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Approach to a better understanding and modelling of β-pyrrolidinoalcohol ligands for enantioselective alkylation

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Abstract

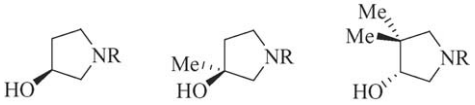
A series of pyrrolidine-based β-amino alcohols derived from malic acid, citramalic acid and pantolactone with primary amines was prepared and their activity as chiral ligands in the enantioselective alkylation of benzaldehyde using diethylzinc was studied.

Keywords: Enantioselective alkylation; β-Amino alcohols; Diethylzinc; Pyrrolidinoalcohols; Benzaldehyde

1. Introduction

The interest in the enantioselective addition of dialkylzinc reagents to aldehydes catalysed by chiral ligands has grown considerably in the last decades. The process constitutes a fundamental and versatile method for obtaining chiral secondary alcohols with high optical purity through the enantioselective formation of carbon–carbon bonds [1–6].

Of the various types of chiral ligands explored in these reactions, β-amino alcohols have proven to be especially efficient catalysts. Ligands of this type with pyrrolidine backbone structures [7–10] have shown very good results in catalytic procedures, namely, alkylations, epoxidations and reductions, among others. The vast application of hydroxypyrrolidines in catalytic reactions and the promising results obtained thus far, justified our attempt to extend some results on the synthesis and application of β-amino alcohols with a pyrrolidine backbone structure derived from tartaric acid [11]. Accordingly, we prepared some analogous ligands of general structures **1**, **2** and **3** derived from malic and citramalic acids and pantolactone, respectively. A comparative study on the activity and enantioselectivity of these ligands in enantioselective alkylations relatively to those previously prepared by us was performed in order to evaluate the extent of the influence of the structural changes in the ligands, namely, the absence of one of the hydroxyl groups and the presence of additional methyl groups on the pyrrolidine backbone.



1 **2** **3**

In this paper we describe the synthesis and characterization of the pyrrolidino alcohols **1**–**3** as well as their application in the enantioselective alkylation of benzaldehyde.

2. Experimental

2.1. General

All solvents were dried prior to use following standard procedures. Reactions carried out in an inert atmosphere used standard Schlenk-type techniques. Diethylzinc (Aldrich) was used as a 1 M solution in hexane. Benzaldehyde was distilled prior to use and stored over 4 Å molecular sieves. Commercially acquired benzylamine was stored over KOH. All other reagents were used as commercially acquired. 1-Naphthylmethylamine was prepared from 1-naphthylacetic acid, according to a previously described procedure [11]. Tosyl chloride was recrystallized prior to use.

Melting points were determined using a Leitz-Wetzler 799 microscope, with a heated plate (values are uncorrected). Optical rotations were measured with an optical activity AA-5

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polarimeter. NMR spectra were recorded on a Bruker AMX 300 (300 and 75.5 MHz, for ^{1}H and ^{13}C, respectively). TMS was used as the internal standard, chemical shifts are referred in δ and coupling constants, *J*, in Hz. Infrared spectra were recorded on a Perkin-Elmer 1720× FTIR. Elemental analyses were carried out on a Fisons Instruments EA 1108 CHNS-O elemental analyser. GC analyses were recorded on a HP 5890A instrument coupled to an HP 3396A integrator using a capillary column (Supelcowax 10, 30 m, 0.25 i.d., 0.25 μm). Mass spectra were recorded on a HP 5973 MSD chromatograph with 70 eV(IE), Agilent 6890 series, equipped with an HP-5MS column (30 m × 0.25 mm × 0.25 μm). HRMS were recorded on a Micromass Autospec.

Alkylation reaction products were identified by comparison with authentic commercially acquired samples and by gc/ms analysis. Catalytic experiments were repeated in order to confirm results. Enantiomeric excesses were determined by using a chiral γ-cyclodextrin capillary column (FS-Lipodex-E, 25 m, 0.25 i.d.) from Machery-Nagel on an HP 5890 A instrument coupled to an HP 3396 A integrator. The absolute configuration of the major enantiomer was determined by comparison with the optical rotation from an isolated sample.

2.2. Malic acid derivatives

2.2.1. (S)-3-Acetoxy-N-benzyl-2,5-dioxopyrrolidine (**5a**)

Prepared as described by Naylor in 31% yield [12]. $[\alpha]_D^{20} = -40.0$ (*c*1.0 MeOH), [lit. −40.6 (*c*1.0 MeOH)]. m.p.: 54–56 °C [lit. 58–60 °C]. ^{1}H NMR ($CDCl_3$): 2.15 (s, 3H), 2.66 (dd, 1H, ABX *system*, *J*18.3, 4.8), 3.16 (dd, 1H, ABX *system*, *J*18.3, 8.7), 4.68 (d, 1H, AB *system*, *J*14.1), 4.77 (d, 1H, AB *system*, *J*14.1), 5.44 (dd, 1H, ABX *system*, *J*8.7, 4.8), 7.26–7.41 (m, 5H). IR (cm^{-1}): 2986, 2945, 1756, 1706, 1431, 1404, 1371, 1343, 1318, 1224, 1170, 1086, 951. Elemental analysis ($C_{13}H_{13}O_4N$): calc. (%): C(63.15), H(5.30): N(5.67); found (%): C(62.82), H(5.36), N(5.93).

2.2.2. (S)-N-Benzyl-3-hydroxypyrrolidine (**1a**)

Prepared as described by Naylor in 54% yield [12]. $[\alpha]_D^{20} = -2.7$ (*c*3.71, $CHCl_3$), [lit. −3.2 (*c*3.69, $CHCl_3$)].

2.2.3. (S)-3-Acetoxy-N-(1-naphthyl)methyl-2, 5-dioxopyrrolidine (**5b**)

Malic acid (0.67 g, 5 mmol) and acetyl chloride (2 ml, 28 mmol) are refluxed for 2 h. After removing excess acetyl chloride the residue is dissolved in 10 ml dry dichloromethane and 1-naphthylamine (2.83 g, 18 mmol) is added. The reaction is stirred for 18 h at room temperature. Acetyl chloride (2 ml, 28 mmol) is added and the reaction refluxed for 5 h. After evaporating to dryness, the residue is chromatographed on silica gel using AcOEt/Hex (1:1) as eluent. The resulting product (49% yield) is crystallised from ethyl acetate/hexane.

$[\alpha]_D^{20} = -30.0$ (*c*1.0, CH_2Cl_2). m.p.: 79–80 °C. ^{1}H NMR ($CDCl_3$): 2.10 (s, 3H), 2.71 (dd, 1H, ABX *system*, *J*18.4, 4.8), 3.15 (dd, 1H, ABX *system*, *J*18.4, 8.8), 5.16 (d, 1H, AB *system*, *J*14.7), 5.21 (d, 1H, AB *system*, *J*14.7), 5.44 (dd, 1H, ABX *system*, *J*8.8, 4.8), 7.41–7.61 (m, 4H), 7.81–7.88 (m, 2H), 8.26 (d, 1H, *J*8.4). IR (cm^{-1}): 1749, 1715, 1433, 1405, 1379, 1346, 1227, 1184, 1070, 1042, 949, 789, 772, 738. Elemental analysis ($C_{17}H_{15}O_4N$): calc. (%): C(68.68), H(5.09): N(4.71), found (%): C(68.64), H(5.17), N(4.97).

2.2.4. (S)-3-Hydroxy-N-(1-naphthyl)methylpyrrolidine (**1b**)

To $LiAlH_4$ (0.2 g, 5.4 mmol) in 20 ml dry THF, is added dropwise a solution of (*S*)-3-acetoxy-*N*-benzyl-2,5-dioxopyrrolidine (0.50 g, 1.7 mmol) in 20 ml dry THF. After the addition is complete, the reaction is refluxed for 2h. The reaction mixture is cooled and ethyl acetate is added to destroy excess hydride, after which 0.2 ml water, 0.2 ml NaOH 15% and 0.6 ml water are added successively. The resulting solution is filtered through celite and the solid washed with THF. After drying over anhydrous $MgSO_4$, the solution is filtered and the solvent evaporated. The resulting product (44%) is chromatographed on silica gel using ethyl ether/triethylamine (80:20) as eluent. $[\alpha]_D^{20} = -2.0$ (*c*10.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): 1.68–1.73 (m, 1H), 2.13–2.22 (m, 2H), 2.31–2.39 (m, 1H), 2.54 (dd, 1H, *J*4.9, 10.0), 2.70 (dl, 1H), 2.86–2.93 (m, 1H), 4.00 (d, 1H, AB *system*, *J*13.0 Hz), 4.04 (d, 1H, AB *system*, *J*13.0), 4.25–4.29 (m, 1H), 7.25–7.52 (m, 4H), 7.75–7.78 (m, 1H), 7.83–7.86 (m, 1H), 8.23–8.26 (m, 1H). ^{13}C NMR ($CDCl_3$): 34.94, 52.37, 57.99, 63.02, 71.45, 124.30, 125.19, 125.59, 125.83, 126.71, 127.91, 128.45, 132.18, 133.75, 134.66. IR (cm^{-1}): 3054, 2987, 1422, 1263, 896, 727. *m/z* (EI): 227 (M^+, 20%), 182 (13), 141 (100), 115 (24), 86 (13).

2.2.5. (S)-3-Acetoxy-N-[(R)-(1′-phenyl)ethyl]-2, 5-dioxopyrrolidine (**5c**)

Prepared as described for **5b** using (3.35 g, 25 mmol) malic acid and (*R*)-1-phenylethylamine (11.6 ml, 90 mmol) The residue is chromatographed on silica gel using AcOEt/Hex (3:1) as eluent. The resulting product is obtained as an oil (30%). $[\alpha]_D^{20} = +30.4$ (*c*1.15, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): 1.82 (d, 3H, *J*7.3), 2.15 (s, 3H), 2.63 (dd, 1H, ABX *system*, *J*18.3, 5.1), 3.09 (dd, 1H, ABX *system*, *J*18.3, 8.8), 5.41 (dd, 1H, ABX *system*, *J*8.8, 5.1), 5.44 (q, 1H, *J*7.3), 7.26–7.34 (m, 5H). IR (cm^{-1}): 1749, 1711, 1392, 1374, 1250, 1224, 1193, 1051, 1106, 700.

2.2.6. (S)-[N-(R)-(1′-phenyl)ethyl]-3-hydroxypyrrolidine (**1c**)

Prepared as described for **1b** using (1 g, 3.83 mmol) (*S*)-3-acetoxy-*N*-(*R*)-(1′-phenyl)ethyl-2,5-dioxopyrrolidine. The residue is purified by column chromatography using CH_2Cl_2/MeOH/NH_3 (150:8:1) as eluent. The pure product is obtained in 43% yield. $[\alpha]_D^{20} = +40.0$ (*c*1.0, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): 1.38 (d, 3H, *J*6.6), 1.66–1.71 (m, 1H), 2.11–2.20 (m, 1H), 2.24–2.33 (m, 1H), 2.49 (dd, 1H, *J*10.1, 5.3), 2.61–2.67 (m, 1H), 2.79 (dd, 1H, *J*10.1, 2.0), 3.24 (q, 1H, *J*6.6), 4.29–4.35 (m, 1H), 7.26–7.32 (m, 5H). ^{13}C NMR ($CDCl_3$): 22.50, 34.85, 51.44, 61.55, 65.53, 70.69, 127.05, 128.28, 144.22. IR (cm^{-1}): 3450, 3435, 3414, 2970, 2808, 1450, 1366, 1320, 1139, 1092, 766, 701. *m/z* (EI): 191 (M^+, 4%), 176 (100), 114 (16), 105 (44), 91 (11), 77 (12). HRMS (EI+): *m/z* 191.1308 ($C_{12}H_{17}NO$ [M^+], 191.1310).

*2.2.7. (S)-3-Acetoxy-N-[(S)-(1′-phenyl)ethyl]-2, 5-dioxopyrrolidine (**5d**)*

Prepared as described for **5b** using (3.35 g, 25 mmol) malic acid and (*S*)-1-phenylethylamine (11.6 ml, 90 mmol). The residue is chromatographed on silica gel using AcOEt/Hex (3:1) as eluent. The resulting product is obtained as a white solid in 50% yield. $[\alpha]_D^{20} = -105$ (*c*1.0, CH_2Cl_2). m.p.: 99–103 °C. ^{1}H NMR ($CDCl_3$): 1.83 (d, 3H, *J*7.3), 2.15 (s, 3H), 2.62 (dd, 1H, ABX *system*, *J*18.3, 5.1), 3.10 (dd, 1H, ABX *system*, *J*18.3, 8.8), 5.33 (dd, 1H, ABX *system*, *J*8.8, 5.1), 5.45 (q, 1H, *J*7.3), 7.26–7.36 (m, 3H), 7.43–7.46 (m, 2H). IR (cm^{-1}): 2986, 2941, 1737, 1719, 1400, 1378, 1337, 1248, 1232, 1190, 1085, 1047, 938, 766, 719, 701.

*2.2.8. (S)-[N-(S)-(1′-phenyl)ethyl]-3-hydroxypyrrolidine (**1d**)*

Prepared as described for **1b** using (1.5 g, 5.74 mmol) (*S*)-3-acetoxy-*N*-(*S*)-(1′-phenyl)ethyl-2,5-dioxopyrrolidine. The residue is purified by column chromatography using CH_2Cl_2/MeOH/NH_3 (150:8:1) as eluent. The pure product is obtained in 36% yield. $[\alpha]_D^{20} = -55$ (*c*1.0, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): 1.38 (d, 3H, *J*6.5), 1.74–1.77 (m, 1H), 2.14–2.8 (m, 1H), 2.19–2.26 (m, 1H), 2.46 (dd, 1H, *J*10.5, 5.0), 2.49–2.51 (m, 1H), 2.96–3.00 (m, 1H), 3.24 (q, 1H, *J*6.5), 4.25–4.29 (m, 1H), 7.21–7.24 (m, 5H). ^{13}C NMR ($CDCl_3$): 22.77, 34.77, 50.84, 61.76, 65.31, 71.16, 126.99, 127.11, 128.35, 144.91. IR (cm^{-1}): 3055, 2987, 1422, 1265, 1176, 896, 705. *m/z* (EI): 191 (M^+, 5%), 176 (100), 114 (15), 105 (28), 91 (9), 77 (7). HRMS (EI+): *m/z* 191.1307 ($C_{12}H_{17}NO$ [M^+], 191.1310).

*2.2.9. (S)-Diethyl malate (**6**)*

Concentrated sulphuric acid (1 ml) was added to a solution of (*S*)-malic acid (13.4 g, 0.1 mol) in 100 ml absolute ethanol and the mixture was refluxed for 5 h with a calcium chloride tube. The ethanol was evaporated, water was added and the aqueous phase extracted several times with ethyl acetate. The joint organic phases were washed with a saturated sodium bicarbonate solution and water. After drying with anhydrous $MgSO_4$, and evaporating the solvent, an oil is obtained (80%). $[\alpha]_D^{21} = -11.1$ (pure), [lit. −10.7 (pure)] [13]. ^{1}H NMR ($CDCl_3$): 1.25–1.31 (m, 6H), 2.78 (dd, 1H, ABX *system*, *J*9.6, 3.8), 2.84 (dd, 1H, ABX *system*, *J*9.6, 2.6); 3.61 (bs, 1H), 4.17 (q, 2H, *J*4.2), 4.21–4.31 (m, 2H), 4.51 (bs, 1H). IR (cm^{-1}): 3505, 3485, 2984, 1373, 1737, 1180, 1027, 1107.

*2.2.10. (S)-2-(1′-Ethoxyethyloxy)diethyl malate (**7**)*

Prepared according to Hungerbuhler [14]. The product (94%) is obtained as an oil. ^{1}H NMR ($CDCl_3$) diastereoisomer mixture: 1.16, 1.18 (2t, 3H, $J = J'$7.0), 1.24–1.36 (m, 9H), 2.74–2.78 (m, 2H), 3.45–3.72 (m, 2H), 4.13–4.26 (m, 5H), 4.85 (2q, 1H, $J = J'$5.4). IR (cm^{-1}): 3466, 3376, 2985, 1736, 1348, 1272, 1217, 1184, 1109, 1026.

*2.2.11. (S)-2-(1′- Ethoxyethyloxy)-1,4-butanediol (**8**)*

Prepared according to Hungerbuhler [14]. Evaporation of the solvent gives the product (81%) as an oil. ^{1}H NMR ($CDCl_3$) diastereoisomer mixture: 1.23 (t, 3H, *J*7.2), 1.36, 1.37 (2d, 3H, $J = J'$5.3), 1.71–1.73 (m, 2H), 3.54–3.75 (m, 7H), 4.72, 4.83 (2q, 1H, $J = J'$5.3). IR (cm^{-1}): 3462, 3448, 3405, 3391, 3372, 2980, 2935, 1725, 1652, 1447, 1381, 1341, 1248, 1127, 1096, 1050, 991.

*2.2.12. (S)-2-(1′-Ethoxyethyloxy)-1,4-ditosyloxybutane (**9**)*

Prepared according to Nagel [15]. The resulting product (91%) is used directly in the next step of the synthetic sequence.

*2.2.13. (S)-N-Benzyl-3-(1′-ethoxyethyloxy)-pyrrolidine (**10**)*

(*S*)-2-(1′-Ethoxyethyloxy)-1,4-ditosyloxybutane (4.9 g, 10 mmol), benzylamine (4 ml, 36 mmol) and 30 ml de dry isopropanol are refluxed in an inert atmosphere for 24 h. After evaporating the solvent, the residue is treated with a saturated sodium hydrogencarbonate solution and then extracted with ethyl acetate. Joint organic phases are dried over anhydrous $MgSO_4$, filtered and the solvent evaporated. The resulting oil is chromatographed on silica using AcOEt/MeOH (95:5) as eluent to give the pure product in 55% yield. ^{1}H NMR ($CDCl_3$) diastereoisomer mixture: 1.15, 1.17 (2t, $J = J'$7.0), 1.28 (d, 3H, *J*5.3), 1.76–1.82 (m, 1H), 2.03–2.15 (m, 1H), 2.43–2.64 (m, 3H), 2.77–2.88 (m, 1H), 3.40–3.47 (m, 1H), 3.50 (d, 1H, AB *system*, *J*13.0), 3.56–3.62 (m, 1H), 3.65 (d, 1H, AB *system*, *J*13.0), 4.30–4.34 (m, 1H), 4.66, 4.68 (2q, 1H, *J*5.4, *J′*5.3), 7.26–7.32 (m, 5H).

*2.2.14. (S)-N-Benzyl-3-hydroxypyrrolidine (**1a**)*

Prepared according to Nagel [15]. The product is purified by column chromatography on silica gel using CH_2Cl_2/MeOH/NH_3 (150:8:1) as eluent. The pure product was obtained in 32% yield. $[\alpha]_D^{20} = -2.7$ (*c*3.77, $CHCl_3$), [lit. −3.2 (*c*3.69, $CHCl_3$)]. ^{1}H NMR ($CDCl_3$): 1.72–1.76 (m, 1H), 2.05–2.36 (m, 2H), 2.54 (dd, 1H, *J*5.2, 10.1), 2.67 (dd, 1H, *J*2.1, 10.1), 2.83–2.90 (m, 1H), 3.63 (s, 2H), 4.30–4.36 (m, 1H), 7.26–7.33 (m, 5H). ^{13}C NMR ($CDCl_3$): 34.69, 52.37, 60.12, 62.69, 70.77, 127.06, 128.18, 128.87, 138.07. IR (cm^{-1}): 3369, 3340, 2957, 2804, 1448, 1340, 1126, 1093, 747. *m/z* (EI): 177 (M^+, 31%), 157 (13), 132 (25), 100 (14), 91 (100), 86 (13), 65 (15).

2.3. Citramalic acid derivatives

*2.3.1. (S)-Methyl citramalate (**14**)*

Citramalic acid (3 g, 20.25 mmol) was dissolved in100 ml methanol and 5 ml concentrated sulphuric acid were added. The mixture was stirred at room temperature and monitored by tlc until the total consumption of the reagent (around 48 h). The tlc is developed using a solution of *p*-anisaldehyde (2 ml of *p*-anisaldehyde, 2 ml concentrated H_2SO_4, 36 ml ethanol 95% and 5–6 drops acetic acid).

A saturated solution of $NaHCO_3$ is added until neutralization and excess methanol is evaporated. The aqueous phase is extracted with ethyl acetate and the joint organic phases are washed with water. After drying over anhydrous $MgSO_4$, filtering and evaporating the solvent, an oil is obtained (70%) and used directly in the next step of the synthetic sequence without

further purification. $[\alpha]_D^{19} = +26.1$ (c1.15, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): 1.45 (s, 3H); 2.69 (d, 1H, AB *system*, *J*16.5); 2.98 (d, 1H, AB *system*, *J*16.5); 3.69 (s, 3H); 3.80 (s, 3H). IR (cm^{-1}): 3512, 3481, 3452, 2956, 1739, 1440, 1406, 1205, 1182, 1120.

2.3.2. (S)-2-(1′-Ethoxyethyloxy)-methyl citramalate (**15**)

Methyl citramalate (2.5 g, 14.2 mmol) was dissolved in 35 ml ethylvinyl ether. The solution was cooled in an ice bath, placed in an inert atmosphere and 60 μl of trifluoroacetic acid were added. The reaction was left at room temperature for 3 days.

Sodium carbonate (0.2 g) was added and the reaction was stirred for an additional 30 min. The solids were filtered and the ether evaporated. An oil (87%) was obtained and used directly. ^{1}H NMR ($CDCl_3$) diastereoisomer mixture: 1.13, 1.16 (2t, 3H, $J = J'7$); 1.26–1.33 (m, 3H); 1.53, 1.58 (2s, 3H); 2.80 (d, 0.5H, AB *system*, *J*16.3); 2.86 (s, 1H); 3.01 (d, 0.5H, AB *system*, J16.3); 3.41–3.51 (m, 2H); 3.66 (s, 3H); 3.67 (s, 3H); 5.01 (approx. q, *J*5.3). IR (cm^{-1}): 2985, 1743, 1439, 1383, 1352, 1301, 1198, 1169, 1108, 1080, 1029, 979.

2.3.3. (S)-2-(1′-Ethoxyethyloxy)-2-methyl-1,4-butanediol (**16**)

Dry ethyl ether (100 ml) was placed in a two-necked round bottomed flask equipped with an addition funnel, magnetic stirring and under an inert atmosphere. After cooling to −10 °C lithium aluminium hydride (0.87 g, 23 mmol) was added. To this suspension, at −10 °C, a solution of (*S*)-2-(1′-ethoxyethyloxy)-methyl citramalate (3.5 g; 14.1 mmol) in 50 ml dry ethyl ether was added and the reaction stirred for 24 h at room temperature.

Ethyl acetate was added drop wise, followed by 0.9 ml water, 0.9 ml NaOH, 15% and finally 1.8 ml water. After stirring at room temperature for 30 min the solution is filtered with Celite and dried over anhydrous $MgSO_4$. After filtering and evaporating the solvent the product is obtained as an oil in 90% yield. ^{1}H NMR ($CDCl_3$) diastereoisomer mixture: 1.18–1.26 (m, 6H); 1.31, 1.33 (2d, 3H, $J = J'1.5$); 1.53–1.81 (m, 1H); 1.88–1.97 (m, 1H); 3.44–3.60 (m, 4H); 3.70–4.00 (m, 2H); 4.82–5.00 (m, 1H). IR (cm^{-1}): 3463, 3424, 3416, 2978, 2936, 2888, 1448, 1384, 1344, 1242, 1114, 1081, 1054, 970.

2.3.4. (S)-2-(1′-Ethoxyethyloxy)-2-methyl-1,4-dimesyloxybutane (**17**)

To a solution of (*S*)-2-(1′-ethoxyethyloxy)-2-methyl-1,4-dimesyloxybutanediol (2 g, 10.4 mmol) in 50 ml of dry dichloromethane, triethylamine (3.5 ml, 25 mmol) was dropwise added at 0 °C and under an inert atmosphere, followed by mesyl chloride (1.94 ml, 25 mmol). After addition is complete, the reaction is left at room temperature until consumption of the reagent, controlled by tlc.

The reaction mixture is transferred to a separatory funnel and extracted with water and saturated $NaHCO_3$. The organic phase is dried over anhydrous $MgSO_4$ filtered and the solvent evaporated. The resulting product, an oil (89%) is used directly in the next step of the synthetic sequence.

A sample was purified by column chromatography on silica gel using ethyl acetate/hexane (3:1) as eluent. Proton nmr analysis allowed us to conclude that it was the product, however, without the protecting group. ^{1}H NMR ($CDCl_3$): 1.33 (s, 3H); 1.96–2.07 (m, 2H); 2.63 (bs, 1H); 3.04 (s, 3H); 3.10 (s, 3H); 4.09 (d, 1H, AB *system*, *J*6.9); 4.12 (d, 1H, AB *system*, *J*6.9); 4.41–4.46 (m, 2H). IR (cm^{-1}): 3027, 2979, 2941, 1731, 1466, 1350, 1250, 1172, 963, 843.

2.3.5. (S)-N-Benzyl-3-hydroxy-3-methyl-pyrrolidine (**2a**)

In a round bottomed flask (*S*)-2-(1′-ethoxyethyloxy)-2-methyl-1,4-dimesyloxybutane (3.24 g, 9.3 mmol) is added to 60 ml dry isopropanol. Benzylamine (3.6 ml, 33.5 mmol) is added and the reaction is refluxed in an inert atmosphere for about 18 h. The solvent is evaporated and the residue is taken up in a saturated $NaHCO_3$ solution and extracted several times with ethyl acetate. The joint organic phases are dried over anhydrous $MgSO_4$ filtered and the solvent evaporated.

The product is purified by column chromatography on silica gel using dichloromethane/methanol/NH_3 (150:8:1) as eluent. A second chromatography was required using ethyl acetate/methanol (92:8) in order to eliminate benzylamine that was still contaminating the product. The pure product was obtained in 63% yield. $[\alpha]_D^{19} = -15$ (c1.0, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): 1.32 (s, 3H); 1.84–1.89 (m, 2H); 2.22 (d, 1H, AB *system*, *J*9.5); 2.27–2.35 (m, 1H); 2.70 (d, 1H, AB *system*, *J*9.5); 2.89–2.97 (m, 2H); 3.61 (s, 2H); 7.22–7.31 (m, 5H). ^{13}C NMR ($CDCl_3$): 25.74; 40.47; 53.69; 59.96; 67.59; 77.17; 126.92; 128.14; 128.70; 138.56. IR (cm^{-1}): 3420, 3397, 3353, 3028, 2966, 2925, 2798, 1373, 1258, 1125, 1071, 1028, 958, 928, 742, 700. *m/z* (EI): 191 (M^+, 26%); 133 (43); 120 (10); 100 (24); 91 (100); 65 (14). HRMS (EI+): *m/z* 191.1312 ($C_{12}H_{17}NO$ [M^+], 191.1310).

2.4. Pantolactone derivatives

2.4.1. (R)-3,3-Dimethyl-1,2,4-butanetriol (**19**)

Prepared according to Broquet [16]. The product is obtained as an oil in 87% yield. $[\alpha]_D^{20} = -20$ (c1.0, ethanol) lit. −16 (c1.06, ethanol). ^{1}H NMR ($CDCl_3$): 0.91 (s, 3H), 0.94 (s, 3H), 3.08 (bs, 3H), 3.62–3.80 (m, 4H), 3.93–4.02 (m, 1H).

2.4.2. (R)-3,3-Dimethyl-2-hydroxy-1,4-ditosyloxybutane (**20**)

Prepared according to Brunner [17]. The product is used in the next step without further purification (37% yield). $[\alpha]_D^{20} = -5$ (c1.0, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): 0.97 (s, 3H), 1.03 (s, 3H), 2.31 (s, 3H), 2.40 (s, 3H), 3.49 (d, 1H, AB *system*, *J*8.0), 3.60 (d, 1H, AB *system*, *J*8.0), 3.83–3.90 (m, 2H), 4.06–4.10 (m, 1H), 7.13 (d, 2H, *J*8.0), 7.29 (d, 2H, *J*8.2), 7.66 (d, 2H, *J*8.0), 7.74 (d, 2H, *J*8.2). IR (cm^{-1}): 3054, 2987, 1422, 1361, 1263, 1190, 1178, 896, 727, 668, 666.

2.4.3. (R)-4,4-Dimethyl-N-benzyl-3-hydroxypyrrolidine (**3a**)

(*R*)-3,3-Dimethyl-2-hydroxy-1,4-ditosyloxybutane (3.75 g, 8.5 mmol) and benzylamine (3.3 ml, 30.5 mmol) in 50 ml dry isopropanol are refluxed in an inert atmosphere for 24 h. The solvent is evaporated, the residue is treated with a saturated sodium

hydrogencarbonate solution and extracted with ethyl acetate. The organic phase is dried over anhydrous $MgSO_4$, filtered and the solvent evaporated. The resulting oil is chromatographed on silica using AcOEt/MeOH (95:5) as eluent (40% yield). $[\alpha]_D^{20} = +20.0$ (c1.0, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): 1.05 (s, 3H), 1.06 (s, 3H), 2.27 (d, 1H, AB *system*, *J*9.1), 2.53 (d, 1H, AB *system*, *J*9.1), 2.59 (dd, 1H, ABX *system*, *J*10.1, 3.2), 2.91 (dd, 1H, ABX *system*, *J*10.1, 5.3), 3.61 (aprox. s, 2H), 3.74 (dd, 1H, ABX *system*, *J*5.3, 3.2), 5.2 (bs, 1H), 7.26–7.32 (m, 5H). ^{13}C NMR ($CDCl_3$): 22.0, 27.9, 41.8, 60.2, 61.5, 66.0, 79.1, 127.1, 128.3, 128.7, 138.4. IR (cm^{-1}): 3435, 3407, 3374, 2951, 2925, 1090, 697. *m/z* (EI): 205 (M^+, 38%), 133 (61), 91 (100), 65 (14) HRMS (EI+): *m/z* 205.1470 ($C_{13}H_{19}NO$ [M^+], 205.1467).

2.5. (3S,4S)-N-Benzyl-3-hydroxy-4-methoxymethyloxypyrrolidine

2.5.1. (3S,4S)-N-Benzyl-3-benzyloxy-4-hydroxypyrrolidine (**22**)

To a solution of (3*S*,4*S*)-*N*-benzyl-3,4-dihydroxypyrrolidine (4 g, 20.7 mmol) in 120 ml dry THF in a two necked round bottomed flask 0.455 g (2.07 mmol) of $(CH_3)_2SnCl_2$ and 5.72 g (41.4 mmol) of K_2CO_3 were added with stirring. After placing the mixture in an inert atmosphere, 2.9 ml (24.8 mmol) of benzoyl chloride were added and stirring continued at room temperature for 3 days.

The THF was evaporated and water and ethyl acetate were added to the residue. The aqueous phase was extracted with more ethyl acetate and the joint organic phases were washed with water and dried over anhydrous $MgSO_4$. After filtering and evaporating the product was purified by column chromatography with CH_2Cl_2/MeOH (95:5). Yield: 50%. ^{1}H NMR ($CDCl_3$): 2.64 (dd, 1H, *J*5.0, 9.8), 2.84 (dd, 1H, *J*3.8, 10.8), 3.04 (dd, 1H, *J*6.3, 9.8), 3.14 (dd, 1H, *J*7.0, 10.8), 3.64 (d, 1H, AB *system*, *J*12.8), 3.73 (d, 1H, AB *system*, *J*12.8), 4.30–4.35 (m, 1H), 5.02–5.06 (m, 1H), 7.26–7.33 (m, 5H), 7.42–7.47 (m, 2H), 7.56–7.58 (m, 1H), 8.00–8.07 (m, 2H). IR (cm^{-1}): 3054, 2987, 1718, 1442, 1263, 896, 727, 666. *m/z* (EI): 298 [(M+1)$^+$, 0.2%]; 175 (21); 158 (40); 91 (100); 77 (31). HRMS (EI+): *m/z* 298.1442 ($C_{18}H_{20}NO_3$ [MH]$^+$, 298.1443).

2.5.2. (3S,4S)-N-Benzyl-3-benzyloxy-4-methoxymethyloxypyrrolidine (**23**)

(3*S*,4*S*)-*N*-benzyl-3-benzyloxy-4-hydroxypyrrolidine (2.96 g, 9.96 mmol) is placed in a round bottomed flask with 50 ml recently distilled dimethoxymethane. After cooling in an ice bath, phosphorous pentoxide (3.5 g, 24.9 mmol) is slowly added over a period of one hour. The reaction is left at room temperature for at least 48 h.

A saturated sodium hydrogen carbonate solution is slowly added and when effervescence stops, dichloromethane is added and the aqueous phase is extracted several times with this solvent. The joint organic phases are dried over anhydrous $MgSO_4$, filtered and the solvent evaporated. The product is was purified by column chromatography with AcOEt/hexane (1:1). yield: 58%. $[\alpha]_D^{28} = +10$ (c1.0, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): 2.57 (dd, 1H, *J*5.1, 10.0), 2.74 (dd, 1H, *J*3.2, 10.8), 3.07–3.14 (m, 2H), 3.34 (s, 3H), 3.63 (d, 1H, AB *system*, *J*13.0), 3.71 (d, 1H, AB *system*, *J*13.0), 4.35–4.40 (m, 1H), 4.66 (d, 1H, AB *system*, *J*6.8), 4.79 (d, 1H, AB *system*, *J*6.8), 5.28–5.33 (m, 1H), 7.23–7.37 (m, 5H), 7.40–7.47 (m, 2H), 7.53–7.59 (m, 1H), 8.02–8.08 (m, 2H). IR (cm^{-1}): 2987, 1719, 1422, 1263, 896, 753, 666. *m/z* (EI): 312 [(M+1)$^+$, 1.6%]; 158 (51); 91 (100); 77 (26). HRMS (EI+): *m/z* 342.1710 ($C_{20}H_{24}NO_4$ [MH]$^+$, 342.1705).

2.5.3. (3S,4S)-N-Benzyl-3-hydroxy-4-methoxymethyloxypyrrolidine (**24**)

Methanol (60 ml) and 1.74 g NaOH were added to (3*S*,4*S*)-*N*-benzyl-3-benzyloxy-4-methoxymethyloxypyrrolidine (1.92 g, 5.63 mmol) and the solution stirred at room temperature until the complete disappearance of the reagent, controlled by tlc using AcOEt/hexane (1:1).

The methanol was evaporated and ethyl acetate and water were added. The aqueous phase is extracted several times with this solvent. The joint organic phases are washed with water, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated to give the product (82%). $[\alpha]_D^{21} = +40$ (c1.0, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): 2.48 (dd, 1H, *J*5.2, 10.2), 2.63 (dd, 1H, *J*4.3, 9.9), 2.83 (dd, 1H, *J*6.1, 9.9), 3.08 (dd, 1H, *J*7.1, 10.2), 3.39 (s, 3H), 3.59 (d,1H, AB *system*, *J*12.8), 3.67 (d,1H, AB *system*, *J*12.8), 3.92–3.97 (m, 1H), 4.13–4.18 (m, 1H), 4.66 (d, 1H, AB *system*, *J*6.8), 4.70 (d, 1H, AB *system*, *J*6.8), 7.26–7.32 (m, 5H). ^{13}C NMR($CDCl_3$): 55.62, 58.25, 59.57, 60.15, 76.55, 85.37, 96.62, 127.12, 128.27, 128.79, 138,12. IR (cm^{-1}): 3054, 2987, 1422, 1265, 896, 742. *m/z* (EI): 237 (M^+, 1%); 192 (6); 177 (7); 160 (12); 132 (14); 91 (100); 65 (7). HRMS (EI+): *m/z* 237.1360 ($C_{13}H_{19}NO_3$ [M^+], 237.1365).

2.6. General procedure for enantioselective alkylation reactions

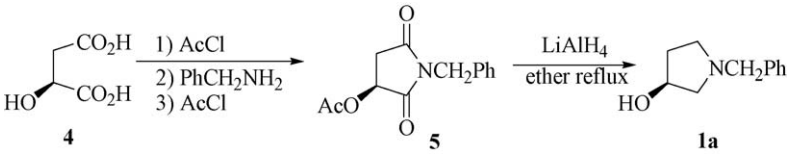
To the chiral ligand (0.15 mmol) and benzaldehyde (1 mmol) in an inert atmosphere, 4 ml cyclohexane were added. The temperature of the reaction mixture was lowered to 0 °C and diethylzinc (2 mmol, as a 1 M hexane solution) was added. The reaction was stirred at the same temperature for 24 h. After this time a saturated ammonium chloride solution (1 ml) followed by 2 M HCl (1 ml) were added and the reaction mixture was extracted with diethyl ether. The organic phases were washed with water and brine and dried over anhydrous magnesium sulphate. The resulting solution was analysed by gc in order to determine the ee of the 1-phenyl-1-propanol.

3. Results and discussion

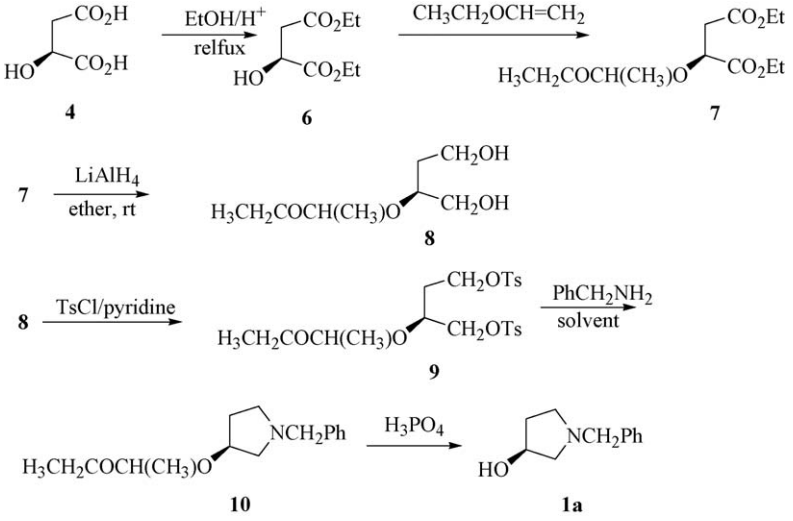
3.1. Ligand synthesis

3.1.1. Malic acid derivatives

We found two procedures in the literature for the synthesis of *N*-benzyl-3-hydroxypyrrolidine **1a** with purposes other than their application as chiral ligands. The first procedure is described by Naylor [12] and the second by Nagel [15]. Both authors state that if the synthesis is carried out in refluxing xylene followed by hydride reduction, epimerization may



Scheme 1.



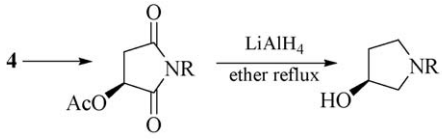
Scheme 2.

occur. Therefore, they propose alternative synthetic sequences to obtain an optically pure product.

The Naylor procedure involves a three-step synthetic sequence: reaction of malic acid **4** with acetyl chloride and benzylamine to give the cyclic compound **5** followed by reduction with lithium aluminium hydride to give the chiral ligand **1a**, Scheme 1.

The Nagel procedure is a somewhat longer synthetic sequence, which involves six steps, Scheme 2. After esterification of the carboxyl groups, the hydroxyl is protected with ethyl vinyl ether to give **7** as a mixture of diastereoisomers. Reduction of the ester group followed by tosylation of the hydroxyls gives the ditosylated compound **9**, which is subsequently reacted with benzylamine to give the pyrrolidine **10**. Finally, treatment with phosphoric acid removes the protecting group to give chiral ligand **1a**.

We started out by preparing **1a** using the two sequences in order to determine whether any epimerization occurred. The specific rotation of the products obtained by both pathways was found to be the same, thus allowing us to conclude that both sequences lead to products of identical optical purity. Being the overall yield of the Naylor procedure slightly higher, we chose this procedure for the synthesis of other malic acid derivatives using naphthymethylamine, (*R*)-phenylethylamine and (*S*)-phenylethylamine, **1b**–**1d**, Scheme 3.



5b R = naphthylmethyl
5c R = *(R)*-phenylethyl
5d R = *(S)*-phenylethyl

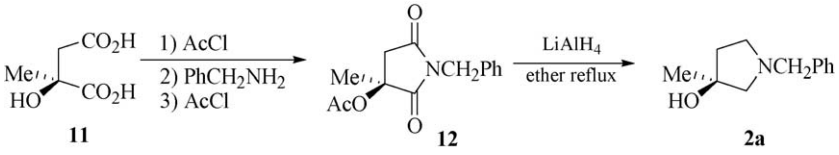
1b R = naphthylmethyl
1c R = *(R)*-phenylethyl
1d R = *(S)*-phenylethyl

Scheme 3.

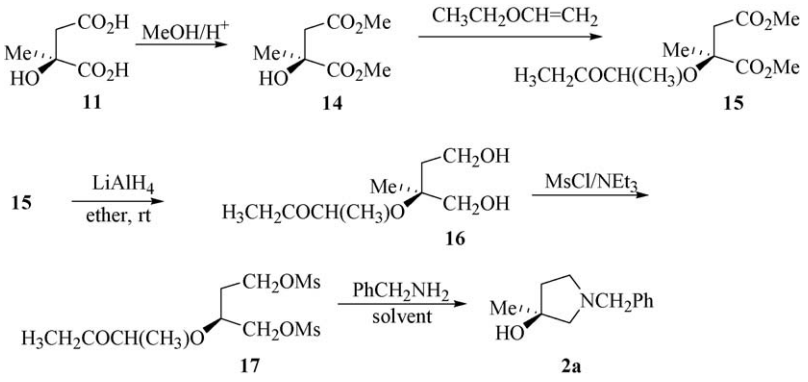
3.1.2. Citramalic acid derivatives

The structural similarities between citramalic **11** and malic acids **4** led us to initially use the Naylor procedure to synthesize *N*-benzyl-3-hydroxy-3-methylpyrrolidine **2a**, Scheme 4.

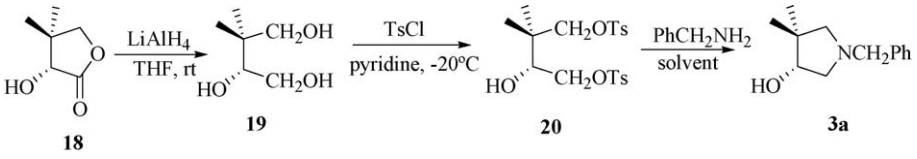
However, after reaction of **11** with acetyl chloride followed by treatment with benzylamine, nmr analysis of the product revealed it to actually be **13**, which resulted from the elimination of a water molecule. We therefore decided to use the Nagel procedure, making changes in some of the reactions in order to improve the overall synthesis, Scheme 5. Milder conditions



Scheme 4.

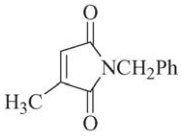


Scheme 5.



Scheme 6.

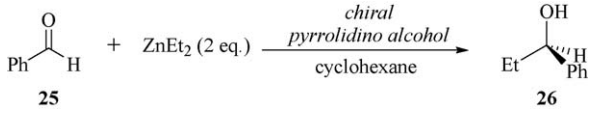
were used for the esterification procedure, namely, standing in methanol with sulphuric acid at room temperature. Also, instead



of the ditosylated derivative we chose to prepare the more reactive dimesylated **17** so as to improve the yield of the reaction. Based on nmr analysis, we found that after reaction with benzylamime the resulting product was chiral ligand **2a** and not the hydroxyl protected precursor. Removal of the protecting group occurred during the work-up of the product.

3.1.3. Pantolactone derivatives

Using (*R*)-pantolactone **18**, *N*-benzyl-4,4-dimethyl-3-hydroxypyrrolidine **3a** was prepared [16] according to Scheme 6. The first step of the sequence involved the reduction of the lactone to the triol **19**, which was subsequently treated at −20 °C in the presence of 1.5 equivalents of tosyl chloride per group to be tosylated. Under these reaction conditions, the ditosylated product **20** is essentially formed, with only small quantities of the tritosylated derivative. This allows the mixture



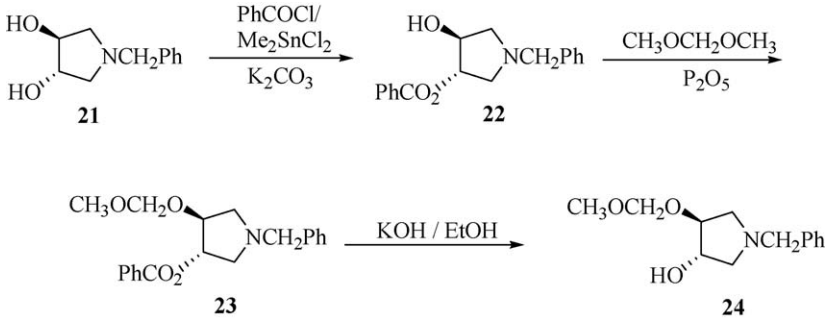
Scheme 8.

to be directly used in the next step of the synthetic sequence without further purification, the reaction with benzylamine to give the chiral ligand **3a**.

Ligand **24** was also included in the catalytic studies. We prepared this ligand following the synthetic sequence described in Scheme 7. Pyrrolidine alcohol **21**, prepared according to a previously described procedure [11], was treated with benzoyl chloride and dichlorodimethyltin, selectively giving monobenzoyl derivative **22**. The reaction with dimethoxymethane gives intermediate **23**, which after being submitted to hydrolysis originated chiral ligand **24**.

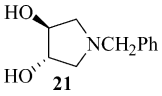
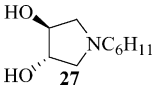
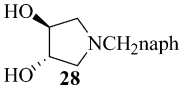
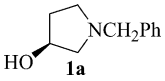
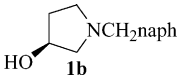
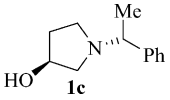
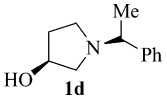
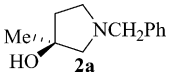
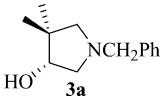
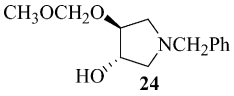
3.2. Enantioselective alkylations

Our new pyrrolidine-based amino alcohols were tested in the enantioselective alkylation of benzaldehyde, Scheme 8, with



Scheme 7.

Table 1
Results for the enantioselective alkylation of benzaldehyde in the presence of pyrrolidino alcohols as catalysts[a]

Entry	Ligand	Conversion (%)[b]	1-phenyl-1-propanol (%)[b,c]	ee (%)[d]/abs. configuration
1	 **21**	99	93	72(*R*)
2	 **27**	97	94	75(*R*)
3	 **28**	93	67	80(*R*)
4	 **1a**	78	77	53(*S*)
5	 **1b**	63	86	54(*S*)
6	 **1c**	69	65	56(*S*)
7	 **1d**	67	82	38(*S*)
8	 **2a**	73	56	33(*S*)
9	 **3a**	94	92	56(*R*)
10	 **24**	80	64	43(*R*)

[a]Reactions were carried out at 0 °C for 24 h after the addition of a 1 M hexane solution of diethylzinc (2 mmol) to **3** (0.15 mmol) and benzaldehyde (1 mmol) in cyclohexane.
[b] Determined by gc.
[c] Relatively to converted benzaldehyde.
[d] Determined by chiral gc.

diethyl zinc using previously established reaction conditions [11]: treatment of the aldehyde with diethylzinc in the presence of the chiral ligand at 0 °C for 24 h. The results of these reactions are summarized in Table 1.

Under the reaction conditions used, all ligands proved to be efficient as catalysts in the alkylation reactions, conversions ranging from 63–94%. In all cases studied, besides the desired chiral 1-phenyl-1-propanol **26**, benzyl alcohol is formed as a by-product, its formation having been attributed to a secondary process in which benzaldehyde is reduced by the zinc alkoxide of the ethylation product, 1-phenyl-1-propanoxide.

One of our objectives in preparing and studying malic acid, citramalic acid and pantolactone derived chiral ligands was to compare their performance with similar tartaric acid derivatives which were previously studied and reported [11]. Three representative ligands of this type are **21**, **27** and **28**, entries 1–3 of Table 1.

From the results reported in Table 1 (entries 4–9) it is clear that the new ligands tested are less selective than the tartaric acid derivatives. Among the malic acid derivatives (Table 1, entries 4–7), there were no significant changes in ee with the *N*-substituent, contrary to what was observed with the tartaric acid derivatives where visible changes were observed with the nature of this group.

With the ligands which resulted from the reaction with both enantiomers of phenylethylamine (Table 1, entries 6, 7), we analysed the effect of an additional chiral center directly adjacent to the nitrogen. The presence of the (*R*) chiral center proved to be irrelevant while the (*S*) chiral center caused a decrease in the ee of the reaction product.

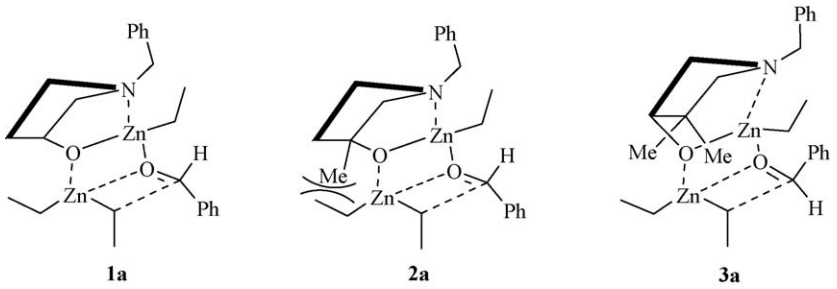


Fig. 1. Transition state structures for **1a**, **2a** and **3a**.

The selectivity observed with the citramalic acid derivative was much lower than in the case of the malic acid derivatives (Table 1, entry 8).

With the pantolactone derivative, results were identical to the malic acid derivatives: (Table 1, entry 9).

The structural changes which were introduced in the novel ligands that we synthesized in this work showed no advantage relatively to the previously studied ligands. However, we believe that they were useful in helping to achieve a better understanding of the induction of chirality by pyrrolidinoalcohol chiral ligands. It can therefore be helpful for the design of more efficient inducers of chirality.

The possible structures for the most stable transition states for the three types of new ligands are presented in Fig. 1. With these structures we can explain the stereochemistry of the product alcohol which is due to the approach of the ethyl group to the *Si* face of the aldehyde in the case of the malic and citramalic acid derivatives and the approach of the ethyl group to the *Re* face of the aldehyde in the case of the pantolactone derivative.

The transition state structures can also help interpret the effect of the methyl substituents. In the citramalic acid derivative **2a** there is some steric crowding due to the methyl group being on the carbinol carbon, which is very close to the point of coordination with the zinc metal. This is likely not to benefit chiral induction.

In the pantolactone derivative **3a**, the two methyls in the carbon adjacent to the carbinol carbon do not seem to significantly alter the transition state when compared to the malic acid ligands **1a** and therefore no changes are observed in the ee of the products.

In order to better understand the differences in selectivity between these new ligands and the tartaric acid derivatives, namely if they are due to the absence of the second hydroxyl, the second chiral center or both, we prepared and tested **24** with two chiral centers but only one free hydroxyl group.

When we used ligand **24** in the enantioselective alkylation of benzaldehyde, 1-phenyl-1-propanol was obtained with an ee of 43% (Table 1, entry 10).

Comparing the selectivity of the various *N*-benzyl ligands **1**, **4**, **8**–**10**, it is clear that this ee is most similar to those obtained with the malic, citramalic and pantolactone ligands. This seems to indicate that it is the lack of the second free hydroxyl and not of a second chiral center which is responsible for the lower selectivity of the new ligands herein described.

We questioned ourselves as to the exact function of the second free hydroxyl group. X-ray diffraction studies of this type of ligand revealed the existence of intermolecular hydrogen bonding between the hydroxyls of different ligands originating a well defined rigid network [11,18]. It is possible that this type of intermolecular hydrogen bonding may exist in solution between the catalytically active species, which result from the reaction of the ligand with the diethylzinc. If this is so, limitations would certainly be imposed on the formation of the transition state, favoring the preferential approach of one of the faces of the aldehyde, therefore enhancing the selectivity of the processs.

Another possibility is that the second hydroxyl reacts with an additional molecule of diethylzinc since two equivalents of this reagent are being used relatively to the substrate. This would also contribute to the formation of some type of network where zinc is found between the ligand molecules. Once again this would impose limitations on the formation of the transition state, thus improving selectivity.

Either one of these proposals can explain the differences in selectivity observed with the ligands studied. Additional studies with **24** are underway so that the differences in selectivity of the mono and dihydroxylated pyrrolidinoalcohols may be clearly explained and thus more efficient ligands may be designed.

4. Conclusions

Pyrrolidine-based β-amino alcohols derived from malic acid, citramalic acid and pantolactone were prepared and found to be efficient chiral ligands in the enantioselective alkylation of benzaldehyde using diethylzinc. The selectivity of these ligands was compared to previously prepared tartaric acid derived pyrrolidino alcohols and although they did not prove to be better chiral inducers, they apparently gave some insight into the mechanism of chiral induction and contributed to the design of new ligands. Further studies are underway in order to allow for a clear interpretation of the results described.

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