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SYNTHESIS OF A SERIES OF STRUCTURAL ANALOGUES OF THE CINCHONA ALKALOIDS†

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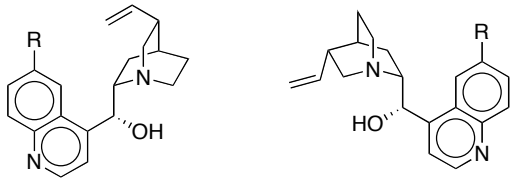
Abstract – Five olefins, each possessing an aryl (Ar) group, an aliphatic moiety, and a protected amino group as *N*-Teoc (-$CO_2(CH_2)_2$TMS) or N_3 at the aliphatic end, were converted to the corresponding epoxides with high ee. The amino group was generated by deprotection of the *N*-Teoc group with CsF or by Staudinger reaction of the azide group at elevated temperatures, under which the intramolecular epoxide ring-opening with the resulting amino group took place concomitantly to afford the analogues of the Cinchona alkaloids.

The Cinchona alkaloids are an important class of compounds not only as drugs but also as catalysts for asymmetric reactions (Figure 1).[1] Discrimination of a prochiral element by the quinoline ring and the polar functional groups is the key step for the enantioselection. Except a few cases, most of the reactions with the natural Cinchona alkaloids and their derivatives have shown the moderate levels of



quinine (**1a**): R = OMe
cinchonidine (**1b**): R = H

quinidine (**2a**): R = OMe
cinchonine (**2b**): R = H

Figure 1. The major constitutes of the Cinchona alkaloids.

† In celebration of the 75th birthday of Professor Ekkehard Winterfeldt.

selectivity and reactivity. One approach to improve the efficiency is the structural modification on the quinoline and quinuclidine rings by synthesis.[2–4] However, except for our syntheses, the previous syntheses suffer from the low efficiency and the poor flexibility.

Recently, we have established a synthesis of quinine (**1a**) and quinidine (**2a**),[5] which features stereocontrolled construction of the cis 3,4-disubstituted piperidine as the precursor of the quinuclidine ring, epoxide ring formation, and its opening by the piperidine nitrogen, furnishing the quinine framework.[6,7] Use of the Teoc protective group (Teoc = $-CO_2(CH_2)_2TMS$) is the additional advantage of the synthesis. The Teoc group is easily installed onto the nitrogen atom and removed with CsF. With these procedures in hand, we explored a method to afford a series of Cinchona analogues **3** with the quinuclidine ring and **4** with the piperidine ring (Figure 2). As the Ar part, we selected **a**–**d**, and, in practice, synthesized compounds **3d**, **4a**–**d**, and *ent*-**4d** (the enantiomer of **4d**) to evaluate high potential of the present method.

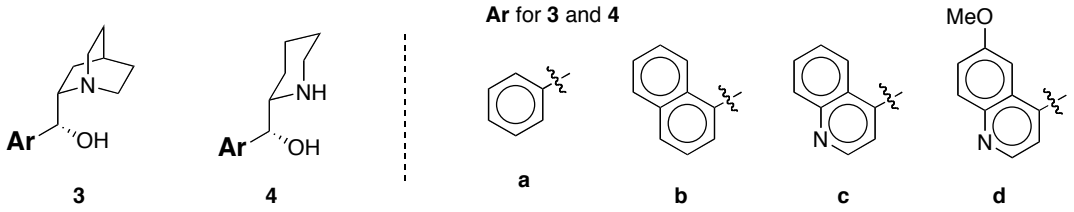
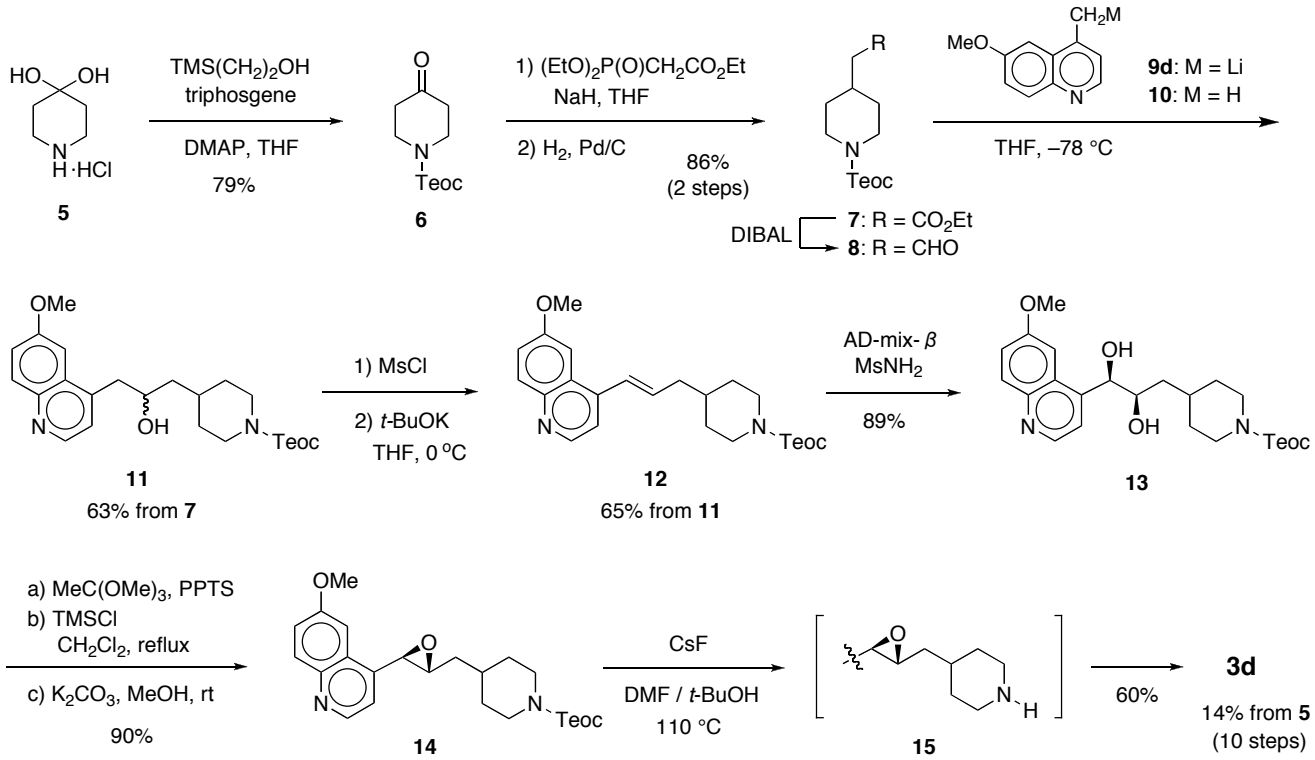


Figure 2. Cinchona analogues **3** and **4**.

We envisioned olefin **12** as the key intermediate leading to the first target **3d**[8] (Scheme 1). The synthesis commenced with protection of commercially available piperidone·HCl·H_2O adduct **5** with TeocCl (generated in situ from triphosgene and $TMS(CH_2)_2OH$) and an amine base. Among the four amines examined (Et_3N, pyridine, DMAP, *N*-Me-imidazole), DMAP afforded *N*-Teoc-piperidone **6** most efficiently (79% yield).[9] Horner-Wadsworth-Emmons reaction of **6** followed by hydrogenation produced ester **7**, which was reduced to aldehyde **8** in good yield. Reaction of **8** with anion **9d** derived from **10** and LDA gave alcohol **11** in 63% yield, which was converted stereoselectively to the key olefin **12** (J = 15 Hz for olefin protons) by elimination of MsOH with *t*-BuOK in THF.

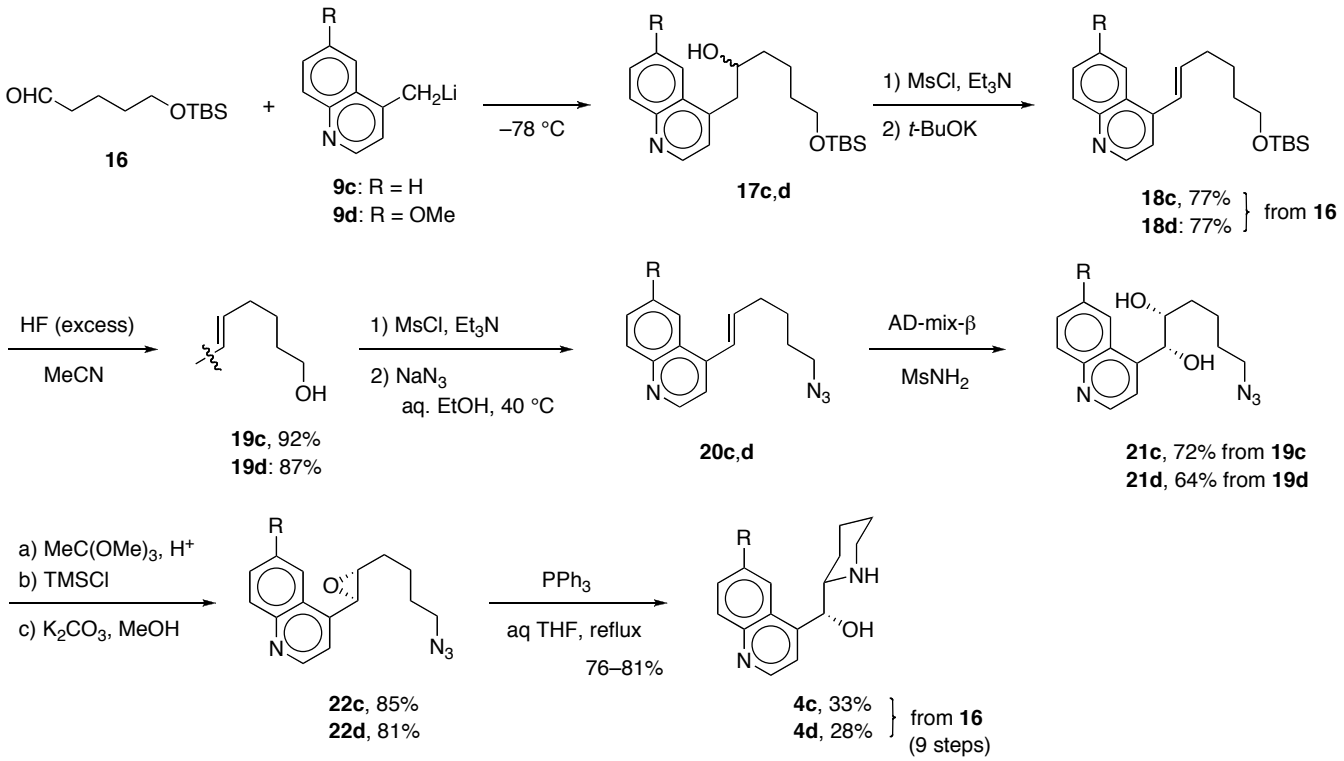
To complete the synthesis, olefin **12** was subjected to the Sharpless asymmetric dihydroxylation (AD)[10] with AD-mix-β and the resulting diol **13** (> 99% ee by chiral HPLC, Chiralcel OD-H, hexane/*i*-PrOH = 90 : 10, 0.5 mL/min, 40.2 and 60.1 min for the major and minor isomers, respectively) was converted efficiently to epoxide **14** by the standard procedure.[11] Finally, **14** was exposed to CsF at 110 °C, under



Scheme 1. Synthesis of **3d**.

which deprotection of the Teoc group and intramolecular epoxide ring-opening by the piperidine nitrogen of **15** took place in one pot to furnish **3d**[12] in 60% yield. Overall yield from **5** in 10 steps was 14%. Since the anion **9d** obviously can be replaced by another anion such as that used in the later Schemes, various aryl groups would by systematically installed as Ar in **3** by using the present method.[13]

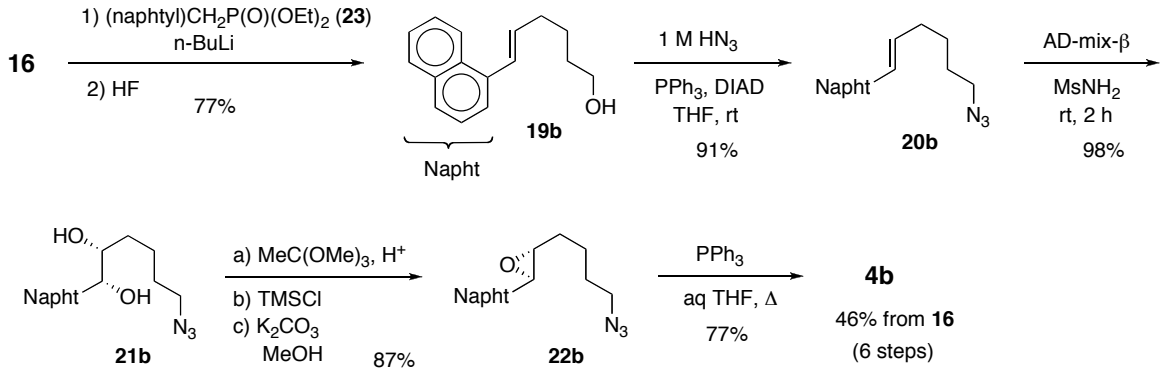
For the synthesis of the piperidines **4**, we chose an azide group that is convertible to an amino group by Staudinger reaction.[14,15] Reaction of aldehyde **16**[16] with the anion **9d** produced alcohol **17d**, which was converted to the trans olefin **18d** (J = 15 Hz for olefin protons) through elimination of MsOH in 77% yield from aldehyde **16** (Scheme 2). The TBS group was removed with HF and the resulting hydroxy group was substituted by an azide group using the Mitsunobu reaction[17] (HN_3, DIAD, PPh_3). However, close R_f values between azide **20d** and a by-product derived probably from DIAD prevented complete separation by chromatography, and the contamination, even though a small quantity, substantially impeded the AD reaction. We then took a detour through mesylation and substitution with NaN_3 to afford azide **20d** in 65% yield (2 steps). AD reaction of **20d** with AD-mix-β proceeded cleanly to afford diol **21d** (>99% ee by chiral HPLC), which was transformed into the epoxy-azide **22d** in good yield. Finally, Staudinger reaction with PPh_3 in refluxing aqueous THF furnished the target **4d**[4d] in 81% yield.[18] Total yield in 9 steps was 28%.



Scheme 2. Synthesis of **4c** and **4d**. For **c** series, R = H; **d** series, R = OMe.

Similarly, **4c**[19] of a cinchonine/cinchonidine analogue was synthesized in 33% overall yield from aldehyde **16** through diol **21c** of > 99% ee in 9 steps (Scheme 2).

The azide strategy was applied to synthesis of phenyl and naphthyl derivatives **4a**,**b**. The first step in the synthesis of **4b** (Scheme 3) was Wittig-type olefination of aldehyde **16** with phosphonate **23**[20] to afford, after hydrolysis of the TBS group, the trans olefin **19b** exclusively in 77% yield. An azide group was attached to **19b** by using Mitsunobu reaction to produce **20b** in 91% yield. The by-product derived from DIAD was easily separated by chromatography. The resulting transformation including



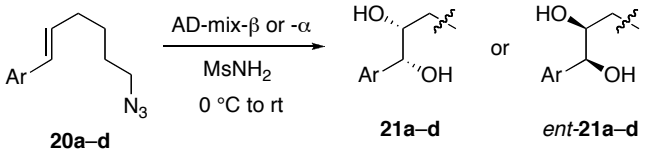
Scheme 3. Synthesis of **4b**.

AD reaction with AD-mix-β, epoxidation, and Staudinger reaction[14] of the resulting epoxy-azide **22b** proceeded smoothly to afford naphthyl derivative **4b**[4a] in good yield. The overall yield from **16** in 6 steps was 46%.

Similar transformation starting with reaction between aldehyde **16** and $PhCH_2P(O)(OEt)_2$ proceeded efficiently as well, furnishing phenyl derivative **4a**[4b,4c,21,22] in 52% overall yield from **16** (Scheme is not shown).

In the above syntheses of the Cinchona derivatives, AD-mix-β was used to create the stereocenters of the natural configuration. High selectivity and yields were also attained with AD-mix-α as summarized in Table 1. The diol products *ent*-**21a–d** are convertible to the enantiomers of **4a–d**. In practice, *ent*-**21d** was transformed into *ent*-**4d** with a similar efficiency.

Table 1. Results of AD reaction of **20a–d**.



	21 from AD-mix-β		*ent*-**21** from AD-mix-α		chiral	hexane :
substrate	yield[a]	%ee[b]	yield[a]	%ee[b]	column	*i*-PrOH
20a	81	>98	88	>99	Chiralcel OJ-H	90 : 10
20b	98	>99	91	>98	Chiralcel OD-H	80 : 20
20c	84	>99	85	>99	Chiralcel OD-H	90 : 10
20d	98	>99	98	>98	Chiralcel OD-H	90 : 10

[a] Isolated yields. [b] Determined by chiral HPLC.

In summary, we have established a method for the synthesis of a series of analogues possessing the key structural features of the Cinchona alkaloids.[23] Both enantiomers are now accessible with an equal effort. Moreover, the method would be applicable to diversity-oriented synthesis to find an efficient catalyst.

ACKNOWLEDGEMENT

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9. To a solution of DMAP (996 mg, 8.15 mmol) in THF (30 mL) was added triphosgene (484 mg, 1.63 mmol) at 0 °C. After 20 min, 2-(trimethylsilyl)ethanol (0.70 mL, 4.90 mmol) was added. The solution was stirred at 0 ºC for 30 min before addition of 4-piperidone derivative **5** (500 mg, 3.26 mmol). The resulting solution was stirred at rt for 20 h to afford piperidone **6** (631 mg, 79%) after chromatography on silica gel (CH_2Cl_2/EtOAc).
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12. The previous synthesis of **3d** suffers from low stereoselectivity in the construction of the olefin moiety, while availability of the starting compound is not clearly indicated.[2a] *Cf*. B. Lygo, J. Crosby, T. R. Lowdon, and P. G. Wainwright, *Tetrahedron Lett*., 1997, **38**, 2343.
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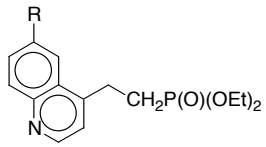
20. Although the phosphonates **i** (R = H, OMe) will produce olefins **12**, **19c**,**d** directly, we did not use **i** due to additional steps required for its preparation (5 steps).



i (R = H, OMe)

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23. Specific rotations and ^{1}H NMR spectra of **3d**, **4a**–**d** synthesized were as follows. **3d**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40–1.71 (m, 3 H), 1.72–2.28 (m, 4 H), 2.72–3.04 (m, 3 H), 3.13–3.28 (m, 1 H), 3.48–3.69 (m, 1 H), 3.87 (s, 3 H), 5.21–5.46 (m, 1 H), 5.74 (d, *J* = 3 Hz, 1 H), 7.20–7.23 (m, 1 H), 7.35 (dd, *J* = 9, 2 Hz, 1 H), 7.57 (d, *J* = 4 Hz, 1 H), 8.01 (d, *J* = 9 Hz, 1 H), 8.73 (d, *J* = 4 Hz, 1 H). **4a**: $[\alpha]^{25}_D$ –40.9 (*c* 0.22, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10–1.83 (m, 6 H), 2.54 (dt, *J* = 3, 12 Hz, 1 H), 2.63–2.74 (m, 1 H), 2.98 (d, *J* = 12 Hz, 1 H), 3.13 (br s, 2 H), 4.57 (d, *J* = 5 Hz, 1 H), 7.21–7.38 (m, 5 H). **4b**: $[\alpha]^{26}_D$ –74.5 (*c* 0.53, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.99–1.82 (m, 6 H), 2.54 (dt, *J* = 3, 12 Hz, 1 H), 2.85–3.08 (m, 2 H), 3.52 (br s, 2 H), 5.44 (d, *J* = 5

Hz, 1 H), 7.28 (t, *J* = 7 Hz, 1 H), 7.35–7.47 (m, 2 H), 7.68 (d, *J* = 7 Hz, 1 H), 7.73 (d, *J* = 8 Hz, 1 H), 7.83 (d, *J* = 8 Hz, 1 H), 8.00 (d, *J* = 9 Hz, 1 H). **4c**: $[\alpha]^{26}_{D}$ –62.1 (*c* 0.47, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.02–1.83 (m, 6 H), 2.64 (dt, *J* = 3, 12 Hz, 1 H), 2.99 (dt, *J* = 11, 3 Hz, 1 H), 3.11 (d, *J* = 12 Hz, 1 H), 4.20 (br s, 2 H), 5.52 (d, *J* = 3 Hz, 1 H), 7.34 (ddd, *J* = 8, 7, 1 Hz, 1 H), 7.57–7.68 (m, 2 H), 7.91 (d, *J* = 8 Hz, 1 H), 8.07 (d, *J* = 8 Hz, 1 H), 8.80 (d, *J* = 5 Hz, 1 H). **4d**: $[\alpha]^{23}_{D}$ = –95.9 (*c* 0.17, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.97–1.78 (m, 7 H), 2.69 (dt, *J* = 12, 2 Hz, 1 H), 3.06 (dt, *J* = 11, 3 Hz, 1 H), 3.22 (dm, *J* = 10 Hz, 1 H), 3.69 (br s, 1 H), 3.92 (s, 3 H), 5.48 (br s, 1 H), 7.21 (s, 1 H), 7.31 (dd *J* = 9, 2 Hz, 1 H), 7.54 (d, *J* = 4.5 Hz, 1 H), 7.97 (d, *J* = 9 Hz, 1 H), 8.68 (d, *J* = 4.5 Hz, 1 H).