DIASTEREOSELECTIVE SYNTHESIS OF 2,6-DISUBSTITUTED 3-HYDROXY PIPERIDINE DERIVATIVES BY AN APPLICATION OF RADICAL CYCLIZATION

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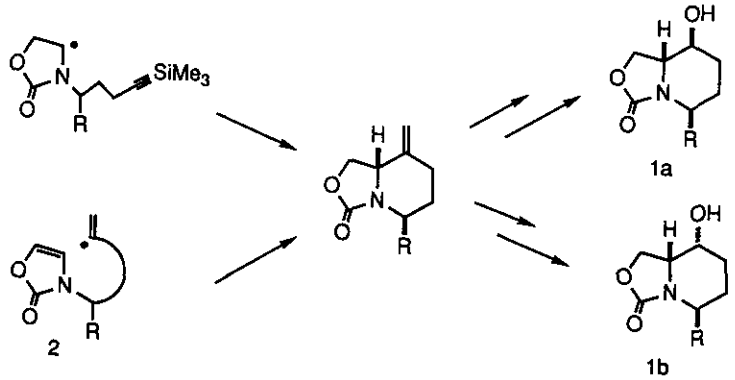
Abstract — *N*-[α-(2-Bromo-1-butenyl)-α-methyl]oxazolin-2-one (**7**) and *N*-[α-(2-bromo-1-butenyl)-α-pyranyloxyethyl]oxazolin-2-one (**14**), obtained by starting with ethyl acetoacetate, were treated with tributyltin hydride in the presence of AIBN afforded the cyclization products (**8**) and (**15**), respectively, with high diastereoselectivity. Conversion of the 8-methyleneoxazolidinopiperidine (**15**) to the 6-hydroxyethyl-2-hydroxymethyl-3-hydroxypiperidine derivative (**18**) was described.

In the previous paper,[1] we reported the diastereoselective synthesis of heterocyclic ring systems fused with oxazolidin-2-one by an application of α-acylaminoradical cyclization at an unsaturated component. The method was extensively applied, at the initial stage, to a synthesis of **1a** and **1b**[2] that are protected forms of 2,6-disubstituted 3-hydroxypiperidine derivatives . Successively, we investigated a modification of the procedure giving this type of compounds, which should be potentially useful intermediates in a synthesis of prosopis piperidine alkaloids.[3] There is a

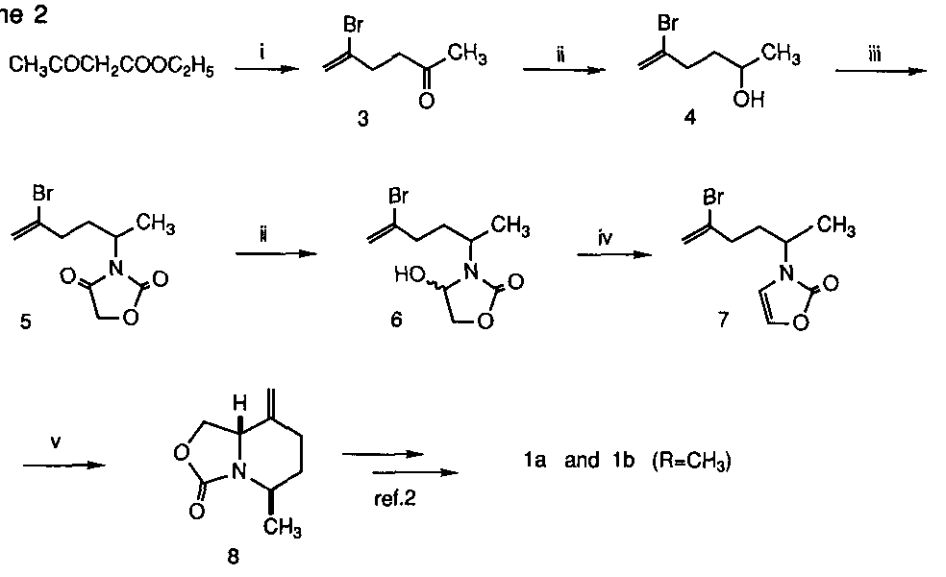
Scheme 1

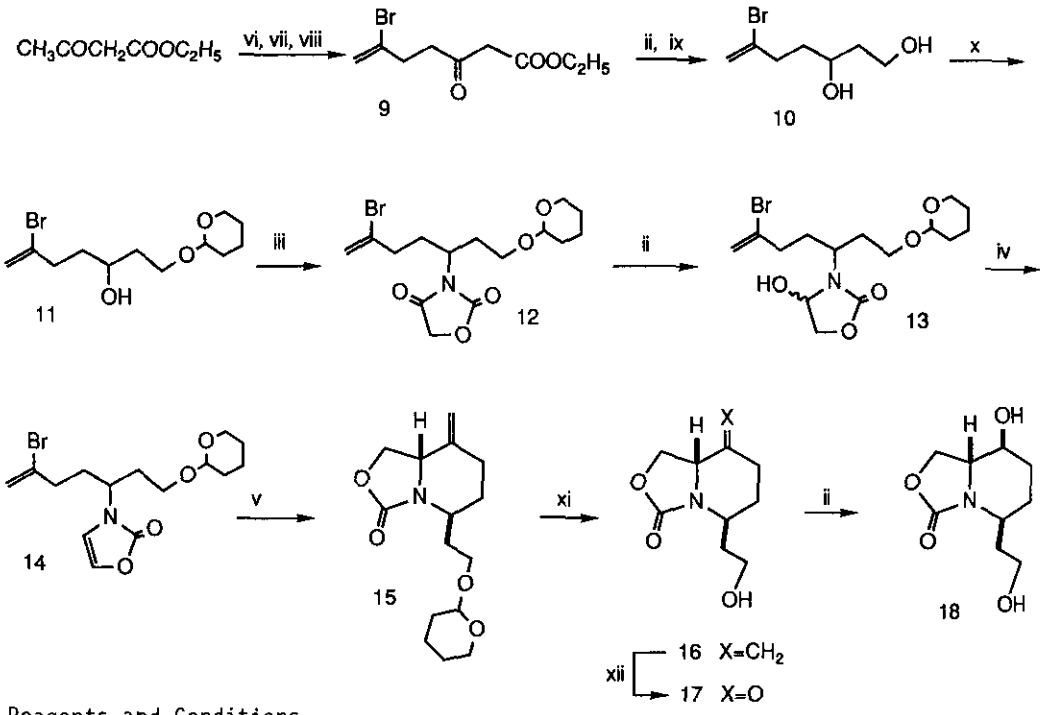


particular interest in an intramolecular C-C bond formation by the reaction of the vinyl radical(2)[4] with the olefinic carbon at the 4,5-position of oxazolin-2-one. Our study was focused on a synthesis of the versatile intermediate possessing a substituent at the 5-position of oxazolidinopiperidine ring (Scheme 1). The results of our studies are described in this paper.

At first, we prepared two precursors used for the radical cyclization according to the method outlined in the Scheme 2. Reduction of the ketone (**3**), obtained by bromoallylation of ethyl acetoacetate with 2,3-dibromo-1-propene by the usual way, with $NaBH_4$ yielded the alcohol (**4**). Reaction of **4** with oxazolidine-2,4-dione by the Mitsunobu's method[6] (i-PrOCON=NCOOPr-i, Ph_3P, THF) afforded the *N*-substituted oxazolidine-2,4-dione (**5**) in 76 % yield. Reduction of **5** followed by treatment of **6** with methanesulfonyl chloride in the presence of triethylamine in CH_2Cl_2 afforded **7**[5] (70 % yield from **5**) through spontaneous eliminaion of methanesulfonic acid. For the synthesis of prosopinine and related compounds, an introduction of a functional group in an alkyl substituent at the 5-position of oxazolidinpiperidine would be essential. Then, in a similar way, **14** was prepared aiming at a synthesis of 5-hydroxyethyloxazolopiperidine derivative (**18**) as follows. Condensation of ethyl acetoacetate with 2,3-dibromo-1-propene by an application of the dianion procedure (NaH, then BuLi-THF) yielded the ketone (**9**), in 82 % yield, which was converted to the diol (**10**) in 77 % yield through two step sequence ($NaBH_4$-MeOH, and then $LiAlH_4$-THF). The selective protection of the primary hydroxyl group with pyranyl group (1.1 equiv. of 3,4-dihydro-2H-pyran, catalytic amount of pyridinium *p*-toluenesulfonate , CH_2Cl_2) gave the mono-ol (**11**) in nearly quantitative

Scheme 2





Reagents and Conditions

i. Na-EtOH, 2,3-dibromo-1-propene ii. $NaBH_4$-MeOH iii. oxazolidine-2,4-dione, $(i\text{-}PrOCON{=})_2$, Ph_3P iv. $MeSO_2Cl/Et_3N$, CH_2Cl_2 v. n-Bu_3SnH/AIBN vi. NaH-THF vii. n-BuLi viii. 2,3-dibromo-1-propene ix. $LiAlH_4$-THF x. dihydropyran-CH_2Cl_2, PPTS xi. p-TsOH, MeOH xii. O_3-MeOH, MeSMe

yield. Condensation of **11** with oxazolidine-2,4-dione, followed by reduction of **12** and subsequent methanesulfonylation of **13** afforded **14** as in a preparation of **7.**

Benzene solution of **7** was heated under reflux in the presence of tributyltin hydride and a catalytic amount of AIBN to yield the desired cyclization product (**8**) in 72 % yield, which was identical with an authentic specimen[2] in all respects. The formation of **8** was found to proceed with high diastereoselectivity without formation of the alternative stereoisomer. Conversion of **8** to **1a** and **1b** (R=CH_3) has been already accomplished previously.[2]

The cyclization of **14** was also successfully achieved to yield **15** in 52 % yield accompanying with a formation of the debromination product in 15 % yield. On the contrary to this result, in the cyclization of **7,** formation of the debromination product was not observed. Furthermore, the reaction rate for the cyclization of **14** was comparatively very slow and the reaction required more than 48 h until most of **14** was consumed. Deprotection of **15** by heating in methanol in the presence of *p*-toluene-

sulfonic acid yielded **16**,[5] the ^{1}H nmr spectrum of which showed signals at δ around 4.15, characteristic of *trans*-oriented 5-H with 8a-H,[2] though they were partially overlapped with signals due to 8a-H and one of 1-H_2.[2] This result is consistent with those reported previously.[2] Ozonolysis of **16** yielded the ketone (**17**),[5] which was subsequently reduced with $NaBH_4$ to afford **18**[5] (oil, 83 % yield). The relative configuration at 8-H and 8a-H was easily deduced as trans from the signals at δ around 3.52 (8-H and 8a-H , m) , characteristic signals of 8-H and 8a-H taking *trans*-configuration , in their ^{1}H nmr spectra (400 MHz).[2]

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5. All new compounds described in this paper gave satisfactory spectral data. Selected spectral data are as follows. **7**: ^{1}H Nmr ($CDCl_3$, 400 MHz), δ 1.35 (3H, d, *J*, 6.5 Hz), 5.39 (1H, d, *J*, 2 Hz), 5.59 (1H, d, *J*, 2 Hz), 6.60 (1H, d, *J*, 2Hz), 6.83 (1H, d, *J*, 2 Hz). **16**: ^{1}H Nmr ($CDCl_3$, 400 MHz) δ 3.54-3.58 (1H, m,), 4.15-4.27 (1H, m), 4.23-4.27 (1H, m), 4.51-4.58 (1H, m), 4.69 (1H, s), 4.97 (1H, s). Ir ($CHCl_3$) 1730 cm^{-1} (C=O). **17**: ^{1}H Nmr ($CDCl_3$, 400 MHz) δ 4.09-4.22 (2H, m), 4.40-4.46 (1H, m), 4.60-4.67 (1H, m). **18**: ^{1}H Nmr ($CDCl_3$,400 MHz) δ 3.44--3.60 (2H, m), 4.08-4.17 (1H, m), 4.20 (1H, dd, *J*, 6.4, 8.9 Hz), 4.56 (1H, dd, *J*, 8.2, 8.9 Hz). Ir ($CHCl_3$,) 3450 (OH), 1730 cm^{-1} (C=O).
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