THE ASYMMETRIC SYNTHESIS OF 4,4-DIMETHYL-3-SUBSTITUTEDBUTYROLACTONES

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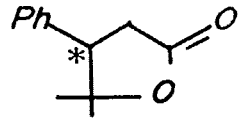
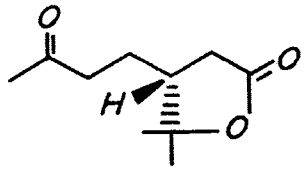
Chiral 4,4-dimethyl-3-phenyl and 3-(3-oxobutyl)butyrolactones have been prepared in high enantiomeric excesses by a mild acid catalysed cleavage and lactonisation of the Michael adducts obtained from asymmetric additions of isopropenyl magnesium bromide to α,β-unsaturated carboxylic amides derived from l-ephedrine.

The synthesis of 4,4-dimethyl-3-substitutedbutyrolactones has received a significant amount of attention,[1] as these compounds are easily elaborated to pyrethroid acids.[1-3] However, there have been only a few reports of the enantioselective synthesis of this type of lactone,[2,4,5] the highest optical purity (80% ee) being obtained for a preparation of (-)-4,4-dimethyl-3-phenylbutyrolactone ((-)-1a).[5]

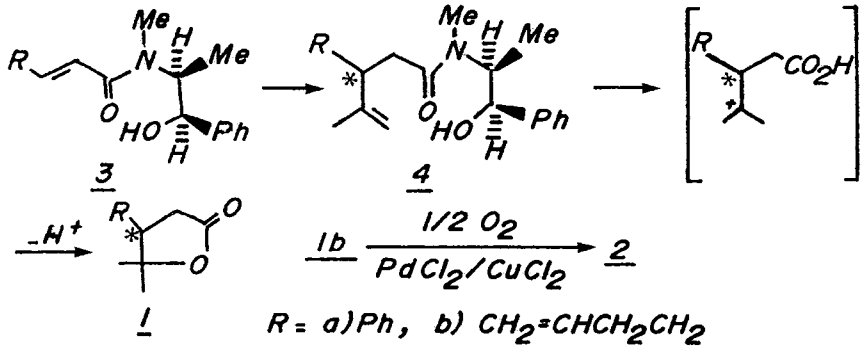


1a



2

We wish to report here a new strategy for the efficient enantioselective synthesis of (+)-1a together with (R)-(-)-4,4-dimethyl-3-(3-oxobutyl)butyrolactone (2), a natural product isolated from Psuedomonas flava[6] and a synthon for trans-chrysanthemic acid.[3] We reasoned that a chiral 3-isopropenylalkanoic acid upon acid treatment might give a chiral 4,4-dimethyl-3-substitutedbutyrolactone in a manner similar to that documented for other 4-alkenoic acids,[7] involving protonation of the double bond to give the tertiary carbocation and subsequent lactonisation. For the preparation of chiral 3-isopropenyl carboxylic acids we adapted a procedure originally reported by Mukaiyama and Iwasawa.[8] Thus the α,β-unsaturated carboxylic amides 3a[8] and 3b[9], derived from l-ephedrine and the appropriate (E)-3-alkenoic acid chloride,[8] were each added to an excess of isopropenylmagnesium bromide[10] to give the Michael adducts 4a and 4b[9] as shown below.



Mild acid hydrolysis[11] of 4a and 4b gave in one step the chiral lactones 1a[12] and 1b[9] respectively, without isolation of the

3-isopropenyl carboxylic acids. Lactonisation may in fact be occuring directly from the amides, as has been demonstrated for the esters of some 4-alkenoic acids.[7] Chiral lactone 1a exhibited greater than 99% enantiomeric excess (ee) when compared to the literature value.[12] The determination of the enantiomeric excess of 1b, previously undetermined,[9] was based on its conversion to the known chiral lactone 2[6] by palladium-catalysed oxidation[13] of 1b. Product 2 isolated from 1b exhibited an 88% ee and hence 1b must also exhibit at least an 88% ee. Attempts to separate a mixture of 1a and its enantiomer (prepared from an experiment conducted under conditions known to lead to lower enantioselectivities) on a Pirkle column[14] were unsuccessful. The use of a chiral shift reagent[15] in determining the ee of a mixture of 1a and its enantiomer by nmr methods was also unsuccessful and hence we must still rely on the determination of the ee of 1a, 1b and 2 on optical rotation measurements.

We are currently investigating various modifications and applications of this synthetic strategy to the synthesis of other more complex chiral lactones.

EXPERIMENTAL

Melting points were determined using a Koffler hot stage melting point apparatus and are uncorrected. Optical rotations were determined using a Perkin-Elmer 141 polarimeter at 21 ^{o}C +/- 2 ^{o}C. Infrared spectra were recorded on a Pye Unicam SP1000 infrared photometer using KBr discs. Nuclear magnetic resonance

spectra for protons (^{1}H nmr) and for carbon (^{13}C nmr) were recorded on a Bruker AM300 (300 MHz) spectrometer and are expressed in ppm (δ values) relative to tetramethylsilane as internal reference in deuteriochloroform ($CDCl_3$).

4,4-Dimethyl-3-phenylbutyrolactone (1b)

To 0.781 g of magnesium in 1 mL of THF and 5 mL of ether was added dropwise 2.86 mL of isopropenyl bromide in 6 mL of ether. The Grignard reaction was initiated by ultrasound.[9,16] After the Grignard reagent was completely formed, 50 mL of ether was added and the resulting solution cooled to -78 °C. A solution of N-(3-phenyl-2-propenoyl)-1-ephedrine (3a) (0.948 g, 0.321 mmol) in 8 mL of ether was added dropwise to the stirred solution. The total THF-ether ratio was 1:69. The reaction mixture was stirred under argon for 120 h, while the temperature was maintained at -60 °C. The reaction mixture was then allowed to warm up to -10 °C and 75 mL of pH 7 buffer (phosphate/NaOH) was added. The crude reaction product, obtained after the usual work-up[8] and flash chromatography[17] using ethyl acetate-hexane (1:4), gave the desired N-(4-methyl-3-phenyl-4-pentenoyl)-1-ephedrine (4a) in 81% yield as 0.875 g of a colourless oil: ^{1}H nmr ($CDCl_3$) δ 7.31-7.07 (m, 10 H, C_6H_5), 4.85 (d, 1 H, J = 12 H_z, $CHOH$), 4.70-3.84 (m, 3 H, CH_2=C, $NCHCH_3$), 2.73-2.61 (m, 1 H, $PhCHCCH_3$), 2.53 (s, 3 H, N-CH_3), 1.62 (s, 3 H, CH_3CCH_2), 1.06 (d, 3 H, J = 3 H_z, CH_3CH); ms m/z 337 (M^+).

A solution of 0.273 g (0.081 mmol) of 4a in 15 mL of ethanolic HCl was refluxed overnight. Evaporation of the solvent and recrystallization of the product from chloroform-hexane gave in 43% yield 0.066 g of pure 1a, mp: 91-93 °C (lit[12] mp: 91-92 °C); ir (KBr) 1780 (CO) cm^{-1}; ^1H nmr ($CDCl_3$) δ 7.45-7.20 (m, 5 H, $C_6\underline{H}_5$), 3.52 (t, 1 H, J = 9 H_z), $C\underline{H}CH_2CO_2$), 3.10-2.85 (m, 2 H, $C\underline{H}_2CO_2$), 1.56 (s, 3 H, $C\underline{H}_3$), 1.05 (s, 3 H, $C\underline{H}_3$); ^{13}C nmr ($CDCl_3$) δ 175.4 ($\underline{C}$=O), 136.7 (q-$\underline{C}$-Ar), 128.7 ($\underline{o}$-C-Ar), 127.8 ($\underline{m}$ and $\underline{p}$-C-Ar), 87.2 ($\underline{C}$-O), 51.2 ($\underline{C}CH_2CO$), 34.5 ($\underline{C}H_2CO$), 27.7, 23.2 ($\underline{C}H_3$, $\underline{C}H_3$); ms m/z 190 (M^+), 13), 175 (13), 162 (24), 132 (14), 131 (19), 105 (57), 104 (100), 103 (40), 91 (16), 78 (33), 77 (34), 51 (24), 43 (35), 39 (16); $[\alpha]_D^{26}$ = 78.59° ($\underline{c}$ 0.59, CH_2Cl_2) (lit.[5] $[\alpha]_D^{26}$ = -78.79°).

4,4-Dimethyl-3-(3-oxobutyl)butyrolactone (2).

The 1,4-addition adduct N-(3-isopropenyl-6-heptenoyl)-1-ephedrine (4b)[9] was prepared as described above for 4a, the important modification of our previous procedure[9] being the low THF-ether ratio.

A solution of 0.366 g (0.116 mmol) of 4b was heated to reflux in 15 mL of ethanolic HCl overnight as previously described.[9] The product obtained after evaporation of the solvent was distilled in a Kugelrohr apparatus to give in 56% yield 0.110 g of 1b[9] as a colourless liquid: $[\alpha]_D^{26}$ = -43.19° ($\underline{c}$ 0.78, $CHCl_3$) (lit.[9] $[\alpha]_D^{26}$ = -24.85°).

Palladium-catalysed oxidation of 1b as previously described[13] in 1.75 mL of DMF and 0.25 mL of water gave a crude product contaminated with DMF. Flash chromatography of the product using ethyl acetate-hexane (1:4) and bulb to bulb distillation of the purified product in a Kugelrohr apparatus gave, after recrystallization from chloroform-hexane, in 69% yield 0.825 g of 2; mp: 59-60 °C (lit.[18] mp: 63-64 °C); ir (KBr) 1775 (lactone CO), 1725 (C-O) cm^{-1}; ^1H nmr ($CDCl_3$) δ 2.67-2.57 (m, 1 H, $C\underline{H}CH_2CO_2$), 2.35-2.23 (m, 4 H, $C\underline{H}_2CO_2$ and $CH_3COC\underline{H}_2$), 2.21 (s, 3 H, $C\underline{H}_3CO$), 1.90-1.50 (m, 2 H, $CH_3COCH_2C\underline{H}_2$), 1.46 (s, 3 H, $C\underline{H}_3$), 1.28 (s, 3 H, $C\underline{H}_3$); ^{13}C nmr δ 207.2 ($CH_3\underline{C}O$), 175.1 ($\underline{C}O_2$), 86.6 ($(CH_3)_2\underline{C}O$), 45.1 ($(CH_3)_2C-\underline{C}$), 41.8 ($CH_3CO\underline{C}H_2$), 34.7 ($\underline{C}H_2CO_2$), 30.0 ($\underline{C}H_3CO$), 27.3 and 21.8 ($2\underline{C}H_3$), 23.2 ($CH_3COCH_2\underline{C}H_2$); anal. calcd for $C_{10}H_{16}O_3$: C, 65.19, H, 8.75. Found: C, 65.25, H, 9.17.

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References and Notes

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11. Amides 4a and 4b (0.1 mmol) were each dissolved in 3% HCl in water/ethanol (1:10)(15 mL) and refluxed overnight.
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