A new approach to the stereoselective synthesis of trans-3-carbamoyl-\(\beta\)-lactam moieties

Anna Zakaszewska, Ewelina Najda-Mocarska and Sławomir Makowiec*

One-pot synthesis of optically active 1,4-disubstituted-3-carbamoyl-azetidinones from 5-\{(N-arylamino)-(hydroxyl)methylene\}-2,2-dimethyl-1,3-dioxa-4,6-diones and chiral aldimines is achieved via thermal generation of carbamoyl ketenes and subsequent [2+2] cycloaddition. Three possible chiral induction approaches were tested and \((R)-(+)\)-1-phenylethylamine was confirmed as the best chiral auxiliary. Among the four possible diastereoisomers, only two with significant excess of one were formed.

Introduction

Cardiovascular diseases are still the leading cause of death in developed countries.\(^1\) Atherosclerosis associated with the pathological metabolism of fats and cholesterol plays a significant role in the development of these diseases. Among the many methods of treating this type of disorder, the therapy that aims at reducing the level of plasma cholesterol is one of the newest and the most promising methods.\(^2\) Ezetimibe, the first NPC1L1 inhibitor, is a drug used alone or in combination with statins to treat hypercholesterolemia.\(^3\) Despite some suspicions of carcinogenicity, its effectiveness is not to be doubted. Since the discovery of ezetimibe,\(^4\) NPC1L1 inhibitors with various similar structures have been developed, such as AZD 4121 (Astra Zeneca),\(^5\) AVE5530 (Sanofi-Aventis),\(^6\) and SCH-48461\(^7\) (Fig. 1).

In 1980, Watanabe proposed an unconventional method for the construction of \(\beta\)-lactam rings, based on the thermal decomposition of 5-acyl-2,2-dimethyl-1,3-dioxa-4,6-diones to 2-oxo-ketenes and their subsequent reaction with aldimine.\(^8\) Recently, we have focused our research efforts on the formation of \(\beta\)-lactams during [2+2] cycloaddition of aldimines to \(\beta\)-oxo-ketenes generated from 5-carbamoyl-2,2-dimethyl-1,3-dioxadiones (1) under pyrolytic conditions.\(^9\) On a representative series of models, we have observed the exclusive formation of trans \(\beta\)-lactam rings.

However, the presence of a trans configuration is not the only necessary criterion that increases the potential of cholesterol absorption inhibitors, since only one from a pair of enantiomers can exhibit biological activity.\(^10\) Therefore, we hypothesize that the application of a recently developed method along with suitable chiral induction would lead to the formation of only one diastereoisomer of 3-carbamoyl \(\beta\)-lactam. Such a method could be a simple one-pot procedure for the formation of ezetimibe-like scaffolds.

Our previous research carried out with 5-acyl-2,2-dimethyl-1,3-dioxadiones as a source of ketenes and chiral aldimines confirmed our hypothesis. However, yields of azetidinones obtained with chiral induction compared to those obtained by experiments conducted without chiral induction were worse.\(^11\)

Results and discussion

Our study discusses a methodology for synthesizing diastereoisomerically enriched 3-carbamoyl-\(\beta\)-lactams and proposes an exhaustive study on the relationship between the type and position...
of chiral induction on the obtained diastereoisomeric excess. From a theoretical perspective, in the case of [2+2] cycloaddition of 2-carbamoyl ketenes (2) to aldmines (3), three potential approaches of chiral induction are possible (Scheme 1).

The first approach is to attach a chiral moiety to 2,2-dimethyl-1,3-dioxao-4,6-dione, for example, an isocyanate derivative of amino acid esters is attached or an aeylation reaction with N-protected amino acids is carried out.\(^\text{12,13}\) An undeniable advantage of this approach is the ease of preparation of 5-carbamoyl-2,2-dimethyl-1,3-dioxadiones (1) or 5-acyl-2,2-dimethyl-1,3-dioxadiones and the inexhaustible source of chiral auxiliaries. On the other hand, the relatively long distance between the chiral center and the newly formed bond could be a significant disadvantage, which may reduce diastereoisomeric excess. We tested such an approach by reacting \((S)-5\text{-}[1\text{-}hydroxy\text{-}2\text{-}[phtaloylamino]propyldiene]\text{-}2\text{-}2\text{-}dimethyl\text{-}1,3\text{-}dioxane\text{-}4,6\text{-}dione (5) with \(N\)-benzylidene propan-2-amine (3ad) in boiling toluene that was previously saturated with gaseous HCl. We obtained azetidinone (6) with negligible diastereoisomeric excess (Scheme 2).

The second approach to introduce chiral induction is to use chiral aldimine derived from chiral amine and aldehyde. This approach is widely followed in the synthesis of chiral azetidinones by [2+2] cycloaddition using ketenes generated in a conventional manner by acyl chlorides or azides.\(^\text{14}\) This method has significant advantages such as the ease of preparation of aldimines and a wide range of commercially available chiral amines. Moreover, the application of arylmethylamines is indeed a chiral auxiliary strategy, which allows removing the amine moiety after undergoing oxidative cleavage.\(^\text{15}\) Therefore, in the preliminary study, we made to react compounds 5-[hydroxy-\((\text{phenylamino})\text{methylene}\text{-}2\text{-}2\text{-}dimethyl\text{-}1,3\text{-}dioxane\text{-}4,6\text{-}dione (1a) and \((R)\)-N-benzylidene-1-phenylethanamine (3aa) in boiling toluene previously saturated with HCl. As a result, we obtained a mixture of diastereoisomers \((3S, 4S)-2\text{-}\text{oxo-N},4\text{-diphenyl}-1\text{-}((R)\text{-}1\text{-}phenylethyl)\text{azetidine-3-carboxamide (7aaa) and (3R, 4R)-2\text{-}\text{oxo-N},4\text{-diphenyl}-1\text{-}((R)\text{-}1\text{-}phenylethyl)\text{azetidine-3-carboxamide (8aaa)} in a ratio of 63:37, with an overall yield of 45% (entry 1 Table 1). These results paved the way for in-depth research to analyze the broad scope of these models. We used aldimines prepared from \((R)\text{-}[1\text{-}phenylethylamidine, \((R)\text{-}[1\text{-}(1\text{-}naphthyl)ethylamidine and \((R)\text{-}[1\text{-}(2\text{-}naphthyl)ethylamidine as a source of asymmetric induction. Ketenes were generated from 5-[hydroxy-\((\text{arylaminomethylene})\text{-}2\text{-}2\text{-}dimethyl\text{-}1,3\text{-}dioxane\text{-}4,6\text{-}diones (1a-i). Alkylamino derivatives of 1 were excluded from the research as they tend to form six-membered 1,3-oxazine R,4-dienes instead of azetidinones.\(^\text{16}\) From Table 1 we can conclude that it is difficult to find a regular tendency between the structures and the diastereoisomeric excess obtained. In some cases, certain reactions appeared to be very sensitive to the “butterfly effect.” A small, negligible change in the structure that does not cause any significant differences in electron or steric effects turned out to be important. For example, substituting a methyl group in the \(p\)-hydrogen position of a ketene moiety drastically reduces de (entry 12 vs. 20, Table 1), whereas a strong electron-donating (entry 15, Table 1) or an electro-accepting group in para position (entry 22, Table 1) has a weaker effect. However, some regularities are observed. A bulky alkyl tertiary group in most cases leads to higher de (entries 12–16, 18–22, Table 1), but introducing an allyl group in such a tertiary system lowers the de (entries 23, 24, Table 1). Aiming to increase the diastereoselectivity, we checked whether a lower reaction temperature would lead to better results. Based on our previous experience with ketenes generated from 5-carbamoyl-2,2-dimethyl-1,3-dioxadiones (1),\(^\text{9}\) we have confirmed that the lowest acceptable temperature for the effective course of reaction is 80 °C. Although the reaction time was elongated up to 28 h, the yield obtained by reacting (1a) with \((S)-N\text{-}[2\text{-}2\text{-}dimethylpropylene]\text{-}1\text{-}phenylethanamine (3ea) in boiling benzene was worse and de was lower (entry 13, Table 1). We also carried out the aforementioned experiment in boiling DCE, but the result was unsatisfactory (entry 14, Table 1). Eventually, we checked whether the application of MW irradiation instead of heating would improve de, but the yield and amount of by-products obtained were unacceptable.

The \(^1\text{H}-\text{NMR} \text{ spectra of prepared } \beta\text{-lactams 7aaa-ahd and 8aaa-8ahd showed coupling constants for H-C(2) and H-C(3) in the range of 2.0–2.8 Hz in all cases, indicating the exclusive formation of trans products. Products 7aaa-ahd and 8aaa-8ahd possess three stereogenic centers, including one with a fixed configuration; hence, considering that only trans-\(\beta\text{-lactam}-\text{w} were obtained, only two diastereoisomers \((1'R, 2R, 3R)\text{ and } (1'R, 2S, 3S)\text{ should exist. To assign absolute configuration for 7aea and 8aea diastereoisomers NOESY experiments and conformational analysis with HyperChem software using an MM+ force field for each compound were carried out. The NOESY spectrum of the first diastereoisomer eluted from column chromatography, 7aea, revealed interactions between...}
the H–C(1) methine proton and the tert-butyl group and between the H–C(1) methine and the H–C(2) \( \beta \)-lactam proton, whereas the spectrum of the second diastereoisomer \( \text{8aea} \) showed interaction only between the H–C(1) methine proton and the tert-butyl group.

Calculation of the lowest energy conformation revealed that in the \( (1^R, 2^S, 3^S) \) diastereoisomer the short interatomic distance between H–C(1) methine and the H–C(2) \( \beta \)-lactam proton was 0.27 nm, whereas that of the second diastereoisomer with configuration \( (1^R, 2^R, 3^R) \) was 0.35 nm which was significantly longer (Fig. 2). The distances between H-atoms in the lowest energy conformation were compared with the interaction observed by NOESY experiments and the results strongly suggest that the configuration of \( \text{7aea} \) is \( (1^R, 2^S, 3^S) \) whereas that of \( \text{8aea} \) is \( (1^R, 2^R, 3^R) \). For other models such as \( \text{7cea} / \text{8cea} \) and \( \text{7ifa} / \text{8ifa} \) interatomic distances in the lowest energy conformation identically correlated with the interaction observed by NOESY experiments.

Taking into account the plausible reaction mechanism for ring closing in [2+2] azetidinone formation,\(^{17} \) it has been emphasized that the most promising manner for effective chiral induction would be placing an asymmetric atom as close to the reaction center as possible, that is, in the aldehyde moiety of aldimine. Such an approach is frequently used in the classical Staudinger reaction for stereoselective formation of azetidinone rings.\(^{18} \) These reactions when carried out under

Table 1  Stereoselective synthesis of trans-3-carbamoyl-\( \beta \)-lactams

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\(^a\) Configuration assigned based on NOESY spectral results and conformational analysis. \(^b\) Reaction in benzene. \(^c\) Reaction in DCE.
Basic conditions have a broad scope of chiral auxiliaries—mainly protected carbohydrate derivatives—\(^{19}\) including commercially available compounds.

In the process carried out in this study, saturation with HCl excludes all the aforementioned chiral precursors and therefore we had to develop a novel approach. In such cases, aldehydes derived from \(N\)-protected amino acids can act as good alternatives for carbohydrate derivatives that are to be used as chiral auxiliaries. We synthesized \((S)-2-(1-(\text{isopropylimino})\text{propan-2-yl})\text{isoindoline-1,3-dione}^{20}\) based on alaninal; however, when 5-[hydroxy(phenylamino)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione (1a) in boiling toluene was saturated with HCl, we obtained a complex mixture of products without any traces of the azetidinone product (the crude reaction mixture was tested using \(^1\text{H} \text{NMR for specific signals (Scheme 3). To examine whether it is a property of the amino acid derivatives, we carried out additional experiments under the same reaction conditions. When compound 1a was reacted with aldimines of aliphatic aldehydes containing \(\alpha\)-hydrogen, ((\(R\))-\(N\)-(2-ethylhexylidene)-1-phenylethana)mine and \((R\)-\(N\)-(2-methylbutylidene)-1-phenylethanalamine), the desired azetidone was not observed (Scheme 4). These results, observed only for aldimines containing \(\alpha\)-hydrogen, strongly suggest the course of side reactions through enolization of aldimine catalyzed by HCl.

Moreover, we also synthesized (1\(R\), 2\(S\), 5\(R\))-2-isopropyl-5-methylcyclohexanecarbaldehyde, which is an excellent chiral auxiliary and can be easily prepared from \((-\)-menthone) by Wittig reaction with (methoxymethyl)triphenylphosphonium chloride.\(^{21}\) However, this model has limitations because of the presence of \(\alpha\)-hydrogen. From the reaction mixture composed of 1a and \(N\)-((1\(R\), 2\(S\), 5\(R\))-2-isopropyl-5-methylcyclohexyl)methylene)propan-2-amine (3gd), we isolated \(N^4\)-isopropyl-\(N^4\)-((\(\text{E}\))-((2\(R\), 5\(S\))-2-isopropyl-5-methylcyclohexylidene)methyl)-\(N^3\)-phenylmalonamide (9), which confirmed the enolization of aldimine during the reaction with 1a\(^{22}\) (Scheme 5).

Our attempts toward the stereoselective methylation of (1\(R\), 2\(S\), 5\(R\))-2-isopropyl-5-methylcyclohexanecarbaldehyde on the \(\alpha\)-position failed. Because our reaction conditions exclude any other type of aldehyde, we thoroughly investigated CA for synthesizing tertiary aldehydes by stereoselective methods. Hara et al. recently published a series of papers regarding asymmetric \(\alpha\)-allylation of aldehydes.\(^{23}\) We prepared (\(R\))-2-methyl-2-phenylpent-4-enal according to their procedure with 95% ee and transformed it into aldimine 3hd. The reaction of (\(R\))-\(N\)-(2-methyl-2-phenylpent-4-en-1-yldiene)propan-2-amine 3hd with 5-[hydroxy(phenylamino)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione (1a) under optimal conditions led to the formation of two diastereoisomers of trans-1-isopropyl-2-oxo-\(N\)-phenyl-4-((\(R\))-2-phenylpent-4-en-2-yl)azetidine-3-carboxamide with 50% yield, but unfortunately with no diastereoselectivity (Scheme 6).

**Conclusions**

We have developed a process for the stereoselective formation of 3-carbamoyl-\(\beta\)-lactams; one diastereoisomer was formed in excess, with a trans configuration in the azetidinone ring. A wide range of representative models were prepared. 5-[Hydroxy(arylaminomethylene]-2,2-dimethyl-1,3-dioxane-4,6-diones (1a-i) were applied as a source of ketenes for [2+2] cycloaddition to aldimines. Chiral induction proved to be the most effective when a chiral center was present in the amine moiety of the aldimine. Surprisingly, the application of chiral aldehydes with a chiral center closer to the newly formed bond entailed much lower diastereoisomeric excess values.

**Experimental**

**Materials and general methods**

Reagents were purchased from Sigma-Aldrich or Acros. Toluene was distilled from potassium under argon and stored over...
molecular sieves. DCM was distilled over P2O5 and stored over molecular sieves. Commercially unavailable reagents were prepared according to the procedures mentioned in the literature: 5-[hydroxy[(phenylamino)methylene]-2,2-dimethyl-1,3-dioxo-4,6-dione 1a, 5-[hydroxy[(4-nitrophenyl)amino]methylene]-2,2-dimethyl-1,3-dioxo-4,6-dione 1b, 5-[hydroxy[(3-chlorophenyl)amino]methylene]-2,2-dimethyl-1,3-dioxo-4,6-dione 1c, 5-[hydroxy[(4-methoxyphenyl)amino]methylene]-2,2-dimethyl-1,3-dioxo-4,6-dione 1d, and 5-[hydroxy[(2-(methylamino)methylene]methyl]-2,2-dimethyl-1,3-dioxo-4,6-dione 1f. Chiral imines 3aa-hd were prepared according to the procedure mentioned in the literature.27 Analytical TLC was performed on aluminum sheets of UV-254 Merck silica gel. Flash chromatography was performed using 40–63 micron Zeocrom silica gel. 1H and 13C spectra were recorded on Varian Gemini 200, Bruker Avance III HD 400 MHz and Varian Unity Plus 500 spectrometers, chemical shifts (δ) are given in ppm relative to internal Me4Si; coupling constants (J) are given in Hz. High resolution mass spectra (HRMS) were recorded on a MicroMas Quattro LCT mass spectrometer. Melting points were determined with a Warsztat Elektromechaniczny W-wa apparatus and are not corrected. The ratio of the diastereoisomers was determined based on isolated yields as well as by integration of 1H spectra.

5-[Hydroxy[(3-methylphenyl)amino]methylene]-2,2-dimethyl-1,3-dioxo-4,6-dione (1e)

To a cooled to 0 °C solution of Meldrum’s acid (0.72 g, 5 mmol) in dry DFM (5 ml), Et3N (1.4 ml, 10 mmol) was added. The mixture was stirred for 10 min and 3-methylphenylisocyanate (0.665 g, 5 mmol) was added. The stirring was continued for 15 min at 0 °C and 1 h at RT. The reaction mixture was poured into 2 M HCl ice cooled aqueous solution (30 ml). The solid precipitate was filtered and washed with cold water. Crystalization from AcOEt/hexane gave 0.860 g, 62% yield; mp 98–101 °C. 

1H NMR (400 MHz, CDCl3): δ 13.13 (s, 1H), 12.18 (s, 1H), 7.32–7.27 (m, 3 H), 7.12–7.08 (m, 1 H), 2.40 (s, 3 H), 1.79 (s, 6 H), 13C NMR (100 MHz, CDCl3): δ 170.7, 169.1, 164.3, 160.7 (d, JCF = 10 Hz), 130.7 (d, JCF = 8 Hz), 116.2 (d, JCF = 24 Hz), 110.6 (d, JCF = 26 Hz), 105.4, 73.9, 26.3. HRMS (ESI+): m/z calcd for C13H11FNO5Na [M – H]− 276.0872, found. 276.0864.

5-[Hydroxy[(4-methylphenyl)amino]methylene]-2,2-dimethyl-1,3-dioxo-4,6-dione (1g)

To a cooled to 0 °C solution of Meldrum’s acid (0.72 g, 5 mmol) in dry DFM (5 ml) was added Et3N (1.4 ml, 10 mmol). The mixture was stirred for 10 min and 4-methylphenylisocyanate (0.685 g, 5 mmol) was added. The stirring was continued for 15 min at 0 °C and 1 h at RT. The reaction mixture was poured into 2 M HCl ice cooled aqueous solution (30 ml). The solid precipitate was filtered and washed with cold water. Crystalization from AcOEt/hexane gave 0.900 g, 65% yield; mp 118–120 °C. 

1H NMR (400 MHz, CDCl3): δ 15.65 (s, 1H), 11.10 (s, 1H), 7.40–7.33 (m, 2 H), 7.21–7.17 (m, 1 H), 7.00–6.95 (m, 1 H), 1.79 (s, 6 H), 13C NMR (100 MHz, CDCl3): δ 171.0, 169.3, 164.2, 162.8 (d, JCF = 245 Hz), 136.3 (d, JCF = 10 Hz), 130.5 (d, JCF = 9 Hz), 117.4 (d, JCF = 3 Hz), 113.3 (d, JCF = 21 Hz), 109.6 (d, JCF = 26 Hz), 105.4, 73.9, 26.3. HRMS (ESI+): m/z calcd for C13H11FNO5Na [M – H]− 280.0621, found. 280.0610.

5-[Hydroxy[(3-fluorophenyl)amino]methylene]-2,2-dimethyl-1,3-dioxo-4,6-dione (1h)

To a cooled to 0 °C solution of Meldrum’s acid (0.72 g, 5 mmol) in dry DFM (5 ml) was added Et3N (1.4 ml, 10 mmol). The mixture was stirred for 10 min and 3-fluorophenylisocyanate (0.685 g, 5 mmol) was added. The stirring was continued for 15 min at 0 °C and 1 h at RT. The reaction mixture was poured into 2 M HCl ice cooled aqueous solution (30 ml). The solid precipitate was filtered and washed with cold water. Crystalization from AcOEt/hexane gave 0.899 g, 64% yield; mp 102–104 °C. 

1H NMR (400 MHz, CDCl3): δ 16.06 (s, 1H), 11.23 (s, 1H), 7.40–7.33 (m, 2 H), 7.21–7.18 (m, 1 H), 7.00–6.95 (m, 1 H), 1.79 (s, 6 H), 13C NMR (100 MHz, CDCl3): δ 171.0, 169.3, 164.2, 162.8 (d, JCF = 245 Hz), 136.3 (d, JCF = 10 Hz), 130.5 (d, JCF = 9 Hz), 117.4 (d, JCF = 3 Hz), 113.3 (d, JCF = 21 Hz), 109.6 (d, JCF = 26 Hz), 105.4, 73.9, 26.3. HRMS (ESI+): m/z calcd for C13H11FNO5Na [M – H]− 280.0621, found. 280.0622.

2-(1-Isopropyl-2-oxo-4-phenylazetidin-3-yl)-1-oxopropan-2-yl)sioindoline-1,3-dione (6)

To a solution of 5 (0.345 g, 1 mmol) in dry toluene (10 ml) was added N-benzylidenepropan-2-amine (3ad) (0.294 g, 2 mmol). The reaction mixture was cooled to 0 °C and saturated with dry HCl over 20 min. The resulting mixture was stirred and heated to reflux for 2 h. After completion of the reaction, the solvent was removed under vacuum, and the residue was purified with flash chromatography (EtOAc: Hex 1:3, SiO2) giving one fraction, a mixture of two diastereoisomers (170 mg, 0.43 mmol, 43%, ratio 53:47, yellow oil). Overall de = 6%. 1H NMR (500 MHz, CDCl3): δ: 7.89–7.85 (m, 1 H, ArH), 7.78–7.76 (m, 1 H, ArH), 7.73–7.72 (m, 1 H, ArH), 7.70–7.68 (m, 1 H, ArH), 7.38–7.37 (m, 2 H, ArH), 7.30–7.19 (m, 3 H, ArH), 5.03–4.98 (m, 1 H, CH2CH3, H-4), 4.91 (q, 0.53 H, J = 7.5 Hz, CH3CH3), 4.85 (d, 0.47 H, J = 2.5 Hz, H-4), 4.18 (d, 0.53 H, J = 2.5 Hz, H-3), 4.04 (d, 0.47 H, J = 2.5 Hz, H-3), 3.74–3.65 (m, 1 H, CH(CH3)2), 1.75 (d, 1.59 H, J = 7.5 Hz, CH3CH3), 1.60 (d, 1.41 H, J = 7.5 Hz, CH3CH3), 1.21 (d, 1.59 H, J = 6.5 Hz, CH3CH3), 1.41 (d, 1.41 H, J = 6.5 Hz, CH3CH3), 1.00 (d, 3 H, J = 6.5 Hz, CH3CH3) ppm. 13C NMR (100 MHz, CDCl3)
δ: 198.4 (maj), 196.6 (min), 167.6 (maj), 167.3 (min), 162.1 (maj), 162.5 (min), 137.7 (min), 137.6 (maj), 134.2, 134.1, 134.0, 132.0, 131.6, 129.0, 128.9, 128.8, 128.6, 126.8, 123.5, 123.4, 68.1 (min), 55.7 (maj), 54.8 (min), 54.6 (maj), 54.1 (min), 45.8 (maj), 45.7 (min), 21.1 (min), 21.0 (maj), 20.3 (maj), 20.2 (min), 14.3 (min), 13.6 (maj), ppm.

N1-Isopropyl-N1-[(E)-(2R,5S)-2-isopropyl-5-methylenecyclohexylidene]-N2-phenylmalonamide (9)

To a solution of 1a (0.263 g, 1 mmol) in dry toluene (10 ml) was added N1-[(1R,2S,5R)-2-isopropyl-5-methylenecyclohexyl]methylene)-propan-2-amine (3g) (0.418 g, 2 mmol). The reaction mixture was cooled to 0 °C and saturated with dry HCl over 20 min. The resulting mixture was stirred and heated to reflux for 2 h. After completion of the reaction, the solvent was removed under vacuum, and the residue was purified by flash chromatography (EtOAc : Hex 1 : 3, SiO2) giving one fraction, a mixture of two diastereoisomers (29 mg, 0.08 mmol, 8%).1H NMR (400 MHz, CDCl3) δ: 10.44 (s, 1 H, NH), 7.61–7.59 (m, 2 H, ArH), 7.36–7.32 (m, 2 H, ArH), 7.13–7.09 (m, 1 H, ArH), 5.63 (s, 1 H, CH=C), 4.89 (q, 1 H, J = 6.8 Hz, CH3(CH3)), 3.40 (d, 1 H, J = 18.0 Hz, C(O)CH2C(O)), 3.29–3.26 (m, 1 H), 2.16–2.09 (m, 1 H), 1.95–2.03 (m, 3 H), 1.75–1.67 (m, 1 H), 1.58–1.45 (m, 1 H), 1.44–1.33 (m, 1 H), 1.30–1.21 (m, 1 H), 1.15 (d, 3 H, J = 6.8 Hz, CH3), 1.12 (d, 3 H, J = 6.8 Hz, CH3), 1.05 (d, 3 H, J = 6.8 Hz, CH3), 0.95 (d, 3 H, J = 6.8 Hz, CH3), 0.91 (d, 3 H, J = 6.8 Hz, CH3).

General procedure for the stereoselective preparation of 3-carbamoyl-azetidin-2-ones (7aa-hd) and (8aa-hd)

To a solution of 1a-i (1 mmol) in dry toluene (10 ml) was added aldime 3aa-hd (2 mmol). The reaction mixture was cooled to 0 °C and saturated with dry HCl over 20 min. The resulting mixture was stirred and heated to reflux for 2 h. After completion of the reaction, the solvent was removed under vacuum, and the residue was purified as specified below.

2-Oxo-N4-diphenyl-1-(1-phenylethyl)azetidine-3-carboxamide (7aa) and (8aa)

Purification by flash chromatography (EtOAc : Hex 1 : 3, SiO2) gave one fraction, a mixture of two diastereoisomers (167 mg, 0.45 mmol, 45%, ratio 63:37, yellow oil). Overall de = 26%.

1H NMR (500 MHz, CDCl3) δ: 8.33 (s, 0.63 H, NH), 8.31 (s, 0.37 H, NH), 7.55 (d, 0.63 H, J = 8 Hz, ArH), 7.48 (d, 1 H, J = 8 Hz, ArH), 7.37–7.28 (m, 6.74 H, ArH), 7.27–7.21 (m, 4.37 H, ArH), 7.20–7.16 (m, 1.26 H, ArH), 7.13–7.08 (m, 1 H, ArH), 4.94 (q, 0.63 H, J = 7.5 Hz, CHCH3), 4.84 (d, 0.63 H, J = 2.0 Hz, H-4), 4.82 (d, 0.37 H, J = 2.0 Hz, H-4), 4.41 (q, 0.37 H, J = 7.5 Hz, CHCH3), 3.95 (d, 0.63 H, J = 2.0 Hz, H-3), 3.92 (d, 0.37 H, J = 2.0 Hz, H-3), 1.80 (d, 1.11 H, J = 7.5 Hz, CH3), 1.41 (d, 1.89 H, J = 7.5 Hz, CH3) ppm.13C NMR (125 MHz, CDCl3) δ: 165.5 (major), 165.4 (min), 163.7 (min), 163.4 (major), 140.6, 139.5, 137.9, 137.7, 137.6, 136.8, 129.2, 129.1, 129.0, 128.9, 128.0, 127.4, 127.2, 127.1, 127.0, 124.8, 124.7, 120.2, 120.1, 63.5 (major), 63.4 (min), 57.8 (major), 57.4 (min), 55.2 (min), 53.7 (major), 20.2 (min), 19.5 (major) ppm. HRMS (ESI+): m/z calcd for C23H18N2O4Na [M + Na+] 393.1579, found. 393.1566.

N4-(4-Chlorophenyl)-2-oxo-4-phenyl-1-(1-phenylethyl)azetidine-3-carboxamide (7aba) and (8aba)

Purification by flash chromatography (EtOAc : Hex 1 : 3, SiO2) gave one fraction, a mixture of two diastereoisomers (255 mg, 0.63 mmol, 63%, ratio 70:30, yellow oil). Overall de = 40%.

1H NMR (500 MHz, CDCl3) δ: 8.38 (s, 0.7 H, NH), 8.36 (s, 0.3 H, NH), 7.55 (d, 0.7 H, J = 8.5 Hz, ArH), 7.47 (d, 1 H, J = 8.5 Hz, ArH), 7.34–7.30 (m, 3 H, ArH), 7.29–7.25 (m, 3 H, ArH), 7.24–7.21 (m, 3 H, ArH), 7.18–7.06 (m, 3.3 H, ArH), 4.90 (q, 0.7 H, J = 7.5 Hz, CHCH3), 4.81 (s, 1 H, H-4), 4.43 (q, 0.3 H, J = 7.0 Hz, CHCH3), 3.91 (d, 0.7 H, J = 2.0 Hz, H-3), 3.89 (d, 0.3 H, J = 2.0 Hz, H-3), 1.77 (d, 0.9 H, J = 7.0 Hz, CH3), 1.43 (d, 2.1 H, J = 7.5 Hz, CH3) ppm.13C NMR (125 MHz, CDCl3) δ: 165.3 (major), 162.5 (min), 163.4 (major), 163.2 (major), 140.2, 139.2, 137.6, 137.5, 136.5, 135.4, 134.9, 134.8, 129.4, 129.3, 129.2, 129.1, 129.0, 128.5, 128.4, 128.2, 127.4, 127.0, 124.9, 124.8, 124.6, 124.3, 122.7, 122.6, 122.4, 120.2, 63.6 (min), 62.7 (major), 58.0 (major), 57.2 (major), 49.9 (min), 48.5 (major), 19.3 (min), 19.2 (major) ppm. HRMS (ESI+): m/z calcd for C22H17N2O4ClNa [M + Na+] 443.1735, found. 443.1725.
2-(4-Chlorophenyl)-1-(1-naphthalen-2-yl)ethyl)-4-oxo-N-phenylazetidine-3-carboxamide (7bba) and (8bba)

Purification by flash chromatography (EtOAc: Hex 1:3, SiO₂) gave one fraction, a mixture of two diastereoisomers (207 mg, 0.50 mmol, 50%, ratio 63 : 37, yellow oil). Overall de = 26%.

1H NMR (500 MHz, CDCl₃): δ: 7.76–7.21 (m, 10 H, ArH), 4.89–4.85 (m, 1.26 H, CH₃), 7.41–7.21 (m, 10 H, ArH), 4.89–4.85 (m, 1.26 H, CH₃), 1.90–1.71 (m, 4 H, ArH) ppm. 13C NMR (125 MHz, CDCl₃): δ: 165.1 (maj), 164.1 (min), 163.8 (min), 159.7 (maj), 159.4 (min), 159.1 (min), 158.8 (maj), 158.5 (min), 156.0 (maj), 155.8 (min), 140.6 (maj), 140.4 (min), 139.7 (min), 138.6 (maj), 138.3 (maj), 138.0 (min), 137.5 (maj), 137.2 (min), 136.2 (maj), 136.1 (min), 129.7 (min), 129.5 (maj), 129.2 (min), 129.1 (maj), 129.0 (min), 128.7 (maj), 128.5 (min), 128.2 (maj), 128.0 (min), 127.9 (maj), 127.7 (min), 126.9 (maj), 126.7 (min), 126.3 (maj), 126.1 (min), 125.8 (maj), 125.6 (min), 125.4 (maj), 125.2 (min), 124.9 (maj), 124.6 (min), 124.3 (maj), 123.4 (min), 119.9, 119.7, 64.9 (min), 64.5 (maj), 57.0 (min), 55.6 (maj), 49.7 (min), 49.2 (maj), 20.2 (maj), 19.9 (min) ppm. HRMS (ESI+): m/z calcd for C₂₂H₂₁ClN₂O₃Na [M + Na⁺] 438.1430, found. 438.1432.

2-(4-Chlorophenyl)-1-(1-naphthalen-1-yl)ethyl)-4-oxo-N-phenylazetidine-3-carboxamide (7aca) and (8aca)

Purification by flash chromatography (EtOAc: Hex 1:3, SiO₂) gave one fraction, a mixture of two diastereoisomers (120 mg, 0.30 mmol, 30%, ratio 53 : 47, yellow oil). Overall de = 6%.

1H NMR (500 MHz, CDCl₃): δ: 8.98 (s, 1 H, NH), 8.19–8.15 (m, 0.53 H, ArH), 7.86–7.84 (m, 0.47 H, ArH), 7.55–7.50 (m, 2 H, ArH), 7.33–7.21 (m, 6 H, ArH), 7.18–7.13 (m, 2 H, ArH), 7.12–7.08 (m, 1 H, ArH), 6.88–6.85 (m, 2 H, ArH), 4.92 (q, 0.53 H, J = 7.5 Hz, CH₂CH₃), 4.77–4.73 (m, 1 H, H-4), 4.36 (q, 0.47 H, J = 7.5 Hz, CH₂CH₃), 3.96 (d, 0.53 H, J = 2.5 Hz, H-3), 3.89 (d, 0.47 H, J = 2.5 Hz, CH₃), 1.39 (d, 1.4 H, J = 7.0 Hz, CH₃) ppm.

13C NMR (125 MHz, CDCl₃): δ: 165.5 (maj), 165.6 (min), 163.8 (min), 165.2 (maj), 160.2, 160.1, 140.7, 139.5, 137.8, 137.7, 132.2, 129.7, 129.2, 129.1, 128.9, 128.8, 128.6, 128.5, 128.4, 128.2, 128.0, 127.9, 126.2, 126.2, 125.6, 125.4, 124.9, 124.8, 120.1, 63.5 (maj), 63.4 (min), 57.3 (maj), 56.8 (min), 55.2 (min), 54.0 (maj), 19.8 (min), 19.6 (maj) ppm. HRMS (ESI+): m/z calcd for C₂₃H₂₃ClN₂O₃Na [M + Na⁺] 427.1189, found. 427.1200.
2-(4-Fluorophenyl)-4-oxo-N-phenyl-1-(1-phenylethyl)azetidine-3-carboxamide (7ada) and (8ada)

Purification by flash chromatography (EtOAc:Hex 1:3, SiO₂) gave one fraction, a mixture of two diastereoisomers (271 mg, 0.70 mmol, 70%, ratio 75:25, yellow oil). Overall de = 50%.

1H NMR (500 MHz, CDCl₃) δ: 8.37 (s, 0.75 H, NH), 8.32 (s, 0.25 H, NH), 7.55–7.50 (m, 1.74 H, ArH), 7.41–7.34 (m, 1.26 H, ArH), 7.37–7.31 (m, 1.26 H, ArH), 7.12–7.07 (m, 1 H, ArH), 4.59 (q, 0.26 H, J = 7.5 Hz, CH₂CH₃), 4.39 (q, 0.26 H, J = 2.5 Hz, H-4), 3.87 (d, 0.74 H, J = 2.5 Hz, CH₂CH₂), 3.72 (d, 0.74 H, J = 2.5 Hz, H-4), 3.71 (d, 0.26 H, J = 2.5 Hz, H-3), 3.67 (d, 0.26 H, J = 2.5 Hz, H-4), 1.85 (d, 0.78 H, J = 7.5 Hz, CH₂), 1.75 (d, 2.22 H, J = 7.5 Hz, CH₃), 0.96 (s, 2.36 H, Bu), 0.88 (s, 6.63 H, Bu) ppm.

13C NMR (125 MHz, CDCl₃) δ: 166.6 (min), 165.5 (maj), 164.2 (maj), 164.1 (min), 141.5 (maj), 141.2 (min), 137.8 (maj), 137.7 (min), 129.2, 129.1, 128.9, 128.0, 127.7, 127.2, 126.8, 124.7 (min), 124.6 (maj), 120.1 (min), 120.0 (maj), 66.6 (maj), 64.3 (maj), 57.4 (min), 56.7 (min), 55.1 (maj), 55.0 (maj), 32.5, 26.5, 26.1, 21.4 (maj), 20.5 (min) ppm. HRMS (ESI⁺): m/z calcd for C₂₂H₂₂N₂O₂Na [M + Na⁺] 373.1892, found. 373.1902.

2-(tert-Butyl)-N-(4-methoxyphenyl)-4-oxo-1-(1-phenylethyl)azetidine-3-carboxamide (7dea) and (8dea)

Purification by flash chromatography (EtOAc:Hex 1:4:12, SiO₂) gave one fraction, a mixture of two diastereoisomers (175 mg, 0.46 mmol, 46%, ratio 70:30, yellow oil). Overall de = 40%.

1H NMR (500 MHz, CDCl₃) δ: 8.59 (s, 0.7 H, NH), 8.33 (s, 0.3 H, NH), 7.45–7.40 (m, 3.3 H, ArH), 7.37–7.33 (m, 2 H, ArH), 7.30–7.25 (m, 1.7 H, ArH), 6.84–6.78 (m, 2 H, ArH), 4.60 (q, 0.3 H, J = 7.0 Hz, CH₂CH₃), 4.50 (q, 0.7 H, J = 7.0 Hz, CH₂CH₂), 3.87 (d, 0.7 H, J = 2.5 Hz, H-3), 3.78 (s, 0.9 H, OCH₃), 3.77 (s, 2.1 H, OCH₃), 3.72 (d, 0.7 H, J = 2.5 Hz, H-4), 3.70 (d, 0.3 H, J = 2.5 Hz, H-3), 3.66 (d, 0.3 H, J = 2.5 Hz, H-4), 1.85 (d, 0.9 H, J = 7.5 Hz, CH₃), 1.75 (d, 2.1 H, J = 7.5 Hz, OCH₃), 0.95 (s, 2.66 H, Bu), 0.87 (s, 6.34 H, Bu) ppm.

13C NMR (125 MHz, CDCl₃) δ: 166.8 (min), 166.6 (maj), 163.9, 156.7 (min), 156.5 (maj), 141.6 (maj), 141.2 (min), 131.0 (maj), 130.9 (min), 129.1 (maj), 128.9 (maj), 127.9 (maj), 127.7 (maj), 127.2 (maj), 126.8 (min), 121.7 (min), 121.6 (maj), 114.3 (min), 114.2 (maj), 66.6 (maj), 64.4 (min), 57.3 (maj), 56.6 (min), 55.7 (min), 55.5 (maj), 55.0 (min), 54.9 (maj), 32.5, 26.5, 26.1 (maj), 21.4 (maj), 20.5 (min) ppm. HRMS (ESI⁺): m/z calcd for C₂₂H₂₂N₂O₂Na [M + Na⁺] 403.1998, found. 403.2005.

2-(tert-Butyl)-N-(3-chlorophenyl)-4-oxo-1-(1-phenylethyl)azetidine-3-carboxamide (7cea) and (8cea)

Purification by flash chromatography (EtOAc:Hex 1:5, SiO₂) gave one fraction, a mixture of two diastereoisomers (161 mg, 0.42 mmol, 42%, ratio 71:29, yellow oil). Overall de = 42%.

1H NMR (500 MHz, CDCl₃) δ: 9.02 (s, 0.71 H, NH), 8.66 (s, 0.29 H, NH), 7.71 (s, 1H, ArH), 7.42–7.40 (m, 1.29 H, ArH), 7.36–7.33 (m, 2 H, ArH), 7.30–7.25 (m, 2 H, ArH), 7.23–7.17 (m, 1 H, ArH), 7.15–7.11 (m, 0.71 H, ArH), 7.06–7.00 (m, 1 H, ArH), 4.60 (q, 0.29 H, J = 7.5 Hz, CH₂CH₃), 4.50 (q, 0.71 H, J = 7.5 Hz, CH₂CH₂), 3.93–3.91 (m, 0.71 H, H-3), 3.81–3.78 (m, 0.71 H, H-3), 3.76–3.74 (m, 0.29 H, H-4), 3.71–3.69 (m, 0.29 H, H-4), 1.85 (d, 0.87 H, J = 7.0 Hz, CH₃), 1.77 (d, 2.13 H, J = 7.0 Hz, CH₃), 0.95 (s, 2.59 H, Bu), 0.87 (s, 6.43 H, Bu) ppm.

13C NMR (125 MHz, CDCl₃) δ: 166.5, 164.3, 141.4 (maj), 141.1 (min), 138.9 (maj), 138.8 (min), 134.8 (min), 134.7 (maj), 130.1 (min), 130.0 (maj), 129.1 (min), 128.9 (min), 128.0 (maj), 127.8 (maj), 127.2 (maj), 126.8 (min), 124.6 (min), 124.5 (maj), 120.1 (min), 119.9 (min), 117.9 (min), 117.7 (maj), 66.4 (maj), 64.2 (min), 57.5 (maj), 56.7 (min), 55.2 (maj), 55.1 (min), 32.5, 26.5, 26.1 (maj), 21.4 (maj), 20.5 (min) ppm. HRMS (ESI⁺): m/z calcd for C₂₂H₂₂ClN₂O₂Na [M + Na⁺] 470.1502, found. 407.1509.
2-(tert-Butyl)-1-(1-naphthalen-2-yl)ethyl)-4-oxo-N-phenylazetidine-3-carboxamide (7aea) and (8aea)

Purification by flash chromatography (EtOAc : Hex 1 : 5, SiO₂) gave one fraction, a mixture of two diastereoisomers (208 mg, 0.32 mmol, 52%, ratio 55 : 45, yellow oil). Overall de = 10%.

¹H NMR (500 MHz, CDCl₃) δ: 8.57 (s, 0.55 H, NH), 8.45 (s, 0.45 H, NH), 7.86–7.78 (m, 3.90 H, ArH), 7.72–7.66 (m, 0.55 H, ArH), 7.61–7.54 (m, 2.55 H, ArH), 7.51–7.45 (m, 2.55 H, ArH), 7.32–7.26 (m, 2.45 H, ArH), 7.16–7.04 (m, 1 H, ArH), 4.80 (q, 0.45 H, J = 7.5 Hz, CH₂CH₃), 4.66 (q, 0.55 H, J = 7.5 Hz, CH₂CH₃), 3.91 (d, 0.55 H, J = 2.5 Hz, H-3, H-4), 3.78–3.75 (m, 1 H, H-3 H-4), 3.66 (d, 0.32 H, J = 2.8 Hz, CH₃), 1.89 (d, 1.05 H, J = 7.2 Hz, CH₃), 1.77 (d, 1.95 H, J = 7.2 Hz, CH₃), 1.01 (s, 3.15 H, tert-But), 0.92 (s, 5.85 H, tert-But) ppm.

¹³C NMR (100 MHz, CDCl₃) δ: 166.7 (min), 166.5 (maj), 164.0 (maj), 163.9 (min, 141.4 (maj), 141.1 (min), 135.6 (maj), 135.5 (min), 130.5 (maj), 130.4 (min), 128.9 (min), 128.7 (maj), 128.4 (min), 128.2 (maj), 127.8 (min), 127.5 (maj), 126.9 (maj), 126.7 (min), 126.6 (min), 126.5 (maj), 124.9 (min), 124.8 (maj), 122.0 (min), 121.7 (maj), 66.8 (min), 64.3 (maj), 57.1 (maj), 56.6 (min), 54.6 (min), 54.4 (maj), 32.3, 26.3 (min), 25.9 (maj), 21.1 (maj), 20.3 (min), 17.7 (maj), 14.2 (min) ppm. HRMS (ESI⁺): m/z calcd for C₂₃H₂₈N₂O₂Na [M + Na]⁺ 387.2061, found. 387.2048, 387.2046, 387.2042.

2-(tert-Butyl)-4-oxo-1-(1-phenylethyl)azetidine-3-carboxamide (7aea) and (8aea)

Purification by flash chromatography (EtOAc : Hex 1 : 4, SiO₂) gave one fraction, a mixture of two diastereoisomers (172 mg, 0.35 mmol, 35%, ratio 68 : 32, yellow oil). Overall de = 36%.

¹H NMR (500 MHz, CDCl₃) δ: 8.38 (s, 0.68 H, NH), 8.30 (s, 0.32 H, NH), 7.47–7.34 (m, 6 H, ArH), 7.32–7.29 (m, 1 H, ArH), 7.16–7.11 (m, 2 H, ArH), 4.60 (q, 0.32 H, J = 7.2 Hz, CH₂CH₃), 4.52 (q, 0.68 H, J = 7.2 Hz, CH₂CH₃), 3.85 (d, 0.68 H, J = 2.8 Hz, CH₃), 3.71–3.69 (m, 1 H, H-3 H-4), 3.66 (d, 0.32 H, J = 2.8 Hz, H-4), 2.35–2.32 (m, 3 H, ArCH₃), 1.87 (d, 0.96 H, J = 7.2 Hz, CH₃), 1.76 (d, 2.04 H, J = 7.2 Hz, CH₃), 0.98 (s, 2.84 H, tert-But), 0.90 (s, 6.15 H, tert-But) ppm.

¹³C NMR (100 MHz, CDCl₃) δ: 166.5 (min), 166.3 (maj), 163.9 (maj), 163.8 (min, 141.3 (maj), 141.0 (min), 135.0 (maj), 134.9 (min), 134.1 (min), 134.0 (maj), 129.5 (min), 129.4 (maj), 128.9 (min), 128.7 (maj), 127.7 (min), 127.5 (maj), 127.0 (maj), 126.5 (min), 119.9 (min), 119.8 (maj), 66.6 (maj), 64.2 (min), 57.0 (maj), 56.5 (min), 54.7 (min), 54.6 (maj), 32.3, 26.3 (min), 25.9 (maj), 21.1 (maj), 20.8, 20.3 (min) ppm. HRMS (ESI⁺): m/z calcd for C₂₃H₂₈N₂O₂Na [M + Na]⁺ 387.2061, found. 387.2061.
N-(4-Fluorophenyl)-2-(2-methylpent-4-en-2-yl)-4-oxo-1-(1-phenylethyl)azetidine-3-carboxamide (7fa) and (8fa)

Purification by flash chromatography (EtOAc:Hex 1:4–1:3; SiO$_2$) gave one fraction, a mixture of two diastereoisomers (193 mg, 0.49 mmol, 49%, ratio 64:36, yellow oil). Overall de = 28%. $^1$H NMR (400 MHz, CDCl$_3$) δ: 8.59 (s, 0.64 H, NH), 8.40 (s, 0.36 H, NH), 7.54–7.50 (m, 2 H, ArH), 7.45–7.42 (m, 1 H, ArH), 7.40–7.34 (m, 2 H, ArH), 7.32–7.29 (m, 2 H, ArH), 7.05–6.97 (m, 2 H, ArH), 5.81–5.70 (m, 1 H, CH$_2$CH–CH$_2$), 5.08–5.05 (m, 1 H, CH$_2$CH–CH$_2$), 4.64 (q, 0.36 H, J = 7.2 Hz, CH$_2$CH), 4.51 (q, 0.64 H, J = 7.2 Hz, CH$_2$CH), 3.97 (d, 0.64 Hz, J = 2.4 Hz, H-3), 3.80–3.79 (m, 1 H, CH-3), 3.77 (d, 0.36 H, J = 2.4 Hz, H-4), 2.09–2.01 (m, 2 H, CH$_2$CH–CH$_2$), 1.87 (d, 0.96 Hz, J = 7.2 Hz, CH$_2$CH), 1.78 (d, 2.04 Hz, J = 7.2 Hz, CH$_2$CH), 0.97 (s, 2.88 H, $^3$Bu) ppm. 13C NMR (100 MHz, CDCl$_3$) δ: 166.4 (min), 166.2 (maj), 162.9 (maj), 161.9 (min), 159.9 (d, J$_{CF}$ = 242 Hz) (min), 159.3 (d, J$_{CF}$ = 242 Hz) (maj), 141.3 (min), 141.1 (maj), 133.6 (d, J$_{CF}$ = 3 Hz) (maj), 133.5 (d, J$_{CF}$ = 3 Hz) (min), 128.9 (min), 128.7 (maj), 127.8 (maj), 127.5 (maj), 127.0 (min), 126.6 (maj), 121.6 (d, J$_{CF}$ = 8 Hz) (min), 121.4 (d, J$_{CF}$ = 8 Hz) (maj), 115.5 (d, J$_{CF}$ = 22 Hz) (min), 115.3 (d, J$_{CF}$ = 22 Hz) (maj), 66.3 (maj), 64.1 (min), 57.2 (maj), 56.5 (min), 54.8 (min), 54.7 (maj), 32.3, 26.3 (min), 25.9 (maj), 21.1 (maj), 20.3 (mpm). HRMS (ESI$^+$): m/z calcd for C$_{32}$H$_{29}$F$_{2}$O$_7$N$_2$Na $[M + Na]^+$ 578.1954, found. 578.1942.

1-Isopropyl-2-oxo-N-phenyl-4-(2-phenylpent-4-en-2-yl)azetidine-3-carboxamide (7ahd) and (8ahd)

Purification by flash chromatography (EtOAc:Hex 1:4–1:3; SiO$_2$) gave one fraction, a mixture of two diastereoisomers (188 mg, 0.5 mmol, 50%, ratio 50:50, yellow oil). Overall de = 30%. $^1$H NMR (400 MHz, CDCl$_3$) δ: 8.50 (s, 0.5 H, NH), 7.95 (s, 0.5 H, NH), 7.57–7.54 (m, 1 H, ArH), 7.46–7.21 (m, 8 H, ArH), 7.12–7.03 (m, 1 H, ArH), 5.67–5.56 (m, 0.5 H, CH$_2$CH–CH$_2$), 5.42–5.31 (m, 0.5 H, CH$_2$CH–CH$_2$), 5.14–4.93 (m, 2 H, CH$_2$CH–CH$_2$), 4.41 (d, 0.5 H, J = 2.0 Hz, H-4), 4.30 (d, 0.5 H, J = 2.0 Hz, H-3), 3.84 (d, 0.5 H, J = 2.0 Hz, H-4), 3.54 (d, 0.5 H, J = 2.0 Hz, H-4), 3.44 (sept, 0.5 H, J = 6.8 Hz, CH(CH$_3$)$_2$), 2.91 (dd, 0.5 H, J = 6.8 Hz, CH(CH$_3$)$_2$), 2.17 (d, 0.5 H, J = 14.0 Hz, J = 5.6 Hz, CH$_2$CH–CH$_2$), 2.83 (dd, 0.5 H, J = 14.0 Hz, J = 5.6 Hz, CH$_2$CH–CH$_2$), 2.70 (sept, 0.5 H, J = 6.4 Hz, CH(CH$_3$)$_2$), 2.44 (dd, 0.5 H, J = 14.0 Hz, J = 8.4 Hz, CH$_2$CH–CH$_2$), 2.33 (dd, 0.5 H, J = 14.0 Hz, J = 8.4 Hz, CH$_2$CH–CH$_2$), 1.46 (d, 1.5 H, J = 6.8 Hz, CH(CH$_3$)$_2$), 1.44 (s, 1.5 H, CH$_3$), 1.40 (s, 1.5 H, CH$_3$), 1.25 (d, 1.5 H, J = 6.8 Hz, CH(CH$_3$)$_2$), 1.19 (d, 1.5 H, J = 6.4 Hz, CH(CH$_3$)$_2$), 0.91 (d, 1.5 H, J = 6.4 Hz, CH(CH$_3$)$_2$), ppm. 13C NMR (100 MHz, CDCl$_3$) δ: 169.3, 166.2, 164.0, 163.5, 141.3, 141.0, 137.5, 129.1, 129.0, 128.9, 128.9, 128.8, 127.8, 127.5, 127.0, 126.6, 124.5, 124.4, 120.0, 119.9, 119.8, 119.7, 83.1, 66.5, 64.1, 62.2, 57.1, 56.5, 54.8, 54.6, 42.4, 32.3, 28.0, 27.5, 27.4, 26.3, 25.9, 21.1, 20.3 ppm.