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Transformation of *trans*-4-Aryl-3-chloro-1-(2-chloroethyl)azetidin-2-ones into 3-Aryl-2-(ethylamino)propan-1-ols via Intermediate 1-(1-Aryl-2-chloro-3-hydroxypropyl)aziridines and *trans*-2-Aryl-3-(hydroxymethyl)aziridines

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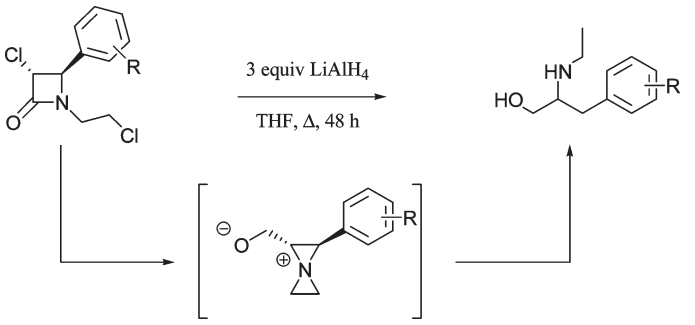
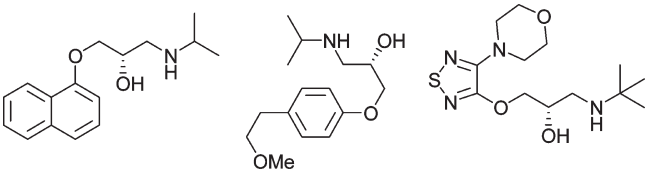


trans-4-Aryl-3-chloro-1-(2-chloroethyl)azetidin-2-ones, prepared through cyclocondensation of chloroketene and the appropriate imines in a diastereoselective way, were unexpectedly transformed into 3-aryl-2-(ethylamino)propan-1-ols using $LiAlH_4$ in THF under reflux. A stepwise analysis showed that the initially formed 1-(1-aryl-2-chloro-3-hydroxypropyl)aziridines were converted into *trans*-2-aryl-3-(hydroxymethyl)aziridines, most probably *via N*-spiro bis-aziridinium intermediates, which were subsequently prone to undergo ring opening by $LiAlH_4$ to afford 3-aryl-2-(ethylamino)propan-1-ols.

Introduction

The synthesis of β-amino alcohols merits considerable attention since these compounds play an important role in synthetic organic chemistry, for example, as auxiliaries and ligands in asymmetric synthesis.[1] The two heteroatoms allow great flexibility, as one or both can be bound to a Lewis acid, transition metal, or achiral starting material.[1] In addition, a variety of β-amino alcohols exhibits various pharmacological properties, and the β-amino alcohol moiety is present as a key structural unit in different biologically active compounds. For example, the β-blockers propranolol **1**, metoprolol **2**, and timolol **3** are used for treating abnormal heart rhythm, high blood pressure, heart failure, and angina.[2]



1 **2** **3**

Apart from their relevance as potential β-lactam antibiotics,[3] azetidin-2-ones have also been recognized as valuable and flexible synthons for further elaboration toward a large variety of nitrogen-containing compounds ("β-lactam synthon method").[4] In particular, azetidin-2-ones bearing

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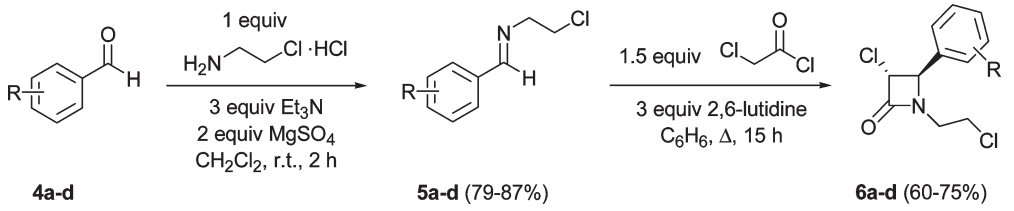
SCHEME 1



halogenated side chains are very useful starting materials for rearrangements as a result of their high intrinsic reactivity, which is based on the combination of a strained four-membered ring, a nucleophilic nitrogen (after elaboration), and a halogenated carbon atom. In that respect, intensive research on the synthetic applicability of the mainly unexplored class of 4-(haloalkyl)azetidin-2-ones has resulted in the efficient and diastereoselective preparation of a broad variety of functionalized azaheterocycles, including aziridines, azetidines, piperidines, pyrrolidines, azepanes, pyrrolidin-2-ones, oxolanes, bicyclic β-lactams, and bicyclic γ-lactams.[5]

One of the most straightforward transformations of β-lactams comprises their reductive ring opening toward γ-amino alcohols.[6] The presence of halogenated carbon atoms in these substrates is of synthetic relevance, as this can lead to further rearrangements toward azaheterocyclic compounds. In previous work, we have demonstrated the applicability of halogen-containing β-lactams for the construction of stereodefined aziridines upon treatment with $LiAlH_4$, e.g., the conversion of *N*-(2-chloroethyl)azetidin-2-ones into 1-(3-hydroxypropyl)-aziridines[6e] and the reductive ring contraction of 3-chloro-β-lactams into 3-(hydroxymethyl)aziridines.[6g] However, up to now, the reactivity of halogenated β-lactams bearing a halogenated side chain toward $LiAlH_4$ has not been explored.

TABLE 1. Synthesis of *N*-(Arylmethylidene)-(2-chloroethyl)amines 5 and *trans*-4-Aryl-3-chloro-1-(2-chloroethyl)-β-lactams 6

entry	R	compound **5** (yield)	compound **6** (yield)[a]	*cis*/*trans* (**6**)[b]
1	4-Me	**5a** (79%)	**6a** (75%)	3/97
2	H	**5b** (87%)	**6b** (60%)	3/97
3	4-Cl	**5c** (79%)	**6c** (69%)	5/95
4	3-OMe	**5d** (84%)	**6d** (66%)	5/95

[a]After purification by column chromatography (SiO_2). [b]Based on ^1H NMR analysis of the reaction mixture.

SCHEME 2

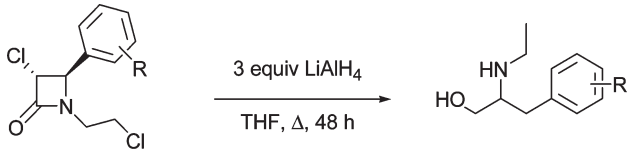


TABLE 2. Transformation of *trans*-4-Aryl-3-chloro-1-(2-chloroethyl)-β-lactams 6 into 3-Aryl-2-(ethylamino)propan-1-ols 7

entry	R	compound (yield)[a]
1	4-Me	**7a** (61%)
2	H	**7b** (70%)
3	4-Cl	**7c** (65%)
4	3-OMe	**7d** (68%)

[a]After recrystallization from hexane/EtOAc (1/30).

In this paper, the applicability of *trans*-4-aryl-3-chloro-1-(2-chloroethyl)azetidin-2-ones regarding their treatment with lithium aluminum hydride was evaluated for the first time. The chemistry of 3-chloro-β-lactams comprises a mainly unexplored field in the literature, although these compounds are very useful substrates for further elaboration due to their unique synthetic properties, e.g., dehalogenation toward 3-unsubstituted azetidinones[7] and conversion into different 3-substituted azetidines.[8] In addition, the use of *N*-(ω-haloalkyl)-β-lactams has been studied to a very limited extent, for example, toward the synthesis of 1,4-diazepan-5-ones,[9] bicyclic β-lactams,[5a,10] and aziridines.[6e] In this work, both structural features were combined into a new type of substrate, i.e., 3-chloro-1-(2-chloroethyl)-β-lactams, which were unexpectedly transformed into 2-(ethylamino)propan-1-ols upon treatment with $LiAlH_4$ in THF under reflux through a number of rearrangements.

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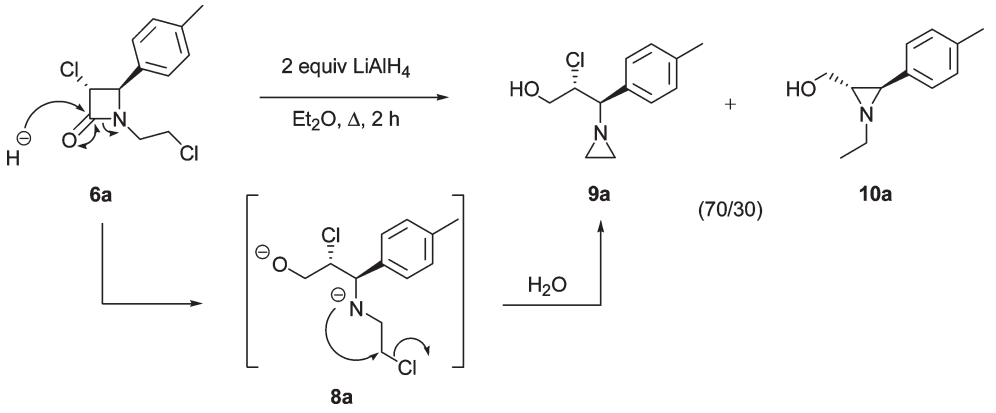
SCHEME 3



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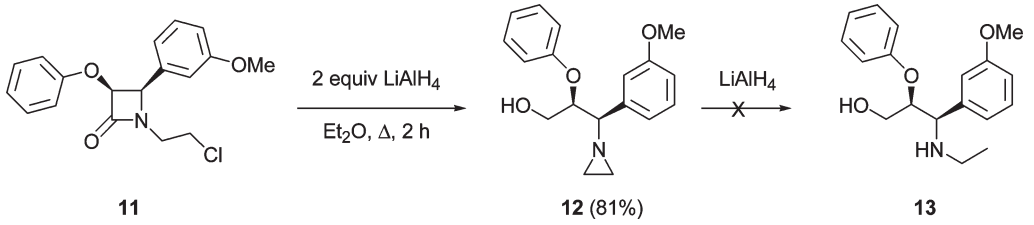

Results and Discussion

The synthesis of *trans*-4-aryl-3-chloro-1-(2-chloroethyl)-β-lactams, in which the two halogen atoms reside in both cases in the β-position with respect to the nitrogen atom, was accomplished by Staudinger's ketene−imine cycloaddition reaction. Thus, treatment of *N*-(arylmethylidene)-(2-chloroethyl)amines **5**, prepared via imination of different benzaldehydes **4** in dichloromethane in the presence of $MgSO_4$ and Et_3N utilizing 1 equiv of 2-chloroethylamine hydrochloride, with 1.5 equiv of chloroacetyl chloride and 3 equiv of 2,6-lutidine in benzene gave the premised *trans*-4-aryl-3-chloro-1-(2-chloroethyl)-β-lactams **6** (Scheme 1, Table 1).

In accordance with previous results on β-lactam synthesis,[6g,8] the latter β-lactams **6** were obtained stereoselectively (*cis*/*trans* 3−5/95−97) after a reflux period of 15 h, and separation of both isomers was performed by means of column chromatography on silica gel. The *trans*-selectivity could be deduced on the basis of the ^{1}H NMR spectra of β-lactams **6**, as the observed coupling constants between the 3-H and 4-H protons varied between 1.1 and 2.0 Hz ($CDCl_3$), which corresponds well with those reported in the literature for *trans*-β-lactams.[11] It should be noted that dichlorinated β-lactams **6** represent a novel class of substrates suitable for further elaborations.

The stereochemical outcome of this Staudinger reaction can be rationalized as follows. It is well-known that the specific ketene substituent plays an important role in the diastereoselectivity of the Staudinger reaction. When the ketene, *in situ* generated from an acid chloride in the presence of a base, is substituted with a chloro atom (Moore ketene), *E*/*Z*-isomerization across the iminium bond of the zwitterionic intermediates followed by conrotatory ring closure will mostly afford the thermodynamically more stable *trans*-β-lactams, while the use of e.g. Bose-Evans ketenes (alkoxy ketenes) generally results in the diaseteroselective formation of *cis*-β-lactams.[12]

TABLE 3. Treatment of 1-[3-Hydroxy-1-(3-methoxyphenyl)-2-phenoxy]-aziridine 12 with $LiAlH_4$

entry	molar equiv $LiAlH_4$	solvent	temp	time (h)	result
1	2	THF or Et_2O	rt	48	no reaction
2	4	THF or Et_2O	reflux	48	no reaction

In previous work, the reductive ring opening of azetidin-2-ones by means of $LiAlH_4$ has been described as an efficient approach toward β- and γ-aminoalcohols.[6] In analogy, *trans*-4-aryl-3-chloro-1-(2-chloroethyl)-β-lactams **6** were treated with 3 molar equiv of $LiAlH_4$ in THF under reflux for 48 h, resulting in full conversion of the starting material. Spectroscopic analysis of the obtained reaction products revealed their molecular structure to be 3-aryl-2-(ethylamino)propan-1-ols **7**, quite unexpectedly (Scheme 2, Table 2). It should be noted that although this class of β-amino alcohols is known in the literature,[13] the above-described methodology for the selective preparation of these amino alcohols **7** is totally different from the synthesis reported in the literature.[13]

In order to elucidate the mechanistic background of this intriguing transformation, β-lactam **6a** was subjected to different reaction conditions, involving variation of the reaction time, solvent, and number of molar equivalents of $LiAlH_4$. First, *trans*-3-chloro-1-(2-chloroethyl)-4-(4-methylphenyl)-β-lactam **6a** was treated with 2 molar equiv of lithium aluminum

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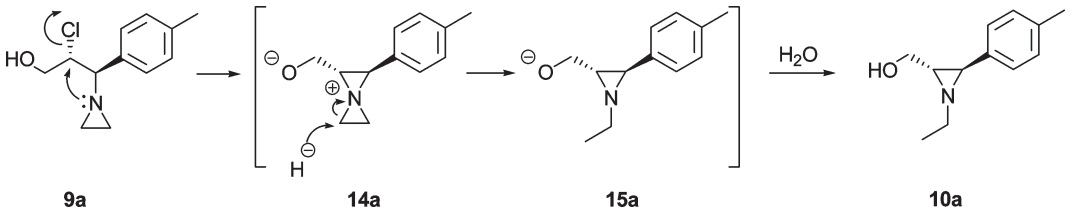
SCHEME 5



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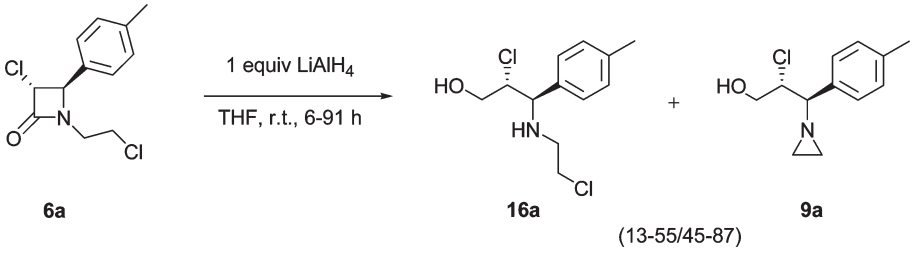

hydride in diethyl ether under reflux for 2 h.[6e] This process resulted in 1,2-fission of the amide bond, followed by intramolecular displacement of the chloride at the primary carbon atom by the nucleophilic nitrogen, giving rise to the initially expected 1-[2-chloro-3-hydroxy-1-(4-methylphenyl)]aziridine **9a**. Interestingly, next to the latter aziridine **9a**, a substantial amount of *trans*-1-ethyl-3-hydroxymethyl-2-(4-methylphenyl)-aziridine **10a** was observed in the crude reaction mixture as well (Scheme 3, ratio **9a**/**10a** = 70/30).[6g]

The unexpected formation of *N*-ethylaziridine **10a** can be rationalized in two ways. In a first approach, the nucleophilic nitrogen in intermediate **8a**, formed after cleavage of the amide bond of β-lactam **6a**, displaces the chloride at the secondary carbon atom to afford aziridine **10a** in a direct way (followed by reductive removal of the chloro atom to furnish the *N*-ethyl group). Since a primary electrophilic carbon atom is more likely to be attacked than a secondary, this competition could not explain the observed ratio (70/30). Alternatively, the presence of the latter aziridine **10a** can be explained by a possible ring transformation of aziridine **9a**. Considering the *in situ* activation of the aziridine moiety by the Lewis acid character of aluminum, aziridine **10a** can be formed either by hydride-induced aziridine ring opening followed by intramolecular substitution of the chloro atom or by initial formation of a *N*-spiro bis-aziridinium intermediate, which is subsequently prone to undergo ring opening by hydride.

In order to shed light on the underlying mechanism, *cis*-1-(2-chloroethyl)-4-(3-methoxyphenyl)-3-phenoxyazetidin-2-one **11**, prepared in 78% overall yield via imination followed by the Staudinger reaction, was transformed into 1-[3-hydroxy-1-(3-methoxyphenyl)-2-phenoxy]aziridine **12** upon treatment with 2 molar equiv of $LiAlH_4$ in diethyl ether under reflux.[6e] Treatment of the latter aziridine **12** with $LiAlH_4$ (2 or 4 molar equiv) did not result in any conversion, and the starting material was recovered completely after every attempt (Scheme 4, Table 3). Obviously, aziridine **12** is highly reluctant to undergo hydride-induced ring opening to furnish 3-(*N*-ethylamino)-3-(3-methoxyphenyl)-2-phenoxypropan-1-ol **13**, pointing to a reaction mechanism involving the formation and consecutive ring opening of *N*-spiro bis-aziridinium salt **14a** for the conversion of aziridine **9a** to aziridine **10a** (Scheme 5). It should be noted that although reaction mechanisms consistent with the formation of bicyclic aziridinium salts are well-known,[5a,14] the occurrence of 1-azoniaspiro[2.2]pentanes **14** as such has not been described before in the literature, apart from one paper in which the *N*-spiro bis-aziridinium ion is suggested to be a stable and isolable molecule on the basis of *ab initio* studies.[15] Nonetheless, an alternative reaction mechanism involving initial epoxide formation, followed by either *N*-spiro bis-aziridinium formation and consecutive hydride-induced ring opening, or hydride-promoted aziridine and epoxide ring opening in a concerted manner, should not be excluded.

TABLE 4. Reduction of *trans*-3-Chloro-1-(2-chloroethyl)-4-(4-methylphenyl)-β-lactam 6a in THF at Room Temperature

entry	molar equiv $LiAlH_4$	solvent	temp	time (h)	result
1	1	THF	rt	6	**16a**/**9a** = 55/45
2	1	THF	rt	19	**16a**/**9a** = 25/75
3	1	THF	rt	91	**16a**/**9a** = 13/87

TABLE 5. Transformation of *trans*-4-Aryl-3-chloro-1-(2-chloroethyl)-β-lactams 6a,b into 1-(1-Aryl-2-chloro-3-hydroxypropyl)aziridines 9a,b

entry	substrate	R	reaction conditions	compound (yield)[a]
1	**6a**	4-Me	1 molar equiv $LiAlH_4$, THF, rt, 91 h	**9a** (40%)
2	**6b**	H	1 molar equiv $LiAlH_4$, THF, rt, 91 h	**9b** (55%)

[a]After purification by column chromatography (SiO_2).

In order to prevent hydride-induced ring transformation of aziridine **9a** toward aziridine **10a**, milder reaction conditions were applied for the reduction of β-lactam **6a**. Thus, treatment of β-lactam **6a** with 1 molar equiv of $LiAlH_4$ in THF at room temperature for 6−91 h afforded a mixture of γ-aminoalcohol **16a** and aziridine **9a** in varying amounts

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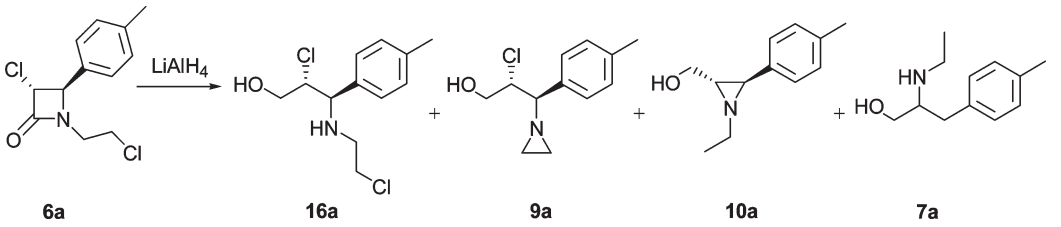
SCHEME 7



SCHEME 8

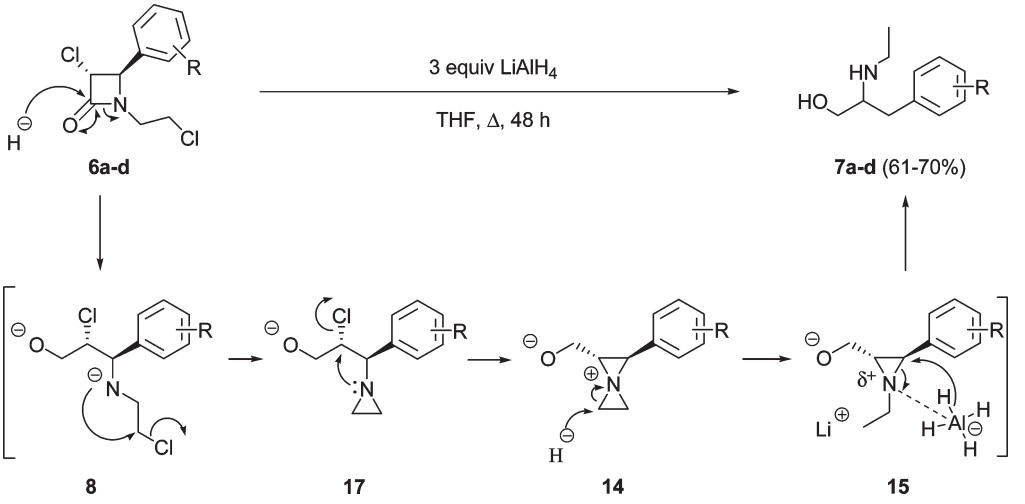


TABLE 6. Reduction of *trans*-3-Chloro-1-(2-chloroethyl)-4-(4-methylphenyl)-β-lactam 6a under Different Reaction Conditions

entry	molar equiv $LiAlH_4$	solvent	temp	time (h)	Result[a]	yield (%)
1	1	THF	reflux	2	**16a**/**9a**/**10a** = 45/45/10	80
2	2	THF	reflux	2	**9a**/**10a** = 72/28	85
3	2	THF	rt	18	**9a**/**10a** = 67/33	81
4	2	THF	rt	20	**9a**/**10a** = 62/38	82
5	2	THF	rt	100	**9a**/**10a** = 67/33	75
6	2	Et_2O	reflux	1	**9a**/**10a** = 73/27	68
7	2	Et_2O	reflux	2	**9a**/**10a** = 70/30	72
8	2	Et_2O	reflux	3	**9a**/**10a** = 62/38	87
9	2	Et_2O	reflux	4	**9a**/**10a**/**7a** = 48/33/19	83
10	2	THF	reflux	7	**10a**/**7a** = 50/50	65
11	3	Et_2O	reflux	1	**9a**/**10a** = 71/29	69
12	3	Et_2O	reflux	5	**9a**/**10a**/**7a** = 58/22/20	79
13	3	Et_2O	reflux	20	**10a**/**7a** = 25/75	82
14	3	THF	reflux	48	**7a**	82
15	4	THF	reflux	1	**10a**/**7a** = 58/42	73

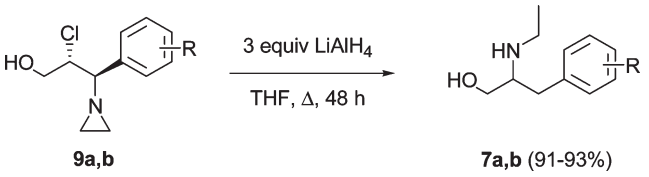
[a]Based on ^1H NMR analysis of the reaction mixtures

(Scheme 6, Table 4). From a mechanistic point of view, these results can be rationalized considering the conversion of β-lactam **6a** into aziridine **9a** via intermediate γ-aminoalcohol **16a**, as mentioned before. In this way, 1-(1-aryl-2-chloro-3-hydroxypropyl)aziridines **9a,b** were isolated in pure form and in good yields after purification by column chromatography on silica gel (Table 5). Interestingly, all four hydrogen atoms of aziridines **9a,b** were observed as separate doublets of doublets with characteristic aziridine chemical shifts (1.05−2.20 ppm, $CDCl_3$). Also, spectroscopic analysis by ^{13}C NMR revealed different δ-values for the two aziridine carbon atoms (25.22−25.28 ppm and 31.62−31.64 ppm, $CDCl_3$). These findings are in accordance with analogous results reported in the literature for C-unsubstituted aziridines.[6e,16]

In the next stage, different attempts were made to tune the reaction selectivity toward aziridine **10a** starting from β-lactam **6a** upon treatment with $LiAlH_4$ (Scheme 7, Table 6). From the presented results, it can be deduced that although complete conversion of aziridine **9a** into aziridine **10a** was achieved by establishing more forcing reaction conditions, the inherent reactivity of the intermediate 2-arylaziridine **10a** toward $LiAlH_4$ resulted in fast ring opening toward β-amino alcohol **7a** at higher temperatures. In this transformation, $LiAlH_4$ is responsible for both the activation of the aziridine ring, resulting in a considerable weakening of the C2−N bond due to benzylic stabilization of the developing carbenium ion,

(16) Kim, H. Y.; Talukdar, A.; Cushman, M. *Org. Lett.* **2006**, *8*, 1085.

SCHEME 9



9a,b **7a,b** (91-93%)

TABLE 7. Transformation of 1-(1-Aryl-2-chloro-3-hydroxypropyl)-aziridines 9a,b into 3-Aryl-2-(ethylamino)propan-1-ols 7a,b

entry	R	compound (yield)
1	4-Me	**7a** (91%)
2	H	**7b** (93%)

and for the delivery of the nucleophilic hydride, which subsequently induces ring opening in a regioselective manner.[6g] Moreover, an additional activation by an internal hydrogen bond between the hydroxyl group and the aziridine nitrogen atom facilitates the ring opening toward β-amino alcohol **7a**.[17]

These detailed experiments finally culminated in a straightforward and efficient synthesis of 3-aryl-2-(ethylamino)propan-1-ols **7** from *trans*-4-aryl-3-chloro-1-(2-chloroethyl)-β-lactams **6** upon treatment with 3 molar equiv of $LiAlH_4$ in THF under reflux for 48 h (Table 6, entry 14) through formation and subsequent conversion of intermediates **8**, **17**, **14**, and **15** (Scheme 8).

To provide additional evidence for this reaction mechanism, 3-aryl-2-(ethylamino)propan-1-ols **7a,b** were synthesized in excellent yields by reduction of 1-(1-aryl-2-chloro-3-hydroxypropyl)aziridines **9a,b** using 3 molar equiv of $LiAlH_4$ in THF under reflux for 48 h (Scheme 9, Table 7).

In conclusion, a number of 3-aryl-2-(ethylamino)propan-1-ols were synthesized in an efficient way by reduction of the corresponding *trans*-4-aryl-3-chloro-1-(2-chloroethyl)-β-lactams using $LiAlH_4$ in THF under reflux. This reaction proceeded through an unexpected conversion of the initially formed 1-(1-aryl-2-chloro-3-hydroxypropyl)aziridines into *trans*-2-aryl-1-ethyl-3-(hydroxymethyl)aziridines via *N*-spiro bis-aziridinium salts. The intermediacy of *N*-spiro bis-aziridinium salts was thus reported for the first time. Alternatively, reduction of the starting compounds by $LiAlH_4$ in THF at room temperature afforded 1-(1-aryl-2-chloro-3-hydroxypropyl)aziridines in good yields.

Experimental Section

Synthesis of *trans*-4-Aryl-3-chloro-1-(2-chloroethyl)azetidin-2-ones 6. As a representative example, the synthesis of *trans*-3-chloro-1-(2-chloroethyl)-4-(4-methylphenyl)azetidin-2-one **6a** is described here. To a solution of *N*-(4-methylphenylmethylidene)-(2-chloroethyl)amine **5a** (10 mmol) in dry benzene (50 mL) was added 2,6-lutidine (30 mmol, 3 equiv), and the resulting mixture was heated under reflux. Immediately thereafter, chloroacetyl chloride (15 mmol, 1.5 equiv) was added to the boiling mixture, followed by a reflux period of 15 h. Afterward, the resulting suspension was filtered in order to remove 2,6-lutidine hydrochloride, after which the filtrate was washed with an aqueous solution of 1 M HCl (2 × 15 mL). The organic phase was dried over $MgSO_4$, followed by removal of the drying agent and evaporation of the solvent in vacuo. Purification by means of column chromatography on silica gel (hexane/EtOAc 6/1) afforded pure *trans*-3-chloro-1-(2-chloroethyl)-4-(4-methylphenyl)azetidin-2-one **6a**.

(17) Lee, K.-D.; Suh, J.-M.; Park, J.-H.; Ha, H.-J.; Choi, H. G.; Park, C. S.; Chang, J. W.; Lee, W. K.; Dong, Y.; Yun, H. *Tetrahedron* **2001**, *57*, 8267.

***trans*-3-Chloro-1-(2-chloroethyl)-4-(4-methylphenyl)azetidin-2-one 6a.** (75%) Yellow oil. R_f = 0.10 (hexane/EtOAc 6/1). ^{1}H NMR ($CDCl_3$): δ 2.39 (3H, s); 3.20 (1H, ddd, J = 14.6, 7.4, 5.2 Hz); 3.51−3.68 (2H, m); 3.84 (1H, ddd, J = 14.6, 6.1, 5.2 Hz); 4.54 and 4.70 (2H, 2 × d, J = 1.6 Hz); 7.20−7.28 (4H, m). ^{13}C NMR ($CDCl_3$): δ 21.2 (CH_3); 41.3 (CH_2); 42.7 (CH_2); 63.3 (CH); 66.9 (CH); 126.7 (CH); 130.0 (CH); 131.6 (C); 139.8 (C); 164.1 (C). IR (cm^{-1}): $\nu_{C=O}$ = 1767. MS: m/z (%) 258/60/2 (M^+ + 1, 100). Anal. Calcd for $C_{12}H_{13}Cl_2NO$: C 55.83; H 5.08; N 5.43. Found: C 55.70; H 5.46; N 5.47.

Synthesis of 1-(1-Aryl-2-chloro-3-hydroxypropyl)aziridines 9. As a representative example, the synthesis of *anti*-1-[2-chloro-3-hydroxy-1-(4-methylphenyl)propyl]aziridine **9a** is described here. To an ice-cooled solution of *trans*-3-chloro-1-(2-chloroethyl)-4-(4-methylphenyl)azetidin-2-one **6a** (8 mmol) in THF (50 mL) was added $LiAlH_4$ (8 mmol, 1 molar equiv) in small portions. Subsequently, the resulting suspension was stirred at room temperature for 91 h, after which water (10 mL) was added cautiously at 0 °C in order to neutralize the excess of $LiAlH_4$. Afterward, the mixture was filtered through a pad of Celite, and the filtrate was dried over $MgSO_4$. Removal of the drying agent through filtration and evaporation of the solvent in vacuo afforded *anti*-1-[2-chloro-3-hydroxy-1-(4-methylphenyl)propyl]-aziridine **9a**, which was purified by column chromatography on silica gel (hexane/EtOAc 3/2).

***anti*-1-[2-Chloro-3-hydroxy-1-(4-methylphenyl)propyl]aziridine 9a.** (40%) White crystals. Mp = 68.7 °C. R_f = 0.06 (hexane/EtOAc 3/2). ^{1}H NMR ($CDCl_3$): δ 1.05 (1H, dd, J = 6.5, 4.4 Hz); 1.76 (1H, dd, J = 5.7, 4.1 Hz); 1.80 (1H, dd, J = 6.5, 4.1 Hz); 2.18 (1H, dd, J = 5.7, 4.4 Hz); 2.36 (3H, s); 3.00 (1H, d, J = 4.4 Hz); 3.77−3.84 (1H, m); 4.08 (1H, d, J = 12.7 Hz); 4.16−4.22 (2H, m); 7.18 and 7.28 (4H, 2 × d, J = 8.2 Hz). ^{13}C NMR ($CDCl_3$): δ 21.2 (CH_3); 25.2 (CH_2); 31.6 (CH_2); 63.8 (CH_2); 66.1 (CH); 76.9 (CH); 127.7 (CH); 129.2 (CH); 136.5 (C); 137.8 (C). IR (cm^{-1}): ν_{OH} = 3188. MS: m/z (%) 226/8 (M^+ + 1, 100). Anal. Calcd for $C_{12}H_{16}ClNO$: C 63.85; H 7.14; N 6.21. Found: C 63.62; H 7.54; N 6.41.

Synthesis of 3-aryl-2-(ethylamino)propan-1-ols 7. As a representative example, the synthesis of 2-(*N*-ethylamino)-3-(4-methylphenyl)propan-1-ol **7a** is described here. To an ice-cooled solution of *trans*-3-chloro-1-(2-chloroethyl)-4-(4-methylphenyl)azetidin-2-one **6a** (2 mmol) in THF (30 mL) was added $LiAlH_4$ (6 mmol, 3 molar equiv) in small portions. Subsequently, the resulting suspension was heated under reflux for 48 h, after which water (5 mL) was added cautiously at 0 °C in order to neutralize the excess of $LiAlH_4$. Afterward, the mixture was filtered through a pad of Celite, and the filtrate was dried over $MgSO_4$. Removal of the drying agent through filtration and evaporation of the solvent in vacuo afforded 2-(*N*-ethylamino)-3-(4-methylphenyl)propan-1-ol **7a**, which was purified by recrystallization from EtOAc/hexane (1/30).

2-(*N*-Ethylamino)-3-(4-methylphenyl)propan-1-ol 7a. (61%) White crystals. Mp = 102.3 °C. Recrystallization from EtOAc/hexane (1/30). ^{1}H NMR ($CDCl_3$): δ 1.05 (3H, t, J = 7.2 Hz); 1.80 (2H, s(broad)); 2.33 (3H, s); 2.59−2.78 (4H, m); 2.84−2.92 (1H, m); 3.29 and 3.60 (2H, 2 × dd, J = 10.5, 5.5, 3.9 Hz); 7.06 and 7.11 (4H, 2 × d, J = 8.0 Hz). ^{13}C NMR ($CDCl_3$): δ 15.6 (CH_3); 21.0 (CH_3); 37.7 (CH_2); 41.2 (CH_2); 60.0 (CH); 62.4 (CH_2); 129.0 (CH); 129.3 (CH); 135.5 (C); 135.9 (C). IR (cm^{-1}): $\nu_{OH,NH}$ = 3254. MS: m/z (%) 194 (M^+ + 1, 100). Anal. Calcd for $C_{12}H_{19}NO$: C 74.57; H 9.91; N 7.25. Found: C 74.24; H 10.26; N 7.09.

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Supporting Information Available: Spectral data of compounds **6b−d**, **9b**, and **7c,d** and ^{1}H NMR and ^{13}C NMR spectra of compounds **6a−d**, **9a,b**, and **7a,c,d**. This material is available free of charge via the Internet at http://pubs.acs.org.