Synthesis I. Geibel et al. Feature

Formation of Bicyclic Cyclopentenone Derivatives by Robinson-Type Annulation of Cyclic β-Oxoesters Containing a 1,4-Diketone Moiety

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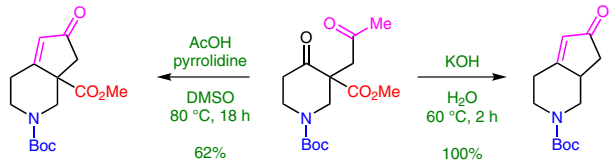

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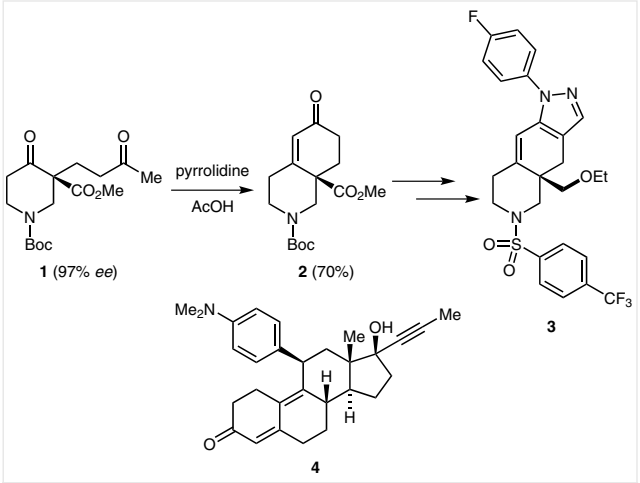
Abstract Robinson-type cyclopentannulations of cyclic β-oxoesters possessing a 1,4-diketone moiety are accomplished under four different Brønsted basic reaction conditions. Using pyrrolidine/acetic acid in DMSO, an oxohexahydrocyclopenta[*a*]indene (42%) and an *N*-Boc-protected oxohexahydrocyclopenta[*c*]pyridine derivative (62%) are obtained with retention of the ester moieties. The latter compound defines an interesting new scaffold for medicinal chemistry with three positions allowing further derivatizations. The use of KO*t*Bu in DMSO or NaH in toluene leads to cyclopentene derivatives with either partial ester saponification and decarboxylation or displacement of the ester moiety within the carbon skeleton. With aqueous KOH, the cyclopentannulations are successful in almost all cases, but with the ester moieties cleaved off. The respective bicyclic and tricyclic products are obtained in good to excellent yields. The 1,4-diketone starting materials are prepared by cerium-catalyzed oxidative coupling of β-oxoesters with isopropenyl acetate. Alternatively, a two-step sequence consisting of α-propargylation followed by palladium-catalyzed alkyne hydration is used.

Keywords heterocyclic compounds, piperidine derivatives, cyclopentenone, Robinson annulation, ketones, diketones, alicyclic compounds, bicyclic compounds, alkyne hydration

Since its first report in 1935,[1] the synthesis of cyclohexenone derivatives from 1,5-diketones via an intramolecular aldol reaction has been one of the most widely used tools in organic chemistry and was consequently named Robinson annulation in honor of its inventor.[2] Selected from the myriad examples in the literature, the synthesis of octahydroisoquinolone **2** from 1,5-diketone **1** is shown in Scheme 1.[3] Compound **2** is the intermediate product for the preparation of CORT 108297 (**3**).[4] Starting from compound **2**, a sulfonamide moiety was introduced after *N*-Boc deprotection, the ethyl ester group was reduced, the resulting primary alcohol alkylated and a pyrazole annulated to the B-ring. CORT 108297 (**3**) is a new and promising glucocorticoid receptor antagonist for the treatment of psychotic depressions.[5] The activity profile of compound **3** is comparable to that of mifepristone (**4**) (RU 486), however, the main advantage of CORT 108297 (**3**) is that it shows, in contrast to mifepristone (**4**), no progesterone receptor antagonism. Due to this adverse effect, mifepristone cannot be prescribed to pregnant patients.



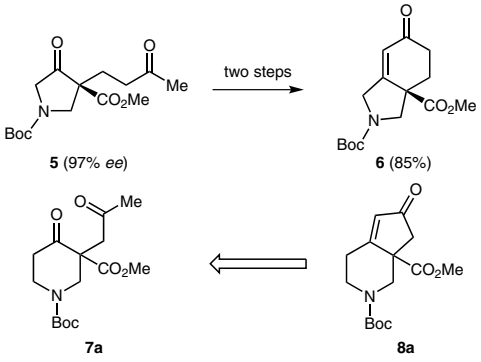
Scheme 1 Robinson annulation of heterocyclic 1,5-diketone **1** furnishing compound **2** as an intermediate product for the synthesis of CORT 108297 (**3**), and the structure of mifepristone (**4**) (RU 486)

Recently, we reported on the synthesis of hexahydroisoindole derivative **6** by Robinson annulation of pyrrolidine derivative **5** (Scheme 2), which can be regarded as the A-*nor* homologue of compound **2** and was therefore included in structure–activity investigations of derived A-*nor* homologues of CORT 108297 (**3**).[6] The objective of the study presented herein is the preparation of cyclopentannulated

piperidine **8a**, being the B-*nor* homologue of compound **2**, by intramolecular aldol reaction of piperidine derivative **7a** possessing a 1,4-diketone moiety. The targeted cyclopentapiperidine derivative **8a** is reasonably envisioned as a further intermediate product for related studies in a medicinal chemistry context. There is literature precedent for this kind of cyclopentannulation,[7] although the number of examples is not as extensive as for the Robinson annulation reaction to cyclohexenone derivatives. Examples of strongly basic reactions conditions for this transformation are NaH in toluene,[8] KO*t*Bu in DMSO,[9] and KOH in water or ethanol.[10]

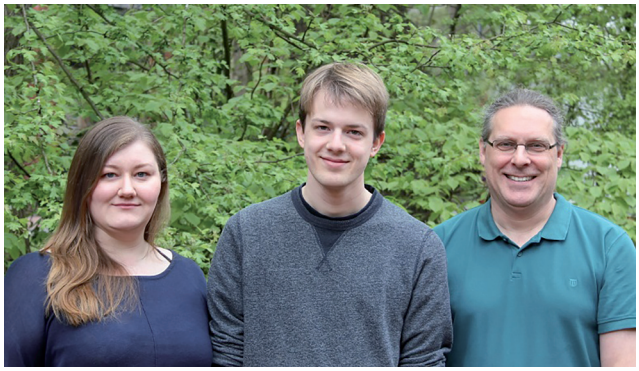
In addition to piperidine derivatives **7a** and **7b**, we also included other cyclic 1,4-diketones in our study, i.e., the alicyclic congeners **9a–d**, the indanone derivative **10** and the benzannulated representatives with a six-membered ring **11a** and **11b** (Figure 1). All the compounds shown in Figure 1 were racemates and were prepared according to two different pathways, as discussed in further detail below.

First of all, we investigated our standard conditions [polar protic (buffered) with pyrrolidine and AcOH (1 equiv each) in DMSO] that had already been successfully utilized for the Robinson annulation of 1,5-diketone **1** furnishing compound **2**. However, even after tedious variation of the reaction parameters: stoichiometry, temperature or the solvent, we were only successful in two cases (Scheme 3). Fortunately, the target reaction of this study proceeded to furnish the piperidine derivative **8a** in 62% yield. Changing the



Scheme 2 Robinson annulation of heterocyclic 1,5-diketone **5** and the projected preparation of cyclopentannulated piperidine **8a** from 1,4-diketone **7a**

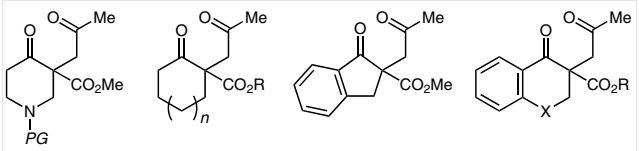
Biographical Sketches



Jens Christoffers (right) was born in 1966 and grew up in northern Germany. He received his diploma from Universität Marburg, Germany in 1992 before moving to Bonn, where he completed his doctorate in 1994 in the group of Professor K. H. Dötz. After a postdoctorate with Professor R. G. Bergman in Berkeley, USA, he joined the group of Professor S. Blechert at TU Berlin in 1996, where he finished his habilitation in 2000. From 2001 to 2006 he was Associate Professor at Universität Stuttgart, and since 2006 is a Full Professor at Universität Oldenburg. His current research interests are in the fields of heterocyclic chemistry and homogeneous catalysis with focus on catalytic oxidation reactions utilizing molecular oxygen.

Irina Geibel (left) was born in Maikain, Kazakhstan in 1986. She obtained her B.Sc. in chemistry from Universität Oldenburg in 2012, where she performed research with Professor Jürgen Martens in the field of multicomponent reactions. She received her M.Sc. with honors in 2014 and is currently finishing her Ph.D. in the group of Professor Christoffers. Her research is focused on cerium-catalyzed, oxidative C–C coupling reactions toward 1,4-diketones and δ-lactones as well as subsequent transformations of these products.

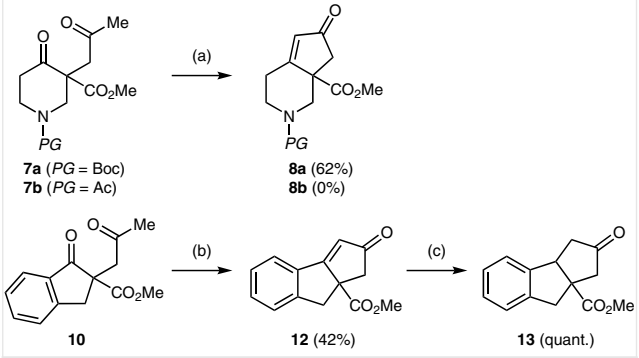
Christoph Kahrs (center) was born in 1993 in Germany. He received his B.Sc. in chemistry from Universität Oldenburg in 2014 in the group of Professor Jürgen Martens in the field of multicomponent reactions. He joined the group of Professor Christoffers in 2016 for his master's thesis, which he finished with honors. For his Ph.D. thesis, he is currently working in the field of functional coordination polymers based on sulfonic acids.



7a (*PG* = Boc) **7b** (*PG* = Ac) | **9a** (*n* = 0, R = Et) **9b** (*n* = 1, R = Et) **9c** (*n* = 2, R = Me) **9d** (*n* = 1, R = *t*Bu) | **10** | **11a** (X = CH_2, R = Et) **11b** (X = NAc, R = Me)

Figure 1 1,4-Diketones submitted to cyclopentannulation experiments

carbamate protecting group to *N*-acetyl in starting material **7b** resulted in unspecified decomposition under similar reaction conditions for unknown reasons. The other successful case was the cyclization of the indanone **10** furnishing cyclopentindene derivative **12**, also in fair yield. In the formation of products **8a** and **12**, the methoxycarboxyl group was retained, which was not always the case in the experiments presented below. The cyclopentene ring of compound **12** could be catalytically hydrogenated with the corresponding product **13** being obtained in quantitative yield. Needless to say, the relative configuration in this case must be *cis*, as is always the case for two annulated five-membered rings. Actually, the formation of compound **12** is a very interesting issue, since it is the only example of a product with two annulated five-membered rings from throughout this entire study.

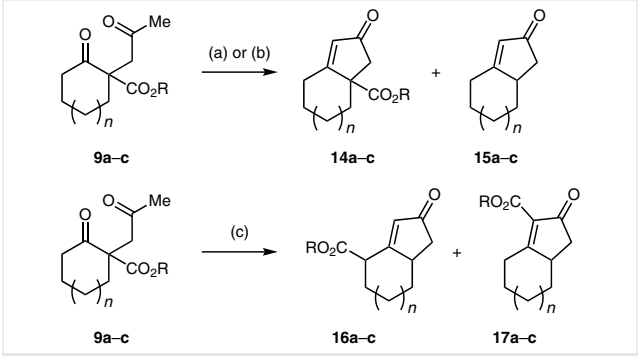


7a (*PG* = Boc) **7b** (*PG* = Ac) | **8a** (62%) **8b** (0%)

10 | **12** (42%) | **13** (quant.)

Scheme 3 Cyclopentannulation and subsequent catalytic hydrogenation. *Reagents and conditions*: (a) pyrrolidine (1.0 equiv), AcOH (1.0 equiv), DMSO, 80 °C, 18 h; (b) pyrrolidine (1.0 equiv), AcOH (1.0 equiv), DMSO, 100 °C, 18 h; (c) H_2 (2.5 atm), cat. Pd/C, EtOAc, 50 °C, 2 d.

We then turned our attention to other Brønsted basic reaction conditions that had precedent in the literature. First of all, we investigated the use of KO*t*Bu in DMSO,[9] which was performed with exclusion of moisture in order to prevent ester saponification, followed by decarboxylation. As a first albeit disappointing result, the conversion of piperidine derivatives **7a** and **7b** led to unspecified decomposition under these reaction conditions. The alicyclic congeners **9b** and **9c** gave annulation products, however, not chemoselectively (Scheme 4 and Table 1). Apart from the expected products **14b** (up to 51% yield) and **14c** (13–15%), the alkoxydecarboxylated compounds **15b** (up to 48%) and **15c** (up to 37%) were also obtained. We therefore decided to use NaH in toluene,[8] also under strictly anhydrous conditions. Now we indeed avoided alkoxydecarboxylation, but observed, for our purpose, a useless, but very remarkable result, which actually contradicts literature reports:[8b] while compounds **14b** and **14c** were not detectable, the constitutional isomers **16b**, **16c** and **17c** were obtained (see Table 1 for yields), where the alkoxycarbonyl moiety seemed to formally migrate within the carbon skeleton. Actually, this isomerization could be mechanistically interpreted as the result of a sequence of retro-Dieckmann and Dieckmann reactions. Anyhow, for the cyclopentanone derivative **9a**, none of the respective products **14a**, **15a**, **16a** or **17a** (with two annulated five-membered rings) could be isolated. Furthermore, reactions of the benzannulated starting materials **10**, **11a** and **11b** did not result in formation of the expected products under either of the conditions (a), (b) or (c).



9a–c | **14a–c** | **15a–c**

9a–c | **16a–c** | **17a–c**

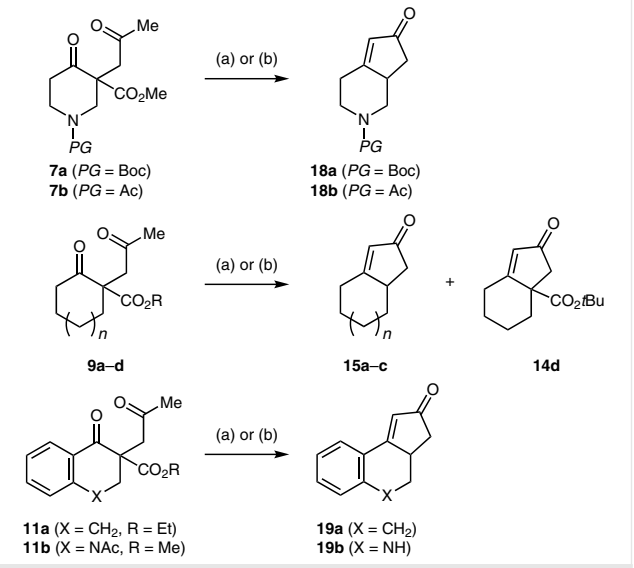
Scheme 4 Attempts toward the cyclization of alicyclic 1,4-diketones **9a–c**. *Reagents and conditions*: (a) KO*t*Bu (1.2 equiv), DMSO, 50 °C, 20 h; (b) KO*t*Bu (1.2 equiv), DMSO, 100 °C, 20 h; (c) NaH (4 equiv), toluene, 111 °C, 18 h; for n, R and yields see Table 1.

Table 1 Results of the Conversions of the Alicyclic Starting Materials Shown in Scheme 4

Starting material	Conditions[a]	Yield of **14**	Yield of **15**	Yield of **16**	Yield of **17**
9a (*n* = 0, R = Et)	(a), (b) or (c)	0%	0%	0%	0%
9b (*n* = 1, R = Et)	(a)	34%	48%	0%	0%
9b (*n* = 1, R = Et)	(b)	51%	8%	0%	0%
9c (*n* = 2, R = Me)	(a)	13%	37%	0%	0%
9c (*n* = 2, R = Me)	(b)	15%	4%	0%	0%
9b (*n* = 1, R = Et)	(c)	0%	0%	85%	0%
9c (*n* = 2, R = Me)	(c)	0%	0%	33%	35%

[a] For conditions (a), (b) and (c), see the caption to Scheme 4.

Finally, we attempted to achieve cyclopentannulation for all the starting materials collected in Figure 1 under strongly basic, protic conditions[10] by using aqueous KOH solution (15% w/w), although we expected that such conditions would result in saponification and decarboxylation in almost every case (Scheme 5). Both piperidine derivatives **7a** and **7b** were converted smoothly at 60 °C to furnish the two annulation products **18a** and **18b** in very good yields (100% and 92%, respectively) (Table 2, entries 1 and 2). At 120 °C, however, no unique products were isolable, presumably due to cleavage of the *N*-Boc and *N*-Ac moieties and subsequent reactions of the secondary amino function. In the aliphatic series, the cyclopentenone derivative **9a** did not give any unique product (entry 3). The six- and seven-membered homologues **9b** and **9c** gave cyclization products **15b** and **15c** with very good results at 120 °C (entries 4 and 5). At 60 °C, the yield for the seven-membered ring product **15c** was a little lower (64%) (entry 5). We also investigated whether a *tert*-butyl ester would be resistant toward saponification under these conditions. At 60 °C, the ester moiety was not preserved completely, and the product **14d** was obtained in only 17% yield (entry 6). At 120 °C, the *tert*-butyloxycarbonyl group was completely cleaved and compound **15b** was isolated in 97% yield, which is almost equal to that starting with ethyl ester **9b**. In the benzannulated series, the indanone derivative **10** gave no defined products. The six-membered tetralone **11a** and the tetrahydroquinoline derivative **11b** gave very good yields of products **19a**,**b** at both temperatures (entries 7 and 8). In the case of starting material **11b**, which is an aniline derivative, the *N*-acetyl group is cleaved off.



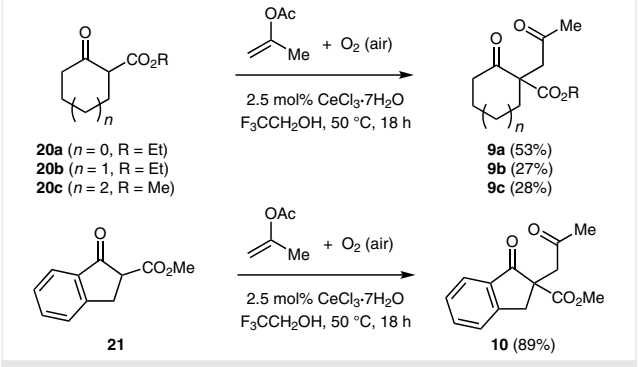
Scheme 5 Cyclization and dealkoxycarbonylation of 1,4-diketones **7**, **9** and **11** under strongly basic, protic conditions. *Reagents and conditions*: (a) 15% aqueous KOH, 60 °C, 2–9 h; (b) as (a), but 120 °C; for *PG*, *n*, R, X and yields see Table 2.

Table 2 Results of the Conversions of the 1,4-Diketones Shown in Scheme 5

Entry	Starting material	Conditions (a)[a] Main/By-product (yield)	Conditions (b)[a] Product (yield)
1	**7a** (*PG* = Boc)	**18a** (100%)	**18a** (0%)
2	**7b** (*PG* = Ac)	**18b** (92%)	**18b** (0%)
3	**9a** (*n* = 0, R = Et)	**15a** (0%)	**15a** (0%)
4	**9b** (*n* = 1, R = Et)	**15b** (95%)	**15b** (95%)
5	**9c** (*n* = 2, R = Me)	**15c** (64%)	**15c** (91%)
6	**9d** (*n* = 1, R = *t*Bu)	**15b** (79%)/**14d** (17%)	**15b** (97%)
7	**11a** (X = CH_2, R = Et)	**19a** (97%)[b]	**19a** (94%)[c]
8	**11b** (X = NAc, R = Me)	**19b** (65%)[d]	**19b** (61%)[e]

[a] For conditions (a) and (b) see the caption to Scheme 5. The reaction time was generally 2 h; for exceptions, see footnotes b–e.
[b] Time: 6 h.
[c] Time: 9 h.
[d] Time: 8 h.
[e] Time: 5 h.

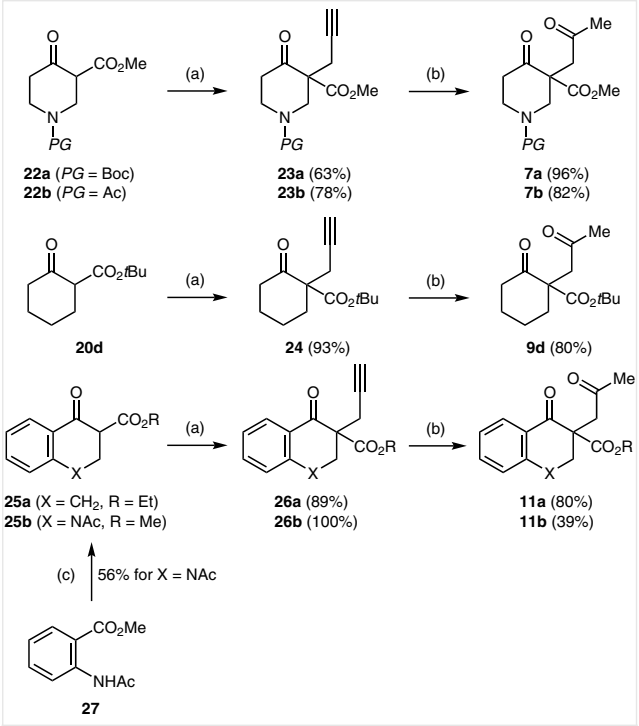
As mentioned above, the starting materials depicted in Figure 1 were accessed according to two different routes. The first method used the cerium-catalyzed aerobic coupling of β-oxoesters **20** and **21** with isopropenyl acetate furnishing the 1,4-diketones **9** and **10** (Scheme 6). This new reaction was recently developed by us and can be regarded as an oxidative Umpolung.[11]



Scheme 6 Cerium-catalyzed aerobic coupling of β-oxoesters **20** and **21** with isopropenyl acetate furnishing 1,4-diketones **9** and **10**

Since the above-mentioned one-step method did not give reliable results in every case, we have also chosen an alternative two-step protocol, which was less atom economic and more cost intensive. The first step was the alkylation of the respective β-oxoesters **20d**, **22a**,**b**, and **25a**,**b** with propargyl bromide and K_2CO_3 in acetone (Scheme 7), which gave the appropriate α-propargylated compounds **23a**,**b**, **24**, and **26a**,**b** in good to excellent yields (63–100%).[12] Compound **25b** was previously unknown and prepared by annulation (conjugated addition to methyl acrylate and subsequent Dieckmann condensation) of *N*-acetyl anthrani-

late **27**. The second step was the catalytic alkyne hydration, which is nowadays often reported with very popular gold catalysts.[13] However, in our hands, gold catalysis led to unsatisfying results. The same is also true for the use of thulium triflate [$Tm(OTf)_3$], as reported recently,[14] that did not yield preparatively useful amounts of the 1,4-diketones in our cases. Nevertheless, we eventually came across a report by Xu et al.,[15] who recommended $PdCl_2$ as catalyst for the hydration of alkynylphosphonates. Indeed, using their procedure, the 1,4-diketones **7a**,**b**, **9d**, and **11a** could be obtained in yields of 80–96%. Only isoquinoline derivative **11b** gave a poorer result (39% yield).



Scheme 7 Synthesis of 1,4-diketones in two steps via α-propargyl derivatives. *Reagents and conditions*: (a) $BrCH_2C{\equiv}CH$ (2.0 equiv), K_2CO_3 (1.2 equiv), acetone, 60 °C, 2–6 h; (b) $PdCl_2$ (2 mol%), H_2O in 1,4-dioxane, 80 °C, 10 min to 8 h; (c) $CH_2{=}CHCO_2Me$ (1.1 equiv), KO*t*Bu (1.1 equiv), THF, 23 °C, 3 d. For detailed reaction times of the procedures (a) and (b), see the experimental section.

In conclusion, we have prepared cyclic oxoesters with a 1,4-dicarbonyl unit following two different routes, and subsequently submitted them to intramolecular aldol condensation furnishing bicyclic and tricyclic cyclopentenone derivatives. First of all, 1,4-diketones **9a–c**, and **10** were prepared in 27–89% yields by cerium-catalyzed aerobic coupling of oxoesters **20a–c** and **21** with isopropenyl acetate, following an oxidative Umpolung strategy reported by us recently.[11] Alternatively, although requiring more work and being cost intensive, 1,4-diketones **7a**,**b**, **9d**, and **11a**,**b** were prepared in two steps by α-propargylation of oxoesters **20d**, **22a**,**b**, and **25a**,**b** furnishing the alkynes **23a**,**b**, **24**, and **26a**,**b** as intermediate products (yields of 63–100%), which were subsequently submitted to palladium-catalyzed hydration (yields of 39–96%).

We then turned to the annulation reactions and used a protocol (pyrrolidine and acetic acid in DMSO) that had been successfully applied before for the cyclohexenone annulation of the respective 1,5-diketone **5**.[3] We were able to cyclize the *N*-Boc protected compound **7a** yielding the cyclopentapiperidine **8a** (62%) with the ester moiety preserved, which is an important result, as this compound could be a synthetic precursor of the B-*nor* analogue of CORT 108297 (**3**) and therefore was the actual target compound of our study. With a more general view, compound **8a** holds three functionalities allowing for further derivatizations and defines therefore a new scaffold for lead discovery in medicinal chemistry. Nevertheless, this result seems to be a little fortunate, because neither the *N*-acetyl congener **7b** nor the other 1,4-diketones **9a–d** and **11a**,**b** gave cyclization products under these reaction conditions. An exception was the preparation of the tricyclic product **12** (42%) from indanone derivative **10**, which is the only compound accessed by us via annulation of two five-membered rings. When using a stronger Brønsted base, albeit under aprotic (and anhydrous) reaction conditions, as were KO*t*Bu in DMSO or NaH, the alkoxycarbonyl groups were either to some extent cleaved and subsequently decarboxylated (products **15b**,**c**, 37–48%) or were displaced within the carbon skeleton (products **16b**,**c** in yields of 85% and 33%, and compound **17c** in 35% yield), most probably due to a sequence of retro-Dieckmann and Dieckmann processes. We finally decided to intentionally accept ester saponification and decarboxylation and conducted the cyclizations in aqueous KOH. Indeed, we obtained the corresponding bicyclic products **18a**,**b**, **15b**,**c**, and the tricyclic products **19a**,**b** without alkoxycarbonyl moieties in good to excellent yields.

Compounds **20d**,[16] **22b**,[17] and **27**[18] are known in the literature and were prepared according to the published procedures. The syntheses of oxoesters **21**,[11] **25a**,[11] **22a**,[3] and 1,4-diketones **9a**,[11] **9b**,[11] **9c**[11] and **10**[11] were reported by us earlier. All other starting materials were commercially available. Preparative column chromatography was carried out using Merck SiO_2 (35–70 µm, type 60 A) with hexanes, *tert*-butyl methyl ether (MTBE), EtOH and MeOH as eluents. TLC was performed on Merck aluminum plates coated with SiO_2 F_{254}. Melting points were recorded using a Gallenkamp apparatus. IR spectra were recorded on a Bruker Tensor 27 spectrophotometer equipped with a 'GoldenGate' diamond ATR unit. ^1H and ^{13}C NMR spectra were recorded on Bruker Avance DRX 500 and 300 instruments. Multiplicities of carbon signals were determined with DEPT experiments. HRMS spectra were obtained with a Waters Q-TOF Premier (ESI) spectrometer.

Pd-Catalyzed Hydration; General Procedure A (GP A)

$PdCl_2$ (2 mol%) and H_2O (50 g/mol) were added to a solution of α-propargyl-β-oxo ester (1.0 equiv) in 1,4-dioxane (3 L/mol) and the resulting mixture was stirred for 10 min to 8 h at 80 °C. The solvent was removed in vacuo and the crude product purified by column chromatography to give the respective 1,4-diketone.

1-*tert*-Butyl 3-Methyl 4-Oxo-3-(2-oxopropyl)piperidine-1,3-dicarboxylate (7a)

According to GP A, a mixture of α-propargyl-β-oxo ester **23a** (310 mg, 1.05 mmol), $PdCl_2$ (4 mg, 21 µmol) and H_2O (3 drops, 66 mg) in 1,4-dioxane (3 mL) was heated at 80 °C for 30 min. The crude mixture was purified by column chromatography (SiO_2, MTBE, R_f = 0.44) to yield the title compound **7a** (316 mg, 1.01 mmol, 96%) as a colorless oil. The NMR spectra showed partly broadened and doubled signal sets due to the carbamate moiety.

IR (ATR): 2999 (w), 2958 (w), 2903 (w), 1694 (vs), 1471 (m), 1427 (m), 1365 (m), 1294 (w), 1248 (m), 1230 (m), 1163 (vs), 1098 (w), 1072 (m), 971 (m), 893 (m), 869 (w), 733 (w) cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.37 (s, 9 H), 2.09 (s, 3 H), 2.41 (dt, *J* = 15.6 Hz, *J* = 4.0 Hz, 1 H), 2.77 (d, *J* = 18.0 Hz, 1 H), 2.73–2.85 (m, 1 H), 2.92–3.08 (m, 1 H), 3.19–3.41 (m, 1 H), 3.28 (ddd, *J* = 13.4 Hz, *J* = 10.6 Hz, *J* = 4.4 Hz, 1 H), 3.56–3.66 (m, 3 H), 4.01–4.11 (m, 1 H), 4.21–4.35 (m, 1 H).

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 28.01 (3 CH_3), 29.76 (CH_3), 39.14 (CH_2), 42.28 (1/2 CH_2), 43.24 (1/2 CH_2), 44.64 (1/2 CH_2), 44.74 (1/2 CH_2), 49.45 (1/2 CH_2), 49.84 (1/2 CH_2), 52.54 (CH_3), 57.96 (1/2 C), 58.34 (1/2 C), 80.22 (C), 153.73 (1/2 C), 154.07 (1/2 C), 170.38 (C), 204.02 (1/2 C), 204.19 (1/2 C), 204.36 (1/2 C), 204.55 (1/2 C).

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{15}H_{23}NNaO_6$: 336.1418; found: 336.1421.

Methyl 1-Acetyl-4-oxo-3-(2-oxopropyl)piperidine-3-carboxylate (7b)

According to GP A, a mixture of α-propargyl-β-oxo ester **23b** (1.00 g, 4.21 mmol), $PdCl_2$ (15 mg, 84 µmol) and H_2O (9 drops, 204 mg) in 1,4-dioxane (15 mL) was heated at 80 °C for 3 h. The crude mixture was purified by column chromatography (SiO_2, MTBE/MeOH, 16:3, R_f = 0.22) to yield the title compound **7b** (880 mg, 3.45 mmol, 82%) as a colorless oil. The NMR spectra showed doubled signal sets due to rotamers (ratio 3:2).

IR (ATR): 3057 (w), 2984 (w), 2954 (w), 1715 (vs), 1650 (vs), 1432 (s), 1364 (m), 1266 (s), 1227 (m), 1171 (m), 1099 (w), 1046 (w), 1018 (w) cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ (major rotamer) = 2.01 (s, 3 H), 2.05 (s, 3 H), 2.38 (dt, *J* = 15.5 Hz, *J* = 3.8 Hz, 1 H), 2.58 (ddd, *J* = 15.4 Hz, *J* = 11.3 Hz, *J* = 6.8 Hz, 1 H), 2.79 (d, *J* = 18.0 Hz, 1 H), 2.89 (d, *J* = 18.0 Hz, 1 H), 2.98–3.16 (m, 1 H), 3.45–3.53 (m, 1 H), 3.57 (s, 3 H), 4.17 (dd, *J* = 13.9 Hz, *J* = 2.6 Hz, 1 H), 4.47 (ddt, *J* = 13.0 Hz, *J* = 6.4 Hz, *J* = 3.0 Hz, 1 H); δ (minor rotamer) = 2.01 (s, 3 H), 2.03 (s, 3 H), 2.46 (dt, *J* = 15.7 Hz, *J* = 4.1 Hz, 1 H), 2.51–2.62 (m, 1 H), 2.73 (d, *J* = 18.2 Hz, 1 H), 2.82 (ddd, *J* = 17.3 Hz, *J* = 10.0 Hz, *J* = 6.0 Hz, 1 H), 2.98–3.16 (m, 2 H), 3.51 (s, 3 H), 3.86 (ddt, *J* = 13.2 Hz, *J* = 6.4 Hz, *J* = 2.9 Hz, 1 H), 4.59 (dd, *J* = 13.4 Hz, *J* = 2.3 Hz, 1 H).

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ (major rotamer) = 20.54 (CH_3), 29.85 (CH_3), 38.77 (CH_2), 40.37 (CH_2), 44.36 (CH_2), 51.22 (CH_2), 52.76 (CH_3), 58.49 (C), 169.26 (C), 169.97 (C), 202.46 (C), 204.53 (C); δ (minor rotamer) = 20.64 (CH_3), 29.53 (CH_3), 39.02 (CH_2), 44.56 (CH_2), 44.70 (CH_2), 47.01 (CH_2), 52.47 (CH_3), 57.62 (C), 169.12 (C), 170.05 (C), 203.23 (C), 204.58 (C).

HRMS (ESI): *m*/*z* $[M + Li]^+$ calcd for $C_{12}H_{17}LiNO_5$: 262.1261; found: 262.1257.

***tert*-Butyl 2-Oxo-1-(2-oxopropyl)cyclohexane-1-carboxylate (9d)**

According to GP A, a mixture of α-propargyl-β-oxo ester **24** (900 mg, 3.81 mmol), $PdCl_2$ (14 mg, 76 µmol) and H_2O (8 drops, 184 mg) in 1,4-dioxane (12 mL) was heated at 80 °C for 10 min. The crude mixture was purified by column chromatography (SiO_2, hexanes/MTBE, 1:1, R_f = 0.39) to yield the title compound **9d** (778 mg, 3.06 mmol, 80%) as a light yellow oil.

IR (ATR): 2976 (w), 2938 (w), 2868 (w), 1710 (vs), 1450 (w), 1424 (w), 1367 (m), 1312 (w), 1270 (w), 1146 (s), 1132 (s), 1079 (w), 949 (w), 845 (m), 735 (m), 703 (w) cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.47 (s, 9 H), 1.64–1.75 (m, 4 H), 2.03 (ddt, *J* = 13.0 Hz, *J* = 6.4 Hz, *J* = 2.9 Hz, 1 H), 2.17 (s, 3 H), 2.32 (dt, *J* = 10.0 Hz, *J* = 3.1 Hz, 1 H), 2.41–2.47 (m, 1 H), 2.73–2.78 (m, 1 H), 2.78 (d, *J* = 17.2 Hz, 1 H), 2.82 (d, *J* = 17.1 Hz, 1 H).

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 21.98 (CH_2), 26.80 (CH_2), 27.85 (3 CH_3), 30.40 (CH_3), 36.79 (CH_2), 40.44 (CH_2), 48.25 (CH_2), 59.98 (C), 82.24 (C), 170.84 (C), 205.40 (C), 207.56 (C).

HRMS (ESI): *m*/*z* $[M + Li]^+$ calcd for $C_{14}H_{22}LiO_4$: 261.1673; found: 261.1680.

Ethyl 2-(2-Oxopropyl)-1-tetralone-2-carboxylate (11a)

According to GP A, a mixture of α-propargyl-β-oxo ester **26a** (475 mg, 1.85 mmol), $PdCl_2$ (7 mg, 37 µmol) and H_2O (4 drops, 89 mg) in 1,4-dioxane (5 mL) was heated at 80 °C for 2 h. The crude mixture was purified by column chromatography (SiO_2, hexanes/MTBE, 1:1, R_f = 0.29) to yield the title compound **11a** (407 mg, 1.48 mmol, 80%) as a colorless oil.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.13 (t, *J* = 7.1 Hz, 3 H), 2.22 (s, 3 H), 2.42 (ddd, *J* = 13.5 Hz, *J* = 5.1 Hz, *J* = 4.1 Hz, 1 H), 2.47 (ddd, *J* = 13.8 Hz, *J* = 11.4 Hz, *J* = 4.8 Hz, 1 H), 2.87 (dt, *J* = 17.3 Hz, *J* = 4.4 Hz, 1 H), 2.99 (d, *J* = 17.4 Hz, 1 H), 3.05 (ddd, *J* = 16.9 Hz, *J* = 11.5 Hz, *J* = 5.5 Hz, 1 H), 3.08 (d, *J* = 17.4 Hz, 1 H), 4.10–4.19 (m, 2 H), 7.20 (d, *J* = 7.7 Hz, 1 H), 7.30 (t, *J* = 7.6 Hz, 1 H), 7.45 (td, *J* = 7.5 Hz, *J* = 1.4 Hz, 1 H), 8.01 (dd, *J* = 7.9 Hz, *J* = 1.4 Hz, 1 H).

The data were in accordance with literature values.[11]

Methyl 1-Acetyl-4-oxo-3-(2-oxopropyl)-1,2,3,4-tetrahydroquinoline-3-carboxylate (11b)

According to GP A, a mixture of α-propargyl-β-oxo ester **26b** (500 mg, 1.72 mmol), $PdCl_2$ (6 mg, 34 µmol) and H_2O (4 drops, 92 mg) in 1,4-dioxane (8 mL) was heated at 80 °C for 8 h. The crude mixture was purified by column chromatography (SiO_2, MTBE, R_f = 0.22) to yield the title compound **11b** (203 mg, 0.67 mmol, 39%) as a colorless oil. NMR spectra showed partly broadened signal sets due to the amide moiety.

IR (ATR): 2955 (w), 2923 (w), 2853 (w), 1737 (m), 1720 (m), 1672 (vs), 1601 (m), 1480 (m), 1462 (m), 1379 (m), 1293 (w), 1243 (m), 1213 (m), 1171 (w), 1123 (w), 1083 (w), 961 (w), 765 (m) cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 2.14 (s, 3 H), 2.25 (s, 3 H), 3.07 (d, *J* = 18.4 Hz, 1 H), 3.24 (d, *J* = 18.4 Hz, 1 H), 3.62 (s, 3 H), 4.19 (d, *J* = 13.5 Hz, 1 H), 4.65–4.78 (m, 1 H), 7.24 (t, *J* = 7.9 Hz, 1 H), 7.48–7.56 (m, 2 H), 7.97 (dt, *J* = 7.9 Hz, *J* = 1.1 Hz, 1 H).

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 22.71 (CH_3), 29.98 (CH_3), 44.86 (CH_2), 49.66 (CH_2), 52.95 (CH_3), 56.57 (C), 123.98 (CH), 124.90 (C), 125.41 (CH), 128.17 (CH), 134.14 (CH), 143.26 (C), 169.88 (C), 170.10 (C), 191.17 (C), 204.71 (C).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{18}NO_5$: 304.1179; found: 304.1174.

2-*tert*-Butyl 7a-Methyl 6-Oxo-2,3,4,6,7,7a-hexahydro-1*H*-cyclopenta[*c*]pyridine-2,7a-dicarboxylate (8a)

A solution of pyrrolidine (46 mg, 0.64 mmol), glacial AcOH (38 mg, 0.64 mmol) and 1,4-diketone **7a** (199 mg, 0.64 mmol) in DMSO (1.5 mL) was heated for 18 h at 80 °C in a tightly closed reaction vial. After cooling to ambient temperature, the mixture was diluted with brine (30 mL) and extracted with MTBE (2 × 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered and the solvent was removed in vacuo. The residue was purified by column chromatography (SiO_2, MTBE, R_f = 0.43) to yield the title compound **8a** (117 mg, 0.40 mmol, 62%) as a yellow oil.

IR (ATR): 2978 (w), 2895 (w), 2863 (w), 1703 (s), 1696 (vs), 1629 (m), 1422 (m), 1365 (m), 1311 (w), 1292 (w), 1274 (w), 1238 (m), 1199 (w), 1165 (s), 1123 (m), 1050 (w), 1036 (w), 956 (w), 898 (w), 847 (w) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.46 (s, 9 H), 2.26 (d, *J* = 18.8 Hz, 1 H), 2.49–2.91 (m, 5 H), 3.70 (s, 3 H), 4.26–4.59 (m, 1 H), 4.94 (d, *J* = 13.1 Hz, 1 H), 6.03 (s, 1 H).

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 28.21 (3 CH_3), 29.52 (CH_2), 43.51 (CH_2), 43.75 (CH_2), 52.70 (CH_3), 53.20 (CH_2), 53.87 (C), 80.44 (C), 129.47 (CH), 153.87 (C), 171.88 (C), 177.26 (C), 204.45 (C).

HRMS (ESI): *m*/*z* [M + Li]$^+$ calcd for $C_{15}H_{21}LiNO_5$: 302.1574; found: 302.1584.

Methyl 2-Oxo-1,2,8,8a-tetrahydrocyclopenta[*a*]indene-8a-carboxylate (12)

A solution of pyrrolidine (100 mg, 1.40 mmol), glacial AcOH (85 mg, 1.40 mmol) and 1,4-diketone **10** (346 mg, 1.41 mmol) in DMSO (3 mL) was heated for 18 h at 100 °C in a tightly closed reaction vial. After cooling to ambient temperature, the mixture was diluted with brine (10 mL) and extracted with MTBE (2 × 5 mL). The combined organic extracts were dried ($MgSO_4$), filtered and the solvent was removed in vacuo. The residue was purified by column chromatography (SiO_2, hexanes/MTBE, 1:1, R_f = 0.31) to yield the title compound **12** (135 mg, 0.59 mmol, 42%) as a red oil.

IR (ATR): 2972 (w), 2953 (w), 1730 (s), 1707 (vs), 1626 (s), 1197 (s), 1166 (s), 755 (s), 729 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.64 (d, *J* = 16.8 Hz, 1 H), 2.92 (d, *J* = 15.4 Hz, 1 H), 2.98 (d, *J* = 16.8 Hz, 1 H), 3.61 (s, 3 H), 3.84 (d, *J* = 15.4 Hz, 1 H), 6.26 (s, 1 H), 7.32–7.34 (m, 1 H), 7.39–7.47 (m, 2 H), 7.59 (d, *J* = 7.6 Hz, 1 H).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 39.59 (CH_2), 47.82 (CH_2), 53.06 (CH_3), 62.15 (C), 121.65 (CH), 124.55 (CH), 125.74 (CH), 127.63 (CH), 132.32 (CH), 133.44 (C), 147.71 (C), 173.23 (C), 180.38 (C), 207.62 (C).

HRMS (ESI): *m*/*z* [M + Li]$^+$ calcd for $C_{14}H_{12}LiO_3$: 235.0941; found: 235.0938.

Methyl 2-Oxo-1,2,3,3a,8,8a-hexahydrocyclopenta[*a*]indene-8a-carboxylate (13)

A mixture of Pd/C (10% w/w, 3 mg), enone **12** (25 mg, 0.11 mmol) and EtOAc (10 mL) was stirred under a H_2 atmosphere (2.5 bar) for 48 h at 50 °C. After filtration through SiO_2 [MTBE, R_f = 0.36 (hexanes/MTBE, 2:1)], the title compound **13** (25 mg, 0.11 mmol, 100%) was isolated as a colorless oil.

IR (ATR): 2954 (w), 2927 (w), 2859 (w), 1729 (vs), 747 (s) cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.22 (d, *J* = 18.7 Hz, 1 H), 2.67 (d, *J* = 19.1 Hz, 1 H), 2.88–2.94 (m, 2 H), 3.08 (d, *J* = 16.1 Hz, 1 H), 3.75 (d, *J* = 16.1 Hz, 1 H), 3.80 (s, 3 H), 4.13 (d, *J* = 8.9 Hz, 1 H), 7.17–7.19 (m, 1 H), 7.25–7.29 (m, 3 H).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 41.29 (CH_2), 42.71 (CH_2), 46.90 (CH_2), 50.50 (CH), 52.54 (CH_3), 56.18 (C), 124.46 (CH), 125.26 (CH), 127.44 (CH), 127.75 (CH), 140.49 (C), 143.03 (C), 175.80 (C), 215.83 (C).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{14}NaO_3$: 253.0835; found: 253.0830.

Annulation Using KO*t*Bu in DMSO; General Procedure B (GP B)

Under an anhydrous and inert atmosphere (N_2), a solution of KO*t*Bu (1.2 equiv) and 1,4-diketone **9b** or **9c** (1 equiv) in anhydrous DMSO (8 L/mol) was stirred for 20 h at the temperature given below. After cooling to ambient temperature, the mixture was acidified with HCl (10%, ca. 3 L/mol) to pH 4 and extracted with MTBE (3 × 25 L/mol). The combined organic layers were washed with brine (40 L/mol) and H_2O (40 L/mol), dried ($MgSO_4$), filtered and the solvent was removed in vacuo. The residue was purified by column chromatography (SiO_2, hexanes/MTBE, 1:2) to yield the indenone-carboxylate **14b** or **14c** in the first fraction and the indenone **15b** or **15c** in the second fraction.

Ethyl 2-Oxo-3,3a,4,5,6,7-hexahydro-2*H*-indene-3a-carboxylate (14b)

KO*t*Bu (37 mg, 0.33 mmol) and 1,4-diketone **9b** (62 mg, 0.27 mmol) in anhydrous DMSO (3 mL) were reacted according to GP B at 100 °C to furnish compound **14b** (29 mg, 0.14 mmol, 51%) in the first fraction (SiO_2, hexanes/MTBE, 1:2, R_f = 0.44) as a colorless oil. Secondly, product **15b** (3 mg, 22 µmol, 8%) was eluted (R_f = 0.36) as a light yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.25 (t, *J* = 7.1 Hz, 3 H), 1.32 (td, *J* = 13.3 Hz, *J* = 3.8 Hz, 1 H), 1.40 (qt, *J* = 13.2 Hz, *J* = 4.0 Hz, 1 H), 1.54 (qt, *J* = 13.6 Hz, *J* = 3.5 Hz, 1 H), 1.74–1.79 (m, 1 H), 1.98–2.04 (m, 1 H), 2.28 (d, *J* = 18.7 Hz, 1 H), 2.39 (tdd, *J* = 13.5 Hz, *J* = 5.7 Hz, *J* = 1.7 Hz, 1 H), 2.64 (d, *J* = 18.7 Hz, 1 H), 2.68 (dq, *J* = 13.4, *J* = 2.9 Hz, 1 H), 2.79 (ddt, *J* = 13.6 Hz, *J* = 4.1 Hz, *J* = 1.9 Hz, 1 H), 4.13–4.22 (m, 2 H), 5.96 (d, *J* = 1.5 Hz, 1 H).

The data were in accordance with literature values.[19]

2,4,5,6,7,7a-Hexahydro-1*H*-inden-2-one (15b)

KO*t*Bu (49 mg, 0.44 mmol) and 1,4-diketone **9b** (83 mg, 0.37 mmol) in anhydrous DMSO (3 mL) were reacted according to GP B at 50 °C to furnish compound **14b** (26 mg, 0.13 mmol, 34%) in the first fraction (SiO_2, hexanes/MTBE, 1:2, R_f = 0.44) as a colorless oil. Secondly, product **15b** (24 mg, 0.18 mmol, 48%) was eluted (R_f = 0.36) as a light yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.12 (qd, *J* = 12.5 Hz, *J* = 3.4 Hz, 1 H), 1.35–1.57 (m, 2 H), 1.82–1.94 (m, 1 H), 1.97 (dd, *J* = 17.7 Hz, *J* = 6.5 Hz, 1 H), 2.01–2.05 (m, 1 H), 2.15–2.32 (m, 2 H), 2.57 (dd, *J* = 17.7 Hz, *J* = 2.0 Hz, 1 H), 2.60–2.68 (m, 1 H), 2.78–2.83 (m, 1 H), 5.83 (s, 1 H).

The data were in accordance with literature values.[8a]

Methyl 2-Oxo-2,3,3a,4,5,6,7,8-octahydroazulene-3a-carboxylate (14c)

KO*t*Bu (30 mg, 0.27 mmol) and 1,4-diketone **9c** (50 mg, 0.22 mmol) in anhydrous DMSO (2.7 mL) were reacted according to GP B at 100 °C to furnish compound **14c** (7 mg, 34 µmol, 15%) in the first fraction (SiO_2, hexanes/MTBE, 1:2, R_f = 0.42) as a light yellow oil. Secondly, product **15c** (1 mg, 9 µmol, 4%) was eluted (R_f = 0.35) as a colorless oil.

IR (ATR): 2927 (m), 2856 (w), 1726 (vs), 1689 (vs), 1614 (m), 1449 (m), 1412 (w), 1294 (w), 1246 (m), 1193 (m), 1161 (m), 1013 (w), 931 (w), 864 (w), 842 (w) cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.33–1.39 (m, 1 H), 1.44–1.52 (m, 1 H), 1.54–1.59 (m, 1 H), 1.62–1.72 (m, 2 H), 1.77 (ddd, *J* = 13.9 Hz, *J* = 10.1 Hz, *J* = 1.7 Hz, 1 H), 1.82–1.88 (m, 1 H), 2.29 (d, *J* = 18.0 Hz, 1 H), 2.31 (ddd, *J* = 14.1 Hz, *J* = 8.7 Hz, *J* = 1.6 Hz, 1 H), 2.54 (dddd, *J* = 14.5 Hz, *J* = 9.6 Hz, *J* = 3.8 Hz, *J* = 1.2 Hz, 1 H), 2.80 (ddd, *J* = 10.7 Hz, *J* = 7.6 Hz, *J* = 3.8 Hz, 1 H), 2.85 (d, *J* = 18.1 Hz, 1 H), 3.71 (s, 3 H), 5.98 (t, *J* = 1.1 Hz, 1 H).

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 24.76 (CH_2), 28.99 (CH_2), 29.76 (CH_2), 31.38 (CH_2), 36.29 (CH_2), 48.91 (CH_2), 52.74 (CH_3), 57.42 (C), 132.00 (CH), 174.19 (C), 183.28 (C), 206.62 (C).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{16}NaO_3$: 231.0992; found: 231.0991.

2,3,3a,4,5,6,7,8-Octahydroazulen-2-one (15c)

KO*t*Bu (74 mg, 0.66 mmol) and 1,4-diketone **9c** (125 mg, 0.55 mmol) in anhydrous DMSO (4.7 mL) were reacted according to GP B at 50 °C to furnish compound **14c** (15 mg, 72 µmol, 13%) in the first fraction (SiO_2, hexanes/MTBE, 1:2, R_f = 0.42) as a light yellow oil. Secondly, product **15c** (31 mg, 0.21 mmol, 37%) was eluted (R_f = 0.35) as a colorless oil.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.34–1.54 (m, 3 H), 1.65–1.70 (m, 2 H), 1.71–1.77 (m, 1 H), 1.80–1.86 (m, 1 H), 1.91–1.96 (m, 1 H), 2.00 (dd, *J* = 18.4 Hz, *J* = 2.6 Hz, 1 H), 2.66 (dd, *J* = 18.4 Hz, *J* = 6.4 Hz, 1 H), 2.66–2.77 (m, 2 H), 2.91–2.95 (m, 1 H), 5.85 (q, *J* = 1.5 Hz, 1 H).

The data were in accordance with literature values.[20]

Ethyl 2-Oxo-2,4,5,6,7,7a-hexahydro-1*H*-indene-4-carboxylate (16b)

Under an anhydrous and inert atmosphere of N_2, a solution of 1,4-diketone **9b** (46 mg, 0.20 mmol) in anhydrous toluene (0.3 mL) was added to a suspension of NaH (33 mg, 60% in mineral oil, 0.81 mmol) in anhydrous toluene (1.7 mL) and the resulting reaction mixture was stirred for 18 h at 111 °C. After cooling to 0 °C, the mixture was acidified with HCl (10%, ca. 0.5 mL) to pH 4 and extracted with MTBE (3 × 5 mL). The combined organic layers were washed with brine (10 mL) and H_2O (10 mL), dried ($MgSO_4$), filtered and the solvent was removed in vacuo. The crude product was purified by column chromatography (SiO_2, hexanes/MTBE, 1:1, R_f = 0.36) to yield the indenone **16b** (36 mg, 0.17 mmol, 85%) as a colorless oil.

IR (ATR): 2979 (w), 2935 (m), 2859 (w), 1732 (s), 1702 (vs), 1621 (s), 1447 (w), 1369 (w), 1336 (w), 1293 (w), 1270 (m), 1252 (m), 1197 (w), 1168 (m), 1144 (s), 1112 (w), 1060 (w), 1025 (m), 941 (w), 857 (w), 840 (m), 786 (w), 677 (w), 650 (w) cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.19 (qd, *J* = 12.9 Hz, *J* = 3.6 Hz, 1 H), 1.29 (t, *J* = 7.2 Hz, 3 H), 1.38 (qt, *J* = 13.8 Hz, *J* = 4.2 Hz, 1 H), 1.52 (qt, *J* = 13.3 Hz, *J* = 3.4 Hz, 1 H), 1.87 (dtd, *J* = 13.7 Hz, *J* = 3.3 Hz, *J* = 1.7 Hz, 1 H), 2.00–2.05 (m, 1 H), 2.22–2.27 (m, 1 H), 2.31 (td, *J* = 13.9 Hz, *J* = 5.8 Hz, 1 H), 2.84 (ddt, *J* = 14.0 Hz, *J* = 4.1 Hz, *J* = 1.9 Hz, 1 H), 3.00–3.04 (m, 2 H), 4.15–4.25 (m, 2 H), 5.80 (s, 1 H).

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 14.34 (CH_3), 25.16 (CH_2), 26.73 (CH_2), 31.03 (CH_2), 34.15 (CH_2), 46.06 (CH), 59.46 (CH), 61.66 (CH_2), 125.12 (CH), 169.37 (C), 184.30 (C), 201.47 (C).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{16}NaO_3$: 231.0992; found: 231.0992.

Conversion of 1,4-Diketone 9c with NaH in Toluene

Under an anhydrous and inert atmosphere of N_2, a solution of 1,4-diketone **9c** (49 mg, 0.22 mmol) in anhydrous toluene (0.3 mL) was added to a suspension of NaH (35 mg, 60% in mineral oil, 0.87 mmol) in anhydrous toluene (1.7 mL) and the resulting reaction mixture was stirred for 18 h at 111 °C. After cooling to 0 °C, the mixture was acidified with HCl (10%, ca. 0.5 mL) to pH 4 and extracted with MTBE (3 × 5 mL). The combined organic layers were washed with brine (10 mL) and H_2O (10 mL), dried ($MgSO_4$), filtered and the solvent was removed in vacuo. The residue was purified by column chromatography (SiO_2, hexanes/MTBE, 1:2) to yield the azulenone **16c** (15 mg, 72 µmol, 33%) in the first fraction (R_f = 0.39) as a colorless oil. Secondly, the azulenone **17c** (16 mg, 77 µmol, 35%) was eluted (R_f = 0.26) as a colorless oil.

Methyl 2-Oxo-1,2,4,5,6,7,8,8a-octahydroazulene-4-carboxylate (16c)

IR (ATR): 2926 (m), 2856 (w), 1733 (s), 1701 (vs), 1605 (m), 1437 (m), 1342 (m), 1245 (m), 1193 (w), 1148 (s), 1072 (w), 1023 (w), 996 (w), 924 (w), 812 (w) cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.40–1.48 (m, 1 H), 1.49–1.58 (m, 2 H), 1.67–1.78 (m, 3 H), 1.81–1.87 (m, 1 H), 1.97–2.03 (m, 1 H), 2.66–2.72 (m, 1 H), 2.76–2.82 (m, 1 H), 3.08 (d, *J* = 3.5 Hz, 1 H), 3.31–3.36 (m, 1 H), 3.77 (s, 3 H), 5.85 (d, *J* = 1.4 Hz, 1 H).

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 26.65 (CH_2), 28.24 (CH_2), 30.59 (CH_2), 32.85 (CH_2), 33.12 (CH_2), 48.88 (CH), 52.73 (CH_3), 60.78 (CH), 127.86 (CH), 169.82 (C), 187.49 (C), 201.31 (C).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{16}NaO_3$: 231.0992; found: 231.0992.

Methyl 2-Oxo-2,3,3a,4,5,6,7,8-octahydroazulene-1-carboxylate (17c)

IR (ATR): 2925 (m), 2855 (w), 1739 (s), 1707 (vs), 1605 (m), 1436 (m), 1363 (m), 1309 (m), 1230 (m), 1207 (m), 1157 (m), 1111 (w), 1020 (s), 781 (w), 733 (w) cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.33–1.57 (m, 3 H), 1.65–1.93 (m, 4 H), 1.98–2.03 (m, 1 H), 2.10 (dd, *J* = 18.6 Hz, *J* = 2.8 Hz, 1 H), 2.76 (dd, *J* = 18.6 Hz, *J* = 6.9 Hz, 1 H), 3.00–3.10 (m, 3 H), 3.83 (s, 3 H).

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 26.00 (CH_2), 28.87 (CH_2), 30.50 (CH_2), 33.28 (CH_2), 34.58 (CH_2), 43.45 (CH), 44.18 (CH_2), 51.90 (CH_3), 131.04 (C), 164.05 (C), 194.53 (C), 202.84 (C).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{16}NaO_3$: 231.0992; found: 231.0991.

Annulation with Aqueous KOH in Water; General Procedure C (GP C)

Under an inert atmosphere of N_2, aqueous KOH (15% w/w, 2.5 L/mol) was added dropwise over a period of 15 min to a mixture of the respective 1,4-diketone (1.0 equiv) in H_2O (20 L/mol). The mixture was stirred at 60 °C or 120 °C for 2–9 h, then cooled to ambient temperature and extracted with CH_2Cl_2 (3 × 10 L/mol). The combined organic layers were dried ($MgSO_4$), filtered and the solvent removed in vacuo. The crude product was purified by column chromatography to give the cyclopentenone derivatives.

tert-Butyl 1,3,4,6,7,7a-Hexahydro-2*H*-cyclopenta[*c*]pyridin-6-one-2-carboxylate (18a)

According to GP C, 1,4-diketone **7a** (55 mg, 0.18 mmol) and KOH (15% in H_2O, 0.5 mL) in H_2O (4 mL) were reacted for 2 h at 60 °C to furnish the title compound **18a** (42 mg, 0.18 mmol, 100%) as a yellow oil without further chromatographic purification. NMR spectra showed partly broadened signal sets due to rotamers (ratio 1:1).

IR (ATR): 2969 (w), 2932 (w), 2853 (w), 1690 (vs), 1624 (m), 1417 (m), 1365 (m), 1262 (m), 1240 (m), 1161 (s), 1108 (m), 1026 (w), 881 (w) cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.47 (s, 9 H), 1.94 (dd, *J* = 18.8 Hz, *J* = 2.5 Hz, 1 H), 2.31–2.56 (m, 2 H), 2.50 (dd, *J* = 18.7 Hz, *J* = 6.6 Hz, 1 H), 2.62–2.86 (m, 3 H), 4.32–4.60 (m, 2 H), 5.94 (t, *J* = 1.7 Hz, 1 H).

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 28.33 (3 CH_3), 30.68 (CH_2), 38.48 (CH_2), 40.76 (CH), 44.35 (CH_2), 50.68 (CH_2), 80.37 (C), 128.00 (CH), 154.26 (C), 180.14 (C), 207.45 (C).

HRMS (ESI): *m*/*z* [M + Li]$^+$ calcd for $C_{13}H_{19}LiNO_3$: 244.1519; found: 244.1520.

2-Acetyl-1,2,3,4,7,7a-hexahydro-6*H*-cyclopenta[*c*]pyridin-6-one (18b)

According to GP C, 1,4-diketone **7b** (108 mg, 0.42 mmol) and KOH (15% in H_2O, 1.1 mL) were reacted for 2 h at 60 °C. The crude mixture was purified by column chromatography (SiO_2, MTBE/MeOH, 4:1, R_f = 0.27) to yield the title compound **18b** (70 mg, 0.39 mmol, 92%) as a yellow solid (mp 132 °C). This compound has been reported in the literature previously, but was not sufficiently characterized.[21] NMR spectra showed doubled signal sets due to rotamers (ratio 1:1).

IR (ATR): 2917 (w), 2876 (w), 1702 (s), 1673 (m), 1640 (s), 1620 (vs), 1426 (s), 1363 (w), 1264 (m), 1230 (m), 1137 (w), 1016 (m), 878 (w), 841 (w), 685 (w) cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.97 (dd, *J* = 18.7 Hz, *J* = 2.4 Hz, 2 H), 2.14 (s, 3 H), 2.15 (s, 3 H), 2.19 (t, *J* = 12.1 Hz, 1 H), 2.41–2.55 (m, 5 H), 2.75–2.84 (m, 5 H), 3.09 (td, *J* = 13.1 Hz, *J* = 3.1 Hz, 1 H), 4.06 (ddt, *J* = 13.5 Hz, *J* = 6.2 Hz, *J* = 2.0 Hz, 1 H), 4.14 (ddd, *J* = 12.0 Hz, *J* = 4.7 Hz, *J* = 2.0 Hz, 1 H), 4.92 (ddt, *J* = 12.2 Hz, *J* = 5.6 Hz, *J* = 2.0 Hz, 1 H), 5.00 (ddd, *J* = 12.5 Hz, *J* = 6.3 Hz, *J* = 2.2 Hz, 1 H), 5.95 (t, *J* = 1.7 Hz, 1 H), 5.96 (t, *J* = 1.7 Hz, 1 H).

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 21.39 (2 CH_3), 30.32 (C), 31.07 (C), 38.28 (CH_2), 38.53 (CH_2), 40.47 (CH), 41.24 (CH), 41.80 (CH_2), 46.35 (CH_2), 48.02 (CH_2), 52.67 (CH_2), 128.32 (CH), 128.39 (CH), 168.93 (2 C), 178.47 (C), 179.08 (C), 206.57 (C), 207.09 (C).

HRMS (ESI): *m*/*z* [M + Li]$^+$ calcd for $C_{10}H_{13}LiNO_2$: 186.1101; found: 186.1113.

2,4,5,6,7,7a-Hexahydro-1*H*-inden-2-one (15b) from Oxoester 9b

According to GP C, the 1,4-diketone **9b** (100 mg, 0.44 mmol) and KOH (15% in H_2O, 1.1 mL) were reacted for 2 h at 60 °C to yield the title compound **15b** (57 mg, 0.42 mmol, 95%) as a colorless liquid without further chromatographic purification; for characterization see above.

4,5,6,7,8,8a-Hexahydro-1*H*-azulen-2-one (15c)

According to GP C, the 1,4-diketone **9c** (100 mg, 0.44 mmol) and KOH (15% in H_2O, 1.1 mL) were reacted for 2 h at 120 °C. The crude mixture was purified by column chromatography (SiO_2, hexanes/MTBE, 1:2, R_f = 0.36) to yield the title compound **15c** (42 mg, 0.28 mmol, 64%) as a colorless liquid; for characterization see above.

tert-Butyl 2-Oxo-2,3,4,5,6,7-hexahydroindene-3a-carboxylate (14d)

According to GP C, 1,4-diketone **9d** (100 mg, 0.39 mmol) and KOH (15% in H_2O, 1.0 mL) in H_2O (8 mL) were reacted for 2 h at 60 °C. The crude mixture was purified by column chromatography (SiO_2, hexanes/MTBE, 1:1, R_f = 0.39) to yield the title compound **14d** (16 mg, 68 µmol, 17%) in the first fraction as a colorless oil. Secondly, indenone **15b** (42 mg, 0.31 mmol, 79%) was eluted (R_f = 0.26) as a colorless liquid.

IR (ATR): 2975 (w), 2943 (w), 2859 (w), 1717 (vs), 1627 (m), 1447 (w), 1369 (w), 1233 (w), 1154 (s), 1135 (m), 990 (w), 848 (w) cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.22–1.35 (m, 2 H), 1.43 (s, 9 H), 1.54 (qt, *J* = 13.2 Hz, *J* = 3.3 Hz, 1 H), 1.70–1.78 (m, 1 H), 2.00 (ddt, *J* = 10.3 Hz, *J* = 4.8 Hz, *J* = 2.3 Hz, 1 H), 2.24 (d, *J* = 18.7 Hz, 1 H), 2.38 (td, *J* = 13.4 Hz, *J* = 5.8 Hz, 1 H), 2.60 (d, *J* = 18.7 Hz, 1 H), 2.57–2.67 (m, 1 H), 2.73–2.83 (m, 1 H), 5.92 (d, *J* = 1.6 Hz, 1 H).

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 23.16 (CH_2), 27.18 (CH_2), 27.81 (3 CH_3), 29.82 (CH_2), 37.64 (CH_2), 48.00 (CH_2), 54.61 (C), 81.63 (C), 128.14 (CH), 172.27 (C), 182.19 (C), 206.69 (C).

HRMS (ESI): *m*/*z* [M + Li]$^+$ calcd for $C_{14}H_{20}LiO_3$: 243.1567; found: 243.1561.

2,4,5,6,7,7a-Hexahydro-1*H*-inden-2-one (15b) from Oxoester 9d

According to GP C, the 1,4-diketone **9d** (235 mg, 0.92 mmol) and KOH (15% in H_2O, 3 mL) were reacted for 2 h at 120 °C. The crude material was purified by column chromatography (SiO_2, hexanes/MTBE, 1:1, R_f = 0.27) to yield the title compound **15b** (121 mg, 0.89 mmol, 97%) as a colorless liquid; for characterization see above.

3,3a,4,5-Tetrahydro-2*H*-cyclopenta[*a*]naphthalen-2-one (19a)

According to GP C, 1,4-diketone **11a** (100 mg, 0.36 mmol) and KOH (15% in H_2O, 1.0 mL) were reacted for 6 h at 60 °C to yield the title compound **19a** (64 mg, 0.35 mmol, 97%) as a colorless solid (mp 74 °C) without further chromatographic purification.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.63–1.71 (m, 1 H), 2.20 (dd, *J* = 18.3 Hz, *J* = 3.5 Hz, 1 H), 2.29 (dtd, *J* = 12.1 Hz, *J* = 4.8 Hz, *J* = 2.1 Hz, 1 H), 2.79 (dd, *J* = 18.3 Hz, *J* = 6.5 Hz, 1 H), 2.99 (ddd, *J* = 17.2 Hz, *J* = 5.2 Hz, *J* = 2.2 Hz, 1 H), 3.02–3.09 (m, 2 H), 6.39 (d, *J* = 2.0 Hz, 1 H), 7.23–7.28 (m, 2 H), 7.36 (td, *J* = 7.5 Hz, *J* = 1.4 Hz, 1 H), 7.66 (dd, *J* = 7.8 Hz, *J* = 1.3 Hz, 1 H).

The data were in accordance with literature values.[22]

3,3a,4,5-Tetrahydrocyclopenta[*c*]quinolin-2-one (19b)

According to GP C, 1,4-diketone **11b** (96 mg, 0.32 mmol) and KOH (15% in H_2O, 1.0 mL) were reacted for 8 h at 60 °C. The crude mixture was purified by column chromatography (SiO_2, MTBE, R_f = 0.22) to yield the title compound **19b** (39 mg, 0.21 mmol, 65%) as a light yellow oil.

^1H NMR (500 MHz, $CDCl_3$): δ = 2.03–2.08 (m, 1 H), 2.71–2.77 (m, 1 H), 3.08–3.16 (m, 2 H), 3.58–3.67 (m, 1 H), 4.56 (br s, 1 H), 6.28 (d, *J* = 1.7 Hz, 1 H), 6.64 (dd, *J* = 8.3 Hz, *J* = 1.1 Hz, 1 H), 6.73 (ddd, *J* = 8.0 Hz, *J* = 7.1 Hz, *J* = 1.1 Hz, 1 H), 7.20 (ddd, *J* = 8.4 Hz, *J* = 7.1 Hz, *J* = 1.5 Hz, 1 H), 7.49 (dd, *J* = 7.9 Hz, *J* = 1.5 Hz, 1 H).

The data were in accordance with literature values.[23]

Alkylation of Oxoesters; General Procedure D (GP D)

A solution of propargyl bromide (80% w/w in toluene, 2.0 equiv) and K_2CO_3 (1.2 equiv) were added to a mixture of the respective β-oxoester (1.0 equiv) in acetone (3 L/mol). The mixture was heated to reflux for 2–6 h, then cooled to ambient temperature, diluted with H_2O (10 L/mol) and extracted with MTBE (3 × 10 L/mol). The combined organic layers were dried ($MgSO_4$), filtered and the solvent was removed in vacuo. The crude product was purified by column chromatography to give the α-propargyl-β-oxoester derivatives.

1-(*tert*-Butyl) 3-Methyl 4-Oxo-3-propargylpiperidine-1,3-dicarboxylate (23a)

According to GP D, β-oxoester **22a** (600 mg, 2.33 mmol), K_2CO_3 (387 mg, 2.80 mmol) and propargyl bromide (694 mg, 80% w/w in toluene, 4.66 mmol) in acetone (6 mL) were heated to reflux for 4 h. The crude material was purified by column chromatography (SiO_2, hexanes/MTBE, 1:1, R_f = 0.41) to yield the title compound **23a** (435 mg, 1.47 mmol, 63%) as a light yellow oil. NMR spectra showed partly broadened signal sets due to the carbamate moiety.

IR (ATR): 3284 (w), 2977 (w), 2936 (w), 1720 (m), 1693 (vs), 1469 (w), 1421 (m), 1366 (m), 1312 (w), 1249 (m), 1236 (m), 1162 (s), 1131 (s), 971 (m), 860 (w), 769 (w) cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.42 (s, 9 H), 2.00 (t, *J* = 2.7 Hz, 1 H), 2.42 (dt, *J* = 15.1 Hz, *J* = 4.3 Hz, 1 H), 2.61 (dd, *J* = 16.8 Hz, *J* = 2.7 Hz, 1 H), 2.62–2.77 (m, 2 H), 3.23 (ddd, *J* = 13.9 Hz, *J* = 10.7 Hz, *J* = 4.3 Hz, 1 H), 3.31–3.47 (m, 1 H), 3.67 (s, 3 H), 4.10 (dt, *J* = 12.3 Hz, *J* = 5.1 Hz, 1 H), 4.47–4.65 (m, 1 H).

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 21.35 (CH_2), 28.07 (3 CH_3), 39.44 (CH_2), 42.57 (CH_2), 49.51 (CH_2), 52.76 (CH_3), 59.66 (C), 71.65 (CH), 78.65 (C), 80.41 (C), 153.99 (C), 169.38 (C), 202.74 (C).

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{15}H_{21}NNaO_5$: 318.1312; found: 318.1312.

Methyl 1-Acetyl-4-Oxo-3-propargylpiperidine-3-carboxylate (23b)

According to GP D, β-oxoester **22b** (1.40 g, 7.03 mmol), K_2CO_3 (1.17 g, 8.44 mmol) and propargyl bromide (2.09 g, 80% w/w in toluene, 14.1 mmol) in acetone (20 mL) were heated to reflux for 2 h. The crude material was purified by column chromatography (SiO_2, MTBE/EtOH, 8:1, R_f = 0.32) to yield the title compound **23b** (1.30 g, 5.48 mmol, 78%) as a colorless oil. NMR spectra showed doubled signal sets due to rotamers (ratio 3:1).

IR (ATR): 3283 (w), 2954 (w), 2875 (w), 1719 (vs), 1645 (vs), 1425 (s), 1367 (w), 1263 (m), 1212 (m), 1183 (w), 1033 (m), 1016 (m), 957 (w), 848 (w) cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ (major rotamer) = 2.10 (t, *J* = 2.7 Hz, 1 H), 2.29 (s, 3 H), 2.49 (dt, *J* = 14.8 Hz, *J* = 3.9 Hz, 1 H), 2.56 (ddd, *J* = 14.7 Hz, *J* = 11.3 Hz, *J* = 6.5 Hz, 1 H), 2.62 (dd, *J* = 17.3 Hz, *J* = 2.8 Hz, 1 H), 2.78 (dd, *J* = 17.3 Hz, *J* = 2.8 Hz, 1 H), 3.00 (ddd, *J* = 13.4 Hz, *J* = 11.4 Hz, *J* = 4.2 Hz, 1 H), 3.38 (d, *J* = 13.9 Hz, 1 H), 3.73 (s, 3 H), 4.58 (dd, *J* = 13.9 Hz, *J* = 2.7 Hz, 1 H), 4.71 (ddt, *J* = 13.0 Hz, *J* = 6.4 Hz, *J* = 3.1 Hz, 1 H); δ (minor rotamer) = 2.03 (t, *J* = 2.7 Hz, 1 H), 2.15 (s, 3 H), 2.46–2.68 (m, 2 H), 2.80 (dd, *J* = 17.2 Hz, *J* = 2.6 Hz, 1 H), 2.81–2.89 (m, 1 H), 3.33 (d, *J* = 13.8 Hz, 1 H), 3.50–3.58 (m, 1 H), 3.70 (s, 3 H), 3.98 (dddd, *J* = 13.3 Hz, *J* = 6.6 Hz, *J* = 4.3 Hz, *J* = 2.7 Hz, 1 H), 4.97 (dd, *J* = 13.7 Hz, *J* = 2.2 Hz, 1 H).

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ (major rotamer) = 21.08 (CH_3), 21.63 (CH_2), 39.75 (CH_2), 41.21 (CH_2), 51.58 (CH_2), 53.23 (CH_3), 59.75 (C), 72.60 (CH), 77.79 (C), 168.98 (C), 170.06 (C), 201.55 (C); δ (minor rotamer) = 21.20 (CH_3), 21.42 (CH_2), 39.57 (CH_2), 44.85 (CH_2), 47.12 (CH_2), 53.06 (CH_3), 59.41 (C), 71.78 (CH), 78.61 (C), 169.37 (C), 169.53 (C), 202.11 (C).

HRMS (ESI): *m*/*z* $[M + Li]^+$ calcd for $C_{12}H_{15}LiNO_4$: 244.1156; found: 244.1164.

***tert*-Butyl 2-Oxo-1-propargylcyclohexane-1-carboxylate (24)**

According to GP D, β-oxoester **20d** (1.50 g, 7.57 mmol), K_2CO_3 (1.26 g, 9.08 mmol) and propargyl bromide (2.25 g, 80% w/w in toluene, 15.1 mmol) in acetone (25 mL) were heated to reflux for 4 h. The crude material was purified by column chromatography (SiO_2, hexanes/MTBE, 1:1, R_f = 0.57) to yield the title compound **24** (1.67 g, 7.05 mmol, 93%) as a light yellow oil.

IR (ATR): 3283 (w), 2945 (w), 2868 (w), 1713 (vs), 1453 (w), 1369 (m), 1217 (w), 1151 (s), 1091 (w), 845 (w), 650 (w) cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.45 (s, 9 H), 1.51–1.67 (m, 2 H), 1.74–1.81 (m, 2 H), 2.00 (t, *J* = 2.7 Hz, 1 H), 2.01–2.07 (m, 1 H), 2.43–2.46 (m, 2 H), 2.50 (dd, *J* = 17.0 Hz, *J* = 2.7 Hz, 1 H), 2.61 (dq, *J* = 13.7 Hz, *J* = 3.2 Hz, 1 H), 2.70 (dd, *J* = 16.9 Hz, *J* = 2.7 Hz, 1 H).

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 22.34 (CH_2), 24.76 (CH_2), 27.37 (CH_2), 27.81 (3 CH_3), 35.42 (CH_2), 40.81 (CH_2), 60.42 (C), 71.11 (CH), 79.72 (C), 82.38 (C), 169.33 (C), 206.18 (C).

HRMS (ESI): *m*/*z* $[M + Li]^+$ calcd for $C_{14}H_{20}LiO_3$: 243.1567; found: 243.1580.

Ethyl 2-Propargyl-1-tetralone-2-carboxylate (26a)

According to GP D, β-oxoester **25a** (2.00 g, 9.16 mmol), K_2CO_3 (1.52 g, 11.0 mmol) and propargyl bromide (2.72 g, 80% w/w in toluene, 18.3 mmol) in acetone (25 mL) were heated to reflux for 6 h. The crude material was purified by column chromatography (SiO_2, hexanes/MTBE, 10:1, R_f = 0.20) to yield the title compound **26a** (2.09 g, 8.15 mmol, 89%) as a colorless oil.

IR (ATR): 3277 (w), 2981 (w), 2935 (w), 1730 (s), 1685 (vs), 1601 (m), 1455 (m), 1423 (m), 1389 (w), 1366 (m), 1355 (m), 1321 (m), 1293 (m), 1274 (m), 1236 (s), 1211 (s), 1121 (m), 1076 (m), 1018 (m), 965 (w), 939 (m), 919 (w), 897 (m), 861 (w), 808 (w), 788 (m), 745 (m), 646 (m) cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.15 (t, *J* = 7.1 Hz, 3 H), 2.00 (t, *J* = 2.7 Hz, 1 H), 2.44 (ddd, *J* = 13.9 Hz, *J* = 10.9 Hz, *J* = 4.9 Hz, 1 H), 2.63 (dt, *J* = 13.8 Hz, *J* = 4.7 Hz, 1 H), 2.88 (d, *J* = 2.6 Hz, 2 H), 2.95 (dt, *J* = 17.4 Hz, *J* = 4.7 Hz, 1 H), 3.14 (ddd, *J* = 17.4 Hz, *J* = 10.9 Hz, *J* = 4.8 Hz, 1 H), 4.14 (q, *J* = 7.1 Hz, 2 H), 7.22 (d, *J* = 7.7 Hz, 1 H), 7.30 (t, *J* = 7.6 Hz, 1 H), 7.47 (td, *J* = 7.5 Hz, *J* = 1.5 Hz, 1 H), 8.04 (dd, *J* = 7.9 Hz, *J* = 1.5 Hz, 1 H).

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 13.90 (CH_3), 24.21 (CH_2), 25.73 (CH_2), 30.49 (CH_2), 56.55 (C), 61.63 (CH_2), 71.17 (CH), 79.58 (C), 126.72 (CH), 127.99 (CH), 128.69 (CH), 131.61 (C), 133.62 (CH), 143.16 (C), 170.50 (C), 193.70 (C).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{17}O_3$: 257.1172; found: 257.1180.

Methyl 1-Acetyl-4-oxo-3-propargyl-1,2,3,4-tetrahydroquinoline-3-carboxylate (26b)

According to GP D, β-oxoester **25b** (502 mg, 2.03 mmol), K_2CO_3 (337 mg, 2.44 mmol) and propargyl bromide (604 mg, 80% w/w in toluene, 4.06 mmol) in acetone (6 mL) were heated to reflux for 6 h. The crude material was purified by column chromatography (SiO_2, hexanes/MTBE, 1:2, R_f = 0.19) to yield the title compound **26b** (590 mg, 2.03 mmol, 100%) as a yellow oil.

IR (ATR): 3276 (w), 2958 (w), 1739 (m), 1670 (vs), 1602 (m), 1578 (w), 1481 (m), 1379 (m), 1317 (m), 1239 (s), 1212 (vs), 1084 (w), 971 (w), 766 (m), 737 (w), 665 (w) cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 2.01 (t, *J* = 2.7 Hz, 1 H), 2.37 (s, 3 H), 2.88 (dd, *J* = 17.1 Hz, *J* = 2.7 Hz, 1 H), 2.98 (dd, *J* = 17.3 Hz, *J* = 2.7 Hz, 1 H), 3.68 (s, 3 H), 4.12 (d, *J* = 13.6 Hz, 1 H), 4.85–4.94 (m, 1 H), 7.27 (d, *J* = 8.0 Hz, 1 H), 7.52–7.68 (m, 2 H), 8.06 (dt, *J* = 7.8 Hz, *J* = 1.1 Hz, 1 H).

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 21.85 (CH_2), 23.04 (CH_3), 50.33 (CH_2), 53.21 (CH_3), 57.43 (C), 72.12 (CH), 78.31 (C), 124.06 (CH), 124.60 (C), 125.41 (CH), 128.46 (CH), 134.62 (CH), 143.60 (C), 169.32 (C), 170.26 (C), 190.06 (C).

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{16}H_{15}NNaO_4$: 308.0893; found: 308.0899.

Methyl 1-Acetyl-4-oxo-1,2,3,4-tetrahydroquinoline-3-carboxylate (25b)

Under an anhydrous and inert atmosphere (N_2), methyl acrylate (1.47 g, 17.1 mmol) and KO*t*Bu (1.91 g, 17.1 mmol) were added to a cooled (ice/water bath) solution of methyl 2-acetamidobenzoate (**27**) (3.00 g, 15.5 mmol) in anhydrous THF (33 mL). The reaction mixture was stirred for 3 d at 23 °C and then evaporated. The crude product was purified by column chromatography (SiO_2, hexanes/MTBE, 1:1, R_f = 0.18) to yield the oxoester **25b** (2.15 g, 8.68 mmol, 56%) as a yellow solid (mp 126 °C). This product has been reported in the literature previously,[24] but not fully characterized. The product was isolated as a mixture of keto and enol tautomers (ratio 1:5 by ^1H NMR).

IR (ATR): 3353 (m), 3074 (w), 2959 (w), 1708 (m), 1667 (vs), 1583 (m), 1495 (s), 1440 (m), 1379 (m), 1365 (m), 1314 (m), 1260 (m), 1218 (w), 1179 (w), 1087 (w), 950 (w) cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ (keto tautomer) = 2.35 (s, 3 H), 3.70 (dd, *J* = 7.1 Hz, *J* = 4.3 Hz, 1 H), 3.75 (s, 3 H), 4.37–4.41 (m, 1 H), 4.55 (dd, *J* = 13.5 Hz, *J* = 7.2 Hz, 1 H), 7.26–7.29 (m, 1 H), 7.40–7.44 (m, 1 H), 7.57 (ddd, *J* = 8.9 Hz, *J* = 7.2 Hz, *J* = 1.7 Hz, 1 H), 8.05 (dt, *J* = 7.9 Hz, *J* = 1.0 Hz, 1 H); δ (enol tautomer) = 2.22 (s, 3 H), 3.84 (s, 3 H), 4.65 (s, 2 H), 7.26–7.29 (m, 2 H), 7.42 (td, *J* = 7.8 Hz, *J* = 1.6 Hz, 1 H), 7.81 (dd, *J* = 7.8 Hz, *J* = 1.5 Hz, 1 H), 11.97 (br s, 1 H).

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ (keto tautomer) = 22.86 (CH_3), 46.31 (CH_2), 52.60 (CH_3), 53.94 (CH), 123.97 (CH), 124.44 (C), 125.37 (CH), 128.12 (CH), 134.46 (CH), 143.61 (C), 167.93 (C), 169.62 (C), 188.56 (C); δ (enol tautomer) = 22.22 (CH_3), 39.69 (CH_2), 51.73 (CH_3), 97.12 (C), 123.72 (CH), 124.61 (C), 124.67 (CH), 125.34 (CH), 130.70 (CH), 139.53 (C), 162.71 (C), 169.20 (C), 170.22 (C).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{13}H_{13}NO_4$: 247.0839; found: 247.0843.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1590812.

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