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# Synthesis and Biological Evaluation of Azido- and Aziridino-hydroxyl-$\beta$-lactams through Stereo- and Regioselective Epoxide Ring Opening†

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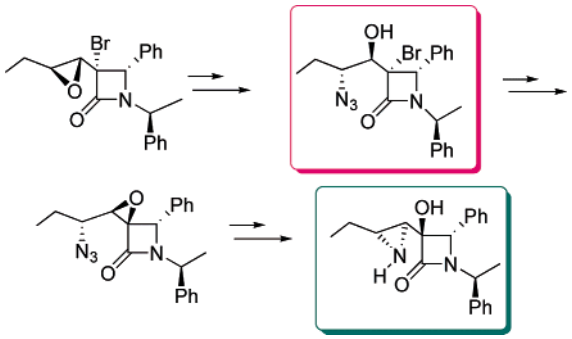


Two new classes of azido- and aziridino-hydroxyl-$\beta$-lactam containing structures have been prepared by means of a stereo- and regioselective epoxide ring opening. The straightforwardness of the procedure makes this strategy useful for the synthesis of potentially bioactive compounds. Some selected examples showed promising activity in acyl CoA-cholesterol acyltransferase inhibition assays.

Azetidin-2-ones are important as key structural elements of the most widely employed class of antibacterial agents; numerous synthetic approaches to azetidin-2-ones have been reported.[1] More recently, azetidin-2-ones have received great attention since the discovery that some representative examples of these compounds have shown potent and selective enzymatic inhibition.[2] Over the past few years, a class of $\beta$-lactam based structures containing hydroxy and keto functions in the C-3 side chain were found to be very potent cholesterol absorption inhibitors (CAI).[3] Ezetimibe is a new example of a $\beta$-lactam containing drug involving inhibition of intestinal cholesterol absorption.[3,4] Since cardiovascular disease is the leading cause of death in the industrialized world, the synthesis of new polyfunctionalized azetidin-2-ones, possessing the minimum requirements for cholesterol absorption control, has received great attention. In a program directed to the synthesis of potential CAI, we became interested in the functionalization of the C-3 side chain; the lipophilic phenyl group was chosen as the substituent in the $\beta$-lactam ring C-4 position, as suggested by the literature for bioactive Ezetimibe analogues.[3a,b]

We have recently reported the synthesis of 3-bromo-3-alkenyl-azetidin-2-ones (**1**)[5] via ketene−imine cycloaddition.[6] This class of compounds is of great interest since the substitution of the bromine in position 3 through $S_N2'$ rearrangement[7] and the transformation of the double bond in the side chain give access to a variety of derivatives.

In this work, the functionalization of the double bond is described with a view to the formation of C−O and C−N bonds. The reactions herein reported are characterized by total stereocontrol in all steps, high overall yield, and access to densely functionalized $\beta$-lactams. Furthermore, only a few examples of C-3 side chain amino and azido function-containing azetidinones are reported in the literature.[8]

The azido group can be easily submitted to further transformations affording amines, aziridines, or cyclic nitrogen-containing compounds. Although the azido function is practically absent in naturally occurring species, it is quite stable in a biological environment, and lacking in toxicity, it has been introduced in a variety of drugs,[9] the most important one being the well-known azidothymidine, AZT.

To this purpose, the treatment of substrates **1a**−**c** with *meta*-chloroperbenzoic acid (MCPBA) performed under concentrated conditions (2 M in $CH_2Cl_2$) allowed the corresponding epoxides to be obtained in a 1:1 mixture and an almost quantitative yield (Scheme 1).[10] The diastereomeric mixture of epoxides **2a**−**c** and **3a**−**c** was separated by flash chromatography.

The first epoxide, **2a**, to be eluted was a solid crystallized from $CHCl_3$, and its structure with the relative epoxide con-

† Dedicated to Professor Achille Umani-Ronchi on the occasion of his 70th birthday.

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**SCHEME 1. Synthesis of Epoxides 2 and 3**

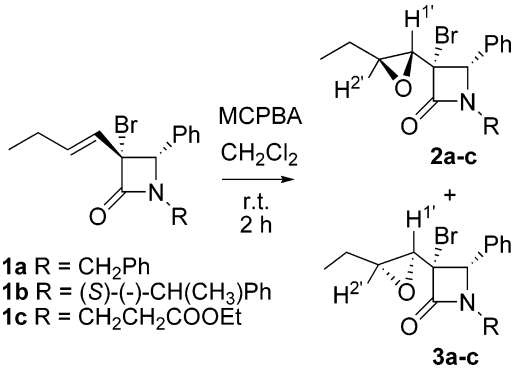


**TABLE 1. $^1$H NMR Data for Compounds 2a−c and 3a−c**

| entry[a] | epoxide | $\delta$ H$^{1'}$ | $\delta$ H$^{2'}$ | $J_{1'-2'}$ |
|---|---|---|---|---|
| 1 | **2a** | 3.27 | 3.57 | 2.2 |
| 2 | **2b** | 3.19 | 3.48 | 2.0 |
| 3 | **2c** | 3.26 | 3.49 | 2.1 |
| 4 | **3a** | 3.38 | 2.82 | 2.1 |
| 5 | **3b** | 3.37 | 2.81 | 2.3 |
| 6 | **3c** | 3.41 | 2.95 | 2.4 |

[a] Spectra recorded in $CDCl_3$ solution at 25 °C.

figuration was established by single-crystal X-ray analysis,[11] thus allowing the (1′*R**,2′*S**) configuration to be attributed to the newly introduced stereogenic centers. As a consequence the (1′*S**,2′*R**) configuration was attributed to the isomer **3a**.

The $^1$H NMR of **2a** shows the hydrogen H$^{1'}$ as a doublet resonating at 3.29 ppm, while the hydrogen H$^{2'}$ is a multiplet deshielded at 3.59 ppm. The coupling constant, $J_{1'-2'} = 2.2$ Hz, accounts for a trans relationship. Semi-empirical calculations[12] are in agreement with the X-ray structure, showing bromide and epoxide in the more stable anti arrangement. NOE analysis of **2a**,**b** and **3a**,**b** confirmed that this conformation is also the preferred one in solution. The irradiation of the hydrogen at C-4 on the lactam ring, indeed, enhances the signal relative to H$^1$. The same experiment performed on isomer **3a**,**b** induced enhancement at H$^2$ of the epoxide.[13] Finally, comparison of the $^1$H NMR chemical shifts for the pairs of compounds **2** and **3** revealed a complete regularity, allowing the relative configuration to be confidently attributed to **2c** and **3c** and the absolute configuration to be attributed to **2b** and **3b**. (Table 1).

The regioselective ring opening of oxiranes provides a convenient way to prepare polyfunctionalized compounds. Successful ring openings of epoxyalcohols with diethylaluminum azide have been reported by Benedetti et al.[14] aiming to prepare 3-amino-1,2-diols that are present in several classes of biologically active compounds. Therefore, the treatment of epoxides **2a**−**c** and **3a**−**c** with $Me_2AlN_3$, prepared in situ from sodium azide and $Me_2AlCl$, gave the corresponding azides **4a**−**c** or **5a**−**c** with a good yield and complete stereo- and regioselectivity (Table 2). The ring opening of the epoxides occurred only on the C-2′ position with inversion of the configuration.

The complete regio- and stereoselectivity can be rationalized by the tendency of the aluminum to become tetrahedral through an intramolecular coordination.[15]

The ab initio geometry-optimized structure of the aluminum complex (DFT/B3LYP/6.31G* minimization) shows that the computed atomic partial charges on C-1′ and C-2′ are very similar. The attack of the azide occurs exclusively on the less hindered C-2′ position since the attack to C-1′ is greatly disfavored by the presence of the vicinal phenyl group more than by the presence of the bulky bromine lying on the opposite face of the lactam ring.

Furthermore, the formation of the aluminum complex, promoting the ionization of the azide, favors the nucleophilic anion attack via $S_N2$ mechanism, with complete inversion of the configuration (Figure 1). Subsequently, upon treatment of compound **4** and **5** with 1 equiv of NaH in dry THF at 0 °C, spiro-epoxides **6** and **7** could be obtained in quantitative yields via the bromine displacement (Table 2).

It is noteworthy that a complete pathway from epoxides **2** and **3** to azides **4** and **5** and then to spiro-epoxides **6** and **7** does not require chromatographic purification, since the products were obtained in high yield and in the absence of byproducts.

We next studied the reduction of the azido group. Extensive experimentation was carried out in order to reduce the azido group in the presence of sensitive functions such as epoxide and bromide.[16]

However, any attempt to reduce the azide **4a** with $NaBH_4$ in refluxing methanol failed. Under these conditions, spiro-epoxide **6a** was obtained in moderate yield. The treatment of **6a** with $BH_2Cl$-$SMe_2$ as well as hydrogenation on Pd/C gave mixtures of products.

Excellent results were observed by reducing azides **6a**−**c** and **7a**−**c** with $Ph_3P$ or $Et_3P$.[17] These reactions allowed aziridines **8a**−**c** and **9a**−**c** to be obtained in yields ranging from 50−80%, via an aza-Payne-like ring opening[18] of the epoxide (Scheme 2).

The $^1$H NMR coupling constants of the aziridine protons ($J_{2-3} = 2.0-3.0$ Hz) account for a trans relationship, confirming the stereochemistry attributed to the starting azides **6** and **7**. In the overall sequence from α-bromoepoxides to aziridines, the stereochemical configuration of both C-1′ and C-2′ carbon atoms has been inverted. The retention of the configuration at C-3, in the last step, arises from mechanistic considerations.[19] A possible mechanism is reported in Scheme 3.

The reaction proceeds by nucleophilic attack of a phospine on the azide, to form an aza-ylide intermediate. The nucleophilic nitrogen atom of the aza-ylide attacks the epoxide, inducing

(11) Crystal data for **2a**: $C_{20}H_{20}Br_1N_1O_2$; MW = 386.28; monoclinic, *P*2(1)/*c*; $a = 8.8729(11)$ Å, $b = 19.734(2)$ Å, $c = 21.236(3)$ Å, $\beta = 92.613(2)°$; $V = 3714.5(8)$ Å$^3$; $Z = 8$; $D_{calc} = 1.381$ Mg/m$^3$; $R_1 = 0.0474$, w$R_2 = 0.1260$ (final); goodness-of-fit on $F^2 = 0.769$. ORTEP plot is reported in Supporting Information.

(12) Structures calculated with AM1 (HYPERCHEM 7.0 package).

(13) See Supporting Information.

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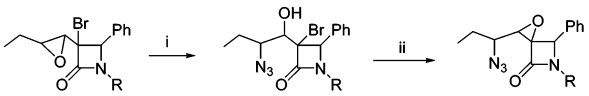
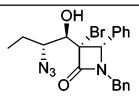
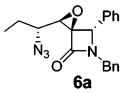
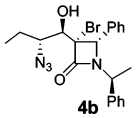
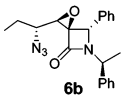
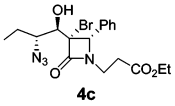
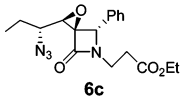
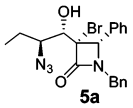
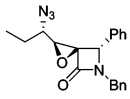
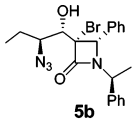
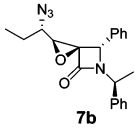
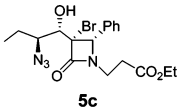
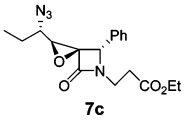
**TABLE 2. Ring Opening of Epoxides 2 and 3 and Synthesis of Epoxides 6 and 7**[a]




| entry | Starting material | Azide | Yield (%) | Epoxide | Yield (%) |
|---|---|---|---|---|---|
| 1 | **2a** |  **4a** | >95 |  **6a** | >95 |
| 2 | **2b** |  **4b** | >95 |  **6b** | >95 |
| 3 | **2c** |  **4c** | >95 |  **6c** | >95 |
| 4 | **3a** |  **5a** | >95 |  **7a** | >95 |
| 5 | **3b** |  **5b** | >95 |  **7b** | >95 |
| 6 | **3c** |  **5c** | 93 |  **7c** | >95 |

[a] Reaction conditions: (i) $NaN_3/Me_2AlCl$, toluene, −78 °C; (ii) NaH, THF, 0 °C.

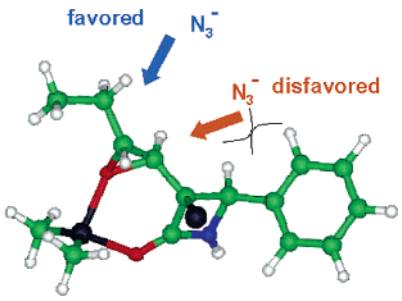
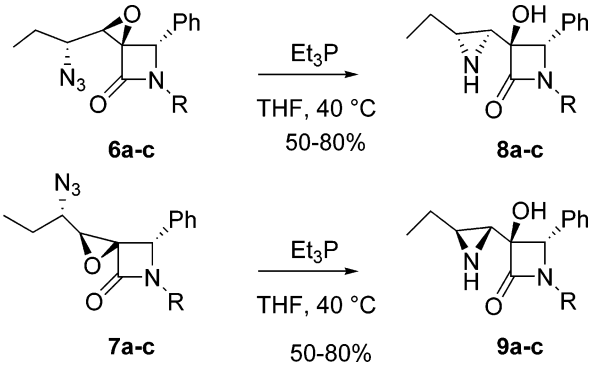



**FIGURE 1.** Azide anion nucleophilic attack on the aluminum complex (ab initio geometry optimized structure with DFT/B3LYP/6.31G*).

the ring opening. Hydrolysis of the adduct produces the aziridine-alcohol and liberates the phosphine oxide.

Finally, representative examples of aziridines and their azido precursors were tested as acyl CoA-cholesterol acyltransferase (ACAT) inhibitors[21] using Lovastatin as a reference standard[22] ($IC_{50}$ = 12 $\mu$M from literature data, $IC_{50}$ = 16.8 $\mu$M when concurrently tested). ACAT is a key enzyme in controlling cholesterol metabolism and represents a promising target for the development of therapeutic agents.[23] Although this test is not strictly correlated with Ezetimibe activity,[24] some indication on the cholesterol absorption inhibition can be deduced, giving rise to the preliminary results reported in Table 3. These promising results do not allow for the elucidation of a structure−activity relationship, but nevertheless the results confirm the

**SCHEME 2. Synthesis of Aziridines 8a−c and 9a−c**




(21) Inhibition tests were performed by MDS Pharma Services on acyl CoA-cholesterol acyltransferase from New Zealand derived albino rabbit intestinal mucosa, using [$^{14}$C]palmitoyl CoA (18 $\mu$M) as a substrate in 1% DMSO−0.2 M potassium phosphate buffer (pH 7.4) and 1.5 mg/mL bovine serum albumin at 25°C.

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**SCHEME 3. Mechanistic Considerations on the Aza-Payne-like Ring Opening of Epoxide to Aziridine[20]**

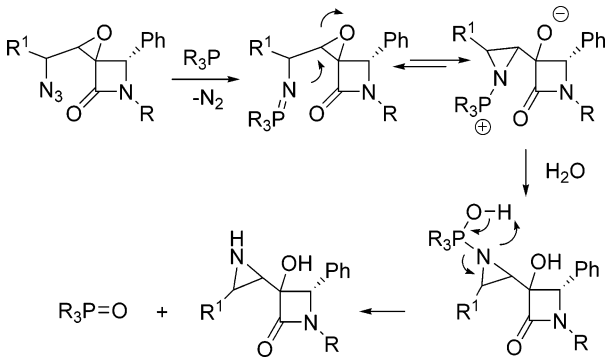

**TABLE 3. ACAT Inhibition Activities of Some Selected Aziridino- and Azido- Derivatives**

| entry | compd | concn ($\mu$M) | % inhibition[a] |
|---|---|---|---|
| 1 | **4b** | 10 | 65 |
| 2 | **5b** | 10 | 60 |
| 3 | **8c** | 10 | 22 |
| 4 | Lovastatin | 16.8 | 50 |

[a] Measured by quantitation of [$^{14}$C]cholesterol ester by column chromatography.

potential application of these molecules as ACAT inhibitors. In vivo assays in a murine model of yperlipidemia are currently underway.

In summary, this investigation gave us the epoxide ring opening with $Me_2AlN_3$ through a fast, regio- and stereoselective process. Subsequent nucleophilic substitution on the bromine atom afforded spiro derivatives in a quantitative yield. Finally the tandem reduction/ring opening reaction of the epoxide gave an easy access to a new class of aziridino-lactams. This chemo-, regio-, and stereoselective method allows the synthesis of hydroxy-aziridine and azido-epoxide-containing azetidin-2-ones. The potential of these products as ACAT inhibitors and the simplicity of the procedure make this strategy useful in bioactive compound synthesis.

## Experimental Section

**General Procedure for the Ring Opening of Epoxides 2a−c and 3a−c.** To a stirred solution of $NaN_3$ (1 mmol) in toluene (3 mL) at 25 °C under nitrogen atmosphere was added dropwise $Me_2AlCl$ (1 mmol, 1 equiv, 1 mL of 1 M solution in hexane). The reaction was stirred for 4 h and then was cooled to −78 °C. Epoxide **2** or **3** (0.5 equiv, 0.5 mmol) was diluted in toluene (0.5 mL) and then was added to the reaction mixture. The solution was stirred overnight, slowly reaching room temperature, and then was diluted with EtOAc, cooled to 5 °C, and added to a aqueous solution (5 mL) containing NaF (1 equiv, 1 mmol, 42 mg). The two phases were stirred for 30 min and then were separated; the organic layer was dried over $Na_2SO_4$, and the solvent was removed under reduced pressure. Compounds **4** and **5** were used in the following step without further purification.

**4a:** HPLC-MS $t_R$ = 13.8 min (M + 1) = 429/431, (M + Na) = 451/453 *m*/*z*; IR (neat) $\nu$ 3420, 2966, 2925, 2108, 1752, 1647, 1457, 1399, 1356, 1264, 1107, 1170 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.08 (t, 3H, $J$ = 7.4 Hz), 1.59−1.74 (m, 1H), 2.04−2.18 (m, 1H), 3.29 (bs, 1H), 3.50 (dt, 1H, $J$ = 3.0, 8.7 Hz), 3.62 (d, 1H, $J$ = 8.7 Hz), 3.88 (d, 1H, $J$ = 14.8 Hz), 4.77 (s, 1H), 4.92 (d, 1H, $J$ = 14.8 Hz), 7.14−7.20 (m, 2H), 7.30−7.47 (m, 8H); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 9.9, 24.5, 44.9, 64.3, 65.7, 73.8, 75.1, 128.2, 128.4, 128.6, 128.7, 129.0, 129.2, 133.0, 134.1, 166.3. Anal. Calcd for $C_{20}H_{21}BrN_4O_2$: C, 55.95; H, 4.93; N, 13.05. Found: C, 55.92; H, 4.90; N, 13.01.

**General Procedure for the Formation of Epoxides 6a−c and 7a−c.** A solution of compound **4** or **5** (1 mmol) and NaH (1.2 equiv, 1.2 mmol, 29 mg) in dry $CH_2Cl_2$ (10 mL) was stirred at 0 °C for 2 h. The reaction was quenched by adding cold water dropwise (1 mL) and was further diluted with water (10 mL), and then layers were separated. The organic layer was dried over $Na_2SO_4$, and the solvent was removed under reduced pressure. Compounds **6** and **7** were isolated pure and used in the following step without further purification.

**6a:** HPLC-MS $t_R$ = 16.0 min (M + 1) = 349, (M + Na) = 371 m/z; IR (neat) $\nu$ 3392, 3058, 3024, 2968, 2924, 2099, 1770, 1496, 1456, 1387, 1261, 1101, 1028 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 1.04 (t, 3H, $J$ = 7.4 Hz), 1.54−1.80 (m, 1H), 1.81−2.00 (m, 1H), 2.81 (d, 1H, $J$ = 8.4 Hz), 3.61 (dt, 1H, $J$ = 5.2, 8.4 Hz), 3.91 (d, 1H, $J$ = 15.0 Hz), 4.64 (s, 1H), 4.98 (d, 1H, $J$ = 15.0 Hz), 7.15−7.44 (m, 10H); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 9.6, 29.7, 44.9, 59.9, 61.6, 62.7, 74.3, 127.4, 128.0, 128.6, 128.7, 128.8, 129.2, 134.0, 134.6, 169.3. Anal. Calcd for $C_{20}H_{20}N_4O_2$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.93; H, 5.80; N, 16.11.

**General Procedure for the Tandem Reduction-Aza-Payne Rearrangement to Compounds 8a−c and 9a−c.** A solution of azido-epoxide **6** or **7** (1 mmol) and $Et_3P$ (1.2 mmol, 1.2 equiv, 1.2 mL of 1 M solution in THF) in dry THF (5 mL) was stirred at reflux under nitrogen atmosphere. After 2 h the reaction was stopped by adding 6 M HCl (2 mL); THF was removed under reduced pressure, and the residue was diluted with EtOAc. The two phases were separated, and a 6 M solution of NaOH was added to the aqueous layer to reach basic pH. The basic aqueous phase was then extracted twice with EtOAc (10 mL); the organic layer was dried over $Na_2SO_4$, and the solvent was removed under reduced pressure to give the pure compounds **8** and **9**.

**8a:** Yield 59%; HPLC-MS $t_R$ = 9.6 min (M + 1) = 323, (M + Na) = 345 *m*/*z*; IR (neat) $\nu$ 3285, 3059, 3032, 1755, 1604, 1495, 1454, 1399, 1355, 1252, 1126, 1027 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 0.46 (t, 3H, $J$ = 7.4 Hz), 0.74−0.93 (m, 2H), 1.47 (bs, 1H), 1.87 (bs, 1H), 4.03 (d, 1H, $J$ = 15.0 Hz), 4.54 (s, 1H), 4.96 (d, 1H, $J$ = 15.0 Hz), 7.17−7.40 (m, 10H); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 10.3, 20.2, 25.8, 29.7, 44.3, 67.0, 85.2, 127.2, 127.8, 128.3, 128.5, 128.8 (2C), 134.6, 134.9, 171.1. Anal. Calcd for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.52; H, 6.88; N, 8.72.

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**Supporting Information Available:** General procedures, complete characterization of compounds **2**−**9**, X-ray data for **2a**, NOESY-1D experiments on **2a** and on **3a**, $^1$H NMR spectra for compounds **2**−**9**, and experimental details on biological assays. This material is available free of charge via the Internet at http://pubs.acs.org.

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