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Preparation of optically pure fused polycyclic scaffolds by Ugi reaction followed by olefin and enyne metathesis

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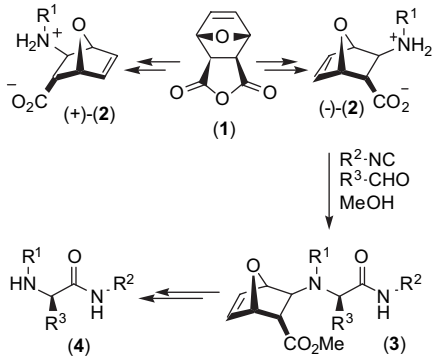
Abstract—Optically pure fused polycyclic scaffolds containing up to eight stereocentres have been synthesised by olefin metathesis and tandem enyne metathesis/Diels–Alder addition of Ugi multicomponent reaction adducts generated from 7-oxa-[2.2.1]-bicyclic amino acid derivatives.

1. Introduction

Multicomponent reactions (MCRs) are a very important class of reactions, which have recently attracted the attention of several academic and industrial researchers, due to their ability to generate quickly and efficiently large collections of compounds amenable for HTS.[1] In this area, the Ugi four-component reaction occupies a leading position since it represents a valuable method to access alpha-acylamino-amides in a straightforward manner.[2]

The power of this reaction has been dramatically increased during the last decades by modifications of the classic procedure. Such modifications include the use of non-classical building blocks, the employment of bifunctional components or the exploitation of post-condensation modifications. All these aspects have been extensively reviewed recently by Doemling.[3] Within our research in the field of intramolecular MCRs, we have recently reported the completely stereoselective Ugi 5-Centre-4-Component Reaction (U-5C-4CR) of an *N*-alkylated bicyclic β-amino acid derivative **2** with a wide variety of aldehydes and isocyanides;[4] and we have demonstrated that the stereochemistry of the newly generated carbon centre is governed by the configuration of the bicyclic unit, which was efficiently prepared in both enantiomerically pure forms from common substrate **1**.[5] We have shown that the bicyclic moiety can be used as a chiral auxiliary and that it can be easily removed at the end of the reaction, yielding optically pure amino acid derivatives **4**. In Scheme 1, the reaction sequence is summarised starting from the symmetric anhydride **1** and using (−)-**2** as chiral auxiliary.



Scheme 1. Optically pure bicyclic amino acid derivatives as chiral auxiliaries in stereoselective Ugi reactions.

[2.2.1]-Bicyclic alkenes have been extensively used in intramolecular ROM/RCM reactions to construct polycyclic ring systems, mainly due to the driving force constituted by the strain release in the ROM step; the conservation of the starting chiral information throughout the process is another advantage of these transformations.[6] However, the final compounds obtained via this route generally do not display many additional handles for decorating the framework with diverse building blocks, a useful feature to render these scaffolds better suited for structure optimisation studies and biological screenings. Moreover, the substances used in these studies are generally available as racemic mixtures, although an example of ROM/RCM on an optically pure 7-oxa-[2.2.1]-bicyclic amino acid derivative has been recently reported.[7]

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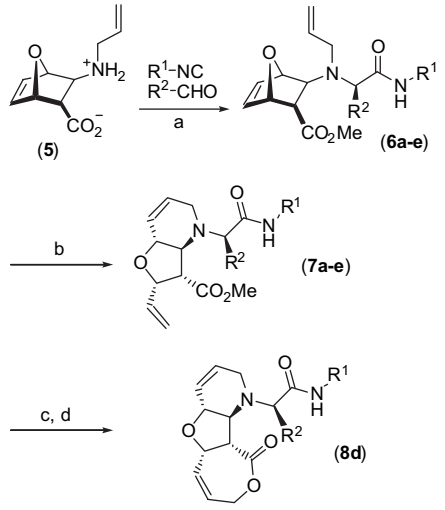
On the other hand, the quest for polyfunctional, structurally complex compounds, acting as smart tools both in understanding the role and functions of emerging biological targets and in validating their biological responses, is becoming more important in the drug discovery process.[8]

In this paper, we report our studies on the coupling of the above-mentioned stereoselective Ugi reaction with two complexity-generating reactions,[9] i.e, ring-opening/ring-closing metathesis (ROM/RCM) and Diels–Alder addition to prepare optically pure polycyclic scaffolds.

2. Results and discussion

Optically pure (−)-*N*-allyl-3-amino-7-oxa-[2.2.1]-bicyclohept-5-ene-2-carboxylic acid was prepared in good yield using a procedure similar to that used to prepare *N*-methyl and *N*-benzyl derivatives,[5] and reacted with different combinations of aldehydes and isocyanides in methanol at room temperature for 2–4 days (Scheme 2). The resulting Ugi adducts were isolated in good yields (Table 1) and as a single diastereoisomer, as previously reported for similar compounds. Optical integrity was previously demonstrated by converting the amino acids, derived from a *retro* Diels–Alder process followed by an enamine deprotection, into the corresponding Mosher's amides.[5]



Scheme 2. Ugi reaction followed by ROM/RCM. Reagents and conditions: (a) MeOH, room temperature; (b) Grubb's II generation catalyst, CH_2Cl_2, room temperature; (c) allyl alcohol, NaH, room temperature; (d) Grubb's I generation catalyst, CH_2Cl_2, reflux.

The subsequent ROM/RCM step was investigated under various conditions; in particular, two different catalysts were tested, and also the presence of an ethylene atmosphere replacing the inert gas was analysed. Optimal conditions were found with 10 mol % of the Grubb's II generation catalyst (benzylidene-1,3-bis-(2,4,6-trimethylphenyl)-2-(imidazolidinylidene)dichloro(tricyclohexylphosphine) ruthenium) under an ethylene atmosphere at a 5 mM concentration of substrate in dichloromethane (Table 1). The reactions with and without ethylene did not display a dramatic difference in reactivity, while the use of Grubb's I generation catalyst (benzylidene-bis(tricyclohexylphosphine)dichlororuthenium) resulted in very poor yield of the desired product. The compounds obtained in this way were fully characterised and their structure unequivocally determined by two-dimensional NMR experiments. Bicyclic systems have been recently used as scaffolds to prepare conformationally constrained peptides and peptidomimetics.[10] We are currently investigating the properties of these molecules as reverse-turn inducers in RGD-based peptidomimetic inhibitors of integrins.[11]

Table 1. Ugi reaction followed by ROM/RCM

Entry	R^1	R^2	Yield (**6**)	Catalyst	Conditions	Yield (**7**)
a	*t*-Bu	*i*-Bu	61	II	Ar	61
b	*t*-Bu	4-NO_2–Ph	70	II	Ar	71
c	Bn	*i*-Bu	71	II	CH_2=CH_2	88
d	Cyclohex	*i*-Pr	69	II	CH_2=CH_2	87
e	*t*-Bu	4-Cl–Ph	46	II	CH_2=CH_2	95
f	*t*-Bu	*i*-Bu	—[a]	I	Ar	10

[a] See, entry a.

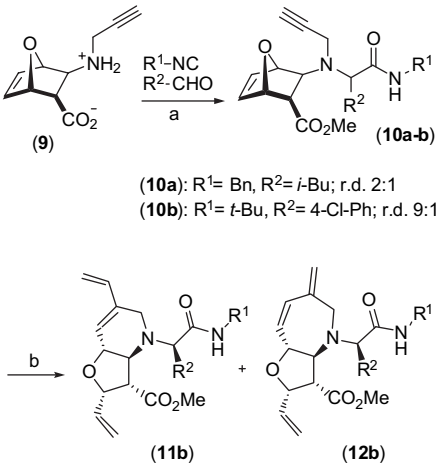
Compound **7d** was further elaborated: after conversion of the methyl ester into the corresponding allyl ester, conditions for the ring-closing metathesis between the two terminal double bonds were investigated. Surprisingly, no product was isolated when the reaction was performed at room temperature, either with generation (I) or (II) catalyst, and with or without an ethylene atmosphere. However, while with the generation (I) catalyst the starting material was recovered unreacted, with the generation (II) catalyst complete consumption of compound **7d** gave rise to polymerisation products.

The desired tricyclic product **8d** was eventually obtained in a satisfactory 78% yield when the reaction was performed with the less reactive catalyst (10%) at reflux in a 5 mM dichloromethane solution under an argon atmosphere. It is worth noting that a similar reaction was reported by Winkler and co-workers, but in that case a larger amount of catalyst (30%) and higher dilution (0.5 mM) were found necessary to isolate the final product in 57% yield.[7]

In order to increase the diversity of these polycyclic molecules, we also explored the possibility of substituting the allyl group on the nitrogen atom with a propargyl group, and to perform the Ugi and the enyne matathesis reactions on the resulting derivative. Bicyclic amino acid **9** was therefore reacted with different combinations of aldehydes and isocyanides and to our surprise stereoselection in this case was not complete (Scheme 3). At this stage, we cannot give an explanation of these unexpected results since, if it can be postulated that a propargyl group, being less bulky than an allyl group, could in principle have a lower effect on the stereoselection, it is difficult to use the same rationale when complete stereoselection is observed with an even less bulky methyl group.[4]

In the case of compound **10b**, however, stereoselection was satisfactory and the major diastereoisomer could be separated from the minor one by chromatographic purification.[12] This propargyl derivative was then subjected to ROM/RCM under different conditions (Table 2).

The reaction did not proceed at all without an ethylene atmosphere, and the starting material was recovered unreacted. There are many reports in which the presence of ethylene



Scheme 3. Ugi reaction with propargylic amino acid followed by ROM/RCM. Reagents and conditions: (a) MeOH, room temperature; (b) See text.

Table 2. ROM/RCM on propargylic derivative **10b**

Entry	Solvent	Catalyst	Conditions	Yield (**11b**)	Yield (**12b**)
a	CH_2Cl_2	II	Ar	—	—
b	CH_2Cl_2	I	Ar	—	—
c	CH_2Cl_2	II	CH_2=CH_2	64	26
d	CH_2Cl_2	I	CH_2=CH_2	79	—
e	Toluene	II	CH_2=CH_2	40[a]	15
f	THF	II	CH_2=CH_2	29[b]	8

[a] Twenty percent of open adduct was also isolated.
[b] Seventeen percent of open adduct was also isolated.

gas was found beneficial during enyne metathesis and indeed also in our case, the reaction proceeded smoothly with the aid of this gas.[13] Interestingly, when the Grubb's II generation catalyst was used, two products were isolated: the 6-*exo* compound **11b** and the less common 7-*endo* compound **12b**;[14] however, when the Grubb's I generation catalyst was used instead, only the 6-*exo* derivative **11b** could be isolated in 78% yield. Other solvents such as toluene and THF were also investigated, but none of them gave results better than DCM.

The diene resulting from this reaction could be further transformed via a Diels–Alder reaction in the presence of a dienophile, and representative compounds **13** and **14** were obtained. Since complete stereocontrol was observed also during the Diels–Alder reaction, highly complex enantiomerically pure polycyclic derivatives could be assembled with this three-step process. Detailed NOE experiments have been conducted on compound **13**, whose structure has been univocally identified as the one shown in Scheme 4. The Diels–Alder reaction could be also performed in situ without the isolation of the diene, by addition of the corresponding alkene; however, due to the high dilution required for the ROM/RCM process, the Diels–Alder reaction was found to be extremely slow under these conditions.

3. Conclusions

In conclusion, in the present paper it has been shown how, starting from simple, easily available precursors, the synthesis of enantiomerically pure fused polycyclic scaffolds containing up to eight stereocentres can be achieved in a straightforward manner, taking advantage of a complexity–diversity generating strategy based on a Ugi multicomponent reaction, a ring-opening/ring-closing metathesis and a Diels–Alder cycloaddition.

Moreover, it is noteworthy that the use of different aldehydes, isocyanides and unsaturated moieties on the secondary amine in the Ugi reaction, together with the presence of differently manipulable functionalities on the final adducts, offers the possibility to diversely decorate these scaffolds to generate new DOS libraries, useful for application in chemical genetics.[15]

With this aim, we are now continuing to work on this project and the results of this research will be reported in due course.

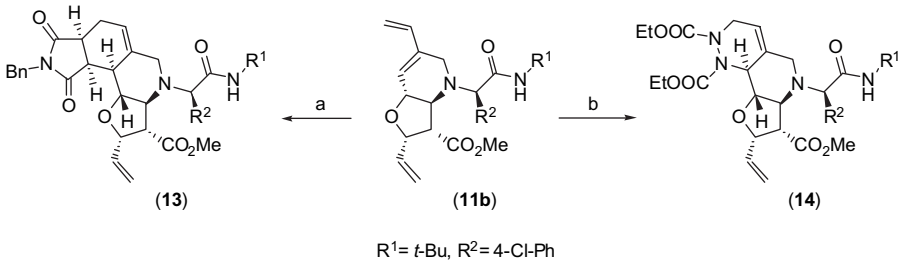
4. Experimental

4.1. General remarks

TLC analyses have been performed on silica TLC plates MERCK 60 F254 (0.25 mm thick). Spots have been observed under the UV light (λ=254 nm) or stained with iodine vapours or with a solution of $(NH_4)MoO_4 \cdot 4H_2O$ and $Ce(SO_4)_2$ in diluted H_2SO_4. Flash chromatographies have been performed on ICN Biomedicals 60A silica (230–400 mesh). Optical rotations were determined with a Jasco DP-181 polarimeter, using a Jasco cylindrical cell 10× 100 mm. Microanalyses were performed on a Heraeus CHN-O-Rapid instrument. Anhydrous solvents and all reagents have been bought from FLUKA or ALDRICH.

4.2. NMR spectra

^{1}H NMRs have been recorded on a VARIAN 'MERCURY 300' at 300 MHz. Chemical shifts are reported in parts per million using TMS (0.00 ppm) as internal standard.



Scheme 4. Diels–Alder reactions on bicyclic diene **11b**. Reagents and conditions: (a) *N*-benzylmaleimide, CH_2Cl_2, room temperature, 78%; (b) Diethylazodicarboxylate, DCM, room temperature, 59%.

J constants are reported in Hertz. ^{13}C NMRs have been recorded on a VARIAN 'MERCURY 300' at 75 MHz. When not indicated, spectra have been recorded at room temperature in $CDCl_3$ as the solvent. Peak attribution is made with the aid of DEPT, 2D COSY, HSQC and TOCSY experiments.

4.3. GC–MS analysis

GC–MS analyses have been performed on an HP-5890 series II with an HP-1 column (530 μm, length 12 m, internal diameter 0.2 mm). Ultrapure helium has been used as carrier gas. Mass spectra (electron impact) were recorded on an HP-5971A spectrometer, coupled to the above chromatograph. Conditions for the GC–MS analyses are as follows: flow: 0.9 mL/min; initial temperature: 100 °C; initial time: 2 min.; rate: 20 °C/min; final temperature: 280 °C; final time: 4 min; injector temperature: 250 °C.

4.4. General procedure for the Ugi reaction

The amino acid (0.29 mmol) was suspended in dry methanol (1 mL), and aldehyde (0.32 mmol) and isocyanide (0.32 mmol) were added in sequence. The reaction was stirred at room temperature under nitrogen for 2–5 days, then concentrated in vacuo and analysed by ^{1}H NMR to determine the diastereomeric ratio. The crude material was then purified by flash chromatography.

4.5. General procedure for the ROM/RCM reaction

The bicyclic derivative (0.18 mmol) was dissolved in dry dichloromethane (30 mL) under argon or ethylene atmosphere. The Grubb's catalyst (0.018 mmol), dissolved in dry dichloromethane (6 mL), was added via syringe and the reaction left stirring overnight. The solvent was then evaporated under reduced pressure and the crude material purified by flash chromatography. For compound **8d**, the reaction was performed at reflux.

4.6. General procedure for the Diels–Alder reaction

The diene (0.18 mmol) and the dienophile (0.27 mmol) are dissolved in dry dichloromethane (2 mL) and stirred for 24 h. The solvent is then evaporated and the crude material purified by flash chromatography.

4.7. Detailed compound characterisation

4.7.1. (1*S*,2*S*,3*S*,4*R*)-Methyl 3-(*N*-((*R*)-1-(*tert*-butylcarbamoyl)-3-methylbutyl)-*N*-allylamino)-7-oxa-bicyclo[2.2.1]hept-5-ene-2-carboxylate (6a). M.W. 378.51; R_f 0.67 (eluent: EtOAc/PE 3:7); $[\alpha]_D^{20}$ −55.4 (*c* 0.66, $CHCl_3$).

^{1}H NMR (300 MHz): δ 0.90 [3H, d, *J* 7]; 0.94 [3H, d, *J* 7]; 1.33 [9H, s]; 1.40 [1H, m]; 1.65–1.85 [2H, m]; 2.93 [1H, t, *J* 4]; 3.31 [1H, d, *J* 4]; 3.32–3.40 [2H, m]; 3.45 [1H, dd, *J* 15, 7]; 3.66 [3H, s]; 4.90 [1H, br s]; 5.07 [1H, d, *J* 4]; 5.11 [1H, dd, *J* 10, 1]; 5.30 [1H, dd, *J* 16, 1]; 5.70–5.82 [1H, m]; 6.34 [1H, dd, *J* 6, 2]; 6.46 [1H, dd, *J* 6, 2]; 6.70 [1H, s].

^{13}C NMR (75 MHz): δ 22.5 (CH_3); 23.0 (CH_3); 25.7 (CH); 28.6 (CH_3); 38.2 (CH_2); 47.2 (CH); 50.4 (C); 50.6 (CH_2); 51.9 (CH_3); 59.8 (CH); 64.3 (CH); 78.5 (CH); 82.8 (CH); 116.8 (CH_2); 135.5 (CH); 136.0 (CH); 137.1 (CH); 172.2 (C); 172.9 (C).

Elem. Anal. Calcd for: C, 66.64; H, 9.05; N, 7.40. Found C, 66.81; H, 9.04; N, 7.39.

4.7.2. (1*S*,2*S*,3*S*,4*R*)-Methyl 3-(*N*-((*R*)-(*tert*-butylcarbamoyl)(4-nitrophenyl)methyl)-*N*-allylamino)-7-oxa-bicyclo[2.2.1]hept-5-ene-2-carboxylate (6b). M.W. 443.49; R_f 0.34 (eluent: EtOAc/PE 3:7); $[\alpha]_D^{20}$ −85.8 (*c* 1.26, $CHCl_3$).

^{1}H NMR (300 MHz): δ 1.40 [9H, s]; 2.98 [1H, t, *J* 4]; 3.09 [1H, dd, *J* 15, 8]; 3.42 [1H, d, *J* 4]; 3.60 [1H, m]; 3.71 [3H, s]; 3.91 [1H, br s]; 4.80 [1H, s]; 5.05 [1H, d, *J* 4]; 5.26 [1H, d, *J* 10]; 5.32 [1H, d, *J* 13]; 5.66–5.80 [1H, m]; 6.18 [1H, dd, *J* 6, 1]; 6.29 [1H, dd, *J* 6, 2]; 7.25 [1H, s]; 7.49 [2H, dd, *J* 7, 2]; 8.24 [2H, dd, *J* 7, 2].

^{13}C NMR (75 MHz): δ 28.4 (CH_3); 47.4 (CH); 50.7 (C); 51.2 (CH_2); 52.1 (CH_3); 63.8 (CH); 65.8 (CH); 78.1 (CH); 80.7 (CH); 118.7 (CH_2); 123.3 (CH); 131.2 (CH); 135.4 (CH); 135.5 (CH); 136.1 (CH); 144.5 (C); 147.3 (C); 169.4 (C); 171.7 (C).

Elem. Anal. Calcd for: C, 62.29; H, 6.59; N, 9.47. Found C, 62.41; H, 6.60; N, 9.45.

4.7.3. (1*S*,2*S*,3*S*,4*R*)-Methyl 3-(*N*-((*R*)-1-(benzylcarbamoyl)-3-methylbutyl)-*N*-allylamino)-7-oxa-bicyclo[2.2.1]hept-5-ene-2-carboxylate (6c). M.W. 412.52; R_f 0.47 (eluent: EtOAc/PE 3:7); $[\alpha]_D^{20}$ −55.5 (*c* 0.65, $CHCl_3$).

^{1}H NMR (300 MHz): δ 0.91 [3H, d, *J* 7]; 0.96 [3H, d, *J* 7]; 1.40–1.50 [1H, m]; 1.70–2.00 [2H, m]; 2.80 [1H, t, *J* 4]; 3.26 [1H, d, *J* 4]; 3.40–3.55 [3H, m]; 3.56 [3H, s]; 4.35 [1H, dd, *J* 15, 6]; 4.47 [1H, dd, *J* 15, 6]; 4.86 [2H, br s]; 5.09 [1H, dd, *J* 10, 1]; 5.17 [1H, dd, *J* 16, 1]; 5.65–5.80 [1H, m]; 6.32 [1H, dd, *J* 6, 1]; 6.42 [1H, dd, *J* 6, 1]; 7.20 [1H, br s]; 7.25–7.40 [5H, m].

^{13}C NMR (75 MHz): δ 22.5 (CH_3); 23.1 (CH_3); 25.7 (C); 38.2 (CH_2); 43.3 (CH_2); 47.4 (CH); 50.2 (CH_2); 52.0 (CH_3); 59.6 (CH); 64.3 (CH); 78.2 (CH); 82.6 (CH); 117.1 (CH_2); 127.3 (CH); 127.8 (CH); 128.6 (CH); 135.8 (CH); 135.9 (CH); 136.8 (CH); 138.6 (C); 172.3 (C); 173.6 (C).

Elem. Anal. Calcd for: C, 69.88; H, 7.82; N, 6.79. Found C, 69.81; H, 7.80; N, 6.80.

4.7.4. (1*S*,2*S*,3*S*,4*R*)-Methyl 3-(*N*-((*R*)-1-(cyclohexylcarbamoyl)-2-methylpropyl)-*N*-allylamino)-7-oxa-bicyclo[2.2.1]hept-5-ene-2-carboxylate (6d). M.W. 390.52; R_f 0.56 (eluent: EtOAc/PE 3:7); $[\alpha]_D^{20}$ −37.1 (*c* 0.52, $CHCl_3$).

^{1}H NMR (300 MHz): δ 0.81 [3H, d, *J* 7]; 0.96 [3H, d, *J* 7]; 1.10–2.50 [11H, m]; 2.66 [1H, d, *J* 10]; 2.91 [1H, dd, *J* 4, 3]; 2.99 [1H, dd, *J* 15, 8]; 3.42 [1H, d, *J* 3]; 3.60 [3H, s]; 3.70–3.90 [2H, m]; 4.85 [1H, br s]; 5.00–5.15 [3H, m]; 5.65–5.80 [1H, m]; 6.16 [1H, d, *J* 8]; 6.32 [1H, dd, *J* 6, 2]; 6.43 [1H, dd, *J* 6, 2].

^{13}C NMR (75 MHz): δ 19.6 (CH_3); 20.1 (CH_3); 24.8 (CH_2); 24.9 (CH_2); 25.5 (CH_2); 27.8 (CH); 33.0 (CH_2); 33.3 (CH_2);

46.3 (CH); 47.4 (CH); 50.3 (CH_2); 51.9 (CH_3); 64.0 (CH); 67.9 (CH); 78.6 (CH); 83.6 (CH); 116.0 (CH_2); 135.8 (CH); 136.1 (CH); 137.5 (CH); 171.5 (C); 172.6 (C).

Elem. Anal. Calcd for: C, 67.66; H, 8.78; N, 7.17. Found C, 67.79; H, 8.76; N, 7.16.

4.7.5. (1*S*,2*S*,3*S*,4*R*)-Methyl 3-(*N*-((*R*)-(*tert*-butylcarbamoyl)(4-chlorophenyl)methyl)-*N*-allylamino)-7-oxa-bicyclo[2.2.1]hept-5-ene-2-carboxylate (6e). M.W. 432.94; R_f 0.58 (eluent: EtOAc/PE 3:7); $[\alpha]_D^{20}$ −64.8 (*c* 0.80, $CHCl_3$).

^{1}H NMR (300 MHz): δ 1.38 [9H, s]; 2.95 [1H, t, *J* 4]; 3.07 [1H, dd, *J* 15, 8]; 3.36 [1H, d, *J* 4]; 3.55–3.65 [1H, m]; 3.70 [3H, s]; 3.87 [1H, br s]; 4.66 [1H, s]; 5.02 [1H, d, *J* 4]; 5.24 [1H, d, *J* 10]; 5.30 [1H, d, *J* 16]; 5.66–5.80 [1H, m]; 6.16 [1H, dd, *J* 6, 2]; 6.24 [1H, dd, *J* 6, 1]; 7.21 [2H, d, *J* 7]; 7.28 [1H, s]; 7.35 [2H, d, *J* 7].

^{13}C NMR (75 MHz): δ 28.5 (CH_3); 47.4 (CH); 50.5 (C); 51.0 (CH_2); 52.1 (CH_3); 63.9 (CH); 66.3 (CH); 78.2 (CH); 80.8 (CH); 118.5 (CH_2); 128.6 (CH); 131.7 (CH); 133.8 (C); 135.1 (C); 135.2 (CH); 135.9 (CH); 136.6 (CH); 170.3 (C); 171.9 (C).

Elem. Anal. Calcd for: C, 63.81; H, 6.75; Cl, 8.19; N, 6.47. Found C, 63.97; H, 6.76; Cl, 8.19; N, 6.46.

4.7.6. (2*S*,3*S*,3a*S*,7a*R*)-Methyl 4-((*R*)-1-(*tert*-butylcarbamoyl)-3-methylbutyl)-2,3,3a,4,5,7a-hexahydro-2-vinylfuro[3,2-*b*]pyridine-3-carboxylate (7a). M.W. 378.51; R_f 0.57 (eluent: EtOAc/PE 2:8); $[\alpha]_D^{20}$ +86.8 (*c* 1.26, $CHCl_3$).

^{1}H NMR (300 MHz): δ 0.84 [3H, d, *J* 7]; 0.88 [3H, d, *J* 7]; 1.38 [9H, s]; 1.40–1.80 [3H, m]; 2.83 [1H, dd, *J* 8, 6]; 3.20–3.40 [4H, m]; 3.72 [3H, s]; 4.05–4.15 [1H, m]; 4.85 [1H, t, *J* 9]; 5.22 [1H, ddd, *J* 10, 1, 1]; 5.33 [1H, ddd, *J* 17, 1, 1]; 5.60–5.80 [2H, m]; 5.99 [1H, ddd, *J* 10, 3, 2]; 6.93 [1H, s].

^{13}C NMR (75 MHz): δ 22.0 (CH_3); 23.1 (CH_3); 24.4 (CH); 28.9 (C); 37.8 (CH_2); 47.6 (CH_2); 51.3 (CH and C); 52.5 (CH_3); 62.4 (CH); 64.0 (CH); 79.9 (CH); 80.9 (CH); 119.4 (CH_2); 124.7 (CH); 127.8 (CH); 134.6 (CH); 169.6 (C); 173.6 (C).

GC–MS 9.0 min (100%) [378 (M), 278 (100%, M−*t*-BuNHCO)].

Elem. Anal. Calcd for: C, 66.64; H, 9.05; N, 7.40. Found C, 66.62; H, 9.05; N, 7.41.

4.7.7. (2*S*,3*S*,3a*S*,7a*R*)-Methyl 4-((*R*)-(*tert*-butylcarbamoyl)(4-nitrophenyl)methyl)-2,3,3a,4,5,7a-hexahydro-2-vinylfuro[3,2-*b*]pyridine-3-carboxylate (7b). M.W. 443.49; R_f 0.31 (eluent: EtOAc/PE 3:7); $[\alpha]_D^{20}$ −48.8 (*c* 1.56, $CHCl_3$)

^{1}H NMR (300 MHz): δ 1.35 [9H, s]; 3.00 [1H, dd, *J* 11, 10]; 3.25 [1H, dd, *J* 11, 8]; 3.33 [1H, dq, J_d 17, J_q 3]; 3.40–3.55 [1H, m]; 3.52 [3H, s]; 4.20 [1H, s]; 4.31 [1H, m]; 4.74 [1H, dd, *J* 10, 8]; 5.19 [1H, dt, J_d 10, J_t 1]; 5.26 [1H, d, *J* 17]; 5.65 [1H, ddd, *J* 17, 10, 8]; 5.70–5.80 [1H, m]; 6.07 [1H, br d, *J* 10]; 6.66 [1H, s]; 7.60 [2H, d, *J* 9]; 8.17 [2H, d, *J* 9].

^{13}C NMR (75 MHz): δ 28.5 (CH_3); 51.2 (CH); 51.3 (C); 51.8 (CH_3); 52.1 (CH_2); 64.9 (CH); 70.6 (CH); 78.4 (CH); 80.7 (CH); 119.4 (CH_2); 123.1 (CH); 125.5 (CH); 127.4 (CH); 129.2 (CH); 134.2 (CH); 146.1 (C); 147.3 (C); 167.7 (C); 172.2 (C).

GC–MS 12.1 min (100%) [443 (M), 343 (100%, M−*t*-BuNHCO), 208 (30%, M−*t*-BuNHCOCHC$_6$H$_4$NO$_2$), 96 (60%)].

Elem. Anal. Calcd for: C, 62.29; H, 6.59; N, 9.47. Found C, 62.37; H, 6.58; N, 9.47.

4.7.8. (2*S*,3*S*,3a*S*,7a*R*)-Methyl 4-((*R*)-1-(benzylcarbamoyl)-3-methylbutyl)-2,3,3a,4,5,7a-hexahydro-2-vinylfuro[3,2-*b*]pyridine-3-carboxylate (7c). M.W. 412.52; R_f 0.66 (eluent: EtOAc/PE 3:7); $[\alpha]_D^{20}$ +88.8 (*c* 0.60, $CHCl_3$).

^{1}H NMR (300 MHz): δ 0.85 [3H, d, *J* 7]; 0.89 [3H, d, *J* 7]; 1.40–1.80 [3H, m]; 3.01 [1H, dd, *J* 8, 6]; 3.20–3.40 [4H, m]; 3.63 [3H, s]; 4.05–4.15 [1H, m]; 4.43 [1H, dd, *J* 15, 6]; 4.52 [1H, dd, *J* 15, 6]; 4.70–4.80 [1H, m]; 5.20 [1H, dd, *J* 10, 1]; 5.29 [1H, dt, J_d 16, J_t 1]; 5.60–5.80 [2H, m]; 5.99 [1H, ddd, *J* 11, 4, 2]; 7.20–7.40 [5H, m]; 7.50 [1H, br s].

^{13}C NMR (75 MHz): δ 22.0 (CH_3); 23.0 (CH_3); 24.5 (CH); 37.7 (CH_2); 43.2 (CH_2); 47.9 (CH_2); 52.3 (CH); 52.5 (CH_3); 62.0 (CH); 63.9 (CH); 79.8 (CH); 80.9 (CH); 119.3 (CH_2); 124.8 (CH); 127.1 (CH); 127.5 (CH); 127.8 (CH); 128.5 (CH); 134.5 (CH); 138.8 (C); 170.6 (C); 173.7 (C).

GC–MS 11.1 min (100%) [412 (M), 278 (100%, M−BnNHCO), 91 (30%)].

Elem. Anal. Calcd for: C, 69.88; H, 7.82; N, 6.79. Found C, 70.09; H, 7.84; N, 6.80.

4.7.9. (2*S*,3*S*,3a*S*,7a*R*)-Methyl 4-((*R*)-1-(cyclohexylcarbamoyl)-2-methylpropyl)-2,3,3a,4,5,7a-hexahydro-2-vinylfuro[3,2-*b*]pyridine-3-carboxylate (7d). M.W. 390.52; R_f 0.65 (eluent: EtOAc/PE 3:7); $[\alpha]_D^{20}$ +123.0 (*c* 1.00, $CHCl_3$).

^{1}H NMR (300 MHz): δ 0.81 [3H, d, *J* 6]; 0.92 [3H, d, *J* 6]; 1.15–2.20 [12H, m]; 3.10–3.30 [4H, m]; 3.63 [3H, s]; 3.70–3.80 [1H, m]; 4.08 [1H, br s]; 4.86 [1H, t, *J* 9]; 5.23 [1H, dd, *J* 10, 1]; 5.33 [1H, d, *J* 16]; 5.60–5.80 [2H, m]; 5.97 [1H, ddd, *J* 10, 4, 2]; 6.97 [1H, d, *J* 7].

^{13}C NMR (75 MHz): δ 19.9 (CH_3); 20.2 (CH_3); 24.8 (CH_2); 24.8 (CH_2); 25.5 (CH_2); 26.0 (CH); 32.9 (CH_2); 33.8 (CH_2); 47.5 (CH_2); 48.0 (CH); 52.6 (CH_3); 52.9 (CH); 63.6 (CH); 71.5 (CH); 80.0 (CH); 80.8 (CH); 119.4 (CH_2); 124.5 (CH); 127.7 (CH); 134.7 (CH); 167.7 (C); 174.0 (C).

GC–MS 10.4 min (100%) [390 (M), 264 (100%, M−cyclohexNHCO)].

Elem. Anal. Calcd for: C, 67.66; H, 8.78; N, 7.17. Found C, 67.74; H, 8.76; N, 7.18.

4.7.10. (2*S*,3*S*,3a*S*,7a*R*)-Methyl 4-((*R*)-(*tert*-butylcarbamoyl)(4-chlorophenyl)methyl)-2,3,3a,4,5,7a-hexahydro-2-vinylfuro[3,2-*b*]pyridine-3-carboxylate (7e). M.W. 432.94; R_f 0.16 (eluent: EtOAc/PE 2:8); $[\alpha]_D^{20}$ −69.6 (*c* 0.72, $CHCl_3$).

^{1}H NMR (300 MHz): δ 1.30 [9H, s]; 3.00 [1H, dd, *J* 12, 10]; 3.21 [1H, dd, *J* 12, 8]; 3.32 [1H, dq, J_d 17, J_q 3]; 3.40–3.50 [1H, m]; 3.48 [3H, s]; 4.04 [1H, s]; 4.20–4.30 [1H, m]; 4.68 [1H, dd, *J* 10, 8]; 5.15 [1H, d, *J* 10]; 5.24 [1H, d, *J* 17]; 5.63 [1H, ddd, *J* 17, 10, 8]; 5.65–5.75 [1H, m]; 6.05 [1H, br d, *J* 10]; 6.32 [1H, s]; 7.30 [4H, m].

^{13}C NMR (75 MHz): δ 28.5 (CH_3); 51.0 (CH); 51.4 (C); 51.8 (CH_3); 52.1 (CH_2); 65.4 (CH); 71.5 (CH); 77.6 (CH); 80.8 (CH); 119.1 (CH_2); 125.7 (CH); 127.8 (CH); 128.3 (CH); 129.9 (CH); 133.7 (C); 134.5 (CH); 136.9 (C); 169.2 (C); 171.7 (C).

GC–MS 11.1 min (100%) [332 (40%, M−*t*-BuNHCO), 208 (50%, M−*t*-BuNHCOCHC$_6$H$_4$Cl), 96 (100%)].

Elem. Anal. Calcd for: C, 63.81; H, 6.75; Cl, 8.19; N, 6.47. Found C, 63.71; H, 6.74; Cl, 8.21; N, 6.47.

4.7.11. (5a*S*,6a*R*,10a*S*,10b*S*)-10-((*R*)-1-(*tert*-Butylcarbamoyl)-3-methylbutyl)-5a,6a,9,10,10a,10b-hexahydropyrido[2,3-*b*]furo[3,2-*c*]oxepin-1-(3*H*)-one (8d). M.W. 388.50; R_f 0.16 (eluent: EtOAc/PE 2:8); $[\alpha]_D^{20}$ +129.0 (*c* 0.70, $CHCl_3$).

^{1}H NMR (300 MHz): δ 0.83 [3H, d, *J* 7]; 0.95 [3H, d, *J* 7]; 1.15–2.00 [10H, m]; 2.00–2.20 [1H, m]; 2.40 [1H, d, *J* 10]; 3.20–3.40 [4H, m]; 3.75–3.85 [1H, m]; 4.10 [1H, br s]; 4.54 [1H, ddd, *J* 13, 7, 1]; 4.64 [1H, dd, *J* 13, 7]; 5.11 [1H, br d, *J* 10]; 5.74 [1H, ddd, *J* 10, 6, 3]; 6.03 [1H, ddd, *J* 10, 4, 2]; 6.10–6.20 [1H, m]; 6.26 [1H, br d, *J* 10]; 7.46 [1H, d, *J* 7].

^{13}C NMR (75 MHz): δ 20.0 (CH_3); 20.3 (CH_3); 24.7 (CH_2); 25.6 (2×CH_2); 26.7 (CH); 32.8 (CH_2); 33.5 (CH_2); 47.8 (CH_2); 48.0 (CH); 54.2 (CH); 62.4 (CH_2); 65.7 (CH); 70.6 (CH); 76.4 (CH); 79.7 (CH); 124.3 (CH); 126.2 (CH); 128.6 (CH); 138.1 (CH); 168.3 (C); 174.2 (C).

GC–MS 11.3 min (100%) [388 (M), 262 (100%, M−cyclohexNHCO), 124 (40%)].

Elem. Anal. Calcd for: C, 68.01; H, 8.30; N, 7.21. Found C, 67.84; H, 8.28; N, 7.22.

4.7.12. (1*S*,2*S*,3*S*,4*R*)-Methyl 3-(*N*-((*RS*)-1-(benzylcarbamoyl)-3-methylbutyl)-*N*-propargylamino)-7-oxa-bicyclo[2.2.1]hept-5-ene-2-carboxylate (10a). Mixture of diastereoisomers; M.W. 410.51; R_f 0.34 (eluent: EtOAc/PE 3:7).

^{1}H NMR (300 MHz): δ 0.90–1.00 [9H, m]; 1.60–1.90 [3H, m]; 2.15 [0.67H, d, *J* 2]; 2.18 [0.33H, d, *J* 2]; 2.84 [0.33H, t, *J* 4]; 2.94 [0.67H, t, *J* 4]; 3.40 [0.67H, d, *J* 4]; 3.48 [0.33H, d, *J* 4]; 3.50–3.75 [3H, m]; 3.58 [2H, s]; 3.62 [1H, s]; 4.30–4.50 [2H, m]; 4.94 [0.67H, d, *J* 5]; 4.96 [1H, s]; 5.06 [0.33H, d, *J* 5]; 6.25–6.45 [2H, m]; 6.83 [0.33H, t, *J* 6]; 7.18 [0.67H, t, *J* 6]; 7.20–7.35 [5H, m].

^{13}C NMR (75 MHz): δ 22.4 (CH_3); 22.7 and 22.9 (CH_3); 25.1 and 25.3 (CH); 36.7 and 37.0 (CH_2); 38.4 and 38.5 (CH_2); 43.2 (CH_2); 47.6 and 48.1 (CH); 51.8 and 51.9 (CH_3); 60.6 and 61.6 (CH); 63.4 and 64.5 (CH); 71.9 and 72.0 (CH); 78.2 and 81.3 (CH); 78.3 (CH); 81.5 and 82.4 (CH); 127.2 and 127.3 (CH); 127.7 and 127.8 (CH); 128.5 (CH); 135.2 and 135.7 (CH); 136.0 and 136.4 (CH); 138.3 and 138.4 (C); 171.9 and 172.3 (C); 172.5 and 173.1 (C).

Elem. anal. (mixture) calcd for: C, 70.22; H, 7.37; N, 6.82. Found C, 70.14; H, 7.35; N, 6.83.

4.7.13. (1*S*,2*S*,3*S*,4*R*)-Methyl 3-(*N*-((*R*)-(*tert*-butylcarbamoyl)(4-chlorophenyl)methyl)-*N*-propargylamino)-7-oxa-bicyclo[2.2.1]hept-5-ene-2-carboxylate (10b). Major diastereoisomer; M.W. 430.92; R_f 0.32 (eluent: EtOAc/PE 3:7); $[\alpha]_D^{20}$ −72.2 (*c* 0.50, $CHCl_3$).

^{1}H NMR (300 MHz): δ 1.37 [9H, s]; 2.26 [1H, t, *J* 2]; 3.10 [1H, t, *J* 4]; 3.36 [1H, dd, *J* 18, 2]; 3.40 [1H, d, *J* 4]; 3.66 [1H, dd, *J* 18, 2]; 3.69 [3H, s]; 4.29 [1H, br s]; 4.77 [1H, s]; 5.06 [1H, d, *J* 4]; 6.22 [1H, dd, *J* 6, 2]; 6.29 [1H, dd, *J* 6, 2]; 7.02 [1H, s]; 7.26–7.36 [4H, m].

^{13}C NMR (75 MHz): δ 28.4 (CH_3); 37.4 (CH_2); 47.1 (CH); 51.0 (C); 52.0 (CH_3); 64.2 (CH); 68.0 (CH); 72.8 (CH); 78.3 (CH); 80.7 (C); 81.0 (CH); 128.6 (CH); 131.3 (CH); 133.9 (C); 134.6 (C); 135.6 (CH); 136.0 (CH); 169.6 (C); 171.7 (C).

Elem. Anal. Calcd for: C, 64.11; H, 6.32; Cl, 8.23; N, 6.50. Found C, 64.23; H, 6.31; Cl, 8.21; N, 6.48.

4.7.14. (2*S*,3*S*,3a*S*,7a*R*)-Methyl 4-((*R*)-(*tert*-butylcarbamoyl)(4-chlorophenyl)methyl)-2,3,3a,4,5,7a-hexahydro-2,6-divinylfuro[3,2-*b*]pyridine-3-carboxylate (11b). M.W. 458.98; R_f 0.77 (eluent: EtOAc/PE 4:6); $[\alpha]_D^{20}$ −25.5 (*c* 0.58, $CHCl_3$).

^{1}H NMR (300 MHz): δ 1.31 [9H, s]; 2.98 [1H, dd, *J* 12, 10]; 3.19 [1H, dd, *J* 12, 9]; 3.32 [1H, br d, *J* 16]; 3.47 [3H, s]; 3.72 [1H, br d, *J* 16]; 4.07 [1H, s]; 4.35 [1H, br d, *J* 9]; 4.69 [1H, dd, *J* 10, 7]; 5.02 [1H, d, *J* 18]; 5.04 [1H, d, *J* 11]; 5.14 [1H, ddd, *J* 10, 2, 1]; 5.22 [1H, ddd, *J* 17, 2, 1]; 5.62 [1H, ddd, *J* 17, 10, 8]; 6.04 [1H, br s]; 6.26 [1H, dd, *J* 18, 11]; 6.28 [1H, s]; 7.20–7.40 [4H, m].

^{13}C NMR (75 MHz): δ 28.6 (CH_3); 51.1 (CH); 51.5 (C); 51.8 (CH_2); 51.8 (CH_3); 65.8 (CH); 72.0 (CH); 78.4 (CH); 81.1 (CH); 113.7 (CH_2); 119.1 (CH_2); 126.0 (CH); 128.4 (CH); 129.9 (CH); 133.7 (C); 134.4 (CH); 135.9 (CH); 136.6 (C); 136.9 (C); 169.2 (C); 171.6 (C).

GC–MS 12.3 min (100%) [458 (M); 358 (100%, M−*t*-BuNHCO), 234 (70%, M−*t*-BuNHCOCHC$_6$H$_4$Cl), 122 (90%)].

Elem. Anal. Calcd for: C, 65.42; H, 6.81; Cl, 7.72; N, 6.10. Found C, 65.48; H, 6.80; Cl, 7.70; N, 6.12.

4.7.15. (*Z*,2*S*,3*S*,3a*S*,8a*R*)-Methyl 4-((*R*)-(*tert*-butylcarbamoyl)(4-chlorophenyl)methyl)-3,3a,4,5,6,8a-hexahydro-6-methylene-2-vinyl-2*H*-furo[3,2-*b*]azepine-

3-carboxylate (12b). M.W. 458.98; R_f 0.64 (eluent: EtOAc/PE 4:6); $[\alpha]_D^{20}$ −96.4 (*c* 0.50, $CHCl_3$).

^{1}H NMR (300 MHz): δ 1.36 [9H, s]; 2.94 [1H, dd, *J* 9, 6]; 3.37 [3H, s]; 3.43 [1H, br d, *J* 15]; 3.60 [1H, dd, *J* 9, 6]; 3.94 [1H, br d, *J* 15]; 4.07 [1H, s]; 4.54 [1H, dd, *J* 9, 8]; 4.93 [1H, br d, *J* 9]; 4.95 [1H, s]; 5.16 [1H, ddd, *J* 10, 1, 1]; 5.17 [1H, s]; 5.30 [1H, ddd, *J* 17, 2, 1]; 5.57 [1H, ddd, *J* 17, 10, 7]; 5.99 [1H, br d, *J* 11]; 6.20 [1H, dd, *J* 11, 2]; 6.56 [1H, s]; 7.20–7.40 [4H, m].

^{13}C NMR (75 MHz): δ 28.7 (CH_3); 51.3 (C); 51.4 (CH_3); 55.6 (CH_2); 56.4 (CH); 70.8 (CH); 71.2 (CH); 79.3 (CH); 80.5 (CH); 118.6 (CH_2); 121.3 (CH_2); 128.7 (CH); 131.3 (CH); 131.3 (CH); 132.2 (CH); 133.2 (CH); 134.1 (C); 134.9 (C); 140.5 (C); 169.9 (C); 171.5 (C).

GC–MS 12.5 min (100%) [458 (M); 358 (100%, M−*t*-BuNHCO), 234 (50%, M−*t*-BuNHCOCHC$_6$H$_4$Cl), 125 (100%)].

Elem. Anal. Calcd for: C, 65.42; H, 6.81; Cl, 7.72; N, 6.10. Found C, 65.28; H, 6.82; Cl, 7.72; N, 6.11.

4.7.16. (2*S*,3*S*,3a*S*,8*S*,9*R*,9a*S*,9b*R*)-*N*-Benzyl-4-((*R*)-(*tert*-butylcarbamoyl)(4-chlorophenyl)methyl)-3-(methoxycarbonyl)-2,3,3a,4,5,7,8,9,9a,9b-decahydro-2-vinylfuro[3,2-*c*]isoquinoline-8,9-dicarboximide (13). M.W. 646.18; R_f 0.22 (eluent: EtOAc/PE 3:7); $[\alpha]_D^{20}$ +60.2 (*c* 0.60, $CHCl_3$).

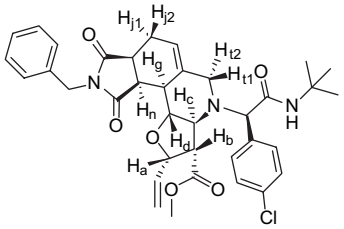
^{1}H NMR (300 MHz): δ 1.36 [9H, s]; 2.05–2.15 [1H, m]; 2.41 [1H, ddd, *J* 11, 6, 4]; 2.69 [1H, ddd, *J* 15, 7, 1]; 3.05 [1H, br d, *J* 16]; 3.10 [1H, ddd, *J* 8, 8, 1]; 3.23 [1H, t, *J* 10]; 3.32 [1H, d, *J* 16]; 3.38 [1H, t, *J* 10]; 3.40 [1H, dd, *J* 8, 6]; 3.58 [3H, s]; 3.94 [1H, s]; 4.51 [1H, d, *J* 14]; 4.62 [1H, d, *J* 14]; 4.67 [1H, t, *J* 10]; 4.89 [1H, dd, *J* 10, 8]; 5.22 [1H, d, *J* 10]; 5.33 [1H, d, *J* 17]; 5.57 [1H, br s]; 5.67 [1H, ddd, *J* 17, 10, 8]; 6.72 [1H, s]; 7.20–7.40 [9H, m].

^{13}C NMR (75 MHz): δ 25.1 (CH_2); 28.6 (CH_3); 39.9 (CH); 40.5 (CH); 42.3 (CH_2); 42.7 (CH); 49.0 (CH_2); 51.5 (C); 52.2 (CH_3); 54.8 (CH); 65.5 (CH); 67.8 (CH); 76.9 (CH); 81.2 (CH); 119.3 (CH_2); 122.1 (CH); 127.8 (CH); 128.2 (CH); 128.2 (CH); 128.5 (CH); 129.7 (CH); 133.1 (C); 134.5 (CH); 135.7 (C); 136.2 (C); 136.3 (C); 168.1 (C); 173.5 (C); 176.9 (C); 179.0 (C).

Elem. Anal. Calcd for: C, 66.91; H, 6.24; Cl, 5.49; N, 6.50. Found C, 67.09; H, 6.23; Cl, 5.50; N, 6.51.

NOE analysis. Given the configurations of C_c and C_d (respectively *S* and *R*), the structure is confirmed by a NOESY signal between H_g and H_c (the two protons are cis, therefore the configuration of C_g is *S*) and by the absence of a signal between H_d and H_n (the two protons are trans, therefore the configuration of C_n is *R*).

Detailed NOE absorbances H_d–H_{t1}: 7%; H_d–H_b: 7%; H_d–H_a: 6%; H_g–H_c: strong, overlapped with H_g–H_n; H_g–H_{j1}: 8%; H_g–H_{t2}: 4%. The signals of H_c and H_n are overlapped in the ^{1}H NMR; it is not possible to determine an NOE absorbance between these two protons.



4.7.17. (2*S*,3*S*,3a*S*,9a*S*,9b*R*)-Diethyl 4-((*R*)-(*tert*-butylcarbamoyl)(4-chlorophenyl)methyl)-2,3,3a,4,5,9,10b-hexahydro-3-methoxycarbonyl-2-vinylfuro[3,2-*h*]pyrido[4,3-*c*]pyridazine-8,9(7*H*,10a*H*)-dicarboxylate (14). M.W. 633.13; R_f 0.49 (eluent: EtOAc/PE 1:1); $[\alpha]_D^{20}$ −104.9 (*c* 0.35, $CHCl_3$).

^{1}H NMR (CD_3OD, 300 MHz): δ 1.20–1.30 [6H, m]; 1.28 [9H, s]; 3.10 [1H, t, *J* 10]; 3.20–3.60 [5H, m]; 3.47 [3H, s]; 4.12 [1H, s]; 4.15–4.30 [4H, m]; 4.43 [1H, dd, *J* 17, 6]; 4.60 [1H, t, *J* 8]; 5.15 [1H, d, *J* 10]; 5.27 [1H, d, *J* 17]; 5.55–5.70 [1H, m]; 5.68 [1H, br s]; 7.20–7.40 [4H, m]; 7.81 [1H, s].

^{13}C NMR (CD_3OD, 75 MHz): δ 14.9 (CH_3); 28.7 (CH_3); 43.4 (CH_2); 52.4 (CH); 52.8 (CH_3); 57.4 (CH_2); 60.1 (C); 63.6 and 64.0 (CH_2); 69.5 (CH); 71.0 (CH); 80.8 (CH); 81.6 (CH); 119.0 (CH_2); 123.6 (CH); 129.3 (CH); 131.9 (CH); 134.9 (C); 136.2 (CH); 138.2 (C); 156.7 and 157.2 (C); 172.2 (C); 172.7 (C).

GC–MS 17.4 min (100%) [532 (200%, M−*t*-BuNHCO), 408 (30%, M−*t*-BuNHCOCHC$_6$H$_4$Cl), 207 (75%), 125 (95%), 95 (100%)].

Elem. Anal. Calcd for: C, 58.81; H, 6.53; Cl, 5.60; N, 8.85. Found C, 58.63; H, 6.53; Cl, 5.59; N, 8.87.

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Supplementary data

Complete product characterisation data of all new compounds and detailed NOE experiments for compound **13**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.06.061.

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