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A FACILE AND EFFICIENT STEREOSELECTIVE SYNTHESIS OF 6-HYDROXY-trans-4a-PHENYLDECAHYDROISOQUINOLINE

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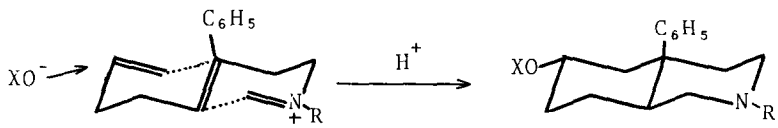
Summary A stereoselective synthesis of 6-oxygenated trans-4a-phenyldecahydroisoquinoline was achieved by treatment of 1-ethoxycarbamoyl-1-phenyl-1,5-hexadiene with paraformaldehyde in formic acid.

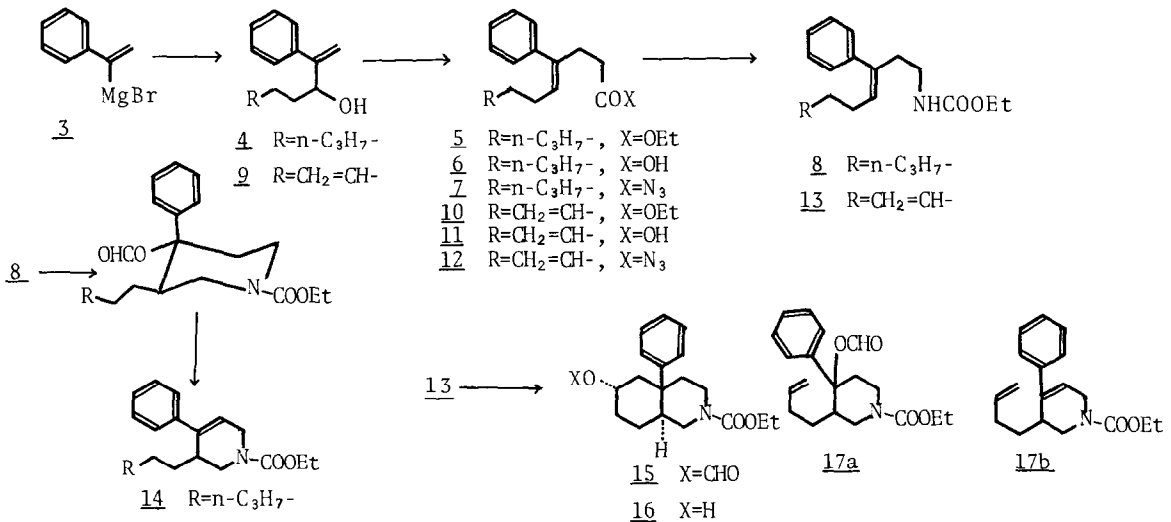
We investigated a stereoselective synthesis of 6-oxygenated trans-4a-phenyldecahydroisoquinoline system, a key structural variant of morphine molecule[1]. Our synthetic strategy is based on the ring-closure of diolefin-iminium species (1), which would provide a solution of two characteristic problems in the construction of the target molecule (2); one is introduction of oxygen function at the 6-position and another is stereoselective formation of trans-decahydroisoquinoline skeleton. Although a number of N-acyliminium-induced cyclization[2] have been applied to a synthesis of alkaloids families[3], polyolefinic heterocyclizations are virtually unknown[4] for that purpose. We describe the results of our studies in this paper.



1 2

First, we examined the ring-closure of monoolefin-iminium ion intermediate, derived from 8 prior to examination of cyclization of the compound of type 1, whether pyridine ring fromed. The desired starting materials were prepared by the following practical methods. The reaction of the Grignard reagent (3), obtained from α-bromostyrene[5] with hexanal gave the allyl alcohol (4). Claisen rearrangement of 4 by the use of triethyl orthoacetate [3 eq. $CH_3C(OEt)_3$, 0.1 eq. phenol, 145°C, 6 h] gave the ester (5) stereoselectively[6]. Hydrolysis of 5 yielded the acid (6; 70 % from 3, 5-10 % EtOH-NaOH, reflux, 2 h). The acid (6) was easily converted to the carbamate (8)[7] through the same manner as Overman reported[8]. The azide (7)[6, Et_3N, acetone, 1.2 eq. ClCOOEt, 0°C, 10 min, then, aq. NaN_3, 0°C ⟶ room temperature, 1 h) was treated with EtOH in toluene (reflux, 6 h) to give 8. In a similar way, the carbamate (13)[9] was obtained starting with the allyl alcohol (9), prepared by the reaction of 3 with pentenal[10], through 10, 11 and 12. The carbamate (8) was treated with paraformaldehyde (1.1 eq.) in formic acid (50°C, 1.5 h) to give rise to a formation of the tetrahydropyridine (14[11]; 70 %). The

formation of the double bond at the 4(5) position would be caused by elimination of formic acid during ring-inversion. Treatment of 13 with paraformaldehyde in formic acid (room temperature, 1.5 h) yielded the desired 6-oxygenated trans-4a-phenylisoquinoline (15)[12], mp 119-121°C, as expected. In this reaction, formation of monocyclization products (17a,b) was not observed. Hydrolysis of 15 (3N NaOH-EtOH, room temperature, 1 h) gave quantitative yield of the 6-hydroxy derivative (16)[13].



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4. 13-azasteroidal compounds were obtained by cyclization of aryl-olefin-N-acyliminium ion system. In these cases, the substituent at the terminal position is phenyl group; J. Dijkink and W. N. Speckamp, Tetrahderon, 34, 173 (1978).
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7. MS; m/e 289 (M^+); ^{1}HNMR ($CDCl_3$) δ 0.67-1.03 (3H, broad t), 1.10-1.52 (11H, m), 1.97 (2H, t,d, J=8 and 8 Hz), 2.53 (2H, t, J=7 Hz), 3.13 (2H, t,d, J=7 and 7 Hz), 4.86 (1H, broad s, NH), 5.56 (1H, t, J=8 Hz), 7.1-7.5 (5H, m).
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9. MS; m/z 274 (MH^+) [electron-impact MS did not give M^+); ^{1}HNMR ($CDCl_3$) δ 1.22 (3H, t, J=7 Hz), 2.07 (4H, m), 2.54 (2H, t, J=6 Hz), 3.14 (2H, d,t, J=6 and 6 Hz), 4.12 (2H, q, J=7 Hz), 4.67 (1H, broad s, NH), 4.87-5.21 (2H, m), 5.44-6.07 (2H, m), 7.11-7.51 (5H, m).
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11. MS; m/e 301 (M^+); ^{1}HNMR ($CDCl_3$) δ 0.67-1.00 (3H, broad t), 1.00-1.67 (11H, m), 2.63 (1H, broad s, $W_{1/2}$=15 Hz), 3.07 (1H, d,d, J=12 and 3 Hz), 3.78 (1H, d,d,d, J=12, 3 and 3 Hz), 4.07-4.40 (4H, m), 4.17 (2H, q, J=7 Hz), 5.81 (1H, t, J=3 Hz), 7.3 (5H, m).
12. MS; m/e 331 (M^+); ^{1}HNMR ($CDCl_3$) δ 1.23 (3H, t, J=7.5 Hz), 2.61-2.88 (1H, m), 3.00 (1H, d,d, J=13 and 3 Hz), 4.13 (2H, q, J=7.5 Hz), 4.91-5.37 (1H, m), 7.07-7.64 (5H, m).
13. MS; m/e 303 (M^+); ^{1}HNMR ($CDCCl_3$) δ 1.22 (3H, t, J=7 Hz), 2.57-2.97 (1H, m), 2.81 (1H, d,d, J=13 and 3 Hz), 3.67-4.19 (3H, m), 4.12 (2H, q, J=7 Hz), 7.43 (5H, m).

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