Investigación

Asymmetric Synthesis of Naturally Occurring b-Hydroxyamides (R)-Tembamide and (R)-Aegeline

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Abstract. Chiral cyanohydrins were synthesized from anisaldehyde and trimethylsilylcyanide catalyzed by a chiral Schiff-base titanium complex. Cyanohydrins were converted into chiral the ß-hydroxyamides, (*R*)-Tembamide and (*R*)-Aegeline.
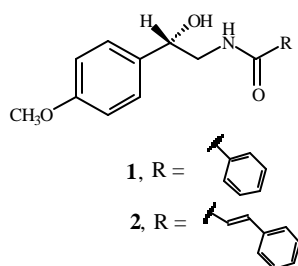**Keywords:** Chiral cyanohydrins, chiral Schiff base-titanium complex, ß-hydroxyamides.

Resumen. Se sintetizaron cianohidrinas quirales a partir de anisaldehído y cianuro de trimetilsililo por medio de la reacción catalizada con un complejo de titanio y una base de Schiff quiral. Las cianohidrinas fueron convertidas a las ß-hydroxyamidas quirales, (*R*)-Tembamida y (*R*)-Aegelina.
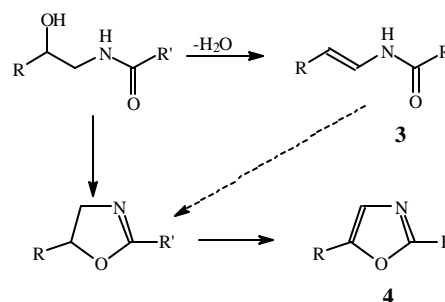**Palabras clave:** Cianohidrinas quirales, bases de Schiff quirales-complejo de titanio, ß-hydroxyamidas.

Introduction

(*R*)-(-)-Tembamide (**1**) and (*R*)-(-)-aegeline (**2**) are two naturally occurring ß-hydroxyamides isolated from *Fagara hyemalis* (St. Hill) Engler and *Aegele marmelos* Correa, respectively, belonging to the family Rutaceae [1-4]. These β-hydroxyamides have been reported to have insecticide and adrenaline-like activity. Extracts of *Aegle marmelos*, containing tembamide (**1**), have been used in the Indian traditional medicine as a control for hypoglycemia [5]. One report also claims that the leaves of *Aegle marmelos* are used in Bangladesh for fertility control [6].

1, R =

2, R =

In addition to their varied biological properties, these ß-hydroxyamides are possible intermediates in the plant biosynthesis of enamides (**3**) and oxazoles (**4**), as they have been isolated from several species of the same family [7-10]. The enamides and oxazoles may be formed from the ß-hydroxyamide (**1** and **2**) by a simple dehydration process to enamide (**3**) or by an internal SN_2 type displacement to oxazoline followed by oxidation to oxazole (**4**) (Scheme 1). In a recent publication we have shown the facile formation of oxazolines from chiral ß-hydroxyamides (*erythro-* and *threo-*) by chemical or thermal induced cyclization processes, where the chirality in the oxazoline is either retained or inverted [11]. To our knowledge, the biosynthetic interconnection between these compounds has not been fully established in the family Rutaceae.
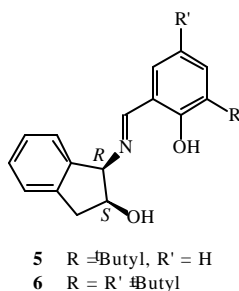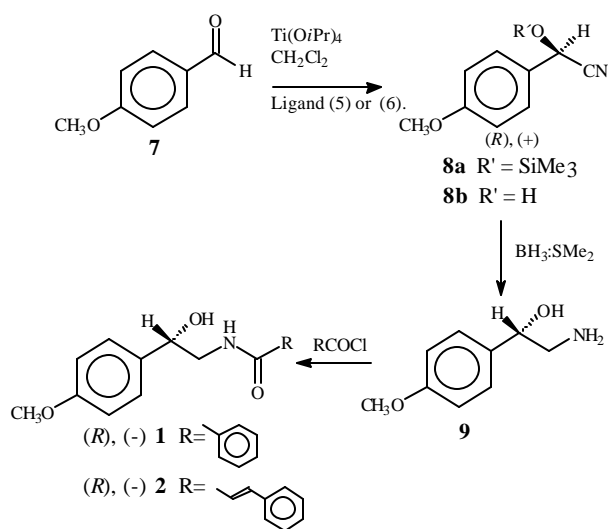

Scheme 1

These two β-hydroxyamides (**1** and **2**) were isolated from Nature as racemic mixtures and later resolved into their enantiomers as tartrate salts [12]. A previous report from this laboratory described the synthesis of racemic tembamide (**1**) and aegeline (**2**) from the cyanohydrin obtained by the addition of trimethylsilylcyanide to anisaldehyde with catalysis by zinc iodide [13]. More recent advances now allow addition of trimethylsilylcyanide to carbonyl groups in an enantioselective fashion, using chiral Lewis acid catalysts [14-17]. In view of their interesting biological and possible biosynthetic roles, we embarked on the enantioselective synthesis of tembamide (**1**) and aegeline (**2**). Here we report the synthesis of a chiral cyanohydrin and its transformation to the chiral ß-hydroxyamides, tembamide (**1**) and aegeline (**2**).

Results and discussion

Recently we reported the asymmetric addition of trimethylsi-lylcyanide to benzaldehyde catalyzed by titanium (IV)-Schiff base complexes derived from a chiral *cis*-indanol system [17]. In this study we discovered that ligands **5** and **6** gave the best enantioselectivity in the hydrocyanation reaction. We believe the reason for this high enantioselectivity is due to the rigid five-membered ring backbone of the *cis*-indanol and the presence of two chiral centers, probably enhancing the chirality in the final cyanohydrin. Further, the X-ray structure of ligand **5** [18] (Fig. 1) suggests that the indanol ring may sterically hinder one face of the carbonyl from cyanide ion attack in the transition state involving the titanium complex.

Fig. 1. Structure of ligand **5**.

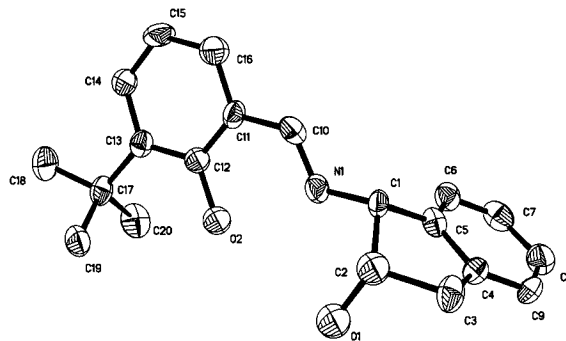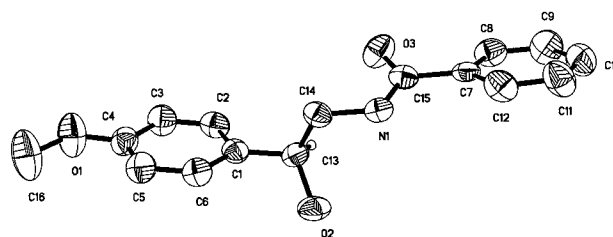**5**   R = *t*Butyl, R' = H
6   R = R' = *t*Butyl

Having shown the versatility of these chiral Schiff base ligands, we turned our attention to exploiting these ligands in the asymmetric synthesis of a variety of oxygenated natural products, such as ß-hydroxyamides **1** and **2**. Here we report the use of ligands **5** and **6** and titanium tetraisopropoxide as catalyst in the addition of trimethylsilylcyanide to anisaldehyde (**7**), giving the cyanohydrin in 95 and 89 % ee, respectively. Reduction of the cyanohydrin (**8**) with diborane gave the ß-amino alcohol (**9**) and subsequent acylation with benzoyl and cinnamoyl chlorides gave tembamide (**1**) and aegeline (**2**), respectively, in high optical purity (95 % ee) (Scheme
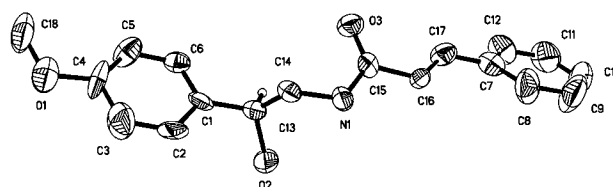
Fig. 2. Tembamide (**1**).

2). Amides (**1**) and (**2**) were characterized by ^{1}H, ^{13}C and X-ray (Figs. 2 and 3) [19, 20].

Conclusions

Chiral cyanohydrins are versatile synthetic intermediates which can be converted to α-hydroxy carboxylic acids, α-hydroxy aldehydes, α-hydroxy ketones. Here we have demonstrated the enantioselective synthesis of a cyanohydrin derived from anisaldehyde and its transformation to the chiral ß-aminoalcohol (**9**) and ß-hydroxyamides **1** and **2** in high optical purity. Although our method is complementary to the one reported by Jackson and co-workers employing a chiral dipeptide and hydrogen cyanide [21], our method has several advantages: it is not necessary to use HCN; in our case using trimethylsilylcyanide as the source for cyanide makes it easier to handle, and the trimethylsilyloxycyanohydrin adduct (**8a**) itself can be purified by distillation under reduced pressure. Further, cyanohydrin with the *S*-configuration can also be synthesized conveniently using ligand **5** with the *S,R*-configuration.

Scheme 2.

Scheme 2

Fig. 3. Aegeline (**2**).

Experimental

¹H and ¹³C NMR spectra were recorded on a Varian Gemini 200 Spectrometer, and on a Varian Unity Inova 500 MHz spectrometer with TMS as internal standard. X-ray data were collected on a Siemens P4 difractometer. Structure solution were performed by direct methods, and structure refinement was done with the program SHELXS [22]. IR spectra were obtained on a Perkin-Elmer 1600 series spectrometer. Enantiomeric excesses were determined using a Hewlet-Packard 6890 gas chromatograph with a 30 m Supelco ß-DEX column. The optical rotations were obtained on a Rudolph Research Flanders automatic polarimeter. Unless otherwise specified all reagents were purchased from Aldrich Chemical Co. and used without further purification.

(*R*)-(-)-2(4-Methoxyphenyl)-2-(trimethylsilyloxy)-acetonitrile, (8a). Under a nitrogen atmosphere, ligand **5** [17] (0.264 g, 0.85 mmol) was stirred with 6 mL CH_2Cl_2 at 23 °C. To the stirred solution Ti(O-*i*-Pr)$_4$ (0.244 g, 0.85 mmol) was added and the mixture stirred at room temperature for 1 h. The solution was then cooled to –780 °C and trimethylsilylcyanide (0.72 mL, 5.65 mmol) and anisaldehyde (0.56 mL, 4.6 mmol) were added and the mixture stirred at –78 °C for 36 h. The crude mixture was passed through a short column of silica gel and the product concentrated and subjected to short path distillation using Kugelrohr oven, fraction boiling at 95 °C/3 mm Hg was collected. Orange-yellow liquid (0.82 g 77 % yield); bp 95 °C/3 mm Hg; $[\alpha]_D = +21.80°$ (c = 1.00, CHCl$_3$) {lit. [21], $[\alpha]_D = +22°$ (c = 1.00, CHCl$_3$)}; IR (film): 1600, 1512,1460, 1250 cm⁻¹; ¹H NMR (200 MHz, CDCl$_3$): δ 7.37 (d, 2H, J = 7.9 Hz), 6.90 (d, 2H, J = 7.9Hz), 5.50 (s, 1H), 3.77 (s, 3H) and 0.18 (s, 9H); ¹³C NMR (50 MHz, CDCl$_3$): δ 160.28, 128.37, 127.86, 119.30, 114.17, 63.17, 55.14 and 0.42.

(*R*)-(+)-2-Hydroxy-2-(4-methoxyphenyl) acetonitrile, (8b). Compound **8a** (0.50 g) was stirred with 1M HCl (10 mL) for 4 h, and the product extracted into dichloromethane. The crude material was recrystallized from dichloromethane/hexane to give 8b (0.48 g) in 95 % yield and 95 % ee. Enantiomeric excess was determined by derivatizing the alcohol with acetic anhydride and injecting into a Hewlet-Packard 6890 gas chromatograph with a 30 m Supelco β-DEX column. The retention times of the enantiomers were 15.17 min (*R*) and 15.45 min (*S*). Mp: 84-87 °C (lit. [23], 74-76 °C); $[\alpha]_D = +47.50°$ (c = 1, CHCl$_3$), {lit. [23], $[\alpha]_D = +48.80°$ (c = 1, CHCl$_3$)}. IR (KBr): 3398, 2247 cm⁻¹; ¹H NMR (200 MHz, CDCl$_3$): δ 7.42 (d, 2H, J = 8.9Hz), 6.93 (d, 2H, J = 8.9Hz), 5.45 (s, 1H), 3.81 (s, 3H) and 3.21 (brs, 1H); ¹³C (50 MHz, CDCl$_3$): δ 160.78, 128.32, 127.66, 119.40, 114.57, 63.22 and 55.35.

Reduction of (8b). Compound 8b (0.5 g, 3 mmol) in dry ether (50 mL) was added to a stirred ice-cold solution of BH$_3$:S Me$_2$ solution (3.07 mL, 6 mmol). The mixture was allowed to stand at room temperature overnight and the excess BH$_3$ was destroyed by addition of methanol. Solvent was removed under reduced pressure to give a brownish oil in 74 % yield (0.38 g). ¹H NMR (200 MHz, CDCl$_3$): δ 7.13 (d, 2H, J = 7.9 Hz), 6.76 (d, 2H, J = 7.9 Hz), 4.42 (m, 1H), 3.71 (s, 3H), 3.1 (brs. 1H) and 2.62 (m, 2H); ¹³C (50 MHz, CDCl$_3$): δ 158.53, 134.89, 126.77, 113.32, 73.49, 54.74 and 48.86.

Acylation of amino alcohol (9). Without further purification, the crude amino alcohol **9** was reacted with benzoyl chloride and *trans*-cinnamoyl chloride under Schotten-Bauman conditions [13] to give (*R*)-(-)-tembamide (**1**) and (*R*)-(-)-aegeline (**2**) [13] in 83 % and 85 % yields, respectively.

(*R*)-(-)-Tembamide (1). White solid (0.53 g, 83 %), Mp: 144-146 °C (lit [12], 156-157 °C); $[\alpha]_D = -58.40°$ (c = 0.53, CHCl$_3$), {lit. [12], $[\alpha]_D = -55.31°$ (c = 0.5, CHCl$_3$)}. IR(KBr): 3345, 3299, 1633, 1245 and 1031 cm⁻¹; ¹H NMR (500 MHz, CDCl$_3$): δ 7.74 (d, 2H, J = 7.1 Hz), 7.48 (t, 1 H, J = 7.4 Hz), 7.39 (t, 2H, J = 7.8 Hz), 7.29 (d, 2H, J = 8.5 Hz), 6.88 (d, 2H, J = 8.7 Hz), 6.69 (br. s 1H), 4.85 (dd, 1H, J$_1$ = 3.2 Hz and J$_2$ = 7.8 Hz) 3.88-3.81 (m, 1H), 3.77 (s, 3H), 3.53-3.39 (m, 1H); ¹³C (125 MHz, CDCl$_3$): δ 168.52, 159.31, 134.12, 133.89, 131.61, 128.55, 127.07, 113.43, 73.19, 55.27 and 47.74.

(*R*)-(-)-Aegeline (2). White solid (0.58 g, 85 %); Mp: 193-195 °C (lit. [12], 196-197 °C); $[\alpha]_D = -39.30°$ (c = 0.45, CHCl$_3$), {lit. [12], $[\alpha]_D = -35.1°$ (c = 0.4, CHCl$_3$)}. IR(KBr): 3368, 3283, 1653, 1596, 1241, 1074 and 1032 cm⁻¹; ¹H NMR (500 MHz, CDCl$_3$): δ 7.57 (d, 1H, J = 15.62 Hz), 7.50 (d, 2H, J = 8 Hz), 7.43 (br. t, 1H, J = Hz), 7.36-7.35 (m, 3H), 7.33 (d, 2H, J = 8 Hz), 6.77 (d, 2H, J = 8 Hz), 6.56 (d, 1H, J = 15.62 Hz), 5.08 (br. s, 1H), 4.79 (dd, 1H, J$_1$ = 3.39 Hz and J$_2$ = 8.19 Hz), 3.80 (s, 3H), 3.72 (ddd, 1H, J$_1$ = 3.5 Hz, J$_2$ = 6.9 Hz and J$_3$ = 13.79 Hz) and 3.35 (ddd, 1H, J$_1$ = 4.6 Hz, J$_2$ = 8.5 Hz and J$_3$ = 13.8 Hz); ¹³C NMR (125 MHz, CDCl$_3$): δ 165.67, 138.89, 134.15, 127.88, 127.04, 126.73, 126.28, 120.71, 112.65, 71.21, 54.18 and 46.74.

Supporting Information Available. The X-ray crystal structure data for **1**, **2** and **5** are available. Tables of final atomic coordinates for the non-hydrogen atoms, anisotropic thermal parameters, complete list of bond distances and angles and complete crystallographic data are included [24].

Acknowledgments

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18. X-ray quality crystals were obtained from a methanol-hexane solution of (**5**). X-ray analysis: empirical formula $C_{20}H_{23}NO_2$, F. W. 309.39, T = 294 K, orthorhombic, space group $P2_12_12_1$, a = 9.0434(12) Å, b = 10.259(2) Å, c = 18.788(3) Å, $\alpha = 90°$, ß = 90°, $\gamma = 90°$, V = 1743.0(5) Å³, z = 4, D_c = 1.179 mg / m³, F (000) = 664, λ = 0.71073 Å, μ= 0.075 mm⁻¹, 2.17° < 2θ < 30.00, R_1 = 0.1079, wR_2 = 0.2006, largest diff. Peak and hole 0.200 and –0.196 eÅ⁻³.
19. X-ray quality crystals were obtained by slow evaporation of a $CDCl_3$ solution of (**1**). X-ray analysis: empirical formula $C_{16}H_{17}NO_3$, F.W. 271.31, T = 294 K, monoclinic, space group I_2 / a, a = 19.188(14) Å, b = 9.560(4) Å, c = 30.90(3) Å, $\alpha = 90°$, ß = 95.45(4)°, $\gamma = 90°$, V = 5643(7) Å³, z = 16, D_c = 1.277 mg / m³, F (000) = 2304, λ = 0.71073 Å, μ = 0.088 mm⁻¹, 2.13° < 2θ < 22.61, R_1 = 0.0968, wR2 = 0.2285, largest diff. Peak and hole 0.315 and –0.357 eÅ⁻³.
20. X-ray quality crystals were obtained by slow evaporation of a $CDCl_3$ solution of (**2**). X-ray analysis: empirical formula $C_{18}H_{19}NO_3$, F.W. 297.34, T = 293 K, monoclinic, space group P_{21}, a = 6.866(5) Å, b = 8.944(4) Å, c = 12.942(12) Å, $\alpha = 90°$, ß = 90.21(4)°, $\gamma = 90°$, V = 794.7(10) Å³, z = 2, D_c = 1.243 mg / m³, F (000)= 316, λ = 0.71073 Å, μ= 0.085 mm⁻¹, 1.57 ° < 2θ < 22.49, R_1 = 0.0851, wR2 = 0.1729, largest diff. Peak and hole 0.199 and –0.205 eÅ⁻³.
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