An Efficient Synthesis of Azetidine-2,3-diones from L-(+)-Diethyl Tartrate

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Abstract: A convenient route to enantiopure azetidine-2,3-diones is described. The chiral ketene generated from commercially available L-(+)-diethyl tartrate on Staudinger cycloaddition with different imines gave spiro-β-lactams in good yields. These spiro-β-lactams were transformed into azetidine-2,3-diones in excellent yields in a two-step process.

Key words: stereoselective synthesis, lactams, imines, cycloaddition, spiro compounds

β-Lactams, being a part of most widely used antibiotics,[1] are a familiar class of compounds in organic synthesis. The resurgence of bacterial activity against traditional antibiotics has inevitably led to the discovery of newer β-lactam antibiotics with modified structures. Recent times have witnessed an upsurge in the number of new varied applications of β-lactams.[2–11] Among these, the most important application that has outgrown most other applications is the use of β-lactams as a synthon for biologically important molecules.[12] One particularly important and useful class of synthons are substituted azetidine-2,3-diones. They have been shown to be promising building blocks[13] and precursors for highly functionalized β-lactams[14] including Sch-48461 and Sch-58235 which display an important cholesterol absorption inhibitory activity (Figure 1).

Apart from synthesis of these functionalized β-lactams, other applications involve synthesis of α-amino acid *N*-carboxy anhydrides which have been used in peptide synthesis.[15] More recently, another elegant application of azetidine-2,3-diones in peptide synthesis has been reported using their reaction with primary amines.[16]

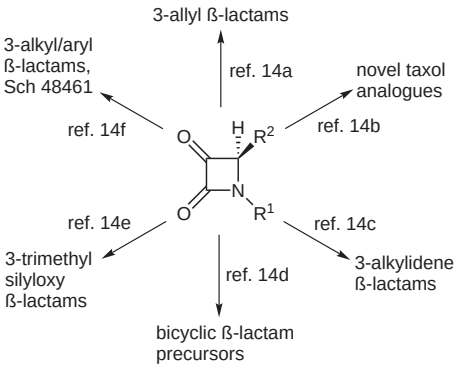

Figure 1 Applications of azetidine-2,3-diones in synthesis

The most widely used method for the synthesis of azetidine-2,3-diones is oxidation of 3-hydroxy β-lactams.[17] However, besides this method few other methods are also available in the literature.[18–21] Most of the reports dealing with the applications of enantiopure azetidine-2,3-diones[13–16] utilize the method of oxidation of corresponding 3-hydroxy β-lactams. Interestingly these chiral 3-hydroxy β-lactams have been synthesized starting with chiral imines. While this has proved to be a useful method, difficulties can be encountered in some cases. Some applications of β-lactams demand presence of aryl groups at N-1 and C-4 positions of the β-lactam.[14f,22] In such cases it becomes difficult to start with a chiral imine. Thus, a method which provides enantiopure azetidine-2,3-diones and simultaneously allows flexibility in the choice of substituents on the imine moiety is desired. Towards this end we have devised a short route to enantiopure azetidine-2,3-diones starting with L-(+)-diethyl tartrate.

Commercially available L-(+)-diethyl tartrate was protected as an acetonide **2** following a reported procedure[23] (Scheme 1). Selective hydrolysis of one of the ester groups of **2** yielded mono acid in good yield, which was subsequently converted into acid chloride **3** by refluxing with oxalyl chloride in dichloromethane. Acid chloride **3** was used as a ketene precursor in Staudinger cycloaddition reaction, which reacted cleanly with imines **4a**–**c** to furnish a diastereomeric mixture of spiro-β-lactams **5a**–**c** and **6a**–**c** in about 60:40 ratio as indicated by the ^{1}H NMR.[24] Both diastereomers displayed a strong band around 1755 cm^{-1} in the IR spectrum indicating the presence of a β-lactam group. The only proton on the lactam ring appeared as a singlet at δ = 5.19 and δ = 4.87 in the major diastereomer **5a** and the minor diastereomer **6a**, respectively, along with other signals from the tartrate moiety. Absolute configurations at the newly generated chiral centers were determined with the help of single crystal X-ray analyses. Major diastereomer **5a** on X-ray analysis[25] (Figure 2) was found to have configuration 3*S*,4*S*. However, the minor isomer could not be obtained in crystalline form.

Figure 3 depicts all the theoretically possible products of Staudinger cycloaddition between the diethyl tartrate derived ketene and imines. With the attack of imine possible

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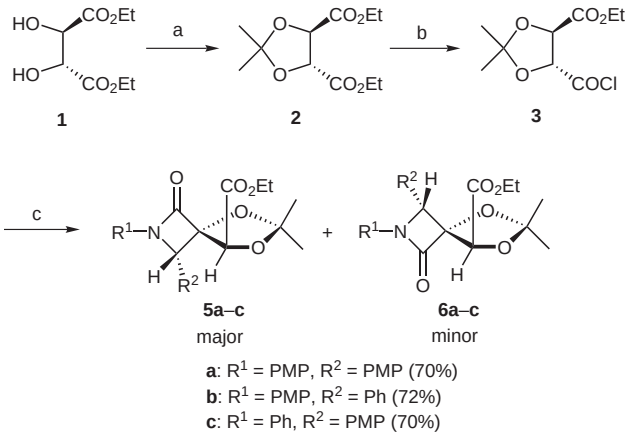


Scheme 1 *Reagents and conditions*: (a) 2,2-dimethoxy propane, benzene, PTSA, reflux, 5 h; (b) (i) NaOH, THF–H_2O, r.t., 4–6 h; (ii) $(COCl)_2$, CH_2Cl_2, reflux, 5 h; (c) $R^1N{=}CHR^2$ (**4a**–**c**), Et_3N, CH_2Cl_2, –40 °C to r.t., 15 h.

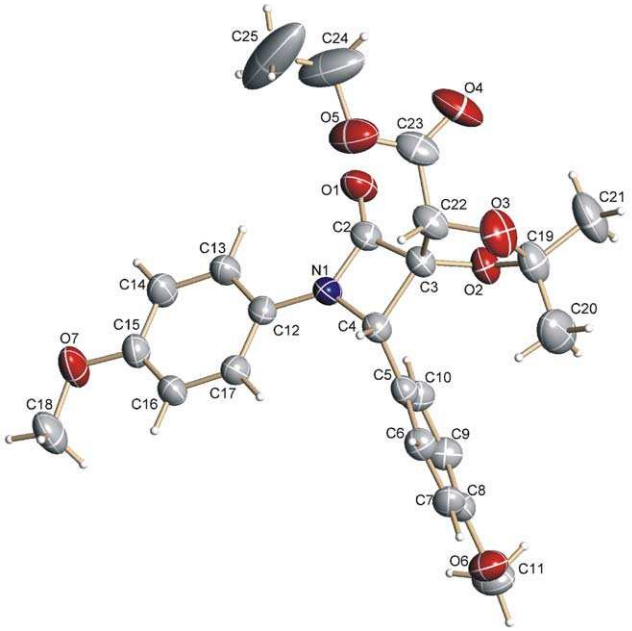


Figure 2 ORTEP diagram of **5a**

from four directions, theoretically four diastereomers are possible. We envisaged that the torquoelectronic effect[26] of the oxygen substituent on the ketene would prohibit attack from its side, thereby completely eliminating the possibility of formation of products **5′** and **6′**. Reaction indeed followed the expected course and the only products obtained were **5a**–**c** and **6a**–**c**, which arise from the attack of imine taking place from the opposite side of the oxygen substituent. The ethoxy carbonyl substituent due to its lesser bulk and distance from the reaction center exerted only little steric influence resulting into low diastereoselectivity. However, both the diastereomers could be easily separated by careful flash column chromatography.

Deprotection of acetonide to furnish diols **7a**–**c** and **8a**–**c** proceeded cleanly using anhydrous $FeCl_3$ in dichloromethane[24,27] (Scheme 2). One of the diols **8b** derived from minor diastereomer **6b** offered crystalline product. It helped to establish the absolute configuration of the β-lactam ring carbons via X-ray analysis.[25] Minor diastereomer **8b** (Figure 4) was found to have 3*R*,4*R* absolute configuration.

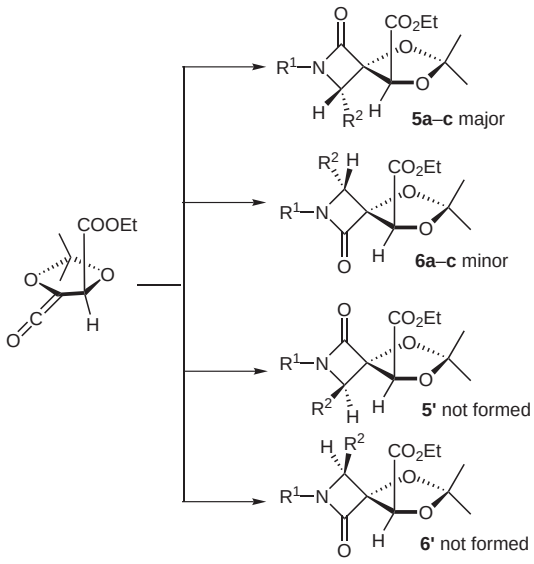
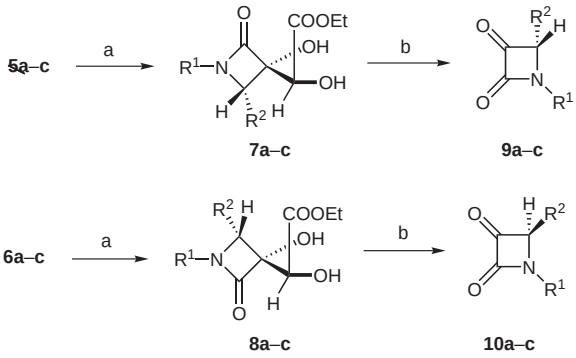


Figure 3 Theoretically possible products from diethyl tartrate derived ketene



Scheme 2 *Reagents and conditions*: (a) $FeCl_3$, CH_2Cl_2, r.t., 2 h; (b) $NaIO_4$, acetone–water, r.t., 6–8 h.

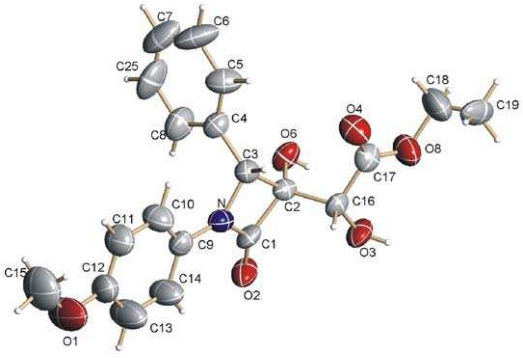


Figure 4 ORTEP diagram of **8b**

The oxidative cleavage of these diols **7a–c** and **8a–c** by sodium periodate in acetone–water mixture[24] provided the corresponding azetidine-2,3-diones **9a–c** and **10a–c** in excellent yields (Table 1). Major diastereomers of spiro-β-lactams yielded (4*S*)-azetidine-2,3-diones, while minor diastereomers furnished (4*R*)-azetidine-2,3-diones.

Table 1 Synthesis of Azetidine-2,3-diones **9a–c** and **10a–c**

Entry	β-Lactam	Diones	Yield (%)[a]	$[\alpha]_D^{26}$ ($CHCl_3$)
1	**5a**	**9a**	74	+53.3 (*c* = 0.9)
2	**5b**	**9b**	78	+123.0 (*c* = 2.0)
3	**5c**	**9c**	81	+80.0 (*c* = 0.8)
4	**6a**	**10a**	77	–54.6 (*c* = 1.5)
5	**6b**	**10b**	74	–123.6 (*c* = 1.1)
6	**6c**	**10c**	75	–79.2 (*c* = 5.3)

[a] Isolated overall yields from spiro-β-lactam **5a–c** and **6a–c**.

Stereoselective reduction of the keto group of racemic azetidin-2,3-diones to the corresponding 3-hydroxy azetidin-2-ones with sodium borohydride is known.[28] To confirm the absolute configuration of azetidin-2,3-diones we carried out reduction of one of the diones (**9b**) to a known 3-hydroxy β-lactam. The spectral data and the specific rotation[29] {(3*R*,4*S*)-3-hydroxy-1-(4-methoxyphenyl)-4-phenyl azetidin-2-one; observed $[\alpha]_D^{26}$ +177.7 (*c* = 0.18, $CHCl_3$); Lit.[29] $[\alpha]_D$ +176.0 (*c* = 1.00, $CHCl_3$)} were in good agreement with those of the reported compound. 3-Hydroxy-4-aryl β-lactams are also important synthetic targets as they have been shown to be synthons for the phenyl isoserine side chain of taxol[30,31] and all the four isomers of cytoxazone.[32]

In conclusion, we have developed a short synthesis of azetidine-2,3-diones from L-(+)-diethyl tartrate. This work represents the first report describing a convenient access to enantiopure azetidine-2,3-diones with aromatic substituents at the N-1 and C-4 positions of the β-lactam. The methodology consists of fewer steps, is operationally simple and can be adopted for large-scale preparation. Enantiopure 3-hydroxy β-lactams can also be accessed easily from azetidine-2,3-diones in good yields.

Acknowledgment

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References and Notes

(1) For reviews on β-lactam antibiotics, see: (a) Durkheimer, W.; Blumbatch, J.; Lattrell, R.; Scheunemann, K. H. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 180. (b) *Chemistry and Biology of β-Lactam Antibiotics*, Vol. 1; Morin, R. B.; Gorman, M., Eds.; Academic Press: New York, **1982**. (c) *Chemistry and Biology of β-Lactam Antibiotics*, Vol. 2; Morin, R. B.; Gorman, M., Eds.; Academic Press: New York, **1982**. (d) *Chemistry and Biology of β-Lactam Antibiotics*, Vol. 3; Morin, R. B.; Gorman, M., Eds.; Academic Press: New York, **1982**. (e) 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. (f) Southgate, R. *Contemp. Org. Synth.* **1994**, *1*, 417. (g) *The Chemistry of β-Lactams*; Page, M. I., Ed.; Chapman and Hall: London, **1992**.

(2) Rothstein, J. D.; Patel, S.; Regan, M. R.; Haenggelli, C.; Huang, Y. H.; Bergles, D. E.; Jin, L.; Hoberg, M. D.; Vidensky, S.; Chung, D. S.; Toan, S. V.; Bruijn, L. I.; Su, Z.-Z.; Gupta, P.; Fisher, P. B. *Nature (London)* **2005**, *433*, 73.

(3) (a) Burnett, D. A.; Caplen, M. A.; Davis, H. R. Jr.; Burrie, R. E.; Clader, J. W. *J. Med. Chem.* **1994**, *37*, 1733. (b) Dugar, S.; Yumibe, N.; Clader, J. W.; Vizziano, M.; Huie, K.; van Heek, M.; Compton, D. S.; Davis, H. R. Jr. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1271. (c) Wu, G. G. *Process Res. Det.* **2004**, *4*, 298.

(4) Han, W. T.; Trehan, A. K.; Wright, J. J. K.; Federici, M. E.; Seiler, S. M.; Meanwell, N. A. *Bioorg. Med. Chem.* **1995**, *3*, 1123.

(5) Borthwick, A. D.; Weingarten, G.; Haley, T. M.; Tomaszewski, M.; Wang, W.; Hu, Z.; Bedard, J.; Jin, H.; Yuen, L.; Mansour, T. S. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 365.

(6) Cainelli, G.; Galletti, P.; Garbisa, S.; Giacomini, D.; Sartor, L.; Quintavalla, A. *Bioorg. Med. Chem.* **2003**, *11*, 5391.

(7) (a) Doherty, J. B.; Ashe, B. M.; Agrenbright, L. W.; Baker, P. L.; Bonney, R. J.; Chandler, G. O.; Dahlgren, M. E.; Dorn, C. P. Jr.; Finke, P. E.; Firestone, R. A.; Fletcher, D.; Hagemann, W. K.; Munford, R.; O'Grady, L.; Maycock, A. L.; Pisano, J. M.; Shah, S. K.; Thompson, K. R.; Zimmerman, M. *Nature (London)* **1986**, *322*, 192. (b) Cvetovich, R. J.; Chartran, M.; Hartner, F. W.; Roberge, C.; Amato, J. S.; Grabowski, E. J. *J. Org. Chem.* **1996**, *61*, 6575.

(8) (a) Zhou, N. E.; Guo, D.; Thomas, G.; Reddy, A. V. N.; Kaleta, J.; Purisima, E.; Menard, R.; Micetich, R. G.; Singh, R. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 139. (b) Setti, E. L.; Davis, D.; Chung, T.; McCarter, J. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2051.

(9) (a) Smith, D. M.; Kazi, A.; Smith, L.; Long, T. E.; Heldreth, B.; Turos, E.; Dou, Q. P. *Mol. Pharmacol.* **2002**, *61*, 1348. (b) Kazi, A.; Hill, R.; Long, T. E.; Kuhn, D. J.; Turos, E.; Dou, Q. P. *Biochem. Pharmacol.* **2004**, *67*, 365.

(10) (a) Alonso, E.; Lopez-Ortiz, F.; del Pozo, C.; Peratta, E.; Macias, A.; Gonzalez, J. *J. Org. Chem.* **2001**, *66*, 6333. (b) Bittermann, H.; Gmeiner, P. *J. Org. Chem.* **2006**, *71*, 97.

(11) Alonso, E.; del Pozo, C.; Gonzalez, J. *Synlett* **2002**, 69.

(12) (a) Broccolo, F.; Carnally, G.; Caltabiano, G.; Cocuzza, C. E. A.; Fortuna, C. G.; Galletti, P.; Giacomini, D.; Musumarra, G.; Musumeci, R.; Quitavalla, A. *J. Med. Chem.* **2006**, *49*, 2804. (b) Alcaide, B.; Almendros, P. *Curr. Med. Chem.* **2004**, *11*, 1921. (c) Deshmukh, A. R. A. S.; Bhawal, B. M.; Krishnaswamy, D.; Govande, V. V.; Shinkre, B. A.; Jayanthi, A. *Curr. Med. Chem.* **2004**, *11*, 1889. (d) Singh, G. S. *Tetrahedron* **2003**, *59*, 7631. (e) Alcaide, B.;

Almendros, P. *Synlett* **2002**, 381. (f) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbid, M. *Synlett* **2001**, 1813. (g) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbid, M. In *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; Wiley-VCH: New York, **1997**, 279.

(13) Palomo, C.; Aizpurua, J. M.; Urchegui, R.; Garcia, J. M. *J. Chem. Soc., Chem. Commun.* **1995**, 2327.

(14) (a) Jayaraman, M.; Manhas, M. S.; Bose, A. K. *Tetrahedron Lett.* **1997**, *38*, 709. (b) Kant, J.; Schwartz, W. S.; Fairchild, C.; Gao, Q.; Huang, S.; Long, B. H.; Kadow, J. F.; Langley, D. R.; Farina, V.; Vyas, D. *Tetrahedron Lett.* **1996**, *37*, 6495. (c) Palomo, C.; Aizpurua, J. M.; Lopez, M. C.; Aurrekoetxea, N.; Oiarbide, M. *Tetrahedron Lett.* **1990**, *31*, 6425. (d) Palomo, C.; Aizpurua, J. M.; Cossio, F. P.; Garcia, J. M.; Lopez, M. C.; Oiarbide, M. *J. Org. Chem.* **1990**, *55*, 2070. (e) Palomo, C.; Aizpurua, J. M.; Lopez, M. C.; Aurrekoetxea, N.; Oiarbide, M. *Tetrahedron Lett.* **1990**, *31*, 2205. (f) Tiwari, D. K.; Gumaste, V. K.; Deshmukh, A. R. A. S. *Synthesis* **2006**, 115.

(15) (a) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Odriozola, B.; Maneiro, E.; Miranda, J. I.; Urchegui, R. *Chem. Commun.* **1996**, 161. (b) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Carreaux, F.; Cuevas, C.; Maneiro, E.; Ontoria, J. M. *J. Org. Chem.* **1994**, *59*, 3123.

(16) Alcaide, B.; Almendros, P.; Aragoncillo, C. *Chem. Commun.* **2000**, 757.

(17) Cossio, F. P.; Lopez, C.; Oiarbide, M.; Palomo, C.; Apariocio, D.; Rubiales, G. *Tetrahedron Lett.* **1988**, *29*, 3133.

(18) Cossio, F. P.; Ganboa, I.; Garcia, J. M.; Lecea, B.; Palomo, C. *Tetrahedron Lett.* **1987**, *28*, 1945.

(19) (a) Manhas, M. S.; Bari, S. S.; Bhawal, B. M.; Bose, A. K. *Tetrahedron Lett.* **1984**, *25*, 4733. (b) Van der Veen, J. M.; Bari, S. S.; Krishnan, L.; Manhas, M. S.; Bose, A. K. *J. Org. Chem.* **1989**, *54*, 5758.

(20) (a) Tufariello, J. J.; Pinto, D. J. P.; Milowsky, A. S.; Reinhardt, D. V. *Tetrahedron Lett.* **1987**, *28*, 5481. (b) Lysek, R.; Lipkowska, Z. U.; Chmielewski, M. *Tetrahedron* **2001**, *57*, 1301. (c) Danh, T. T.; Borsuk, K.; Solecka, J.; Chmielewski, M. *Tetrahedron* **2006**, *62*, 10928.

(21) Kai, H.; Orita, A.; Murai, S. *Synth. Commun.* **1998**, *28*, 1989.

(22) (a) Burnett, D. A.; Caplen, M. A.; Davis, H. R. Jr.; Burrier, R. E.; Clader, J. W. *J. Med. Chem.* **1994**, *37*, 1733. (b) Burnett, D. A. *Tetrahedron Lett.* **1994**, *37*, 7339.

(23) Carmack, M.; Kelly, C. J. *J. Org. Chem.* **1968**, *33*, 2171.

(24) **Typical Procedure for Spiro-β-lactams 5a and 6a**: A solution of acid chloride **3** (0.371 g, 1.84 mmol) in anhyd dichloromethane (10 mL) was added dropwise over a period of 20–30 min to a solution of imine **4a** (0.296 g, 1.23 mmol) and triethyl amine (0.77 mL, 5.53 mmol) in anhyd dichloromethane (20 mL) at –40 °C. After the addition was complete the solution was allowed to attain r.t. and stirred for 15 h (TLC). The reaction mixture was then diluted with dichloromethane and washed with H_2O (2 × 10 mL) and sat. brine solution (10 mL). The combined organic layer was dried over anhyd Na_2SO_4, filtered and concentrated under reduced pressure to get the crude diastereomeric mixture of **5a** and **6a** (0.480 g, 70%). ^{1}H NMR of the crude product showed a 60:40 mixture of diastereomers which were separated by careful flash column chromatography [PE–EtOAc (8:2)].

(3*S*,4*S*,8*R*)-1,2-Bis(4-methoxyphenyl)-6,6-dimethyl-3-oxo-5,7–dioxa-2-azaspiro[3.4]octane-8-carboxylic Acid Ethyl Ester (5a): yield: 42%; colorless crystals; mp 163–164 °C; $[\alpha]_D^{26}$ +1.4 (*c* = 2.7, $CHCl_3$). IR ($CHCl_3$): 1751, 1755 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.04 (s, 3 H, Me), 1.12 (t, *J* = 7.2 Hz, 3 H, OCH_2CH_3), 1.60 (s, 3 H, Me), 3.74 (s, 3 H, Me), 3.81 (s, 3 H, Me), 4.16–4.29 (m, 2 H, OCH_2), 5.02 (s, 1 H, C8-H), 5.19 (s, 1 H, C3-H), 6.79 (d, *J* = 8.9 Hz, 2 H, ArH), 6.91 (d, *J* = 8.9 Hz, 2 H, ArH), 7.25–7.31 (m, 4 H, ArH). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.7, 25.6, 26.5, 55.1, 55.2, 61.8, 68.0, 78.1, 92.5, 113.6, 113.9, 114.1, 118.7, 124.9, 129.2, 130.3, 156.2, 159.8, 163.3, 167.9. MS: *m*/*z* = 442 [M + 1]. Anal. Calcd for $C_{24}H_{27}NO_7$: C, 65.29; H, 6.16; N, 3.17. Found: C, 65.18; H, 6.29; N, 3.03.

(3*R*,4*R*,8*R*)-1,2-Bis(4-methoxyphenyl)-6,6-dimethyl-3-oxo-5,7–dioxa-2-azaspiro[3.4]octane-8-carboxylic Acid Ethyl Ester (6a): yield: 28%; brown viscous liquid; $[\alpha]_D^{26}$ –7.0 (*c* = 2.8, $CHCl_3$). IR ($CHCl_3$): 1751, 1755 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.06 (s, 3 H, Me), 1.11 (t, *J* = 7.2 Hz, 3 H, OCH_2CH_3), 1.47 (s, 3 H, Me), 3.75 (s, 3 H, Me), 3.80 (s, 3 H, Me), 4.18–4.30 (m, 2 H, OCH_2CH_3), 4.87 (s, 1 H, C3-H), 5.03 (s, 1 H, C8-H), 6.79 (d, *J* = 9.0 Hz, 2 H, ArH), 6.87 (d, *J* = 9.0 Hz, 2 H, ArH), 7.25–7.30 (m, 4 H, ArH). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.8, 25.6, 26.1, 55.0, 55.2, 61.7, 65.7, 77.0, 90.9, 113.1, 113.7, 114.2, 118.7, 124.5, 129.1, 130.3, 156.3, 159.7, 163.4, 167.6. MS: *m*/*z* = 442 [M + 1]. Anal. Calcd for $C_{24}H_{27}NO_7$: C, 65.29; H, 6.16; N, 3.17. Found: C, 65.42; H, 6.10; N, 3.25.

Typical Procedure for Diol 7a: To a solution of spiro-β-lactam **5a** (0.200 g, 0.453 mmol) in dichloromethane (10 mL) was added anhyd $FeCl_3$ (0.147 g, 0.907 mmol) at r.t. and stirred for 2 h. After completion of the reaction (TLC) the reaction mixture was passed through a celite bed. The filtrate was concentrated in vacuo to get the crude diol **7a**. The crude product was purified by column chromatography [PE–EtOAc (3:2)] to obtain pure diol **7a** (0.162 g, 89%).

(3*S*,4*S*)-Hydroxy-[3-hydroxy-1,2-bis(4-methoxyphenyl)-4-oxoazetidin-3-yl]acetic Acid Ethyl Ester (7a): yield: 89%; thick brown oil; $[\alpha]_D^{26}$ +20 (*c* = 1.1, $CHCl_3$). IR ($CHCl_3$): 1731, 1735, 3377 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.29 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3), 2.05 (s, 2 H, OH), 3.75 (s, 3 H, OMe), 3.80 (s, 3 H, OMe), 4.32 (quart, *J* = 7.1 Hz, 2 H, OCH_2CH_3), 5.27 (s, 1 H, C*H*COOEt), 5.30 (s, 1 H, C4-H), 6.79 (d, *J* = 9.0 Hz, 2 H, ArH), 6.91 (d, *J* = 8.9 Hz, 2 H, ArH), 7.21–7.30 (m, 4 H, ArH). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.9, 55.1, 55.3, 62.3, 63.3, 71.0, 86.3, 114.1, 119.0, 124.5, 129.0, 130.0, 156.3, 159.8, 164.2, 171.5. MS: *m*/*z* = 402 [M + 1]. Anal. Calcd for $C_{21}H_{23}NO_7$: C, 62.83; H, 5.78; N, 3.49. Found: C, 62.72; H, 5.94; N, 3.60.

(3*R*,4*R*)-Hydroxy-[3-hydroxy-1,2-bis(4-methoxyphenyl)-4-oxo-azetidin-3-yl]acetic Acid Ethyl Ester (8a): yield: 88%; thick brown oil; $[\alpha]_D^{26}$ –25.6 (*c* = 2.5, $CHCl_3$). IR ($CHCl_3$): 1731, 1737, 3371 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.26 (t, *J* = 7.2 Hz, 3 H, OCH_2CH_3), 2.04 (s, 2 H, OH), 3.74 (s, 3 H, OMe), 3.79 (s, 3 H, OMe), 4.30 (quart, *J* = 7.2 Hz, 2 H, OCH_2CH_3), 4.63 (s, 1 H, C4-H), 5.30 (s, 1 H, C*H*COOEt), 6.78 (d, *J* = 9.1 Hz, 2 H, ArH), 6.91 (d, *J* = 8.9 Hz, 2 H, ArH), 7.23–7.30 (m, 4 H, ArH). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.5, 55.2, 55.3, 61.9, 63.2, 71.1, 86.8, 114.1, 119.2, 124.5, 129.1, 130.0, 156.9, 159.7, 164.3, 171.5. MS: *m*/*z* = 402 [M + 1]. Anal. Calcd for $C_{21}H_{23}NO_7$: C, 62.83; H, 5.78; N, 3.49. Found: C, 62.75; H, 5.69; N, 3.32.

Typical Procedure for Dione 9a: To a solution of diol **7a** (0.105 g, 0.261 mmol) in acetone–water (2:1, 6 mL) was added powdered $NaIO_4$ and the solution was stirred for 6–8 h. After completion of the reaction (TLC), the reaction mixture was filtered through a Büchner funnel and the residue was washed with acetone (5 mL). The combined filtrates were evaporated in vacuo to remove acetone. The residue was extracted with dichloromethane (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure to get the crude dione **9a** as a yellow solid. The

crude product was purified by column chromatography [PE–EtOAc (8:2)] to get pure dione **9a** as a yellow solid (0.065 g, 84%).

(4*S*)-1,4-Bis(4-methoxyphenyl)azetidine-2,3-dione (9a): yield: 84%; yellow solid; mp 144 °C; $[\alpha]_D^{26}$ +53.3 (*c* = 0.9, $CHCl_3$). IR ($CHCl_3$): 1755, 1809, 1832 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 3.79 (s, 3 H, OMe), 3.80 (s, 3 H, OMe), 5.51 (s, 1 H, C4-H), 6.85–6.94 (m, 4 H, ArH), 7.24 (d, *J* = 9.3 Hz, 2 H, ArH), 7.46 (d, *J* = 9.1 Hz, 2 H, ArH). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 55.2, 55.4, 74.4, 114.6, 114.8, 119.6, 123.5, 127.7, 129.8, 157.8, 160.1, 160.8, 191.1. MS: *m*/*z* = 298 [M + 1]. Anal. Calcd for $C_{17}H_{15}NO_4$: C, 68.68; H, 5.09; N, 4.71. Found: C, 68.85; H, 5.19; N, 4.62.

(4*R*)-1,4-Bis(4-methoxyphenyl)azetidine-2,3-dione (10a): yield: 85%; $[\alpha]_D^{26}$ –54.6 (*c* = 1.5, $CHCl_3$). The spectral data of **10a** was identical to that of **9a**. Anal. Calcd for $C_{17}H_{15}NO_4$: C, 68.68; H, 5.09; N, 4.71. Found: C, 68.50; H, 5.22; N, 4.67.

(25) **X-ray Data for 5a and 8b**: Single crystals of the **5a** and **8b** were grown by slow evaporation of the solution mixture in EtOAc and PE. The X-ray data of **5a**–**8b** were collected on a SMART APEX CCD single crystal X-ray diffractometer with omega and phi scan mode and different number of scans and exposure times for different crystals using λ(MoK_α) = 0.71073 Å radiation at T = 293 (2) K with oscillation/frame = –0.3°, maximum detector swing angle = –30.0°, beam center = (260.2, 252.5), in plane spot width = 1.24. All the data were corrected for Lorentzian, polarization and absorption effects using SAINT and SADABS programs. The crystal structures were solved by direct method using SHELXS-97 and the refinement was performed by full matrix least squares of F^2 using SHELXL-97.[33]

Crystal Data for 5a ($C_{24}H_{27}NO_7$): M = 441.47; crystal dimensions: 0.52 × 0.47 × 0.33 mm, multirun data acquisition. Total scans = 3, total frames = 1818, exposure/frame = 10.0 s/frame, range = 1.98°–27.00°, completeness to of 27.0°: 100.0%. Crystals belonged to monoclinic, space group $P2_1/c$, *a* = 10.8952(5) Å, *b* = 23.954(1) Å, *c* = 9.4343(5) Å, *β* = 109.280(3)°, *V* = 2324.1(2) $Å^3$, *Z* = 4, D_c = 1.262 mg/m^3, *μ* (MoK_α) = 0.093 mm^{-1}, *T* = 293(2) K, 16695 reflections measured, 4083 unique [I > 2σ(I)], *R* value = 0.0482, wR^2 = 0.1268. X-ray analysis revealed the stereochemistry at C(3) and C(4) positions. The supplementary crystallographic data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.uk/data_request/cif. Please quote the reference number CCDC 647625.

Crystal Data for 8b ($C_{20}H_{21}NO_6$): M = 371.38; crystal dimensions: 0.51 × 0.11 × 0.03 mm, hemisphere data acquisition. Total scans = 3, total frames = 1271, exposure/frame = 15.0 s/frame, range = 2.07°–24.99°, completeness to of 24.99º: 99.4%. Crystals belonged to monoclinic, space group $P2_1$, *a* = 11.324(1) Å, *b* = 5.3940(7) Å, *c* = 15.822(2) Å, *β* = 98.893(3)°, *V* = 954.8(2) $Å^3$, *Z* = 2, D_c = 1.292 mg/m^3, *μ* (MoK_α) = 0.096 mm^{-1}, *T* = 293(2) K, 4764 reflections measured, 2759 unique [I >2σ(I)], *R* value = 0.0696, wR^2 = 0.1552. X-ray analysis revealed the stereochemistry at C(3) and C(4) positions. The end atom C(19) had positional disorder. The supplementary crystallographic data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.uk/data_request/cif. Please quote the reference number CCDC 647624.

(26) Alonso, E.; del Pozo, C.; Gonzalez, J. *J. Chem. Soc., Perkin Trans. 1* **2002**, 571.
(27) Sen, S. E.; Roach, S. L.; Boggs, J. K.; Ewing, G. J.; Magrath, J. *J. Org. Chem.* **1997**, *62*, 6684.
(28) Palomo, C.; Arrieta, A.; Cossio, F. P.; Aizpurua, J. M.; Mielgo, A.; Aurrekoetxea, N. *Tetrahedron Lett.* **1990**, *31*, 6429.
(29) Srirajan, V.; Deshmukh, A. R. A. S.; Bhawal, B. M. *Tetrahedron* **1996**, *52*, 5585.
(30) Denis, J.-N.; Greene, A. E.; Serra, A. A.; Luche, M. J. *J. Org. Chem.* **1986**, *51*, 46.
(31) Denis, J.-N.; Greene, A. E.; Gueritte-Voegelein, F.; Mangatal, L.; Potier, P. *J. Am. Chem. Soc.* **1988**, *110*, 5917.
(32) Mishra, R. K.; Coates, C. M.; Revell, K. D.; Turos, E. *Org. Lett.* **2007**, *9*, 575.
(33) Sheldrick, G. M. *SHELX-97: Program for Crystal Structure Solution and Refinement*; University of Göttingen: Germany, **1997**.