Preparation of Pure Enantiomeric 3-Oxa-2,7-diazabicyclo[3.3.0]octanes and their Conversion to Other Bicyclic Ring-Systems

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1.3-Dipolar Cycloaddition, Nitrones, Bicyclic Heterocyclic Compounds, Diastereoselectivity, Conformation

Pure Enantiomeric (S)-N-benzylalaninol (R_1 = Me) and (S)-N-benzylvalinol (R_1 = i-Pr) were allylated with Br-CH_2-CH=CR_2 R_3 (R_2 = R_3 = H ;R_2 = Ph, R_3 = H ;R_2 = R_3 = Ph). Swern oxidation followed by treatment with methylhydroxylamine afforded nitrones 6 (Me-N(O)=CH-CHR_1-N(CH_2 Ph)CH_2-CH=CR_2 R_3) which underwent an intramolecular 1,3-dipolar cycloaddition providing 3-oxa-2,7-diazabicyclo[3.3.0]octanes, e. g. (1R,5R,8S)-7-benzyl-2,8-dimethyl-3-oxa-2,7-diazabicyclo[3.3.0]octane 7a (R_1 = Me, R_2 = R_3 = H) and (1R,4R,5R,8S)-7-benzyl-2,8-dimethyl-4-phenyl-3-oxa-2,7-diazabicyclo[3.3.0]-octane 7b (R_1 = Me, R_2 = Ph, R_3 = H).

Reductive ring opening of 7a and 7b afforded the corresponding α-hydroxyalkylated pyrrolidines (9a: R_2 = H or 9b: R_2 = Ph, resp.). Condensation of these compounds with benzaldehyde yielded a mixture of diastereomeric 4-oxa-2,8-diazabicyclo[4.3.0]-nonanes: 10a/11a (1R,3S,6R,9S)/(1R,3R,6R,9S) R_1 = Me, R_2 = R_3 = H and 10b /11b (1R,3S,5R,6R,9S)/(1R,3R,5R,6R,9S) R_1 = Me, R_2 = R_3 = Ph. Pyrrolidine 9b was converted to the mesylate which formed (1R,4S,5R,7S)-3-benzyl-4,6-dimethyl-7-phenyl-3,6-diazabicyclo[3.2.0]heptane 13 along with (4R,5S)-1-benzyl-3,5-dimethyl-4-styryl-imidazolidine 15 upon treatment with sodium hydroxide.

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