Cyclobutane Ring Opening Reactions of 1,2,2a,8b-Tetrahydrocyclobuta[*c*]-quinolin-3(4*H*)-ones

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Dedicated to Professor Reinhard W. Hoffmann on the occasion of his 75th birthday

Abstract: Two pathways are presented, which allow for the selective cleavage of the C1/C8b bond in the title compounds. The first reaction was found by serendipity when reductive debenzylation was attempted on a heteroanellated azabicyclo[4.2.0]octane. It yielded an eight-membered lactam ring (azocane). The second transformation relies on a rationally designed 1,2-rearrangement reaction, which was introduced because attempts to induce classical Wagner–Meerwein-type 1,2-shifts did not meet with success. The reaction, a retro-benzilic acid rearrangement, allowed for the conversion of a heteroanellated hydroxycyclobutanecarboxylate into the respective cyclopentadione (76% yield).

Key words: metal reductions, lactams, photochemistry, cyclobutanes, rearrangements, fragmentations

The title compounds, 1,2,2a,8b-tetrahydrocyclobuta[*c*]quinolin-3(4*H*)-ones of general structure **A**, are readily synthesized from appropriate quinolones and alkenes by an inter- or intramolecular [2+2]-photocycloaddition reaction.[1] Recent work in our group has established enantioselective access to this carbon skeleton, employing a hydrogen-bonding chiral template for the required enantioface differentiation.[2] In attempts to extend the photocycloaddition methodology the question was raised, whether chemo- and regioselective ring-opening reactions would be feasible in skeleton **A** (Figure 1).

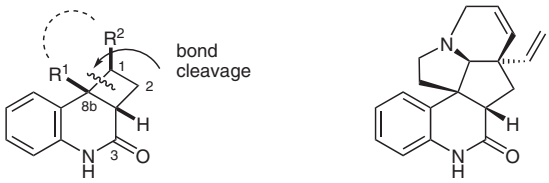
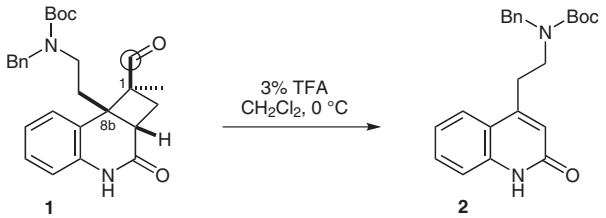


Figure 1 Structure of a generic heteroanellated cyclobutane **A** and of the *Melodinus* alkaloid (+)-meloscine.

Ideally, these reactions should leave at least one of the stereogenic centers formed in the photocycloaddition step intact and should, thus, open new routes to other product classes. A case in point was the pentacyclic skeleton of the *Melodinus* alkaloid meloscine, the lower three rings of which we tried to synthesize[3] by a possible ring extension of the four-membered ring anellated to the dihydroquinolone (as in **A**) to a five-membered ring-anellated product. The substituent R^1 in tetrahydrocyclobutaquinolin-3(4*H*)-one **A** was represented by a 2-aminoethyl group, which was in some cases linked to the group R^2. It was found in our model substrates that complete bond cleavage is possible under reductive conditions and that 1,2-rearrangement can be induced if an additional substituent is present at C1 and it is a strongly electron-donating hydroxy group. The results of our studies are summarized in this account.

Quinolone photocycloaddition products were obtained as previously described.[4] Initial experiments were directed towards a possible ring extension of a cyclobutyliminium ion into a cyclopentyl cation by a Wagner–Meerwein-type 1,2-shift.[5] Typical substrates, which exhibit a substructure of this type, were, however, difficult to synthesize. Photocycloaddition products obtained by intermolecular reactions carried a *N*-benzyl-*N*-(*tert*-butoxycarbonyl)-protected 2-aminoethyl substituent at position C8b as well as an ester group and an additional alkyl substituent at C1. Intramolecular photocycloaddition products displayed similar substitution patterns and oxidation states at the relevant atoms (*vide infra*). Scheme 1 depicts an attempt to generate an iminium ion at the indicated exocyclic carbonyl carbon atom by *N*-(*tert*-butoxycarbonyl) (Boc) deprotection[6] of carbamate **1**[4] to the secondary *N*-benzylamine. Even with small amounts of trifluoroacetic acid at 0 °C, a rapid retro-[2+2] cycloaddition to quinolinone **2** was observed. The cleavage was, under all conditions, faster than the desired deprotection. Similar retro-[2+2] cycloadditions have so far only been observed under UV irradiation (λ = 300 nm) or under thermal conditions in photochemically generated homodimers of quinolin-2(1*H*)-ones such as **2**.[1a,4,7]



Scheme 1 Acid-catalyzed retro-[2+2] cycloaddition of aldehyde **1** to quinolone **2**

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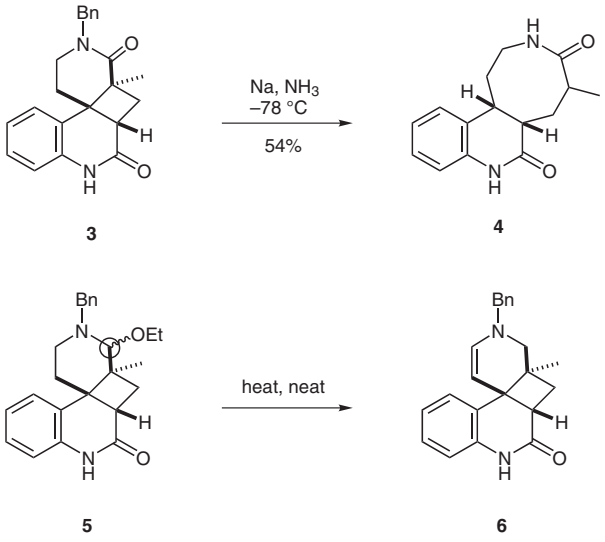
Successful cleavage of the bond between C1 and C8b was achieved when the debenzylation of the intramolecular photocycloaddition product **3** was attempted. Initial experiments conducted under hydrogenolytic[8] and acidic conditions[9] had not led to significant conversion. The use of aluminum(III) chloride in refluxing toluene[10] had resulted in complete decomposition of starting material. Upon treatment of **3** with sodium metal in liquid ammonia, however, the cyclobutane ring was cleaved and the eight-membered lactam **4** was obtained (Scheme 2). When employing stoichiometric amounts (1.0 equiv) of sodium, no significant N-debenzylation was achieved, as indicated by the NMR spectra of the crude product mixture. Thus, it appeared as if the opening was faster than the deprotection. Using a slight excess of sodium metal produced lactam **4** as a single diastereoisomer with the lactam and the dihydroquinolone being *cis*-fused. The relative configuration of the stereogenic center next to the lactam carbonyl group could not be established. While reductive cyclobutane cleavage by alkali metals is known,[11] it has, so far, been restricted to geminal dicarbonyl-substituted substrates[12] or to simple carbocycles.[13] The reaction depicted in Scheme 2 is the first example of a reductive cyclobutane cleavage within a heterocyclic framework under Birch conditions and represents an as yet unprecedented approach to otherwise hardly accessible eight-membered lactams. Attempts to reconnect the ring to an azabicyclo[3.3.0]octane relevant to meloscine (Figure 1) were not undertaken.



Scheme 2 Reductive ring-opening and debenzylation of tetracyclic lactam **3** and ethanol elimination of *N*,*O*-acetal **5**

The construction of a tetracyclic framework with the required oxidation state at the indicated carbon center adjacent to nitrogen was difficult. After numerous attempts however, *N*,*O*-acetal **5** could be generated from a known hydroxycarbamate[4] by a one-pot sequence of *N*-Boc deprotection and in situ oxidation–ring closure with *o*-iodoxybenzoic acid (IBX)[14] in dimethyl sulfoxide. Treatment of *N*,*O*-acetal **5** with acids under various conditions did not, however, result in the desired 1,2-shift. Under drastic conditions, i.e. upon heating a neat sample to 160–180 °C, ethanol elimination was observed, yet the product did not exhibit a rearranged carbon skeleton, but turned out to be enamine **6** (Scheme 2). Mechanistically, an aziridine or an azomethine ylide are conceivable intermediates, which could be formed by 1,3-elimination and which could rearrange to the enamine. Precedence for a related thermal rearrangement exists.[15]

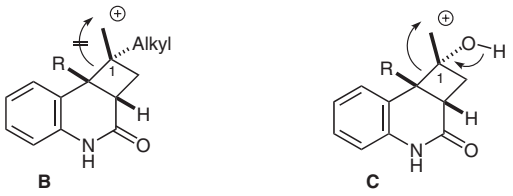


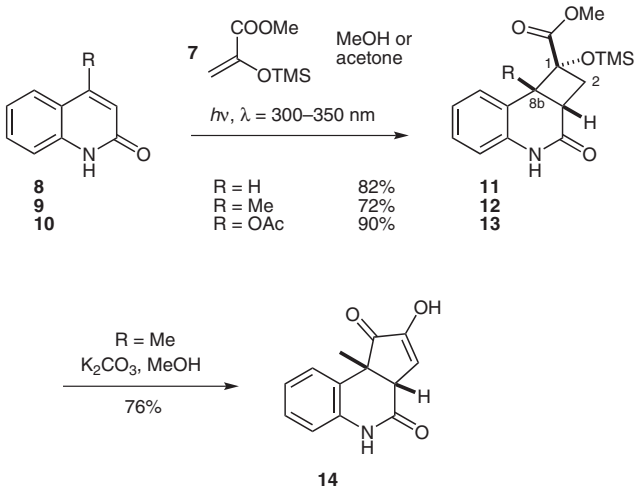
Figure 2 Desired 1,2-shift in cation intermediates of type **B** and increased migration aptitude in intermediates **C** with a hydroxy substituent in position C1

The latter result complemented other experimental evidence that led us to believe that the driving force of the 1,2-rearrangement depicted in intermediate **B** (Figure 2) is for steric or electronic reasons not high enough. In order to increase the nucleophilicity of the migrating group and to stabilize the incipient carbenium ion we considered the replacement of the alkyl group by a hydroxy group at carbon atom C1 a good choice. The rearrangement of intermediate **C** would occur in the sense of a pinacol rearrangement.[16]

Silyl enol ether **7**, easily available from methyl pyruvate,[17] offered itself as a potential olefin component in the [2+2] photocycloaddition to quinolones (Scheme 3). Indeed, the reactions proceeded cleanly with quinolin-2(1*H*)-one (**8**), 4-methylquinolin-2(1*H*)-one (**9**), and 4-acetoxyquinolin-2(1*H*)-one (**10**). Products **11**–**13** were obtained in a highly regio- and diastereoselective fashion. While the regioselectivity can be explained by the high stabilization of a triplet 1,4-diradical intermediate,[18] which bears an aryl substituent on one end and captodative substitution (CO_2Me, OTMS) on the other end, the high simple diastereoselectivity is remarkable. On steric grounds, the large substituents in the four-membered ring, methoxycarbonyl (CO_2Me) at C1 and aryl at C8b, are *trans*-positioned as are the small substituents trimethylsiloxy (OTMS) and R^1. Nonetheless, one would expect, at least, a deterioration of the diastereoselectivity if the size of R^1 increases. This is not the case as in the reactions **8** → **11**, **9** → **12**, and **10** → **13**, a single product was obtained in excellent yield.

It was a pleasant surprise to note that simple treatment of silyl ether **12** with potassium carbonate introduced a 1,2-rearrangement to product **14**. Apparently, the oxy anion generated by silyl deprotection exerts a strong electron-donating pressure, which forces the desired migration. Precedence for such a rearrangement was found in the work of Takeshita et al., who had earlier reported a retro-benzilic acid rearrangement of cyclobutane photoproducts

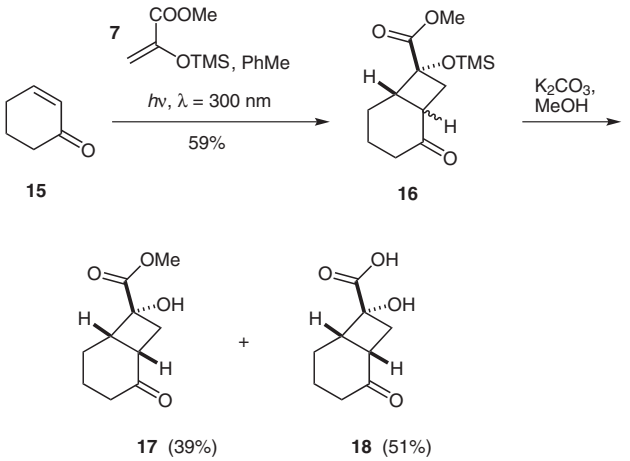
derived from 2,4-dioxopentanoate.[19] In our case, there was no indication of the intermediacy of a free carbanion, but its existence cannot be ruled out. The rearrangement of cyclobutane **12** proceeded very smoothly, and could even be performed directly in the irradiation mixture as a one-pot procedure.



Scheme 3 [2+2] Photocycloaddition of silyl enol ether **7** to quinolones **8**–**10** and subsequent retro-benzilic acid rearrangement of product **12**

Yields seem to be limited mainly by losses in the hydrolytic workup and recrystallization of the polar rearrangement product **14**. The attempted rearrangement of substrate **11** failed, however, because an initial, strongly fluorescent product quickly decomposed in the presence of the base to give a complex, polar mixture. This was most likely due to deprotonation and subsequent elimination/fragmentation reactions. Acetate **13** also displayed widespread fragmentation, but in this case quinolone **10** could be identified as the main product.

With regard to the rearrangement, we further investigated the prerequisites for the migration. More specifically, we tried to find out whether the rearrangement proceeds by the expected cleavage of the C1/C8b bond or by a cleavage of the C1/C2 bond. To this end the photocycloaddition of cyclohex-2-enone (**15**) and silyl enol ether **7** was investigated. Contrary to the excellent diastereoselectivity observed in the reactions with quinolin-2(1*H*)-ones, the reaction yielded an inseparable isomeric mixture, the two main constituents of which being putatively assigned as the *cis*- and *trans*-fused *exo*-HT-diastereoisomers **16** (dr ~ 1:1),[20,21] as well as ~10% of an unidentified, presumably C7 epimeric side product. Treatment of this mixture with potassium carbonate under identical conditions as for **12** resulted in instant OTMS deprotection as well as rapid epimerization at C1 to the thermodynamically more stable *cis*-fused isomer,[20] but no rearrangement was observed. Instead, prolonged stirring at ambient temperature only led to ester saponification, so that after one hour the free carboxylic acid **18** and its corresponding α-hydroxy ester **17** could be isolated, both in diastereomerically pure form (Scheme 4). With the intermediacy of compound **17** clearly proven, it appears safe to assume that a rearrangement would have certainly occurred if a migration of the methylene or methine group had been feasible. It therefore seems as if the rearrangement was only possible for quaternary, heteroatom-free carbon centers, while all rearrangement attempts on substrates lacking this feature failed for both the dihydroquinolone **11/13** and the cyclohexane **16/17** systems.



Scheme 4 [2+2] Photocycloaddition of cyclohex-2-enone (**15**) to silyl enol ether **7** and subsequent reactions induced by treatment of product **16** with potassium carbonate as base

In summary, two reactions were found, which occur by cleavage of the C1/C8b bond in the title compounds. Although of limited generality both reactions allow for useful further functionalization of quinolinones giving access to heteroanellated eight-membered lactams such as **4** and a cyclopentane-1,2-dione **14**.

Photochemical transformations were performed in Duran or quartz glass tubes (d = 1.0 cm) in a merry-go-round apparatus using 16 fluorescent lamps LZC-UVA (λ = 350 nm) or RPR-3000 Å (λ = 300 nm) at 35 °C. TLC: Merck glass sheets (0.25 mm silica gel 60, F254), eluent given in brackets. Detection by UV or coloration with $KMnO_4$. Flash chromatography was performed on silica gel 60 (Merck, 230–400 mesh) (dimensions of columns given as [diameter] × [height]) with the indicated eluent. Common solvents for chromatography [pentane, EtOAc, CH_2Cl_2, MeOH] were distilled prior to use. NMR: Bruker AV-250, AV-360, AV-500. ^1H and ^{13}C NMR spectra were recorded in the indicated solvent at r.t. Chemical shifts are reported relative to solvent residue signals as internal standard. Apparent multiplets, which occur as a result of the accidental equality of coupling constants of magnetically nonequivalent protons are marked as virtual (virt.). The multiplicities of the ^{13}C NMR signals were determined by DEPT experiments. Signals in the NMR spectra which may be interchanged are marked with an asterisk (*). IR: Perkin-Elmer 1600 FT-IR. MS: Finnigan MAT 8200 (EI), Agilent 5937 mass selective GC-MS detector (EI), Finnigan LCQ classic (ESI).

The syntheses of aldehyde **1**, tetracyclic lactam **3**, and silyl enol ether **7** have previously been described.[4,17] *N*,*O*-Acetal **5** was prepared from the literature-known alcohol (±)-*tert*-butyl *N*-benzyl-*N*-{2-[(1*S*,2a*S*,8b*R*)-1-(hydroxymethyl)-1-methyl-3-oxo-1,2,2a,3,4,8b-hexahydrocyclobuta[*c*]quinolin-8b-yl]ethyl}carb-

amate[4] by *N*-Boc deprotection with TFA (CH_2Cl_2) and subsequent treatment of the crude product with IBX (DMSO). 4-Acetoxyquinolin-2(1*H*)-one (**10**) was prepared by acetylation of 2,4-dihydroxyquinoline using a slightly modified literature procedure.[22] All other chemicals were commercially available and used as received.

N-Benzyl-*N*-(*tert*-butoxycarbonyl)-2-(2-oxo-1,2-dihydroquinolin-4-yl)ethylamine (2)

Treatment of aldehyde **1** with 3% TFA in CH_2Cl_2 at 0 °C for 1.0 h gave Boc-protected quinolone **2** in almost quantitative yield. More than 5% TFA in CH_2Cl_2 at r.t. resulted in *N*-Boc cleavage. 10% TFA in CH_2Cl_2 at r.t. gave the Boc-deprotected amine derivative of **2** as the sole product, the spectroscopic data of which have been described previously.[4]

(±)-(5*S*,6a*S*,12b*R*)-5-Methyl-2,3,6,6a,8,12b-hexahydroazocino[5,4-*c*]quinoline-4,7(1*H*,5*H*)-dione (4)

Tetracyclic lactam **3** (100 mg, 289 μmol) was dissolved in liquid NH_3 (50 mL) at –78 °C and treated with very small chunks of Na metal until a dark blue color persisted for more than a minute. The soln was quenched with solid NH_4Cl, and the NH_3 evaporated at r.t. H_2O (25 mL) and sat. aq NH_4Cl (100 mL) were added and the aqueous soln was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were dried (Na_2SO_4) and filtered. The solvent was evaporated and the crude product was purified by flash chromatography (2.5 × 20 cm, CH_2Cl_2–MeOH, 30:1 to 20:1) to give **4** (40 mg, 54%) as a white solid; mp >280 °C; R_f = 0.44 (CH_2Cl_2–MeOH, 10:1, UV).

IR (KBr): 3200 (s, br), 3020 (m, $C_{ar}H$), 2926 (w, $C_{al}H$), 1680 (vs, CO), 1654 (vs, CO), 1481 (m), 1428 (w), 1293 (m), 693 (m), 504 cm^{-1} (m).

^1H NMR (360 MHz, DMSO-d_6): δ = 10.13 (s, 1 H, NHCOAr), 7.35 (dd, ^3J = 8.9 Hz, ^3J = 5.5 Hz, 1 H, N*H*COR), 7.17–7.10 (m, 2 H, H-10, H-12), 6.93 (virt. t, ^3J = 7.4 Hz, 1 H, H-11), 6.88 (d, ^3J = 7.7 Hz, 1 H, H-9), 3.60–3.48 (m, 1 H, CH*H*NH), 3.10–2.95 (m, 2 H, ArCH, C*H*HNH), 2.94–2.86 (m, 1 H, C*H*CH$_3$), 2.78–2.72 (m, 1 H, NHCOC*H*), 1.94 (ddd, ^2J = 14.6 Hz, ^3J = 7.0 Hz, ^3J = 3.4 Hz, 1 H, H-6), 1.82–1.70 (m, 2 H, H-1), 1.53 (ddd, ^2J = 14.6 Hz, ^3J = 10.8 Hz, ^3J = 4.8 Hz, 1 H, H-6), 0.95 (d, ^3J = 6.4 Hz, 3 H, CH_3).

^{13}C NMR (90.6 MHz, DMSO-d_6): δ = 177.1 (s, CONHR), 172.2 (s, CONHAr), 137.3 (s, C8a), 131.0 (s, C-12a), 126.9* (d, C-10H), 124.9* (d, C-12H), 122.2 (d, C-11H), 115.5 (d, C-9H), 42.2 (d, C-6aH), 38.5 (t, CH_2N), 36.3 (d, C-12bH), 33.9* (t, C-1H_2), 33.7* (t, C-6H_2), 31.5 [d, *C*H(CH$_3$)], 18.3 [q, CH(*C*H$_3$)].

MS (EI): *m*/*z* (%) = 258 (18) [M$^+$], 230 (7) [(M – CO)$^+$], 214 (37) [(M – CONH$_2$)$^+$], 201 (18), 186 (21), 172 (10), 159 (23), 146 (33), 44 (100) [CONH$_2^+$].

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{15}H_{18}N_2O_2$: 258.1368; found: 258.1366.

(±)-(1a*S*,7b*S*,11a*R*)-10-Benzyl-11a-methyl-1,10,11,11a-tetrahydro-1a*H*-pyrido[4′,3′:2,3]cyclobuta[1,2-*c*]quinoline-2(3*H*)-one (6)

Enamine **6** was prepared from *N*,*O*-acetal **5** by heating a neat sample to >160 °C with a heat gun or a Kugelrohr. Thus, **5** (15 mg, 39.8 μmol) gave **6** (13 mg) as a yellow glass, which was analyzed without further purification; yellow oil; R_f = 0.63 (EtOAc, UV).

IR (KBr): 3201 (m, br), 2924 (m, $C_{al}H$), 1669 (vs, CO), 1590 (m), 1490 (m), 755 (m, C_{ar}), 699 cm^{-1} (m, C_{Ph}).

^1H NMR (360 MHz, $CDCl_3$): δ = 7.83 (s, 1 H, NH), 7.40–7.25 (m, 5 H, HBn), 7.18 (d, ^3J = 7.5 Hz, 1 H, H-7), 7.14 (virt. dt, ^3J = 7.7 Hz, ^4J = 1.4 Hz, 1 H, H-5), 6.98 (virt. dt, ^3J = 7.6 Hz, ^4J = 0.7 Hz, 1 H, H-6), 6.65 (d, ^3J = 7.9 Hz, 1 H, H-4), 6.41 (d, ^3J = 7.9 Hz, 1 H, =CHN), 4.53 (d, ^3J = 7.9 Hz, 1 H, CCH=), 4.15–4.05 (m, 2 H, CH_2Ph), 2.96 (dd, ^3J = 10.8 Hz, ^3J = 2.7 Hz, 1 H, COCH), 2.86 (dd, ^2J = 11.2 Hz, ^3J = 10.8 Hz, 1 H, H-1$_{exo}$), 2.49 (d, ^2J = 11.9 Hz, 1 H, NCH*H*), 2.21 (d, ^2J = 11.9 Hz, 1 H, NC*H*H), 2.00 (dd, ^2J = 11.2 Hz, ^3J = 2.7 Hz, 1 H, H-1$_{endo}$), 0.85 (s, 3 H, CH_3).

^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 173. 6 (s, CO), 138.1 (s, C_{ar}), 137.4 (s, C_{ar}), 137.3 (d, =CHN), 129.0 (d, C-7H), 128.5 (d, C-BnH), 128.1 (d, C-BnH), 127.8 (d, C-BnH), 127.4 (d, C-5H), 126.0 (s, C_{ar}), 123.2 (d, C-6H), 114.7 (d, C-4H), 104.0 (d, C*C*H=), 59.4 (t, CH_2Ph), 53.6 (t, NCH_2), 44.7* (s, C-7b), 44.0* (s, C-11a), 43.6 (d, CO*C*H), 33.5 (C-1H_2), 22.4 (q, CH_3).

MS (ESI): *m*/*z* = 331 [M + H$^+$], 1143, 1473.

4-Acetoxyquinolin-2(1*H*)-one (10)

Acetylation of 2,4-dihydroxyquinoline with an excess of Ac_2O[22] and Et_3N (1.0 equiv) gave **10** as white needles; yield: 48%; mp 214–216 °C; R_f = 0.73 (CH_2Cl_2–MeOH, 10:1, UV). Spectroscopic data have not been previously published.

IR (KBr): 3496 (s, br, NH), 2843 (s, $C_{al}H$), 1763 (s, COMe), 1670 (vs, CONH), 1503 (s), 1434 (m), 1381 (m), 911 (m), 762 (m), 508 cm^{-1} (m).

^1H NMR (250 MHz, DMSO-d_6): δ = 11.91 (br, 1 H, NH), 7.65 (d, ^3J = 8.0 Hz, 1 H, H-5), 7.56 (t, ^3J = 7.3 Hz, 1 H, H-7), 7.37 (d, ^3J = 8.0 Hz, 1 H, H-8), 7.20 (t, ^3J = 7.4 Hz, 1 H, H-6), 6.41 (s, 1 H, H-3), 2.42 (s, 3 H, CH_3).

^{13}C NMR (63 MHz, DMSO-d_6): δ = 168.1 (s, COMe), 162.3 (s, CONH), 156.1 (s, C-4), 139.0 (s, C-8a), 131.5 (d, C-7H), 122.5 (d, C-5H), 122.0 (d, C-6H), 115.5 (d, C-8H), 114.8 (s, C-4a), 112.3 (d, C-3H), 20.8 (q, CH_3).

MS (EI): *m*/*z* (%) = 203 (34) [M$^+$], 161 (100) [(M – Ac)$^+$], 133 (15), 119 (35), 43 (34) [Ac$^+$].

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{11}H_9NO_3$: 203.0582; found: 203.0584.

(±)-Methyl (1*R*,2a*S*,8b*R*)-3-Oxo-1-(trimethylsiloxy)-1,2,2a,3,4,8b-hexahydrocyclobuta[*c*]quinoline-1-carboxylate (11)

Quinolin-2(1*H*)-one (**8**, 250 mg, 1.72 mmol) and silyl enol ether **7** (3.25 mL, 3.00 g, 17.2 mmol, 10 equiv) were dissolved in MeOH (83 mL) and irradiated at λ = 350 nm for 1.5 h. After evaporation of the solvent, the crude product was purified by flash chromatography (3.0 × 20 cm, pentane–EtOAc, 2:1 to 1:1) to give **11** (452 mg, 82%) as a white solid; mp 135–138 °C; R_f = 0.58 (EtOAc, UV).

IR (KBr): 3204 (m), 3070 (w, $C_{ar}H$), 2953 (w, $C_{al}H$), 1741 (s, COOMe), 1672 (vs, CONH), 1594 (m), 1495 (m), 1394 (s), 847 (s), 757 cm^{-1} (m).

^1H NMR (250 MHz, $CDCl_3$): δ = 9.04 (br, 1 H, NH), 7.17 (t, ^3J = 7.0 Hz, 1 H, H-6), 7.01–6.96 (m, 2 H, H-7, H-8), 6.80 (d, ^3J = 7.9 Hz, 1 H, H-5), 4.17 (dd, ^3J = 9.1 Hz, ^4J_w = 1.9 Hz, 1 H, H-8b), 3.82 (s, 3 H, OCH_3), 3.34 (ddd, $^3J_{exo}$ = 9.3 Hz, ^3J = 9.1 Hz, $^3J_{endo}$ = 6.0 Hz, 1 H, COCH), 3.13 (ddd, ^2J = 12.0 Hz, ^3J = 9.3 Hz, ^4J_w = 1.9 Hz, 1 H, H-2$_{exo}$), 2.51 (dd, ^2J = 12.0 Hz, ^3J = 6.0 Hz, 1 H, H-2$_{endo}$), –0.12 [s, 9 H, Si(CH$_3$)$_3$].

^{13}C NMR (63 MHz, $CDCl_3$): δ = 173.5 (s, COOMe), 171.6 (s, CONH), 138.0 (s, C-4a), 130.6 (d, C-8H), 128.3 (d, C-6H), 122.8 (d, C-7H), 117.7 (s, C-8a), 115.5 (d, C-5H), 78.6 (s, C-1), 52.4 (q, OCH_3), 46.4 (d, ArCH), 40.2 (t, C-2H_2), 32.1 (d, CO*C*H), 1.0 [q, Si(CH$_3$)$_3$].

MS (EI): *m*/*z* (%) = 319 (2) [M$^+$], 159 (8), 145 (100) [QuinH$^+$], 117 (8), 89 (9) [TMSO$^+$], 73 (8) [TMS$^+$], 59 (4), 43 (5) [$C_3H_7^+$].

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{16}H_{21}NO_4Si$: 319.1240; found: 319.1244.

(±)-Methyl (1*R*,2a*S*,8b*R*)-8b-Methyl-3-oxo-1-(trimethylsiloxy)-1,2,2a,3,4,8b-hexahydrocyclobuta[*c*]quinoline-1-carboxylate (12)

4-Methylquinolin-2(1*H*)-one (**9**, 250 mg, 1.57 mmol) and silyl enol ether **7** (1.52 mL, 1.37 g, 7.85 mmol, 5 equiv) were dissolved in MeOH (77 mL) and irradiated at λ = 350 nm for 1.5 h. After evaporation of the solvent, the crude product was purified by flash chromatography (3.0 × 20 cm, pentane–EtOAc, 2:1 to 1:1) to give **12** (378 mg, 72%) as a white solid; mp 148–150 °C; R_f = 0.46 (pentane–EtOAc, 1:1, UV).

IR (KBr): 3434 (w, br, CONH), 3063 (w, $C_{ar}H$), 2961 (w, $C_{al}H$), 1728 (s, COOMe), 1672 (vs, CONH), 1591 (m), 1490 (m), 1399 (s), 1181 (m), 751 cm^{-1} (m).

^{1}H NMR (360 MHz, $CDCl_3$): δ = 9.24 (br, 1 H, NH), 7.22 (d, ^3J = 7.7 Hz, 1 H, H-8), 7.18 (t, ^3J = 7.6 Hz, 1 H, H-6), 7.01 (t, ^3J = 7.5 Hz, 1 H, H-7), 6.81 (d, ^3J = 7.4 Hz, 1 H, H-5), 3.84 (s, 3 H, OCH_3), 3.12 (dd, ^2J = 9.9 Hz, ^3J = 9.2 Hz, 1 H, H-2$_{exo}$), 3.04 (dd, ^3J = 9.2 Hz, ^3J = 8.5 Hz, 1 H, COCH), 2.21 (dd, ^2J = 9.9 Hz, ^3J = 8.5 Hz, 1 H, H-2$_{endo}$), 1.35 (s, 3 H, CH_3), –0.12 [s, 9 H, $Si(CH_3)_3$].

^{13}C NMR (63 MHz, $CDCl_3$): δ = 173.3 (s, COOMe), 170.7 (s, CONH), 135.9 (s, C-4a), 131.4 (d, C-8H), 128.0 (d, C-6H), 122.6 (s, C-8a), 122.5 (d, C-7H), 115.6 (d, C-5H), 80.4 (s, C-1) 52.0 (q, OCH_3), 51.1 (s, C-8b), 38.6 (d, CO*C*H), 37.1 (t, C-2H_2), 25.4 (q, CH_3), 0.8 [q, $Si(CH_3)_3$].

MS (EI): *m*/*z* (%) = 333 (1) [M^+], 159 (100) [QuinCH_3^+], 130 (10), 89 (4), 73 (6), 59 (3).

HRMS (EI): *m*/*z* [M^+] calcd for $C_{17}H_{23}NO_4Si$: 333.1396; found: 333.1394.

(±)-Methyl (1*R*,2a*S*,8b*R*)-8b-Acetoxy-3-oxo-1-(trimethylsiloxy)-1,2,2a,3,4,8b-hexahydrocyclobuta[*c*]quinoline-1-carboxylate (13)

4-Acetoxyquinolin-2(1*H*)-one (**10**, 300 mg, 1.48 mmol) and silyl enol ether **7** (2.49 mL, 2.57 g, 14.8 mmol, 10 equiv) were dissolved in acetone (71 mL) and irradiated at λ = 300 nm for 2.5 h. After evaporation of the solvent, the crude product was purified by flash chromatography (3.5 × 20 cm, pentane–EtOAc, 1:1 to 1:2) to give **13** (502 mg, 90%) as a white solid; mp 203–206 °C; R_f = 0.30 (pentane–EtOAc, 1:1, UV).

IR (KBr): 3447 (w, br, CONH), 3081 (w, $C_{ar}H$), 2955 (w, $C_{al}H$), 1741 (s, br, COO), 1680 (vs, CONH), 1597 (m), 1398 (s), 1181 (m), 1044 (s), 756 cm^{-1} (m).

^{1}H NMR (360 MHz, $CDCl_3$): δ = 9.74 (br, 1 H, NH), 7.33 (d, ^3J = 7.9 Hz, 1 H, H-8), 7.26 (t, ^3J = 7.9 Hz, 1 H, H-6), 7.02 (t, ^3J = 7.8 Hz, 1 H, H-7), 6.91 (d, ^3J = 7.7 Hz, 1 H, H-5), 3.87 (s, 3 H, OCH_3), 3.59 (virt. t, ^3J = 10.1 Hz, 1 H, COCH), 3.06 (virt. t, $^3J \approx {}^2J$ = 10.6 Hz, 1 H, H-2$_{exo}$), 1.93–1.87 (m, 4 H, H-2$_{endo}$, CH_3), –0.10 [s, 9 H, $Si(CH_3)_3$].

^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 171.8 (s, COOMe), 169.2* (s, COMe), 169.1* (s, CONH), 137.5 (s, C-4a), 131.5 (d, C-8H), 130.0 (d, C-6H), 122.2 (d, C-7H), 116.0 (s, C-8a), 115.7 (d, C-5H), 81.8 (s, C-8b), 80.4 (s, C-1) 52.5 (q, OCH_3), 40.4 (d, CO*C*H), 34.6 (t, C-2H_2), 20.8 (q, CH_3), 0.8 [q, $Si(CH_3)_3$].

MS (EI): *m*/*z* (%) = 377 (4) [M^+], 203 (46), 161 (100) [QuinOH^+], 119 (6), 89 (10) [$TMSO^+$], 73 (14) [TMS^+], 59 (6), 43 (22) [Ac^+].

HRMS (EI): *m*/*z* [M^+] calcd for $C_{18}H_{23}NO_6Si$: 377.1295; found: 377.1284.

(±)-(3a*S*,9b*R*)-2-Hydroxy-9b-methyl-5,9b-dihydro-1*H*-cyclopenta[*c*]quinoline-1,4(3a*H*)-dione (14)

Cyclobutane **12** (50 mg, 150 μmol) was stirred in MeOH (5.0 mL) with an excess of K_2CO_3 at r.t. for 4.0 h. Sat. aq. NH_4Cl (40 mL) was added and the mixture extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were dried (Na_2SO_4) and filtered. After evaporation of the solvent enone **14** (26 mg, 76%) was obtained as an off-white solid.

In an alternative one-pot procedure, irradiation of 4-methylquinolin-2(1*H*)-one (**9**, 250 mg, 1.57 mmol) and silyl enol ether **7** (1.50 mL, 1.37 g, 7.85 mmol, 5 equiv) in MeOH (70 mL) and direct treatment of the irradiation mixture with K_2CO_3 followed by aqueous workup and recrystallization (CH_2Cl_2–pentane) afforded crystalline enone **14** (170 mg, 47%); mp 110–113 °C; R_f = 0.40 (EtOAc, UV). Additional purification by flash chromatography was not successful.

IR (KBr): 3200 (vs, br, OH), 1715 (s, CO), 1655 (vs, CONH), 1590 (m), 1495 (w), 1387 (m), 1149 (m), 1099 (m), 756 cm^{-1} (m).

^{1}H NMR (360 MHz, DMSO-d_6): δ = 10.43* (br, 1 H, OH), 10.08* (br, 1 H, NH), 7.48 (d, ^3J = 7.7 Hz, 1 H, H-9), 7.16 (t, ^3J = 7.6 Hz, 1 H, H-7), 6.99 (t, ^3J = 7.6 Hz, 1 H, H-8), 6.87 (d, ^3J = 7.9 Hz, 1 H, H-6), 6.40 (d, ^3J = 3.2 Hz, 1 H, =CH), 3.47 (d, ^3J = 3.2 Hz, 1 H, COCH), 1.42 (s, 3 H, CH_3).

^{13}C NMR (63 MHz, DMSO-d_6): δ = 203.0 (s, CO), 167.6 (s, CONH), 153.3 (s, COH), 135.5 (s, C-4a), 128.0* (d, C_7H), 127.6* (d, C_9H), 126.8 (d, =CH), 122.6 (d, C-8H), 121.9 (s, C-9a), 115.2 (d, C-6H), 48.2 (d, CO*C*H), 47.3 (s, C-9b), 26.4 (q, CH_3).

MS (EI): *m*/*z* (%) = 229 (100) [M^+], 214 (18) [$(M - CH_3)^+$], 200 (7), 184 (15), 172 (22), 159 (34) [QuinCH_3^+], 130 (27), 43 (83) [$C_3H_7^+$], 41 (38) [C_2HO^+].

HRMS (EI): *m*/*z* [M^+] calcd for $C_{13}H_{11}NO_3$: 229.0739; found: 229.0734.

(±)-Methyl (1*R*/*S*,6*R*,7*R*/*S*)-2-Oxo-7-(trimethylsiloxy)bicyclo[4.2.0]octane-7-carboxylate (16)

Cyclohex-2-en-1-one (**15**, 303 mg, 3.15 mmol, 50.0 mM) and silyl enol ether **7** (3.35 mL, 3.08 g, 17.7 mmol, 5.6 equiv) in toluene (63 mL) were irradiated in quartz-glass tubes (λ = 300 nm) for 10.0 h. After evaporation of the solvent, the crude product was purified by flash chromatography (3.5 × 25 cm, pentane–EtOAc, 10:1) to give **16** (500 mg, 59%) as a colorless oil; R_f = 0.60 (pentane–EtOAc, 2:1, $KMnO_4$). Compound **16** was an inseparable diastereomeric mixture of two *exo*-HT-photocycloaddition products (6*R*,7*S*), as well as ~10% of an unidentified diastereoisomer. The mixture was used directly in the next step

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.76 (s, 3 H, OCH_3), 3.72 (s, 3 H, OCH_3), 3.20–3.08 (m, 2 H), 2.94–2.88 (m, 2 H), 2.69–2.58 (m, 2 H), 2.45–2.20 (m, 6 H), 2.20–2.07 (m, 2 H) 1.95–1.65 (m, 6 H), 0.16 [s, 9 H, $Si(CH_3)_3$], 0.12 [s, 9 H, $Si(CH_3)_3$].

^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 213.0/208.7 (s, CO), 174.9/172.5 (s, COOMe), 79.8/75.7 (s, C-7), 54.5/45.3 (d, C-6H), 52.1/52.0 (q, OCH_3), 47.9/38.0 (d, C-1H), 40.4/38.4 (t, C-8H_2), 39.1/36.4 (t, C-3H_2), 27.8/21.8 (t, C-4H_2), 24.7/21.4 (t, C-5H_2), 1.30/1.18 [q, $Si(CH_3)_3$].

MS (EI): *m*/*z* (%) = 270 (5) [M^+], 255 (7) [$(M - Me)^+$], 211 (16) [$(M - COOMe)^+$], 200 (20), 185 (60), 169 (55) [$(185–Me)^+$], 159 (100), 89 (50) [$OTMS^+$], 73 (45) [TMS^+].

HRMS (EI): *m*/*z* [M^+] calcd for $C_{13}H_{22}O_4Si$: 270.1287; found: 270.1282.

(±)-Methyl (1*R*,6*R*,7*S*)-7-Hydroxy-2-oxobicyclo[4.2.0]octane-7-carboxylate (17) and (±)-(1*R*,6*R*,7*S*)-7-Hydroxy-2-oxobicyclo[4.2.0]octane-7-carboxylic Acid (18)

Diastereomeric mixture **16** (80 mg, 300 μmol) was stirred in MeOH (5.0 mL) with an excess of K_2CO_3 at r.t. for 1.0 h. Sat. aq NH_4Cl (40 mL) and H_2O (40 mL) were added and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic phases were

dried (Na_2SO_4) and filtered. After evaporation of the solvent the crude product was purified by flash chromatography to give the diastereomerically pure ester **17** (23 mg, 39%) as a colorless oil. The remaining aqueous phase was acidified to pH 1 with concd aq HCl and extracted with EtOAc (3 × 10 mL). The combined extracts were dried (Na_2SO_4) and the solvent was evaporated to give the diastereomerically pure carboxylic acid **18** (28.0 mg, 51%) as a colorless oil.

(±)-Methyl (1*R*,6*R*,7*S*)-7-Hydroxy-2-oxobicyclo[4.2.0]octane-7-carboxylate (17)

Colorless oil; R_f = 0.24 (pentane–EtOAc, 1:1, $KMnO_4$).

IR (film): 3468 (s, br, OH), 2953 (s, $C_{al}H$), 1714 (vs, CO), 1700 (vs, CO), 1439 (m), 1374 (m), 1276 (s), 1244 (s), 1211 (s), 1180 (s), 1096 (m), 1046 cm^{-1} (m).

^1H NMR (360 MHz, $CDCl_3$): δ = 3.83 (s, 3 H, OCH_3), 3.42 (s, 1 H, OH), 3.12 (dddd, $^3J_{cis}$ = 8.3 Hz, ^3J = 8.2 Hz, ^3J = 6.3 Hz, ^4J = 2.5 Hz, 1 H, H-6), 2.97 (ddd, ^3J = 9.4 Hz, ^3J = 8.4 Hz, $^3J_{cis}$ = 8.3 Hz, 1 H, H-1), 2.85 (ddd, ^2J = 12.5 Hz, ^3J = 9.4 Hz, ^4J = 2.5 Hz, 1 H, H-8$_{exo}$), 2.45 (ddd, ^2J = 17.4 Hz, ^3J = 7.8 Hz, ^3J = 5.7 Hz, 1 H, H-3), 2.38 (br. dd, ^2J = 12.5 Hz, ^3J = 8.4 Hz, 1 H, H-8$_{endo}$), 2.29 (ddd, ^2J = 17.4 Hz, ^3J = 7.8 Hz, ^3J = 5.4 Hz, 1 H, H-3), 2.21–2.11 (m, 1 H, H-4), 1.98–1.88 (m, 1 H, H-5), 1.85–1.74 (m, 1 H, H-4), 1.75–1.66 (m, 1 H, H-5).

^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 212.9 (s, CO), 176.1 (s, COOMe), 73.3 (s, C-7), 53.1 (q, OCH_3), 44.5 (d, C-6H), 39.1 (t, C-3H_2), 37.6 (d, C-1H), 37.4 (t, C-8H_2), 21.5 (t, C-4H_2), 21.2 (t, C-5H_2).

HRMS (EI): *m*/*z* [M^+] calcd for $C_{10}H_{14}O_4$: 198.0892; found: 198.0889.

(±)-(1*R*,6*R*,7*S*)-7-Hydroxy-2-oxobicyclo[4.2.0]octane-7-carboxylic Acid (18)

Colorless oil; R_f = 0.00 (pentane–EtOAc, 1:1, $KMnO_4$).

^1H NMR (360 MHz, $CDCl_3$): δ = 5.64 (v br, 1 H, COOH), 3.80 (br, 1 H, OH), 3.24 (dddd, $^3J_{cis}$ = 8.2 Hz, ^3J = 7.8 Hz, ^3J = 6.9 Hz, ^4J = 2.2 Hz, 1 H, H-6), 3.03 (ddd, ^3J = 9.5 Hz, ^3J = 8.3 Hz, $^3J_{cis}$ = 8.2 Hz, 1 H, H-1), 2.93 (dd, ^2J = 12.4 Hz, ^3J = 9.5 Hz, 1 H, H-8$_{exo}$), 2.55–2.30 (m, 3 H, H-3, H-8$_{endo}$), 2.22–2.14 (m, 1 H, H-4), 2.01–1.91 (m, 1 H, H-5), 1.90–1.82 (m, 1 H, H-4), 1.77–1.67 (m, 1 H, H-5).

^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 214.0 (s, CO), 179.4 (s, COOH), 73.1 (s, C-7), 44.6 (d, C-6H), 39.1 (t, C-3H_2), 37.7 (d, C-1H), 37.3 (t, C-8H_2), 21.5 (t, C-4H_2), 21.2 (t, C-5H_2).

HRMS (EI): *m*/*z* [M^+] calcd for $C_9H_{12}O_4$: 184.0736; found: 184.0743.

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