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AN EFFICIENT DIASTEREOSELECTIVE SYNTHESIS OF 6-HYDROXY-4a-[3,4-CROWNED(15-CROWN-5)PHENYL]-trans-DECAHYDROISOQUINOLINE

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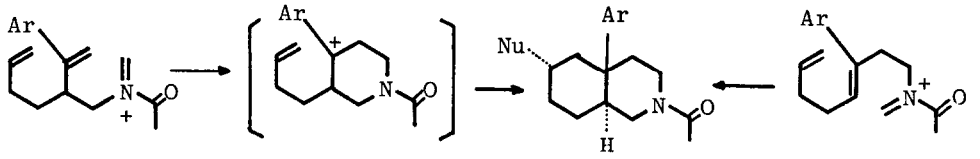
A high diastereoselective synthesis of 6-hydroxy-4a-aryl-trans-decahydroisoquinoline derivatives was achieved by an application of N-acyliminium ion-induced polyene cyclization procedure.

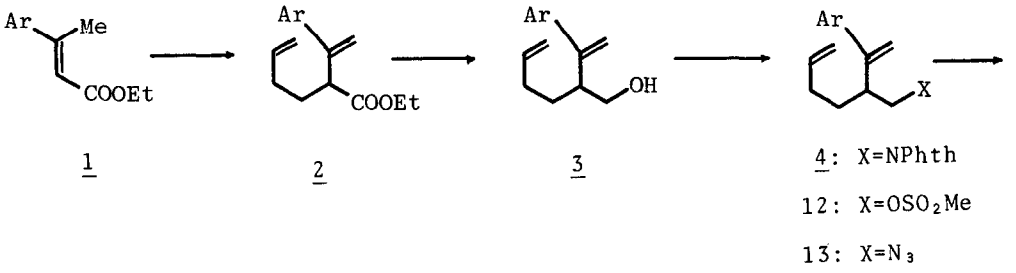
The field of biomimetic polyene cyclization has been used to a synthesis of complex multicyclic compounds with excellent stereochemical control.[1,2] Allyl alcohols, epoxides, acetals, or sulfonates have been used as suitable cationic initiators for successful polyene cyclizations. The use of N-acyliminium ions has been found to achieve remarkable stereocontrol synthesis of N-polycyclic compounds.[3] We have investigated a diastereoselective synthesis of 6-hydroxy-4a-aryl-trans-decahydroisoquinoline ring system,[3d] a key structural variant of morphine molecule, by using N-acyliminium ion as a cationic initiator. The search for potent analgesics based on the morphine ring system has been an area of considerable interest for many years[4] and new structural variants in this field are still required in the hope of finding significant analgesics without undesired side effects. Introduction of crown ether system might serve as a new type of ligand for elucidation of the mechanism of opiate.[5] From these points of view, We planned a synthesis of the title compound. Our synthetic strategy is based on the trans-fusion controlled ring closure of polyene-N-acyliminium ion system (Eq. 1).



Eq. 1

At the first stage, we describe a synthesis of 4a-(4-methoxyphenyl)- and 4a-(3,4-dimethoxyphenyl)-trans-decahydroisoquinolines.

α-Butenylation of the esters 1a,b (LDA, 1-iodo-3-butene, THF, -78°C ⟶ room temperature) gave the corresponding esters 2a[6] (80 %) and 2b (70 %), respectively. Reduction of 2a,b ($LiAlH_4$, Et_2O, 0°C, 2 h) gave the alcohols 3a,b which were condensed with phthalimide by Mitsunobu's method[7] to give the corresponding N-substituted phthalimide 4a (82 %, mp 70-71°C) and 4b (80 %, mp 82-83°C), respectively. Decomposition of 4a,b ($NH_2NH_2 \cdot H_2O$, work up), followed by methoxy-

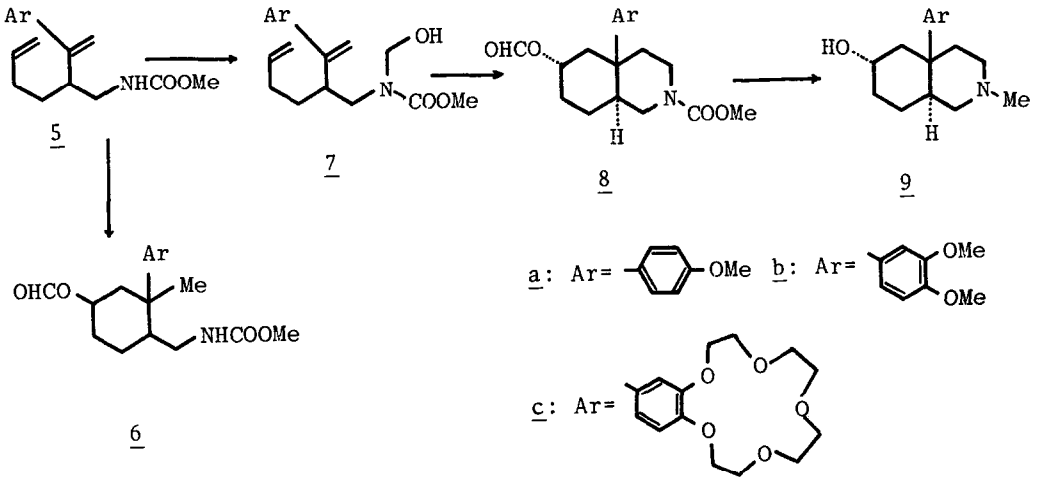


1 2 3

4: X=NPhth

12: X=OSO_2Me

13: X=N_3

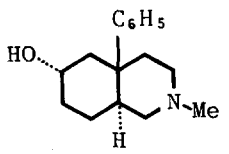


5 7 8 9

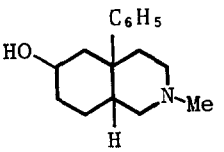
6

a: Ar= b: Ar=

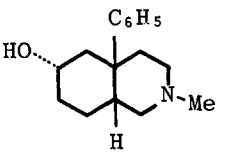
c: Ar=



10



11a



11b

carbonylation with methyl chloroformate yielded 5a and 5b, respectively. Cyclization of 5a with paraformaldehyde in formic acid resulted in a formation of 6a (20 %), δ 7.98 (OCHO), 1.33 (C-CH_3), without yielding the desired double cyclization product 8a. However, hydroxymethylation of 5a,b ($CsCO_3$, paraformaldehyde, THF),[8] followed by cyclization with formic acid gave the desired corresponding 4a-arylisoquinolines 8a[6] (72 %) and 8b[6] (73.6 %), respectively. Reduction of 8a,b ($LiAlH_4$, THF) afforded the corresponding 6-hydroxy-2-methylisoquinolines 9a[6] (82 %, mp 74-76°C) and 9b[6] (64 %, mp 104-107°C), respectively. In order to determine the ring-juncture of 9, the 4a-phenyl analog 10 (mp 69-71°C) was prepared by starting from the ester 1 (Ar=C_6H_5) according to the same procedure as above and compared with the known cis-fused two epimeric isomers 11a,b.[9] The characteristic physical data of 10 were considerably different from those of 11a,b appeared in the literature. Therefore, the ring-juncture of 4a-phenyldecahydroisoquinolines obtained by this method was assigned as trans rather than cis. The equatorial configuration of the hydroxyl group at 6-position was also easily deduced from the magnitude of the coupling constants for C-6 proton bearing oxygen function, which was clearly visible in their ^{1}H-NMR spectra. The signals were broadened ($W_{1/2}$= 30 Hz) by large diaxial coupling interactions. In the case of axial-oriented isomers, half-band width of equatorial 6-H should be in the range of around 15 Hz because of the smaller proton-proton coupling constants from the Karplus relation.[10] Thus, the ring-closure was found to proceed with high diastereoselectivity.

The method was successively applied to a synthesis of 4a-[3,4-crowned(15-crown-5)phenyl] analog 9c starting from 3,4-crowned(15-crown-5)acetophenone.[11] Wittig reaction of 3,4-crowned(15-crown-5)acetophenone [$(EtO)_2POCH_2COOEt$, NaH, DMF, 60°C] gave the ester 1c (52 %, mp 63-65°C). α-Butenylation of 1c (LDA, 1-iodo-3-butene, THF, -78°C ⟶ room temperature) yielded the ester 2c (86 %), reduction of which ($LiAlH_4$, Et_2O, 0°C, 2 h) gave the alcohol 3c. Since conversion of 3c to the corresponding amine leading to 5c by Mitsunobu's method was not successful, a preparation of 5c was carried out through the following procedure. Methansulfonate 12, derived from 3c, was treated with NaN_3 (DMF, 70°C, 4 h) to give the azide 13 (60 %), IR (neat) 2045 cm^{-1}. Reduction of 13 ($LiAlH_4$, THF), followed by methoxycarbonylation gave 5c (54 % from 12). Hydroxymethylation of 5c ($CsCO_3$, Paraformaldehyde, THF) afforded 7c, which was treated with formic acid to give the desired 4a-crowned-phenyl isoquinoline 8c[6] (59 %, mp 132-134°C). Reduction of 8c ($LiAlH_4$, THF) afforded 9c (80 %), δ 2.06 (NCH_3).

References and Notes

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6. All new compounds gave satisfactory microanalyses, IR, ^{1}H-NMR (90 MHz), and Mass spectral data. Analytical data for some of them were obtained by high resolution mass spectra. Selected spectral data are as follows. 8a: ^{1}H-NMR ($CDCl_3$) δ 7.97 (1H, s), 7.33 (2H, d, J=9 Hz), 6.92 (2H, d, J=9 Hz), 5.10 (1H, m, $W_{1/2}$= 25 Hz), 3.80 (3H, s), 3.66 (3H, s), 3.00 (1H, dd, J= 2 and 12 Hz), 2.73 (1H, d with small spliting, J=12 Hz), 2.43-1.23 (11H, m), MS m/e 347 (M^+). 8b: ^{1}H-NMR ($CDCl_3$) δ 7.93 (1H, s), 6.94 (3H, s), 5.11 (1H, m, $W_{1/2}$= 30 Hz), 3.90 (6H, s), 3.68 (3H, s), 3.04 (1H, dd, J=3 and 12 Hz), 2.78 (1H, d with small spliting, J=12 Hz), 2.48-1.14 (11H, m), MS m/e 377 (M^+). 9a: ^{1}H-NMR ($CDCl_3$) δ 7.35 (2H, d, J=9 Hz), 6.93 (2H, d, J=9 Hz), 3.66-4.12 (1H, m), 3.82 (3H, s), 2.10 (3H, s), MS m/e 275 (M^+). 9b: ^{1}H-NMR ($CDCl_3$) δ 6.90 (3H, broad s), 3.86 (6H, s), 3.57-3.97 (1H, m), 2.09 (3H, s), MS m/e 305 (M^+). 8c: ^{1}H-NMR ($CDCl_3$) δ 7.91 (1H, s), 6.86 (3H, broad s), 5.07 (1H, m, $W_{1/2}$= 30 Hz), 4.20-4.03 (4H, m), 3.97-3.78 (4H, m), 3.70 (8H, s), 3.59 (3H, s), 2.99 (1H, dd, J=2 and 13 Hz), 2.70 (1H, broad d, J=13 Hz), 2.40-1.20 (11H, m).
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