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[2+2] Cycloaddition reactions of 1-benzyl-2,4-diphenyl-1,3-diazabuta-1,3-diene with chiral ketenes

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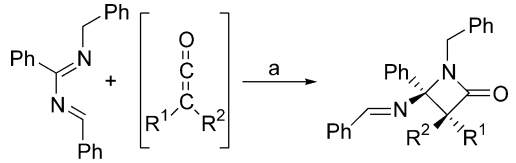
Abstract—The [2+2] cycloaddition reactions of 1-benzyl-2,4-diphenyl-1,3-diaza-1,3-butadiene with β-(dimethylphenylsilyl)ketene, β-menthoxyketene and Evans–Sjögren ketene were investigated. The results and some chemical transformations of the obtained cycloadducts are reported. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

Recently, we reported that cycloaddition reactions of 1-benzyl-1,3-diazabuta-1,3-diene **1a** with ketenes **2a**–**h** proceed directly to [2+2] cycloaddition products giving rise to the 1-benzyl-4-(benzylidene-amino)-4-phenyl-azetidin-2-ones **3a**–**h** in good yields, Scheme 1, Table 1.[1]

Moreover, diastereoselectivity for the cycloaddition reactions involving monosubstituted ketenes was demonstrated by ^{1}H NMR spectra analysis and NOE-difference experiments, performed for azetidinones **3a**,**c**,**d**,**f**, showing the presence of a single diastereomer with *cis* relationship between the benzylidene-amino group at C-4 and the hydrogen at C-3.



1a **2a-h** **3a-h**

Scheme 1. *Reagents and conditions*: (a) TEA, toluene, 0°C to rt, 3–24 h.

Table 1. Compounds **3a**–**h**

	R^1	R^2	Yield (%)
3a	Ph	H	57
3b	Ph	Ph	64
3c	Cl	H	71
3d	CH=CH_2	H	78
3e	Me	Me	54
3f	OMe	H	73
3g	Cl	Cl	65
3h	N_3	H	95

The diastereoselectivity achieved in these reactions prompted us to extend our investigations to the enantioselective synthesis of azetidin-2-ones as potential useful building blocks for natural products and the preparation of biologically active compounds.[2]

2. Results and discussion

Over the past years exciting results have been obtained in the enantioselective synthesis of β-lactams, performing the Staudinger[3] reaction with imines and different monosubstituted chiral ketenes.[4] Among these we choose to test the reactivity of β-silylalkylketene **2i**[5], β-menthoxyketene **2j**[6] and Evans–Sjögren ketenes **2k**,**l**[7] with **1a** in order to obtain β-lactams bearing a trisubstituted stereogenic center at the C(3) position and a quaternary stereogenic center at C(4), Scheme 2.

The reaction between **1a** and ketene **2i**, generated in situ from the corresponding acid chloride and triethylamine, was performed in dry toluene at 0°C, Scheme 2. The reaction products were separated by flash chromatography and further purified by crystallization.

1-Benzyl-4-(benzylidene-amino)-3-[(dimethyl-phenyl-silanyl)-phenyl-methyl]-4-phenyl-azetidin-2-ones **3j** and **k** were obtained with a total yield of 75% and with a de of 10%. The absolute configurations around C3 and C4 of **3j** and **k** were tentatively assigned as (3*R*,4*R*,3′*R*) and (3*S*,4*S*,3′*R*), respectively, through combined NMR spectroscopy (^{1}H NMR, COSY and NOESY) and conformational analysis experiments,[8] Fig. 1.

Keywords: [2+2] cycloaddition; 1,3-diaza-1,3-butadiens; chiral ketenes; azetidin-2-ones.

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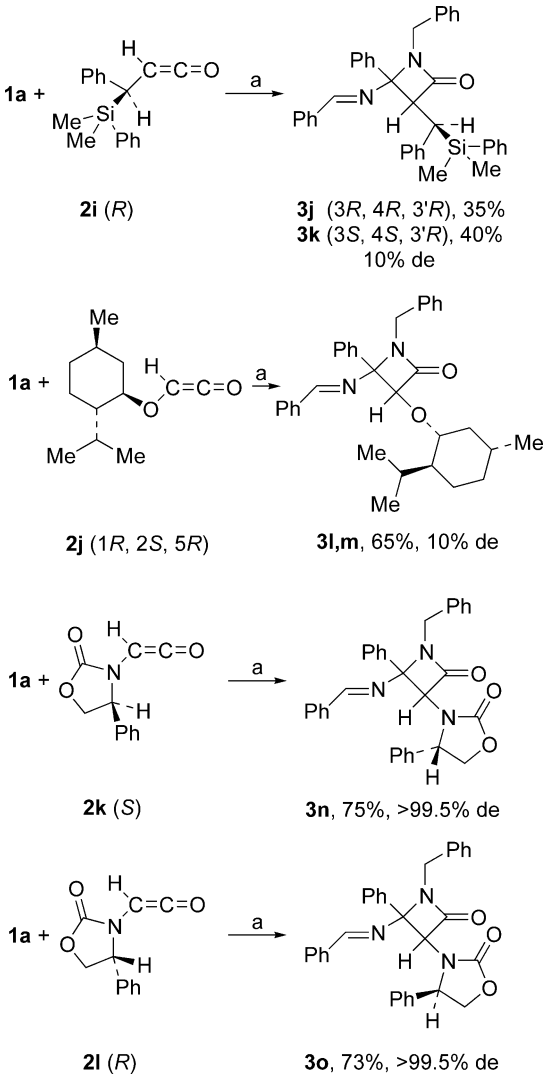


Scheme 2. *Reagents and conditions*: (a) TEA, toluene, 0°C to rt, 24 h.

The ^{1}H NMR spectrum of compound **3k** showed two doublets at 3.70 and 2.53 ppm with J=6.6 Hz, which can be easily attributed, on the basis of COSY analysis, to C3–H and Cα–H, respectively. Moreover, proton–proton NOE interactions were observed between C3–H and Cα–H and C3–H and CH=N. Conformational analysis, performed for the rotation around the C3–Cα bond with AM1 semi-empirical SCF computational method,[9] predicts a minimum for a set of conformers with dihedral angle H–C3–Cα–H ranging from −110 to −70°, Fig. 1. These values applied to the Karplus equation provide a theoretical $^3J_{H-C3-C\alpha-H}$ of 0–7 Hz.

In contrast, the ^{1}H NMR of compound **3j** showed for C3–H and Cα–H two doublets centered at 3.68 and 2.43 ppm, respectively, with J=13.4 Hz. However, for **3j**, proton–proton NOE interactions were observed only between C3–H and CH=N. Moreover, conformational analysis performed for the rotation around the C3–Cα bond predicts a minimum for a set of conformers with dihedral angle H-C3-Cα-H ranging from 140 to 180°, corresponding to a calculated $^3J_{H-C3-C\alpha-H}$ of 7–15 Hz, Fig. 1. All the obtained results are in agreement with the reported structures for **3j** and **k**.

Similar results were obtained when **1a** was reacted, under the same conditions, with ketene **2j**, Scheme 2. The reaction affords, after usual purification procedures, 1-benzyl-4-(benzylidene-amino)-3-menthoxy-4-phenyl-azetidin-2-ones **3l** and **m** in 65% yield and with a de of 10%. However, due to the complexity of the menthoxy substituent, stereochemical assignments have been made, by means of NOESY experiment, only for C3–H and CH=N substituents which also in this case result in a *cis* relationship.

Finally, the reactions of **1a** with (4*S*) and (4*R*)-3-(2-oxo-vinyl)-4-phenyl-oxazolidin-2-ones **2k** and **l**, run under the usual reaction conditions, gave in both cases a single

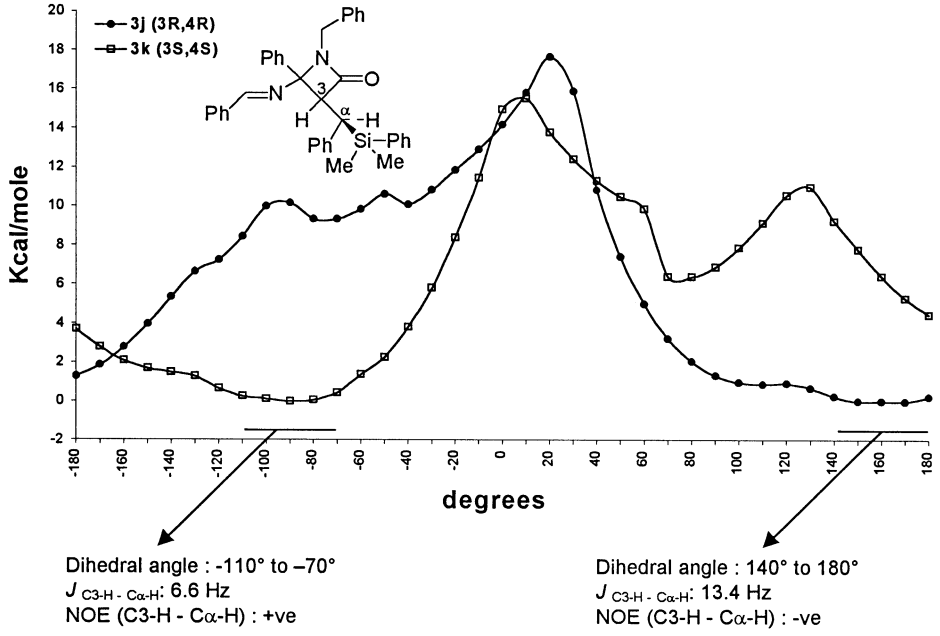
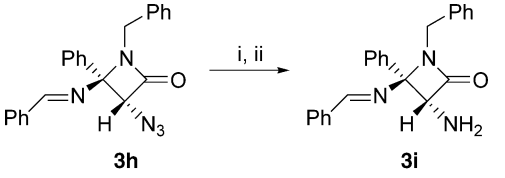


Figure 1. C3H–CαH rotational energy chart for the diastereoisomers **3j** and **k**.

β-lactam product as demonstrated by ^{1}H NMR spectroscopic analysis of the corresponding crude reaction mixtures. After usual purification procedures, the azetidin-2-ones **3n** (from **2k**) and **3o** (from **2l**) were obtained in 73–75% yields and with a de>99.5%. Also in this case, the NOESY experiment showed a *cis* relationship between C3–H and CH=N moiety, Scheme 2.

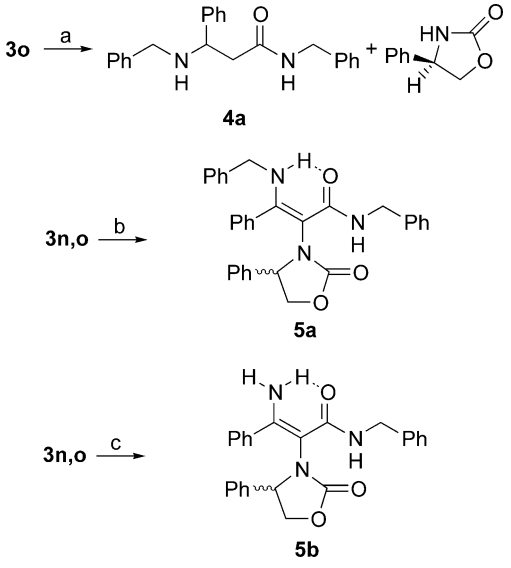
As reported in the literature, the Evans–Sjögren ketene has been widely used to perform highly diastereoselective cycloadditions,[10] moreover this chiral auxiliary acts also as a N-protecting group, yielding by reductive Birch cleavage, enantiomerically pure 3-amino-azetidin-2-ones.[11] Thus, starting from **3n** and **o**, our goal was to synthesize enantiomerically pure 3-amino-1-benzyl-4-(benzylidene-amino)-4-phenyl-azetidin-2-one **3i** which was already obtained as a racemate by treatment of **3h** with Triphenylphosphine,[12] Scheme 3.



Scheme 3. *Reagents and conditions*: (i) Ph_3P, THF, rt; (ii) H_2O, 65%.

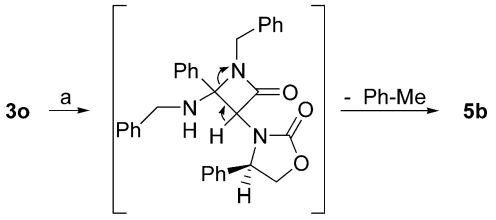
However, Birch reduction of **3o** yields, by C=N double bond reduction and 4-phenyl-oxazolidinone elimination, the *N*-benzyl-3-benzylamino-3-phenylpropionamide **4a** and 4-phenyl-oxazolidinone as a mixture of inseparable compounds, Scheme 4.

As reported in the literature,[7,11a] catalytic C=C double bond reduction as well as Birch cleavage of both the *N*-benzyl group and the oxazolidinone moiety can be successfully performed for some 1-benzyl-3-(4-phenyloxazolidinyl)-4-styryl-azetidin-2-ones. However, in our case, catalytic hydrogenation of **3n** or **o** gave, in nearly quantitative yields, the *N*-benzyl-3-benzylamino-2-(2-oxo-4-phenyl-oxazolidin-3-yl)-3-phenyl-acrylamide **5a** when the reaction was performed with anhydrous ammonium formate in methanol[13], and the 3-amino-*N*-benzyl-2-(2-oxo-4-phenyl-oxazolidin-3-yl)-3-phenyl-acrylamide **5b** when the reaction was performed under hydrogen atmosphere in methylene chloride, Scheme 4. Failing the NOE experiments, the *cis* relationship between amino and amido groups in the phenyl-acrylamides **5a** and **b** was assigned on the basis of the likely hydrogen bond. This assumption was confirmed by the unexpectedly high chemical shift of amino group for **5a** (δ=10.18) and **5b** (δ=6.83–7.14, obscured by aromatic protons).



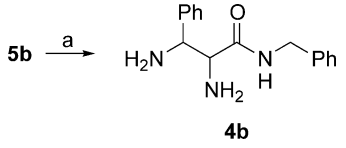
Scheme 4. *Reagents and conditions*: (a) Li, NH_3, THF/*t*-BuOH 10:1, −78°C, 2 min., 62%. (b) HCO_2NH_4, Pd/C, MeOH, reflux, 94%. (c) H_2 (760 Torr), Pd/C, CH_2Cl_2, rt, 90–95%.

Both reactions proceed through the intermediacy of an unstable *gem*-diamine as demonstrated by the $NaBH_4$ selective reduction of the C=N double bond[14] of **3o** which also affords **5b**, Scheme 5.



Scheme 5. *Reagents and conditions*: (a) $NaBH_4$, THF, rt, 48%.

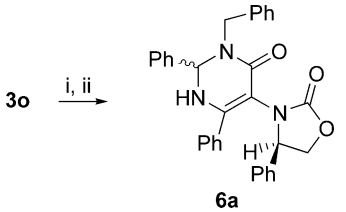
Moreover, Birch reduction of **5b** results in the isolation of 2,3-diamino-*N*-benzyl-3-phenyl-propionamide **4b**, Scheme 6.



Scheme 6. *Reagents and conditions*: (a) Li, NH_3, THF/*t*-BuOH 10:1, −78°C, 2 min, 98%.

The instability of azetidin-2-ones **3n**,**o** to reductive conditions prompted us to extend our investigations to other simple techniques for removing the chiral auxiliary.

Easy removal of the oxazolidinone with trimethylsilyliodide has been described[15] for sensitive β-lactams. Thus treatment of **3o** with TMSI/HMDS and DBU yielded exclusively the 3-benzyl-5-(2-oxo-4-phenyl-oxazolidin-3-yl)-2,6-diphenyl-2,3-dihydro-1*H*-pyrimidin-4-one **6a**, as a single diastereomer (see below), Scheme 7.



Scheme 7. *Reagents and conditions*: (i) TMSI, HMDS, CH_3CN, rt; (ii) DBU, 0°C to rt, 90%.

The structure of **6a** was assigned on the basis of analytical and spectroscopic data. In particular, elemental analysis and EI-MS are in agreement with a molecular formula of $C_{32}H_{27}N_3O_3$ and a molecular weight of 501 Da. The ^{1}H NMR spectrum showed the disappearance of the azomethinic proton at δ_H 8.26 and a doublet for C2–H centred at $-_H$ 5.49, with J=1.1 Hz, which collapse to a singlet by treatment with D_2O. ^{13}C APT showed the presence of seven quaternary C_{sp2} carbons and NOESY and HMBC interactions (Fig. 2) are consistent with the proposed structure. Finally, COSY and HETCOR experiments permit the complete assignment of both ^{1}H and ^{13}C NMR spectroscopic resonances.

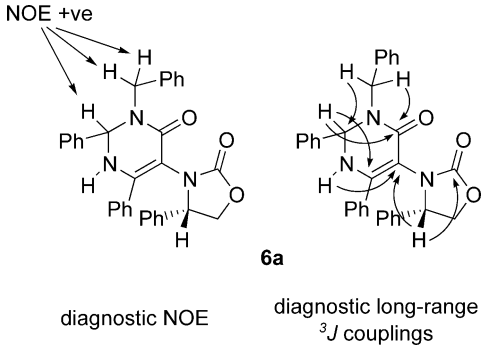
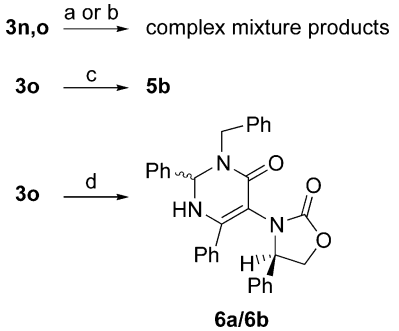


Figure 2.

Moreover, we tested the reactivity of **3n**,**o** under oxidative (CAN[16], $K_2S_2O_8$[17]) and hydrolytic (LiOH, HCl) conditions. However, both CAN and $K_2S_2O_8$ gave complex reaction mixtures, whereas the reaction performed with LiOH in H_2O/THF afforded, starting from **3o**, by base catalyzed hydrolysis of the C=N double bond and azetidinone ring opening, the 3-phenylpropenamide **5b**, Scheme 8.

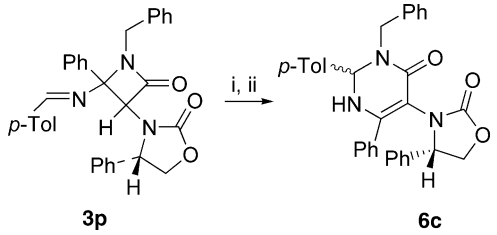
Finally, hydrolysis of **3o** with 6N HCl results in the isolation (80%) of a 1:1 diastereomeric mixture of **6a** and **b**, which were easily separated by flash chromatography, Scheme 8.



Scheme 8. *Reagents and conditions*: (a) CAN, H_2O/THF,rt. (b) $K_2S_2O_8$, THF, rt. (c) LiOH, H_2O/THF, rt, 93%. (d) HCl 6N, rt, 81%.

In our opinion, the mechanism involved in the HCl or TMSI mediated reactions involves, starting from azetidin-2-one **3o**, proton or TMSI addition to the C=N double bond followed by cleavage of the N–C4 bond and cyclization of an open chain intermediate. Finally, appropriate work-up of the reaction mixture resulted in the isolation of pyrimidinones **6**. It is worth noting that, in the reaction performed with TMSI, the cyclization step is affected by the presence on the nitrogen atom of a bulky TMS group, which induces the formation of a single diastereoisomer.

An alternative reaction pathway involving C3–C4 bond breaking was ruled out by performing the TMSI mediated reaction with the azetidin-2-one **3p** bearing a 4-methylphenyl substituent at the imino residue. As depicted in Scheme 9, the pyrimidinone **6c** was the sole reaction product.



Scheme 9. *Reagents and conditions*: (i) TMSI, HMDS, CH_3CN, rt; (ii) DBU, 0°C to rt, 83%.

Although our goal of synthesizing new optically active β-lactams has not been completely achieved, we consider noteworthy the new features accomplished in the field of β-lactams and oxazolidinone substituted β-lactams.

3. Experimental

3.1. General details

All chemicals and solvents are commercially available and were used after distillation or treatment with drying agents. 'PE' refers to the fraction of petroleum ether with boiling point of 40–60°C. 'EtOAc' means ethyl acetate. 'TEA' means triethylamine. All organic solutions from work-ups were dried by exposure to anhydrous sodium sulfate for 20 min. Merck silica gel 60 F_{254} thin-layer plates were employed for thin layer chromatography. Merck silica gel (230–400 mesh) was employed for flash column chromatography. Melting points, measured with a Stuart Scientific SMP3 apparatus, are uncorrected. Infrared spectra were recorded on a FT-IR Perkin Elmer 16 PC spectrophotometer, using thin films between NaCl plates in the cases of liquid samples and KBr tablets for solid samples. NMR chemical shifts are reported in parts per million (ppm). Coupling constants (J) are reported in Hertz (Hz). Unless otherwise stated, proton NMR spectra were recorded in $CDCl_3$, on Varian-Gemini 200 or Bruker 300 Avance spectrometers, at 200 or 300 MHz, with residual chloroform as the internal reference (δ_H=7.27 ppm). J_{vic} is referred to a vicinal coupling. J_{gem} is referred to as geminal coupling. Unless otherwise stated, ^{13}C NMR spectra were recorded in $CDCl_3$, on the same spectrometers, at 50.3 or 75.4 MHz, with the central peak of chloroform as the internal reference (δ_C=77.3 ppm). The APT sequence was used to distinguish the methine and methyl carbon signals from those due to methylene and quaternary carbons. Two-dimensional NMR experiments (COSY, HETCOR, HMBC and NOESY) were used, where appropriate, to aid in the assignment of signals in the proton and ^{13}C NMR spectra. Low-resolution mass spectra were run on a

Finnigam TSQ-700 spectrometer using CI method. The specific rotations were performed on a Perkin–Elmer 241 polarimeter. 1,3-Diaza-1,3-butadiene **1a**,**b**, ketenes **2a**–**g** and azetidinones **3a**–**g** are known compounds and were prepared according to described methods[1]. β-silylalkylketene **2i**, β-menthoxyketene **2j** and Evans–Sjögren ketenes **2k**,**l** formally derived from, respectively, 3(*S*)-(dimethylphenylsilyl)-3-phenyl-propionyl chloride[4], menthoxy-acetyl chloride[5] and (2-oxo-4-phenyl-oxazolidin-3-yl)-acetyl chloride[6] were synthesized in agreement to reported literature.

3.2. 1-Benzyl-4-(benzylidene-amino)-4-phenyl-azetidin-2-ones 3h,i–p

A solution of appropriate acyl chloride (1.2 mmol) in dry toluene (8 mL) was added slowly (over a period of 1 h) to a nitrogen flushed, well stirred and ice-water cooled solution of 1,3-diaza-1,3-butadiene **1a** or **b** (1.0 mmol) and triethylamine (2.3 mmol) in dry toluene (14 mL). After complete addition of acyl chloride, the reaction mixture was stirred for 3–24 h at room temperature. It was then thoroughly washed first with a cold saturated solution of $NaHCO_3$ (14 mL) and then with cold water (15 mL). The organic layer was dried over anhydrous Na_2SO_4 and freed from solvent under reduced pressure at 40°C. The crude product was purified by crystallisation and/or by flash chromatography.

3.2.1. 3-Azido-1-benzyl-4-(benzylidene-amino)-4-phenyl-azetidin-2-one 3h. Reaction time: 3 h; purified by crystallization; yield 86%; white solid; mp 112–113°C (PE); ^{1}H NMR (200 MHz): 3.93 (d, 1H, CH_2, J_{gem}=15.0 Hz), 4.93 (d, 1H, CH_2, J_{gem}=15.0 Hz), 4.55 (s, 1H, CH) 7.17–7.59 (m, 13H, arom.), 7.60–7.66 (m, 2H, arom.), 7.92 (s, 1H, CH=N); ^{13}C NMR (50.3 MHz): 45.3 (CH_2), 77.1 (CH), 87.9 (N–C–N), 128.1, 128.6, 128.7, 128.8, 128.9, 129.0, 129.3, 129.4, 131.9 (CH arom.), 134.9, 135.0, 136.4 (C arom.), 159.8 (CH=N), 164.3 (C=O); IR (KBr, cm^{-1}): 1642 (ν C=N), 1756 (ν C=O), 2108 (ν N_3); elem. anal., found (calcd for $C_{23}H_{19}N_5O$): C 72.25 (72.42), H 4.96 (5.02), N 18.39 (18.36).

3.2.2. (3*R*,4*R*,3′*R*)-1-Benzyl-4-(benzylidene-amino)-3-[(dimethyl-phenyl-silanyl)-phenyl-methyl]-4-phenyl-azetidin-2-one 3j. Reaction time: 24 h; purified by flash chromatography (PE/EtOAc 95:5); yield 35%; white solid; mp 154–155°C (diisopropyl ether); ^{1}H NMR (200 MHz): 0.19 (s, 3H, CH_3–Si), 0.46 (s, 3H, CH_3–Si), 2.43 (d, 1H, CH–Si, J_{vic}=13.4 Hz), 3.68 (d, 1H, J_{vic}=13.4 Hz, CH–C=O), 3.84 (d, 1H, CH_2, J_{gem}=15.0 Hz), 4.91 (d, 1H, CH_2, J_{gem}=15.0 Hz), 6.22 (d, 2H, *J*=6.4 Hz, arom.), 6.80–7.01 (m, 4H, arom.), 7.12–7.43 (m, 19H, arom.), 7.74 (s, 1H, CH=N); ^{13}C NMR (50.3 MHz): −2.6, −2.1 (CH_3), 34.2 (CH–Si), 44.8 (CH_2), 68.8 (*C*H–C=O), 87.4 (N–C–N), 124.7, 127.5, 127.6, 127.8, 127.9, 128.1, 128.2, 128.5, 128.7, 128.9, 129.2, 129.5, 131.2, 135.0 (CH arom.; one signal obscured), 135.9, 136.9, 137.6, 140.6 (C arom.; one signal obscured), 157.9 (CH=N), 169.7 (C=O); IR (KBr, cm^{-1}): 1648 (ν C=N), 1748 (ν C=O); elem. anal., found (calcd for $C_{38}H_{36}N_2OSi$): C 80.40 (80.81), H 6.37 (6.42), N 5.03 (4.96).

3.2.3. (3*S*,4*S*,3′*R*)1-Benzyl-4-(benzylidene-amino)-3-[(dimethyl-phenyl-silanyl)-phenyl-methyl]-4-phenyl-azetidin-2-one 3k. Reaction time: 24 h; purified by flash chromatography (PE/EtOAc 95:5); yield 40%; yellow oil; ^{1}H NMR (200 MHz): 0.06 (s, 3H, CH_3–Si), 0.32 (s, 3H, CH_3–Si), 2.53 (d, 1H, CH–Si, J_{vic}=6.6 Hz), 3.84 (d, 1H, CH_2, J_{gem}=15.0 Hz), 3.70 (d, 1H, CH–C=O, J_{vic}=6.6 Hz), 4.63 (d, 1H, CH_2, J_{gem}=15.0 Hz), 6.71 (m, 2H, arom.), 7.00–7.04 (m, 3H, arom.), 7.22–7.51 (m, 20H, arom.), 7.81 (s, 1H, CH=N); ^{13}C NMR (50.3 MHz): −4.1, −3.0 (CH_3), 35.0 (CH–Si), 45.0 (CH_2), 66.8 (*C*H–C=O), 87.1 (N–C–N), 124.9, 127.7, 127.9, 128.0, 128.3, 128.7, 128.8, 128.9, 129.0, 129.4, 131.5, 134.6 (CH arom.; three signals obscured), 135.7, 136.6, 137.0, 137.6, 139.7 (C arom.; one signal obscured), 158.0 (CH=N), 170.1 (C=O); IR (KBr, cm^{-1}): 1644 (ν C=N), 1750 (ν C=O); elem. anal., found (calcd for $C_{38}H_{36}N_2OSi$): C 80.31 (80.81), H 6.28 (6.42), N 4.58 (4.96).

3.2.4. 1-Benzyl-4-(benzylidene-amino)-3-menthoxy-4-phenyl-azetidin-2-one 3l. Reaction time: 24 h; purified by flash chromatography (PE/EtOAc 95:5); yield 29%; yellow oil; ^{1}H NMR (200 MHz): 0.76 (d, 6H, *CH*$_3$–CH–CH_3 and *CH*$_3$–CH(CH_2)$_2$, J_{vic}=7.0 Hz), 0.84 (d, 3H, CH_3–CH–*CH*$_3$, J_{vic}=7.0 Hz), 0.90–1.30 (m, 4H, CH_2 menthoxy), 1.40–1.60 (m, 4H, CH_2 and CH menthoxy), 2.19 (d sept., 1H, CH_3–*CH*–CH_3, J_{vic}=7.0 and 2.2 Hz), 3.19 (dt, 1H, CH–O menthoxy, J_{vic}=10.4 and 4.2 Hz), 3.71 (d, 1H, CH_2–Ph, J_{gem}=14.8 Hz), 4.38 (s, 1H, CH–C=O), 4.85 (d, 1H, CH_2–Ph, J_{gem}=14.8 Hz), 7.20–7.60 (m, 13H, arom.), 7.60–7.70 (m, 2H, arom.), 7.83 (s, 1H, Ph–CH=N); ^{13}C NMR (50.3 MHz): 16.8, 21.3, 22.5 (CH_3), 23.7, 34.6, 41.2 (CH_2 menthoxy), 25.9, 31.9, 48.5, (CH menthoxy), 45.0 (CH_2–Ph), 82.4 (CH–O menthoxy), 89.2 (N–C–N), 94.6, (*C*H–C=O), 128.2, 128.4, 128.7, 129.1, 129.3, 129.7, 129.9, 131.7 (CH arom.; one signal obscured), 136.0, 136.8, 137.4 (C arom.), 158.5 (CH=N), 168.5 (C=O); IR (NaCl, cm^{-1}): 1646 (ν C=N), 1766 (ν C=O), 1062 (ν C–O); elem. anal., found (calcd for $C_{33}H_{38}N_2O_2$): C 80.01 (80.13), H 7.89 (7.74), N 5.13 (5.66).

3.2.5. 1-Benzyl-4-(benzylidene-amino)-3-menthoxy-4-phenyl-azetidin-2-one 3m. Reaction time: 24 h; purified by flash chromatography (PE/EtOAc 95:5); yield 36%; yellowish oil; ^{1}H NMR (200 MHz): 0.25 (d, 3H, *CH*$_3$–CH–CH_3, J_{vic}=6.9 Hz), 0.60 (d, 3H, CH_3–CH–*CH*$_3$, J_{vic}=7.1 Hz), 0.86 (d, 3H, CH_3–CH(CH_2)$_2$, J_{vic}=6.4 Hz), 0.70–1.70 (m, 4H, CH_2 menthoxy), 1.40–1.60 (m, 4H, CH_2 and CH menthoxy), 2.06 (m, 1H, CH_3– *CH*(CH_2)$_2$), 3.01 (dt, 1H, CH–O menthoxy, J_{vic}=10.6 and 4.2 Hz), 3.76 (d, 1H, CH_2–Ph, J_{gem}=15.0 Hz), 4.47 (s, 1H, CH–C=O),4.86 (d, 1H, CH_2–Ph, J_{gem}=15.0 Hz), 7.22–7.57 (m, 13H, arom.), 7.65–7.70 (m, 2H, arom.), 7.84 (s, 1H, CH=N); ^{13}C NMR (50.3 MHz): 16.2, 21.3, 22.7 (CH_3), 23.3, 34.7, 40.9 (CH_2 menthoxy), 25.1, 31.9, 48.0, (CH menthoxy), 44.9 (CH_2–Ph), 81.4 (CH–O menthoxy), 89.4 (N–C–N), 92.7, (*C*H–C=O), 128.2, 128.6, 128.7, 129.1, 129.2, 129.5, 129.7, 129.8, 131.7 (CH arom.), 136.0, 136.6, 137.4 (C arom.), 158.5 (CH=N), 169.2 (C=O); IR (NaCl, cm^{-1}): 1062 (ν C–O), 1644 (ν C=N), 1766 (ν C=O); elem. anal., found (calcd for $C_{33}H_{38}N_2O_2$): C 80.54 (80.13), H 7.95 (7.74), N 5.50 (5.66).

3.2.6. (+)-1-Benzyl-4-(benzylidene-amino)-3-(2-oxo-4-phenyl-oxazolidin-3-yl)-4-phenyl-azetidin-2-one 3n. Reaction time: 24 h; purified by flash chromatography

(PE/EtOAc 7:3); yield 75%; white solid; mp 160°C; $[\alpha]^{21}_D$=+135° (*c* 0.006, $CHCl_3$); ^{1}H NMR (200 MHz): 4.00 (dd, 1H, CH_2 oxazolidinone, J_{vic}=7.3 Hz and J_{gem}=8.9 Hz), 4.33 (t, 1H, CH_2 oxazolidinone, J_{vic}=J_{gem}=8.9 Hz), 4.39 (d, 1H, CH_2–Ph, J_{gem}=15.4 Hz), 4.47 (s, 1H, CH–C=O), 4.77 (m, 2H, CH_2–Ph and CH oxazolidinone), 7.00–7.06 (dd, 2H, arom.), 7.19–7.44 (m, 16H, arom.), 7.53–7.58 (dd, 2H, arom.), 8.26 (s, 1H, CH=N); ^{13}C NMR (50.3 MHz): 45.5 (CH_2–Ph), 60.0 (CH oxazolidinone), 70.9 (CH_2 oxazolidinone), 72.6, (*C*H–C=O), 88.8 (N–C–N), 128.0, 128.2, 128.6, 128.9, 129.0, 129.1, 129.1, 129.2, 129.3, 129.4, 129.6, 132.0 (CH arom.), 135.2, 135.7, 137.2 (C arom.; one signal obscured), 157.6 (C=O oxazolidinone), 160.9 (CH=N), 169.2 (C=O); IR (NaCl, cm^{-1}): 1644 (ν C=N), 1756, 1775 (ν C=O); elem. anal., found (calcd for $C_{32}H_{27}N_3O_3$): C 76.54 (76.63), H 5.39 (5.43), N 8.42 (8.38).

3.2.7. (−)-1-Benzyl-4-(benzylidene-amino)-3-(2-oxo-4-phenyl-oxazolidin-3-yl)-4-phenyl-azetidin-2-one 3o. Reaction time: 24 h; purified by flash chromatography (PE/EtOAc 7:3); yield 73%; white solid; mp 159°C; $[\alpha]^{21}_D$=−133° (*c* 0.006, $CHCl_3$); ^{1}H NMR, ^{13}C NMR and IR data are identical to **3n**; elem. anal., found (calcd for $C_{32}H_{27}N_3O_3$): C 76.24 (76.63), H 5.36 (5.43), N 8.35 (8.38).

3.2.8. (+)-1-Benzyl-4-[(4-methyl-benzylidene-amino]-3-(2-oxo-4-phenyl-oxazolidin-3-yl)-4-phenyl-azetidin-2-one 3p. Reaction time: 24 h; purified by flash chromatography (PE/EtOAc 7:3); yield 83%; white solid; mp 85–88°C; $[\alpha]^{21}_D$=+149° (*c* 0.006, $CHCl_3$); ^{1}H NMR (200 MHz): 2.40 (s, 3H, CH_3), 4.00 (dd, 1H, CH_2 oxazolidinone, J_{vic}=7.3 Hz and J_{gem}=8.8 Hz), 4.34 (t, 1H, CH_2 oxazolidinone, J_{vic}=J_{gem}=8.8 Hz), 4.41 (d, 1H, CH_2–Ph, J_{gem}=15.4 Hz), 4.49 (s, 1H, CH–C=O), 4.73 (d, 1H, CH_2=Ph, J_{gem}=15.4 Hz), 4.80 (dd, 1H, CH oxazolidinone, J_{vic}=7.3 and 8.8 Hz), 7.02–7.07 (dd, 2H, arom.), 7.17–7.38 (m, 16H, arom.), 7.47 (d, 2H, arom. *p*-tolyl, *J*=8.1 Hz), 8.24 (s, 1H, CH=N); ^{13}C NMR (50.3 MHz): 21.6 (CH_3), 45.1 (CH_2–Ph), 59.7, (CH oxazolidinone), 70.5 (CH_2 oxazolidinone), 72.2, (*C*H–C=O), 88.4 (N–C–N), 127.6, 127.8, 128.3, 128.5, 128.6, 128.7, 128.8, 128.9, 129.0, 129.2, 129.4 (CH arom.), 132.9, 135.0, 136.8, 139.9, 142.1 (C arom.), 157.3 (C=O oxazolidinone), 160.4 (CH=N), 163.5 (C=O); IR (NaCl, cm^{-1}): 1637 (ν C=N), 1759, 1779 (ν C=O); elem. anal., found (calcd for $C_{33}H_{29}N_3O_3$): C 76.81 (76.87), H 5.61 (5.67), N 8.22 (8.15).

3.3. 3-Amino-1-benzyl-4-(benzylidene-amino)-4-phenyl-azetidin-2-one 3i

Triphenylphosphine[12] (0.068 g, 0.26 mmol) was added to a solution of **3h** (0.1 g, 0.26 mmol) in THF (0.5 mL) containing one little boiling-stone to regularize the effervescence (N_2). When the effervescence ceased, water (0.02 mL, 1.11 mmol) was added and the reaction mixture left at room temperature overnight. The reaction crude was then diluted with ethyl acetate (10 mL) and washed with a saturated solution of $NaHCO_3$ (3×15 mL). The organic layer was dried and freed from solvent under reduced pressure at 40°C. The crude product was purified by flash chromatography (PE/EtOAc 4:6); yield 65%; yellow oil; ^{1}H NMR (200 MHz): 1.49 (bs, 2H, NH_2), 3.87 (d, 1H, CH_2, J_{gem}=15.0 Hz), 4.96 (d, 1H, CH_2, J_{gem}=15.0 Hz), 4.09 (s, 1H, CH) 7.20–7.58 (m, 13H, arom.), 7.60–7.67 (m, 2H, arom.), 7.91 (s, 1H, CH=N); ^{13}C NMR (50.3 MHz): 44.9 (CH_2), 75.8 (CH), 90.0 (N–C–N), 127.5, 127.9, 128.1, 128.5, 128.7, 128.9, 129.1, 129.4, 131.3 (CH arom.), 135.5, 136.9, 137.1 (C arom.), 158.1 (CH=N), 170.5 (C=O); IR (KBr, cm^{-1}): 1645 (ν C=N), 1756 (ν C=O), 3302, 3366 (ν NH_2); elem. anal., found (calcd for $C_{23}H_{21}N_3O$): C 77.54 (77.72), H 5.78 (5.96), N 11.95 (11.82).

3.4. Birch reduction[7,11a] of 3o and 5b

To a well stirred dark-blue solution of lithium shots (0.033 g, 4.8 mmol) in liquid ammonia (9 mL), cooled at −78°C, a solution of **3o** or **5b** (0.40 mmol) in Bu^t–OH/THF 1:10 (3 mL) was added, and the mixture was stirred at −78°C for 3 min. The lithium excess was quenched with solid ammonium chloride (12 equiv., 0.26 g) whereas the ammonia was allowed to distil from the reaction mixture at room temperature. The residual solvents were then removed under reduced pressure and the reaction mixture treated with water (8 mL), acidified with HCl 3N to pH 3 for 3 min, basified with NaOH 2N to pH 10 and finally extracted with methylene chloride. The organic layer was dried and freed from solvent under reduced pressure at 40°C giving rise to crude propionamides **4a** or **b**.

3.4.1. *N*-Benzyl-3-benzylamino-3-phenylpropionamide 4a. Purified by flash chromatography (PE/AcOEt/TEA 6:2:2); yield 62%; yellowish oil (lit. 92–93°C);[18] ^{1}H NMR (200 MHz): 2.00 (bs, 1H, NH amine), 2.45–2.69 (m, 2H, 2nd order system, CH–CH_2–C=O), 3.48 (d, 1H, Ph–CH_2–NH–CH, J_{gem}=12.7 Hz), 3.61 (d, 1H, Ph–CH_2–NH–CH, J_{gem}=12.7 Hz), 4.04 (dd, 1H, CH, J_{vic}=4.1 and 9.8 Hz), 4.40 (m, 2H, Ph–CH_2–NH–C=O), 7.20–7.50 (m, 15H, arom.), 7.84 (bs, 1H, NH amide); ^{13}C NMR (50.3 MHz): 43.5, 44.2, 51.3 (CH_2), 59.3 (CH), 126.8, 127.2, 127.4, 127.7, 128.0, 128.4, 128.8, 129.3 (CH arom.; one signal obscured), 138.5, 139.6, 142.5 (C arom.), 171.1 (C=O amide); IR (NaCl, cm^{-1}): 1650 (ν C=O), 3290 (ν NH); *m/z* 345 (M^++H, 100%).

3.4.2. 2,3-Diamino-*N*-benzyl-3-phenyl-propionamide 4b. The resulting crude product was characterized without further purification; yield 98%; yellowish oil; ^{1}H NMR (200 MHz, benzene): 1.67 (bs, 4H, NH_2), 3.57 (d, 1H, CH, J_{vic}=5.9 Hz), 4.37 (m, 2H, CH_2), 5.47 (d, 1H, CH, J_{vic}=5.9 Hz), 7.10–7.14 (m, 2H arom.), 7.20–7.47 (m, 8H, arom.), 7.50 (bs, 1H, NH); ^{13}C NMR (50.3 MHz, $CDCl_3$): 43.5, (CH_2–NH), 58.9 (CH), 61.3 (CH), 127.7, 127.9, 128.1, 128.2, 129.0 (CH arom.; one signal obscured), 138.7, 141.5 (C arom.), 173.5 (C=O); IR (NaCl, cm^{-1}): 1650 (ν C=O), 3264, 3280 (ν NH); *m/z* 270 (M^++H, 100%).

3.5. *N*-Benzyl-3-benzylamino-2-(2-oxo-4-phenyl-oxazolidin-3-yl)-3-phenyl-acrylamide 5a

To a well stirred suspension of azetidinone **3n** (0.1 g, 0.2 mmol) and an equal weight of 10% Pd/C in dry methanol (5 mL), anhydrous ammonium formate[13] (0.063 g,

1 mmol) was added in a single portion under nitrogen. The reaction mixture was stirred under reflux and monitored by TLC (PE/AcOEt 1:1). After 2 h, the catalyst was removed by filtration through a celite pad washing with methanol and chloroform. The combined organic filtrate was dried and freed from solvent under reduced pressure. The crude product was purified by flash chromatography (PE/AcOEt 8:2); yield 94%; white solid; mp 71–73°C (PE); ^{1}H NMR (200 MHz): 3.62 (t, 1H, CH_2 oxazolidinone, J_{vic}=J_{gem}=8.7 Hz), 3.86 (dd, 1H, CH oxazolidinone, J_{vic}=5.0 and 8.7 Hz), 4.05–4.18 (m, 5H, CH_2 benzylics and one H of CH_2 oxazolidinone), 5.56 (brt, 1H, NH, J_{vic}=6.0 Hz), 6.93–6.99 (m, 2H, arom.), 7.10–7.54 (m, 18H, arom.), 10.18 (brt, 1H, NH, J_{vic}=6.1 Hz); ^{13}C NMR (50.3 MHz): 43.0, (CH_2–N), 48.5 (CH_2–N), 63.0 (CH), 69.0 (CH_2 oxazolidinone), 96.2 (C_{sp2}), 127.0, 127.2, 127.3, 127.5, 127.7, 128.2, 128.5, 128.7, 129.3, 129.4, 129.6, 129.7 (CH arom.), 133.3, 138.3, 138.6, 138.8 (C arom.), 159.1 (C=O oxazolidinone), 162.5 (C_{sp2}), 169.3 (C=O amide); IR (KBr, cm^{-1}): 1608 (ν C=O amide), 1742 (ν C=O oxazolidinone), 3396 (ν NH); *m/z* 504 (M^++H, 100%).

3.6. 3-Amino-*N*-benzyl-2-(2-oxo-4-phenyl-oxazolidin-3-yl)-3-phenyl-acrylamide 5b

To a solution of azetidinone **3n** or **p** (0.2 mmol) in dry methylene chloride (10 mL), a catalytic amount of 10% Pd/C (0.01 g) was added and the reaction mixture was shaken under hydrogen[7,11a] at atmospheric pressure for 4 h. The catalyst was then removed by filtration through a celite pad washing carefully with methylene chloride. The combined organic filtrate was dried and freed from solvent under reduced pressure. The resulting crude product was purified by flash chromatography (PE/AcOEt 75:25); yield 90–95%; white solid; mp 224°C (PE); ^{1}H NMR (200 MHz, benzene): 3.32 (t, 1H, one H of CH_2 oxazolidinone, J_{vic}=J_{gem}=11.2 Hz), 3.55–3.64 (m, 2H, CH and one H of CH_2 oxazolidinone), 4.16 (dd, 1H, Ph–*CH*$_2$–NH, J_{vic}=6.2 Hz and J_{gem}=15.0 Hz), 4.45 (dd, 1H, Ph–*CH*$_2$–NH, J_{vic}=6.2 Hz and J_{gem}=15.0 Hz), 6.14 (brt, 1H, NH, J_{vic}=6.2 Hz), 6.83–7.14 (m, 15H, arom. and NH_2), 7.35–7.42 (m, 2H, arom.); ^{13}C NMR (50.3 MHz, $CDCl_3$): 43.3, (CH_2–N), 62.8 (CH), 69.5 (CH_2 oxazolidinone), 96.7 (C_{sp2}), 127.4, 127.5, 127.7, 128.0, 128.8, 129.6, 130.5 (CH arom.; two signals obscured), 137.1, 137.9, 139.0 (C arom.), 159.1 (C_{sp2}), 159.1 (C=O oxazolidinone), 168.8 (C=O amide); IR (KBr, cm^{-1}): 1636 (ν C=O amide), 1728 (ν C=O oxazolidinone), 3264, 3394 (ν NH).

3.7. Selective reduction with $NaBH_4$[14]

To a solution of **3o** (0.05 g, 0.1 mmol) in THF (3 mL), $NaBH_4$ (0.003 g, 0.06 mmol) was added. The mixture was stirred at room temperature and the progress monitored by TLC (EP/AcOEt 1:1). After 24 h, the solution was diluted with water (30 mL) and extracted with AcOEt (3×15 mL). The combined organic layers were dried and freed from solvent at reduced pressure. The crude product was purified by flash chromatography (EP/AcOEt 75:25) to afford **5b** (0.03 g, 48%).

3.8. 3-Benzyl-5-(2-oxo-4-phenyl-oxazolidin-3-yl)-2,6-diphenyl-2,3-dihydro-1*H*-pyrimidin-4-one 6a and 3-benzyl-5-(2-oxo-4-phenyl-oxazolidin-3-yl)-2-tolyl-6-phenyl-2,3-dihydro-1*H*-pyrimidin-4-one 6c

To a stirred solution of azetidinone **3o** or **p** (0.4 mmol) in acetonitrile (5 mL), hexamethyldisilazane (0.210 mL, 1 mmol) and trimethylsilyl iodide (TMSI)[15] (0.142 mL, 1 mmol) were added at room temperature. The reaction mixture was stirred for 4–6 h, then cooled at 0°C and treated with DBU (0.149 mL, 2.5 mmol). Stirring was continued overnight at room temperature, then the mixture was quenched with 5 equiv. of HCl 1N (2 mL, 2 mmol), diluted with water (10 mL) and extracted with ethyl acetate (3×15 mL). The aqueous phase was adjusted to pH 10 with NaOH 1N then extracted again with ethyl acetate (2×15 mL). The organic layer was finally dried and the solvent evaporated in vacuo to give crude **6a** and **c**, respectively, which were purified by flash chromatography (PE/AcOEt 7:3).

3.8.1. 6a. yield 90%; white solid; mp 217–218°C (PE/AcOEt); ^{1}H NMR (300 MHz): 3.58 (d, 1H, CH_2–Ph, J_{gem}=15.3 Hz), 4.07 (t, 1H, CH_2 oxazolidinone, J_{vic}=J_{gem}=9.0 Hz), 4.32 (bd, 1H, NH, J_{vic}=1.1 Hz), 4.68 (t, 1H, CH_2 oxazolidinone, J_{vic}=J_{gem}=9.0 Hz), 5.26 (t, 1H, CH oxazolidinone, J_{vic}=J_{gem}=9.0 Hz), 5.35 (d, 1H, CH_2–Ph, J_{gem}=15.3 Hz), 5.49 (d, 1H, CH, J_{vic}=1.1 Hz), 6.74 (d, 2H, arom. J=7.3 Hz), 7.03 (t, 2H, arom., J=7.3 Hz), 7.14–7.45 (m, 16H, arom.); ^{13}C NMR (75.4 MHz): 46.7, (CH_2–Ph), 63.5 (CH), 70.2 (CH_2), 71.9 (CH), 101.4 (C_{sp2}), 127.7, 128.2, 128.3, 128.4, 128.6, 128.8, 129.3, 129.5, 130.4, 130.6, (CH arom.; two signals obscured), 133.6, 137.1, 137.6, 138.1 (C arom.), 155.4 (C=O), 160.8 (C_{sp2}), 163.4 (C=O); IR (KBr, cm^{-1}): 1616 (ν C=O pyrimidinone), 1742 (ν C=O oxazolidinone), 3286 (ν NH); *m/z* 501 (M^++H, 55%); elem. anal., found (calcd for $C_{32}H_{27}N_3O_3$): C 75.92 (76.63), H 4.46 (5.43), N 8.25 (8.38).

3.8.2. 6c. yield 83%; white solid; mp 178–182°C (PE); ^{1}H NMR (200 MHz): 2.36 (s, 3H, CH_3) 3.58 (d, 1H, Ph–CH_2–Ph, J_{gem}=15.4 Hz), 4.08 (t, 1H, CH_2 oxazolidinone, J_{vic}=J_{gem}=9.0 Hz), 4.28 (bs, 1H, NH), 4.69 (t, 1H, CH_2 oxazolidinone, J_{vic}=J_{gem}=9.0 Hz), 5.26 (bt, 1H, CH oxazolidinone, J_{vic}=J_{gem}=9.0 Hz), 5.36 (d, 1H, CH_2–Ph, J_{gem}=15.4 Hz), 5.46 (d, 1H, CH, J_{vic}=1.3 Hz), 6.76 (d, 2H, arom. J=7.0 Hz), 7.01–7.43 (m, 17H, arom.); ^{13}C NMR (50.3 MHz): 21.3 (CH_3), 46.3 (CH_2–Ph), 63.1 (CH), 69.9 (CH_2), 71.3 (CH), 100.8 (C_{sp2}), 127.3, 127.8, 128.0, 128.1, 128.2, 128.5, 128.9, 129.2, 129.8, 130.3 (CH arom.; one signal obscured), 133.4, 134.9, 136.9, 137.3, 140.1 (C arom.), 155.2 (C=O), 160.5 (C_{sp2}), 163.2 (C=O); IR (KBr, cm^{-1}): 1614, (ν C=O pyrimidinone) 1747 (ν C=O oxazolidinone), 3253 (ν NH); *m/z* 501 (M^++H, 55%); elem. anal., found (calcd for $C_{32}H_{27}N_3O_3$): C 75.92 (76.63), H 4.46 (5.43), N 8.25 (8.38).

3.9. Alkaline hydrolysis of 3o

A suspension of azetidinone **3o** (0.1 g, 0.2 mmol) and LiOH (0.084 g, 2 mmol) in H_2O/THF 3:1 (10 mL) was stirred at room temperature for 4 h. The reaction mixture was then

diluted with HCl 0.1N to neutral pH and extracted with ethyl acetate (3×15 mL). The organic layer was dried and the solvent evaporated in vacuo yielding pure **5b** (0.076 g, 93%).

3.10. Acidic hydrolysis of 3o

A suspension of azetidinone **3o** (0.1 g, 0.2 mmol) in HCl 6N (10 mL) was stirred at room temperature for 4 h. The reaction mixture was then diluted with $NaHCO_3$ to neutral pH and extracted with ethyle acetate (3×15 mL). The organic layer was dried and the solvent evaporated in vacuo. Purification by flash chromatography (PE/AcOEt 7:3) yields progressively **6a** (0.039 g, 39%) and **6b** (0.042 g, 42%).

3.10.1. 3-Benzyl-5-(2-oxo-4-phenyl-oxazolidin-3-yl)-2,6-diphenyl-2,3-dihydro-1*H*-pyrimidin-4-one 6b. White solid; mp 197°C (PE/AcOEt); ^{1}H NMR (200 MHz): 3.66 (d, 1H, CH_2–Ph, J_{gem}=15.1 Hz), 3.94 (t, 1H, CH_2 oxazolidinone, J_{vic}=J_{gem}=9.0 Hz), 4.55 (t, 1H, CH_2 oxazolidinone, J_{vic}=J_{gem}=9.0 Hz), 4.95 (t, 1H, CH oxazolidinone, J_{vic}=J_{gem}=9.0 Hz), 5.01 (d, 1H, NH, J_{vic}=5.3 Hz), 5.47 (d, 1H, CH, J_{vic}=5.3 Hz), 5.55 (d, 1H, CH_2–Ph, J_{gem}=15.1 Hz), 6.49 (d, 2H, arom. J=7.5 Hz), 6.85 (t, 2H, arom., J=7.5 Hz), 7.05–7.45 (m, 16H, arom.); ^{13}C NMR (50.3 MHz): 47.5, (CH_2–Ph), 63.7 (CH), 68.7 (CH), 70.2 (CH_2), 102.2 (C_{sp2}), 126.6, 128.0, 128.3, 128.4, 128.6, 128.7, 128.8, 128.9, 129.1, 129.2, 129.3, 130.9 (CH arom.), 133.5, 137.1, 137.4, 139.8 (C arom.), 154.1 (C=O), 160.7 (C_{sp2}), 162.7 (C=O); IR (KBr, cm^{-1}): 1610 (ν C=O pyrimidinone), 1756 (ν C=O oxazolidinone), 3262, 3396 (ν NH); elem. anal., found (calcd for $C_{32}H_{27}N_3O_3$): C 76.18 (76.63) H 4.35 (5.43) N 8.22 (8.38).

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