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Dihydropyridazine Derivatives with Cyclopenta-, Benzo-, Furo-, Thiopyrano- and Pyrido-Annulation

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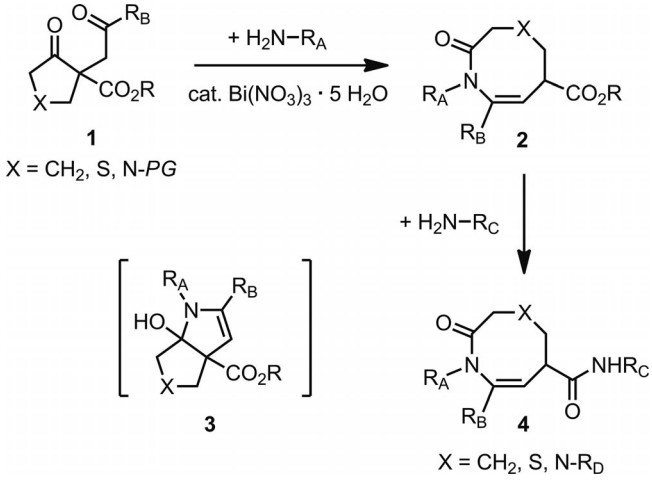
Regioisomeric [*c*]annulated pyridazines were prepared from arylhydrazines and carbocyclic or heterocyclic β-oxo esters with an α-phenacetyl moiety. With AcOH/EtOH, the hydrazones were preferentially formed at the endocyclic ketone, which are further cyclized with trifluoroacetic acid (TFA)/CH_2Cl_2 to give 2,4a-dihydropyridazines. Use of TFA/CH_2Cl_2 led hydrazones at the exocyclic benzoyl group, which reacted further to give 1,4-dihydro-4a*H*-pyridazines. In this investigation, examples of the rare or unknown heterocyclic systems furo[3,4-*c*]-, thiopyrano[4,3-*c*]- and pyrido[4,3-*c*]pyridazine were prepared.

Introduction

Following on from our discovery that 1,4-dicarbonyl compounds **1** (X = CH_2) react in a bismuth-catalyzed ring expansion reaction with primary amines to furnish eight-membered ring lactams **2** (Scheme 1),[1] we have used this reaction for the preparation of a model library of hexahydroazocinones **4** (X = CH_2). The interconversion of the five-membered ring in starting materials **1** to an eight-membered ring in products **2** is assumed to proceed through intermediate **3** with a bicyclo[3.3.0] skeleton. Apart from R_A originating from the amine R_A-NH_2 and R_B introduced by 1,4-diketone **1**, a third point of diversity R_C was installed by saponification and amidation of the carboxylate function (Scheme 1).[2] Furthermore, we have been able to convert tetrahydrothiophenes **1** (X = S) and pyrrolidines (X = N-*PG*) to respective thiazocinones **4** (X = S)[3] and diazocinones (X = N-R_D),[4] the latter having a fourth point of diversity R_D, which was introduced after deprotection of secondary amine N-*PG*. Attempts for the preparation of benzoannulated congeners were however of limited success.[5] In the course of our ongoing search for heterocyclic scaffolds suitable for the development of combinatorial libraries,[6] we envisioned cyclic 1,4-diketones **1** could also be converted with hydrazines **5** to give annulated dihydropyridazines. Because hydrazines as unsymmetrical 1,2-dinucleophiles could preferentially attack one of the two carbonyl groups of 1,4-dielectrophiles **1**, we were expecting to face a regioselectivity problem during this transformation. In contrast to fully-unsaturated aromatic cogeners,[7] annulated aliphatic partially saturated pyridazines have been rarely reported in the literature,[8] despite their simple retrosynthetic breakdown into hydrazines and 1,4-dicarbonyl compounds. Moreover, the aromatic or partially-hydrogenated pyridazine moiety could be regarded of a privileged structural motif in medicinal chemistry.[9] Therefore we would like to report the scope and limitations, as well as the envisioned regiochemistry problems, of dihydropyridazine formation from various 1,4-diketones of general formula **1** and a number of different hydrazines **5**.



Scheme 1. Synthesis of eight-membered-ring lactam libraries **4** from 1,4-diketones **1** and amines.

Results and Discussion

In preliminary studies we had prepared cyclopenta-annulated 2,5-dihydropyridazine **8a** in two steps from oxo ester **1a**, which was first converted under acidic conditions in po-

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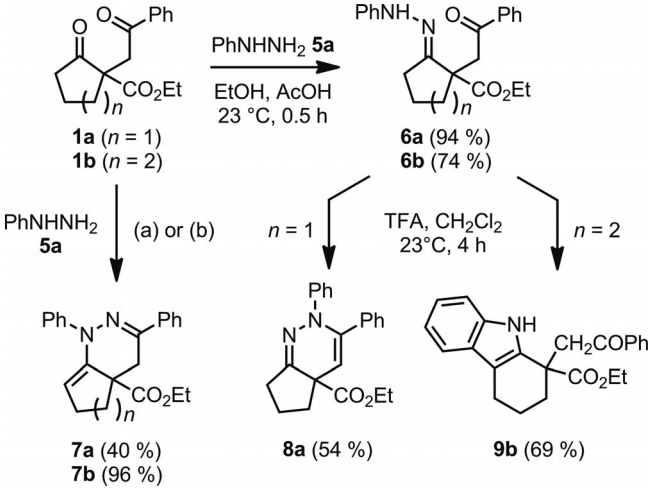
lar protic solvent to give hydrazone **6a** in 94% yield after crystallization (Scheme 2).[1] In contrast to our proposed mechanism of azocanone formation through intermediate **3** (see Scheme 1), hydrazine **5a** preferentially reacted with the endocyclic carbonyl group of compound **1a**. Subsequent treatment of hydrazone **6a** in strongly-acidic polar aprotic medium gave annulation product **8a** in 54% yield.[1] Our attempts to transfer that earlier result to hydrazone **6b**, which was obtained from cyclohexanone derivative **1b** in 74% yield, led to indole annulation product **9b** instead of a pyridazine. This was not surprising, because the reaction conditions were typical for a Fischer indolization.[10] Because we were aiming to avoid the latter process, we started to look for alternative conditions. Finally, the conversion of oxo ester **1b** with hydrazine **5a** under acidic conditions in polar aprotic solvent and without isolation of any hydrazone gave 1,4-dihydro-5*H*-pyridazine derivative **7b** in excellent yield. The formation of compound **7b** was the result of a first attack of hydrazine **5a** to the benzoyl group of compound **1b**. Because the reaction time was prolonged relative to the preparation of hydrazone **6b**, which crystallized from the reaction mixture, we assumed several equilibrating species within the reaction mixture and formation of compound **7b** as the thermodynamic product. Conversion of cyclopentanone derivative **1a** under similar reaction conditions led to the formation of regioisomer **7a**, the isolated yield of this compound was however rather low and could not be increased by varying the reaction conditions.



Scheme 2. Preliminary studies towards dihydropyridazine formation. Conditions for **7a**: (a) 1.5 equiv. **5a**, 0.5 equiv. AcOH, CH_2Cl_2, 23 °C, 3 h; then + 0.5 equiv. TFA, 23 °C, 2.5 h. For **7b**: (b) 1.1 equiv. **5a**, 0.6 equiv. TFA, CH_2Cl_2, 23 °C, 3 h.

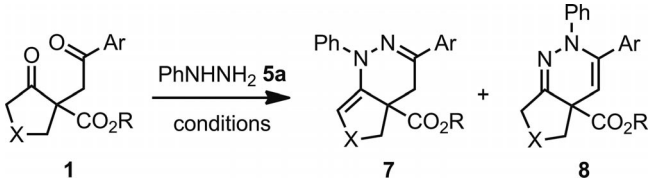
Regioisomers **7** and **8** could be clearly distinguished by ^{1}H NMR spectroscopy. Elucidation of their constitution was also accomplished by NMR spectroscopy, as outlined for compounds **6a**, **7a**, and **8a**. For compound **1a**, the ^{13}C-NMR signals of both ketones could be assigned by comparison to literature values:[11] 197 ppm for the benzoyl group and 215 ppm for the alicyclic C=O. Upon formation of hydrazone **6a**, the arylketone moiety was retained (δ = 198 ppm), whereas the signal previously at δ = 215 ppm was replaced by an imine resonance at δ = 143 ppm (NMR spectroscopic data of **1a**, **6a** and **8a** are known but are listed in the experimental section for reference). This actually proved the regiochemistry of hydrazone formation at the alicyclic ketone. Furthermore, ^{1}H NMR spectra of compounds **1a** and **6a** showed an AX-system for the diastereotopic methylene protons next to the benzoyl moiety (δ_A = 3.5, 3.2 ppm, δ_X = 3.8, 4.1 ppm, J_{AX} = 18.5, 18.1 Hz for **1a** and **6a**, respectively). Compound **7a** showed the same signals shifted to higher field: δ_A = 2.5 ppm, δ_X = 3.8 ppm, J_{AX} = 16.8 Hz. An additional sp^2-CH resonance was detected in the ^{1}H NMR spectrum of compound **7a** (δ = 2.5 ppm) with coupling (t, 2.5 Hz) to the adjacent CH_2 group, as established by a ^{1}H,^{1}H-COSY experiment. In contrast, compound **8a** had a CH_2–CH_2–CH_2 unit (established by HMBC, HMQC and ^{1}H,^{1}H-COSY) with complex J(^{1}H,^{1}H) coupling patterns and an olefinic singlet at δ = 4.8 ppm with a ^2J(^{1}H,^{13}C)-correlation (by HMBC) to the quaternary aliphatic signal indicating the depicted constitution. The diagnostic spectroscopic features of compounds **7a** and **8a** appeared in all compounds **7** (a characteristic AX-system with J_{AX} = 17 Hz at δ_A = 2.4–2.8 and δ_X = 3.4–3.8 ppm) as well as compounds **8** (singlet at 4.4–4.7 ppm) confirming the assignment of the respective regioisomers.

We aimed to transfer the formation of dihydropyridazines **7** with $PhNHNH_2$ (**5a**) to other 1,4-diketones **1** (Scheme 3, Table 1). Starting with variations of the ring size and introduction of heteroatoms, two out of several investigated reaction conditions turned out to be privileged, because most of the optimal results were obtained with them [(a) and (b) as specified in Table 1]. Results with starting materials **1a** and **1b** are given in Table 1, Entries 1 and 2. With seven-membered ring congener **1c**, no unique product was isolated (Table 1, Entry 3). Introduction of heteroatoms in the five-membered ring gave only for tetrahydrofuran derivative **1d** a respective product **7d** in poor yield (15%) and containing small amounts of regioisomer **8d** (2%; Table 1, Entry 4). Furo[3,4-*c*]pyridazine derivatives, like compound **7d**, are rarely reported in the literature.[12] Starting with tetrahydrothiophene **1e** and pyrrolidines **1f** and **1g**, no unique products were isolated (Table 1, Entries 5–7). We then investigated oxa-, thia-, and azacyclohexanone derivatives **1h**–**1k**. For tetrahydropyran **1h**, no unique product was isolated (Table 1, Entry 8). Tetrahydrothiopyran **1i** gave product **7i** together with its regioisomer **8i**, both in moderate yields (35% and 20%, respectively; Table 1, Entry 9). Compounds **7i** and **8i** were not separable by column chromatography. The thiopyrano[4,3-*c*]pyridazine ring system, as in compounds **7i** and **8i**, was not reported in the literature before, but with another pyrido[3′,2′:5,6]-annulation.[13] Piperidine derivatives with either a Boc or Cbz-protective group at nitrogen gave both pyridopyridazines **7j** and **7k** (Table 1, Entries 10 and 11). As expected, the yield for Cbz-protected compound **7k** was higher (43%) than for Boc-protected product **7j** (15%), because the latter protecting group was expected to be labile under the reaction conditions. Pyrido[4,3-*c*]pyridazine derivatives, like compounds **7j** and **7k**, are rarely reported in the literature.[14]

Table 1. Formation of regioisomeric annulated 1,4-dihydropyridazines **7** and **8**. Residues X, R and Ar, conditions and yields.

Entry	Starting material	X	R	Ar	Conditions[a]	Products (yield)[b]
1	**1a**	CH_2	Et	Ph	(a)	**7a** (40%)
2	**1b**	CH_2CH_2	Et	Ph	(b)	**7b** (96%)
3	**1c**	$CH_2CH_2CH_2$	Me	Ph	(a) or (b)	–[c]
4	**1d**	O	Me	Ph	(a)	**7d** (15%), **8d** (2%)[d]
5	**1e**	S	Me	Ph	(a) or (b)	–[c]
6	**1f**	N(Boc)	Me	Ph	(a) or (b)	–[c]
7	**1g**	N(Cbz)	Me	Ph	(a) or (b)	–[c]
8	**1h**	CH_2O	Et	Ph	(a) or (b)	–[c]
9	**1i**	CH_2S	Me	Ph	(b)	**7i** (35%), **8i** (20%)[d]
10	**1j**	CH_2N(Boc)	Me	Ph	(b)	**7j** (15%)
11	**1k**	CH_2N(Cbz)	Me	Ph	(b)	**7k** (43%)
12	**1l**	CH_2CH_2	Et	4-$MeOC_6H_4$	(b)	**7l** (78%)
13	**1m**	CH_2CH_2	Et	4-BrC_6H_4	(b)	**7m** (48%), **8m** (15%)[d]
14	**1n**	CH_2CH_2	Et	4-$NO_2C_6H_4$	(b)	**7n** (46%), **8n** (10%)[d]
15	**1o**	CH_2CH_2	Et	2,4-$(MeO)_2C_6H_3$	(b)	**8o** (45%)

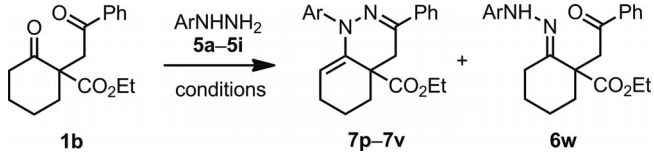
[a] Conditions: (a) 1.5 equiv. **5a**, 0.5 equiv. AcOH, CH_2Cl_2, 23 °C, 3 h; then + 0.5 equiv. TFA, 23 °C, 2.5 h; (b) 1.1 equiv. **5a**, 0.6 equiv. TFA, CH_2Cl_2, 23 °C, 3 h. [b] Yields of isolated products. [c] No unique product isolated. [d] Regioisomers **7** and **8** were not separated.



Scheme 3. Conversion of 1,4-diketones **1a**–**1o** with phenylhydrazine (**5a**).

We then continued by varying the aromatic residue Ar of the 1,4-diketone motif by introducing electron accepting and donating substituents (for the synthesis of starting materials **1** vide infra). For this purpose we chose X = CH_2CH_2, because cyclohexanone derivative **1b** was the compound with be best result so far (96% yield of pyridazine **7b**; Table 1, Entry 2). A *para*-methoxy substituent in starting material **1l** did not significantly influence the outcome of the reaction (78% yield of product **7l**; Table 1, Entry 12). In contrast, *para*-bromo and -nitro groups (starting materials **1m** and **1n**) shifted the regioselectivity slightly towards formation of byproducts **8m** (15%) and **8n** (10%; Table 1, Entries 13 and 14), which was actually hardly understood from an electronic point of view, because preferential initial attack of hydrazine **5a** at the benzoyl moiety would be assumed with an electron withdrawing aromatic system Ar. With two donor substituents (starting material **1o**; Table 1, Entry 15), one of them even sterically congesting, attack of hydrazine **5a** at the benzoyl group seems to be completely blocked, thus, no regioisomer **7o** was observed, only product **8o** was isolated.

In addition, conversion of cyclohexanone derivative **1b** with several phenylhydrazine derivatives **5b**–**5i** was investigated (Scheme 4, Table 2; for the synthesis of starting materials **5** vide infra). For comparison, formation of product **7b** is listed as Table 2, Entry 1. In all cases (except Table 2, Entry 9) only the formation of regioisomer **7** was observed, although products **7q** and **7v** contained small amounts of regioisomers **8q** and **8v** (3% and 4%, respectively). Whereas *ortho*-chloro and -methoxy substituents seemed to have no significant negative influence on the yield (Table 2, Entries 2–4), an *ortho*-methyl group gave a low yield of product **7t** (18%; Table 2, Entry 6). This effect was not clearly understood, because *para*-methoxy and -methyl groups (Table 2, Entries 5 and 7) had opposite effects. *para*-Iodophenyl derivative **7v** (77% yield; Table 2, Entry 8) was ready for further diversifying transformations through cross-coupling reactions. In contrast to hydrazines **5a**–**5h**, 2,3-dinitro congener **5i** led to no isolable materials under standard conditions (a), but after heating in THF as solvent, hydrazone **6w** was obtained from the reaction mixture (72%; Table 2, Entry 9).



Scheme 4. Conversion of 1,4-diketone **1b** with various arylhydrazines **5a**–**5i**.

Table 2. Formation of annulated 1,4-dihydropyridazines **7** from 1,4-diketone **1b**. Residues Ar, conditions and yields.

Entry	Hydrazine	Ar	Conditions[a]	Products (yield)[b]
1	**5a**	Ph	(a)	**7b** (96%)
2	**5b**	2-ClC_6H_4	(a)	**7p** (75%)
3	**5c**	3,4-$Cl_2C_6H_3$	(a)	**7q** (78%), **8q** (3%)[c]
4	**5d**	2-$MeOC_6H_4$	(a)	**7r** (53%)
5	**5e**	4-$MeOC_6H_4$	(a)	**7s** (35%)
6	**5f**	2-MeC_6H_4	(a)	**7t** (18%)
7	**5g**	4-MeC_6H_4	(a)	**7u** (66%)
8	**5h**	4-IC_6H_4	(a)	**7v** (77%), **8v** (4%)[c]
9	**5i**	2,4-$(NO_2)_2C_6H_3$	(b)	**6w** (72%)

[a] Conditions: (a) 1.1 equiv. **5**, 0.6 equiv. TFA, CH_2Cl_2, 23 °C, 3 h; (b) 1.0 equiv. **5**, 0.6 equiv. TFA, THF, 67 °C, 3 h. [b] Yields of isolated products. [c] Regioisomers **7** and **8** were not separated.

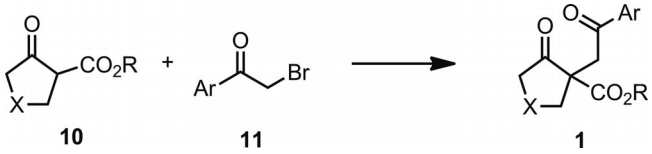
The synthesis of starting materials **1** was achieved by alkylation of respective β-oxo esters **10** with α-bromoacetophenones **11** as shown in Scheme 5. Compounds **1a**–**1c**,[15] **1d**, **1e**,[3] and **1f**[4] were known from the literature and pre-

Table 3. Conditions and yields for the α-alkylation of β-oxo esters **10** with α-bromo ketones **11**.

Entry	Oxo ester[a]	X	R	Bromo ketone [equiv.]	Ar	Conditions[b]	Product [yield]
1	**10g**	N(Cbz)	Me	**11a** (1.1)	Ph	(a)	**1g** (44%)
2	**10h**	CH_2O	Et	**11a** (1.1)	Ph	(a)	**1h** (72%)
3	**10i**	CH_2S	Me	**11a** (1.1)	Ph	(a)	**1i** (49%)
4	**10j**	CH_2N(Boc)	Me	**11a** (1.1)	Ph	(a)	**1j** (74%)
5	**10k**	CH_2N(Cbz)	Me	**11a** (1.1)	Ph	(a)	**1k** (70%)
6	**10b**	CH_2CH_2	Et	**11l** (2.0)	4-$MeOC_6H_4$	(a)	**1l** (54%)
7	**10b**	CH_2CH_2	Et	**11m** (1.2)	4-BrC_6H_4	(b)	**1m** (44%)
8	**10b**	CH_2CH_2	Et	**11n** (1.2)	4-$NO_2C_6H_4$	(a)	**1n** (13%)
9	**10b**	CH_2CH_2	Et	**11o** (1.1)	2,4-$(MeO)_2C_6H_3$	(a)	**1o** (47%)

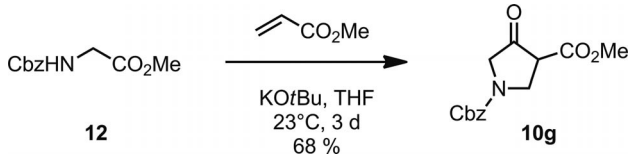
[a] 1.0 equiv. was used. [b] Conditions: (a) K_2CO_3, acetone, 40 °C, 19 h; (b) NaH, THF, 60 °C, 17 h; K_2CO_3 or NaH were used in equimolar amounts relative to respective bromo ketone **11**.

pared accordingly. Results and reaction conditions for products **1g**–**1o** are collected in Table 3. In general, K_2CO_3 in acetone was used, except for product **1m** (Table 3, Entry 7) were we used NaH in THF. Yields ranged from 45–75%, except for *para*-nitro substituted product **1n**, were it was lower (13%; Table 3, Entry 8).



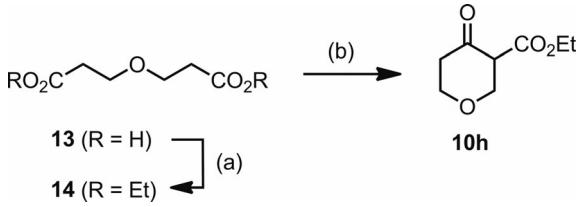
Scheme 5. Synthesis of 1,4-diketones **1** by α-alkylation of β-oxo esters **10** with α-bromoacetophenones **11**. For conditions and yields see Table 3.

Oxo esters **10i**,[16] **10j**,[17] and **10k**[18] were literature known and were prepared accordingly. Compound **10g** had not been reported before, thus, we prepared it by conjugate addition of *N*-Cbz methyl gycinate (**12**)[19] to methyl acrylate followed by Dieckmann condensation as reported for the *N*-Boc-protected congener.[4] The conversion was performed as a two-step-, one-flask-protocol and product **10g** was isolated in 68% yield after chromatographic purification (Scheme 6).



Scheme 6. Synthesis of oxo ester **10g** by conjugate addition of *N*-Cbz-GlyOMe (**12**) to methyl acrylate followed by Dieckmann condensation.

Compound **10h** was known in the literature,[20] reported protocols for acylation of tetrahydropyranone were however not reproducible. We therefore prepared oxo ester **10h** by Dieckmann condensation of diethyl ester **14** in analogy to a procedure reported for the dipropyl ester (Scheme 7).[21] Diethyl ester **14** was obtained by esterification from diacid **13**.[22]



Scheme 7. Synthesis of tetrahydropyranonecarboxylate **10h** from diacid **13**. Reagents, conditions and yields: (a) cat. H_2SO_4, EtOH, $CHCl_3$, Dean–Stark trap, 95 °C, 20 h, 50%; (b) 2.2 equiv. LDA, THF, –78 °C, 15 min, 18%.

α-Bromo ketones **11l**,[23] **11m**[24] and **11n**[25] were known from the literature and are commercially available. During the bromination of 2,4-dimethoxyacetophenone, bromination of the aromatic ring cannot be avoided,[26] thus, bromo ketone **11o** was prepared by Friedel–Crafts acylation of 1,3-dimethoxybenzene with bromoacetyl bromide.[27]

Hydrazines **5a** and **5i** were commercially available. Hydrazines **5b**,[28] **5c**,[29] **5d**,[30] **5e**,[31] **5f**,[32] **5g**[33] and **5h**[34] were reported in the literature. We prepared compounds **5b**, **5d**, **5e**, **5f** and **5g** according to a reported procedure[35] and compounds **5c** and **5h** following a slightly different procedure.[36]

Conclusions

The reaction of cyclic β-oxo esters **1** bearing an α-phenacetyl moiety with arylhydrazines **5** could lead to two regioisomeric hydrazones. With AcOH in EtOH, hydrazone formation at the endocyclic carbonyl group (products **6**) was observed. In two cases, hydrazones **6** could be further transformed with TFA/CH_2Cl_2 to a [*c*]annulated 2,4a-dihydropyridazine **8a** or an indole derivative **9b**. With TFA/CH_2Cl_2 or AcOH/CH_2Cl_2, hydrazones at the exocyclic benzoyl group were formed as intermediate products, which cannot be isolated, but further cyclize under reaction conditions to furnish [*c*]annulated 1,4-dihydro-4a*H*-pyridazines **7**. We have investigated conversion of 15 different carbocyclic and heterocyclic 1,4-diketones **1** with nine different arylhydrazines **5**. New 1,4-dihydro-4a*H*-pyridazines **7** were isolated in 16 cases. Among them were rare furo[3,4-*c*]- (**7d**) and pyrido[4,3-*c*]pyridazines (**7j** and **7k**) or even unknown

ring systems like thiopyrano[4,3-*c*]pyridazine **7i**. The yields ranged between 15 and 96%, with the majority between 40 and 80%. In four cases regioisomeric 2,4a-dihydropyridazines **8** were obtained as byproducts (10–20%) or even the only product (**8o**, 45%). Five of starting materials **1** gave no useful results.

Experimental Section

General: Preparative column chromatography was carried out with Merck SiO_2 (0.035–0.070 mm, type 60 A) with hexane, toluene and *tert*-butyl methyl ether (MTBE) as eluents. TLC was performed with Merck SiO_2 F_{254} plates on aluminum sheets. ^1H- and ^{13}C-NMR spectra were recorded with a Bruker Avance DRX 500. Multiplicities of carbon signals were determined with DEPT experiments. MS and HRMS spectra were obtained with a Finnigan MAT 95 (CI) and a Waters Q-TOF Premier (ESI) spectrometer. IR spectra were recorded with a Bruker Tensor 27 spectrometer equipped with a "GoldenGate" diamond ATR unit. Elemental analyses were measured with a Euro EA-CHNS from HEKAtech. Preparation and spectroscopic data of compounds **1a**,[37] **6a**[1] and **8a**[1] were reported by us earlier. NMR spectroscopic data for these three compounds are however listed below for comparison.

Ethyl 1-(Benzoylmethyl)cyclopentane-1-carboxylate (1a): ^1H NMR ($CDCl_3$, 500 MHz): δ = 1.24 (t, J = 7.1 Hz, 3 H), 2.03–2.17 (m, 3 H), 2.53–2.69 (m, 3 H), 3.48 (d, J = 18.6 Hz, 1 H), 3.86 (d, J = 18.6 Hz, 1 H), 4.17 (q, J = 7.1 Hz, 2 H), 7.43–7.49 (m, 2 H), 7.55–7.60 (m, 1 H), 7.93–7.97 (m, 2 H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ = 14.00 (CH_3), 19.86 (CH_2), 33.40 (CH_2), 37.76 (CH_2), 43.48 (CH_2), 57.47 (C), 61.66 (CH_2), 128.11 (2 CH), 133.47 (2 CH), 136.31 (C), 170.71 (C), 196.74 (C), 215.11 (C) ppm.

Ethyl 1-(Benzoylmethyl)-2-phenylhydrazonocyclopentane-1-carboxylate (6a): ^1H NMR ($CDCl_3$, 500 MHz): δ = 1.20 (t, J = 7.1 Hz, 3 H), 1.83 (ddd, J = 7.7, J = 9.8, J = 13.1 Hz, 1 H), 1.94–2.00 (m, 1 H), 2.16–2.25 (m, 1 H), 2.35–2.42 (m, 1 H), 2.48 (ddd, J = 3.9, J = 9.4, J = 17.2 Hz, 1 H), 2.77 (ddd, J = 3.4, J = 7.3, J = 13.0 Hz, 1 H), 3.23 (d, J = 18.1 Hz, 1 H), 4.11 (d, J = 18.1 Hz, 1 H), 4.16 (q, J = 7.0 Hz, 2 H), 6.80–6.83 (m, 1 H), 6.98–7.01 (m, 2 H), 7.17–7.21 (m, 2 H), 7.36 (s, 1 H), 7.44–7.48 (m, 2 H), 7.54–7.57 (m, 1 H), 7.98–8.00 (m, 2 H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ = 14.08 (CH_3), 22.46 (CH_2), 26.25 (CH_2), 35.60 (CH_2), 45.69 (CH_2), 54.44 (C), 61.00 (CH_2), 112.90 (2 CH), 119.92 (CH), 128.06 (2 CH), 128.54 (2 CH), 129.11 (2 CH), 133.03 (CH), 137.09 (C), 145.36 (C), 153.46 (C), 173.27 (C), 197.97 (C) ppm.

Ethyl 1-(2-Oxo-2-phenylethyl)-2-(2-phenylhydrazono)cyclohexanecarboxylate (6b): Phenylhydrazine (**5a**; 111 mg, 1.03 mmol) and AcOH (72 mg, 1.2 mmol) were added to a solution of 1,4-diketone **1b** (298 mg, 1.03 mmol) in EtOH (2 mL) and the reaction mixture was stirred for 90 min at 23 °C. The precipitated solid was filtered off and dried to furnish hydrazone **6b** (290 mg, 766 µmol, 74%) as a colorless solid. M.p. 153 °C. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.32 (t, J = 6.5 Hz, 3 H), 1.45–1.50 (m, 1 H), 1.64–1.69 (m, 1 H), 1.72–1.81 (m, 2 H), 1.96–1.98 (m, 1 H), 2.45 (d, J = 12.3 Hz, 1 H), 2.50–2.56 (m, 1 H), 2.78 (d, J = 14.6 Hz, 1 H), 3.33 (d, J = 16.6 Hz, 1 H), 3.90 (d, J = 16.6 Hz, 1 H), 4.29–4.32 (m, 2 H), 6.58 (d, J = 7.5 Hz, 2 H), 6.68 (t, J = 6.7 Hz, 1 H), 6.92 (t, J = 7.0 Hz, 2 H), 7.20 (br. s, 1 H), 7.52 (t, J = 7.0 Hz, 2 H), 7.63 (t, J = 6.8 Hz, 1 H), 8.06 (d, J = 7.1 Hz, 2 H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 14.15 (CH_3), 22.16 (CH_2), 23.44 (CH_2), 25.60 (CH_2), 37.81 (CH_2), 45.41 (CH_2), 53.31 (CH_2), 60.98 (CH_2), 112.73 (2 CH), 119.34 (CH), 128.23 (2 CH), 128.49 (2 CH), 128.70 (2 CH), 132.76 (CH), 137.39 (C), 145.23 (C), 146.61 (C), 174.75 (C), 197.30 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3339 (m), 3063 (w), 2974 (w), 2955 (w), 2933 (w), 1715 (s), 1687 (m), 1600 (m), 1446 (m), 1236 (m), 1219 (m), 1195 (m), 1141 (m), 1124 (m), 1034 (m), 744 (vs), 689 (vs) cm^{-1}. HRMS (ESI): calcd. for $C_{23}H_{26}N_2NaO_3$ [M + Na^+] 401.1841; found 401.1848.

Ethyl 2,3-Diphenyl-2,5,6,7-tetrahydrocyclopenta[*c*]pyridazine-4a-carboxylate (8a): ^1H NMR ($CDCl_3$, 500 MHz): δ = 1.14 (t, J = 7.1 Hz, 3 H), 1.78–1.86 (m, 1 H), 1.93–2.06 (m, 2 H), 2.64–2.71 (m, 2 H), 2.89 (ddd, J = 6.5, J = 9.0, J = 16.8 Hz, 1 H), 4.05–4.12 (m, 2 H), 4.79 (s, 1 H), 6.85–6.89 (m, 1 H), 7.03–7.05 (m, 2 H), 7.07–7.11 (m, 2 H), 7.18–7.23 (m, 5 H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ = 14.05 (CH_3), 22.50 (CH_2), 30.17 (CH_2), 37.06 (CH_2), 51.05 (C), 61.17 (CH_2), 101.22 (CH), 121.16 (2 CH), 122.55 (CH), 127.99 (3 CH), 128.20 (2 CH), 128.69 (2 CH), 135.51 (C), 140.38 (C), 143.52 (C), 153.38 (C), 172.89 (C) ppm.

Ethyl 1-(2-Oxo-2-phenylethyl)-2,3,4,9-tetrahydro-1*H*-carbazole-1-carboxylate (9b): TFA (47 mg, 0.40 mmol) was added to a solution of hydrazone **6b** (98 mg, 0.26 mmol) in CH_2Cl_2 (5 mL) and the solution was stirred for 4 h at 23 °C. After removal of all volatile materials in vacuo, the residue was purified by using chromatography (SiO_2, hexane/MTBE = 2:1, R_f = 0.37), to yield indole **9b** (65 mg, 0.18 mmol, 69%) as a colorless solid. M.p. 125 °C. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.20 (t, J = 7.2 Hz, 3 H), 1.89–1.94 (m, 1 H), 1.98–2.07 (m, 2 H), 2.35–2.39 (m, 1 H), 2.71–2.82 (m, 2 H), 3.59 (d, J = 18.2 Hz, 1 H), 3.89 (d, J = 18.2 Hz, 1 H), 4.14–4.24 (m, 2 H), 7.05 (t, J = 7.4 Hz, 1 H), 7.13 (t, J = 7.6 Hz, 1 H), 7.30 (d, J = 8.1 Hz, 1 H), 7.40–7.50 (m, 3 H), 7.56 (t, J = 7.4 Hz, 1 H), 7.95 (d, J = 7.6 Hz, 2 H), 8.76 (s, 1 H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 14.36 (CH_3), 20.58 (CH_2), 21.26 (CH_2), 35.42 (CH_2), 44.90 (C), 49.43 (CH_2), 61.53 (CH_2), 111.24 (CH), 111.77 (C), 118.53 (CH), 119.16 (CH), 122.09 (CH), 127.03 (C), 128.33 (2 CH), 128.89 (2 CH), 133.47 (C), 133.83 (CH), 135.94 (CH), 136.68 (CH), 175.28 (C), 199.80 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3066 (w), 1661 (s), 1596 (m), 1578 (m), 1447 (m), 1329 (m), 1304 (m), 1218 (s), 1178 (m), 1065 (m), 1040 (s), 1015 (s), 799 (m), 714 (s), 689 (m), 644 (m) cm^{-1}. HRMS (ESI): calcd. for $C_{23}H_{23}NNaO_3$ [M + Na^+] 384.1576; found 384.1583.

Ethyl 1,3-Diphenyl-4,4a,5,6-tetrahydro-1*H*-cyclopenta[*c*]pyridazine-4a-carboxylate (7a): Phenylhydrazine (**5a**; 177 mg, 1.64 mmol) and AcOH (33 mg, 0.55 mmol) were added to a solution of 1,4-diketone **1a** (300 mg, 1.09 mmol) in CH_2Cl_2 (3.3 mL) and the reaction mixture was stirred for 3 h at 23 °C. Then TFA (63 mg, 0.55 mmol) was added and stirring was continued for 2.5 h. After removal of all volatile materials in vacuo, the residue was purified by using chromatography (SiO_2, hexane/MTBE = 20:1, R_f = 0.22) to yield pyridazine **7a** (150 mg, 430 µmol, 40%) as a yellowish oil. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.17 (t, J = 7.1 Hz, 3 H), 1.93 (td, J = 8.9, J = 12.9 Hz, 1 H), 2.41 (ddd, J = 2.2, J = 8.9, J = 15.2 Hz, 1 H), 2.47 (d, J = 16.8 Hz, 1 H), 2.65 (dd, J = 8.3, J = 13.1 Hz, 1 H), 2.70–2.79 (m 1 H), 3.78 (d, J = 16.8 Hz, 1 H), 4.11 (q, J = 7.2 Hz, 2 H), 5.37 (t, J = 2.5 Hz, 1 H), 7.08 (t, J = 7.3 Hz, 1 H), 7.30 (t, J = 7.3 Hz, 1 H), 7.33–7.39 (m, 4 H), 7.55–7.57 (m, 2 H), 7.78 (d, J = 7.5 Hz, 2 H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 14.15 (CH_3), 28.26 (CH_2), 35.42 (CH_2), 36.95 (CH_2), 50.62 (C), 61.23 (CH_2), 106.02 (CH), 120.66 (2 CH), 123.35 (CH), 125.27 (2 CH), 127.96 (CH), 128.26 (2 CH), 128.67 (2 CH), 136.82 (C), 137.92 (C), 141.32 (C), 145.59 (C), 174.02 (C) ppm. IR (ATR): $\tilde{\nu}$ = 2960 (w), 2929 (w), 2326 (w), 2194 (w), 1982 (w), 1761 (m), 1726 (s), 1687 (m), 1595 (m), 1493 (s), 1446 (m), 1369 (m), 1300 (s), 1190 (s), 1095 (s), 1015 (s), 913 (m), 756 (s), 691 (s) cm^{-1}. HRMS (ESI): calcd. for $C_{22}H_{23}N_2O_2$ [M + H^+] 347.1760; found 347.1750.

Ethyl 1,3-Diphenyl-1,4,4a,5,6,7-hexahydrobenzo[*c*]pyridazine-4a-carboxylate (7b): Phenylhydrazine (**5a**; 121 mg, 1.14 mmol) and TFA (74 mg, 0.62 mmol) were added to a solution of 1,4-diketone **1b** (300 mg, 1.04 mmol) in CH_2Cl_2 (3.5 mL) and the reaction mixture was stirred for 3 h at 23 °C. After removal of all volatile materials in vacuo, the residue was purified by using chromatography (SiO_2, hexane/MTBE = 10:1, R_f = 0.34) to yield pyridazine **7b** (359 mg, 1.00 mmol, 96%) as a yellowish oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.09 (t, J = 7.1 Hz, 3 H), 1.54–1.59 (m, 1 H), 1.63–1.75 (m, 2 H), 2.06–2.13 (m, 1 H), 2.23–2.32 (m, 2 H), 2.45 (d, J = 17.1 Hz, 1 H), 3.50 (d, J = 17.1 Hz, 1 H), 4.05 (q, J = 7.1 Hz, 2 H), 5.40 (t, J = 3.6 Hz, 1 H), 6.96 (t, J = 7.3 Hz, 1 H), 7.16–7.19 (m, 1 H), 7.22–7.27 (m, 4 H), 7.47 (d, J = 8.1 Hz, 2 H), 7.65 (d, J = 7.9 Hz, 2 H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 14.23 (CH_3), 19.31 (CH_2), 24.78 (CH_2), 35.05 (2 CH_2), 41.95 (C), 61.43 (CH_2), 108.59 (CH), 122.05 (2 CH), 123.07 (CH), 124.84 (2 CH), 127.65 (CH), 128.22 (2 CH), 128.58 (2 CH), 135.69 (C), 138.01 (C), 138.92 (C), 146.41 (C), 174.30 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3059 (w), 2979 (w), 2934 (w), 2865 (w), 1723 (s), 1590 (m), 1491 (s), 1445 (m), 1267 (m), 1186 (s), 1024 (m), 758 (s), 693 (s), 633 (s) cm^{-1}. HRMS (ESI): calcd. for $C_{23}H_{25}N_2O_2$ [M + H$^+$] 361.1916; found 361.1921.

Methyl 1,3-Diphenyl-1,4,4a,5-tetrahydrofuro[3,4-*c*]pyridazine-4a-carboxylate (7d) and Methyl 2,3-Diphenyl-4a,5,6,7-tetrahydrofuro-[*c*]pyridazine-4a-carboxylate (8d): Following the procedure reported for compound **7a**, 1,4-diketone **1d** (100 mg, 380 µmol), phenylhydrazine (**5a**; 62 mg, 0.57 mmol), AcOH (11 mg, 0.19 mmol) and TFA (22 mg, 0.19 mmol) were reacted in CH_2Cl_2 (1.2 mL). Chromatography (SiO_2, hexane/MTBE = 2:1, R_f = 0.15) gave a mixture of regioisomers **7d** (19 mg, 57 µmol, 15%) and **8d** (3 mg, 9 µmol, 2%) as a yellowish oil. ^{1}H NMR (500 MHz, $CDCl_3$), major regioisomer **7d**: δ = 2.66 (d, J = 16.9 Hz, 1 H), 3.59 (d, J = 16.9 Hz, 1 H), 3.62 (s, 3 H), 4.22 (d, J = 9.6 Hz, 1 H), 4.94 (d, J = 9.6 Hz, 1 H), 6.52 (s, 1 H), 6.93 (t, J = 7.3 Hz, 1 H), 7.24–7.32 (m, 5 H), 7.45 (d, J = 8.2 Hz, 2 H), 7.69 (d, J = 7.8 Hz, 2 H) ppm; minor regioisomer **8d**: δ = 3.64 (s, 3 H), 3.85 (d, J = 8.8 Hz, 1 H), 4.44 (d, J = 14.0 Hz, 1 H), 4.70 (s, 1 H), 4.74 (d, J = 14.0 Hz, 1 H), 6.85 (t, J = 7.2 Hz, 1 H), 7.05 (t, J = 7.8 Hz, 2 H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$), major regioisomer **7d**: δ = 34.89 (CH_2), 49.91 (CH_3), 53.54 (C), 80.12 (CH_2), 117.77 (2 CH), 117.91 (C), 122.76 (CH), 125.54 (2 CH), 128.61 (CH), 128.82 (2 CH), 129.49 (2 CH), 131.63 (CH), 138.19 (C), 140.01 (C), 145.58 (C), 173.51 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3060 (w), 3033 (w), 2912 (w), 1732 (s), 1598 (m), 1495 (s), 1290 (m), 1212 (s), 1172 (m), 1127 (m), 1096 (s), 765 (s), 694 (s), 636 (m) cm^{-1}. HRMS (ESI): calcd. for $C_{20}H_{18}N_2NaO_3$ [M + Na$^+$] 357.1215; found 357.1223.

Methyl 1,3-Diphenyl-1,4,4a,5,6,7-hexahydrothiopyrano[4,3-*c*]pyridazine-4a-carboxylate (7i) and Methyl 2,3-Diphenyl-2,4a,5,6,7,8-hexahydrothiopyrano[4,3-*c*]pyridazine-4a-carboxylate (8i): Following the procedure given for compound **7b**, 1,4-diketone **1i** (480 mg, 1.64 mmol), phenylhydrazine (**5a**; 195 mg, 1.80 mmol) and TFA (112 mg, 0.980 mmol) were reacted in CH_2Cl_2 (5.6 mL). Chromatography (SiO_2, hexane/MTBE = 10:1, R_f = 0.27) gave a mixture of regioisomers **7i** (211 mg, 580 µmol, 35%) and **8i** (118 mg, 320 µmol, 20%) as a yellowish solid. ^{1}H NMR (500 MHz, $CDCl_3$), major regioisomer **7i**: δ = 2.69–2.73 (m, 1 H), 2.78 (d, J = 13.7 Hz, 1 H), 2.94–2.97 (m, 1 H), 3.19–3.22 (m, 1 H), 3.38 (d, J = 13.4 Hz, 1 H), 3.46 (d, J = 17.2 Hz, 1 H), 3.71 (s, 3 H), 5.53 (s, 1 H), 7.07–7.10 (m, 2 H), 7.31–7.35 (m, 4 H), 7.52 (d, J = 7.7 Hz, 2 H), 7.68 (d, J = 7.7 Hz, 2 H) ppm; minor regioisomer **8i**: δ = 2.69–2.73 (m, 1 H), 2.88–2.89 (m, 1 H), 2.94–2.97 (m, 1 H), 3.25–3.26 (m, 1 H), 3.38 (d, J = 13.4 Hz, 1 H), 3.42–3.43 (m, 1 H), 3.80 (s, 3 H), 4.55 (s, 1 H), 6.92 (t, J = 7.3 Hz, 1 H), 6.97 (d, J = 7.8 Hz, 2 H), 7.07–7.10 (m, 2 H), 7.13–7.18 (m, 3 H), 7.26 (d, J = 7.1 Hz, 2 H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$), major regioisomer **7i**: δ = 26.27 (CH_2), 33.49 (CH_2), 35.92 (CH_2), 42.70 (C), 52.91 (CH_3), 105.06 (CH), 122.90 (2 CH), 124.64 (2 CH), 127.90 (CH), 128.07 (CH), 128.24 (2 CH), 128.77 (2 CH), 137.22 (C), 137.54 (C), 138.09 (C), 146.13 (C), 173.18 (C) ppm; minor regioisomer **8i**: δ = 28.94 (CH_2), 34.46 (CH_2), 37.67 (CH_2), 48.79 (C), 52.73 (CH_3), 101.35 (CH), 123.25 (2 CH), 123.83 (CH), 123.89 (CH), 127.95 (2 CH), 127.98 (2 CH), 128.12 (2 CH), 135.53 (C), 140.32 (C), 143.41 (C), 143.62 (C), 171.77 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3056 (w), 2950 (w), 2906 (w), 1730 (s), 1593 (m), 1491 (s), 1297 (m), 1262 (m), 1194 (s), 1156 (m), 1136 (m), 1029 (w), 758 (s), 691 (s) cm^{-1}. HRMS (ESI): calcd. for $C_{21}H_{20}N_2NaO_2S$ [M + Na$^+$] 387.1143; found 387.1137.

6-*tert*-Butyl 4a-Methyl 1,3-Diphenyl-1,4,4a,5,6,7-hexahydropyrido[4,3-*c*]pyridazine-4a,6-dicarboxylate (7j): Following the procedure given for compound **7b**, 1,4-diketone **1j** (640 mg, 1.70 mmol), phenylhydrazine (**5a**; 257 mg, 2.38 mmol) and TFA (116 mg, 1.02 mmol) were reacted in CH_2Cl_2 (5.8 mL). Chromatography (SiO_2, hexane/MTBE = 10:1, R_f = 0.29) gave pyridazine **7j** (133 mg, 250 µmol, 15%) as a yellowish oil. A double signal set is observed due to *E*/*Z*-isomers (ratio 1.0:0.73) at the carbamate C–N bond. ^{1}H NMR (500 MHz, $CDCl_3$), major conformer: δ = 1.49 (s, 9 H), 2.31 (d, J = 17.1 Hz, 1 H), 2.88–2.96 (m, 2 H), 3.37 (d, J = 16.5 Hz, 2 H), 3.69 (s, 3 H), 4.58–4.65 (m, 2 H), 5.26 (br. s, 1 H), 7.09–7.14 (m, 2 H), 7.33–7.38 (m, 3 H), 7.52 (d, J = 7.3 Hz, 2 H), 7.71 (d, J = 7.3 Hz, 2 H) ppm; minor conformer: δ = 1.48 (s, 9 H), 2.31 (d, J = 17.1 Hz, 1 H), 2.88–2.96 (m, 1 H), 2.96–3.04 (m, 1 H), 3.74 (s, 3 H), 4.41–4.45 (m, 1 H), 4.58–4.65 (m, 2 H), 4.76 (d, J = 16.0 Hz, 1 H), 5.18 (br. s, 1 H), 7.01 (d, J = 7.3 Hz, 1 H), 7.09–7.14 (m, 2 H), 7.33–7.38 (m, 2 H), 7.52 (d, J = 7.3 Hz, 2 H), 7.71 (d, J = 7.3 Hz, 2 H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$), major conformer: δ = 28.34 (3 CH_3), 30.03 (CH_2), 42.16 (C), 42.65 (CH_2), 50.73 (CH_2), 52.96 (CH_3), 80.20 (C), 102.54 (CH), 123.59 (CH), 124.40 (CH), 124.79 (2 CH), 127.98 (2 CH), 128.29 (2 CH), 128.84 (2 CH), 137.33 (C), 138.02 (C), 143.51 (C), 145.90 (C), 153.81 (C), 172.61 (C) ppm; minor conformer: δ = 28.29 (3 CH_3), 29.67 (CH_2), 41.97 (C), 43.44 (CH_2), 49.43 (CH_2), 52.67 (CH_3), 80.09 (C), 102.49 (CH), 122.77 (CH), 123.37 (2 CH), 124.79 (2 CH), 128.17 (CH), 128.29 (2 CH), 128.84 (2 CH), 135.47 (C), 138.02 (C), 143.51 (C), 145.90 (C), 153.81 (C), 172.57 (C) ppm. IR (ATR): $\tilde{\nu}$ = 2975 (w), 2952 (w), 2930 (w), 1734 (m), 1696 (s), 1597 (m), 1493 (m), 1423 (m), 1365 (m), 1236 (m), 1198 (s), 1163 (s), 1153 (s), 1124 (s), 754 (s), 691 (s) cm^{-1}. HRMS (ESI): calcd. for $C_{26}H_{30}N_3O_4$ [M + H$^+$] 448.2236; found 448.2231.

6-Benzyl 4a-Methyl 1,3-Diphenyl-1,4,4a,5,6,7-hexahydropyrido-[4,3-*c*]pyridazine-4a,6-dicarboxylate (7k): Following the procedure given for compound **7b**, 1,4-diketone **1k** (145 mg, 350 µmol), phenylhydrazine (**5a**; 42 mg, 0.39 mmol) and TFA (24 mg, 0.21 mmol) were reacted in CH_2Cl_2 (1.2 mL). Twofold chromatography (SiO_2, toluene/MTBE = 10:1, R_f = 0.34, then hexane/MTBE = 3:1, R_f = 0.20) gave pyridazine **7k** (70 mg, 0.15 mmol, 43%) as a yellowish oil. A double signal set is observed due to *E*/*Z*-isomers (ratio ≈ 1:1) at the carbamate C–N bond. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.32 (t, J = 16.6 Hz, 2 H), 2.88–2.94 (m, 2 H), 3.41 (s, 3 H), 3.45–3.53 (m, 5 H), 3.66–3.78 (m, 2 H), 4.44–4.57 (m, 2 H), 4.60–4.75 (m, 2 H), 5.04–5.16 (m, 6 H), 7.00–7.11 (m, 4 H), 7.17–7.20 (m, 2 H), 7.24–7.30 (m, 16 H), 7.41 (d, J = 7.9 Hz, 4 H), 7.60–7.63 (m, 4 H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 29.85 (CH_2), 29.97 (CH_2), 41.99 (C), 42.18 (C), 43.35 (2 CH_2), 50.08 (CH_2), 50.36 (CH_2), 52.78 (CH_3), 52.95 (CH_2), 67.39 (2 CH_2), 101.22 (CH), 101.97 (CH), 122.85 (2 CH), 123.44 (2 CH), 123.62 (2 CH), 123.70 (2 CH), 124.51 (2 CH), 124.82 (2 CH), 127.92 (2 CH),

128.00 (2 CH), 128.04 (2 CH), 128.18 (2 CH), 128.30 (4 CH), 128.52 (2 CH), 128.87 (4 CH), 133.80 (C), 134.26 (C), 136.41 (C), 136.55 (C), 137.31 (2 C), 138.21 (C), 138.60 (C), 145.85 (2 C), 154.62 (C), 154.88 (C), 172.09 (C), 172.34 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3062 (w), 3033 (w), 2951 (w), 2924 (w), 2849 (w), 1732 (m), 1702 (s), 1594 (m), 1493 (m), 1445 (m), 1430 (m), 1336 (m), 1294 (m), 1262 (m), 1227 (s), 1197 (s), 1121 (m), 759 (m), 732 (m), 693 (s) cm^{-1}. HRMS (ESI): calcd. for $C_{29}H_{27}N_3NaO_4$ [M + Na^+] 504.1899; found 504.1909.

Ethyl 3-(4-Methoxyphenyl)-1-phenyl-1,4,4a,5,6,7-hexahydrobenzo[*c*]pyridazine-4a-carboxylate (7l): Following the procedure given for compound **7b**, 1,4-diketone **1l** (1.00 g, 3.14 mmol), phenylhydrazine (**5a**; 373 mg, 3.45 mmol) and TFA (214 mg, 1.88 mmol) were reacted in CH_2Cl_2 (11 mL). Chromatography (SiO_2, hexane/MTBE = 10:1, R_f = 0.24) gave pyridazine **7l** (955 mg, 2.45 mmol, 78%) as a yellowish solid. M.p. 113 °C. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.16 (t, J = 7.1 Hz, 3 H), 1.62 (t, J = 12.0 Hz, 1 H), 1.69–1.82 (m, 2 H), 2.13–2.17 (m, 1 H), 2.29–2.37 (m, 2 H), 2.49 (d, J = 17.1 Hz, 1 H), 3.54 (d, J = 17.1 Hz, 1 H), 3.80 (s, 3 H), 4.11 (q, J = 7.1 Hz, 2 H), 5.46 (br. s, 1 H), 6.86 (d, J = 8.6 Hz, 2 H), 7.01 (t, J = 7.2 Hz, 1 H), 7.30 (t, J = 7.7 Hz, 2 H), 7.53 (d, J = 8.2 Hz, 2 H), 7.66 (d, J = 8.6 Hz, 2 H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 14.19 (CH_3), 19.26 (CH_2), 24.73 (CH_2), 35.00 (CH_2), 35.10 (CH_2), 42.00 (C), 55.25 (CH_3), 61.34 (CH_2), 108.22 (CH), 113.63 (2 CH), 121.79 (2 CH), 122.73 (CH), 126.12 (2 CH), 128.50 (2 CH), 130.81 (C), 135.69 (C), 138.97 (C), 146.45 (C), 159.46 (C), 174.30 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3002 (w), 2957 (w), 2935 (w), 2858 (w), 2837 (w), 1723 (s), 1598 (m), 1511 (m), 1494 (s), 1453 (m), 1297 (m), 1240 (m), 1214 (m), 1183 (s), 1157 (m), 1084 (m), 1037 (m), 1025 (m), 836 (s), 764 (s), 698 (s) cm^{-1}. HRMS (ESI): calcd. for $C_{24}H_{27}N_2O_3$ [M + H^+] 391.2022; found 391.2029.

Ethyl 3-(4-Bromophenyl)-1-phenyl-1,4,4a,5,6,7-hexahydrobenzo[*c*]-pyridazine-4a-carboxylate (7m) and Ethyl 3-(4-Bromophenyl)-2-phenyl-2,4a,5,6,7,8-hexahydrobenzo[*c*]pyridazine-4a-caboxylate (8m): Following the procedure given for compound **7b**, 1,4-diketone **1m** (181 mg, 491 µmol), phenylhydrazine (**5a**; 58 mg, 0.54 mmol) and TFA (33 mg, 0.29 mmol) were reacted in CH_2Cl_2 (1.7 mL). Chromatography (SiO_2, hexane/MTBE = 10:1, R_f = 0.36) gave a mixture of regioisomers **7m** (104 mg, 240 µmol, 48%) and **8m** (41 mg, 90 µmol, 15%) as a yellowish oil. ^1H NMR (500 MHz, $CDCl_3$), major regioisomer **7m**: δ = 1.15 (t, J = 7.1 Hz, 3 H), 1.49–1.64 (m, 2 H), 1.69–1.78 (m, 2 H), 2.11–2.18 (m, 1 H), 2.32–2.36 (m, 1 H), 2.48 (d, J = 17.1 Hz, 1 H), 3.49 (d, J = 17.0 Hz, 1 H), 4.07–4.14 (m, 2 H), 5.46–5.47 (m, 1 H), 7.04 (t, J = 7.3 Hz, 1 H), 7.30 (t, J = 7.9 Hz, 2 H), 7.42 (d, J = 8.5 Hz, 2 H), 7.50 (d, J = 8.1 Hz, 2 H), 7.57 (d, J = 6.6 Hz, 2 H) ppm; minor regioisomer **8m**: δ = 1.20 (t, J = 7.1 Hz, 3 H), 1.69–1.78 (m, 2 H), 1.89–1.91 (m, 1 H), 2.27–2.30 (m, 2 H), 2.51–2.54 (m, 2 H), 2.64–2.67 (m, 1 H), 4.14–4.25 (m, 2 H), 4.57 (s, 1 H), 6.91 (t, J = 7.3 Hz, 1 H), 6.97 (d, J = 8.0 Hz, 2 H), 7.00 (d, J = 8.4 Hz, 2 H), 7.10 (t, J = 7.8 Hz, 2 H), 7.27–7.29 (m, 2 H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$), major regioisomer **7m**: δ = 14.21 (CH_3), 19.21 (CH_2), 24.71 (CH_2), 34.67 (CH_2), 34.90 (CH_2), 41.74 (C), 61.49 (CH_2), 109.00 (CH), 121.52 (C), 122.08 (2 CH), 123.32 (CH), 126.24 (2 CH), 128.62 (2 CH), 131.36 (2 CH), 135.41 (C), 136.84 (C), 137.60 (C), 146.15 (C), 174.17 (C) ppm; minor regioisomer **8m**: δ = 14.17 (CH_3), 22.82 (CH_2), 24.71 (CH_2), 32.35 (CH_2), 37.31 (CH_2), 47.11 (C), 61.25 (CH_2), 104.54 (CH), 121.91 (C), 122.57 (2 CH), 123.32 (CH), 128.31 (2 CH), 129.54 (2 CH), 131.17 (2 CH), 135.09 (C), 138.25 (C), 143.69 (C), 147.03 (C), 172.36 (C) ppm. IR (ATR): $\tilde{\nu}$ = 2979 (w), 2935 (w), 2865 (w), 2836 (w), 1724 (s), 1594 (m), 1577 (w), 1310 (m), 1295 (m), 1267 (m), 1189 (s), 1072 (m), 909 (m), 825 (m), 751 (m), 732 (m), 695 (m), 632 (s) cm^{-1}. HRMS (ESI): calcd. for $C_{23}H_{24}BrN_2O_2$ [M + H^+] 439.1021; found 439.1030.

Ethyl 3-(4-Nitrophenyl)-1-phenyl-1,4,4a,5,6,7-hexahydrobenzo[*c*]pyridazine-4a-carboxylate (7n) and Ethyl 3-(4-Nitrophenyl)-2-phenyl-2,4a,5,6,7,8-hexahydrobenzo[*c*]pyridazine-4a-caboxylate (8n): Following the procedure given for compound **7b**, 1,4-diketone **1n** (75 mg, 0.22 mmol), phenylhydrazine (**5a**; 26 mg, 0.24 mmol) and TFA (15 mg, 0.13 mmol) were reacted in CH_2Cl_2 (0.8 mL). Chromatography (SiO_2, hexane/MTBE = 5:1, R_f = 0.31) gave a mixture of regioisomers **7n** (41 mg, 0.10 mmol, 46%) and **8n** (9 mg, 0.02 mmol, 10%) as a yellowish oil. ^1H NMR (500 MHz, $CDCl_3$), major isomer **7n**: δ = 1.15 (t, J = 7.1 Hz, 3 H), 1.61–1.66 (m, 1 H), 1.71–1.81 (m, 2 H), 2.13–2.21 (m, 1 H), 2.32 (ddd, J = 4.5 Hz, J = 8.9 Hz, J = 17.9 Hz, 1 H), 2.38–2.40 (m, 1 H), 2.52 (d, J = 17.0 Hz, 1 H), 3.55 (d, J = 17.0 Hz, 1 H), 4.07–4.15 (m, 2 H), 5.51 (dd, J = 3.5 Hz, J = 5.0 Hz, 1 H), 7.10 (t, J = 7.1 Hz, 1 H), 7.34 (t, J = 7.9 Hz, 2 H), 7.50 (d, J = 7.6 Hz, 2 H), 7.81 (d, J = 9.0 Hz, 2 H), 8.15 (d, J = 9.0 Hz, 2 H) ppm; minor isomer **8n**: δ = 1.21 (t, J = 7.1 Hz, 3 H), 1.55–1.60 (m, 2 H), 1.61–1.66 (m, 1 H), 1.71–1.81 (m, 2 H), 1.91–1.94 (m, 1 H), 2.55–2.56 (m, 1 H), 2.65–2.69 (m, 1 H), 4.16–4.26 (m, 2 H), 4.71 (s, 1 H), 6.92 (t, J = 7.4 Hz, 1 H), 6.96 (d, J = 7.6 Hz, 2 H), 7.10 (t, J = 7.1 Hz, 2 H), 7.30 (d, J = 8.7 Hz, 2 H), 8.01 (d, J = 8.8 Hz, 2 H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$), major isomer **7n**: δ = 14.66 (CH_3), 19.60 (CH_2), 25.16 (CH_2), 34.84 (CH_2), 35.28 (CH_2), 42.03 (C), 62.09 (CH_2), 110.79 (CH), 122.99 (2 CH), 124.12 (2 CH), 124.64 (CH), 125.22 (2 CH), 129.21 (2 CH), 135.73 (C), 136.35 (C), 144.45 (C), 146.23 (C), 146.98 (C), 174.37 (C) ppm; minor isomer **8n**: δ = 14.61 (CH_3), 23.19 (CH_2), 30.12 (CH_2), 32.72 (CH_2), 37.76 (CH_2), 47.64 (C), 61.91 (CH_2), 107.16 (CH), 122.87 (2 CH), 123.79 (2 CH), 124.23 (CH), 128.75 (2 CH), 128.99 (2 CH), 137.98 (C), 143.33 (C), 143.83 (C), 147.61 (C), 147.89 (C), 172.46 (C) ppm. IR (ATR): $\tilde{\nu}$ = 2980 (w), 2935 (w), 2864 (w), 2837 (w), 1725 (m), 1594 (m), 1553 (m), 1511 (m), 1491 (m), 1338 (vs), 1191 (s), 1109 (m), 854 (m), 753 (m), 695 (m) cm^{-1}. HRMS (ESI): calcd. for $C_{23}H_{24}N_3O_4$ [M + H^+] 406.1767; found 406.1763.

Ethyl 3-(2,4-Dimethoxyphenyl)-2-phenyl-2,4a,5,6,7,8-hexahydrobenzo[*c*]pyridazine-4a-carboxylate (8o): Following the procedure given for compound **7b**, 1,4-diketone **1o** (100 mg, 290 µmol), phenylhydrazine (**5a**; 35 mg, 0.32 mmol) and TFA (15 mg, 0.13 mmol) were reacted in CH_2Cl_2 (1.0 mL). Chromatography (SiO_2, hexane/MTBE = 2:1, R_f = 0.49) gave pyridazine **8o** (54 mg, 13 µmol, 45%) as an orange oil. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.24 (t, J = 7.1 Hz, 3 H), 1.49 (dt, J = 12.8, J = 3.0 Hz, 1 H), 1.57 (dt, J = 12.9, J = 3.6 Hz, 1 H), 1.67 (td, J = 13.2, J = 3.4 Hz, 1 H), 1.86–1.89 (m, 1 H), 2.46–2.49 (m, 1 H), 2.55 (dd, J = 5.2, J = 13.3 Hz, 1 H), 2.64–2.67 (m, 1 H), 3.27 (s, 3 H), 3.73 (s, 3 H), 3.79 (d, J = 11.7 Hz, 1 H), 4.11–4.26 (m, 2 H), 4.39 (s, 1 H), 6.09 (d, J = 2.1 Hz, 1 H), 6.38 (dd, J = 2.3, J = 8.4 Hz, 1 H), 6.83 (t, J = 7.1 Hz, 1 H), 6.96–7.01 (m, 4 H), 7.12 (d, J = 8.3 Hz, 1 H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 14.27 (CH_3), 22.91 (CH_2), 25.45 (CH_2), 32.39 (CH_2), 37.14 (CH_2), 46.85 (C), 55.02 (CH_3), 55.26 (CH_3), 60.92 (CH_2), 98.30 (CH), 102.07 (CH), 104.17 (CH), 118.02 (C), 122.33 (2 CH), 122.88 (CH), 127.30 (2 CH), 131.84 (CH), 137.36 (C), 144.40 (C), 144.74 (C), 157.34 (C), 161.33 (C), 173.09 (C) ppm. IR (ATR): $\tilde{\nu}$ = 2933 (w), 2859 (w), 2838 (w), 1725 (s), 1608 (m), 1598 (m), 1504 (m), 1496 (m), 1464 (m), 1308 (m), 1283 (m), 1209 (s), 1033 (w) cm^{-1}. HRMS (ESI): calcd. for $C_{25}H_{28}N_2NaO_4$ [M + Na^+] 443.1947; found 443.1959.

Ethyl 1-(2-Chlorophenyl)-3-phenyl-1,4,4a,5,6,7-hexahydrobenzo[*c*]-pyridazine-4a-carboxylate (7p): Following the procedure given for compound **7b**, 1,4-diketone **1b** (150 mg, 520 µmol), 2-chlorophenyl-

hydrazine (**5b**; 81 mg, 0.57 mmol) and TFA (15 mg, 0.13 mmol) were reacted in CH_2Cl_2 (1.8 mL). Chromatography (SiO_2, hexane/MTBE = 10:1, R_f = 0.33) gave pyridazine **7p** (155 mg, 390 μmol, 75%) as a yellowish oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.24 (t, J = 7.1 Hz, 3 H), 1.65 (dd, J = 3.4, J = 13.0 Hz, 1 H), 1.75–1.84 (m, 2 H), 2.18–2.28 (m, 2 H), 2.42 (dt, J = 13.3, J = 3.7 Hz, 1 H), 2.48 (d, J = 16.7 Hz, 1 H), 3.58 (d, J = 16.7 Hz, 1 H), 4.15–4.26 (m, 2 H), 4.73 (t, J = 4.3 Hz, 1 H), 7.23 (t, J = 7.7 Hz, 1 H), 7.25–7.28 (m, 2 H), 7.32–7.37 (m, 2 H), 7.49 (d, J = 8.0 Hz, 1 H), 7.60 (d, J = 7.9 Hz, 1 H), 7.73 (d, J = 8.0 Hz, 2 H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 14.23 (CH_3), 19.48 (CH_2), 24.48 (CH_2), 33.96 (CH_2), 34.49 (CH_2), 42.04 (C), 61.40 (CH_2), 103.90 (CH), 125.04 (2 CH), 127.41 (CH), 127.58 (CH), 127.77 (CH), 128.24 (2 CH), 129.47 (CH), 130.40 (CH), 132.42 (C), 136.08 (C), 137.81 (C), 140.11 (C), 143.14 (C), 173.88 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3061 (w), 2978 (w), 2932 (w), 2869 (w), 2837 (w), 1722 (s), 1585 (w), 1479 (m), 1444 (m), 1292 (m), 1194 (vs), 1113 (m), 1024 (m), 759 (m), 693 (m), 632 (m), 600 (m), 536 (m) cm^{-1}. HRMS (ESI): calcd. for $C_{23}H_{23}ClN_2NaO_2$ [M + Na$^+$] 417.1346; found 417.1336.

Ethyl 1-(3,4-Dichlorophenyl)-3-phenyl-1,4,4a,5,6,7-hexahydrobenzo[*c*]pyridazine-4a-carboxylate (7q) and Ethyl 2-(3,4-Dichlorophenyl)-3-phenyl-2,4a,5,6,7,8-hexahydrobenzo[*c*]pyridazine-4a-carboxylate (8q): Following the procedure given for compound **7b**, 1,4-diketone **1b** (150 mg, 520 μmol), 3,4-dichlorophenylhydrazine (**5c**; 100 mg, 570 μmol) and TFA (15 mg, 0.13 mmol) were reacted in CH_2Cl_2 (1.8 mL). Chromatography (SiO_2, hexane/MTBE = 10:1, R_f = 0.35) gave a mixture of regioisomers **7q** (174 mg, 410 μmol, 78%) and **8q** (7.0 mg, 16 μmol, 3%) as a yellowish oil. ^{1}H NMR (500 MHz, $CDCl_3$), major isomer **7q**: δ = 1.14 (t, J = 7.1 Hz, 3 H), 1.61–1.66 (m, 1 H), 1.70–1.81 (m, 2 H), 2.14–2.21 (m, 1 H), 2.31–2.39 (m, 2 H), 2.53 (d, J = 17.3 Hz, 1 H), 3.57 (d, J = 17.3 Hz, 1 H), 4.09 (q, J = 7.1 Hz, 2 H), 5.58 (t, J = 4.2 Hz, 1 H), 7.27–7.36 (m, 4 H), 7.41 (dd, J = 2.4, J = 8.8 Hz, 1 H), 7.65 (d, J = 2.3 Hz, 1 H), 7.70 (d, J = 7.6 Hz, 2 H) ppm; minor isomer **8q**: 1.20 (t, J = 7.1 Hz, 3 H), 4.14–4.25 (m, 2 H), 4.66 (s, 1 H), 6.62 (dd, J = 2.4, J = 8.8 Hz, 1 H), 7.04 (d, J = 8.8 Hz, 1 H) 7.11–7.13 (m, 2 H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$), major isomer **7q**: δ = 14.17 (CH_3), 19.08 (CH_2), 24.70 (CH_2), 34.83 (CH_2), 35.32 (CH_2), 41.81 (C), 61.57 (CH_2), 111.02 (CH), 120.00 (CH), 122.18 (CH), 124.95 (2 CH), 125.04 (C), 128.20 (CH), 128.31 (2 CH), 129.99 (C), 132.19 (C), 134.85 (C), 137.36 (C), 140.68 (C), 145.75 (C), 174.03 (C) ppm. IR (ATR): $\tilde{\nu}$ = 2980 (w), 2937 (w), 2866 (w), 2837 (w), 1725 (m), 1585 (m), 1471 (s), 1445 (m), 1266 (m), 1180 (m), 1126 (m), 1112 (m), 1023 (m), 760 (m), 737 (m), 693 (m), 631 (m) cm^{-1}. HRMS (ESI): calcd. for $C_{23}H_{22}Cl_2N_2NaO_2$ [M + Na$^+$] 451.0956; found 451.0943.

Ethyl 1-(2-Methoxyphenyl)-3-phenyl-1,4,4a,5,6,7-hexahydrobenzo[*c*]pyridazine-4a-carboxylate (7r): Following the procedure given for compound **7b**, 1,4-diketone **1b** (150 mg, 520 μmol), 2-methoxyphenylhydrazine (**5d**; 79 mg, 0.57 mmol) and TFA (15 mg, 0.13 mmol) were reacted in CH_2Cl_2 (1.8 mL). Chromatography (SiO_2, hexane/MTBE = 10:1, R_f = 0.32) gave pyridazine **7r** (107 mg, 270 μmol, 53%) as a yellowish oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.12 (t, J = 7.1 Hz, 3 H), 1.47–1.54 (m, 1 H), 1.62–1.68 (m, 2 H), 2.09–2.14 (m, 2 H), 2.28 (dt, J = 12.8, J = 3.2 Hz, 1 H), 2.38 (d, J = 16.3 Hz, 1 H), 3.42 (d, J = 16.5 Hz, 1 H), 3.76 (s, 3 H), 4.03–4.13 (m, 2 H), 4.62 (br. s, 1 H), 6.92 (t, J = 8.9 Hz, 2 H), 7.13–7.18 (m, 2 H), 7.22 (t, J = 7.6 Hz, 2 H), 7.37 (t, J = 6.8 Hz, 1 H), 7.58 (d, J = 7.7 Hz, 2 H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 14.67 (CH_3), 20.05 (CH_2), 24.95 (CH_2), 34.18 (CH_2), 34.94 (CH_2), 42.51 (C), 56.54 (CH_3), 61.71 (CH_2), 103.13 (CH), 113.34 (CH), 121.69 (CH), 125.35 (2 CH), 127.76 (CH), 128.04 (CH), 128.57 (2 CH), 129.42 (CH), 135.51 (C), 137.13 (C), 138.65 (C), 139.08 (C), 156.22 (C), 174.53 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3058 (w), 2975 (w), 2933 (w), 2835 (w), 1721 (m), 1584 (m), 1498 (m), 1460 (m), 1444 (m), 1293 (m), 1271 (m), 1243 (m), 1194 (s), 1159 (s), 1123 (m), 1024 (s), 752 (s), 693 (m) cm^{-1}. HRMS (ESI): calcd. for $C_{24}H_{27}N_2O_3$ [M + H$^+$] 391.2022; found 391.2021.

Ethyl 1-(4-Methoxyphenyl)-3-phenyl-1,4,4a,5,6,7-hexahydrobenzo[*c*]pyridazine-4a-carboxylate (7s): Following the procedure given for compound **7b**, 1,4-diketone **1b** (150 mg, 520 μmol), 4-methoxyphenylhydrazine (**5e**; 79 mg, 0.57 mmol) and TFA (15 mg, 0.13 mmol) were reacted in CH_2Cl_2 (1.8 mL). Chromatography (SiO_2, hexane/MTBE = 10:1, R_f = 0.32) gave pyridazine **7s** (69 mg, 0.18 mmol, 35%) as a yellowish oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.16 (t, J = 7.1 Hz, 3 H), 1.59–1.61 (m, 1 H), 1.70–1.76 (m, 2 H), 2.11–2.18 (m, 1 H), 2.24–2.27 (m, 1 H), 2.35 (dt, J = 13.2, J = 4.0 Hz, 1 H), 2.46 (d, J = 16.7 Hz, 1 H), 3.53 (d, J = 17.0 Hz, 1 H), 3.79 (s, 3 H), 4.11 (q, J = 7.1 Hz, 2 H), 5.20 (br. s, 1 H), 6.87 (d, J = 8.5 Hz, 2 H), 7.20–7.23 (m, 1 H), 7.30 (t, J = 7.6 Hz, 2 H), 7.41 (d, J = 8.5 Hz, 2 H), 7.67 (d, J = 8.0 Hz, 2 H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 14.23 (CH_3), 19.40 (CH_2), 24.68 (CH_2), 34.40 (CH_2), 34.90 (CH_2), 41.97 (C), 55.50 (CH_3), 61.38 (CH_2), 106.16 (CH), 113.95 (2 CH), 124.67 (2 CH), 124.71 (2 CH), 127.42 (CH), 128.17 (2 CH), 136.38 (C), 137.95 (C), 138.04 (C), 139.78 (C), 156.27 (C), 174.25 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3062 (w), 2978 (w), 2933 (w), 2868 (w), 2835 (w), 1723 (m), 1506 (s), 1444 (m), 1293 (m), 1241 (s), 1178 (s), 1111 (m), 1028 (m), 830 (m), 759 (m), 692 (m) cm^{-1}. HRMS (ESI): calcd. for $C_{24}H_{26}N_2NaO_3$ [M + Na$^+$] 413.1841; found 413.1837.

Ethyl 1-(2-Methylphenyl)-3-phenyl-1,4,4a,5,6,7-hexahydrobenzo[*c*]pyridazine-4a-carboxylate (7t): Following the procedure given for compound **7b**, 1,4-diketone **1b** (150 mg, 520 μmol), 2-methylphenylhydrazine (**5f**; 70 mg, 0.57 mmol) and TFA (15 mg, 0.13 mmol) were reacted in CH_2Cl_2 (1.8 mL). Chromatography (SiO_2, hexane/MTBE = 10:1, R_f = 0.38) gave pyridazine **7t** (35 mg, 90 μmol, 18%) as a yellowish oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.18 (t, J = 7.1 Hz, 3 H), 1.49–1.60 (m, 1 H), 1.72–1.78 (m, 2 H), 2.10–2.20 (m, 2 H), 2.26 (s, 3 H), 2.34 (dt, J = 13.1, J = 3.1 Hz, 1 H), 2.42 (d, J = 14.8 Hz, 1 H), 3.53 (d, J = 16.6 Hz, 1 H), 4.08–4.20 (m, 2 H), 4.56 (br. s, 1 H), 7.14–7.17 (m, 1 H), 7.20–7.23 (m, 3 H), 7.28 (t, J = 7.6 Hz, 2 H), 7.35–7.37 (m, 1 H), 7.66 (d, J = 7.7 Hz, 2 H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 14.20 (CH_3), 18.04 (CH_3), 19.47 (CH_2), 24.49 (CH_2), 33.79 (CH_2), 34.74 (CH_2), 42.24 (C), 61.36 (CH_2), 102.82 (CH), 124.75 (2 CH), 126.53 (CH), 126.69 (CH), 127.49 (CH), 127.70 (CH), 128.20 (2 CH), 130.85 (CH), 135.79 (C), 136.25 (C), 137.92 (C), 138.90 (C), 144.29 (C), 173.99 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3059 (w), 3025 (w), 2981 (w), 2934 (w), 2870 (w), 2837 (w), 1724 (s), 1585 (m), 1493 (m), 1447 (m), 1294 (m), 1270 (m), 1190 (s), 1126 (m), 1068 (m), 1025 (m), 761 (m), 695 (m), 633 (s) cm^{-1}. HRMS (ESI): calcd. for $C_{24}H_{27}N_2O_2$ [M + H$^+$] 375.2073; found 375.2070.

Ethyl 1-(4-Methylphenyl)-3-phenyl-1,4,4a,5,6,7-hexahydrobenzo[*c*]pyridazine-4a-carboxylate (7u): Following the procedure given for compound **7b**, 1,4-diketone **1b** (150 mg, 520 μmol), 4-methylphenylhydrazine (**5g**; 70 mg, 0.57 mmol) and TFA (15 mg, 0.13 mmol) were reacted in CH_2Cl_2 (1.8 mL). Chromatography (SiO_2, hexane/MTBE = 10:1, R_f = 0.37) gave pyridazine **7u** (128 mg, 340 μmol, 66%) as a yellowish oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.15 (t, J = 7.1 Hz, 3 H), 1.55–1.63 (m, 1 H), 1.69–1.76 (m, 2 H), 2.11–2.18 (m, 1 H), 2.26–2.37 (m, 2 H), 2.31 (s, 3 H), 2.48 (d, J = 17.1 Hz, 1 H), 3.54 (d, J = 17.1 Hz, 1 H), 4.10 (q, J = 7.1 Hz, 2 H), 5.35 (br. s, 1 H), 7.11 (d, J = 8.1 Hz, 2 H), 7.21–7.24 (m, 1 H), 7.30 (t, J = 7.6 Hz, 2 H), 7.40 (d, J = 8.1 Hz, 2 H), 7.69 (d, J = 7.8 Hz, 2 H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 14.45 (CH_3), 19.56 (CH_2), 21.08 (CH_3), 24.94 (CH_2), 34.95 (CH_2), 35.21 (CH_2),

42.12 (C), 61.62 (CH_2), 107.72 (CH), 122.76 (2 CH), 124.94 (2 CH), 127.71 (CH), 128.40 (2 CH), 129.41 (2 CH), 133.12 (C), 136.10 (C), 138.22 (C), 138.50 (C), 144.17 (C), 175.54 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3029 (w), 2975 (w), 2934 (w), 2864 (w), 2835 (w), 1725 (m), 1509 (m), 1445 (w), 1267 (w), 1191 (m), 760 (w), 694 (w), 632 (s) cm^{-1}. HRMS (ESI): calcd. for $C_{24}H_{26}N_2NaO_2$ [M + Na^+] 397.1892; found 397.1866.

Ethyl 1-(4-Iodophenyl)-3-phenyl-1,4,4a,5,6,7-hexahydrobenzo[*c*]pyridazine-4a-carboxylate (7v) and Ethyl 2-(4-Iodophenyl)-3-phenyl-2,4a,5,6,7,8-hexahydrobenzo[*c*]pyridazine-4a-carboxylate (8v): Following the procedure given for compound **7b**, 1,4-diketone **1b** (150 mg, 520 μmol), 4-iodophenylhydrazine (**5h**; 133 mg, 570 μmol) and TFA (15 mg, 0.13 mmol) were reacted in CH_2Cl_2 (1.8 mL). Chromatography (SiO_2, hexane/MTBE = 10:1, R_f = 0.27) gave a mixture of regioisomers **7v** (194 mg, 400 μmol, 77%) and **8v** (10 mg, 21 μmol, 4%) as a red solid. M.p. 44 °C. ^{1}H NMR (500 MHz, $CDCl_3$), major isomer **7v**: δ = 1.07 (t, J = 7.1 Hz, 3 H), 1.53–1.59 (m, 1 H), 1.63–1.71 (m, 2 H), 2.08–2.11 (m, 1 H), 2.23–2.31 (m, 2 H), 2.45 (d, J = 17.3 Hz, 1 H), 3.50 (d, J = 17.2 Hz, 1 H), 4.03 (q, J = 7.1 Hz, 2 H), 5.47 (t, J = 4.2 Hz, 1 H), 7.18–7.21 (m, 1 H), 7.25–7.28 (m, 4 H), 7.51 (d, J = 8.6 Hz, 2 H), 7.63 (d, J = 7.7 Hz, 2 H) ppm; minor isomer **8v**: δ = 1.13 (t, J = 7.2 Hz, 3 H), 2.60 (d, J = 14.8 Hz, 1 H), 4.07–4.18 (m, 2 H), 4.56 (s, 1 H), 6.68 (d, J = 8.5 Hz, 2 H), 7.06 (d, J = 6.3 Hz, 2 H), 7.13 (d, J = 7.0 Hz, 2 H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$), major isomer **7v**: δ = 14.67 (CH_3), 19.61 (CH_2), 25.18 (CH_2), 35.36 (CH_2), 35.60 (CH_2), 42.26 (C), 61.95 (CH_2), 85.84 (C), 110.39 (CH), 123.72 (2 CH), 125.30 (2 CH), 128.40 (CH), 128.72 (2 CH), 135.51 (C), 137.90 (2 CH), 138.07 (C), 140.28 (C), 146.56 (C), 174.58 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3059 (w), 2978 (w), 2934 (w), 2865 (w), 2835 (w), 1723 (s), 1579 (m), 1481 (vs), 1444 (m), 1301 (m), 1266 (m), 1184 (s), 1170 (s), 1110 (m), 1022 (m), 818 (m), 758 (s), 691 (s) cm^{-1}. HRMS (ESI): calcd. for $C_{23}H_{24}IN_2O_2$ [M + H^+] 487.0882; found 487.0891.

Ethyl 2-[2-(2,4-Dinitrophenyl)hydrazono]-1-(2-oxo-2-phenylethyl)-cyclohexanecarboxylate (6w): 2,4-Dinitrophenylhydrazine **5i** (151 mg, 690 μmol) and TFA (47 mg, 0.41 mmol) were added to a solution of 1,4-diketone **1b** (200 mg, 690 μmol) in THF (2.4 mL) and the resulting reaction mixture was stirred for 3 h under reflux. After removal of all volatile materials in vacuo, the residue was purified by using chromatography (SiO_2, hexane/MTBE = 3:1, R_f = 0.22) to yield hydrazone **6w** (233 mg, 500 μmol, 72%) as an orange solid. M.p. 75 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.30 (t, J = 7.1 Hz, 3 H), 1.47–1.56 (m, 1 H), 1.58–1.66 (m, 1 H), 1.78–1.84 (m, 2 H), 2.05–2.08 (m, 1 H), 2.44–2.47 (m, 1 H), 2.74–2.86 (m, 2 H), 3.35 (d, J = 16.7 Hz, 1 H), 3.80 (d, J = 16.7 Hz, 1 H), 4.23–4.36 (m, 2 H), 6.86 (d, J = 9.6 Hz, 1 H), 7.52–7.55 (m, 3 H), 7.68 (t, J = 7.4 Hz, 1 H), 8.03 (d, J = 7.5 Hz, 2 H), 8.98 (d, J = 2.5 Hz, 1 H), 11.20 (s, 1 H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 14.58 (CH_3), 22.37 (CH_2), 26.09 (CH_2), 26.32 (CH_2), 38.57 (CH_2), 45.71 (CH_2), 54.50 (C), 62.02 (CH_2), 116.45 (CH), 123.73 (CH), 128.64 (2 CH), 129.36 (2 CH), 129.59 (C), 129.75 (CH), 133.98 (CH), 137.26 (C), 138.09 (C), 145.34 (C), 158.95 (C), 174.11 (C), 197.06 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3323 (w), 2941 (w), 2865 (w), 1727 (m), 1688 (m), 1618 (s), 1591 (m), 1517 (m), 1504 (m), 1334 (s), 1312 (m), 1221 (m), 1198 (m), 1137 (m), 763 (m), 744 (m), 630 (s) cm^{-1}. HRMS (ESI): calcd. for $C_{23}H_{24}N_4NaO_7$ [M + Na^+] 491.1543; found 491.1542.

1-Benzyl 3-Methyl 4-Oxo-3-(2-oxo-2-phenylethyl)pyrrolidine-1,3-dicarboxylate (1g): Phenacyl bromide (105 mg, 530 μmol) and K_2CO_3 (73 mg, 0.53 mmol) were added to a solution of β-oxo ester **10g** (134 mg, 480 μmol) in acetone (1 mL) and the resulting mixture was stirred for 19 h at 40 °C. Then water (10 mL) was added and the aqueous phase was extracted with MTBE (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered and the solvent was evaporated to yield 1,4-diketone **1g** (83 mg, 0.21 mmol, 44%) after chromatography (SiO_2, hexane/MTBE = 2:1, R_f = 0.13) as a colorless oil. A double signal set is observed due to *E*/*Z*-isomers (ratio 1.0:0.95) at the carbamate C–N bond. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.65–3.74 (m, 4 H), 3.71 (s, 6 H), 3.85 (s, 2 H), 4.16–4.28 (m, 4 H), 4.39–4.46 (m, 2 H), 5.19 (s, 4 H), 7.32–7.38 (m, 10 H), 7.46 (t, J = 7.5 Hz, 4 H), 7.58 (t, J = 7.5 Hz, 2 H), 7.92 (d, J = 7.8 Hz, 4 H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 42.83 (CH_2), 43.04 (CH_2), 52.54 (CH_2), 52.70 (CH_2), 52.95 (CH_2), 53.07 (CH_2), 53.59 (2 CH_3), 56.70 (C), 57.68 (C), 67.62 (2 CH_2), 128.21 (4 CH), 128.38 (2 CH), 128.40 (4 CH), 128.74 (4 CH), 129.00 (4 CH), 134.20 (2 CH), 135.72 (2 C), 136.56 (2 C), 154.86 (C), 155.03 (C), 169.35 (C), 169.62 (C), 196.31 (C), 196.37 (C), 205.94 (C), 206.57 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3063 (w), 3032 (w), 2955 (w), 2920 (w), 1769 (m), 1704 (s), 1681 (s), 1449 (m), 1418 (m), 1352 (m), 1270 (m), 1211 (m), 1180 (m), 1120 (m), 911 (m), 754 (m), 730 (s), 689 (s) cm^{-1}. HRMS (ESI): calcd. for $C_{22}H_{21}NNaO_6$ [M + Na^+] 418.1267; found 418.1274.

Ethyl 4-Oxo-3-(2-oxo-2-phenylethyl)tetrahydro-2*H*-pyran-3-carboxylate (1h): Following the procedure given for compound **1g**, oxo ester **10h** (413 mg, 2.40 mmol), phenacyl bromide (**11a**; 525 mg, 2.64 mmol) and K_2CO_3 (365 mg, 2.64 mmol) were reacted in acetone (4.8 mL). Chromatography (SiO_2, hexane/MTBE = 1:1, R_f = 0.38) gave 1,4-diketone **1h** (502 mg, 1.73 mmol, 72%) as a colorless solid. M.p. 90 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.26 (t, J = 7.1 Hz, 3 H), 2.53–2.57 (m, 1 H), 3.05 (ddd, J = 7.3, J = 11.0, J = 15.4 Hz, 1 H), 3.38 (d, J = 17.7 Hz, 1 H), 3.51 (d, J = 17.7 Hz, 1 H), 3.89–3.95 (m, 2 H), 4.22–4.28 (m, 3 H), 4.43 (d, J = 11.4 Hz, 1 H), 7.44 (t, J = 7.7 Hz, 2 H), 7.56 (t, J = 7.4 Hz, 1 H), 7.91 (d, J = 7.6 Hz, 2 H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 13.97 (CH_3), 39.53 (CH_2), 40.79 (CH_2), 60.04 (C), 62.00 (CH_2), 68.26 (CH_2), 73.97 (CH_2), 128.09 (2 CH), 128.64 (2 CH), 133.42 (CH), 136.50 (C), 170.73 (C), 196.00 (C), 202.88 (C) ppm. IR (ATR): $\tilde{\nu}$ = 2979 (w), 2931 (w), 2865 (w), 1733 (s), 1714 (s), 1710 (s), 1451 (m), 1385 (m), 1364 (m), 1300 (m), 1252 (m), 1220 (s), 1197 (m), 1106 (m), 1003 (m), 746 (m), 693 (m), 632 (s) cm^{-1}. HRMS (CI, isobutane): calcd. for $C_{16}H_{18}O_5$ [M + H^+] 291.1232; found 291.1227. $C_{16}H_{19}O_5$ (290.31): calcd. C 66.19, H 6.25; found C 66.19, H 6.39.

Methyl 4-Oxo-3-(2-oxo-2-phenylethyl)tetrahydro-2*H*-thiopyran-3-carboxylate (1i): Following the procedure given for compound **1g**, oxo ester **10i** (300 mg, 1.72 mmol), phenacyl bromide (**11a**; 376 mg, 1.89 mmol) and K_2CO_3 (261 mg, 1.89 mmol) were reacted in acetone (3.5 mL). Chromatography (SiO_2, hexane/MTBE = 1:1, R_f = 0.38) gave 1,4-diketone **1i** (248 mg, 0.850 mmol, 49%) as a yellowish solid. M.p. 86 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.80–2.88 (m, 2 H), 2.97–3.09 (m, 2 H), 3.26 (s, 2 H), 3.50 (A-part of an AB-system, J = 17.3 Hz 1 H), 3.61 (B-part of an AB-system, J = 17.3 Hz, 1 H), 3.75 (s, 3 H), 7.40 (t, J = 7.7 Hz, 2 H), 7.51 (t, J = 7.3 Hz, 1 H), 7.88 (d, J = 7.8 Hz, 2 H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 29.78 (CH_2), 37.62 (CH_2), 41.96 (CH_2), 42.64 (CH_2), 52.71 (CH_3), 60.68 (C), 127.89 (2 CH), 128.47 (2 CH), 133.24 (CH), 136.26 (C), 171.31 (C), 196.06 (C), 204.25 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3002 (w), 2968 (w), 2951 (w), 2931 (w), 1734 (s), 1706 (s), 1596 (m), 1448 (m), 1430 (m), 1418 (m), 1364 (m), 1317 (m), 1291 (m), 1208 (s), 1136 (m), 1130 (m), 1004 (m), 968 (m), 779 (m), 754 (m), 691 (m) cm^{-1}. HRMS (CI, isobutane): calcd. for $C_{15}H_{17}O_4S$ [M + H^+] 293.0848; found 293.0840.

1-*tert*-Butyl 3-Methyl 4-Oxo-3-(2-oxo-2-phenylethyl)piperidine-1,3-dicarboxylate (1j): Following the procedure given for compound **1g**,

oxo ester **10j** (1.15 g, 4.47 mmol), phenacyl bromide (**11a**; 979 mg, 4.92 mmol) and K_2CO_3 (680 mg, 4.92 mmol) were reacted in acetone (14 mL). Chromatography (SiO_2, hexane/MTBE = 2:1, R_f = 0.14) gave 1,4-diketone **1j** (1.24 g, 3.31 mmol, 74%) as a colorless solid. M.p. 45 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.40 (s, 9 H), 2.60 (d, J = 14.9 Hz, 1 H), 2.84–2.97 (m, 1 H), 3.44–3.79 (m, 4 H), 3.72 (s, 3 H), 4.15 (s, 1 H), 4.34–4.50 (m, 1 H), 7.44 (t, J = 7.1 Hz, 2 H), 7.56 (t, J = 7.0 Hz, 1 H), 7.92 (d, J = 7.8 Hz, 2 H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 28.47 (3 CH_3), 39.51 (CH_2), 41.12 (CH_2), 42.69 (CH_2), 50.02 (CH_2), 53.08 (CH_3), 58.56 (C), 80.72 (C), 128.32 (2 CH), 128.88 (2 CH), 133.77 (CH), 136.44 (C), 154.46 (C), 171.03 (C), 196.22 (C), 204.60 (C) ppm. IR (ATR): $\tilde{\nu}$ = 2977 (w), 2954 (w), 2932 (w), 1737 (m), 1686 (s), 1424 (m), 1366 (m), 1295 (m), 1249 (m), 1220 (m), 1157 (s), 1132 (m), 1000 (m), 756 (m), 739 (m), 690 (m) cm^{-1}. HRMS (ESI): calcd. for $C_{20}H_{25}NNaO_6$ [M + Na$^+$] 398.1580; found 398.1570.

1-Benzyl 3-Methyl 4-Oxo3-(2-oxo-phenylethyl)piperidine-1,3-dicarboxylate (1k): Following the procedure given for compound **1g**, oxo ester **10k** (524 mg, 1.80 mmol), phenacyl bromide (**11a**; 384 mg, 1.98 mmol) and K_2CO_3 (274 mg, 1.98 mmol) were reacted in acetone (3.6 mL). Chromatography (SiO_2, hexane/MTBE = 1:1, R_f = 0.25) gave 1,4-diketone **1k** (517 mg, 1.26 mmol, 70%) as a colorless oil. A double set of broad signals is observed due to *E*/*Z*-isomers (ratio 1.0:0.62) at the carbamate C–N bond. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.64 (d, J = 15.6 Hz, 2 H), 2.89–2.99 (m, 2 H), 3.44–3.48 (m, 3 H), 3.54–3.58 (m, 8 H), 3.64–3.72 (m, 2 H), 3.81 (d, J = 17.8 Hz, 1 H), 4.29–4.33 (m, 2 H), 4.46–4.57 (m, 2 H), 5.05–5.19 (m, 4 H), 7.31–7.35 (m, 10 H), 7.44 (t, J = 7.6 Hz, 4 H), 7.57 (t, J = 7.3 Hz, 2 H), 7.86–7.90 (m, 4 H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$), major conformer: δ = 38.91 (CH_2), 40.96 (CH_2), 42.85 (CH_2), 49.53 (CH_2), 52.67 (CH_3), 57.77 (C), 67.49 (CH_2), 127.62 (2 CH), 127.91 (CH), 128.08 (2 CH), 128.43 (2 CH), 128.57 (2 CH), 133.53 (CH), 135.92 (C), 136.04 (C), 154.85 (C), 170.58 (C), 196.00 (C), 203.67 (C) ppm; minor conformer: δ = 39.13 (CH_2), 41.27 (CH_2), 42.85 (CH_2), 49.87 (CH_2), 52.79 (CH_3), 57.43 (C), 67.49 (CH_2), 127.62 (2 CH), 127.91 (CH), 128.08 (2 CH), 128.43 (2 CH), 128.57 (2 CH), 133.53 (CH), 135.92 (C), 136.37 (C), 155.08 (C), 170.74 (C), 196.27 (C), 203.87 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3065 (w), 3031 (w), 2953 (w), 1737 (m), 1695 (s), 1473 (w), 1447 (m), 1430 (m), 1355 (w), 1293 (m), 1277 (m), 1248 (m), 1217 (s), 1127 (m), 999 (m), 909 (m), 755 (m), 737 (m), 691 (m), 643 (m), 609 (m) cm^{-1}. HRMS (CI, isobutane): calcd. for $C_{23}H_{24}NO_6$ [M + H$^+$] 410.1604; found 410.1593.

Ethyl 1-[2-(4-Methoxyphenyl)-2-oxoethyl]-2-oxocyclohexanecarboxylate (1l): Following the procedure given for compound **1g**, oxo ester **10b** (1.00 g, 5.88 mmol), 4-methoxyphenacyl bromide (**11l**; 1.62 g, 7.06 mmol) and K_2CO_3 (976 mg, 7.06 mmol) were reacted in acetone (12 mL). Chromatography (SiO_2, hexane/MTBE = 2:1, R_f = 0.23) gave 1,4-diketone **1l** (1.01 g, 3.16 mmol, 54%) as a yellowish oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.24 (t, J = 7.1 Hz, 3 H), 1.74–1.83 (m, 4 H), 2.04–2.06 (m, 1 H), 2.41–2.45 (m, 1 H), 2.50–2.53 (m, 1 H), 2.75–2.82 (m, 1 H), 3.35 (d, J = 17.3 Hz, 1 H), 3.50 (d, J = 17.3 Hz, 1 H), 3.84 (s, 3 H), 4.16–4.25 (m, 2 H), 6.90 (d, J = 8.6 Hz, 2 H), 7.91 (d, J = 8.6 Hz, 2 H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 14.01 (CH_3), 22.00 (CH_2), 26.71 (CH_2), 36.58 (CH_2), 40.51 (CH_2), 43.68 (CH_2), 55.43 (CH_3), 58.75 (C), 61.44 (CH_2), 113.62 (2 CH), 129.86 (C), 130.30 (2 CH), 163.48 (C), 172.08 (C), 195.42 (C), 207.40 (C) ppm. IR (ATR): $\tilde{\nu}$ = 2938 (w), 2865 (w), 2842 (w), 1728 (m), 1710 (s), 1679 (m), 1600 (s), 1510 (m), 1312 (m), 1260 (m), 1223 (s), 1170 (s), 1027 (m), 631 (s) cm^{-1}. HRMS (CI, isobutane): calcd. for $C_{18}H_{23}O_5$ [M + H$^+$] 319.1545; found 319.1538.

Ethyl 1-[2-(4-Bromophenyl)-2-oxoethyl]-2-oxocyclohexanecarboxylate (1m): NaH (60% in mineral oil, 57 mg, 1.4 mmol) and 4-bromophenacyl bromide (**11m**; 395 mg, 1.42 mmol) were added at 60 °C to a solution of oxo ester **10b** (200 mg, 1.18 mmol) in THF (1.2 mL) and the reaction mixture was stirred at this temperature for 17 h. Then water (5 mL) and brine (5 mL) were added and the mixture was extracted with MTBE (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered and the solvent was removed in vacuo. Chromatography (SiO_2, hexane/MTBE = 5:1, R_f = 0.23) yielded 1,4-diketone **1m** (191 mg, 520 µmol, 44%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.25 (t, J = 7.1 Hz, 3 H), 1.71–1.83 (m, 4 H), 2.04–2.08 (m, 1 H), 2.42–2.45 (m, 1 H), 2.47–2.52 (m, 1 H), 2.80–2.87 (m, 1 H), 3.29 (d, J = 17.3 Hz, 1 H), 3.47 (d, J = 17.3 Hz, 1 H), 4.17–4.27 (m, 2 H), 7.57 (d, J = 8.6 Hz, 2 H), 7.79 (d, J = 8.6 Hz, 2 H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 14.03 (CH_3), 21.98 (CH_2), 26.84 (CH_2), 36.90 (CH_2), 40.52 (CH_2), 43.87 (CH_2), 59.06 (C), 61.60 (CH_2), 128.25 (C), 129.59 (2 CH), 131.83 (2 CH), 135.56 (C), 171.94 (C), 196.04 (C), 207.30 (C) ppm. IR (ATR): $\tilde{\nu}$ = 2939 (w), 2865 (w), 1728 (m), 1708 (s), 1687 (s), 1585 (m), 1397 (m), 1215 (s), 1193 (s), 1133 (m), 1071 (s), 1006 (m), 626 (m) cm^{-1}. HRMS (CI, isobutane): calcd. for $C_{17}H_{20}BrO_4$ [M + H$^+$] 367.0545; found 367.0540.

Ethyl 1-[2-(4-Nitrophenyl)-2-oxoethyl]-2-oxocyclohexanecarboxylate (1n): Following the procedure given for compound **1g**, oxo ester **10b** (500 mg, 2.94 mmol), 4-nitrophenacyl bromide (**11n**; 1.43 g, 5.88 mmol) and K_2CO_3 (813 mg, 5.88 mmol) were reacted in acetone (6 mL). Chromatography (SiO_2, hexane/MTBE = 3:1, R_f = 0.16) gave 1,4-diketone **1n** (122 mg, 370 µmol, 13%) as a yellowish oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.27 (t, J = 7.1 Hz, 3 H), 1.69–1.83 (m, 4 H), 2.07–2.13 (m, 1 H), 2.43–2.51 (m, 2 H), 2.85–2.93 (m, 1 H), 3.29 (d, J = 17.2 Hz, 1 H), 3.49 (d, J = 17.2 Hz, 1 H), 4.22–4.28 (m, 2 H), 8.07 (d, J = 8.7 Hz, 2 H), 8.28 (d, J = 8.7 Hz, 2 H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 14.48 (CH_3), 22.37 (CH_2), 27.40 (CH_2), 37.70 (CH_2), 40.95 (CH_2), 44.69 (CH_2), 60.05 (C), 62.21 (CH_2), 124.22 (2 CH), 129.51 (2 CH), 141.89 (C), 150.70 (C), 172.24 (C), 196.20 (C), 207.73 (C) ppm. IR (ATR): $\tilde{\nu}$ = 2941 (w), 2868 (w), 1730 (m), 1697 (s), 1605 (w), 1526 (s), 1347 (s), 1318 (m), 1214 (m), 1197 (m), 1013 (m), 856 (m), 633 (m) cm^{-1}. HRMS (CI, isobutane): calcd. for $C_{17}H_{20}NO_6$ [M + H$^+$] 334.1291; found 334.1294.

Ethyl 1-[2-(2,4-Dimethoxyphenyl)-2-oxoethyl]-2-oxocyclohexanecarboxylate (1o): Following the procedure given for compound **1g**, oxo ester **10b** (90 mg, 0.53 mmol), 2,4-dimethoxyphenacyl bromide (**11o**; 150 mg, 580 µmol) and K_2CO_3 (80 mg, 0.58 mmol) were reacted in acetone (1.1 mL). Chromatography (SiO_2, hexane/MTBE = 2:1, R_f = 0.20) gave 1,4-diketone **1o** (86 mg, 0.25 mmol, 47%) as a colorless solid. M.p. 83 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.23 (t, J = 7.1 Hz, 3 H), 1.71–1.83 (m, 4 H), 2.00–2.05 (m, 1 H), 2.37–2.41 (m, 1 H), 2.47–2.50 (m, 1 H), 2.76–2.83 (m, 1 H), 3.39 (A-part of an AB-system, J = 18.2 Hz, 1 H), 3.50 (B-part of an AB-system, J = 18.2 Hz, 1 H), 3.82 (s, 3 H), 3.86 (s, 3 H), 4.14–4.25 (m, 2 H), 6.41 (d, J = 1.4 Hz, 1 H), 6.49 (dd, J = 1.7, J = 8.8 Hz, 1 H), 7.78 (d, J = 8.7 Hz, 1 H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 14.49 (CH_3), 22.44 (CH_2), 27.22 (CH_2), 37.04 (CH_2), 41.00 (CH_2), 49.58 (CH_2), 55.89 (CH_3), 55.94 (CH_3), 59.50 (C), 61.65 (CH_2), 98.68 (CH), 105.55 (CH), 121.20 (C), 133.28 (CH), 161.23 (C), 164.92 (C), 172.95 (C), 196.90 (C), 208.13 (C) ppm. IR (ATR): $\tilde{\nu}$ = 2977 (w), 2955 (w), 2932 (w), 2863 (w), 1730 (m), 1702 (m), 1666 (m), 1311 (m), 1298 (m), 1257 (m), 1221 (m), 1210 (m), 1177 (s), 1136 (s), 1127 (s), 1074 (m), 1025 (m), 842 (m) cm^{-1}. HRMS (CI, isobutane): calcd. for $C_{19}H_{25}O_6$ [M + H$^+$] 349.1651; found 349.1649.

1-Benzyl 3-Methyl 4-Oxopyrrolidine-1,3-dicarboxylate (10g): Methylacrylate (193 mg, 2.24 mmol) and KO*t*Bu (276 mg, 2.46 mmol) were added at 0 °C to a solution of carbamate **12** (500 mg, 2.24 mmol) in THF (4 mL) and the mixture was stirred at 23 °C for 3 d. Afterwards the solvent was removed in vacuo, the residue was dissolved in CH_2Cl_2 (15 mL) and the pH-value was adjusted to 1 with hydrochloric acid (1 mol/L). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvent was evaporated to yield pyrrolidine **10g** (424 mg, 1.53 mmol, 68%) after chromatography (SiO_2, hexane/MTBE = 1:2, R_f = 0.16) as a colorless oil. A double signal set is observed due to keto-enol-tautomers (ratio 1.0:0.50). ^{1}H NMR (500 MHz, $CDCl_3$); ketone: δ = 3.76 (s, 3 H), 3.88–3.98 (m, 2 H), 4.07–4.11 (m, 1 H), 4.27 (s, 2 H), 5.11–5.17 (m, 2 H), 7.32–7.36 (m, 5 H) ppm; enol: δ = 3.78 (s, 3 H), 3.88–3.98 (m, 1 H), 4.07–4.11 (m, 2 H), 4.27 (s, 1 H), 5.11–5.17 (m, 2 H), 7.32–7.36 (m, 5 H), 10.01 (s, 1 H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$), ketone: δ = 48.54 (CH_2), 50.94 (CH_2), 51.45 (CH), 52.85 (CH_2), 67.44 (CH_2), 127.86 (CH), 128.00 (2 CH), 128.41 (2 CH), 135.98 (C), 154.38 (C), 167.64 (C), 203.45 (C) ppm; enol: δ = 48.79 (CH_2), 51.28 (CH_2), 51.38 (CH_3), 67.07 (CH_2), 96.87 (C), 128.00 (2 CH), 128.20 (CH), 127.47 (2 CH), 136.34 (C), 154.29 (C), 166.80 (C), 167.50 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3274 (m, br.), 2956 (w), 2934 (w), 2891 (w), 2869 (w), 1699 (s), 1682 (s), 1641 (m), 1456 (m), 1425 (m), 1365 (m), 1329 (m), 1224 (m), 1217 (m), 1121 (s), 1045 (m), 767 (m), 730 (s), 690 (m) cm^{-1}. HRMS (CI, isobutane): calcd. for $C_{14}H_{16}NO_5$ [M + H$^+$] 278.1028; found 278.1022.

Diethyl 3,3′-Oxydipropanoate (14): EtOH (1.49 g, 32.4 mmol) and conc. H_2SO_4 (128 mg, 1.30 mmol) were added to a solution of acid **13** (1.05 g, 6.48 mmol) in $CHCl_3$ (30 mL) and the mixture was stirred for 20 h in an inverse Dean–Stark trap under reflux. The organic phase was washed with water (20 mL) and brine (20 mL) and then dried ($MgSO_4$), filtered and evaporated to yield ester **14** (705 mg, 3.23 mmol, 50%) after chromatography (SiO_2, hexane/MTBE = 2:1, R_f = 0.35) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.23 (t, J = 7.1 Hz, 6 H), 2.53 (t, J = 6.4 Hz, 4 H), 3.69 (t, J = 6.4 Hz, 4 H), 4.11 (q, J = 7.1 Hz, 4 H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 14.15 (2 CH_3), 35.01 (2 CH_2), 60.46 (2 CH_2), 66.33 (2 CH_2), 171.48 (2 C) ppm. IR (ATR): $\tilde{\nu}$ = 2982 (w), 2935 (w), 2905 (w), 2876 (w), 1731 (s), 1373 (m), 1258 (m), 1181 (s), 1111 (m), 1063 (m), 1029 (m) cm^{-1}. HRMS (CI, isobutane): calcd. for $C_{10}H_{19}O_5$ [M + H$^+$] 219.1232; found 219.1231.

Ethyl 4-Oxotetrahydro-2*H*-pyran-3-carboxylate (10h): *n*BuLi (1.6 mol/L hexane, 16.5 mL, 26.4 mmol) was added at –78 °C under an inert atmosphere (N_2) to a solution of anhydrous *i*Pr_2NH (2.67 g, 26.4 mmol) in absolute THF (24 mL) and afterwards the mixture was stirred at 0 °C for 15 min. This solution was then added at –78 °C to a solution of diester **14** (2.95 g, 13.5 mmol) in absolute THF (36 mL) and stirring was continued for 15 min. After warming to ambient temperature, water (40 mL), hydrochloric acid (100 mL, 1 mol/L) and hexane (40 mL) were added and the layers were separated. The aqueous phase was extracted with EtOAc (3 × 50 mL) and the combined organic extracts were dried ($MgSO_4$), filtered and the solvent was evaporated to yield β-oxo ester **10h** (422 mg, 2.45 mmol, 18%) after chromatography (SiO_2, hexane/MTBE = 5:1, R_f = 0.38) as a colorless liquid. A double signal set is observed owing to keto-enol-tautomers (ratio 0.30:1.0). ^{1}H NMR (500 MHz, $CDCl_3$), ketone: δ = 1.27 (t, J = 7.1 Hz, 3 H), 2.50–2.55 (m, 1 H), 2.63–2.68 (m, 1 H), 3.44 (t, J = 5.9 Hz, 1 H), 3.93–4.01 (m, 2 H), 4.07 (dd, J = 11.6 Hz, J = 4.9 Hz, 1 H) 4.18–4.22 (m, 3 H) ppm; enol: δ = 1.27 (t, J = 7.1 Hz, 3 H), 2.35–2.37 (m, 2 H), 3.82 (t, J = 5.5 Hz, 2 H), 4.18–4.22 (m, 2 H), 4.25 (s, 2 H), 11.82 (s, 1 H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$), ketone: δ = 14.09 (CH_3), 42.05 (CH_2), 57.87 (CH), 61.56 (CH_2), 68.22 (CH_2), 69.70 (CH_2), 167.80 (C), 201.43 (C) ppm; enol: δ = 14.24 (CH_3), 28.76 (CH_2), 60.35 (CH_2), 63.05 (CH_2), 63.97 (CH_2), 97.43 (C), 168.84 (C), 170.15 (C) ppm. IR (ATR): $\tilde{\nu}$ = 2980 (w), 2938 (w), 2915 (w), 2856 (w), 1739 (w), 1719 (m), 1661 (s), 1628 (m), 1403 (w), 1368 (w), 1306 (s), 1285 (m), 1240 (m), 1218 (s), 1193 (m), 1100 (m), 1052 (m), 722 (w), 630 (m) cm^{-1}. HRMS (CI, isobutane): calcd. for $C_8H_{13}O_4$ [M + H$^+$] 173.0814; found 173.0811.

2-Bromo-1-(2,4-dimethoxyphenyl)ethanone (11o): Anhydrous $AlCl_3$ (995 mg, 7.46 mmol) was added to a solution of 1,3-dimethoxybenzene (1.03 g, 7.46 mmol) in bromoacetyl bromide (1.51 g, 7.46 mmol) and the mixture was stirred for 1 h at 23 °C. Water (20 mL) was carefully added and the aqueous phase was extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with hydrochloric acid (40 mL, 1 mol/L), then dried ($MgSO_4$), filtered and the solvent was evaporated. Chromatography [hexane/MTBE = 10:1, then 3:1, R_f(hexane/MTBE = 10:1) = 0.11] gave phenacyl bromide **11o** (666 mg, 2.57 mmol, 34%) as a colorless solid. M.p. 103 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.85 (s, 3 H), 3.91 (s, 3 H), 4.55 (s, 2 H), 6.44 (d, J = 2.2 Hz, 1 H), 6.55 (dd, J = 2.2, J = 8.8 Hz, 1 H), 7.89 (d, J = 8.8 Hz, 1 H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 37.97 (CH_2), 55.62 (CH_3), 55.70 (CH_3), 98.23 (CH), 105.85 (CH), 117.84 (C), 133.82 (CH), 160.88 (C), 165.37 (C), 190.16 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3013 (w), 2979 (w), 2948 (w), 1661 (s), 1596 (m), 1574 (m), 1453 (m), 1334 (m), 1275 (s), 1212 (m), 1182 (s), 1112 (m), 1020 (s), 992 (m), 828 (m), 633 (m) cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%) = 258 (5) [M$^+$], 165 (100), 137 (4), 121 (8), 106 (9), 77 (12).

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C{^{1}H} NMR spectra of all products.

Acknowledgments

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