

Asymmetric aldol reactions of an *N*-propionyl derivative of chiral auxiliary derived from terpene alcohol *cis*-myrtanol with benzaldehyde

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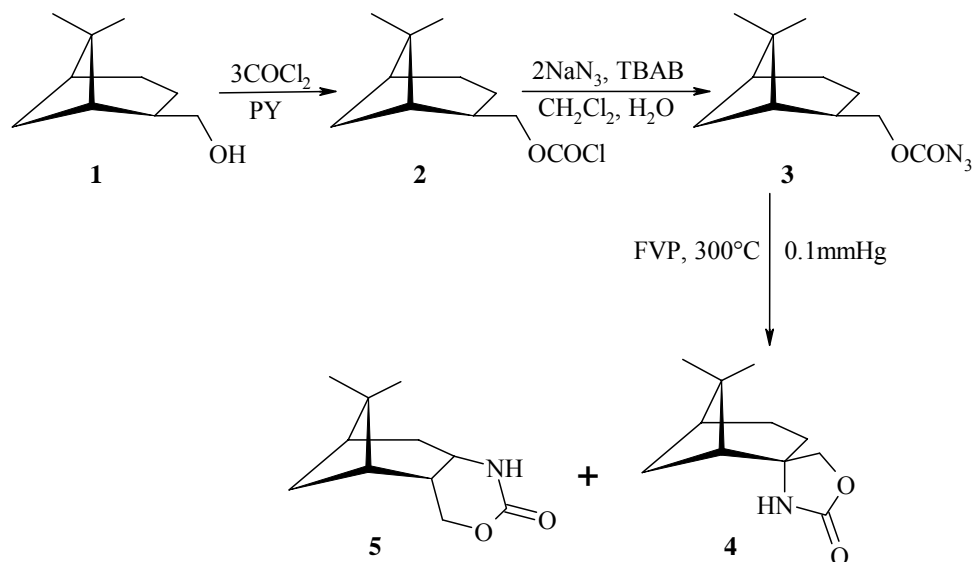
Abstract

The asymmetric aldol reaction was carried out by deprotonating an *N*-propionyl derivative of alcohol-derived terpene "*cis*-myrtanol", chiral auxiliary with lithium diisopropylamide (LDA), and then treating the *Z*-lithium enolate with benzaldehyde. Unfortunately, analysis of ¹H NMR spectrum of the crude aldol product showed poor diastereoselectivity. The boron enolate methodology was adopted to improve it. The boron enolate was generated by treatment of the *N*-propionyl derivative with Bu₂BOTf and diisopropylethylamine and then treated with benzaldehyde. Analysis of ¹H NMR spectrum of the crude aldol product obtained revealed an excellent diastereoselectivity.

Keywords: *cis*-Myrtanol, chiral auxiliary, *Z*-lithium enolate, boron enolate, diastereoselectivity

Introduction

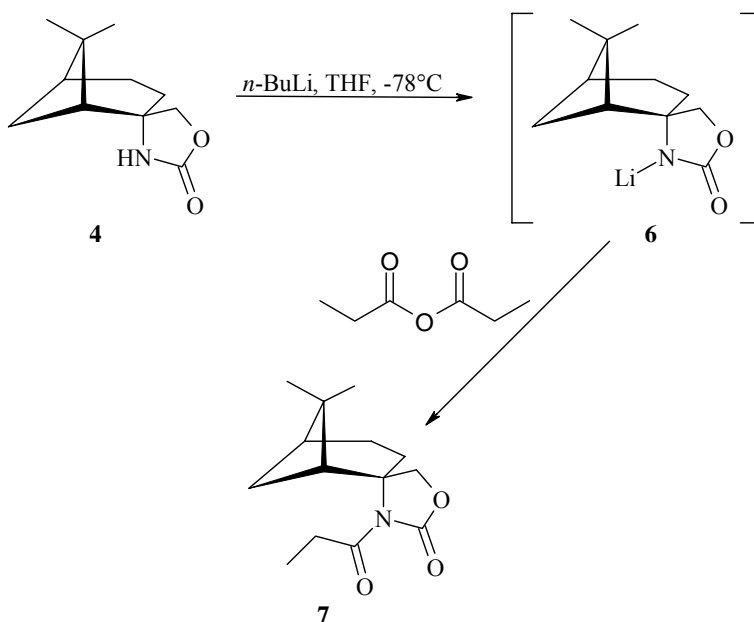
The stereospecific intramolecular nitrene insertion process was chosen as a synthetic route for the synthesis of the chiral oxazolidinone auxiliaries¹⁻⁷ using as starting materials cheap, readily available chiral alcohol. This nitrene route to chiral oxazolidinones has been used previously by Paryzek⁸ and by Alewood⁹ in the field of steroid chemistry. The chiral substrate selected for investigation was the terpene alcohol *cis*-myrtanol **1** which is commercially available. This starting material was chosen and employed by Cadogan *et al*⁷ for the synthesis of the chiral spiro-oxazolidinone auxiliary **4** (Scheme 1). Azidoformate **3** was synthesized from **1** according to the sequence shown in Scheme 1. The azidoformate **3** was subsequently thermally decomposed by flash vacuum pyrolysis (300°C, 0.1mmHg). This produced a mixture consisting of the spiro-oxazolidinone **4** and the six-membered oxazinone **5** in the ratio 4:1 respectively. Flash column chromatography of the crude mixture allowed the spiro-oxazolidinone **4** to be isolated in a yield of 56%⁷ (Scheme 1).



Scheme 1

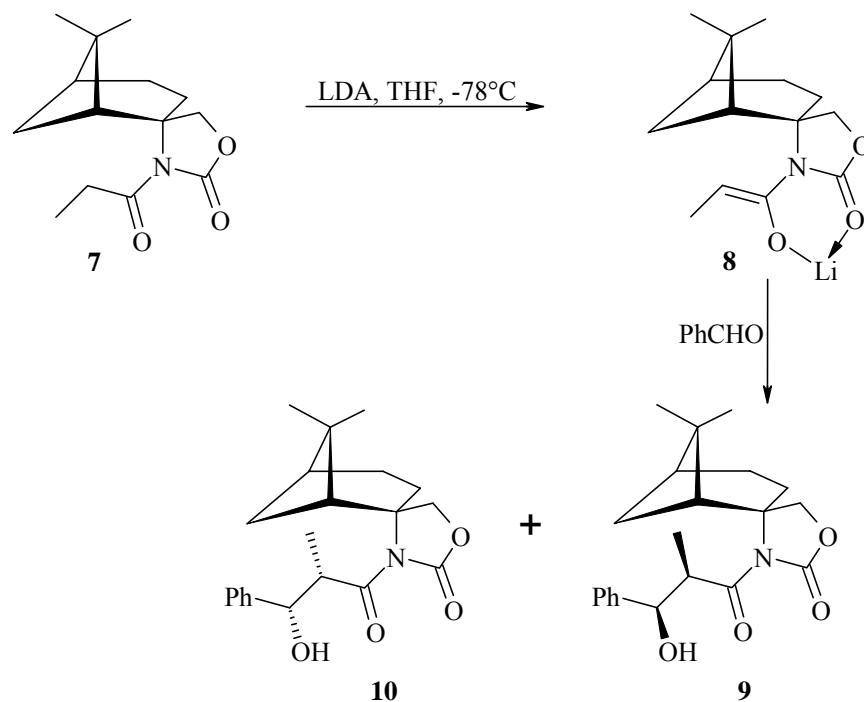
Results and Discussion

The method used by Evans *et al*^{10,11} was employed for the preparation of the *N*-propionyl derivative **7** of chiral auxiliary **4**. In essence, solution of chiral auxiliary **4** in anhydrous THF (tetrahydrofuran) was treated with *n*-butyllithium at -78°C , followed by acylation of the resulting anion **6** with, cheap and readily available acylation reagent, freshly distilled propionic anhydride (Scheme 2), leading to an 80% yield of the desired *N*-propionyl derivative **7**.



Scheme 2

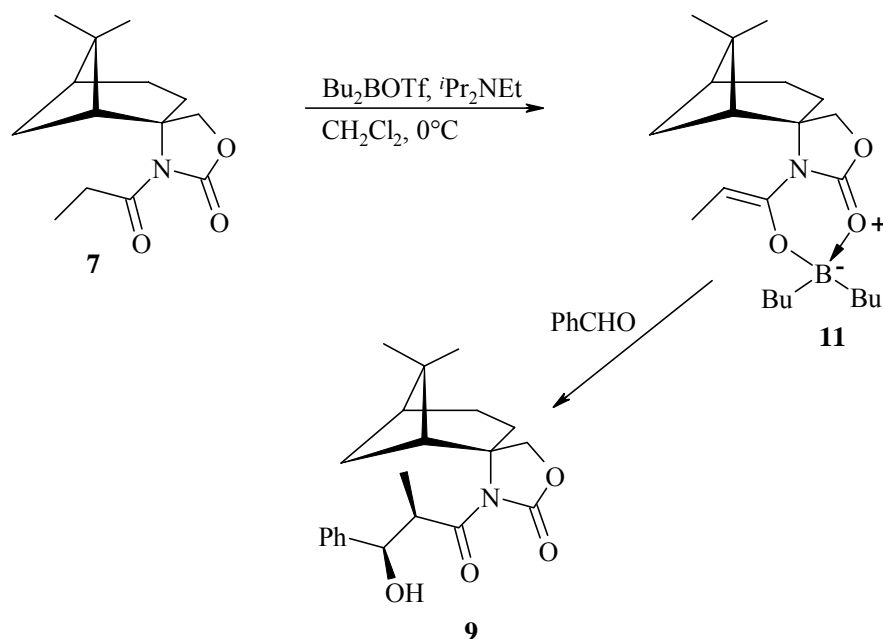
The asymmetric aldol reaction was carried out by deprotonating *N*-propionyl derivative **7** with lithium diisopropylamide (LDA), and then treating the resulting *Z*-lithium enolate **8** with freshly distilled benzaldehyde (Scheme 3). The reaction was allowed to proceed for a period of 30 seconds in order to obtain a kinetic product mixture, rather than an equilibrated thermodynamic product. After work-up, the crude aldol product was isolated by flash column chromatography as a pale yellow gum in good yield (70%), and then examined by high field ^1H NMR spectroscopy. The resonances of interest were doublets in the chemical shift range 5.15-4.75 ppm arising from the carbinol proton PhCHOH . Analysis revealed that only two *syn* diastereomers **9** and **10** ($^3J = 3.9$ and 5.9Hz) has been formed in a ratio of 70:30, respectively, giving a 40% diastereomeric excess (*d.e.*). The above assignments were made by measuring the vicinal coupling constants of the carbinol protons and using the known fact¹² that, for this proton, $^3J_{syn}$ is typically 3-6 Hz, and $^3J_{anti}$ is typically 7-9 Hz.



Scheme 3

It has been shown by a number of workers¹³⁻¹⁵ that lithium-mediated aldol reactions exhibit poor levels of diastereoselection. It should be noted that the poor diastereoselectivity can be attributed to a less “tight” transition state compared to other enolate systems, *e.g.* that of boron, due to the relatively long Li-O bond length¹⁶. Furthermore, lithium does not possess true ligands, other than those of solvent, *e.g.* alkyl groups, which would make steric interactions in the aldol transition state greater.

After this slightly poor demonstration of selectivity with the lithium-based-enolate **8**, attention was turned towards boron-mediated aldol reaction to improve the diastereoselectivity of this aldol reaction. In this procedure, the boron enolate **11** was generated by treatment of the *N*-propionyl derivative **7** with 1.1 equiv. of dibutylboron triflate (Bu_2BOTf) and diisopropylethylamine and allowed to react with freshly distilled benzaldehyde for thirty minutes at -78°C (Scheme 4). Once complete, the solution was warmed to room temperature for one and three quarter hours and worked-up to yield the crude aldol product as a pale yellow oil in acceptable yield (65%). The crude product was purified by flash column chromatography to yield a single diastereomer (*d.e.* = >99%) as shown by high field ^1H NMR spectroscopy. Despite the poor yield (37%), the level of asymmetric induction imparted by the auxiliary **4** under these specific conditions is excellent and ^{13}C NMR spectroscopy indicated only one aldol product had been formed. Analysis of ^1H NMR 400 MHz spectrum confirmed that the product was a *syn* isomer due to the presence of small vicinal coupling constants ($J= 3.9$ Hz) with one doublet at 5.12 ppm arising from the PhCHOH proton.

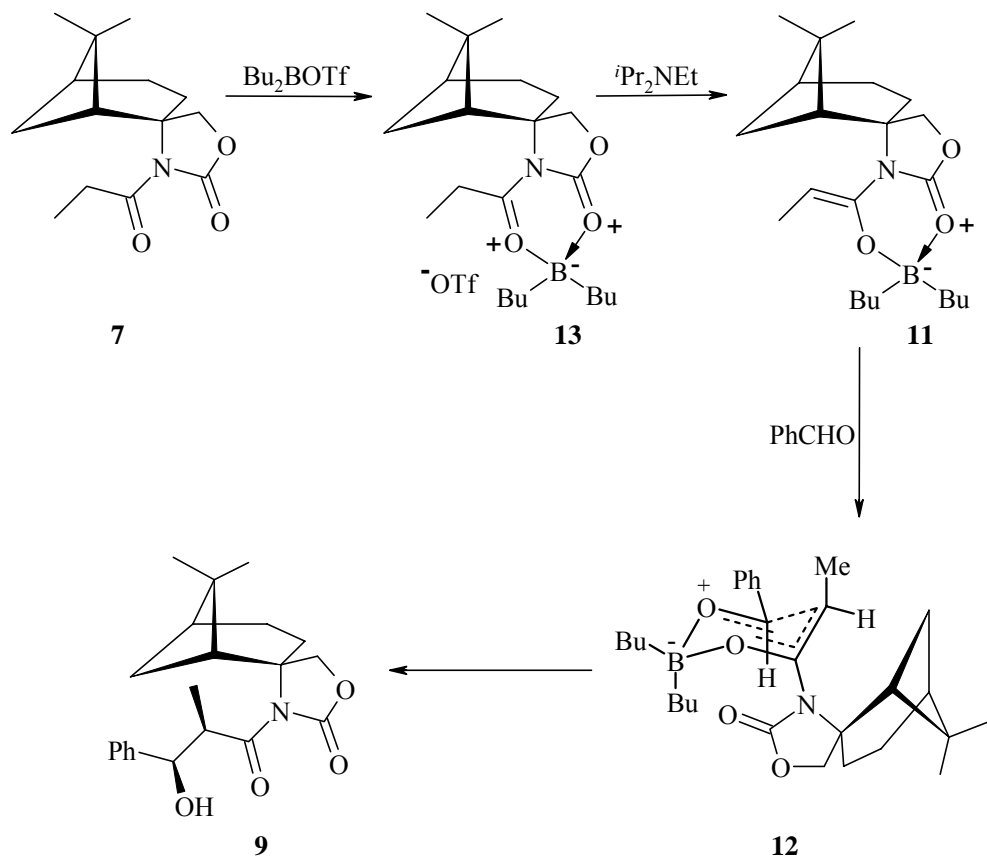


Scheme 4

This high level of asymmetric induction imparted by oxazinone **4** in this model aldol reaction is attributed to formation of the six-membered Zimmerman-Traxler transition state **12** as shown in Scheme 5.

From a mechanistic viewpoint, when the dibutylboron triflate is added to **7**, the boron initially co-ordinates to the *N*-acyl carbonyl groups in a tetrahedral fashion to form complex **13**. Subsequent treatment with diisopropylethylamine forms the boron enolate **11** (Scheme 5). Upon benzaldehyde addition to **11**, the B-O bond pertaining to the six-membered imide ring is cleaved,

and the auxiliary rotates 180° about the N-C bond, allowing the boron to co-ordinate to the carbonyl oxygen of the incoming aldehyde. This results into the formation of the six-membered Zimmerman-Traxler transition state **12** as depicted in Scheme 5. It is worth noting that in the transition state **12**, attack of the benzaldehyde occurs on the $C_{\alpha-re}$ face of the enolate since the bulk of the auxiliary shields the $C_{\alpha-si}$ face.



Scheme 5

The absolute stereochemistry of this single diastereomer **9** produced from the aldol reaction as expected from the mechanism discussed above has the *syn* ($2'R,3'R$) configuration, because it fits with the transition state **12** depicted in scheme 5. This indicates that the $C_{\alpha-re}$ face of the enolate had been attacked by $C_{\alpha-si}$ face of benzaldehyde.

Experimental Section

Preparation of 6,6-dimethyl-3'-propionyl-2'*H*-spiro[bicyclo[3.1.1]heptane-2,4'-[1,3]oxazolidin]-2'-one (7). To a solution of chiral auxiliary **4** (0.50 g, 2.56 mmol) in dry THF (20ml), at -78°C under argon, was added *n*-butyllithium (1.76ml of 1.6M solution, 2.82 mmol, 1.1 eq) *via* syringe.

After stirring for 30 minutes a solution of freshly distilled propionic anhydride (0.521g, 4.00mmol, 1.56 eq) in THF (5ml) was added dropwise *via* syringe. The resulting solution was stirred at -78°C for 5 minutes before being allowed to warm to room temperature and then stirred at this temperature for 30 minutes. TLC analysis revealed that the reaction was complete and quenching was effected with saturated aqueous sodium carbonate solution. After stirring for 10 minutes at room temperature, the layers were separated and the aqueous layer extracted with dichloromethane (3x20ml). The combined organic extracts were washed successively with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution, dried over (MgSO₄), filtered and evaporated to yield a pale yellow oil which was purified by flash chromatography (50g silica) using *n*-hexane:ether (3:1) as elution solvent, followed by Kugelrohr distillation to yield **7** as a colorless oil (0.512g, 80%); Bp= 105°C/0.03mmHg; $[\alpha]_D^{22} = +85.2^\circ$ (c =2.46, CH₂Cl₂); FTIR (thin film) ν_{\max} 1778 (oxazolidinone C=O), 1707 (C=O) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 4.17 (1H, d, *J*=8.5 Hz, CH_aH_bO), 3.89 (1H, d, *J*=8.5 Hz, CH_aH_bO), 2.94 (1H, dq, *J*=18.0, 7.3 Hz, CH_aH_bCH₃), 2.74 (1H, dq, *J*=18.0, 7.3 Hz, CH_aH_bCH₃), 2.23 (1H, m, C1-*H*), 2.14 (1H, m, C5-*H*), 2.11 (1H, m, C7-*H*_a), 1.97 (1H, m, C4-*H*_a), 1.90 (1H, m, C7-*H*_b), 1.78 (2H, m, C3-*H*₂), 1.65 (1H, m, C4-*H*_b), 1.23 (3H, s, CH₃), 1.07 (3H, t, *J*=7.3 Hz, CH₃CH₂), 0.97 (3H, s, CH₃) ppm; ¹³C NMR (100.2 MHz, CDCl₃) δ 175.01(C=O), 154.86(oxazolidinone C=O), 74.03(CH₂O), 69.49(quat C, C2), 50.72(CH, C1), 40.55(CH, C5), 39.80(quat C, C6), 30.80(CH₂CH₃), 27.27(CH₃), 26.80(CH₂, C3), 24.07(CH₂, C7), 23.97(CH₂, C4), 22.92(CH₃), 8.43(CH₃CH₂) ppm; MS (FAB) *m/z* 32(57%), 41(38), 57(base), 135(81), 196(35), 252(64 M+H); Accurate mass (FAB) Found: 252.15996 (M+H); C₁₄H₂₂NO₃ requires 252.15997.

Aldol reaction of 6,6-dimethyl-3'-propionyl-2'H-spiro[bicyclo[3.1.1]heptane-2,4'-[1,3]oxazolidin]-2'-one (7) with benzaldehyde in the presence of lithium diisopropylamide (LDA). A solution of LDA (1.32mmol, 1.1eq) was prepared by the dropwise addition of *n*-butyllithium (0.84ml of 1.6M solution, 1.32mmol, 1.1eq) to a solution of anhydrous diisopropylamine (0.134g, 1.32mmol, 1.1eq) in dry THF (10ml) at 0°C under argon. The solution was stirred at 0°C for 30 minutes, cooled to -78°C and treated with a solution of *N*-propionyl derivative **7** (0.30g, 1.20mmol, 1eq) in THF (10ml). The reaction mixture was stirred at this temperature for a further 30 minutes before addition of a solution of freshly distilled benzaldehyde (0.14g, 1.23mmol, 1.1eq) in dry THF (2ml) with rapid stirring. The reaction mixture was quenched after 30 seconds with saturated aqueous ammonium chloride solution (5ml), water (20ml) was added and the products were extracted into ether (3x20ml). The combined ether layers were washed with water (10ml), dried over magnesium sulfate and evaporated to dryness *in vacuo* to give the residue which was subjected to flash column chromatography using hexane:ether (4:1) elution. The first fraction to be eluted was found to be unreacted starting material **7** (0.037g, 29% recovery). The second fraction to be eluted was the aldol product as a pale yellow gum (0.296g, 70%). Analysis of this product by 400 MHz ¹H NMR spectroscopy showed that only two *syn* diastereomers **9** and **10** (³*J* = 3.9 and 5.9Hz) had

formed in the ratio of 70:30 respectively (diastereomeric excess = 40%) (these ratios were determined by integration of the doublets in the range 5.15-4.75 ppm, arising from the PhCHOH protons).

Aldol reaction of 6,6-dimethyl-3'-propionyl-2'H-spiro[bicyclo[3.1.1]heptane-2,4'-[1,3]oxazolidin]-2'-one (7) with benzaldehyde in the presence of Bu₂BOTf. To a solution of *N*-propionyl derivative 7 (0.25g, 1mmol, 1.0eq) in anhydrous dichloromethane (10ml) at 0°C under argon was added di-*n*-butylboron triflate (1M in dichloromethane, 1.1ml, 1.1mmol, 1.1eq) followed by diisopropylethylamine (0.23g, 1.8mmol, 1.8eq) in dry dichloromethane (*ca.* 5ml). The resulting pale yellow solution was stirred at 0°C for 1 hour before being cooled to -78°C. A solution of freshly distilled benzaldehyde (0.16g, 1.5mmol, 1.5eq) in dichloromethane (2ml) was added dropwise to the boron enolate solution and the reaction mixture was stirred for 30 minutes, whereupon the temperature was allowed to rise to 20°C. The mixture was stirred for a further 2 hours, quenched with a pH 7 phosphate buffer (30ml) and then extracted into dichloromethane (3x20ml). After evaporation *in vacuo*, the residue was dissolved in methanol (30ml) and the solution cooled to 0°C before being treated with hydrogen peroxide (100 volumes, 3ml) at this temperature. The reaction mixture was then stirred at room temperature overnight, sodium sulfite solution (10ml) was added and the mixture evaporated *in vacuo*. The residue was extracted with dichloromethane (3x20ml) and the combined organic extracts dried over magnesium sulfate, filtered and evaporated *in vacuo* to yield the crude aldol product as a pale yellow oil (0.236g, 65%). Examination of the 400 MHz ¹H NMR spectrum of this crude aldol product confirmed that only one *syn* diastereomer 9 (³*J* = 3.9 Hz) had been formed. (diastereomeric excess =>99%) (only one doublet at 5.12 ppm arising from the PhCHOH proton). The crude product was subjected to flash column chromatography using hexane:ether (4:1) for elution. The first fraction to be eluted was unreacted starting material 7 (0.074g, 30%) and the second fraction contained the *syn* diastereomer 3'-((3*R*)-hydroxy-(2*R*)-methyl-3-phenylpropionyl)-6,6-dimethyl-2'H-spiro[bicyclo[3.1.1]heptane-2,4'-[1,3]oxazolidin]-2'-one 9 as a colorless solid (0.127g, 37%); mp 124.5-125.8°C; FTIR (nujol) ν_{\max} 3544 (OH), 1772 (oxazolidinone C=O), 1747 (C=O) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.42-7.21 (5H, cm, Ph), 5.12 (1H, d, *J* = 3.9Hz, CHOH), 4.19 (1H, d, *J* = 8.5 Hz, CH_aH_bO), 3.95 (1H, d, *J* = 8.5 Hz, CH_aH_bO), 3.77 (1H, dq, *J* = 7.3, 3.9Hz, CHCH₃), 2.98 (1H, broad s, OH), 2.25 (1H, m, C1-H), 2.17 (1H, m, C5-H), 2.15 (1H, m, C7-H_a), 2.01 (1H, m, C4-H_a), 1.93 (1H, m, C7-H_b), 1.79 (2H, m, C3-H₂), 1.67 (1H, m, C4-H_b), 1.27 (3H, s, CH₃), 1.04 (3H, s, CH₃) 1.02 (3H, d, *J* = 7.3Hz, CH₃CH) ppm; ¹³C NMR (100.2 MHz, CDCl₃) δ 179.33(C=O), 154.89(oxazolidinone C=O), 141.21(Ar C), 128.03(Ar 2CH), 127.12(Ar CH), 125.98(Ar 2CH), 73.82(CHOH), 72.49(CH₂O), 69.51(quat C, C2), 50.76(CH, C1), 45.99(CHCH₃), 40.58(CH, C5), 39.86(quat C, C6), 27.31(CH₃), 26.82(CH₂, C3), 24.10(CH₂, C7), 23.99(CH₂, C4), 22.93(CH₃), 8.47(CH₃CH) ppm; Accurate mass (FAB) Found: 358.20267 (M+H); C₂₁H₂₈NO₄ requires 358.20183.

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