Total Synthesis of Virantmycin

Stereospecific Construction of Contiguous Quaternary and Tertiary Stereocenters by Rearrangement from Indoline-2-methanol to 2,2,3-Trisubstituted Tetrahydroquinoline: Application to an Efficient Total Synthesis of Natural Virantmycin**

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The stereoselective construction of chiral quaternary stereocenters is one of the most challenging problems in synthetic organic chemistry.[1] Substituted tetrahydroquinolines and tetrahydroisoquinolines have attracted considerable attention from organic and medicinal chemists, primarily because they display a wide range of physiological activities.[1c,2] These ring systems are present in various important natural products.[2] Moreover, chiral quaternary centers are often essential for these compounds. For example, chiral contiguous quaternary and tertiary stereocenters are found in virantmycin (**6a**),[3] a potent antiviral agent (Scheme 1). Recently, Shibasaki et al. reported an elegant synthesis of 1,1-disubstituted tetrahy-

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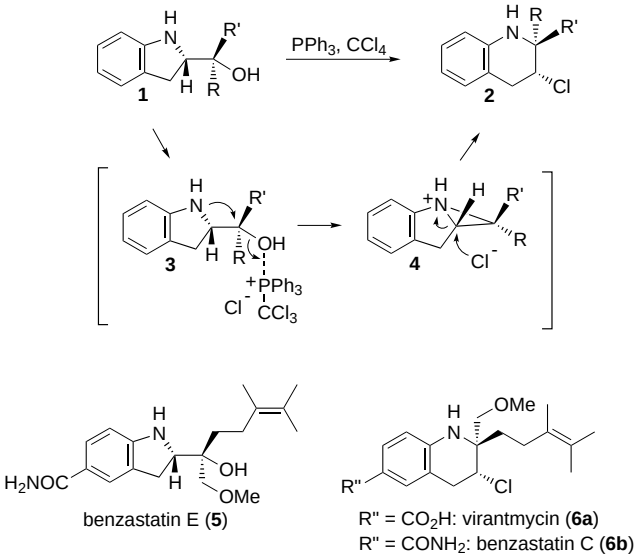
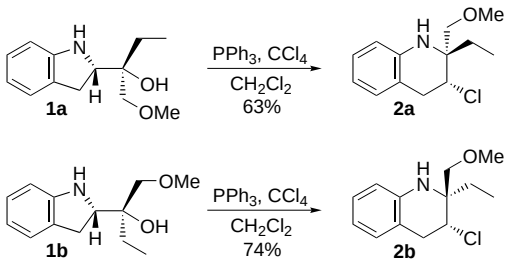


Scheme 1.



Scheme 2.

droisoquinolines by a catalytic, enantioselective Reissert-type reaction.[1c] However, efficient stereoselective synthesis of 2,2-disubstituted tetrahydroquinolines still remains to be solved. Herein we describe an indoline-2-methanol to tetrahydroquinoline rearrangement in which contiguous quaternary and tertiary stereogenic centers are constructed in one step. This reaction was successfully applied to an efficient total synthesis of natural virantmycin (**6a**).

Kim et al. reported the isolation from *Streptomyces nitrosporeus* 30643 of a novel class of indoline alkaloids, that is benzastatins such as benzastatin E (**5**), and tetrahydroquinoline alkaloids, namely, benzastatin C (**6b**) and its congeners, which are structurally related to virantmycin (**6a**).[4] The structures of these alkaloids suggested that an aziridine intermediate, such as **4**, is involved in their biosyntheses.[5] Based on this hypothesis, we designed the triphenylphosphane/CCl_4-mediated rearrangement from α,α-disubstituted indoline-2-methanol **1** to 2,2,3-trisubstituted tetrahydroquinoline **2** via the aziridine **4**, followed by ring opening by attack of chloride anion (Scheme 1).[6] This type of rearrangement is a useful method of accessing various chiral 2,2,3-trisubstituted tetrahydroquinoline derivatives in conjunction with our previously developed, highly diastereoselective synthesis of optically active α,α-disubstituted indoline-2-methanol compounds **1** by Grignard addition to 2-acylindoline.[7]

We investigated the reaction by using optically active alcohol **1a**[7] as starting material (Scheme 2). Treatment of **1a** with PPh_3 (3 equiv) and CCl_4 (10 equiv) in CH_2Cl_2 under reflux for 30 min afforded tetrahydroquinoline **2a** as a single isomer in 63% yield. The same treatment of diastereomer **1b**[7] gave **2b** as a sole isomer in 74% yield.[8,9] Relative configurations of **2a** and **2b** were determined by comparison with the corresponding authentic racemic samples, reported by Shirahama et al.[10] The absolute configuration of **2a** was determined to be 2*R*,3*R* by X-ray analysis of (1*S*,2*R*,4*R*)-(−)-camphorsultam[11] derivative **7** (Figure 1),[12] which was derived from **2a** in a two-step sequence. Treatment of **2b** with nBu_3SnH and azobisisobutyronitrile afforded the dechlorinated derivative, which was identical with the dechlorinated compound derived from **2a** except for the optical rotation. On the basis of these results, the rearrangement is considered to be stereospecific.[13] Table 1 presents the results of the rearrangement of various chiral indoline-2-methanol derivatives. All the reactions provide single isomers in moderate to good yield.[14] The reaction of **1c** (enantiomer of **1a**) provided the antipode of **2a** (entry 1). Use of polymer-supported triphenylphosphane gave the same result (entry 6). Thus, this rearrangement provides a new method for the synthesis of various optically active 2,2,3-trisubstituted tetrahydroquinolines.

The utility of this reaction was clearly demonstrated by an efficient total synthesis of the potent antiviral agent virantmycin (**6a**)[3] in its natural form. Several total syntheses of (±)- or *ent*-virantmycin are known.[15,16] However, the naturally occurring form of virantmycin has not been synthesized to date. The synthesis of (−)-virantmycin is outlined in Scheme 3. Acylindoline **9**,[7] which was prepared from commercially available (*S*)-(−)-indoline-2-carboxylic acid (**8**) in four steps (37%), was treated with iodine monochloride to afford iodide **10** in 91% yield. Iodide **10** was subjected to diastereoselective Grignard addition[7] with 2,3-dimethyl-3-pentenylmagnesium bromide[17] to give *tert*-alcohols as a 95/5 mixture of separable isomers, as determined by HPLC analysis of the product mixture. The Boc protecting group of the major isomer was removed by treatment with HCO_2H to afford **11**.[18] The resulting amino alcohol **11** was treated with tri-*n*-butylphosphane (20 equiv)[19] and CCl_4 (30 equiv) to provide tetrahydroquinoline **12** as a single isomer in 45% yield. The tetrahydroquinoline **12** was carbonylated by reaction with 1 atm of CO in H_2O/DMF in the presence of catalytic $Pd(OAc)_2$ and K_2CO_3 to give

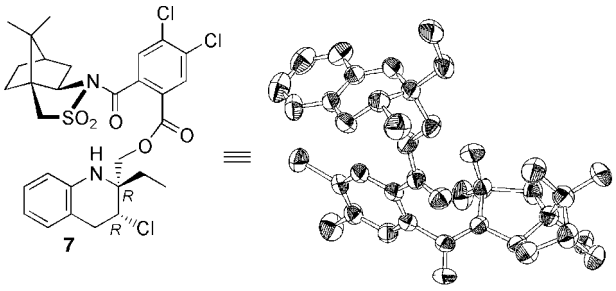
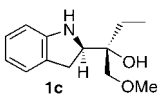
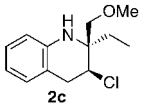
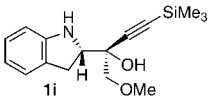
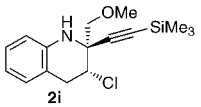
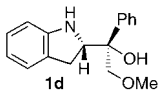
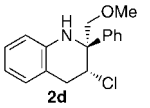
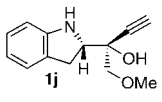
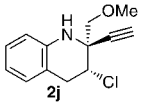
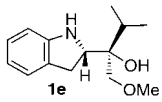
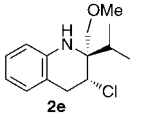
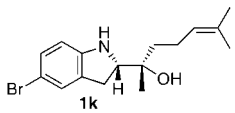
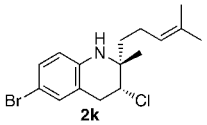
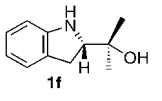
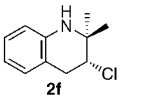
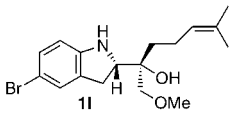
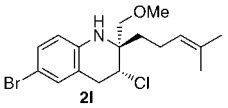
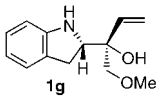
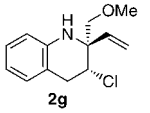
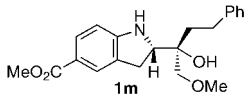
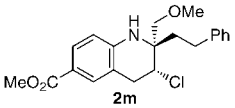
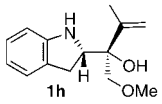
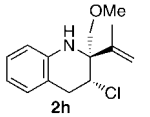
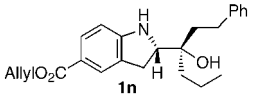
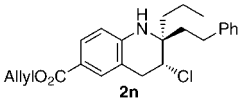
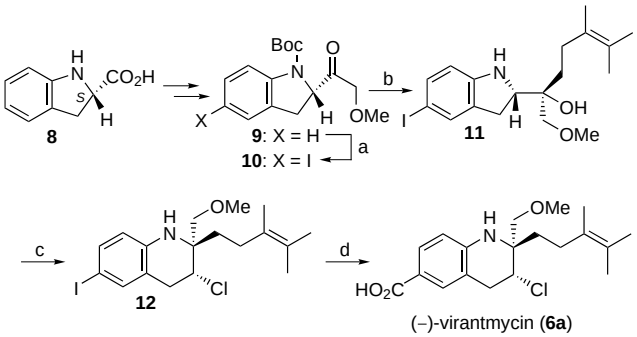


Figure 1. X-ray structure of the (1*S*,2*R*,4*R*)-(−)-camphorsultam derivative of **2a**.

Table 1: Rearrangement of indoline **1** to tetrahydroquinoline **2**.

Entry[a]	Indoline **1**[b]	Tetrahydroquinoline **2**[c]	Yield [%][d]	Entry[a]	Indoline **1**[b]	Tetrahydroquinoline **2**[c]	Yield [%][d]
1	 **1c**	 **2c**	63	7	 **1i**	 **2i**	63
2	 **1d**	 **2d**	63	8	 **1j**	 **2j**	55
3	 **1e**	 **2e**	53	9	 **1k**	 **2k**	62
4	 **1f**	 **2f**	65	10	 **1l**	 **2l**	41
5	 **1g**	 **2g**	31	11	 **1m**	 **2m**	50
6	 **1h**	 **2h**	37 (44)[e]	12	 **1n**	 **2n**	52

[a] All the reactions conducted were with Ph_3P (3 equiv) and CCl_4 (10 equiv), except for entry 6. [b] For synthesis of indoline **1**, see ref. [7]. [c] The absolute stereochemistry was tentatively assigned by analogy with the reaction mechanism, except for **2c** (enantiomer of **2a**). [d] Yield of isolated product after column chromatography. [e] Polymer-supported triphenylphosphane (5 equiv) was used.



Scheme 3. Reagents and conditions: a) ICl, 2,6-di-*tert*-butyl-4-methylpyridine, CH_2Cl_2, 0 °C→RT, 91 %; b) 1) $Me_2C{=}C(Me)(CH_2)_2MgBr$, THF, −78 °C, 73 %; 2) HCO_2H, CH_2Cl_2, 50 °C, 59 %; c) $(nBu)_3P$, CCl_4, CH_2Cl_2, reflux, 45 %; d) CO 1 atm, K_2CO_3, $Pd(OAc)_2$, H_2O/DMF, RT, 53 % (80 % based on recovered starting material); Boc = 1,1-dimethylethoxycarbonyl.

(−)-virantmycin (**6a**) in 53 % yield (80 % based on recovered starting material). Synthetic **6a** was identical in all respects to natural virantmycin[3,16] [^{1}H NMR, ^{13}C NMR spectra, and $[\alpha]_D^{24} = -15.0$ ($c = 0.84$ in $CHCl_3$) (ref.[16,20] $[\alpha]_D^{18} = -11.1$ ($c = 0.175$ in $CHCl_3$))]. This synthesis required only nine steps from indoline **8**.

In summary, we have developed a novel synthesis of chiral trisubstituted tetrahydroquinolines in which contiguous quaternary and tertiary stereogenic centers are constructed in analogy to the hypothetical biosynthetic pathway. The reaction was applied to the first total synthesis of natural virantmycin in only nine steps from commercially available starting material. We believe that our rearrangement reaction provides some support for the proposed biosynthetic pathway of virantmycin and related tetrahydroquinoline alkaloids via an aziridine intermediate. Further applications of this methodology to complex polycyclic tetrahydroquinoline alkaloids are underway.

Experimental Section

2a: Triphenylphosphane (135 mg, 0.420 mmol) was added to a solution of **1a** (31 mg, 0.14 mmol) and CCl_4 (135 μL, 1.40 mmol) in CH_2Cl_2 (3 mL) at 40 °C (bath temp.). The mixture was stirred under reflux for 1 h, and then concentrated. Purification by column chromatography on silica gel (*n*-hexane/AcOEt 10/1 to 2/1) gave tetrahydroquinoline **2a** as a colorless oil (21 mg, 63 %): $[\alpha]_D^{24} = +7.2$ ($c = 0.45$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.01$ (t, $J =$ 8.1 Hz, 1H), 6.96 (d, $J = 8.1$ Hz, 1H), 6.63 (t, $J = 8.1$ Hz, 1H), 6.53 (d, $J = 8.1$ Hz, 1H), 4.33 (dd, $J = 6.6$, 5.2 Hz, 1H), 3.99 (br s, 1H), 3.53 (d, $J = 9.2$ Hz, 1H), 3.48 (d, $J = 9.2$ Hz, 1H), 3.35 (s, 3H), 3.30 (dd, $J =$ 16.8, 5.2 Hz, 1H), 3.05 (dd, $J = 16.8$, 6.6 Hz, 1H), 1.76 (dq, $J = 14.9$, 7.3 Hz, 1H), 1.66 (dq, $J = 14.9$, 7.3 Hz, 1H), 0.92 ppm (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 142.3$, 129.4, 127.4, 117.6, 117.2, 114.7, 73.5, 59.4, 57.6, 57.0, 33.9, 27.2, 7.1 ppm; IR ($CHCl_3$ solution): $\tilde{\nu} = 3422$, 2972, 2935, 2896, 1607, 1588, 1482, 1312, 1260, 1112, 980, 960, 834 cm^{-1}; HRMS calcd for $C_{13}H_{18}NOCl$ [M^+]: 239.1077; found 239.1075.

2b: $[\alpha]_D^{24} = -30.2$ ($c = 0.67$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.01$ (t, $J = 8.0$ Hz, 1H), 6.97 (d, $J = 8.0$ Hz, 1H), 6.67 (t, $J = 8.0$ Hz, 1H), 6.57 (d, $J = 8.0$ Hz, 1H), 4.44 (dd, $J = 7.0$, 5.0 Hz, 1H), 3.99 (br s, 1H), 3.42 (1H, d, $J = 9.5$ Hz), 3.40 (d, $J = 9.5$ Hz, 1H),

3.35 (s, 3H), 3.24 (dd, $J = 16.5$, 5.0 Hz, 1H), 3.09 (dd, $J = 16.5$, 6.5 Hz, 1H), 1.82 (dq, $J = 14.5$, 7.5 Hz, 1H), 1.72 (dq, $J = 14.5$, 7.5 Hz, 1H), 0.94 ppm (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 142.1$, 129.3, 127.3, 117.8, 117.7, 115.0, 75.1, 59.3, 57.9, 57.5, 34.0, 25.4, 7.5 ppm; IR ($CHCl_3$ solution): $\tilde{\nu} = 3424$, 2972, 2935, 2883, 1607, 1588, 1498, 1481, 1307, 1156, 1111, 962 cm^{-1}; HRMS: calcd for $C_{13}H_{18}NOCl$ [M^+]: 239.1077, found: 239.1081.

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[6] Cossy et al. reported a ring-expansion reaction of *N*-benzylpyrrolidine-2-methanol derivatives to *N*-3-chloropiperidine derivatives using MsCl (Ms = methanesulfonyl). They reported that the rearrangement does not proceed with α,α-disubstituted *N*-benzylpyrrolidine-2-methanol derivatives. J. Cossy, C. Dumas, D. Gomez Pardo, *Eur. J. Org. Chem.* **1999**, 1693. Under the same conditions, α,α-disubstituted indoline-2-methanols do not undergo the rearrangement reaction, probably because of steric hindrance.

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[8] The same reactions of corresponding α-monosubstituted or unsubstituted indoline-2-methanols gave complex mixtures.

[9] No racemization occurs during the rearrangement, this is confirmed by the resulting tetrahydroquinoline **2a** which is optically pure by chiral HPLC analysis. Daicel Chiralcel OJ ($\varnothing = 0.46$ cm × 25 cm), *n*-hexane/*i*PrOH (95/5), 1 mL min^{-1}.

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[11] N. Harada, N. Koumura, M. Robillard, *Enantiomer* **1997**, *2*, 303.

[12] CCDC 202237 (**7**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

[13] There is no direct evidence for the formation of an aziridine intermediate such as **4**. A stepwise sequence may be possible (1. formation of tertiary chloride; 2. intermolecular cyclization to an aziridine; 3. ring opening by the attack of chloride anion). However, we could not obtain the tertiary chloride by treatment of **1a** with various chlorinating agents. Also, treatment of **1a** under Mitsunobu conditions gave no aziridine compound (starting material was recovered). For the ring-opening reaction of an aziridine, such as **4**, with chloride anions to provide tetrahydroquinoline **2**, see ref. [10].

[14] All the other products were highly polar materials which were not isolated.

[15] Syntheses of (±)-virantmycin: a) M. L. Hill, R. A. Raphael, *Tetrahedron Lett.* **1986**, *27*, 1293; b) M. L. Hill, R. A. Raphael, *Tetrahedron* **1990**, *46*, 4587; c) Y. Morimoto, F. Matsuda, H. Shirahama, *Synlett* **1991**, 202 and ref. [10]; d) H. Steinhagen, E. J. Corey, *Org. Lett.* **1999**, *1*, 823.

[16] Synthesis of *ent*-virantmycin: Y. Morimoto, F. Matsuda, H. Shirahama, *Tetrahedron* **1996**, *52*, 10631.

[17] A. N. De Silva, C. L. Francis, D. Ward, *Aust. J. Chem.* **1993**, *46*, 1657.

[18] The configurations of the newly created asymmetric centers in the Grignard adduct were determined after NOE experiments on the acetonide derivative of **11**. See ref. [7].

[19] When we used triphenylphosphane in the reaction, an undesired deiodinated product and an indole derivative (dehydration followed by isomerization) were obtained. However, using tri-*n*-butylphosphane instead of triphenylphosphane prevented these side reactions.

[20] Initially, the optical rotation of (−)-virantmycin was reported as −0.05 in ref. [3]. Later, the optical rotation of (−)-virantmycin was reexamined and reported as −11.1 by Shirahama and co-workers.[16]

