An Efficient and Diastereoselective Synthesis of *trans* β-Lactams and β-Aminocarbonyl Compounds

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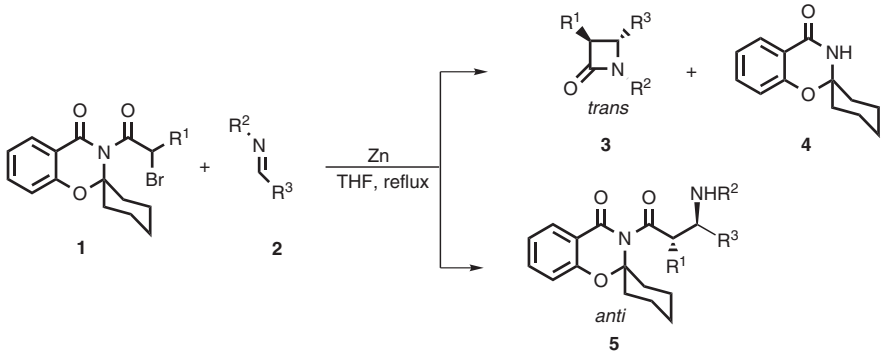
Abstract: Efficient and diastereoselective syntheses of *trans* β-lactams and *anti* β-aminocarbonyl compounds from carboximide **1** and imines **2** under the classical Reformatsky reaction conditions are described. An enolate-imine mechanism has been proposed for this reaction.

Key words: β-lactams, imines, Reformatsky reaction, β-aminocarbonyl compounds

The discovery of penicillin and cephalosporin focused the attention of synthetic chemists on *cis* β-lactams. Interest turned to *trans* β-lactams when thienamycin and several other antibiotics were found to belong to the *trans* family.[1] Some *trans* β-lactams are good cholesterol absorption inhibitors.[2] The ketene-imine cycloaddition (Staudinger reaction) and the ester enolate-imine condensation (Gilman–Speeter reaction) are two major methods for the synthesis of β-lactams. Some earlier studies were directed toward the formation of *trans* β-lactams using the Staudinger reaction, but special conditions, such as high-power microwave irradiation[1] were required and usually gave low yields.[3] The Gilman–Speeter reaction gave almost always a mixture of *cis* and *trans* β-lactams with the *cis* isomer predominating.[4] The synthesis of *trans* β-lactams using chiral imines also has been reported.[5] Herein, we would like to disclose a novel method for the stereoselective synthesis of *trans* β-lactams.

Initially, we found that the Refomatsky-type reaction of carboximide **1**, which could be prepared easily from inexpensive salicylamide according to the literature procedure,[6] with imine derived from aniline and phenyl aldehyde afforded 100% *trans* β-lactam and the auxiliary **4** could be recycled (Scheme 1). The reaction proceeded in THF under reflux, and was finished within 10–20 minutes. The *trans* configuration was determined by the H-3/H-4 coupling constant values (J_{trans} = 1.5–2.5 Hz; J_{cis} = 4.5–6.0 Hz). This fact demonstrated that the use of the auxiliary **4** led to an efficient asymmetric induction. We then examined other imines and the results are summarized in Table 1.

As shown in Table 1, imines derived from anilines and aromatic or aliphatic aldehydes gave good-to-satisfactory yields (50–82%) (Table 1, entries 1–19). Unfortunately, *N*-benzylimine did not react (Table 1, entry 20). Comparison of the ^{1}H NMR spectra of the crude β-lactams with existing literature data[7] indicated that only the *trans* isomers were available. There was no β-amino carbonyl **5** formed as the by-products in these reactions, which is usually a big trouble for the reported Reformatsky-type reactions. This may be due to the good leaving ability of the auxiliary **4**, which facilitates the cyclization of the intermediate (vide infra). However, β-aminocarbonyl compounds **5** were the only products when R^1 was *ortho*-methoxyphenyl group (Scheme 1). As shown in Table 2, the imines derived from both aromatic (Table 2, entries 1–4, 6 and 7) and aliphatic aldehydes (Table 2, entries 5 and 8) afforded *anti* β-aminocarbonyl compounds **5** in good yields (70–85%).



1 2 3 4 5

Scheme 1

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Table 1 Diastereoselective Synthesis of β-Lactams

Entry	R^1	R^2	R^3	β-Lactam[a]	Yield[b] (%)
1	Me	Ph	Ph	**3a**	75
2	Me	Ph	4-ClPh	**3b**	76
3	Me	Ph	4-MeOPh	**3c**	80
4	Me	Ph	3,4-(OCH_2O)Ph	**3d**	71
5	Me	4-MeOPh	Ph	**3e**	75
6	Me	4-MeOPh	4-ClPh	**3f**	72
7	Me	4-MeOPh	4-MeOPh	**3g**	82
8	Me	4-MeOPh	3,4-(OCH_2O)Ph	**3h**	79
9	Me	4-ClPh	Ph	**3i**	66
10	Me	4-ClPh	4-ClPh	**3j**	50
11	Me	4-ClPh	4-MeOPh	**3k**	75
12	Me	4-ClPh	3,4-(OCH_2O)Ph	**3l**	70
13	Et	Ph	Ph	**3m**	83
14	Et	4-MeOPh	4-ClPh	**3n**	79
15	Et	Ph	4-MeOPh	**3o**	80
16	Et	4-MeOPh	3,4-(OCH_2O)Ph	**3p**	82
17	Me	Ph	*trans*-Styryl	**3q**	75
18	Et	Ph	*trans*-Styryl	**3r**	81
19	Me	4-MeOPh	*iso*-Propyl	**3s**	80
20	Me	Bn	Ph	–	No reaction

[a] Determined by ^1H NMR to be 100% *trans*.
[b] Isolated yield based on imine.

Table 2 Diastereoselective Synthesis of β-Amino Carbonyls

Entry	R^1	R^2	R^3	β-Amino carbonyl	Yield[a] (%)
1	Me	2-MeOPh	Ph	**5a**	83
2	Me	2-MeOPh	4-MeOPh	**5b**	76
3	Me	2-MeOPh	4-ClPh	**5c**	85
4	Me	2-MeOPh	4-FPh	**5d**	80
5	Me	2-MeOPh	*iso*-Propyl	**5e**	70
6	Et	2-MeOPh	Ph	**5f**	82
7	Et	2-MeOPh	4-ClPh	**5g**	80
8	Et	2-MeOPh	*iso*-propyl	**5h**	80

[a] Isolated yield based on imine.

Two possible mechanisms are suggested for the formation of *trans* β-lactams: the ketene-imine mechanism and the enolate-imine mechanism (Scheme 2). The former hypothesized that ketene **6** formed by treatment of **1** with Zn could be added to imine to give the *trans* β-lactam. However, this mechanism could not explain the production of **5**. The latter mechanism hypothesized that the chair-like transition state **8** involving the imine and the (*Z*)-enolate[8] gave the intermediate **9**, which cyclized to produce the *trans* β-lactam. The existence of the (*Z*)-enolate **7**, which was different from the traditional (*E*)-enolate, had been proved by the literature.[6] Formation of β-amino carbonyl compounds **5** could also be well explained by this mechanism. When R^1 was *ortho*-methoxyphenyl group, the strong electronegativity of R^1 reduced the nucleophilicity of the nitrogen,[9] which hindered the subsequent cyclization of **9** and **5** formed. Therefore, the enolate-imine mechanism was more reasonable. Though the structural determination was not made, we could deduce from the mechanism that the stereochemistry of the β-amino carbonyl was *anti*.

In conclusion, we have developed an efficient method for the synthesis of *trans* β-lactams **3** and *anti* β-amino carbonyl compounds **5** by the Reformatsky-type reaction of imines **2** with carboximide **1**, which was derived from the recyclable auxiliary **4**. The reaction gave high diastereoselectivity and satisfactory to good yields.

All chemicals were obtained from commercial suppliers and used without further purification. Melting points are uncorrected. Flash column chromatography was carried out on 300–500 mesh silica gel. IR spectra were recorded on a Perkin-Elmer 983 FT-IR spectrometer. ^{1}H NMR spectra were recorded on a Bruker Avance DMX 500 instrument. ESI–MS data were obtained on a Bruker Esquire 3000 plus instrument. HRMS data were recorded on a Bruker FT-ICR-MS Apex III apparatus.

Synthesis of *trans* β-Lactams 3 and *anti* β-Aminocarbonyl Compounds 5; General Procedure

A mixture of carboximide **1** (1.2 mmol), imines **2** (1 mmol) and zinc dust (2 mmol) in THF (5 mL) was refluxed for 10–20 min, cooled and poured into water (5 mL), and then extracted with CH_2Cl_2 (3 × 5 mL). The combined extracts were washed with brine, dried over anhyd Na_2SO_4, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel (eluted with hexane–EtOAc) to give the products.

***trans*-3-Methyl-1,4-diphenylazetidin-2-one[10] (3a)**

Colorless oil.

IR (KBr): 1745 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.48 (d, *J* = 7.4 Hz, 3 H), 3.13 (dq, *J* = 2.4, 7.4 Hz, 1 H, H-3), 4.58 (d, *J* = 2.4 Hz, 1 H, H-4), 7.02–7.05 (m, 1 H) 7.22–7.39 (m, 9 H).

ESI–MS: *m*/*z* = 238 [M + 1]$^+$.

***trans*-4-(4-Chlorophenyl)-3-methyl-1-phenylazetidin-2-one[4a] (3b)**

Colorless oil.

IR (film): 1748 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.49 (d, *J* = 7.4 Hz, 3 H), 3.15 (dq, *J* = 2.3, 7.4 Hz, 1 H, H-3), 4.56 (d, *J* = 2.3 Hz, 1 H, H-4), 7.18–7.40 (m, 9 H).

ESI–MS: *m*/*z* = 272 [M + 1]$^+$.

***trans*-4-(4-Methoxyphenyl)-3-methyl-1-phenylazetidin-2-one[4a] (3c)**

Yellow solid; mp 76–77 °C.

IR (KBr): 1745 cm^{-1}.

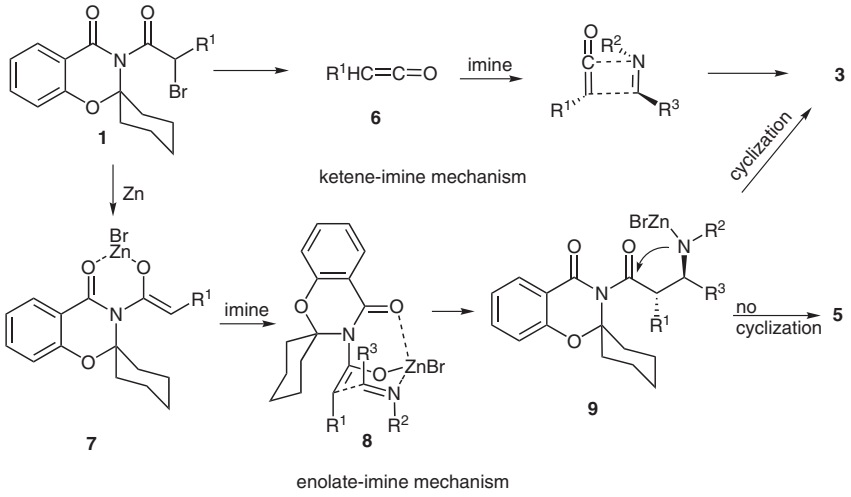
^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.48 (d, *J* = 7.4 Hz, 3 H), 3.11 (dq, *J* = 2.2, 7.4 Hz, 1 H, H-3), 3.73 (s, 3 H), 4.56 (d, *J* = 2.2 Hz, 1 H, H-4), 6.76–7.38 (m, 9 H).

ESI–MS: *m*/*z* = 268 [M + 1]$^+$.

***trans*-3-Methyl-4-[3,4-(methyleneoxy)phenyl]-1-phenylazetidin-2-one[4a] (3d)**

Colorless oil.

IR (film): 1746 cm^{-1}.



Scheme 2

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.45 (d, *J* = 7.4 Hz, 3 H), 3.09 (dq, *J* = 2.3, 7.4 Hz, 1 H, H-3), 4.49 (d, *J* = 2.3 Hz, 1 H, H-4), 5.95 (m, 2 H), 6.78–7.30 (m, 8 H).

ESI–MS: *m*/*z* = 281 $[M + 1]^+$.

***trans*-1-(4-Methoxyphenyl)-3-methyl-4-phenylazetidin-2-one[4b] (3e)**
Colorless oil.

IR (film): 1749 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.46 (d, *J* = 7.4 Hz, 3 H), 3.10 (dq, *J* = 2.2, 7.4 Hz, 1 H, H-3), 3.80 (s, 3 H), 4.53 (d, *J* = 2.2 Hz, 1 H, H-4), 6.89–7.29 (m, 9 H).

ESI–MS: *m*/*z* = 268 $[M + 1]^+$.

***trans*-4-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-methylazetidin-2-one[4b] (3f)**
Colorless oil.

IR (film): 1745 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.46 (d, *J* = 7.4 Hz, 3 H), 3.10 (dq, *J* = 2.2, 7.4 Hz, 1 H, H-3), 3.79 (s, 3 H), 4.49 (d, *J* = 2.2 Hz, 1 H, H-4), 6.87–7.24 (m, 8 H).

ESI–MS: *m*/*z* = 302 $[M + 1]^+$.

***trans*-1,4-Bis(4-methoxyphenyl)-3-methylazetidin-2-one[4b] (3g)**
Colorless oil.

IR (film): 1743 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.46 (d, *J* = 7.4 Hz, 3 H), 3.08 (dq, *J* = 2.2, 7.4 Hz, 1 H, H-3), 3.74 (s, 3 H), 3.80 (s, 3 H), 4.49 (d, *J* = 2.2 Hz, 1 H, H-4), 6.76–7.27 (m, 8 H).

ESI–MS: *m*/*z* = 298 $[M + 1]^+$.

***trans*-1-(4-Methoxyphenyl)-3-methyl-4-[3,4-(methyleneoxyl)phenyl]azetidin-2-one[4b] (3h)**
Colorless oil.

IR (film): 1746 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.44 (d, *J* = 7.4 Hz, 3 H), 3.07 (dq, *J* = 1.8, 7.4 Hz, 1 H, H-3), 3.74 (s, 3 H), 4.45 (d, *J* = 1.8 Hz, 1 H, H-4), 5.94 (m, 2 H), 6.77–7.24 (m, 7 H).

ESI–MS: *m*/*z* = 312 $[M + 1]^+$.

***trans*-1-(4-Chlorophenyl)-3-methyl-4-phenylazetidin-2-one[4a] (3i)**
Colorless oil.

IR (film): 1748 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.49 (d, *J* = 7.4 Hz, 3 H), 3.15 (dq, *J* = 2.3, 7.4 Hz, 1 H, H-3), 4.56 (d, *J* = 2.3 Hz, 1 H, H-4), 7.18–7.40 (m, 9 H).

ESI–MS: *m*/*z* = 272 $[M + 1]^+$.

***trans*-1-(4-Chlorophenyl)-4-(4-methoxyphenyl)-3-methylazetidin-2-one[4a] (3k)**
Colorless oil.

IR (film): 1746 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.46 (d, *J* = 7.4 Hz, 3 H), 3.10 (dq, *J* = 2.2, 7.4 Hz, 1 H, H-3), 3.79 (s, 3 H), 4.49 (d, *J* = 2.2 Hz, 1 H, H-4), 6.87–7.24 (m, 8 H).

ESI–MS: *m*/*z* = 302 $[M + 1]^+$.

***trans*-1-(4-Chlorophenyl)-3-methyl-4-[3,4-(methyleneoxyl)phenyl]azetidin-2-one[4a] (3l)**
Colorless oil.

IR (film): 1745 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.46 (d, *J* = 7.4 Hz, 3 H), 3.11 (dq, *J* = 2.3, 7.4 Hz, 1 H, H-3), 4.47 (d, *J* = 2.3 Hz, 1 H, H-4), 5.96 (m, 2 H), 6.77–7.24 (m, 7 H).

ESI–MS: *m*/*z* = 316 $[M + 1]^+$.

***trans*-3-Ethyl-1,4-diphenylazetidin-2-one[4a] (3m)**
Colorless oil.

IR (film): 1757 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.09 (t, *J* = 7.4 Hz, 3 H), 1.85 (m, 1 H), 1.95 (m, 1 H), 3.06 (m, 1 H, H-3), 4.67 (d, *J* = 2.2 Hz, 1 H), 7.02–7.46 (m, 10 H).

ESI–MS: *m*/*z* = 274 $[M + 23]^+$.

***trans*-4-(4-Chlorophenyl)-3-ethyl-1-(4-methoxyphenyl)azetidin-2-one[4a] (3n)**
Colorless oil.

IR (film): 1747 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.09 (t, *J* = 7.5 Hz, 3 H), 1.85 (m, 1 H), 1.96 (m, 1 H), 3.00 (m, 1 H, H-3), 3.74 (s, 3 H), 4.61 (d, *J* = 2.1 Hz, 1 H, H-4), 7.02–7.46 (m, 8 H).

ESI–MS: *m*/*z* = 338 $[M + 23]^+$.

***trans*-3-Ethyl-4-(4-methoxyphenyl)-1-phenylazetidin-2-one[4b] (3o)**
Colorless oil.

IR (film): 1748 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.09 (t, *J* = 7.4 Hz, 3 H), 1.85 (m, 1 H), 1.95 (m, 1 H), 3.03 (m, 1 H, H-3), 3.79 (s, 3 H), 4.62 (d, *J* = 2.1 Hz, 1 H, H-4), 6.89 (m, 3 H), 7.01 (m, 1 H), 7.21–7.29 (m, 5 H).

ESI–MS: *m*/*z* = 282 $[M + 1]^+$.

***trans*-3-Ethyl-1-phenyl-4-[3,4-(methyleneoxy)phenyl]azetidin-2-one[4a] (3p)**
Colorless oil.

IR (film): 1743 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.08 (t, *J* = 7.4 Hz, 3 H), 1.84 (m, 1 H), 1.94 (m, 1 H), 3.00 (m, 1 H, H-3), 3.73 (s, 3 H), 4.54 (d, *J* = 2.1 Hz, 1 H, H-4), 5.94 (m, 2 H), 5.94 (m, 2 H), 6.77–6.84 (m, 3 H), 7.23 (m, 2 H).

ESI–MS: *m*/*z* = 326 $[M + 1]^+$.

***trans*-3-Methyl-1-phenyl-4-(*trans*-styryl)azetidin-2-one[10] (3q)**
Colorless oil.

IR (film): 1748 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.44 (d, *J* = 7.4 Hz, 3 H), 3.13 (dq, *J* = 1.7, 7.4 Hz, 1 H, H-3), 4.24 (dd, *J* = 1.1, 8.1 Hz, 1 H, H-4), 6.28 (dd, *J* = 8.4, 15.9 Hz, 1 H), 6.80 (d, *J* = 15.9 Hz, 1 H), 7.05–7.45 (m, 10 H).

ESI–MS: *m*/*z* = 264 $[M + 1]^+$, 549 $[2 \times M + Na]^+$.

***trans*-3-Ethyl-1-phenyl-4-(*trans*-styryl)azetidin-2-one[4a] (3r)**
Colorless oil.

IR (film): 1754 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.09 (t, *J* = 7.4 Hz, 3 H), 1.83 (m, 1 H), 1.94 (m, 1 H), 3.06 (m, 1 H, H-3), 4.33 (dd, *J* = 1.9, 8.4 Hz, 1

H, H-4), 6.30 (dd, *J* = 8.4, 15.9 Hz, 1 H), 6.78 (d, *J* = 15.9 Hz, 1 H), 7.03–7.50 (m, 10 H).

ESI–MS: *m*/*z* = 278 $[M + 1]^+$, 577 $[2 \times M + Na]^+$.

***trans*-4-Isopropyl-3-methyl-1-(4-methoxyphenyl)azetidin-2-one[4b] (3s)**
Colorless oil.

IR (film): 1749 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.05 (m, 6 H), 1.48 (d, *J* = 7.4 Hz, 3 H), 2.45 (m, 1 H, H-3), 3.12 (dq, *J* = 2.2, 1.4 Hz, 1 H), 3.74 (s, 3 H), 4.61 (m, 1 H), 6.71–7.22 (m, 4 H).

ESI–MS: *m*/*z* = 234 $[M + 1]^+$.

***anti*-3-[3-(2-Methoxyanilino)-2-methyl-3-phenylpropionyl]spiro[2*H*-1,3-benzoxazine-2,1′-cyclohexan]-4(3*H*)-one (5a)**
White crystal; mp 176–178 °C.

IR (KBr): 3380, 1718, 1678 cm^{-1}.

^1H NMR (125 MHz, $CDCl_3$): δ = 1.08 (d, *J* = 7.9 Hz, 3 H), 1.40–2.30 (m, 10 H), 3.61 (qd, *J* = 7.9 Hz, *J* = 9.9 Hz, 1 H), 3.83 (s, 3 H), 4.60 (d, *J* = 9.9 Hz, 1 H), 6.47–8.05 (m, 13 H).

^{13}C NMR (500 MHz, $CDCl_3$): δ = 16.79, 22.56, 22.65, 24.55, 32.79, 33.10, 51.08, 55.96, 61.97, 95.88, 110.02, 111.18, 116.34, 117.43, 117.74, 121.42, 122.48, 127.57, 127.77, 128.60, 136.15, 137.22, 141.82, 147.03, 155.68, 164.02, 183.26.

ESI–MS: *m*/*z* = 485 $[M + 1]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{30}H_{33}N_2O_4^+$: 485.2435; found: 485.2438.

***anti*-3-[3-(2-Methoxyanilino)-3-(4-methoxyphenyl)-2-methylpropionyl]spiro[2*H*-1,3-benzoxazine-2,1′-cyclohexan]-4(3*H*)-one (5b)**
White crystal; mp 185–187 °C.

IR (KBr): 3385, 1715, 1679 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.08 (d, *J* = 6.8 Hz, 3 H), 1.40–2.30 (m, 10 H), 3.52 (qd, *J* = 6.8 Hz, *J* = 9.9 Hz, 1 H), 3.73 (s, 3 H), 3.82 (s, 3 H), 4.54 (d, *J* = 9.9 Hz, 1 H), 5.80 (br s, 1 H), 6.42–8.04 (m, 12 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.78, 22.56, 22.63, 24.48, 33.01, 33.15, 51.08, 55.96, 55.90, 61.97, 95.86, 110.02, 111.18, 116.34, 117.43, 117.74, 121.42, 122.48, 127.57, 127.77, 128.60, 136.15, 137.22, 141.82, 147.03, 155.68, 164.02, 183.26.

ESI–MS: *m*/*z* = 515 $[M + 1]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{31}H_{35}N_2O_5^+$: 515.2540; found: 515.2538.

***anti*-3-[3-(2-Methoxyanilino)-3-(4-chlorophenyl)-2-methylpropionyl]spiro[2*H*-1,3-benzoxazine-2,1′-cyclohexan]-4(3*H*)-one (5c)**
White crystal; mp 174–176 °C.

IR (KBr): 3388, 1718, 1678 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.08 (d, *J* = 6.9 Hz, 3 H), 1.40–2.30 (m, 10 H), 3.54 (qd, *J* = 6.9 Hz, *J* = 9.9 Hz, 1 H), 3.83 (s, 3 H), 4.57 (d, *J* = 9.9 Hz, 1 H), 5.90 (br s, 1 H), 6.35–8.04 (m, 12 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.79, 22.56, 22.61, 24.53, 32.84, 33.10, 50.78, 55.94, 61.35, 95.85, 110.05, 111.16, 116.68, 117.45, 117.64, 121.36, 122.53, 128.58, 128.82, 129.12, 136.24, 136.90, 140.48, 147.08, 155.65, 164.06, 182.85.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{30}H_{32}ClN_2O_4^+$: 519.2045; found: 519.2037.

***anti*-3-[3-(2-Methoxyanilino)-3-(4-fluorophenyl)-2-methylpropionyl]spiro[2*H*-1,3-benzoxazine-2,1′-cyclohexan]-4(3*H*)-one (5d)**
White crystal; mp 167–170 °C.

IR (KBr): 3383, 1714, 1675 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.07 (d, *J* = 6.8 Hz, 3 H), 1.40–2.30 (m, 10 H), 3.58 (qd, *J* = 6.8 Hz, *J* = 9.9 Hz, 1 H), 3.84 (s, 3 H), 4.58 (d, *J* = 9.9 Hz, 1 H), 6.40–8.04 (m, 12 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.81, 22.56, 22.63, 24.54, 32.83, 33.10, 51.02, 55.95, 61.28, 95.87, 110.04, 111.15, 115.42, 115.59, 116.55, 117.45, 117.68, 121.38, 122.53, 128.59, 129.19, 129.26, 136.23, 137.02, 147.06, 155.66, 161.32, 163.26, 164.07, 183.01.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{30}H_{32}FN_2O_4^+$: 503.2341; found: 503.2338.

***anti*-3-[3-(2-Methoxyanilino)-2,4-dimethylpentanoyl]spiro[2*H*-1,3-benzoxazine-2,1′-cyclohexan]-4(3*H*)-one (5e)**
Colorless oil.

IR (film): 3424, 2932, 1718, 1683 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.7 Hz, 6 H), 1.33 (d, *J* = 6.7 Hz, 3 H), 1.50–2.15 (m, 11 H), 3.43 (qd, *J* = 6.8 Hz, *J* = 8.9 Hz, 1 H), 3.64 (dd, *J* = 3.5 Hz, *J* = 8.9 Hz, 1 H), 3.80 (s, 3 H), 4.70 (br s, 1 H), 6.54–7.99 (m, 8 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.43, 16.57, 21.05 22.51 24.44, 30.84, 32.91, 33.34, 47.99, 55.90, 62.12, 95.90, 110.05, 110.68, 115.62, 117.36, 121.52, 122.36, 128.51, 135.88, 139.56, 146.34, 155.51, 163.62, 183.99.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{27}H_{35}N_2O_4^+$: 451.2591; found: 451.2588.

***anti*-3-[2-{(2-methoxyanilino)(phenyl)methyl}-butanoyl]-spiro[2*H*-1,3-benzoxazine-2,1′-cyclohexan]-4(3*H*)-one (5f)**
Yellow crystal; mp 157–160 °C.

IR (KBr): 3380, 1718, 1678 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 7.5 Hz, 3 H), 1.49–2.43 (m, 12 H), 3.76 (m, 1 H), 3.82 (s, 3 H), 4.64 (t, *J* = 8.5 Hz, 1 H), 6.04 (d, *J* = 7.6 Hz, 1 H), 6.40–8.04 (m, 13 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 11.71, 22.62, 22.69, 24.36, 24.54, 32.71, 33.24, 56.05, 56.58, 59.93, 96.16, 110.11, 110.79, 116.09, 117.36, 117.81, 121.46, 122.42, 127.40, 127.71, 128.54, 128.66, 136.09, 137.51, 141.95, 147.05, 155.52, 164.21, 181.83.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{31}H_{35}N_2O_4^+$: 499.2591; found: 499.2595.

***anti*-3-[2-{(2-Methoxyanilino)(4-chlorophenyl)methyl}butanoyl]spiro[2*H*-1,3-benzoxazine-2,1′-cyclohexan]-4(3*H*)-one (5g)**
Colorless oil.

IR (KBr): 3376, 2934, 1716, 1681 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 7.4 Hz, 3 H), 1.49–2.43 (m, 12 H), 3.75 (m, 1 H), 3.82 (s, 3 H), 4.62 (t, *J* = 8.1 Hz, 1 H), 6.04 (d, *J* = 7.3 Hz, 1 H), 6.40–8.04 (m, 12 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 11.75, 22.63, 22.69, 24.39, 24.55, 32.82, 33.28, 56.03, 56.33, 59.38, 96.16, 110.13, 110.78, 116.45, 117.41, 117.67, 121.41, 122.49, 128.63, 128.76, 129.13, 133.05, 136.26, 137.21, 140.63, 147.11, 155.51, 164.31, 181.39.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{31}H_{34}ClN_2O_4^+$: 533.2202; found: 533.2199.

***anti*-3-[3-(2-Methoxyanilino)-2-ethyl-4-methylpentanoyl]-spiro[2*H*-1,3-benzoxazine-2,1′-cyclohexan]-4(3*H*)-one (5h)**
Colorless oil.

IR (film): 3424, 2932, 1718, 1683 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.96 (m, 9 H), 1.47–2.32 (m, 13 H), 3.60 (m 2 H), 3.07 (s, 3 H), 4.70 (d, *J* = 9.6 Hz, 1 H), 6.54–7.99 (m, 8 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 11.83, 18.03, 21.33, 22.66, 22.67 24.08, 24.46, 31.76, 32.97, 33.09, 53.02, 55.98, 59.65, 96.06, 110.12, 115.19, 117.38, 118.03, 121.53, 122.46, 128.64, 135.92, 139.90, 146.44, 155.41, 163.73, 182.53.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{28}H_{37}FN_2O_4^+$: 465.2748; found: 465.2745.

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References

(1) Bose, A. K.; Banik, B. K.; Manhas, M. S. *Tetrahedron Lett.* **1995**, *36*, 213.
(2) Clader, J. W. *J. Med. Chem.* **2004**, *47*, 1.
(3) (a) Alcaide, B.; Vicente-Rodriguez, A. *Tetrahedron Lett.* **1998**, *39*, 6589. (b) Alcaide, B.; Vicente-Rodriguez, A. *Tetrahedron Lett.* **1999**, *40*, 2005.
(4) (a) Hart, D. J.; Ha, D. C. *Chem. Rev.* **1989**, *89*, 1447. (b) Chen, L.; Zhao, G.; Ding, Y. *Tetrahedron Lett.* **2003**, *44*, 2611.
(5) Cainelli, G.; Panunzio, M.; Bandini, E.; Martelli, G.; Spunta, G. *Tetrahedron* **1996**, *5*, 1685.
(6) Kondo, K.; Seki, M.; Kuroda, T.; Yamanaka, T.; Iwasaki, T. *J. Org. Chem.* **1997**, *62*, 2877.
(7) Kagan, H. B.; Basselier, J. J.; Luche, J. L. *Tetrahedron Lett.* **1964**, *16*, 941.
(8) (a) Cainelli, G.; Panunzio, M.; Bandini, E.; Martelli, G.; Spunta, G. *Tetrahedron* **1996**, *5*, 1685. (b) Fukuzawa, S. I.; Matsuzawa, H.; Yoshimitsu, S. I. *J. Org. Chem.* **2000**, *65*, 1702.
(9) Adrian, J. C. Jr.; Barkin, J. L.; Hassib, L. *Tetrahedron Lett.* **1999**, *40*, 2457.
(10) Townes, J. A.; Evans, M. A.; Queffelec, J.; Taylor, S. J.; Morken, J. P. *Org. Lett.* **2002**, *4*, 2537.