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

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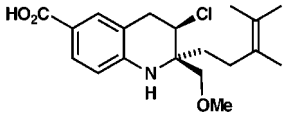
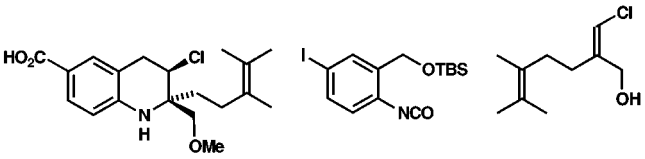
ABSTRACT



virantmycin

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 (±)-virantmycin.[2] 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.[3] The building blocks for the assembly of the virantmycin structure were the isocyanate **2** and the allylic alcohol **3**.

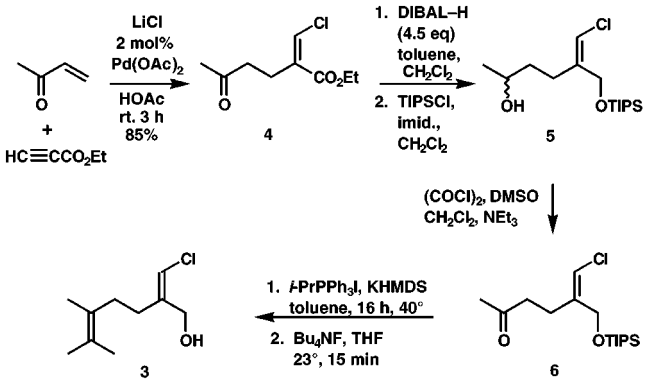


1 2 3

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 °C for 2 h to form 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[4] with 2.5 equiv of phosgene in CH_2Cl_2 and saturated aqueous $NaHCO_3$ 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 $Pd(OAc)_2$ provided

Scheme 1



3 4 5 6

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

(2) The naturally occurring form of virantmycin has not yet been synthesized; for syntheses of (±)- 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.

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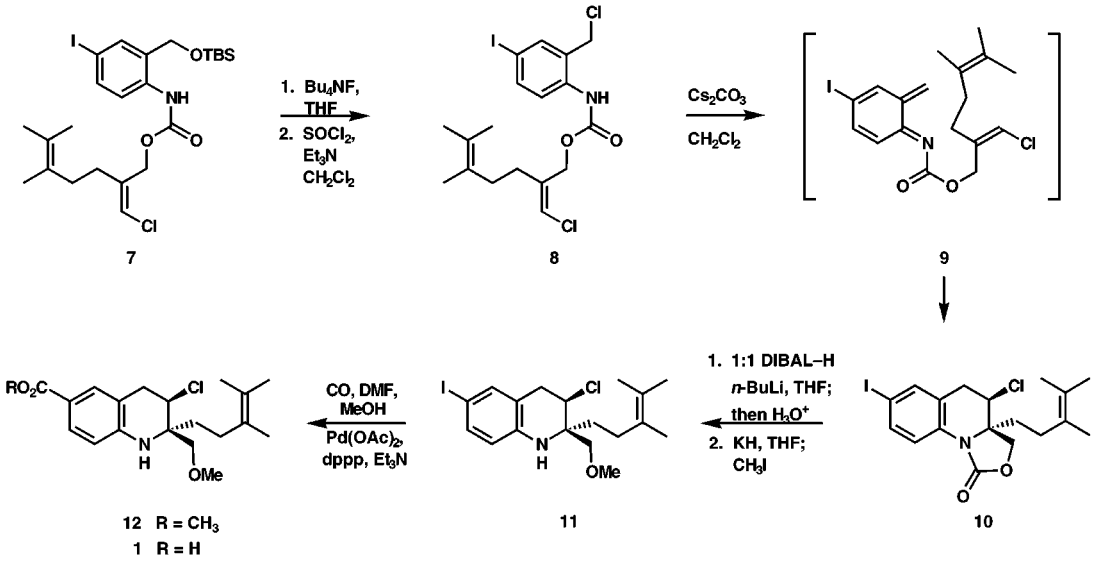
Scheme 2



the keto ester **4** (85%) with 93:7 *Z*/*E* selectivity.[5] 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_3N 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 (±)-virantmycin is outlined in Scheme 2. The carbamate **7** was prepared from the isocyanate **2** and the allylic alcohol **3** by reaction in CH_2Cl_2 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 $SOCl_2$ and 1.2 equiv of Et_3N in CH_2Cl_2 at 23 °C for 3 h (75%). Stirring of **8** in CH_2Cl_2 solution at 23 °C for 48 h with 5 equiv of Cs_2CO_3 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**.[6] 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)[7] 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_3N in the presence of 0.2 equiv of $Pd(OAc)_2$ and 0.22 equiv of 1,3-bis(diphenylphosphino)propane (dppp) at 75 °C for 6 h to give the methyl ester of (±)-virantmycin (**12**; 85%). The ^1H and ^{13}C NMR, infrared, and mass spectral data for synthetic **12** were identical with those previously reported.[2a,b] Hydrolysis of **12** using 3 equiv of LiOH in 3:1 CH_3CN/H_2O produced (±)-virantmycin (**1**), which was identical spectroscopically and chromatographically with an authentic sample.[8]

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

Acknowledgment. We are indebted to the National Institutes of Health and the Deutscher Akademischer Austauchdienst (DAAD) for financial assistance of this research.

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(4) Nowick, J. S.; Holmes, D. L.; Noronha, G.; Smith, E. M.; Nguyen, T. M.; Huang, S.-L. *J. Org. Chem.* **1996**, *61*, 3929.

(5) (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.

(6) 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** → **10**.

(7) Kim, S.; Ahn, K. H. *J. Org. Chem.* **1984**, *49*, 1717.

(8) Graciously provided by Prof. Satoshi Ōmura, to whom we are very grateful.