## A Simple Convergent Approach to the Synthesis of the Antiviral Agent Virantmycin

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ABSTRACT



The antiviral agent (±)-virantmycin has been synthesized from two simple building blocks (2 and 3) in eight steps, as outlined in Scheme 2.

This paper reports the development of a short and convergent approach to the synthesis of the potent antiviral agent virantmycin  $(1)^1$  and its initial demonstration in a synthesis of  $(\pm)$ -virantmycin.<sup>2</sup> The key methodology underlying this approach is the construction of the hydroquinoline system by the generation and trapping of an *o*-azaxylylene intermediate, as recently reported from this laboratory.<sup>3</sup> The building blocks for the assembly of the virantmycin structure were the isocyanate **2** and the allylic alcohol **3**.



The isocyanate 2 was synthesized from commercially available 2-aminobenzyl alcohol by the sequence (1) iodination with 1 equiv of ICl in HOAc at 23  $^{\circ}$ C for 2 h to form

(1) Omura, S., Nakagawa, A. Tetrahedron Lett. 1981, 22, 2199.

(2) The naturally occurring form of virantmycin has not yet been synthesized; for syntheses of  $(\pm)$ - or *ent*-virantmycin see: (a) Hill, M. L.; Raphael, R. A. *Tetrahedron Lett.* **1986**, 27, 1293. (b) Hill, M. L.; Raphael, R. A. *Tetrahedron* **1990**, 46, 4587. (c) Morimoto, Y.; Matsuda, F.; Shirahama, H. *Synlett* **1991**, 202. (d) Morimoto, Y.; Matsuda, F.; Shirahama, H. *Tetrahedron* **1996**, 52, 10609.

(3) Steinhagen, H.; Corey, E. J. Angew. Chem., Int. Ed. 1999, 38, 1928.

2-amino-5-iodobenzyl alcohol (74%), (2) O-silylation with 1.1 equiv of *tert*-butyldimethylsilyl chloride (TBSCl), 2.5 equiv of imidazole, and a catalytic amount of 4-(dimethylamino)pyridine (DMAP) in dimethylformamide at 23 °C for 2 h (97%), and (3) isocyanate formation<sup>4</sup> with 2.5 equiv of phosgene in CH<sub>2</sub>Cl<sub>2</sub> and saturated aqueous NaHCO<sub>3</sub> with stirring of the biphasic mixture at 23 °C for 1 h (>99%).

The allylic alcohol **3** was prepared by the sequence outlined in Scheme 1. Reaction of ethyl propiolate with 4 equiv of methyl vinyl ketone and LiCl (4 equiv) in HOAc at 23 °C in the presence of 2 mol % of Pd(OAc)<sub>2</sub> provided



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the keto ester **4** (85%) with 93:7 Z/E selectivity.<sup>5</sup> Reduction of **4** with diisobutylaluminum hydride and subsequent selective silylation of the primary hydroxyl function with triisopropylsilyl chloride (TIPSCl) afforded the secondary alcohol **5** (55% overall), which was transformed by Swern oxidation (initially at -60 °C with warming after addition of Et<sub>3</sub>N to room temperature over 4 h) into the corresponding methyl ketone **6** (94%). Wittig isopropylidination and desilylation of **6** gave **3** in 92% overall yield.

The completion of the synthesis of  $(\pm)$ -virantmycin is outlined in Scheme 2. The carbamate **7** was prepared from the isocyanate **2** and the allylic alcohol **3** by reaction in CH<sub>2</sub>-Cl<sub>2</sub> in the presence of 0.2 equiv of DMAP at 23 °C for 1.5 h (84%) and converted to the chloro carbamate **8** by sequential desilylation at 23 °C for 15 min (92%) and chlorination with 1.1 equiv of SOCl<sub>2</sub> and 1.2 equiv of Et<sub>3</sub>N in CH<sub>2</sub>Cl<sub>2</sub> at 23 °C for 3 h (75%). Stirring of **8** in CH<sub>2</sub>Cl<sub>2</sub> solution at 23 °C for 48 h with 5 equiv of Cs<sub>2</sub>CO<sub>3</sub> resulted in completely stereoselective formation of the hydroquinoline derivative **10** (90%) by way of an internal [4 + 2] cycloaddition of the intermediate *o*-azaxylylene **9**.<sup>6</sup> Reductive cleavage of the cyclic urethane subunit of 10 was effected by a mild and novel procedure consisting of treatment at -78 °C with 1 equiv of diisobutyl-*n*-butylaluminum hydride (from an equimolar mixture of n-BuLi and DIBAL-H)<sup>7</sup> followed by quenching with aqueous acid. The resulting amino alcohol (53% yield, not optimal) was methylated to 11 and methoxycarbonylated by reaction with 1 atm of CO in MeOH-dimethylformamide-Et<sub>3</sub>N in the presence of 0.2 equiv of Pd(OAc)<sub>2</sub> and 0.22 equiv of 1,3-bis(diphenylphosphino)propane (dppp) at 75 °C for 6 h to give the methyl ester of ( $\pm$ )-virantmycin (12; 85%). The <sup>1</sup>H and <sup>13</sup>C NMR, infrared, and mass spectral data for synthetic 12 were identical with those previously reported.<sup>2a,b</sup> Hydrolysis of 12 using 3 equiv of LiOH in 3:1 CH<sub>3</sub>CN/H<sub>2</sub>O produced (±)virantmycin (1), which was identical spectroscopically and chromatographically with an authentic sample.8

The synthesis of  $(\pm)$ -virantmycin reported herein is simple and expeditious and should, with appropriate modification, be applicable to the synthesis of the natural enantiomer of virantmycin (1).

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<sup>(5) (</sup>a) Wang, Z.; Lu, X. J. Org. Chem. **1996**, 61, 2254. (b) Wang, Z.; Lu, X. Tetrahedron Lett. **1997**, 29, 5213. (c) Wang, Z.; Lu, X. J. Chem. Soc., Chem. Commun. **1996**, 535.

<sup>(6)</sup> Any *E*-isomeric chloroolefin which may be present in the starting material **8** is lost in this step because it does not undergo cyclization under the conditions of the conversion  $8 \rightarrow 10$ .

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<sup>(7)</sup> Kim, S.; Ahn, K. H. J. Org. Chem. 1984, 49, 1717.

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