An Efficient Synthesis of 2,3-Aziridino-γ-lactones from Azetidin-2-ones

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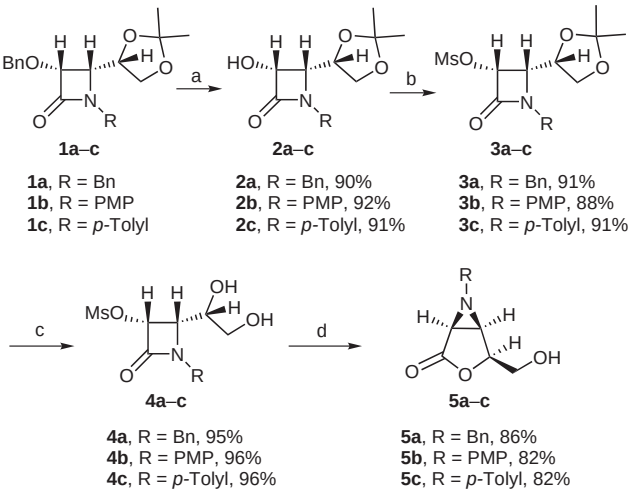
Abstract: An efficient synthesis of enantiopure 2,3-aziridino-γ-lactones from azetidin-2-ones is described. Acid-catalyzed tandem intramolecular azetidinone ring opening followed by aziridine ring formation via elimination of a mesylate group is the key step in this synthesis. 2,3-Aziridino-γ-lactones are important precursors for biologically important glutamic acid derivatives.

Key words: azetidin-2-ones, aziridines, lactones, glutamic acid

The β-lactam skeleton, apart from composing the partial structure of a variety of β-lactam antibiotics,[1–3] has been recognized as a useful building block in the synthesis of a variety of pharmaceutically useful products.[4] The strain energy associated with the four-membered azetidin-2-one ring makes it susceptible to nucleophilic ring cleavage. The selective bond cleavage of the strained ring coupled with the possibility of further transformations make this molecule a powerful building block.[5] There have been many efforts made in exploring new aspects of β-lactam chemistry using enantiomerically pure β-lactams as versatile intermediates for the synthesis of heterocyclic non β-lactam structures,[6] aromatic β-amino acids, and their derivatives,[7] oligopeptides,[4c] labelled peptides, and azetidines, which can be further converted to polyamines, polyamino alcohols, amino sugars, and polyamino ethers.[4a]



Scheme 1 *Reagents and conditions*: a) 10% Pd/C, $HCOONH_4$, MeOH, reflux, 0.5 h; b) MsCl, Et_3N, CH_2Cl_2, –10 °C, r.t., 2 h; c) PTSA, THF–H_2O, reflux, 12–24 h; d) HCl–MeOH (20%), reflux, 18–24 h.

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For the last couple of years we have engaged in using azetidin-2-ones as synthons[8] for the synthesis of biologically useful organic molecules. As a part of this research program we herein report an efficient synthesis of enantiopure 2,3-aziridino-γ-lactones from 3-benzyloxyazetidin-2-ones **1**.

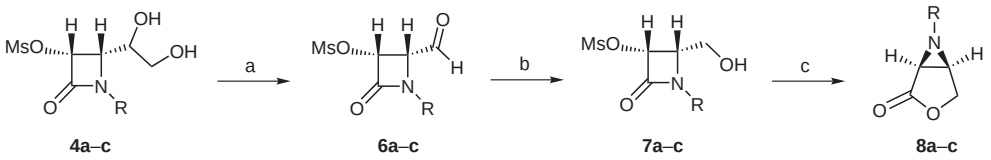
2,3-Aziridino-γ-lactones are very important intermediates in the synthesis of biologically useful 3,4-dihydroxy glutamic acids, analogues of L-glutamic acid, an important excitatory neurotransmitter of the central nervous system.[9] The regioselective nucleophilic opening of the aziridine ring also gives a variety of useful products[10] including α-amino acids, such as polyoxamic acid[10a] and β-amino acids.[10c] The regioselectivity of the ring cleavage is mainly controlled by the hardness and softness of the nucleophile.[10b] There are few reports[11] on the synthesis of 2,3-aziridino-γ-lactone analogues; some of these are multi-step reactions (12–14 steps)[11c,e] that give low overall yield of the desired product. We wish to report a short and efficient synthesis of 2,3-aziridino-γ-lactones from optically pure 3-benzyloxy-β-lactams. The key step in this synthesis is the selective intramolecular nucleophilic β-lactam ring opening followed by aziridine ring formation via elimination of the mesylate group (Scheme 1).

The starting 3-benzyloxy-azetidin-2-one (**1a**) was obtained in good yield[12] and enantiopurity by Staudinger's ketene-imine cycloaddition reaction. The ketene was generated in situ from benzyloxyacetyl chloride using triethylamine and the imine was prepared by the reaction of D-glyceraldehyde acetonide with benzylamine. The benzyl group was removed by transfer hydrogenation[13] using ammonium formate and Pd/C (10%) to provide the corresponding 3-hydroxy-β-lactam **2a** in very good yield. It was then converted to its meslylate **3a** by its reaction with methanesulfonyl chloride in the presence of triethylamine.[12b] The removal of the acetonide group was achieved by refluxing **3a** in THF–H_2O with a catalytic amount of PTSA giving dihydroxy-β-lactam **4a** in excellent yield. Dihydroxy-β-lactam **4a** was refluxed in methanolic HCl (20%) for 18 hours (monitored by TLC). The extractive work-up with ethyl acetate gave 2,3-aziridino-γ-lactone **5a** as a thick oil. The IR spectrum of **5a** showed a strong absorption band at 1780 cm^{-1} for the γ-lactone carbonyl group and the ^1H NMR spectrum did not show a singlet for the methyl group indicating the elimination of the mesylate group during the aziridine ring formation. One of the aziridine ring protons appeared as a doublet at 2.80 ppm (J = 4.5 Hz) and the other proton appeared as a doublet of doublet at 3.14 ppm (J = 3.1 and 4.5 Hz). The

Table 1 Synthesis of 2,3-Aziridino-γ-lactones **5a–c** and **8a–c**

Entry.	Compound	R[a]	Reaction time (h)	Mp (°C)	Yield (%)[b]	$[\alpha]_D^{30}$ ($CHCl_3$)
1	**5a**	Bn	20	Thick oil	86	–40.0 (*c* 1.5)
2	**5b**	PMP	24	Thick oil	82	+1.0 (*c* 1.75)
3	**5c**	*p*-Tolyl	18	Thick oil	82	+16.0 (*c* 0.5)
4	**8a**	Bn	8	Thick oil	80	–1.6 (*c* 0.9)
5	**8b**	PMP	15	92–94	81	+18.0 (*c* 1.0)
6	**8c**	*p*-Tolyl	17	95–96	83	+60.0 (*c* 1.5)

[a] PMP = 4-Methoxyphenyl.
[b] Isolated yields.



4a–c **6a–c** **7a–c** **8a–c**

4a, R = Bn
4b, R = PMP
4c, R = *p*-Tolyl

6a, R = Bn, 80%
6b, R = PMP, 85%
6c, R = *p*-Tolyl, 90%

7a, R = Bn, 82%
7b, R = PMP, 84%
7c, R = *p*-Tolyl, 80%

8a, R = Bn, 80%
8b, R = PMP, 81%
8c, R = *p*-Tolyl, 83%

Scheme 2 *Reagents and conditions*: a) $NaIO_4$ supported on silica gel, MeOH, r.t., 3.5 h; b) $NaBH_4$, MeOH–THF, r.t., 3 h; c) HCl–MeOH (20%), reflux, 8–17 h.

benzyl protons appeared as two doublets at 3.35 and 3.82 ppm (J = 13.0 Hz). Spectral data clearly revealed the formation of 2,3-aziridino-γ-lactone **5a** via one-pot azetidinone ring opening followed by aziridine ring formation.[14] Other 2,3-aziridino-γ-lactones **5b**,**c** were also prepared (Table 1) from **1b**,**c** following the above synthetic procedure (Scheme 1) and were characterized by spectral analyses.

The formation of 2,3-aziridino-γ-lactone was further confirmed by the synthesis of aziridino-γ-lactone **8a** and comparing its spectral data with the reported racemic compound (Scheme 2).[11b] Oxidative cleavage, by silica gel supported sodium metaperiodate,[15] of dihydroxy-β-lactam **4a** gave 4-formyl-β-lactam **6a**, which on reduction with sodium borohydride gave hydroxy-β-lactam **7a** in good yield. This was further subjected to intramolecular nucleophilic ring cleavage. Compound **7a** was refluxed with methanolic HCl for eight hours to afford 2,3-aziridino-γ-lactone **8a** in very good yield. The IR and NMR spectral data[16] of **8a** was found to be exactly similar with that reported for the racemic compound.[11b] This confirms the formation of aziridino-γ-lactones via tandem nucleophilic azetidinone ring opening and aziridine ring formation. Other aziridino-γ-lactones **8b**,**c** were also prepared in good yields (Table 1, Scheme 2).

In conclusion, we have demonstrated an efficient synthesis of 2,3-aziridino-γ-lactones using azetidin-2-ones as synthons. One-pot nucleophilic azetidinone ring opening followed by the formation of an aziridine ring is the key step in this synthesis. The generality of this synthetic procedure was established by the preparation of 2,3-aziridino-γ-lactones **5a–c** and **8a–c**.

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References

(1) For reviews on β-lactam antibiotics, see: (a) Dürkheimer, W.; Blumbach, J.; Lattrell, R.; Scheunemann, K. H. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 180. (b) *Chemistry and Biology of β-Lactam Antibiotics*, Vol. 1-3; Morin, R. B.; Gorman, M., Eds.; Academic Press: New York, **1982**. (c) Coulton, S.; Hunt, E. In *Recent Progress in the Chemical Synthesis of Antibiotics and Related Microbial Products*, Vol. 2; Lukacs, G., Ed.; Springer-Verlag: Berlin, **1993**, 621. (d) Southgate, R. *Contemp. Org. Synth.* **1994**, *1*, 417.

(2) *The Chemistry of β-Lactams*; Page, M. I., Ed.; Chapman and Hall: London, **1992**.

(3) For comprehensive general reviews, see: (a) Koppel, G. A. In *Small Ring Heterocycles*, Vol. 42; Hasner, A., Ed.; Wiley: New York, **1983**, 219. (b) Backes, J. In *Houben–Weyl Methoden der organischem Chemie*, Vol. E16B; Muller, E.; Bayer, O., Eds.; Thieme: Stuttgart, **1991**, 31. (c) de Kimpe, N. In *Comprehensive Heterocyclic Chemistry II*, Vol. 1B; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V.; Padwa, A., Eds.; Pergamon: Oxford, **1996**, 507.

(4) (a) Ojima, I. In *The Chemistry of β-Lactams*; Georg, G. I., Ed.; VCH: New York, **1993**, 197; and references cited therein. (b) Palomo, C.; Aizpurua, J.; Ganboa, I. In *Enantioselective Synthesis of Beta-Amino Acids*; Juaristi, E., Ed.; Wiley-VCH: New York, **1997**, 279; and references cited therein. (c) For a review on this subject see: Ojima, I.; Delaloge, F. *Chem. Soc. Rev.* **1997**, *26*, 377.

(5) (a) Alcaide, B.; Almendros, P. *Chem. Soc. Rev.* **2001**, *30*, 226. (b) Alcaide, B.; Almendros, P. *Synlett* **2002**, 381.

(6) Alcaide, B.; Almendros, P. *Curr. Med. Chem.* **2004**, *11*, 1921.

(7) Palomo, C.; Aizpurua, J.; Ganboa, I. In *Enantioselective Synthesis of Beta-Amino Acids*; Juaristi, E., Ed.; Wiley-VCH: New York, **1997**, 279–357; and references cited therein.
(8) (a) Jayaraman, M.; Deshmukh, A. R. A. S.; Bhawal, B. M. *Tetrahedron* **1996**, *52*, 8989. (b) Jayaraman, M.; Puranik, V. G.; Bhawal, B. M. *Tetrahedron* **1996**, *52*, 9005. (c) Srirajan, V.; Deshmukh, A. R. A. S.; Puranik, V. G.; Bhawal, B. M. *Tetrahedron: Asymmetry* **1996**, *7*, 2733. (d) Krishnaswamy, D.; Govande, V. V.; Deshmukh, A. R. A. S. *Synthesis* **2003**, 1903. (e) Deshmukh, A. R. A. S.; Bhawal, B. M.; Krishnaswamy, D.; Govande, V. V.; Shinkre, B. A.; Jayanthi, A. *Curr. Med. Chem.* **2004**, *11*, 1889; and references cited therein. (f) Shirode, N. M.; Kulkarni, K. C.; Gumaste, V. K.; Deshmukh, A. R. A. S. *Arkivoc* **2005**, *(i)*, 53.
(9) (a) Yan, Z.; Weaving, R.; Dauban, P.; Dodd, R. H. *Tetrahedron Lett.* **2002**, *43*, 7593. (b) Dauban, P.; De Saint-Fuscien, C.; Acher, F.; Prezeau, L.; Barbet, I.; Pin, J.-P.; Dodd, R. H. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 129. (c) Dauban, P.; De Saint-Fuscien, C.; Dodd, R. H. *Tetrahedron* **1999**, *55*, 7589. (d) Dauban, P.; Chiaroni, A.; Riche, C.; Dodd, R. H. *J. Org. Chem.* **1996**, *61*, 2488.
(10) (a) Tarrade, A.; Dauban, P.; Dodd, R. H. *J. Org. Chem.* **2003**, *68*, 9521; and references cited therein. (b) McCoull, W.; Davis, F. A. *Synthesis* **2000**, 1347; and references cited therein. (c) Dodd, R. H. *Molecules* **2000**, *5*, 293; and references cited therein. (d) Dauban, P.; Dubois, L.; Tran Huu Dau, E.; Dodd, R. H. *J. Org. Chem.* **1995**, *60*, 2035. (e) Dubois, L.; Mehta, A.; Tourette, E.; Dodd, R. H. *J. Org. Chem.* **1994**, *59*, 434.
(11) (a) Luisi, R.; Capriati, V.; Florio, S.; Di Cunto, P.; Musio, B. *Tetrahedron* **2005**, *61*, 3251. (b) de Saint-Fuscien, C.; Tarrade, A.; Dauban, P.; Dodd, R. H. *Tetrahedron Lett.* **2000**, *41*, 6393. (c) Dauban, P.; Hofmann, B.; Dodd, R. H. *Tetrahedron* **1997**, *53*, 10743. (d) Dauban, P.; Dodd, R. H. *J. Org. Chem.* **1997**, *62*, 4277. (e) Dubois, L.; Dodd, R. H. *Tetrahedron* **1993**, *49*, 901. (f) Krutius, O.; Eremeev, A. V.; Sekacis, I. *Latv. PSR Zinat. Akad. Vestis, Kim. Ser.* **1988**, 487, *Chem. Abstr.* **1989**, *110*, 114582.
(12) (a) Banik, B. K.; Manhas, M. S.; Kaluza, Z.; Barakat, K. J.; Bose, A. K. *Tetrahedron Lett.* **1992**, *33*, 3603. (b) Banik, B. K.; Mathur, C.; Wagle, D. R.; Manhas, M. S.; Bose, A. K. *Tetrahedron* **2000**, *56*, 5603.
(13) Bieg, T.; Szeja, W. *Synthesis* **1985**, 76.
(14) A typical procedure for the synthesis of (1*S*,4*S*,5*R*)-6-benzyl-4-hydroxymethyl-3-oxa-6-aza-bicyclo[3.1.0]hexan-2-one(**5a**): Dihydroxyazetidin-2-one (**4a**; 0.5 g, 1.58 mmol) was dissolved in methanolic HCl (20%, 10 mL) and the reaction mixture was refluxed for 20 h. After the reaction was over (TLC), MeOH was removed under reduced pressure and sat. $NaHCO_3$ was added to the residue. It was then extracted with EtOAc (3 × 20 mL) and the combined organic extract was washed with brine (10 mL). It was then dried over anhyd Na_2SO_4 and the solvent was removed under reduced pressure to provide a thick oil, which was quickly purified by flash column chromatography (acetone–petroleum ether, 4:1) to furnish **5a** (0.300 g, 86%) as a thick oil.
$[\alpha]_D^{30}$ –40 (*c* 1.5, $CHCl_3$); IR ($CHCl_3$): 3417, 1780 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ = 7.34–7.38 (m, 5 H), 4.46–4.53 (m, 1 H), 3.78–3.94 (m, 2 H), 3.82 (d, *J* = 13.0 Hz, 1 H), 3.35 (d, *J* = 13.0 Hz, 1 H), 3.14 (dd, *J* = 3.1, 4.5 Hz, 1 H), 2.80 (d, *J* = 4.5 Hz, 1 H), 2.26 (br s, 1 H); ^{13}C NMR (50.32 MHz, $CDCl_3$): δ =171.8, 136.8, 128.6, 127.8, 127.7, 79.3, 61.6, 60.8, 42.8, 40.0; MS (70 eV): *m*/*z* = 242 (M^+); Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.73; H, 5.98; N, 6.40. Found: C, 65.50; H, 6.01; N, 6.24.
(15) Zhong, Y.-L.; Shing, T. K. M. *J. Org. Chem.* **1997**, *62*, 2622.
(16) (1*S*,5*R*)-6-Benzyl-3-oxa-6-azabicyclo[3.1.0]hexan-2-one (**8a**) was synthesized from 3-hydroxymethyl-azetidin-2-one (**7a**) following the procedure described for compound **5a**.[14] **8a**: Thick oil, 80%; $[\alpha]_D^{30}$ –1.6 (*c* 0.9, $CHCl_3$); IR ($CHCl_3$): 1774 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ = 7.30–7.40 (m, 5 H), 4.34 (d, *J* = 9.8 Hz, 1 H), 4.21 (dd, *J* = 9.8, 3.1 Hz, 1 H), 3.74 (d, *J* = 13.5 Hz, 1 H), 3.47 (d, *J* = 13.5 Hz, 1 H), 2.96 (dd, *J* = 4.5, 3.1 Hz, 1 H), 2.72 (d, *J* = 4.5 Hz, 1 H); ^{13}C NMR (50.32 MHz, $CDCl_3$): δ = 172.3, 137.0, 128.6, 127.8, 127.7, 69.5, 61.1, 42.1, 39.7; MS (70 eV): *m*/*z* = 190 (M^+); Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.81; H, 5.86; N, 7.40. Found: C, 69.62; H, 5.43; N, 7.19.