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Stereocontrolled Functionalization in Acyclic Systems by Exploiting Internal 1,2-Asymmetric Induction – Generation of Polypropionate and Related Motifs

Stephen Hanessian,* Yonghua Gai and Wengui Wang

Department of Chemistry, Université de Montréal, C.P. 6128, Succ. Centre-ville, Montreal, QC, Canada, H3C 3J7

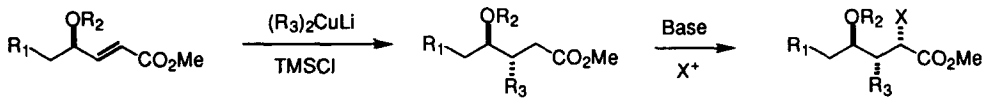
Abstract: Conjugate organocuprate additions to α,β-unsaturated esters that have a γ-ether substitutent take place with high *anti*-selectivity. Potassium ester enolates can react with electrophiles to give the corresponding α-hydroxy α-alkyl, and α-azido esters with an overall *anti/syn* orientation of three vicinal groups relative to the initial resident chiral center.

The stereocontrolled introduction of vicinal functional groups in acyclic carbon chains presents a major challenge in the realm of natural product synthesis,[1] as well as in unnatural molecules with therapeutic potential.[2] Subunits harboring vicinal, alternating, and remotely situated functional groups such as hydroxy, alkyl, amino, etc. are common targets for synthesis. Moreover the introduction of functional diversity in acyclic or cyclic scaffolds is also of great interest in the general area of combinatorial approaches to drug discovery and lead optimization.[3]

The polypropionate biosynthetic subunit is prevalent in a multitude of natural products, and the advent of asymmetric processes has greatly advanced our capabilities in generating hydroxy-methyl-hydroxy triad units.[4] The majority of these methods rely on elegantly conceived elements of stereocontrol based on the use of chiral auxiliaries, chiral catalysts, on the manipulation of cyclic chiral templates, or other methods.[5]

We have previously reported that the addition of lithium dimethylcuprate to acyclic α,β-unsaturated esters that contain a γ-alkoxy substituent (ex. BOM, MOM, etc.) on a stereogenic center led to a high preponderance of the *anti*-orientated C-methyl product (internal 1,2-asymmetric induction).[6] Plausible mechanistic rationales were proposed by us and other groups[7] to explain the stereochemical outcome of these conjugate addition reactions (Scheme 1).

Scheme 1



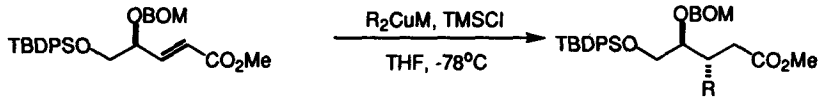
R_1 = alkoxy, alkyl, aryl
R_2 = BOM, MOM, MTM, etc.

anti- product
1,2-induction

R_3 = Me
X = OH, alkyl, etc.

In this paper we describe the extension of these reactions to other organoalkyl groups, and we offer a general approach to the generation of a polypropionate-derived triad unit in acyclic systems. Table 1 shows the results of conjugate addition with a readily available α,β-unsaturated ester.[6] Preparatively good to excellent yields of the corresponding ethyl, butyl, vinyl, and 2-propenyl adducts were obtained as virtually single isomers after chromatography.[8,9] Stereochemical proof was provided by chemical correlation to the corresponding 3-substituted lactones which were prepared by known procedures.[10]

Table 1



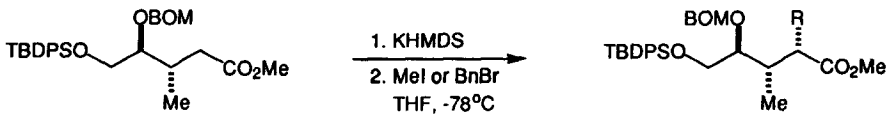
Entry	R	M [a]	Yield [b]	Anti/Syn [c]	$[\alpha]_D$ [d]
1	Methyl	Li	93%	>50:1	-21.7
2	Ethyl	MgBr	73%	>50:1	-21.1
3	Butyl	Li	90%	>50:1	-22.0
4	Vinyl	MgBr	70%	>12:1	-19.5
5	2-Propenyl	Li	60%	> 8:1	-17.1

a. From commercially available reagent; for experimental conditions, see ref. 6; b. Yield of isolated product after flash chromatography; c. Ratio determined by ^{1}H-NMR of crude product before chromatography; d. Optical rotation was measured at 25°C in $CHCl_3$ in degrees.

While the alkyl ether nature of the γ-substituent was required for high selectivity in the conjugate additions, the R_1 substituent in the δ-position allowed greater flexibility (Scheme 1). Thus, alkyl and aryl groups[11] were tolerated without affecting the stereoselectivity of the additions (see below).

Having demonstrated the generality of 1,2-induction in the γ-substituted α,β-unsaturated ester motif shown in Table 1, we explored the prospects of electrophilic additions of the corresponding enolates (Scheme 1). Treatment of the adduct from lithium dimethylcuprate with KHMDS and methyl iodide or benzyl bromide gave excellent yields of the 2*S*, 3*S*-dimethyl, and 2*S*-benzyl-3*S*-methyl substituted analogs essentially as single products (Table 2). The *syn*-relationship of the 2,3-alkyl groups was established by cyclization to the corresponding butyrolactone derivatives and correlation with authentic samples.[12] This method provides an expedient route to enantiomerically pure acyclic compounds that contain vicinal *syn*-related alkyl substituents.[13]

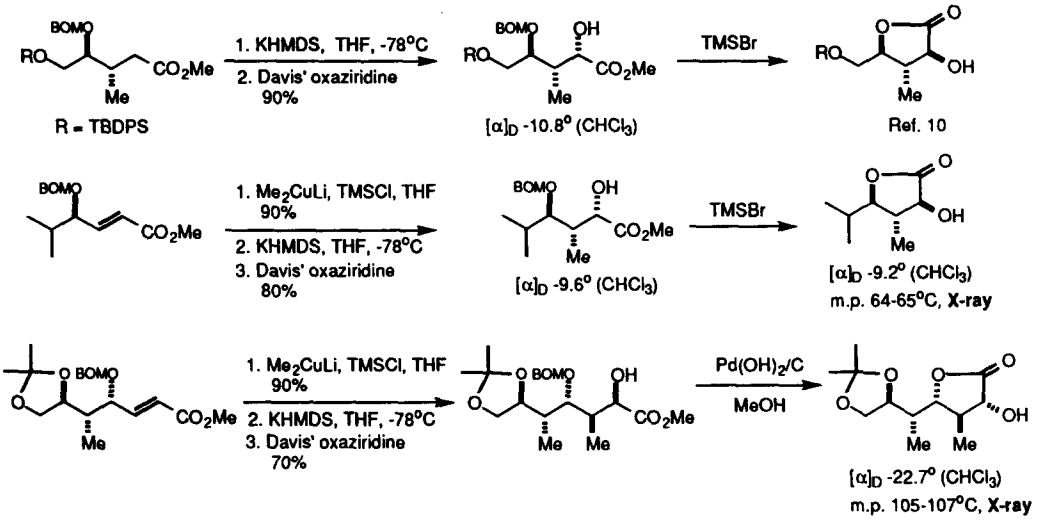
Scheme 2



R= Me, 95%, syn/anti> 20:1
R= Bn, 91%, syn/anti >20:1

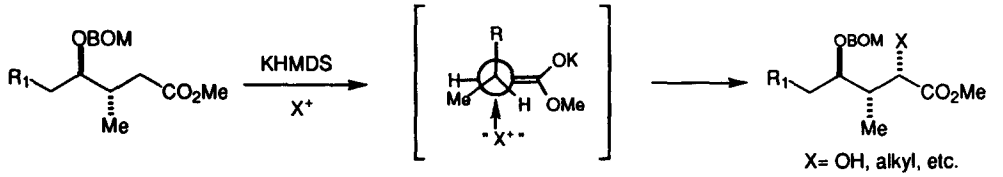
For the purposes of generating a propionate biosynthetic triad, we next studied the hydroxylation of enolates (Scheme 3). The combination of KHMDS and the Davis oxaziridine reagent[14] proved to be optimal for providing enantiomerically pure products after chromatography. In each instance, and regardless of the nature or size of the γ-substituent on the chain, hydroxylation took place to give *syn*-selectivity vis-a-vis the C-3 methyl group. The level of 1,2-*syn* induction was dependent on the size of the C-3 alkyl group, since hydroxylation of the enolates derived from the ethyl, vinyl and 2-propenyl esters (Table 1, entries, 2, 4, 5) were less selective ~70-80% yield, 80:20 *syn/anti*). It is of interest that hydroxylation of the enolate of 3*R*-ethyl-5*S*-(tert-butyldiphenylsiloxy)-4-H-furanone, led to a 1:1 mixture of α-hydroxylactones, possibly because of the presence of sterically compromising groups near either face of the enolate. Thus, acyclic stereocontrol as illustrated in this Letter wins over analogous reactions in cyclic counterparts.

Scheme 3



The hydroxylation of β-alkyl substituted enolate esters has a precedent in the work of Morizawa[15] who showed that *syn*-selectivity was prevalent with racemic 3-trifluoromethyl butyrate with the Davis reagent as well as with the Vedejs-Mimoun MoOPh reagent.[16] A plausible mechanistic rationale[15] is presented in Figure 1, which is also applicable to other electrophiles.

Figure 1



In conclusion, we have reported versatile methods for the synthesis of enantiomerically pure (or highly enriched) five carbon (and higher) acyclic ester motifs that harbor three or more contiguous substituents consisting of combinations of alkyl and hydroxy groups, starting from a single resident ether substituent of

defined stereogenicity.[17] These patterns of substitution are otherwise difficult to obtain, particularly from acyclic precursors and the methodology described here should find numerous applications in the synthesis of functionally diverse, enantiopure molecules.

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