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Asymmetric synthesis of (*R*)-(−)-carnitine

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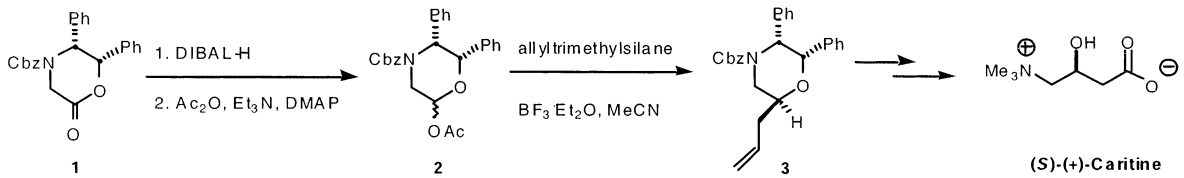
Abstract—A $TiCl_4$-promoted Mukaiyama-type aldol reaction of the ketenesilyl acetal of ethyl acetate with the lactone carbonyl of (5*R*,6*S*)-4-(benzyloxycarbonyl)-5,6-diphenyl-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (**1**) proceeds with a high degree of diastereoselectivity. The TBDMS-protected hemiketal thus obtained was efficiently converted into highly enantiomerically enriched (*R*)-(−)-carnitine by following an elimination–reduction protocol. This approach further demonstrates the utility of commercially available glycine template **1** as a potential substrate for the asymmetric synthesis of both enantiomers of carnitine.

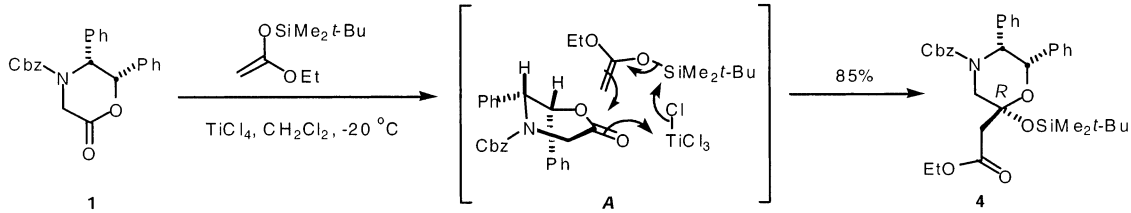
The asymmetric syntheses of carnitine and its analogs have attracted considerable interest in recent years due to their potential biological activity. (*R*)-(−)-Carnitine plays an important role in biochemical pathways for the β-oxidation of fatty acids and is involved in other important metabolic functions, both as free carnitine and as acyl carnitines.[1,2] In addition, clinical applications as a hypolipidemic agent in hemodialysis patients,[3] as well as in the treatment of myocardial ischaemia[4] and seizure[5] have been developed. The antipode, (*S*)-(+)-carnitine acts as competitive inhibitor of carnitine acyltransferase[6] causing depletion of carnitine.

Several approaches have been reported in the literature for the synthesis of carnitine and its analogs including asymmetric syntheses,[7] utilization of chiral, non-racemic starting materials,[8] chemical resolution,[9] enzymatic or microbial techniques[10] and others.[11]

We have recently reported[12] the asymmetric synthesis of (*S*)-(+)-carnitine from (5*R*,6*S*)-4-(benzyloxycarbonyl)-5,6-diphenyl-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (**1**)[13] by conducting a stereoselective allylation on the protected hemiacetal (**2**) derived from **1** (Scheme 1). The allyl oxazine **3** thus obtained was readily converted into (*S*)-(+)-carnitine.[12] Herein, we report an efficient



Scheme 1.



Scheme 2.

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method for the synthesis of (*R*)-(−)-carnitine by employing the same glycine template **1** as a starting material but using distinctly different chemistry.

We envisaged that reversal of stereochemistry at C2 in **3** could result into the formation of (*R*)-(−)-carnitine. This led us to investigate the asymmetric Mukaiyama-type aldol reaction[14] on the lactone carbonyl of **1**. Thus, reaction of **1** with the *t*-butyldimethylsilylketene acetal of ethyl acetate in the presence of $TiCl_4$ at −50°C (CH_2Cl_2, 12 h) resulted in the formation of the TBDMS protected hemiketal **4** as a single diastereomer (by ^1H NMR analysis of the crude product) in moderate yield (57%). The yield of the reaction was further improved by reducing the reaction time (−20°C, 30 min, 85% yield, Scheme 2).

The stereochemistry of the newly created stereogenic center in **4** was determined as '*R*' by ^1H NMR NOE measurements that revealed a *syn*-relationship for the C5 and C6 protons of the oxazine ring with the protons α to ester carbonyl group. The stereochemical outcome of the Mukaiyama-type aldol reaction is presumed to be a manifestation of a transition state (***A***) where nucleophilic addition occurs on the less hindered face of **1**, as shown in Scheme 2.

Treatment of **4** with $BF_3{\cdot}Et_2O$ (CH_2Cl_2, 0°C, 8 h) cleanly generated the elimination product **5** in 95% yield (no elimination product with an exocyclic double bond was detected by ^1H NMR at this reaction temperature). Hydrogenation of **5** to the all *syn*-substituted oxazine **6** could not be achieved with 10% Pd/C (20 mol%, 80 psi of H_2, EtOH, rt, 12 h) and resulted in the recovery of starting material (no Cbz-deprotection was observed under these reaction conditions either). However, hydrogenation of **5** with $PdCl_2$ (20 mol%, 100 psi of H_2, EtOH, 2 equiv. conc. HCl, rt, 18 h) resulted in the formation of the desired all *syn*-substituted oxazine **6** in quantitative yield and with a 94:6 diastereomeric ratio (by ^1H NMR, Scheme 3).

The stereochemistry of newly created stereogenic center in the major diastereomer of **6** was determined as '*R*' by ^1H NMR NOE measurements that revealed a *syn*-relationship of the protons at C2, C5 and C6 of the oxazine ring. The high degree of asymmetric induction in the reduction step can be explained by adsorption on the catalyst surface and subsequent hydrogenation of the double bond from the sterically less hindered face of the molecule.

Hydrolysis of ester group in **6** (1 M NaOH, THF, rt, 12 h) and subsequent neutralization of the reaction mixture with 1 M HCl followed by hydrogenolysis (2.2 equiv. $PdCl_2$, 120 psi of H_2, 75–80°C, 3 h) and treatment with DOWEX 50WX2-100 ion-exchange resin generated the desired β-hydroxy-γ-aminobutyric acid **7**[15] ($[\alpha]_D^{25}=-18.0$ (*c* 1, H_2O); lit.[15a] $[\alpha]_D^{25}=-20.5$ (*c* 1.75, H_2O)) in a one pot reaction (91% yield from **6**).

Although a one-pot conversion of **7** to (*R*)-(−)-carnitine (**9**) has been reported in literature, the yield of the reaction was very low (<10%)[10a] and hence, we adopted a more efficient two step procedure which we have recently reported for the synthesis of (*S*)-(+)-carnitine.[12] Thus, reductive methylation of **7** with aq. CH_2O (10% Pd/C, 80 psi of H_2, rt, 36 h) generated the desired dimethylamino compound **8** in quantitative yield. Quaternization of **8** with CH_3I (DMF, rt, 24 h) followed by treatment with Amberlite IRA-400 (OH) ion-exchange resin generated (*R*)-(−)-carnitine **9**[7–10] ($[\alpha]_D^{25}=-29.2$ (*c* 2, H_2O); lit.[9a] $[\alpha]_D=-31.3$ (*c* 10, H_2O)) in 83% yield (Scheme 3). Experimental data is provided for all new compounds.[16]

In summary, we have demonstrated an efficient method for the synthesis of (*R*)-(−)-carnitine by employing an asymmetric Mukaiyama type aldol reaction on lactone carbonyl of commercially available (5*R*,6*S*)-4-(benzyloxycarbonyl)-5,6-diphenyl-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (**1**)[13] and subsequent elimination–reduction protocol. Since, oxazinone (**1**) has also been used as a starting material for the synthesis of (*S*)-(+)-carnitine,[12] this further demonstrates the utility of this glycine template as a potential substrate for the stereodivergent synthesis of both enantiomers of carnitine. Current efforts are focused on synthesis of other peptide isosteres of biological importance, based on this methodology.

Acknowledgements

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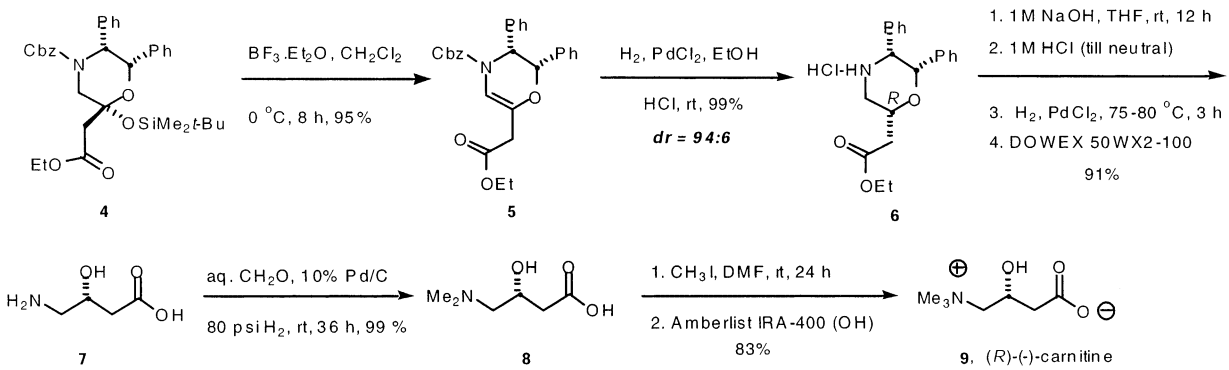

Scheme 3.

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16. **(2*R*,5*R*,6*S*)-2-(*tert*-Butyldimethylsilyloxy)-2-ethoxycarbonylmethyl-5,6-diphenyl-morpholine-4-carboxylic acid benzyl ester (4)**: To a stirred solution of **1** (1.935 g, 5 mmol) in anhydrous CH_2Cl_2 (40 mL) was added at −20°C the *t*-butyldimethylsilylketene acetal of ethyl acetate (5.05 g, 25 mmol) which was followed by a dropwise addition of $TiCl_4$ (2.74 mL, 25 mmol) over a period of 10 min. The reaction mixture was stirred at −20°C for 30 min after which it was quenched by adding satd aqueous NH_4Cl. The mixture was warmed to ambient temperature and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried (anhydrous Na_2SO_4) and concentrated to provide crude **4** which on purification by flash chromatography on silica gel (95:5 petroleum ether:ethyl acetate, followed by 9:1 petroleum ether:ethyl acetate) furnished 2.51 g (85%) of **4** as a clear colorless gum; $[\alpha]_D^{25}=-85.8$ (*c* 1, $CHCl_3$); ^{1}H NMR (300 MHz, DMSO-d_6, 393 K): δ 7.38–7.07 (m, 15H), 5.51 (d, 1H, $J=4.2$ Hz), 5.46 (d, 1H, $J=4.2$ Hz), 5.23 (d, 1H, $J=12.6$ Hz), 5.15 (d, 1H, $J=12.6$ Hz), 4.45 (d, 1H, $J=13.5$ Hz), 4.13–3.97 (m, 2H), 3.23 (d, 1H, $J=13.5$ Hz), 3.04 (d, 1H, $J=13.5$ Hz), 2.77 (d, 1H, $J=13.5$ Hz), 1.14 (t, 3H, $J=7.2$ Hz), 0.93 (s, 9H), 0.27 (s, 3H), 0.26 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6, 373 K): δ 167.8, 154.1, 137.5, 136.0, 135.7, 128.8, 127.6, 127.1, 126.9, 126.6, 126.2, 124.9, 97.1, 74.9, 66.4, 59.2, 55.5, 46.3, 24.9, 16.9, 13.1, −3.0, −3.4; IR ($CHCl_3$): 1737, 1700, 1604, 1585 cm^{-1}; HRMS (FAB+) calcd for $C_{34}H_{44}NO_6Si$ (*m*/*z*): 590.2937, found (*m*/*z*): 590.2931.

(5*R*,6*S*)-2-Ethoxycarbonylmethyl-5,6-diphenyl-5,6-dihydro-[1,4]oxazine-4-carboxylic acid benzyl ester (5): To a stirred solution of **4** (1.762 g, 3 mmol) in CH_2Cl_2 (40 mL) was added at 0°C $BF_3{\cdot}Et_2O$ (0.76 mL, 6 mmol) dropwise over a period of 10 min and the resulting solution was stirred at 0°C for 8 h. It was then quenched with water at 0°C, warmed to ambient temperature and extracted with CH_2Cl_2. The combined organic layer was dried (Na_2SO_4) and concentrated to provide crude **5** which on purification by flash chromatography on silica gel (9:1 petroleum ether:ethyl acetate, followed by 8:2 petroleum ether:ethyl acetate) furnished 1.3 g (95%) of **5** as a clear colorless gum; $[\alpha]_D^{25}=+235.1$ (*c* 1, $CHCl_3$); ^{1}H NMR (300 MHz, DMSO-d_6, 373 K): δ 7.30–6.97 (m, 15H), 6.74 (s, 1H), 5.37 (d, 1H, $J=3.0$ Hz), 5.32 (d, 1H, $J=3.0$ Hz), 5.19 (d, 1H, $J=12.6$ Hz), 5.12 (d, 1H, $J=12.6$ Hz), 4.17 (q, 2H, $J=7.5$ Hz), 3.39 (d, 1H, $J=16.2$ Hz), 3.31 (d, 1H, $J=16.2$ Hz), 1.22 (t, 3H, $J=7.5$ Hz); ^{13}C NMR (75 MHz, DMSO-d_6, 373 K): δ 168.6, 150.6, 136.2, 136.1, 135.7, 133.5, 127.6, 127.2, 127.0, 126.8, 126.5, 125.7, 104.4, 77.4, 66.5, 59.6, 58.5, 37.0, 13.3; IR ($CHCl_3$): 1737, 1707, 1605, 1585 cm^{-1}; HRMS (FAB+) calcd for $C_{28}H_{27}NO_5$ (*m*/*z*): 457.1889, found (*m*/*z*): 457.1896.

(2*R*,5*R*,6*S*)-2-Ethoxycarbonylmethyl-5,6-diphenyl-morpholine hydrochloride (6): To a solution of **5** (0.3 g, 0.65 mmol) in EtOH (30 mL) was added 10 M HCl (130 μL, 1.3 mmol) and $PdCl_2$ (0.023 g, 0.13 mmol) and the mixture was hydrogenated at 100 psi of H_2 and at ambient temperature for 18 h. Removal of catalyst by

filtration through a plug of Celite and removal of solvent furnished 0.235 g (99%) of crude **6** (*dr* = 94:6 by ^{1}H NMR) as a white solid which was pure by NMR; $[\alpha]_D^{25} = -8.4$ (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, CD_3OD, 300 K): δ 7.64–7.10 (m, 10H), 5.36 (d, 1H, $J = 3.2$ Hz), 4.98 (d, 1H, $J = 3.2$ Hz), 4.60–4.53 (m, 1H), 4.24 (q, 2H, $J = 7.2$ Hz), 3.43–3.27 (m, 2H), 2.93 (d, 2H, $J = 6.0$ Hz), 1.30 (t, 3H, $J = 7.2$ Hz); ^{13}C NMR (75 MHz, CD_3OD, 300 K): δ 171.5, 137.9, 132.7, 132.3, 130.7, 129.8, 129.2, 128.7, 126.5, 78.9, 72.7, 62.2, 58.4, 41.6, 38.9, 14.7; IR ($CHCl_3$): 1738, 1586 cm^{-1}; HRMS (FAB+) calcd for $C_{20}H_{24}NO_3$ (m/z): 326.1756, found (m/z): 326.1765.

(*R*)-4-Amino-3-hydroxybutanoic acid (7):[15] To the solution of **6** (0.2 g, 0.55 mmol) in THF (10 mL) was added 1 M NaOH (2.75 mL, 2.75 mmol) and the mixture was stirred at ambient temperature for 12 h after which it was neutralized with 1 M HCl and diluted by adding 5 mL water. The resulting solution was hydrogenated with $PdCl_2$ (0.216 g, 1.22 mmol) at 75–80°C and 120 psi of H_2 for 3 h. The mixture was then cooled to ambient temperature, the catalyst was removed by filtration through a plug of Celite and the filtrate concentrated and triturated with Et_2O. The residue thus obtained was dissolved in water and passed through DOWEX 50WX2-100 ion-exchange resin and the resin was washed with distilled water. Elution of the resin with 3% aq. NH_4OH furnished 0.06 g (91%) of **7** which was pure by NMR; $[\alpha]_D^{25} = -18.0$ (*c* 1, H_2O); lit.[15a] $[\alpha]_D^{25} = -20.5$ (*c* 1.75, H_2O); ^{1}H NMR (400 MHz, D_2O, 300 K): δ 4.21–4.15 (m, 1H), 3.14 (dd, 1H, $J = 3.2$, 13.2 Hz), 2.93 (dd, 1H, $J = 9.2$, 13.2 Hz), 2.41 (d, 2H, $J = 6.4$ Hz); ^{13}C NMR (75 MHz, D_2O, 300 K): δ 173.9, 61.0, 39.6, 37.9.