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New advances in stereoselective Meyers' lactamization. Application to the diastereoselective synthesis of β-substituted oxazoloazepinones

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ABSTRACT

A stereoselective approach to the preparation of 7,5-fused bicyclic lactams based on Meyers' lactamization is presented. The lactamization step is conducted at 0 °C with 6-oxohexanoic acid **1** and with various chiral aminoalcohols in the presence of 2-fluoro-1-ethylpyridinium tetrafluoroborate (FEP) as an activating agent. Under these mild conditions, bicyclic lactams **2**–**4** were obtained in satisfactory yields and diastereoselectivities up to 95%. To account for the high level of diastereoselection, the mechanistic aspects of Meyers' lactamization were investigated by means of in situ infrared spectroscopy. Finally, the lactam enolate derived from **2** was subjected to reaction with various electrophiles, furnishing the corresponding β-substituted oxazoloazepinones **5–9** in good yields (up to 86%) and in moderate to excellent diastereoselectivities ranging from 27% to 95% de.

1. Introduction

Seven-membered nitrogen heterocycles are constituents of a large number of compounds with interesting pharmacological properties such as balanol, a potent inhibitor of the protein kinase C enzyme, which has attracted a lot of synthetic efforts in the last few years.[1] The γ-secretase inhibitor LY411575 (IC_{50}<1 nM in HEK cells) discovered by researchers at Eli Lilly and presently studied for potential use in the treatment of central nervous disorders should also be mentioned.[2] The azepine fragment is also encountered in stemoamide,[3] a pyrroloazepine alkaloid isolated from *Stemona Tuberosa*, the roots of which have been used in traditional Asian folk medicine for the treatment of respiratory diseases (Fig. 1).[4] Among the various strategies already investigated for the preparation of these biologically active products, only a few report general methods for the construction of the seven-membered heterocyclic ring.

To fill in this gap, Meyers attempted to extend the well-known diastereoselective formation of 5,5- and 6,5-fused bicyclic lactams[5] to the construction of larger 7,5-fused bicyclic lactams from ω-keto acids.[6] Unfortunately, under routine cyclodehydration conditions, both the yield and the diastereoselectivity were revealed to be rather modest, likely due to a lack of rigidity of the larger seven-membered ring. The limitation of Meyers' methodology in constructing larger chiral 7,5-fused bicyclic lactams was also pointed out more recently by Wünsch,[7] who observed the total absence of diastereoselectivity during the preparation of oxazolo[3]benzazepinones by lactamization of an ω-keto acid and (*R*)-phenylglycinol. Alternatively, we had previously shown that 2-fluoro-1-ethylpyridinium tetrafluoroborate (FEP) or Mukaiyama's reagent could advantageously replace conventional thermal conditions by means of carboxylic acid activation, to afford 5,5- and 6,5-fused bicyclic lactams with high diastereoselectivities under much milder conditions.[8] An axially chiral 7,5-fused bicyclic lactam, closely related to the circumdatin family of natural products, could be

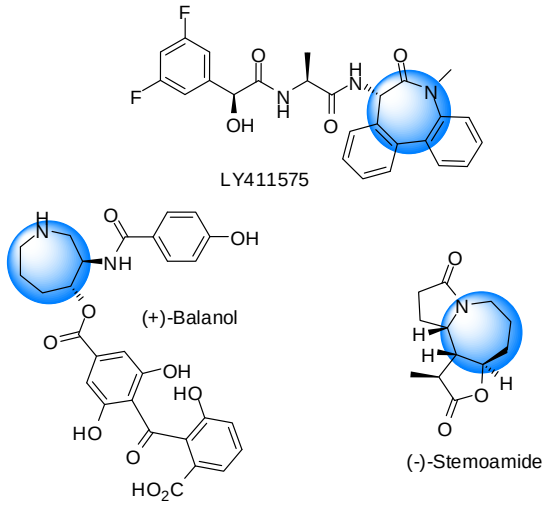

Figure 1. Biological active compounds containing seven-membered nitrogen heterocycles.

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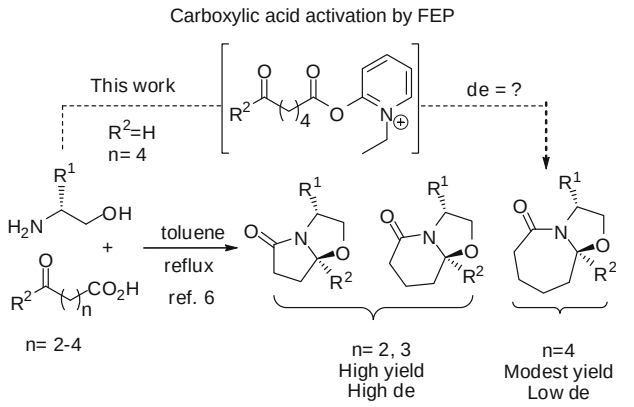
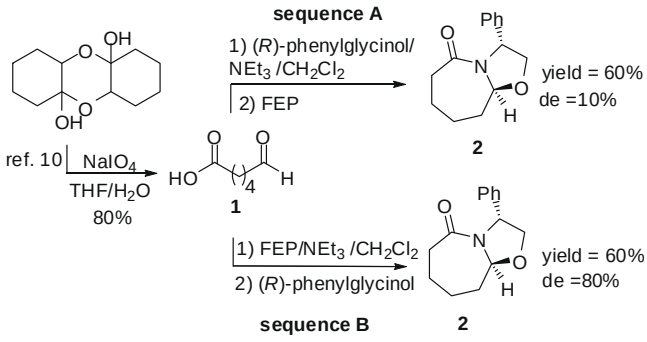
prepared under these new activation conditions, while classical dehydrating conditions led mainly to the degradation of starting material.[9] Herein, we report a useful extension of these mild lactamization conditions to the preparation of oxazoloazepinones (Scheme 1). In addition, an evaluation of the potential of these 7,5-fused bicyclic lactams as chiral templates is reported during the alkylation of the corresponding lactam enolates.



Scheme 1. Scope and limitation of Meyers' bicyclic lactam formation under dehydrating conditions.

2. Results and discussion

The required 6-oxohexanoic acid **1** was prepared in 80% yield by a Baeyer–Villiger oxidation of the commercially available 2-hydroxycyclohexanone dimer.[10] The lactamization was then carried out in dichloromethane at 0 °C in the presence of FEP, to afford the desired 7,5-fused bicyclic lactam **2** in 60% yield. Interestingly, the diastereoselectivity was found to be markedly influenced by the sequence of the reagent addition. While disappointing results (de = 10%) were obtained by adding (*R*)-phenylglycinol followed by FEP to a solution of 6-oxohexanoic acid **1** and NEt_3 (sequence **A**), the diastereoselectivity could be significantly enhanced (de = 80%) by first introducing the activating agent FEP followed by (*R*)-phenylglycinol (sequence **B**). This result designates the formation of the activated ester prior to the formation of the oxazolidine intermediate as a prerequisite for obtaining satisfactory diastereoselectivities (Scheme 2).



Scheme 2. FEP-promoted diastereoselective lactamization of 6-oxohexanoic acid **1**.

To highlight the formation of various intermediates in the lactamization process, sequences **A** and **B** were monitored by in situ infrared spectroscopy (Figs. 2 and 3). Both sequences started with the addition of NEt_3 to a solution of 6-oxohexanoic acid **1** in dichloromethane. Whereas the initial spectra of 6-oxohexanoic acid **1** showed two bands at 1710 cm^{-1} and 1725 cm^{-1} that are attributed to the carboxylic and aldehyde functions, respectively, upon addition of triethylamine a new absorbance appeared at 1370 cm^{-1}, that is, associated with the formation of the corresponding carboxylate salt. The disappearance of the aldehyde C=O stretch (1725 cm^{-1}) after adding (*R*)-phenylglycinol, in conjunction with the absence of any imine band (usually located near 1650 cm^{-1}), suggested the rapid formation of the oxazolidine intermediate as the main product. A quantitative ^{13}C NMR experiment of a solution of 6-oxohexanoic acid **1** and (*R*)-phenylglycinol in $CDCl_3$ confirmed the presence of the oxazolidine as a mixture of two diastereomers with a slight diastereomeric enrichment of 57:43. Sequence **A** was finally completed with the addition of FEP, to afford the desired oxazoloazepinone **2** within a few minutes as indicated by the appearance of a new band at 1650 cm^{-1}, that is, assigned to the lactam C=O vibration. The NMR analysis of the crude product showed a modest diastereoselectivity of 55:45 that is roughly the same as the one measured in the oxazolidine intermediate. This result suggests that the stereochemical outcome of the whole lactamization process arises from the oxazolidine formation, which may be considered as the stereodetermining step (Fig. 2).

In sequence **B**, FEP was first added to the carboxylate salt of **1** to produce the activated ester as observed by the appearance of a new absorbance at 1840 cm^{-1} (Fig. 3). Upon addition of (*R*)-phenylglycinol, an additional peak at 1650 cm^{-1} appeared, revealing that lactamization occurred within a few minutes. Subsequent ^1H NMR analysis of the crude product showed that the desired oxazoloazepinone **2** was formed in up to 80% de. Unfortunately, no other intermediates could be observed by in situ infrared spectroscopy

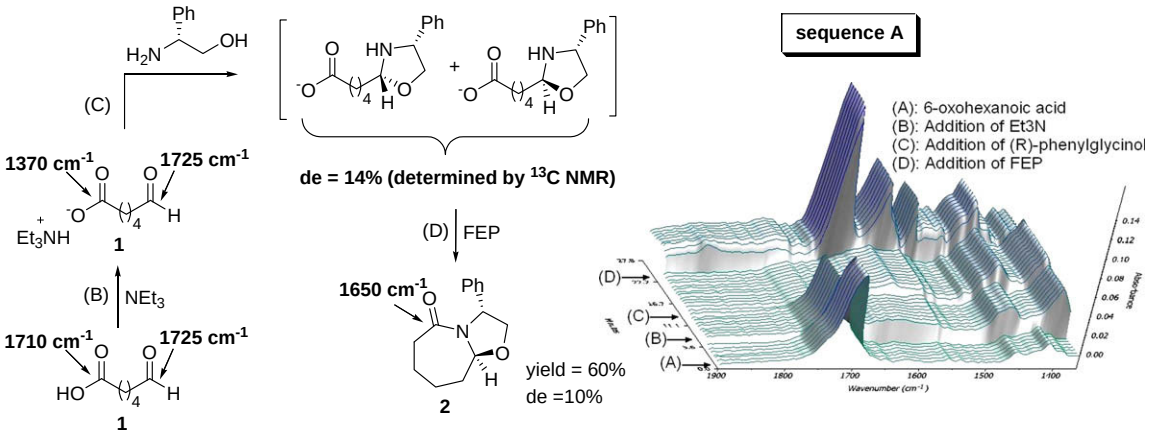


Figure 2. Monitoring the lactamization process by in situ infrared spectroscopy (sequence **A**).

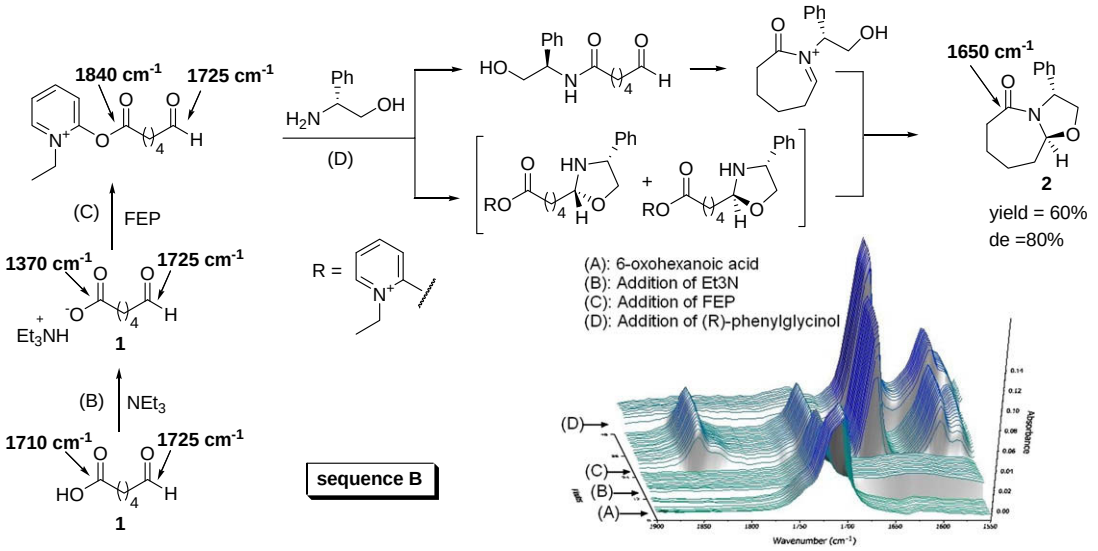


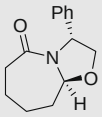
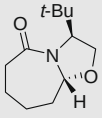
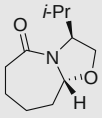
Figure 3. Monitoring the lactamization process by in situ infrared spectroscopy (sequence **B**).

due to the fast conversion of the activated ester into the desired oxazoloazepinone **2**. At this stage, two mechanisms were envisioned to explain the formation of the oxazoloazepinone **2** from the activated ester. The first involves the formation of the oxazolidine, which would subsequently react with the activated ester to yield oxazoloazepinone **2** similarly to sequence **A**. Alternatively, (*R*)-phenylglycinol may react first with the activated ester to furnish an ω-amido aldehyde. The diastereoselective lactamization would then take place via the formation of an acyliminium species, followed by the oxazolidine ring formation resulting from the preferential attack of the alcohol on one face of the iminium. The highly diastereoselective cyclisation of an ω-amido acetal into oxazolo[3]benzazepinone reported by Wünsch[11] is consistent with this mechanistic scenario and argues in favor of the formation of an ω-amido aldehyde as an intermediate. Attempts to determine the relative configuration of the major diastereoisomer by NOESY experiments failed. The stereochemistry at the N,O-acetal stereocenter of the oxazoloazepinone **2** may be, however, reasonably assigned as (*S*) by comparison with the literature data (Fig. 3).[12]

Although phenylglycinol is usually designated as the chiral auxiliary of choice for synthetic applications on account of the facile cleavage of the chiral appendage, (*S*)-*tert*-leucinol and (*S*)-valinol were also considered in this study (Table 1). The performances of (*S*)-*tert*-leucinol did not surpass those of (*R*)-phenylglycinol, affording the oxazoloazepinone **3** in only 45% yield and 81% de (entries 1 and 2). The lactamization conducted with (*S*)-valinol proceeded with a high diastereoselectivity, as only one diastereomer could be detected on the ^{1}H NMR spectra of the crude product, however, at the expense of the yield not exceeding 31% (entry 3). To complete this study, other reaction parameters, such as temperature (−78 °C, 20 °C, or 40 °C) and solvents (CH_3CN, $CHCl_3$, or DMF), were briefly examined during the formation of oxazoloazepinone **2** without any improvement of yield or diastereoselectivity.

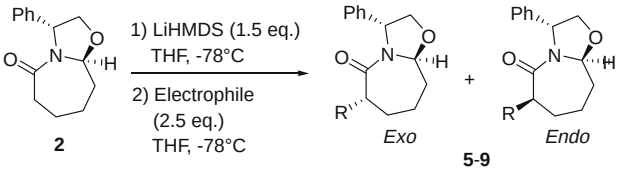
With these new chiral oxazoloazepinones in hand, diastereoselective functionalization at C-6 of the oxazoloazepinone **2** was then investigated (Table 2). Whereas alkylation of enolates derived from 5,5- and 6,5-fused bicyclic lactams has already been extensively exploited,[5,13] it remains almost unexplored with 7,5-fused bicyclic lactams,[11] most likely due to the lack of general stereo-

Table 1
Lactamization of 6-oxohexanoic acid **1** with various aminoalcohols[a]

Entry	Aminoalcohol	Lactam	Yield[b] (%)	de[c] (%)
1	(*R*)-Phenylalaninol	 **2**	60	80
2	(*S*)-*tert*-Leucinol	 **3**	45	80
3	(*S*)-Valinol	 **4**	31	>95

[a] Lactamization was conducted following the procedure **B** at 0 °C using compound **1** (1 equiv), NEt_3 (2 equiv), FEP (1.1 equiv), and aminoalcohol (1 equiv).
[b] Isolated yield.
[c] Determined by ^{1}H NMR and chiral GC.

Table 2
Alkylation of lactam enolate derived from oxazoloazepinone **2**



Entry	Electrophile	R	Product	Yield (%)	de[a] (%)
1	MeI	Me	**5**	73[b]	60
2	$C_6H_5CH_2Br$	Bn	**6**	65	62
3	AllylBr	$CH_2CH{=}CH_2$	**7**	86	27
4	Ph_2CO	$C(OH)Ph_2$	**8**	60	>95
5	TrN_3[c]	N_3	**9**	>95[d]	>95

[a] Diastereomeric excesses were determined by chiral GC and ^{1}H NMR.
[b] 4 Equiv of LiHMDS was necessary to drive the reaction to completion.
[c] Tr = triisopropyl-*p*-toluenesulfonyl.
[d] Conversion determined by ^{1}H NMR.

selective access to these larger bicyclic lactams. A survey of the literature revealed that while LDA provides rather poor yields during the alkylation of various oxazolopiperidinones, much better yields have been reached with comparable or higher level of diastereoselectivity by using LiHMDS.[13]

After optimization of the reaction conditions, treatment of oxazoloazepinone **2** with LiHMDS at −78 °C in THF gave rise to the corresponding lactam enolate, which was subsequently trapped with various electrophiles. In all cases, the reaction proceeded with excellent conversions and isolated yields, ranging between 60% and 86%. The diastereoselectivity was shown to be highly substrate dependent, affording the β-substituted oxazoloazepinones **5**–**9** in 27–95% de. Whereas methyl iodide and benzyl bromide afforded oxazoloazepinones **5** and **6** with very similar levels of diastereoselection (60% and 62%, respectively), allylbromide furnished oxazoloazepinone **7** in only 27% de (entries 1–3). The more sterically hindered benzophenone and triisopropyl-*p*-toluenesulfonylazide led to high diastereoselectivities, providing oxazoloazepinones **8** and **9** in up to 95% de (entries 4 and 5). It should be noted that although azidation of **2** occurred with complete conversion, we did not succeed in the separation of the residual triisopropyl-*p*-toluenesulfonylazide derivatives, used in excess, from the 6-azidooxazoloazepinone **9**. All our efforts to determine the configuration of the new stereocenter at C-6 of the various oxazoloazepinones **5–9** by X-ray analysis and NOESY experiments failed. A preferential *endo*-facial selectivity was observed by Wünsch during the diastereoselective alkylation of an oxazolo[3]benzazepinone, which is structurally closely related to our oxazoloazepinones.[7,11] Although the literature data strongly argue in favor of the preferential formation of the *endo*-diastereomer, it would be hazardous to conclude on the configuration at C-6 in oxazoloazepinones **5-9**. Indeed, whereas numerous literature reports mention a preferential *endo*-facial selectivity during the alkylation of 5,5-fused bicyclic lactams,[5] an *exo*-facial selectivity has also been reported in many cases with 6,5-fused bicyclic lactams.[13a–d]

3. Conclusion

Meyers' methodology was successfully applied to the stereoselective synthesis of new 7,5-bicyclic lactams. The lactamization was conducted under mild conditions with 6-oxohexanoic acid **1** and with various chiral aminoalcohols in the presence of FEP as activating agent. Oxazoloazepinones **2**–**4** were obtained in good yields with diastereoselectivities of up to 95%. The sequence of the reagent addition proved to be crucial in achieving good diastereoselectivities. In an effort to gain insight into the difference in the diastereoselectivity between sequences **A** and **B**, both lactamization procedures were monitored by in situ infrared spectroscopy. Lastly, to probe the synthetic potential of what can be considered as new chiral templates for the stereoselective functionalization of seven-membered ring heterocycles, alkylation of the corresponding lactam enolates was investigated affording the β-substituted oxazoloazepinones **5-9** in good yields and diastereoselectivities up to 95%.

4. Experimental

4.1. General methods

All solvents were dried according to the common methods and were distilled before use. IR spectra were recorded on ELMER IRTF 1650 spectrometer. Melting points were determinated using WME Kofler apparatus. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 300 Avance (300 MHz). Chemical shifts are reported in δ (ppm). In the case of diastereomeric mixture, spectral data of the minor isomer are given in square brackets. Gas chromatography was performed on a Varian 3300 chromatograph fitted with a DB5 capillary column (l = 30 m, ∅ = 0.25 mm, df = 0.25 μm) for reaction monitoring or on a Chirasil-Dex CB® chiral capillary column (l = 25 m, ∅ = 0.25 mm, df = 0.25 μm) for diastereomeric excesses determination. EI-MS were performed on a GCQ Thermoquest spectrophotometer coupled to a Finnigan-GCQ chromatograph equipped with a DB5-MS capillary column (l = 25 m, ∅ = 0.25 mm, df = 0.25 μm). Other mass spectra (IC, FAB) were recorded on JEOL JMS AX-500 by the Mass Spectrometry Laboratory at the University of Rouen. Elemental analysis was carried out at the University of Rouen (Microanalytical Service Laboratory) on a CARLO ERBA 1160. Optical rotation was measured at 20 °C in CH_2Cl_2 or $CHCl_3$ on a PERKIN–ELMER 341 micropolarimeter. All reactions were carried out under an argon atmosphere, and were monitored by thin-layer chromatography with Merck 60F-254 precoated silica (0.2 mm) on aluminum. Flash chromatographies were performed with SDS silica gel, 70–230 mesh (Merck). Preparative layer chromatographies were performed with Merck 60 HF254 precoated silica on glass. The solvent systems were given v/v.

4.2. 6-Oxohexanoic acid 1

To a solution of 2-hydroxycyclohexanone dimer (3.42 g, 30.0 mmol) in a 60% aqueous THF solution (300 mL) was added sodium periodate (6.42 g, 30.0 mmol). The solution was stirred for 10 h at room temperature. Thereafter, sodium periodate (3.21 g, 15.0 mmol) was again added, and the solution was stirred for an additional 6 h. The reaction mixture was diluted with AcOEt (300 mL), and washed with brine. The organic phase was extracted and dried over $MgSO_4$. Flash chromatography of the residue (eluent: ethylacetate/cyclohexane: 1/1) (stain reagent for TLC: phosphomolybdic acid reagent) provided 6-oxohexanoic acid **1** as a clear oil (3.12 g, 80%). ^{1}H NMR 300 MHz, ($CDCl_3$) δ 9.65 (s, 1H); 2.22 (s, 2H); 2.12 (s, 2H); 1.43 (s, 4H). ^{13}C NMR 75 MHz, ($CDCl_3$) δ 203.3; 179.4; 43.6; 33.9; 24.3; 21.6. IR υ (cm^{-1}) (KBr): 3446; 2948; 1722; 1411. Anal. Calcd for $C_6H_{10}O_3$: C, 55.37; H, 7.74; O, 36.88. Found: C, 55.25; H, 7.71; O, 36.81.

4.3. (3*R*,9a*RS*)-Hexahydro-3-phenyloxazolo[3,2-*a*]azepin-5(6*H*)-one 2 (procedure B)

To a solution of 6-oxohexanoic acid **1** (1.00 g, 7.68 mmol) in dry CH_2Cl_2 (50 mL) at 0 °C was added triethylamine (2.16 mL, 15.5 mmol). Then, 2-fluoro-1-ethylpyridinium tetrafluoroborate salt (FEP) (1.80 g, 8.45 mmol) was slowly added. The mixture was stirred for 20 min at 0 °C after which (*R*)-phenylglycinol (1.05 g, 7.68 mmol) was added, and the resulting solution was stirred for 45 min at the same temperature. Water (50 mL) was added, and the organic phase was extracted twice with CH_2Cl_2 (50 mL). After drying over $MgSO_4$, the combined organic layers were removed under vacuum. The desired oxazoloazepinone **2** was obtained in 80% de (measured by ^{1}H NMR and GC analyses of the crude product). Flash chromatography (AcOEt/cyclohexane 1/1) allowed us to isolate the pure (3*R*,9a*S*)-**2** and a (3*R*,9a*R*)-enriched mixture of both diastereomers in 60% yield (1.07 g). (3*R*,9a*S*)-**2**: white solid (mp: 132–133 °C). ^{1}H NMR 300 MHz, ($CDCl_3$) δ 7.30–7.19 (H_{Ar}, 5H, m); 5.15 (H-3, 1H, d, J = 5.3 Hz); 5.08 (H-9a, 1H, d, J = 9.6 Hz); 4.11–4.00 (H-2, 2H, m); 2.58 (H-6, 1H, dd, J = 14.9, 7.2 Hz); 2.30–2.19 (H-6′ + H9, 2H, m); 1.99–1.95 (H-8, 1H, m); 1.86–1.80 (H-7, 1H, m); 1.68–1.48 (H-9′ + H-8′ + H-7′, 3H, m). ^{13}C NMR 75 MHz, ($CDCl_3$) δ 171.7 (C-5); 141.1 (Cq_{Ar}); 128.5; 127.4; 126.7 (CH_{Ar}); 90.9 (C-9a); 72.7 (C-2); 60.0 (C-3); 38.7 (C-6); 34.7 (C-9); 26.6 (C-8); 23.3 (C-7). IR υ (cm^{-1}) (KBr): 3440; 2932; 2861; 1644; 1422. Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06; O, 13.83. Found: C, 72.57; H, 4.31; N, 6.19. $[\alpha]_D^{20} = -59.1$ (c 1.15, CH_2Cl_2). (3*R*,9a*R*)-**2**: ^{1}H

NMR (300 MHz, $CDCl_3$) δ [(3*R*,9a*R*)/(3*R*,9a*S*) mixture : 65/35] 7.30–7.11 (H_{Ar}, 5H, m); 5.36 (H-9a, 1H, d, J = 9.6 Hz); 5.11–5.06 (H-3, 1H, m); 4.24 (H-2, 1H, dd, J = 8.6, 6.2 Hz); 3.79 (H-2, 1H, dd, J = 8.8, 3.0 Hz); 2.42 (H-6, 1H, dd, J = 14.1, 7.2 Hz); 2.29–2.18 (H-6, 1H, m); 1.98–1.45 (H-7 to H-9, 6H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ [(3*R*,9a*R*)/(3*R*,9a*S*) mixture : 65/35] 170.8 (C-5); 140.7 (Cq_{Ar}); 128.6 ; 127.5 ; 126.3 (CH_{Ar}); 91.0 (C-9a); 72.4 (C-2); 60.2 (C-3); 38.5 (C-6); 34.7 (C-9); 26.2 (C-8); 23.1 (C-7).

4.4. (3*S*,9a*RS*)-Hexahydro-3-*tert*-butyloxazolo[3,2-*a*]azepin-5(6*H*)-one 3

The title compound was prepared according to procedure **B** from 6-oxohexanoic acid **1** (185 mg, 1.42 mmol), triethylamine (0.4 mL, 2.84 mmol), 2-fluoro-1-ethylpyridinium tetrafluoroborate salt (FEP) (333 mg, 1.56 mmol), and (*S*)-*tert*-leucinol (166 mg, 1.42 mmol). The desired oxazoloazepinone **3** was obtained in 81% de (measured by ^{1}H NMR and GC analyses of the crude product). Flash chromatography (cyclohexane/ethyl acetate 1/1) of the residue provided compound **3** (134 mg, 45%) as an inseparable mixture of diastereomers (3*R*,9a*S*)-**3** and (3*R*,9a*R*)-**3** in an 87/13 ratio. (3*R*,9a*S*)-**3** [chemical shift data of (3*R*,9a*R*)-**3** appear in square brakets]: ^{1}H NMR 300 MHz, ($CDCl_3$) δ [5.10 (H-9a, 1H, m)]; 4.87 (H-9a, 1H, m); [4.20-4.18 (H-3, 1H, m)]; 4.00–3.95 (H-2, 2H, m); [3.85–3.81 (H-2, 2H, m)]; 3.57 (H-3, 1H, dd, J = 9.0, 6.2 Hz); 2.60 (H-6, 1H, dd, J = 15.8, 7.3 Hz); 2.56-1.40 (H-6 to H9 + [H-6 to H9], 7H + [8H], m); 0.95–0.80 (CH_3 + [CH_3], 9H + [9H], *s*). ^{13}C NMR 75 MHz, ($CDCl_3$) δ 175.0, [173.4] (C-5); 91.5, [91.2] (C-9a); 67.5, [66.2] (C-2); 64.6, [63.8] (C-3); 39.5, [38.7] (C-6); [36.4], 35.5 (C-*t*Bu); 34.2, [30.0] (C-9); 27.6, [27.4] (CH_3); 27.2, [25.9], 23.9, [23.3] (C-7 and C-8). CI-MS *m/z* 212 ($M+H^+$). HR-MS calcd for $C_{12}H_{21}NO_2$ $(MH)^+$ *m/z* 212.1634, found: 212.1650.

4.5. (3*S*,9a*R*)-Hexahydro-3-*iso*-propyloxazolo[3,2-*a*]azepin-5(6*H*)-one 4

The title compound was prepared according to procedure **B** from 6-oxohexanoic acid **1** (446 mg, 3.42 mmol), triethylamine (1.0 mL, 6.84 mmol), 2-fluoro-1-ethylpyridinium tetrafluoroborate salt (FEP) (803 mg, 3.77 mmol), and (*S*)-valinol (353 mg, 3.42 mmol). The desired oxazoloazepinone **4** was obtained in up to 95% de (measured by ^{1}H NMR and GC analyses of the crude product). Flash chromatography (cyclohexane/ethyl acetate 1/1) of the residue provided compound **4** (205 mg, 31%) as a colorless oil. ^{1}H NMR 300 MHz ($CDCl_3$) δ 5.90 (H-9a, 1H, d, J = 8.3 Hz); 3.96–3.88 (H-2, 2H, m); 3.63 (H-3, 1H, dd, J = 8.9, 6.0 Hz); 2.54 (H-6, 1H, dd, J = 15.2, 7.5 Hz); 2.24–1.77 (5H, m); 1.51–1.45 (3H, m); 0.87 (CH_3, 3H, d, J = 5.3 Hz); 0.85 (CH_3, 3H, d, J = 5.3 Hz). ^{13}C NMR 75 MHz, ($CDCl_3$) δ 172.9 (C-5); 90.7 (C-9a); 67.8 (C-2); 62.2 (C-3); 39.1 (C-6); 35.1 (C-9); 30.9 (C-10); 27.0 (C-8); 23.7 (C-7); 19.8, 18.9 (CH_3). EI-MS *m/z* 197; 154; 114; 95; 67. HR-MS calcd for $C_{11}H_{19}NO_2$ $(MH)^+$ *m/z* 197.1416, found: 197.1414.

4.6. (3*R*,6*R*,9a*S*)- and (3*R*,6*S*,9a*S*)-6-methyl-3-phenyl-2,3,6,7,8,9-hexahydrooxazolo[3,2-*a*]azepin-5(9a*H*)-one 5

4.6.1. General procedure C for the alkylation of oxazoloazepinone (3*R*,9a*S*)-2

To a precooled (−78 °C) solution of oxazoloazepinone (3*R*,9a*S*)-**2** (1 equiv, 0.2 mmol) in THF (5 mL), LiHMDS (1 M in THF, 1.5 equiv) was added dropwise. After stirring the solution at −78 °C for 1 h, methyl iodide (43 μL, 0.687 mmol) was added, and stirring was continued until complete consumption of the starting lactam. The reaction mixture was quenched by the addition of brine (10 mL), and the resulting mixture was extracted with ethyl acetate (2 × 10 mL). The combined organic extracts were dried over $MgSO_4$, and concentrated to afford the crude product. The diastereomeric excess was measured by ^{1}H NMR and GC analyses (de = 60%). Both diastereomers were separated by flash chromatography on silica gel (AcOEt/cyclohexane 20/80) in 73% yield (41 mg). Under these chromatographic conditions, the minor diastereoisomer was eluted before the major diastereomer. Compound **5** (major diasteromer): white solid (mp: 74–76 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39–7.23 (H_{Ar}, 5H, m); 5.30–5.17 (H-3 + H-9a, 2H, m); 4.14–4.05 (H-2, 2H, m); 2.95–2.86 (H-6, 1H, m); 2.65–2.32 (H-9, 1H, m); 1.82–1.69 (H-7 + H-8 + H-9, 5H, m); 1.27 (CH_3, 3H, d, J = 7.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2 (C-5); 142.0 (Cq_{Ar}); 128.8; 127.7; 127.0 (CH_{Ar}); 89.9 (C-9a); 72.9 (C-2); 61.4 (C-3); 42.4 (C-6); 35.1 (C-9); 29.7 (C-7); 19.5 (C-8); 14.5 (CH_3). EI-MS *m/z* 245; 148; 120; 119; 117; 104; 91; 77; 69; 55; 41. IR ν (cm^{-1}) (KBr) 3030; 2919; 1634; 1497; 1461; 1423; 1386; 1092; 711. HR-MS calcd for $C_{15}H_{20}NO_2$ $(MH)^+$ *m/z* 246.1494, found: 246.1511. $[\alpha]_D^{20} = -22.6$ (*c* 1.15, $CHCl_3$). Compound **5** (minor diasteromer): glassy solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42–7.24 (H_{Ar}, 5H, m); 5.22–5.20 (H-3 + H-9a, 2H, m); 4.18–4.08 (H-2, 2H, m); 2.34–2.17 (H-6 + H-9, 2H, m); 2.03–1.97 (H-8, 1H, m); 1.80–1.48 (H-7 + H-8 + H-9, 4H, m); 1.15 (CH_3, 3H, d, J = 6.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9 (C-5); 141.6 (Cq_{Ar}); 128.9; 127.8; 127.2 (CH_{Ar}); 90.8 (C-9a); 72.7 (C-2); 60.7 (C-3); 41.0 (C-6); 35.0 (C-9); 32.5 (C-7); 26.8 (C-8); 18.3 (CH_3). HR-MS calcd for $C_{15}H_{20}NO_2$ $(MH)^+$ *m/z* 246.1494, found: 246.1487. $[\alpha]_D^{20} = -60.0$ (*c* 0.2, $CHCl_3$).

4.7. (3*R*,6*R*,9a*S*)- and (3*R*,6*S*,9a*S*)-6-benzyl-3-phenyl-2,3,6,7,8,9-hexahydrooxazolo[3,2-*a*]azepin-5(9a*H*)-one 6

According to general procedure **C** from oxazoloazepinone (3*R*,9a*S*)-**2** (49 mg, 0.21 mmol), LiHMDS (0.318 mL, 0.318 mmol) and benzyl bromide (66 μL, 0.687 mmol) furnish **6** The diastereoisomeric excess (de = 62%) was measured by ^{1}H NMR and GC analyses from the crude product. Flash chromatography (AcOEt/cyclohexane 10/90) furnished a mixture of diastereomers in a 84/16 ratio (44 mg, 65%). Compound **6** (84/16 diastereoisomeric ratio): ^{1}H NMR (300 MHz, $CDCl_3$) [chemical shift data of the minor diastereomer appear in square brakets] δ 7.36–7.11 (H_{Ar} and [H_{Ar}], 20H, m); 5.23–5.01 (H-3 + H-9a and [H-3 + H-9a], 4H, m); 4.05–3.99 (H-2 and [H-2], 4H, m); [3.28–3.24 (H-6, 1H, m)]; 3.05–1.31 (other H and [other H], 17H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ [173.1], 174.2 (C-5); 141.9, [141.4], [140.9], 139.0 (Cq_{Ar}); [129.8], 129.3, 129.0, [128.9], 128.8, [128.7], [127.9], 127.8, [127.2], 127.1, 126.9, [126.5] (CH_{Ar}); [90.8], 89.9 (C-9a); 72.9, [72.8] (C-2); 61.6, [60.7] (C-3); 49.8, [48.1] (C-6); [37.7], [34.9], 34.9, 34.6 (CH_2-benzyl + C-9); [28.8], 25.8 (C-7); [26.9], 19.7 (C-8); 14,5 (CH_3). IR ν (cm^{-1}) (neat) 3438; 2932; 2866; 1638; 1495; 1453; 751; 714; 699. HR-MS calcd for $C_{21}H_{24}NO_2$ $(MH)^+$ *m/z* 322.1807, found: 322.1816.

4.8. (3*R*,6*R*,9a*S*)- and (3*R*,6*S*,9a*S*)-6-allyl-3-phenyl-2,3,6,7,8,9-hexahydrooxazolo[3,2-*a*]azepin-5(9a*H*)-one 7

According to general procedure **C** from oxazoloazepinone (3*R*,9a*S*)-**2** (50 mg, 0.22 mmol), LiHMDS (0.324 mL, 0.324 mmol) and allyl bromide (47 μL, 0.543 mmol) afforded **7**. The diastereomeric excess (de = 27%) was measured by ^{1}H NMR and GC analyses from the crude product. Flash chromatography (AcOEt/cyclohexane 30/70) allowed us to isolate the pure major diastereomer and a minor-enriched mixture of both diastereomers in 86% (51 mg). The major diastereomer was eluted before the minor diastereomer. Compound **7** (major diastereomer): colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36–7.18 (H_{Ar}, 5H, m); 5.82–5.70 (CH_{allyl}, 1H, m); 5.17–5.14 (H-3 + H-9a, 2H, m); 5.01–4.96 (CH_{2allyl}, 2H, m); 4.11–4.01 (H-2, 2H, m); 2.61–2.53 (CH_2, 1H, m); 2.19–2.10 (H-

7 + H-6, 2H, m); 2.04–1.93 (CH_2, 1H, m); 1.77–1.71 (H-8, 1H, m); 1.68–1.57 (H-7′ + H-9, 3H, m); 1.37–1.25 (H-8′, 1H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0 (C-5); 141.4 (Cq_{Ar}); 137.4 (CH_{allyl}); 128.9; 127.8; 127.2 (CH_{Ar}); 117.0 (CH_{2allyl}); 90.8 (C-9a); 72.8 (C-2); 60.6 (C-3); 46.0 (C-6); 36.3 (CH_2); 35.0 (C-7); 29.3 (C-8); 26.9 (C-9). IC-MS *m/z* 272.0. IR ν (cm^{-1}) (neat) 3392; 2927; 2860; 1647;1455; 1418; 1091; 713. HR-MS calcd for $C_{17}H_{22}NO_2$ $(MH)^+$ *m/z* 272.1650, found: 246.1647. $[\alpha]_D^{20} = -70.0$ (*c* 0.3, $CHCl_3$). Compound **7** (minor diastereomer): ^{1}H NMR (300 MHz, $CDCl_3$) δ (major/minor mixture : *56/44*) 7.30–7.00 (H_{Ar}, 5H, m); 5.70–5.50 (CH_{allyl}, 1H, m); 5.10–4.80 (H-3 + H-9a + CH_{2allyl}, 4H, m); 4.00–3.80 (H-2, 2H, m); 2.05–1.00 (H-6 to H-9 + CH_2, 9H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9 (C-5); 141.9 (Cq_{Ar}); 135.7 (CH_{allyl}); 128.8; 127.7; 127.0 (CH_{Ar}); 117.4 (CH_{2allyl}); 89.8 (C-9a); 72.9 (C-2); 61.5 (C-3); 47.8 (C-6); 34.9 (CH_2); 32.8 (C-7); 26.7 (C-9); 19.5 (C-8). IC-MS *m/z* 272.0. IR ν (cm^{-1}) (neat) 3464; 3066; 3031; 2954; 2862; 1645; 1491; 1448; 1419; 715.

4.9. (3*R*,6*R*,9a*S*)- or (3*R*,6*S*,9a*S*)-6-(hydroxydiphenylmethyl)-3-phenyl-2,3,6,7,8,9-hexahydro-oxazolo[3,2-*a*]azepin-5(9a*H*)-one 8

According to general procedure **C** from oxazoloazepinone (3*R*,9a*S*)-**2** (52 mg, 0.23 mmol), LiHMDS (0.337 mL, 0.337 mmol) and benzophenone (103 mg, 0.563 mmol) afforded **8** (54 mg, 60%) as a single diastereoisomer after flash chromatography (CH_2Cl_2/cyclohexane from 40/60 to 90/10). Pale yellow solid (mp: 174–176 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39–7.37 (H_{Ar}, 2H, m); 7.25–7.01 (H_{Ar}, 13H, m); 5.77 (OH, 1H, br s); 4.89–5.83 (H-3 + H-9a, 2H, m); 3.89–3.86 (H-2, 2H, m); 3.43–3.39 (H-6, 1H, m); 2.29–2.21 (H-9, 1H, m); 2.15–2.04 (H-9′, 1H, m); 1.80–1.71 (H-8 + H-7, 3H, m); 1.40–1.34 (H-8′, 1H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9 (C-5); 146.0, 144.8, 141.8 (Cq_{Ar}); 128.9, 128.3, 127.8, 127.5, 127.4, 127.3, 126.6 (CH_{Ar}); 89.8 (C-9a); 81.3 (C_q); 73.2 (C-2); 61.4 (C-3); 53.7 (C-6); 30.5 (C-9); 24.0, 21.8 (C-7 and C-8). CI-MS *m/z* 414.0. IR ν (cm^{-1}) (neat) 3336; 3029; 2953; 2869; 1617; 1493; 1448; 756; 701. HR-MS calcd for $C_{27}H_{28}NO_3$ $(MH)^+$ *m/z* 414.2069, found: 414.2083. $[\alpha]_D^{20} = -37.5$ (*c* 1.0, $CHCl_3$).

4.10. (3*R*,6*R*,9a*S*)- or (3*R*,6*S*,9a*S*)-6-azido-3-phenyl-2,3,6,7,8,9-hexahydro-oxazolo[3,2-*a*]azepin-5(9a*H*)-one 9

According to general procedure **C** from oxazoloazepinone (3*R*,9a*S*)-**2** (50 mg, 0.22 mmol), LiHMDS (0.324 mL, 0.324 mmol) and trisyl azide (100 mg, 0.324 mol) provided **9** as a single diastereomer along with some residual trisyl azide derivatives which are unseparable by flash chromatography (AcOEt/cyclohexane 5/95 to 30/70) **8** : ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32–7.18 (H_{Ar}, 5H, m); 5.3 (H-9a, 1H, d, *J* = 9.4 Hz); 5.06 (H-3, 1H, d, *J* = 4.7 Hz); 4.31 (H-6, 1H, d, *J* = 6.4 Hz); 4.13–4.00 (H-2, 2H, m); 2.30–1.60 (H-7 and/or H-8 and/or H-9, 4H, m); 1.21–1.16 (H-7 and/or H-8 and/or H-9, 2H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7 (C-5); 140.8 (Cq_{Ar}); 128.6, 127.7, 126.9 (CH_{Ar}); 89.4 (C-9a); 72.6 (C-2); 66.7 (C-6); 60.9 (C-3); 34.4, 28.0, 18.8 (C-7, C-8 and C-9). ESI-MS *m/z* 273.4 (MH^+). IR ν (cm^{-1}) (neat) 2098; 1652.

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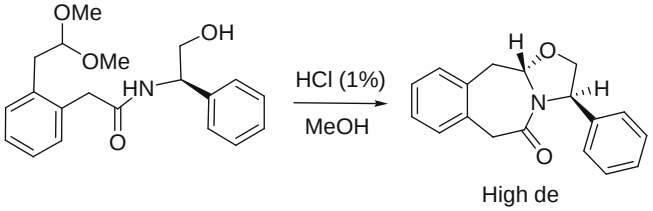

12. The (*S*)-configuration at the new N,O-acetal stereocenter, obtained from (*R*)-phenylglycinol, is in accordance with the diastereoselection observed during the formation of 5,5-, 6,5- and 7,5-fused bicyclic lactams, see Refs. 5, 6, 8, 9 This is also coherent with the diastereoselection observed during the formation of oxazolo[3]benzoazepinone by lactamization of ω-amido acetals under mild acidic conditions, see Ref. 11.
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