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(+)(1R,2R,5R) 2-Hydroxy-3-pinanone as Chiral Auxiliary in Erythro-selective Aldol Reactions

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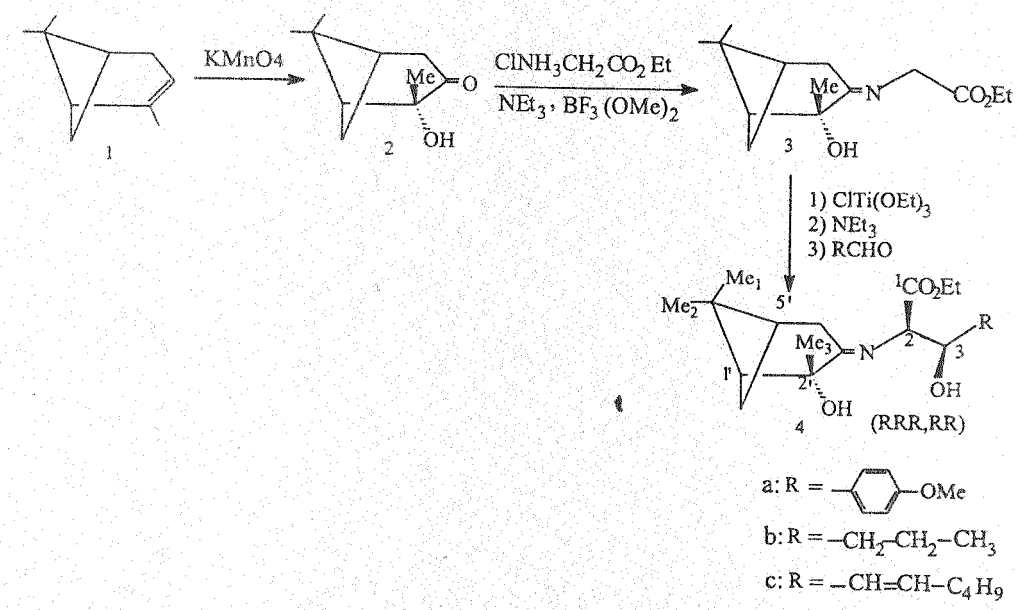
Schiff bases derived from (+)(1R,2R,5R) 2-hydroxy-3-pinanone and glycine ethyl ester can easily undergo diastereo- and enantio-selective aldol reactions controlled by a titanium complex to yield aldol adducts which provide after hydrolysis β-hydroxy-α-amino acids.

Key Words: (+)(1R,2R,5R) 2-Hydroxy-3-pinanon, Chiral auxiliary, Aldol Reactions

INTRODUCTION

Recently, asymmetric aldol reactions were the subject of extensive investigations because of the high diastereo- and enantioselectivity obtained which constitutes of it a powerful approach to optically active β-hydroxy-α-amino acids and complex molecules. Although the enantioselective approaches have been shown to be attractive, the use of chiral auxiliaries attached to the enolate moiety



Scheme-1

remains the most common and predictable method for affecting asymmetric aldol reactions **(Scheme-1).**

The application of chiral auxiliaries and reagents derived from α-pinene in asymmetric synthesis is well known[1, 2]. However, this natural and readily available starting material has been scarcely employed to build chiral auxiliaries for aldol reactions[3–5].

EXPERIMENTAL

IR spectra were recorded on Shimadzu FT-8201PC, for ^1H (250 MHz) and ^{13}C (250 MHz) NMR spectra: Bruker-Avance-DPX 250, δ in ppm and the coupling constant J in Hz. TMS was used as internal standard. All air and moisture-sensitive reactions were performed under dry nitrogen in dried flasks. All starting materials were used after purification, (–)α-pinene and titanium tetraethoxide are expected. All solvents were distilled. Column chromatography was performed using silica gel 230–400 mesh from Merck. Chromatography on preparative plates was performed using 60 G Merck silica gel (2 mm). Analytical thin layer chromatography (TLC) was performed on Merck plates silica gel 60 F_{254} (0.2 mm); the spots were detected with UV light and iodine.

General procedure for aldol reaction

To a cold (0°C) solution of the Schiff base **(3)** (0.9 g; 3.55 mmol) in dry dichloromethane (5 mL) was added dropwise a solution of $(EtO)_3TiCl$ (3.55 mmol; 1 equiv.) in dichloromethane (3 mL) and the mixture stirred for 30 min at 0°C; then NEt_3 (14.2 mmol; 4 equiv.) was added and the mixture stirred again for 30 min at 0°C. The aldehyde (7.1 mmol; 2 equiv.) was added dropwise. After 7 h at 0°C under stirring, the mixture was poured into a cold, saturated solution of NaCl (30 mL). Titanium oxide was filtered off and the aqueous phase extracted with Et_2O (3 × 30 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under vacuum. After column chromatography followed by preparative plates chromatography, aldol adducts were isolated and elucidated by the usual spectroscopic methods IR, ^1H NMR and ^{13}C NMR.

Ethyl (1′R,2′R,5′R,2R,3R)-3-hydroxy–2-[(2′-hydroxypinan-3′-ylene)-amino]-3-(*p*-methoxy phenyl) propanoate **(4a):** yellow oil (60%); TLC: $R_f = 0.35$ (Et_2O/hexane; 70/30): IR (ν, cm^{-1}): 3379 ν(OH, br); 1736 ν(C═O); 1659 ν(C═N). ^1H NMR ($CDCl_3$): δ = 0.87 (S, 3H, Me_1); 1.29 (t, 3H, CH_3 ester, $^3J = 7$); 1.35(S, 3H, Me_2); 1.55 (S, 3H, Me_3); 1.6 (d, 1H, $^3J = 11$); 2.06 (m, 2H); 2.18 (S, 1H, OH); 2.35 (m, 1H); 2.60 (br, 2H); 3.88 (S, 3H, OCH_3); 4.23 (m, 4H, CH_2 ester +2CH, H-2; H-3); 7.01 (d, 2H, $CH_{arom.}$; $^3J = 9$); 7.85 (d, 2H, $CH_{arom.}$; $^3J = 9$).^{13}C NMR ($CDCl_3$): δ = 14.14 (CH_3); 22.79 (CH_3); 27.21 (CH_3); 27.97 (CH_3); 28.05 (CH_2); 33.91 (CH_2); 38.14 (CH_3); 38.56 (CH); 39.21 (C); 50.45 (CH); 52.24 (CH_2 ester); 61.07 (CH); 76.39 (CH); 76.39 (C); 76.54 (C); 113.4 ($CH_{arom.}$); 114.27 ($CH_{arom.}$); 130.15 (C); 131.98 (C); 170.27 (C═N); 181.012 (C═O).

Ethyl (1′R,2′R,5′R,2R,3R)-3-hydroxy–2-[(2′-hydroxypinan-3′-ylene)-amino] hexanoate **(4b):** yellow oil (0.33 g; 65%). $R_f = 0.39$ Et_2O/hexane/MeOH : 50/50/05). IR (ν, cm^{-1}): 3394 ν(OH, br); 1736 ν(C═O); 1659 ν(C═N). ^1H NMR

($CDCl_3$): $\delta = 0.79$ (S, 3H, Me_1); 0.88 (t, 3H, $^3J = 7$); 1.18 (t, 3H, CH_3 ester, $^3J = 7$); 1.29 (S, 3H, Me_2); 1.44 (S, 3H, Me_3); 1.50 (m, 2H); 1.65 (d, 1H, $^3J = 11$); 2.03 (m, 4H, 2CH + CH_2); 2.18 (S, 1H, OH); 2.25 (m, 1H); 2.55 (br, 2H); 3.55 (S, 1H, OH); 4.00 (d, 1H, $^3J = 6$); 4.12 (m, 3H,CH + CH_2 ester.^{13}C NMR ($CDCl_3$): $\delta = 14.14$ (CH_3); 22.10 (CH_3); 22.57 (CH_3 ester); 22.86 (CH_3); 27.32 (CH_3); 27.67 (CH_2); 29.78 (CH_2); 30.4 (CH_2); 36.9 (CH_2); 39.2 (CH); 39.64 (C); 50.23 (CH); 51.53 (CH_2 ester); 61.76 (CH); 76.47 (CH); 76.98 (C); 170.02 (C=N); 173.45 (C=O).

Ethyl (1′R,2′R,5′R,2R,3R)-3-hydroxy–2-[(2′-hydroxypinan-3′-ylene)-amino] non-4-enoate (**4c**): yellow oil (50%); TLC: $R_f = 0.3$ (Et_2O/hexane: 70/30). IR (ν, cm^{-1}): 3364 ν(OH, br); 1743 ν(C=O); 1666 ν(C=N); ^1H NMR ($CDCl_3$): $\delta = 0.89$ (S, 6H, Me_1 + CH_3); 1.23 (br, 7H, 2CH_2 + CH_3 ester, $^3J = 7$); 1.3 (S, 3H, Me_2); 1.46 (S, 3H, Me_3); 1.5 (m, 1H); 2.03 (m, 4H, 2CH + CH_2C=); 2.29 (m, 1H); 2.60 (br, 2H); 3.25 (S, 1H, OH); 4.14 (m, 3H, CH_2 ester + CH, H-2); 4.54 (t, 1H, H-3, $^3J = 9$); 5.47 (dd, 1H, CH=, $^3J = 15$, $^3J = 7$)); 5.74 (dt, 1H, CH=, $^3J = 15$, $^3J = 7$).

RESULTS AND DISCUSSION

In the present work, a recent methodology for the enantio- and diastereoselective preparation of some aldol adducts which give after hydrolysis and reduction optically active aminodiols is described.

The chiral auxiliary (+)(1R,2R,5R) 2-hydroxy-3-pinanone (**2**) can easily be obtained from the inexpensive (–)α-pinene (**1**) by oxidation with potassium permanganate[6–8]. The Schiff base of glycine ethyl ester (**3**) was prepared in 85% yield by refluxing **2** and glycine ethyl ester hydrochloride in benzene, in the presence of NEt_3 and catalytic amount of boron trifluoride-dimethyl ether using a Dean-Stark trap[9]. The formation of the corresponding titanium enolate was realized by the successive addition of 1 equivalent of $(EtO)_3TiCl$ (which was prepared according to Holloway's procedure[10]) to the iminoglycinate (**3**), then the addition of 1 or 2 equivalents of NEt_3. Aldol reactions were realized by the formation of the titanium enolate in the case of the non-enolysable *p*-methoxybenzaldehyde or by the addition of the aldehyde to the titanium enolate formed before hand, in the case of *n*-butanal and *trans*-2-heptenal. These different steps are summarized in **Scheme-1.**

We report our first results concerning enantio- and diastereoselective aldol reactions of a Schiff base derived from the chiral auxiliary (+)(1R,2R,5R) 2-hydroxy-3-pinanone with three aldehydes (*p*-methoxybenzaldehyde, *n*-butanal and *trans*-2-heptenal). These aldehydes were chosen on the basis of chemical structure similarity with those used by Solladie-Cavallo *et al.*[11, 12] and gave high erythro diastereoselectivity (*p*-nitrobenzaldehyde, acetaldehyde and *trans*-2-decenal). Two chiral centres are created and four diastereomers can be formed. Under the best conditions, three isomers, among the four possible, were obtained, one of them being widely major (ee > 95%). The three products were detected by thin layer chromatography and were separated by preparative plates. The chemical yields were low, despite the experimental conditions employed, the starting Schiff

base being recovered. The best results were found with *p*-methoxybenzaldehyde which gave the aldol adduct with traces of the other diastereomers. The hydrolysis of the aldol adducts will give β-hydroxy-α-amino acids which will produce after reduction aminodiols of biological interest[12]; the inducer of chirality will be recovered in good chemical yield and can be reused.

The structures of the obtained compounds were elucidated by the usual spectroscopic methods such as IR, ^{1}H NMR and ^{13}C NMR. The (R,R,R,R,R) absolute configuration of the aldol adducts **4a**, **4b** and **4c** was determined by ^{1}H NMR and was attributed by correlation with similar compounds[11, 13].

Conclusion

In conclusion, the use of (+)(1R,2R,5R) 2-hydroxy-3-pinanone as chiral auxiliary and the direct generation ($(EtO)_3TiCl/NEt_3/0°C$) of titanium enolates constitutes a new efficient method for the rapid access to erythro-selective aldol reactions and to synthesize new chiral products which give after hydrolysis β-hydroxy-α-amino acids.

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