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An efficient route for the construction of cyclopenta[*b*]quinoline derivatives via intramolecular cyclopropanation

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Abstract—A one-pot process to introduce diazoacetoacetate functionality into quinoline was identified with excellent yield and regioselectivity. An intramolecular cyclopropanation of the resulting adducts gave tetracyclic cyclopenta[*b*]quinoline derivatives in nearly quantitative yields. A synthetic utility of the tetracyclic derivatives was examined by a simple ring opening reaction to afford cyclopenta[*b*]quinoline in a good yield.

1. Introduction

The quinoline ring systems are important structural units in naturally occurring alkaloids and synthetic compounds with interesting biological activities.[1] Cyclopenta[*b*]quinoline derivatives are of particular importance among the quinoline analogues due to their wide range of biological activities[2] such as antiinflammatory activity,[2a] antimalarial activity,[2b] and cholinesterase inhibition activity.[2c] Additionally, cyclopenta[*b*]quinoline moiety is present in certain natural products such as isoschizogaline[2d] and isoschizogamine.[2d,e] Therefore, the development of simple and convenient methodologies for synthesis of cyclopenta[*b*]quinoline derivatives is an interesting and attractive endeavor for both organic and medicinal chemists.

Nucleophilic addition to activated quinoline C=N bonds has been reported to be an efficient method to prepare 2-substituted quinoline derivatives.[3] As a result of the addition reaction, the remaining olefin C=C bond functionality in the quinoline would be more reactive due to dearomatization of the quinoline ring. We envisioned that the C=C bonds would be feasible to undergo cyclopropanation reaction with carbenoids, and an intramolecular fashion of such a reaction would result in ring fused cyclopenta[*b*]quinoline derivatives.

Chemical modifications with diazocarbonyl compounds have been of long-standing interest,[4a] and both acid and base promoted aldol reactions have been developed for this purpose. Diazoacetoacetates were widely used for such modifications.[4] The unattached diazo functionality after the modification can be used in further catalytic metal carbene reactions to generate more complex molecules. Calter's group reported that boron enolates of diazoacetoacetates underwent condensation with aldehydes.[5] Recently, similar reaction was reported by Wang's group with titanium(IV) enolates.[6] In both cases, stoichiometric amounts of the Lewis acids were required to achieve full conversion. Doyle et al. developed an improved addition reaction of methyl 3-(*tert*-butyldimethylsilanoxy)-2-diazobut-3-enoate[7] with both aldehydes and imines, but with catalytic amounts of lanthanide triflates or scandium-(III) triflates.[8] However, methyl 3-(*tert*-butyldimethylsilanoxy)-2-diazobut-3-enoate is unstable and difficult to handle.

2. Results and discussion

Herein, we wish to report an addition reaction of methyl 3-(*tert*-butyldimethylsilanoxy)-2-diazobut-3-enoate to quinolines in situ activated by an acyl chloride. Due to the enhanced reactivity of the activated quinoline C=N, no additional Lewis acid catalyst was necessary to achieve high yields. Additionally, the diazo functionality in the resulting adduct underwent rhodium(II)-catalyzed intramolecular cyclopropanation to give tetracyclic cyclopenta[*b*]quinoline derivatives quantitatively.

To simplify the manipulation for the quinoline addition reaction, we were able to conduct the reaction in a four-component one-pot fashion without using isolated methyl

Keywords: Cyclopenta[*b*]quinoline; Cyclopropanation; Dirhodium(II); Diazo compounds; Carbene.
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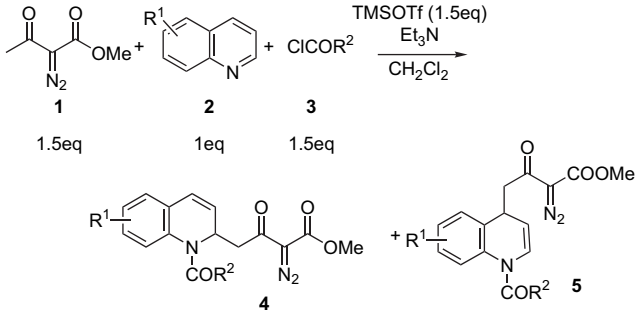
3-(*tert*-butyldimethylsilanoxy)-2-diazobut-3-enoate. It was found that the reaction media for the activation of quinoline were applicable for the in situ generation of methyl 3-(*tert*-butyldimethylsilanoxy)-2-diazobut-3-enoate from TMSOTf and methyl diazoacetoacetate. Thus, methyl diazoacetoacetate, TMSOTf, triethylamine, alkyl chloroformate, quinolines were sequentially added to methylene dichloride to afford substituted quinoline derivatives **4** and **5** in nearly quantitative yields (Scheme 1). A plausible reaction pathway for the one-pot reaction to generate adducts **4c** and **5c** is shown in Scheme 2. A similar one-pot reaction strategy was reported previously in the addition reactions of in situ formed silyl enol ethers with an imidazole activated by an alkyl chloroformate.[9]



Scheme 1. One-pot synthesis of the 2-substituted adducts **4** by the sequential addition of methyl diazoacetoacetates, trimethylsilyltriflate, triethylamine, quinoline, and alkyl chloroformate.

Initially, the effects of various acyl chlorides on the reaction were examined, as shown in Table 1 (entries 1–4). The addition to the quinoline activated by benzoyl chloride proceeded smoothly to afford regioisomeric adducts **4a** and **5a** in a nearly quantitative yield favoring the desired 2-substituted isomer **4a** (**4a/5a**=86:14). Similar regioselectivity was observed with the use of methyl chloroformate instead of benzoyl chloride (**4b/5b**=85:15), but the improved regioselectivity was obtained with ethyl chloroformate (**4c/5c**=88:12). The best result of **4d/5d**=98:2 was obtained when benzyl chloroformate was used in the reaction (Table 1, entry 4). Considering the high regioselectivity, as well as easy deprotection of the resulting *N*-Cbz groups (Cbz=carbobenzyloxy), benzyl chloroformate was chosen as the activating reagent through out the study. A number of substituted quinoline derivatives were applied in the reaction under the conditions with the CbzCl/TMSOTf/Et_3N/CH_2Cl_2 system.

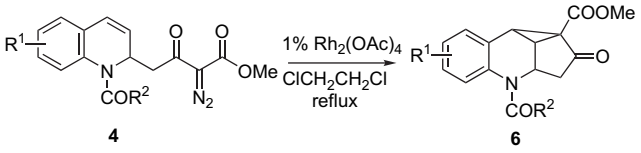
Table 1. The effect of various chloroformate esters and quinoline substitutions on the reaction

Entry	R^1 (**2**)	R^2	Isolated yields of **4** and **5**[a] (%)	Ratio of **4**/**5**[b]
1	H (**2a**)	C_6H_5	99 (**4a+5a**)	86:14
2	H (**2a**)	MeO	99 (**4b+5b**)	85:15
3	H (**2a**)	EtO	99 (**4c+5c**)	88:12
4	H (**2a**)	BnO	98 (**4d+5d**)	98:2
5	2-Me (**2b**)	BnO	NR[c]	NR[c]
6	3-Me (**2c**)	BnO	99 (**4e+5e**)	98:2
7	4-Me (**2d**)	BnO	99 (**4f+5f**)	95:5
8	6-Me (**2e**)	BnO	99 (**4g+5g**)	96:4
9	6-MeO (**2f**)	BnO	95 (**4h+5h**)	99:1
10	6-NO_2 (**2g**)	BnO	95 (**4i+5i**)	98:2
11	8-MeO (**2h**)	BnO	NR[c]	NR[c]

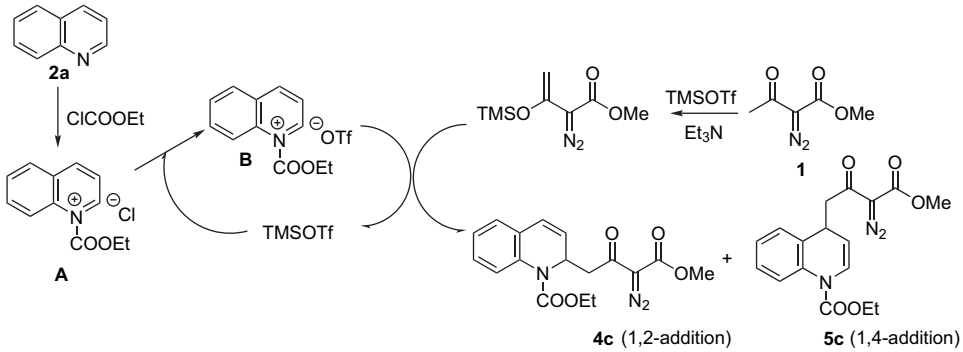
[a] Isolated yields after chromatography.
[b] Determined by ^1H NMR of crude reaction mixtures.
[c] No desired reaction occurred.

The reaction was very sensitive to the substituents on both 2- and 8-position of the quinoline. No reaction occurred with 2- or 8-substituted quinolines under the standard reaction conditions (Table 1, entries 5 and 11). This was probably owing to the steric bulkiness at 2- or 8-position preventing the acyl chloride to activate corresponding quinoline. All other 3-, 4- or 6- substituted quinolines gave the desired adducts in nearly quantitative yields with excellent regioselectivity (Table 1, entries 6–10).

The potential of this addition process for synthetic transformations was examined through diazo decomposition (Scheme 3). Treatment of adducts **4** with 1.0 mol % dirhodium(II) acetate led to the formation of tetracyclic cyclopenta[*b*]quinoline analogues quantitatively in most cases. Exceptions are **4a** and **4e**, which gave the intramolecular cyclopropanation products in a relatively lower yield (Table 2, entries 1 and 5). The structure of cyclopropanation products **6** was confirmed by a single-cystal X-ray analysis of **6c** (Fig. 1).[10] To the best of our knowledge, the tetracyclic compounds **6** were a new type of cyclopenta[*b*]quinoline analogues, and might be of general interests to medicinal chemists for the evaluation of potential biological activities.

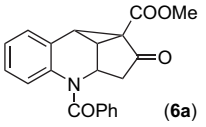
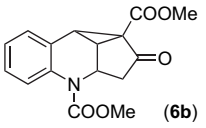
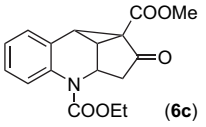
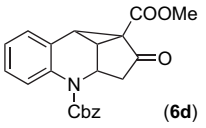
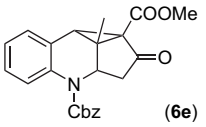
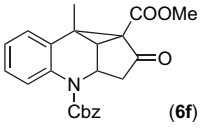
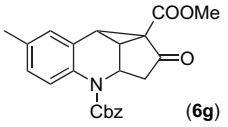
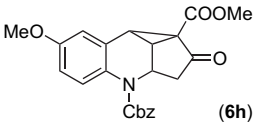
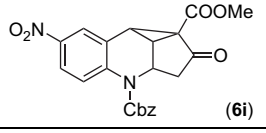


Scheme 3. Intramolecular cyclopropanation reaction of **4**.



Scheme 2. A representative reaction mechanism to generate adducts **4** and **5**.

Table 2. Intramolecular cyclopropane reaction of **4**[a]

Entry	4	Product (**6**)	Yield[b] of **6** (%)
1	**4a**	 (**6a**)	85
2	**4b**	 (**6b**)	100
3	**4c**	 (**6c**)	100
4	**4d**	 (**6d**)	100
5	**4e**	 (**6e**)	87
6	**4f**	 (**6f**)	100
7	**4g**	 (**6g**)	100
8	**4h**	 (**6h**)	100
9	**4i**	 (**6i**)	100

[a] All reactions were carried out in refluxing $ClCH_2CH_2Cl$ in the presence of $Rh_2(OAc)_4$ (1 mol %).
[b] Isolated yields after chromatography.

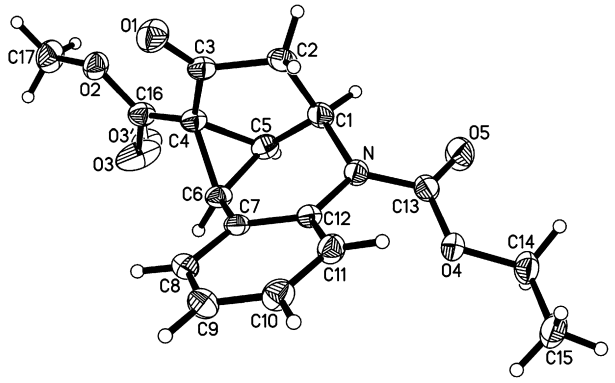
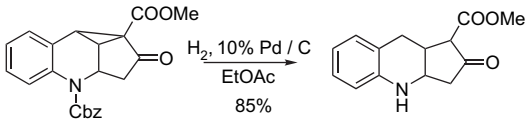


Figure 1. X-ray structure of **6c**.

Compounds **6** could also serve as valuable synthetic intermediates for other quinoline derivatives. For example, ring opening reaction of **6d** occurred smoothly under hydrogenolysis to give cyclopenta[*b*]quinoline **7** in 85% yield with an unoptimized reaction condition. Meanwhile, the Cbz group was removed simultaneously under such a condition (Scheme 4).



Scheme 4. The open-ring reaction of tetracyclic compound **6d**.

3. Conclusion

In summary, we have developed a one-pot process to introduce diazoacetoacetate functionality into quinoline with both excellent yield and regioselectivty. The synthetic utility of the adducts has been demonstrated by intramolecular cyclopropanation to give tetracyclic cyclopenta[*b*]quinoline derivatives **6** in nearly quantitative yields. This method provides an alternative entry to access cyclopenta[*b*]quinoline derivatives.

4. Experimental section

4.1. General

All chemicals were purchased from commercial suppliers and used without further purification. Melting points are uncorrected. NMR spectra were recorded on a Brucker-300 MHz spectrometer. HRMS (ESI) Mass spectra were recorded on BRUKER FT-MS. Dichloromethane was distilled over calcium hydride. 1,2-Dichloroethane was dried over anhydrous $CaCl_2$ without further purification. All reactions were carried out under argon atmosphere in well-dried glassware.

4.2. Typical procedure for the one-pot synthesis of diazo adducts 4

Methyl diazoacetoacetate (1 mmol) was dissolved in CH_2Cl_2 (4 ml), and TMSOTf (222 mg, 1 mmol) and triethylamine (101 mg, 1 mmol) were added successively at 5–8 °C under an inert atmosphere. The mixture was allowed to stir at the same temperature for additional 1 h. Acyl chloride (1 mmol) and quinolines (0.67 mmol) were added to the mixture, and the resulting reaction mixture was allowed to stir for 3–8 h until completion. Solvent was removed and the crude product was subject to ^1H NMR analysis for the determination of **4/5** ratio. The crude product was purified by flash chromatography on silica gel eluting with EtOAc/light petroleum ether to give (**4+5**).

4.2.1. Methyl 2-diazo-4-[2-(1-benzoxy-1,2-dihydro)quinoline]-3-oxobutyrate (4a). R_f=0.25 (10% EtOAc/light petroleum ether); yellow solid, mp=105–108 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.21–7.32 (m, 5H), 7.08–7.09 (m, 1H), 6.98–6.99 (m, 1H), 6.80–6.82 (m, 1H), 6.58–6.61 (m, 1H), 6.49–6.50 (m, 1H), 6.28–6.33 (m, 1H), 5.68–5.73 (m, 1H), 3.79 (s, 3H), 3.28 (dd, J_1=14.8 Hz, J_2=6.4 Hz,

1H), 2.78 (dd, J_1=14.8 Hz, J_2=7.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.2, 169.7, 161.8, 135.3, 135.1, 130.3, 129.6, 129.0, 127.9, 126.9, 126.8, 126.1, 125.9, 125.2, 124.8, 75.6, 52.1, 49.3, 42.9; HRMS: calcd for $C_{21}H_{17}N_3O_4Na$: 398.1111, $[M+Na]^+$; found: 398.1113.

4.2.2. Methyl 2-diazo-4-[2-(1-methoxycarbonyl-1,2-dihydro)quinoline]-3-oxobutyrate (4b). R_f=0.25 (10% EtOAc/light petroleum ether); white solid, mp=78–80 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52–7.54 (m, 1H), 7.19–7.24 (m, 1H), 7.05 (m, 2H), 6.46–6.47 (m, 1H), 6.11–6.16 (m, 1H), 5.47–5.54 (m, 1H), 3.77 (s, 3H), 3.75 (s, 3H), 3.18 (dd, J_1=15.1 Hz, J_2=6.4 Hz, 1H), 2.74 (dd, J_1=15.1 Hz, J_2=7.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.1, 161.6, 154.5, 133.9, 128.4, 127.6, 126.6, 126.2, 125.3, 124.6, 124.3, 75.6, 52.9, 52.1, 49.5, 43.5; HRMS: calcd for $C_{16}H_{15}N_3O_5Na$: 352.0904, $[M+Na]^+$; found: 352.0904.

4.2.3. Methyl 2-diazo-4-[2-(1-ethoxycarbonyl-1,2-dihydro)quinoline]-3-oxobutyrate (4c). R_f=0.25 (10% EtOAc/light petroleum ether); yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56–7.58 (m, 1H), 7.19–7.24 (m, 1H), 7.06–7.07 (m, 2H), 6.47–6.50 (m, 1H), 6.12–6.15 (m, 1H), 5.51–5.53 (m, 1H), 4.16–4.28 (m, 2H), 3.79 (s, 3H), 3.18 (dd, J_1=14.8 Hz, J_2=6.4 Hz, 1H), 2.74 (dd, J_1=14.8 Hz, J_2=7.6 Hz, 1H), 1.25–1.31 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.3, 161.7, 154.1, 134.1, 128.3, 127.7, 126.7, 126.2, 125.5, 124.7, 124.3, 75.6, 62.2, 52.2, 49.5, 43.6, 14.3; HRMS: calcd for $C_{17}H_{17}N_3O_5Na$: 366.1060, $[M+Na]^+$; found: 366.1064.

4.2.4. Methyl 2-diazo-4-[2-(1-benzyloxycarbonyl-1,2-dihydro)quinoline]-3-oxobutyrate (4d). R_f=0.25 (10% EtOAc/light petroleum ether); white solid, mp=103–105 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58–7.63 (m, 1H), 7.19–7.35 (m, 6H), 7.07 (m, 2H), 6.48–6.51 (m, 1H), 6.12–6.17 (m, 1H), 5.55–5.57 (m, 1H), 5.14–5.27 (m, 2H), 3.73 (s, 3H), 3.18 (dd, J_1=14.6 Hz, J_2=5.8 Hz, 1H), 2.74 (dd, J_1=14.6 Hz, J_2=7.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.9, 161.5, 153.7, 135.8, 133.8 (overlap), 128.4, 128.0, 127.8, 127.7, 126.6, 126.1, 125.4, 124.6, 124.3, 75.9, 67.6, 52.0, 49.7, 43.3; HRMS: calcd for $C_{22}H_{19}N_3O_5Na$: 428.1217, $[M+Na]^+$; found: 428.1227.

4.2.5. Methyl 2-diazo-4-[2-(3-methyl-1-benzyloxycarbonyl-1,2-dihydro)quinoline]-3-oxobutyrate (4e). R_f=0.25 (10% EtOAc/light petroleum ether); white solid, mp=98–101 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58–7.61 (m, 1H), 7.01–7.31 (m, 8H), 6.27 (s, 1H), 5.17–5.35 (m, 3H), 3.75 (s, 3H), 3.24–3.28 (m, 1H), 2.43–2.51 (m, 1H), 2.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.8, 161.5, 153.8, 137.3, 135.9, 132.4, 128.4, 127.9, 127.7, 127.5, 126.8, 125.3, 124.7, 124.3, 121.4, 75.8, 67.6, 53.9, 51.9, 40.7, 20.1; HRMS: calcd for $C_{23}H_{21}N_3O_5Na$: 442.1373, $[M+Na]^+$; found: 442.1378.

4.2.6. Methyl 2-diazo-4-[2-(4-methyl-1-benzyloxycarbonyl-1,2-dihydro)quinoline]-3-oxobutyrate (4f). R_f=0.25 (10% EtOAc/light petroleum ether); yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58–7.63 (m, 1H), 7.09–7.33 (m, 7H), 5.95–5.98 (m, 1H), 5.44–5.50 (m, 1H), 5.14–5.27 (m, 2H), 3.73 (s, 3H), 3.14 (dd, J_1=14.6 Hz, J_2=5.7 Hz, 1H), 2.74 (dd, J_1=14.6 Hz, J_2=8.0 Hz, 1H), 2.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.2, 161.6, 153.8, 136.0, 133.8, 130.7, 128.4 (overlap), 128.0, 127.9, 127.5 (overlap), 124.9, 124.3, 123.1, 75.7, 67.7, 52.1, 49.5, 43.4, 18.3; HRMS: calcd for $C_{23}H_{21}N_3O_5Na$: 442.1373, $[M+Na]^+$; found: 442.1382.

4.2.7. Methyl 2-diazo-4-[2-(6-methyl-1-benzyloxycarbonyl-1,2-dihydro)quinoline]-3-oxobutyrate (4g). R_f=0.25 (10% EtOAc/light petroleum ether); white solid, mp=100–102 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53–7.56 (m, 1H), 7.30–7.37 (m, 5H), 7.02–7.05 (m, 1H), 6.89 (s, 1H), 6.44–6.48 (m, 1H), 6.13–6.16 (m, 1H), 5.52–5.56 (m, 1H), 5.14–5.27 (m, 2H), 3.73 (s, 3H), 3.19 (dd, J_1=14.6 Hz, J_2=5.8 Hz, 1H), 2.74 (dd, J_1=14.6 Hz, J_2=7.9 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.8, 161.5, 153.8, 135.9, 133.8, 131.3, 128.3 (overlap), 127.9, 127.8 (overlap), 126.6, 126.4, 125.4, 124.5, 75.8, 67.6, 51.9, 49.7, 43.3, 20.6; HRMS: calcd for $C_{23}H_{21}N_3O_5Na$: 442.1373, $[M+Na]^+$; found: 442.1366.

4.2.8. Methyl 2-diazo-4-[2-(6-methoxy-1-benzyloxycarbonyl-1,2-dihydro)quinoline]-3-oxobutyrate (4h). R_f=0.25 (10% EtOAc/light petroleum ether); white solid, mp=108–110 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44–7.56 (m, 1H), 7.25–7.34 (m, 5H), 6.76–6.79 (m, 1H), 6.60–6.62 (m, 1H), 6.43–6.47 (m, 1H), 6.13–6.18 (m, 1H), 5.51–5.57 (m, 1H), 5.12–5.16 (m, 2H), 3.76 (s, 3H), 3.72 (s, 3H), 3.15 (dd, J_1=14.6 Hz, J_2=5.7 Hz, 1H), 2.70 (dd, J_1=14.6 Hz, J_2=8.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.8, 161.5, 156.2, 153.8, 135.9, 128.8, 128.3, 127.9, 127.7, 127.6, 126.9, 125.8, 125.4, 113.2, 110.8, 75.8, 67.5, 51.9, 49.6, 43.1; HRMS: calcd for $C_{23}H_{21}N_3O_6Na$: 458.1323, $[M+Na]^+$; found: 458.1325.

4.2.9. Methyl 2-diazo-4-[2-(6-nitro-1-benzyloxycarbonyl-1,2-dihydro)quinoline]-3-oxobutyrate (4i). R_f=0.25 (10% EtOAc/light petroleum ether); yellow solid, mp=158–161 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08–8.12 (m, 1H), 7.987.99 (m, 1H), 7.83–7.86 (m, 1H), 7.29–7.39 (m, 5H), 6.57–6.61 (m, 1H), 6.29–6.34 (m, 1H), 5.59–5.66 (m, 1H), 5.29 (d, J=12.2 Hz, 1H), 5.23 (d, J=12.2 Hz, 1H), 3.78 (s, 3H), 3.25 (dd, J_1=14.8 Hz, J_2=5.9 Hz, 1H), 2.72 (dd, J_1=14.8 Hz, J_2=7.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.5, 161.5, 156.2, 153.3, 143.7, 139.9, 135.1, 130.4, 128.6, 128.5, 128.2, 126.9, 124.7, 124.2, 122.9, 121.5, 75.8, 68.6, 52.2, 50.3, 43.8; HRMS: calcd for $C_{22}H_{18}N_4O_7Na$: 473.1068, $[M+Na]^+$; found: 473.1070.

4.2.10. Methyl 2-diazo-4-[4-(1-methoxycarbonyl-1,4-dihydro)quinoline]-3-oxobutyrate (5b). R_f=0.26 (12% EtOAc/light petroleum ether); yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97–7.80 (m, 1H), 6.98–7.24 (m, 4H), 5.42–5.46 (m, 1H), 3.92–3.97 (m, 1H), 3.88 (s, 3H), 3.78 (s, 3H), 2.99–3.15 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.3, 161.5, 152.9, 136.4, 130.2, 128.2, 126.7, 126.6, 125.0, 121.3, 112.5, 76.1, 53.3, 52.2, 48.4, 33.9; HRMS: calcd for $C_{16}H_{15}N_3O_5Na$: 352.0904, $[M+Na]^+$; found: 352.0922.

4.2.11. Methyl 2-diazo-4-[4-(1-ethoxycarbonyl-1,4-dihydro)quinoline]-3-oxobutyrate (5c). R_f=0.25 (12% EtOAc/light petroleum ether); yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98–8.01 (m, 1H), 6.99–7.24 (m, 4H), 5.40–5.44 (m, 1H), 4.31 (q, J=7.1 Hz, 2H), 3.93 (m,

1H), 3.77 (s, 3H), 3.05–3.15 (m, 2H), 1.36 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.4, 161.4, 152.4, 136.4, 130.1, 128.1, 126.7, 126.5, 124.9, 121.2, 112.1, 76.1, 62.4, 52.2, 48.4, 33.8, 14.4; HRMS: calcd for $C_{17}H_{17}N_3O_5Na$: 366.1060, $[M+Na]^+$; found: 366.1068.

4.3. General procedure for the cyclopropanation of diazo adducts 4

To a refluxing $ClCH_2CH_2Cl$ (5 mL) solution of $Rh_2(OAc)_4$ (1 mol %) was added the adduct **4** (0.5 mmol) in 3 mL of $ClCH_2CH_2Cl$ over 30 min under argon atmosphere. After completion of the addition, the reaction mixture was cooled to room temperature. Solvent was removed and the crude product was purified by flash chromatography on silica gel eluting with EtOAc/light petroleum ether to give **6**.

4.3.1. Methyl 3-benzoyl-1-oxo-2,2a,3,7b,7c,8-hexahydro-1*H*-bicyclo[3.1.0]hex-5-eno [4,5,6-*bc*]quinoline-7c-carboxylate (6a). R_f=0.25 (30% EtOAc/light petroleum ether); white solid, mp=210–212 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27–7.42 (m, 4H), 7.03–7.08 (m, 1H), 6.87–6.92 (m, 1H), 6.52–6.56 (m, 1H), 5.99–6.01 (m, 1H), 3.81 (s, 3H), 3.57–3.60 (m, 1H), 3.33–3.38 (m, 1H), 2.95 (dd, J_1=19.6 Hz, J_2=10.9 Hz, 1H), 1.78 (d, J=19.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.8, 168.9, 167.8, 136.3, 134.7, 131.0, 130.8, 128.7, 128.3, 127.9, 126.0, 125.9, 123.1, 52.8, 47.1, 46.1, 44.5, 33.6, 30.3; HRMS: calcd for $C_{21}H_{17}NO_4Na$: 370.1050, $[M+Na]^+$; found: 370.1051.

4.3.2. Dimethyl 1-oxo-1,2,2a,7c-tetrahydro-7b*H*-bicyclo[3.1.0]hex-5-eno[4,5,6-*bc*]quinoline-3,7c(8*H*)-dicarboxylate (6b). R_f=0.25 (30% EtOAc/light petroleum ether); white solid, mp=158–160 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36–7.40 (m, 2H), 7.20–7.26 (m, 1H), 7.11–7.14 (m, 1H), 5.67–5.73 (m, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 3.423.45 (m, 1H), 3.23–3.28 (m, 1H), 2.84 (dd, J_1=19.7 Hz, J_2=11.0 Hz, 1H), 1.71 (d, J=19.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.8, 167.8, 154.0, 135.0, 130.8, 128.3, 125.7, 125.2, 123.1, 53.3, 52.7, 47.5, 45.6, 44.6, 32.6, 30.4; HRMS: calcd for $C_{16}H_{15}NO_5Na$: 324.0842, $[M+Na]^+$; found: 324.0842.

4.3.3. 3-Ethyl 7c-methyl 1-oxo-1,2,2a,7c-tetrahydro-7b*H*-bicyclo[3.1.0]hex-5-eno[4,5,6-*bc*]quinoline-3,7c(8*H*)-dicarboxylate (6c). R_f=0.25 (30% EtOAc/light petroleum ether); white solid, mp=111–113 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37–7.47 (m, 2H), 7.20–7.26 (m, 1H), 7.08–7.13 (m, 1H), 5.68–5.74 (m, 1H), 4.07–4.28 (m, 2H), 3.77 (s, 3H), 3.42–3.45 (m, 1H), 3.25–3.29 (m, 1H), 2.84 (dd, J_1=19.6 Hz, J_2=11.0 Hz, 1H), 1.70 (d, J=19.6 Hz, 1H), 1.23–1.34 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.9, 167.8, 153.5, 135.1, 130.7, 128.2, 125.4, 125.2, 123.1, 62.3, 52.6, 47.2, 45.4, 44.6, 32.6, 30.4, 14.3; HRMS: calcd for $C_{17}H_{17}NO_5Na$: 338.0999, $[M+Na]^+$; found: 338.1000.

4.3.4. 3-Benzyl 7c-methyl 1-oxo-1,2,2a,7c-tetrahydro-7b*H*-bicyclo[3.1.0]hex-5-eno[4,5,6-*bc*]quinoline-3,7c(8*H*)-dicarboxylate (6d). R_f=0.25 (30% EtOAc/light petroleum ether); yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32–7.40 (m, 7H), 7.09–7.16 (m, 2H), 5.70–5.76 (m, 1H), 5.32 (d, J=12.3 Hz, 1H), 5.18 (d, J=12.3 Hz, 1H), 3.79 (s, 3H), 3.43–3.46 (m, 1H), 3.24–3.29 (m, 1H), 2.85 (dd, J_1=19.2 Hz, J_2=11.1 Hz, 1H), 1.73 (d, J=19.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.8, 167.8, 153.3, 135.6, 134.9, 130.7, 128.5, 128.3 (overlap), 128.0, 125.6, 125.3, 123.2, 68.0, 52.7, 47.5, 45.6, 44.5, 32.6, 30.3; HRMS: calcd for $C_{22}H_{19}NO_5Na$: 400.1155, $[M+Na]^+$; found: 400.1143.

4.3.5. 3-Benzyl 7c-methyl 8-methyl-1-oxo-1,2,2a,7c-tetrahydro-7b*H*-bicyclo[3.1.0]hex-5-eno[4,5,6-*bc*]quinoline-3,7c(8*H*)-dicarboxylate (6e). R_f=0.25 (30% EtOAc/light petroleum ether); yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33–7.40 (m, 7H), 7.08–7.22 (m, 2H), 5.45–5.49 (m, 1H), 5.36 (d, J=12.2 Hz, 1H), 5.18 (d, J=12.3 Hz, 1H), 3.81 (s, 3H), 3.35 (s, 1H), 2.84 (dd, J_1=19.8 Hz, J_2=11.0 Hz, 1H), 1.71 (d, J=19.8 Hz, 1H), 1.59 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.6, 167.0, 153.7, 135.8, 135.4, 130.4, 128.6, 128.4, 128.1, 125.6, 125.2, 124.4, 68.1, 54.2, 52.7, 51.9, 43.4, 40.7, 34.3, 15.6; HRMS: calcd for $C_{23}H_{21}NO_5Na$: 414.1312, $[M+Na]^+$; found: 414.1321.

4.3.6. 3-Benzyl 7c-methyl 7b-methyl-1-oxo-1,2,2a,7c-tetrahydro-7b*H*-bicyclo[3.1.0]hex-5-eno[4,5,6-*bc*]quinoline-3,7c(8*H*)-dicarboxylate (6f). R_f=0.25 (30% EtOAc/light petroleum ether); yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33–7.46 (m, 7H), 7.14–7.20 (m, 2H), 5.61–5.65 (m, 1H), 5.33 (d, J=12.3 Hz, 1H), 5.18 (d, J=12.3 Hz, 1H), 3.82 (s, 3H), 3.14 (m, 1H), 2.74 (dd, J_1=19.4 Hz, J_2=11.0 Hz, 1H), 1.73 (d, J=19.4 Hz, 1H), 1.58 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.6, 166.2, 153.3, 135.7, 134.6, 129.0, 128.7, 128.5, 128.3, 128.0, 127.9, 125.9, 125.3, 67.9, 52.6, 51.1, 48.2, 44.5, 36.9, 33.4, 20.0; HRMS: calcd for $C_{23}H_{21}NO_5Na$: 414.1317, $[M+Na]^+$; found: 414.1301.

4.3.7. 3-Benzyl 7c-methyl 6-methyl-1-oxo-1,2,2a,7c-tetrahydro-7b*H*-bicyclo[3.1.0]hex-5-eno[4,5,6-*bc*]quinoline-3,7c(8*H*)-dicarboxylate (6g). R_f=0.25 (30% EtOAc/light petroleum ether); white solid, mp=135–138 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28–7.38 (m, 6H), 7.21 (s, 1H), 7.01–7.04 (m, 1H), 5.68–5.74 (m, 1H), 5.31 (d, J=12.3 Hz, 1H), 5.15 (d, J=12.3 Hz, 1H), 3.79 (s, 3H), 3.41 (m, 1H), 3.23–3.28 (m, 1H), 2.84 (dd, J_1=19.6 Hz, J_2=11.1 Hz, 1H), 2.26 (s, 3H), 1.73 (d, J=19.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.8, 167.8, 153.4, 135.7, 135.4, 132.3, 130.9, 129.0, 128.5, 128.2, 127.9, 125.0, 122.9, 67.9, 52.6, 47.5, 45.7, 44.5, 32.6, 0.4, 20.6; HRMS: calcd for $C_{23}H_{21}NO_5Na$: 414.1317, $[M+Na]^+$; found: 414.1326.

4.3.8. 3-Benzyl 7c-methyl 6-methoxy-1-oxo-1,2,2a,7c-tetrahydro-7b*H*-bicyclo[3.1.0]hex-5-eno[4,5,6-*bc*]quinoline-3,7c(8*H*)-dicarboxylate (6h). R_f=0.25 (30% EtOAc/light petroleum ether); white solid, mp=125–128 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25–7.36 (m, 6H), 6.89–6.90 (m, 1H), 6.75–6.79 (m, 1H), 5.68–5.74 (m, 1H), 5.31 (d, J=12.3 Hz, 1H), 5.15 (d, J=12.3 Hz, 1H), 3.79 (s, 3H), 3.75 (s, 3H), 3.40–3.44 (m, 1H), 3.23–3.28 (m, 1H), 2.84 (dd, J_1=19.6 Hz, J_2=11.0 Hz, 1H), 1.73 (d, J=19.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.8, 167.8, 157.1, 153.5, 135.8, 128.5, 128.2, 128.0, 127.8, 126.6, 124.3, 115.2, 114.3, 67.9, 55.4, 52.7, 47.6, 45.9, 44.5, 32.8, 30.6; HRMS: calcd for $C_{23}H_{21}NO_6Na$: 430.1261, $[M+Na]^+$; found: 430.1270.

4.3.9. 3-Benzyl 7c-methyl 6-nitro-1-oxo-1,2,2a,7c-tetrahydro-7b*H*-bicyclo[3.1.0]hex-5-eno[4,5,6-*bc*]quinoline-3,7c(8*H*)-dicarboxylate (6i). R_f=0.20 (30% EtOAc/light petroleum ether); yellow solid, mp=174–176 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (d, J_1=2.5 Hz, 1H), 8.07 (dd, J_1=2.5 Hz, J_2=9.1 Hz, 1H), 7.72 (d, J_2=9.1 Hz, 1H), 7.38 (s, 5H), 5.78–5.84 (m, 1H), 5.33 (d, J=12.1 Hz, 1H), 5.22 (d, J=12.1 Hz, 1H), 3.81 (s, 3H), 3.51–3.54 (m, 1H), 3.28–3.33 (m, 1H), 2.94 (dd, J_1=19.7 Hz, J_2=11.1 Hz, 1H), 1.71 (d, J=19.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.6, 167.1, 152.7, 144.3, 141.2, 134.9, 128.7, 128.3, 126.3, 125.5, 124.2, 123.6, 68.8, 52.9, 47.7, 45.3, 44.7, 31.5, 29.3; HRMS: calcd for $C_{22}H_{18}N_2O_7Na$: 445.1006, $[M+Na]^+$; found: 445.1009.

4.4. Procedure for the preparation of cyclopenta[*b*]quinoline derivative 7

To a solution of **6d** (170 mg, 0.45 mmol) in EtOAc (10 ml) was added 10% Pd on carbon (60 mg). The reaction mixture was charged with an atmosphere of H_2 and allowed to stir at room temperature for 14 h. The catalyst was filtered off, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with 20% EtOAc/light petroleum ether to give **7** as a white solid (94 mg, 85% yield).

4.4.1. Methyl 2-oxo-2,3,3a,4,9,9a-hexahydro-1*H*-cyclopenta[*b*]quinoline-1-carboxylate 7. R_f=0.25 (20% EtOAc/light petroleum ether); white solid, mp=120–122 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.98–7.02 (m, 2H), 6.66–5.71 (m, 1H), 6.45–6.48 (m, 1H), 3.99–4.01 (m, 1H), 3.77–3.81 (m, 1H), 3.76 (s, 3H), 3.03–3.18 (m, 3H), 2.73–2.80 (m, 1H), 2.59–2.66 (m, 1H), 2.34–2.40 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.4, 169.5, 142.6, 130.1, 127.2, 118.2, 116.3, 113.8, 55.6, 52.5, 48.9, 48.2, 38.2, 27.3; HRMS: calcd for $C_{14}H_{15}NO_3Na$: 268.0944, $[M+Na]^+$; found: 268.0950.

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References and notes

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10. Crystallographic data for the structure of **6c** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-625735. These data can be obtained online free of charge [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44)-1223-336-003, or mail to: deposit@ccdc.cam.ac.uk].