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β-Lactam-synthon-interceded diastereoselective synthesis of functionally enriched thioxo-imidazolidines, imidazolidin-2-ones, piperazine-5,6-diones and 4,5-dihydroimidazoles

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ABSTRACT

The manuscript explicates simple and convenient protocols for the diastereoselective synthesis of functionally decorated thioxo-imidazolidines, imidazolidin-2-ones, piperazine-5,6-diones and 4,5-dihydroimidazoles using β-lactam synthon approach with an extension towards one-pot synthesis. Since the developed methodology does not employ either the use of Lewis acid conditions or Pd-catalyzed customary procedures, the developed route can be easily modulated for the synthesis of functionalized imidazoles with acid-sensitive functionalities and do not suffer from typical intricacies associated with conventional methods.

1. Introduction

Nitrogen containing heterocycles constitute important core fragments in different natural products and pharmaceutical agents imparting unique physical and biological properties.[1] The chemistry of imidazoles, in particular, has attracted more attention recently due to their reactivity and novel biological properties. Differently substituted imidazoles have been regarded as antihelmintic,[2] analgesic,[3] antibacterial,[4] antifungal,[5] antiviral,[6] antitubercular,[7] anticancer[8] and COX-2/LOX inhibitors.[9] In addition, many of the substituted diaryl imidazoles are potential inhibitors of the p38 MAP kinase,[10] glucagon[11] and CB1 cannabinoid receptor antagonists[12] as well as modulators of P-glycoprotein mediated multidrug resistance (MDR).[13] Fused imidazole derivatives viz. benzoimidazoles and phenanthroimidazole[14] have been used in fabrication of light emitting devices and dye-sensitized solar cells.[15] Recent advances in the areas of green chemistry and organometallic chemistry have extended the utility of imidazoles as ionic liquids[16] and *N*-heterocyclic carbenes.[17] Similarly, imidazolidin-2-ones have shown potential as HIV protease inhibitor[18] with potent activity as 5HT3 antagonists[19] implicated in anxiety, emesis and drug abuse. Di-substituted imidazolidin-2-ones have been reported as potent neurokinin antagonists[20] while spiro imidazolidin-2-one has shown ability to protect against the epilepsy.[21] They are also considered as important chiral auxiliaries to induce stereoselectivity in reactions.[22] The structural motif piperazine diones has also been considered as a privileged scaffold with a variety of therapeutic potential being an important constituent of antibiotics, synthetic vaccines and in chemotherapy.[23] They also constitute an important class of herbicides mainly as protoporphyrinogen-IX oxidase inhibitors with advantage such as high resistance to soil leaching, slow development of weed resistance[24] and low toxicity.

A number of reports have appeared in the literature for the synthesis of 1,2,4,5-tetrasubstituted imidazoles.[25,26] Generally, their synthesis involved a four-component condensation of a 1,2-diketone, α-hydroxyketone or α-ketomonoxime with an aldehyde, primary amine and ammonium acetate using microwaves,[25a] heteropolyacid,[25b] $BF_3 \cdot SiO_2$,[25c] silica gel/$NaHSO_4$[25d] or $HClO_4$–SiO_2[25e] and ionic liquids[25f] Such imidazoles have also been synthesized by the cycloaddition reaction of mesoionic 1,3-oxazolium-5-olates with *N*-(arylmethylene) benzenesulfonamides,[26a] hetero-Cope rearrangement,[26b] condensation of a 1,2-diketone with an aryl nitrile and primary amine under microwave irradiation.[26c] However, most of these reactions either require protic or Lewis acid conditions, which are not compatible with acid-sensitive functionalities or require amino acetal or ketal subunits prepared via several synthetic steps. The reported protocols for the synthesis of

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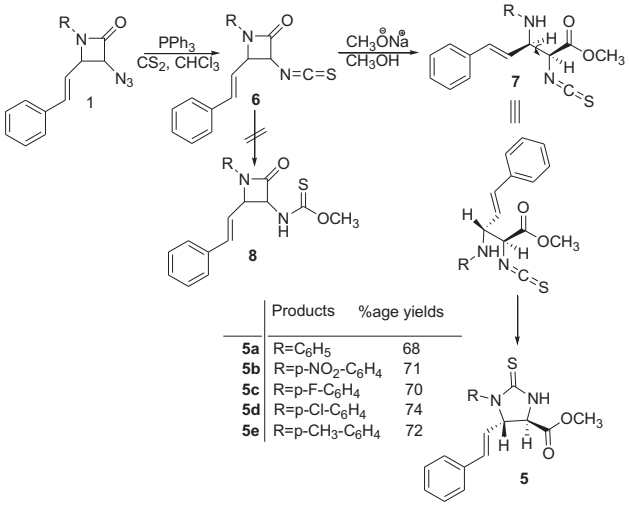
imidazolidin-2-ones employed palladium catalyzed allylic alkylation,[27] alkene diamination,[28] ureidomercuriation[29] and rearrangement of amino acids using bromine.[30] These protocols are invariably associated with a number of disadvantages ranging from the isolation of complex mixture of products, alkene isomerization, preference for (*E*)-alkene over the (*Z*)-isomer for the carboamination along with longer reaction times and incomplete conversions.

Thus, in continuation with our pursuit for the synthesis of novel heterocyclic compounds with medicinal potential,[31] and our recent exposure to the prospective of β-lactam synthon approach for the synthesis of novel heterocyclic compounds,[32] we have recently reported diastereoselective synthesis of thioxo-imidazolidines en route to multi-functionalized imidazoles.[32d] The present manuscript provides a detailed account on the extension of this protocol for the synthesis of functionalized imidazolines, imidazolidin-2-ones and piperazine-5,6-diones.

2. Results and discussion

Thus, the treatment of racemic *cis*-3-azido-azetidin-2-ones **1**, prepared via Staudinger reaction,[31a] with sodium methoxide in dry methanol at room temperature resulted in the isolation of equimolar diastereomeric mixtures of corresponding β-amino esters **2** and **3**. The diastereomeric mixture of **2** and **3** was utilized as such for further synthetic endeavours viz. an initial Staudinger reaction with triphenylphosphine followed by the treatment with carbon disulfide. This synthetic sequence resulted in the isolation of diastereomeric mixture of *cis* and *trans* (1-aryl-5-styryl-2-thioxo-imidazolidin-4-yl)-acetic acid methyl esters **4** and **5** presumably via intramolecular cyclization of 2-isothiocyanato-3-methylamino-5-phenyl-pent-4-enoic acid methyl esters (**I** and **II**) as shown in Scheme 1. The careful chromatographic separation of 2-thioxo-imidazolidines enabled the isolation and characterization of **4** and **5** with the help of spectral data and analytical evidences. The stereochemistry assigned to **4** and **5** was on the basis of coupling constant J=9.6 Hz for cis-isomer and J=5.7 Hz for trans-isomer, respectively.

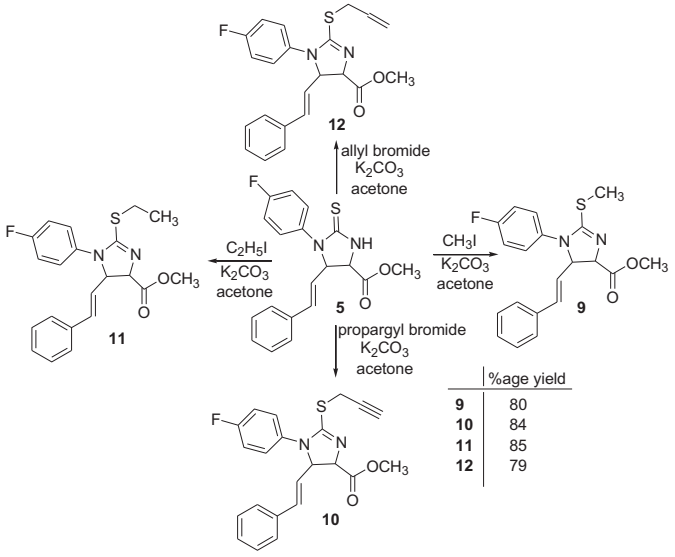
The diastereoselectivity in the above sequence of reactions has been achieved by introducing an electrophilic site viz. isothiocyanate prior to amidolysis of β-lactam ring, which would result in the preference of intramolecular cyclization over epimerization as observed in Scheme 1. Thus, the treatment of racemic 3-azido-azetidin-2-one with triphenylphosphine and carbon disulphide led to the synthesis of 3-isothiocyanato-1-phenyl-4-styryl-azetidin-2-one **6**. This upon amidolysis with sodium methoxide resulted in diastereoselective synthesis of *trans*-2-thioxo-imidazolidines **5** via aminoesters **7** as shown in Scheme 2. The absence of even traces of **4** as well as 3-thiocarbamic acid *O*-methyl ester **8** in the ^{1}H NMR of crude reaction mixture ruled out epimerization and is suggestive of the fact that the relaxation of ring strain is the driving force for the described transformation.



	Products	%age yields
5a	R=C_6H_5	68
5b	R=p-NO_2-C_6H_4	71
5c	R=p-F-C_6H_4	70
5d	R=p-Cl-C_6H_4	74
5e	R=p-CH_3-C_6H_4	72

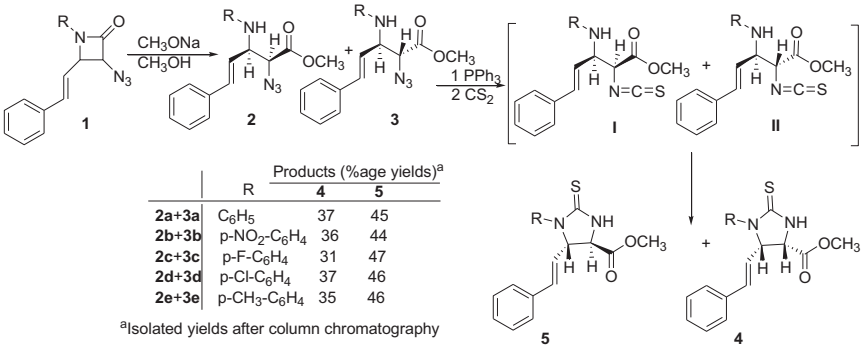
Scheme 2. Diastereoselective synthesis of *trans*-2-thioxo-imidazolidines.

The diastereoselectively synthesized **5** was further utilized for the synthesis of structurally diverse 4,5-dihydroimidazoles in quantitative yields via usual synthetic steps as depicted in Scheme 3.



	%age yield
9	80
10	84
11	85
12	79

Scheme 3. Synthesis of multi-functionalized 4,5-dihydroimidazoles.

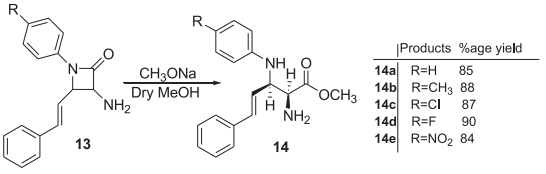


	R	Products (%age yields)[a] 4	5
2a+3a	C_6H_5	37	45
2b+3b	p-NO_2-C_6H_4	36	44
2c+3c	p-F-C_6H_4	31	47
2d+3d	p-Cl-C_6H_4	37	46
2e+3e	p-CH_3-C_6H_4	35	46

[a]Isolated yields after column chromatography

Scheme 1. Synthetic sequence for the preparation of 2-thioxo-imidazolidines.

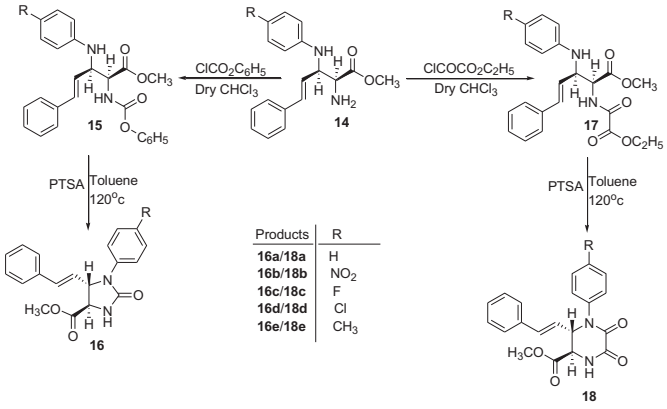
The above-developed protocol has been further extended towards the diastereoselective synthesis of functionalized imidazolidin-2-ones and piperazine-5,6-diones. The synthetic approach involved an initial amidolysis of racemic *cis*-3-amino-2-azetidinones **13**, obtained from **1** using Zn/NH_4Cl reduction protocol,[33] to yield the corresponding α-aminoesters **14** in a diastereoselective manner. The absence of diastereomeric mixture in **13** as was observed in amidolysis of **1** can thus be attributed to the strong electron withdrawing nature of azido group, which makes the hydrogen at α-position acidic and facilitates enolization. Such enolization is, however, discouraged by the presence of polar donating $-NH_2$ group resulting in the isolation of corresponding *cis*-α-aminoesters **14** in a highly diastereoselective manner (Scheme 4).



Products		%age yield
14a	R=H	85
14b	R=CH_3	88
14c	R=Cl	87
14d	R=F	90
14e	R=NO_2	84

Scheme 4. Diastereoselective synthesis of *cis*-α-aminoesters via base assisted amidolysis.

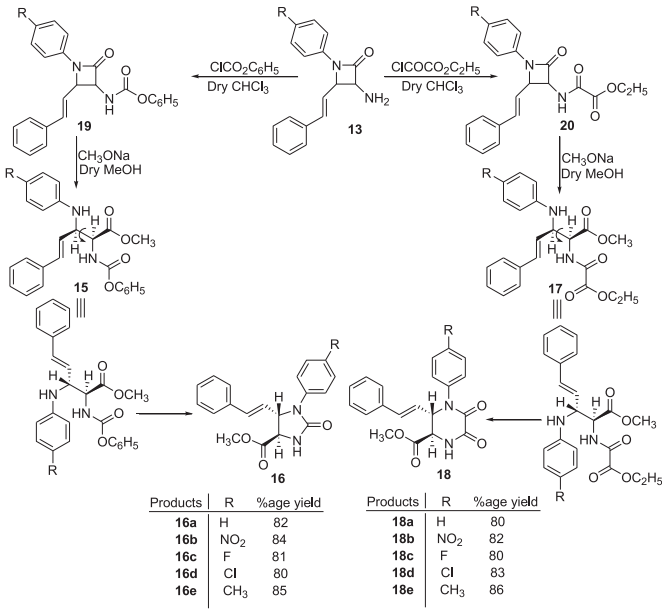
The synthesized *cis*-α-aminoesters **14** were then reacted with phenyl chloroformate to yield the corresponding *cis*-2-phenoxy carbonyl amino-5-phenyl-3-arylamino-pent-4-enoic acid methyl esters **15**, which upon subsequent refluxing in toluene in the presence of *p*-toluene sulfonic acid led to the isolation of 1,4,5-trisubstituted *trans*-imidazolidin-2-ones **16**. Similar protocol involving an initial treatment of **14** with ethyl oxalylchloride with subsequent heating in toluene in the presence of *p*-TsOH led to the diastereoselective formation of 1,2,3-trisubstituted *trans*-piperazine-5,6-diones **18** in good to excellent yields. The trans-stereochemistry to these products were assigned on the basis of observed coupling constant viz. J=5.4 Hz for **16** and J=2.1 Hz for **18**, respectively (Scheme 5).



Products	R
16a/18a	H
16b/18b	NO_2
16c/18c	F
16d/18d	Cl
16e/18e	CH_3

Scheme 5. Diastereoselective synthesis of *trans*-imidazolidin-2-one and piperazine-5,6-dione.

Since the above methodology involved an initial formation of α-aminoesters **15** and **17** having appropriately placed electrophilic and nucleophilic viz. alkoxy and *N*-aryl amino groups, it was felt worthwhile to explore the single pot version of the above synthetic protocols. This could be achieved by introducing an electrophilic site viz. carbonylamino and ethoxyoxalyl amino prior to the amidolysis of β-lactam ring. Thus the treatment of racemic 3-amino-2-azetidinone **13** with phenyl chloroformate/ethyl chloro-oxalyl chloride led to the synthesis of **19**/**20**, respectively. The amidolytic cleavage of **19** and **20** using sodium methoxide led to the diastereoselective formation of corresponding *trans*-imidazolidin-2-one **16** and piperazine-5,6-diones **18**, respectively, without the isolation of corresponding amino esters **15** and **17**. The formation of diastereomerically pure trans-product, without the formation of corresponding cis-isomer even in traces as confirmed by ^{1}H NMR of crude reaction mixture, is a consequence of bringing closer the latent functionalities involving C–C bond rotation in the amino-esters as shown in Scheme 6.



Products	R	%age yield
16a	H	82
16b	NO_2	84
16c	F	81
16d	Cl	80
16e	CH_3	85

Products	R	%age yield
18a	H	80
18b	NO_2	82
18c	F	80
18d	Cl	83
18e	CH_3	86

Scheme 6. Single-pot synthesis of imidazolidin-2-one and piperazine-5,6-dione.

3. Conclusions

In conclusion, we have urbanized a convenient synthetic protocol for the diastereoselective synthesis of functionalized thioxo-imidazolidines, 4,5-dihydroimidazoles, imidazolidin-2-ones and piperazine-5,6-diones utilizing β-lactam synthon protocol. The synthesized precursors with latent functionalities can be easily utilized for further transformations to biologically and medicinally important imidazole/piperazine based scaffolds. Since the reaction does not employ protic or Lewis acid conditions, the strategy can be easily modulated for the synthesis of imidazoles with acid-sensitive functionalities. Further, the developed protocol for the synthesis of imidazolidine-2-ones does not suffer from typical intricacies associated with conventional methodologies viz. the utilization of palladium catalyst, alkene isomerization and preference for (*E*)-alkene over (*Z*)-isomer along with incomplete conversions and longer reaction times.

4. Experimental section

4.1. General

Melting points were determined by open capillary using Veego Precision Digital Melting Point apparatus (MP-D) and are uncorrected. IR spectra were recorded on a Shimadzu D-8001 spectrophotometer. ^{1}H NMR spectra were recorded in deuterochloroform with Jeol 300 (300 MHz) spectrometers using TMS as internal standard. Chemical shift values are expressed as parts per million downfield from TMS and J values are in hertz. Splitting patterns are indicated as s: singlet, d: doublet, t: triplet, m: multiplet, dd: double doublet, ddd: doublet of a doublet of

a doublet, and br: broad peak. ^{13}C NMR spectra were recorded on Jeol 300 (75 MHz) spectrometers in deuterochloroform using TMS as internal standard. Mass spectra were recorded on Shimadzu GC–MS-QP-2000 mass spectrometer. Elemental analyses were performed on Heraus CHN-O-Rapid Elemental Analyzer. Column chromatography was performed on a silica gel (60–120 mesh). All the starting materials as well as the products were racemates.

4.2. Sodium methoxide assisted intermolecular amidolysis of 3-azido-azetidin-2-one

To a solution of 3-azido-β-lactam **1** (1 mmol) in dry methanol was added a solution of sodium methoxide (0.3 mmol) in dry methanol. The reaction mixture was allowed to stir at room temperature and the progress was monitored using TLC using a mixture of (80:20) hexane/ethyl acetate. On completion, the reaction mixture was quenched with water (10 ml) and extracted with chloroform (2×50 ml). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure to yield diastereomeric mixture of β-amino esters **2** and **3** as pale yellow viscous liquids.

*4.2.1. 2(SR)-Azido-5-phenyl-3(SR)-phenylamino-pent-4-enoic acid methyl ester (**2a**) and 2(RS)-azido-5-phenyl-3(SR)-phenylamino-pent-4-enoic acid methyl ester (**3a**).* Yellow oil. δ_H ($CDCl_3$, 300 MHz): 3.77 (s, 3H, $-OCH_3$), 3.81 (s, 3H, $-OCH_3$), 4.38 (a pair of d, J=3.6, 3.9 Hz, 2H, H^4, $H^{4'}$), 4.57 (dd, J=6.0, 4.3 Hz, 2H, H^5, $H^{5'}$), 6.09 (a pair of dd, 2H, J=6.3, 6.9, 15.9, 16.2 Hz, H^6, $H^{6'}$), 6.55–6.66 (m, 6H, H^7, $H^{7'}$, 4H, ArH), 7.07–7.17 (m, 4H, aromatic), 7.21–7.44 (m, 12H, aromatic). δ_C ($CDCl_3$, 75 MHz): 52.7, 52.8, 56.9, 57.0, 64.9, 66.2, 114.1, 114.2, 118.5, 118.8, 124.6, 126.5, 126.6, 126.7, 127.9, 128.0, 128.2, 128.5, 129.2, 129.5, 133.1, 133.8, 136.1, 145.6, 168.8, 168.9. ν_{max} (KBr)/cm^{-1} 2100, 1750, 1582, 1500. m/z 323 (M^+).

*4.2.2. 2(SR)-Azido-3(SR)-(4-nitro-phenylamino)-5-phenyl-pent-4-enoic acid methyl ester (**2b**) and 2(RS)-azido-3(SR)-(4-nitro-phenylamino)-5-phenyl-pent-4-enoic acid methyl ester (**3b**).* Yellow oil. δ_H ($CDCl_3$, 300 MHz): 3.78 (s, 3H, $-OCH_3$), 3.81 (s, 3H, $-OCH_3$), 4.36 (a pair of d, J=3.6, 3.9 Hz, 2H, H^4, $H^{4'}$), 4.57–4.61 (m, 2H, H^5, $H^{5'}$),6.09 (a pair of dd, 2H, J=6.3, 6.9, 15.9, 16.2 Hz, H^6, $H^{6'}$), 6.54–6.65 (m, 6H, H^7, $H^{7'}$, 4ArH), 7.08–7.16 (m, 4H, H, aromatic), 7.25–7.46 (m, 10H, aromatic). δ_C ($CDCl_3$, 75 MHz): 52.8, 52.9, 57.0, 57.1, 63.8, 64.2, 115.2, 115.3, 124.2, 126.0, 126.6, 126.7, 128.1, 128.2, 128.5, 128.6, 128.7, 129.0, 129.1, 129.3, 133.3, 134.0, 135.8, 135.9, 144.2, 144.7, 168.7, 168.8. ν_{max} (KBr)/cm^{-1}2100, 1750, 1582, 1500. m/z 368 (M^+).

*4.2.3. 2(SR)-Azido-3(SR)-(4-fluoro-phenylamino)-5-phenyl-pent-4-enoic acid methyl ester (**2c**) and 2(RS)-azido-3(SR)-(4-fluoro-phenylamino)-5-phenyl-pent-4-enoic acid methyl ester (**3c**).* Yellow oil. δ_H ($CDCl_3$, 300 MHz): 3.79 (s, 3H, $-OCH_3$), 3.81 (s, 3H, $-OCH_3$), 4.18 (s, 1H, NH), 4.37 (a pair of d, J=3.6, 3.9 Hz, 2H, H^4, $H^{4'}$), 4.57 (m, 2H, H^5, $H^{5'}$), 6.09 (a pair of dd, 2H, J=6.3, 6.9, 15.9, 16.2 Hz, H^6, $H^{6'}$), 6.60–6.67 (m, 2H, , H^7, $H^{7'}$, 4H, ArH), 6.85–6.91 (m, 4H, aromatic), 7.22–7.32 (m, 10H, aromatic). δ_C ($CDCl_3$, 75 MHz): 52.8, 52.9, 57.2, 57.8, 63.9, 64.3, 115.4, 115.5, 115.6, 115.8, 115.9, 116.1, 124.5, 126.4, 126.6, 126.7, 128.1, 128.2, 128.6, 128.7, 133.2, 134.0, 134.8, 136.0, 141.9, 142.4, 168.8, 168.9. ν_{max} (KBr)/cm^{-1} 2100,1750,1582, 1500. m/z 344 (M^+).

*4.2.4. 2(SR)-Azido-3(SR)-(4-chloro-phenylamino)-5-phenyl-pent-4-enoic acid methyl ester (**2d**) and 2(RS)-azido-3(SR)-(4-chloro-phenylamino)-5-phenyl-pent-4-enoic acid methyl ester (**3d**).* Yellow oil. δ_H ($CDCl_3$, 300 MHz): 3.76 (s, 3H, $-OCH_3$), 3.80 (s, 3H, $-OCH_3$), 4.17 (s, 1H, NH), 4.38 (a pair of d, J=3.6, 3.9 Hz, 2H, H^4 $H^{4'}$), 4.57 (m, 2H, H^5, $H^{5'}$), 6.08 (a pair of dd, 2H, J=6.3, 6.9, 15.9, 16.2 Hz, H^6, $H^{6'}$), 6.56–6.65 (m, 2H, H^7, $H^{7'}$, 4H, ArH), 7.08–7.15 (m, 4H, aromatic), 7.23–7.34 (m, 10H, aromatic). δ_C ($CDCl_3$, 75 MHz): 52.8, 52.9, 57.0, 57.1, 63.8, 64.2, 115.2, 115.3, 124.1, 126.0, 126.6, 126.7, 128.1, 128.2, 128.6, 128.7, 128.8, 129.1, 129.2, 129.3, 133.3, 134.0, 135.8, 135.9, 144.2, 144.7, 168.7, 168.8. ν_{max} (KBr)/cm^{-1}2100,1750,1582, 1500. m/z 357(M^+).

*4.2.5. 2(SR)-Azido-5-phenyl-3(SR)-p-tolylamino-pent-4-enoic acid methyl ester (**2e**) and 2(RS)-azido-5-phenyl-3(SR)-p-tolylamino-pent-4-enoic acid methyl ester (**3e**).* Yellow oil. δ_H ($CDCl_3$, 300 MHz): 2.21 (s, 3H, CH_3), 2.23 (s, 3H, CH_3), 3.74 (s, 3H, $-OCH_3$), 3.80 (s, 3H, $-OCH_3$), 4.38 (a pair of d, J=3.3, 3.9 Hz, 2H, H^4, $H^{4'}$), 4.58–4.63 (m, 2H, H^5, $H^{5'}$), 6.09 (a pair of dd, 2H, J=6.3, 6.9, 15.9, 16.2 Hz, H^6, $H^{6'}$), 6.56–6.68 (m, 6H, H^7, $H^{7'}$, 4ArH), 6.98 (a pair of d, 4H, J=7.4, 6.3 Hz, ArH), 7.02–7.34 (m, 10H, H, aromatic). δ_C ($CDCl_3$, 75 MHz): 20.3, 20.4, 52.8, 52.9, 57.3, 57.4, 64.8, 66.2, 114.4, 114.5, 124.7, 126.5, 126.6, 126.7, 126.8, 127.9, 128.0, 128.2, 128.4, 128.5, 128.6, 129.7, 129.9, 133.0, 133.7, 136.1, 143.2, 168.9, 169.0. ν_{max} (KBr)/cm^{-1}2100,1750,1582, 1500. m/z 337 (M^+).

4.3. Typical procedure for the preparation of diastereomeric mixture of thioxo-imidazolidines 4 and 5

To a stirred solution of β-amino esters **2** and **3** (1 mmol) in dry chloroform was added a solution of triphenylphosphine (1.2 mmol) in dry chloroform. On completion of the reaction, carbon disulphide (5.0 mmol) was added and the solution was allowed to stir for 14 h and the progress was monitored using TLC. The reaction mixture was then concentrated under reduced pressure and purified via column chromatography using (35:65) ethyl acetate/hexane mixture.

*4.3.1. 1-Phenyl-5(RS)-styryl-2-thioxo-imidazolidine-4(RS)-carboxylic acid methyl ester (**5a**).* Yellow oil. Found: C, 71.35; H, 3.94, N, 4.53. $C_{19}H_{13}NO_2S$ requires C, 71.45; H, 4.10; N, 4.39%. δ_H ($CDCl_3$, 300 MHz): 3.79 (s, 3H, $-OCH_3$), 4.32 (d, J=5.7 Hz, 1H, H^4), 5.07 (dd, J=5.7, 8.4 Hz, 1H, H^5), 6.12 (dd, J=8.4, 15.9 Hz, 1H, H^6), 6.48 (d, J=15.9 Hz, 1H, H^7), 7.17–7.39 (m, 10H, aromatic), 7.42 (s, 1H, NH). δ_C ($CDCl_3$, 75 MHz): 52.8, 61.3, 67.2, 120.1, 125.6, 127.8, 128.6, 128.9, 129.2, 132.9, 134.6, 136.3, 136.9, 168.8, 183.0. ν_{max} (KBr)/cm^{-1} 1750, 1500, 1210. m/z 319 (M^+).

*4.3.2. 1-Phenyl-5(SR)-styryl-2-thioxo-imidazolidine-4(RS)-carboxylic acid methyl ester (**4a**).* White solid. Found: C, 71.37; H, 3.98, N, 4.52. $C_{19}H_{13}NO_2S$ requires C, 71.45; H, 4.10; N, 4.39%. Mp 153–154 °C. δ_H ($CDCl_3$, 300 MHz): 3.69 (s, 3H, $-OCH_3$), 4.88 (d, J=9.6 Hz, 1H, H^4), 5.14 (dd, J=9.3, 9.6 Hz, 1H, H^5), 6.05 (dd, J=9.3, 15.6 Hz, 1H, H^6), 6.50 (d, J=15.6 Hz, 1H, H^7), 6.93 (s, 1H, NH), 7.23–7.37 (m, 10H, aromatic). δ_C ($CDCl_3$, 75 MHz): 52.7, 60.2, 67.8, 121.0, 126.7, 128.7, 128.8, 129.1, 129.4, 133.1, 134.9, 136.5, 137.2, 168.4, 182.9. ν_{max} (KBr)/cm^{-1} 1750, 1500, 1210. m/z 319 (M^+).

*4.3.3. 1-(4-Nitro-phenyl)-5(RS)-styryl-2-thioxo-imidazolidine-4(RS)-carboxylic acid methyl ester (**5b**).* Yellow oil. Found: C, 59.43; H, 4.35, N, 11.12. $C_{19}H_{17}N_3O_4S$ requires C, 59.52; H, 4.47; N, 10.96%. δ_H ($CDCl_3$, 300 MHz): 3.86 (s, 3H, $-OCH_3$), 4.31 (d, J=5.7 Hz, 1H, H^4), 5.10 (dd, J=5.7, 8.4 Hz, 1H, H^5), 6.17 (dd, J=8.4, 15.6 Hz, 1H, H^6), 6.51 (d, J=15.6 Hz, 1H, H^7), 6.54 (s, 1H, NH), 7.23–7.36 (m, 5H, H, aromatic), 7.76 (d, 2H, J=8.7 Hz, ArH), 8.20 (d, 2H, J=8.7 Hz, ArH). δ_C ($CDCl_3$, 75 MHz): 52.7, 61.3, 67.1, 120.4, 125.3, 127.6, 128.7, 128.6, 129.0, 132.6, 134.7, 136.5, 136.6, 168.7, 182.9. ν_{max} (KBr)/cm^{-1} 1750, 1500, 1210. m/z 384 (M^+).

*4.3.4. 1-(4-Nitro-phenyl)-5(SR)-styryl-2-thioxo-imidazolidine-4(RS)-carboxylic acid methyl ester (**4b**).* Yellow solid. Found: C, 62.56; H, 3.24, N, 7.72. $C_{19}H_{12}N_2O_4S$ requires C, 62.63; H, 3.32; N, 7.69%. Mp

158–160 °C. δ_H ($CDCl_3$, 300 MHz): 3.71 (s, 3H, $-OCH_3$), 4.89 (d, J=9.9 Hz, 1H, H^4), 5.31 (dd, J=9.6, 9.9 Hz, 1H, H^5), 6.03 (dd, J=9.6, 15.9 Hz, 1H, H^6), 6.61 (d, J=15.9 Hz, 1H, H^7), 6.86 (s, 1H, NH), 7.24–7.37 (m, 5H, aromatic), 7.74 (d, 2H, J=9.0 Hz, ArH), 8.21 (d, 2H, J=9.0 Hz, ArH). δ_C ($CDCl_3$, 75 MHz): 52.9, 60.6, 68.4, 121.8, 127.1, 127.4, 128.8, 129.6, 129.9, 135.5, 135.9, 136.7, 137.7, 168.5, 183.0. ν_{max} (KBr)/cm^{-1} 1751, 1510, 1200. m/z 384 (M^+).

*4.3.5. 1-(4-Fluoro-phenyl)-5(RS)-styryl-2-thioxo-imidazolidine-4(RS)-carboxylic acid methyl ester (**5c**).* Yellow oil. Found: C, 63.87; H, 4.72, N, 8.04. $C_{19}H_{17}FN_2O_2S$ requires C, 64.03; H, 4.81; N, 7.86%. δ_H ($CDCl_3$, 300 MHz): 3.86 (s, 3H, $-OCH_3$), 4.34 (d, J=5.7 Hz, 1H, H^4), 5.10 (dd, J=5.7, 8.7 Hz, 1H, H^5), 6.17 (dd, J=8.7, 15.6 Hz, 1H, H^6), 6.50 (d, J=15.6 Hz, 1H, H^7), 6.68 (s, 1H, NH), 7.02–7.36 (m, 9H, H, aromatic). δ_C ($CDCl_3$, 75 MHz): 52.8, 60.7, 68.6, 115.4, 115.7, 123.8, 126.1, 126.5, 128.0, 128.9, 133.5, 134.6, 135.7, 168.9, 182.0. ν_{max} (KBr)/cm^{-1} 1750, 1500, 1210 m/z 357 (M^+).

*4.3.6. 1-(4-Fluoro-phenyl)-5(SR)-styryl-2-thioxo-imidazolidine-4(RS)-carboxylic acid methyl ester (**4c**).* White solid. Found: C, 63.93; H, 4.65, N, 8.03. $C_{19}H_{17}FN_2O_2S$ requires C, 64.03; H, 4.81; N, 7.86%. Mp 156–158 °C. δ_H ($CDCl_3$, 300 MHz): 3.69 (s, 3H, $-OCH_3$), 4.89 (d, J=9.9 Hz, 1H, H^4), 5.12 (dd, J=9.3, 9.9 Hz, 1H, H^5), 6.07 (dd, J=9.3, 15.6 Hz, 1H, H^6), 6.48 (d, J=15.6 Hz, 1H, H^7), 6.94 (s, 1H, NH), 7.01–7.37 (m, 9H, H, aromatic). δ_C ($CDCl_3$, 75 MHz): 50.7, 58.3, 66.2, 113.8, 114.1, 119.3, 124.8, 124.9, 126.8, 127.8, 132.0, 133.1, 135.3, 166.6, 181.3. ν_{max} (KBr)/cm^{-1} 1750, 1500, 1210. m/z 357 (M^+).

*4.3.7. 1-(4-Chloro-phenyl)-5(RS)-styryl-2-thioxo-imidazolidine-4(RS)-carboxylic acid methyl ester (**5d**).* Yellow oil. Found: C, 61.00; H, 4.42, N, 7.67. $C_{19}H_{17}ClN_2O_2S$ requires C, 61.20; H, 4.60; N, 7.51%. δ_H ($CDCl_3$, 300 MHz): 3.78 (s, 3H, $-OCH_3$), 4.33 (d, J=5.7 Hz, 1H, H^4), 5.07 (dd, J=5.7, 8.4 Hz, 1H, H^5), 6.10 (dd, J=8.4, 15.9 Hz, 1H, H^6), 6.47 (d, J=15.9 Hz, 1H, H^7), 7.16–7.38 (m, 9H, H, aromatic), 7.42 (s, 1H, NH). δ_C ($CDCl_3$, 75 MHz): 53.1, 61.1, 68.7.7, 124.2, 126.7, 128.5, 128.7, 128.9, 129.1, 133.1, 134.9, 136.0, 136.5, 169.3, 182.0. ν_{max} (KBr)/cm^{-1} 1750, 1500, 1210. m/z 373 (M^+).

*4.3.8. 1-(4-Chloro-phenyl)-5(SR)-styryl-2-thioxo-imidazolidine-4(RS)-carboxylic acid methyl ester (**4d**).* White solid. Found: C, 61.02; H, 4.43, N, 7.65. $C_{19}H_{17}ClN_2O_2S$ requires C, 61.20; H, 4.60; N, 7.51%. Mp 163–164 °C. δ_H ($CDCl_3$, 300 MHz): 3.70 (s, 3H, $-OCH_3$), 4.86 (d, J=9.9 Hz, 1H, H^4), 5.14 (dd, J=9.6, 9.9 Hz, 1H, H^5), 6.04 (dd, J=9.6, 15.9 Hz, 1H, H^6), 6.50 (d, J=15.9 Hz, 1H, H^7), 6.68 (s, 1H, NH), 7.25–7.35 (m, 9H, H, aromatic). δ_C ($CDCl_3$, 75 MHz): 52.7, 60.2, 67.9, 121.0, 126.7, 128.7, 128.7, 128.8, 129.1, 133.2, 135.0, 136.5, 137.3, 168.2, 183.1. ν_{max} (KBr)/cm^{-1} 1750, 1500, 1210. m/z 373 (M^+).

*4.3.9. 5(RS)-Styryl-2-thioxo-1-p-tolyl-imidazolidine-4(RS)-carboxylic acid methyl ester (**5e**).* Yellow oil. Found: C, 72.13; H, 3.83, N, 4.62. $C_{19}H_{13}NO_2S$ requires C, 72.05; H, 4.53; N, 4.20%. δ_H ($CDCl_3$, 300 MHz): 2.31(s, 3H, CH_3), 3.86 (s, 3H, $-OCH_3$), 4.32 (d, J=5.7 Hz, 1H, H^4), 5.12 (dd, J=5.7, 8.7 Hz, 1H, H^5), 6.19 (dd, J=8.7, 15.6 Hz, 1H, H^6), 6.50 (d, J=15.6 Hz, 1H, H^7), 6.53 (s, 1H, NH), 7.16 (d, 2H, J=8.4 Hz, ArH), 7.22–7.31 (m, 7H, aromatic). δ_C ($CDCl_3$, 75 MHz): 21.2, 52.8, 60.2, 67.1, 120.3, 125.4, 127.7, 128.8, 128.7, 129.1, 132.7, 134.8, 136.4, 136.7, 168.8, 183.1. ν_{max} (KBr)/cm^{-1} 1750, 1500, 1210 m/z 333 (M^+).

*4.3.10. 5(SR)-Styryl-2-thioxo-1-p-tolyl-imidazolidine-4(RS)-carboxylic acid methyl ester (**4e**).* White solid. Found: C, 71.85; H, 4.38, N, 4.32. $C_{19}H_{13}NO_2S$ requires C, 72.05; H, 4.53; N, 4.20%. Mp 160–162 °C. δ_H ($CDCl_3$, 300 MHz): 2.30 (s, 3H, CH_3), 3.69 (s, 3H, $-OCH_3$), 4.86 (d, J=9.9 Hz, 1H, H^4), 5.10 (dd, J=9.9, 9.6 Hz, 1H, H^5), 6.17 (dd, J=9.6, 15.9 Hz, 1H, H^6), 6.48 (d, J=15.9 Hz, 1H, H^7), 6.57 (s, 1H, NH), 7.15 (d, 2H, J=8.4 Hz, ArH), 7.23–7.31 (m, 7H, aromatic). δ_C ($CDCl_3$, 75 MHz): 21.1, 52.6, 60.3, 68.1, 121.5, 126.7, 127.4, 128.6, 129.7, 129.9, 135.2, 135.3, 136.9, 137.6, 168.4, 183.3. ν_{max} (KBr)/cm^{-1} 1751, 1510, 1200. m/z 333 (M^+).

4.4. Typical procedure for the diastereoselective synthesis of 1,2,4,5-tetrahydroimidazoles

To a stirred solution of 3-azido-β-lactams (1 mmol) in dry chloroform was added a solution of triphenylphosphine (1.2 mmol) in dry chloroform. On completion of the reaction, carbon disulphide (5.0 mmol) was added and the progress was monitored using TLC using a mixture of (70:30) hexane/ethyl acetate. The synthesized 3-isothiocyanato-β-lactams were purified using column chromatography with a solution of (5:95) ethyl acetate/hexane. The purified 3-isothiocyanato-β-lactam (1 mmol) was dissolved in dry methanol and a solution of sodium methoxide (0.3 mmol) was added to it. The reaction mixture after completion was quenched with water (10 mmol) and extracted with chloroform (2×50 ml). The combined organic layers were dried over anhydrous sodium sulfate, concentrated under reduced pressure and purified via column chromatography using a solution of (35:65) ethyl acetate/hexane to yield *trans*-thioxo-imidazolines **5**. To the stirred solution of thioxo-imidazolines (1.0 mmol) in dry acetone were added K_2CO_3 (5.0 mmol) and the alkyl halide (1.2 mmol) at room temperature. On completion of the reaction as monitored by TLC, the reaction mixture was filtered, washed with water (25 ml) extracted with dichloromethane (2×25 ml). The combined organic layer was dried upon anhydrous sodium sulfate and concentrated under reduced pressure to form the corresponding 1,2,4,5-tetrahydroimidazoles.

*4.4.1. 1-(4-Fluoro-phenyl)-2-methylsulfanyl-5(SR)-styryl-4,5-dihydro-1H-imidazole-4(SR)-carboxylic acid methyl ester (**9**).* Yellow oil. Found: C, 64.73; H, 5.29, N, 7.44. $C_{20}H_{19}FN_2O_2S$ requires C, 64.85; H, 5.17; N, 7.56%. δ_H ($CDCl_3$, 300 MHz): 2.11 (s, 3H, CH_3), 4.92 (t, J=9.0, 10.2 Hz, 1H, H^5), 5.05 (d, J=10.5 Hz, 1H, H^4), 6.04 (dd, J=9.0, 15.9 Hz, 1H, H^6), 6.45 (d, J=15.9 Hz, 1H, H^7), 6.51 (d, 2H, J=8.2 Hz, ArH), 6.82 (d, 2H, J=8.2 Hz, ArH), 7.16–7.28 (m, 5H, ArH). δ_C ($CDCl_3$, 75 MHz): 18.9, 53.0, 71.6, 72.4, 117.2, 117.6, 125.3, 128.2, 129.9, 130.1, 130.4, 130.7, 137.6, 137.7, 166.2, 171.5. m/z 370 (M^+).

*4.4.2. 1-(4-Fluoro-phenyl)-2-prop-2-ynylsulfanyl-5(SR)-styryl-4,5-dihydro-1H-imidazole-4(SR)-carboxylic acid methyl ester (**10**).* Yellow oil. Found: C, 67.50; H, 3.72, N, 7.31. $C_{19}H_{17}FN_2O_2S$ requires C, 67.68; H, 3.87; N, 7.18%. δ_H ($CDCl_3$, 300 MHz): 2.24 (t, J=1.5, 2.7 Hz, 1H, acetylinic), 3.65 (s, 3H, $-OCH_3$), 3.94 (dABq, 2H, J=1.5, 2.7, 11.2 Hz, CH_2), 4.95 (dd, J=9.0, 10.2 Hz, 1H, H^5), 5.05 (d, J=10.5 Hz, 1H, H^4), 6.08 (dd, J=9.0 Hz, 15.9 Hz, 1H, H^6), 6.44 (d, J=15.9 Hz, 1H, H^7), 7.00 (d, 2H, J=9.0 Hz, ArH), 7.16–7.28 (m, 7H, H, aromatic). δ_C ($CDCl_3$, 75 MHz): 37.0, 53.3, 71.8, 72.9, 73.3, 80.0, 117.5, 117.8, 125.1, 128.1, 129.8, 130.0, 130.1, 130.2, 137.3, 137.4, 166.4, 171.8. m/z 391 (M+).

*4.4.3. 2-Ethylsulfanyl-1-(4-fluoro-phenyl)-5(SR)-styryl-4,5-dihydro-1H-imidazole-4(SR)-carboxylic acid methyl ester (**11**).* Yellow oil. Found: C, 65.48; H, 5.60, N, 7.44. $C_{21}H_{21}FN_2O_2S$ requires C, 65.60; H, 5.51; N, 7.29%. δ_H ($CDCl_3$, 300 MHz): 1.27 (t, J=7.2 Hz, 3H, CH_3), 3.15 (q, J=7.2 Hz, 2H, CH_2), 4.95 (t, J=9.0, 10.2 Hz, 1H, H^5), 5.02 (d, J=10.5 Hz, 1H, H^4), 6.07 (dd, J=9.0, 15.9 Hz, 1H, H^6), 6.47 (d, J=15.9 Hz, 1H, H^7), 6.53 (d, 2H, J=8.2 Hz, ArH), 6.87 (d, 2H, J=8.2 Hz, ArH), 7.12–7.31 (m, 5H, ArH). δ_C ($CDCl_3$, 75 MHz): 15.9, 19.7, 53.2, 71.8, 72.5, 117.8, 118.3, 125.8, 128.0, 129.9, 130.2, 130.8, 131.2, 137.6, 137.9, 166.5, 171.9. m/z 384 (M^+).

*4.4.4. 1-(4-Fluoro-phenyl)-2-methylsulfanyl-5-styryl-4,5-dihydro-1H-imidazole-4-carboxylic acid methyl ester (**12**).* Yellow oil. Found: C, 65.69; H, 5.29, N, 7.01. $C_{22}H_{22}FN_2O_2S$ requires C, 66.65; H, 5.34; N,

7.07%. δ_H ($CDCl_3$, 300 MHz): 4.04(d, J=1.4 Hz, 2H, $-CH_2-$), 3.64 (s, 3H, $-OCH_3$), 4.93 (d, J=9.0, 9.6 Hz, 1H, H^5), 5.05 (d, J=9.6 Hz, 1H, H^4), 5.17 (m, 2H, allylic $-CH_2-$), 5.7 (m, 1H, CH), 6.07 (dd, J=9.0, 15.9 Hz, 1H, H^6), 6.45 (d, J=15.9 Hz, 1H, H^7), 7.04 (d, 2H, J=8.6 Hz, ArH), 7.16–7.28 (m, 7H, H, aromatic). δ_C ($CDCl_3$, 75 MHz): 28.2, 53.3, 63.2, 67.9, 115.9, 117.5, 117.8, 125.1, 128.1, 129.8, 130.0, 130.1, 130.2, 132.7, 137.3, 137.4, 166.4, 171.8. m/z 397 (M^+).

4.5. Typical procedure for the sodium methoxide assisted intermolecular amidolysis of 3-amino-azetidin-2-one

To a solution of 3-amino-β-lactam **13** (1 mmol) in dry methanol was added a solution of sodium methoxide (0.3 mmol) in dry methanol. The reaction mixture was allowed to stir at room temperature and the progress was monitored using TLC using a mixture of (60:40) hexane/ethyl acetate. On completion, the reaction mixture was quenched with water (10 ml) and extracted with chloroform (2×50 ml). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure to yield *cis*-α-amino ester **14** as pale yellow viscous liquid.

*4.5.1. 2(SR)-Amino-5-phenyl-3(RS)-phenylamino-pent-4-enoic acid methyl ester (**14a**).* Yellow liquid. Found: C, 72.87; H, 6.92, N, 9.52. $C_{18}H_{20}N_2O_2$ requires C, 72.95; H, 6.80; N, 9.45%. Yield: 90%. δ_H ($CDCl_3$, 300 MHz): 3.68 (s, 3H, $-OCH_3$), 4.42 (dd, J=5.4, 9.0 Hz, 1H, H^2), 4.7 (d, J=5.4 Hz, 1H, H^1), 6.15 (dd, J=9.0, 15.9 Hz, 1H, H^3), 6.68 (d, J=15.9 Hz, 1H, H^4), 6.83–7.04 (m, 5H, ArH), 7.14–7.30 (m, 5H, ArH). δ_C ($CDCl_3$, 75 MHz): 50.4, 61.0, 61.8, 112.4, 116.5, 123.6, 126.2, 127.3, 127.7, 128.4, 129.5, 134.7, 143.5, 172.0. m/z 296 (M^+).

4.6. Typical procedure for the diastereoselective synthesis of imidazolidin-2-one and piperazine-5,6-dione

To a stirred solution of *cis*-α-amino ester (1 mmol) in a dry chloroform was added phenyl chloroformate/ethyloxalyl chloride (1 mmol) at 0 °C and the solution was allowed to stir for 2 h. The progress of reaction was monitored by using TLC and on completion, the reaction mixture was treated with a saturated solution of sodium bicarbonate and extracted with chloroform (2×50 ml). The combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to yield *cis*-2-phenoxy carbonyl amino-5-phenyl-3-arylamino-pent-4-enoic acid methyl esters **15**/*cis*-2-(ethoxy oxalyl amino)-5-phenyl-3-arylamino-pent-4-enoic acid methyl esters **17**. Compound **15**/**17** was then refluxed in toluene in the presence of *p*-toluene sulfonic acid for 12 h. On completion, as evidenced by TLC, the reaction mixture was concentrated under reduced pressure and purified via column chromatography using a mixture of ethyl acetate/hexane (60:40) to yield the corresponding imidazolidin-2-one **16**/piperazine-5,6-dione **18**, respectively.

*4.6.1. 2(SR)-Phenoxycarbonylamino-5-phenyl-3(RS)-phenylamino-pent-4-enoic acid methyl ester (**15a**).* Yellow Liquid. Found: C, 72.03; H, 5.93; N, 6.60. $C_{25}H_{24}N_2O_4$ requires C, 72.10; H, 5.81; N, 6.73%. Yield: 82%. δ_H ($CDCl_3$, 300 MHz): 3.68 (s, 3H, $-OCH_3$), 4.68 (dd, J=4.8, 6.0 Hz, H^2), 4.96 (dd, J=4.8, 7.2 Hz, H^1), 6.02 (dd, J=6.0, 15.9 Hz, H^3), 6.69 (d, J=15.9 Hz, H^4), 6.83–7.04 (m, 5H, ArH), 7.14–7.28 (m, 10H, ArH), 7.87 (d, J=7.2 Hz, NH, exchangeable with D_2O). δ_C ($CDCl_3$, 75 MHz): 54.5, 57.9, 69.0, 112.5, 116.9, 123.3, 124.0, 125.7, 126.2, 127.1, 127.3, 128.5, 129.7, 130.0, 131.4, 133.3, 135.7, 160.1, 170.7. m/z 416 (M^+).

*4.6.2. 2(SR)-(Ethoxyoxalyl amino)-5-phenyl-3(RS)-phenylamino-pent-4-enoic acid methyl ester (**17a**).* Yellow Liquid. Found: C, 69.56; H, 6.24, N, 7.39. $C_{22}H_{24}N_2O_4$ requires C, 69.46; H, 6.36; N, 7.36%. Yield: 85%. δ_H ($CDCl_3$, 300 MHz): 1.32 (t, J=7.2 Hz, 3H, CH_3), 3.68 (s, 3H, $-OCH_3$), 4.31 (q, J=7.2 Hz, 2H, CH_2), 4.66 (dd, J=4.8, 6.0 Hz, H^2), 4.93 (dd, J=4.8, 7.2 Hz, H^1), 6.06 (dd, J=6.0, 15.9 Hz, H^3), 6.62 (d, J=15.9 Hz, H^4), 7.14–7.40 (m, 10H, ArH), 7.82 (d, J=7.2 Hz, NH, exchangeable with D_2O). δ_C ($CDCl_3$, 75 MHz): 12.7, 19.7, 56.5, 58.5, 69.2, 112.3, 116.9, 123.3, 126.2, 127.4, 127.7, 128.4, 129.3, 130.1, 133.0, 160.2, 160.3, 183.4. m/z 380 (M^+).

*4.6.3. 2-Oxo-1-phenyl-5(SR)-styryl-imidazolidin-4(RS)-carboxylic acid methyl ester (**16a**).* White solid. Found: C, 70.66; H, 5.71, N, 8.75. $C_{19}H_{18}N_2O_3$ requires C, 70.79; H, 5.63; N, 8.69%. Mp 221–222 °C. Yield: 68%. δ_H ($CDCl_3$, 300 MHz): 3.68 (s, 3H, $-OCH_3$), 4.95 (dd, J=5.4, 6.2 Hz, 1H, H^3), 5.38 (dd, J=5.5, 9.0 Hz, 1H, H^4), 5.42 (d, J=8.94 Hz, 1H, NH, exchangeable with D_2O), 6.10 (dd, J=6.1, 16.04 Hz, 1H, H^2), 6.72 (d, J=16.04 Hz, 1H, H^1), 7.00–7.24 (m, 6H, ArH), 7.30–7.65 (m, 4H, ArH). δ_C ($CDCl_3$, 75 MHz): 52.6, 59.8, 60.4, 117.9, 122.1, 126.6, 128.5, 128.7, 129.4, 134.2, 134.5, 135.7, 138.2, 156.7, 163.2. ν_{max} (KBr)/cm^{-1} 1759, 1697. m/z 322 (M^+).

*4.6.4. 1-(4-Nitro-phenyl)-2-oxo-5(SR)-styryl-imidazolidin-4(RS)-carboxylic acid methyl ester (**16b**).* White solid. Found: C, 62.02; H, 4.73, N, 11.49. $C_{19}H_{17}N_3O_5$ requires C, 62.12; H, 4.66; N, 11.44%. Mp 225–227 °C. Yield: 69%. δ_H ($CDCl_3$, 300 MHz): 2.34 (s, 3H, $-CH_3$), 3.69 (s, 3H, $-OCH_3$), 4.95 (dd, J=5.4, 6.3 Hz, 1H, H^3), 5.32 (dd, J=5.2, 9.0 Hz, 1H, H^4), 5.41 (d, J=8.90 Hz, 1H, NH, exchangeable with D_2O), 6.17 (dd, J=6.4, 16.04 Hz, 1H, H^2), 6.75 (d, J=16.08 Hz, 1H, H^1), 7.14–7.30 (m, 5H, ArH), 7.90 (d, J=8.2 Hz, 2H, ArH), 8.17 (d, J=8.2 Hz, 2H, ArH). δ_C ($CDCl_3$, 75 MHz): 52.9, 59.9, 60.7, 117.5, 122.4, 126.5, 128.6, 128.8, 129.5, 134.1, 134.7, 135.4, 144.3, 156.1, 163.2. ν_{max} (KBr)/cm^{-1} 1759, 1697 m/z 367 (M^+).

*4.6.5. 1-(4-Fluoro-phenyl)-2-oxo-5(SR)-styryl-imidazolidin-4(RS)-carboxylic acid methyl ester (**16c**).* White solid. Found: C, 67.10; H, 5.07, N, 8.11. $C_{19}H_{17}FN_2O_3$ requires: C, 67.05; H, 5.03; N, 8.23%. Mp 215–216 °C. Yield: 68%. δ_H ($CDCl_3$, 300 MHz): 3.67 (s, 3H, $-OCH_3$), 4.96 (dd, J=5.4, 6.1 Hz, 1H, H^3), 5.35 (dd, J=5.4, 9.0 Hz, 1H, H^4), 5.40 (d, J=9.0 Hz, 1H, NH, exchangeable with D_2O), 6.14 (dd, J=6.2, 16.08 Hz, 1H, H^2), 6.72 (d, J=16.04 Hz, 1H, H^1), 6.95–7.30 (m, 7H, aromatic), 7.62 (d, J=8.2 Hz, 2H, ArH). δ_C ($CDCl_3$, 75 MHz): 52.9, 60.1, 60.8, 117.4, 122.0, 126.7, 128.6, 128.9, 129.7, 134.3, 134.9, 135.2, 147.7, 156.4, 163.5. ν_{max} (KBr)/cm^{-1} 1759, 1697. m/z 340 (M^+).

*4.6.6. 1-(4-Chloro-phenyl)-2-oxo-5(SR)-styryl-imidazolidin-4(RS)-carboxylic acid methyl ester (**16d**).* White solid. Found: C, 63.82; H, 4.78, N, 7.90. $C_{19}H_{17}ClN_2O_3$ requires C, 63.96; H, 4.80; N, 7.85%. Mp 224–225 °C. Yield: 72%. δ_H ($CDCl_3$, 300 MHz): 3.69 (s, 3H, $-OCH_3$), 4.97 (dd, J=5.1, 6.3 Hz, 1H, H^3), 5.38 (dd, J=5.3, 9.0 Hz, 1H, H^4), 5.42 (d, J=8.96 Hz, 1H, NH, exchangeable with D_2O), 6.12 (dd, J=6.3, 16.04 Hz, 1H, H^2), 6.71 (d, J=16.04 Hz, 1H, H^1), 7.14–7.30 (m, 7H, ArH), 7.58 (d, J=8.2 Hz, 2H, ArH). δ_C ($CDCl_3$, 75 MHz): 52.5, 60.3, 60.5, 117.5, 122.5, 126.4, 128.0, 129.1, 129.4, 134.0, 134.6, 135.6, 136.2, 156.1, 163.5. ν_{max} (KBr)/cm^{-1} 1759, 1697. m/z 356 (M^+).

*4.6.7. 2-Oxo-5(SR)-styryl-1-p-tolyl-imidazolidin-4(RS)-carboxylic acid methyl ester (**16e**).* White solid. Found: C, 71.27; H, 6.06, N, 8.37. $C_{20}H_{20}N_2O_3$ requires C, 71.41; H, 5.99; N, 8.33%. Mp 219–220 °C. Yield: 75%. δ_H ($CDCl_3$, 300 MHz): 2.31 (s, 3H, $-CH_3$), 3.68 (s, 3H, $-OCH_3$), 4.93 (dd, J=5.4, 6.2 Hz, 1H, H^3), 5.33 (dd, J=5.4, 9.0 Hz, 1H, H^4), 5.43 (d, J=8.92 Hz, 1H, NH, exchangeable with D_2O), 6.18 (dd, J=6.2, 16.08 Hz, 1H, H^2), 6.73 (d, J=16.04 Hz, 1H, H^1), 7.11 (d, J=8.28 Hz, 2H, ArH), 7.28–7.40 (m, 7H, ArH). δ_C ($CDCl_3$, 75 MHz): 20.9, 52.7, 59.9, 60.9, 117.2, 122.3, 126.7, 128.5, 128.7, 129.6, 134.2, 134.9, 135.6, 136.1, 156.2, 163.4. ν_{max} (KBr)/cm^{-1} 1759, 1698. m/z 336 (M^+).

*4.6.8. 5,6-Dioxo-4-phenyl-3(SR)-styryl-piperazine-2(RS)-carboxylic acid methyl ester (**18a**).* White solid. Found: C, 68.66; H, 5.11, N, 7.91. $C_{20}H_{18}N_2O_4$ requires C, 68.56; H, 5.18; N, 8.00%. Mp 233–234 °C.

Yield: 68%. δ_H ($CDCl_3$, 300 MHz): 3.78 (s, 3H, $-OCH_3$), 4.30 (dd, J=2.3, 5.0 Hz, 1H, H^4), 4.92 (dd, J=2.3, 6.8 Hz, 1H, H^3), 6.34 (dd, J=6.8, 15.6 Hz, 1H, H^2), 6.52 (d, J=15.6 Hz, 1H, H^1), 7.00–7.30 (m, 8H, aromatic), 7.64 (m, 2H, ArH), 8.10 (d, J=5.0 Hz, NH, exchangeable with D_2O). δ_C ($CDCl_3$, 75 MHz): 52.7, 59.7, 60.4, 117.2, 122.5, 126.7, 128.1, 128.9, 129.2, 134.1, 134.4, 135.8, 136.2, 156.0, 163.2, 171.9 ν_{max} (KBr)/cm^{-1} 1749, 1693, 1681. m/z 350 (M^+).

*4.6.9. 4-(4-Nitro-phenyl)-5,6-dioxo-3(SR)-styryl-piperazine-2(RS)-carboxylic acid methyl ester (**18b**).* White solid. Found: C, 60.66; H, 4.20, N, 10.66. $C_{20}H_{17}N_3O_6$ requires C, 60.76; H, 4.33; N, 10.63%. Mp 238–239 °C. Yield: 66%. δ_H ($CDCl_3$, 300 MHz): 3.79 (s, 3H, $-OCH_3$), 4.32 (dd, J=2.0, 5.1 Hz, 1H, H^4), 4.93 (dd, J=2.0, 6.6 Hz, 1H, H^3), 6.35 (dd, J=6.6, 15.9 Hz, 1H, H^2), 6.50 (d, J=15.9 Hz, 1H, H^1), 7.14–7.30 (m, 5H, aromatic), 7.90 (d, J=8.2 Hz, 2H, ArH), 8.10 (d, J=5.1 Hz, NH, exchangeable with D_2O), 8.17(d, J=8.2 Hz, 2H, ArH). δ_C ($CDCl_3$, 75 MHz): 52.9, 59.8, 60.6, 117.3, 122.6, 126.8, 128.2, 128.8, 129.3, 134.0, 134.6, 135.6, 144.4, 156.1, 163.0, 171.5. ν_{max} (KBr)/cm^{-1} 1749, 1693,1681. m/z 395 (M^+).

*4.6.10. 4-(4-Fluoro-phenyl)-5,6-dioxo-3(SR)-styryl-piperazine-2(RS)-carboxylic acid methyl ester (**18c**).* White solid. Found: C, 65.13; H, 4.76, N, 7.67. $C_{20}H_{17}FN_2O_4$ requires C, 65.21; H, 4.65; N, 7.60%. Mp 234–235 °C. Yield: 67%. δ_H ($CDCl_3$, 300 MHz): 3.80 (s, 3H, $-OCH_3$), 4.33 (dd, J=2.0, 5.1 Hz, 1H, H^4), 4.91 (dd, J=2.0, 6.6 Hz, 1H, H^3), 6.34 (dd, J=6.6, 15.9 Hz, 1H, H^2), 6.51 (d, J=15.9 Hz, 1H, H^1), 6.95 (d, J=8.2 Hz, 2H aromatic), 7.14–7.30 (m, 5H, aromatic), 7.62 (d, J=8.2 Hz, 2H aromatic), 8.09 (d, J=5.1 Hz, NH, exchangeable with D_2O). δ_C ($CDCl_3$, 75 MHz): 52.7, 59.6, 60.4, 117.4, 122.6, 126.7, 128.3, 128.9, 129.3, 134.1, 134.8, 135.6, 136.0, 156.0, 163.2, 172.4. ν_{max} (KBr)/cm^{-1} 1749, 1693, 1681. m/z 368 (M^+).

*4.6.11. 4-(4-Chloro-phenyl)-5,6-dioxo-3(SR)-styryl-piperazine-2(RS)-carboxylic acid methyl ester (**18d**).* White solid. Found: C, 62.30; H, 4.57, N, 7.37. $C_{20}H_{17}ClN_2O_4$ requires C, 62.42; H, 4.45; N, 7.28%. Mp 243–244 °C. Yield: 71%. δ_H ($CDCl_3$, 300 MHz): 3.82 (s, 3H, $-OCH_3$), 4.34 (dd, J=2.2, 5.2 Hz, 1H, H^4), 4.90 (dd, J=2.2, 6.8 Hz, 1H, H^3), 6.35 (dd, J=6.8, 15.6 Hz, 1H, H^2), 6.50 (d, J=15.6 Hz, 1H, H^1), 7.14–7.30 (m, 7H, ArH), 7.58 (d, J=8.20 Hz, 2H, ArH), 8.10 (d, J=5.2 Hz, NH, exchangeable with D_2O). δ_C ($CDCl_3$, 75 MHz): 52.8, 59.7, 60.4, 117.2, 122.5, 126.7, 128.4, 128.7, 129.4, 134.1, 134.9, 135.8, 136.0, 156.1, 163.5, 172.1. ν_{max} (KBr)/cm^{-1} 1749, 1693, 1681. m/z 384 (M^+).

*4.6.12. 5,6-Dioxo-3(SR)-styryl-4-p-tolyl-piperazine-2(RS)-carboxylic acid methyl ester (**18e**).* White Solid. Found: C, 69.28; H, 5.66, N, 7.70. $C_{21}H_{20}N_2O_4$ requires C, 69.22; H, 5.53; N, 7.69%. Mp 239–240 °C. Yield: 73%. δ_H ($CDCl_3$, 300 MHz): 2.53 (s, 3H, $-CH_3$), 3.81 (s, 3H, $-OCH_3$), 4.37 (dd, J=2.1, 5.0 Hz, 1H, H^4), 4.91 (dd, J=2.1, 6.9 Hz, 1H, H^3), 6.37 (dd, J=6.9, 15.9 Hz, 1H, H^2), 6.55 (d, J=15.9 Hz, 1H, H^1), 7.12 (d, J=8.28 Hz, 2H, ArH), 7.23–7.37 (m, 7H, ArH), 8.09 (d, J=5.0 Hz, NH, exchangeable with D_2O). δ_C ($CDCl_3$, 75 MHz): 20.7, 52.5, 59.9, 60.6, 117.1, 122.3, 126.5, 128.4, 128.7, 129.6, 134.1, 134.9, 135.6, 136.0, 156.2, 163.8, 172.3. ν_{max} (KBr)/cm^{-1} 1749, 1693,1681. m/z 364 (M^+).

4.7. Typical procedure for single-pot synthesis of imidazolidin-2-one and piperazine-5,6-dione

To a stirred solution of 3-amino-β-lactam (1 mmol) in a dry chloroform was added phenyl chloroformate/ethyloxalyl chloride (1 mmol) at 0 °C and the solution was allowed to stir for 2 h. The progress of reaction was monitored by using TLC and on completion, the reaction mixture was treated with a saturated solution of sodium bicarbonate and extracted with chloroform (2×50 ml). The combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to yield (2-oxo-1-phenyl-4-styryl-azetidin-3-yl)-carbamic acid phenyl ester **19** and *N*-(2-oxo-1-aryl-4-styryl-azetidin-3-yl)-oxalamic acid ethyl ester **20**, respectively, purified via column chromatography using a mixture of (30:70) ethyl acetate/hexane mixture. To a stirred solution of **19** and **20** (1 mmol) in dry methanol was added a solution of sodium methoxide (0.3 mmol) in dry methanol. The reaction mixture was allowed to stir at room temperature and the progress was monitored using TLC. On completion, the reaction mixture was quenched with water (10 ml) and extracted with chloroform (2×50 ml). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure to yield imidazolidin-2-one **16** and piperazine-5,6-dione **18**, which were recrystallized using a mixture of (20:80) chloroform/hexane mixture.

*4.7.1. (2-Oxo-1-phenyl-4(RS)-styryl-azetidin-3(SR)-yl)-carbamic acid phenyl ester (**19a**).* Yellow liquid. Found: C, 74.87; H, 5.41, N, 7.21. $C_{24}H_{20}N_2O_3$ requires C, 74.98; H, 5.24; N, 7.29%. Yield: 86%. δ_H ($CDCl_3$, 300 MHz): 4.64 (dd, J=6.0, 4.8 Hz, H^2), 4.92 (dd, J=4.8, 7.2 Hz, H^1), 6.08 (dd, J=6.0, 15.9 Hz, H^3), 6.61 (d, J=15.9 Hz, H^4), 7.07–7.31 (m, 15H, ArH), 7.82 (d, J=7.2 Hz, NH, exchangeable with D_2O). δ_C ($CDCl_3$, 75 MHz): 57.4, 59.2, 120.3, 121.4, 123.3, 124.1, 125.5, 126.2, 127.2, 127.7, 128.4, 128.7, 128.9, 134.6, 140.8, 153.1, 157.6, 179.9. m/z 384 (M^+).

*4.7.2. N-(2-Oxo-1-phenyl-4(RS)-styryl-azetidin-3(SR)-yl)-oxalamic acid ethyl ester (**20a**).* Yellow liquid. Found: C, 69.15; H, 5.58, N, 7.56. $C_{21}H_{20}N_2O_4$ requires C, 69.22; H, 5.53; N, 7.69%. Yield: 89%. δ_H ($CDCl_3$, 300 MHz): 1.31 (t, J=7.2 Hz, 3H, CH_3), 4.30 (q, J=7.2 Hz, CH_2), 4.64 (dd, J=4.8, 6.0 Hz, H^2), 4.92 (dd, J=4.8, 7.2 Hz, H^1), 6.08 (dd, J=6.0, 15.9 Hz, H^3), 6.61 (d, J=15.9 Hz, H^4), 7.10–7.24 (m, 6H, ArH), 7.30–7.32 (m, 4H, ArH), 7.82 (d, J=7.2 Hz, NH, exchangeable with D_2O). δ_C ($CDCl_3$, 75 MHz): 12.8, 56.3, 58.5, 59.6, 120.3, 123.6, 124.2, 126.3, 127.4, 127.8, 128.5, 128.7, 134.6, 140.8, 160.2, 160.3, 170.5. m/z 364 (M^+).

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References and notes

1. (a) Kumar, V.; Mahajan, M. P. In *Pyrimidines and Imidazoles in Heterocycles in Natural Product Synthesis*; Majumdar, K. C., Chattopadhyay, S. K., Eds.; Wiley-VCH: Weinheim, 2011; Chapter 14, pp 507–533; (b) Laufer, S. A.; Zimmermann, W.; Ruff, K. J. *J. Med. Chem.* **2004**, *47*, 6311.
2. Dutta, S. *Acta Pharm.* **2010**, *60*, 229.
3. Gupta, P.; Hameed, S.; Jain, R. *Eur. J. Med. Chem.* **2004**, *39*, 805.
4. Antolini, M.; Bozzoli, A.; Ghiron, C.; Kennedy, G.; Rossi, T.; Ursini, A. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1023.
5. Ellis, G. P.; Epstein, C.; Fitzmaurice, C.; Golberg, L.; Lord, G. H. *J. Pharm. Pharmacol.* **1964**, *16*, 400.
6. Ram, V. J.; Vanden Berghe, D. A.; Vlietinck, A. *Justus Liebigs Ann. Chem.* **1987**, *9*, 797.
7. Tanaka, F.; Takeuchi, S.; Tanaka, N.; Yonehara, H.; Umezawa, H.; Sumiki, Y. *J. Antibiot.* **1961**, *14*, 161.
8. Nicolaou, K. C.; Xu, J. Y.; Kim, S.; Pfefferkorn, J.; Ohshima, T.; Vourloumis, D.; Hosokawa, S. *J. Am. Chem. Soc.* **1998**, *34*, 8661.
9. Barta, T. E.; Stealey, M. A.; Collins, P. W.; Weier, R. M. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3443.
10. Murry, J. A. *Drug Discov. Dev.* **2003**, *6*, 945.
11. De Laszlo, S. E.; Hacker, C.; Li, B.; Kim, D.; MacCoss, M.; Mantlo, N.; Pivnichny, J. V.; Colwell, L.; Koch, G. E.; Cascieri, M. A.; Hagmann, W. K. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 641.
12. Eyers, P. A.; Craxton, M.; Morrice, N.; Cohen, P.; Goedert, M. *Chem. Biol.* **1998**, *5*, 321.
13. Newman, M. J.; Rodarte, J. C.; Benbatoul, K. D.; Romano, S. J.; Zhang, C.; Krane, S.; Moran, E. J.; Uyeda, R. T.; Dixon, R.; Guns, E. S.; Mayer, L. D. *Cancer Res.* **2000**, *60*, 2964.
14. (a) Fang, Z.; Wang, S.; Zhao, L.; Xu, Z.; Ren, J.; Wang, X. *Mater. Lett.* **2007**, *61*, 4803; (b) Ge, Z.; Hayakawa, T.; Ando, S.; Ueda, M.; Akiike, T.; Miyamoto, H. *Chem. Mater.* **2008**, *20*, 2532; (c) Lai, M. Y.; Chen, C. H.; Huang, W. S.; Lin, J. T.; Ke, T. H.; Chen, L. Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 581; (d) Fang, Z.; Wang, S.;

Zhao, L.; Xu, Z.; Ren, J.; Wang, X. *Mater. Chem. Phys.* **2008**, *107*, 305; (e) Chen, C. H.; Huang, W. S.; Lai, M. Y.; Tsao, W. C.; Lin, J. T.; Wu, Y. H. *Adv. Funct. Mater.* **2009**, *19*, 2661.
15. (a) Shin, R. Y. C.; Kietzke, T.; Sudhakar, S.; Dodabalapur, A.; Chen, Z. K.; Sellinger, A. *Chem. Mater.* **2007**, *19*, 1892; (b) Tsai, M. S.; Hsu, Y. C.; Lin, J. T.; Chen, H. C.; Hsu, C. P. *J. Phys. Chem. C* **2007**, *111*, 18785; (c) Chang, Y. T.; Hsu, S. L.; Chen, G. Y.; Su, M. H.; Singh, T. A.; Diau, E. W. G. *Adv. Funct. Mater.* **2008**, *18*, 2356; (d) Chang, Y. T.; Hsu, S. L.; Su, M. H.; Wei, K. H. *Adv. Funct. Mater.* **2009**, *21*, 2093; (e) Velusamy, M.; Hsu, C. Y.; Lin, J. T.; Chang, C. W.; Hsu, C. P. *Chem. Asian J.* **2010**, *5*, 87.
16. (a) Dupont, J.; DeSouza, R. F.; Suarez, P. A. Z. *Chem. Rev.* **2002**, *102*, 3667; (b) Nara, S. J.; Naik, P. U.; Harjani, J. R.; Salunkhe, M. M. *Indian J. Chem.* **2001**, *45B*, 2257; (c) Chowdhury, S.; Mohan, R. S.; Scott, J. L. *Tetrahedron* **2007**, *63*, 2363.
17. (a) Bourissou, D.; Guerret, O.; Gabbai, F. P.; Bertrand, G. *Chem. Rev.* **2000**, *100*, 39; (b) Arnold, P. L.; Liddle, S. T. *Chem. Commun.* **2006**, 3959; (c) Kuhl, O. *Chem. Soc. Rev.* **2007**, *36*, 592.
18. (a) Spaltenstein, A.; Almond, M. R.; Bock, W. J.; Cleary, D. G.; Furfine, E. S.; Hazen, R. J.; Kazmierski, W. M.; Salituro, F. G.; Tung, R. D.; Wright, L. L. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1159; (b) Kazmierski, W. M.; Furfine, E.; Gray-Nunez, Y.; Spaltenstein, A.; Wright, L. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5685.
19. Heidempergher, F.; Pillan, A.; Pinciroli, V.; Vaghi, F.; Arrigoni, C.; Bolis, G.; Caccia, C.; Dho, L.; McArthur, R.; Varasi, M. *J. Med. Chem.* **1997**, *40*, 3369.
20. (a) Shue, H.-J.; Chen, X.; Shih, N.-Y.; Blythin, D. J.; Paliwal, S.; Lin, L.; Gu, D.; Schwerdt, J. H.; Shah, S.; Reichard, G. A.; Piwinski, J. J.; Duffy, R. A.; Lachowicz, J. E.; Coffin, V. L.; Liu, F.; Nomeir, A. A.; Morgan, C. A.; Varty, G. B. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3896; (b) Shue, H.-J.; Chen, X.; Schwerdt, J. H.; Paliwal, S.; Blythin, D. J.; Lin, L.; Gu, D.; Wang, C.; Reichard, G. A.; Wang, H.; Piwinski, J. J.; Duffy, R. A.; Lachowicz, J. E.; Coffin, V. L.; Nomeir, A. A.; Morgan, C. A.; Varty, G. B.; Shih, N. Y. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1065.
21. Byrtus, H.; Obniska, J.; Czopek, A.; Kaminski, K.; Pawlowski, M. *Bioorg. Med. Chem.* **2011**, *20*, 6149.
22. Wang, D.; Zhang, B.; He, C.; Wu, P.; Duan, C. *Chem. Commun.* **2010**, 4728.
23. Chai, C. L. L.; Hockless, D. C. R.; Weerasauria, K. D. V. *Polyhedron* **1997**, *16*, 1577.
24. Li, B.; Xiang, D.; Hsu, C. T.; Liu, Z. L.; Wu, C.; Yang, H. Z. *Molecules* **2005**, *10*, 1119.
25. (a) Balalaie, S.; Arabanian, A. *Green Chem.* **2002**, *2*, 274; (b) Heravi, M. M.; Derikvand, F.; Bamoharram, F. F. *J. Mol. Catal., A: Chem.* **2007**, *263*, 112; (c) Sadeghi, B.; Mirjalili, B. B. F.; Hashemi, M. M. *Tetrahedron Lett.* **2008**, *49*, 2575; (d) Karimi, A. R.; Alimohammadi, Z.; Azizian, J.; Mohammadi, A. A.; Mohammadizadeh, M. R. *Catal. Commun.* **2006**, *7*, 728; (e) Kantevari, S.; Vuppalapati, S. V. N.; Biradar, D. O.; Nagarapu, L. *J. Mol. Catal., A: Chem.* **2007**, *266*, 109; (f) Siddiqui, S. A.; Narkhede, U. C.; Palimkar, S. S.; Daniel, T.; Lahoti, R. J.; Srinivasan, K. V. *Tetrahedron* **2005**, *61*, 3539.
26. (a) Consonni, R.; Croce, P. D.; Ferraccioli, R.; Rosa, C. L. *J. Chem. Res., Synop.* **1991**, 188; (b) Lantos, I.; Zhang, W. Y.; Shui, X.; Eggleston, D. S. *J. Org. Chem.* **1993**, *58*, 7092; (c) Balalaie, S.; Hashemi, M. M.; Akhbari, M. *Tetrahedron Lett.* **2003**, *44*, 1709; (d) Sharma, G. V. M.; Jyothi, Y.; Sree Lakshmi, P. *Synth. Commun.* **2006**, *36*, 2991.
27. Overman, L. E.; Remarchuk, T. P. *J. Am. Chem. Soc.* **2002**, *124*, 12.
28. (a) Muniz, K.; Hovelmann, C. H.; Streuff, J. *J. Am. Chem. Soc.* **2008**, *130*, 763; (b) Du, H.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* **2007**, *129*, 11688; (c) Bar, G. L. J.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *J. Am. Chem. Soc.* **2005**, *127*, 7308.
29. Danishefsky, S.; Taniyama, E.; Webb, R. R., II. *Tetrahedron Lett.* **1983**, *24*, 11.
30. (a) Doyle, M. P.; Khou, Q. L.; Raab, C. E.; Roos, G. H. P.; Simonsen, S. H.; Lynch, V. *Inorg. Chem.* **1996**, *35*, 6064; (b) Doyle, M. P.; Colyer, J. T. *Tetrahedron: Asymmetry* **2003**, *14*, 3601; (c) Doyle, M. P.; Morgan, J. P.; Fettinger, J. C.; Zavalij, P. Y.; Colyer, J. T.; Timmons, D. J.; Carducci, M. D. *J. Org. Chem.* **2005**, *70*, 5291.
31. (a) Singh, P.; Sachdeva, S.; Raj, R.; Kumar, V.; Mahajan, M. P.; Nasser, S.; Vivas, L.; Gut, J.; Rosenthal, P. J.; Feng, T. S.; Chibale, K. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 4561; (b) Singh, P.; Kaur, S.; Kumar, V.; Bedi, P. M. S.; Mahajan, M. P.; Sehar, I.; Pal, H. C.; Saxena, A. K. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 3017; (c) Singh, P.; Raj, R.; Kumar, V.; Mahajan, M. P.; Bedi, P. M. S.; Kaur, T.; Saxena, A. K. *Eur. J. Med. Chem.* **2012**, *47*, 594; (d) Singh, P.; Singh, P.; Kumar, M.; Gut, J.; Rosenthal, P. J.; Kumar, K.; Kumar, V.; Mahajan, M. P.; Bisetty, K. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 57; (e) Anand, A.; Singh, P.; Mehra, V.; Amandeep; Kumar, V.; Mahajan, M. P. *Tetrahedron Lett.* **2012**, 2417; (f) Kumar, K.; Singh, P.; Kremer, L.; Guérardel, Y.; Biot, C.; Kumar, V. *Dalton Trans.* **2012**, *41*, 5778.
32. (a) Anand, A.; Bhargava, G.; Kumar, V.; Mahajan, M. P. *Tetrahedron Lett.* **2010**, *51*, 2312; (b) Singh, P.; Bhargava, G.; Kumar, V.; Mahajan, M. P. *Tetrahedron Lett.* **2010**, *51*, 4272; (c) Raj, R.; Mehra, V.; Singh, P.; Kumar, V.; Bhargava, G.; Mahajan, M. P.; Handa, S.; Slaughter, L. M. *Eur. J. Org. Chem.* **2011**, *14*, 2697; (d) Singh, P.; Mehra, V.; Anand, A.; Kumar, V.; Mahajan, M. P. *Tetrahedron Lett.* **2011**, *52*, 5060.
33. Lin, W.; Zhang, X.; He, Z.; Jin, Y.; Gong, L.; Mi, A. *Synth. Commun.* **2002**, *32*, 3279.