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Application of an Ugi type reaction to an *N*-silyl-4,4-disubstituted 1,4-dihydropyridine

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ABSTRACT

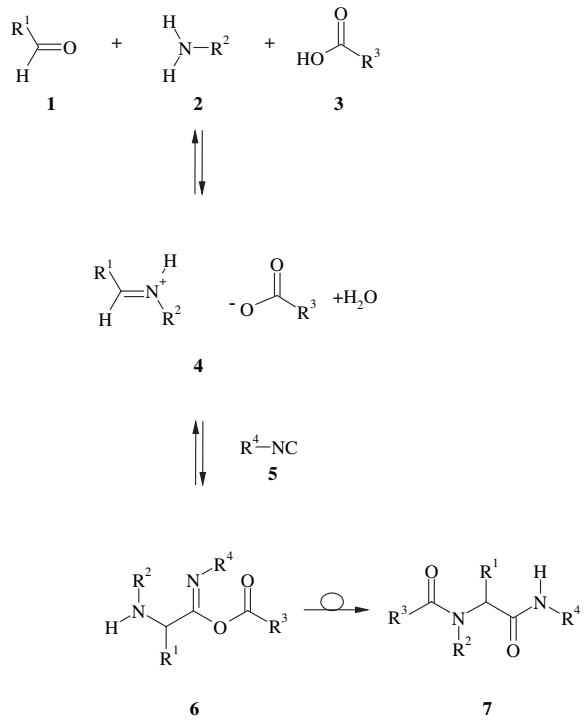
Ugi type reactions of an *N*-silyl-4,4-disubstituted 1,4-dihydropyridine with various isocyanides and carboxylic acids provided 2-carbamoylated 1,2,3,4-tetrahydropyridine derivatives in good yields and with high stereoselectivities.

1. Introduction

The Ugi four-component reaction (U-4CR) has first been described in 1959 but represents still one of the most important and prominent variants of multicomponent reactions (MCRs) to date.[1] Being highly efficient and versatile the Ugi four-component reaction (U-4CR) provides a rapid and reliable access to a plethora of α-acylaminoamide derivatives **7**. Accordingly, the U-4CR, besides being widely used, became the conceptual basis of many related four-component reactions, the development of which was driven to a great extent by the field of combinatorial chemistry in the pharmaceutical industry emerging at the beginning of the 1990s. Thus, many multicomponent reactions related to the Ugi reactions playing an important role in the drug discovery process are available now.

A considerably simplified reaction mechanism of the classical Ugi four-component reaction (U-4CR) is shown in Scheme 1. The sequence starts with the condensation of the aldehyde **1** with the amine **2** in the presence of the carboxylic acid **3**, which results in the formation of the iminium salt **4**. In the key step both, the electrophilic iminium ion and the nucleophilic carboxylate function of the iminium salt **4** add to the terminal carbon of the isocyanide **5**. Rearrangement of the thus formed unstable intermediate **6** results finally in the formation of the Ugi product **7**.

An interesting extension of the Ugi reaction has been reported by Lavilla et al.[2] By employing *N*-alkyl-dihydropyridines **8** as starting material for the Ugi reaction the authors established an efficient access to α-carbamoylated piperidine derivatives **11**. The transformation was accomplished by treating starting material **8** with p-toluenesulfonic acid (**10**) and isocyanide **9**, the acid transforming **8** into an iminium ion, which was then trapped by the isocyanide **9** in the second step of the reaction sequence (Scheme 2). Experiments undertaken by the authors to perform these transformations in an enantioselective manner using (+)-camphorsulfonic acid as a chiral proton source, however, failed.



Scheme 1. Considerably simplified reaction mechanism of the U-4CR.

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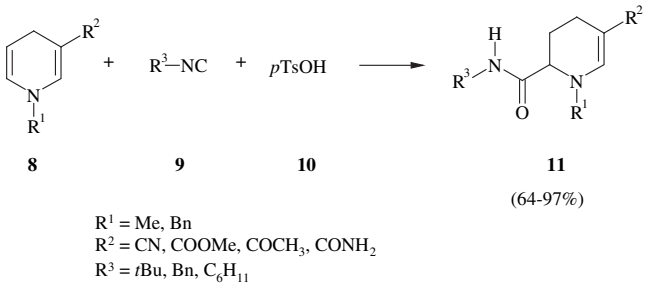
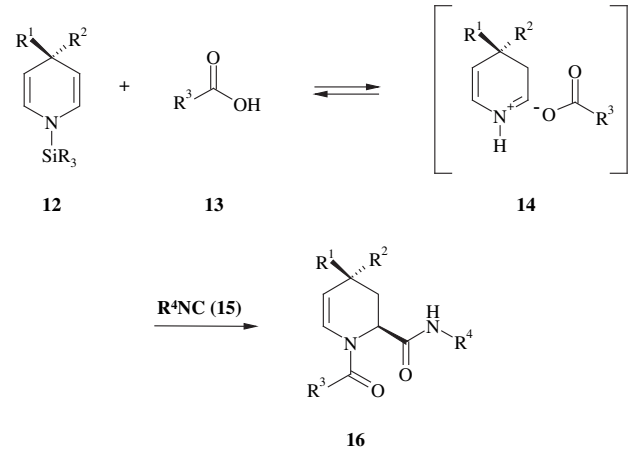


Scheme 2. α-Carbamoylation of 1,4-dihydropyridines **8**.

The piperidine ring is a common subunit in many biological active molecules and natural products.[3] Short and versatile routes to substituted piperidine derivatives are therefore of tremendous value. Allowing multiple functionalization reactions dihydropyridines are of great interest as building blocks for the preparation of piperidine derivatives and of piperidine ring containing heterocycles.[4] For instance 1,2-dihydropyridine derivatives have successfully been employed as key intermediates in the total synthesis of (+)-Leuciduline[5] and (+)-Melazocin.[6] 1,4-Dihydropyridines were successfully used, for example, as intermediates in the synthesis of alkaloids of the ervitsine–ervatamine group.[7]

So far, for practical reasons, mainly 4-unsubstituted and 4-monosubstituted 1,4-dihydropyridines have been employed as building blocks for the construction of more complex molecules whereas 4,4-disubstituted 1,4-dihydropyridines have rarely been used for this purpose. This is certainly due to the fact that up to now the preparation of 4,4-disubstituted 1,4-dihydropyridines in general has been an inefficient and laborious multistep process. Recently, we reported on a new method that allows the preparation of 4,4-disubstituted 1,4-dihydropyridines **12** in a straightforward manner, by the direct addition of organomagnesium derivatives to *N*-silylpyridinium ions.[8] To demonstrate the utility of the resulting 4,4-disubstituted, *N*-silylprotected 1,4-dihydropyridines **12** as building blocks for the construction of more complex molecules and inspired by the Ugi reaction, we decided to study the transformation of these compounds into α-carbamoylated 1,2,3,4-tetrahydropyridine derivatives **16**. In this paper we report on the successful implementation of this plan (Scheme 3).



Scheme 3. Proposed Ugi reaction process with 1,4-dihydropyridines **12**.

2. Results and discussion

We envisaged that the 1,4-dihydropyridine derivatives **12** should be particularly useful for the preparation of α-carbamoylated piperidine derivatives by Ugi type reactions. In addition to the variability of the 4-substituents the 1,4-dihydropyridines **12** offer further structural flexibility, which is inferred by the lability of the *N*-silyl group. Ugi reactions are typically performed under acidic reaction conditions, necessary to generate iminium ions as integral part of the reaction sequence. When applied to 1,4-dihydropyridines **12** acidic reaction conditions in addition to transforming **12** into an iminium salt are likely to also cause a desilylation reaction. Accordingly, as reactive intermediate the *N*-desilylated cyclic iminium ion **14** should form. But with the iminium ion **14** as intermediate the Ugi reaction can proceed along the common pathway leading to Ugi products provided with an *N*-acyl group resulting from the carboxylic acid used in the reaction. Thus, now depending on the carboxylic acid **13** selected for the Ugi reaction final products with different *N*-acyl groups can be obtained. As compared to the reactions described by Lavilla et al.[2] (Scheme 2), where the *N*-substituent of the starting material **8** by being stable remains unchanged, Ugi reactions with the *N*-silyl 1,4-dihydropyridines **12** would introduce additional flexibility by also allowing variation of the *N*-substituent (Scheme 3). Accordingly, it seemed particularly worthwhile to explore the use of *N*-silyl-1,4-dihydropyridines as starting material in Ugi type reactions.

As a model substrate for this study, the easily accessible *N*-triisopropylsilyl protected 1,4-dihydropyridine **17** was selected.[8] In a first attempt, **17** was treated in dichloromethane at room temperature for 17 h with 2 equiv of *tert*-butyl isocyanide (**23**) and 3.5 equiv acetic acid (**18**). As no reaction occurred, the experiment was repeated at 40 °C. In this case after 5 h at least traces of the desired reaction product **26** could be detected by ^{1}H NMR spectroscopy.

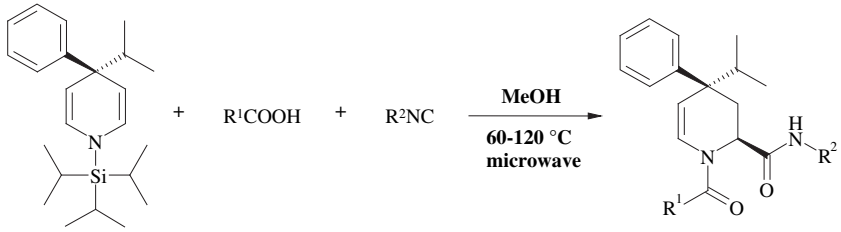
Ugi reactions are well known to proceed best in polar protic solvents.[9] Therefore, in a further experiment dichloromethane was replaced by methanol and, in addition, the reaction temperature was raised to 65 °C. Whereas before only minute amounts of the desired Ugi product **26** had formed, now even 55% of **26** could be isolated (Table 1, entry 1). The reaction proceeded as well, when acetic acid (**18**) was replaced by benzoic acid (**19**) keeping the reaction conditions the same. With 48%, the yield for the Ugi product, the *N*-benzoyl derivative **27**, was in this case again quite satisfying (Table 1, entry 2).

For reactions performed under microwave irradiation instead with conventional heating often positive effects with respect to the reaction time and the yield are observed. Therefore, we repeated the reactions mentioned above, with acetic acid (**18**) or benzoic acid (**19**), in a microwave reactor (Table 1, compare entries 1 and 2 with 3 and 4). We were pleased to find that under these conditions the replacing of the conventional heating in an oil bath by microwave irradiation not only shortened the reaction time, but also increased the yields of **26** from 55% to 69% and **27** from 48% to 62%, respectively.

Next, dihydropyridine **17** was reacted with *tert*-butyl isocyanide (**23**) in the presence of different carboxylic acids **20**–**22** (Table 1, entries 5–7). First, formic acid (**20**) was implemented as reagent yielding 74% of the *N*-formylated reaction product **28** (Table 1, entry 5). To increase the synthetic possibilities, the products resulting from the Ugi reaction can be used for, in the next reactions with the tetrahydropyridine **17** and the isonitrile **23**, 3-chloropropionic acid (**21**) and chloroacetic acid (**22**) were employed as reaction partners. Also, these reactions proceeded smoothly providing the desired tetrahydropyridines **29** and **30** in yields of 59% and 64%, respectively (Table 1, entries 6 and 7).

To further broaden the scope of this reaction finally the structure of the isocyanide used was varied, too (Table 1, entries 8–10). The reaction performed with methyl isocyanoacetate (**24**) in the presence of either acid **18** or **19** led to the desired tetrahydropyridines **31** and **32** in yields of 75% and 80%, respectively. Also, the acid labile 1-isocyanocyclohexene (**25**) could be employed

Table 1
α-Carbamoylation of model substrate **17**[a]



17 **18-22** **23-25** **26-33**

Entry	Carboxylic acid		Isocyanide		*t* (h)	*T* (°C)	Product	
	No. (R^1)	equiv	No. (R^2)	equiv			No.	Yield[b] (%)
1	**18** (Me)	3.5	**23** (*t*-Bu)	2.0	5.0	65[b]	**26**	55
2	**19** (Ph)	3.5	**23** (*t*-Bu)	2.0	5.0	65[c]	**27**	48
3	**18** (Me)	3.5	**23** (*t*-Bu)	2.0	1.5	120	**26**	69
4	**19** (Ph)	3.5	**23** (*t*-Bu)	2.0	1.5	120	**27**	62
5	**20** (H)	3.5	**23** (*t*-Bu)	2.0	1.5	100	**28**	74
6	**21** (CH_2CH_2Cl)	3.0	**23** (*t*-Bu)	2.0	1.5	110	**29**	59
7	**22** (CH_2Cl)	3.5	**23** (*t*-Bu)	2.0	1.0	100	**30**	64
8	**18** (Me)	4.0	**24** (CH_2CO_2Me)	1.5	1.8	100	**31**	75
9	**19** (Ph)	4.0	**24** (CH_2CO_2Me)	1.5	1.8	100	**32**	80
10	**20** (H)	2.5	**25**[d]	1.5	1.5	110	**33**	32

[a] Racemic compounds though the structure of only one enantiomer is shown.
[b] Isolated yield.
[c] Heating with oil bath.
[d] 1-Isocyanocyclohexene (**25**).

successfully providing in the presence of formic acid (**20**) the α-carbamoylated reaction product **33** in 32% yield (Table 1, entry 10).

All final products **26**–**33** were obtained as single diastereomers. Also, the yields given in Table 1 refer to this pure form. Though the crude products of the above described Ugi reactions were subjected to a careful analysis by ^{1}H and ^{13}C NMR spectroscopy, no clear conclusion regarding the diastereoselectivity of the reaction could be drawn. Various side products were present in the reaction mixture, but because of their small quantities their identification was considered a fruitless endeavor. But as no serious efforts had to be made to isolate compounds **26**–**33** in diastereomerically pure form, it should be justified, to assume that the formation of compounds **26**–**33** had proceeded with a reasonable or even high diastereoselectivity.

To determine the relative configuration of the Ugi products that had been synthesized in this study, compound **26**, for which suitable crystals had been obtained, was subjected to an X-ray analysis. As indicated by the structure obtained from this X-ray analysis given in Figure 1, in **26** the tetrahydropyridine ring adopts a pseudo-chair conformation with the carbamoyl substituent in 2-position and the phenyl substituent in 4-position both occupying a pseudo-axial orientation and residing on the same side. From an energetic point of view the found structure will represent the most favored geometry as the sterically more demanding isopropyl group (as compared to the phenyl group) in the 4-position occupies a pseudo-equatorial orientation, whereas the pseudo-axial orientation of the carbamoyl group in the 2-position allows for a partly release of the $A^{(1,3)}$ strain arising from the adjacent *N*-acyl group.

According to the ^{1}H NMR spectra of compounds **26**–**33**, the stereochemistry found for **26**, by X-ray analysis, with the 2-carbamoyl group and the 4-phenyl group in cis-orientation is likely to apply to all other Ugi products **27**–**33** as well. For all Ugi products, **26**–**33**, two different sets of signals are observed in the ^{1}H NMR spectra taken at room temperature (for **27** and **32** the ^{1}H NMR spectra were taken at −25 °C). These arise from the presence of two conformational isomers with respect to the *N*-acyl moiety as evidenced by significant chemical shift differences especially experienced by the 2-H proton of the piperidine ring ($\Delta\Delta\delta \sim 0.4$–$0.5$ ppm). For all compounds the two sets of signals arising from the two rotamers of the *N*-acyl moiety were very similar with respect to chemical shift and coupling pattern and coupling constants. This was also true for the protons in the 2- and 3-position of the piperidine ring, which should suffer a significant change of their chemical shift and coupling constants when a change of the relative configuration occurs (Table 2, Experimental part). As this is not the case, it seems reasonable to assume, that the relative configuration displayed by compound **26** according to the X-ray analysis applies also to all other Ugi products, **27**–**33**.

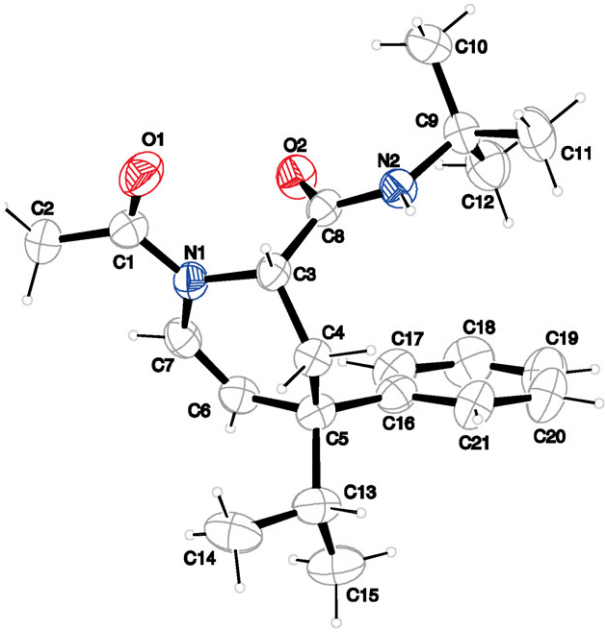
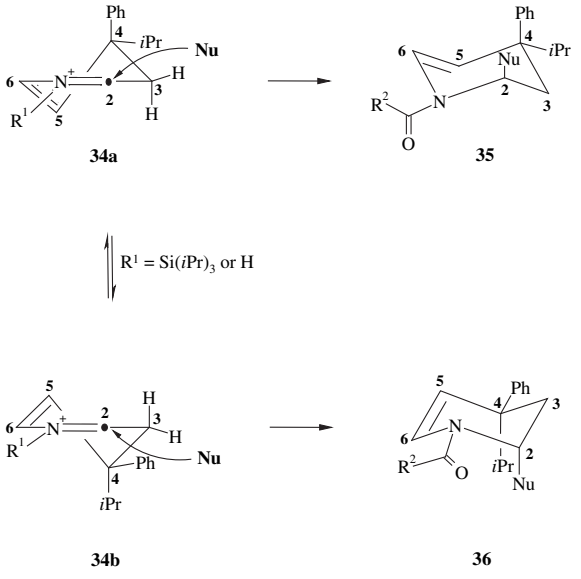


Figure 1. X-ray structure of **26**.

As a rationale for the stereoselection observed for the transformation of the *N*-silyl-1,4-dihydropyridine **17** to the Ugi products **26–33**, the model in Scheme 4 is proposed. The iminium ion **34**, with R^1 being either a proton or a TIPS group, will adopt a pseudo-chair conformation that can exist in two conformations.[10] From these two conformations, **34a** and **34b**, conformer **34a** with the isopropyl group in an equatorial and the phenyl group in an axial orientation—in the 4-position of the piperidine ring—should clearly predominate over **34b** with the opposite arrangement. For stereoelectronic reasons the nucleophile will add along the trajectories indicated in formula **34a** and **34b**. From these the approach as indicated in **34b** should be favored as it suffers less steric interactions arising from the axial oriented substituent in 4-position, which is in this case a phenyl group, which is sterically less demanding than the isopropyl group displayed in an axial position in **34b**. Accordingly, the reaction pathway indicated in **34a** benefits from both, the preponderance of the underlying conformer **34a** and the more favorable trajectory for the nucleophile addition. When the reaction along this pathway predominates (**34a**→**35**), which should be the case for the reasons given above, then as major isomer the addition product **35** in which the added nucleophile and the 4-phenyl substituent reside on the same side of the piperidine ring should form. Actually, this is in line with the relative configuration of the Ugi products **26–33**, which display this stereochemistry.



Scheme 4. Model for stereoselection of Ugi type reactions performed with **17**.

3. Conclusions

In summary, we have developed a straightforward method for the transformation of *N*-silyl-1,4-dihydropyridine **17** as a model compound to α-carbamoylated piperidine derivatives **26–33** by an Ugi type reaction. This reaction has been realized for a series of different carboxylic acids and isocyanides and was found to proceed with high diastereoselectivities and with good yields.

4. Experimental section

Methanol was freshly dried using a standard procedure.[11] 4-Isopropyl-4-phenyl-1-triisopropylsilyl-1,4-dihydropyridine (**17**)[8] and 1-isocyanocyclohexene (**25**)[12] were synthesized according to a literature procedure. Flash chromatography was performed with 40–63 mesh silica gel. Preparative HPLC was performed with a Hibar® LiChrosorb® Si 60 column (5 μm, 25×250 nm). Microwave reactions were performed using flame-dried reaction vessels under argon atmosphere in a Biotage Initiator. ^{1}H and ^{13}C NMR spectra were recorded on a JNMR-GX 400 (Joel, 400 MHz) or a JNMR-GX 500 (Joel, 500 MHz) spectrometer, respectively. Septets are abbreviated with sept. Rotameric ratios were determined from the respective ^{1}H NMR spectra at 25 °C. ^{13}C NMR peaks are referred to major and minor rotamers when clearly determinable. Infrared spectra were obtained on a Perkin Elmer Model 1600 FTIR spectrometer. Microanalytical data for carbon, hydrogen, and nitrogen were determined on a Heraeus Rapid Analyser and on a Elementar Vario EL Analyser.

4.1. Typical Ugi procedure

A solution of **17** in MeOH was mixed with the corresponding isocyanide followed by the addition of the carboxylic acid. The reaction vessels were sealed and heated in the microwave reactor at the temperature and time given. After removal of the solvent the residue was dissolved in CH_2Cl_2 and the organic layer was once washed with a HCl solution (0.2 M) and once with brine. After drying over $MgSO_4$ the solvent was removed in vacuo and the residue was purified by column chromatography and if necessary by subsequent preparative HPLC.

4.2. (2*RS*,4*SR*)-1-Acetyl-*N*-*tert*-butyl-4-isopropyl-4-phenyl-1,2,3,4-tetrahydropyridine-2-carboxamide (26)

According to standard procedure from **17** (50.0 mg, 0.141 mmol) in MeOH (3 mL), **23** (23.4 mg, 0.281 mmol, 31.7 μL, 2.0 equiv), and acetic acid (**18**) (29.7 mg, 0.492 mmol, 28.3 μL, 3.5 equiv) at 120 °C for 1.5 h. After column chromatography (*n*-pentane/EtOAc, 28:72) and preparative HPLC (*n*-heptane/EtOAc, 25:75, 20 mL/min, t_R=20.2 min) **26** was isolated. Yield 33 mg (69%), colorless solid, mp 167–169 °C. TLC: R_f=0.38 (SiO_2, EtOAc). ^{1}H NMR (400 MHz, tetrachloroethane, 130 °C): δ=0.70 (d, $^3J_{H,H}$=5.3 Hz, 3H, CH(CH_3)$_2$), 0.86 (d, $^3J_{H,H}$=5.3 Hz, 3H, CH(CH_3)$_2$), 0.90 (br s, 9H, C(CH_3)$_3$), 1.84–1.94 (m, 1H, CH(CH$_3$)$_2$), 2.14–2.27 (m, 1H, NCHCH_2), 2.18 (s, 3H, COCH_3), 2.95 (d, $^3J_{H,H}$=14.1 Hz, 1H, NCHCH_2), 4.59 (br s, 1H, NCHCH$_2$), 4.90 (br s, 1H, NH), 5.40 (d, $^3J_{H,H}$=8.5 Hz, 1H, NCH=CH), 7.13–7.20 (m, 2H, NCH=CH, H_{para}), 7.22–7.35 (m, 4H, $H_{arom.}$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ=17.5 (q, 1C, CH(CH_3)$_2$), 17.6 (q, 1C, CH(CH_3)$_2$), 17.7 (q, 1C, CH(CH_3)$_2$), 17.5 (q, 1C, CH(CH_3)$_2$), 21.5 (q, 1C, COCH_3), 21.6 (q, 1C, COCH_3), 27.9 (q, 3C, C(CH_3)$_3$), 28.1 (q, 3C, C(CH_3)$_3$), 31.4 (t, 1C, NCHCH_2, major), 32.2 (t, 1C, NCHCH_2, minor), 38.2 (d, 1C, CH(CH$_3$)$_2$), 38.9 (d, 1C, CH(CH$_3$)$_2$), 42.3 (s, 1C, C(CH$_3$)$_3$), 42.8 (s, 1C, C(CH$_3$)$_3$), 50.6 (s, 1C, CHCH$_2$C), 50.9 (s, 1C, CHCH$_2$C), 53.3 (d, 1C, NCHCH$_2$, minor), 57.6 (d, 1C, NCHCH$_2$, major), 111.6 (d, 1C, NCH=CH, minor), 112.8 (d, 1C, NCH=CH, major), 121.7 (d, 1C, NCH=CH, major), 124.6 (d, 1C, NCH=CH, minor), 125.3 (d, $C_{arom.}$), 126.1 (d, $C_{arom.}$), 126.3 (d, $C_{arom.}$), 127.4 (d, $C_{arom.}$), 127.5 (d, $C_{arom.}$), 127.9 (d, $C_{arom.}$), 128.0 (d, $C_{arom.}$), 128.2 (d, $C_{arom.}$), 129.0 (d, $C_{arom.}$), 144.5 (s, 1$C_{arom.}$), 144.9 (s, 1$C_{arom.}$), 167.7 (s, 1C, CO), 168.3 (s, 1C, CO), 168.4 (s, 1C, CO), 168.9 (s, 1C, CO) ppm. IR (KBr): ν=3428, 3314, 3059, 2963, 2961, 2929, 2873, 1672, 1645, 1542, 1425, 1385 cm^{-1}. MS (CI, CH_5^+): *m*/*z* (%)=343 (86, [M+H]$^+$), 299 (36), 270 (52), 242 (78), 227 (36), 183 (21), 156 (45), 102 (100). Anal. Calcd for $C_{21}H_{30}N_2O_2$ (342.49): C, 73.65; H, 8.83; N, 8.18. Found: C, 73.61; H, 8.66; N, 8.19.

4.3. (2*RS*,4*SR*)-1-Benzoyl-*N*-*tert*-butyl-4-isopropyl-4-phenyl-1,2,3,4-tetrahydropyridine-2-carboxamide (27)

According to standard procedure from **17** (50.0 mg, 0.141 mmol) in MeOH (3 mL), **23** (23.4 mg, 0.282 mmol, 31.7 μL, 2.0 equiv), and

benzoic acid (**19**) (60.3 mg, 0.494 mmol, 3.5 equiv) at 120 °C for 1.5 h. After column chromatography (*n*-pentane/EtOAc, 70:30) and preparative HPLC (cyclohexane/EtOAc, 60:40, 20 mL/min, t_R=11.9 min) **27** was isolated. Yield 35 mg (62%) colorless solid, mp 158–160 °C. TLC: R_f=0.77 (SiO_2, EtOAc). ^{1}H NMR (400 MHz, tetrachloroethane, 125 °C): δ=0.71 (d, $^3J_{H,H}$=5.8 Hz, 3H, CH(CH_3)$_2$), 0.89 (d, $^3J_{H,H}$=5.8 Hz, 3H, CH(CH_3)$_2$), 0.95 (br s, 9H, C(CH_3)$_3$), 1.89–1.99 (m, 1H, CH(CH_3)$_2$), 2.28–2.37 (m, 1H, NCHCH_2), 2.97 (d, $^3J_{H,H}$=14.5 Hz, 1H, NCHCH_2), 4.78 (br s, 1H, NCHCH_2), 5.03 (br s, 1H, NH), 5.35 (d, $^3J_{H,H}$=8.3 Hz, 1H, NCH=CH), 7.00 (d, $^3J_{H,H}$=8.3 Hz, 1H, NCH=CH), 7.14–7.21 (m, 1H, $H_{arom.}$), 7.23–7.63 (m, 4H, $H_{arom.}$), 7.43–7.55 (m, 5H, $H_{arom.}$) ppm. ^{13}C NMR (125 MHz, tetrachloroethane, 100 °C): δ=17.7 (q, 1C, CH(CH_3)$_2$), 17.8 (q, 1C, CH(CH_3)$_2$), 28.3 (q, 3C, C(CH_3)$_3$), 32.6 (t, 1C, NCHCH_2), 38.6 (d, 1C, CH(CH_3)$_2$), 43.2 (s, 1C, C(CH_3)$_3$), 50.7 (s, 1C, CHCH$_2$C), 55.4 (d, 1C, NCHCH$_2$), 112.2 (d, 1C, NCH=CH), 125.4 (d, 1C, NCH=CH), 126.2 (d, 1C, $C_{arom.}$), 127.5 (d, 2C, $C_{arom.}$), 127.8 (d, 2C, $C_{arom.}$), 128.0 (d, 2C, $C_{arom.}$), 128.6 (d, 2C, $C_{arom.}$), 130.6 (d, 1C, $C_{arom.}$), 134.8 (d, 1C, $C_{arom.}$), 144.9 (s, 1C, $C_{arom.}$), 167.8 (s, 1C, CO), 169.3 (s, 1C, CO) ppm. IR (KBr): ν=3428, 3359, 3058, 2963, 2929, 2873, 1685, 1634, 1622, 1535, 1421, 1383 cm^{-1}. MS (CI, CH_5^+): *m*/*z* (%)=405 (66, [M+H]$^+$), 361 (24), 332 (93), 304 (33), 227 (90), 183 (55), 156 (26), 105 (100). $C_{26}H_{32}N_2O_2$ (404.56): Anal. Calcd for C, 77.19; H, 7.87; N, 6.92. Found C, 77.00; H, 8.06; N, 6.88.

4.4. (2*RS*,4*SR*)-*N*-*tert*-Butyl-1-formyl-4-isopropyl-4-phenyl-1,2,3,4-tetrahydropyridine-2-carboxamide (28)

According to standard procedure from **17** (50.0 mg, 0.141 mmol) in MeOH (3 mL), **23** (23.4 mg, 0.282 mmol, 31.7 μL, 2.0 equiv), and formic acid (**20**) (22.7 mg, 0.494 mmol, 18.6 μL, 3.5 equiv) at 100 °C for 1.5 h. The residue was purified twice by column chromatography (I: CH_2Cl_2/EtOAc, 70:30 and SC II: CH_2Cl_2/EtOAc, 50:50). Yield 34 mg (74%) colorless solid, mp 129–131 °C. TLC: R_f=0.58 (SiO_2, EtOAc). ^{1}H NMR (400 MHz, tetrachloroethane, 125 °C): δ=0.67 (d, $^3J_{H,H}$=6.8 Hz, 3H, CH(CH_3)$_2$), 0.86 (d, $^3J_{H,H}$=6.8 Hz, 3H, CH(CH_3)$_2$), 0.90 (s, 9H, C(CH_3)$_3$), 1.92 (sept., $^3J_{H,H}$=6.8 Hz, 1H, CH(CH_3)$_2$), 2.15–2.26 (m, 1H, NCHCH_2), 2.94 (d, $^3J_{H,H}$=12.3 Hz, 1H, NCHCH_2), 4.62 (br s, 1H, NCHCH_2), 4.86 (br s, 1H, NH), 5.44 (br s, 1H, NCH=CH), 6.79 (br s, 1H, NCH=CH), 7.12–7.20 (m, 1H, H_{para}), 7.20–7.35 (m, 4H, $H_{arom.}$), 8.35 (s, 1H, CHO) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ=17.3 (q, 1C, CH(CH_3)$_2$), 17.7 (q, 1C, CH(CH_3)$_2$, minor), 17.8 (q, 1C, CH(CH_3)$_2$, major), 28.0 (q, 3C, C(CH_3)$_3$, minor), 28.1 (q, 3C, C(CH_3)$_3$, major), 31.2 (t, 1C, NCHCH_2, major), 31.4 (t, 1C, NCHCH_2, major), 38.3 (t, 1C, CH(CH_3)$_2$, major), 38.7 (t, 1C, CH(CH_3)$_2$, minor), 44.0 (s, 1C, C(CH_3)$_3$), 50.8 (s, 1C, CHCH$_2$C, major), 51.1 (s, 1C, CHCH$_2$C, minor), 52.6 (d, 1C, NCHCH$_2$, major), 56.5 (d, 1C, NCHCH$_2$, minor), 112.4 (d, 1C, NCH=CH, major), 114.6 (d, 1C, NCH=CH, minor), 120.0 (d, 1C, NCH=CH, minor), 123.9 (d, 1C, NCH=CH, major), 124.6 (d, 1C, $C_{arom.}$), 127.4 (d, 1C, $C_{arom.}$), 127.6 (d, 1C, $C_{arom.}$), 128.0 (d, 1C, $C_{arom.}$), 128.1 (d, 1C, $C_{arom.}$), 144.1 (s, 1C, $C_{arom.}$, minor), 144.5 (s, 1C, $C_{arom.}$, major), 161.0 (s, 1C, CO, minor), 161.3 (s, 1C, CO, major), 166.7 (s, 1C, CHO, major), 168.2 (s, 1C, CHO, minor) ppm. IR (KBr): ν=3434, 3321, 3053, 2963, 2929, 2867, 1698, 1654, 1541, 1358 cm^{-1}. MS (CI, CH_5^+): *m*/*z* (%)=329 (100, [M+H]$^+$), 301 (89), 257 (31), 156 (27). Anal. Calcd for $C_{20}H_{28}N_2O_2$ (328.46): C, 73.14; H 8.59; N, 8.53. Found: C, 72.82; H, 8.94; N, 8.45.

4.5. (2*RS*,4*SR*)-*N*-*tert*-Butyl-1-(3-chloropropionyl)-4-isopropyl-4-phenyl-1,2,3,4-tetrahydropyridine-2-carboxamide (29)

According to standard procedure from **17** (100 mg, 0.281 mmol) in MeOH (4.5 mL), **23** (46.7 mg, 0.562 mmol, 63.3 μL, 2.0 equiv), and 3-chloropropionic acid (**21**) (91.6 mg, 0.844 mmol, 3.5 equiv) at 110 °C for 1.5 h. After column chromatography (CH_2Cl_2/EtOAc, 90:10) and preparative HPLC (*n*-heptane/EtOAc, 50:50, 18 mL/min, t_R=18.1 min) **29** was isolated. Yield 65 mg (59%), colorless solid, mp 104–105 °C. TLC: R_f=0.62 (SiO_2, EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ=0.60 (d, $^3J_{H,H}$=7.2 Hz, 0.53×3H, CH(CH_3)$_2$), 0.61 (d, $^3J_{H,H}$=6.6 Hz, 0.47×3H, CH(CH_3)$_2$), 0.79 (d, $^3J_{H,H}$=6.6 Hz, 0.47×3H, CH(CH_3)$_2$), 0.83 (d, $^3J_{H,H}$=7.2 Hz, 0.53×3H, CH(CH_3)$_2$), 0.81 (s, 0.47×9H, C(CH_3)$_3$), 0.84 (s, 0.53×9H, C(CH_3)$_3$), 1.78 (sept., $^3J_{H,H}$=6.6 Hz, 0.47×1H, CH(CH_3)$_2$), 1.87 (sept., $^3J_{H,H}$=7.2 Hz, 0.53×1H, CH(CH_3)$_2$), 2.19 (dd, $^3J_{H,H}$=14.4/6.6 Hz, 1H, NCHCH_2), 2.58–2.67 (m, 0.47×1H, CH_2CH$_2$Cl), 2.83 (dt, $^3J_{H,H}$=17.0/5.5 Hz, 0.47×1H, CH_2CH$_2$Cl), 2.88–2.98 (m, 0.53×2H, CH_2CH$_2$Cl, NCHCH_2), 3.06 (dt, $^3J_{H,H}$=14.3/5.7 Hz, 0.47×1H, NCHCH_2), 3.10–3.17 (m, 0.53×1H, CH_2CH$_2$Cl), 3.74–3.80 (m, 0.47×1H, CH$_2$CH_2Cl), 3.81–3.88 (m, 0.53×1H, CH$_2$CH_2Cl), 3.88–3.99 (m, 1H, CH$_2$CH_2Cl), 4.35 (d, $^3J_{H,H}$=5.7 Hz, 0.47×1H, NCHCH$_2$), 4.86 (dd, $^3J_{H,H}$=6.6/2.0 Hz, 0.53×1H, NCHCH$_2$), 4.97 (br s, 0.53×1H, NH), 5.10 (br s, 0.47×1H, NH), 5.40 (dd, $^3J_{H,H}$=8.9/1.6 Hz, 0.53×1H, NCH=CH), 5.53 (dd, $^3J_{H,H}$=9.0/1.8 Hz, 0.47×1H, NCH=CH), 6.95 (d, $^3J_{H,H}$=8.9 Hz, 0.53×1H, NCH=CH), 7.12–7.30 (m, 5H, $H_{arom.}$), 7.54 (d, $^3J_{H,H}$=9.0 Hz, 0.47×1H, NCH=CH) ppm. Rotameric ratio: 47:53. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ=17.5 (q, 1C, CH(CH_3)$_2$), 17.6 (q, 1C, CH(CH_3)$_2$), 17.7 (q, 1C, CH(CH_3)$_2$), 17.8 (q, 1C, CH(CH_3)$_2$), 27.8 (q, 3C, C(CH_3)$_3$), 28.1 (q, 3C, C(CH_3)$_3$), 31.5 (t, 1C, NCHCH_2, minor), 32.2 (t, 1C, NCHCH_2, major), 36.0 (t, 1C, CH_2CH$_2$Cl, major), 36.1 (t, 1C, CH_2CH$_2$Cl, minor), 38.2 (d, 1C, CH(CH$_3$)$_2$, major), 38.9 (t, 1C, CH$_2$CH$_2$Cl, minor), 39.1 (d, 1C, CH(CH$_3$)$_2$, minor), 40.0 (t, 1C, CH$_2$CH$_2$Cl, major), 42.5 (s, 1C, C(CH$_3$)$_3$), 42.9 (s, 1C, C(CH$_3$)$_3$), 50.7 (s, 1C, CHCH$_2$C), 51.1 (s, 1C, CHCH$_2$C), 53.7 (d, 1C, NCHCH$_2$, major), 56.6 (d, 1C, NCHCH$_2$, minor), 112.7 (d, 1C, NCH=CH, major), 113.5 (d, 1C, NCH=CH, minor), 121.7 (d, 1C, NCH=CH, minor), 123.4 (d, 1C, NCH=CH, major), 126.2 (d, $C_{arom.}$), 126.4 (d, $C_{arom.}$), 127.4 (d, $C_{arom.}$), 127.45 (d, $C_{arom.}$), 127.5 (d, $C_{arom.}$), 127.9 (d, $C_{arom.}$), 128.1 (d, $C_{arom.}$), 144.3 (s, 1$C_{arom.}$), 144.7 (s, 1$C_{arom.}$), 167.8 (s, 1C, CO), 167.9 (s, 1C, CO), 168.0 (s, 1C, CO) ppm. IR (KBr): ν=3429, 3304, 2965, 1678, 1648, 1548 cm^{-1}. MS (CI, CH_5^+): *m*/*z* (%)=391 (53, [M+H]$^+$), 347 (19), 318 (20), 290 (20), 227 (25), 183 (59), 156 (100). Anal. Calcd for $C_{22}H_{31}ClN_2O_2$ (390.96): C, 67.59; H, 7.99; N, 7.17; Cl 9.07. Found: C 67.51; H, 8.16; N, 7.11; Cl, 9.25.

4.6. (2*RS*,4*SR*)-*N*-*tert*-Butyl-1-(2-chloroacetyl)-4-isopropyl-4-phenyl-1,2,3,4-tetrahydropyridine-2-carboxamide (30)

According to standard procedure from **17** (100 mg, 0.281 mmol) in MeOH (4.0 mL), **23** (46.7 mg, 0.562 mmol, 63.3 μL, 2.0 equiv), and 2-chloroacetic acid (**22**) (93.1 mg, 0.983 mmol, 3.5 equiv) at 100 °C for 1.0 h. After column chromatography (*n*-pentane/CH_2Cl_2/EtOAc, 40:20:40) and preparative HPLC (*n*-heptane/EtOAc, 50:50, 18 mL/min, t_R=19.0 min) **30** was isolated. Yield 68 mg (64%), colorless solid, mp 170–172 °C. TLC: R_f=0.63 (SiO_2, EtOAc). ^{1}H NMR (400 MHz, tetrachloroethane, 125 °C): δ=0.68 (d, $^3J_{H,H}$=6.9 Hz, 3H, CH(CH_3)$_2$), 0.86 (d, $^3J_{H,H}$=6.9 Hz, 3H, CH(CH_3)$_2$), 0.89 (s, 9H, C(CH$_3$)$_3$), 1.85–1.95 (m, 1H, CH(CH$_3$)$_2$), 2.20–2.29 (m, 1H, NCHCH_2), 2.97 (d, $^3J_{H,H}$=14.4 Hz, 1H, NCHCH_2), 4.12 (d, $^3J_{H,H}$=12.4 Hz, 1H, CH$_2$Cl), 4.24 (d, $^3J_{H,H}$=12.4 Hz, 1H, CH$_2$Cl), 4.69 (br s, 1H, NCHCH$_2$), 4.93 (br s, 1H, NH), 5.50 (d, $^3J_{H,H}$=7.8 Hz, 1H, NCH=CH), 7.06 (br s, 1H, NCH=CH), 7.13–7.21 (m, 1H, H_{para}), 7.21–7.33 (m, 4H, $H_{arom.}$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ=17.4 (q, 1C, CH(CH_3)$_2$, minor), 17.5 (q, 1C, CH(CH_3)$_2$, major), 17.7 (q, 1C, CH(CH_3)$_2$, minor), 17.8 (q, 1C, CH(CH_3)$_2$, major), 27.8 (q, 3C, C(CH_3)$_3$, minor), 27.9 (q, 3C, C(CH_3)$_3$, major), 31.3 (t, 1C, NCHCH_2, major), 31.4 (t, 1C, NCHCH_2, minor), 38.3 (d, 1C, CH(CH$_3$)$_2$, major), 38.4 (d, 1C, CH(CH$_3$)$_2$, minor), 40.4 (t, 1C, CH$_2$Cl, major), 40.5 (t, 1C, CH$_2$Cl, minor), 42.6 (s, 1C, CHCH$_2$C, minor), 42.7 (s, 1C, CHCH$_2$C, major), 50.7 (s, 1C, C(CH$_3$)$_3$, major), 50.8 (s, 1C, C(CH$_3$)$_3$, minor), 53.5 (d, 1C, NCHCH$_2$, major), 57.0 (s, 1C, NCHCH$_2$, minor), 114.0 (d, 1C, NCH=CH, major), 114.8 (d, 1C, NCH=CH, minor), 122.0 (d, 1C,

NCH=CH, minor), 123.3 (d, 1C, NCH=CH, major), 126.2 (d, $C_{arom.}$), 126.5 (d, $C_{arom.}$), 127.4 (d, $C_{arom.}$), 127.5 (d, $C_{arom.}$), 127.9 (d, $C_{arom.}$), 128.2 (d, $C_{arom.}$), 144.3 (s, $C_{arom.}$), 164.3 (s, 2C, CO), 167.0 (s, 2C, CO) ppm. IR (KBr): ν=3340, 3054, 3025, 2970, 2272, 2871, 1680, 1660, 1637, 1543, 1427, 1366 cm^{-1}. MS (CI, CH_5^+): m/z (%)=377 (44, $[M+H]^+$), 304 (100), 276 (75), 227 (41), 184 (28). Anal. Calcd for $C_{21}H_{29}ClN_2O_2$ (376.93): C, 66.92; H, 7.76; N, 7.43; Cl, 9.41. Found: C, 67.04; H, 7.67; N, 7.15; Cl, 9.14.

4.7. (2*RS*,4*SR*)-Methyl 2-[(1-acetyl-4-isopropyl-4-phenyl-1,2,3,4-tetrahydropyridine-2-yl)carbonylamino] ethanoate (31)

According to standard procedure from **17** (50.0 mg, 0.141 mmol) in MeOH (2.5 mL), **24** (21.0 mg, 0.211 mmol, 19.3 μL, 1.5 equiv), and acetic acid (**18**) (33.9 mg, 0.562 mmol, 32.3 μL, 3.5 equiv) at 100 °C for 1.8 h. After column chromatography (isohexane/EtOAc, 5:95) and preparative HPLC (*n*-heptane/EtOAc, 50:50, 20 mL/min, t_R=21.7 min) **31** was isolated. Yield 38 mg (75%), colorless solid, mp 208–209 °C. TLC: R_f=0.40 (SiO_2, EtOAc). ^{1}H NMR (400 MHz, tetrachloroethane, 125 °C): δ=0.78 (d, $^3J_{H,H}$=6.8 Hz, 3H, CH(CH_3)$_2$), 0.96 (d, $^3J_{H,H}$=6.8 Hz, 3H, CH(CH_3)$_2$), 1.78–1.92 (m, 1H, CH(CH$_3$)$_2$), 2.27 (s, 3H, COCH$_3$), 2.23–2.34 (m, 1H, NCHCH_2), 2.90–3.06 (m, 2H, NHCH_2, NCHCH_2), 3.46 (dd, $^3J_{H,H}$=18.0/4.8 Hz, 1H, NHCH_2), 3.76 (s, 3H, COOCH$_3$), 4.86 (br s, 1H, NCHCH$_2$), 5.44 (d, $^3J_{H,H}$=9.3 Hz, 1H, NCH=CH), 5.64 (br s, 1H, NH), 7.08–7.31 (6H, NCH=CH, 5H$_{arom.}$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ=17.2 (q, 1C, CH(CH_3)$_2$, minor), 17.3 (q, 1C, CH(CH_3)$_2$, major), 17.4 (q, 1C, CH(CH_3)$_2$, minor), 17.5 (q, 1C, CH(CH_3)$_2$, major), 21.3 (q, 1C, OCH$_3$, minor), 21.4 (q, 1C, OCH$_3$, major), 32.5 (t, 1C, NCHCH_2, major), 32.7 (t, 1C, NCHCH_2, minor), 37.5 (d, 1C, CH(CH$_3$)$_2$, major), 37.6 (d, 1C, CH(CH$_3$)$_2$, minor), 40.5 (t, 1C, NHCH$_2$, minor), 40.7 (t, 1C, NHCH$_2$, major), 42.9 (s, 1C, CHCH$_2$C, minor), 43.2 (s, 1C, CHCH$_2$C, major), 52.2 (q, 1C, COOCH$_3$, major), 52.5 (q, 1C, COOCH$_3$, minor), 53.7 (d, 1C, NCHCH$_2$, major), 56.3 (d, 1C, NCHCH$_2$, minor), 110.9 (d, 1C, NCH=CH, major), 111.6 (d, 1C, NCH=CH, minor), 122.6 (d, 1C, NCH=CH, minor), 125.0 (d, 1C, NCH=CH, major), 126.0 (d, 1C, $C_{arom.}$), 126.1 (d, 1C, $C_{arom.}$), 127.3 (d, 1C, $C_{arom.}$), 127.4 (d, 1C, $C_{arom.}$), 127.9 (d, 1C, $C_{arom.}$), 144.6 (s, 1C, $C_{arom.}$, minor), 144.9 (s, 1C, $C_{arom.}$, minor), 168.5 (s, 1C, CO, major), 168.8 (s, 1C, CO, minor), 168.9 (s, 1C, CO, major), 169.4 (s, 1C, CO, minor), 169.7 (s, 1C, CO, minor), 170.1 (s, 1C, CO, major) ppm. MS (CI, CH_5^+): m/z (%)=359 (53), 315 (28 $[M+H]^+-C_3H_7$), 270 (100), 242 (22), 198 (9), 156 (23). Anal. Calcd for $C_{19}H_{25}N_2O_4$, (359.44): C, 67.02; H, 7.31; N, 7.82. Found: C 66.79; H, 6.99; N, 7.82.

4.8. (2*RS*,4*SR*)-Methyl 2-[(1-benzoyl-4-isopropyl-4-phenyl-1,2,3,4-tetrahydropyridine-2-yl)carbonylamino] ethanoate (32)

According to standard procedure from **17** (50.0 mg, 0.141 mmol) in MeOH (2.5 mL), **24** (21.0 mg, 0.211 mmol, 19.3 μL, 1.5 equiv), and benzoic acid (**19**) (68.9 mg, 0.562 mmol, 3.5 equiv) at 100 °C for 1.8 h. After column chromatography (*n*-pentane/EtOAc, 30:70) and preparative HPLC (*n*-heptane/EtOAc, 25:75, 20 mL/min, t_R=11.1 min) **32** was isolated as a colorless solid. Yield 47 mg (80%), mp 65–69 °C. TLC: R_f=0.63 (SiO_2, EtOAc). ^{1}H NMR (500 MHz, tetrachloroethane, 90 °C): δ=0.69 (d, $^3J_{H,H}$=6.4 Hz, 3H, CH(CH_3)$_2$), 0.91 (d, $^3J_{H,H}$=6.4 Hz, 3H, CH(CH_3)$_2$), 1.93–2.03 (m, 1H, CH(CH$_3$)$_2$), 2.33 (dd, $^3J_{H,H}$=14.2/6.0 Hz, 1H, NCHCH_2), 2.86–3.00 (m, 2H, NCHCH_2, NHCH_2), 3.40 (dd, $^3J_{H,H}$=18.6/4.8 Hz, 1H, NHCH_2), 3.73 (s, 3H, CH$_3$), 4.96 (br s, 1H, NCHCH$_2$), 5.29 (br s, 1H, NCH=CH), 5.79 (br s, 1H, NH), 6.99 (br s, 1H, NCH=CH), 7.09–7.17 (m, 1H, H$_{arom.}$), 7.18–7.30 (m, 4H, H$_{arom.}$), 7.43–7.58 (m, 5H, H$_{arom.}$) ppm. ^{13}C NMR (125 MHz, tetrachloroethane, 90 °C): δ=17.7 (q, 1C, CH(CH_3)$_2$), 17.8 (q, 1C, CH(CH_3)$_2$), 33.0 (t, 1C, NCHCH_2), 37.8 (d, 1C, CH(CH$_3$)$_2$), 41.1 (d, 1C, NHCH$_2$), 43.6 (s, 1C, CHCH$_2$C), 52.2 (q, 1C, CH$_3$), 52.6 (d, 1C, NCHCH$_2$), 111.5 (d, 1C, NCH=CH), 125.9 (d, 1C, NCH=CH), 126.1 (d, 1C, $C_{arom.}$), 127.6 (d, 2C, $C_{arom.}$), 127.8 (d, 2C, $C_{arom.}$), 127.9 (d, 2C, $C_{arom.}$), 128.7 (d, 2C, $C_{arom.}$), 130.7 (d, 1C, $C_{arom.}$), 134.4 (s, 1C, $C_{arom.}$), 144.6 (s, 1C, $C_{arom.}$), 168.7 (s, 1C, CO), 169.5 (s, 1C, CO), 170.0 (s, 1C, CO) ppm. IR (KBr): ν=3240, 3059, 3028, 2958, 2876, 1754, 1664, 1640, 1531, 1411, 1367 cm^{-1}. MS (CI, CH_5^+): m/z (%)=421 (35, $[M+H]^+$), 377 (30), 332 (100), 304 (25), 260 (28), 156 (19), 105 (57). MS (EI, 70 eV): m/z (%)=377 (17, $M^+-C_3H_7$), 260 (30), 156 (21), 105 (100). Anal. Calcd for $C_{25}H_{28}N_2O_4$, (420.51): C, 71.41; H, 6.71; N, 6.66. Found C, 71.21; H, 6.64; N, 6.58.

4.9. (2*RS*,4*SR*)-*N*-Cyclohex-1-en-1-yl(1-formyl-4-isopropyl-4-phenyl-1,2,3,4-tetrahydropyridine)-2-carboxamide (33)

According to standard procedure from **17** (60.0 mg, 0.169 mmol) in MeOH (3.0 mL), **25** (27.2 mg, 0.253 mmol, 1.5 equiv), and formic acid (**20**) (19.5 mg, 0.422 mmol, 16.0 μL, 2.5 equiv) at 110 °C for 1.5 h. The residue was purified twice by column chromatography (*n*-pentane/EtOAc, 50:50). **33** was isolated. Yield 18.8 mg (32%), colorless solid, mp 176–178 °C. TLC: R_f=0.54 (SiO_2, EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ=0.62 (d, $^3J_{H,H}$=6.7 Hz, 3H, CH(CH_3)$_2$), 0.82 (d, $^3J_{H,H}$=6.7 Hz, 0.32×3H, CH(CH_3)$_2$), 0.83 (d, $^3J_{H,H}$=6.7 Hz, 0.68×3H, CH(CH_3)$_2$), 1.32–1.48 (m, 4H, CH$_2$), 1.50–1.65 (m, 2H, CH$_2$), 1.78–1.98 (m, 3H, CH$_2$+CH(CH$_3$)$_2$), 2.15 (dd, $^3J_{H,H}$=14.4/6.5 Hz, 0.68×1H, NCHCH_2), 2.22 (dd, $^3J_{H,H}$=14.3/6.3 Hz, 0.32×1H, NCHCH_2), 2.89 (dd, $^3J_{H,H}$=14.4/1.7 Hz, 0.68×1H, NCHCH_2), 2.99 (dd, $^3J_{H,H}$=14.3/1.9 Hz, 0.32×1H, NCHCH_2), 4.33 (dd, $^3J_{H,H}$=6.3/1.9 Hz, 0.32×1H, NCHCH$_2$), 4.75 (dd, $^3J_{H,H}$=6.5/1.7 Hz, 0.68×1H, NCHCH$_2$), 5.26–5.30 (m, 0.68×1H, NHC=CH), 5.32–5.35 (m, 0.32×1H, NHC=CH), 5.40 (d, $^3J_{H,H}$=8.5 Hz, 0.68×1H, NCH=CH), 5.55 (d, $^3J_{H,H}$=8.8 Hz, 0.32×1H, NCH=CH), 5.92 (br s, 0.68×1H, NH), 5.94 (br s, 0.32×1H, NH), 6.79 (d, $^3J_{H,H}$=8.5 Hz, 0.68×1H, NCH=CH), 7.06–7.23 (m, 5H, H$_{arom.}$), 7.33 (d, $^3J_{H,H}$=8.8 Hz, 0.32×1H, NCH=CH), 7.99 (s, 0.32×1H, CHO), 8.37 (s, 0.68×1H, CHO) ppm. Rotameric ratio: 68:32. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ=17.5 (q, 1C, CH(CH_3)$_2$), 17.7 (q, 1C, CH(CH_3)$_2$, minor), 17.8 (q, 1C, CH(CH_3)$_2$, major), 21.6 (t, 1C, CH$_2$, minor), 21.7 (t, 1C, CH$_2$, major), 22.2 (t, 1C, CH$_2$, minor), 22.3 (t, 1C, CH$_2$, major), 23.7 (d, 1C, CH(CH$_3$)$_2$), 27.0 (t, 1C, CH$_2$, major), 27.1 (t, 1C, CH$_2$, minor), 31.9 (t, 1C, CH$_2$, minor), 32.0 (t, 1C, CH$_2$, major), 37.8 (t, 1C, CH$_2$, major), 38.0 (t, 1C, CH$_2$, minor), 44.3 (s, 1C, CHCH$_2$C, major), 44.4 (s, 1C, CHCH$_2$C, minor), 52.3 (d, 1C, NCHCH$_2$, major), 56.4 (s, 1C, NCHCH$_2$, minor), 112.6 (d, 1C, NHC=CH, minor), 112.7 (d, 1C, NCH=CH, major), 113.3 (d, 1C, NHC=CH, major), 114.9 (d, 1C, NCH=CH, minor), 120.3 (d, 1C, NCH=CH, minor), 124.0 (d, 1C, NCH=CH, major), 126.0 (d, $C_{arom.}$), 126.1 (d, $C_{arom.}$), 127.3 (d, $C_{arom.}$), 127.4 (d, $C_{arom.}$), 127.8 (d, $C_{arom.}$), 127.9 (d, $C_{arom.}$), 131.3 (s, 1C, NHC=CH, minor), 131.5 (s, 1C, NHC=CH, major), 143.6 (s, 1C$_{arom.}$), 144.1 (s, 1C$_{arom.}$), 160.0 (d, 1C, CHO, minor), 161.4 (d, 1C, CHO, major), 165.6 (s, 1C, CO, major), 166.9 (s, 1C, CO, minor) ppm. IR (KBr): ν=3283, 3202, 3056, 2966, 2925, 1685, 1666, 1651, 1544, 1351 cm^{-1}. IR (KBr): ν=3353, 2970, 2887, 1749, 1657, 1539, 1410, 1400, 1368, 1341, 1201 cm^{-1}. MS (CI, CH_5^+): m/z (%)=353 (25, $[M+H]^+$), 256 (40), 245 (42), 228 (100), 184 (22), 156 (70). HRMS (EI, 70 eV): calcd for $C_{22}H_{28}N_2O_2$ $[M]^+$ 352.2151; found 352.2170.

Supplementary data

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC 735022. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk). Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.10.020.

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