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Synthesis of optically pure 2,3,4-trisubstituted tetrahydrofurans via a two-step sequential Michael-Evans aldol cyclization strategy: total synthesis of (+)-magnolone

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ABSTRACT

Synthesis of optically pure 2,3,4-trisubstituted tetrahydrofurans is described employing a two-step Michael-Evans aldol cyclization strategy. The approach is successfully applied for the total synthesis of furano lignan natural product (+)-magnolone.

Devising newer protocols for synthesizing substituted tetrahydrofurans, in general, has been the focus of synthetic organic chemists for some time owing to the presence of this core unit in many natural products[1] possessing diverse array of biological activities.[2] In particular, construction of stereo-defined optically pure 2,3,4-trisubstituted tetrahydrofurans, representing core structure of furano lignan class of natural products,[3] has been an attractive target. It has generally been noticed that the natural products belonging to this class display '2,3-*trans*,3,4-*trans*' stereochemistry[4] (e.g., sesaminone **1**, magnolone **2**) however, other stereochemical arrangements such as '2,3-*cis*,3,4-*trans*'[5] (e.g., sylvone **3**) and '2,3-*trans*, 3,4-*cis*' (e.g., 2,6-diaryl, 3,7-dioxabicyclo [3,3,0] octane lignans or furofuran lignans **4**)[6] are also known (Fig. 1).

Recent review by Wolfe et al.[7] broadly covers most of the transformations related to the synthesis of tetrahydrofurans in optically pure form, however, very few methods are known which could directly be used for the total synthesis of tetrahydrofuran lignans. It appears that there are only two suitable methods to synthesize furano lignans which involve either the Lewis acid-mediated coupling of cyclic allyl siloxanes with aldehydes[8] or [1,3]-rearrangement of 1,3-dioxepins.[9] Therefore, developing a simple, efficient and stereo-divergent protocol to access 2,3,4-trisubstituted tetrahydrofurans, applicable for the synthesis of furano lignan natural products appears to be demanding.

In this context, we envisioned that the conjugate addition to **5** followed by aldol and intramolecular cyclization sequence, as shown in Scheme 1, may lead to stereoselective construction of trisubstituted tetrahydrofuran skeleton efficiently. Furthermore, this strategy was envisaged to be attractive as the desired stereochemistry at various centres of tetrahydrofuran could easily be tuned at will. For illustration, the stereochemistry of R group at C-4 will de-

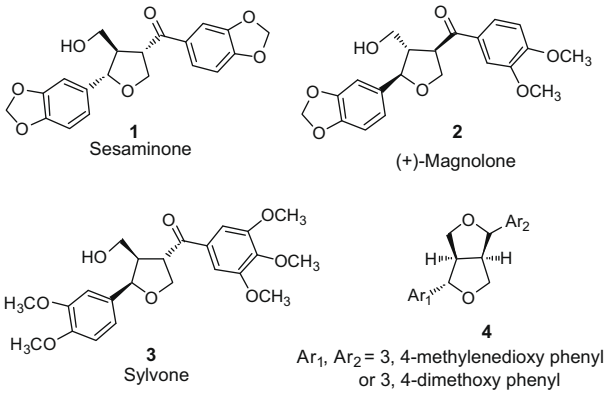

Figure 1. Structures of furo and furofuran lignans.

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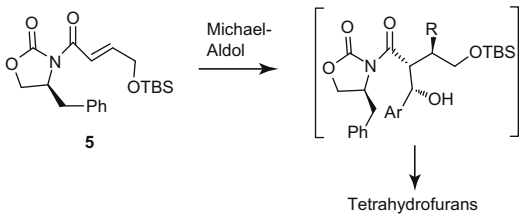


Scheme 1. Synthetic strategy for substituted tetrahydrofurans.

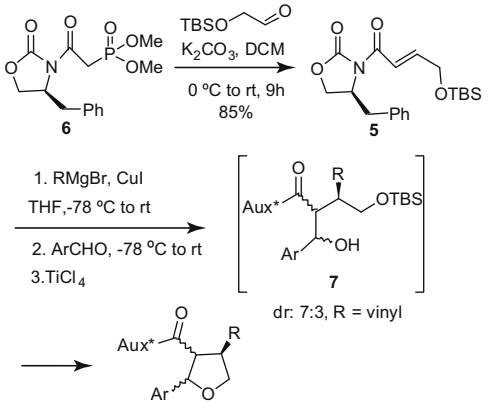
pend upon the Evans chiral auxiliary whereas the stereochemistry at C-2 and C-3 centres of THF ring could easily be controlled employing either Evans *syn*- or *anti*-aldol reaction protocols.[10]

In this Letter, we disclose our preliminary and successful results of a two-step strategy to construct stereo-defined 2,3,4-trisubstituted tetrahydrofurans employing Michael-Evans aldol cyclization sequence.

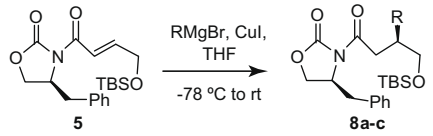
We initiated the proposed synthesis of 2,3,4-trisubstituted tetrahydrofurans by carrying out first one-pot Michael-aldol-cyclization sequence starting from **5** (Scheme 2). Compound **5** was easily prepared in 85% yield by Horner–Wadsworth–Emmons reaction[11] of phosphonate[12] **6** with 2-(*tert*-butyldimethylsiloxy) acetaldehyde[13] in the presence of K_2CO_3. Compound **5** upon treatment with a solution of alkyl magnesium bromide (1.2 equiv) and CuI (1.5 equiv) in THF (−78 °C to rt) followed by sequential addition of *p*-anisaldehyde (1.2 equiv) and $TiCl_4$ (2 equiv) at −78 °C gave corresponding inseparable mixture of diastereomeric tetrahydrofurans.

This observation led us to examine the diastereomeric purity of the Michael-aldol reaction product **7**, which was found to be a mixture (*dr* 7:3, determined by ^{1}H NMR). Therefore, we decided to adopt two-step protocol from **5** to obtain substituted THFs. Michael addition (Scheme 3) of various organocuprates (prepared by mixing corresponding Grignard reagent (1.2 equiv) and dry CuI (1.5 equiv) in THF at −78 °C) to **5** gave corresponding conjugate adducts **8a–c** with very high diastereomeric purity[14,15] (see Scheme 3), determined by HPLC (mobile phase: MeOH/H_2O (90:10), flow rate: 1.0/min, column: Grace Denali RP-18 (250 × 4.6 mm)) analysis. Pure diastereomers were easily separated by column chromatography (Silica Gel 100–200, eluent: ethyl acetate/pet ether (5:95)).

Reaction of diastereomerically pure **8c** with $TiCl_4$ (2.5 equiv), DIPEA (3 equiv) and *p*-anisaldehyde (1.2 equiv) in DCM at −78 °C (Evans *syn*-aldol reaction condition) (Scheme 4) followed by usual work-up and purification gave, to our delight, diastereomerically pure 2,3-*trans*, 3,4-*trans* trisubstituted tetrahydrofuran **9c** in 67% yield.[16]

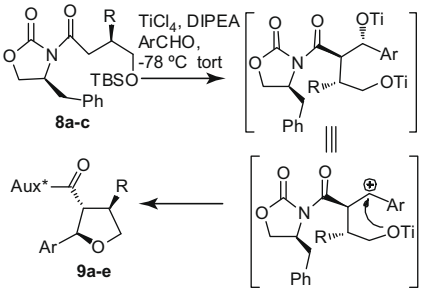


Scheme 2. Initial strategy for tetrahydrofurans.



8	R	Yield (%)	*dr*
a	Me	90	98:2
b	Vinyl	95	>99:1
c	Prop-1-enyl	88	97:3

Scheme 3. Michael addition reaction on **5**.



	R	ArCHO	9	Yield(%)
8a	Me	*p*-anisaldehyde	a	72
8b	Vinyl	*p*-anisaldehyde	b	80
8c	Prop-1-enyl	*p*-anisaldehyde	c	67
8b	Vinyl	piperonal	d	82
8c	Prop-1-enyl	piperonal	e	78

Scheme 4. Synthesis of tetrahydrofurans using Evans *syn*-aldol reaction.

The relative stereochemistry of the substituents in **9c** was assigned by detailed 2D NMR spectroscopy (COSY and NOESY) and finally confirmed by single crystal X-ray analysis (Fig. 2).[17] The inverted stereochemistry at C-2 benzylic carbon suggests that tetrahydrofuran ring formation involved thermodynamically favoured intramolecular S_N1 type nucleophilic substitution at benzylic position. In order to study the generality of this reaction, various reactions combining different aldehydes and conjugate adducts (**8a–c**) were carried out and the results are presented in Scheme 4.

With these successful results, we decided to apply this protocol for the total synthesis of tetrahydrofuran lignan natural product (+)-magnolone[18] (**2**). Compound **2** is a trisubstituted 7′-oxo tetrahydrofuran lignan isolated from the leaves of *magnolia coco*. and has been used in the treatment of impaired liver function and cancer.

Yamauchi and Nakato[19] have synthesized this molecule employing *erythro* selective aldol condensation followed by a stereoselective intramolecular S_N1 cyclization in the presence of acid catalyst starting from (*S*)-benzyl-3-pent-4-enoyloxazolidin-2-one, and also assigned the absolute configuration as (7*S*,8*R*,8'*S*).

We began the synthesis of **2** starting from tetrahydrofuran derivative **9d**. $LiBH_4$ reduction of **9d** in THF at 0 °C followed by protection of primary alcohol moiety as –OTBS provided **10** in 98% yield. Dihydroxylation of **10** using OsO_4 (cat.), trimethyl amine N-oxide (TMO, 1.2 equiv), in THF/*t*-BuOH/H_2O (2:4:1) gave corresponding diol which on cleavage using $NaIO_4$ (1.2 equiv) in THF/H_2O (2:1) provided corresponding aldehyde **11** in 90% yield. Reaction of **11** with 4-lithio-1,2-dimethoxy benzene (1.2 equiv) in THF

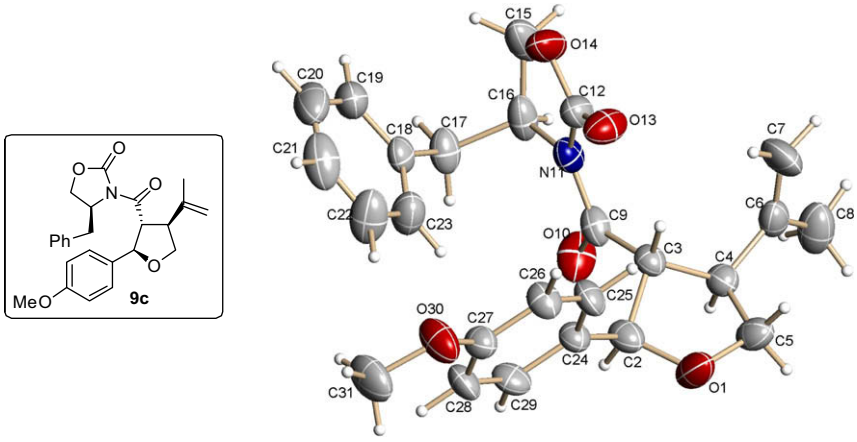
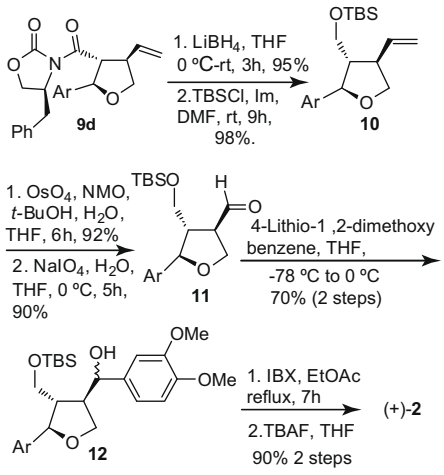


Figure 2. ORTEP diagram of **9c**. Ellipsoids are drawn at 40% probability.



Scheme 5. Total synthesis of (+)-magnolone.

at −78 °C gave **12** in 70% yield. Oxidation of **12** using IBX (2 equiv) in refluxing ethyl acetate followed by TBS deprotection (TBAF, 1.2 equiv/THF) gave **2** in 44% overall yield starting from **9d**. The spectral data of **2** ($[\alpha]_D^{29.4}$ +23.5 (*c* 0.15, $CHCl_3$), Lit.[18] $[\alpha]_D^{20}$ +31 (*c* 0.2, $CHCl_3$)) were found to be in excellent agreement with those of literature values reported for (+)-magnolone (Scheme 5).

In conclusion, we have developed a concise and stereo-divergent method for the synthesis of optically pure 2,3,4-trisubstituted tetrahydrofurans. The significance of this strategy is successfully demonstrated by applying for the total synthesis of furo lignan (+)-magnolone. Total synthesis of other similar furo lignans is in progress.

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15. Data for conjugate adduct **8c**: thick colourless liquid. $[\alpha]_D^{27.4}$ +30.26 (*c* 1.0, $CHCl_3$). IR (neat) ν_{max}; 3027, 2955, 2857, 1783, 1702, 1647, 1604, 1497, 1471, 1387, 1353, 1256, 1216, 1100, 1005, 938, 895, 837, 758, 701, 666 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) 7.17–7.36 (m, 5H), 4.71–4.86 (m, 2H), 4.59–4.71 (m, 1H), 4.14–4.17 (m, 2H), 3.68 (dd, *J* = 5.44, 9.73 Hz, 1H), 3.52 (dd, *J* = 7.33, 9.73 Hz, 1H), 3.30 (dd, *J* = 2.91, 13.14 Hz, 1H), 3.14–3.18 (m, 2H), 2.80–2.88 (m, 1H), 2.70 (dd, *J* = 9.86, 13.52 Hz, 1H), 1.79 (s, 3H), 0.89 (s, 9H), 0.05 (s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$), 172.3, 153.4, 145.4, 135.2, 129.4, 128.8, 127.2, 111.6, 65.9, 65.4, 55.1, 44.8, 37.8, 36.0, 25.8, 21.6, 18.2, −5.4. Mass (ESI-MS); *m*/*z* 440.62 $(M+Na)^+$. Anal. Calcd for $C_{23}H_{35}NO_4Si$: C, 66.15; H, 8.45; N, 3.35; O, 15.32; Si, 6.73. Found: C, 66.11; H, 8.40; N, 3.25.
16. *General procedure for the Evans syn-aldol cyclization reaction*: To a solution of conjugate adduct (e.g., **8c**) (2.50 mmol) in dry DCM (15 mL) at −78 °C was added dropwise $TiCl_4$ (6.30 mmol), followed by DIPEA (7.50 mmol). The mixture was allowed to stir at this temperature for 30 min. Aldehyde (3.0 mmol) in DCM (8 mL) was added dropwise at −78 °C and the mixture slowly warmed up to rt. The reaction was quenched with aqueous solution of NH_4Cl. DCM layer separated, aqueous layer was extracted with DCM (2 × 10 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The resultant residue was purified by column chromatography to obtain substituted tetrahydrofurans (e.g., **9c**) in good yields.
Data for substituted tetrahydrofurans **9c**: mp 121–123 °C. $[\alpha]_D^{26.5}$ −25.28 (*c* 1.0, $CHCl_3$). IR (neat) ν_{max}; 3019, 2920, 2401, 1783, 1689, 1613, 1516, 1382, 1386, 1215, 1030, 928, 757, 668 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) 7.35 (d, *J* = 8.53 Hz, 2H), 7.21–7.25 (m, 3H), 6.99–7.02 (m, 2H), 6.88 (d, *J* = 8.78 Hz, 2H), 5.06 (d, *J* = 9.03 Hz, 1H), 4.78–4.85 (m, 3H), 4.63–4.69 (m, 1H), 4.25 (t, *J* = 8.79 Hz, 1H), 4.00–4.09 (m, 3H), 3.80 (s, 3H), 3.54 (dd, *J* = 9.04, 16.82 Hz, 1H), 3.11 (dd, *J* = 3.27, 13.56 Hz, 1H), 2.53 (dd, *J* = 9.29, 13.30 Hz, 1H), 1.82 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$), 172.8, 159.7, 152.5, 142.9, 134.8, 130.6, 129.3, 128.9, 128.1,

127.3, 113.9, 113.1, 86.2, 71.8, 65.5, 55.2, 54.2, 53.1, 37.7, 19.0. Mass (ESI-MS); m/z 444.38 $(M+Na)^+$, 460.35 $(M+K)^+$. Anal. Calcd for $C_{25}H_{27}NO_5$: C, 71.24; H, 6.46; N, 3.32; O, 18.98. Found: C, 71.20; H, 6.32; N, 3.28.

17. CCDC number for compound **9c** is 736220.
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