Structures of Saturated 5*H*-Pyrrolo[1,2-*a*][3,1]benzoxazin-1(2*H*)-ones Prepared from 4-Oxopentanoic Acid and Cyclic Amino Alcohols

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Saturated heterocycles containing two condensed heterocyclic rings and a carbo(bi)cyclic ring have been prepared by the reaction of 4-oxopentanoic acid (**1**) with (bi)cyclic amino alcohols. 5*H*-Pyrrolo[1,2-*a*][3,1]benzoxazin-1(2*H*)-ones **2**–**5** were formed in the reaction of **1** with *trans*- or *cis*-2-(hydroxymethyl)cyclohexylamines or -cyclohexenylamines. With di-*endo*- or di-*exo*-3-aminobicyclo[2.2.1]hept-2-yl- or -hept-5-en-2-ylmethanols, **1** yielded the corresponding derivatives **6**–**9** that are methylene-bridged in the cyclohexane or cyclohexene rings. The stereoselectivity of the syntheses were high; only for **5**, **7** and **9** were both C-3a epimers produced in observable amounts. The structures were established by means of NMR spectroscopic methods by applying standard pulse techniques.

Introduction

4-Oxopentanoic (levulinic) acid (**1**) is often used for preparing fused heterocycles.[1] For example, pyrrolo[1,2-*a*]-benzimidazoles have been obtained by reaction with phenylenediamine.[2−7] Similarly, reaction with anthranilic hydrazides has yielded pyridazino[3,2-*b*]quinazolines,[8] and pyrrolo[2,1-*a*]quinazolinones have been produced with anthranilamides.[9,10] Several chiral oxopyrrolooxazoles have been prepared by cyclisation with 2-amino alcohols, and they have been further used as precursors for the synthesis of a wide variety of optically pure quaternary-carbon compounds.[11−14] This condensation into bicyclic lactams has been observed to be highly stereoselective.

Surprisingly, we have found only one example in the literature where 1-amino-3-hydroxy compounds have been utilised in this manner (to yield oxazine-condensed heterocycles).[15] Since the fused heterocyclic compounds synthesised from 4-oxopentanoic acid proved to have significant pharmacological activity,[2,7,8] it seemed plausible to prepare fused 1,3-N,O-heterocycles possessing biological activity. As we have recently synthesised similar compounds from 3-aroylpropionic and -isobutyric acids with cyclic amino alcohols and characterised their structures using NMR spectroscopic and X-ray methods,[16,17] the present work, in which 4-oxopentanoic acid is the starting compound, complements the earlier studies and enables a comparison of the different structures and spectroscopic evaluations in the series.

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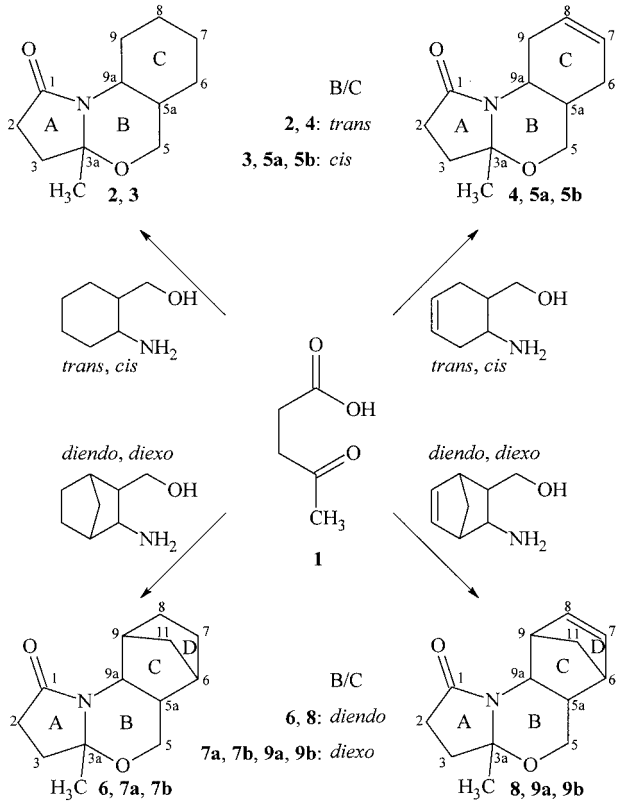
Results and Discussion

Synthesis

4-Oxopentanoic acid (**1**) was heated under reflux in toluene with *trans*- or *cis*-2-(hydroxymethyl)cyclohexylamine or -4-cyclohexenylamine in the presence of a catalytic amount of *p*-toluenesulfonic acid (PTSA) to yield the tricyclic, saturated compound **2** or **3**, or the partially unsaturated 5*H*-pyrrolo[1,2-*a*][3,1]benzoxazin-1(2*H*)-one **4** or **5**. The reaction of **1** with di-*endo*- or di-*exo*-3-aminobicyclo[2.2.1]-hept-2-yl- or -hept-5-en-2-ylmethanol resulted in the fully saturated, methylene-bridged tetracyclic derivative **6** or **7**, or the partially unsaturated tetracyclic derivative **8** or **9** (Scheme 1).

All of these new tricyclic and tetracyclic derivatives can potentially have the methyl substituent either far from or close to the cyclohexane/ene or norbornane/ene annulation hydrogen atoms, or in the case of the *trans* derivatives **2** and **4**, to one of them. The structure determination is important not only for elucidating this relationship, but also because of the possible change in structure of the starting amino alcohol that may occur depending on the reaction conditions.[18−20] Compounds **5**, **7** and **9** proved to be mixtures of two epimers, whereas the others were stereochemically pure by NMR spectroscopy. In each case, the predominant diastereoisomer is indicated by an **a** and the minor epimer by a **b** suffixed to the compound number.



Scheme 1

NMR Spectroscopic Study

The assignment of the ^1H and ^{13}C NMR spectral chemical shifts was accomplished by the application of conventional 1D and 2D NMR experiments (standard ^1H and $^{13}C\{^1H\}$, DEPT, selective INEPT, NOE difference, DQF-COSY, long-range DQF-COSY, f_1-decoupled CH shift, COLOC, HMBC) as described in the Exp. Sect. ^1H NMR chemical shifts and coupling constants were extracted from the 1D spectra using PERCH NMR software.[21] ^1H and ^{13}C NMR chemical shifts and $^1H,^1H$ coupling constants for compounds **2**−**9** are presented in Tables 1, 2 and 3, respectively. The stereostructures, as obtained from semiempirical PM3 calculations based on the configurations determined below, are portrayed in Figure 1.

Stereochemical conclusions were made on the basis of the values of $^1H,^1H$ coupling constants as well as NOE difference experiments. Of prime interest was the relative orientation of the methyl substituent with respect to the annulation hydrogen atoms (5a-H and 9a-H), and the conformation adopted by the carbo- and heterocyclic rings. Because of the fusion with the pyrrolo ring, the benzoxazine moiety was expected to be conformationally rigid. In agreement with this hypothesis, sub-spectra resulting from the presence of multiple conformers were not observed in either the ^1H or ^{13}C NMR spectra for any of the compounds studied at 25 °C. Compounds **3**, **7** and **8** were also subjected to low-temperature measurements down to −60 °C, for which dynamic effects were not in evidence.

Pyrrolobenzoxazinones 2 and 4 with *trans* B/C Rings

There are three chiral centres in compounds **2** and **4**, two of them (C-5a and C-9a) defining the ring fusion between the oxazine and carbocyclic rings, and the third (C-3a) bearing the methyl substituent. The relative configuration of carbon atoms C-5a and C-9a is fixed as (*R**,*R**) by the *trans* fusion of the starting material, which leaves two possible diastereoisomers with respect to C-3a as products. It was evident from the ^1H or ^{13}C NMR spectra of **2** and **4** that only one of the two possible isomers was present. Since NOE difference measurements showed a clear enhancement for the methyl proton resonance (4.7% for **2** and 6.3% for **4**) upon irradiating 5-H_{ax}, and since a large coupling constant indicative of a diaxial relationship was observed between 5-H_{ax} and 5a-H (11.4 Hz for both **2** and **4**), it could be established that 5-H_{ax} is *syn* and 5a-H is *anti* to the methyl group in the oxazine ring. Therefore the relative configuration is (3a*R**,5a*R**,9a*R**) in both *trans*-fused compounds.

In **2**, the carbocyclic ring is unambiguously in a chair conformation as evidenced by the large vicinal coupling

Table 1. ^1H NMR chemical shifts for compounds **2**−**9** in $CDCl_3$ at 25 °C (δ_{TMS} = 0.00 ppm)

	2-H_{anti}	2-H_{syn}	3-H_{anti}	3-H_{syn}	5-H_{ax}	5-H_{eq}	5a-H	6-H_{ax}	6-H_{eq}	7-H_{ax}	7-H_{eq}	8-H_{ax}	8-H_{eq}	9-H_{ax}	9-H_{eq}	9a-H	CH_3
2	2.43	2.31	2.00	2.00	3.59	3.67	1.68	0.94	1.53	1.31	1.70	1.22	1.89	2.25	2.57	3.16	1.54
3	2.40	2.42	2.03	2.09	4.11	3.56	2.07	1.59	1.62	1.16	1.51	1.29	1.77	1.76	1.82	4.20	1.61
4	2.42	2.31	2.00	2.06	3.65	3.81	1.94	1.72	2.00	5.60	–	5.70	–	2.84	3.14	3.49	1.52
5a	2.42	2.43	2.06	2.11	3.93	3.56	2.18	2.41	1.80	5.59	–	5.62	–	2.39	2.37	4.50	1.64
5b[a]	2.34*	2.37*	1.97*	2.06*	4.12	3.63	1.86	2.38	1.95	5.68	–	5.71	–	2.33	3.43	3.96	1.55
	2-H_{anti}	2-H_{syn}	3-H_{anti}	3-H_{syn}	5-H_{syn}	5-H_{anti}	5a-H	6-H	7-H_{exo}	7-H_{endo}	8-H_{exo}	8-H_{endo}	9-H	9a-H	11-H_{syn}	11-H_{anti}	CH_3
6[b]	2.37	2.32	1.98	2.11	4.07	3.77	1.99	2.18	1.37*	1.65	1.36*	1.35*	3.22	3.76	1.40*	1.37*	1.41
7a	2.36	2.45	2.04	1.93	3.61	3.73	1.84	2.20	1.55	1.14	1.52	1.38	2.22	4.12	2.31	1.18	1.50
7b[c]	2.42*	2.32*	1.92*	1.98*	3.79*	3.40*	1.90	1.90	1.49	1.19	(1.61)	(1.45)	3.81	3.43	1.64	1.20	1.39
8	2.29	2.42	1.95	2.14	3.40	4.01	2.66	2.89	6.35	–	6.23	–	3.34	4.15	1.44	1.56	1.36
9a	2.38	2.33	1.93	2.05	3.98	3.48	1.83	2.53	6.23	–	6.07	–	4.35	3.31	1.67	1.45	1.38
9b	2.36	2.47	2.06	1.97	3.69	3.83	1.78	2.78	6.28	–	6.16	–	2.77	4.04	2.39	1.48	1.49

[a] Values of geminal protons marked with an asterisk may be interchanged. [b] Values marked with an asterisk may be interchanged. [c] The assignment of asterisked values is based on **9a**; values in parentheses are uncertain.

Table 2. ^{13}C NMR chemical shifts for compounds **2**−**9** in $CDCl_3$ at 25 °C (δ_{TMS} = 0.00 ppm); relative stereochemistries are also provided

	Stereochemistry	C-1	C-2	C-3	C-3a	C-5	C-5a	C-6	C-7	C-8	C-9	C-9a	C-11	CH_3
2	(3a*R**5a*R**9a*R**)	174.56	30.27	33.52	92.16	66.87	40.93	27.01	24.82	26.02	28.73	57.44	–	19.97
3	(3a*R**5a*R**9a*S**)	172.78	29.52	36.39	89.84	61.72	33.63	26.91	21.53	25.20	27.70	49.11	–	24.13
4	(3a*R**5a*R**9a*R**)	173.06	30.21	33.82	91.49	65.95	36.47	26.51	123.84	126.01	28.44	52.78	–	19.37
5a	(3a*R**5a*R**9a*S**)	173.12	29.45	36.57	90.16	62.71	31.57	25.84	124.28	123.65	25.85	45.40	–	24.27
5b	(3a*R**5a*S**9a*R**)	172.61	30.42	34.65	91.43	65.63	32.49	23.66	124.66	124.79	26.43	48.77	–	20.39
6	(3a*R**5a*S**9a*R**)	171.96	29.07	34.27	88.53	61.90	33.19	41.52	22.45	21.74	40.34	50.74	36.51	21.62
7a	(3a*R**5a*R**9a*S**)	173.52	30.37	33.72	90.77	62.27	42.14	41.20	28.42	28.81	41.57	53.87	35.84	26.38
7b	(3a*R**5a*S**9a*R**)	172.09	30.48	33.07	90.73	62.12	42.90	39.58	29.47	26.36	37.56	56.89	33.93	23.10
8	(3a*R**5a*R**9a*S**)	175.43	29.22	37.55	88.23	62.93	34.45	44.30	137.63	136.92	46.96	52.71	48.17	23.87
9a	(3a*R**5a*S**9a*R**)	172.13	30.46	33.22	90.59	64.38	37.53	45.28	139.41	135.07	43.56	52.19	43.30	22.89
9b	(3a*R**5a*R**9a*S**)	173.94	30.54	34.10	90.74	62.58	34.41	46.89	137.91	138.29	46.15	50.75	44.89	26.35

Table 3. $^1H,^1H$ coupling constants [Hz] for compounds **2**−**9** in $CDCl_3$ at 25 °C

	$2_{anti}, 2_{syn}$	$2_{anti}, 3_{anti}$	$2_{anti}, 3_{syn}$	$2_{syn}, 3_{anti}$	$2_{syn}, 3_{syn}$	$3_{anti}, 3_{syn}$	$5_{ax}, 5_{eq}$	$5_{ax}, 5a$	$5_{eq}, 5a$	$5a, 6_{ax}$	$5a, 6_{eq}$	$5a, 9a$	$6_{ax}, 6_{eq}$	$6_{ax}, 7_{eq}$	$6_{eq}, 7_{ax}$
2	−17.17	10.74	4.71	7.66	9.10	−13.11	−11.84	11.39	4.77	11.94	3.39	10.60	−13.33	13.01	3.89	3.59
3	−15.09	10.09	2.55	10.21	8.92	−12.66	−11.86	12.41	4.55	6.16	1.00	5.53	−14.33	13.91	4.70	4.10
4	−17.19	10.16	2.77	9.57	9.27	−12.61	−11.97	11.40	5.13	11.24	5.29	11.03	−17.60	2.70	–	4.86
5a	−17.13	10.07	2.46	10.11	9.19	−12.71	−11.81	12.25	4.41	8.23	0.96	5.57	−19.06	2.80	–	4.44
5b	[a]	[a]	[a]	[a]	[a]	−12.8	−11.74	3.25	2.8	[a]	[a]	8.5	[a]	[a]	–	[a]

	$6_{eq}, 7_{eq}$	$7_{ax}, 7_{eq}$	$7_{ax}, 8_{ax}$	$7_{ax}, 8_{eq}$	$7_{eq}, 8_{ax}$	$7_{eq}, 8_{eq}$	$8_{ax}, 8_{eq}$	$8_{ax}, 9_{ax}$	$8_{ax}, 9_{eq}$	$8_{eq}, 9_{ax}$	$8_{eq}, 9_{eq}$	$9_{ax}, 9_{eq}$	$9_{ax}, 9a$	$9_{eq}, 9a$
2	2.94	−13.35	13.23	3.94	3.67	2.82	−13.58	13.24	3.36	3.61	3.38	−13.49	12.02	3.64
3	2.22	−13.67	13.12	3.32	3.32	3.11	−13.50	13.23	3.31	3.73	3.35	−13.03	12.90	5.02
4	–	–	10.04	–	–	–	–	2.53	5.73	–	–	−17.83	10.98	5.02
5a	–	–	10.08	–	–	–	–	3.05	4.93	–	–	−13.89	10.10	7.54
5b	–	–	[a]	–	–	–	–	[a]	[a]	–	–	[a]	5.0	3.4

	$2_{anti}, 2_{syn}$	$2_{anti}, 3_{anti}$	$2_{anti}, 3_{syn}$	$2_{syn}, 3_{anti}$	$2_{syn}, 3_{syn}$	$3_{anti}, 3_{syn}$	$5_{syn}, 5_{anti}$	$5_{syn}, 5a$	$5_{anti}, 5a$	5a, 6	5a, 9a	6, 7_{exo}	6, 7_{endo}
6[b]	−17.08	9.80	0.91	11.37	8.45	−12.21	−12.39	7.38	3.20	4.63	11.20	2.8	2.27
7a	−16.78	9.46	0.78	12.23	8.17	−12.28	−12.53	2.94	5.54	0.71	9.50	4.63	0.53
7b	[a]	[a]	[a]	[a]	[a]	[a]	−11.63	6.81	9.16	[a]	7.7	[a]	[a]
8	−16.64	9.44	0.79	12.36	8.17	−12.05	−12.21	10.76	9.22	3.64	10.33	3.06	–
9a	−17.06	9.79	1.31	11.22	8.62	−12.40	−11.73	6.72	8.37	1.68	7.55	2.98	–
9b	−16.87	9.11	0.81	12.35	7.97	−12.33	−12.64	2.83	5.50	1.48	9.25	3.11	–

	6, 11_{syn}	6, 11_{anti}	$7_{exo}, 7_{endo}$	$7_{exo}, 8_{exo}$	$7_{exo}, 8_{endo}$	$7_{endo}, 8_{exo}$	$7_{endo}, 8_{endo}$	$8_{exo}, 8_{endo}$	$8_{exo}, 9$	$8_{endo}, 9$	9, 9a	9, 11_{syn}	9, 11_{anti}
6[b]	1.98	0.95	−9.28	13.2	(−5.85)	(−1.05)	11.32	−8.85	4.1	0.1	4.21	1.79	−0.3
7a	1.78	1.46	−12.32	12.43	4.09	4.88	8.97	−12.44	4.46	0.74	0.66	1.70	1.29
7b	[a]	[a]	[a]	[a]	[a]	[a]	[a]	[a]	[a]	[a]	[a]	[a]	[a]
8	1.38	2.07	–	5.77	–	–	–	–	3.09	–	3.45	1.45	1.90
9a	1.29	1.61	–	5.71	–	–	–	–	3.22	–	1.06	1.58	2.05
9b	1.21	1.6	–	5.69	–	–	–	–	2.89	–	1.63	0.60	1.6

[a] Not detected. [b] Large uncertainties, particularly for the values in parentheses, exist for some of the $^1H,^1H$ couplings in the norbornane moiety because of strongly overlapping signals. The number of significant figures is based on the standard deviations given by the spin analysis (PERCH NMR software).

constants typical for adjacent diaxial protons (Table 3) and by several w-type, long-range couplings observed in long-range DQF-COSY experiments. In **4**, the fragment C-6−C-7−C-8−C-9 is planar because of the double bond between C-7 and C-8, but the couplings $^3J_{5a\text{-}H,6\text{-}Hax}$, $^3J_{5a\text{-}H,9a\text{-}H}$ and $^3J_{9\text{-}Hax,9a\text{-}H}$ are of similar magnitudes to the corresponding values in **2**, which indicates that the annulation region of the carbocycle is essentially the same. Thus, the carbocyclic ring in **4** is in a half-chair conformation. The oxazine ring is in a chair conformation in both **2** and **4**, which is indicated by the diaxial coupling pattern in the 5-H_{ax}−5a-H−9a-H sequence together with observed NOEs between 5-H_{ax} and CH_3, 9a-H and CH_3, and 5-H_{ax} and 9a-H. We assume that this ring is slightly flattened because of the lactamide nitrogen atom, analogous to observations made in previous studies.[16,17] The presence of a transoid, homoallylic five-bond coupling[22] (ca. 1 Hz) between 9a-H and 2-H_{syn} was observed for these compounds, suggesting that the

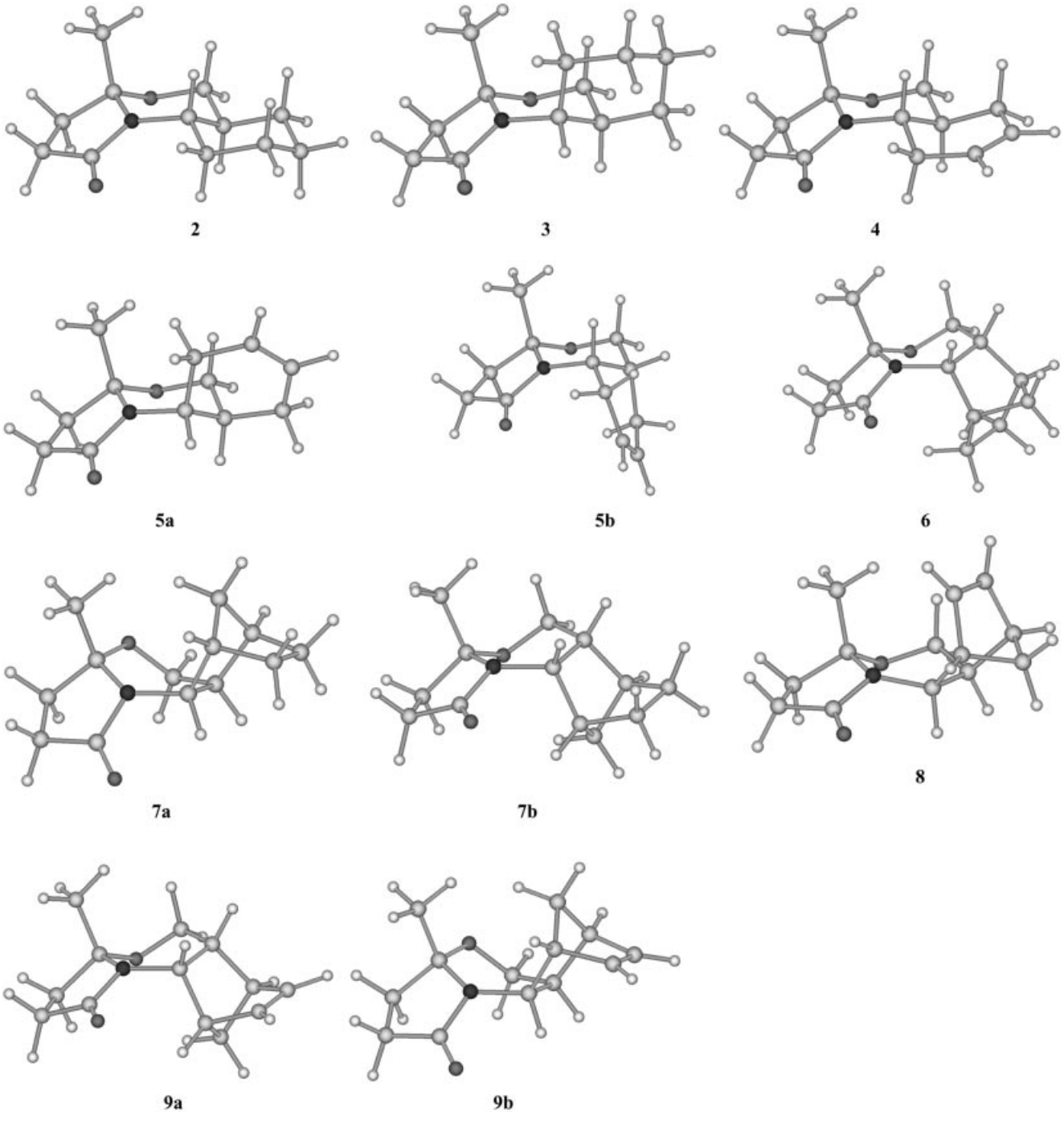


Figure 1. The stereostructures of compounds **2**−**9** as determined by semiempirical PM3 calculations

C-1−N-10 bond has partial double bond character, which is consistent with the proposed flattening of the oxazine ring.

The pyrrolo protons can be either *syn* or *anti* with respect to the 3a-methyl group, with *syn*-protons being identified as such by their receiving an NOE enhancement upon irradiation of the methyl protons. The geminal coupling constant between 2-H_{syn} and 2-H_{anti} protons is very negative (ca. −17 Hz) in both compounds as a result of the π-electron effect resulting from the adjacent carbonyl bond lying favourably with respect to the 2-H_{syn}−C-2−2-H_{anti} bond angle.[23] The partial double bond character of the C-1−N-10 bond implies that the C-3a−N-10−C-1−C-2 fragment of the pyrrolo ring must be relatively planar. It is therefore assumed that the pyrrolo ring is predominantly in an envelope conformation with C-3 as the flap atom. It then follows

from the coupling pattern of the pyrrolo protons (for both **2** and **4**) that the flap atom C-3 and the methyl substituent must lie on opposite sides of the plane of the pyrrolo ring.

Pyrrolobenzoxazinones 3 and 5 with *cis* B/C Rings

As observed for compounds **2** and **4**, only one diastereoisomer was present for **3**. For **5**, however, an observable amount (8%) of a minor epimer was detected.

The *cis* fusion of compounds **3**, **5a** and **5b** was readily confirmed by the medium-sized vicinal coupling constants between 5a-H and 9a-H (5.5, 5.6 and 8.5 Hz, respectively) corresponding to ax−eq or eq−ax arrangements. Consistent with this notion, the sum of the carbon atom chemical shifts for the carbocycle in these compounds is considerably smaller (by 13−21 ppm) in comparison to their *trans*-fused counterparts, which is a well-known consequence[24,25] for sterically strained structures. In **3** and **5a** there is a large coupling between 5-H_{ax} and 5a-H (12.4 and 12.3 Hz, respectively), which implies that 5a-H is axial and 9a-H equatorial with respect to the oxazine ring and, consequently, that the oxazine ring is in an *N*-out[26] conformation. The aforementioned coupling, in addition to the observed NOE enhancements between all the possible two-spin combinations of CH_3, 5-H_{ax} and 9-H_{ax}, and the w-type long-range coupling between 5-H_{eq} and 9a-H, suggests that the oxazine ring is in a chair conformation in both of these compounds. From these data it also follows that the relative configuration of both **3** and **5a** is (3a*R**,5a*R**,9a*S**). That the cyclohexane ring in **3** is also in a chair conformation is again evident from the large vicinal coupling constants typical for diaxial protons. As for **4**, the carbocycle of **5a** is also in a half-chair conformation because of the C-7−C-8 double bond. In contrast to the *trans*-fused compounds, the $\sin^2\varphi\,\sin^2\varphi'$-dependent[27,28] homoallylic $^5J_{9a\text{-H},2\text{-H}syn}$ couplings had zero values in **3** and **5a**, indicating that the torsion angle between 9a-H and C-1 is now much closer to 0°. Such an arrangement also places 9a-H in the deshielding zone of the lactamide carbonyl bond, which is clearly reflected by the considerable downfield shift (> 1 ppm) experienced by this proton in comparison to the *trans*-fused derivatives. These characteristic spectral features of 9a-H have already been noted in previous studies on similar structures.[16,24] The carbon atom chemical shifts exhibit the expected behaviour when comparing **3** to **2** and **5a** to **4**. Thus, in the *cis* compounds there is a decrease in the values of the chemical shifts of C-3a, C-5, C-5a and C-9a owing to various *syn*-axial, γ-gauche and other comparable effects[29] present in the *cis* form, as well as an increase in the CH_3 shift likely attributable to the methyl group being slightly bent away from the axial position because of steric demands.

The spin simulation of the upfield region of the proton spectrum was not possible for **5b** because of overlap with the dominating **5a** isomer. From the low-field region, however, it was possible to extract the coupling constants $J_{5\text{-Hax},5a\text{-H}}$, $J_{5\text{-Heq},5a\text{-H}}$ and $J_{5a\text{-H},9a\text{-H}}$, and the lack of large diaxial values suggests that it exhibits the expected "*N*-in"-type[26] *cis* fusion. An NOE enhancement (2.2%) was also observed for the 5-H_{ax} signal when irradiating the CH_3 protons, which indicates a (3a*R**,5a*S**,9a*R**) configuration for **5b**. In this structure, the carbocycle and the methyl group are on opposite sides of the plane of the oxazine ring. The resulting relief of steric strain in comparison to **5a** is clearly seen in the carbon atom chemical shifts: C-5 is deshielded since C-7 and C-9 no longer occupy γ-gauche positions, as is C-9a because the now-axial (with respect to the oxazine ring) 9a-H is not disturbed by the carbonyl group. This phenomenon is also directly apparent from the upfield shift of the 9a-H resonance; 9-H_{eq}, on the other hand, experiences an expected downfield shift because of the vicinity of the carbonyl oxygen atom, which is in agreement with the structure proposed for **5b**. The methyl substituent can also occupy an axial position that closely resembles the one in the *trans*-fused compounds. This arrangement is confirmed nicely by the similar CH_3 ^1H or ^{13}C NMR chemical shift values in **2**, **4** and **5b**. The spectral features of **5b** stated above are consistent with the oxazine ring being in a chair conformation. The cyclohexene moiety most likely occupies a half-chair conformation analogous to that of **5a**, though the lack of coupling data precludes firm conclusions.

The coupling behaviour of the pyrrolo protons of compounds **3** and **5a** is similar to that of the *trans*-fused compounds **2** and **4**, suggesting that the previously deduced pyrrolo ring conformation is valid for all of the cyclohexane/ene condensed compounds. As an additional verification to the proposed pyrrolo ring conformation, the geometry of compound **3** was optimised using DFT calculations at the B3LYP/6-31G(d,p) level[30−34] of theory. In the optimised structure, the pyrrolo ring had indeed adopted an envelope conformation with C-3 as the flap atom. The C-1−C-2−C-3−C-3a torsion angle (−26°) in this structure was well in agreement qualitatively with the observed coupling constants, implying, for example, a relatively large value for $J_{2\text{-H}syn,3\text{-H}anti}$ (observed: 10.2 Hz) and a small one for $J_{2\text{-H}anti,3\text{-H}syn}$ (observed: 2.6 Hz). This torsion angle was one of the constraints used in the PM3 molecular modelling of compounds **2**−**5** presented in Figure 1.

Di-*endo*-Fused Norbornane/ene Derivatives 6 and 8

In **6** and **8**, the conformation of the norbornane skeleton is reflected by the observation, wherever expected, of w-type, long-range $^1H,^1H$ couplings within the skeleton. The same is true for the di-*exo*-fused derivatives considered later. Thus, we are left with three stereochemical questions of interest: whether the norbornane moiety is di-*endo*-fused (as expected from the stereochemistries of the starting materials), how the bridgehead protons 5a-H and 9a-H are orientated with respect to the methyl substituent, and, finally, what are the conformations of the hetero rings?

Norbornane/ene fused compounds, such as **6**−**9**, are readily identified as being either di-*endo*- or di-*exo*-condensed from their $^3J_{5a\text{-H},9a\text{-H}}$ values: di-*exo*-protons have larger vicinal coupling constants (> 10 Hz) than di-*endo*-protons (< 10 Hz).[35] Thus, **6** and **8** are di-*endo*-fused ($^3J_{5a\text{-H},9a\text{-H}}$ = 11.2 and 10.3 Hz, respectively). For **6**, the observed w-type, long-range couplings between 5a-H, 7-H_{exo} and 9a-H, 8-

H_{exo} provided an additional verification of the fusion. In **8**, there was an NOE enhancement (ca. 3−4%) for one of the 11-H signals when irradiating the 5a-H and 9a-H resonances, which also confirms the di-*endo*-fusion.

In considering the relative orientation of the methyl group with respect to the annulation hydrogen atoms, since the irradiation of one of the 5-H protons (labelled as 5-H_{syn}) of compound **6** results in an intensity increase of the CH_3 and 5a-H proton resonances (5.7 and 8.9%, respectively), whereas the irradiation of the other proton (5a-H_{anti}) does not change the intensity of the methyl protons, it is straightforward to state that the methyl group and the annulation protons are on the same side of the heterocyclic ring. Interestingly, in **8** there was an NOE enhancement in the 7-H and 8-H signals (0.8 and 2.0%) when irradiating CH_3. From this effect it follows that in **8** the 5a-H and 9a-H protons must be on the opposite side of the oxazine ring with respect to the CH_3 group. It is obvious that in **6** such a folding would result in strong steric interactions between the methyl group and the *endo* protons at positions 7 and 8.

Since in **6** and **8** there is a strong NOE correlation between 5-H_{syn} and CH_3, it is necessary that these groups occupy (pseudo-)axial positions. On the other hand, the fragment C-5−C-5a−C-9a−N-10 must be almost planar because of the fused norbornane/ene moiety. Under these constraints, molecular modelling suggests a sofa-like[36] conformation for the oxazine ring where O-4 is below and the methyl substituent is above the plane defined by C-5−C-5a−C-9a−N-10−C-3a. Such a conformation has also been observed by X-ray measurements for other similar di-*endo*-fused derivatives[16,17] and can, therefore, be considered quite probable also for compounds **6** and **8**.

The coupling pattern of the pyrrolo protons is very uniform for all of the norbornane/ene-fused compounds we have studied, which again suggests that the pyrrolo ring conformation is invariant in this subset. As $J_{2\text{-H}anti,3\text{-H}syn}$ is even smaller (ca. 1 Hz) in these compounds than in compounds **2**−**5** and, correspondingly, $J_{2\text{-H}syn,3\text{-H}anti}$ is larger, it can be concluded that the envelope conformation is now more puckered than in the cyclohexane/ene-condensed derivatives. Consistent with this conformation, DFT optimisation of **8** revealed a somewhat larger value (−29°) for the C-1−C-2−C-3−C-3a torsion angle than that calculated for **3** (−26°), with the conformation of the pyrrolo ring still being an envelope with C-3 as the flap atom. The calculation gave a value of 89° for the torsion angle between 2-H_{anti} and 3-H_{syn}, nicely in agreement with the nearly vanishing coupling constant.

Di-*exo*-Fused Norbornane/ene Derivatives 7 and 9

Contrary to the diastereoisomerically pure di-*endo*-fused analogues, di-*exo*-fused compounds **7** and **9** were both composed of a mixture of two diastereoisomers **a** and **b** in ratios of 96:4 and 82:18, respectively. The expected conformation and the di-*exo* fusion of the norbornane/ene moiety in **7a**, **9a** and **9b** was verified in the same manner as for **6** and **8**. The low proportion of **7b** (4%) made it impossible to observe any meaningful long-range $^1H,^1H$ couplings within the norbornane moiety, as the corresponding spectral area was dominated by the major isomer. The di-*exo* fusion of **7b** is revealed by the small value of the 5a-H, 9a-H coupling constant (7.7 Hz) as previously mentioned.

In **7a**, the observed NOE enhancement in the CH_3 protons (5.0%) when irradiating one of the 11-H protons (11-H_{syn}) proves the *syn* relationship of the methyl substituent and the norbornane methylene bridge. As a consequence, the *endo* protons at the ring-fusion sites must be *anti* to the methyl group. The NOE measurements for **7a** revealed a curious spatial proximity between the 3-H_{anti} and 5-H_{anti} protons (*anti* with respect to the methyl group). Under such a restraint, semiempirical calculations suggest a somewhat distorted twist conformation for the oxazine ring where C-3a and C-5a are in isoclinal ring positions and 5-H_{anti} is in a pseudo-axial position. This places 11-H_{syn} close to the lone pair of the ring oxygen atom, which is indeed reflected by the considerable deshielding experienced by this proton compared to 11-H_{anti}. A downfield shift of the methyl carbon atom is observed relative to **6** and **8**, which agrees well with the assumption that the substituent is now isoclinally orientated instead of being in a more-hindered pseudo-axial position.

In **9a**, irradiation of the CH_3 protons increased the intensity of the 9a-H signal by 2.2%. Thus, the annulation protons are *syn* to the methyl group. This arrangement is also evident from the remarkable downfield shift of 9-H with respect to **7a**, as the opposite folding of the norbornane skeleton has placed the proton in the vicinity of the carbonyl group. It is interesting that the major diastereoisomers of **7** and **9** do not share the same relative stereochemistry, as the introduction of the C-7−C-8 double bond in **9** should not impose notable changes in the steric demands in comparison to **7**. The conformation of the six-membered heterocycle in **9a**, as suggested by semiempirical modelling, is similar to that of **6**. However, the methyl group is probably slightly bent out from the pseudo-axial position since the NOE enhancement of 5-H_{syn} upon irradiation of the CH_3 unit was only 1.0%.

The stereochemistries of the minor diastereoisomers are subsequently fixed by determination of the structures of the major epimers. Thus, the structure of **7b** is similar to that of **9a**, whereas **9b** resembles **7a**. This assignment is also evident from a comparison of the 9-H, 9a-H, 11-H_{syn} and methyl group (both ^1H and ^{13}C NMR) chemical shifts as well as the $J_{5\text{-H}syn,5\text{-H}anti}$, $J_{5\text{-H}syn,5a\text{-H}}$ and $J_{5a\text{-H},9a\text{-H}}$ coupling constants.

Conclusions

A series of 3a-methyl-substituted, saturated 5*H*-pyrrolo[1,2-*a*][3,1]benzoxazin-1(2*H*)-ones, together with their 6,9-methylene-bridged analogues, have been synthesised and their stereostructures characterised by NMR spectroscopy.

Comparing the 3a-methyl-substituted cyclohexane/ene condensed products **2**−**5** with the 3a-aryl-substituted ana-

Table 4. Physical and analytical data for compounds **2**−**9**

Compound	Formula	Ratio[a]	M.p. [°C]	Yield (%)	Found (calcd.) C	Found (calcd.) H	Found (calcd.) N
2	$C_{12}H_{19}NO_2$	−	59−61[b]	87	68.91 (68.85)	9.29 (9.15)	6.66 (6.69)
3	$C_{12}H_{19}NO_2$	−	118−120[c]	92	68.61 (68.85)	9.27 (9.15)	6.59 (6.69)
4	$C_{12}H_{17}NO_2$	−	64−66[d]	85	69.57 (69.54)	8.33 (8.27)	6.86 (6.76)
5a + **5b**	$C_{12}H_{17}NO_2$	92:8	56−58[c]	85	69.65 (69.54)	8.26 (8.27)	6.70 (6.76)
6	$C_{13}H_{19}NO_2$	−	105−107[d]	75	70.60 (70.56)	8.70 (8.65)	6.30 (6.33)
7a + **7b**	$C_{13}H_{19}NO_2$	96:4	74−76[d]	90	70.46 (70.56)	8.59 (8.65)	6.24 (6.33)
8	$C_{13}H_{17}NO_2$	−	143−145[c]	70	71.19 (71.21)	7.90 (7.81)	6.39 (6.39)
9a + **9b**	$C_{13}H_{17}NO_2$	82:18	[e]	71	71.01 (71.21)	7.97 (7.81)	6.15 (6.39)

[a] Diastereoisomeric ratio as obtained on NMR spectral samples. Solvent of crystallisation: [b] Benzene. [c] Ethyl acetate. [d] Diethyl ether. [e] Colourless oil.

logues studied previously,[16,17] we see that the replacement of the 3a substituent has little effect on the product stereochemistry. With the exception of a small amount (8%) of the minor epimer present in product **5**, the synthesis of these compounds was stereoselective and the relative stereochemistry of the products unaffected by the change of the C-3a substituent.

The differences between the 3a analogues are more pronounced in the case of the norbornane/ene-fused derivatives, **6**−**9**. The di-*endo*-fused products **6** and **8** consisted of only one diastereoisomer, but only **8** had a structure similar to its 3a-aryl-substituted analogues.[16,17] The inversed configuration of C-3a in **6**, as compared to its aryl-substituted analogue, must be due to steric reasons: *syn*-folding of the norbornane moiety and the methyl group would lead to strong nonbonded interactions between the *endo* protons (at the 7 and 8 positions) and the methyl group. As these di-*endo* protons are missing from **8**, its usual behaviour is easy to understand. The di-*exo*-fused derivatives **7** and **9** were mixtures of the two possible C-3a diastereoisomers, whereas in the 3a-aryl-substituted analogues only *syn* alignment between the 3a substituent and the methylene bridge of the norbornane was observed. This observation again could be attributable to steric interactions between the methyl group and the norbornane 11-H_{syn} proton.

It is worth noting that in compounds **2**−**5**, changing the C-7−C-8 bond order does not result in a change in the relative stereochemistry of the product (apart from the minor form **5b**) but in **6**−**9** it actually reverses the relative stability of the two diastereoisomers.

Experimental Section

NMR Measurements: NMR spectra were recorded with JEOL JNM-LA400 (operating at 399.78 MHz for ^{1}H and 100.54 MHz for ^{13}C) and JEOL JNM-A500 (500.16 MHz for ^{1}H and 125.78 MHz for ^{13}C) FT NMR spectrometers using $CDCl_3$ solutions of samples in 5-mm diameter NMR tubes. The deuterium signal of the solvent served as a field-frequency lock and tetramethylsilane (TMS) as an internal reference (δ = 0.00 ppm for both ^{1}H and ^{13}C). Temperature control was set at 25 °C for normal-temperature measurements and was decreased down to −60 °C for the low-temperature measurements. Standard, vendor-supplied pulse sequences[37] were used in all experiments. 1D ^{1}H NMR spectra were acquired using 8 kHz spectral width and 32 k data points with 16−64 scans. 1D ^{13}C NMR spectra with broadband proton decoupling consisted of 65 k data points with a 27−30 kHz frequency range and were accumulated until sufficient S/N ratio was achieved (100−5000 scans). An exponential weighting function with 0.3−0.5 Hz line-broadening factor was applied prior to Fourier transformation. In NOE difference measurements, saturation times of 7−10 s were used and the integral of the irradiated signal was given a reference value of −100% in order to estimate the percentage NOE enhancement for the other proton signals. DEPT 135° experiments were optimised for 145 Hz $J_{C,H}$ couplings, other parameters being similar to basic ^{13}C NMR measurement. Selective INEPT measurements were optimised for long-range $J_{C,H}$ couplings in the range of 2−12 Hz as needed. For 2D correlation experiments, suitable spectral widths were selected from the corresponding 1D spectra. Zero filling (t_2: ×1 or ×2, t_1: ×2 or ×4), together with exponential multiplication (0.3 Hz) and sinebell (130% of the FID length and shifted −30%) apodisation, was generally employed when processing the spectra. Homonuclear 2D correlation experiments included phase-sensitive DQF-COSY and long-range DQF-COSY (with 200-ms delay), whereas heteronuclear experiments consisted of f_1-decoupled CH-shift and COLOC, HMBC-BIRD or gradient-selected HMBC. CH-shift measurements were optimised for 145 Hz $^1J_{C,H}$ couplings, and long-range couplings of 8 Hz. Spin analysis of the ^{1}H NMR spectra was performed with PERCH NMR software.[21] For DFT calculations, Gaussian 98 software[38] was utilised.

Preparation of the 3a-Methyloctahydro- (2 and 3) and -3,3a,5a,6,9,9a-hexahydro-5*H*-pyrrolo[1,2-*a*][3,1]benzoxazin-1(2*H*)-ones (4 and 5) and Di-*endo* (6 and 8) and Di-*exo* (7 and 9) 6,9-Methano Analogues: 4-Oxopentanoic acid (**1**, 1.2 g, 0.010 mol, Acros 12.514.01 levulinic acid, 98+%), a cyclic or bicyclic amino alcohol [1.3 g of *cis*- or *trans*-2-(hydroxymethyl)cyclohexyl-1-amine,[39] or 1.3 g of *cis*- or *trans*-2-(hydroxymethyl)-4-cyclohexenyl-1-amine,[40] or 1.4 g of di-*exo*- or di-*endo*-3-aminobicyclo[2.2.1]hept-2-ylmethanol or 1.4 g of -hept-5-en-2-ylmethanol;[41,42] 0.010 mol], and PTSA (0.05 g) in toluene (50 mL) was heated under reflux for 2 h. After evaporation of the solvent, the residue was transferred to a chromatography column (alumina, Acros, activated, basic, 50−200 μ) and eluted with EtOAc. The physical data for compounds **2**−**9** are listed in Table 4.

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