Inter- and Intramolecular Hetero Diels-Alder Reactions, 41[1]

Unusual Stereocontrol in Intramolecular Hetero Diels-Alder Reactions of 2-Aza-1,3-butadienes. A Stereoselective Sequential Synthesis of Annulated Tetrahydropyridines

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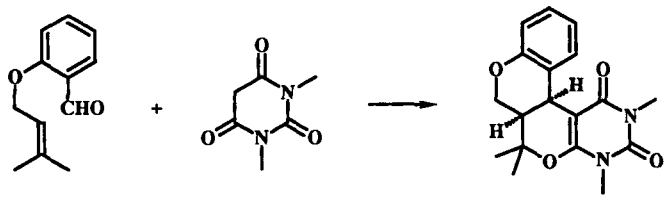
Condensation of aldehydes **1a–e** with 5-amino-3-methylisoxazole (**4**) gives the corresponding imines **5a–e** with a 2-aza-1,3-butadiene moiety, which cyclize selctively, e.g. **5a** to form the *trans*-fused tetrahydropyridine **7a** and **5c** to yield the *cis*-fused cycloadduct **8c**. The astounding difference in the selectivity of these reactions is explained by electronic effects and suggests a change in the dominating interactions of the orbitals in the transition structure. The structure of **7a** is elucidated by an X-ray analysis.

The hetero Diels-Alder reaction is today one of the most efficient methods for the synthesis of many types of heterocycles[2]. In the more elegant procedures the cyclization is carried out in an intramolecular mode, and the heterodiene is formed in situ only, which allows the reaction to be run as a sequential transformation starting with simple substrates[2a]. Thus, the tandem Knoevenagel hetero Diels-Alder reaction of aromatic aldehydes **1** with 1,3-dicarbonyl compounds such as **2** affords annulated dihydropyrans **3** via an intermediately formed 1-oxa-1,3-butadiene in high yield and with excellent selectivity[3]. With aliphatic aldehydes *trans*-fused dihydropyrans are formed nearly exclusively[4]. Asymmetric induction in these transformations can be brought about either by a stereogenic center in the chain or in the 1,3-dicarbonyl compound[5] or by use of chiral Lewis acids[6]; the method has already been used extensively in the synthesis of natural products[2a]. In this paper we describe an extension of the protocol for the synthesis of annulated tetrahydropyridines by an intramolecular hetero Diels-Alder reaction of 2-aza-1,3-butadienes, which are formed in situ by condensation of an enamine with an unsaturated aldehyde bearing a hetero dienophile moiety. Several intermolecular Diels-Alder reactions of 2-aza-1,3-butadienes have been described[7], however, only a few examples of intramoleclar reactions of this type are known[8]. A novel tandem cyclization via an intermediately formed 2-aza-1,3-butadiene has recently been published by Heathcock[9].

For our investigations the benzaldehydes **1a–e** and the aminoisoxazole **4** were used. The synthesis **1a–e** was accomplished by alkylation of the corresponding hydroxybenzaldehydes with the appropriate allyl bromides in acetone in the presence of potassium carbonate in 80–90% yield[10].

For the performance of the tandem-condensation azabutadiene Diels-Alder reaction a solution of the benzaldehydes **1a–e** and the aminoisoxazole **4** in xylene was heated for 50 h at 138°C. The reaction is quite unusual since its selectivity strongly depends on the substituents at the aromatic ring system and the dienophile moiety. Thus, in the reaction of **1a** with **4** the *trans*-annulated tetracyclic tetrahydropyridine **7a** was obtained in 62% yield as the only isolable product. If the reaction was performed at 80°C for 6 h, the imine **5a** with an 2-aza-1,3-butadiene moiety could be isolated in 72% yield. Heating of **5a** at 138°C for 50 h afforded **7a** in 62% yield besides 12% of the substrate and some polymeric material. This clearly proves that **5a** is an intermediate on the way to **7a**. The second intermediate **6a** is assumed to be the primarily formed cycloadduct, which gives the stable aromatic isoxazole moiety by a 1,3-hydrogen shift; however, as expected, this intermediate was not detected.



1d **2** **3**

***cis* : *trans* = >100 : 1**

In the reaction of **1b** with **4** two diastereomeric *trans*- and *cis*-fused cycloadducts could be formed; however, only the *trans*-fused cycloadduct **7b** with an equatorially orientated methoxycarbonyl group was obtained. Thus, the configuration of the double bond in **1b** is retained which would be in agreement with a concerted mechanism. Quite surprisingly the tandem reaction of **1c** with **4** at 138°C for 50 h gave exclusively the *cis*-fused compound **8c** in 68% yield.

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The stereoselectivity is lost in the reaction of **1d** and **1e** with **4**. In these transformations the *trans*- and *cis*-fused cycloadducts **7d** and **8d** as well as **7e** and **8e** were formed as mixtures of about 1.4:1 in 63% yield for **7d/8d** and about 5:1 for **7e/8e** in 62% yield. In the latter case again two *cis* and *trans* diastereomers could be formed; however, only the diastereomers **7e** and **8e** with equatorially orientated methyl groups were isolated.

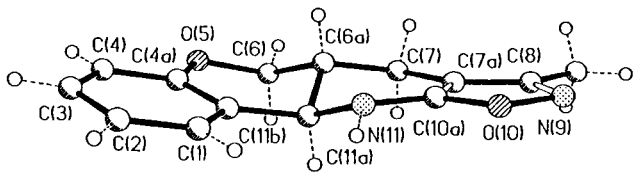


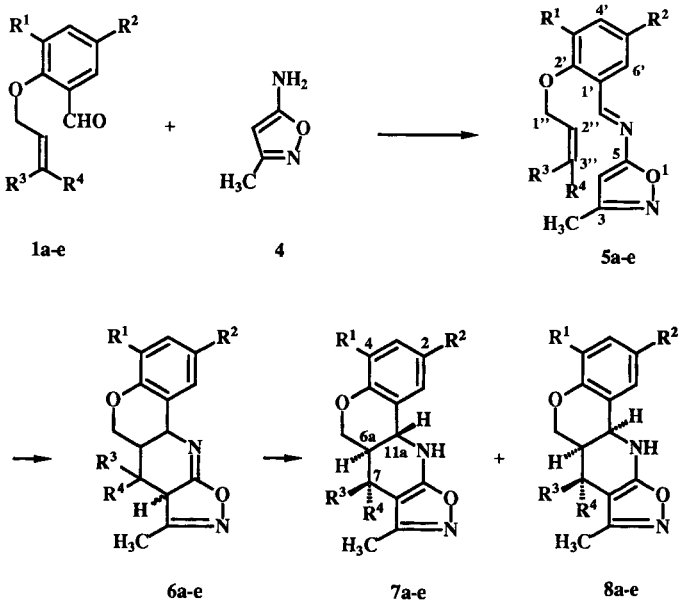
Figure 1. Molecular structure of **7a**

The configuration and conformation of the cycloadducts were determined by ^{1}H-NMR spectra and X-ray analysis (Figure 1). For **5a** the imino hydrogen resonates at $\delta = 9.27$ as a singlet. The other signals correspond to the resonances of the starting materials. In the Diels-Alder adduct **7a** the *trans* configuration of the newly formed stereogenic centers is deduced from the signals at $\delta = 2.10-2.28$ for 6-H and 4.35 for 11a-H with a coupling constant of $J_{6a\text{-}H,11a\text{-}H} = 10.0$ Hz. In the NMR spectrum of **7b** a similar pattern for 6a-H and 11a-H is found. 6a-H shows an additional coupling of $J_{6a\text{-}H,7\text{-}H_{ax}} = 3.9$ Hz, clearly indicating that the methoxycarbonyl group at C-7 must have an equatorial orientation. For 6a-H and 11a-H of **8c** signals are observed in the NMR spectrum at $\delta = 2.02$ and 4.14 with $J_{6a\text{-}H,11a\text{-}H} = 4.5$ Hz. From these values it can be deduced that in **8c** a *cis* annulation exists. The product mixtures **7d/8d** and **7e/8e** show resonances lines at $\delta = 1.84-2.02$ for 6a-H and 4.03 to 4.35 for 11a-H with $J_{6a\text{-}H,11a\text{-}H} = 10.5-11.1$ Hz for the *trans*-annulated cycloadducts **7d** and **7e** and $J_{6a\text{-}H,11a\text{-}H} = 4.8-5.0$ Hz for the *cis*-annulated compounds **8d** and **8e**. These values are in agreement with the foregoing discussion. Interestingly, in **7e** a long-range coupling of $J = 2.0$ Hz between 6a-H and N-H is observed; in all other compounds, this coupling does not exist, again indicating that the substituent at C-7 must be equatorial.

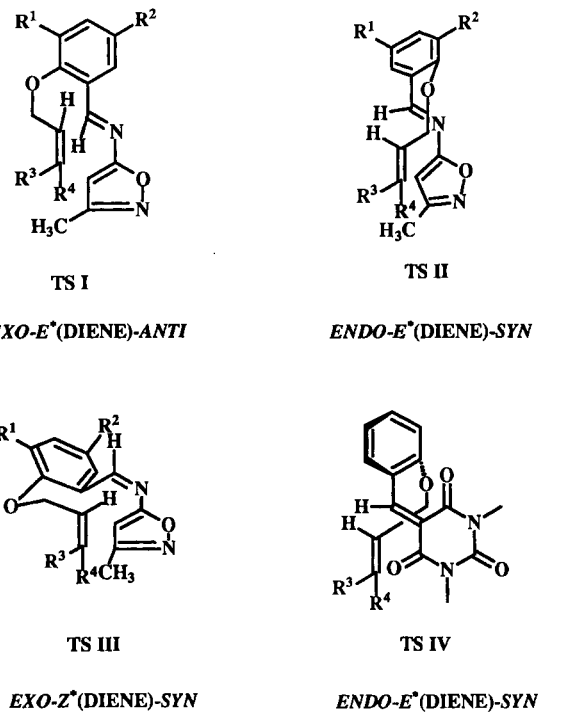
Table 1. Tandem imine formation hetero Diels-Alder reaction of **1a–e** with **4**

Substrates	Products[a]	Yield (%)[b]	Ratio of 7/8[c]
4 and **1a**	**7a**	62	>100:1
1b	**7b**	67	>100:1
1c	**8c**	68	<1:100
1d	**7d/8d**	63	1.4:1
1e	**7e/8e**	62	5.0:1

[a] All products were obtained as racemic mixtures. – [b] Yields are based on **4**. – [c] Determined from the ^{13}C-NMR spectra of the crude product mixtures.



1, 5-8	R^1	R^2	R^3	R^4
a	H	H	H	H
b	H	H	H	CO_2Me
c	Cl	Cl	CH_3	CH_3
d	H	H	CH_3	CH_3
e	H	H	H	CH_3



*EXO-E**(DIENE)-*ANTI*

*ENDO-E**(DIENE)-*SYN*

*EXO-Z**(DIENE)-*SYN*

*ENDO-E**(DIENE)-*SYN*

The observed stereochemistry in the different cycloadditions is quite unusual and can only be explained by assuming steric and electronic effects as well as a change in the mechanism. It is well understood, if we assume a concerted mechanism, that the *trans*-annulated products **7** can only be formed via an *exo-E**(diene)-*anti* (TS I) and the *cis*-annulated products **8** via an *endo-E**(diene)-*syn* (TS II) or an *exo-*

*E**(diene)-*syn* transition state (TS III). In the reaction of 1-oxa-1,3-butadienes with enol ethers and alkenes it has been shown by experiments and calculations that the overlap of the $LUMO_{Oxadiene}$-$HOMO_{Dienophile}$ is dominating. However, in the reaction of the 2-aza-1,3-butadiene moiety in **5a–e** a change of the dominating interaction may occur, according to the energy of the HOMO of the dienophile. It can also be assumed that the cycloaddition may no longer be a concerted process in all cases as it has been shown for the analogous 1-oxa-1,3-butadienes. This has been confirmed by AM1-CI[11] calculations[12]. As has been discussed for the reaction of **1d** with **2**[2a], the *cis*-fused product **3**, which is obtained exclusively in this tranformation, is presumably formed via an *endo-E**(diene)-*syn* transition structure (TS IV). Thus, we deduce from this and other experiments as well as calculations that due to a favorable overlap of the orbitals the plane of the benzene ring is orthogonal to the heterodiene in the *endo-E**(diene)-*syn* transition structure whereas the angle between the benzene ring and the heterodiene in the *exo-E**(diene)-*anti* transition structure should be about 60°. Clearly, this would minimize steric interactions between the non-reacting CO group and the substituents at the aromatic ring system in the *endo-E**(diene)-*syn* transition structure (TS IV). However, such steric interactions are less pronounced in TS I since there is no substituent at the nitrogen; thus, the *exo-E**(diene)-*anti* transition structure is favorable. Therefore, mixtures of the *trans*- and *cis*-fused compounds are obtained in the reaction of **1d** and **1e** with **4**. The pronounced selectivity in the reaction of **1c** with **4** as compared to the reaction of **1e** and **1d** with **4** may be explained by an electronic interaction of one of the chloro substituents at the benzene ring with the electron pair at the nitrogen in the *exo-E**(diene)-*anti* transition structure (TS I) favoring the formation of the *cis*-annulated compound presumably via the *endo-E**(diene) geometry (TS II). Finally, the high *trans*-selectivity in the reaction of **1a** and **1b** with **4** may be explained by assuming a change of the dominating interaction of the orbitals due to the lower energy of the HOMO of the dienophile in **5a** and **5b**. It is likely that this causes a change of the bond orders in the transition structures as compared to the reaction of **1d** with **4** or **1d** with **2**, favoring an *exo-E-anti* attack. It may even be possible that in these cases the bond between position 4 of the 2-azabutadiene and the dienophile moiety in TS I is formed to a higher extent than the second bond which would be contrary to the cycloadditions of the oxabutadienes.

Noteworthy, it has been shown that the observed *trans*- and *cis*-selectivities are due to a kinetic control, since heating of the pure diastereomers **7** and **8** in decaline at 200°C for 24 h did not lead to an isomerization.

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Experimental

^1H and ^{13}C NMR: Varian XL-200, VRX-500 and FT-80 A; multiplicities were determined with the APT pulse sequence; assignments marked with an asterisk may be interchanged. – MS: Varian MAT 311 A; high resolution: Varian MAT 731. – IR: Bruker IFS 25. – UV: Varian Cary 219. – Melting points: Kofler melting point apparatus (corrected values). – Elemental analyses: Analytical laboratory of the university. – All solvents were distilled prior to use. All reactions were monitored by TLC (Machery-Nagel Alugram Sil G/UV_{254}). Products were isolated by column chromatography (CC) on SiO_2 (CC: ICN Silica 63–200, 60 A, ICN Biochemicals, Eschwege). Solvents used for TLC and column chromatography: A, petroleum ether/ethyl acetate (9:1), B, petroleum ether/ethyl acetate (4:1), C, petroleum ether/ethyl acetate (2:1). All chiral compounds are obtained as racemic mixtures.

The *O*-substituted salicylaldehydes **1a–e** were prepared according to methods described in the literature[10]. 5-Amino-3-methylisoxazole (**4**) is commercially available.

Tandem Imine Formation Hetero-Diels-Alder Reaction of **1a–e** *with* **4** *via 2-Aza-1,3-butadienes*

General Procedure: A solution of the benzaldehyde derivatives **1a–e** (300–500 mg, 1.85–2.84 mmol) and 5-amino-3-methylisoxazole (**6**) (181–278 mg, 1.85–2.84 mmol) in xylene (50 ml) was heated for 50 h under reflux. After cooling to room temp. the solvent was evaporated in vacuo and the residue purified by chromatography on silica gel (150–220 g, 60–200 mesh, solvent as indicated).

X-ray Structure Analysis of **7a**[13]: $C_{14}H_{14}N_2O_2$ (242.3); monoclinic; space group $P2_1/n$; a = 505.6(1), b = 919.2(2), c = 2588.3(9) pm; β = 91.47(1)°; V = 120.26(6) nm^3; Z = 4; d_x = 1.34 Mg/m^3; m = 0.0085 mm^{-1}; Siemens-Stoe AED2 diffractometer; Mo-K_α (λ = 71.073 pm); monochromator: highly orientated graphite crystal; T = 293 K; scan $7.0° < 2\Theta < 45.0°$; reciprocal lattice segment, index ranges: $-5 < h < 5$, $-1 < k < 9$, $-11 < l < 27$; 1588 reflexions collected; 1573 (R_{int} > 0.0364) independent reflexions; 1244 [$F > 3.0\sigma(F)$] observed reflexions. Direct methods were used for solution (SHELXTL[14] and full-matrix least squares for refinement; R = 0.0702, R_w = 0.0715 (281 parameters).

Table 2. Atomic coordinates (× 10^4) and equivalent isotropic displacement parameters (× 10^{-1}) [pm^2] of **7a**, U(eq) defined as 1/3 of the trace of orthogonalized U_{ij} tensor

	x	y	z	U(eq)
C(1)	2217(7)	2358(4)	3728(1)	70(1)
C(2)	3091(8)	1169(4)	4004(2)	88(2)
C(3)	2234(9)	979(4)	4505(2)	85(2)
C(4)	534(9)	1944(5)	4711(1)	80(2)
C(4A)	-390(7)	3124(4)	4431(1)	61(1)
C(5)	-2078(5)	4031(3)	4678(1)	76(1)
C(6)	-3180(7)	5216(4)	4387(1)	64(1)
C(6A)	-1241(6)	5871(3)	4015(1)	52(1)
C(7)	-2418(6)	7232(4)	3749(1)	56(1)
C(8)	-667(6)	8726(3)	2935(1)	51(1)
C(81)	-2226(7)	10106(4)	2933(1)	67(1)
N(9)	1060(5)	8506(3)	2574(1)	59(1)
O(10)	2159(4)	7088(2)	2681(1)	58(1)
C(10A)	929(6)	6580(3)	3101(1)	47(1)
N(11)	1569(5)	5239(3)	3286(1)	50(1)
C(11A)	-485(6)	4678(3)	3635(1)	50(1)
C(11B)	472(6)	3361(3)	3927(1)	52(1)

3-Methyl-5-[2-(2-propenyloxy)benzylideneamino]isoxazole (**5a**): The reaction of **1a** (300 mg, 1.85 mmol) with **4** (181 mg, 1.85 mmol) yielded 277 mg (72%) of **5a** as colorless crystals on heating in xylene at 80°C for 6 h. R_f = 0.33 (solvent A), m.p. 57°C (ethanol). – IR (KBr): $\tilde{\nu}$ = 3078, 3050, 3038 (C=CH), 2994, 2984, 2966, 2924 (CH), 1648 (C=N). – UV (acetonitrile): λ_{max} (lg ε) = 191.5 nm (1.866),

257.5 (1.113), 347.0 (1.728). – ^{1}H NMR (80 MHz, $CDCl_3$): δ = 2.30 (s, 3H, 3-CH_3), 4.65 (dt, *J* = 4.5/2.0 Hz, 2H, CH_2-1″), 5.30 (dq, *J* = 10.5/2.0 Hz, 1H, 3″-H_{cis}), 5.45 (dq, *J* = 17.5/2.0 Hz, 1H, 3″-H_{trans}), 6.00 (s, 1H, 4-H), 6.10 (m_c, 1H, 2″-H), 6.91 (d, *J* = 7.5 Hz, 1H, 3′-H), 7.02 (t, *J* = 7.6 Hz, 1H, 5′-H), 7.45 (m_c, 1H, 4′-H), 8.13 (dd, *J* = 7.5/1.5 Hz, 1H, 6′-H), 9.27 (s, 1H, CH=N). – ^{13}C NMR (200 MHz, $CDCl_3$): δ = 10.59 (3-CH_3), 69.21 (C-1′), 110.9 (C-3″)*, 112.5 (C-3′), 117.9 (C-2′), 120.3 (C-5′), 127.6 (C-2″), 128.2 (C-6′), 132.5 (C-4′), 134.2 (C-4), 155.7 (C-1′)*, 157.6 (C=N), 160.7 (C-3)*, 166.0 (C-5). – MS (70 eV): *m/z* (%) = 243 (10) [M^+ + H], 242 (36) [M^+], 145 (100) [$M^+ - C_4H_5N_2O$].

$C_{14}H_{14}N_2O_2$ Calcd. 242.1055 Found 242.1055 (MS)

(6aRS,11aRS)-6a,7,11,11a-Tetrahydro-8-methyl-6H-[1]benzopyrano[4,3-b]isoxazolo[4,5-e]pyridine (**7a**): Heating of **5a** (200 mg, 0.83 mmol) in xylene for 50 h under reflux yielded 184 mg (62%) of **7a** as colorless crystals. R_f = 0.08 (solvent B), m.p. 192°C (ethyl acetate/petroleum ether). – IR (KBr): $\tilde{\nu}$ = 3194 cm^{-1} (NH), 3064, 3012 (C=CH), 2974, 2946, 2912 (CH), 1648 (C=N). – UV (acetonitrile): λ_{max} (lg ε) = 197.0 nm (3.687), 228.0 (0.969), 249.5 (1.668). – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.10–2.28 (m, 2H, 6a-H, 7-H_{eq}), 2.20 (s, 3H, 8-CH_3), 2.55 (dd, *J* = 12.5/3.5 Hz, 1H, 7-H_{ax}), 3.98 (t, *J* = 11.5 Hz, 1H, 6-H_{ax}), 4.35 (dd, *J* = 10.0/4.5 Hz, 1H, 11a-H), 4.48 (dd, *J* = 11.2/3.2 Hz, 1H, 6-H_{eq}), 4.55 (m_c, 1H, NH, D_2O), 6.92 (dd, *J* = 8.3/1.3 Hz, 1H, 4-H), 7.03 (td, *J* = 7.5/1.2 Hz, 1H, 2-H), 7.25 (m_c, 1H, 3-H), 7.34 (dt, *J* = 7.8/1.3 Hz, 1H, 1-H). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 10.40 (8-CH_3), 20.34 (C-7), 34.18 (C-6a), 53.80 (C-11a), 68.58 (C-6), 90.50 (C-7a), 117.0 (C-4), 121.0 (C-2), 121.4 (C-4a), 125.1 (C-1), 129.2 (C-3), 153.9 (C-11b), 159.1 (C-8), 166.3 (C-10a). – MS (70 eV): *m/z* (%) = 243 (8) [M^+ + H], 242 (48) [M^+], 198 (20) [$M^+ - C_3H_8$], 131 (100) [$C_9H_7O^+$], 57 (12) [$C_3H_5O^+$], 43 (20) [$C_3H_7^+$].

$C_{14}H_{14}N_2O_2$ (242.3) Calcd. C 69.35 H 5.80
Found C 69.40 H 5.85

Methyl (6aRS,11aRS)-6a,7,11,11a-Tetrahydro-8-methyl-6H-[1]-benzopyrano[4,3-b]isoxazolo[4,5-e]pyridine-7α-carboxylate (**7b**): The reaction of **1b** (500 mg, 2.27 mmol) with **4** (222 mg, 2.27 mmol) according to the general procedure yielded 456 mg (67%) of **7b** as a colorless solid. R_f = 0.43 (solvent C), m.p. 210°C (ethanol). – IR (KBr): $\tilde{\nu}$ = 3392 cm^{-1} (NH), 3084, 3064, 3036 (C=CH); 2964, 2926 (C–H), 1728 (C=O), 1644 (C=N). – UV (acetonitrile): λ_{max} (lg ε) = 197.0 nm (3.302), 227.5 (0.797), 246.6 (0.815). – ^{1}H NMR (200 MHz, DMSO): δ = 1.98 (s, 3H, 8-CH_3), 2.20 (dddd, *J* = 11.2/11.2/11.2/3.9 Hz, 1H, 6a-H), 3.49 (d, *J* = 10.8 Hz, 1H, 7-H), 3.78 (s, 3H, OCH_3), 4.08 (t, *J* = 11.2 Hz, 1H, 6-H_{ax}), 4.30 (dd, *J* = 11.2/3.9 Hz, 1H, 6-H_{eq}), 4.50 (d, *J* = 10.8 Hz, 1H, 11a-H), 6.85 (dd, *J* = 8.1/1.0 Hz, 1H, 4-H), 6.99 (td, *J* = 8.0/1.2 Hz, 1H, 2-H), 7.23 (m_c, 1H, 3-H), 7.60 (d, *J* = 7.9 Hz, 1H, 1-H), 7.62 (s br, 1H, NH, D_2O). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 10.60 (8-CH_3), 38.14 (C-6a), 39.74 (C-11a), 52.53 (OCH_3), 53.24 (C-7), 66.85 (C-6), 98.30 (C-7a)*, 117.2 (C-4), 120.5 (C-2), 121.3 (C-4a), 125.0 (C-1), 129.5 (C-3), 153.7 (C-11b), 160.0 (C-8)*, 166.2 (C-10a)*, 172.2 (C=O). – MS (70 eV): *m/z* (%) = 300 (38) [M^+], 241 (100) [$M^+ - CO_2CH_3$], 59 (8) [$CO_2CH_3^+$].

$C_{16}H_{16}N_2O_4$ (300.2) Calcd. C 63.99 H 5.33
Found C 64.02 H 5.29

(6aRS,11aSR)-2,4-Dichloro-6a,7,11,11a-tetrahydro-7,7,8-trimethyl-6H-[1]benzopyrano[4,3-b]isoxazolo[4,5-e]pyridine (**8c**): The reaction of **1c** (500 mg, 1.93 mmol) with **4** (189 mg, 1.93 mmol) according to the general procedure yielded 445 mg (68%) of **8c** as colorless crystals; R_f = 0.12 (solvent A), m.p. 239°C (ethanol). – IR (KBr): $\tilde{\nu}$ = 3232 cm^{-1} (NH), 3080 (C=CH), 2978, 2928 (CH), 1624 (C=N). – UV (acetonitrile): λ_{max} (lg ε) = 205 nm (2.500), 238 (0.753), 296 (0.200). – ^{1}H NMR (200 MHz, DMSO): δ = 1.22 (s, 3H, 7-CH_3 ax), 1.29 (s, 3H, 7-CH_3 eq), 1.88 (s, 3H, 8-CH_3), 2.02 (dt, *J* = 11.5/4.5 Hz, 1H, 6a-H), 3.70 (t, *J* = 11.4 Hz, 1H, 6-H_{ax}), 4.15 (d, *J* = 4.5 Hz, 1-H, 11a-H), 4.52 (ddd, *J* = 11.5/4.5/1.5 Hz, 1H, 6-H_{eq}), 7.38 (s br, 1H, NH, D_2O), 7.45 (d, *J* = 2.8 Hz, 1H, 3-H), 7.60 (d, *J* = 2.8 Hz, 1H, 1-H). – ^{13}C NMR (50 MHz, DMSO): δ = 11.62 (8-CH_3), 25.15 (7-CH_3 ax), 28.16 (7-CH_3 eq), 29.60 (C-7), 37.49 (C-6a), 52.52 (C-12a), 64.37 (C-6), 85.69 (C-7a), 120.8 (C-4a), 122.5 (C-4), 125.2 (C-2), 127.8 (C-1), 130.2 (C-3), 148.1 (C-11b), 158.1 (C-8), 164.0 (C-10a). – MS (70 eV): *m/z* = 339 (44) [M^+], 338 (70) [M^+ – H], 323 (12) [$M^+ - CH_3$], 69 (20) [$C_5H_9^+$], 43 (100) [$C_3H_7^+$].

$C_{16}H_{16}Cl_2N_2O_2$ (339.2) Calcd. C 56.68 H 4.75
Found C 56.72 H 4.80

(6aRS,11aRS)- and (6aRS,11aSR)-6a,7,11,11a-Tetrahydro-7,7,8-trimethyl-6H-[1]benzopyrano[4,3-b]isoxazolo[4,5-e]pyridine (**7d** and **8d**): The reaction of **1d** (400 mg, 2.10 mmol) with **4** (206 mg, 2.10 mmol) according to the general procedure yielded 358 mg (63%) of **7d** and **8d** as a 1.4:1.0 mixture. Column chromatography afforded 209 mg of the *trans*-fused cycloadduct **7d** and 149 mg of the *cis*-fused cycloadduct **8d**. **7d**: R_f = 0.16 (solvent A), m.p. 153°C (ethyl acetate). – IR (KBr): $\tilde{\nu}$ = 3322 cm^{-1} (NH), 3062, 3040 (C=CH), 2962, 2930 (CH), 1636 (C=N), 1452, 1366 (CH_3). – UV (acetonitrile): λ_{max} (lg ε) = 197.5 nm (3.282), 240.0 (1.206). – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.12 (s, 3H, 7-CH_3 ax), 1.45 (s, 3H, 7-CH_3 eq), 1.96 (td, *J* = 11.1/3.2 Hz, 1H, 6a-H), 2.30 (s, 3H, 8-CH_3), 3.31 (t, *J* = 11.1 Hz, 1H, 6H_{ax}), 4.35 (d, *J* = 10.5 Hz, 1H, 11a-H), 4.46 (dd, *J* = 11.1/3.2 Hz, 1H, 6H_{eq}), 4.52 (s br, 1H, NH, D_2O), 6.88 (dd, *J* = 8.2/1.2 Hz, 1H, 4-H), 6.99 (td, *J* = 7.5/1.1 Hz, 1H, 2-H), 7.22 (m_c, 1H, 3-H), 7.34 (d, *J* = 7.8 Hz, 1H, 1-H). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 11.95 (8-CH_3), 24.34 (7-CH_3 ax), 25.56 (7-CH_3 eq), 31.32 (C-7), 44.86 (C-6a), 50.17 (C-11a), 64.81 (C-6), 99.87 (C-7a), 116.9 (C-4), 121.0 (C-2), 121.9 (C-4a), 125.6 (C-1), 128.9 (C-3), 153.9 (C-11b), 159.3 (C-8), 164.8 (C-10a). – MS (70 eV): *m/z* (%) = 270 (14) [M^+], 255 (15) [$M^+ - CH_3$], 184 (100) [$M^+ - C_5H_{10}O$].

$C_{16}H_{18}N_2O_2$ (270.3) Calcd. C 71.09 H 6.80
Found C 71.02 H 6.71

8d: R_f = 0.10 (solvent A), m.p. 173°C (ethyl acetate). – IR (KBr): $\tilde{\nu}$ = 3376 cm^{-1} (NH), 3076 (C=CH), 2980, 2926 (CH), 1626 (C=N), 1460, 1370 (CH_3). – UV (acetonitrile): λ_{max} (lg ε) = 197.0 nm (2.408), 227.5 (0.487), 249.5 (0.501). – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.33 (s, 3H, 7-CH_3 ax), 1.39 (s, 3H, 7-CH_3 eq), 2.00 (s, 3H, 8-CH_3), 2.02 (m_c, 1H, 6a-H), 3.82 (t, *J* = 11.1 Hz, 1H, 6H_{ax}), 4.03 (dd, *J* = 4.8/1.5 Hz, 1H, 11a-H), 4.34 (ddd, *J* = 11.1/4.0/1.5 Hz, 1H, 6H_{eq}), 4.47 (s br, 1H, NH, D_2O), 6.82 (dd, *J* = 8.0/1.1 Hz, 1H, 4-H), 6.89 (td, *J* = 7.5/1.1 Hz, 1H, 2-H), 7.17 (ddd, *J* = 8.2/8.0/1.8 Hz, 1H, 3-H), 7.31 (dd, *J* = 7.5/1.9 Hz, 1H, 1-H). – ^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.43 (8-CH_3), 26.30 (7-CH_3 ax), 28.98 (7-CH_3 eq), 30.55 (C-6a), 39.52 (C-11a), 53.34 (C-7), 63.36 (C-6), 88.59 (C-7a), 116.7 (C-4), 113.4 (C-2), 120.8 (C-4a), 128.6 (C-1), 131.8 (C-3), 153.8 (C-11b), 159.9 (C-8), 163.4 (C-10a). – MS (70 eV): *m/z* (%) = 270 (100) [M^+], 255 (6) [$M^+ - CH_3$], 69 (28) [$C_5H_9^+$], 59 (78) [$C_4H_{11}^+$], 43 (48) [$C_3H_{11}^+$].

$C_{16}H_{18}N_2O_2$ (270.3) Calcd. C 71.09 H 6.80
Found C 71.02 H 6.71

(6aRS,7RS,11aRS)- and (6aRS,7RS,11aSR)-6a,7,11,11a-Tetrahydro-7α,8-dimethyl-6H-[1]benzopyrano[4,3-b]isoxazolo[4,5-e]-pyridine (**7e** and **8e**): The reaction of **1e** (500 mg, 2.84 mmol) with **4** (278 mg, 2.84 mmol) according to the general procedure yielded 451 mg (62%) of **7e** and **8e** as a 5:1 mixture. Column chromatography afforded 376 mg of **7e** and 75 mg of **8e** as colorless solids.

7e: R_f = 0.31 (solvent C), m.p. 205° (ethyl acetate). – IR (KBr): $\tilde{\nu}$ = 3224 cm^{-1} (NH), 3064 (C=CH), 2984, 2964 (CH), 1636 (C=N), 1450, 1318 (CH_3). – UV (acetonitrile): λ_{max} (lg ε) = 274.0 (0.514), 228.0 (1.028), 248.0 (1.113). – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.35 (d, *J* = 6.7 Hz, 3H, 7-CH_3), 1.84 (dddd, *J* = 10.5/10.5/11.2/3.5 Hz, 1H, 6a-H), 2.53 (dq, *J* = 10.2/6.7 Hz, 1H, 7-H), 3.88 (t, *J* = 11.5 Hz, 1H, 6H_{ax}), 4.35 (d, *J* = 10.5 Hz, 1H, 11a-H), 4.53 (dd, *J* = 11.1/3.5 Hz, 6-H_{eq}), 4.54 (s br, 1H, NH, D_2O), 6.88 (dd, *J* = 8.0/1.2 Hz, 1H, 4-H), 6.98 (td, *J* = 7.5/1.1 Hz, 1H, 2-H), 7.22 (m_c, 1H, 3-H), 7.30 (dt, *J* = 7.5/1.1 Hz, 1H, 1-H). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 12.04 (8-CH_3), 17.18 (7-CH_3), 27.74 (C-6a), 41.99 (C-11a), 53.97 (C-7), 67.33 (C-6), 95.58 (C-7a), 116.9 (C-4), 121.0 (C-2), 121.5 (C-4a), 125.1 (C-1), 129.2 (C-3), 153.9 (C-11b), 159.2 (C-8), 165.4 (C-10a). – MS (70 eV): *m/z* (%) = 256 (38) [M^+], 158 (34) [$M^+ - C_4H_8N_2O$], 131 (100) [$C_9H_7O^+$], 44 (46) [$C_3H_8^+$].

$C_{15}H_{16}N_2O_2$ (256.1) Calcd. C 70.29 H 6.29
Found C 70.18 H 6.31

8e: R_f = 0.22 (solvent C), m.p. 200 °C (ethyl acetate). – IR (KBr): $\tilde{\nu}$ = 3214 cm^{-1} (NH), 3072, 3034 (C=CH), 2976, 2910 (CH), 1636 (C=N), 1540, 1340 (CH_3). – UV (acetonitrile): λ_{max} (lg ε) = 197.5 nm (3.106), 225.0 (0.723), 253 (0.625). – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.38 (d, *J* = 6.5 Hz, 3H, 7-CH_3 ax), 1.92 (dddd, *J* = 7.9/5.0/5.0/2.3 Hz, 1H, 6a-H), 2.29 (s, 3H, 8-CH_3), 3.58 (dqd, *J* = 7.9/6.5/2.0 Hz, 1H, 7-H_{eq}), 4.03 (d, *J* = 5.0 Hz, 1H, 11a-H), 4.26 (dd, *J* = 11.5/3.0 Hz, 1H, 6H), 4.35 (dd, *J* = 11.5/4.5 Hz, 1H, 6-H), 4.56 (s br, 1H, NH, D_2O), 6.79 (dd, *J* = 8.1/1.1 Hz, 1H, 4-H), 6.88 (td, *J* = 7.9/1.2 Hz, 1H, 2-H), 7.07–7.16 (m, 2H, 3-H, 1-H). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 11.46 (8-CH_3), 20.03 (7-CH_3), 30.79 (C-6), 36.99 (C-11a), 46.61 (C-7), 96.43 (C-7a), 116.7 (C-4), 120.6 (C-2), 123.8 (C-4a), 128.1 (C-1), 130.3 (C-3), 153.0 (C-11b), 159.4 (C-8), 164.6 (C-10a). – MS (70 eV): *m/z* (%) = 256 (100) [M^+], 131 (60) [$C_9H_7O^+$], 44 (42) [$C_3H_8^+$].

$C_{15}H_{16}N_2O_2$ (256.1) Calcd. C 70.29 H 6.29
Found C 70.20 H 6.21

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