ASYMMETRIC ALDOL REACTIONS OF *N*-PROPIONYL DERIVATIVES OF 1,3-OXAZIN-2-ONE AND OXAZOLIDIN-2-ONE CHIRAL AUXILIARIES DERIVED FROM [(1*S*)-*ENDO*]-(-)-BORNEOL *VIA* LITHIUM ENOLATE WITH DIFFERENT ALDEHYDES

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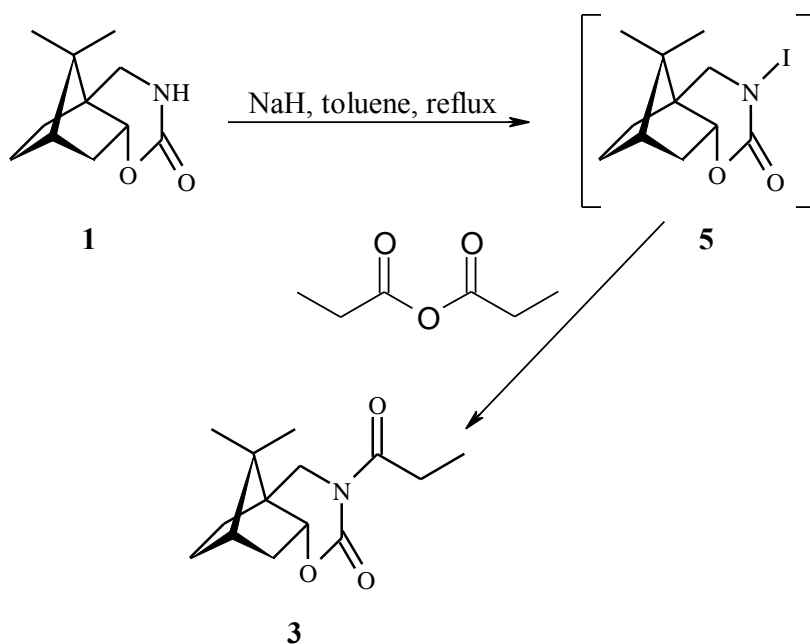
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Abstract

The work concerning this investigation involves preparation of lithium enolates of *N*-propionyl derivatives of 1,3-oxazin-2-one and oxazolidin-2-one chiral auxiliaries derived from [(1*S*)-*endo*]-(-)-borneol by deprotonating *N*-propionyl derivatives with lithium diisopropylamide (LDA). It also involves condensation of these lithium enolates with different aldehydes in asymmetric aldol reactions. The stereochemical outcome for these aldol reactions is measured in terms of diastereomeric excess (*d.e.*) which is determined by analysis of the crude aldol products by high-field ^{1}H NMR spectroscopy.
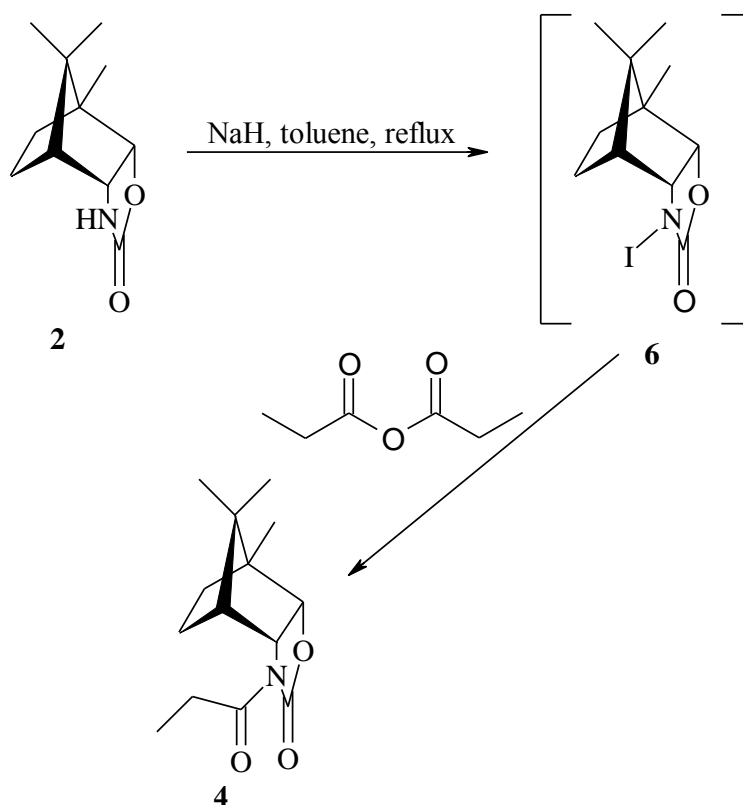
Introduction

The six-membered 1,3-oxazin-2-one **1** was synthesised as a *ca*. 1:1 mixture with the tricyclic oxazolidin-2-one **2**[1-2] by application of the INIR (Intramolecular Nitrene Insertion Reaction) method[3] to the terpene-alcohol [(1*S*)-*endo*]-(-)-borneol.

Methods used by Evans *et al*[4] were employed by Banks *et al*[1] and Abbas *et al*[2] for the preparation of the *N*-propionyl derivatives **3** and **4** of chiral auxiliaries **1** and **2**, respectively. In a variant of this procedure, a new procedure was employed for this

purpose. Thus, chiral auxiliaries **1** and **2** were treated individually with different base, sodium hydride, under reflux in anhydrous toluene to form anions **5** and **6**, respectively, which were then cooled to room temperature and treated with, the alternative acylation reagent, freshly distilled propionic anhydride (Schemes 1 and 2). This procedure led to excellent yields 98% and 96% of *N*-propionyl derivatives **3** and **4**, respectively.
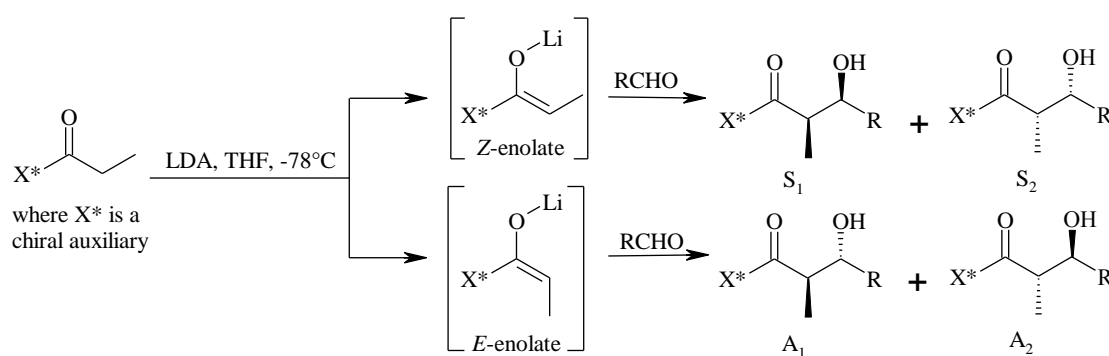

Scheme 1

Scheme 2

Results and discussion

The work concerning this investigation involves pre-formed lithium enolates and their condensation with an aldehyde in an asymmetric aldol reaction. The ability of such reagents to form rigid chelates with metal ions coupled with the masking of one face of the enolate by the auxiliary moiety (X^*) makes these reagents one of the most reliable and versatile tools for the selective synthesis of carbon-carbon bonds with the simultaneous generation of two new chiral centers[5,6] (Scheme 3). As shown, the geometry of the reacting enolate (*Z* or *E*) is crucial in determination of the configuration of the aldol product(s) with the possibility of obtaining four different stereoisomers, *viz.* S_1 and S_2 (*syn*), and A_1 and A_2 (*anti*). The composition of the product mixture depends

very much on the auxiliary (X^*) chosen and the type of enolate (and choice of metal) that is generated bearing in mind that only one *syn-* and one *anti-*isomer can be formed from each face of the enolate provided the latter exhibits fixed geometry. Numerous studies have led to the development of various methodologies for *syn-* and *anti-* aldol reactions.[7-10]
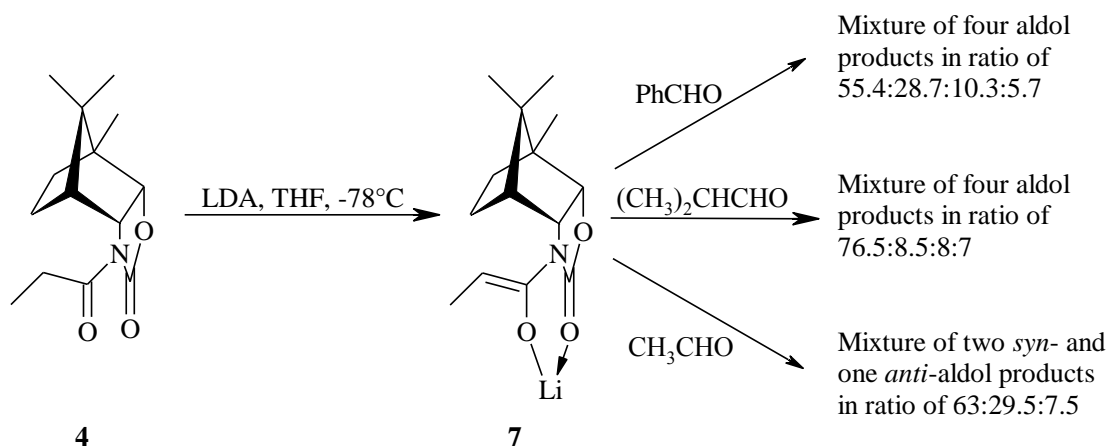

Scheme 3

The stereochemical outcome for the aldol reactions of the *N*-propionyl derivatives with aldehydes is measured in terms of diastereomeric excess (*d.e.*) which is determined by analysis of the crude aldol product by high-field ^{1}H NMR spectroscopy. From the spectra obtained, the most informative region was the chemical shift range that contained the doublet of resonances arising from the carbinol proton (RC*H*-OH) for each diastereomer.

Banks *et al*[1] reported that reaction of the lithium enolate **7**, generated by deprotonating *N*-propionyl derivative **4** with lithium diisopropylamide (LDA), with benzaldehyde, and quenching after thirty seconds, yielded a colorless crystalline solid which was shown by high field ^{1}H NMR spectroscopy to be a mixture of the four
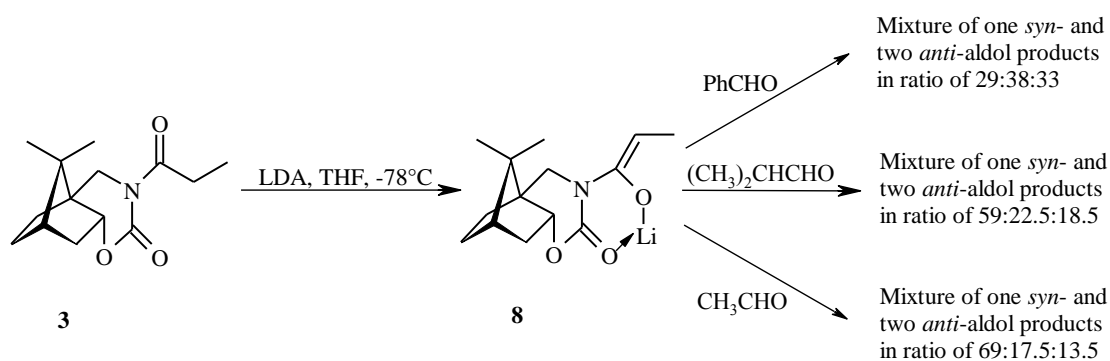
possible aldol products (S_1, S_2, A_1, A_2) in a ratio of 55.4:28.7:10.3:5.7 (Scheme 4), giving *d.e.* of 11%.

Scheme 4

In analogues to Banks results[1], Abbas reported in PhD thesis[11] that the $Z(O)$ lithium enolate **8** was prepared by deprotonating *N*-propionyl derivative **3** with lithium diisopropylamide (LDA) and then treated with freshly distilled benzaldehyde. Only short reaction period of 30 seconds was allowed in order that a kinetic product mixture, rather that an equilibrated thermodynamic product, would be obtained. After work-up, the crude aldol product was isolated as a colorless gum in excellent yield (90%). Examination of the crude aldol product by high-field ^{1}H NMR and ^{13}C NMR spectroscopy showed that a mixture of only three aldol products had been formed (Scheme 5). One of these was found to be a *syn* diastereomer (^3J= 2.6 Hz), whilst the other two proved to be *anti* diastereomers (^3J= 11.5 Hz), all of which were formed in a ratio of (29:38:33 respectively), *i.e.* without diastereomeric excess. These ratios were determined by integration of the doublets in the range 5.28-4.97 ppm, arising from the

PhC*H*OH protons. The above *syn*:*anti* assignments were made by measuring the vicinal

coupling constants of the carbinol protons and using the known fact[12] that, for this

proton, $^3J_{syn}$ is typically 3-6 Hz, and $^3J_{anti}$ is typically 7-9 Hz.

Scheme 5

These poor levels of diastereoselection attained with lithium enolates in these

reactions has been noted by other workers[4, 13-16] and can be attributed to a less "tight"

transition state compared to other enolate systems due to the relatively long Li-O bond

length.[17] In addition, lithium does not possess true ligands (*i.e.* ligands other than those

of solvent, for example, alkyl groups), which would make steric interactions in the aldol

transition state greater.[18]

To evaluate the scope of these lithium enolate-mediated aldol condensations,

reactions of lithium enolates **7** and **8** with other aldehydes were attempted. Reaction of

lithium enolate **7** with isobutyraldehyde and quenching after two minutes yielded a

colorless crystalline solid in excellent yield (90%). A longer reaction time was allowed

due to the less reactivity of isobutyraldehyde because of the poorer electrophilic quality

of the carbonyl group compared to that of benzaldehyde. This is due to the absence of

the aromatic group as well as the increased steric demand imposed by the isopropyl group. Examination of the crude aldol product by high field ^{1}H NMR spectroscopy showed that a mixture of the four possible aldol products had been formed in a ratio of (76.5:8.5:8:7), giving acceptable *d.e.* of 53% (Scheme 4). These ratios were determined by integration of the doublets of doublets in the range 3.8-3.0 ppm, arising from the carbinol $(CH_3)_2CHCHOH$ protons. The major isomer was identified to be a *syn* diastereomer (^{3}J= 2.7 Hz), whilst the other *syn* diastereomer (^{3}J= 4.0 Hz), and the other two isomers proved to be *anti* diastereomers (^{3}J= 6.9 and 8.2 Hz, respectively).

Reaction of lithium enolate **8** with isobutyraldehyde and quenching after two minutes yielded the crude aldol product as a colorless gum in excellent yield (92%). Analysis of the crude aldol product by high field ^{1}H NMR spectroscopy revealed the presence of three aldol products in a ratio of (59:22.5:18.5) (Scheme 5), giving an improved *d.e.* of 18% compared to the benzaldehyde reaction. These ratios were determined by integration of the doublets of doublets in the range 3.8-3.0 ppm, arising from the carbinol $(CH_3)_2CHCHOH$ protons. One of these isomers was found to be a *syn* diastereomer (^{3}J= 2.7 Hz), whilst the other two isomers proved to be *anti* diastereomers (^{3}J= 10.4 Hz).

Treatment of lithium enolate **7** with acetaldehyde, allowing the reaction to proceed for two minutes for this less hindered system, afforded an oil which was shown by ^{1}H NMR spectroscopy to be only the starting material *N*-propionyl derivative **4**. The same reaction of lithium enolate **7** with acetaldehyde was repeated and determined to be complete by thin-layer chromatography after three hours, giving a pale yellow gum in good yield (65%). The crude aldol product was examined by high field ^{1}H NMR spectroscopy which showed a mixture of only three aldol products had been formed

(Scheme 4). Two of these were found to be *syn* diastereomer (^3J= 3.2 and 3.5 Hz, respectively) in ratio of 2:1, whilst, the other isomer proved to be *anti* diastereomer (^3J= 10.3 Hz), all of which were formed in a ratio of (63:29.5:7.5, respectively), giving *d.e.* of 26%. These ratios were determined by integration of the doublets of quartets in the range 3.9-3.4 ppm, arising from the carbinol CH$_3$C*H*OH protons.

Reaction of lithium enolate **8** with acetaldehyde and quenching after three hours yielded the crude aldol product as a pale yellow gum in poor yield (43%). Analysis of the crude aldol product by high field ^{1}H NMR spectroscopy revealed the presence of three aldol products in a ratio of (69:17.5:13.5) (Scheme 5), giving an improved *d.e.* of 38% compared to the benzaldehyde and isobutyraldehyde reactions. These ratios were determined by integration of the doublets of quartets in the range 4.0-3.5 ppm, arising from the carbinol CH$_3$C*H*OH protons. The major isomer was found as usual to be a *syn* diastereomer (^3J= 3.1 Hz), whilst the other two isomers found to be *anti* diastereomers (^3J= 10.5 Hz).

The resistance of acetaldehyde to react with lithium enolate was a striking observation considering that one could not account for it on the basis of steric arguments, although it could be argued that the enolization of the aldehyde by the LDA suppresses the aldol reaction. Enolization is less likely to occur in the case of isobutyraldehyde due to steric interactions between the isopropyl groups of the aldehyde and the LDA, which inhibit this process. This enolization is obviously not a problem in the benzaldehyde case, as it has no enolisable proton and hence it reacts readily. Such a hypothesis has been put forward by Banks *et al*[19] to explain the unreactive nature of aldehydes with α–hydrogens.

Experimental

Tetrahydrofuran (THF) was distilled over KOH followed by distillation over sodium metal in the presence of benzophenone and stored under nitrogen. The infrared spectra were obtained by Nicolet Magna 520 FTIR spectrophotometer using nujol mulls, on sodium chloride plates. ^{1}H NMR spectra were recorded by Bruker AC-250 spectrometer and Bruker DP X 400 MHz spectrometer using $CDCl_3$ as a solvent and TMS as internal standard. FAB and accurate mass measurements were obtained on a Kratos MS-50 TC spectrometer.

General procedure of asymmetric aldol reactions of lithium enolates of *N*-propionyl derivatives 3 and 4 with different aldehydes.

A solution of lithium diisopropylamide (LDA) (2.18mmol, 1.1eq.) was prepared by the dropwise addition of 1.6M *n*-butyllithium (1.36 ml, 2.18mmol, 1.1eq.) to a solution of anhydrous diisopropylamine (0.221g, 2.18mmol, 1.1eq.) in dry tetrahydrofuran (30ml) 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 derivatives **3** or **4** (0.497g, 1.98mmol, 1eq.) in tetrahydrofuran (5ml). The reaction mixture was stirred at this temperature for a further 30 minutes before addition of a solution of freshly distilled aldehyde (2.18mmol, 1.1eq.) in dry tetrahydrofuran with rapid stirring. The reaction mixture was quenched after period depends on the type of aldehyde, with saturated aqueous ammonium chloride solution (5ml), water (50ml) was added and the products were extracted into ether (3x20ml). The combined organic layers were washed with water (10ml), dried over

magnesium sulfate and evaporated to dryness *in vacuo* to yield the crude aldol product for NMR spectroscopic analysis.

Aldol condensation of the *Z(O)* lithium enolate of *N*-propionyl derivative 3.

a) With benzaldehyde[11].

The reaction mixture was quenched after 30 seconds with saturated aqueous ammonium chloride solution (5ml), water (30ml) was added and the product was extracted into ether (3x20ml). The combined organic layers were washed with water (10ml), dried over magnesium sulfate and evaporated to dryness *in vacuo* to yield the crude aldol product as a colorless gum (0.627g, 90%), analysis of which by 250 MHz ^{1}H NMR spectroscopy by integration of the doublets in the range 5.28-4.97 ppm, arising from the PhC*H*OH protons showed that only one *syn* diastereomer (^3J= 2.6 Hz) and two *anti* diastereomers (^3J= 11.5 Hz) had been formed in the ratio of 29:38:33, respectively; FTIR (nujol) ν_{max}: 3486 (OH), 1763 (C=O), 1676 (C=O) cm^{-1}; Accurate mass (FAB); Found: 358.20092; $C_{21}H_{28}NO_4$ (M+H) requires 358.20183.

b) With isobutyraldehyde.

The reaction mixture was quenched after two minutes with saturated aqueous ammonium chloride solution (5ml) and concentrated *in vacuo*. Water (40ml) was added and the product was extracted with dichloromethane (3x25ml). The combined organic extracts were washed thoroughly with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered and evaporated to yield a colorless gum (0.587g, 92%). Analysis of this crude aldol product by 400 MHz ^{1}H NMR spectroscopy by integration of the doublets of doublets in the range 3.8-3.0 ppm, arising from the $(CH_3)_2$CHC*H*OH protons showed only one *syn* diastereomer (^3J= 2.7 Hz) as a major product, and two *anti* diastereomers (^3J= 10.4 Hz)

had been formed in the ratio of 59:22.5:18.5, respectively, giving *d.e.* of (18%); FTIR (nujol) ν_{max}: 3352 (OH), 1760 (C=O), 1736 (C=O) cm^{-1}; Accurate mass (FAB); Found: 324.21698; $C_{18}H_{30}NO_4$ (M+H) requires 324.21747.

c) With acetaldehyde.

The reaction mixture was quenched after three hours with saturated aqueous ammonium chloride solution (5ml) and concentrated *in vacuo*. Water (40ml) was added and the product was extracted with dichloromethane (3x25ml). The combined organic extracts were washed thoroughly with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered and evaporated to yield a pale yellow gum (0.220g, 43%). Analysis of the crude aldol product by 400 MHz ^{1}H NMR spectroscopy by integration of the doublets of quartets in the range 4.0-3.5 ppm, arising from the CH$_3$C*H*OH protons showed only one *syn* diastereomer (^3J= 3.1 Hz) as a major product, and two *anti* diastereomers (^3J= 10.5 Hz) had been formed in the ratio of 69:17.5:13.5, respectively, giving *d.e.* of (38%); FTIR (nujol) ν_{max}: 3444 (OH), 1766 (C=O), 1672 (C=O) cm^{-1}; Accurate mass (FAB); Found: 296.18581; $C_{16}H_{26}NO_4$ (M+H) requires 296.18617.

Aldol condensation of the *Z(O)* lithium enolate of *N*-propionyl derivative 4.

a) With isobutyraldehyde.

The reaction mixture was quenched after two minutes with saturated aqueous ammonium chloride solution (5ml) and concentrated *in vacuo*. Water (40ml) was added and the product was extracted with dichloromethane (3x25ml). The combined organic extracts were washed thoroughly with saturated aqueous sodium bicarbonate solution

and saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered and evaporated to yield an oil (0.577g, 90%) which crystallized on standing. This was shown by 400 MHz ^{1}H NMR spectroscopy to contain a mixture of all four possible isomers with a ratio of 76.5:8.5:8:7, giving *d.e.* of (53%). These values were determined by measuring the ratio of the doublets of doublets for the carbinol $(CH_3)_2CHCHOH$ resonances, which resonate at δ 3.8-3.0 ppm. The major isomer was identified to be a *syn* diastereomer (^3J = 2.6 Hz), whilst the other *syn* diastereomer (^3J = 4.0 Hz) and the other two isomers proved to be *anti* diastereomers (^3J = 6.3 and 8.2 Hz, respectively); FTIR (nujol) ν_{max}: 3340 (OH), 1762 (C=O), 1728 (C=O) cm^{-1}; Accurate mass (FAB), Found: 324.21735; $C_{18}H_{30}NO_4$ (M+H) requires 324.21747.

b) With acetaldehyde.

The reaction mixture was quenched after three hours with saturated aqueous ammonium chloride solution (5ml) and concentrated *in vacuo*. Water (40ml) was added and the product was extracted with dichloromethane (3x25ml). The combined organic extracts were washed thoroughly with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered and evaporated to yield a pale yellow gum (0.332g, 65%). Analysis of the crude aldol product by 400 MHz ^{1}H NMR spectroscopy by integration of the doublets of quartets in the range 3.9-3.4 ppm, arising from the CH_3CHOH protons showed two *syn* diastereomers in a ratio of 2:1 (^3J= 3.2 and 3.5 Hz, respectively) and one *anti* diastereomer (^3J= 10.3 Hz) had been formed in the ratio of 63:29.5:7.5, respectively,

giving *d.e.* of (26%); FTIR (nujol) ν_{max}: 3460 (OH), 1764 (C=O), 1677 (C=O) cm^{-1};

Accurate mass (FAB); Found: 296.18603; $C_{16}H_{26}NO_4$ (M+H) requires 296.18617.

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