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AN EFFICIENT APPROACH TOWARD VIRANTMYCIN: STEREOSPECIFIC CONSTRUCTION OF TETRAHYDROQUINOLINE RING SYSTEM EMPLOYING INTRAMOLECULAR NITRENE-ADDITION REACTION

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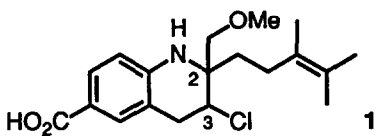
Summary: An efficient and stereospecific synthesis of the tetrahydroquinoline ring system of the structurally unique alkaloid, virantmycin (**1**), has been achieved using intramolecular addition reaction of nitrene to olefin as a key step.

The unusual alkaloid, virantmycin (**1**), isolated from the fermentation broth of *Streptomyces nitrosporeus* by Omura *et al.* in 1981, has been found to possess antifungal and potent inhibitory activity against various RNA and DNA viruses.[1] Its gross structure has been established as unique tetrahydroquinoline skeleton[2,3] and the two multi-step syntheses have been reported.[4,5]

In an effort to develop the efficient synthetic scheme for **1**, we found that the tetrahydroquinoline ring can be constructed effectively employing stereospecific intramolecular addition of nitrene, generated by photolysis of aryl azide,[7] to olefin. Although some stereospecific intermolecular nitrene-addition to olefin have been reported,[8] utilization of the nitrene-addition for organic synthesis has been hitherto restricted because of low yields of the desired aziridines. In this communication we wish to report the stereospecific synthesis of a diastereomeric pair of the tetrahydroquinoline systems **6** and **8** *via* intramolecular nitrene-addition reaction of the azide-olefins **3** and **4**, respectively, and unambiguous assignment for relative configuration of **6** and **8**.

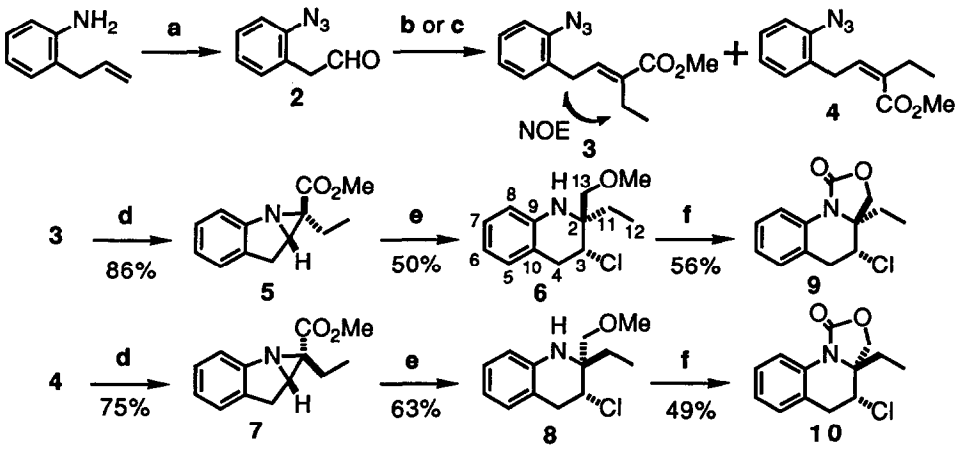


1 Virantmycin

The syntheses of azide-olefins **3** and **4** required for nitrene-addition reaction were carried out by stereoselective olefination of the aldehyde **2** easily prepared from 2-allylaniline[9] (Scheme 1). The Wittig reaction of aldehyde **2** with methyl 2-(triphenylphosphoranylidene)-butyrate[10] yielded *E*-olefin **3** with the stereoselectivity of 32 : 1. On the other hand, the Horner-Emmons reaction of **2** with methyl 2-[bis(2,2,2-trifluoroethyl)phosphono]butyrate[11] under Still's condition[12] provided *Z*-olefin **4** with the stereoselectivity of 8 : 1. The stereochemistry of the olefins **3** and **4** was proven by the chemical shifts of their vinyl protons [**3**, δ 6.77 (t, J=7.3 Hz); **4**, δ 5.94 (t, J=7.3 Hz)] and the presence of NOE shown in **3**.

The crucial nitrene-addition reaction by photolysis[7] of the azide-olefins **3** and **4** proceeded with complete stereospecificity to afford aziridines **5** and **7** in good yields, respectively. The stereochemistry of the aziridines **5** and **7** was supported from the high field shifts of the protons in the functional groups (CO_2CH_3 or CH_2CH_3) *cis* to an aromatic ring in their ^{1}H-NMR spectra [**5**, CO_2CH_3, δ 3.80 (3H, s), CH_2CH_3, δ 1.50 (1H, dq, J=14.7, 7.3 Hz) and δ 1.20 (1H, dq, J=14.7, 7.3 Hz), CH_2CH_3, δ 0.84 (3H, t, J=7.3 Hz); **7**, CO_2CH_3, δ 3.25 (3H, s), CH_2CH_3, δ 2.09 (1H, dq, J=14.7, 7.3 Hz) and δ 1.66 (1H, dq, J=14.7, 7.3 Hz), CH_2CH_3, δ 1.04 (3H, t, J=7.3 Hz)]. Reduction of methyl ester, methylation, and the regioselective ring opening of aziridine with inversion[13] gave two diastereomeric compounds **6** and **8** which contained the same ring system as **1**.

It seemed to be difficult to prove the stereochemistry of compounds **6** and **8** deduced from the stereospecific reaction sequences by their NOE experiments, because these piperidine ring systems were conformationally flexible as shown by the presence of some NOEs observed in the NOESY spectra of compounds **6** and **8** (Fig. 1) and ambiguity for the assignment of each proton of 4-H_2 to equatorial or axial orientation remained.[14] In order to fix the conformation of piperidine ring, cyclic carbamates **9** and **10** were derived from **6** and **8**, respectively. As shown in Fig. 2, coupling constants between 3-H and 4-H_2 in **9** and **10**



a. 1) HCl, $NaNO_2$, then NaN_3 (83%), 2) OsO_4, N-methylmorpholine N-oxide / acetone-H_2O, 3) $NaIO_4$ / THF-H_2O (63%, 2 steps). **b**. EtC(=PPh_3)CO_2Me / CH_2Cl_2 / rt / 30 h (80%, **3** : **4** = 32 : 1). **c**. EtCH[P(O)(OCH_2CF_3)$_2$]CO_2Me, KN(TMS)$_2$, 18-crown-6 / THF / -78 °C→rt / 4 h (50%, **3** : **4** = 1 : 8). **d**. hν / toluene / rt. **e**. 1) $LiAlH_4$ / THF / 0 °C, 2) KH / THF, then MeI, 3) Et_4NCl, TFA / CH_2Cl_2 / -15 °C / 20 min. **f**. 1) $AlCl_3$, ^{n}PrSH / CH_2Cl_2,[15] 2) Im_2CO (10 equiv.) / toluene.

Scheme 1.

revealed that these compounds possessed conformationally rigid piperidine ring system. Furthermore, the stereochemistry of compounds **6** and **8** was unambiguously confirmed from NOE experiments with **9** and **10** (Fig. 2).

In conclusion we have established an efficient and stereospecific route to the tetrahydroquinoline ring system of virantmycin (**1**) utilizing intramolecular nitrene-addition reaction as a key step. The application of this strategy to the total synthesis of natural product will be reported in due course.

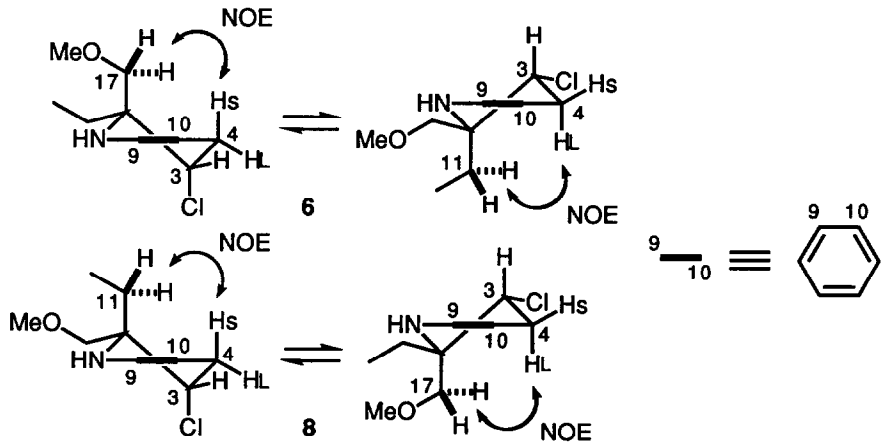


Fig. 1. NOEs observed in compounds **6** and **8**.

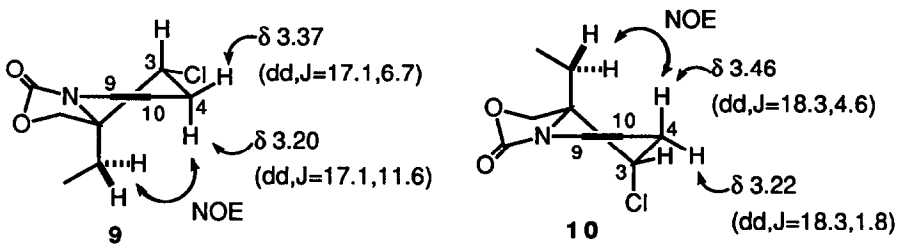


Fig. 2. NOEs observed in cyclic carbamates **9** and **10**.

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6, δ 7.02 (1H, t, J=7.9 Hz, 7-H), 6.97 (1H, d, J=7.9 Hz, 5-H), 6.68 (1H, t, J=7.9 Hz, 6-H), 6.58 (1H, d, J=7.9 Hz, 8-H), 4.45 (1H, dd, J=6.7, 4.9 Hz, 3-H), 3.41 (2H, s, 13-H_2), 3.35 (3H, s, 13-OMe), 3.25 (1H, dd, J=17.1, 4.9 Hz, 4-Hs), 3.08 (1H, dd, J=17.1, 6.7 Hz, 4-H_L), 1.63-1.90 (2H, m, 11-H_2), 0.94 (3H, t, J=7.3 Hz, 12-H_3); **8**, δ 7.03 (1H, t, J=7.9 Hz, 7-H), 6.97 (1H, d, J=7.9 Hz, 5-H), 6.67 (1H, t, J=7.9 Hz, 6-H), 6.56 (1H, d, J=7.9 Hz, 8-H), 4.35 (1H, dd, J=6.7, 4.9 Hz, 3-H), 4.01 (1H, br s, NH), 3.54 (1H, d, J=9.2 Hz, 13-H), 3.49 (1H, d, J=9.2 Hz, 13-H'), 3.37 (3H, s, 13-OMe), 3.31 (1H, dd, J=17.1, 4.9 Hz, 4-Hs), 3.06 (1H, dd, J=17.1, 6.7 Hz, 4-H_L), 1.58-1.86 (2H, m, 11-H_2), 0.93 (3H, t, J=7.3 Hz, 12-H_3).
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