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Stereoselective Alkylation of Methyl (2-tributylstannyl)tetrahydrofuran-3-ylcarboxylate Lithium Enolate:- Access to 2,3,3-Trisubstituted Tetrahydrofurans.

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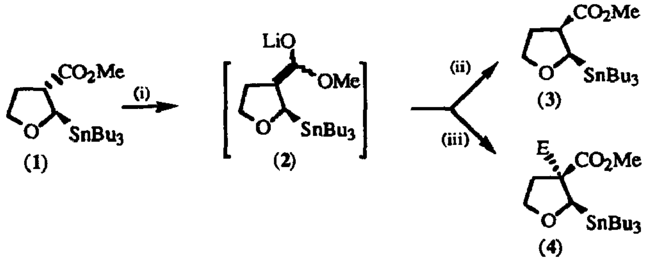
Abstract: *A stereoselective synthesis of 2,3,3 -trifunctionalised tetrahydrofurans is described.*

We have recently shown[1] that deprotonation of the *trans*-ester (1) under conditions of kinetic control (LDA, 1.1 eq.; THF; -78 °C; 30 mins.) generates the stable enolate (2) which upon reprotonation (NH_4Cl; -78 °C) affords the *cis*-ester (3) in good overall yield (66%), **Scheme 1**. We now wish to report that alkylation of the enolate (2) with a variety of alkylating agents (E^+) proceeds rapidly at -78 °C in THF affording the alkylated tetrahydrofurans (4) in generally high yields (**Table**).

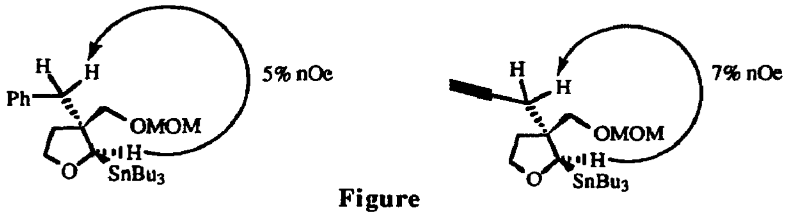


Reagents and conditions:- (i) LDA, 1.1 eq.; THF; -78°C; (ii) NH_4Cl; -78°C 66%; (iii) E^+; THF; -78°C.

Scheme 1

An examination of the high field ^1H and ^{13}C nmr spectra of the crude reaction products suggests that alkylation occurs with very high levels of 1,2-asymmetric induction (d.s. > 99:1). As expected, alkylation takes place *anti*- to the relatively bulky tin-residue, as confirmed by a series of nOe difference experiments on a series of MOM-derivatives, **Figure**. In the case of the alkylation ractions of (2) with MOM-Cl and Davis oxaziridine, (**Table**, entries 5 and 6), functionalisation proceded in lower yields, although we have made no attempts to optimize these reactions. Surprisingly, the β-hydroxy stannane (**10**) appears to be stable towards silica gel chromatography.

The stereoselective alkylation of the enolate (2) in combination with the stereospecific functionalisation of the C-Sn bond in related substrates[1] can be put to good effect in a highly efficient synthesis of 2,3,3-trisubstituted tetrahydrofurans as illustrated below (**Scheme 2**).



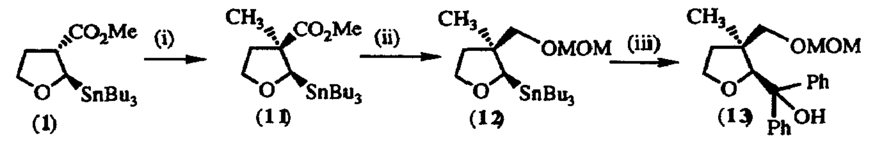
Figure

Table

Entry	Electrophile, E+	(Product)/Yield (%)§
1	C_3H_5Br	(5); 78
2	$PhCH_2Br$	(6); 80
3	C_3H_3Br	(7); 76
4	$CH_3.CO.CH_3$	(8); 83
5	$MeOCH_2Cl$	(9); 45 (+ 12% (3))
6	[O]¶	(10); 34

§ Characterised by ^{1}H nmr; ir; high resolution mass spectrometry and/or combustion microanalysis; ¶ [O] = Davis oxaziridine

Generation of the enolate (2) under standard conditions followed by reaction with methyl iodide (1 eq.; -78 °C) afforded the stannane (11) as the only detectable product. Conversion of the ester (11) into the MOM-ether (12) (97% overall yield) and subsequent transmetallation at -78 °C followed by alkylation with benzophenone (THF; -20 °C) afforded the carbinol (13) in excellent yield (90%), with overall retention of configuration at C_2. The relative stereochemistry between C_2 and C_3 proved difficult to establish on the basis of nOe studies and was finally confirmed upon the basis of a single crystal X-ray structure determination[2].



Reagents and conditions:- (i) a. LDA, 1.1 eq.; THF; -78°C; b. MeI; -78°C; 81% (ii) a. Dibal-H, 2 eq.; 0°C; b. MOM-Cl, 1.1 eq.; Hunig's base; 97%; (iii) a.^{n}BuLi, 1.1 eq.; THF; -78°C; b. Ph_2CO, 1.1 eq.; -20°C; 90%.

Scheme 2

In conclusion we have demonstrated that the ester (1) has the chemical equivalence of the homoenolate di-anion[3] (14). Synthetic applications of this synthon are under investigation and will be reported elsewhere.

Acknowledgements

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References and notes

1. Zhao, Y.; Beddoes, R. L.; Quayle, P. *Tetrahedron Letters*, **1994**, *35*, 0000; preceding paper.
2. Zhao, Y.; Beddoes, R. L.; Quayle, P.; unpublished observations.
3. For related intermediates see Nakahira, H.; Ryu, I.; Ikebe, M.; Kambe, N.; Sonoda, N. *Angew. Chem., Int. Ed. Engl.*, **1991**, *30*, 177.

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