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Chiral amine-induced stereoselectivity in *trans*-β-lactam formation via Staudinger cycloaddition

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ABSTRACT

A series of chiral *trans*-β-lactams was obtained via Staudinger cycloaddition with low to moderate diastereoselectivity (up to 54% *de*) induced by a chiral amine component of the imine. It was shown that the direct connection of nitrogen to a chiral centre is crucial to induce chirality; moderate asymmetric induction was achieved by using isomeric 1-phenylethylamines, which are among the cheapest chiral sources on the market, while low diastereoselectivity was obtained from 3-aminomethylpinane, where the chiral centres are distant from nitrogen by a methylene group. It was shown, that an increase of the reaction temperature from 110 °C to 140 °C led to commensurable results but speeded-up the transformation significantly. The absolute configurations of phenylethylamine derivatives were determined by X-ray analysis of selected samples.

1. Introduction

Azetidine-2-ones, so-called β-lactams, are heterocyclic systems of great importance as they exist as structural subunits in many products of interest as pharmaceuticals and synthetic building blocks.[1–5] The subsequent development of a number of classes of β-lactam antibiotics has made this family of four-membered ring amides one of the most successful classes of therapeutic agents to date.[6–10] The stereoisomerically pure azetidinones receive special attention as the ring stereochemistry is closely related with their biological activities. For instance, the penicillin and cephalosporin antibiotics possess *cis*-β-lactam units, whereas thienamycins and trinems have *trans*-β-lactam moieties.

Azetidinones are of widespread interest from the synthetic point of view because of their reactivity.[11] However, their skeleton is one of the most difficult to synthesize due to the ring strain.[12] Among the various methods reported for the construction of β-lactam ring,[13–17] the Staudinger [2+2] ketene-imine cycloaddition reaction regarded as one of the most fundamental and versatile routes for their stereoselective synthesis.[18] The organized transition state of the reaction offers diverse options to design suitable partners of ketene and imine so that the product stereoselectivity can be efficiently controlled by the competition between the direct ring-closure and the isomerization of the imine moiety in the zwitterionic intermediates generated from imines and ketenes. Ideally, there are three sites where a selectivity-directing group can be located: the ketene, the aldehyde component of the imine, and the amine component of the imine. In general, electron donating ketene substituents and electron-withdrawing imine substituents accelerate the direct ring-closure, leading to a preference for *cis*-β-lactam formation; while electron-withdrawing ketene substituents and electron donating imine substituents slow the direct ring-closure, leading to a preference for *trans*-β-lactam formation. The presence of a chiral centre at the adjacent sites of the reacting groups can also dictate the preference for a particular diastereomer. Various chiral acid derivatives, as ketene precursors, and chiral imines have been reported to effect moderate to very high diastereoselectivity in β-lactam ring construction.[19–22] The asymmetric Staudinger reaction has been successfully achieved with chiral ketenes and with imines derived from chiral aldehydes and achiral amines, while the number of reports on the asymmetric induction caused by the amine auxiliary is quite limited, despite their broad variability on the market. Chiral *cis*-azetidinones are obtained by using L-alanine methyl ester,[23] *D*-threonine derivatives,[24] chiral diols,[25] 1-phenylethylamine,[26] 1-naphthylethylamine,[27] as chiral auxiliaries; while, to the best of our knowledge, only Lassatella et al.

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report[28] on the 'unexpected formation of chiral *trans*-β-lactams' via Staudinger-like cycloaddition of chiral *N*,*N*-dialkylhydrazones to α-aminoketene, the selectivity being controlled by the temperature.[29]

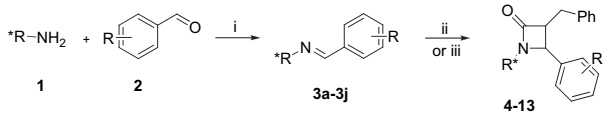
In this paper, we report our study on the diastereoselectivity in the formation of *trans*-β-lactams via Staudinger cycloaddition induced by a chiral amine component of the imine.

2. Results and discussion

The relatively cheap commercial chiral amines, (+)-aminomethylpinane and the isomeric 1-phenylethylamines, were chosen as selectivity-directing sources in an attempt to investigate the influence of the remoteness of the amine chiral centre from nitrogen on the reaction selectivity. Additionally, molecules containing a pinane unit have shown variable biological efficacies, while the benzyl position of the amino group in phenylethylamines was expected to assist the nucleophilic attack and to speed-up the reaction.

A set of aromatic aldehydes with electron donating substituents was used aiming to slow the direct closure and to accelerate the isomerization of the zwitterionic intermediate; 4-dimethylamino-, 3,4-dimethoxy-, and 2,4,6-trimethoxybenzaldehyde and *o*-vanillin, the latter leading to products possessing bulky substituents at the *o*-position (**12**,**13**).

The imine intermediates **3** were obtained quantitatively by irradiating mixtures of an amine **1** and aldehyde **2** in a microwave oven (Scheme 1), while the classical methods, such as azeotropic distillation with Dean–Stark trap or in the presence of water-trapping agents, led to low conversions and decomposition took place during the purifications. The microwave transformation was very fast and clean, no impurities or reagents were detected by NMR spectroscopy, which allowed using these relatively unstable products without chromatography purification.



R*-NH$_2$ \ R	4-Me$_2$N	3,4-(MeO)$_2$	2,4,6-(MeO)$_3$	2-OH-3-OMe/ 2-(OCOR)-3-OMe
(+)-3-aminomethylpinane	**3a / 4**	**3b / 5**		
(*S*)-1-phenylethylamine	**3c / 6**	**3e / 8**	**3g / 10**	**3i / 12**
(*R*)-1-phenylethylamine	**3d / 7**	**3f / 9**	**3h / 11**	**3j / 13**

Scheme 1. Preparation of azetidinones **4**–**13**. i) MWI, 600–800 W, 2–4 min; ii) $PhCH_2CH_2COCl$ (1 equiv for **4**–**11**, 2 equiv for **12**,**13**), Et_3N, toluene, reflux, 24 h; iii) $PhCH_2CH_2COCl$ (1 equiv for **4**–**11**, 2 equiv for **12**,**13**), Et_3N, xylene, reflux, 2–3 h.

The imines **3** were converted into the target azetidinones **4**–**13** via Staudinger [2+2] ketene-imine cycloaddition by using 3-phenylpropionyl chloride as a ketene precursor and triethylamine as a base (Scheme 1). In the case of azetidinones **12** and **13** formation, the cycloaddition reaction was performed in two-fold excess of ketene precursor due to the presence of a free hydroxyl group. The reactions were initially performed in refluxing toluene in an attempt to achieve β-lactam ring formation with *trans*-selectivity, in accordance with the observed by Lassatella et al.[28,29] dependence of the ring stereochemistry on the reaction temperature. The transformations proceeded in a relatively clean way and the azetidinones **4**–**13** were isolated in good to high yields, as shown in Table 1.

The products were obtained diastereoselectively as pairs of isomers with the desired *trans*-C_3,C_4-configuration, i.e., (3*R*,4*S*) and (3*S*,4*R*). The isomeric ratios were determined on the basis of the relative integral intensities of the proton NMR resonances, which are in areas free of other signals; C*H*-4 and CH_2-N for **4**-**5** and C*H*-4, C*H*-Me, and CH_3 for **6**–**13** crude products. These diastereoisomers were separated by high performance flash chromatography (HPFC) on silica gel. As they posses very close or equal R_f-values, a mobile phase with a gradient of polarity was used and pure isomers or enriched fractions were isolated, respectively.

The absolute configurations of the phenylethylamine azetidinones **6**–**13** were determined by X-ray analysis of selected samples of the isomers with lower R_f-values. The latter are solid products in some cases, while the less polar ones are always viscous oils. The crystals were grown by slow diffusion of hexane into chloroform solutions of the enantiomeric products (3*S*,4*R*)-**6** and (3*R*,4*S*)-**7**. The thermal ellipsoid plots with labeling schemes obtained are given in Figure 1.

As can be seen from Table 1, low to moderate asymmetric induction in the ring construction was achieved by using phenylethylamine auxiliary (entries 3–10), while almost equimolar mixtures of *trans*-isomers were obtained from aminomethylpinane derivatives (entries 1 and 2), where the chiral centres are distant from the nitrogen. A comparison between 4-dimethylamino and methoxy derivatives shows that all phenylethylamine products were formed with similar efficacy, while the selectivity was moderately influenced by the substituents on the aldehyde moiety. Commensurable superiority of the less polar isomer was observed in the formation of dimethylamino and 3,4-dimethoxy substituted β-lactams (26/32 vs 26/26; entries 3,4 vs 5,6), while better selectivity was achieved with bulky electron donating substituent in *o*-position (26/32 vs 42/44; entries 3,4 vs 9,10) and the best with three methoxy groups (26/32 vs 52/54; entries 3,4 vs 7,8).

The dependence of the selectivity on the reaction temperature was studied on the example of the phenylethylamine derivatives products **6**–**13** (entries 3–10). The lower temperature experiments for the preparation of **7** led to decomposition at 60 °C, where side-product formation was only detected, and lower conversion with the same selectivity at 80 °C. When the temperature was increased by performing the reaction in refluxing xylene, similar yields and selectivities were obtained (Table 1, pathway B vs pathway A) but much faster then in toluene (2 h vs 24 h). The only exception from the common pattern of behaviour was the formation of vanillin derivatives **12** and **13**, where decomposition was detected in xylene resulting in a serious decrease of the yields.

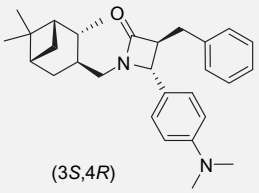
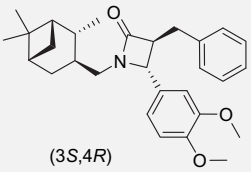
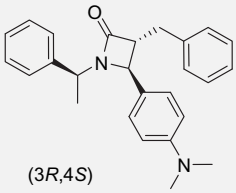
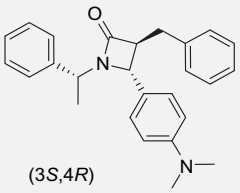
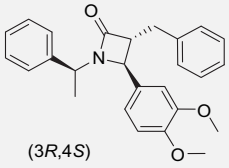
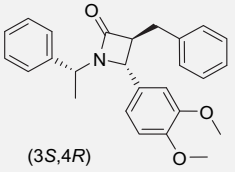
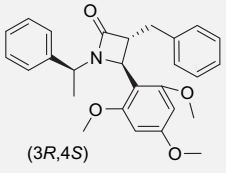
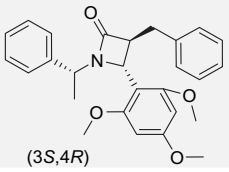
In summary, ten pairs of β-lactams with *trans*-C_3,C_4-configuration were obtained via Staudinger cycloaddition with low to moderate diastereoselectivity induced by a chiral amine component of the imine. It was found that 1-phenylethylamine is effective as a chiral auxiliary, contrary to aminomethylpinane, where the chiral centres are distant from the nitrogen. The absolute configurations of all four possible *trans*-isomers of the four phenylethylamine derivatives were determined by X-ray analysis of selected samples. It was shown, that the transformation goes with commensurable yields and selectivities in refluxing toluene and xylene, but with much different rates, making the xylene protocol the method of choice.

3. Experimental

3.1. General procedures

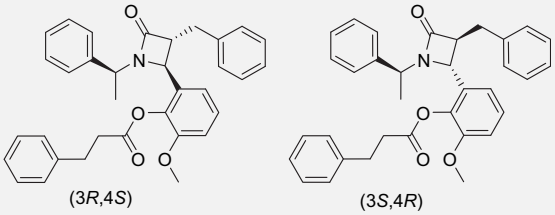
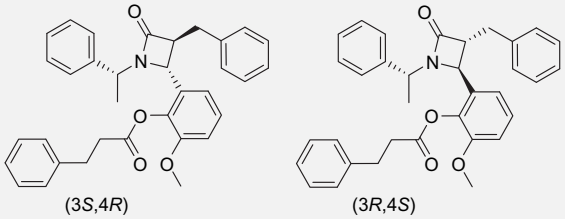
All reagents were purchased from Aldrich, Merck and Fluka and were used without any further purification. Toluene and xylene were dried over sodium wire. The microwave irradiated reactions (MWI) were performed in domestic household oven Panasonic NN-S255W. Fluka silica gel/TLC-cards 60778 with fluorescent indicator 254 nm were used for TLC chromatography and R_f-values determination. The purifications were carried out on a Biotage HorizonTM HPFC system on silica gel. The melting points were determined in capillary tubes on MEL-TEMP 1102D-230 VAC

Table 1
Preparation of azetidin-2-ones **4**–**13**

Entry	Starting imine	Conditions[a]	Product			
			No.	Structure[b]	Yield[c] %	*de*[d] %
1	**3a**	A	**4**	 (3*S*,4*R*) (3*R*,4*S*)	72	10
2	**3b**	A	**5**	 (3*S*,4*R*) (3*R*,4*S*)	70	6
3	**3c**	A B	**6**	 (3*R*,4*S*) (3*S*,4*R*)	87 92	26 28
4	**3d**	A B	**7**	 (3*S*,4*R*) (3*R*,4*S*)	69 86	32 34
5	**3e**	A B	**8**	 (3*R*,4*S*) (3*S*,4*R*)	73 67	26 24
6	**3f**	A B	**9**	 (3*S*,4*R*) (3*R*,4*S*)	66 79	26 26
7	**3g**	A B	**10**	 (3*R*,4*S*) (3*S*,4*R*)	76 83	52 48
8	**3h**	A B	**11**	 (3*S*,4*R*) (3*R*,4*S*)	89 73	54 48

(*continued on next page*)

Table 1 (*continued*)

Entry	Starting imine	Conditions[a]	Product			
			No.	Structure[b]	Yield[c] %	*de*[d] %
9	**3i**	A B	**12**	 (3*R*,4*S*) (3*S*,4*R*)	72 <10	42 43
10	**3j**	A B	**13**	 (3*S*,4*R*) (3*R*,4*S*)	61 <10	44 44

[a] A: 110 °C, 24 h; B: 140 °C, 2–3 h.
[b] The major diastereoisomer is drawn first.
[c] After HPFC purification on silica gel.
[d] Determined by ^{1}H NMR spectra of the crude mixtures.

apparatus without corrections. The IR spectra were taken on a Bruker Tensor 27 as chloroform solutions and were quoted in cm^{-1}. The NMR spectra were recorded on a Bruker Avance DRX 250 and Bruker Avance II+ 600 (indicated) spectrometers in deuterochloroform; the chemical shifts were quoted in ppm in δ-values against tetramethylsilane (TMS) as an internal standard and the coupling constants were calculated in Hertz. The assignments of signals were confirmed by 2D techniques (COSY, NOESY, HSQC, HMBC). The low resolution mass spectra were taken on a HP 5973 Mass Selective Detector, the high resolution mass spectra on a DFS High Resolution Magnetic Sector MS, Thermo Scientific. The optical rotations were recorded on a Perkin–Elmer Polarimeter 241 (Na-lamp, 589 nm, 1 dm cell, *c* 1 in $CHCl_3$).

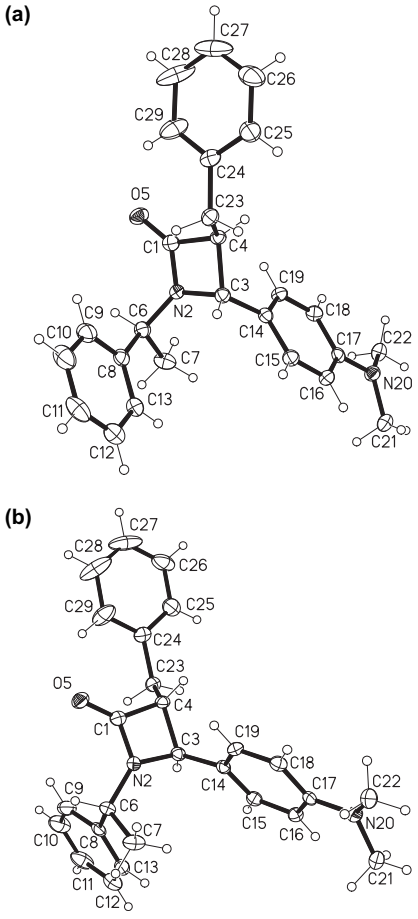


Figure 1. Thermal ellipsoid plot (50% probability level) and labeling scheme of the structure of: a) (3*S*,4*R*)-**6**; b) (3*R*,4*S*)-**7**.

3.2. Preparation of imines 3

3.2.1. General procedure. A mixture of a chiral amine **1** (1 mmol) and an aromatic aldehyde **2** (1 mmol) was irradiated in a domestic household microwave oven in an open vessel with a power of 600–800 W for 2–4 min. The clean crude products (NMR) were used in the next step without purification.

3.2.2. N-(4-Dimethylaminobenzylidene)-1-((1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl)methanamine ***3a****.* 295 mg, 99% yield; IR 513, 592, 787, 821, 947, 1068, 1166, 1234, 1307, 1366, 1443, 1472, 1526, 1604, 1637, 1678, 2822, 2900, 2980; ^{1}H NMR (250 MHz) 0.83 (d, 1H, *J* 9.4, $^1/_2$ CH_2-7), 1.03 (s, 3H, CH_3), 1.06 (d, 3H, *J* 7.1, CH_3-2), 1.19 (s, 3H, CH_3), 1.54 (m, 1H, $^1/_2$ CH_2-4), 1.74–1.92 (m, 3H), 2.02–2.31 (m, 3H), 2.95 (s, 6H, 2×CH_3–N), 3.43 (m, 1H, $^1/_2$ CH_2–N═), 3.61 (m, 1H, $^1/_2$ CH_2–N═), 6.66 (d, 2H, *J* 8.9, C*H*-3 and C*H*-5 Ar), 7.60 (d, 2H, *J* 8.9, C*H*-2 and C*H*-6 Ar), 8.14 (s, 1H, C*H*═N); (250 MHz) ^{13}C NMR 21.7 (*C*H_3), 22.9 (*C*H_3), 28.0 (*C*H_3), 32.4 (*C*H_2), 33.5 (*C*H_2), 37.4 (*C*H), 39.0 (C_{quat}-6), 40.1 (*C*H_3–N), 40.9 (*C*H), 41.8 (*C*H), 48.1 (*C*H), 70.7 (*C*H_2–N═), 111.6 (*C*H-3 and *C*H-5 Ar), 124.7 (C_{quat}-1 Ar), 129.4 (*C*H-2 and *C*H-6 Ar), 151.8 (C_{quat}-4 Ar), 160.4 (*C*H═N); MS *m*/*z* 298.

3.2.3. N-(3,4-Dimethoxybenzylidene)-1-((1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl)methanamine ***3b****.* 309 mg, 98% yield; IR 592, 613, 645, 731, 807, 871, 1026, 1136, 116+1, 1238, 1267, 1327, 1340, 1383, 1420, 1453, 1464, 1512, 1586, 1598, 1644, 1683, 2836, 2903; ^{1}H NMR (250 MHz) 0.84 (d, 1H, *J* 9.4, $^1/_2$ CH_2-7), 1.04 (s, 3H, CH_3), 1.08 (d, 3H, *J* 7.1, CH_3-2), 1.20 (s, 3H, CH_3), 1.55 (m, 1H, $^1/_2$ CH_2-4), 1.76–1.94 (m, 3H), 2.04–2.33 (m, 3H), 3.48 (m, 1H, $^1/_2$

CH_2–N=), 3.64 (m, 1H, $^1/_2$ CH_2–N=), 3.88 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 6.86 (d, 1H, *J* 8.2, C*H*-5 Ar), 7.16 (dd, 1H, *J* 1.8, 8.2, C*H*-6 Ar), 7.43 (d, 1H, *J* 1.8, C*H*-2 Ar), 8.20 (s, 1H, C*H*=N); ^{13}C NMR (250 MHz) 21.7 (CH_3), 23.0 (CH_3), 28.0 (CH_3), 32.5 (CH_2), 33.6 (CH_2), 37.3 (CH), 39.0 (C_{quat}-6), 40.9 (CH), 41.8 (CH), 48.14 (CH), 55.8 (OCH_3), 70.5 (CH_2–N=), 108.9 (CH-2 Ar), 110.5 (CH-5 Ar), 122.8 (CH-6 Ar), 129.7 (C_{quat}-1 Ar), 149.3 (C_{quat}-3 or C_{quat}-4 Ar), 151.2 (C_{quat}-3 or C_{quat}-4 Ar), 160.0 (CH=N); MS *m*/*z* 315.

3.2.4. (S)-N-(4-Dimethylaminobenzylidene)-1-phenylethylamine ***3c***[30]. 249 mg, 99% yield; IR 522, 703, 761, 815, 970, 1064, 1183, 1228, 1317, 1362, 1384, 1448, 1489, 1524, 1609, 1636, 2825, 2843, 2923, 2966, 3025; ^{1}H NMR (250 MHz) 1.57 (d, 3H, *J* 6.7, CH_3–CH), 2.96 (s, 6H, 2×CH_3–N), 4.46 (q, 1H, *J* 6.7, 13.3, CH–CH_3), 6.66 (d, 2H, *J* 8.8, C*H*-3 and C*H*-5 Ar), 7.19 (t, 1H, *J* 7.1, C*H*-4 Ph), 7.30 (dd, 2H, *J* 7.1, 7.6, C*H*-3 and C*H*-5 Ph), 7.41 (d, 2H, *J* 7.6, C*H*-2 and C*H*-6 Ph), 7.64 (d, 2H, *J* 8.8, C*H*-2 and C*H*-6 Ar), 8.22 (s, 1H, C*H*=N); ^{13}C NMR (250 MHz) 24.8 (CH_3–CH), 40.2 (CH_3–N), 69.4 (CH–CH_3), 111.6 (CH-3 and CH-5 Ar), 124.7 (C_{quat}-1 Ar), 126.58 (CH-4 Ph), 126.6 (CH-2 and CH-6 Ph), 128.2 (CH-3 and CH-5 Ph), 129.5 (CH-2 and CH-6 Ar), 145.8 (C_{quat}-1 Ph), 152.0 (C_{quat}-4 Ar), 159.3 (CH=N); MS *m*/*z* 252.

3.2.5. (R)-N-(4-Dimethylaminobenzylidene)-1-phenylethylamine ***3d***. 246 mg, 98% yield; IR 523, 704, 762, 816, 972, 1064, 1181, 1230, 1320, 1362, 1383, 1449, 1490, 1526, 1607, 1638, 2827, 2841, 2923, 2964, 3025; ^{1}H NMR (250 MHz) 1.57 (d, 3H, *J* 6.7, CH_3–CH), 2.98 (s, 6H, 2×CH_3–N), 4.47 (q, 1H, *J* 6.7, 13.3, CH–CH_3), 6.68 (d, 2H, *J* 8.9, C*H*-3 and C*H*-5 Ar), 7.20 (t, 1H, *J* 7.1, C*H*-4 Ph), 7.31 (dd, 2H, *J* 6.9, 7.6, C*H*-3 and C*H*-5 Ph), 7.42 (d, 2H, *J* 6.9, C*H*-2 and C*H*-6 Ph), 7.65 (d, 2H, *J* 8.8, C*H*-2 and C*H*-6 Ar), 8.23 (s, 1H, C*H*=N); ^{13}C NMR (250 MHz) 24.9 (CH_3–CH), 40.2 (CH_3–N), 69.4 (CH–CH_3), 111.6 (CH-3 and CH-5 Ar), 124.7 (C_{quat}-1 Ar), 126.5 (CH-4 Ph), 126.6 (CH-2 and CH-6 Ph), 128.3 (CH-3 and CH-5 Ph), 129.6 (CH-2 and CH-6 Ar), 145.8 (C_{quat}-1 Ph), 152.0 (C_{quat}-4 Ar), 159.4 (CH=N); MS *m*/*z* 252.

3.2.6. (S)-N-(3,4-Dimethoxybenzylidene)-1-phenylethylamine ***3e***. 263 mg, 98% yield; recrystallization from heptane; mp 71–72 °C; IR 541, 641, 704, 764, 813, 871, 927, 969, 1020, 1078, 1141, 1188, 1263, 1386, 1419, 1448, 1511, 1600, 1642, 2843, 2925, 2968, 3027, 3061; ^{1}H NMR (250 MHz) 1.58 (d, 3H, *J* 6.7, CH_3–CH), 3.88 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 4.51 (q, 1H, *J* 6.6, 13.2, CH–CH_3), 6.86 (d, 1H, *J* 8.2, C*H*-5 Ar), 7.18 (dd, 1H, *J* 1.8, 8.3, C*H*-6 Ar), 7.25 (td, 1H, *J* 1.4, 7.3, C*H*-4 Ph), 7.33 (m, 2H, C*H*-3 and C*H*-5 Ph), 7.42 (dd, 2H, *J* 1.5, 7.6, C*H*-2 and C*H*-6 Ph), 7.48 (d, 1H, *J* 1.8, C*H*-2 Ar), 8.26 (s, 1H, C*H*=N); ^{13}C NMR (250 MHz) 24.7 (CH_3–CH), 55.8 (OCH_3), 55.9 (OCH_3), 69.4 (CH–CH_3), 109.1 (CH-2 Ar), 110.4 (CH-5 Ar), 122.9 (CH-6 Ar), 126.6 (CH-2 and CH-6 Ph), 126.7 (CH-4 Ph), 128.3 (CH-3 and CH-5 Ph), 129.7 (C_{quat}-1 Ar), 145.2 (C_{quat}-1 Ph), 149.2 (C_{quat}-3 or C_{quat}-4 Ar), 151.2 (C_{quat}-3 or C_{quat}-4 Ar), 158.8 (CH=N); MS *m*/*z* 269.

3.2.7. (R)-N-(3,4-Dimethoxybenzylidene)-1-phenylethylamine ***3f***[31]. 265 mg, 98% yield; IR 541, 641, 704, 764, 813, 871, 927, 969, 1020, 1077, 1141, 1188, 1264, 1386, 1419, 1448, 1511, 1600, 16414, 2843, 2925, 2968, 3026, 3060; ^{1}H NMR (250 MHz) 1.58 (d, 3H, *J* 6.7, CH_3–CH), 3.90 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 4.52 (q, 1H, *J* 6.6, 13.3, CH–CH_3), 6.86 (d, 1H, *J* 8.2, C*H*-5 Ar), 7.17 (dd, 1H, *J* 1.8, 8.2, C*H*-6 Ar), 7.23 (td, 1H, *J* 1.4, 7.3, C*H*-4 Ph), 7.33 (m, 2H, C*H*-3 and C*H*-5 Ph), 7.42 (dd, 2H, *J* 1.5, 7.7, C*H*-2 and C*H*-6 Ph), 7.48 (d, 1H, *J* 1.8, C*H*-2 Ar), 8.27 (s, 1H, C*H*=N); ^{13}C NMR (250 MHz) 24.8 (CH_3–CH), 55.9 (OCH_3), 56.0 (OCH_3), 69.4 (CH–CH_3), 109.2 (CH-2 Ar), 110.4 (CH-5 Ar), 123.0 (CH-6 Ar), 126.6 (CH-2 and CH-6 Ph), 126.8 (CH-4 Ph), 128.4 (CH-3 and CH-5 Ph), 129.8 (C_{quat}-1 Ar), 145.3 (C_{quat}-1 Ph), 149.3 (C_{quat}-3 or C_{quat}-4 Ar), 151.3 (C_{quat}-3 or C_{quat}-4 Ar), 158.9 (CH=N); MS *m*/*z* 269.

3.2.8. (S)-N-(2,4,6-Trimethoxybenzylidene)-1-phenylethylamine ***3g***. 296 mg, 99% yield; IR 541, 591, 700, 762, 811, 952, 1034, 1060, 1129, 1156, 1205, 1228, 1333, 1415, 1455, 1603, 1636, 2838, 2966; ^{1}H NMR (250 MHz) 1.60 (d, 3H, *J* 6.6, CH_3–CH), 3.81 (s, 6H, 2×OCH_3), 3.82 (s, 3H, OCH_3), 4.47 (q, 1H, *J* 6.6, 13.2, CH–CH_3), 6.11 (s, 2H, C*H*-3 and C*H*-5 Ar), 7.20 (td, 1H, *J* 1.3, 7.4, C*H*-4 Ph), 7.32 (m, 2H, C*H*-3 and C*H*-5 Ph), 7.48 (dd, 2H, *J* 1.3, 7.5, C*H*-2 and C*H*-6 Ph), 8.55 (s, 1H, C*H*=N); ^{13}C NMR (250 MHz) 25.2 (CH_3–CH), 55.3 (OCH_3), 56.0 (2×OCH_3), 71.0 (CH–CH_3), 90.8 (CH-3 and CH-5 Ar), 107.9 (C_{quat}-1 Ar), 126.3 (CH-4 Ph), 126.6 (CH-2 and CH-6 Ph), 128.1 (CH-3 and CH-5 Ph), 146.2 (C_{quat}-1 Ph), 154.6 (CH=N), 160.7 (C_{quat}-2 and C_{quat}-6 Ar), 162.3 (C_{quat}-4 Ar); MS *m*/*z* 299.

3.2.9. (R)-N-(2,4,6-Trimethoxybenzylidene)-1-phenylethylamine ***3h***. 295 mg, 99% yield; IR 542, 593, 701, 763, 813, 953, 1036, 1061, 1131, 1157, 1206, 1229, 1335, 1416, 1456, 1605, 1637, 2839, 2967; ^{1}H NMR (250 MHz) 1.60 (d, 3H, *J* 6.6, CH_3–CH), 3.81 (s, 6H, 2×OCH_3), 3.82 (s, 3H, OCH_3), 4.46 (q, 1H, *J* 6.6, 13.2, CH–CH_3), 6.11 (s, 2H, C*H*-3 and C*H*-5 Ar), 7.20 (td, 1H, *J* 1.3, 7.2, C*H*-4 Ph), 7.31 (m, 2H, C*H*-3 and C*H*-5 Ph), 7.48 (dd, 2H, *J* 1.3, 7.5, C*H*-2 and C*H*-6 Ph), 8.55 (s, 1H, C*H*=N); ^{13}C NMR (250 MHz) 25.2 (CH_3–CH), 55.3 (OCH_3), 56.0 (2×OCH_3), 71.0 (CH–CH_3), 90.8 (CH-3 and CH-5 Ar), 107.9 (C_{quat}-1 Ar), 126.3 (CH-4 Ph), 126.6 (CH-2 and CH-6 Ph), 128.1 (CH-3 and CH-5 Ph), 146.2 (C_{quat}-1 Ph), 154.6 (CH=N), 160.7 (C_{quat}-2 and C_{quat}-6 Ar), 162.3 (C_{quat}-4 Ar); MS *m*/*z* 299.

3.2.10. (S)-N-(2-Hydroxy-3-methoxybenzylidene)-1-phenylethylamine ***3i***. 252 mg, 99% yield; IR 535, 700, 738, 764, 840, 968, 1093, 1255, 1270, 1383, 1419, 1466, 1628, 2930, 2971, 3061; ^{1}H NMR (600 MHz) 1.62 (d, 3H, *J* 6.7, CH_3–CH), 3.90 (s, 3H, OCH_3), 4.56 (q, 1H, *J* 6.7, 13.3, CH–CH_3), 6.80 (t, 1H, *J* 7.9, C*H*-5 Ar), 6.87 (dd, 1H, *J* 1.4, 7.9, C*H*-4 Ar), 6.92 (dd, 1H, *J* 1.4, 7.9, C*H*-6 Ar), 7.25 (td, 1H, *J* 1.5, 7.3, C*H*-4 Ph), 7.34 (td, 2H, *J* 1.5, 7.4, C*H*-3 and C*H*-5 Ph), 7.37 (dd, 2H, *J* 1.5, 7.4, C*H*-2 and C*H*-6 Ph), 8.40 (s, 1H, C*H*=N) 14.18 (s, 1H, O*H*); ^{13}C NMR (600 MHz) 25.2 (CH_3–CH), 56.1 (OCH_3), 68.2 (CH–CH_3), 113.9 (CH-4 Ar), 117.9 (CH-5 Ar), 118.6 (C_{quat}-1 Ar), 122.9 (CH-6 Ar), 126.3 (CH-2 and CH-6 Ph), 127.2 (CH-4 Ph), 128.7 (CH-3 and CH-5 Ph), 143.7 (C_{quat}-1 Ph), 148.4 (C_{quat}-3 Ar), 151.8 (C_{quat}-4 Ar), 163.4 (CH=N); MS *m*/*z* 255.

3.2.11. (R)-N-(2-Hydroxy-3-methoxybenzylidene)-1-phenylethylamine ***3j***. 249 mg, 98% yield; IR 536, 700, 738, 764, 840, 968, 1093, 1255, 1270, 1383, 1419, 1466, 1628, 2932, 2971, 3061; ^{1}H NMR (600 MHz) 1.63 (d, 3H, *J* 6.7, CH_3–CH), 3.91 (s, 3H, OCH_3), 4.57 (q, 1H, *J* 6.7, 13.3, CH–CH_3), 6.80 (t, 1H, *J* 7.9, C*H*-5 Ar), 6.87 (dd, 1H, *J* 1.5, 7.8, C*H*-4 Ar), 6.92 (dd, 1H, *J* 1.4, 7.9, C*H*-6 Ar), 7.26 (td, 1H, *J* 1.5, 7.4, C*H*-4 Ph), 7.34 (td, 2H, *J* 1.5, 7.4, C*H*-3 and C*H*-5 Ph), 7.37 (dd, 2H, *J* 1.5, 7.4, C*H*-2 and C*H*-6 Ph), 8.40 (s, 1H, C*H*=N) 14.17 (s, 1H, O*H*); ^{13}C NMR (600 MHz) 25.2 (CH_3–CH), 56.1 (OCH_3), 68.2 (CH–CH_3), 113.9 (CH-4 Ar), 117.9 (CH-5 Ar), 118.6 (C_{quat}-1 Ar), 122.9 (CH-6 Ar), 126.3 (CH-2 and CH-6 Ph), 127.3 (CH-4 Ph), 128.7 (CH-3 and CH-5 Ph), 143.7 (C_{quat}-1 Ph), 148.5 (C_{quat}-3 Ar), 151.8 (C_{quat}-4 Ar), 163.4 (CH=N); MS *m*/*z* 255.

3.3. Preparation of azetidin-2-ones 4–13

3.3.1. General procedure. To a refluxing solution of imine **3** (1 mmol) and Et_3N (1.5 mmol) in toluene or xylene (15 mL) 3-phenylpropionyl chloride (1 mmol for **4**-**11**; 2 mmol for **12** and **13**) was added and the mixture was refluxed for 24 h (in toluene) or for 2–3 h (in xylene). The products were partitioned between water and toluene/xylene. The organic phase was washed with brine, dried over Na_2SO_4, evaporated to dryness, and purified by PHFC on silica gel. Mobile phase with a gradient of polarity from ether: hexane 10:90 to ether:hexane 80:20 was used. The enriched fractions of stereoisomers of the products **4**, **5**, and **9** were isolated, instead of pure isomers, due to much closed R_f-values.

The yields and selectivities are summarized in Table 1.

The *trans*-3,4-isomers of aminomethylpinane derivatives **4** and **5** are indicated as **a** and **b** for simplicity; the less polar isomer is **a**,

the more polar is **b**. The couple components have equal R_f-values and only partial separations were achieved.

3.3.2. 3-Benzyl-4-(4-(dimethylamino)phenyl)-1-(((1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl)methyl)azetidin-2-one ***4***. IR 700, 823, 947, 1074, 1122, 1274, 1289, 1354, 1454, 1525, 1615, 1748, 2809, 2857, 2870, 2923, 3027, 3062, 3086, 3370; MS *m*/*z* 430; HRMS (EI): calcd for $C_{29}H_{38}N_2O$ (M^+): 430.2984, found: 430.2965.

3.3.2.1. Isomer ***4a***. R_f 0.26 (ether:hexane 1:1), 0.40 (ether:hexane 2:3, three times developed plates); colourless oil; ^{1}H NMR (600 MHz) 0.60 (d, 1H, *J* 9.7, ½ C*H*$_2$-7 Pin), 0.89 (s, 3H, C*H*$_3$), 0.98 (d, 3H, *J* 7.2, C*H*$_3$-2 Pin), 1.14 (s, 3H, C*H*$_3$), 1.28 (ddd, 1H, *J* 2.4, 6.3, 13.2, ½ C*H*$_2$-4 Pin), 1.61 (dtd, 1H, *J* 1.9, 7.1, 14.2, C*H*-3 Pin), 1.69 (td, 1H, *J* 2.0, 6.7, C*H*-2 Pin), 1.72 (t, 1H, C*H*-1 Pin), 1.80 (m, 1H, C*H*-5 Pin), 1.83 (m, 1H, ½ C*H*$_2$-4 Pin), 2.20 (ddt, 1H, *J* 2.2, 6.3, 12.2, ½ C*H*$_2$-7 Pin), 2.49 (dd, 1H, *J* 8.2, 13.9, ½ C*H*$_2$-N), 2.94 (s, 6H, 2×C*H*$_3$–N), 3.08 (dd, 1H, *J* 7.1, 14.7, ½ C*H*$_2$), 3.16 (dd, 1H, *J* 5.3, 14.7, ½ C*H*$_2$), 3.27 (ddd, 1H, *J* 1.9, 5.3, 7.8, C*H*-3), 3.46 (dd, 1H, *J* 5.9, 13.9, ½ C*H*$_2$–N), 4.24 (d, 1H, *J* 1.9, C*H*-4), 6.67 (d, 2H, *J* 8.7, C*H*-3 and C*H*-5 Ar), 7.08 (d, 2H, *J* 8.7, C*H*-2 and C*H*-6 Ar), 7.19 (tt, 1H, *J* 1.4, 7.1, C*H*-4 Ph), 7.23 (dt, 2H, *J* 1.6, 6.7, C*H*-2 and C*H*-6 Ph), 7.27 (td, 2H, *J* 1.4, 7.2, C*H*-3 and C*H*-5 Ph); ^{13}C NMR (600 MHz) 21.7 (*C*H$_3$-2 Pin), 23.0 (*C*H$_3$), 27.9 (*C*H$_3$), 32.9 (*C*H$_2$-4 Pin), 33.7 (*C*H$_2$-7 Pin), 34.2 (*C*H$_2$), 36.0 (*C*H-1 Pin), 38.6 (*C*$_{quat}$-6 Pin), 40.4 (*C*H$_3$-N), 41.0 (*C*H-3 Pin), 41.4 (*C*H-5 Pin), 47.8 (*C*H-2 Pin), 48.8 (*C*H$_2$-N), 60.4 (*C*H-3), 61.3 (*C*H-4), 112.5 (*C*H-3 and *C*H-5 Ar), 124.8 (*C*$_{quat}$), 126.4 (*C*H-4 Ph), 127.5 (*C*H-2 and *C*H-6 Ar), 128.4 (*C*H-3 and *C*H-5 Ph), 129.0 (*C*H-2 and *C*H-6 Ph), 138.2 (*C*$_{quat}$), 150.5 (*C*$_{quat}$), 170.1 (*C*═O).

3.3.2.2. Isomer ***4b***. R_f 0.26 (ether:hexane 1:1), 0.37 (ether:hexane 2:3, three times developed plates); colourless oil; ^{1}H NMR (600 MHz) 0.67 (d, 1H, *J* 9.8, ½ C*H*$_2$-7 Pin), 0.83 (d, 3H, *J* 7.2, C*H*$_3$-2 Pin), 0.91 (s, 3H, C*H*$_3$), 1.16 (s, 3H, C*H*$_3$), 1.40 (dd, 1H, *J* 2.6, 7.8, ½ C*H*$_2$-4 Ar), 1.61 (tdd, 1H, *J* 1.7, 7.0, 13.9, C*H*-3 Ar), 1.69 (m, 3H, C*H*-1, C*H*-2, and ½ C*H*-4 Ar), 1.82 (m, 1H, C*H*-5 Ar), 2.24 (m, 1H, ½ C*H*$_2$-7 Ar), 2.62 (dd, 1H, *J* 3.4, 13.6, ½ C*H*$_2$–N), 2.94 (s, 6H, 2×C*H*$_3$–N), 3.06 (dd, 1H, *J* 8.4, 14.7, ½ C*H*$_2$), 3.14 (dd, 1H, *J* 5.1, 14.7, ½ C*H*$_2$), 3.27 (m, 1H, C*H*-3), 3.32 (dd, 1H, *J* 9.6, 13.6, ½ C*H*$_2$–N), 4.20 (d, 1H, *J* 1.9, C*H*-4), 6.67 (d, 2H, *J* 8.8, C*H*-3 and C*H*-5 Ar), 7.05 (d, 2H, *J* 8.8, C*H*-2 and C*H*-6 Ar), 7.19 (tt, 1H, *J* 1.4, 7.1, C*H*-4 Ph), 7.23 (dt, 2H, *J* 1.7, 6.7, C*H*-2 and C*H*-6 Ph), 7.26 (td, 2H, *J* 1.4, 7.4, C*H*-3 and C*H*-5 Ph); ^{13}C NMR (600 MHz) 21.4 (*C*H$_3$-2 Pin), 22.9 (*C*H$_3$), 27.9 (*C*H$_3$), 32.1 (*C*H$_2$-4 Pin), 33.7 (*C*H$_2$-7 Pin), 34.2 (*C*H$_2$), 34.6 (*C*H-1 Pin), 38.7 (*C*$_{quat}$-6 Pin), 40.4 (*C*H$_3$–N), 40.6 (*C*H-3 Pin), 41.4 (*C*H-5 Pin), 47.6 (*C*H-2 Pin), 48.0 (*C*H$_2$–N), 59.6 (*C*H-4), 60.1 (*C*H-3), 112.5 (*C*H-3 and *C*H-5 Ar), 124.6 (*C*$_{quat}$), 126.4 (*C*H-4 Ph), 127.4 (*C*H-2 and *C*H-6 Ar), 128.4 (*C*H-3 and *C*H-5 Ph), 129.6 (*C*H-2 and *C*H-6 Ph), 138.1 (*C*$_{quat}$), 150.5 (*C*$_{quat}$), 170.2 (*C*═O).

3.3.3. 3-Benzyl-4-(3,4-dimethoxyphenyl)-1-(((1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl)methyl)azetidin-2-one ***5***. IR 755, 1028, 1139, 1162, 1239, 1263, 1454, 1465, 1517, 1594, 1605, 1748, 2837, 2871, 2907, 2935, 3026, 3062, 3484; MS *m*/*z* 447; HRMS (EI): calcd for $C_{29}H_{37}NO_3$ (M^+): 447.2773, found: 447.2748.

3.3.3.1. Isomer ***5a***. R_f 0.12 (ether:hexane 1:1); colourless oil; ^{1}H NMR (600 MHz) 0.55 (d, 1H, *J* 9.8, ½ C*H*$_2$-7 Pin), 0.84 (s, 3H, C*H*$_3$), 0.94 (d, 3H, *J* 7.2, C*H*$_3$-2 Pin), 1.09 (s, 3H, C*H*$_3$), 1.24 (ddd, 1H, *J* 2.6, 5.9, 13.4, ½ C*H*$_2$-4 Pin), 1.57 (dtd, 1H, *J* 1.9, 7.1, 14.2, C*H*-3 Pin), 1.64 (m, 1H, C*H*-2 Pin), 1.70 (m, 1H, C*H*-1 Pin), 1.68 (m, 1H, C*H*-5 Pin), 1.57 (m, 1H, ½ C*H*$_2$-4 Pin), 2.16 (m, 1H, ½ C*H*$_2$-7 Pin), 2.49 (dd, 1H, *J* 8.3, 13.8, ½ C*H*$_2$-N), 2.98 (dd, 1H, *J* 9.0, 14.4, ½ C*H*$_2$), 3.14 (dd, 1H, *J* 4.9, 14.6, ½ C*H*$_2$), 3.19 (m, 1H, C*H*-3), 3.86 (dd, 1H, *J* 6.0, 13.9, ½ C*H*$_2$-N), 3.72 (s, 3H, OC*H*$_3$), 3.80 (s, 3H, OC*H*$_3$), 4.21 (d, 1H, *J* 1.9, C*H*-4), 6.74 (d, 1H, *J* 8.2, C*H*-5 Ar), 6.65 (d, 1H, *J* 2.0, 8.2, C*H*-6 Ar), 6.46 (d, 1H, *J* 2.0, C*H*-2 Ar), 7.19 (tt, 1H, *J* 1.4, 7.1, C*H*-4 Ph), 7.23 (dt, 2H, *J* 1.6, 6.7, C*H*-2 and C*H*-6 Ph), 7.28 (td, 2H, *J* 1.4, 7.1, C*H*-3 and C*H*-5 Ph); ^{13}C NMR (600 MHz) 21.7 (*C*H$_3$-2 Pin), 22.9 (*C*H$_3$), 27.8 (*C*H$_3$), 33.0 (*C*H$_2$-4 Pin), 33.6 (*C*H$_2$-7 Pin), 34.1 (*C*H$_2$), 36.0 (*C*H-1 Pin), 38.6 (*C*$_{quat}$-6 Pin), 40.9 (*C*H-3 Pin), 41.3 (*C*H-5 Pin), 47.7 (*C*H-2 Pin), 49.2 (*C*H$_2$-N), 55.8 (*C*H$_3$–O), 60.8 (*C*H-3), 61.4 (*C*H-4), 108.8 (*C*H-2 Ar), 111.1 (*C*H-5 Ar), 118.7 (*C*H-6 Ar), 126.5 (*C*H-4 Ph), 128.5 (*C*H-3 and *C*H-5 Ph), 129.0 (*C*H-2 and *C*H-6 Ph), 130.2 (*C*$_{quat}$), 138.1 (*C*$_{quat}$), 148.9 (*C*$_{quat}$-OCH$_3$), 149.3 (*C*$_{quat}$-OCH$_3$), 169.8 (*C*═O).

3.3.3.2. Isomer ***5b***. R_f 0.12 (ether:hexane 1:1); colourless oil; ^{1}H NMR (600 MHz) 0.63 (d, 1H, *J* 9.8, ½ C*H*$_2$-7 Pin), 0.78 (d, 3H, *J* 7.2, C*H*$_3$-2 Pin), 0.85 (s, 3H, C*H*$_3$), 1.10 (s, 3H, C*H*$_3$), 1.38 (ddd, 1H, *J* 2.5, 5.8, 12.7, ½ C*H*$_2$-4 Pin), 1.45 (tdd, 1H, *J* 1.8, 7.0, 13.9, C*H*-3 Pin), 1.69 (m, 3H, C*H*-1, C*H*-2, and ½ C*H*-4 Pin), 1.71 (m, 1H, C*H*-5 Pin), 2.20 (m, 1H, ½ C*H*$_2$-7 Pin), 2.63 (dd, 1H, *J* 3.9, 13.4, ½ C*H*$_2$–N), 2.96 (dd, 1H, *J* 9.0, 14.5, ½ C*H*$_2$), 3.14 (dd, 1H, *J* 4.9, 14.6, ½ C*H*$_2$), 3.18 (m, 1H, C*H*-3), 3.30 (dd, 1H, *J* 10.0, 13.5, ½ C*H*$_2$–N), 3.71 (s, 3H, OC*H*$_3$), 3.80 (s, 3H, OC*H*$_3$), 4.16 (d, 1H, *J* 1.9, C*H*-4), 6.74 (d, 1H, *J* 8.2, C*H*-5 Ar), 6.66 (dd, 1H, *J* 2.0, 8.2, C*H*-6 Ar), 6.45 (d, 1H, *J* 2.0, C*H*-2 Ar), 7.19 (tt, 1H, *J* 1.4, 7.1, C*H*-4 Ph), 7.23 (dt, 2H, *J* 1.7, 6.7, C*H*-2 and C*H*-6 Ph), 7.26 (td, 2H, *J* 1.4, 7.1, C*H*-3 and C*H*-5 Ph); ^{13}C NMR (600 MHz) 21.4 (*C*H$_3$-2 Pin), 22.9 (*C*H$_3$), 27.8 (*C*H$_3$), 32.1(*C*H$_2$-4 Pin), 33.7 (*C*H$_2$-7 Pin), 34.3 (*C*H$_2$), 34.5 (*C*H-1 Pin), 38.7 (*C*$_{quat}$-6 Pin), 40.5 (*C*H-3 Pin), 41.3 (*C*H-5 Pin), 47.5 (*C*H-2 Pin), 48.3 (*C*H$_2$-N), 55.8 (*C*H$_3$–O), 59.7 (*C*H-4), 60.58 (*C*H-3), 108.6 (*C*H-2 Ar), 111.1 (*C*H-5 Ar), 118.6 (*C*H-6 Ar), 126.5 (*C*H-4 Ph), 128.5 (*C*H-3 and *C*H-5 Ph), 129.1 (*C*H-2 and *C*H-6 Ph), 130.1 (*C*$_{quat}$), 138.0 (*C*$_{quat}$), 148.9 (*C*$_{quat}$-OCH$_3$), 149.3 (*C*$_{quat}$-OCH$_3$), 170.0 (*C*═O).

3.3.4. 3-Benzyl-4-(4-(dimethylamino)phenyl)-1-((S)-1-phenylethyl)azetidin-2-one ***6***. MS *m*/*z* 384; HRMS (EI): calcd for $C_{26}H_{28}N_2O$ (M^+): 384.2202, found: 384.2199.

*3.3.4.1. (3R,4S)-****6***. R_f 0.27 (ether:hexane 1:1), 0.40 (ether:hexane 1:1, two times developed plates); colourless oil; IR 701, 757, 825, 1166, 1350, 1371, 1525, 1599, 1613, 1743, 2736, 2805, 2931, 2979, 3028, 3061, 3085, 3446; ^{1}H NMR (600 MHz) 1.71 (d, 3H, *J* 7.2, C*H*$_3$–CH), 2.93 (s, 6H, 2×C*H*$_3$–N), 3.05 (m, 2H, C*H*$_2$), 3.27 (ddd, 1H, *J* 2.1, 5.3, 7.4, C*H*-3), 3.93 (d, 1H, *J* 2.1, C*H*-4), 4.09 (q, 1H, *J* 7.2, 14.3, C*H*–CH$_3$), 6.62 (d, 2H, *J* 8.7, C*H*-3 and C*H*-5 Ar), 6.94 (m, 2H, C*H* Ph), 6.95 (d, 2H, *J* 8.7, C*H*-2 and C*H*-6 Ar), 7.19 (m, 6H, C*H* Ph), 7.26 (m, 2H, C*H* Ph); ^{13}C NMR (600 MHz) 20.4 (*C*H$_3$–CH), 33.6 (*C*H$_2$), 40.2 (*C*H$_3$–N), 54.2 (*C*H–CH$_3$), 58.6 (*C*H-4), 59.4 (*C*H-3), 112.2 (*C*H-3 and *C*H-5 Ar), 124.6 (*C*$_{quat}$), 126.2 (*C*H Ar), 126.3 (*C*H Ar), 126.9 (*C*H Ar), 127.4 (*C*H Ar), 127.8 (*C*H Ar), 128.2 (*C*H Ar), 128.2 (*C*H Ar), 129.0 (*C*H Ar), 137.8 (*C*$_{quat}$), 141.5 (*C*$_{quat}$), 150.2 (*C*$_{quat}$), 169.6 (*C*═O); $[\alpha]_D$ −21.3° (*c* 1, $CHCl_3$).

*3.3.4.2. (3S,4R)-****6***. R_f 0.21 (ether:hexane 1:1), 0.32 (ether:hexane 1:1, two times developed plates); white crystals (hexane); mp 105–106 °C; IR 697, 757, 797, 827, 1227, 1367, 1386, 1456, 1497, 1525, 1616, 1731, 2809, 2906, 2935, 2984, 3028, 3058, 3086, 3448; ^{1}H NMR (600 MHz) 1.23 (d, 3H, *J* 7.2, C*H*$_3$-CH), 2.94 (s, 6H, 2×C*H*$_3$–N), 3.02 (m, 2H, C*H*$_2$), 3.29 (ddd, 1H, *J* 2.1, 5.3, 7.4, C*H*-3), 3.90 (d, 1H, *J* 2.1, C*H*-4), 4.94 (q, 1H, *J* 7.2, 14.3, C*H*–CH$_3$), 6.62 (d, 2H, *J* 8.7, C*H*-3 and C*H*-5 Ar), 6.94 (m, 2H, C*H* Ph), 6.95 (d, 2H, *J* 8.7, C*H*-2 and C*H*-6 Ar), 7.19 (m, 6H, C*H* Ph), 7.26 (m, 2H, C*H* Ph); ^{13}C NMR (600 MHz) 18.5 (*C*H$_3$–CH), 33.4 (*C*H$_2$), 40.1 (*C*H$_3$–N), 51.2 (*C*H–CH$_3$), 58.9 (*C*H-4), 59.2 (*C*H-3), 112.0 (*C*H-3 and *C*H-5 Ar), 125.8 (*C*$_{quat}$), 126.1 (*C*H Ar), 126.3 (*C*H Ar), 126.9 (*C*H Ar), 127.5 (*C*H Ar), 127.8 (*C*H Ar), 128.2 (*C*H Ar), 128.2 (*C*H Ar), 129.0 (*C*H Ar), 137.8 (*C*$_{quat}$), 141.5 (*C*$_{quat}$), 150.2 (*C*$_{quat}$), 170.0 (*C*═O); $[\alpha]_D$ +18.6° (*c* 1, $CHCl_3$).

3.3.5. 3-Benzyl-4-(4-(dimethylamino)phenyl)-1-((R)-1-phenylethyl)azetidin-2-one ***7***. MS *m*/*z* 384; HRMS (EI): calcd for $C_{26}H_{28}N_2O$ (M^+): 384.2202, found: 384.2184.

*3.3.5.1. (3S,4R)-****7***. R_f 0.27 (ether:hexane 1:1), 0.40 (ether:hexane 1:1, two times developed plates); colourless oil; IR 701, 755, 1349, 1454, 1496, 1519, 1612, 1677, 1742, 2933, 3007, 3028, 3062, 3334; ^{1}H

NMR (600 MHz) 1.71 (d, 3H, *J* 7.2, C*H*$_3$–CH), 2.93 (s, 6H, 2×C*H*$_3$–N), 3.05 (m, 2H, C*H*$_2$), 3.27 (ddd, 1H, *J* 2.1, 5.3, 7.4, C*H*-3), 3.93 (d, 1H, *J* 2.1, C*H*-4), 4.09 (q, 1H, *J* 7.2, 14.3, C*H*–CH$_3$), 6.62 (d, 2H, *J* 8.7, C*H*-3 and C*H*-5 Ar), 6.94 (m, 2H, C*H* Ph), 6.95 (d, 2H, *J* 8.7, C*H*-2 and C*H*-6 Ar), 7.19 (m, 6H, C*H* Ph), 7.26 (m, 2H, C*H* Ph); ^{13}C NMR (600 MHz) 20.4 (*C*H$_3$–CH), 33.6 (*C*H$_2$), 40.2 (*C*H$_3$–N), 54.2 (*C*H–CH$_3$), 58.6 (*C*H-4), 59.4 (*C*H-3), 112.2 (*C*H-3 and *C*H-5 Ar), 124.6 (*C*$_{quat}$), 126.2 (*C*H Ar), 126.3 (*C*H Ar), 126.9 (*C*H Ar), 127.4 (*C*H Ar), 127.8 (*C*H Ar), 128.2 (*C*H Ar), 128.2 (*C*H Ar), 129.0 (*C*H Ar), 137.8 (*C*$_{quat}$), 141.5 (*C*$_{quat}$), 150.2 (*C*$_{quat}$), 169.6 (*C*═O); [α]$_D$ +21.8° (*c* 1, CHCl$_3$).

*3.3.5.2. (3R,4S)-**7**.* R_f 0.21 (ether:hexane 1:1), 0.32 (ether:hexane 1:1, two times developed plates); white crystals (hexane); mp 105–106 °C; IR 700, 755, 1351, 1454, 1496, 1520, 1610, 1675, 1737, 2807, 2933, 2979, 3005, 3028, 3062, 3086, 3325; ^{1}H NMR (600 MHz) 1.23 (d, 3H, *J* 7.2, C*H*$_3$–CH), 2.94 (s, 6H, 2×C*H*$_3$–N), 3.02 (m, 2H, C*H*$_2$), 3.29 (ddd, 1H, *J* 2.1, 5.3, 7.4, and C*H*-5 Ar), 6.94 (m, 2H, C*H* Ph), 6.95 (d, 2H, *J* 8.7, C*H*-2 and C*H*-6 Ar), 7.19 (m, 6H, C*H* Ph), 7.26 (m, 2H, C*H* Ph); ^{13}C NMR (600 MHz) 18.5 (*C*H$_3$–CH), 33.4 (*C*H$_2$), 40.1 (*C*H$_3$–N), 51.2 (*C*H–CH$_3$), 58.9 (*C*H-4), 59.2 (*C*H-3), 112.0 (*C*H-3 and *C*H-5 Ar), 125.8 (*C*$_{quat}$), 126.1 (*C*H Ar), 126.3 (*C*H Ar), 126.9 (*C*H Ar), 127.5 (*C*H Ar), 127.8 (*C*H Ar), 128.2 (*C*H Ar), 128.2 (*C*H Ar), 129.0 (*C*H Ar), 137.8 (*C*$_{quat}$), 141.5 (*C*$_{quat}$), 150.2 (*C*$_{quat}$), 170.0 (*C*═O); [α]$_D$ −20.9° (*c* 1, CHCl$_3$).

*3.3.6. 3-Benzyl-4-(3,4-dimethoxyphenyl)-1-((S)-1-phenylethyl)azetidin-2-one **8**.* MS *m*/*z* 401; HRMS (EI): calcd for $C_{26}H_{27}NO_3$ (M$^+$): 401.1991, found: 401.1986.

*3.3.6.1. (3R,4S)-**8**.* R_f 0.11 (ether:hexane 1:1), 0.23 (ether:hexane 1:1, two times developed plates); colourless oil; IR 701, 760, 1028, 1138, 1163, 1238, 1264, 1311, 1374, 1422, 1454, 1464, 1496, 1517, 1593, 1605, 1745, 2836, 2934, 3028, 3062, 3469, 3593; ^{1}H NMR (600 MHz) 1.68 (d, 3H, *J* 7.2, C*H*$_3$–CH), 3.01 (dd, 1H, *J* 8.4, 14.6, $^1/_2$ C*H*$_2$), 3.13 (dd, 1H, *J* 5.1, 14.6, $^1/_2$ C*H*$_2$), 3.25 (ddd, 1H, *J* 2.0, 5.1, 7.8, C*H*-3), 3.66 (s, 3H, OC*H*$_3$), 3.84 (s, 3H, OC*H*$_3$), 4.02 (d, 1H, *J* 2.1, C*H*-4), 4.30 (q, 1H, *J* 7.2, 14.3, C*H*–CH$_3$), 6.37 (d, 1H, *J* 2.0, C*H*-2 Ar), 6.62 (dd, 1H, *J* 2.0, 8.2, C*H*-6 Ar), 6.74 (d, 1H, *J* 8.2, C*H*-5 Ar), 6.99 (dd, 2H, *J* 2.0, 7.8, C*H* Ph), 7.21 (m, 6H, C*H* Ph), 7.28 (m, 2H, C*H* Ph); ^{13}C NMR (600 MHz) 19.8 (*C*H$_3$–CH), 33.8 (*C*H$_2$), 53.9 (*C*H–CH$_3$), 55.5 (OCH$_3$), 55.7 (OCH$_3$), 58.8 (*C*H-4), 59.8 (*C*H-3), 108.8 (*C*H-2 Ar), 110.8 (*C*H-5 Ar), 118.7 (*C*H-6 Ar), 126.4 (*C*H Ph), 126.6 (*C*H Ph), 127.2 (*C*H Ph), 128.3 (*C*H Ph), 128.4 (*C*H Ph), 129.1 (*C*H Ph), 130.2 (*C*$_{quat}$), 137.7 (*C*$_{quat}$), 141.2 (*C*$_{quat}$), 148.6 (*C*$_{quat}$-OCH$_3$), 149.0 (*C*$_{quat}$-OCH$_3$), 169.6 (*C*═O); [α]$_D$ −34.6° (*c* 1, CHCl$_3$).

*3.3.6.2. (3S,4R)-**8**.* R_f 0.10 (ether:hexane 1:1), 0.18 (ether:hexane 1:1, two times developed plates); colourless oil; IR 700, 731, 759, 913, 1028, 1139, 1162, 1238, 1264, 1314, 1376, 1422, 1454, 1464, 1496, 1518, 1594, 1605, 1744, 2836, 2934, 2975, 3002, 3028, 3062, 3086, 3360, 3469; ^{1}H NMR (600 MHz) 1.33 (d, 3H, *J* 7.2, C*H*$_3$–CH), 2.93 (dd, 1H, *J* 8.3, 14.7, $^1/_2$ C*H*$_2$), 3.07 (dd, 1H, *J* 5.3, 14.7, $^1/_2$ C*H*$_2$), 3.27 (ddd, 1H, *J* 2.1, 5.3, 7.8, C*H*-3), 3.69 (s, 3H, OC*H*$_3$), 3.85 (s, 3H, OC*H*$_3$), 3.96 (d, 1H, *J* 2.1, C*H*-4), 4.84 (q, 1H, *J* 7.2, 14.3, C*H*–CH$_3$), 6.54 (d, 1H, *J* 2.0, C*H*-2 Ar), 6.64 (dd, 1H, *J* 2.0, 8.2, C*H*-6 Ar), 6.74 (d, 1H, *J* 8.2, C*H*-5 Ar), 7.07 (dd, 2H, *J* 2.0, 7.8, C*H* Ph), 7.14 (d, 2H, *J* 7.1, C*H* Ph), 7.21 (m, 6H, C*H* Ph); ^{13}C NMR (600 MHz) 19.0 (*C*H$_3$–CH), 33.9 (*C*H$_2$), 52.4 (*C*H–CH$_3$), 55.7 (OCH$_3$), 55.8 (OCH$_3$), 59.6 (*C*H-4), 59.9 (*C*H-3), 109.1 (*C*H-2 Ar), 111.0 (*C*H-5 Ar), 119.2 (*C*H-6 Ar), 126.4 (*C*H Ph), 126.6 (*C*H Ph), 127.1 (*C*H Ph), 128.3 (*C*H Ph), 128.4 (*C*H Ph), 129.0 (*C*H Ph), 130.2 (*C*$_{quat}$), 137.7 (*C*$_{quat}$), 141.2 (*C*$_{quat}$), 148.6 (*C*$_{quat}$-OCH$_3$), 149.0 (*C*$_{quat}$-OCH$_3$), 169.6 (*C*═O); [α]$_D$ +27.4° (*c* 1, CHCl$_3$).

*3.3.7. 3-Benzyl-4-(3,4-dimethoxyphenyl)-1-((R)-1-phenylethyl)azetidin-2-one **9**.* MS *m*/*z* 401; HRMS (EI): calcd for $C_{26}H_{27}NO_3$ (M$^+$): 401.1991, found: 401.1985.

*3.3.7.1. (3S,4R)-**9**.* R_f 0.11 (ether:hexane 1:1), 0.23 (ether:hexane 1:1, two times developed plates); colourless oil; IR 701, 734, 759, 1028, 1138, 1163, 1238, 1264, 1311, 1422, 1454, 1464, 1496, 1517, 1594, 1605, 1745, 2836, 2934, 3001, 3028, 3062, 3085, 3471; ^{1}H NMR (600 MHz) 1.68 (d, 3H, *J* 7.2, C*H*$_3$–CH), 3.01 (dd, 1H, *J* 8.4, 14.6, $^1/_2$ C*H*$_2$), 3.13 (dd, 1H, *J* 5.1, 14.6, $^1/_2$ C*H*$_2$), 3.25 (ddd, 1H, *J* 2.1, 5.1, 7.8, C*H*-3), 3.66 (s, 3H, OC*H*$_3$), 3.84 (s, 3H, OC*H*$_3$), 4.02 (d, 1H, *J* 2.1, C*H*-4), 4.30 (q, 1H, *J* 7.2, 14.3, C*H*-CH$_3$), 6.37 (d, 1H, *J* 2.0, C*H*-2 Ar), 6.62 (dd, 1H, *J* 2.0, 8.2, C*H*-6 Ar), 6.74 (d, 1H, *J* 8.2, C*H*-5 Ar), 6.99 (dd, 2H, *J* 2.0, 7.8, C*H* Ph), 7.21 (m, 6H, C*H* Ph), 7.28 (m, 2H, C*H* Ph); ^{13}C NMR (600 MHz) 19.8 (*C*H$_3$–CH), 33.8 (*C*H$_2$), 53.9 (*C*H–CH$_3$), 55.5 (OCH$_3$), 55.7 (OCH$_3$), 58.8 (*C*H-4), 59.8 (*C*H-3), 108.8 (*C*H-2 Ar), 110.8 (*C*H-5 Ar), 118.7 (*C*H-6 Ar), 126.4 (*C*H Ph), 126.6 (*C*H Ph), 127.2 (*C*H Ph), 128.3 (*C*H Ph), 128.4 (*C*H Ph), 129.1 (*C*H Ph), 130.2 (*C*$_{quat}$), 137.7 (*C*$_{quat}$), 141.2 (*C*$_{quat}$), 148.6 (*C*$_{quat}$-OCH$_3$), 149.0 (*C*$_{quat}$-OCH$_3$), 169.6 (*C*═O).

*3.3.7.2. (3R,4S)-**9**.* R_f 0.10 (ether:hexane 1:1), 0.18 (ether:hexane 1:1, two times developed plates); colourless oil; IR 700, 735, 759, 1028, 1139, 1162, 1238, 1264, 1314, 1377, 1422, 1454, 1464, 1496, 1518, 1594, 1605, 1745, 2836, 2852, 2934, 2956, 3029, 3062, 3086, 3469; ^{1}H NMR (600 MHz) 1.33 (d, 3H, *J* 7.2, C*H*$_3$–CH), 2.93 (dd, 1H, *J* 8.3, 14.7, $^1/_2$ C*H*$_2$), 3.07 (dd, 1H, *J* 5.3, 14.7, $^1/_2$ C*H*$_2$), 3.27 (ddd, 1H, *J* 2.1, 5.3, 7.8, C*H*-3), 3.69 (s, 3H, OC*H*$_3$), 3.85 (s, 3H, OC*H*$_3$), 3.96 (d, 1H, *J* 2.1, C*H*-4), 4.84 (q, 1H, *J* 7.2, 14.3, C*H*-CH$_3$), 6.54 (d, 1H, *J* 2.0, C*H*-2 Ar), 6.64 (dd, 1H, *J* 2.0, 8.2, C*H*-6 Ar), 6.74 (d, 1H, *J* 8.2, C*H*-5 Ar), 7.07 (dd, 2H, *J* 2.0, 7.8, C*H* Ph), 7.14 (d, 2H, *J* 7.1, C*H* Ph), 7.21 (m, 6H, C*H* Ph); ^{13}C NMR (600 MHz) 19.0 (*C*H$_3$–CH), 33.9 (*C*H$_2$), 52.4 (*C*H–CH$_3$), 55.7 (OCH$_3$), 55.8 (OCH$_3$), 59.6 (*C*H-4), 59.9 (*C*H-3), 109.1 (*C*H-2 Ar), 111.0 (*C*H-5 Ar), 119.2 (*C*H-6 Ar), 126.4 (*C*H Ph), 126.6 (*C*H Ph), 127.1 (*C*H Ph), 128.3 (*C*H Ph), 128.4 (*C*H Ph), 129.0 (*C*H Ph), 130.2 (*C*$_{quat}$), 137.7 (*C*$_{quat}$), 141.2 (*C*$_{quat}$), 148.6 (*C*$_{quat}$-OCH$_3$), 149.0 (*C*$_{quat}$-OCH$_3$), 169.8 (*C*═O).

*3.3.8. 3-Benzyl-4-(2,4,6-trimethoxyphenyl)-1-((S)-1-phenylethyl)azetidin-2-one **10**.* MS *m*/*z* 431; HRMS (EI): calcd for $C_{27}H_{29}NO_4$ (M$^+$): 431.2097, found: 431.2081.

*3.3.8.1. (3R,4S)-**10**.* R_f 0.36 (ether:hexane 4:1); mp 64–65 °C; IR 700, 815, 918, 953, 1036, 1120, 1153, 1204, 1227, 1325, 1453, 1495, 1590, 1606, 1731, 2841, 2938, 2970, 3001, 3026, 3060, 3085, 3447; ^{1}H NMR (600 MHz) 1.53 (d, 3H, *J* 7.1, C*H*$_3$–CH), 3.01 (A part of ABX, dd, 1H, *J* 8.2, 14.5, $^1/_2$ C*H*$_2$), 3.07 (B part of ABX, dd, 1H, *J* 5.1, 14.5, $^1/_2$ C*H*$_2$), 3.58 (s, 6H, OC*H*$_3$-2 and OC*H*$_3$-6 Ar), 3.66 (ddd, 1H, *J* 2.2, 5.1, 8.2, C*H*-3), 3.77 (s, 3H, OC*H*$_3$-4 Ar), 4.32 (q, 1H, *J* 7.1, 14.2, C*H*-CH$_3$), 4.82 (d, 1H, *J* 2.2, C*H*-4), 5.94 (s, 2H, C*H*-3 and C*H*-5 Ar), 6.90 (m, 2H, C*H* Ph), 7.10 (m, 3H, C*H* Ph), 7.18 (m, 1H, C*H* Ph), 7.23 (m, 4H, C*H* Ph); ^{13}C NMR (600 MHz) 19.0 (*C*H$_3$–CH), 34.6 (*C*H$_2$), 50.4 (*C*H-4), 52.8 (*C*H-CH$_3$), 54.8 (*C*H-3), 55.3 (OCH$_3$-4), 55.4 (OCH$_3$-2 and OCH$_3$-6), 90.4 (*C*H-3 and *C*H-5 Ar), 104.5 (*C*$_{quat}$-1 Ar), 126.1 (*C*H Ph), 126.7 (*C*H Ph), 126.8 (2 *C*H Ph), 127.9 (2 *C*H Ph), 128.2 (2 *C*H Ph), 129.2 (2 *C*H Ph), 138.9 (*C*$_{quat}$ Ph), 141.3 (*C*$_{quat}$ Ph), 160.2 (*C*$_{quat}$-2 and *C*$_{quat}$-6 Ar), 161.1 (*C*$_{quat}$-4 Ar), 170.3 (*C*═O); [α]$_D$ +2.7° (*c* 1, CHCl$_3$).

*3.3.8.2. (3S,4R)-**10**.* R_f 0.28 (ether:hexane 4:1); colourless oil; IR 700, 732, 818, 912, 953, 1040, 1061, 1124, 1155, 1206, 1229, 1328, 1393, 1421, 1438, 1454, 1467, 1496, 1590, 1607, 1734, 2841, 2936, 3028, 3062, 3086, 3458; ^{1}H NMR (600 MHz) 1.21 (d, 3H, *J* 7.1, C*H*$_3$–CH), 2.93 (A part of ABX, dd, 1H, *J* 8.3, 14.6, $^1/_2$ C*H*$_2$), 3.01 (B part of ABX, dd, 1H, *J* 5.0, 14.6, $^1/_2$ C*H*$_2$), 3.64 (s, 6H, OC*H*$_3$-2 and OC*H*$_3$-6 Ar), 3.72 (ddd, 1H, *J* 2.2, 5.0, 8.3, C*H*-3), 3.79 (s, 3H, OC*H*$_3$-4 Ar), 4.76 (d, 1H, *J* 2.2, C*H*-4), 4.80 (q, 1H, *J* 7.1, 14.2, C*H*–CH$_3$), 6.02 (s, 2H, C*H*-3 and C*H*-5 Ar), 6.98 (m, 2H, C*H* Ph), 7.15 (m, 3H, C*H* Ph), 7.20 (m, 5H, C*H* Ph); ^{13}C NMR (600 MHz) 17.6 (*C*H$_3$–CH), 34.4 (*C*H$_2$), 50.7 (*C*H-4), 51.3 (*C*H–CH$_3$), 54.7 (*C*H-3), 55.2 (OCH$_3$-4), 55.4 (OCH$_3$-2 and OCH$_3$-6), 90.4 (*C*H-3 and *C*H-5 Ar), 105.6 (*C*$_{quat}$-1 Ar), 126.1 (*C*H Ph), 127.0 (*C*H Ph), 127.2 (2 *C*H Ph), 128.1 (2 *C*H Ph), 128.2 (2 *C*H Ph), 129.1 (2 *C*H Ph), 138.8 (*C*$_{quat}$ Ph), 140.4 (*C*$_{quat}$ Ph), 160.2 (*C*$_{quat}$-2 and *C*$_{quat}$-6 Ar), 161.2 (*C*$_{quat}$-4 Ar), 170.2 (*C*═O); [α]$_D$ −4.1° (*c* 1, CHCl$_3$).

3.3.9. 3-Benzyl-4-(2,4,6-trimethoxyphenyl)-1-((R)-1-phenylethyl)azetidin-2-one ***11***. MS *m*/*z* 431; HRMS (EI): calcd for $C_{27}H_{29}NO_4$ (M^+): 431.2097, found: 431.2091.

*3.3.9.1. (3S,4R)-**11***. R_f 0.36 (ether:hexane 4:1); mp 64–65 °C; IR 700, 817, 952, 1039, 1061, 1122, 1155, 1206, 1229, 1327, 1421, 1454, 1467, 1496, 1591, 1607, 1735, 2840, 2938, 2972, 3028, 3062, 3086, 3468; ^{1}H NMR (600 MHz) 1.53 (d, 3H, *J* 7.1, C*H*$_3$–CH), 3.01 (A part of ABX, dd, 1H, *J* 8.2, 14.5, $^1/_2$ C*H*$_2$), 3.07 (B part of ABX, dd, 1H, *J* 5.1, 14.5, $^1/_2$ C*H*$_2$), 3.58 (s, 6H, OC*H*$_3$-2 and OC*H*$_3$-6 Ar), 3.66 (ddd, 1H, *J* 2.2, 5.1, 8.2, C*H*-3), 3.77 (s, 3H, OC*H*$_3$-4 Ar), 4.32 (q, 1H, *J* 7.1, 14.2, C*H*–CH$_3$), 4.82 (d, 1H, *J* 2.2, C*H*-4), 5.94 (s, 2H, C*H*-3 and C*H*-5 Ar), 6.90 (m, 2H, C*H* Ph), 7.10 (m, 3H, C*H* Ph), 7.18 (m, 1H, C*H* Ph), 7.23 (m, 4H, C*H* Ph); ^{13}C NMR (600 MHz) 19.0 (*C*H$_3$–CH), 34.6 (*C*H$_2$), 50.4 (*C*H-4), 52.8 (*C*H–CH$_3$), 54.8 (*C*H-3), 55.3 (OCH$_3$-4), 55.4 (OCH$_3$-2 and OCH$_3$-6), 90.4 (*C*H-3 and *C*H-5 Ar), 104.5 (C_{quat}-1 Ar), 126.1 (*C*H Ph), 126.7 (*C*H Ph), 126.8 (2 *C*H Ph), 127.9 (2 *C*H Ph), 128.2 (2 *C*H Ph), 129.2 (2 *C*H Ph), 138.9 (C_{quat} Ph), 141.3 (C_{quat} Ph), 160.2 (C_{quat}-2 and C_{quat}-6 Ar), 161.1 (C_{quat}-4 Ar), 170.3 (*C*=O); $[\alpha]_D$ −0.1° (*c* 1, $CHCl_3$).

*3.3.9.2. (3R,4S)-**11***. R_f 0.28 (ether:hexane 4:1); colourless oil; IR 700, 818, 953, 1124, 1155, 1206, 1230, 1422, 1454, 1467, 1496, 1591, 1607, 1735, 2841, 2937, 2974, 3028, 3062, 3460; ^{1}H NMR (600 MHz) 1.21 (d, 3H, *J* 7.1, C*H*$_3$–CH), 2.93 (A part of ABX, dd, 1H, *J* 8.3, 14.6, $^1/_2$ C*H*$_2$), 3.01 (B part of ABX, dd, 1H, *J* 5.0, 14.6, $^1/_2$ C*H*$_2$), 3.64 (s, 6H, OC*H*$_3$-2 and OC*H*$_3$-6 Ar), 3.72 (ddd, 1H, *J* 2.2, 5.0, 8.3, C*H*-3), 3.79 (s, 3H, OC*H*$_3$-4 Ar), 4.76 (d, 1H, *J* 2.2, C*H*-4), 4.80 (q, 1H, *J* 7.1, 14.2, C*H*–CH$_3$), 6.02 (s, 2H, C*H*-3 and C*H*-5 Ar), 6.98 (m, 2H, C*H* Ph), 7.15 (m, 3H, C*H* Ph), 7.20 (m, 5H, C*H* Ph); ^{13}C NMR (600 MHz) 17.6 (*C*H$_3$–CH), 34.4 (*C*H$_2$), 50.7 (*C*H-4), 51.3 (*C*H-CH$_3$), 54.7 (*C*H-3), 55.2 (OCH$_3$-4), 55.4 (OCH$_3$-2 and OCH$_3$-6), 90.4 (*C*H-3 and *C*H-5 Ar), 105.6 (C_{quat}-1 Ar), 126.1 (*C*H Ph), 127.0 (*C*H Ph), 127.2 (2 *C*H Ph), 128.1 (2 *C*H Ph), 128.2 (2 *C*H Ph), 129.1 (2 *C*H Ph), 138.8 (C_{quat} Ph), 140.4 (C_{quat} Ph), 160.2 (C_{quat}-2 and C_{quat}-6 Ar), 161.2 (C_{quat}-4 Ar), 170.2 (*C*=O); $[\alpha]_D$ +0.3° (*c* 1, $CHCl_3$).

3.3.10. 3-Benzyl-4-(2-(2-phenylethylcarbonyloxy)-3-methoxyphenyl)-1-((S)-1-phenylethyl)azetidin-2-one ***12***. MS *m*/*z* 519; HRMS (EI): calcd for $C_{34}H_{33}NO_4$ (M^+): 519.2410, found: 519.2404.

*3.3.10.1. (3R,4S)-**12***. R_f 0.22 (ether:hexane 1:1), 0.35 (ether:-hexane 1:1, two times developed plates); colourless oil; IR 700, 754, 1125, 1171, 1276, 1310, 1441, 1454, 1481, 1496, 1587, 1606, 1746, 2840, 2937, 3028, 3062, 3086, 3481; ^{1}H NMR (600 MHz) 1.61 (d, 3H, *J* 7.1, C*H*$_3$–CH), 2.80 (t, 2H, *J* 7.7, C*H*$_2$–CO), 2.90 (dd, 1H, *J* 5.4, 14.6, $^1/_2$ C*H*$_2$), 2.95 (t, 2H, *J* 7.6, C*H*$_2$-Ph ester), 3.04 (dd, 1H, *J* 6.1, 14.6, $^1/_2$ C*H*$_2$), 3.36 (td, 1H, *J* 2.1, 6.0, C*H*-3), 3.72 (s, 3H, OC*H*$_3$), 4.05 (d, 1H, *J* 2.2, C*H*-4), 4.08 (q, 1H, *J* 7.1, 14.2, C*H*-CH$_3$), 6.74 (dd, 1H, *J* 1.2, 7.8, C*H* Ar), 6.86 (m, 3H, Ar), 7.07–7.33 (m, 14H, Ph); ^{13}C NMR (600 MHz) 20.3 (*C*H$_3$–CH), 30.6 (*C*H$_2$-Ph ester), 33.3 (*C*H$_2$-Ph), 35.1 (*C*H$_2$–CO), 52.5 (*C*H-4), 54.9 (*C*H-CH$_3$), 55.9 (OCH$_3$), 58.8 (*C*H-3), 111.7 (*C*H-Ar), 118.9 (*C*H-Ar), 126.3 (*C*H-Ar), 126.55 (*C*H-Ar), 126.6 (2×*C*H-Ar), 126.7 (*C*H-Ar), 127.2 (*C*H-Ar), 128.3 (2×*C*H-Ar), 128.4 (2×*C*H-Ar), 128.45 (2×*C*H-Ar), 128.5 (2×*C*H-Ar), 129.5 (2×*C*H-Ar), 130.9 (C_{quat}), 137.4 (C_{quat}), 138.4 (C_{quat}), 140.2 (C_{quat}), 141.1 (C_{quat}), 151.2 (C_{quat}), 169.5 (*C*=O), 170.5 (*C*=O); $[\alpha]_D$ +27.6° (*c* 1, $CHCl_3$).

*3.3.10.2. (3S,4R)-**12***. R_f 0.18 (ether:hexane 1:1), 0.27 (ether:hexane 1:1, two times developed plates); colourless oil; IR 699, 748, 770, 1078, 1125, 1170, 1275, 1310, 1378, 1441, 1454, 1481, 1496, 1587, 1605, 1747, 2850, 2931, 3004, 3029, 3062, 3087, 3487; ^{1}H NMR (600 MHz) 1.19 (d, 3H, *J* 7.1, C*H*$_3$–CH), 2.76 (t, 2H, *J* 7.8, C*H*$_2$–CO), 2.85 (dd, 1H, *J* 5.5, 14.6, $^1/_2$ C*H*$_2$), 2.96 (m, 3H, $^1/_2$ C*H*$_2$ and C*H*$_2$-Ph ester), 3.32 (td, 1H, *J* 2.2, 5.8, C*H*-3), 3.74 (s, 3H, OC*H*$_3$), 4.11 (d, 1H, *J* 2.2, C*H*-4), 4.86 (q, 1H, *J* 7.2, 14.3, C*H*–CH$_3$), 6.86 (dd, 1H, *J* 1.3, 8.1, C*H* Ar), 6.97 (m, 3H, Ar), 7.08–7.36 (m, 14H, Ph); ^{13}C NMR (600 MHz) 18.2 (*C*H$_3$–CH), 30.6 (*C*H$_2$-Ph ester), 33.1 (*C*H$_2$-Ph), 35.1 (*C*H$_2$–CO), 51.7 (*C*H–CH$_3$), 51.8 (*C*H-4), 55.9 (OCH$_3$), 59.5 (*C*H-3), 111.5 (*C*H-Ar), 118.9 (*C*H-Ar), 126.4 (*C*H-Ar), 126.6 (*C*H-Ar), 126.7 (*C*H-Ar), 127.1 (2×*C*H-Ar), 127.3 (*C*H-Ar), 128.3 (2×*C*H-Ar), 128.4 (2×*C*H-Ar), 128.45 (2×*C*H-Ar), 128.6 (2×*C*H-Ar), 129.3 (2×*C*H-Ar), 132.4 (C_{quat}), 137.3 (C_{quat}), 138.0 (C_{quat}), 139.8 (C_{quat}), 140.1 (C_{quat}), 151.1 (C_{quat}), 169.8 (*C*=O), 170.3 (*C*=O); $[\alpha]_D$ −11.1° (*c* 1, $CHCl_3$).

3.3.11. 3-Benzyl-4-(2-(2-phenylethylcarbonyloxy)-3-methoxyphenyl)-1-((R)-1-phenylethyl)azetidin-2-one ***13***. MS *m*/*z* 519; HRMS (EI): calcd for $C_{34}H_{33}NO_4$ (M^+): 519.2410, found: 519.2408.

*3.3.11.1. (3S,4R)-**13***. R_f 0.22 (ether:hexane 1:1), 0.35 (ether:-hexane 1:1, two times developed plates); colourless oil; IR 700, 765, 1126, 1276, 1310, 1441, 1454, 1481, 12,937, 2979, 3005, 3028, 3062, 3086, 3504; ^{1}H NMR (600 MHz) 1.61 (d, 3H, *J* 7.1, C*H*$_3$–CH), 2.80 (t, 2H, *J* 7.7, C*H*$_2$–CO), 2.90 (dd, 1H, *J* 5.4, 14.6, $^1/_2$ C*H*$_2$), 2.95 (t, 2H, *J* 7.6, C*H*$_2$-Ph ester), 3.04 (dd, 1H, *J* 6.1, 14.6, $^1/_2$ C*H*$_2$), 3.36 (td, 1H, *J* 2.1, 6.0, C*H*-3), 3.72 (s, 3H, OC*H*$_3$), 4.05 (d, 1H, *J* 2.2, C*H*-4), 4.08 (q, 1H, *J* 7.1, 14.2, C*H*–CH$_3$), 6.74 (dd, 1H, *J* 1.2, 7.8, C*H* Ar), 6.86 (m, 3H, Ar), 7.07–7.33 (m, 14H, Ph); ^{13}C NMR (600 MHz) 20.3 (*C*H$_3$–CH), 30.6 (*C*H$_2$-Ph ester), 33.3 (*C*H$_2$-Ph), 35.1 (*C*H$_2$–CO), 52.5 (*C*H-4), 54.9 (*C*H–CH$_3$), 55.9 (OCH$_3$), 58.8 (*C*H-3), 111.7 (*C*H-Ar), 118.9 (*C*H-Ar), 126.3 (*C*H-Ar), 126.55 (*C*H-Ar), 126.6 (2×*C*H-Ar), 126.7 (*C*H-Ar), 127.2 (*C*H-Ar), 128.3 (2×*C*H-Ar), 128.4 (2×*C*H-Ar), 128.45 (2×*C*H-Ar), 128.5 (2×*C*H-Ar), 129.5 (2×*C*H-Ar), 130.9 (C_{quat}), 137.4 (C_{quat}), 138.4 (C_{quat}), 140.2 (C_{quat}), 141.1 (C_{quat}), 151.2 (C_{quat}), 169.5 (*C*=O), 170.5 (*C*=O); $[\alpha]_D$ −31.1° (*c* 1, $CHCl_3$).

*3.3.11.2. (3R,4S)-**13***. R_f 0.18 (ether:hexane 1:1), 0.27 (ether:hexane 1:1, two times developed plates); colourless oil; IR 700, 753, 1078, 1126, 1170, 1275, 1310, 1379, 1441, 1454, 1481, 1496, 1587, 1605, 1748, 2841, 2934, 2977, 3029, 3062, 3087, 3486; ^{1}H NMR (600 MHz) 1.19 (d, 3H, *J* 7.1, C*H*$_3$–CH), 2.76 (t, 2H, *J* 7.8, C*H*$_2$–CO), 2.85 (dd, 1H, *J* 5.5, 14.6, $^1/_2$ C*H*$_2$), 2.96 (m, 3H, $^1/_2$ C*H*$_2$ and C*H*$_2$-Ph ester), 3.32 (td, 1H, *J* 2.2, 5.8, C*H*-3), 3.74 (s, 3H, OC*H*$_3$), 4.11 (d, 1H, *J* 2.2, C*H*-4), 4.86 (q, 1H, *J* 7.2, 14.3, C*H*–CH$_3$), 6.86 (dd, 1H, *J* 1.3, 8.1, C*H* Ar), 6.97 (m, 3H, Ar), 7.08–7.36 (m, 14H, Ph); ^{13}C NMR (600 MHz) 18.2 (*C*H$_3$–CH), 30.6 (*C*H$_2$-Ph ester), 33.1 (*C*H$_2$-Ph), 35.1 (*C*H$_2$–CO), 51.7 (*C*H–CH$_3$), 51.8 (*C*H-4), 55.9 (OCH$_3$), 59.5 (*C*H-3), 111.5 (*C*H-Ar), 118.9 (*C*H-Ar), 126.4 (*C*H-Ar), 126.6 (*C*H-Ar), 126.7 (*C*H-Ar), 127.1 (2×*C*H-Ar), 127.3 (*C*H-Ar), 128.3 (2×*C*H-Ar), 128.4 (2×*C*H-Ar), 128.45 (2×*C*H-Ar), 128.6 (2×*C*H-Ar), 129.3 (2×*C*H-Ar), 132.4 (C_{quat}), 137.3 (C_{quat}), 138.0 (C_{quat}), 139.8 (C_{quat}), 140.1 (C_{quat}), 151.1 (C_{quat}), 169.8 (*C*=O), 170.3 (*C*=O); $[\alpha]_D$ +10.0° (*c* 1, $CHCl_3$).

3.4. X-ray crystallographic investigations

Colourless prism-shaped crystals of dimensions 0.32×0.12×0.03 mm or 0.56×0.34×0.12 mm were selected for structural analysis of (3*S*,4*R*)-**6** and (3*R*,4*S*)-**7**, respectively. Intensity data for this compound were collected using a diffractometer with a Bruker APEX ccd area detector[32] and graphite-monochromated Mo *K*α radiation (λ=0.71073 Å). The samples were cooled to 100(2) K. Cell parameters were determined from a non-linear least squares fit of 3859 or 4702 peaks in the range $2.64<\theta<27.77°$ or $2.21<\theta<27.89°$. A total of 9167 or 9859 data were measured in the range $1.89<\theta<26.00°$ using ω oscillation frames. The data were corrected for absorption by the semi-empirical method[33] giving minimum and maximum transmission factors of 0.973 and 0.996 or 0.956 and 0.992. The data were merged to form a set of 4058 or 4120 independent data with *R*(int)=0.0329 or 0.0350 and a coverage of 99.8% or 99.9%.

The orthorhombic space group $P2_12_12_1$ was determined for both compounds by systematic absences and statistical tests and verified by subsequent refinement. The structures were solved by direct methods and refined by full-matrix least squares methods on F^2.[34]

Hydrogen atom positions were initially determined by geometry and refined by a riding model. Non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atom displacement parameters were set to 1.2 (1.5 for methyl) times the displacement parameters of the bonded atoms. A total of 262 parameters were refined for both samples against 4058 or 4120 data to give $wR(F^2)$=0.0989 or 0.1045 and S=1.007 or 1.004 for weights of $w=1/[\sigma^2(F^2)+(0.0460\ P)^2+0.3000\ P]$ or $w=1/[\sigma^2(F^2)+(0.0500\ P)^2+0.4000\ P]$, where $P=[F_o^2+2F_c^2]/3$. The final $R(F)$ was 0.0434 for the 3513 or 3669 observed, [$F>4\sigma(F)$], data. The largest shift/s.u. was 0.000 in the final refinement cycles. The final difference map had maxima and minima of 0.177 or 0.210 and −0.209 e/Å^3 or −0.169 e/Å^3, respectively.

Full crystallographic data for this paper in cif-format can be obtained free of charge from the Cambridge Crystallographic Data Centre.[35]

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