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Synthetic approaches to *Cinchona* alkaloids: the C-8/C-9 disconnection strategy

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Abstract—When conducted in DMSO, the Hünig's base-promoted condensation of 3-quinuclidinone with quinoline-4-carboxaldehyde gave an equimolar mixture of epimeric aldols **8** with an excellent yield.

Quinine (**1**), the most celebrated member of the *Cinchona* alkaloids, has played a dominant role in human therapeutics for the treatment of malaria (Fig. 1). In organic chemistry, quinine and related alkaloids have been widely used as chiral substrates for achieving chiral discrimination/recognition, e.g. as resolving agents for acids, as ligands for asymmetric synthesis,[1] as chiral solvating agents in NMR spectroscopy and as selectors in the elaboration of chiral stationary/mobile phases for chromatographic resolution. After a long period of exploratory studies, there has been a resurgence of interest in developing synthetic routes to the *Cinchona* alkaloids, culminating in several successful approaches to quinine. A consistent theme among these syntheses was the creation of the quinuclidine system at the late stages by heterocyclization between N-1 and C-8 (Woodward–Doering,[2] Uskoković–Gutzwiller,[3] Gates–Schreiber,[4] Taylor–Martin,[5] Brown,[6] Wilson[7]) or N-1 and C-6 (Stork[8]). In comparison, the C-8/C-9 disconnection strategy, involving the condensation of a pre-existing quinuclidine unit with a quinoline moiety, has been much less studied.

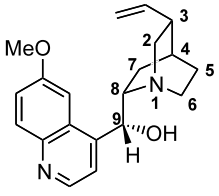
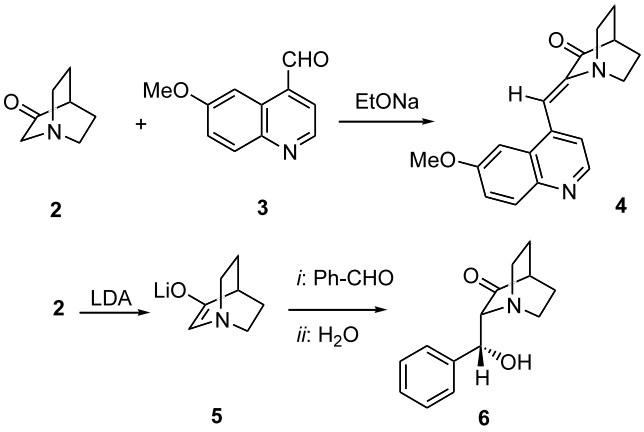


Figure 1. Structure of quinine (**1**).

The first investigation in the area was reported by Coffen who established that the sodium ethoxide-promoted condensation of a mixture of 3-quinuclidinone (**2**) and 6-methoxyquinoline-4-carboxaldehyde (**3**) furnishes in 90% yield (*Z*)-6′-methoxy-7-oxo-8-rubene (**4**).[9] Thus, in such operating conditions, the (desired) initial aldol adduct suffered an irreversible dehydration reaction, affording α,β-ethylenic carbonyl compound **4**. The



Scheme 1.

Keywords: aldols; alkaloids; amines; quinolines; quinuclidines.

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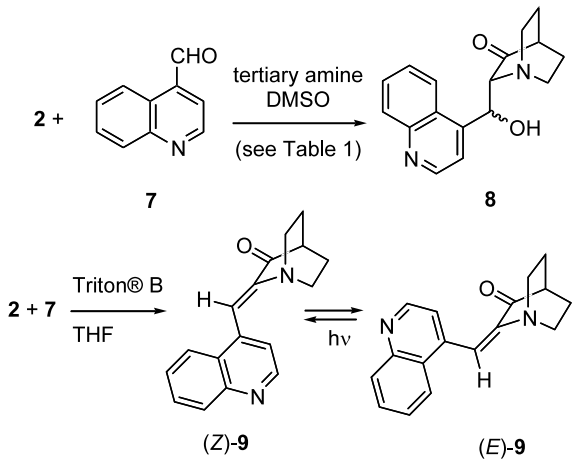


Scheme 2.

critical problem of the interception of the intermediary aldol was partly solved by Stotter some years later, who preformed the lithium enolate of 3-quinuclidinone (**5**) by treating ketone **2** with LDA. Subsequent condensation of this enolate with benzaldehyde at −78°C produced stereoselectively aldol (*erythro*)-**6** with a 83% yield. However, probably because of its reduced electrophilicity, aldehyde **3** proved unsuitable in the condensation with enolate **5** (Scheme 1).[10] In connection with our sustained research efforts in the *Cinchona* alkaloids series, directed towards their synthesis[11] and their use as chiral ligands in asymmetric catalysis,[12] we recently reinvestigated the above 'aldol route', taking advantage of the recent developments in the field. Results from this endeavor are reported hereafter.

Condensation between both commercially available 3-quinuclidinone (**2**) and quinoline-4-carboxaldehyde (**7**)[13] was attempted first; selected results are depicted in Scheme 2 and are listed in Table 1. These results are strongly dependent upon the nature of the base added and of the solvent of the reaction. In THF, all experiments that employed tertiary amines as a base returned only unchanged starting materials (Table 1, entries 1–4), while the utilization of the strongly basic quaternary ammonium hydroxide Triton® B yielded almost quantitatively (*Z*)-7-oxo-8-rubene (*Z*-**9**) (entry 5), an outcome that parallels completely conversion [**2**+**3**→**4**]. However, when DMSO was employed as solvent a dramatic increase in reactivity was gained,[14] the utilization of tertiary amines furnishing now the desired aldols **8** (obtained as a nearly equimolar mixture of diastereomers) (entries 7–10); the best catalyst was found to be the moderately basic Hünig's base, producing **8** in 90% yield (entry 7). Somewhat surprisingly, when the condensation [**2**+**7**] was conducted in DMSO, *in the absence of any external base*, a substantial amount of aldols **8** was formed (30%, entry 6). Presumably, the driving force for this autocatalytic aldol condensation was the intrinsic basicity of **2** ($^{MeCN}pK_B$ of quinuclidine: 19.5). Although aldols **8** were obtained as an equimolar mixture of diastereomers, reflecting a thermodynamic control (while the formation of the single aldol (*erythro*)-**6**[10] implicates a kinetically-controlled addition process),[15] it is noteworthy that addition [**2**+**7**→**8**] realizes the first aldol-type condensation between a quinuclidinone and a quinoline–carboxaldehyde, thus opening future prospects for a synthetic approach to *Cinchona* alkaloids based on the C-8/C-9 disconnection strategy. The identity of aldols **8**[16] was corroborated by dehydration which led to an equimolar mixture of enones (*Z*)-**9** and (*E*)-**9** (Burgess' inner salt: $Et_3N^+SO_2N^-COOMe$,[17] benzene, 80°C, quantitative yield). Configurational assignment of enone (*Z*)-**9**[18] was definitively secured by single-crystal X-ray diffraction analysis (Fig. 2). Incidentally, we have observed that the irradiation, using visible light, of (*Z*)-**9** in CCl_4 in the presence of a trace of I_2 gave a photostationary mixture of (*Z*)-**9** and (*E*)-**9** containing ca. 40% of (*Z*)-**9**.[19,20]

Table 1. Compounds produced via condensation between **2** and **7**

Entry	Solvent	Base added[a]	SM (%)[b]	**8** (%)[c]	(*Z*)-**9** (%)[d]
1	THF	Hünig's base[e]	100	0	0
2	–	2,6-Di-*tert*-butylpyridine	100	0	0
3	–	DMAP[f]	100	0	0
4	–	Proton-Sponge®[g]	100	0	0
5	–	Triton® B[h]	0	0	95
6	DMSO	No base added	70	30	0
7	–	Hünig's base	10	90	0
8	–	2,6-Di-*tert*-butylpyridine	50	50	0
9	–	DMAP	50	50	0
10	–	Proton-Sponge®	50	50	0

[a] All reactions were performed at 30°C during 2 weeks, employing a stoichiometric ratio of **2** and **7** and 1.5 equiv. of base.
[b] Recovered starting materials.
[c] Yield determined by ^1H NMR (equimolar mixture of diastereomers).
[d] Yield determined by ^1H NMR (single *Z* isomer).
[e] Hünig's base: *N*,*N*-di*iso*propylethylamine.
[f] DMAP: 4(dimethylamino)pyridine.
[g] Proton-Sponge®: 1,8-bis(dimethylamino)naphthalene.
[h] Triton® B: benzyltrimethylammonium hydroxide (40 wt.% solution in MeOH); in that case the reaction was completed after 2 h at 20°C.

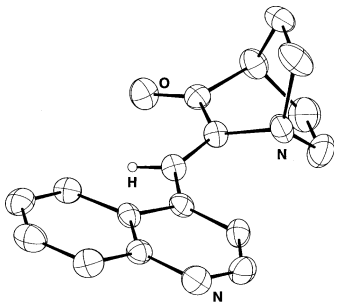
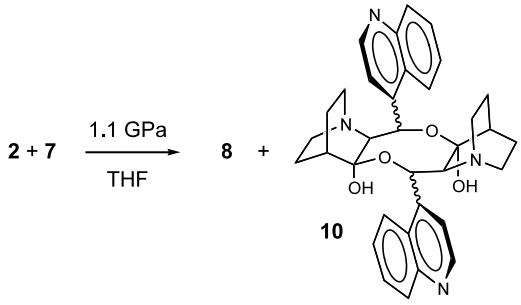


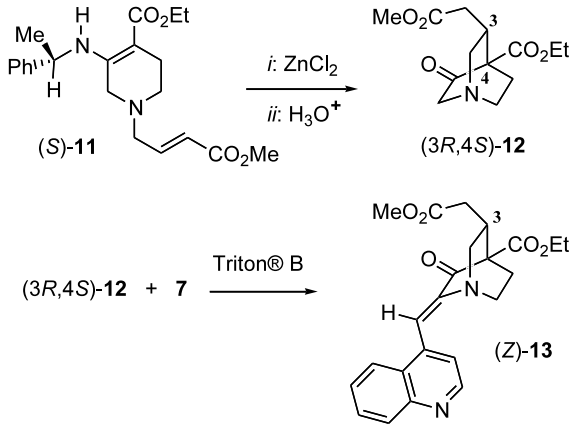
Figure 2. ORTEP view of (*Z*)-**9** with labeled heteroatoms. Thermal ellipsoids are scaled to 50% probability level. Hydrogen atom shown is drawn to an arbitrary scale.



Scheme 3.

Another interesting outcome was obtained when a stoichiometric mixture of **2** and **7** was pressurized at 1.1 GPa in THF at 50°C during 3 days: dimer **10** was isolated in 40% yield, along with aldols **8** (60% yield). Compound **10**,[21] a cream solid almost insoluble in usual solvents, was assigned a molecular formula of $C_{34}H_{36}N_4O_4$, established by elemental analysis and mass spectroscopy (MALDI), corresponding to the condensation of two molecules of aldols **8**, and its bis-hemiacetal structure (of unidentified stereochemistry) was deduced from its IR spectrum which revealed the *absence* of C=O absorption. When stirred in CD_3OD at 65°C, dimer **10** progressively dissolved, a process which, in fact, involved a cycloreversion of the bis-hemiacetal core of the molecule, restoring an equimolar epimeric mixture of progenitors **8**. On the other hand, treatment of **10** with Burgess' inner salt[17] in benzene at 80°C gave an equimolar mixture of enones (*Z*)-**9** and (*E*)-**9** (40% combined yield), together with aldehyde **7** (40% yield), the latter issuing from a concomitant retro-aldol type cleavage of the transient aldols **8** (Scheme 3).

Encouraged by our success with the synthesis of aldols **8**, we have also investigated the condensation of functionalized quinuclidinone (3*R*,4*S*)-**12** (quinine numbering) (synthesized with a 80% de and a 90% ee through asymmetric bridging annulation of enamino ester (*S*)-**11**)[11] with aldehyde **7**. Unfortunately, all experiments performed in DMSO in the presence of a tertiary amine proved unsatisfactory, since returning invariably unchanged starting materials, a failure which may be attributed to the marked steric hindrance of **12**, compared with the unsubstituted parent ketone **2**. However, exposure of a stoichiometric mixture of **7** and **12** to Triton® B in THF led to enone (*Z*)-**13**[22] in 70% yield. Upon irradiation of (*Z*)-**13** with visible light, a photostationary state was reached in which the (*Z*)-**13**/(*E*)-**13** ratio is about 1:3 (Scheme 4).



Scheme 4.

In conclusion, our original objective was to develop a new synthetic approach to *Cinchona* alkaloids based on the C-8/C-9 disconnection strategy. The results thus far obtained show that the addition of 3-quinuclidinone (**2**) with aldehyde **7** proceeded smoothly when conducted in DMSO in the presence of Hünig's base, producing the desired aldols **8** with an excellent yield. Although our initial purpose was found to be thwarted by the failure of the aldol condensation between functionalized quinuclidinone **12** and aldehyde **7**, the experience gained during this study may have paved the way for an eventual, hopefully highly successful, solution.

Acknowledgements

Dr. O. Laprévote (ICSN, CNRS, Gif sur Yvette) is gratefully acknowleged for his invaluable advice in mass spectroscopy.

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13. In a preliminary experiment we have established that, in complete analogy with aldehyde **3**,[10] aldehyde **7** proved unsuitable in the condensation with enolate **5**, revealing its reduced electrophilicity.
14. For a crucial role of DMSO as a solvent in the *uncatalyzed* aldol addition of trimethylsilyl ketene acetals, see: Génisson, Y.; Gorrichon, L. *Tetrahedron Lett.* **2000**, *41*, 4881–4884.
15. However, Stotter pointed out that a facile subsequent equilibration of aldol (*erythro*)-**6** took place in the presence of a trace of DCl, producing an equimolar mixture of *erythro* and *threo* isomers.[10]
16. Aldols **8** (1.2:1 mixture of diastereomers): White solid, mp 145–152°C (Büchi apparatus) 157–158°C (Kofler bench); IR (neat, cm^{-1}) ν: 3300–2500, 1724. Major diastereomer: ^1H NMR (400 MHz, $CDCl_3$): δ 8.81 (d, $J=4.9$ Hz, 1H), 8.09–7.96 (m, 2H), 7.68–7.56 (m, 2H), 7.54–7.45 (m, 1H), 5.83 (d, $J=6.5$ Hz, 1H), 4.84 (br. s, OH), 3.58–3.46 (m, 2H), 3.00–2.70 (m, 3H), 2.49–2.42 (m, 1H), 2.25–2.13 (m, 1H), 2.03–1.81 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 217.9 (C=O), 150.0 (CH), 148.1 (C), 147.6 (C), 130.2 (CH), 128.8 (CH), 126.4 (CH), 125.7 (C), 122.8 (CH), 119.7 (CH), 72.9 (CH), 67.5 (CH), 49.4 (CH_2), 43.3 (CH_2), 40.3 (CH), 26.5 (CH_2), 25.0 (CH_2). Minor diastereomer: ^1H NMR (400 MHz, $CDCl_3$, pertinent data): δ 8.83 (d, $J=4.9$ Hz, 1H), 5.71 (d, $J=4.6$ Hz, 1H), 4.97 (br. s, OH), 3.40–3.30 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 221.5 (C=O), 150.1 (CH), 148.0 (C), 147.3 (C), 130.2 (CH), 129.0 (CH), 126.7 (CH), 125.6 (C), 123.0 (CH), 118.6 (CH), 72.7 (CH), 70.5 (CH), 48.6 (CH_2), 43.1 (CH_2), 40.8 (CH), 27.1 (CH_2), 24.5 (CH_2).
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18. Enone (*Z*)-**9**: Yellow crystals, mp 148°C (Büchi apparatus) 155°C (Kofler bench); IR (neat, cm^{-1}) ν 1710; ^1H NMR (400 MHz, $CDCl_3$): δ 8.95 (d, $J=4.5$ Hz, 1H), 8.15 (d, $J=7.8$ Hz, 1H), 8.13 (d, $J=7.5$ Hz, 1H), 8.12 (d, $J=4.5$ Hz, 1H), 7.77 (s, 1H), 7.74 (dt, $J=7.5$, 1.2 Hz, 1H), 7.60 (dt, $J=7.8$, 1.1 Hz, 1H), 3.21 (dt, $J=13.8$, 7.8 Hz, 2H), 3.03 (dt, $J=13.2$, 7.6 Hz, 2H), 2.73 (t, $J=2.7$ Hz, 1H), 2.09 (dt, $J=8.2$, 2.7 Hz, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 204.9 (C=O), 149.8 (CH), 148.3 (2C), 137.5 (C), 130.0 (CH), 129.0 (CH), 126.8 (CH), 126.7 (C), 123.1 (CH), 122.6 (CH), 118.7 (CH), 47.4 ($2CH_2$), 39.9 (CH), 25.3 ($2CH_2$). Anal. Calcd: C, 77.25; H, 6.10; N, 10.60. Found: C, 77.13; H, 6.19; N, 10.59. Crystal data for 2-(quinolin-4-ylmethylene)-1-aza-bicyclo[2.2.2] octan-3-one: Yellow crystal of 0.25×0.31×0.35 mm, $C_{17}H_{16}N_2O$, $M_w=264.32$; orthorhombic, space group *P*bn21, $Z=8$, $a=7.864(3)$, $b=14.946(3)$, $c=22.960(3)$ Å, $\alpha=\beta=\gamma=90°$, $V=2698.7(12)$ $Å^3$, $d_c=1.301$ g cm^{-3}, $F(000)=1120$, $\lambda=0.710693$ Å (MoKα), $\mu=0.082$ mm^{-1}; 3826 reflections measured ($0\le h\le 10$, $0\le k\le 19$, $-30\le l\le 30$) on a Nonius CAD4 diffractometer. The structure was solved with SIR92[23] and refined with CRYSTALS 2000.[24] Hydrogen atoms riding. Refinement converged to $R(gt)=0.0545$ for the 3636 observed reflections having $I\ge 3\sigma(I)$, and $wR(gt)=0.0595$, goodness-of-fit $S=1.0893$. Residual electron density: −0.55 and 0.58 e $Å^{-3}$. Full crystallographic results have been deposited as Supplementary Material (CIF file) at the Cambridge Crystallographic Data Centre, UK (CCDC 205474).
19. Enone (*E*)-**9**: ^1H NMR (400 MHz, $CDCl_3$): δ 8.90 (d, $J=4.4$ Hz, 1H), 8.14 (d, $J=8.2$ Hz, 1H), 8.12 (d, $J=4.5$ Hz, 1H), 7.86 (d, $J=8.2$ Hz, 1H), 7.69 (dt, $J=8.1$, 1.2 Hz, 1H), 7.54 (dt, $J=7.9$, 1.2 Hz, 1H), 7.19 (s, 1H), 3.23 (m, 4H), 2.57 (t, $J=2.9$ Hz, 1H), 2.02 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 202.6 (C=O), 149.5 (CH), 148.3 (C), 148.0 (C), 147.6 (CH), 139.3 (C), 130.0 (CH), 127.5 (C), 126.5 (CH), 126.1 (C), 123.7 (CH), 121.0 (CH), 48.8 ($2CH_2$), 41.7 (CH), 25.0 ($2CH_2$).
20. Equilibration of (*Z*)-**4** into *Z*/*E* mixture under acidic conditions was reported by Coffen. Furthermore, this author established that (*E*)-**4** slowly rearranged to (*Z*)-**4** on standing.[9]
21. Dimer **10**: Cream solid, mp 142–146°C (Büchi apparatus) 192°C (Kofler bench) (note the amazing difference in mp, ca. 50°C, between the 'instantaneous' mp determined by sprinkling the substance on a hot bench, and the one measured on a capillary tube apparatus, due to the rapid rearrangement of **10** to **8** upon gradual heating); IR (neat, cm^{-1}): ν 3300–2500; MS (MALDI, direct laser desorption) *m*/*z*: 565 (M+1), 564 (*M*), 563 (M−1), 519 (M−CO_2). Anal. calcd: C, 72.32; H, 6.43; N, 9.92. Found: C, 71.80; H, 5.86; N, 9.35.
22. Enone (*Z*)-**13** (9:1 mixture of diastereomers at C-3): IR (neat, cm^{-1}): ν 1728 (br). Major diastereomer (3*R*): ^1H NMR (200 MHz, $CDCl_3$): δ 8.88 (d, $J=4.7$ Hz, 1H), 8.07 (m, 2H), 7.80–7.54 (m, 3H), 7.19 (s, 1H), 4.22 (q, $J=7.0$ Hz, 2H), 3.59 (s, 3H), 3.52–3.44 (m, 1H), 3.18–297 (m, 3H), 2.70–2.42 (m, 2H), 2.25–1.97 (m, 3H), 1.27 (t, $J=7.0$ Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 198.1 (C=O), 172.4 (O-C=O), 169.5 (O-C=O), 150.0 (CH), 148.5 (C), 146.8 (C), 137.2 (C), 134.2 (CH), 130.4 (CH), 129.4 (CH), 127.2 (CH), 126.9 (C), 123.2 (CH), 120.7 (CH), 61.4 (CH_2), 55.4 (CH_2), 55.1 (C), 51.7 (CH_3), 47.5 (CH_2), 38.5 (CH_2), 36.4 (CH), 29.4 (CH_2), 14.1 (CH_3).
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