Construction of Contiguous Quaternary and Tertiary Carbon Centres *via* the Asymmetric Michael Reaction

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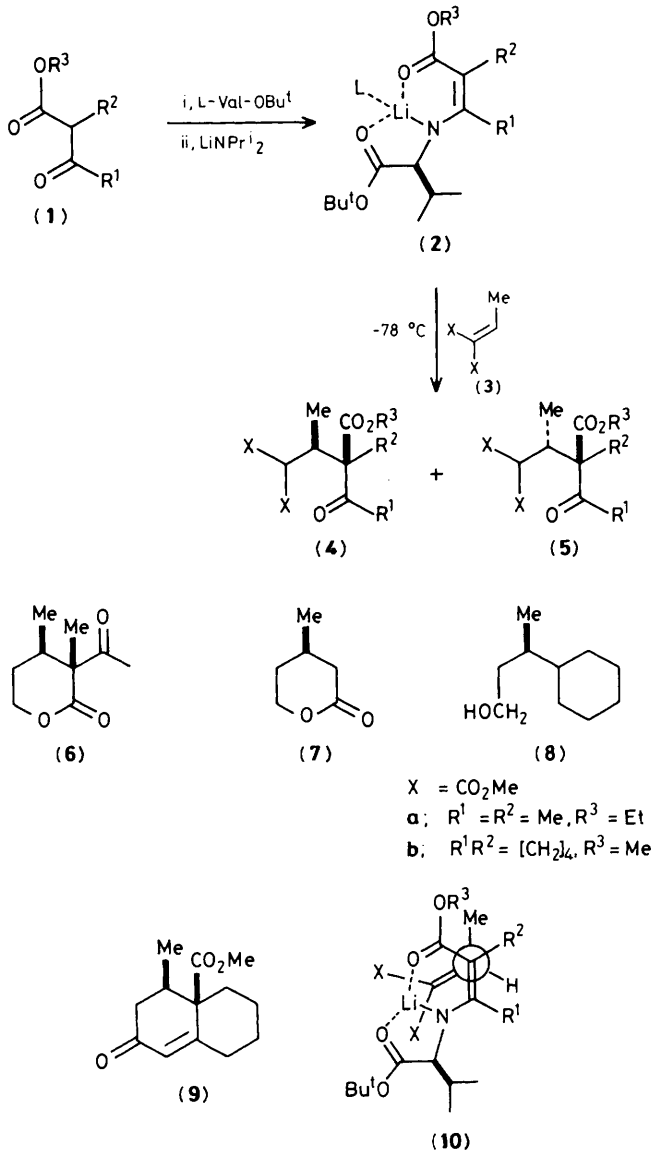
Michael reactions of chiral lithioenamines of α-alkyl β-oxo esters with methyl ethylidenemalonate afforded, after hydrolysis, adducts having contiguous quaternary and tertiary carbon centres, with nearly complete enantio- and diastereo-selectivity.

Control of absolute and relative stereochemistry in the formation of contiguous chiral carbon centres *via* Michael reactions has been of recent interest.[1] Although the Michael reaction has been shown to be effective in the stereocontrolled formation of contiguous tertiary carbon centres,[2–4] no method which creates contiguous quaternary and tertiary carbon centres with high selectivity has been developed. We now describe such a method, proceeding with high enantio-

Table 1. Representative results.

Run	(**1**)/(**2**)	Solvent	Ligand (equiv.)	Major product	$[\alpha]_D(CHCl_3)(°)$	(**4**) : (**5**)	E.e.(%)[a]	Yield (%)
1	(**2a**)	THF	None	(**4a**)	+5.89	30:1	99	54
2	(**2a**)	Toluene	None	(**4a**)	+4.96	13:1		72
3	(**2a**)	Toluene	THF(1)	(**4a**)	+5.54	43:1		79
4	(**2a**)	Toluene	$PO(NMe_2)_3$(2)	(**4a**)	+5.72	200:1	99	94
5	(**2b**)	THF	None	(**4b**)	+107	200:1	99	87
6	(**2b**)	Toluene	$PO(NMe)_3$(2)	(**4b**)	+107	200:1	99	86
7[b]	(**1a**)	Toluene	$PO(NMe)_3$(2)	(**5a**)		1:3		49
8[c]	(**1a**)	EtOH	None	(**4a**) + (**5a**)		1:1		45
9[c]	(**1b**)	EtOH	None	(**4b**)		4:1		76

[a] Enantiomeric excess. [b] $LiNPr^i_2$ used as base; reaction temperature −20 °C. [c] K_2CO_3 used as base; reaction temperature 25 °C. [b c] Products were racemic.



(1) (2) (3) (4) (5) (6) (7) (8) (9) (10)

and diastereo-selectivity, involving the use of chiral enamines of α-alkyl β-oxo esters as Michael donors.[5]

The reaction of the lithioenamine (**2a**) prepared from the oxo ester (**1a**) and L-valine t-butyl ester,[5] with methyl ethylidenemalonate (**3**) in the presence of hexamethylphosphoramide (2 equiv.) in toluene at −78 °C proceeded smoothly to afford, after hydrolysis, the adduct (**4a**) as sole product (run 4).† Representative results are summarized in Table 1. The stereochemistry of (**4a**) was determined by conversion into the lactone (**6**) [i, $(HOCH_2)_2$, *p*-$MeC_6H_4SO_3H/C_6H_6$, 73%; ii, NaCN/Me_2SO, 73%; iii, KOH/aq. EtOH; iv, $ClCO_2Et$/THF (tetrahydrofuran), then $NaBH_4$, 66%; v, KH/THF, 87%; vi, *p*-$MeC_6H_4SO_3H/Me_2CO$, 66%], identical with the compound prepared from (*R*)-(**7**)[6] (i, $LiNPr^i_2$/MeI/$PO(NMe_2)_3$/THF, 70%; ii, $LiNPr^i_2$/AcCN/$PO(NMe_2)_3$/THF, 62%). The enantio- and diastereoiso-meric purities were also determined by ^1H n.m.r. in the presence and in the absence of the shift reagent Eu(hfc)$_3$.‡ The reaction of the cyclic enamine (**2b**) with (**3**) also afforded enantio- and diastereoiso-merically pure product (**4b**) (runs 5 and 6). The absolute stereochemistry was determined by conversion into (*R*)-(**8**)[7] [i, aq. HCl/AcOH; ii, CH_2N_2, 43%; iii, $(HSCH_2)_2$, BF_3OEt_2/CH_2Cl_2, 84%; iv, $LiAlH_4$/THF, 91%; v, Raney Ni/EtOH, 41%]. The relative stereochemistry of (**4b**) was determined by correlation with the known compound (**9**)[8] [from (±)-(**4b**; X = CO_2Bu^t):§ i, CF_3CO_2H, then heat, 89%; ii, AcCl/Ac_2O; iii, MeLi/THF; iv, *p*-$MeC_6H_4SO_3H/C_6H_6$, 20%].

The stereochemical outcome of the reaction of the α-alkyl β-oxo esters (**1a** and **b**) with (**3**) is of interest. As shown in Table 1 (runs 7—9), poor diastereoselectivity was obtained, demonstrating the advantage of the lithioenamine reaction in terms of both enantio- and diastereo-selectivity.

The high enantio- and diastereo-selectivity exhibited by the lithioenamine reaction may be attributed to the properties of the intermediate structure (**10**); the reagent (**3**) will attack the chiral lithioenamine (**2**) from the α-face as a result of initial co-ordination of the carbonyl oxygen of (**3**) to the lithium cation of (**2**), placing the methyl substituent in the less sterically demanding region.

Since the chiral lithioenamines (**2**) are readily available, the present procedure may provide a simple and practical approach to the construction of contiguous quaternary and tertiary carbon centres.¶

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† All new compounds described here provided satisfactory analytical and spectroscopic data.

‡ Two separate peaks for the quaternary methyl group appeared in the presence of the chiral shift reagent.

§ The diastereoisomerically pure (±)-(**4b**) (X = CO_2Bu^t), prepared by the reaction of (**1b**) and (**3**; X = CO_2Bu^t) followed by recrystallization, was converted into (**4b**; X = CO_2Me) (CF_3CO_2H, then CH_2N_2; 91%).

¶ Typical experimental procedure (run 4 of Table 1). To a cooled (−78 °C) solution of lithium di-isopropylamide (13 mmol) in toluene (30 ml) was added a solution of (**2a**) (13 mmol) in toluene (20 ml). After stirring for 1 h at −78 °C, hexamethylphosphoramide (26 mmol) was added. After stirring for another 1 h, the malonate (**3**; X = CO_2Me) (10 mmol) in toluene (20 ml) was added and the whole was stirred for 1.5 h. After the addition of aq. 20% HCl (100 ml), the mixture was stirred for 4 h at room temperature. Extractive work-up followed by silica gel column chromatography [hexane–ethyl acetate (10 : 1)] afforded (**4a**) (94%).