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Novel Synthesis of 1-substituted meso-3,4-dihydroxypyrrolidines with a $RuCl_3$-catalyzed Key Reaction

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RESEARCH ARTICLE

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Abstract

meso-1-Substituted-3,4-dihydroxypyrrolidines were synthesized in three steps from (Z)-but-2-ene-1,4-diol involving RuCl3-catalyzed cis-dihydroxylation of (Z)-but-2-ene-1,4-diyl dimethanesulfonate. In this key step RuCl3-catalysis allowed us to avoid the use of more toxic OsO_4. The final cyclization reaction was performed with three different aromatic amines to yield the desired 3,4- dihydroxypyrrolidines.

Keywords

meso-1-substituted-3,4-dihydroxypyrrolidines, ruthenium catalyst, cis-dihydroxylation

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1 Introduction

Efficient synthetic routes to *N*-substituted *cis*-3,4-dihydroxypyrrolidines being versatile precursors of several biologically active compounds gained increasing importance in recent years [1-4]. Several of the related pyrrolidines are TNF-α converting enzyme inhibitors [1], angiogenesis inhibitors [2,3], anti-tumor agents [4] or antiviral agents [5], which may be useful in the treatment of hepatitis C [4], various types of cancer [2-4], diabetic retinopathy [2] or autoimmune diseases such as rheumatoid arthritis [1,3].

meso-3,4-Dihydroxypyrrolidines can be synthesized from *meso*-tartaric acid [6], or *meso*- dihalobutane-2,3-diols [7,8] as starting materials. However, the most common method to form *meso*-3,4-dihydroxypyrrolidines applies reaction of 3-pyrroline with *N*-methylmorpholine *N*-oxide and catalytic amount of OsO_4 [2,3,9]. Although OsO_4 is a selective catalyst for *cis*-dihydroxylation, its use is inconvenient due to its high price and toxicity (damaging the respiratory system, can cause blindness and necrosis). Moreover, OsO_4 is a very volatile compound (its vapor pressure is 900 Pa at 20 °C, it sublimes at room temperature) which enhance the risk of its toxic effects.

meso-Compounds are ideal substrates in stereoselective synthesis [10] by selective biocatalysis [11], because selective functionalization of the enantiotopic hydroxy functions can lead to enantiopure products in high yield. Lipase-catalyzed biotransformations of *meso*- diols [12] or racemates from *meso*-diols [13] indicated already the versatility of *meso*- componds as starting materials to obtain enantiopure products.

Our aim was to develop a convenient method for the *cis*-dihydroxylation step using a cheaper, less hazardous and less toxic catalyst. Use of ruthenium catalysts has been reported already in *cis*-dihydroxylations of olefins to produce *cis*-diols selectively in rapid reactions with medium to good yields [14-17]. In the most cases, RuO_4 was generated *in situ* in the reactions from $RuCl_3$ and $NaIO_4$, and hydrolysis of the ruthenium-diester formed from the olefins with this RuO_4 catalyst gave the *cis*-diol [15,16]. The most frequent side reaction in this process is overoxidation resulting in formation of aldehydes and ketones from the olefins [15-17]. The side reactions could

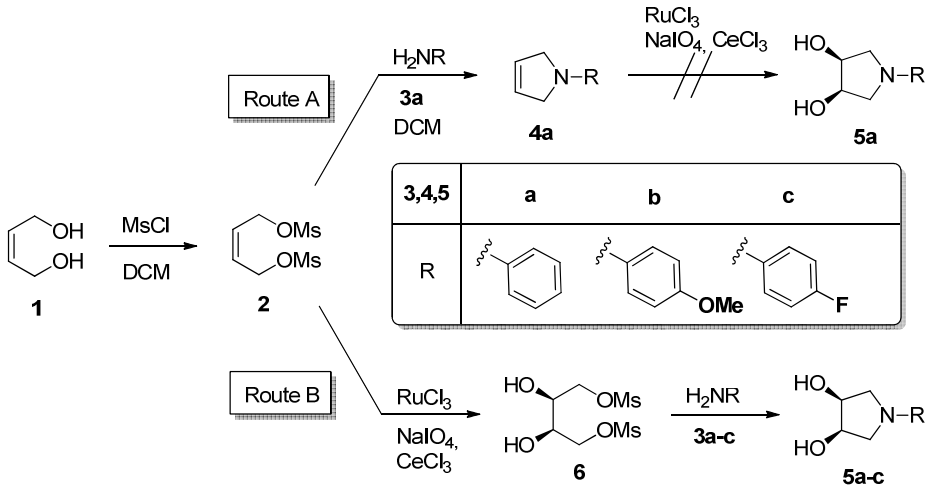

Fig. 1 Synthetic routes to *meso*-3,4-dihydroxypyrrolidines **5a-c**

be suppressed by addition of *Lewis acids* to the system to promote the hydrolysis of the Ru-diester [15,16]. A study on the effects of various *Lewis acids* showed that $CeCl_3$ as additive in the dihydroxylations of olefins resulted in high yields and the best diol-aldehyde ratio [16]. Ru nanoparticles immobilized on hydroxyapatite [18], or a polymer incarcerated ruthenium catalyst [19] allowed recovery of the catalyst and rendered the reactions easy-to-perform and more economical. Moreover, heterogenization of Ru-catalysts opened up the way for carrying out the reactions in continuous-flow reactor.

Our goal in this study was to develop a novel synthetic route to 1-substituted *meso*-3,4- dihydroxypyrrolidines involving Ru-catalzed *cis*-dihydroxylation as the key reaction.

2 Results and discussion

For synthesis of the desired *meso*-3,4-dihydroxypyrrolidines, our first approach was the *cis*-dihydroxylation of *N*-substituted-3-pyrrolidines (Route A in Fig. 1) by analogy of Plietker's method (use of catalytic amounts of $RuCl_3$ and $CeCl_3$ as *Lewis acid*) which was successfully applied to cyclic olefins [16]. Although *N*-phenyl-3-pyrrolidine (**4a**) was obtained smoothly in two steps from (*Z*)-but-2-ene-1,4-diol (**1**) in good yield [20], no product formation in the Ru-catalyzed *cis*-dihydroxylation reaction of *N*-phenyl-3-pyrrolidine (**4a**) was observed.

Because RuCl3 was successfully used in oxidation of (*Z*)-1,4-bis(benzyloxy)but-2-ene and (*Z*)-but-2-ene-1,4-diyl diacetate [11], we decided to invert the *cis*-dyhydroxylation and the cyclization steps (Route B in Fig. 1) and perform the *cis*-dihydroxylation on (*Z*)-but-2- ene-1,4-diyl dimethanesulfonate (**2**). Fortunately, after optimization of the reaction, *meso*-**6** was produced in 66% yield. Under the optimized conditions at 40 mmol scale, $RuCl_3xH_2O$ was used as ruthenium source and the appropriate reaction time was 15 min.

After the successful *cis*-dihydroxlation of open-chain dimethanesulfonate (**2**), cyclization of the formed *meso*-diol (**6**) was investigated with three aromatic amines (**3a**–**c**).

The reaction conditions for cyclization of *meso*-diol (**6**) were investigated using aniline (**3a**) as aromatic amine (Table 1). In the course of the first synthetic trial (Route A, Fig. 1), cyclization of (*Z*)-but-2-ene-1,4-diyl dimethanesulfonate (**2**) was performed in dichloromethane. However in the case of the *meso*-diol (**6**), it was not soluble in dichloromethane under argon. Thus, solvent was changed to acetonitrile (Entries 1,2). At room temperature no product formation was observed even using one week reaction time. At reflux temperature without inert atmosphere only negligible amount of product (**5a**) was formed. Next, when only 1.2 equivalents of aniline (**3a**) and triethylamine as antacid were used (Entries 3–5), **5a** formed in low yield after even 7 h reflux (Entry 3). Although by increasing the triethylamine/acetonitrile ratio the yields were increased (Entry 3–5), substantial degree of side reactions were observed on TLC after a few hours reflux excluding the possibility of prolongation of the cyclization under these conditions. When the reaction was performed in neat triethylamine, similarly low amount of product (**5a**) was formed (Entry 6). Significant increase of the yield could be achieved by addition of 2 equiv. of KI (promoting the S*N*1 reaction) or KI and TEBACl (Entries 7, 8). Next, to enhance the solubility of the starting material (**6**), solvent was changed to ethanol, which is also favorable for S*N*1 reactions (Entries 9–12). Because in ethanol the reaction could be prolonged without any side reaction, the yield of the desired product (**5a**) increased significantly. In these cases, KI or KI and TEBACl could be used as well. Finally, the reaction was carried out also in isopropanol as a higher boiling alcohol to test whether the higher temperature can favor the reaction (Entry 13) but no further increase in the yield was observed.

The same conditions resulted in the highest yield of the *meso*-1-phenylpyrrolidine-3,4-diol (**5a**) in the cyclization of **6** with aniline (**3a**) were used in the cyclization reactions of the other amines (**3b** and **3c**; Table 2). The best result of the cyclization was achieved with *p*- fluoroaniline (**3c**, Entry 3) to give *meso*-1-(4-fluorophenyl)pyrrolidine-3,4-diol (**5c**) as a new molecule in high yield (83%).

Table 1 Conditions for cyclization of *meso*-diol (**6**) with aniline (**3a**)

Entry	Solvent	Antacid	Aniline equiv.	KI equiv.	TEBACI equiv.	Time h	Temp.	Yield %
1	CH_3CN	aniline	3	-	-	168	25°C	n.r.[a]
2	CH_3CN	aniline	3	-	-	168	reflux	n.r.[a]
3	CH_3CN/Et_3N 15/1	Et_3N	1.2	-	-	7	reflux	1.5[b]
4	CH_3CN/Et_3N 4/1	Et_3N	1.2	-	-	3	reflux	1.5[b]
5	CH_3CN/Et_3N 1/2	Et_3N	1.2	-	-	3	reflux	5[b]
6	Et_3N	Et_3N	1.2	-	-	3	reflux	8[b]
7	Et_3N	Et_3N	1.2	2	-	3	reflux	17[b]
8	Et_3N	Et_3N	1.2	2	0.2	3	reflux	25[b]
9	EtOH	aniline	3	2	-	20	reflux	35[c]
10	EtOH	aniline	3	2	0.2	5	reflux	35[c]
11	EtOH	aniline	3	2	0.2	30	reflux	55[c]
12	EtOH	aniline	3	2	0.2	48	reflux	66[c]
13	n-PrOH	aniline	3	2	0.2	48	reflux	65[c]

[a]No reaction

[b]Yield after preparative TLC

[c]Yield after vacuum chromatography

Table 2 Cyclization of the *meso*-diol (**6**) with different amines (**3a–c**)

Entry	Amine	Product	Yield (%)
1	aniline (**3a**)	**5a**	66
2	*p*-anisidine (**3b**)	**5b**	68
3	*p*-fluoroaniline (**3c**)	**5c**	83

3 Experimental

3.1 Materials and methods

All chemicals and starting materials were purchased from Sigma-Aldrich (Saint Louis, MO, USA) and Alfa Aesar Europe (Karlsruhe, Germany) and used without further purification. Prior to use, solvents from Merck KGaA (Darmstadt, Germany) were dried and/or freshly distilled.

TLC was carried out using Kieselgel 60 F254 (Merck) sheets. Spots were visualized under UV light (254 nm and 365 nm) or by treatment with 5% ethanolic phosphomolybdic acid solution and heating of the dried plates. The NMR spectra were recorded on a Bruker DRX-300 spectrometer operating at 300 MHz for 1H and 75 MHz for 13C, and signals are given in ppm on the δ scale. Infrared spectra were recorded on a Bruker ALPHA FT-IR spectrometer and wavenumbers of bands are listed in cm^{-1}.

3.2 Route A: Preparation of N-phenyl-3-pyrroline (4a) from (Z)-but-2-ene-1,4-diyl dimethanesulfonate (2)

(*Z*)-But-2-ene-1,4-diyl dimethanesulfonate (**2**) as orange crystals was prepared from (*Z*)- but-2-ene-1,4-diol (**1**) according to the published method [20]. Mp.: 55 °C; 1H NMR ($CDCl_3$): 3.05 (6H, s, CH_3), 4.85 (4H, d, J = 5.0 Hz, CH_2), 5.95 (2H, t, J = 5.0 Hz, CH); ^{13}C NMR ($CDCl_3$): 38.19 (2xCH_3), 64.30 (2xCH_2),128.27 (2xCH); IR (KBr): 550, 931, 1173, 1351, 2942, 3034.

N-phenyl-3-pyrroline (**4a**) was prepared from the dimethanesulfonate (**2**) by cyclization according to published method [20]. All physical and spectral data of the product (**4a**) were in agreement with the published ones [20].

3.3 Route B: Preparation of 1-substituted meso-3,4-dihydroxypyrrolidines (5a-c) via cis- dihydroxylation of (Z)-but-2-ene-1,4-diyl dimethanesulfonate (2) followed by cyclization

cis-Dihydroxylation of (*Z*)-but-2-ene-1,4-diyl dimethanesulfonate (2) [16]:

$NaIO_4$ (12.8 g, 60 mmol) and $CeCl_3$ (0.99 g, 4 mmol) were added to distilled water (18 mL) and the mixture was gently heated at 50–60 °C until a bright yellow suspension was formed (ca. 10 min). The suspension was cooled down 0–5°C and acetonitrile (50 mL) and ethyl acetate (60 mL) were added to it. After stirring this mixture for 5 min at 0–5°C, a solution of $RuCl_3xH_2O$ (52 mg) in distilled water (1 mL) was added and stirring was continued for 2 min. To the so formed oxidizing mixture was added a solution of (*Z*)-but-2- ene-1,4-diyl dimethanesulfonate (**2**) (9.77 g, 40 mmol) in acetonitrile (10 ml) and the reaction mixture was stirred intensively for 15 min at 0–5°C. The reaction mixture was diluted with ethyl acetate (120 mL) and Na_2SO_4 (20 g) was added. After stirring for 1 min, the solids were filtered out and the organic phase was washed with saturated Na_2SO_3 solution (160 mL). The organic phase was dried over Na_2SO_4 than the solvent was evaporated in vacuum. The residual pale yellow crystals were recrystallized from dichloromethane (10 mL) to give the desired diol (**6**) as white crystals in 70 % yield.

Mp.: 111°C; R_f = 0,33 (hexane:EtOAc 2:8); 1H NMR (DMSO-d_6): 3.17 (6H, s, 2 CH_3), 3.64 (2H, s, 2 CH), 4.18 (2H,

dd, J = 10.1, 5.3 Hz, 2 CH-*H*), 4.33 (2H, d, J = 10.1 Hz, 2 C*H*-H), 5.51 (2H, d, J = 5.3 Hz, OH); ^{13}C NMR (DMSO-d6): 36.65 (2 CH_3), 68.62 (2 CH_2), 72.03 (2 CH); IR (KBr): 525, 533, 853, 956, 1080, 1183, 1348, 3036, 3440, 3507.

Cyclization of *meso*-2,3-dihydroxybutane-1,4-diyl dimethanesulfonate (**6**) with different amines (**3a-c**):

To the solution of aromatic amine (15 mmol; 1.40 g of **3a**, 1.85 g of **3b**, 1.67 g of **3c**) in ethanol (40 mL) were added the dimethanesulfonate (**6**, 1.39 g, 5 mmol), dried KI (1.66 g, 10 mmol) and TEBACl (0.228 g, 1 mmol) and the reaction mixture was stirred under reflux for 48 h. After cooling the reaction mixture to room temperature, the salts were filtered off and the ethanol was removed under vacuum. The crude product was purified by vacuum column chromatography (silica gel, gradient elution from hexane:ethylacetate – 2:8 to ethyl acetate).

meso-1-phenylpyrrolidine-3,4-diol (**5a**): white crystals; yield: 66%; mp.: 157°C; TLC: R_f = 0.51 (hexane:EtOAc 2:8); ^{1}H NMR (DMSO-d_6): 3.06 (2H, dd, J = 9.6 Hz, J = 4.2 Hz, CH-*H*), 3.37 (2H, dd, J = 9.3 Hz, J = 5.4 Hz, CH-*H*), 4.10–4.17 (2H, m, J = 3.3 Hz, 2C*H*- OH), 4.88 (2H, d, J = 4.4 Hz, OH), 6.45 (2H, d, J = 8.1 Hz, 2CH), 6.56 (1H, t, J = 7.2 Hz, CH), 7.13 (2H, t, J = 7.8 Hz, 2CH); ^{13}C NMR (DMSO-d_6): 52.36 ($2CH_2$), 70.60 (2CH), 111.00 (2CH), 115.04 (C), 129.01 (2CH), 147.67 (C-N); IR (KBr): 692, 745, 1101, 1341,1381, 1506, 1600, 2852, 2910, 3312, 3439.

meso-1-(4-methoxyphenyl)pyrrolidine-3,4-diol (**5b**): light brown crystals; yield: 68 %; mp.: 160°C; TLC: R_f = 0.49 (hexane:EtOAc 2:8); ^{1}H NMR (DMSO-d_6): 3.02 (2H, d, J = 5.3 Hz, CH-*H*), ~3,35 (2H, CH-*H*), 3.64 (3H, s, CH_3), 4.12 (2H, s, 2C*H*-OH), 4.84 (2H, s, 2OH), 6.40 (2H, d, J = 7.6 Hz, CH), 6.78 (2H, d, J = 7.6 Hz, CH); ^{13}C NMR (DMSO-d_6): 53.38 (CH_3), 55.84 ($2CH_2$), 71.07 (2CH), 112.11 (2CH), 115.22 (2CH), 143.02 (C-N), 150.63 (*C*- OCH_3); IR (KBr): 518, 773, 794, 812, 1030, 1105, 1179, 1243, 1276, 1370, 1480, 1517, 2829, 2900, 2927, 2955, 3356.

meso-1-(4-fluorophenyl)pyrrolidine-3,4-diol (**5c**): white crystals; yield: 83 %; mp.: 142.5°C; TLC: R_f = 0.41 (hexane:EtOAc 2:8); ^{1}H NMR (MeOH-d_4): 3.20 (2H, dd, J = 9.5, 4.1 Hz, CH-*H*), 3.46 (2H, dd, J = 9.4, 5.6 Hz, CH-*H*), 4.25–4. 31 (2H, m, 2C*H*-OH), 6.46 (2H, dd, J = 9.1 Hz, J = 4.3 Hz, 2CH), 6.90 (2H, t, J = 8.9 Hz, 2CH); ^{13}C NMR (MeOH-d_4): 54.01 ($2CH_2$), 72.67 (2CH), 112.98 (d, J = 7.3 Hz, 2CH), 116.39 (d, J = 22.3 Hz, 2CH), 146.21 (d, J=0.9 Hz, *C*-N), 156.55 (d, J = 232.1 Hz, *C*-F); IR (KBr): 509, 548, 780, 813, 1109, 1212, 1380, 1470, 1518, 1608, 2843, 2924, 3267, 3468.

4 Conclusion

New and convenient methods were developed for preparation of drug-like *meso*-3,4-dihydroxypyrrolidines involving *cis*-dihydroxylation as a key step. In the key step leading to the (*Z*)-2,3-dihydroxybut-1,4-diyl dimethanesulfonate in good yield, $RuCl_3$ was applied in catalytic amounts instead of the expensive and very toxic OsO_4. The optimized reaction conditions of the cyclization of the dihydroxylated dimethanesulfonate with aniline (KI and TEBACl promoting the S_N1 reaction in ethanol, 48 h, reflux) proved to be applicable with other amines as well.

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