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An Enantioselective Synthesis of 3,4-Benzo-5-oxacephams

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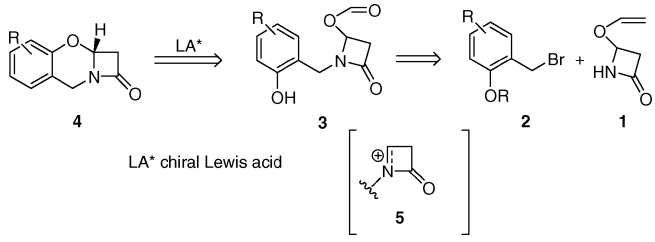
The title compounds represent an interesting group of β-lactam antibiotics and active inhibitors of β-lactamase enzymes. All these compounds have one structural feature in common, an alkoxy fragment located at C4 of the azetidin-2-one ring. The most common strategy for the synthesis of 4-alkoxyazetidinons involves intramolecular nucleophilic substitution at C4 that leads to ring closure. Such a displacement proceeds via the flat intermediate that supposedly has the structure of a mezomeric acyl ammonium cation. We herein report a novel and enantioselective, chiral Lewis acid mediated cyclization that affords the corresponding 5-oxacepham with excellent optical and chemical yields of up to 50 %. This may suggest that the high asymmetric induction is a result of a kinetic resolution of the initially formed racemic oxacepham. (© Wiley-VCH Verlag GmbH & Co. KGaA, 69451 Weinheim, Germany, 2009)

Introduction

The *N*-acyliminium ions are important intermediates in organic synthesis, especially in the context of the preparation of various nitrogen-containing natural products.[1] Such reactive intermediates can act as electron-deficient carbocations toward weak nucleophiles, which provides useful methodologies for both inter- and intramolecular carbon–carbon and carbon–heteroatom bond formation.[2] The *N*-acyliminium ions are typically generated in acidic media from lactams bearing a leaving group in the α-position to the nitrogen atom. Since the middle of the 1960s, cationic cyclization involving benzenoid, alkene or alkyne nucleophiles, and *N*-acyliminium ions has found a broad application in the synthesis of cyclic systems. However, in noticeable contrast to numerous examples of β-lactam synthesis,[3] there have only been a few examples reported of the use of nucleophiles other than carbon-based ones in the intramolecular addition to *N*-acyliminium ions.

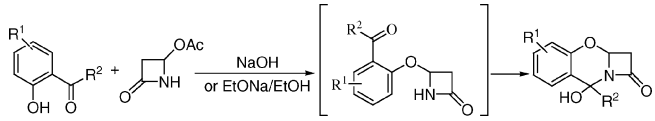
5-Oxacephams and clavams represent an interesting group of β-lactam antibiotics and β-lactamase inhibitors.[4] All these compounds have one structural feature in common – an alkoxy fragment at C4 of the azetidin-2-one ring. One of the most common strategies for the synthesis of such compounds calls for nucleophilic substitution at C4 of azetidin-2-one, which can either constitute the ring closure step or can be followed by the closure of a five- or six-membered ring by intramolecular alkylation of the nitrogen atom. The weak point of such a strategy relates to low asymmetric induction in cases where C3 of the azetidin-2-one ring is unsubstituted and the stereogenic center is located in the nucleophile or to the exclusive formation of the *trans*-functionalized ring if C3 bears a substituent.

In connection with our interest in the synthesis of 5-dethia-5-oxacephams,[5] herein, for the first time, we report a highly enantioselective approach to the construction of 3,4-benzo-5-oxacephams **4**. This new approach is based on the chiral Lewis acid promoted intramolecular nucleophilic substitution at C4 of 4-formyloxy-azetidinones **3**, which leads to ring closure (Scheme 1).



Scheme 1. Synthetic strategy.

Racemic 3,4-benzo-5-oxacephams have been synthesized by the base-catalyzed (NaOH or EtONa/EtOH) condensation of salicylaldehyde or *o*-hydroxyphenones with 4-acetoxyazetidinone.[6] It is likely a two-step process occurs by nucleophilic substitution of the acetoxy group, followed by addition of the NH group of azetidinone to the carbonyl group of phenone (Scheme 2).[6]



Scheme 2. Base-catalyzed formation of substituted 3,4-benzo-5-oxacephams.

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Result and Discussion

We assumed that treatment of the *N*-alkylated azetidinone of type **3**, which bears the *o*-hydroxybenzyl substituent at the nitrogen atom, with a chiral Lewis acid would result in cyclization. This leads to a nonracemic 3,4-benzo-5-oxacepham skeleton **4**. Such displacement would likely proceed via a presumed planar intermediate having an *N*-acyliminium cationic structure **5** (Scheme 1). The desired cyclization precursor **3** should be accessible from the readily available 4-vinyloxyazetidinone (**1**)[7] and suitably substituted benzyl bromides **2** (Scheme 3).

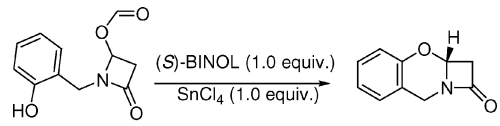
Reaction of **3a** in CH_2Cl_2 with Lewis acids such as $BF_3{\cdot}OEt_2$ or TMSOTf gave (±)-**4a** in a good yield. However, **3a** was less prone to undergo the desired ring closure when other acids such as $SnCl_4$, $SnCl_2$/TMSCl, $Yb(OTf)_3$, or $In(OTf)_3$ were used. No reaction was observed with TFA, TsOH, $(PhO)_3B$, or Et_3Al.

Over the past few years, several examples of the enantioselective addition of carbon nucleophiles to the prochiral iminium intermediates have appeared.[8] These results prompted us to investigate whether the corresponding azetidinones of type **3** could be substrates in the chiral Lewis acid catalyzed enantioselective cyclization reaction.

Our initial studies indicated that azetidinone **3a** does not undergo ring closure in the presence of chiral phosphoric acids[8,9] and a variety of metal–ligand combinations.[10] However, when **3a** was stirred in CH_2Cl_2 in the presence of a stoichiometric mixture of (*S*)-BINOL and $SnCl_4$ at 0 °C for 3 h,[11] the cyclization proceeded smoothly to give (+)-**4a** in a 35% yield after silica gel column chromatography (Table 1, Entry 3) with 85% *ee*. The reaction was carried out until the disappearance of substrate (TLC monitored).

Note that when the reaction temperature was decreased to –20 °C, a lower enantioselectivity was observed (Entry 2). If toluene or diethyl ether were used as the solvent, the yield was practically unchanged, but the enantioselectivity was reduced to 80 and 72%, respectively. There was no reaction when THF was used as a solvent. All attempts to reduce the ratio of substrate **3** to chiral ligand were unsuccessful. The use of 0.5 equiv. of chiral acid reduced the yield to 50% of that found for the primary experiment. Having the first positive result, we investigated the enantioselective cyclization under the same conditions by varying the chiral ligands (Table 2). When either the (*S*)-3,3′-bisphenyl-BINOL or the (*S*)-3,3′-bis-α-naphthyl-BINOL were employed, **4a** was obtained in a moderate yield (35 and 39%, respectively) and excellent enantioselectivity (98 and 99% *ee*, respectively). The presence of bromide at the 6- and 6′-positions of the binaphthol molecule had little effect on the chemical yield, but the enantioselectivity decreased visibly. Application of (*S*,*S*)-TADOL **9** instead of BINOL ligands **6**–**8** gave a similar conversion providing ent-**4a**, but affected the enantioselectivity (Table 2). In all reactions, the ligands were recovered by column chromatography in an 80–90% yield without loss of enantiomeric purity.

Table 1. Evaluation of reaction conditions.

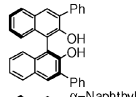
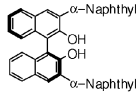
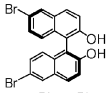
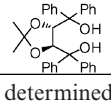


3a **4a**

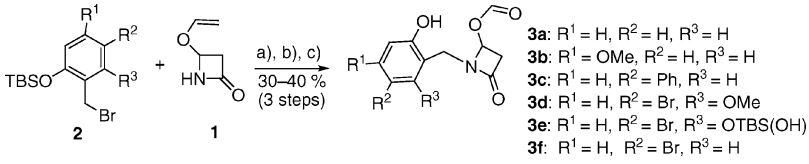
Entry	Solvent	Temperature [°C]	Time [h]	Yield [%][a]	*ee* [%][b]
1	CH_2Cl_2	–40	10	0	–
2	CH_2Cl_2	–20	6	30	78
3	CH_2Cl_2	0	3	35	85
4	toluene	0	3	34	80
5	Et_2O	0	3	32	72
6	THF	0	10	0	–

[a] Isolated yield determined after flash chromatography on SiO_2. [b] Enantiomeric excess was determined by chiral HPLC.

Table 2. Ligand evaluation studies for enantioselective formation of **4a** in the presence of 1 equiv. of ligand/$SnCl_4$ as a catalyst (CH_2Cl_2, 0 °C, 3 h).

Entry	Ligand		Yield [%][a]	*ee* [%][b]	Enantiomer
1	**6**		38	98	*R*
2	**7**		39	99	*R*
3	**8**		30	64	*R*
4	**9**		34	80	*S*

[a] Isolated yield determined after flash chromatography on SiO_2. [b] Enantiomeric excess was determined by chiral HPLC.



Scheme 3. Preparation of *N*-benzyl-substituted azetidinones **3**.

Subsequently, we analyzed the scope of this asymmetric reaction with various *N*-benzylated azetidinones **3**. As shown in Table 3, the enantiomeric excess as well as the yield of products is dependent on the nature of the substituents on the phenol ring.

Table 3. Cyclizations of **3** in the presence of 1 equiv. of (*S*)-3,3′-bis-α-naphthyl-BINOL **7**/$SnCl_4$ as a catalyst (CH_2Cl_2, 0 °C, 3 h).

Entry	Substrate **3**	Product **4**	Yield [%][a]	*ee* [%][b]
1	**3a**	**4a**	39	99
2[c]	**3a**	ent-**4a**	42	99
3	**3b**	**4b**	49	82
4	**3c**	**4c**	45	92
5	**3d**	**4d**	50	95
6	**3e**	**4e**	52	0
7	**3f**	**4f**	0	–

[a] Isolated yield determined after flash chromatography on SiO_2. [b] Enantiomeric excess was determined by chiral HPLC. [c] (*R*)-3,3′-bis-α-naphthyl-BINOL was used as a chiral ligand.

The low yield of the reaction in the presence of chiral catalysts, which never exceeds 50%, may suggest that the high asymmetric induction is a result of a kinetic resolution of the initially formed racemic oxacepham. This mechanistic proposition is strongly supported by the partial asymmetric destruction of racemic **4a** in the presence of the chiral catalyst. Cepham **4a** in CH_2Cl_2 solution in the presence of a stoichiometric mixture of (*S*)-BINOL and $SnCl_4$ at 0 °C leads to the enantiomerically enhanced compound ent-**4a** in 25% yield and 56% *ee* after 1.5 h and in 15% yield and 85% *ee* after 3 h.

To assign the absolute configuration at the C6 carbon atom in compounds **4**, we applied circular dichroism spectroscopy (CD). Building on the presence of two appropriately oriented chromophores in the investigated molecules, namely, an amide and a phenyl/phenoxy chromophores, the exciton chirality method (ECCD) was used for this purpose.[12] On the basis of the data obtained, we were able to assign the (6*R*) configuration to compound (+)-**4a** (Figure 1). Similarly, the CD data allowed the determination of the absolute configuration of the remaining compounds **4**. In a further effort to corroborate the conclusion made on the basis of ECCD, time-dependent density functional theory (TDDFT) calculations were used to simulate the CD spectrum of compound **4b**. As can be seen in Figure 1, the experimental and simulated CD curves are in excellent agreement and thus provide independent proof for the configurational assignment made.

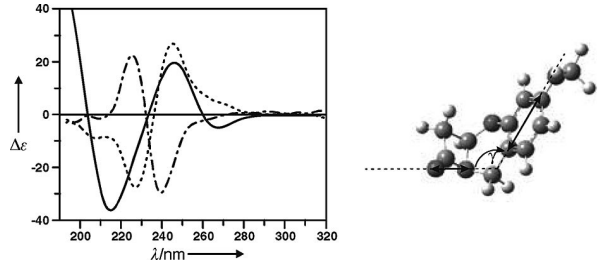
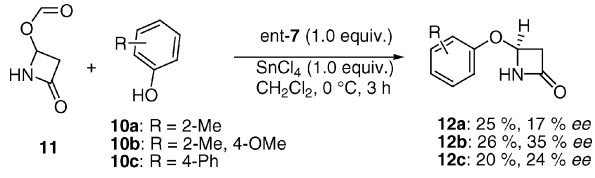


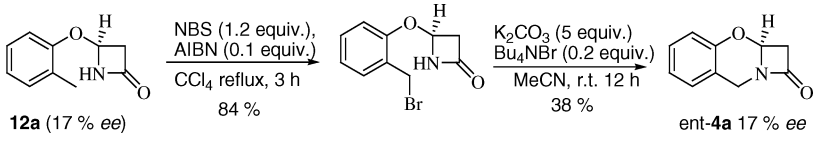
Figure 1. Experimental CD spectra of ent-**4a** (-·-) and **4b** (···) and simulated CD spectrum of **4b** (−) (left). Lowest energy conformer of **4b** calculated at the B3LYP 6-31G++ (d,p) level.

The scope of this transformation was further extended to the intermolecular reaction, which leads to compounds of type **12** (Scheme 4). In all cases, a moderate chemical yield and enantioselectivity, much lower than that for the intramolecular process, was observed under standard cyclization conditions. Furthermore, it was interesting to note that phenols **10** react with azetidinone **11**[7] in the presence of chiral phosphoric acids[8,9] as catalyst to produce the expected 4-phenoxy-azetidinones **12** in good yield (70–80%), but as racemic mixtures. The low asymmetric induction for the intermolecular process is worth mentioning as it implies that the generation of a defined absolute configuration at C4 of azetidinone in this fashion[6] has little chance of being successful.



Scheme 4. Intermolecular enantioselective formation of **12**.

The compound **12a** (17% *ee*) was subsequently transformed into ent-**4a** (17% *ee*) by NBS bromination of the methyl group, followed by intramolecular alkylation of the nitrogen atom (Scheme 5).



Scheme 5. Intramolecular *N*-benzylation leading to ent-**4a**.

Conclusions

In conclusion, for the first time, an enantioselective approach to the synthesis of oxygen analogues of cephalosporins is described. The key step of the method is based on the chiral Lewis acid mediated, intramolecular alkylation of a phenol hydroxy group by the *N*-acyliminium ion generated from the 4-formyloxyazetidinone fragment. However, the mechanism of the reaction requires further studies. It is important to note that while the chiral complex has to be used in a stoichiometric amount, the chiral ligand could easily be recovered from the post-reaction mixture for reuse without any appreciable loss of enantiomeric purity of the product.

Experimental Section

Typical Procedure for Enantioselective Formation of 4: Solution of **7** (75 mg, 0.14 mmol, 1.0 equiv.) in CH_2Cl_2 (5 mL) at 0 °C was treated with a 1 M solution of $SnCl_4$ in CH_2Cl_2 (140 μL, 1 equiv.) under argon. After 15 min, compound **3a** (31 mg, 0.14 mmol) was added. The reaction mixture was stirred for 3 h (disappearance of substrate, TLC monitored) and diluted with saturated $NaHCO_3$ (5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The organic extracts were combined and dried with $MgSO_4$. The solution was filtered, and the filtrate evaporated. The crude product was purified by column chromatography (silica gel, 7:3 hexanes/methyl-*tert*-butyl ether) to yield 9.6 mg (0.055 mmol) of **4a** as a yellow liquid. Yield: 39%, 99% *ee*. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.02 (d, J = 15.0 Hz, 1 H, CH_2), 3.36 (ddd, J = 15.0, 3.0, 2.1 Hz, 1 H, CH_2), 4.21 (d, J = 16.4 Hz, 1 H, CH_2–N), 4.57 (d, J = 16.4 Hz, 1 H, CH_2–N), 5.27 (d, J = 3.0 Hz, 1 H, CH–O), 6.94 (d, J = 8.2 Hz, 1 H, 4-H), 7.00 (tm, J = 7.6 Hz, 1 H, 3-H), 7.07 (d, J = 7.6 Hz, 1 H, 5-H), 7.20 (tm, J = 8.2 Hz, 1 H, 5-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 38.9 (CH_2N), 46.3 (CH_2), 75.3 (CH–O), 117.8 (C-1), 118.4 (C-3), 122.4 (C-5), 127.2 (C-4), 128.5 (C-6), 152.2 (C-2), 167.3 (C=O) ppm. MS (HR-ESI): calcd. for $C_{10}H_{10}NO_2$ [M+ H]$^+$ 176.0706; found 176.0697. $C_{10}H_9NO_2$ (175.18): calcd. C 68.56, H 5.18, N 8.00, O 18.27; found C 68.59, H 5.20, N 8.03. IR (film): $\tilde{\nu}$ = 1774 cm^{-1}. $[\alpha]_D^{26}$ = +36 (c = 0.02, CH_2Cl_2), chiral HPLC (OD-H, hexane/IPA = 9:1, 1.0 mL/min), t_R [*S*] = 24.5 (minor) t_R [*R*] = 37.2 (major).

Supporting Information (see footnote on the first page of this article): Detailed procedures and spectroscopic data of cyclization precursors and 3,4-benzo-5-oxacephams are presented.

Acknowledgments

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[10] A combination of different Lewis acids [$TiCl_4$, $Br_2Ti(OiPr)_4$, $ZnCl_2$] and various ligands (box-type, salen ligands) were tested. In all cases, the expected 3,4-benzo-5-oxacephams were formed in very low yields, as racemic mixtures.
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