture afforded also compound **32**: yield 56 mg, 47%.

(1′*R*,2′*R*,3′*R*,8a′*R*)-1′,2′-Bis(benzyloxy)-3′-[(benzyloxy)methyl]-spiro[cyclopropane-1,8′-(2,3,8,8a-tetrahydroindolizin)]-7′(1′*H*)-one (28): Pale yellow oil, yield 109 mg, 44%. $[\alpha]_D^{20}$ = –16.7 (c = 0.36, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.56–0.66 (m, 1 H, *c*Pr-H), 0.72–0.95 (m, 2 H, *c*Pr-H), 1.54 (ddd, J = 10.2, 6.7, 3.7 Hz, 1 H, *c*Pr-H), 3.53 (d, J = 6.0 Hz, 1 H, 8a-H), 3.67 (dd, J = 6.5, 3.2 Hz, 1 H, 3-H), 3.87 (dd, J = 6.3, 3.0 Hz, 1 H, 1-H), 3 ppm. 95 (t, J = 3.0 Hz, 1 H, 2-H), 4.21 (d, J = 6.7 Hz, 1 H, CH_2Ph), 4.35–4.65 (m, 7 H, CH_2Ph), 5.05 (d, J = 7.4 Hz, 1 H, 6-H), 7.1–7.5 (m, 16 H, Ar-H, 5-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 8.6 (t, *c*Pr-C), 13.9 (t, *c*Pr-C), 25.7 (s, *c*Pr-C), 63.8 (d, C-3), 65.2 (d, C-8a), 69.0 (t, C-1), 71.5 (t, CH_2Ph), 71.8 (t, CH_2Ph), 73.2 (t, CH_2Ph), 83.0 (d, C-1), 84.2 (d, C-2), 98.5 (d, C-6), 127.4 (d, Ar-C), 127.5 (d, Ar-C), 127.6 (d, Ar-C), 127.7 (d, Ar-C), 127.8 (d, Ar-C), 128.2 (d, Ar-C), 136.6 (s, Ar-C), 136.8 (s, Ar-C), 137.0 (s, Ar-C), 148.9 (d, C-5), 192.3 (s, C=O) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3018, 2987, 1692, 1625, 1586, 1460, 1384 cm^{-1}. HRMS: calcd. for $C_{32}H_{34}NO_4^+$: 496.2482; found 496.2483. The reaction mixture afforded also compound **33**: yield 127 mg, 51%.

4-(2-Bromophenyl)-5-methyl-5-azaspiro[2.5]oct-6-en-8-one (29): Yellow oil, yield 132 mg, 90%. R_f = 0.42 (AcOEt/light petroleum, 1:30). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.59–0.71 (m, 1 H, *c*Pr-H), 0.80–0.98 (m, 1 H, *c*Pr-H), 1.10–1.28 (m, 1 H, *c*Pr-H), 1.43–1.53 (m, 1 H, *c*Pr-H), 2.91 (s, 3 H, Me), 4.54 (s, 1 H, 4-H), 5.02 (d, J = 7.3 Hz, 1 H, 7-H), 7.03 (d, J = 7.3 Hz, 1 H, 6-H), 7.14 (dt, J = 8.0, 1.5 Hz, 1 H, Ar-H), 7.22–7.33 (m, 1 H, Ar-H), 7.51 (dd, J = 8.0, 1.5 Hz, 1 H, Ar-H), 7.84 (dd, J = 8.0, 1.5 Hz, 1 H, Ar-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 9.7 (t, *c*Pr-C), 22.9 (t, *c*Pr-C), 28.9 (s, *c*Pr-C), 41.5 (q, Me), 67.2 (d, C-4), 96.2 (d, C-7), 122.9 (s, Ar-C), 128.4 (d, 2 C, Ar-C), 129.5 (d, Ar-C), 132.4 (d, Ar-C), 139.1 (s, Ar-C), 153.3 (d, C-6), 190.2 (s, C=O) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3020, 3000, 1694, 1595, 1430 cm^{-1}. HRMS: calcd. for $C_{14}H_{15}BrNO^+$: 292.0332; found: 292.0332.

General Procedure for the Preparation of Tetrahydropyridones. Thermal Rearrangement of Adducts 2, 4, and 5: A solution of the respective nitrone cycloadduct **2**, **4**, or **5** (0.5 mmol) in xylenes (0.5 mL) was heated in a screw-cap sealed Sovirel tube at 120 °C for 12 h. After the solution had been cooled to room temperature the solvent was removed in vacuo and the crude material was purified by flash chromatography on silica gel.

4-(2-Bromophenyl)-5-methyl-5-azaspiro[2.5]octan-8-one (23): Yellow oil, yield 96 mg, 65%. R_f = 0.31 (AcOEt/light petroleum, 1:30). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.36–0.43 (m, 1 H, *c*Pr-H) 0.82–0.90 (m, 1 H, *c*Pr-H), 1.25 (m, 2 H, *c*Pr-H), 2.35 (s, 3 H, Me), 2.67 (t, J = 5.8 Hz, 2 H, 7-H), 2.84–2.97 (m, 1 H, 6-H), 3.15–3.21 (m, 1 H, 6-H), 4.11 (s, 1 H, 4-H), 7.09–7.16 (ddd, J = 8.0, 6.6, 2.6 Hz, 1 H, Ar-H), 7.26–7.35 (m, 2 H, Ar-H), 7.54 (d, J = 1.4 Hz, 1 H, Ar-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.3 (t, *c*Pr-C), 18.7 (t, *c*Pr-C), 31.3 (s, *c*Pr-C), 38.2 (q, Me), 43.6 (C-7), 50.3 (t, C-6), 70.1 (d, C-4), 125.4 (s, Ar-C), 127.2 (d, Ar-C), 128.9 (d, Ar-C), 130.9 (d, Ar-C), 132.9 (d, Ar-C), 138.6 (s, Ar-C), 208.5 (s, C=O) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3000, 2956, 1692, 1467, 1439, 1365, 1277, 1102, 1025 cm^{-1}. MS: *m*/*z* (%) = 295 (7) $[M + 2]^+$, 293 (7) $[M]^+$, 223 (23), 138 (100), 127 (43). $C_{14}H_{16}BrNO$ (294.19): calcd. C 57.16, H 5.48, N 4.76; found C 57.01, H 5.49, N 4.70.

(3a′*R*,9a*S*,9b*S*)-2′,2′-Dimethylspiro[cyclopropane-1,9′-(hexahydro-[1,3]dioxolo[4,5-*a*]indolizin)]-8(4*H*)-one (32): Pale orange oil, yield 82 mg, 69%. R_f = 0.15 (AcOEt/light petroleum, 3:7). $[\alpha]_D^{20}$ = –103.0 (c = 0.75, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.72–0.93 (m, 2 H, *c*Pr-H), 1.18–1.27 (m, 2 H, *c*Pr-H), 1.28 (s, 3 H, Me), 1.48 (s, 3 H, Me), 2.44–2.61 (m, 3 H, 7-H, 6-H), 2.65–2.84 (m, 1 H, 6-H), 2.90 (d, J = 6.5 Hz, 1 H, 9a-H), 3.22 (dd, J = 10.2, 5.1 Hz, 1 H, 4-H), 3.50 (dd, J = 10.2, 6.5 Hz, 1 H, 4-H), 4.09 (t, J = 6.5 Hz, 1 H, 3a-H), 4.74 (dd, J = 6.5, 5.1 Hz, 1 H, 9a-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 10.4 (t, *c*Pr-C), 16.2 (t, *c*Pr-C), 24.9 (q, Me), 26.9 (q, Me), 30.0 (s, *c*Pr-C), 38.1 (t, C-7), 49.2 (t, C-6), 59.6 (t, C-4), 69.3 (d, C-9a), 77.9 (d, C-3a), 80.4 (d, C-9b), 113.8 (s, acetonide group), 207.4 (s, C=O) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 2981, 2939, 2870, 1697, 1458, 1382, 1210, 1060 cm^{-1}. MS: *m*/*z* (%) = 238 (7) $[M + 1]^+$, 237 (48) $[M]^+$, 236 (97), 178 (88), 137 (100). $C_{13}H_{19}NO_3$ (237.30): calcd. C 65.80, H 8.07, N 5.90; found C 65.99, H 8.45, N 5.58.

(1′*R*,2′*R*,3′*R*,8a′*R*)-1′,2′-Bis(benzyloxy)-3′-[(benzyloxy)methyl]-spiro[cyclopropane-1,8′-(hexahydroindolizin)]-7′(1′*H*)-one (33): Yellow oil, yield 236 mg, 95%. R_f = 0.50 (AcOEt/petroleum ether, 3:7). $[\alpha]_D^{20}$ = –25.0 (c = 1.04, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.66–0.83 (m, 1 H, *c*Pr-H), 0.98–1.21 (m, 1 H, *c*Pr-H), 1.25–1.42 (m, 2 H, *c*Pr-H), 2.37–2.53 (m, 2 H, 6-H), 2.56–2.76 (m, 2 H, 5-H), 3.20–3.33 (m, 2 H, 3-H, 8a-H), 3.35–3.47 (m, 3 H, 2-H, CH_2Ph), 3.52–3.68 (m, 3 H, 2-H, 1-H), 4.44 (s, 2 H, CH_2Ph), 4.48 (AB system, part B, 1 H, CH_2Ph), 4.54 (s, 2 H, CH_2Ph), 4.57 (AB system, part A, 1 H, CH_2Ph), 7.18–7.45 (m, 15 H, Ar-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.1 (t, *c*Pr-C), 14.5 (t, *c*Pr-C), 29.5 (s, *c*Pr-C), 37.4 (t, C-6), 45.2 (t, C-5), 65.5 (d, C-3), 65.9 (d, C-8a), 69.3 (t, C-1), 71.6 (t, CH_2Ph), 72.2 (t, CH_2Ph), 73.1 (t, CH_2Ph), 85.1 (d, C-2), 85.6 (d, C-1), 127.3 (d, Ar-C), 127.5 (d, 2 C, Ar-C), 127.6 (d, Ar-C), 127.7 (d, Ar-C), 127.8 (d, Ar-C), 127.9 (d, Ar-C), 128.2 (d, Ar-C), 128.3 (d, Ar-C), 137.2 (s, Ar-C), 137.4 (s, Ar-C), 137.7 (s, Ar-C), 208.6 (s, C=O) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3010, 2865, 1696, 1584, 1454, 1363 cm^{-1}. HRMS: calcd. for $C_{32}H_{36}NO_4^+$: 498.2639; found 498. 2638.

Supporting Information (see also the footnote on the first page of this article): ^{13}C NMR spectra of compounds **25**, **27**, **28**, **29**, and **33**.

Acknowledgments

Britta Valentin, Sokrates exchange student from the University of Göttingen (Germany), is acknowledged for her experimental contribution to this work. Brunella Innocenti and Maurizio Passaponti are acknowledged for their technical assistance.

[1] a) A. de Meijere (Ed.), *Houben-Weyl, Methods of Organic Chemistry, Carbocyclic Three Membered Ring Compounds*, Thieme, Stuttgart, **1997**, vol. E17; b) O. G. Kulinkovich, *Chem. Rev.* **2003**, *103*, 2597–2632; c) H. N. C. Wong, M.-Y. Hon, C.-W. Tse, Y.-C. Yip, J. Tanko, T. Hudlicky, *Chem. Rev.* **1989**, *89*, 165–198; d) D. H. Gibson, C. H. Deluy, *Chem. Rev.* **1974**, *74*, 605–623.

[2] a) V. Ming, B. L. Pagenkopf, *Tetrahedron* **2005**, *61*, 321–347; b) H.-U. Reissig, R. Zimmer, *Chem. Rev.* **2003**, *103*, 1151–1196; c) H.-U. Reissig, *Top. Curr. Chem.* **1998**, *194–198*, 73–135.

[3] a) A. Brandi, S. Cicchi, F. M. Cordero, A. Goti, *Chem. Rev.* **2003**, *103*, 1213–1269; b) A. Goti, F. M. Cordero, A. Brandi, *Top. Curr. Chem.* **1996**, *178*, 1–97.

[4] a) F. M. Cordero, F. De Sarlo, A. Brandi, *Monatsh. Chem.* **2004**, *135*, 649–669; b) A. Brandi, F. M. Cordero, F. De Sarlo, A. Goti, A. Guarna, *Synlett* **1993**, 1–8.

[5] a) E. Ochoa, M. Mann, D. Sperling, J. Fabian, *Eur. J. Org. Chem.* **2001**, 4223–4231; b) A. Hassner, C. Stumer, *Organic Synthesis Based on Name Reactions, Tetrahedron Organic Chemistry Series, 22*, 2nd ed., Pergamon Press, Oxford, **2002**, p. 42.

[6] J. E. Baldwin, *Chem. Rev.* **2003**, *103*, 1197–1212.

[7] a) S. Cicchi, J. Revuelta, A. Zanobini, M. Betti, A. Brandi, *Synlett* **2003**, 2305–2308; b) J. Revuelta, S. Cicchi, A. Brandi, *J. Org. Chem.* **2005**, *70*, 5636–5642.

[8] J. Revuelta, S. Cicchi, A. Brandi, *Tetrahedron Lett.* **2004**, *45*, 8375–8377.

[9] For reviews on the synthesis of alkylidenecyclopropanes, see ref.[1a] and: A. Brandi, A. Goti, *Chem. Rev.* **1998**, *98*, 589–635.

[10] a) A. Goti, B. Anichini, A. Brandi, A. de Meijere, L. Citti, S. Nevischi, *Tetrahedron Lett.* **1995**, *36*, 5811–5814; b) C. Zorn, B. Anichini, A. Goti, A. Brandi, S. I. Kozhushkov, A. de Meijere, L. Citti, *J. Org. Chem.* **1999**, *64*, 7846–7855.

[11] S. Cicchi, M. Corsi, A. Brandi, A. Goti, *J. Org. Chem.* **2002**, *67*, 1678–1681.

[12] F. Cardona, E. Faggi, F. Liguori, M. Cacciarini, A. Goti, *Tetrahedron Lett.* **2003**, *44*, 2315–2318.

[13] R. D. Hinton, E. G. Janzen, *J. Org. Chem.* **1992**, *57*, 2646–2651.

[14] S. Cicchi, A. Bonanni, F. Cardona, J. Revuelta, A. Goti, *Org. Lett.* **2003**, *5*, 1773–1776, and references cited therein.

[15] G. A. Molander, *Org. React.* **1994**, *46*, 211–367.

[16] B. A. Steinhoff, I. A. Guzei, S. S. Stahl, *J. Am. Chem. Soc.* **2004**, *126*, 11268–11278.

[17] H. Okumoto, T. Jinnai, H. Shimizu, Y. Harada, H. Mishima, A. Suzuki, *Synlett* **2000**, 629–630.

[18] Y. Ito, T. Hirao, T. Saegusa, *J. Org. Chem.* **1978**, *43*, 1011–1013.

[19] For a similar effect of a 1,1-disubstituted cyclopropane ring, see: A. Goti, B. Anichini, A. Brandi, S. Kozhushkov, C. Gratkowski, A. de Meijere, *J. Org. Chem.* **1996**, *61*, 1665–1672.

Received: September 26, 2007
Published Online: December 18, 2007

