New method for the synthesis of α-substituted tetrahydrofuran-2-methanols through diastereoselective addition of THF to aldehydes mediated by Et_3B in the presence of air

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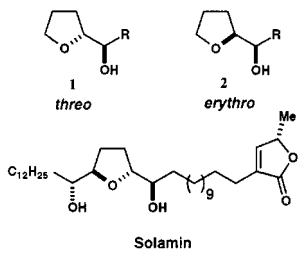
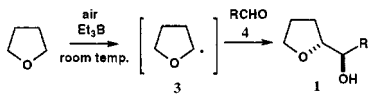
The tetrahydrofuranyl radical, generated from THF with Et_3B in the presence of air, was found to react with aldehydes *threo*-selectively to afford α-substituted tetrahydrofuran-2-methanols, the common structural motifs of biologically active acetogenin polyketides, in moderate yields.

α-Substituted tetrahydrofuran-2-methanols **1** and **2** are common structural units present in acetogenins that possess important biological properties, such as antineoplastic and immunosuppressive activity.[1] Numerous attempts have thus been made to



elaborate these structural units,[2–4] but the direct addition of tetrahydrofuranyl synthons to aldehydes is a rare case of a carbon–carbon bond-forming reaction in the convergent synthesis of acetogenins.[5,6] The authors have accordingly established a new method for the stereoselective synthesis of **1** through the addition of tetrahydrofuranyl radical **3** generated from THF with Et_3B in the presence of air[7] to aldehydes **4**, thereby facilitating the construction of core structural motifs of acetogenins (Scheme 1). To the best of our knowledge, the



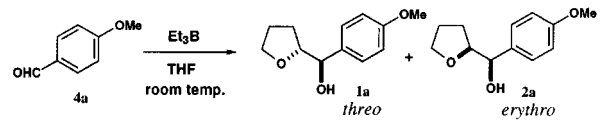
Scheme 1

radical addition of THF to aldehydes to give *threo*-α-substituted tetrahydrofuran-2-methanols **1** stereoselectively is presented in this paper for the first time.[8]

The results of the addition of THF to 4-methoxybenzaldehyde **4a**, mediated by Et_3B either in the presence or absence of air at room temperature, are listed in Table 1.†‡

The radical reaction in the presence of air, which is necessary for radical initiation,[7,9] proceeded *threo*-selectively (*ca.* 90 : 10) to afford alcohols (**1a** and **2a**) along with unchanged aldehyde **4a**. It should be emphasized that the continuous admission of air greatly enhanced the efficiency of the reaction. The chemical yield was also increased by additional amounts of reagents, but it was not significantly improved by prolonged reaction time. Its

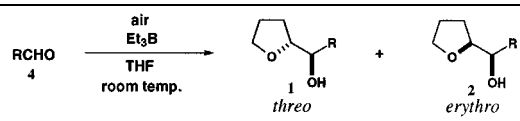
Table 1 Radical reaction of THF with 4-methoxybenzaldehyde **4a**[a]



	Reagents/equiv.				
Entry	Et_3B	THF	*t*/h	Yield (%)[f]	**1a**:**2a**[g]
1[b]	3	31	12	42 (37)	91:9
2[b]	3	31	36	44 (38)	90:10
3[c]	3	31	12	4 (81)	88:12
4[bd]	1	10	12	11 (70)	90:10
5[be]	3	31	12	1 (99)	93:7

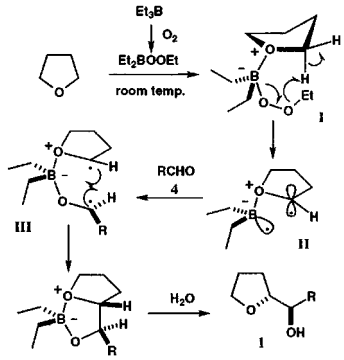
[a] Unless otherwise stated, aldehyde (1.0 mmol) and 1.0 M THF solution of Et_3B (3.0 ml) were used. [b] Air was introduced through a syringe needle with a balloon (*ca.* 10–20 ml h^{-1}). [c] The reaction was carried out under argon. [d] Aldehyde (1.0 mmol) and 1.0 M THF solution of Et_3B (1.0 ml) were used [e] Galvinoxyl (0.3 equiv.) added. [f] Isolated yields: yields of recovered aldehyde **4a** are given in parentheses. [g] Ratio determined from the ^1H NMR spectrum of the diastereomeric mixture.

Table 2 Radical reaction of THF with aldehydes **4**[a]



	Reagents/equiv.						
Entry	Et_3B	THF	*t*/h	**4**	R	Yield (%)[b]	**1**:**2**[c]
1	3	31	12	**4a**	4-$MeOC_6H_4$	42 (37)	91:9
2	3	31	17	**4b**	1,3-benzodioxol-5-yl	47 (38)	89:11
3	3	31	12	**4c**	Ph	44 (21)	85:15
4	3	31	12	**4d**	2-BrC_6H_4	45 (20)	71:29
5	3	31	12	**4e**	$C_{12}H_{25}$	37 (—)[d]	62:38
6	3	31	12	**4f**	c-C_6H_{11}	32 (—)[d]	54:46[e]

[a] Aldehydes (1.0 mmol) and 1.0 M THF solution of Et_3B (3.0 ml) were used. Air was introduced through a syringe needle with a balloon (*ca.* 10–20 ml h^{-1}). [b] Isolated yields: yields of recovered aldehydes **4** are given in parentheses. [c] Ratio determined from the ^1H NMR spectrum of the diastereomeric mixture or based on isolated yields of the corresponding acetates derived from the crude products. [d] Unreacted aldehyde **4** was not recovered. [e] Stereochemistry of the major isomer yet to be determined.



Scheme 2

inhibition by radical inhibitors such as galvinoxyl[10] clearly indicated that the reaction proceeds *via* a radical mechanism (entry 5 in Table 1). The radical reaction was also applied to representative aldehydes **4b**–**f**.

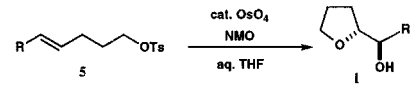
Table 2 demonstrates the general applicability of the present method to various aldehydes, though in only moderate yields.[11] The *threo*-selectivity of the addition was generally high for aromatic aldehydes, and low to moderate in the cases of aliphatic and *ortho*-substituted aromatic aldehydes (entries 4, 5 and 6 in Table 2).§ The reasons for the stereochemical outcome remain unclear but a transition state (**III**) in which boron atoms tether radical **3** to aldehydes **4** may be reasonably assumed (Scheme 2).[12]

In summary, a new method has been established for the stereoselective synthesis of *threo*-α-substituted tetrahydrofuran-2-methanols **1** by addition of tetrahydrofuranyl radical **3**, generated from THF with Et_3B in the presence of air, to aldehydes **4**. This method is quite easy to conduct and readily provides access to common structural motifs of biologically important acetogenins. It may thus be considered a superior means for the synthesis of these natural products. The mechanism of the reaction and potential applications to total synthesis of acetogenins are presently under investigation.

Notes and references

† Representative procedure: To 4-methoxybenzaldehyde **4a** (136 mg, 1.0 mmol) was added 1.0 M Et_3B in THF (3.0 ml, 3.0 mmol) at room temperature. The mixture was stirred at the same temperature with continuous bubbling of air through a syringe needle with a balloon (flow rate; 10–20 ml h^{-1}) for 12 h. The mixture was treated with AcOH and then extracted with CH_2Cl_2, and washed with sat. $NaHCO_3$. The organics were dried over $MgSO_4$. Following solvent evaporation, the residue was purified by column chromatography on silica gel (EtOAc–hexane 1:2) to afford a colorless solid consisting of α-(4-methoxyphenyl)tetrahydrofuran-2-methanols (88 mg, 42%) as a diastereomixture (**1a**:**2a** = 91:9) and unreacted aldehyde **4a** (51 mg, 37%).

‡ The relative configuration of the major adducts **1** was unambiguously determined by comparison of ^{1}H NMR spectral data with those of authentic *threo*-alcohols prepared by dihydroxylation of (*E*)-allyl tosylate **5**.



§ Satisfactory analytical (high-resolution mass) and spectral (IR, ^{1}H NMR, and MS) data were obtained for new compounds.

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