CHEMISTRY
AN ASIAN JOURNAL
www.chemasianj.org

Accepted Article

Title: Furan Derived Chiral Bicycloaziridino Lactone Synthon: Collective Syntheses of Oseltamivir Phosphate (Tamiflu), (S)-Pipecolic acid and its 3-Hydroxy Derivatives

Authors: S. P. Chavan, Appasaheb L. Kadam, Shrikrishna S. Shinde, and Rajesh G. Gonnade

To be cited as: *Chem. Asian J.* 10.1002/asia.201901523

Link to VoR: http://dx.doi.org/10.1002/asia.201901523

A Journal of
ACES Asian Chemical Editorial Society

A sister journal of Angewandte Chemie and Chemistry – A European Journal

WILEY-VCH

10.1002/asia.201901523

WILEY-VCH

Furan Derived Chiral Bicycloaziridino Lactone Synthon: Collective Syntheses of Oseltamivir Phosphate (Tamiflu), (*S*)-Pipecolic acid and its 3-Hydroxy Derivatives

Subhash P. Chavan,*[a],[b] Appasaheb L. Kadam,[a],[b] Shrikrishna S. Shinde,[a] and Rajesh G. Gonnade[b],[c]

Abstract: The unified synthetic strategy for oseltamivir phosphate (tamiflu), (*S*)-pipecolic acid, and its 3-hydroxy derivatives from furan derived common chiral bicycloaziridino lactone synthon is described here. Key features are short (4-steps), enantiopure, and decagram scale synthesis of common chiral synthon from furan and its first-ever application in the total synthesis of biologically active compounds by taking the advantages of high functionalization ability of chiral synthon.

Introduction

Aziridines are useful synthons in the synthesis of a wide variety of alkaloids and medicinally important drug molecules due to their unique chemical reactivity.[1] The inherent ring strain of aziridine ring allows the regioselective and stereoselective transformation of this small *N*-containing ring system for its elegant use in the synthesis of biologically active molecules.[2] In the past decade, considerable progress has been made in the field of stereoselective synthesis of aziridines. However, regioselectivity and stereoselectivity, as well as complexity associated with the catalysts to be prepared and, most importantly, synthesis of aziridine synthon, which is stable at room temperature for its practical use in the synthesis of bioactive compounds are the main challenges and need further improvement.[3]

Due to our continued interest in the synthesis of biologically active compounds that are having societal importance,[4] synthetic studies towards tamiflu, pipecolic acid, and its 3-hydroxy derivatives were initiated in our group using chiral aziridine as a building block. Tamiflu (**1,** oseltamivir phosphate) which is neuraminidase inhibitor was first developed by Gilead Sciences for the treatment of swine flu (H5N1 human flu), whereas pipecolic acid and its 3-hydroxy derivatives (**2**, **3**, and **4**) are important building blocks for the synthesis of various biologically active compounds (**Figure 1**).

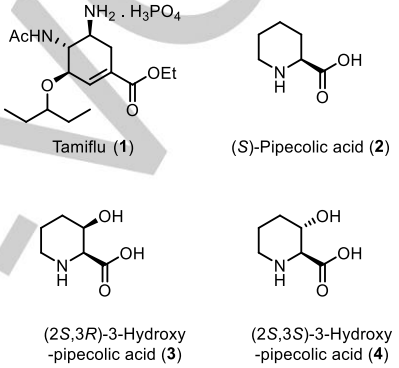


Figure 1. Structures of tamiflu and piperidine alkaloids.

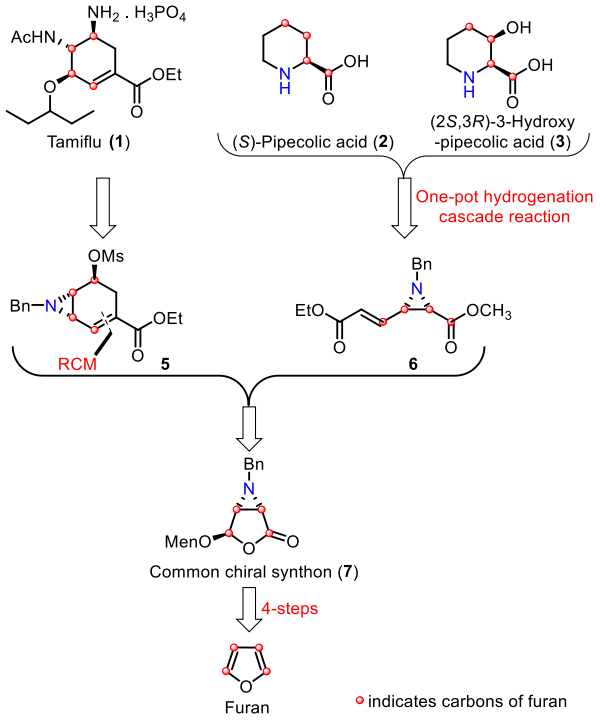
To date, several synthetic approaches for the synthesis of tamiflu, pipecolic acid, and its 3-hydroxy derivatives are reported in the literature.[5,6] Out of these, there are only a few reports in which chiral aziridines were used as the starting material. Of note, in literature reports, there is a lack of scalable route for the synthesis of a common aziridine building block in less number of steps for the collective synthesis of bioactive compounds using simple reagents and reaction conditions.[3] In that context, development of synthetic methodologies for the scalable asymmetric synthesis of aziridine building block in lower number of steps using simple reagents and reaction conditions is highly desirable. In the present report, a unified synthetic strategy for the synthesis of tamiflu, pipecolic acid, and its 3-hydroxy derivatives using furan derived common chiral bicycloaziridino lactone synthon is described.

The retrosynthetic plan is outlined in **Scheme 1**. We envisioned that the common chiral synthon **7** could be an ideal choice for the collective synthesis of tamiflu and piperidine class of alkaloids in enantioselective fashion. Core skeleton **5** of tamiflu (**1**) could be synthesized by using ring-closing metathesis (RCM) of diene derived from common chiral synthon **7**, whereas piperidine alkaloids (*S*)-pipecolic acid (**2**) and (2*S*,3*R*)-3-hydroxypipecolic acid (**3**) could be constructed through regioselective ring-opening and reductive cyclization of functionalized vinyl aziridine **6** derived from common chiral synthon **7**. The common chiral synthon **7**, in turn, could be obtained from a non-chiral starting material furan by taking the advantages of chiral resolution of bromo-butenolide using menthol as a chiral auxiliary.

[a] Dr. S. P. Chavan, A. L. Kadam, S. S. Shinde
Division of Organic Chemistry
CSIR-National Chemical Laboratory
Pune 411008, India
E-mail: sp.chavan@ncl.res.in
[b] Dr. S. P. Chavan, A. L. Kadam, Dr. R. G. Gonnade
Academy of Scientific and Innovative Research (AcSIR)
New Delhi 110025, India
[c] Dr. R. G. Gonnade
Physical and Materials Chemistry Division
CSIR-National Chemical Laboratory
Pune 411008, India

Supporting information for this article is given via a link at the end of the document.

10.1002/asia.201901523



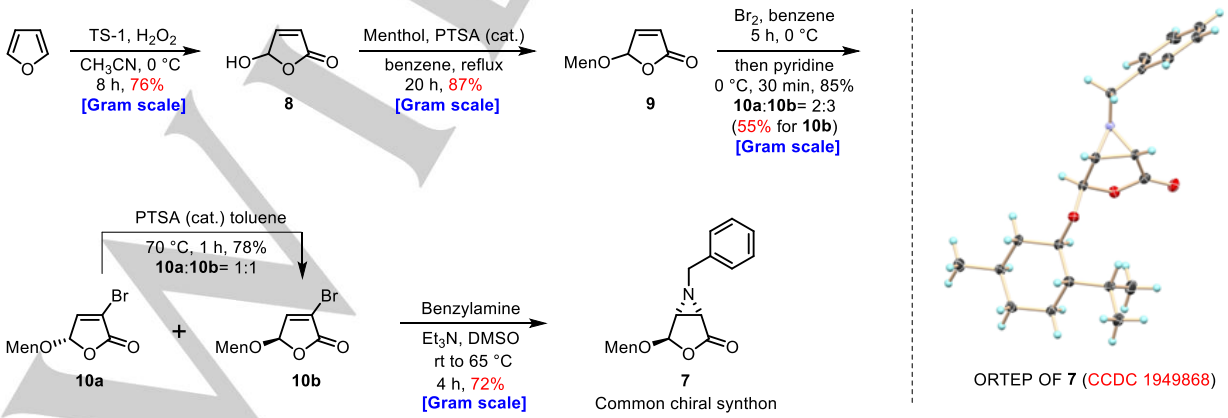
Scheme 1. Retrosynthetic analysis.

Results and Discussion

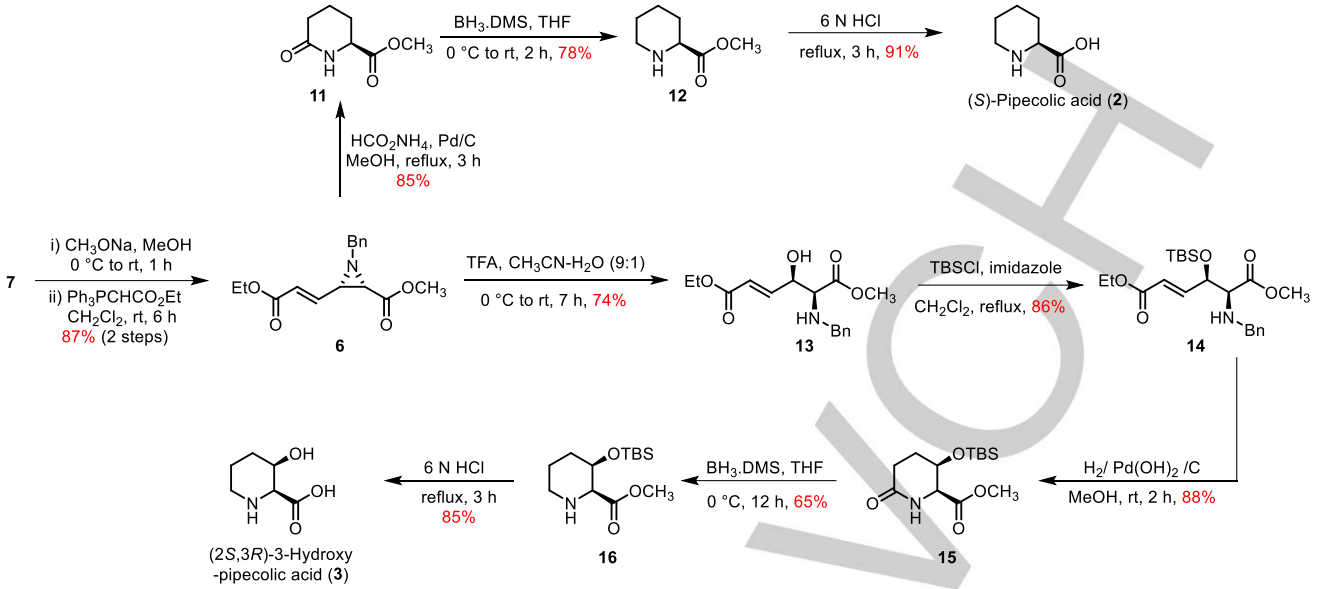
Synthesis commenced with the commercially available starting material furan (**Scheme 2**). Synthesis of hydroxy lactone **8** from furan was achieved using a method developed by Kumar *et al.*[7] Furan on treatment with catalytic amount of titanium silicate molecular sieve (TS-1) catalyst and H_2O_2 in acetonitrile at 0 °C underwent oxidation to furnish 5-hydroxy-2(5*H*)-furanone **8** in 76% yield. The hydroxy-butenolide **8** was then refluxed with (–)-menthol in benzene in the presence of a catalytic amount of PTSA with azeotropic removal of water formed during the reaction to obtain product **9** containing a mixture of diastereomers in 87% combined yield.[8] Compound **9** was then treated with bromine in benzene at 0 °C for 5 h followed by treatment with pyridine at 0 °C to provide bromo-butenolides **10a** and **10b** as a mixture of diastereomers (ratio 2: 3) in 85% yield.[9] The major diastereomer **10b** was obtained in an enantiomerically pure form by recrystallization from *n*-hexane at -18 °C. The filtrate from recrystallization containing compound **10a** as a major diastereomer was treated with PTSA in toluene at 70 °C to obtain a mixture of **10a** and **10b** in 1:1 ratio in 78% yield and an additional amount of **10b** was obtained by the repetitions of the process of crystallization. The global yield obtained for the enantiomerically pure diastereomer **10b** was 55% from compound **9**. The spectral and analytical data obtained for **10b** were in complete agreement with the reported data.[9] In the next step, bromo-butenolide **10b** was treated with benzylamine and triethylamine in DMSO for 30 min at room temperature followed by heating at 65 °C for 4 h to furnish *cis*–aziridine **7** in 72% yield. Synthesis of common chiral bicycloaziridino lactone synthon **7** was achieved in four steps in 26% overall yield. The structure and absolute stereochemistry of synthon **7** were unequivocally confirmed by single-crystal X-ray analysis.

The main advantages of this methodology are decagram scale synthesis, lower number of reaction steps and enantiopure synthesis of aziridine skeleton from the non-chiral starting material. Here, it is noteworthy to mention that unlike other aziridine synthons, bicycloaziridino lactone **7** is a crystalline solid and has remarkably high stability at room temperature (Bicycloaziridino lactone **7** was stable for more than a year at room temperature without either decomposition or formation of side products).

To the best of our knowledge, the application of chiral bicycloaziridino lactone synthon **7** for the total synthesis of natural products is not reported in the literature. However, very closely related elegant work was reported by Dodd *et al.* involving the 3-step preparation of a similar chiral aziridino-γ-lactone synthon from ribonolactone and its application in natural product synthesis.[10] It may also be noted that Dodd *et al.* employed a chiral pool strategy against the current method, which describes a recyclable chiral auxiliary strategy to incorporate chirality.



Scheme 2. Synthesis of common chiral bicycloaziridino lactone synthon **7** from furan.

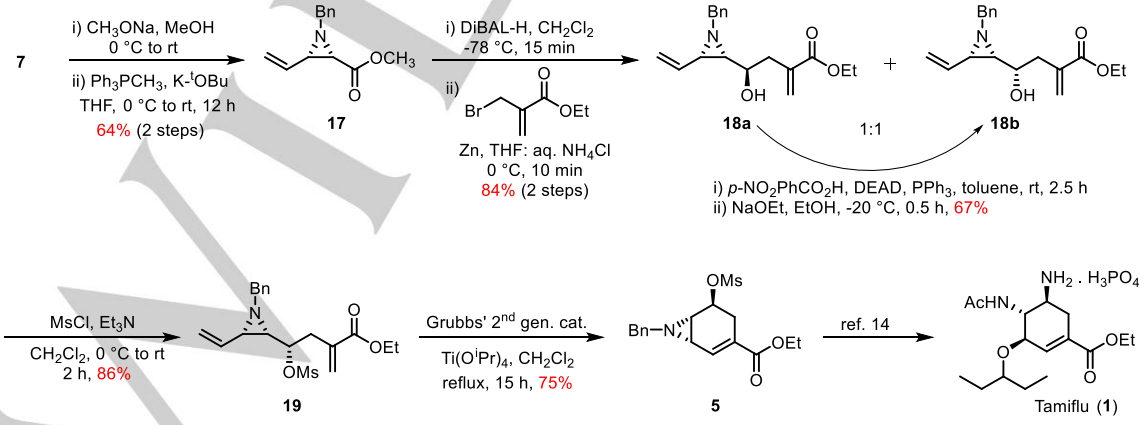


Scheme 3. Total synthesis of (*S*)-pipecolic acid and (2*S*,3*R*)-3-hydroxypipecolic acid from synthon **7**.

Moreover, using the current method, it is possible to synthesize opposite enantiomer of synthon **7** by utilizing the bromo-butenolide **10a** or by employing D-menthol as the chiral auxiliary. Syntheses of tamiflu, (*S*)-pipecolic acid, and its 3-hydroxy derivatives were undertaken to showcase the accessibility of diverse skeletons of bioactive molecules from synthon **7**. Furthermore, the synthetic approach described in this manuscript was inspired from the drawbacks of our previous syntheses of these molecules[4c,e,f] which employed chiral pool strategy and the disadvantages of these syntheses which involved separation of the diastereomeric mixture of aziridine synthon, protection-deprotection sequence and the sensitive acetal deprotection using Lewis acid in case of tamiflu synthesis. The current protocol utilizing common chiral synthon **7** overcomes most of the drawbacks encountered in our previous syntheses.

Based on this delibrations, lactone **7** was treated with $NaOCH_3$ in MeOH, and the crude aldehyde obtained was subjected for two carbon Wittig homologation to obtain vinyl aziridine **6** in 87% yield over 2 steps (**Scheme 3**). In the next step, vinyl aziridine **6** was subjected to transfer hydrogenation using ammonium formate and Pd/C in MeOH under reflux, to provide methyl-6-oxopipecolate **11** in 85% yield. Here, one-pot aziridine opening, olefin reduction, debenzylation, and cyclization were observed under hydrogenation condition.[11] Lactam **11** was reduced using BH_3.DMS to the corresponding amine **12** in 78% yield. In the last step, amino-ester **12** was treated with 6 N HCl under reflux to obtain (*S*)-pipecolic acid (**2**) in 91% yield. The spectral and analytical data obtained for (*S*)-pipecolic acid (**2**) were in complete agreement with the reported data.[4e]

For the total synthesis of (2*S*,3*R*)-3-hydroxypipecolic acid, vinyl aziridine **6** was regioselectively opened using TFA in CH_3CN-H_2O (9:1) to obtain amino-alcohol **13** in 74% yield (**Scheme 3**).



Scheme 4. Formal total synthesis of tamiflu from synthon **7**.

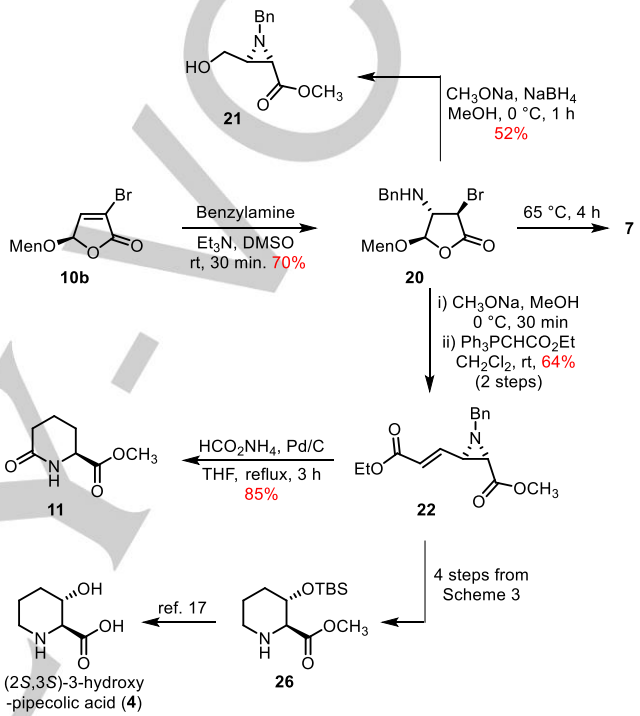
Amino-alcohol **13** was then treated with TBSCl and imidazole in CH_2Cl_2 to obtain TBS protected alcohol **14** in 86% yield. In the next step, compound **14** was subjected to hydrogenation using $Pd(OH)_2$ to afford lactam **15** in 88% yield. Lactam **15** was reduced using BH_3.DMS to the corresponding amine **16** in 65% yield. In the last step, amine **16** was subjected to ester hydrolysis and deprotection of the TBS group using 6 N HCl under reflux condition to furnish (2*S*,3*R*)-3-hydroxypipecolic acid (**3**) in 85% yield. The spectral and analytical data obtained for (2*S*,3*R*)-3-hydroxypipecolic acid (**3**) were in complete agreement with the reported data.[12]

After successful completion of the total synthesis of (*S*)-pipecolic acid and (2*S*,3*R*)-3-hydroxypipecolic acid, we turned our attention towards the synthesis of tamiflu (**1**) using bicycloaziridino lactone **7** as a key intermediate. Here, it was thought that the aziridine part of synthon **7** could be easily converted into 1,2-*trans*-diamine of the target molecule whereas lactone moiety could be converted into the six-membered core skeleton of tamiflu (**Scheme 4**). To this end, synthone **7** was treated with $NaOCH_3$ in MeOH, and the corresponding aldehyde was subjected to one carbon Wittig homologation to afford vinyl aziridine **17** in 64% yield over 2 steps. In the next step, ester **17** was reduced to the corresponding aldehyde using DiBAL-H at -78 °C followed by allylation using addition of allyl zinc reagent prepared by the reaction of zinc and ethyl 2-(bromomethyl)acrylate to the crude aldehyde to successfully produce the homoallyl alcohols **18a** and **18b** in 84% yield over 2 steps in the 1:1 ratio.

At this stage, we hopefully assumed that compound **18b** had the relative stereochemistry as shown in **Scheme 4**, although the relative stereochemistry was not confirmed until after it was converted into the known intermediate for tamiflu prepared by a different route. Nonetheless, the undesired diastereomer **18a** was effectively converted into the desired compound **18b** in 67% yield using Mitsunobu inversion followed by hydrolysis.[13] The compound **18b** was treated with mesyl chloride to obtain mesylate **19** in 86% yield.

After getting required diene **19** in hand, the next task was the construction of tamiflu skeleton using ring-closing metathesis (RCM). Towards this, diene **19** was subjected for RCM using Grubbs' 2nd generation catalyst and titanium isopropoxide as a Lewis acid to obtain tamiflu skeleton **5** in 75% yield. The spectral and analytical data of compound **5** were in good agreement with the reported data.[14] This constitutes the formal total synthesis of tamiflu (**1**) from furan in 10 steps in 7.5% overall yield.

Furthermore, during the synthesis of bicycloaziridino lactone **7** from bromo-butenolide **10b**, we observed the formation of amino-lactone **20** at room temperature in 30 min in 70% isolated yield (**Scheme 5**). The stereochemistry of Br substituent with respect to amine in compound **20** was found to be *trans* and subsequently confirmed by ^{1}H NMR analysis (J= 5.8 Hz), which was found to be in accordance with the literature values.[15] To check the synthetic utility of amino-lactone **20** for the synthesis of chiral aziridine, it was treated with $NaOCH_3$ followed by $NaBH_4$ in MeOH at 0 °C to furnish aziridine **21** in 52% yield. The stereochemistry of aziridine **21** was found to be *trans* (J= 2.9 Hz by ^{1}H NMR) as shown in **Scheme 5**. Furthermore, aldehyde obtained from amino-lactone **20** was subjected for two carbon Wittig homologation to obtain *trans*-vinyl aziridine **22** in 64 % yield over 2 steps. Aziridine **22** under transfer hydrogenation condition was converted into the methyl-6-oxopipecolate **11** in 85% yield. The methyl-6-oxopipecolate **11** derived from *cis*-vinyl aziridine **6** and *trans*-vinyl aziridine **22** has the same spectral and analytical data along with specific rotation,[16] which in turn confirmed the assigned relative and absolute stereochemistry of *trans*-vinyl aziridine **22** and aziridine **21**.



Scheme 5. Formal total synthesis of (2*S*,3*S*)-3-hydroxypipecolic acid **(4)**.

Subsequently, trans-vinyl aziridine **22** was effectively converted into protected 3-hydroxypipecolic acid methyl ester **26** using the same sequence used in the synthesis of (2S,3R)-3-hydroxypipecolic acid **3** (**Scheme 5**). Since the last step for the synthesis of (2S,3S)-3-hydroxypipecolic acid **4** from compound **26** is well documented in the literature,[17] this constitutes the formal total synthesis of (2S,3S)-3-hydroxypipecolic acid **4**.

Conclusions

To conclude, a unified synthetic strategy for tamiflu, (*S*)-pipecolic acid, and its 3-hydroxy derivatives from common chiral bicycloaziridino lactone synthon **7** derived from furan has been accomplished. Common chiral synthon **7** was synthesized in only 4 steps on decagram scale quantity from furan. Moreover, the synthesis of synthon **7** was achieved using simple reagents and reaction conditions in an enantiomerically pure form. Other key features are the first-ever application of synthon **7** in total synthesis tamiflu and piperidine class of alkaloids, successful

functionalization of bicycloaziridino lactone **7** to highly functionalized vinyl aziridine **6** and Lewis acid-catalyzed RCM of aziridine containing diene for the construction of tamiflu framework. Scalable synthesis of enantiomerically pure bicycloaziridino lactone **7** in lower number of steps using easily available and inexpensive reagents makes this protocol attractive. The utility and versatility of the synthon **7** for the synthesis of natural products/scaffolds have been demonstrated, and the remarkable stability of this strained synthon at room temperature would be very valuable in the synthesis of a variety of molecules of interest.

Experimental Section

General: All reactions were carried out in oven-dried glassware under a positive pressure of argon or nitrogen unless otherwise mentioned with magnetic stirring. Air sensitive reagents and solutions were transferred *via* syringe or cannula and were introduced to the apparatus *via* rubber septa. All reagents, starting materials and solvents were obtained from commercial suppliers and used as such without further purification. Reactions were monitored by thin-layer chromatography (TLC) with 0.25 mm pre-coated silica gel plates (60 F254). Visualization was accomplished with either UV light, iodine adsorbed on silica gel or by immersion in an ethanolic solution of phosphomolybdic acid (PMA), p-anisaldehyde, 2,4-DNP, $KMnO_4$ or ninhydrin solution followed by heating with a heat gun for ~15 sec. Melting points are uncorrected. The ^{1}H NMR spectra were recorded on Bruker AV 200, 400, and 500 MHz NMR spectrometers using solvent residue signal as an internal standard [^{1}H NMR: $CDCl_3$ (7.27), DMSO-d_6 (2.50); ^{13}C NMR: $CDCl_3$ (77.00), DMSO-d_6 (39.51)]. The ^{13}C NMR spectra were recorded on 200 NMR (50 MHz), 400 NMR (100 MHz), and 500 NMR (125 MHz) spectrometers. HRMS (ESI) were taken on an Orbitrap (quadrupole plus ion trap) and TOF mass analyzer. The IR spectra were recorded on the FT-IR spectrometer. Column chromatographic separations were carried out on silica gel (60–120 mesh and 230–400 mesh).

5-Hydroxyfuran-2(5*H*)-one (8).

To a cooled (0 °C) solution of furan (25 g, 0.368 mol, 1 equiv) in acetonitrile (250 mL), was added TS-1 catalyst (5 g) and stirred for 10 min at 0 °C. Then 30% H_2O_2 (70 mL, 0.618 mol, 1.68 equiv) was added dropwise and the mixture was stirred for 8 h and allowed to attain room temperature gradually. The catalyst was filtered off, the filtrate was concentrated at room temperature under reduced pressure, extracted with EtOAc (3 X 200 mL) and washed with brine. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* followed by purification of the obtained residue by silica gel (230–400 mesh) column chromatography using EtOAc–PE (40:60) to afford pure product **8** as a white solid (28 g, 76% yield). R_f: 0.2 (EtOAc–PE= 50:50); M. p.: 53–55 °C (lit.[7] M.p. = 54 °C); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.33 (dd, *J* = 1.1, 5.6 Hz, 1H), 6.27 (s, 1H), 6.22 (dd, *J* = 1.1, 5.6 Hz, 1H), 5.32 (br s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 171.3, 152.0, 124.6, 98.7.

(*R*)-5-(((1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl)oxy)furan-2(5*H*)-one (9).

To the stirred solution of 5-hydroxy-2-(5*H*)-furanone (**8**) (30 g, 0.3 mol, 1 equiv) in benzene, (-)-menthol (29.6 g, 0.19 mol, 0.95 equiv) and catalytic amount of *p*-TSA (190 mg, 1 mmol, 0.1 equiv) were added and the reaction mixture was refluxed for 20 h with azeotropic removal of water. After completion, the reaction mixture was cooled to room temperature and washed with water and brine, dried over anhydrous Na_2SO_4 and filtered. Concentration of organic layer *in vacuo* followed by purification of the obtained residue by silica gel (230–400 mesh) column chromatography using EtOAc–PE (02:98) afforded the mixture of diastereomers in the ratio 60:40 as a viscous solid (62 g, 87 % yield). The mixture of diastereomers was used in the next reaction without further separation. For analytical purpose, the mixture of diastereomers was subjected for recrystallization using light petroleum ether at –23 °C to obtain enantiomerically pure **9** as a white crystalline solid.R_f : 0.4 (EtOAc–PE= 10:90); M. p.: 70 °C (lit.[8] Mp = 70.5–70.7 °C); $[\alpha]_D^{25}$ –136 (*c* 1, EtOH). {lit.[8] $[\alpha]_D$ –136.4, (*c* 1, EtOH)}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.16 (dd, *J* = 1.0, 5.7 Hz, 1H), 6.20 (dd, *J* = 1.1, 5.7 Hz, 1H), 6.08 (s, 1H), 3.65 (dt, *J* = 4.4, 10.6 Hz, 1H), 2.21–2.00 (m, 2H), 1.75–1.59 (m, 2H), 1.53–1.33 (m, 1H), 1.33–1.15 (m, 1H), 1.15–0.96 (m, 3H), 0.95 (d, *J* = 6.5 Hz, 3H), 0.87 (d, *J* = 6.9 Hz, 3H), 0.80 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 170.7, 150.9, 124.7, 100.4, 79.1, 47.7, 40.3, 34.1, 31.4, 25.3, 23.1, 22.2, 20.8, 15.7; HRMS (ESI) *m/z* calcd for $C_{14}H_{22}O_3Na$ $[M + Na]^+$: 261.1461, found: 261.1460.

(*R*)-3-Bromo-5-(((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl)oxy)furan-2(5*H*)-one (10b).

To a stirred, ice cold (0 °C) solution of mixture of diastereomers of **9** (30 g, 0.126 mol, 1 equiv) in dry benzene (300 mL), was added solution of bromine (6.5 ml, 0.126 mol, 1 equiv) in benzene dropwise and the reaction mixture was stirred at same temperature for 6 h. The progress of the reaction was monitored by TLC. After that pyridine (12.2 ml, 0.151 mol, 1.2 equiv) was added dropwise at 0 °C and the reaction mixture was stirred for 30 min. After completion, reaction mixture was treated with water and extracted with EtOAc (3 X 500 mL). The combined organic layer was washed with brine (100 mL), dried over anhydrous Na_2SO_4 and filtered. Concentration of organic layer *in vacuo* followed by purification of the obtained residue by silica gel (230–400 mesh) column chromatography using EtOAc–PE (02:98) afforded diastereoisomeric mixture of **10a** and **10b** as a yellow oil. Pure **10b** was separated as a white crystalline solid by crystallization with *n*-hexane at -18 °C. Additional amount of pure **10b** was recovered from the remaining filtrate from crystallization by successive epimerization at 70 °C in toluene using PTSA as a catalyst, followed by the above-mentioned method of purification and recrystallization. (22 g, 55% yield). R_f : 0.5 (EtOAc–PE= 10:90); M. p.: 88–90 °C (lit.[9] Mp = 70.5–70.7 °C); IR ($CHCl_3$): ν_{max} 1770, 1624 cm^{-1}; $[\alpha]_D^{25}$ –121.6 (*c* 3, $CHCl_3$), {lit.[9] $[\alpha]_D$ –121.1 (*c* 1.82, $CHCl_3$)}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.23 (s, 1H), 6.02 (s, 1H), 3.66 (dt, *J* = 4.2, 10.7 Hz, 1H), 2.16–2.05 (m, 2H), 1.72–1.63 (m, 2H), 1.47–1.35 (m, 1H), 1.30–1.22 (m, 1H), 1.07–0.97 (m, 2H), 0.95 (d, *J* = 6.5 Hz, 3H), 0.88 (d, *J* = 7.2 Hz, 3H), 0.86–0.82 (m, 1H), 0.79 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 166.1, 147.5, 117.7, 99.7, 79.4, 47.7, 40.3, 34.1, 31.4, 25.2, 23.0, 22.1, 20.8, 15.6; HRMS (ESI) *m/z* calcd for $C_{14}H_{21}O_3BrNa$ $[M + Na]^+$: 339.0566, found: 339.0567.

(1*S*,4*R*,5*R*)-6-Benzyl-4-(((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl)oxy)-3-oxa-6-azabicyclo[3.1.0]hexan-2-one (7).

To a stirred solution of bromolactone **10b** (15 g, 0.047 mol, 1 equiv) in DMSO (150 mL), triethylamine (7.32 mL, 0.052 mol, 1.1 equiv) followed by benzyl amine (5.18 mL, 0.047 mol, 1 equiv) was added at room temperature. The reaction mixture was stirred at room temperature for 30 min and then heated at 65 °C for 4 h. The progress of the reaction was monitored by TLC. After completion, reaction mixture was treated with cold water (150 mL) and extracted with EtOAc (3 X 200 mL). The combined organic layer was washed with water (2 X 200 mL) and brine (100 mL), dried over anhydrous Na_2SO_4 and filtered. Concentration of organic layer *in vacuo* followed by purification of the obtained residue by

silica gel (230–400 mesh) column chromatography using EtOAc–PE (10:90) afforded pure product **7** as a white solid (11.73 g, 72% yield). R_f: 0.3 (EtOAc–PE= 15:85); M. p.: 149–151 °C; IR ($CHCl_3$): ν_{max} 3022, 1779, 1216, 765 cm^{-1}; $[\alpha]_D^{25}$ –227.6 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.40–7.28 (m, 5H), 5.49 (s, 1H), 3.67 (d, *J* = 13.3 Hz, 1H), 3.56 (dt, *J* = 4.1, 10.8 Hz, 1H), 3.49 (d, *J* = 13.3 Hz, 1H), 2.91 (d, *J* = 4.1 Hz, 1H), 2.74 (d, *J* = 4.1 Hz, 1H), 2.12–2.02 (m, 2H), 1.71–1.61 (m, 2H), 1.44–1.31 (m, 1H), 1.27–1.18 (m, 1H), 1.06–0.94 (m, 2H), 0.93 (d, *J* = 6.4 Hz, 3H), 0.88 (d, *J* = 7.3 Hz, 3H), 0.85–0.80 (m, 1H), 0.78 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.5, 136.7, 128.6 (2C), 127.9 (2C), 127.7, 99.1, 77.4, 60.7, 47.7, 45.5, 39.9, 38.7, 34.2, 31.3, 25.3, 23.0, 22.2, 20.8, 15.6; HRMS (ESI) *m/z* calcd for $C_{21}H_{29}O_3NNa$ $[M + Na]^+$: 366.2040, found: 366.2037.

Methyl (2*S*,3*S*)-1-benzyl-3-((*E*)-3-ethoxy-3-oxoprop-1-en-1-yl)aziridine-2-carboxylate (6).

To a stirred solution of bicyclolactone **7** (1.5 g, 4.37 mmol, 1 equiv) in anhydrous MeOH (15 mL), was added NaOMe (236 mg, 4.37 mmol, 1 equiv) at 0 °C and the reaction mixture was stirred for 1 h while gradually warming to room temperature. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was treated with saturated aq. NH_4Cl and extracted with EtOAc (3 X 20 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4, and filtered. The concentration of the organic layer *in vacuo* afforded crude aldehyde which was used in the next reaction without further purification.

To a stirred solution of aldehyde in CH_2Cl_2 (30 mL) was added (carbethoxymethylene) triphenylphosphorane (1.83 g, 5.24 mmol, 1.2 equiv) and the reaction mixture was stirred for 6 h at room temperature. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was concentrated to dryness and residue was extracted with EtOAc (3 X 50 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4 and filtered. The concentration of organic layer *in vacuo* followed by purification of the obtained residue by silica gel (230–400 mesh) column chromatography using EtOAc–PE (10:90) afforded pure product **6** as a yellow solid (1.1 g, 87% yield). R_f: 0.5 (EtOAc–PE= 30:70); M. p.: 71–73 °C; IR ($CHCl_3$): ν_{max} 1716, 1651, 1215, 770 cm^{-1}; $[\alpha]_D^{25}$ +12.7 (*c* 1.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.38–7.28 (m, 5H), 6.86 (dd, *J* = 8.5, 15.9 Hz, 1H), 6.11 (d, *J* = 15.9 Hz, 1H), 4.22–4.13 (m, 2H), 3.76 (d, *J* = 14.0 Hz, 1H), 3.73 (s, 3H), 3.64 (d, *J* = 14.0 Hz, 1H), 2.62 (d, *J* = 6.7 Hz, 1H), 2.57 (t, *J* = 7.3 Hz, 1H), 1.27 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.6, 165.4, 142.4, 136.9, 128.5 (2C), 127.8 (2C), 127.4, 125.2, 63.2, 60.4, 52.3, 45.7, 44.9, 14.1; HRMS (ESI) *m/z* calcd for $C_{16}H_{20}O_4N$ $[M + H]^+$: 290.1387, found: 290.1382.

Methyl (*S*)-6-oxopiperidine-2-carboxylate (11).

To a stirred solution of compound **6** (0.5 g, 1.73 mmol, 1 equiv) in MeOH (10 mL), were added ammonium formate (1.09 g, 17.3 mmol, 10 equiv) and 10% Pd/C (50 mg) and refluxed for 3 h under nitrogen atmosphere. The reaction mass was filtered through celite, organic layer was concentrated *in vacuo* and purification of the obtained residue by silica gel (230–400 mesh) column chromatography using EtOAc–PE (90:10) afforded pure product **11** as a pale yellow liquid (231 mg, 85% yield). R_f: 0.2 (EtOAc–PE= 100:00); IR ($CHCl_3$): ν_{max} 3019, 1739, 1666 cm^{-1}; $[\alpha]_D^{25}$ –9.0 (*c* 0.5, $CHCl_3$), {lit.[16] $[\alpha]_D$ –9.6 (*c* 1.06, $CHCl_3$)}; ^1H NMR ($CDCl_3$, 200 MHz): δ 6.59 (br s, 1H), 4.16–4.01 (m, 1H), 3.77 (s, 3H), 2.43–2.29 (m, 2H), 2.27–2.02 (m, 1H), 1.96–1.67 (m, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 171.6 (2C), 54.6, 52.6, 30.9, 25.3, 19.3; HRMS (ESI) *m/z* calcd for $C_7H_{11}O_3NNa$ $[M + Na]^+$: 180.0631, found: 180.0630.

Methyl (*S*)-piperidine-2-carboxylate (12).

To a stirred, cooled (0 °C) solution of amide **11** (0.2 g, 1.27 mmol, 1 equiv) in anhydrous THF (5 mL), BH_3·DMS (0.36 mL, 3.82 mmol, 3 equiv) was added dropwise. The resulting reaction mixture was further stirred at 5 °C for 20 h. Methanol (excess) was added to the reaction mixture, stirred for 4 h and concentrated under reduced pressure. Water (10 mL) was added and the reaction mixture was extracted using CH_2Cl_2 (3 × 10 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4 and filtered. Concentration of organic layer *in vacuo* followed by purification of the obtained residue by silica gel (230–400 mesh) column chromatography using EtOAc–PE (40:60) afforded pure product **12** as a colorless thick liquid (142 mg, 78% yield). R_f : 0.2 (EtOAc–PE= 50:50); IR ($CHCl_3$): ν_{max} 3414, 1730 cm^{-1}; $[\alpha]_D^{25}$–1.25 (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 4.02 (br s, 1H), 3.80 (s, 3H), 3.46–3.25 (m, 2H), 2.81–2.57 (m, 1H), 2.12–1.99 (m, 1H), 1.86–1.48 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 171.7, 64.1, 52.6, 52.1, 27.9, 23.9, 21.7; HRMS (ESI) *m/z* calcd for $C_7H_{13}O_2NNa$ $[M + Na]^+$: 166.0838, found: 166.0836.

(*S*)-Piperidine-2-carboxylic acid (2).

A mixture of amine **12** (100 mg, 0.69 mmol, 1 equiv) and 6 N HCl (10 mL) was kept at 120 °C for 3 h. The solvent was removed under reduced pressure and the residue was dissolved in H_2O (50 mL). The mixture was loaded on an ion-exchange column (DOWEX 50W X8) and eluted with H_2O and then with aq. NH_3 solution. The eluate of aq. NH_3 was concentrated to dryness under reduced pressure to give **2** (82 mg, 91%) as a white solid. R_f : 0.4 (CH_2Cl_2–MeOH–NH_4OH= 9:1:1); M. p.: 270–272 °C, (lit.[4e] 271–274 °C); $[\alpha]_D^{25}$ –25.5 (*c* 1, H_2O), {lit.[4e] $[\alpha]_D$ –25.9 (*c* 1, H_2O)}; ^1H NMR (D_2O, 400 MHz): δ 3.85 (dd, *J* = 3.4, 11.7 Hz, 1H), 3.44–3.36 (m, 1H), 3.03–2.93 (m, 1H), 2.23 (dd, *J* = 3.1, 13.9 Hz, 1H), 1.89–1.78 (m, 2H), 1.73–1.51 (m, 3H); ^{13}C NMR (D_2O, 100 MHz): δ 172.1, 57.1, 43.8, 25.8, 21.4, 21.3; MS (ESI) *m/z*: 152.28 $(M+Na)^+$.

1-Ethyl 6-methyl (4*R*,5*S*,*E*)-5-(benzylamino)-4-hydroxyhex-2-enedioate (13).

To a stirred solution of ester **6** (1.1 g, 3.80 mmol, 1 equiv) in CH_3CN:H_2O (9:1, 20 mL), was added TFA (0.58 mL, 7.61 mmol, 2 equiv) dropwise at 0 °C. The reaction mixture was slowly warmed to room temperature and stirred until complete disappearance of starting material (~ 7 h). Reaction mixture was quenched by excess $NaHCO_3$, water (10 mL) was added and extracted with EtOAc (3 × 50 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4 and filtered. Concentration of organic layer *in vacuo* followed by purification of the obtained residue by silica gel (230–400 mesh) column chromatography using EtOAc–PE (30:70) afforded pure product **13** as a thick yellow liquid (865 mg, 74% yield). R_f: 0.3 (EtOAc–PE= 30:70); IR ($CHCl_3$): ν_{max} 3422, 1721, 1659 cm^{-1}; $[\alpha]_D^{25}$ +2.9 (*c* 2, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.35–7.31 (m, 2H), 7.30–7.26 (m, 3H), 6.90 (dd, *J* = 4.6, 15.6 Hz, 1H), 6.14 (dd, *J* = 1.5, 15.6 Hz, 1H), 4.36–4.32 (m, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.84 (d, *J* = 13.0 Hz, 1H), 3.75 (d, *J* = 13.0 Hz, 1H), 3.73 (s, 3H), 3.28 (d, *J* = 6.1 Hz, 1H), 2.70 (br s, 2H), 1.30 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 172.8, 166.1, 146.0, 138.7, 128.5 (2C), 128.3 (2C), 127.5, 122.3, 71.0, 64.6, 60.5, 52.6, 52.3, 14.2; HRMS (ESI) *m/z* calcd for $C_{16}H_{22}O_5N$ $[M + H]^+$: 308.1492, found: 308.1491.

1-Ethyl 6-methyl (4*R*,5*S*,*E*)-5-(benzylamino)-4-((*tert*-butyldimethylsilyl)oxy)hex-2-enedioate (14).

To a stirred solution of hydroxyl amino ester **13** (0.85 g, 2.76 mmol, 1 equiv), imidazole (376 mg, 5.53 mmol, 2 equiv) and DMAP (34 mg, 0.27

mmol, 0.1 equiv) in CH_2Cl_2 (20 mL), was added TBSCl (0.83 g, 5.53 mmol, 2 equiv) dissolved in CH_2Cl_2 (10 mL) slowly at 0 °C after which reaction was heated to reflux for 6 h until completion of reaction. The progress of the reaction was monitored by TLC. After completion, reaction mixture was concentrated to dryness and residue was extracted with CH_2Cl_2 (3 X 50 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4 and filtered. Concentration of organic layer *in vacuo* followed by purification of the obtained residue by silica gel (230–400 mesh) column chromatography using EtOAc–PE (10:90) afforded TBS ether **14** as thick colorless liquid (1 g, 86% yield). R_f : 0.5 (EtOAc–PE= 20:80); IR ($CHCl_3$): ν_{max} 3417, 3023, 1720, 1655 cm^{-1}; $[\alpha]_D^{25}$ –5.0 (*c* 3, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz): (mixture of invertomers) δ 7.38–7.31 (m, 4H), 7.31–7.24 (m, 1H), 7.08–7.00 (m, 1H), 6.00 (d, *J* = 16.0 Hz, 1H), 4.68–4.62 (m, 1H), 4.27 (q, *J* = 6.9 Hz, 2H), 4.00 (dd, *J* = 2.9, 13.5 Hz, 1H), 3.77–3.76 (m, 3H), 3.66 (dd, *J* = 2.7, 13.4 Hz, 1H), 3.34 (br s, 1H), 2.18 (br s, 1H), 1.39–1.33 (m, 3H), 0.92–0.91 (m, 9H), 0.05–0.03 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 172.8, 166.1, 147.9, 139.7, 128.2 (2C), 128.1 (2C), 127.0, 121.8, 73.4, 64.9, 60.4, 51.82, 51.78, 25.6 (3C), 18.0, 14.2, -4.5, -5.4; HRMS (ESI) *m/z* calcd for $C_{22}H_{36}O_5NSi$ $[M + H]^+$: 422.2357, found: 422.2361.

Methyl (2*S*,3*R*)-3-((*tert*-butyldimethylsilyl)oxy)-6-oxopiperidine-2-carboxylate (15).

The amino ester **14** (0.85 g, 2.01 mmol, 1 equiv) was dissolved in methanol (10 mL) and to that was added catalytic amount of palladium hydroxide over carbon (10%, 20 mg). The resulting reaction mixture was stirred under hydrogen atmosphere using balloon pressure for 2 h. The reaction mixture was filtered through Celite and the filtrate was concentrated *in vacuo*. Purification of the obtained residue by silica gel (230–400 mesh) column chromatography using EtOAc–PE (90:10) afforded lactam **15** as white solid (0.51 g, 88% yield). R_f : 0.2 (EtOAc–PE= 90:10); M. p.: 70–72 °C; IR ($CHCl_3$): ν_{max} 3410, 1741, 1664, 1216 cm^{-1}; $[\alpha]_D^{25}$ –47.3 (*c* 0.8, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 6.21 (br s, 1H), 4.56–4.52 (m, 1H), 4.11 (d, *J* = 2.7 Hz, 1H), 3.77 (s, 3H), 2.62–2.51 (m, 1H), 2.38–2.29 (m, 1H), 2.03–1.87 (m, 2H), 0.82 (s, 9H), 0.07 (s, 3H), 0.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.7, 169.2, 64.8, 60.5, 52.5, 27.6, 25.8, 25.4 (3C), 17.8, -4.5, -5.5; HRMS (ESI) *m/z* calcd for $C_{13}H_{25}O_4NNaSi$ $[M + Na]^+$: 310.1445, found: 310.1441.

Methyl (2*S*,3*R*)-3-((*tert*-butyldimethylsilyl)oxy)piperidine-2-carboxylate (16).

To the stirred solution of lactam **15** (0.4 g, 1.39 mmol, 1 equiv) in anhydrous THF (20 mL), was added BH_3·DMS (0.39 mL, 4.18 mmol, 3 equiv) dropwise at 0 ºC. The resulting reaction mixture was further stirred at 5 ºC for 20 h. Methanol (excess) was added to the reaction mixture, stirred for 4 h and concentrated under reduced pressure. Water (10 mL) was added and the reaction mixture was extracted using CH_2Cl_2 (3 × 10 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4 and filtered. Concentration of organic layer *in vacuo* followed by purification of the obtained residue by silica gel (230–400 mesh) column chromatography using EtOAc–PE (30:70) afforded amine **16** as a thick colorless liquid (247 mg, 65% yield). R_f : 0.2 (EtOAc–PE= 50:50); IR ($CHCl_3$): ν_{max} 3420, 1730 cm^{-1}; $[\alpha]_D^{25}$ –10.2 (*c* 0.4, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz): δ 4.16 (br s, 1H), 3.67 (s, 3H), 3.43 (d, *J* = 1.5 Hz, 1H), 3.14–3.07 (m, 1H), 2.61–2.54 (m, 1H), 2.15 (br s, 1H), 1.87–1.81 (m, 1H), 1.75–1.57 (m, 2H), 1.33–1.26 (m, 1H), 0.84 (s, 9H), 0.03 (s, 3H), -0.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 171.9, 66.6, 63.4, 51.6, 45.2, 31.8, 25.6 (3C), 20.2, 17.9, -4.6, -5.4; HRMS (ESI) *m/z* calcd for $C_{13}H_{28}O_3NSi$ $[M + H]^+$: 274.1833, found: 274.1832.

(2*S*,3*R*)-3-Hydroxypiperidine-2-carboxylic acid (3).

A mixture of amine **16** (100 mg, 0.36 mmol, 1 equiv) and 6 N HCl (10 mL) was kept at 120 ºC for 3 h. The solvent was removed under reduced pressure and the residue was dissolved in H_2O (50 mL). The mixture was loaded on an ion-exchange column (DOWEX 50W X8) and eluted with H_2O and then with aq. NH_3 solution. The eluate of aq. NH_3 was concentrated to dryness under reduced pressure to give **3** (45 mg, 85%) as a white solid. R_f : 0.2 ($CHCl_3$-MeOH-30% NH_4OH= 3:5:2); M. p.: 235–238 °C (decomp); IR (neat): ν_{max} 3357, 1625, 1405 cm^{-1}; $[\alpha]_D^{25}$ –53.6 (*c* 0.6, H_2O), {lit.[12] $[\alpha]_D$ –52.8 (*c* 0.6, H_2O)}; ^1H NMR (D_2O, 400 MHz): δ 4.44 (br s, 1H), 3.61 (s, 1H), 3.35 (d, *J* = 10.4 Hz, 1H), 2.99–2.89 (m, 1H), 1.98–1.86 (m, 2H), 1.78–1.62 (m, 2H); ^{13}C NMR (D_2O, 100 MHz): δ 172.3, 64.1, 62.2, 43.6, 28.7, 15.8; HRMS (ESI) *m/z* calcd for $C_6H_{12}O_3N$ $[M + H]^+$: 146.0812, found: 146.0811.

Methyl (2*S*,3*S*)-1-benzyl-3-vinylaziridine-2-carboxylate (17).

To a stirred solution of bicyclolactone **7** (1.5 g, 4.37 mmol, 1 equiv) in anhydrous MeOH (15 mL), was added NaOMe (236 mg, 4.37 mmol, 1 equiv) at 0 °C and the reaction mixture was stirred for 1 h while gradually warming to room temperature. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was treated with saturated aq. NH_4Cl and extracted with EtOAc (3 X 20 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4 and filtered. The concentration of the organic layer *in vacuo* afforded crude aldehyde which was used in the next reaction without further purification.

To a stirred solution of methyltriphenylphosphonium bromide (5.46 g, 15.3 mmol, 3.5 equiv) in THF (30 mL), was added potassium *tert*-butoxide (1.57 g, 13.99 mmol, 3.2 equiv) at 0 °C and stirred for 1 h. To this, the above-obtained solution of aldehyde in THF (10 mL) was added dropwise at 0 °C and the reaction mixture was stirred for 6 h while warming to room temperature. The progress of the reaction was monitored by TLC. After completion, reaction mixture was treated with saturated aq. NH_4Cl and extracted with EtOAc (3 X 100 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4 and filtered. Concentration of organic layer *in vacuo* followed by purification of the obtained residue by silica gel (230–400 mesh) column chromatography using EtOAc–PE (10:90) afforded pure product **17** as a pale yellow liquid (610 mg, 64% yield). R_f : 0.5 (EtOAc–PE= 10:90); IR ($CHCl_3$): ν_{max} 1738, 1646 cm^{-1}; $[\alpha]_D^{25}$ +12.5 (*c* 4, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 7.31–7.15 (m, 5H), 5.88–5.65 (m, 1H), 5.35 (dd, *J* = 1.5, 17.3 Hz, 1H), 5.19 (dd, *J* = 1.5, 10.3 Hz, 1H), 3.66 (s, 3H), 3.61 (s, 2H), 2.47–2.37 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 169.3, 137.4, 133.2, 128.3 (2C), 127.7 (2C), 127.2, 119.5, 63.2, 52.0, 47.9, 44.1; HRMS (ESI) *m/z* calcd for $C_{13}H_{16}O_2N$ $[M + H]^+$: 218.1176, found: 218.1173.

Ethyl (*S*)-4-((2*S*,3*S*)-1-benzyl-3-vinylaziridin-2-yl)-4-hydroxy-2-methylenebutanoate (18b).

To a stirred solution of *cis*-vinyl aziridine-2-carboxylate **17** (0.5 g, 2.30 mmol, 1 equiv) in dry CH_2Cl_2 (15 mL) was added DIBAL-H (4.6 mL, 1 M solution in toluene, 4.60 mmol, 2 equiv) at -78 °C slowly over period of 10 min and the reaction mixture was stirred at same temperature for 30 min. The reaction was quenched by the careful addition of pre-cooled MeOH (2 mL) and allowed to warm to 0 °C. Roche's salt (saturated solution of sodium potassium tartrate, 5 mL) was added and stirred for 0.5 h. The compound was extracted with CH_2Cl_2 (3 X 20 mL), and the combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to furnish crude aldehyde which was used for the next reaction without further purification.

To the solution of crude aldehyde obtained from the above reaction in THF (10 mL), was added ethyl 2-(bromomethyl)acrylate (0.53 g, 2.76 mmol, 1.2 equiv), activated zinc powder (0.45 g, 6.91 mmol, 3 equiv) and saturated aq. solution of NH_4Cl (5 mL) at 0 °C. The reaction mixture was stirred at 0 °C for an additional 10 min. The reaction mixture was filtered through a simple filter paper and thoroughly washed with ethyl acetate (3 X 10 mL). Water was added to the filtrate, and the organic layer was separated, dried over anhydrous Na_2SO_4, filtered and concentrated to give a crude residue that was purified by silica gel (230–400 mesh) column chromatography using EtOAc–PE (15:85) to afford pure product **18a** as a colorless syrup (290 mg, 42% yield). Further elution of the column with EtOAc–PE (20:80) as eluent furnished **18b** (290 gm, 42% yield) as a thick colorless liquid.

To the solution of **18a** (100 mg, 3.32 mmol, 1 equiv) in toluene (10 mL), were added triphenylphosphine (217 mg, 0.83 mmol, 2.5 equiv), *p*-nitrobenzoic acid (138 mg, 0.83 mmol, 2.5 equiv) and DEAD (0.13 mL, 0.83 mmol, 2.5 equiv) at room temperature under nitrogen atmosphere. The reaction mixture was stirred at the same temperature for 2.5 h, and the progress of the reaction was monitored by TLC. To the reaction mass, water (5 mL) was added and the compound was extracted with EtOAc (3 X 20 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to furnish a crude product which was used for the next reaction without further purification.

The above crude product was dissolved in absolute ethanol (5 mL) and to the solution was added NaOEt (25 mg, 0.36 mmol, 1.1 equiv) at -20 °C. The reaction mixture was stirred further for 0.5 h at same temperature. Drops of acetic acid were added to the reaction mixture to adjust the pH to 7. The solution was diluted with water (5 mL) and extracted with EtOAc (3 X 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by silica gel (230–400 mesh) column chromatography using EtOAc–PE (20:80) to afford pure product **18b** as a thick colorless liquid (67 mg, 67% yield over two steps). R_f : 0.2 (EtOAc–PE= 50:50); IR ($CHCl_3$): ν_{max} 3425, 1709, 1634 cm^{-1}; $[\alpha]_D^{25}$ +27.3 (*c* 3.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.35–7.14 (m, 5H), 6.17 (d, *J* = 1.4 Hz, 1H), 5.74–5.57 (m, 1H), 5.55 (d, *J* = 1.4 Hz, 1H), 5.35–5.07 (m, 2H), 4.12 (q, *J* = 7.2 Hz, 2H), 3.63–3.41 (m, 3H), 2.54 (br s, 1H), 2.45–2.29 (m, 2H), 2.20 (t, *J* = 7.2 Hz, 1H), 1.79 (t, *J* = 6.8 Hz, 1H), 1.22 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 167.1, 138.6, 136.7, 134.3, 128.4 (2C), 128.0 (2C), 127.6, 127.2, 118.3, 68.0, 63.9, 60.7, 50.0, 46.4, 37.8, 14.1; HRMS (ESI) *m/z* calcd for $C_{18}H_{24}O_3N$ [M + H]$^+$: 302.1751, found: 302.1752.

Ethyl (*R*)-4-((2*S*,3*S*)-1-benzyl-3-vinylaziridin-2-yl)-4-hydroxy-2-methylenebutanoate (18a)

Rf : 0.25 (EtOAc–PE= 50:50); IR (CHCl3): vmax 3425, 1709, 1634 cm-1; $[\alpha]_D^{25}$ +16.5 (c 4, CHCl3); 1H NMR (CDCl3, 200 MHz): δ 7.31–7.17 (m, 5H), 6.16 (d, J = 1.4 Hz, 1H), 5.90–5.69 (m, 1H), 5.53 (d, J = 1.1 Hz, 1H), 5.39–5.12 (m, 2H), 4.15 (q, J = 7.2 Hz, 2H), 3.72–3.62 (m, 2H), 3.45 (d, J = 13.3 Hz, 1H), 2.83 (br s, 1H), 2.51–2.29 (m, 2H), 2.21 (t, J = 7.1 Hz, 1H), 1.77 (t, J = 6.9 Hz, 1H), 1.24 (t, J = 7.1 Hz, 3H); 13C NMR (CDCl3, 50 MHz): δ 167.9, 138.6, 137.2, 134.7, 128.3 (2C), 128.1 (2C), 127.6, 127.1, 118.1, 68.8, 63.7, 61.0, 49.0, 46.0, 37.9, 14.1; HRMS (ESI) m/z calcd for C18H24O3N [M + H]+: 302.1751, found: 302.1752.

Ethyl (*S*)-4-((2*S*,3*S*)-1-benzyl-3-vinylaziridin-2-yl)-2-methylene-4-((methylsulfonyl)oxy)butanoate (19).

To a stirred solution of alcohol **18b** (0.15 g, 0.49 mmol, 1 equiv) in CH_2Cl_2 (15 mL), was added triethylamine (0.24 mL, 1.74 mmol, 3.5 equiv) followed by mesyl chloride (0.11 mL, 1.49 mmol, 3 equiv) at 0 °C. The reaction mixture was allowed to stir at room temperature for 2 h under nitrogen atmosphere. The completion of reaction was monitored by TLC and reaction mixture was poured in cold water. The compound was extracted with CH_2Cl_2 (3 X 10 mL) and the combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to furnish a residue which was purified by silica gel (230–400 mesh) column chromatography using EtOAc–PE (20:80) to afford pure product **19** as a yellow liquid (163 mg, 86% yield). R_f : 0.5 (EtOAc–PE= 30:70); IR ($CHCl_3$): ν_{max} 1711, 1637, 1206 cm^{-1}; $[\alpha]_D^{25}$ +32.8 (*c* 3, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.36–7.26 (m, 5H), 6.33 (s, 1H), 5.73 (s, 1H), 5.72–5.64 (m, 1H), 5.40 (d, *J* = 17.1 Hz, 1H), 5.28 (d, *J* = 10.4 Hz, 1H), 4.48 (dt, *J* = 4.6, 8.7 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.54 (s, 2H), 2.78–2.72 (m, 1H), 2.65 (s, 3H), 2.64–2.59 (m, 1H), 2.30 (t, *J* = 6.7 Hz, 1H), 2.07 (dd, *J* = 7.0, 9.5 Hz, 1H), 1.30 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 166.2, 138.0, 134.5, 133.2, 129.5, 128.5 (2C), 128.4 (2C), 127.5, 119.2, 82.3, 64.0, 60.8, 47.8, 45.6, 38.0, 36.6, 14.1; HRMS (ESI) *m/z* calcd for $C_{19}H_{26}O_5NS$ [M + H]$^+$: 380.1526, found: 380.1527.

Ethyl (1*S*,5*S*,6*S*)-7-benzyl-5-((methylsulfonyl)oxy)-7-azabicyclo[4.1.0]hept-2-ene-3-carboxylate (5).

To the solution of the olefin compound **19** (100 mg, 0.26 mmol, 1 equiv) in dry CH_2Cl_2 (100 mL), were added titanium tetraisopropoxide (0.04 mL, 0.13 mmol, 0.5 equiv) and Grubbs' 2nd generation catalyst (22 mg, 0.026 mmol, 0.1 equiv). The reaction mixture was refluxed for 15 h and the completion of the reaction was monitored with TLC. The reaction mixture was filtered through celite bed and thoroughly washed with CH_2Cl_2 (3 X 50 mL). Concentration of organic layer *in vacuo* followed by purification of the obtained residue by silica gel (230–400 mesh) column chromatography using EtOAc–PE (15:85) afforded compound **5** as yellow liquid (69 mg, 75% yield). R_f : 0.4 (EtOAc–PE= 30:70); IR ($CHCl_3$): ν_{max} 1707, 1641, 1358, 1217 cm^{-1}; $[\alpha]_D^{25}$ –65.6 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.37–7.28 (m, 6H), 5.45–5.41 (m, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.65 (d, J = 13.4 Hz, 1H), 3.57 (d, J = 13.4 Hz, 1H), 3.02 (s, 3H), 2.97 (t, J = 1.9 Hz, 1H), 2.61 (td, J = 2.5, 5.7 Hz, 1H), 2.50 (td, J = 3.8, 17.5 Hz, 1H), 2.31 (t, J = 5.3 Hz, 1H), 1.30 (t, J = 6.9 Hz, 3H); 13C NMR (CDCl3, 100 MHz): δ 166.0, 137.9, 136.4, 128.5 (2C), 127.7 (2C), 127.4, 126.8, 73.6, 62.7, 60.9, 44.0, 38.8, 35.6, 27.6, 14.2; HRMS (ESI) m/z calcd for C17H22O5NS [M + H]+: 352.1213, found: 352.1213.

(3*R*,4*S*,5*R*)-4-(Benzylamino)-3-bromo-5-(((1*R*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl)oxy)dihydrofuran-2(3*H*)-one (20).

To a stirred solution of bromolactone **10b** (10 g, 0.031 mol, 1 equiv) in DMSO (100 mL), were added triethylamine (4.88 mL, 0.035 mol, 1.1 equiv) followed by benzyl amine (3.45 mL, 0.031 mol, 1 equiv) at room temperature. The reaction mixture was stirred at room temperature for 30 min. The progress of the reaction was monitored by TLC. After completion, reaction mixture was treated with cold water (100 mL) and extracted with EtOAc (3 X 100 mL). The combined organic layer was washed with water (2 X 50 mL) and brine (50 mL), dried over anhydrous Na_2SO_4 and filtered. Concentration of organic layer *in vacuo* followed by purification of the obtained residue by silica gel (230–400 mesh) column chromatography using EtOAc–PE (10:90) afforded pure product **20** as a pale yellow liquid (9.37 g, 70% yield). R_f : 0.3 (EtOAc–PE= 10:90); IR ($CHCl_3$): ν_{max} 3427, 1770 cm^{-1}; $[\alpha]_D^{25}$ –104.5 (*c* 2.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.39–7.29 (m, 5H), 5.51 (d, *J* = 3.3 Hz, 1H), 4.29 (d, *J* = 5.8 Hz, 1H), 3.92 (s, 2H), 3.65–3.49 (m, 2H), 2.32–2.05 (m, 2H), 1.98 (br s, 1H), 1.74–1.62 (m, 2H), 1.50–1.17 (m, 3H), 0.97–0.87 (m, 8H), 0.79 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 170.1, 138.5, 128.7 (2C), 128.2 (2C), 127.7, 104.1, 78.4, 68.0, 51.6, 47.6, 41.4, 39.5, 34.2, 31.3, 25.1, 22.8, 22.2, 20.9, 15.5; HRMS (ESI) *m/z* calcd for $C_{21}H_{31}O_3NBr$ [M + H]$^+$: 424.1482, found: 424.1479.

Methyl (2*S*,3*S*)-1-benzyl-3-(hydroxymethyl)aziridine-2-carboxylate (21).

To a stirred, cooled (0 °C) solution of compound **20** (1 g, 2.36 mmol, 1 equiv) in MeOH (40 mL), were added $NaOCH_3$ (127 mg, 2.36 mmol, 1 equiv) followed by $NaBH_4$ (89 mg, 2.36 mmol, 1 equiv) and the reaction mixture was stirred for 1 h at 0 °C. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was treated with 1 N HCl to adjust the pH to 7 and extracted with EtOAc (3 X 50 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4 and filtered. Concentration of organic layer *in vacuo* followed by purification of the obtained residue by silica gel (230–400 mesh) column chromatography using EtOAc–PE (30:70) afforded pure product **21** as a colorless liquid (0.27 g, 52% yield). R_f: 0.2 (EtOAc–PE= 50:50); IR ($CHCl_3$): ν_{max} 3417, 1730 cm^{-1}; $[\alpha]_D^{25}$ +72.2 (*c* 3, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 7.40–7.26 (m, 5H), 4.03 (d, J = 13.4 Hz, 1H), 3.93 (d, J = 13.4 Hz, 1H), 3.82–3.72 (m, 1H), 3.70 (s, 3H), 3.59 - 3.41 (m, 1H), 2.75 (d, J = 2.9 Hz, 1H), 2.60 (q, J = 3.2 Hz, 1H), 2.41 (br s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 169.3, 138.7, 128.4 (2C), 128.2 (2C), 127.2, 61.0, 54.5, 52.2, 46.9, 37.4; HRMS (ESI) m/z calcd for C12H16O3N [M + H]+: 222.1125, found: 222.1124.

Methyl (2*S*,3*R*)-1-benzyl-3-((*E*)-3-ethoxy-3-oxoprop-1-en-1-yl)aziridine-2-carboxylate (22).

To a stirred solution of compound **20** (1.5 g, 3.54 mmol, 1 equiv) in anhydrous MeOH (15 mL), was added NaOMe (191 mg, 3.54 mmol, 1 equiv) at 0 °C and the reaction mixture was stirred for 30 min at that temperature. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was treated with saturated aq. NH_4Cl and extracted with EtOAc (3 X 20 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4, and filtered. The concentration of the organic layer *in vacuo* afforded crude aldehyde which was used in the next reaction without further purification.

To a stirred solution of aldehyde in CH_2Cl_2 (30 mL), was added (carbethoxymethylene) triphenylphosphorane (1.48 g, 4.25 mmol, 1.2 equiv) and the reaction mixture was stirred for 6 h at room temperature. The progress of the reaction was monitored by TLC. After completion, reaction mixture was concentrated to dryness and residue was extracted with EtOAc (3 X 50 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4 and filtered. Concentration of organic layer *in vacuo* followed by purification of the obtained residue by silica gel (230–400 mesh) column chromatography using EtOAc–PE (10:90) afforded pure product **22** as a pale yellow liquid (0.66 g, 64% yield). R_f: 0.5 (EtOAc–PE= 30:70); IR ($CHCl_3$): ν_{max} 1716, 1651, 1215, 770 cm^{-1}; $[\alpha]_D^{25}$ +29.41 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): (mixture of invertomers) δ 7.41–7.22 (m, 5H), 6.99–6.56 (m, 1H), 6.33–6.00 (m, 1H), 4.31–4.13 (m, 2H), 4.13–3.79 (m, 2H), 3.72 (s, 3H), 3.20–2.92 (m, 1H), 2.76–2.61 (m, 1H), 1.29 (t, *J* =7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): (mixture of invertomers) δ 168.6, 165.7, 145.3, 140.2, 138.4, 137.6, 128.4, 128.0, 127.8, 127.2, 123.5, 60.6, 60.5, 56.5, 54.7, 54.6, 52.4, 46.2, 45.7, 44.5, 42.8, 14.2; HRMS (ESI) *m/z* calcd for $C_{16}H_{20}O_4N$ [M + H]$^+$: 290.1387, found: 290.1384.

1-Ethyl 6-methyl (4*S*,5*S*,*E*)-5-(benzylamino)-4-hydroxyhex-2-enedioate (23).

To a stirred solution of ester **22** (0.6 g, 2.07 mmol, 1 equiv) in CH_3CN:H_2O (9:1, 20 mL), was added TFA (0.32 mL, 4.15 mmol, 2 equiv) dropwise at 0 °C. The reaction mixture was slowly warmed to room temperature and stirred until complete disappearance of starting material (~ 7 h). Reaction mixture was quenched by excess $NaHCO_3$, water (10 mL) was added and extracted with EtOAc (3 × 50 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4 and filtered. Concentration of organic layer *in vacuo* followed by purification of the obtained residue by silica gel (230–400 mesh) column chromatography using EtOAc–PE (30:70) afforded pure product **23** as a yellow solid (452 mg, 71% yield). R_f : 0.3 (EtOAc–PE= 30:70); M. p.: 77–79 °C; IR ($CHCl_3$): ν_{max} 3427, 3021, 1722, 1651 cm^{-1}; $[\alpha]_D^{25}$ +35.35 (*c* 1.7, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.37–7.27 (m, 5H), 6.78 (dd, *J* = 4.2, 15.6 Hz, 1H), 6.11 (dd, *J* = 1.9, 15.6 Hz, 1H), 4.57–4.53 (m, 1H), 4.19 (q, *J* = 7.0 Hz, 2H), 3.93 (d, *J* = 13.0 Hz, 1H), 3.76 (s, 3H), 3.68 (d, *J* = 13.0 Hz, 1H), 3.57 (d, *J* = 5.3 Hz, 1H), 2.34 (br s, 2H), 1.28 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 172.2, 165.9, 145.1, 138.8, 128.5 (2C), 128.4 (2C), 127.5, 122.8, 70.1, 64.2, 60.5, 52.5, 52.2, 14.1; HRMS (ESI) *m/z* calcd for $C_{16}H_{22}O_5N$ [M + H]$^+$: 308.1492, found: 308.1491.

1-Ethyl 6-methyl (4*S*,5*S*,*E*)-5-(benzylamino)-4-((*tert*-butyldimethylsilyl)oxy)hex-2-enedioate (24).

To a stirred solution of amino alcohol **23** (0.35 g, 1.14 mmol, 1 equiv), imidazole (155 mg, 2.28 mmol, 2 equiv) and DMAP (14 mg, 0.11 mmol, 0.1 equiv) in CH_2Cl_2 (20 mL), was added TBSCl (342 mg, 2.28 mmol, 2 equiv) dissolved in CH_2Cl_2 (10 mL) slowly at 0 °C after which reaction was heated to reflux for 6 h until completion of reaction. The progress of the reaction was monitored by TLC. After completion, reaction mixture was concentrated to dryness and residue was extracted with CH_2Cl_2 (3 X 50 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4 and filtered. Concentration of organic layer *in vacuo* followed by purification of the obtained residue by silica gel (230–400 mesh) column chromatography using EtOAc–PE (10:90) afforded TBS ether **24** as thick yellow liquid (393 mg, 82% yield). R_f: 0.5 (EtOAc–PE= 20:80); IR ($CHCl_3$): ν_{max} 3426, 1719, 1656 cm^{-1}; $[\alpha]_D^{25}$ –6.4 (*c* 2.4, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.33–7.28 (m, 4H), 7.27–7.21 (m, 1H), 6.98 (dd, *J* = 5.3, 15.6 Hz, 1H), 6.00 (dd, *J* = 1.3, 15.4 Hz, 1H), 4.51–4.46 (m, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.86 (d, *J* = 13.4 Hz, 1H), 3.71 (s, 3H), 3.68 (d, *J* = 13.4 Hz, 1H), 3.35 (d, *J* = 5.7 Hz, 1H), 1.98 (br s, 1H), 1.31 (t, *J* = 7.1 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 172.8, 166.1, 147.3, 139.3, 128.3 (2C), 128.2 (2C), 127.1, 121.9, 73.5, 66.0, 60.4, 52.2, 51.7, 25.6 (3C), 18.0, 14.2, -4.5, -5.2; HRMS (ESI) *m/z* calcd for $C_{22}H_{36}O_5NSi$ [M + H]$^+$: 422.2357, found: 422.2358.

Methyl (2*S*,3*S*)-3-((*tert*-butyldimethylsilyl)oxy)-6-oxopiperidine-2-carboxylate (25).

The amino ester **24** (0.35 g, 0.83 mmol, 1 equiv) was dissolved in methanol (10 mL) and to that was added catalytic amount of palladium hydroxide over carbon (10%, 20 mg). The resulting reaction mixture was stirred under hydrogen atmosphere using balloon pressure for 2 h. The reaction mixture was filtered through Celite and the filtrate was concentrated *in vacuo*. Purification of the obtained residue by silica gel (230–400 mesh) column chromatography using EtOAc–PE (50:50) afforded lactam **25** as off white solid (215 mg, 90% yield). R_f : 0.3 (EtOAc–PE= 50:50); M. p.: 87 °C; IR ($CHCl_3$): ν_{max} 3404, 1743, 1666 cm^{-1}; $[\alpha]_D^{25}$ –56.0 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 6.62 (br s, 1H), 4.32 (d, *J* = 3.1 Hz, 1H), 4.02 (br s, 1H), 3.75 (s, 3H), 2.59 (td, *J* = 8.8, 17.2 Hz, 1H), 2.30 (td, *J* = 4.6, 17.7 Hz, 1H), 1.86–1.76 (m, 2H), 0.87 (s, 9H), 0.09 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.5, 170.7, 65.4, 62.2, 52.6, 26.5, 26.4, 25.5 (3C), 17.9, -4.9, -5.1; HRMS (ESI) *m/z* calcd for $C_{13}H_{25}O_4NNaSi$ [M + Na]$^+$: 310.1445, found: 310.1442.

Methyl (2*S*,3*S*)-3-((*tert*-butyldimethylsilyl)oxy)piperidine-2-carboxylate (26).

To the stirred solution of lactam **25** (0.2 g, 0.69 mmol, 1 equiv) in anhydrous THF (20 mL), was added BH_3·DMS (0.2 mL, 2.09 mmol, 3 equiv) dropwise at 0 ºC. The resulting reaction mixture was further stirred at 5 °C for 20 h. Methanol (excess) was added to the reaction mixture, stirred for 4 h and concentrated under reduced pressure. Water (10 mL) was added and the reaction mixture was extracted using CH_2Cl_2 (3 × 10 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4 and filtered. Concentration of organic layer *in vacuo* followed by purification of the obtained residue by silica gel (230–400 mesh) column chromatography using EtOAc–PE (50:50) afforded amine **26** as thick yellow liquid (129 mg, 68% yield). R_f : 0.2 (EtOAc–PE= 50:50); IR ($CHCl_3$): ν_{max} 3422, 1737, 1216 cm^{-1}; $[\alpha]_D^{25}$ –12.2 (*c* 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz): δ 3.71 (s, 3H), 3.71–3.66 (m, 1H), 3.20 (d, *J* = 8.4 Hz, 1H), 3.02–2.95 (m, 1H), 2.57–2.49 (m, 1H), 2.01–1.95 (m, 1H), 1.84 (br s, 1H), 1.75–1.70 (m, 1H), 1.52–1.39 (m, 2H), 0.85 (s, 9H), 0.04 (s, 3H), 0.00 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.2, 70.8, 66.2, 51.8, 44.9, 33.8, 25.7, 25.6 (3C), 17.8, -4.3, -5.2; HRMS (ESI) *m/z* calcd for $C_{13}H_{28}O_3NSi$ $[M + H]^+$: 274.1833, found: 274.1833.

Crystallographic data for compound 7

Deposition Number (CCDC) **1949868** contain(s) the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

Acknowledgments

A.L.K. thanks UGC, New Delhi, for the award of a research fellowship. The authors thank CSIR, New Delhi for financial support as part of the XII year plan program under title ORIGIN (CSC-0108) and ACT (CSC-0301). We also thank Dr. H. B. Borate for carefully evaluating the manuscript.

Keywords: Aziridine synthon • Chiral auxiliary • Collective synthesis • Pipecolic acid • Tamiflu •

[1] L. Macha, M. D'hooghe, H. -J. Ha, *Synthesis* **2019**, *51*, 1491–1515.

[2] S. Stankovic, M. D'hooghe, S. Catak, H. Eum, M. Waroquier, V. V. Speybroeck, N. De Kimpe, H. -J. Ha, *Chem. Soc. Rev.,* **2012**, *41*, 643–665.

[3] L. Degennaro, P. Trinchera, R. Luisi, *Chem. Rev.* **2014**, *114*, 7881–7929.

[4] Selected publications from this group (a) S. P. Chavan, R. B. Tejwani, T. Ravindranathan, *J. Org. Chem.* **2001**, *66*, 6197–6201. (b) S. P. Chavan, A. G. Chittiboyina, T. Ravindranathan. S. K. Kamat, U. R. Kalkote, *J. Org. Chem.* **2005**, *70*, 1901–1903. (c) S. P. Chavan, P. N. Chavan, L. B. Khairnar, *RSC Adv.* **2014**, *4*, 11417–11419. (d) S. P. Chavan, K. P. Pawar, S. Garai, *RSC Adv.* **2014**, *4*, 14468–14470. (e) S. P. Chavan, L. B. Khairnar, P. N. Chavan, D. B. Kalbhor, *Tetrahedron: Asymmetry* **2014**, *25*, 1246–1251. (f) S. P. Chavan, L. B. Khairnar, P. N. Chavan, N. B. Dumare, D. B. Kalbhor, R. G. Gonnade, *Tetrahedron Lett*. **2014**, *55*, 6423–6426. (g) S. P. Chavan, A. L. Kadam, P. B. Lasonkar, R. G. Gonnade, *Org. Lett.* **2018**, *20*, 7011–7014. (h) S. P. Chavan, A. L. Kadam, S. A. Kawale, *ACS Omega* **2019**, *4*, 8231–8238.

[5] For reviews on Tamiflu: (a) S. Abrecht, P. Harrington, H. Iding, M. Karpf, R. Trussardi, B. Wirz, U. Zutter, *Chimia* **2004**, *58*, 621–629. (b) M. Shibasaki, M. Kanai, *Eur. J. Org. Chem.* **2008**, 1839–1850. (c) P. Laborda, S. -Y. Wang, J. Voglmeir, *Molecules* **2016**, *21*, 1513.

[6] For reviews on pipecolic acid and its derivatives: (a) C. Kadouri-Puchot, S. Comesse, *Amino Acids* **2005**, *29*, 101–130. (b) A. A. Cant, A. Sutherland, *Synthesis* **2012**, *44*, 1935–1950. (c) A. Cochi, D. G. Pardo, J. Cossy, *Eur. J. Org. Chem.* **2013**, 809–829.

[7] P. Kumar, R. K. Pandey, *Green Chem*. **2000**, *2*, 29–31.

[8] J. C. De Jong, F. Bolhuis, B. L. Feringa, *Tetrahedron Asymmetry,* **1991**, *2*, 1247–1262.

[9] H. Huang, Q. Chen, *Tetrahedron: Asymmetry* **1998**, *9*, 4103–4107.

[10] (a) P. Dauban, A. Chiaroni, C. Riche, R. H. Dodd, *J. Org. Chem.* **1996**, *61,* 2488–2496. (b) Z. Yan, R. Weaving, P. Dauban, R. H. Dodd, *Tetrahedron Lett*. **2002**, *43*, 7593–7595. (c) A. Tarrade, P. Dauban, R. H. Dodd, *J. Org. Chem.* **2003**, *68*, 9521–9524. (d) M. S.Valle, A. Tarrade-Matha, P. Dauban, R. H. Dodd, *Tetrahedron*, **2008**, *64*, 419–432. (e) A. Tarrade-Matha, M. S.Valle,; P. Tercinier, P. Dauban, R. H.Dodd, *Eur. J. Org. Chem.* **2009**, 673–686. (f) M. S. Valle, M. F. Saraiva, P. Retailleau, M. V. de Almeida, R. H. Dodd, *J. Org. Chem.* **2012**, *77*, 5592–5599.

[11] K. S. Ajish Kumar, V. D. Chaudhari, D. D. Dhavale, *Org. Biomol. Chem.* **2008**, *6*, 703–711.

[12] N. B. Kalamkar, V. M. Kasture, D. D. Dhavale, *J. Org. Chem.* **2008**, *73*, 3619–3622.

[13] P. Tapolcsanyi, J. Wolfling, E. Mernyak, G. Schneider, *Monatshefte fur Chemie*, **2004**, *135*, 1129–1136.

[14] S. Terashima, K. Ujita, A. Ishiwata, US 6,790,964 B1, Sep. 14, 2004.

[15] T. Gunasundari, S. Chandrasekaran, *Eur. J. Org. Chem.* **2012**, 6986–6995.

[16] P. K. Upadhyay, P. Kumar, *Synthesis* **2010**, *15*, 2512–2514.

[17] C. Greck, F. Ferreira, J. P. Genet, *Tetrahedron Lett.* **1996**, *37*, 2031–2034.

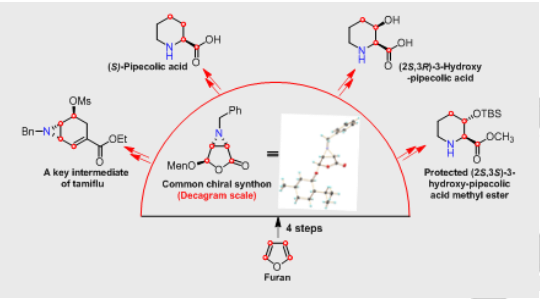
10.1002/asia.201901523

WILEY-VCH

Entry for the Table of Contents

FULL PAPER

The unified synthetic strategy for oseltamivir phosphate (tamiflu), (S)-pipecolic acid and its 3-hydroxy derivatives from furan derived common chiral bicycloaziridino lactone synthon is described. Key features are short (4-steps), enantiopure, and decagram scale synthesis of common chiral synthon from furan and its first-ever application in the total synthesis of biologically active compounds by taking the advantages of high functionalization ability of chiral synthon.



Key Topic*Aziridine Chemistry, Collective Synthesis

Subhash P. Chavan, Appasaheb L. Kadam, Shrikrishna S. Shinde, and Rajesh G. Gonnade*

Page No. – Page No.

Title- Furan Derived Chiral Bicycloaziridino Lactone Synthon: Collective Syntheses of Oseltamivir Phosphate (Tamiflu), (*S*)-Pipecolic acid its 3-Hydroxy derivatives