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Practical synthesis of 3-bromo-5,6-dihydropyridin-2-ones via β,γ-unsaturated α-bromo-ketene/imine cycloaddition☆,☆☆

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Abstract—An approach to 3-bromo-4-alkyl-6-aryl-5,6-dihydropyridin-2-ones and 3-bromo-5-ethyl-6-aryl-5,6-dihydropyridin-2-ones starting from β,γ-unsaturated α-bromoketenes and imines is reported. The presence of a bromine atom on the double bond allows performing aziridination or bromine displacement with an amine. The reaction gave fused bicyclic *N*-allyl-aziridines or 3-amino-substituted 5,6-dihydropyridin-2-ones, depending on the substituents on the six-membered ring.

1. Introduction

Nitrogen-containing heterocyclic compounds are important constituents of biologically active natural products[1] and have attracted considerable attention due to their applications in many fields such as pharmaceuticals and synthetic organic chemistry.[2] In particular, several representative pyridin-2-ones possess significant biological activity as antibacterial, antifungal or free radical scavengers,[3] and may be considered starting materials for the synthesis of more complex molecules.[4] Recently, properly substituted examples of 5,6-dihydropyridin-2-ones have been regarded to be useful intermediates for the preparation of spatially defined scaffolds, constrained counterparts of natural amino acids.[5]

Recently, we have been interested in the synthesis of mimetics of the RGD tripeptide, that is the signaling motif in a variety of extracellular matrix proteins involved in the integrin adhesion mechanism.[6] In this paper we report on the synthesis of a new class of 5,6-dihydropyridin-2-ones, aiming to introduce them as non-peptidic scaffolds in mimetics of the RGD β-turn topology. Numerous methods for the preparation of substituted 5,6-dihydropyridin-2-ones starting from acyclic materials have been reported in the literature but they usually require forcing conditions and are non-general.[7]

Ketenes have long been used in the synthesis of various heterocyclic compounds.[8] In the course of our investigation on the chemistry of unsaturated bromo-ketenes,[9] we have developed a good approach to the synthesis of 3-bromo-4-alkyl-5,6-dihydropyridin-2-ones and 3-bromo-5-ethyl-5,6-dihydropyridin-2-ones.

β,γ-Unsaturated α-bromoketenes were prepared starting from the corresponding acyl halides and triethylamine, and their reactivity in the ketene-imine cycloaddition was examined.

2. Results and discussion

2.1. Synthesis of 3-bromo-5,6-dihydropyridin-2-ones

It is known that when an acyl halide is treated with a base, the corresponding ketene is generated. The labile ketene readily reacts with the Schiff base **2** to give a six membered heterocyclic compound. Starting from both 2-bromo-3-methyl-2-butenoyl chloride **1a** and 2-bromo-3-methyl-2-hexenoyl chloride **1b**, deprotonation occurs on the methyl group, to exclusively give the dehydropyridin-2-one **3** in high yield (Scheme 1).

The amounts of Schiff base and TEA and the effect of the temperature were investigated using the reaction of **1a** and **2a**, and selected results are reported in Table 1.

The reaction of **1a** with 2 equiv. of the imine **2a**, carried out at −78 °C in CH_2Cl_2 in the presence of $AlMe_2Cl$, afforded **3a** in 54% yield after silica gel chromatography, and the remaining product was the corresponding benzylamide

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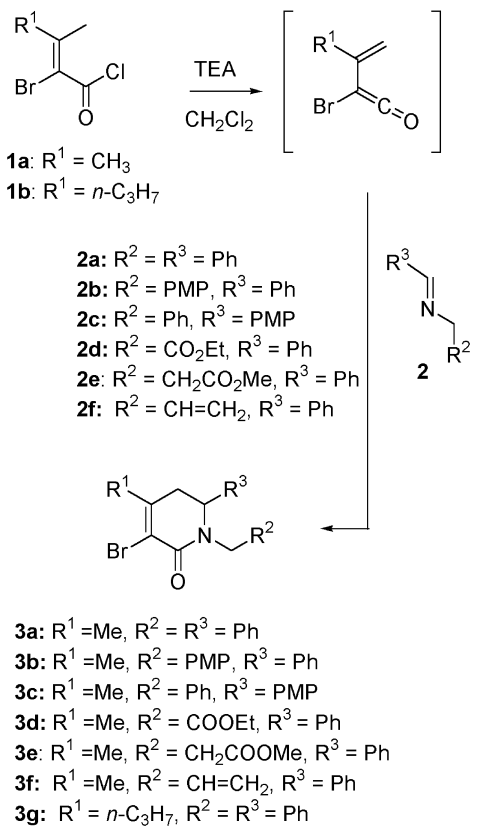


Scheme 1. Formation of β,γ-unsaturated ketenes and reaction with imines **2**.

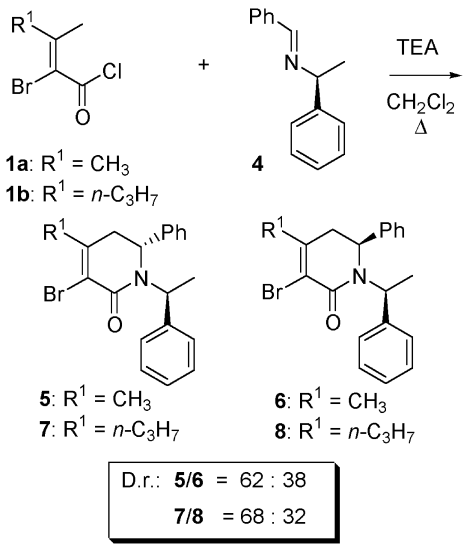
Table 1. Formation of 3-bromo-4-alkyl-5,6-dihydropyridin-2-one **3** via ketene–imine cyclization

Entry[a]	**1** (1 equiv.)	**2** (equiv.)	TEA (equiv.)	*T* (°C)	**3**	Yield (%)[b]
1[c]	**1a**	**2a** (2)	1	−78 to rt	**3a**	54
2	**1a**	**2a** (1)	1	−50 to rt	**3a**	65
3	**1a**	**2a** (1)	2	40	**3a**	92
4	**1a**	**2b** (1)	2	40	**3b**	92
5	**1a**	**2c** (1)	2	40	**3c**	94
6	**1a**	**2d** (1)	2	40	**3d**	34
7	**1a**	**2e** (1)	2	40	**3e**	64
8	**1a**	**2f** (1)	2	40	**3f**	96
9	**1b**	**2a** (1)	2	40	**3g**	94

[a] Reactions were performed in CH_2Cl_2.
[b] Yields correspond to the compounds purified by flash chromatography on silica gel.
[c] Reaction carried out under aluminum-catalyzed conditions.

(entry 1). At −50 °C, in the absence of the Lewis acid, with 1 equiv. of **2a**, dihydropyridinone **3a** was isolated in 65% yield (entry 2). Much better results were obtained when **1a** and **2a** were refluxed in CH_2Cl_2 in the presence of 2 equiv. of TEA (entry 3, 92% yield). These conditions were applied to the reaction of **1a** with imines **2b**-**f**. Excellent results were obtained in both cases, and **3b** and **3c** were obtained in respective yields of 92 and 94% (entries 4 and 5). A lower yield was observed for **3d**, which was obtained from the cyclization of **1a** with the glycine derivative **2d** (entry 6). This result was ascribed to a high degree of autocondensation of the reactive imine. On the other hand, the cycloaddition of **1a** and β-alanine derivative **2e**, gave **3e** in 64% yield (entry 7). When the reaction was performed with the allylamino derivative **2f**, the corresponding dihydropyridinone **3f** was obtained in 96% yield (entry 8). Finally, when acyl chloride **1b** was reacted with **2a** at reflux, **3g** was obtained in 94% yield (entry 9). All of the reactions were monitored by TLC and stopped after disappearance of the imine.

Good yields and moderate diastereoselectivity were observed in the reactions of **1a** and **1b** with the chiral Schiff base **4**, derived by the condensation of benzaldehyde with (*S*)-phenylethylamine, in refluxing CH_2Cl_2. Starting from **1a**, the bromo-dihydropyridin-2-ones **5** and **6** were obtained in a yield of 98% and 62/38 d.r. (Scheme 2).



Scheme 2. Cycloaddition reaction between **1a**-**b** and chiral imine 4″.

Under the same conditions, **1b** gave **7** and **8** in 55% yield and 68/32 d.r. The diastereomeric mixtures of **5/6** and **7/8** were easily separated by flash chromatography and pyridinones were fully characterized by NMR spectroscopy. The isomer **7** was crystallized from ethanol/water. The (6*R*) absolute configuration of the newlycreated stereogenic center in **7** was established by X-ray diffraction,[10] and, according to this result, the (6*S*) configuration to **8** could be assigned (Fig. 1).

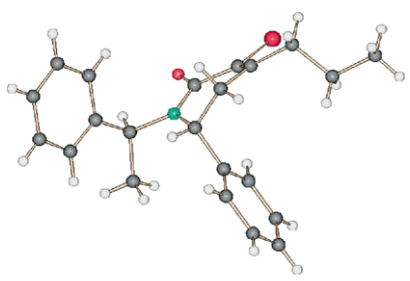


Figure 1. X-ray structure of **7**.

The structure reported in Figure 1, displays **7** in a boat conformation, and the hydrogen of the (*S*)-phenylethylamine group is preferentially in a synperiplanar relationship with the carbonyl of the cycle.

Comparison of the ^{1}H NMR chemical shifts for the pairs of compounds **5/7** and **6/8** revealed a complete regularity and allowed us to confidently attribute the (6*R*) configuration to **5** and the (6*S*) configuration to **6** (Table 2).

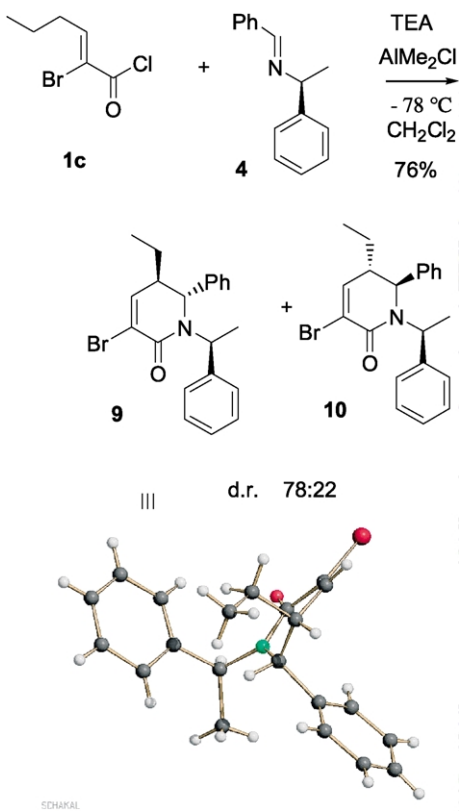
Table 2. ^{1}H NMR data for compounds **5**-**8**

	$\delta^{a}CH_3^{*}$ (ppm)	$\delta^{a}H^{*}$ (ppm)	δH_6 (ppm)	δH_5 (ppm)	$\delta H_{5'}$ (ppm)	J_{5-6} (Hz)	$J_{5'-6}$ (Hz)
5	1.23	6.19	4.39	2.27	2.83	1.2	7.0
6	1.65	5.77	4.57	2.37	3.07	1.5	7.2
7	1.25	6.21	4.42	2.30	2.75	1.8	6.6
8	1.67	5.80	4.60	2.41	3.00	1.5	6.9

[a] Chemical shifts corresponding to (*S*)-phenylethylamino group.

Finally we investigated the behavior of 2-bromo-3-unbranched hexenoyl acyl chloride **1c** in the ketene–imine cyclization with **4**. While the reaction was tested under different conditions, changing the solvent and the temperature, the six-membered heterocyclic compounds **9** and **10** were obtained in 76% total yield and 78:22 d.r. only when the reaction was performed in the presence of one equivalent of $AlMe_2Cl$ at −78 °C and 2 equiv. of **4**.

The two diastereoisomers were easily separated by flash chromatography on silica gel and characterized by ^{1}H NMR analysis, which suggested a 5,6-*trans* relationship for both of them ($J_{5,6}$<0.8 Hz). The major isomer **9** was crystallized from ethanol and its (1′*S*,5*R*,6*R*) absolute configuration was ascertained by X-ray analysis. (Scheme 3).

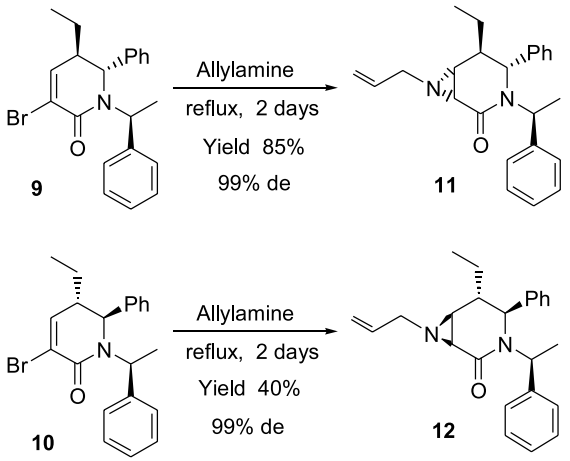


Scheme 3. Synthesis of 5,6-dihydropyridin-2-ones **9** and **10** and X-ray-determined structure of **9**.

2.2. Reactivity of 3-bromo-4-alkyl-5,6-dihydropyridin-2-ones and 3-bromo-5-alkyl-5,6-dihydropyridin-2-ones with allylamine

The presence of the bromine atom on the double bond in the pyridinones makes possible aziridination via the well-known Gabriel–Cromwell reaction.[11] Aziridines have recently received great attention, since they can be considered strained unusual amino acids and they are also useful precursors for the synthesis of various poly-functionalized compounds, such as oxazolines, oxazolidinones, hydroxy amino acids, amino alcohols, etc.[12]

Therefore, we investigated the reactivity of 3-bromo-5,6-dihydropyridin-2-ones in the presence of allylamine. The reaction, carried out on several substrates by refluxing the heterocycle in neat allylamine for 48 h, gave different results depending on the substituents on the six-membered ring. Under these conditions, 3-bromo-5-ethyl-5,6-dihydropyridin-2-ones **9** and **10** gave the corresponding fused bicyclic *N*-allyl-aziridines **11** and **12** in good yield and complete diastereoselectivity (Scheme 4).



Scheme 4. Synthesis of aziridines **11** and **12** via a Gabriel–Cromwell-like reaction.

The assignment of the stereochemistry of the newly created stereocenters in **11** was made by analysis of the coupling constant J_{4-5} and by means of NOESY-1D[13] experiments. The comparison of the vicinal coupling constant (J_{4-5}=1.5 Hz) with literature values[14] referring to similar aziridines, accounted for an anti relationship between the ethyl substituent on C5 and the aziridine ring. Irradiation of the proton at C4 and of the proton at C6 resulted in the enhancement of intensities of the ethyl chain methylene protons, suggesting that they are *cis* to each other. The preferred conformation of (3*R*,4*R*,5*R*,6*R*)-**11**, calculated by means of molecular mechanics energy minimizations of a set of 10^3 geometries generated by Monte Carlo procedure,[15] was in complete agreement with the NOESY-1D signals observed upon irradiation of H_4 and H_5 (Fig. 2). The same considerations allowed to attribute the (3*S*,4*S*,5*S*,6*S*) stereochemistry to **12**.

When the reaction with allylamine was performed on 4-methyl-substituted derivatives, 3-allylamino-4-methyl-5,6-dihydropyridin-2-ones were obtained instead of the

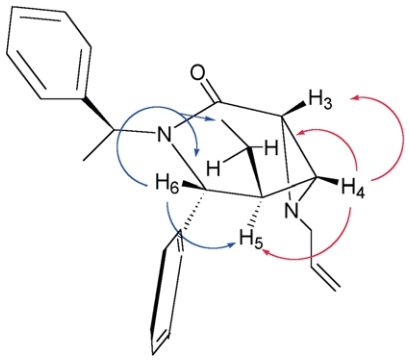
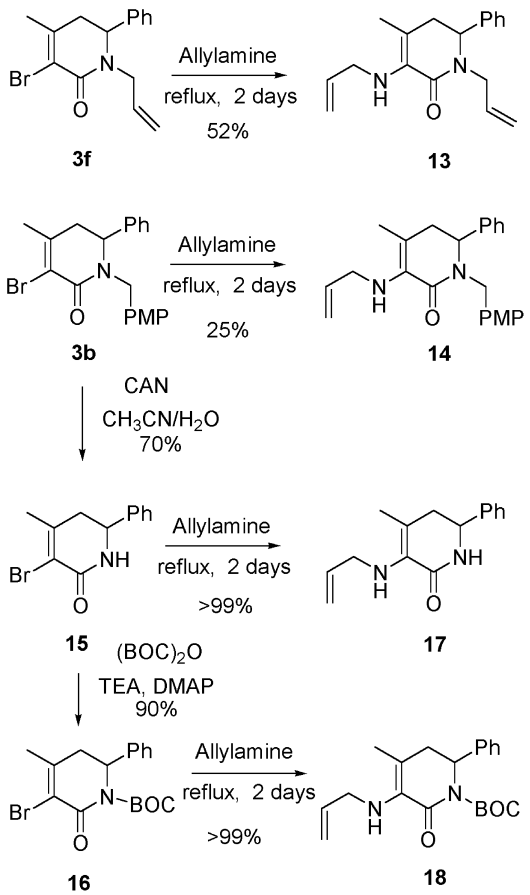


Figure 2. Preferred conformation and NOESY-1D enhancements of **11**.

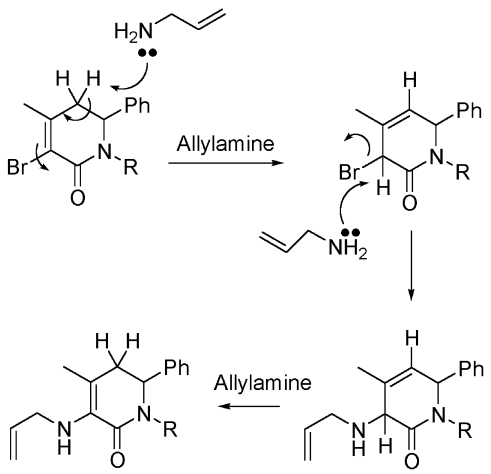
corresponding aziridines. The reaction with **3f** and **3b** gave derivatives **13** and **14** in respective yields of 52 and 25% (Scheme 5).

Finally, deprotection of compound **3b** allowed us to synthesize the dihydropyridin-2-one **15** via cleavage of the *N*-(*p*-methoxybenzyl) group with cerium ammonium nitrate.[16] The reaction carried out in CH_3CN/H_2O at room temperature gave **15** in 70% yield. Upon treatment with TEA, DMAP and di-*tert*-butyldicarbonate in dry THF, **15** was transformed into the corresponding *N*-*tert*-butyloxycarbonyl derivative **16** in 90% yield. The reaction of both **15** and **16** with neat allylamine gave the 3-allylamino-substituted six-membered rings **17** and **18** in quantitative yield (Scheme 5).



Scheme 5. Reactions of allylamine with 3-bromo-4-alkyl-dihydropyridin-2-ones.

The complete chemoselectivity of the reaction between compounds **3b**, **3f**, **15** and **16** and allylamine, can be attributed to the steric hinderance at C_3. In accordance with the nucleophilic substitution of alkyl bromo-2(1*H*)-pyridones and bromo-uracils,[17] a reasonable mechanism could be suggested for the substitution of the vinyl bromide (Scheme 6). The allylamine, acting as a base, promoted the deconjugation of the double bond, so making possible the substitution of the bromine by allylamine itself. Finally the more stable double bond in α,β position was restored.



Scheme 6. Suggested mechanism for the substitution of vinyl bromide by allylamine.

3. Conclusion

A new method for the synthesis of 3-bromo-4-alkyl-5,6-dihydropyridin-2-ones and 3-bromo-5-ethyl-5,6-dihydropyridin-2-ones starting from 3-methyl-β,γ-unsaturated α-bromoketenes and imines has been developed. This one-pot ketene formation/cycloaddition was tested on 2-bromo-3-methyl-2-butenoyl chloride 1a and 2-bromo-3-methyl-2-hexenoyl chloride **1b** in the presence of several different imines. With both substrates, six-membered rings were obtained in good yield. The same reaction gave excellent results even with chiral imines and the ketene derived from 2-bromo-unbranched hexenoyl acyl chloride **1c**. Moreover, the presence of the bromine atom on the double bond makes possible the substitution by allylamine, leading to the formation of aziridines or 3-allylamino derivatives. The reaction gave different results depending on the substituents on the six-membered ring. This class of six membered polyfunctionalized heterocycles could be exploited in the preparation of non-peptidic scaffolds mimicking the β-turn RGD topology.

4. Experimental

4.1. General methods

Unless stated otherwise, solvents and chemicals were obtained from commercial sources and used without further purification. Flash chromatography was performed on silica gel (230–400 mesh). NMR Spectra were recorded with 200, 300, 400 or 600 MHz spectrometers. Chemical shifts were reported as δ values (ppm) relative to the solvent peak of

$CDCl_3$ set at δ=7.27 (^{1}H NMR) or δ=77.0 (^{13}C NMR). Infrared spectra were recorded with an FT-IR spectrometer. Melting points are uncorrected. MS analysis were performed on a liquid chromatograph coupled with an electrospray ionization-mass spectrometer (LC-ESI-MS), using H_2O/CH_3CN as solvent at 25 °C (positive scan 100–500 *m/z*, fragmentor 70 V). Imines **2a-f** and **4** were prepared following a known procedure and characterized by comparison with literature data.[18]

4.2. General procedure for the preparation α-bromo-α,β-unsaturated chlorides 1a-c from α,β-unsaturated acids

To a stirred solution of α,β-unsaturated acid (10 mmol) in CH_2Cl_2 (10 mL), bromine (11 mmol, 0.56 mL) was added dropwise at 0 °C. The mixture was stirred overnight and then washed with a saturated solution of $Na_2S_2O_3$ to remove unreacted bromine. The organic layer was dried over Na_2SO_4 and solvent removed under reduced pressure to give the dibromo acid as a white powder. The product was dissolved in THF (10 mL) then piperidine (40 mmol, 3.9 mL) was added in one portion at 0 °C. The solution was stirred for 24 h at room temperature and then quenched with HCl 6 M (10 mL). After removing THF under reduced pressure, the acid aqueous layer was extracted twice with EtOAc (20 mL). The collected organic layers were dried over Na_2SO_4 and concentrated to give the α-bromo acid as a white powder. $SOCl_2$ (60 mmol, 4.4 mL) was then added to the neat product at 0 °C and the mixture was refluxed for two hours. The α-bromo-α,β-unsaturated chlorides **1a-c** were isolated as *E*/*Z* unseparable mixtures by distilling under reduced pressure.

4.2.1. 2-Bromo-3-methyl-but-2-enoyl chloride 1a. IR (film) ν 2950, 1805 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 2.11 (s, 3H), 2.13 (s, 3H).

4.2.2. 2-Bromo-3-methyl-hex-2-enoyl chloride 1b. IR (film) ν, 2927, 1811 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H (Major isomer) 0.99 (t, 3H, *J*=7.5 Hz), 1.50–1.60 (m, 2H), 2.08 (s, 3H), 2.40 (m, 2H). (Minor isomer) ^{1}H NMR ($CDCl_3$) δ 0.94 (t, 3H, *J*=7.2 Hz), 1.50–1.60 (m, 2H), 2.05 (s, 3H) 2.40 (m, 2H).

4.2.3. 2-Bromo-hex-2-enoyl chloride 1c. IR (film) ν 2955, 1802 cm^{-}1; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H (Major isomer)1.02 (t, 3H, *J*=7.2 Hz), 1.58–1.68 (m, 2H), 2.47 (m, 2H), 7.8 (t, 1H, *J*=6.9 Hz). (Minor isomer) ^{1}H NMR ($CDCl_3$) δ 0.95 (t, 3H, *J*=7.2 Hz), 1.48–1.57 (m, 2H), 2.40 (m, 2H), 6.68 (t, 1H, *J*=7.8 Hz).

4.3. General procedure for the preparation of 5,6-dihydro-pyridin-2-ones 3a-g and 5-8

Acyl chloride **1a-c** (1 mmol) was added to a refluxing solution of imine **2** or **4** (1 mmol, 1 equiv.) and TEA (0.278 mL, 2 mmol, 2 equiv.) in CH_2Cl_2 (5 mL). The reaction was monitored by TLC and quenched with water after disappearance of the imine reagent. The pH of the water layer was then adjusted to neutrality with 0.1 M HCl and diluted with CH_2Cl_2 (10 mL). The separated organic layer was dried over Na_2SO_4 and the solvent was evaporated under vacuum. 5,6-Dihydro-pyridin-2-one **3a-g** were purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 95/5 as eluant).

4.3.1. 1-Benzyl-3-bromo-4-methyl-6-phenyl-5,6-dihydro-pyridin-2-one 3a. Isolated as a pale yellow oil (327 mg, 92%); IR (film) ν 3029, 2930, 1651, 1608, 1453 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.95 (3H, s), 2.52 (1H, dd, *J*=2.4, 17.2 Hz), 3.03 (1H, dd, *J*=7.5, 17.2 Hz), 3.63 (1H, d, *J*=14.7 Hz), 4.56 (1H, dd, *J*=2.4, 7.5 Hz), 5.63 (1H, d, *J*=14.7 Hz), 7.15–7.18 (2H, m), 7.22–7.40 (8H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 24.7 (q), 39.5 (t), 49.5 (t), 56.6 (d), 115.7 (s), 126.4 (d), 127.6 (d), 128.1 (d), 128.2 (d), 128.7 (d), 129.0 (d), 137.5 (s), 139.6 (s), 145.2 (s), 160.7 (s); GC-MS *m/z* 357 (12), 355 (12), 278 (10), 276 (10), 253 (16), 207 (9), 185 (6), 128 (11), 91 (100). Anal. Calcd for $C_{19}H_{18}BrNO$: C, 64.06; H, 5.09; N, 3.93. Found C, 64.08; H, 5.07; N, 3.92.

4.3.2. 3-Bromo-1-(4-methoxy-benzyl)-4-methyl-6-phenyl-5,6-dihydro-pyridin-2-one 3b. Isolated as a pale yellow oil (356 mg, 92%); IR (film) ν 3031, 2932, 1653, 1593, 1460 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.90 (3H, s), 2.47 (1H, dd, *J*=2.4, 17.4 Hz), 2.96 (1H, dd, *J*=7.6, 17.4 Hz), 3.54 (1H, d, *J*=14.6 Hz), 3.77 (3H, s), 4.52 (1H, dd, *J*=2.4, 7.6 Hz), 5.49 (1H, d, *J*=14.6 Hz), 6.80–6.85 (2H, m), 7.12–7.16 (4H, m), 7.30–7.40 (3H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 24.2 (q), 39.1 (t), 48.4 (t), 55.1 (q), 56.0 (d), 113.8 (d), 115.4 (s), 126.1 (d), 127.7 (d), 128.7 (d), 129.2 (d), 129.4 (s), 139.4 (s), 144.9 (s), 158.9 (s), 160.3 (s); LC-ESI-MS rt 11.9 min, *m/z* 386–388 (M+1), 408–410 (M+Na). Anal. Calcd for $C_{20}H_{20}BrNO_2$: C, 62.19; H, 5.22; N, 3.63. Found C, 62.20; H, 5.21; N, 3.65.

4.3.3. 1-Benzyl-3-bromo-6-(4-methoxy-phenyl)-4-methyl-5,6-dihydro-pyridin-2-one 3c. Isolated as a white solid (364 mg, 94%), mp=105–107 °C; IR (nujol) ν 3031, 2928, 1653, 1611, 1449 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.96 (3H, s), 2.47 (1H, dd, *J*=2.6, 17.2 Hz), 2.98 (1H, dd, *J*=7.2, 17.2 Hz), 3.62 (1H, d, *J*=14.8 Hz), 3.82 (3H, s), 4.49 (1H, dd, *J*=2.6, 7.2 Hz), 6.58 (1H, d, *J*=14.8 Hz), 6.88 (2H, d, *J*=8.8 Hz), 7.07 (2H, d, *J*=8.8 Hz), 7.20–7.40 (5H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 24.4 (q), 39.4 (t), 49.0 (t), 55.2 (d), 55.8 (q), 114.1 (d), 115.5 (s), 127.3 (d), 128.0 (d), 128.5 (d), 131.3 (s), 137.4 (s), 145.2 (s), 159.0 (s), 160.2 (s); LC-ESI-MS rt 12.8 min, *m/z* 386–388 (M+1), 408–410 (M+Na). Anal. Calcd for $C_{20}H_{20}BrNO_2$: C, 62.19; H, 5.22; N, 3.63. Found C, 62.18; H, 5.22; N, 3.62.

4.3.4. (3-Bromo-2-oxo-6-phenyl-4-methyl-5,6-dihydro-pyridin-1-yl)-acetic acid ethyl ester 3d. Isolated as a pale yellow oil (120 mg, 34%); IR (film) ν 3034, 2926, 1741, 1656, 1461 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.22 (t, 3H, *J*=7.0 Hz), 2.01 (s, 3H), 2.66 (dd, 1H, *J*=6.0, 17.2 Hz), 3.07 (dd, 1H, *J*=6.6, 17.2 Hz), 3.37 (d, 1H, *J*=17.6 Hz), 4.15 (q, 2H, *J*=7.0 Hz), 4.77 (d, 1H, *J*=17.6 Hz), 4.80 (dd, 1H, *J*=6.6, 6.0 Hz), 7.18–7.22 (m, 2H), 7.50–7.62 (m, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 14.3 (q), 29.3 (q), 41.8 (t), 52.0 (t), 60.2 (d), 114.7 (s), 127.1 (d), 127.7 (d), 128.0 (d), 140.2 (s), 145.4 (s), 162.6 (s), 166.9 (s). GC-MS *m/z* 353 (15), 351 (15), 280 (13), 278 (13), 266 (15), 264 (15), 185 (5), 110 (10), 91 (100). Anal. Calcd for

$C_{16}H_{18}BrNO_3$: C, 54.56; H, 5.15; N, 3.98. Found C, 54.56; H, 5.18; N, 3.94.

4.3.5. 3-(3-Bromo-2-oxo-6-phenyl-4-methyl-5,6-dihydro-pyridin-1-yl)-propionic acid methyl ester 3e. Isolated as a pale yellow oil (226 mg, 64%); IR (film) ν 3029, 2929, 1730, 1653,1460 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ_H 1.92 (s, 3H), 2.56 (dt, 1H, J=5.7, 16.8 Hz), 2.54 (dd, 1H, J=2.2, 17.4 Hz), 2.86 (ddd, 1H, J=5.7, 8.4, 16.8 Hz), 3.14 (dd, 1H, J=7.4, 17.4 Hz), 3.16 (ddd, 1H, J=5.7, 8.4, 13.6 Hz), 3.74 (s, 3H), 4.07 (dt, 2H, J=5.7, 13.6 Hz), 4.88 (dd, 1H, J=7.4, 2.2 Hz), 7.00–7.12 (m, 2H), 7.20–7.36 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 24.0 (q), 32.6 (t), 39.1 (t), 43.8 (t), 51.3 (q), 59.0 (d), 115.2 (s), 125.8 (d), 127.6 (d), 128.5 (d), 139.8 (s), 145.2 (s), 160.4 (s), 172.2 (s); LC-ESI-MS rt 10.7 min, m/z 352–354 (M+1), 374–376 (M+Na). Anal. Calcd for $C_{16}H_{18}BrNO_3$: C, 54.56; H, 5.15; N, 3.98. Found C, 54.54; H, 5.14; N, 3.97.

4.3.6. 1-Allyl-3-bromo-4-methyl-6-phenyl-5,6-dihydro-pyridin-2-one 3f. Isolated as a pale yellow oil (295 mg, 96%); IR (film) ν 2967, 2926, 1653, 1457 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ_H 1.90 (3H, s), 2.54 (1H, dd, J=2.6, 17.2 Hz), 3.09 (1H, dd, J=7.5, 17.2 Hz), 3.19 (1H, dd, J=7.2, 15.4 Hz), 4.63 (1H, dd, J=2.6, 7.5 Hz), 4.74–4.85 (1H, m), 5.05–5.21 (2H, m), 5.68–5.87 (1H, m), 7.12–7.20 (2H, m), 7.25–7.37 (3H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 24.2 (q), 39.1 (t), 48.4 (t), 56.4 (d), 115.5 (s), 117.5 (t), 126.1 (d), 127.7 (d), 128.6 (d), 132.9 (d), 139.5 (s), 145.0 (s), 160.0 (s); LC-ESI-MS rt 11.6 min, m/z 306–308 (M+1), 328–330 (M+Na). Anal. Calcd for $C_{15}H_{16}BrNO$: C, 58.84; H, 5.27; N, 4.57. Found C, 58.87; H, 5.26; N, 4.55.

4.3.7. 1-Benzyl-3-bromo-6-phenyl-4-propyl-5,6-dihydro-pyridin-2-one 3g. Isolated as a pale yellow oil (362 mg, 94%); IR (film) ν 3029, 2928, 1648, 1611, 1454 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 0.75 (3H, t, J=7.5 Hz,), 1.20–1.30 (2H, m), 2.16 (1H, dt, J=7.6, 13.0 Hz), 2.36 (1H, dt, J=7.8, 13.0 Hz), 2.53 (1H, dd, J=2.1, 17.0 Hz), 2.97 (1H, dd, J=7.4, 17.0 Hz), 3.65 (1H, d, J=15.0 Hz), 4.59 (1H, dd, J=2.1, 7.4 Hz), 5.64 (1H, d, J=15 Hz), 7.14–7.17 (2H, m), 7.3–7.39 (8H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 13.4 (q), 19.2 (t), 37.5 (t), 39.1 (t), 49.2 (t), 56.3 (d), 115.4 (s), 126.1 (d), 127.4 (d), 127.8 (d), 128.0 (d), 128.5 (d), 128.7 (d), 137.4 (s), 139.1 (s), 148.3 (s), 160.7 (s); LC-ESI-MS rt 14.7 min, m/z 384–386 (M+1), 406–408 (M+Na). Anal. Calcd for $C_{21}H_{22}BrNO$: C, 65.63; H, 5.77; N, 3.64. Found C, 65.61; H, 5.79; N, 3.64.

4.3.8. (1′*S*,6*R*)-3-Bromo-4-methyl-6-phenyl-1-(1′-phenyl-ethyl)-5,6-dihydro-pyridin-2-one 5. Isolated as a white solid (226 mg, 61%), mp=120–122 °C; IR (nujol) ν 3028, 2930, 16474, 1630, 1452 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 1.23 (3H, d, J=7.4 Hz,), 1.85 (3H, d, $J_{1,3}$=1.2 Hz), 2.27 (1H, dd,, $J_{1,2}$=17.0 Hz, $J_{1,3}$=1.2 Hz), 2.83 (1H, ddd, J=1.2, 7.0, 17.0 Hz) 4.39 (1H, dd, $J_{1,2}$=7.0 Hz, $J_{1,3}$=1.2 Hz), 6.19 (1H, q, J=7.4 Hz), 7.15–7.18 (2H, m), 7.30–7.42 (8H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 16.3 (q), 24.2 (q), 40.3 (t), 52.4 (d), 53.2 (d), 116.0 (s), 126.1 (d), 127.2 (d), 127.4 (d), 127.5 (d), 128.5 (d), 141.4 (s), 141.8 (s), 144.1 (s), 160.2 (s); $[\alpha]_D^{19}$=+29 (c 1.04, $CHCl_3$); LC-ESI-MS rt 13.4 min, m/z 370–372 (M+1), 392–394 (M+Na). Anal. Calcd for $C_{20}H_{20}BrNO$: C, 64.87; H, 5.44; N, 3.78. Found C, 64.90; H, 5.42; N, 3.79.

4.3.9. (1′*S*,6*S*)-3-Bromo-4-methyl-6-phenyl-1-(1′-phenyl-ethyl)-5,6-dihydro-pyridin-2-one 6. Isolated as a white solid (137 mg, 37%), mp=105–107 °C; IR (nujol) ν 3060, 2976, 1727, 1645, 1494 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 1.65 (3H, d, J=7.0 Hz,), 1.84 (3H, s), 2.37 (1H, dd, J=1.5, 16.8 Hz), 3.07 (1H, dd, J=7.2, 16.8 Hz) 4.57 (1H, dd, J=1.5, 7.2 Hz), 5.77 (1H, q, J=7.0 Hz), 6.78–6.82 (2H, m), 6.95–7.05 (6H, m), 7.15–7.18 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 17.7 (q), 24.1 (q), 40.4 (t), 54.3 (2C, d), 116.6 (s), 126.0 (d), 126.8 (d), 127.4 (d), 127.7 (d), 127.8 (d), 128.4 (d), 138.5 (s), 140.5 (s), 143.9 (s), 159.9 (s); $[\alpha]_D^{19}$=−109 (c 0.99, $CHCl_3$); LC-ESI-MS rt 13.0 min, m/z 370–372 (M+1), 392–394 (M+Na). Anal. Calcd for $C_{20}H_{20}BrNO$: C, 64.87; H, 5.44; N, 3.78. Found C, 64.88; H, 5.45; N, 3.76.

4.3.10. (1′*S*,6*R*)-3-Bromo-6-phenyl-1-(1′-phenyl-ethyl)-4-propyl-5,6-dihydro-pyridin-2-one 7. Isolated as a white solid (147 mg, 37%), mp=116–120 °C; IR (nujol) ν 3059, 2928, 1646, 1624, 1452 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 0.67 (3H, t, J=7.2 Hz,), 1.02–1.15 (2H, m), 1.25 (3H, d, J=7.2 Hz), 2.03 (1H, dt, J=7.0, 13.0 Hz), 2.24–2.31 (1H, m), 2.30 (1H, dd, J=1.8, 16.8 Hz), 2.75 (1H, dd, J=6.6, 16.8 Hz), 4.42 (1H, dd, J=1.8, 6.6 Hz), 6.21 (1H, q, J=7.2 Hz), 7.13–7.17 (2H, m), 7.20–7.40 (8H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 13.4 (q), 16.2 (q), 18.9 (t), 38.6 (t), 38.8 (t), 52.2 (d), 53.2 (d), 115.8 (s), 126.0 (d), 127.2 (d), 127.3 (d), 127.5 (d), 128.3 (d), 128.5(d), 141.3 (s), 141.4 (s), 147.5 (s), 160.4 (s); $[\alpha]_D^{19}$=+34 (c 0.93, $CHCl_3$); LC-ESI-MS rt 12.4 min, m/z 398–400 (M+1), 420–422 (M+Na). Anal. Calcd for $C_{22}H_{24}BrNO$: C, 66.33; H, 6.07; N, 3.52. Found C, 66.32; H, 6.06; N, 3.55.

4.3.11. (1′*S*,6*S*)-3-Bromo-6-phenyl-1-(1′-phenyl-ethyl)-4-propyl-5,6-dihydro-pyridin-2-one 8. Isolated as a white solid (71 mg, 18%), mp=95–99 °C; IR (nujol) ν 3030, 2929, 1643, 1453 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 0.66 (3H, t, J=7.2 Hz,), 1.03–1.15 (2H, m), 1.67 (3H, d, J=7.0 Hz), 2.01–2.11 (1H, m), 2.21–2.30 (1H, m), 2.41 (1H, dd, J=1.5, 16.8 Hz), 3.00 (1H, dd, J=6.9, 16.8 Hz), 4.60 (1H, dd, J=1.5, 6.9 Hz), 5.80 (1H, q, J=7.0 Hz), 6.78–6.80 (2H, m), 6.98–7.04 (6H, m), 7.18–7.20 (2H, m); ^{13}C NMR δ_C (50 MHz, $CDCl_3$) 13.5 (q), 17.8 (q), 19.0 (t), 38.8 (t), 38.9 (t), 54.2 (2C, d), 116.4 (s), 126.0 (d), 126.8 (d), 127.4 (d), 127.7 (2C, d), 128.4 (d), 138.5 (s), 140.1 (s), 147.3 (s), 160.2 (s); $[\alpha]_D^{19}$=−81 (c 1.24, $CHCl_3$); LC-ESI-MS rt 13.6 min, m/z 398–400 (M+1), 420–422 (M+Na). Anal. Calcd for $C_{22}H_{24}BrNO$: C, 66.33; H, 6.07; N, 3.52. Found C, 66.35; H, 6.04; N, 3.56.

4.4. Reaction of 1c with imines in the presence of $AlMe_2Cl$

To a stirred solution of acyl chloride **1c** (0.211 g, 1 mmol) in CH_2Cl_2 at −78 °C, $AlMe_2Cl$ (1 mL of a 1 M solution in hexane, 1 equiv.) was added in one portion. After 10 min, a solution of TEA (0.139 mL, 1 mmol, 1 equiv.) in CH_2Cl_2 (2 mL) and a solution of the imine (2 equiv.) in CH_2Cl_2 (2 mL) were added dropwise at the same time. The reaction was monitored by TLC and quenched, after disappearance

of the imine reagent, with a water solution of Seignette salts (Na/K tartrate). The reaction mixture was filtered through a celite pad, diluted with CH_2Cl_2 and washed twice with water. The organic layer was dried over Na_2SO_4 and solvent was removed under reduced pressure. Compounds **9**, **10** were purifed by flash chromatography on silica gel (cyclohexane/Et_2O, 95/5 as eluant).

4.4.1. (1′*S*,5*R*,6*R*)-3-Bromo-5-ethyl-6-phenyl-1-(1′-phenyl-ethyl)-5,6-dihydro-pyridin-2-one 9. Isolated as a white solid (226 mg, 59%), mp=150–152 °C; IR (nujol) ν 3050, 2923, 1666, 1608, 1421 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 0.49 (3H, t, J=7.2 Hz,), 0.82–1.02 (2H, m), 1.21 (3H, d, J=7.2 Hz), 2.0–2.17 (1H, m), 4.29 (1H, bs), 6.29 (1H, q, J=7.2 Hz), 6.61 (1H, dd, $J_{1,2}$=6.6 Hz, $J_{1,3}$=1.2 Hz), 7.13–7.16 (2H, m), 7.30–7.40 (8H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 10.7 (q), 15.9 (q), 25.7 (t), 47.6 (d), 52.2 (d), 56.7 (d), 118.6 (s), 125.9 (d), 127.1 (d), 127.3 (d), 127.9 (d), 128.2 (d), 128.4 (d), 140.0 (s), 140.5 (s), 142.1 (s), 159.0 (s); $[\alpha]_D^{19}$=−66 (*c* 1.14, $CHCl_3$); LC-ESI-MS rt 15.1 min, *m*/*z* 384–386 (M+1), 406–408 (M+Na). Anal. Calcd for $C_{21}H_{22}BrNO$: C, 65.63; H, 5.77; N, 3.64. Found C, 65.61; H, 5.78; N, 3.63.

4.4.2. (1′*S*,5*S*,6*S*)-3-Bromo-5-ethyl-6-phenyl-1-(1′-phenyl-ethyl)-5,6-dihydro-pyridin-2-one 10. Isolated as a dense yellow oil (65 mg, 17%); IR (film) ν 3031, 2926, 1654, 1616, 1452 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 1.09 (3H, t, J=7.2 Hz,), 1.58–1.73 (2H, m), 1.63 (3H, d, J=7.0 Hz), 2.19 (1H, m), 4.41 (1H, bs), 5.85 (1H, q, J=7.0 Hz), 6.61 (1H, dd, J=6.9 Hz, $J_{1,3}$=1.5 Hz), 6.72–6.78 (2H, m), 6.94–7.06 (6H, m), 7.12–7.18 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 11.5 (q), 16.9 (q), 26.8 (t), 47.2 (d), 53.8 (d), 59.3 (d), 119.4 (s), 125.9 (d), 126.7 (d), 127.5 (d), 127.7 (d), 127.8 (d), 128.6 (d), 138.2 (s), 140.4 (s),140.6 (s), 159.0 (s); $[\alpha]_D^{19}$=−28 (*c* 0.97, $CHCl_3$); LC-ESI-MS rt 14.2 min, *m*/*z* 384–386 (M+1), 406–408 (M+Na). Anal. Calcd for $C_{21}H_{22}BrNO$: C, 65.63; H, 5.77; N, 3.64. Found C, 65.66; H, 5.76; N, 3.62.

4.5. Reaction of 3-bromo-5,6-dihydro-pyridin-2-ones with allylamine

3-Bromo-5,6-dihydro-pyridin-2-one (1 mmol) was refluxed in neat allylamine (5 mL) for 2 days. The excess of amine was then removed by evaporation under reduced pressure. The products were purified by flash chromatography on silica gel (eluant: cyclohexane/Et_2O 9/1 for **11** and **12**, cyclohexane/ethyl acetate 8/2 for **13** and **14**).

4.5.1. (1′*S*,3*R*,4*R*,5*R*,6*R*)-3,4-[*N*-(Allyl)-aziridino]-5-ethyl-6-phenyl-*N*-(1′-phenyl-ethyl)-piperidin-2-one 11. Isolated as a white solid (306 mg, 85%), mp=73–75 °C; IR (nujol) ν 3050, 2921, 1641, 1452 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 0.48 (3H, t, J=7.5 Hz), 0.58–0.69 (1H, m), 0.99–1.09 (1H, m), 1.21 (3H, d, J=7.3 Hz), 1.82 (1H, dd, J=1.5, 6.1 Hz), 2.09–2.17 (1H, m), 2.26 (1H, d, J=6.1 Hz), 2.49 (1H, dd, J=5.2, 14.7 Hz), 3.14 (1H, ddt, J=4.2, 14.7, 2.0 Hz), 4.16 (1H, s), 4.69 (1H, dq, J=17.1, 1.8 Hz), 4.86 (1H, dq, J=10.5, 1.8 Hz), 5.55–5.68 (1H, ddt, J=17.1, 10.5, 4.2 Hz), 6.39 (1H, q, J=7.3 Hz), 7.27–7.35 (10H, m); ^{13}C NMR δ_C (100 MHz, $CDCl_3$) 11.5 (q), 17.3 (q), 24.1 (t), 38.9 (d), 43.1 (d), 46.0 (d), 51.2 (d), 58.0 (t), 61.2 (d), 115.5 (t), 126.0 (d), 126.8 (d), 127.8 (d), 128.2 (d), 128.3 (d), 128.4 (d), 134.4 (s), 140.6 (s), 145.1 (d), 169.8 (s); $[\alpha]_D^{19}$=−100.0 (*c* 1.1 $CHCl_3$); LC-ESI-MS rt 15.6 min, *m*/*z* 361 (M+1), 383 (M+Na). Anal. Calcd for $C_{24}H_{28}N_2O$: C, 79.96; H, 7.83; N, 7.77. Found C, 79.98; H, 7.81; N, 7.75.

4.5.2. (1′*S*,3*S*,4*S*,5*S*,6*S*)-3,4-[*N*-(Allyl)-aziridino]-5-ethyl-6-phenyl-*N*-(1′-phenyl-ethyl)-piperidin-2-one 12. Isolated as a white solid (144 mg, 40%), mp=78–80 °C; IR (nujol) ν 3052, 2927, 1639, 1450 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ_H 1.00 (3H, t, J=7.2 Hz,), 1.27 (1H, m), 1.38 (1H, m), 1.70 (3H, d, J=7.2 Hz), 1.90 (1H, dd, J=1.5, 6.0 Hz), 2.18 (1H, d, J=6.0 Hz), 2.31 (1H, bt, J=6.6 Hz), 2.43 (1H, dd, J=15.6, 5.4Hz), 3.10 (1H, dd, J=15.6, 2.4 Hz), 4.35 (1H, s), 4.60 (1H, dd, J=17.4, 1.5 Hz), 4.80 (1H, dd, J=10.8, 1.5 Hz), 5.09 (1H, q, J=7.2 Hz), 5.55 (1H, ddt, J=17.4, 10.8, 4.8 Hz), 7.01–7.15 (7H, m), 7.20–7.35 (3H, m); ^{13}C NMR δ_C (150 MHz, $CDCl_3$) 12.0 (q), 18.2 (q), 25.1 (t), 39.5 (d), 42.9 (d), 46.5 (d), 57.1 (d), 61.1 (t), 62.6 (d), 115.5 (t), 125.6 (d), 126.7 (d), 127.3 (d), 127.8 (d), 128.0 (d), 128.6 (d), 134.4 (s), 140.1 (s), 142.3 (d), 169.6 (s); $[\alpha]_D^{19}$=+11.0 (*c*0.9 $CHCl_3$); LC-ESI-MS rt 17.0 min, *m*/*z* 361 (M+1), 383 (M+Na). Anal. Calcd for $C_{24}H_{28}N_2O$: C, 79.96; H, 7.83; N, 7.77. Found C, 79.95; H, 7.83; N, 7.79.

4.5.3. 1-Allyl-3-allylamino-4-methyl-6-phenyl-5,6-dihydro-pyridin-2-one 13. Isolated as a pale yellow oil (146 mg, 52%); IR (film) ν 3052, 2925, 1638, 1447 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 1.75 (3H, s), 2.35 (1H, dd, J=2.8, 17.2 Hz), 3.05 (1H, dd, J=7.5, 17.2 Hz), 3.16 (1H, dd, J=7.2, 15.3 Hz), 3.42–3.55 (2H, m), 4.58 (1H, dd, J=2.8, 7.5 Hz), 4.76–4.83 (1H, m), 5.04–5.22 (4H, m), 5.68–5.75 (2H, m), 7.18–7.19 (2H, m), 7.22–7.40 (3H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 18.8 (q), 37.2 (t), 47.7 (t), 51.1 (t), 57.0 (d), 115.5 (t), 117.0 (t), 120.8 (s), 126.4 (d), 127.4 (d), 128.4 (d), 133.3 (s), 133.4 (d), 136.6 (d), 140.7 (s), 164.4 (s); LC-ESI-MS rt 12.1 min, *m*/*z* 283 (M+1), 305 (M+Na). Anal. Calcd for $C_{18}H_{22}N_2O$: C, 76.56; H, 7.85; N, 9.92. Found C, 76.55; H, 7.84; N, 9.90.

4.5.4. 3-Allylamino-1-(4-methoxy-benzyl)-4-methyl-6-phenyl-5,6-dihydro-pyridin-2-one 14. Isolated as a pale yellow oil (90 mg, 25%); IR (film) ν 3049, 2932, 1644, 1520 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 1.82 (3H, s), 2.36 (1H, dd, J=2.7, 17.7 Hz), 3.02 (1H, dd, J=7.8, 17.7 Hz), 3.59 (3H, m), 3.90 (3H, s), 4.54 (1H, dd, J=2.7, 7.8 Hz), 5.17 (1H, dq, J=10.5, 1.5 Hz), 5.19 (1H, bs), 5.28 (1H, dq, J=17.1, 1.5 Hz), 5.62 (1H, d, J=15.0 Hz), 6.02 (ddt, J=17.1, 10.5, 6.0 Hz), 6.95 (2H, m), 7.18–7.24 (4H, m), 7.36–7.60 (3H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 18.9 (q), 37.2 (t), 47.8 (t), 51.2 (t), 55.1 (q), 56.6 (d), 113.9 (s), 115.7 (d), 116.1 (t), 120.9 (s), 126.5 (d), 127.2 (d), 128.8 (d), 129.2 (d), 133.4 (s), 136.7 (d), 140.6 (s), 158.9 (s), 164.8 (s); GC-MS *m*/*z* 362(2), 267 (5), 236 (28), 195 (58), 154 (32), 108 (70), 83 (100), 68 (66), 54 (46). Anal. Calcd for $C_{23}H_{26}N_2O_2$: C, 76.21; H, 7.23; N, 7.73. Found C, 76.21; H, 7.22; N, 7.71.

4.6. *N*-*p*-Methoxy-phenyl group removal from dihydro-pyridin-2-one 3b

A solution of CAN (0.548 g, 1 mmol) in water (5 mL) was added dropwise at rt to a stirred solution of **3b** (0.193 g,

0.5 mmol) in CH_3CN (5 mL). After three hours the organic solvent was removed under reduced pressure and the aqueous residue was diluted with ethyl acetate (20 mL) and water (10 mL). The organic layer was separated, dried over Na_2SO_4 and concentrated under reduced pressure. Compound **15** was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 8/2 as eluant).

4.6.1. 3-Bromo-4-methyl-6-phenyl-5,6-dihydro-pyridin-2-one 15. Isolated as a white solid (93 mg, 70%), mp=134–136 °C; IR (film) ν 3304, 3051, 2923, 1640, 1445 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ_H 2.10 (3H, s), 2.63–2.72 (2H, m), 4.74 (1H, t, J=7.8 Hz), 6.00 (1H, bs), 7.35–7.45 (5H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 24.3 (q), 40.6 (t), 54.6 (d), 115.3 (s), 126.2 (d), 128.4 (d), 129.0 (d), 140.2 (s), 148.9 (s), 162.2 (s); GC-MS *m/z* 267 (77), 265 (77), 186 (51), 213 (8), 162 (100), 160 (100), 104 (22), 77 (25), 53 (44). Anal. Calcd for $C_{12}H_{12}NO$: C, 56.16; H, 4.54; N, 5.26. Found C, 56.17; H, 4.55; N, 5.24.

4.7. Preparation of *N-tert*-butyloxycarbonyl-derivative 16

To a stirred solution of **15** (0.267 g, 1 mmol) in CH_2Cl_2 (10 mL) at rt, di-*tert*-butyl dicarbonate (0.436 g, 2 mmol, 2 equiv.), TEA (0.139 mL, 1 mmol, 1 equiv.) and DMAP (0.122 g, 1 mmol, 1 equiv.) were added. After 12 h, the reaction was quenched with water and washed twice with a saturated solution of NH_4Cl (10 mL). The organic layer was dried over Na_2SO_4 and solvent was removed under reduced pressure. Compound **16** was isolated in 90% yield after a quick purification by chromatography on silica gel (cyclohexane/ethyl ether 6/4 as eluant).

4.7.1. 3-Bromo-4-methyl-6-phenyl-1-(*tert*-butyloxycarbonyl)-5,6-dihydro-pyridin-2-one 16. Isolated as a pale yellow oil (328 mg, 90%); IR (film) ν 3042, 2926, 1702, 1644, 1449 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ_H 1.49 (9H, s), 2.02 (3H, s), 2.73 (1H, dd, J=2.6, 17.8 Hz), 3.18 (1H, dd, J=6.6, 17.8 Hz), 5.53 (1H, dd, J=2.6, 6.6 Hz), 7.15–7.45 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 24.7 (q), 27.7 (3C,q), 38.3 (t), 55.5 (d), 83.5 (s), 116.5 (s), 125.4 (d), 128.1 (d), 128.5 (d), 139.9 (s), 149.5 (s), 152.2 (s), 158.8 (s); LC-ESI-MS rt 12.7 min, *m/z* 366–368 (M+1), 388–390 (M+Na). Anal. Calcd for $C_{17}H_{20}NO_3$: C, 55.75; H, 5.50; N, 3.82. Found C, 55.77; H, 5.49; N, 3.79.

4.7.2. 3-Allylamino-4-methyl-6-phenyl-5,6-dihydro-pyridin-2-one 17. Isolated as a pale yellow oil (241 mg, >99%); IR (film) ν 3309, 3050, 2930, 1638, 1441 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 1.92 (3H, s), 2.46 (1H, dd, J=5.4, 16.8 Hz), 2.65 (1H, dd, J=11.7, 16.8 Hz), 3.53 (1H, ddt, J=15.0, 6.0, 1.5 Hz), 3.61 (1H, ddt, J=15.0, 6.0, 1.5 Hz), 4.69 (1H, dd, J=5.4, 11.7 Hz), 5.14 (1H, dq, J=10.2, 1.5 Hz), 5.25 (1H, dq, J=17.1, 1.5 Hz), 5.53 (1H, bs), 5.95 (1H, ddt, J=17.1, 10.2, 6.0 Hz), 7.24–7.45 (5H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 19.0 (q), 39.6 (t), 51.2 (t), 55.5 (d), 113.4 (s), 115.9 (t), 120.4 (s), 126.5 (d), 128.5 (d), 129.1 (d), 136.6 (d), 141.4 (s), 166.7 (d); GC-MS *m/z* 242 (50), 227 (9), 280 (13), 213 (8), 137 (14), 106 (100), 68 (63). Anal. Calcd for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.49; N, 11.56. Found C, 74.33; H, 7.50; N, 11.55.

4.7.3. 3-Allylamino-4-methyl-6-phenyl-1-(*tert*-butyloxycarbonyl)-5,6-dihydro-pyridin-2-one 18. Isolated as a pale yellow oil (340 mg, >99%); IR (film) ν 3052, 2924, 1710, 1639, 1447 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ_H 1.49 (9H, s), 1.91 (3H, s), 2.45 (1H, dd, J=5.0, 17.1 Hz), 2.63 (1H, dd, J=11.7, 17.1 Hz), 3.55 (1H, ddt, J=14.7, 6.0, 1.5 Hz), 3.58 (1H, ddt, J=14.7, 6.0, 1.5 Hz), 4.69 (1H, dd, J=5.0, 11.7 Hz), 5.20 (1H, dq, J=10.5, 1.5 Hz), 5.22 (1H, dq, J=17.1, 1.5 Hz), 6.08 (1H, ddt, J=17.1, 10.2, 6.0 Hz), 7.21–7.48 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 24.5 (q), 28.2 (3C, q), 40.1 (t), 49.2 (t), 54.9 (d), 82.9 (s), 112.9 (s), 115.8 (t), 121.2 (s), 125.8 (d), 128.2 (d), 128.9 (d), 137.5 (d), 140.0 (s), 153.5 (s), 162.4 (s); LC-ESI-MS rt 12.6 min, *m/z* 343 (M+1), 365 (M+Na). Anal. Calcd for $C_{24}H_{28}N_2O$: C, 79.96; H, 7.83; N, 7.77. Found C, 79.98; H, 7.81; N, 7.75. Anal. Calcd for $C_{20}H_{26}N_2O_3$: C, 70.15; H, 7.65; N, 8.18. Found C, 70.14; H, 7.65; N, 8.17.

4.8. X-ray crystallographic determination of compounds 7 and 9

Data were collected at room temperature on a Bruker AXS CCD diffractometer (Mo K_α radiation, λ=0.71073 Å) for compound **7** and on an Enraf-Nonius CAD4 diffractometer (Mo K_α radiation, λ=0.71073 Å) for compound **9**. The data collection, integration and data reduction for **7** were performed using SMART and SAINT programs[19] and an empirical absorption correction was applied using SADABS.[20] The unit cell parameters for **9** were determined by a least-squares fitting of 25 randomly selected strong reflections and an empirical absorption correction was applied using the azimuthal scan method.[21] The structures were solved by direct methods (SIR97)[22] and subsequent Fourier synthesis and refined by full matrix least-squares on F^2 (SHELXTL) Ref. 23 for all non-hydrogen atoms for **7** whereas for **9** only the bromine atom was treated anisotropically because of the poor data/parameter ratio. Hydrogen atoms were placed in calculated positions except for the hydrogen bound to C9 in compound **7** and to C8 in compound **9**.

4.8.1. Compound 7. $C_{22}H_{23}BrNO$, M=397.32, orthorhombic, space group $P2_12_12_1$, a=9.8512(6) Å, b=11.4055(6) Å, c=17.6739(10) Å, V=1985.8(2) $Å^3$, Z=4, $F(000)$=820, μ=2.079 mm^{-1}, D_c=1.329 g/cm^{-3}. The reflections collected were 26095, of which 5796 unique [$R_{(int)}$ =0.0996]; 2887 reflections $I>2\sigma(I)$, R_1=0.0448 and wR_2=0.0984 for 2887 [$I>2\sigma(I)$] and R_1=0.1048 and wR_2=0.1170 for all (5796) intensity data. Goodness-of-fit=0.867, absolute structure parameter of the model: x=0.018 (12), residual electron density in the final Fourier map was 0.392 and −0.406 e $Å^{-3}$. CCDC number is 229760.

4.8.2. Compound 9. $C_{21}H_{22}BrNO$, M=384.31, orthorhombic, space group $P2_12_12_1$, a=7.659(3) Å, b=12.751(2) Å, c=19.087(4) Å, V=1864.0(9) $Å^3$, Z=4, $F(000)$=792, μ=2.212 mm^{-1}, D_c=1.369 g/cm^{-3}. The reflections collected were 2512, of which 2512 unique; 781 reflections [$I>2\sigma(I)$]. R_1=0.0506 and wR_2=0.1238 for 781 [$I>2\sigma(I)$] and R_1=0.2501 and wR_2=0.1833 for all (2512) intensity data. Goodness-of-fit=0.953, absolute structure parameter of the model: x=0.05(3), residual

electron density in the final Fourier map was 0.311 and −0.235 e Å^{-3}. CCDC number is 229761.

5. Supplementary Material

Crystal data and structure refinement for **7** and **9**. Atomic coordinates (×10^4) and equivalent isotropic displacement parameters (Å^2×10^3) for **7** and **9**.

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References and notes

1. *Heterocyclic Chemistry*; 3rd ed., Addison-Wesley Longman, Ltd: England, 1998.
2. *Comprehensive Hetrocyclic Chemistry*; Bird, C. W., Ed.; Pergamon: Oxford, 1996.
3. (a) Fisyuk, A. S.; Bundel, Y. *Chem. Heterocycl. Compd.* **1999**, *35*, 125–145. (b) Arrayas, R. G.; Alcudia, A.; Liebeskind, L. S. *Org. Lett.* **2001**, *3*, 3381–3383. (c) Jones, T. H.; Blum, M. S. *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1983; Vol. 1, pp 33–84. (d) Fodor, G. B.; Colasanti, B. *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1985; Vol. 3, pp 1–90. (e) Strunz, G. M.; Findlay, J. A. *The Alkaloids*; Brossi, A., Ed.; Academic Press: Orlando, 1985; Vol. 26, p 89. (f) Balasubramanian, M.; Keay, J. G. *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: New York, 1996; Vol. 5, p 245. (g) Rubiralta, M.; Giralt, E.; Diez, A. *Piperidine: Structure, Preparation, Reactivity, and Synthetic Applications of Piperidine and its Derivatives*; Elsevier: Amsterdam, 1991. (h) Casinovi, C. G.; Grandolini, G.; Mercantini, R.; Oddo, N.; Olivieri, R.; Tonolo, A. *Tetrahedron Lett.* **1968**, *9*, 3175–3178. (i) Dolle, R. E.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1985**, *107*, 1691–1694. (j) Teshima, Y.; Shin-Ya, K.; Shimazu, A.; Furihata, K.; Chul, H.; Furihata, K.; Hayakawa, Y.; Nagai, K.; Seto, H. *J. Antibiot.* **1991**, *44*, 685–687.
4. (a) Davis, D. A.; Gribble, G. W. *Tetrahedron Lett.* **1990**, *31*, 1081–1084. (b) Fisyuk, A. S.; Poendaev, N. V. *Molecules* **2002**, *7*, 124–128. (c) Hua, D. H.; Zhang, F.; Chen, J. *J. Org. Chem.* **1994**, *59*, 5084–5087. (d) Martin, A. R.; Mallick, S. K.; Caputo, J. F. *J. Org. Chem.* **1974**, *39*, 1808–1811. (e) Smith, R. M. *Tetrahedron* **1979**, *35*, 437–439. (f) Dodson, C. D.; Dyer, L. A.; Searcy, J.; Wright, Z.; Letourneau, D. K. *Phytochemistry* **2000**, *53*, 51–54. (g) Boll, P. M.; Hansen, J.; Simonsen, O.; Thorup, N. *Tetrahedron* **1984**, *40*, 171–175.
5. (a) Hanessian, S.; McNaughton-Smith, G.; Lombart, H.-G.; Lubell, W. D. *Tetrahedron* **1997**, *53*, 12789–12854. (b) Hanessian, S.; Seid, M.; Nilsson, I. *Tetrahedron Lett.* **2002**, *43*, 1991–1994. (c) Gibson, S. E.; Guillo, N.; Tozer, M. J. *Tetrahedron* **1999**, *55*, 585–615. (d) Lee, H. K.; Chun, J. S.; Pak, C. S. *Tetrahedron Lett.* **2001**, *42*, 3483–3486.
6. (a) Nicolaou, K. C.; Trujillo, J. I.; Jandeleit, B.; Chibale, K.; Rosenfeld, M.; Diefenbach, B.; Cheresh, D. A.; Goodman, S. L. *Bioorg. Med. Chem.* **1998**, *6*, 1185–1208. (b) Haubner, R.; Gratias, R.; Diefenbach, B.; Goodman, S. L.; Jonczyk, A.; Kessler, H. *J. Am. Chem. Soc.* **1996**, *118*, 7461–7472. (c) Ojima, I.; Chakravarty, S.; Dong, Q. *Bioorg. Med. Chem.* **1995**, *3*, 337–360.
7. (a) Marson, C. M.; Grabowska, U.; Fallah, A.; Walsgrove, T.; Eggleston, D. S.; Baures, P. W. *J. Org. Chem.* **1994**, *59*, 291–296. (b) Brandstadter, S. M.; Ojima, I.; Hirai, K. *Tetrahedron Lett.* **1987**, *28*, 613–616. (c) Danishefsky, S. J.; Vogel, C. *J. Org. Chem.* **1986**, *51*, 3915–3916. (d) Duran, F.; Ghosez, L. *Tetrahedron Lett.* **1970**, *3*, 245–248.
8. (a) Tidwell, T. T. *Acc. Chem. Res.* **1990**, *23*, 273–279. (b) Hyatt, J. A.; Raynolds, P. W. *Organic Reactions*; Paquette, L. A., Ed.; Wiley: New York, 1994; Vol. 45, pp 159–646. (c) Orr, R. K.; Calter, M. A. *Tetrahedron* **2003**, *59*, 3545–3565.
9. (a) Cardillo, G.; De Simone, A.; Mingardi, A.; Tomasini, C. *Synlett* **1995**, 1131–1132. (b) Cardillo, G.; Fabbroni, S.; Gentilucci, L.; Perciaccante, R.; Tolomelli, A. *Tetrahedron: Asymmetry* **2004**, *15*, 593–601.
10. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 229760 and 229761. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).
11. (a) Nagel, D. L.; Woller, P. B.; Cromwell, N. H. *J. Org. Chem.* **1971**, *36*, 3911–3917. (b) Tarburton, P.; Woller, P. B.; Badger, R. C.; Doomes, E.; Cromwell, N. H. *J. Heterocycl. Chem.* **1977**, *14*, 459–464.
12. (a) Cardillo, G.; Gentilucci, L.; Tolomelli, A. *Aldrichim. Acta* **2003**, *36*, 39–50. (b) Coull, W. M.; Davis, F. A. *Synthesis* **2000**, *10*, 1347–1365. (c) Tanner, D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 599–619. (d) Atkinson, R. S. *Tetrahedron* **1999**, *55*, 1519–1559. (e) Osborn, H. M. I.; Sweeney, J. *Tetrahedron: Asymmetry* **1997**, *8*, 1693–1715.
13. NOESY-1D have been performed with a DPFG (double pulse field gradient) sequence in $CDCl_3$ at 25 °C on a Varian UNITY INOVA 600 MHz (Oxford Magnet).
14. (a) Jeong, J. U.; Tao, B.; Sagasser, I.; Hennings, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1998**, *120*, 6844–6845. (b) Atkinson, R. S.; Kelly, B. J. *J. Chem. Soc., Chem. Commun.* **1988**, 624–625. (c) Pirò, J.; Forns, P.; Blanchet, J.; Bonin, M.; Micouin, L.; Diez, A. *Tetrahedron: Asymmetry* **2002**, *13*, 995–1004.
15. HYPERCHEM 5.1 release Pro, Hypercube Inc, Copyright 1999, and CHEMPLUS™ Release, Hypercube Inc, Copyright 1993–1997.
16. Corey, E. J.; Weidong, L.; Nagamitsu, T. *Angew Chem., Int. Ed. Engl.* **1998**, *37*, 1676–1679.
17. (a) Hung, J.; Werbel, L. M. *Synthesis* **1985**, 80–81. (b) Pessolano, A. A.; Witzel, B. E.; Graham, P. M.; Clark, R. L.; Jones, H.; Dorn, C. P., Jr.; Carty, J.; Shen, T. Y. *J. Heterocycl. Chem.* **1985**, *22*, 265–272. (c) Hirota, K.; Banno, K.; Yamada, Y.; Senda, S. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1137–1142. (d) Senda, S.; Hirota, K.; Banno, K. *J. Med. Chem.* **1972**, *15*, 471–476.
18. (a) Aitken, R. A.; Armstrong, D. P.; Galt, R. H. B.; Mesher, S. T. E. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2139–2145. (b) Smith, P. A. S.; Dang, C. V. *J. Org. Chem.* **1976**, *41*,

2013–2015. (c) Linder, M. R.; Frey, W. U.; Podtech, J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2566–2577. (d) Tsuge, O.; Kanemasa, S.; Yoshioka, M. *J. Org. Chem.* **1988**, *53*, 1384–1391. (e) Afarinkia, K.; Rees, C. W. *Tetrahedron* **1990**, *46*, 7175–7196. (f) Bandini, M.; Cozzi, P. G.; Umani-Ronchi, A.; Villa, M. *Tetrahedron* **1999**, *55*, 8103–8110. (g) Hattori, K.; Yamamoto, H. *Tetrahedron* **1993**, *49*, 1749–1760.

19. SMART and SAINT Software Reference Manuals, version 5.051 (Windows NT Version), Bruker analytical X-ray Instruments Inc: Madison, WI, 1998.
20. Sheldrick, GM. *SADABS: Program for Empirical Absorption Correction*, University of Göttingen: Germany, 1996.
21. North, A. C. T.; Philips, D. C.; Mathews, F. S. *Acta Crystallogr. Sect A* **1968**, *24*, 351.
22. Altomare, A.; Burla, M. C.; Camalli, M.; Cascarano, G. L.; Giacovazzo, C.; Guagliardi, A.; Moliterni, A. G. G.; Polidori, G.; Spagna, R. *J. Appl. Cryst.* **1999**, *32*, 115.
23. Sheldrick, GM. $SHELXTL_{plus}$ Version 5.1 (Windows NT Version) Structure Determination Package; Bruker analytical X-ray Instruments Inc: Madison, WI, 1998.