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Formation and Characterization of a Multicomponent Equilibrium System Derived from *cis*- and *trans*-1-Aminomethylcyclohexane-1,2-diol

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Both cis and trans isomers of amino diols **3**−**6** were prepared stereoselectively. In the reactions between **3**−**6** and phenyl isothiocyanate, the ring closure proceeded regioselectively and resulted only in spiro derivatives of 2-phenyliminooxazolidines **9**, **10**, **13**, and **14**. The reaction of *cis*- (or *trans*-)1-aminomethylcyclohexane-1,2-diol **4** (or **6**) with 1 equiv of an aromatic aldehyde **15a**−**g** in EtOH at room temperature resulted in a complex, multicomponent equilibrium mixture of **16a**−**g** and **18a**−**g** (or **17a**−**g** and **19a**−**g**), in each case consisting of a five-component, ring−chain tautomeric system **16A**−**E** (or **17A**−**E**), involving the Schiff base, two epimeric spirooxazolidines, two epimeric condensed 1,3-oxazines, and some of the four tricyclic compounds **18A**−**D** (or **19A**−**D**). The five-component, ring−chain equilibria were found to be adequately described by the Hammett−Brown linear free energy equation.

Introduction

Aliphatic amino diols play an important role in drug therapy and drug research.[1−6] For example, chloramphenicol, one of the earliest antibiotics, is an amino diol derivative, while other amino diols have been found to act as HIV protease inhibitors,[1−3] and still others have been shown to exert renin inhibitor activity.[5,6] Furthermore, a number of compounds containing a spiromorpholine or spiropiperidine structure closely resembling the amino diols possess marked pharmacological[7] and neurotoxicological effects.[8−10] Outside of the pharmacological interest, amino diols are also useful starting materials for the syntheses of oxazines or oxazolidines, depending upon which hydroxy group undergoes ring closure with the amino group. Since the resulting heterobicycles contain a free hydroxy group, further ring closure can yield heterotricyclic structures. Chiral amino diols also find application as catalysts for enantioselective transformations,[11] and additionally, alicyclic amino diols are potentially excellent starting points for the development of new ring−chain tautomeric systems. Ring−chain tautomeric systems continue to remain the subject of intense interest and are also now appropriately being systematically classified.[12]

Earlier studies on the equilibria between open-chain (i.e., the Schiff base) and ring-closed (1,3-*O*,*N*-heterocycle) species have been conducted utilizing many techniques including ^{1}H NMR spectroscopy,[13−16] which offers superior advantages over other methodologies and readily facilitates quantitation. The tautomeric equilibria of 2-aryl-1,3-*O*,*N*-heterocycles can be described successfully by the Hammett−Brown linear free energy equation:

$$\log K_X = \rho\sigma^+ + \log K_{X=H} \qquad (1)$$

where K_X = [ring]/[chain], ρ is a coefficient that characterizes the sensitivity of the tautomeric system to the influence of the electronic effect of the substituent X, and σ^+ is the Hammett−Brown constant for the substituent

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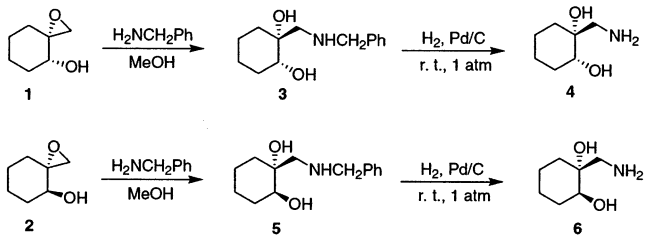
X. Not only can eq 1 describe two- or three-component equilibria of 2-aryl-1,3-*O*,*N*-heterocycles,[13] it can also be applied to more complex systems, e.g. five-component systems containing C-2 epimeric oxazolidine and tetrahydro-1,3-oxazine pairs.[17−20] For $CDCl_3$ solutions at ambient temperature, a value of 0.76 has been obtained for ρ for tetrahydro-1,3-oxazines and 0.60 for oxazolidines.[13]

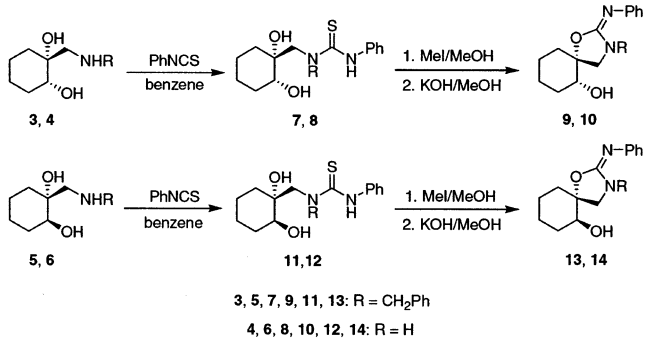
While the chemical behavior of alicyclic 1,2- and 1,3-amino alcohols has been studied extensively, only a few reports combining the characteristics of 1,2- and 1,3-amino alcohols, viz. the alicyclic amino diols, have been published thus far.[11,21,22] In particular, the products of the reaction between an aldehyde and an alicyclic amino diol containing three or more functional groups can potentially present a novel example of ring−chain tautomerism.[23−27]

The aim of the present work was to study the ring closures of stereoisomeric alicyclic amino diols and the ring−chain tautomeric equilibria involved in the ring closures of *cis*- and *trans*-1-aminomethylcyclohexane-1,2-diols with various aromatic aldehydes. It was anticipated that both 1,3-oxazines and oxazolidines could be formed under the reaction conditions applied.

SCHEME 1



SCHEME 2



Results and Discussion

Syntheses of the 1-Aminomethylcyclohexane-1,2-diols 4 and 6. Diastereomeric *cis*- and *trans*-epoxy alcohols **1** and **2** were synthesized stereoselectively by a combination of literature methods.[21,28−30] The synthesis of *cis*-epoxy alcohol **1** started from ethyl 2-oxocyclohexanecarboxylate with $LiAlH_4$ reduction,[28] followed by stereoselective epoxidation of the resulting 2-methylene-1-cyclohexanol with *m*-chloroperbenzoic acid.[29] The trans counterpart **2** was prepared from cyclohexanone by Mannich condensation with paraformaldehyde and dimethylamine hydrochloride.[30] The Mannich base was then subjected to Hofmann's exhaustive methylation, and epoxidation resulting in the epoxy ketone, which was reduced stereoselectively using sodium borohydride in MeOH to provide **2**.

N-Benzylamino diols **3** and **5** were then obtained[21] by the reaction of **1** and **2** (Scheme 1), with benzylamine under very dilute conditions to avoid dimerization. The debenzylation of amino diols **3** and **5** was effected under standard conditions by hydrogenation in the presence of palladium-on-carbon catalyst to produce both *cis*- and *trans*-1-aminomethylcyclohexane-1,2-diols **4** and **6**, in quantitative yield as crystalline bases.

Regioselective Ring Closure of Amino Diols 3−6. To assess the tendencies of amino diols **3**−**6** to furnish either a cyclohexane spirooxazolidine or a cyclohexane-condensed 1,3-oxazine ring, **3**−**6** were each treated with phenyl isothiocyanate, which provided the thiourea derivatives **7**, **8**, **11**, and **12**. After reaction with methyl iodide followed by treatment with base (KOH), these adducts underwent ring closure via methyl mercaptan elimination.[31,32] The spirooxazolidine derivatives **9**, **10**, **13**, and **14** were readily identified as the sole products in each respective case and distinguished from the 1,3-oxazines by the characteristic ^{13}C chemical shifts of C-4, C-5, and C-6 and by 2D heteronuclear NMR experiments. In the HMBC spectra, correlations between the CH_2CHO proton and the O*C*=NPh carbon were not observed, implying that the product of the synthesis was the spirooxazolidine. The reaction sequence is depicted in Scheme 2.

Condensation of Amino Diols 4 and 6 with 1 equiv of an Aromatic Aldehyde. The reaction of the amino diols **4** (or **6**) with seven aromatic aldehydes **15a**−**g** in EtOH after the usual processing (e.g., removal of the solvent at 50 °C and the use of boiling solvent for recrystallization) resulted in a mixture of tricyclic compounds (**18** (or **19**)) in each case instead of the five-component mixture consisting of compounds **16A**−**E** (or **17A**−**E**) (Schemes 3 and 4). Use of milder conditions, though, still resulted in a complex mixture but consisting of the compounds **16** and **18** (or **17** and **19**), i.e., both the tricyclic structures and the expected five-component, ring−chain system were present. In each case, a complex

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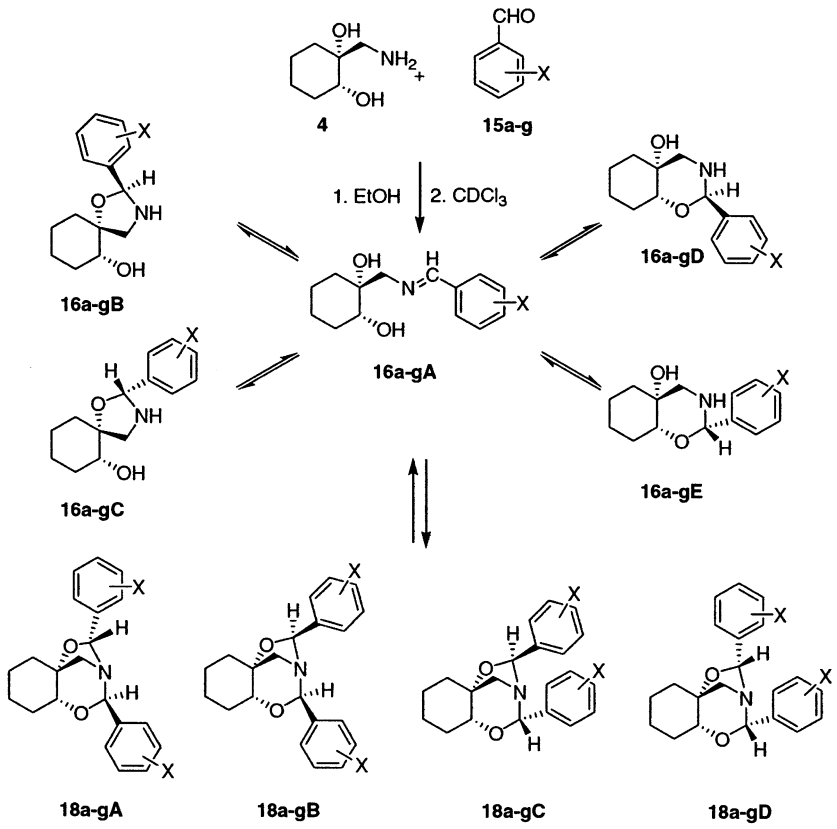
SCHEME 3



a, *p*-NO_2; **b**, *m*-Cl; **c**, *p*-Cl; **d**, H; **e**, *p*-Me; **f**, *p*-OMe; **g**, *p*-NMe_2;

mixture was isolated, with the exception of the 4-nitrophenyl substituent, when the pure compound **16aE** was obtained as the sole crystalline product.

NMR Analysis of Compounds 16−19. Our earlier studies on ring−chain tautomerism[19,20] led us to expect a five-component equilibrium comprised of the two epimeric spirooxazolidines (**16a−gB** and **16a−gC** for compound **4** and **17a−gB** and **17a−gC** for **6**), the two epimeric condensed 1,3-oxazines (**16a−gD** and **16a−gE** for compound **4** and **17a−gD** and **17a−gE** for **6**), and the corresponding Schiff bases (**16a−gA** for compound **4** and **17a−gA** for **6**). However, given the results from the previous section, it was clear that an expanded tautomeric system was involved.

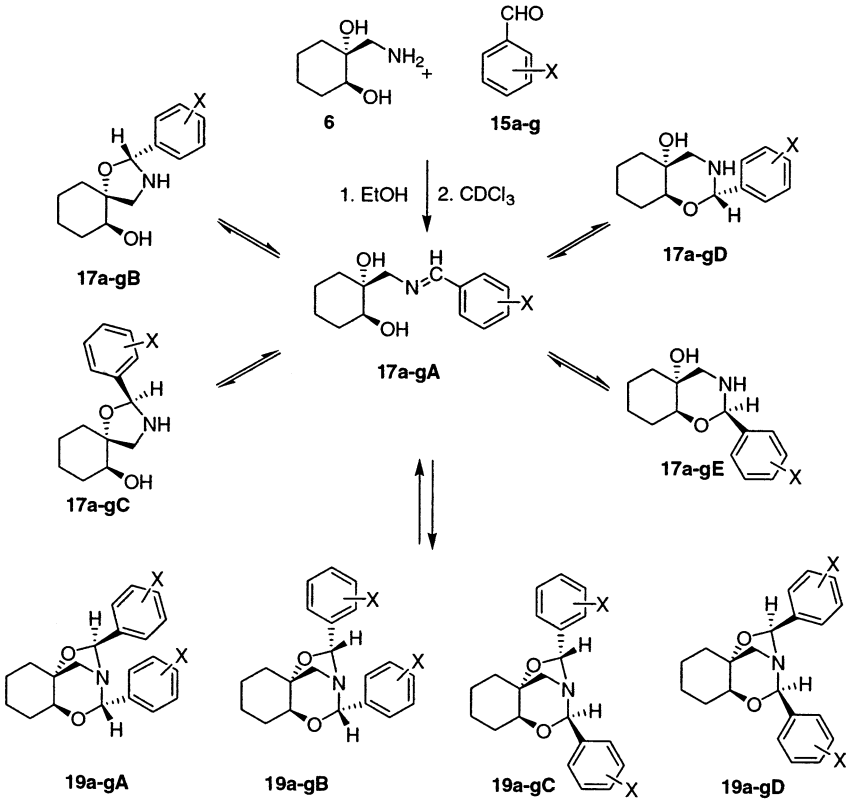
The relative configurations of the various structures were determined by NOESY spectra based on the observation of NOEs between the O−C*H*Ar−N hydrogen and the O−C*H* hydrogen of the ring forms (**16C**, **16E**, **17C**, and **17E**) or one of the O−C*H*Ar−N hydrogens of the tricyclic forms (**18C**, **18D**, **19C**, and **19D**). Interestingly, the conformation of the major component **16E** or **17E** was not forthcoming, since the C−CH_2−NH methylene protons form a degenerate singlet and they therefore do not provide any information regarding possible coupling constants or NOE contacts and hence stereochemical relationships.

For the tautomeric study of these compounds, the samples were dissolved in $CDCl_3$, and as illustrative examples, phenyl derivatives **16d** and **17d** are discussed in detail.

Although the spectrum of the dissolved sample **16d** (or **17d**) was quite complex, structures could readily be assigned due to the well-separated singlets from azomethine hydrogen resonating at 8.21 ppm (or 8.29 ppm) and O−C*H*Ar−N hydrogens resonating in the region 5.25−6.18 ppm (or 5.17−5.75 ppm). The NMR analysis, by the application of various selective 1D and standard 2D homo- and heteronuclear experiments, revealed that the signals in the region 5.25−6.18 ppm (or 5.17−5.75 ppm) belong to 1,3-oxazine **16dE** (or **17dE**) and to the tricyclic compounds **18dB** and **18dC** (or **19dC**). Initially upon dissolution, the tricyclic compounds, the condensed 1,3-oxazine **16dE** (or **17dE**), and the corresponding Schiff base were the major components; the other condensed 1,3-oxazine **16dD** (or **17dD**) and the two epimeric spirooxazolidines were not initially formed. A period of 2 months was found to be adequate for the establishment of an equilibrium resulting in an increase in concentration of the initially minor compounds at the expense of the tricyclic compounds, which were reduced in concentration by a factor of 10.

To test the applicability of the Hammett−Brown linear free energy equation, regression analysis was performed on plots of log *K* versus σ^+ for compounds **16B−D** and **17B−D** (Figures 1 and 2). The tautomeric ratios are based on the integration of the **16B−E**, **17B−E**, **18A−D**, and **19A−D** ring form O−C*H*Ar−N protons and the **16A** and **17A** chain form N=CH proton singlets. Tables 1 and 2 list the chemical shifts of these indicator protons for compounds **16−19** and Tables 3 and 4 the relative

SCHEME 4



a, *p*-NO_2; **b**, *m*-Cl; **c**, *p*-Cl; **d**, H; **e**, *p*-Me; **f**, *p*-OMe; **g**, *p*-NMe_2;

TABLE 1. Chemical Shifts (ppm) of the Indicator Protons[a] for Compounds 16 and 18 in $CDCl_3$

	16A	16B	16C	16D	16E	18A	18B	18C	18D
a	8.33	5.74	5.55	5.67	5.32	–	–	–	–
b	8.14	5.47	5.42	5.57	5.19	–	5.79, 6.08	5.47, 5.57	–
c	8.18	5.59	5.45	5.61	5.21	–	–	5.50, 5.57	–
d	8.21	5.58	5.48	5.66	5.25	–	5.88, 6.18	5.56, 5.71	–
e	8.16	5.54	5.45	5.63	5.21	–	5.84, 6.15	5.51, 5.68	–
f	8.12	5.53	5.43	5.62	5.19	–	5.82, 6.13	5.50, 5.68	–
g	8.04	5.49	5.41	5.63	5.17	–	–	–	–

[a] For **16A**, N=CH; all others, O−C*H*Ar−N.

TABLE 2. Chemical Shifts (ppm) of the Indicator Protons[a] for Compounds 17 and 19 in $CDCl_3$

	17A	17B	17C	17D	17E	19A	19B	19C	19D
a	8.41	5.72	5.61	5.63	5.25	–	–	5.59, 5.68	–
b	8.25	5.62	5.45	5.47	5.14	–	–	5.58, 5.62	–
c	8.29	5.62	5.49	5.51	5.17	–	5.58, 5.61	5.65, 5.76	–
d	8.29	5.62	5.49	5.51	5.17	–	–	5.65, 5.75	–
e	8.17	5.57	5.47	5.51	5.22	–	–	5.52, 5.68	–
f	8.29	5.57	5.44	5.47	5.13	–	–	5.59, 5.72	–
g	8.10	5.53	5.42	5.17	5.10	–	–	–	–

[a] For **17A**, N=CH; all others, O−C*H*Ar−N.

contributions of the compounds to the multicomponent equilibria. Exact thermodynamic comparisons for the condensed 1,3-oxazines and the spirooxazolidines **B**−**E** were performed[20] separately for each of the ring-closed isomers (Table 5). The slopes for the condensed 1,3-oxazines were determined to lie in the range of 0.72−0.75 and those for the spirooxazolidines in the range of 0.62−0.65, in close accord to those described in the literature.[13] Since the plots are linear and the regression coefficients are all higher than 0.96, the systems are deemed to be adequately described by the Hammett−Brown linear free energy equation. An attempt was also made to fit the same relationship to the tricyclic compounds **18B**, **18C**, and **19C**, but the resulting regression coefficients were all generally less than 0.95 using few experimental points. Regarding the mole fractions within the multicomponent equilibria (Tables 3 and 4), the highest amounts of tricyclic compounds were observed for **18dC** (i.e., when benzaldehyde was used) and **19bC** (i.e., when *m*-chlorobenzaldehyde was used), in their respective series.

The sum of the steric and electronic effects of the substituents at positions 4 and 5 (for the oxazolidines) or positions 4, 5, and 6 (for the 1,3-oxazines) can be described by the parameter *c*, which is defined as the difference of the intercept for the 4/5/6-substituted derivatives and the parent 2-aryl-substituted tetrahydro-1,3-oxazine (−0.15) or oxazolidine (−1.10).[16] The value of *c* is positive for some spirooxazolidines (e.g., 0.06 for **16C**, 0.60 for **17B** and 0.83 for **17C**) and also for some condensed 1,3-oxazines (e.g., 0.37 for **16E** and 0.20 for **17E**), which means that the hydroxy-substituted cyclohexane has a stabilizing effect on these ring forms. The negative values of *c* for **16D** (−1.17) and **17D** (−0.53) for the condensed 1,3-oxazines and **16B** (−0.09) for the

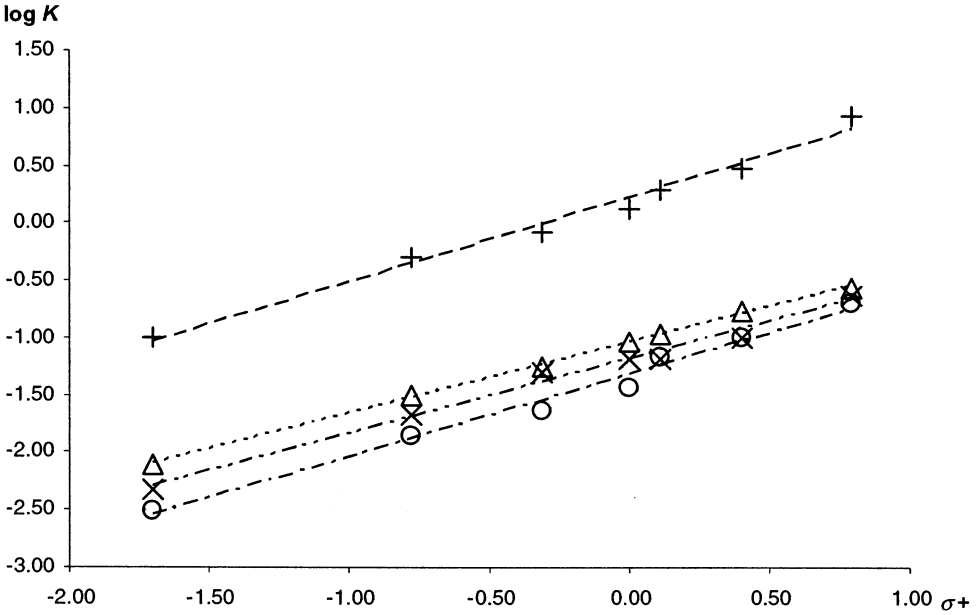


FIGURE 1. Plots of log K_X versus σ^+ values for compounds **16a**−**g**: **B** (x), **C** (△), **D** (○), **E** (+).

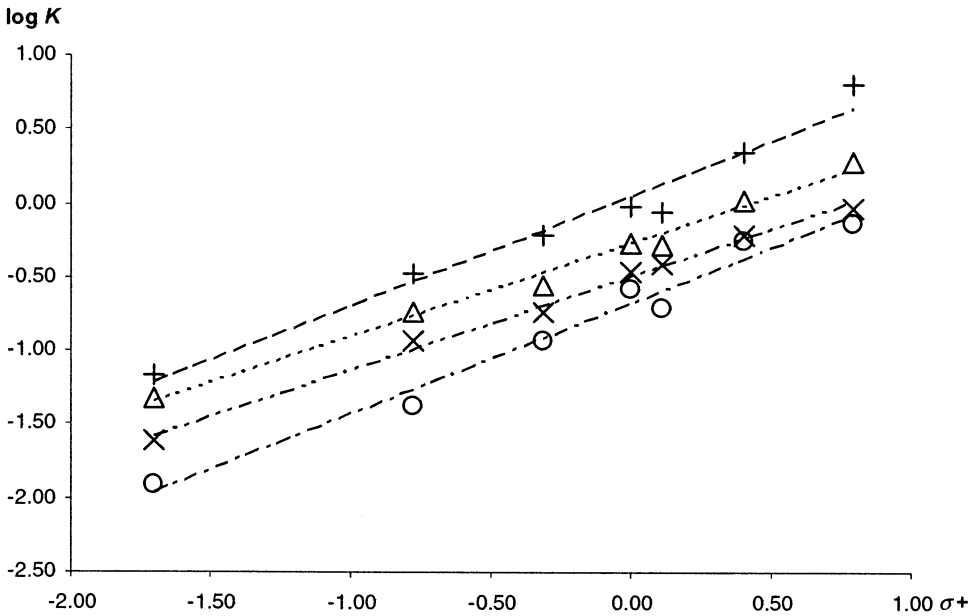


FIGURE 2. Plots of log K_X versus σ^+ values for compounds **17a**−**g**: **B** (x), **C** (△), **D** (○), **E** (+).

TABLE 3. Tautomeric Compositions (%) at Equilibrium and log *K* for Compounds 16a−g and 18a−g in $CDCl_3$ at 300 K

	σ^+	16A	16B	16C	16D	16E	18A	18B	18C	18D	log K_{16B}	log K_{16C}	log K_{16D}	log K_{16E}
a	0.79	9.8	2.3	2.7	2.0	83.3	0.0	0.0	0.0	0.0	−0.6286	−0.5675	−0.6949	0.9295
b	0.40	8.8	0.9	1.5	0.9	26.8	0.0	14.3	46.8	0.0	−1.0022	−0.7747	−1.0074	0.4826
c	0.11	25.7	1.7	2.8	1.7	50.9	0.0	0.0	17.1	0.0	−1.1844	−0.9622	−1.1720	0.2963
d	0	17.9	1.2	1.7	0.6	24.2	0.0	3.2	51.2	0.0	−1.1805	−1.0348	−1.4461	0.1299
e	−0.31	39.3	2.0	2.2	0.9	33.3	0.0	2.3	20.1	0.0	−1.3054	−1.2526	−1.6440	−0.0723
f	−0.78	60.4	1.3	1.9	0.9	30.2	0.0	0.5	5.0	0.0	−1.6757	−1.5129	−1.8508	−0.3013
g	−1.7	89.8	0.4	0.7	0.3	8.8	0.0	0.0	0.0	0.0	−2.3279	−2.1024	−2.5086	−1.0079

spirooxazolidines demonstrate a destabilizing effect of the hydroxy-substituted cyclohexane on these ring forms.

Regarding the possible reaction pathways for the formation of the tricyclic compounds **18** (or **19**), three hypotheses were postulated. On the basis of the well-known literature finding that oxazolidines and tetrahydro-1,3-oxazines can be used as aldehyde sources,[33−36] the tricyclic forms **18** (or **19**) could be formed by the reaction

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TABLE 4. Tautomeric Compositions (%) at Equilibrium and log *K* for Compounds 17a−g and 19a−g in $CDCl_3$ at 300 K

	σ^+	17A	17B	17C	17D	17E	19A	19B	19C	19D	log K_{17B}	log K_{17C}	log K_{17D}	log K_{17E}
a	0.79	8.3	7.6	15.7	6.1	53.4	0.0	0.0	8.9	0.0	−0.0345	0.2800	−0.1331	0.8105
b	0.40	10.0	6.1	10.5	5.5	22.0	0.0	0.0	46.0	0.0	−0.2152	0.0207	−0.2594	0.3421
c	0.11	14.5	5.5	7.6	2.8	12.8	0.0	14.7	42.1	0.0	−0.4163	−0.2788	−0.7091	−0.0520
d	0	19.4	6.6	10.6	5.1	18.6	0.0	0.0	39.7	0.0	−0.4672	−0.2632	−0.5763	−0.0185
e	−0.31	40.2	7.4	11.2	4.7	24.2	0.0	0.0	12.3	0.0	−0.7347	−0.5543	−0.9282	−0.2210
f	−0.78	57.8	6.7	10.7	2.4	19.1	0.0	0.0	3.4	0.0	−0.9382	−0.7333	−1.3830	−0.4803
g	−1.7	86.8	2.1	4.2	1.1	5.8	0.0	0.0	0.0	0.0	−1.6108	−1.3188	−1.9101	−1.1720

TABLE 5. Linear Regression Analysis for Compounds 16, 17, 18B, 18C, and 19C

compound	no. of points	slope (ρ)	intercept (log $K_{X=H}$)	corr coeff	c^a
16B	7	0.65	−1.19	0.988	0.09
16C	7	0.62	−1.04	0.999	0.06
16D	7	0.72	−1.32	0.983	1.17
16E	7	0.74	−0.22	0.986	0.37
17B	7	0.64	−0.50	0.995	0.60
17C	7	0.63	−0.27	0.988	0.83
17D	7	0.75	−0.68	0.976	−0.53
17E	7	0.75	−0.05	0.968	0.20
18B	4	2.29	−0.43	0.953	
18C	5	1.11	−0.05	0.719	
19C	6	0.99	−0.08	0.575	
2-aryloxazolidine[16]	7	0.60	−1.10	0.989	0
2-aryltetrahydro-1,3-oxazine[16]	7	0.76	−0.15	0.998	0

[a] For the meaning of *c*, see the text.

between two condensed 1,3-oxazines **16E** (or **17E**), between the condensed 1,3-oxazine **16E** (or **17E**) and the Schiff base **16A** (or **17A**), or between the condensed 1,3-oxazine **16E** (or **17E**) and an aldehyde **15a**−**g** in the five-component tautomeric system. To select the most appropriate of these different hypotheses, the following experiments were performed.

First, 2D EXSY measurements were carried out in CD_3-OD solutions of the phenyl-substituted systems **16dA**−**E** and **18dA**−**D** (or **17dA**−**E** and **19dA**−**D**), to detect direct magnetization transfers between the indicator protons of tricyclic compounds **18dC** (or **19dC**) and the questionable indicator protons of compounds of different reaction pathways. First-order chemical exchange cross-peaks were observed between the well-separated N=C*H*Ar proton singlet of the corresponding Schiff base **16dA** (or **17dA**) and one of the O−C*H*Ar−N proton of the tricyclic compound **18dC** (or **19dC**) and also between the other O−C*H*Ar−N proton of the **18dC** (or **19dC**) and the indicator proton of the condensed 1,3-oxazine **16dE** (or **17dE**).

However, a reaction pathway involving a slower addition of the condensed 1,3-oxazine to aldehyde cannot be ruled out with the above method, if the reaction rate is too low as compared to the NMR time scale. If the tricyclic forms **18** (or **19**) are formed by the reaction between the condensed 1,3-oxazine and an aldehyde, the pure tricyclic molecules after dissolution decompose under the reaction conditions applied to form the multicomponent equilibrium. On the other hand, the reaction between two condensed 1,3-oxazines **16E** (or **17E**) or between the condensed 1,3-oxazine **16E** (or **17E**) and the Schiff base **16A** (or **17A**) involves an amino diol elimination. Assuming the microscopic reversibility of the reaction, amino diol is necessary for the first step of the decomposition of the pure tricyclic compounds. To test the stability of the pure forms and the effect of amino diol in solution, the pure tricyclic products were prepared. Preparation of the major isomeric tricyclic compounds **18aC** (or **19aC**) was accomplished by reacting the appropriate amino diol **4** (or **6**) with 3 equiv of *p*-nitrobenzaldehyde in EtOH under reflux. After evaporation of the solvent and recrystallization of the resulting crude product, pure samples of **18aC** (or **19aC**) were isolated in each case. After dissolution in $CDCl_3$, the pure *p*-nitrophenyl-substituted **18aC** (or **19aC**) did not decompose during an observation period of 3 months. When amino diol was added to the solution, the multicomponent equilibrium formed immediately.

On the basis of these results, the pathway for the formation of the tricyclic compounds proceeds via the reaction between the condensed 1,3-oxazine and the Schiff base in the five-component ring−chain tautomeric system. For the examined system, this means that the tricyclic compound **18dC** (or **19dC**) was formed from the Schiff base **16dA** (or **17dA**), and the condensed 1,3-oxazine **16dE** (or **17dE**) by aldehyde transfer and amino diol elimination.

Conclusions

Amino diols **3**−**6** were all found to produce solely cyclohexane spirooxazolidine products, i.e. the ring closure under basic conditions occurred highly regioselectively. When amino diol **4** or **6** was condensed with 1 equiv of an aromatic aldehyde, **15a**−**g**, a complex, multicomponent equilibrium mixture consisting of a five-component, ring−chain tautomeric system, involving the Schiff base, two epimeric spirooxazolidines, two epimeric condensed 1,3-oxazines, and some tricyclic compounds, resulted. The reaction pathway for the formation of the tricyclic compounds includes the reaction between one 1,3-oxazine and one Schiff base in the five-component, ring−chain tautomeric system.

The five-component, ring−chain tautomeric system was found to be adequately described by the Hammett−Brown linear free energy equation.

Experimental Section

General Procedures. NMR spectra were recorded at 400 MHz for ^{1}H NMR and at 100 MHz for ^{13}C NMR at 300 K using TMS as an internal reference (0 ppm for both). The number of scans was usually 128. For kinetic measurements, 0.046, 0.19, 0.38, 0.51 and 0.675 M CD_3OD solutions were prepared with respect to both the aldehydes and the amino diols. For

(36) Singh, K.; Deb, P. K.; Behal, S. *Heterocycles* **2001**, *55*, 1937−1942.

2D EXSY spectra, 512 FIDs each consisting of 2048 data points and 40 transients were recorded utilizing a mixing time of 610 ms.

GC analyses were performed using a CHIRASIL-DEX CB column (25 m × 0.25 mm i.d.) maintained isothermally at 130 °C (pressure 70 atm) for the epoxy alcohols. IR spectra were measured with an FT-IR spectrometer. Melting points are uncorrected. Chromatographic separations were performed using Merck Kieselgel 60 (230−400 mesh ASTM) and reactions were monitored using Merck Kieselgel 60 F_{254}-precoated TLC plates (0.25 mm thickness). All chemicals and solvents were used as supplied. Mass spectra were obtained using EI mode (70 eV).

General Procedure for the Preparation of *cis*- and *trans*-1-(Benzylaminomethyl)cyclohexane-1,2-diol (3 and 5). A solution of benzylamine (2.51 g, 23.45 mmol) in MeOH (50 mL) was added to a solution of the corresponding *cis*- or *trans*-epoxy alcohol **1** or **2** (3.0 g, 23.44 mmol) in MeOH (250 mL), and the mixture was refluxed for 48 h. Removal of the solvent provided the yellow, oily amino diol **3** or **5**. The crude product was recrystallized as the HCl salt from EtOH−Et_2O. For subsequent work, the free amino diol base was regenerated.

***cis*-1-(Benzylaminomethyl)cyclohexane-1,2-diol Hydrochloride (3).** Yield: 63%. Mp: 213−214 °C. ^{1}H NMR (DMSO-d_6) δ: 1.07−1.26 (2H, m), 1.27−1.36 (1H, m), 1.37−1.62 (4H, m), 2.77 (1H, d, J = 12.6 Hz), 3.04 (1H, d, J = 12.6 Hz), 3.34 (1H, overlapped with H_2O, m), 4.16 (2H, dd, J = 13.1, 20.1 Hz), 4.73 (1H, s), 5.14 (1H, br s), 7.37−7.46 (3H, m), 7.56−7.63 (2H, m), 8.80 (1H, br s), 9.17 (1H, br s). ^{13}C NMR (DMSO-d_6) δ: 19.8, 23.5, 29.7, 33.4, 50.9, 54.2, 70.5, 72.5, 128.6, 128.9, 130.2, 131.8. IR (KBr) cm^{-1}: 3361, 2933, 992, 699. Anal. Calcd for $C_{14}H_{22}ClNO_2$: C, 61.87; H, 8.16; N, 5.15. Found: C, 61.81; H, 8.14; N, 5.16.

***trans*-1-(Benzylaminomethyl)cyclohexane-1,2-diol Hydrochloride (5).** Yield: 59%. Mp: 206−210 °C. ^{1}H NMR (DMSO-d_6) δ: 1.18−1.38 (4H, m), 1.40−1.64 (3H, m), 1.65−1.78 (1H, m), 2.72 (1H, d, J = 12.6 Hz), 2.98 (1H, d, J = 12.6 Hz), 3.52 (1H, dd, J = 3.0, 5.5 Hz), 4.15 (2H, s), 5.11 (1H, s), 5.15 (1H, br s), 7.36−7.46 (3H, m), 7.55−7.64 (2H, m), 9.00 (2H, br s). ^{13}C NMR (DMSO-d_6) δ: 20.8, 21.1, 29.5, 31.9, 51.0, 52.0, 70.5, 71.2, 128.9, 129.2, 130.7, 132.0. IR (KBr) cm^{-1}: 3155, 2928, 1082, 696. Anal. Calcd for $C_{14}H_{22}ClNO_2$: C, 61.87; H, 8.16; N, 5.15. Found: C, 61.99; H, 8.17; N, 5.14.

General Procedure for the Preparation of *cis*- and *trans*-1-Aminomethylcyclohexane-1,2-diol (4 and 6). To a suspension of palladium-on-carbon (10%, 1.25 g) in MeOH (60 mL) was added the liberated base **3** or **5** (4.50 g, 31.03 mmol) in MeOH (50 mL) and the resulting mixture stirred under a H_2 atmosphere at room temperature. When the reaction was complete as indicated by TLC, the solution was filtered and the solvent removed, affording a colorless oily product **4** or **6** which crystallized upon standing at ca. 4 °C. The crystalline product was recrystallized from EtOAc.

***cis*-1-Aminomethylcyclohexane-1,2-diol (4).** Yield: 98%. Mp: 66−68 °C. ^{1}H NMR (DMSO-d_6) δ: 1.05−1.22 (2H, m), 1.25−1.35 (1H, m), 1.37−1.60 (5H, m), 2.57 (1H, d, J = 12.8 Hz, CH_2–NH_2), 2.68 (1H, d, J = 12.8 Hz, CH_2–NH_2), 3.34 (1H, dd, J = 6.3, 9.1 Hz, H-2), 4.14 (4H, br s, 2 × OH, NH_2). ^{13}C NMR (DMSO-d_6) δ: 20.4 (C-5), 23.7 (C-4), 29.9 (C-3), 33.1 (C-6), 49.3 (*C*H_2–NH_2), 71.3 (C-2), 72.6 (C-1). IR (KBr) cm^{-1}: 3326, 2917, 1519, 1061. Anal. Calcd for $C_7H_{15}NO_2$: C, 57.90; H, 10.41; N, 9.65. Found: C, 58.26; H, 10.70; N, 9.43.

***trans*-1-Aminomethylcyclohexane-1,2-diol (6).** Yield: 98%. Mp: 54−56 °C. ^{1}H NMR (DMSO-d_6) δ: 1.18−1.60 (7H, m), 1.66−1.77 (1H, m), 2.59 (1H, d, J = 12.8 Hz, CH_2–NH_2), 2.85 (1H, d, J = 12.8 Hz, CH_2–NH_2), 3.47 (1H, dd, J = 3.0, 5.5 Hz, H-2), 5.52 (4H, br s, 2 × OH, NH_2). ^{13}C NMR (DMSO-d_6) δ: 20.9 (C-5), 21.1 (C-4), 29.5 (C-3), 31.3 (C-6), 45.7 (*C*H_2–NH_2), 70.3 (C-2), 71.1 (C-1). IR (KBr) cm^{-1}: 3316, 2939, 1505, 1039. Anal. Calcd for $C_7H_{15}NO_2$: C, 57.90; H, 10.41; N, 9.65. Found: C, 58.11; H, 10.55; N, 9.99.

General Procedure for Preparation of the Thiourea Derivatives 7, 8, 11, and 12. Phenyl isothiocyanate (0.70 g, 5.14 mmol) was added to a solution of the appropriate amino diol **3**−**6** (4.26 mmol) in benzene (60 mL) and the resulting solution stirred at room temperature. When the reaction was complete as indicated by TLC, the solvent was removed under vacuum and the resulting crude product was recrystallized from EtOAc−*i*-Pr_2O.

***cis*-1-Benzyl-1-(1,2-dihydroxycyclohexylmethyl)-3-phenylthiourea (7).** Yield: 63%. Mp: 144−146 °C. ^{1}H NMR (DMSO-d_6) δ: 1.13−1.26 (1H, m), 1.34−1.64 (6H, m), 1.77 (1H, d, J = 11.7), 3.33 (overlapped with H_2O, m), 3.52 (1H, br s), 3.86 (1H, d, J = 15.2 Hz), 4.90 (1H, s), 4.97 (1H, d, J = 12.2 Hz), 5.24 (1H, br s), 5.59 (1H, d, J = 8.3 Hz), 7.09 (1H, t, J = 7.3 Hz), 7.23−7.49 (9H, m), 10.32 (1H, br s). ^{13}C NMR (DMSO-d_6) δ: 20.1, 23.6, 29.7, 33.2, 55.6, 57.4, 72.2, 74.8, 124.0, 124.3, 126.8, 127.1, 127.9, 128.2, 137.4, 141.0, 183.3. IR (KBr) cm^{-1}: 3367, 2949, 1525, 1338, 1062. Anal. Calcd for $C_{21}H_{26}N_2O_2S$: C, 68.08; H, 7.07; N, 7.56. Found: C, 67.99; H, 6.89; N, 7.89.

***cis*-1-(1,2-Dihydroxycyclohexylmethyl)-3-phenylthiourea (8).** Yield: 49%. Mp: 124−128 °C. ^{1}H NMR (DMSO-d_6) δ: 1.20−1.30 (2H, m), 1.32−1.44 (2H, m), 1.46−1.63 (3H, m), 1.70−1.79 (1H, m), 3.43 (1H, s), 3.52 (1H, d, J = 12.7 Hz, CH_2–NH), 3.64 (1H, d, J = 11.7 Hz, CH_2–NH), 4.53 (1H, s, OH), 4.66 (1H, s, OH), 7.09 (1H, t, J = 7.3 Hz, *p*-H), 7.31 (2H, t, J = 7.8 Hz, *m*-Hs), 7.45 (2H, d, J = 7.8 Hz, *o*-Hs), 7.49 (1H, br s, NH), 9.77 (1H, s, NH). ^{13}C NMR (DMSO-d_6) δ: 20.5 (C-5), 20.9 (C-4), 29.2 (C-3), 31.0 (C-6), 50.2 (*C*H_2–NH), 71.0 (C-2), 72.2 (C-1), 122.7, 123.9, 128.5, 139.2, 180.4 (C=S). IR (KBr) cm^{-1}: 3291, 2929, 1544, 1035. Anal. Calcd for $C_{14}H_{20}N_2O_2S$: C, 59.97; H, 7.19; N, 9.99. Found: C, 60.03; H, 7.48; N, 10.08.

***trans*-1-Benzyl-1-(1,2-dihydroxycyclohexylmethyl)-3-phenylthiourea (11).** Yield: 95%. Mp: 159−160 °C. ^{1}H NMR (DMSO-d_6) δ: 1.25−1.42 (3H, m), 1.44−1.68 (4H, m), 1.76−1.87 (1H, m), 3.43 (1H, d, J = 11.3 Hz), 3.59 (1H, s), 3.67 (1H, d, J = 14.7 Hz), 5.08 (1H, d, J = 9.8 Hz), 5.21 (1H, s), 5.63 (2H, d, J = 15.7 Hz), 7.09 (1H, t, J = 7.3 Hz), 7.22−7.39 (8H, m), 7.43 (1H, d, J = 7.8 Hz), 10.51 (1H, br s). ^{13}C NMR (DMSO-d_6) δ: 19.3, 20.3, 28.2, 30.1, 55.2, 55.8, 68.7, 74.6, 123.8, 123.9, 126.7, 127.2, 127.9, 128.2, 137.5, 141.0, 183.6. IR (KBr) cm^{-1}: 3290, 2936, 1559, 1367, 739. Anal. Calcd for $C_{21}H_{26}N_2O_2S$: C, 68.08; H, 7.07; N, 7.56. Found: C, 68.55; H, 7.40; N, 7.83.

***trans*-1-(1,2-Dihydroxycyclohexylmethyl)-3-phenylthiourea (12).** Yield: 53%. Mp: 168−170 °C. ^{1}H NMR (DMSO-d_6) δ: 1.11−1.27 (2H, m), 1.29−1.38 (1H, m), 1.39−1.66 (5H, m), 3.51 (1H, d, J = 12.2 Hz, CH_2–NH), 3.71 (1H, d, J = 10.3 Hz, CH_2–NH_2), 4.13 (1H, br s, OH), 4.58 (1H, br s, OH), 7.09 (1H, t, J = 7.3 Hz, *p*-H), 7.31 (2H, t, J = 7.8 Hz, *m*-Hs), 7.47 (2H, d, J = 7.8 Hz, *o*-Hs), 7.62 (1H, s, NH), 9.71 (1H, s, NH). ^{13}C NMR (DMSO-d_6) δ: 20.4 (C-5), 23.2 (C-4), 29.8 (C-3), 33.1 (C-4), 51.8 (CH_2–NH), 71.5 (C-2), 72.1 (C-1), 122.6, 123.9, 128.4, 139.2, 180.5 (C=S). IR (KBr) cm^{-1}: 3339, 2935, 1557, 1018. Anal. Calcd for $C_{14}H_{20}N_2O_2S$: C, 59.97; H, 7.19; N, 9.99. Found: C, 60.30; H, 7.52; N, 9.87.

General Procedure for Preparation of the 2-(Phenylimino)oxazolidine Derivatives 9, 10, 13, and 14. Iodomethane (1.05 g, 7.40 mmol) was added dropwise to a solution of **9**, **10**, **13,** or **14** (1.35 mmol) in MeOH (25 mL). After stirring for 3 h at room temperature, the solvent was removed under vacuum, after which a methanolic solution of KOH (2.5 M, 10 mL) was added to the residue. The resulting solution was then stirred for 4 h, followed by evaporation to dryness. Water (30 mL) was then added to this residue and the resulting suspension extracted with $CHCl_3$ (3 × 40 mL). The organic layer was dried over Na_2SO_4, filtered, and then evaporated to dryness, resulting in a crystalline product which was purified by flash chromatography over silica gel [solvent: Et_2O/Et_3N (9:1) for **9** (R_f = 0.73), toluene/EtOH (4:1) for **10** (R_f = 0.35) and **12** (R_f = 0.39), and toluene/MeOH (9:1) for **11** (R_f = 0.21)].

***cis*-3-Benzyl-2-phenylimino-1-oxa-3-azaspiro[4.5]decan-6-ol (9).** Yield: 55%. Mp: 168−169 °C. ^{1}H NMR (DMSO-d_6) δ: 1.19−1.58 (5H, m, H-7, H-8, 2H-9, H-10), 1.59−1.72 (2H,

m, H-7, H-8), 1.83−1.92 (1H, m, H-10), 3.00 (1H, d, J = 8.1 Hz, H-4), 3.35−3.43 (1H, m, H-6), 3.55 (1H, d, J = 8.1 Hz, H-4), 4.49 (1H, d, J = 15.4 Hz, CH_2–Ph), 4.59 (1H, d, J = 15.4 Hz, CH_2–Ph), 5.06 (1H, d, J = 5.8 Hz, OH), 6.88−6.86 (1H, m, *N*-phenyl), 7.05−7.11 (2H, m, benzyl), 7.13−7.20 (2H, m, benzyl), 7.25−7.31 (1H, m, benzyl), 7.33−7.39 (4H, m, *N*-phenyl). ^{13}C NMR (DMSO-d_6) δ: 21.0 (C-9), 23.0 (C-8), 30.5 (C-7), 34.7 (C-10), 47.6 (*C*H_2–Ph), 51.7 (C-4), 70.7 (C-6), 83.7 (C-5), 120.3 (*N*-phenyl), 123.2 (*N*-phenyl), 126.8 (benzyl), 2 × 127.5 (benzyl), 127.9 (*N*-phenyl), 137.2 (benzyl), 148.1 (*N*-phenyl), 152.7 (C-2). IR (KBr) cm^{-1}: 3225, 2937, 1624, 1085, 696. Anal. Calcd for $C_{21}H_{24}N_2O_2$: C, 74.97; H, 7.19; N, 8.33. Found: C, 75.01; H, 7.01; N, 8.69.

***cis*-2-Phenylimino-1-oxa-3-azaspiro[4.5]decan-6-ol (10).** Yield: 78%. Mp: 110−113 °C. ^{1}H NMR (DMSO-d_6) δ: 1.22−1.73 (7H, m, 2 × H-7, 2 × H-8, 2 × H-9, H-10), 1.80−1.93 (1H, m, H-10), 3.25−3.41 (2H, overlapped with H_2O, m, H-4, H-6), 3.78 (1H, d, J = 11.6 Hz, H-4), 4.85 (1H, d, J = 5.8 Hz, OH), 6.81−6.87 (1H, m), 7.15−7.22 (2H, m), 7.51 (2H, d, J = 7.8 Hz), 8.75 (1H, br s, NH). ^{13}C NMR (DMSO-d_6) δ: 21.5 (C-9), 22.7 (C-8), 31.0 (C-7), 34.4 (C-10), 59.0 (C-4), 70.7 (C-6), 85.5 (C-5), 117.6, 120.1, 128.1, 141.8, 155.3 (C-2). IR (KBr) cm^{-1}: 3069, 2939, 1651, 1092, 691. Anal. Calcd for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.57; H, 7.20; N, 11.66.

***trans*-3-Benzyl-2-phenylimino-1-oxa-3-azaspiro[4.5]-decan-6-ol (13).** Yield: 77%. Mp: 152−153 °C. ^{1}H NMR (DMSO-d_6) δ: 1.14−1.31 (3H, m, H-7, H-8, H-9), 1.47−1.60 (3H, m, H-8, H-9, H-10), 1.66−1.75 (1H, m, H-7), 1.78−1.87 (1H, m, H-10), 3.06 (1H, d, J = 8.3 Hz, H-4), 3.51 (1H, d, J = 8.3 Hz, H-4), 3.54−3.61 (1H, m, H-6), 4.54 (2H, s, CH_2–Ph), 5.23 (1H, d, J = 4.8 Hz, OH), 6.81−6.85 (1H, m, *N*-phenyl), 6.99−7.03 (2H, m, *N*-phenyl), 7.13−7.18 (2H, m, *N*-phenyl), 7.26−7.32 (1H, m, benzyl), 7.35−7.38 (4H, m, benzyl). ^{13}C NMR (DMSO-d_6) δ: 21.7 (C-8, C-9), 31.1 (C-7), 33.7 (C-10), 47.6 (*C*H_2–Ph), 48.7 (C-4), 70.1 (C-6), 85.8 (C-5), 120.3 (phenyl), 123.1 (phenyl), 126.9 (benzyl), 2 × 127.6 (benzyl), 127.8 (phenyl), 137.2 (benzyl), 148.1 (phenyl), 152.4 (C-2). IR (KBr) cm^{-1}: 2936, 1662, 1589, 695. Anal. Calcd for $C_{21}H_{24}N_2O_2$: C, 74.97; H, 7.19; N, 8.33. Found: C, 75.32; H, 7.54; N, 8.47.

***trans*-2-Phenylimino-1-oxa-3-azaspiro[4.5]decan-6-ol (14).** Yield: 74%. Mp: 145−146 °C. ^{1}H NMR (DMSO-d_6) δ: 1.18−1.33 (3H, m, H-7, H-8, H-9), 1.46−1.63 (3H, m, H-8, H-9, H-10), 170−1.84 (2H, m, H-7, H-10), 3.29 (1H, overlapped with H_2O, m, H-4), 3.53−3.60 (1H, m, H-6), 3.78 (1H, d, J = 11.6 Hz, H-4), 4.98 (1H, d, J = 4.8 Hz, OH), 6.81−6.87 (1H, m), 7.15−7.22 (2H, m), 7.48 (2H, br s), 8.83 (1H, br s, NH). ^{13}C NMR (DMSO-d_6) δ: 21.9 (C-8, C-9), 31.2 (C-7), 33.9 (C-10), 56.1 (C-4), 70.4 (C-6), 86.0 (C-5), 117.4, 120.1, 127.9, 141.4, 154.9 (C-2). IR (KBr) cm^{-1}: 2930, 1660, 1449, 745. Anal. Calcd for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.13; H, 7.54; N, 11.10.

General Procedure for the Reaction of Amino Diols 4 and 6 with 1 equiv of an Aromatic Aldehyde. Separate solutions consisting of an aromatic aldehyde **15a**−**g** and an amino diol **4** or **6** were prepared by the direct addition of the aldehyde (1 mmol) to the amino diol (1 mmol) in dry EtOH (10 mL). Each solution was then kept at room temperature for 2 h, after which the bulk of the solvent was removed under vacuum at a temperature below 35 °C, followed by complete drying under high vacuum. The resulting oily products were used for NMR study without further purification, while crystalline crude products were recrystallized from EtOAc−EtOH. In each case though, only a complex mixture was obtained, with the exception of the *p*-nitrophenyl substituent whereby compound **16aE** was isolated pure as a crystalline product. Melting points: **16a**, 143−147 °C; **16b**, 98−100 °C; **16c**, 132−138 °C; **16d**, 114−118 °C; **16e**, 78−82 °C; **16f**, viscous oil; **16g**, 119−120 °C; **17a**, 112−126 °C; **17b**, 164−170 °C; **17c**, 186−188 °C; **17d**, 158−160 °C; **17e**, 170−173 °C; **17f**, a viscous oil; **17g**, 224−237 °C.

2-(4-Nitrophenyl)hexahydro-1,3-benzoxazin-4a-ol (16aE). Yield: 78%. Mp: 143−147 °C. ^{1}H NMR ($CDCl_3$) δ: 1.20 (1H, ddd, J = 5.0, 14.0 Hz, H-5), 1.27−1.41 (1H, m, H-7), 1.52−1.57 (1H, m, H-6), 1.63−1.75 (4H, m, H-5, H-6, 2 × H-8), 1.81−1.84 (1H, m, H-7), 2.92 (2H, s, 2 × H-4), 3.66, (1H, dd, J = 5.0, 10.8 Hz, H-8a), 5.32 (1H, s, H-2), 7.71−7.74 (2H, m, H-2′, H-6′), 8.19−8.22 (2H, m, H-3′, H-5′). ^{13}C NMR ($CDCl_3$) δ: 20.4 (C-6), 24.2 (C-7), 26.9 (C-8), 32.4 (C-5), 55.7 (C-4), 66.3 (C-4a), 81.7 (C-8a), 88.1 (C-2), 123. (C-3′, C-5′), 127.1 (C-2′, C-6′), 146.5 (C-1′), 147.8 (C-4′). MS (70 eV) m/z (%): 278 (M$^+$, 15), 164 (31), 151 (100), 128 (29). Anal. Calcd for $C_{14}H_{18}N_2O_4$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.11; H, 7.03; N, 10.29.

General Preparation of *cis*- and *trans*-8,10-Bis(4-nitrophenyl)-7,11-dioxa-9-azatricyclo[7.2.1.0^{1,6}]dodecane (18aC and 19aC). *p*-Nitrobenzaldehyde (0.45 g, 3 mmol) was added to a solution of amino diol **4** or **6** (0.15 g, 1 mmol) in dry EtOH (20 mL) and the solution refluxed for 10 h, after which the solvent was removed under vacuum and the resulting crude product recrystallized from MeOH.

***cis*-8,10-Bis(4-nitrophenyl)-7,11-dioxa-9-azatricyclo-[7.2.1.0^{1,6}]dodecane (18aC).** Yield: 54%. Mp: 206−210 °C. ^{1}H NMR ($CDCl_3$) δ: 1.28−1.41 (1H, m, H-3), 1.55−1.92 (7H, m, 2 × H-2, H-3, 2 × H-4, 2 × H-5), 2.75 (1H, d, J = 11.6 Hz, H-12), 3.21 (1H, d, J = 11.6 Hz, H-12), 3.81 (1H, dd, J = 5.2, 10.8 Hz, H-1), 5.56 (1H, s, H-8), 5.61 (1H, s, H-10), 7.40−7.45 (2H, m, H-2′, H-6′), 7.84−7.89 (2H, m, H-2″, H-6″), 8.10−8.14 (2H, m, H-3′, H-5′), 8.26−8.30 (2H, m, H-3″, H-5″). ^{13}C NMR ($CDCl_3$) δ: 22.5 (C-4), 23.7 (C-3), 28.5 (C-2), 30.4 (C-5), 59.2 (C-12), 78.5 (C-6), 80.2 (C-1), 89.5 (C-8), 90.6 (C-10), 123.2 (C-3′, C-5′), 123.5 (C-3″, C-5″), 127.0 (C-2′, C-6′), 127.9 (C-2″, C-6″), 146.1 (C-1″), 147.5 (C-4′), 147.8 (C-4″), 148.4 (C-1′). MS (70 eV) m/z (%): 411 (M$^+$, 54), 394 (32), 284 (79), 248 (100). IR (KBr) cm^{-1}: 2942, 1523, 1341. Anal. Calcd for $C_{21}H_{21}N_3O_6$: C, 61.31; H, 5.14; N, 10.21. Found: C, 61.57; H, 5.16; N, 10.45.

***trans*-8,10-Bis(4-nitrophenyl)-7,11-dioxa-9-azatricyclo-[7.2.1.0^{1,6}]dodecane (19aC).** Yield: 45%. Mp: 191−193 °C. ^{1}H NMR ($CDCl_3$) δ: 1.21−1.45 (2H, m, H-3, H-4), 1.79−1.97 (5H, m, H-1, H-3, H-4, 2 × H-5), 2.07−2.14 (1H, m, H-2), 2.60 (1H, dd, J = 1.8, 12.0 Hz, H-12), 3.67 (1H, d, J = 3.8 Hz, H-12), 3.98 (1H, dd, J = 1.7, 6.5, 12.2 Hz, H-1), 5.60 (1H, s, H-8), 5.69 (1H, s, H-10), 7.38−7.44 (2H, m, H-2′, H-6′), 7.84−7.88 (2H, m, H-2″, H-6″), 8.11−8.16 (2H, m, H-3′, H-5′), 8.27−8.31 (2H, m, H-3″, H-5″). ^{13}C NMR ($CDCl_3$) δ: 24.1 (C-4), 24.1 (C-3), 29.0 (C-2), 32.6 (C-5), 53.5 (C-12), 80.7 (C-6), 81.2 (C-1), 86.9 (C-10), 88.4 (C-8), 123.2 (C-3′, C-5′), 123.4 (C-3″, C-5″), 127.0 (C-2′, C-5′), 128.0 (C-2″, C-5″), 146.2 (C-1″), 147.6 (C-4′), 147.8 (C-4″), 148.2 (C-1′). MS (70 eV) m/z (%): 411 (M$^+$, 47), 394 (37), 284 (81), 248 (100). IR (KBr) cm^{-1}: 2937, 1521, 1346. Anal. Calcd for $C_{21}H_{21}N_3O_6$: C, 61.31; H, 5.14; N, 10.21. Found: C, 61.62; H, 5.01; N, 10.63.

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Supporting Information Available: Table of selected ^{1}H and ^{13}C chemical shifts in ppm for compounds **16a**−**g** in $CDCl_3$ and ^{1}H NMR spectra of products **16d** and **17d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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