

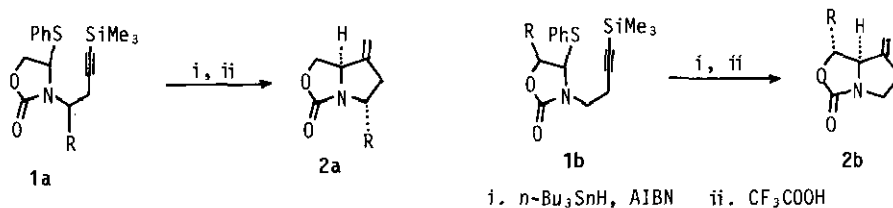
DIASTEREOSELECTIVE SYNTHESIS OF 2,6-DISUBSTITUTED 3-HYDROXYPIPERIDINE, 2-(α -HYDROXY-ALKYL)-3-HYDROXYPIPERIDINE AND 2-(α -HYDROXYALKYL)-3-HYDROXYPYRROLIDINE DERIVATIVES

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Abstract — Reduction of 5-substituted 5,8a-*trans*-oxazolo[3,4-a]pyridin-8-ones (**7a,b**), obtained by an application of α -acylamino radical cyclization at the initial stage, with NaBH_4 and K-Selectride was found to proceed with complete stereocontrol in all cases. Reduction of 1-substituted 1,8a-*trans*-oxazolo[3,4-a]pyridin-8-one (**7c**) and pyrrolidine analogue (**10**) with NaBH_4 and K-Selectride was also found to proceed with high diastereoselectivity.

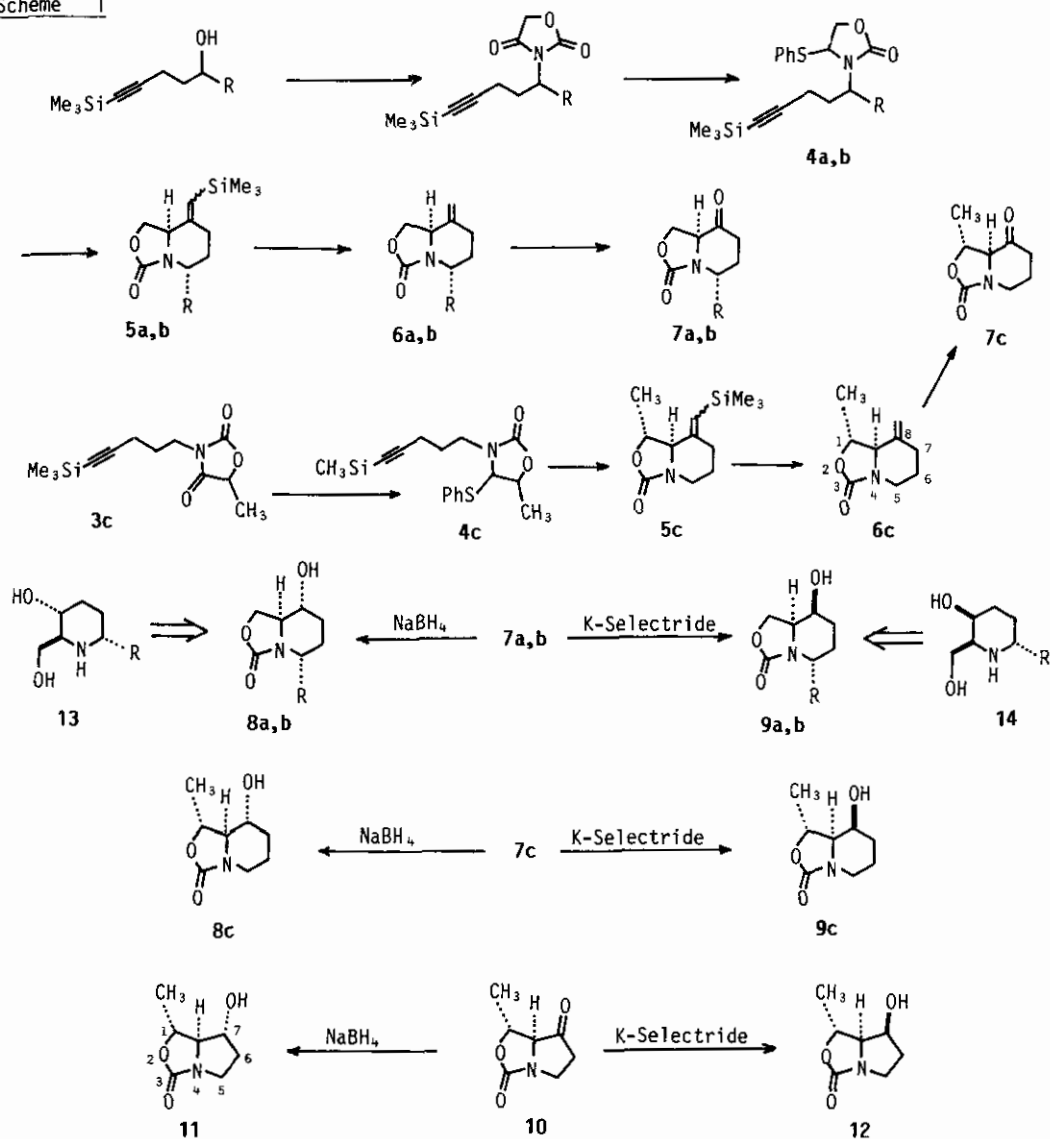
In the previous paper,¹ we reported the diastereoselective synthesis of 1- and 5-substituted tetrahydropyrrolo[1,2-c]oxazoles (**2a,b**) from **1a,b** by an application of α -acylamino radical cyclization.²



The method was extensively applied to a diastereoselective synthesis of 1- and 5-substituted 8-methyleneoxazolo[3,4-a]pyridine derivatives (**6a-c**),³ which were easily converted to the corresponding 8-oxo derivatives (**7a-c**), respectively. As part of our study on a diastereoselective synthesis of 2,3,6-trisubstituted piperidine derivatives (**13**, **14**), which would be interesting from both synthesis and biological evaluation as exemplified by prosopis piperidine alkaloids,⁴ we examined the reduction of **7a,b** with NaBH_4 and K-Selectride. These reactions were found to proceed with complete stereocontrol to give **8,9**. Reduction of **7c**, and **10** gave the corresponding alcohols, potentially useful intermediates for a preparation of the corresponding 3-hydroxy-2-(α -hydroxy-alkyl)piperidine and pyrrolidine analogues. The results are herein described. (See Scheme 1)

At the first stage, 4-phenylthiooxazolidin-2-ones (**4a-c**),⁵ used for generation of the radical species, were prepared by an application of the method reported previously¹ as outlined in the Scheme 1. Condensation of oxazolidine-2,4-dione with corresponding silylated alcohols by the

Scheme 1



For 3-9 a: R=CH₃; b: R=n-Pr

Mitsunobu's method⁶ (Ph₃P, *i*-PrOCON=COO-*i*-Pr, THF) afforded 3a,b. Reduction of 9a,b with NaBH₄, followed by treatment with diphenyl disulfide in benzene in the presence of tri-*n*-butylphosphine yielded 4a,b. In a similar way, 3c, obtained by condensation of 5-methyloxazolidine-2,4-dione and 5-trimethylsilylpentyn-1-ol, was converted to 4c through reduction with NaBH₄ and subsequent replacement of the hydroxy group with phenylthio group.

Benzene solution of **4a-c** (0.01-0.02 M solution) was heated in the presence of tri-*n*-butyltin hydride (1.3 equiv.) and AIBN by the usual way^{1,2} to give the corresponding oxazolo[3,4-*a*]pyridine derivatives (**5a-c**) as a mixture of *E*- and *Z*-isomers (**5a**, 72 %; **5b**, 70 %; **5c**, 68 % yield). Desilylation of **5a-c** with CF₃COOH-CH₂Cl₂ (1:2, room temperature, 14 h) gave nearly quantitative yields of **6a-c**, respectively, as an oil in all cases. The relative configuration at 5-H/8a-H of **6a,b** was assigned as *trans* based on the observation of the signals due to 5-H around at δ 4.0 in their ¹H-nmr (CDCl₃) spectra though they were partially overlapped with signals due to 8a-H and one of 1-H₂. The presence of this lower signals due to 5-H indicates strongly that the substituent at the 5-position takes *cis*-relationship with 8a-H.¹ The ¹H-nmr spectrum of **6c** showed only one CH₃ signal at δ 1.52 (d, J=6 Hz), which is characteristic of signals due to *cis*-oriented CH₃ to 8a-H.¹ The magnitude of J_{1,8a} (=6.5 Hz) also supports the relative configuration at 1-H/8a-H to be *trans*. Conversion of **6a-c** to the 8-oxo derivatives (**7a-c**), an oil, was successfully achieved by ozonolysis procedure (CH₂Cl₂, -78°C, then MeSMe) in nearly quantitative yield in all cases. Reduction of **7a-c** with NaBH₄ (1.5 equiv.) in methanol (0°C, 4 h and then quenched with NaHCO₃ aqueous solution, extract with CHCl₃) yielded **8a**⁵ (mp 88-89°C, 87 % yield), **8b**⁵ (oil, 85 % yield), and **8c**⁵ (oil, 88 % yield), respectively, as a single diastereomer in all cases. The stereochemical course of the reduction is consistent with the propensity of NaBH₄ to reduce unhindered cyclohexanones with axial delivery of hydride to give the thermodynamically more stable products. The relative configuration at 8-H/8a-H of **8a-c** was assigned as *trans* on the basis of the magnitude of J_{8,8a} (for **8a,b**, 9.6 Hz; for **8c**, 9.0 Hz) observed in their ¹H-nmr (CDCl₃, 400 MHz) spectra and the Dreiding model. On the other hand, reduction of **7a-c** with K-Selectride (1.5 equiv. of 1 M solution in tetrahydrofuran) in tetrahydrofuran (-78°C, 2 h and then quenched with 10 % NH₄OH, extract with CHCl₃) afforded **9a**⁵ (mp 141-142°C, 82 % yield), **9b**⁵ (mp 113-114°C, 80 % yield), and **9c**⁵ (oil, 75 % yield), respectively. The relative configuration at 8-H/8a-H of **9a-c** was also determined as *cis* again based on the magnitude of J_{8,8a} (for **9a,b**, 2.2 Hz; for **9c**, 2.1 Hz) and the Dreiding model. Upon reduction of **7a-c** with K-Selectride, hydride attacked from the less hindered side to give the thermodynamically less stable isomers. Thus, reduction of 1- and 5-substituted oxazolo[3,4-*a*]pyridin-8-one with NaBH₄ and K-selectride was found to proceed with complete stereocontrol in both cases. Reduction of the ketone (**10**), obtained by ozonolysis of **2b** (R=CH₃)¹ in 70 % yield as an oil, with NaBH₄ and K-Selectride was also examined. Reduction with NaBH₄ afforded **11**⁵ (oil, 80 % yield) whose relative configuration at 7-H/7a-H was determined as *trans* on the basis of the magnitude of J_{7,7a} (=6.2 Hz) and the Dreiding model. Reduction with K-Selectride gave **12**⁵ (mp 109-110°C, 75 % yield). The magnitude of J_{7,7a} (=3.2 Hz) observed in its ¹H-nmr (CDCl₃, 400 MHz) indicates the relative configuration at 7-H/7a-H to be *cis*. Thus reduction of **10** was found to show the similar

Received, 27th July, 1989

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(5-H, ddd, $J=8.5, 8.8, 10.9$ Hz), 4.21 (7-H, br s), 4.81 (1-H, dq, $J=3.2, 6.5$ Hz). (1-CH₂, d, $J=6.5$ Hz), 3.24 (5-H, ddd, $J=4.5, 8.0, 10.9$ Hz), 3.44 (8-H, dd, $J=3.2, 3.2$ Hz), 3.71 (1-CH₂, d, $J=6.4$ Hz), 3.38 (8-H, dd, $J=4.0, 6.2$ Hz), 4.56 (1-H, dq, $J=4.0, 6.4$ Hz); **12**: δ (CDCl₃) 1.49 (br s), 3.89 (5H, dd, $J=5.2, 12.8$ Hz), 4.64 (1-H, dq, $J=6.4, 6.3$ Hz); **11**: δ (CDCl₃) 1.51 (1-CH₂, (1-CH₂, d, $J=6.3$ Hz), 2.82 (5-H, dt, $J=12.8, 3.4$ Hz), 3.20 (8a-H, dd, $J=2.1, 6.6$ Hz), 3.86 (1H, 4.01 (5-H, m), 4.30 (1-H, dd, $J=8.5, 9.5$ Hz), 4.38 (1-H, dd, $J=5.7, 8.5$ Hz); **9c**: δ (CDCl₃) 1.43 (dd, $J=6.6, 8.5$ Hz); **9b**: δ (CDCl₃) 3.77 (5-H, br s), 3.83 (8a-H, ddd, $J=2.2, 5.7, 9.5$ Hz), 3.96-ddd, $J=2.2, 6.6, 8.8$ Hz), 4.18 (5-H dq, $J=6.0, 7.0$ Hz), 4.30 (1-H, dd, $J=8.5, 8.7$ Hz), 4.36 (1-H, (1-H, dq, $J=6.1, 6.3$ Hz); **9a**: δ (CDCl₃) 1.22 (5-CH₂, d, $J=7$ Hz), 3.79 (8-H, br s), 3.87 (8a-H, 12.9 Hz), 2.97 (5-H, dd, $J=5.5, 9.0$ Hz), 3.47 (8a-H, br s), 3.80 (5-H, dd, $J=5.0, 12.9$ Hz), 4.50 Hz), 4.42 (1-H, $J=7.8, 9.0$ Hz), **8c**: δ (CDCl₃) 1.48 (1-CH₂, d, $J=6.3$ Hz), 2.74 (5-H, dt, $J=3.4, 6.2, 9.6$ Hz), 3.49 (8a-H, ddd, $J=4.0, 7.8, 9.6$ Hz), 3.93-3.87 (5-H, m), 4.25 (1-H, dd, $J=4.0, 9.0$ (1-H, dd, $J=5.1, 8.9$ Hz), 4.43 (1-H, dd, $J=8.0, 8.9$ Hz); **8b**: δ (CDCl₃) 3.45 (8-H, ddd, $J=4.1, J=4.2, 6.2, 9.6$ Hz), 3.56 (8a-H, ddd, $J=5.1, 8.0, 9.6$ Hz), 4.12 (5-H, dq, $J=5.9, 7.0$ Hz), 4.22 Selected spectral data are as follows. **8a**: δ (CDCl₃) 1.23 (5-CH₂, d, $J=7$ Hz), 3.45 (8-H, ddd, characterized by high resolution mass spectra) and IR, ¹H-nmr (90 and 400MHz), and mass spectra.

5. All new compounds described in this paper gave satisfactory microanalyses (some of them were

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pyrrolidine derivatives.

substituted 3-hydroxy-2-hydroxymethylpiperidines, 2-(α -hydroxyalkyl)-3-hydroxypiperidine and

compounds described here would be apparently useful for a diastereoselective synthesis of 6-

behaviour to that of **7c**. The routes to 1- and 5-substituted oxazol[3,4-*a*]pyridin-8-ols and related