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Versatile Chiral Intermediates for Terpenoid Synthesis using Lipase Catalysed Acylation.

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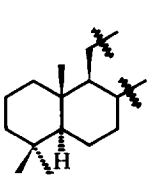
Abstract: The enantioselective transesterification of 1-Hydroxymethyl-5,5,8a-trimethyl-2-oxodecahydronaphthalene (±)-**11** with CCL in vinyl acetate has proved to be a facile method for obtaining versatile chiral intermediates useful in natural product synthesis.

The structural unit **1** with its bicyclo [4.4.0] ring system and three pendant methyl groups is an important 'core' found in a variety of natural products like drimanes, labdanes, hopanes etc. Due to the biological activity of several members of these groups especially the antifeedant activity of Polygodial **2**, Warburganal **3** and Albicanyl acetate **4**, much attention has been paid to their synthesis both in racemic and optically active forms.[1] While most asymmetric synthesis of **2** and **3** have commenced from higher terpenes such as sclareol, abietic acid and manool, Mori *et al.* have utilized bakers yeast reduction of a prochiral ketone as the asymmetry inducing step. For the synthesis of **4**, Fukumoto *et al.* have employed enantiomerically pure Wieland-Miescher ketone.[2] The enantiomer of **1**, *viz.* **5**, even though rare, is found in the biologically active marine natural products[3] zonarol **6**, isozonarol **7** and zonaroic acid **8**.



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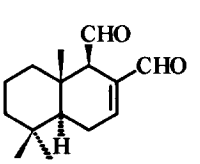

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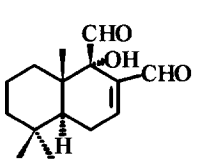

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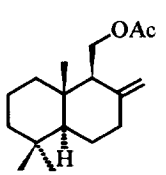

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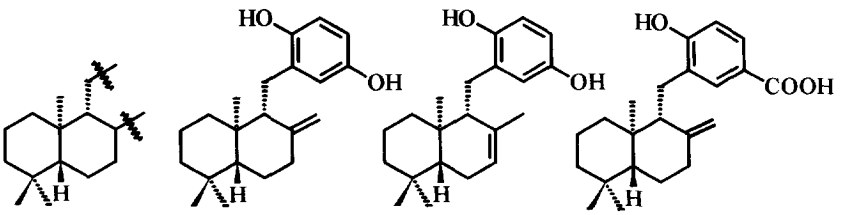
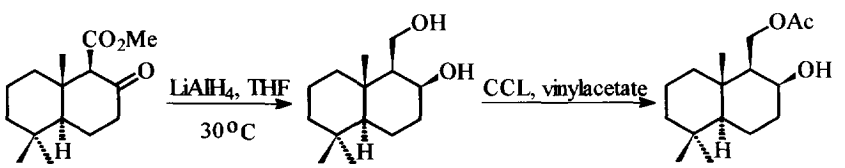


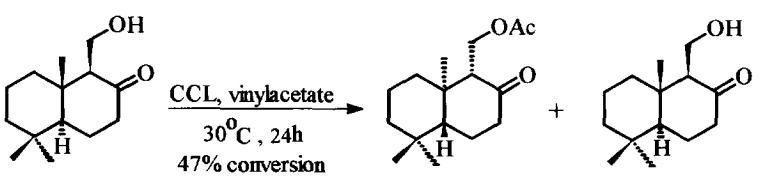
5 6 7 8

In connection with an ongoing programme on the structure - activity relationship of antifeedants, we required access to both **1** and **5**. Therefore, an enzymatic resolution of a suitably functionalised [4.4.0] ring system seemed to be the method of choice. The use of lipases in organic solvents for regio and stereoselective esterification with various acylating agents like vinyl acetate, ethyl acetate, ethyl propionate etc, of 1,2 and 1,3-diols have been demonstrated.[4] Following this lead to reach our objective, we commenced with the well known β-ketoester[5] **9** which was reduced to the diol **10**. However, in our hands, lipase catalysed transesterification of **10** led to facile acylation at the primary site but with poor enantioselectivity under a variety of conditions.[6]



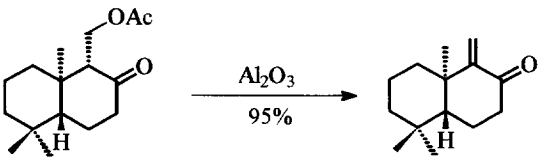
(±)-**9** (±)-**10** (±)

Subsequently, we examined the lipase catalysed transesterification of the ketoalcohol **11**. The use of Porcine pancreatic lipase (PPL), Lipase PS (Amano) and Lipase AY (Amano) with vinyl acetate as the acylating agent did not bring about appreciable conversion even after several days. However, promising results were obtained using Candida cylindracea lipase (CCL). Thus treatment of (±) -**11** with CCL in vinyl acetate at 30°C for 24h resulted in 47% conversion to the ketoacetate (+) -**12** of 68% ee. A single crystallisation of the above acetate using pentane as solvent readily furnished material of 92% ee. The enantiomeric excess was ascertained by ^{1}H nmr using Eu(hfc)$_3$ as shift reagent.



(±)-**11** (+)-**12** (-)-**11**

While the ketoacetate (+) -12 has the potential for conversion to the natural products 6 - 8 as well as the unnatural isomers of 2 - 4, its versatility was amplified by conversion to the enone (+)-13 (95% yield), $[\alpha]^{25}_D$ = +73.6 (c 1.00, $CHCl_3$) through simple adsorption on neutral alumina followed by elution with 20% ethyl acetate in petroleum ether.[7] (+)-13 has been converted to the marine natural product 6 by Mori earlier.[8]



(+) - 12 (+)- 13

For obtaining pure ketoalcohol (-)-11, a sequential enzymatic acylation method was used. The ketoalcohol remaining after the separation of (+)-12 had only a moderate enantiomeric excess of 53%. To take advantage of the higher selectivity shown by CCL for the (+) isomer, a second transesterification was carried out on the above material. This resulted in ketoacetate (+)-12 of poor ee, but provided unreacted ketoalcohol (-) -11(50%) of 82% ee which on crystallisation from hexane readily furnished product of 97% ee, $[\alpha]^{24}_D$ -37.2 (c 0.46 , $CHCl_3$). In this case, the enantiomeric excess was calculated based on reported rotation available in literature.[2b,9]

Experimental:

PPL was purchased from Aldrich Chemical Co and CCL from Fluka. Lipase PS and Lipase AY were gifted by Amano Pharmaceutical Co, Japan.

Lipase catalysed acylation of (±)1-Hydroxymethyl-5,5,8a-trimethyl-2-oxodecahydronaphthalene 11.

To a solution of (±)-11 (520 mg, 2.32 mmol) in vinyl acetate (45 mL) was added Candida cylindrcea lipase (CCL, 24U/mg, 780 mg) and stirred at 30°C. Additional amount of lipase, 100 mg each, was added at 15 h and at 20h after commencement and the reaction stirred for a total period of 24 h. Lipase was then filtered off and washed with ethyl acetate. Combined filtrate was concentrated under reduced pressure and the residue chromatographed over silica gel using 10% ethyl acetate in petroleum ether as eluent to furnish (+)-1-[(acetyl-oxy)methyl]-5,5,8a-trimethyl-2-oxodecahydronaphthalene 12 (290 mg, 47%, 68% ee) and (-)-ketoalcohol 11 (250 mg, 48%, 53% ee). Crystallisation of enantiomerically enriched acetate 12 (290 mg, 68% ee) from pentane furnished (+) -12 (144 mg) with >92%ee. Recrystallisation of >92%ee sample (140 mg) finally furnished (+) 12 (100 mg, >98% ee). (Found: C, 72.38 H, 9.85. $C_{16}H_{26}O_3$ requires C, 72.14; H, 9.84 %); $[\alpha]^{24}_D$ +35.06 (*c* 0.96 , $CHCl_3$); ν_{max} (KBr) 2979, 1744,1723,1464,1045cm^{-1}; δ_H (200 MHz, $CDCl_3$) 0.77 (3H, s), 0.86 (3H, s), 0.98 (3H, s), 1.2-1.8 (9H), 2.0 (3H, s), 2.05-2.6 (3H, m), 4.19 (2H, m); δ_C (22.4 MHz, $CDCl_3$) 15.1, 18.6, 20.7, 21.4, 23.5, 33.3, 33.4, 38.9, 41.5, 41.7, 41.8, 53.6, 58.6, 62.1, 170.7, 209.1 .

The ketoalcohol (-)-11 (200 mg) of 53% ee obtained above was resubmitted to transesterification under same conditions using CCL (300 mg) and vinyl acetate (20 mL). Reaction was stopped after 18h and crude mixture was chromatographed over silica gel to furnish ketoacetate 12 (90 mg, <13% ee) and further enriched (-)-11

(100 mg, 50%). A single crystallisation of this alcohol from hexane furnished enantiomerically pure (-) -11 (50 mg) of 97% ee, $[\alpha]^{25}_D$ -37.2 (*c* 0.46, $CHCl_3$) {lit[9] $[\alpha]_D$ -38.3 (*c* 1.0), lit [2b], $[\alpha]_D$ -38.9 (*c* 1.24 , $CHCl_3$).

Conversion of (+)-12 to (+)-1-Methylene-5,5,8a-trimethyl-2-oxodecahydronaphthalene 13.

(+) -12 (100 mg,0.38 mmol) of > 98% ee was adsorbed on a short column of neutral alumina (Brockmann grade 1, 5g) and on elution with 10% ethyl acetate in petroleum ether after 1h readily furnished enantiomerically pure enone (+)-13 (73 mg, 95%, 98% ee). $[\alpha]^{25}_D$ +73.6 (*c* 1.00, $CHCl_3$) {lit,[8] $[\alpha]^{23}_D$ +71.9 (*c* 0.695, $CHCl_3$), lit, [9] $[\alpha]^{23}_D$ - 75 (*c* 1.0 , $CHCl_3$, for (-) -13)}

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