Stereoselective synthesis of a chiral synthon, 2,2,5-trisubstituted tetrahydropyran, based on simultaneous 1,3- and 1,6-asymmetric induction *via* nucleophilic acetal cleavage reaction of the bicyclic acetal: a total synthesis of (−)-malyngolide

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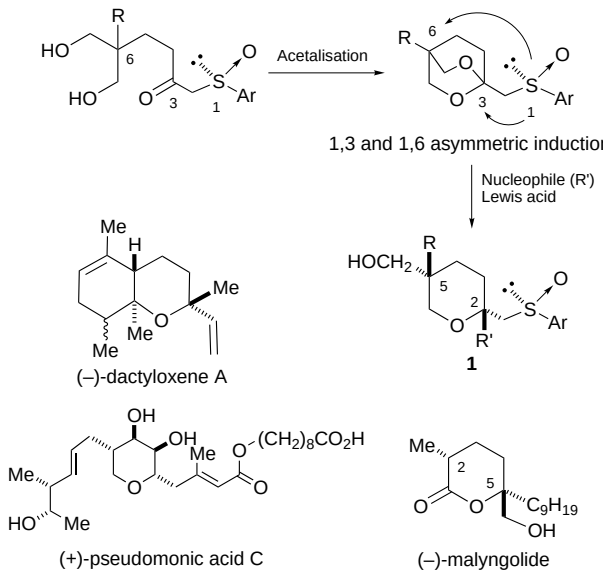
A chiral 2,2,5-trisubstituted tetrahydropyran is synthesised efficiently *via* facial and group selective nucleophilic acetal cleavage reaction of a bicyclic acetal, wherein simultaneous 1,3- and 1,6-asymmetric induction from a sulfinyl chirality is accomplished with high diastereoselectivity; this chiral synthon is successfully applied to a total synthesis of (−)-malyngolide.

The development of a methodology for remote asymmetric induction is one of the most challenging problems in organic synthesis.[1,2] In addition, the simultaneous installation of chiral centres separated by more than two carbons is a very difficult task. We have previously reported a novel asymmetric desymmetrisation of a prochiral 1,3-diol *via* diastereoselective acetal cleavage reaction.[2] The results prompted us to develop a methodology for simultaneous 1,3- and 1,6-asymmetric induction *via* a nucleophilic acetal cleavage reaction,[3] wherein a chiral sulfinyl group controls both the diastereotopic C–O bond cleavage and diastereofacial nucleophilic addition, thereby yielding chiral 2,2,5-trisubstituted tetrahydropyrans with two chiral centres at the C_2 and C_5 positions (Scheme 1).† The resulting tetrahydropyran derivative **1** is considered as a useful chiral synthon for various natural products, *i.e.* (−)-dactyloxene A,[4] (+)-pseudomonic acid C[5] and (−)-malyngolide.[6]

Here we describe a novel method of synthesising 2,2,5-trisubstituted tetrahydropyran based on simultaneous 1,3- and 1,6-asymmetric induction with high diastereoselectivity *via* group and facial selective nucleophilic acetal cleavage reactions and apply this chiral synthon to a total synthesis of (−)-malyngolide.



Scheme 1

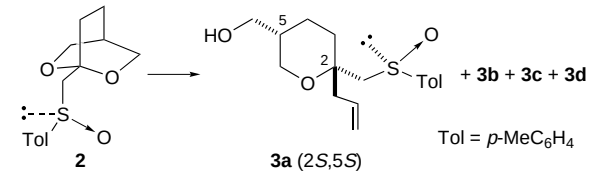
Upon treatment with a mixture of the bicyclic acetal **2**[2] and allyltrimethylsilane with $TiCl_4$, nucleophilic acetal cleavage reaction took place at −78 °C to produce allylated alcohol **3a** along with the three diastereomeric isomers **3b–d**‡ (67 : 10 : 17 : 6) (Table 1). Selectivity was increased by lowering the reaction temperature; CH_2Cl_2 was the most suitable solvent. The best result was obtained when $TiCl_4$ (5 equiv.) was added to a mixture of substrate and allyltrimethylsilane (10 equiv.) in CH_2Cl_2 at −100 °C. In this case, the ratio of **3a** and its three other isomers was 84 : 6 : 7 : 3.

The absolute configuration of the major product **3a** was inferred from the relative configuration determined by single crystal X-ray analysis of the p-nitrobenzoate§ and the known absolute configuration of the sulfoxide.¶

The reaction was rationalised as follows: $TiCl_4$ coordinates between the sulfinyl oxygen and one of the acetal oxygens to form the chelation intermediates **A** or **B**, in which the bulky tolyl group located at equatorial position (Fig. 1). The intermediate **A** is more favourable than **B**, since the electropositive sulfur atom is located between electronegative oxygens and is *anti* to the bulky 7-methylene group in the intermediate **A**.[7] The C–O bond coordinated by $TiCl_4$ is weakened or cleaved to produce transition state **C** or tight ion pair intermediate **D**, respectively. Allyltrimethylsilane reacts with the bicyclic acetal from the backside of the breaking C–O bond *via* an S_N2-type substitution (transition state **C**) or an S_N1-like mechanism (intermediate **D**)[8] to give the (2*S*,5*S*)-isomer **3a** diastereoselectively as a potential multifunctional chiral synthon.

We planned to apply this chiral synthon to the synthesis of a marine antibiotic, (−)-malyngolide.[6] Although various synthe-

Table 1 Nucleophilic acetal cleavage reaction of the bicyclic acetal **2**



2 **3a** (2*S*,5*S*)

Conditons (equiv.)	Yield (%)[a]	Ratio[b] **3a** : **3b** : **3c** : **3d**
$TiCl_4$ (5), Me_3Si(allyl) (5), CH_2Cl_2, −20 °C	91	19 : 26 : 48 : 7
$TiCl_4$ (5), Me_3Si(allyl) (5), CH_2Cl_2, −78 °C	93	67 : 10 : 17 : 6
$TiCl_4$ (5), Me_3Si(allyl) (5), CH_2Cl_2, −100 °C	92	79 : 6 : 9 : 6
$TiCl_4$ (5), Me_3Si(allyl) (5), PhMe, −78 °C	63	66 : 10 : 16 : 8
$TiCl_4$ (5), Me_3Si(allyl) (5), THF, −78 °C	0	—
$TiCl_4$ (5), Me_3Si(allyl) (10), CH_2Cl_2, −100 °C	90	84 : 6 : 7 : 3

[a] Isolated yield. [b] The ratio was determined by 500 MHz ^{1}H NMR spectroscopic measurements.

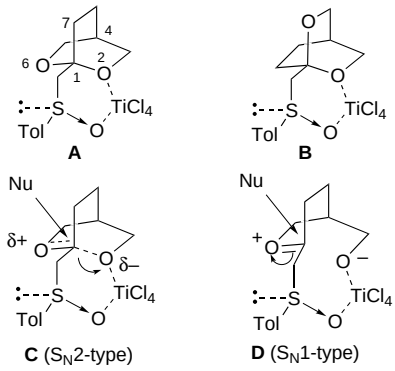
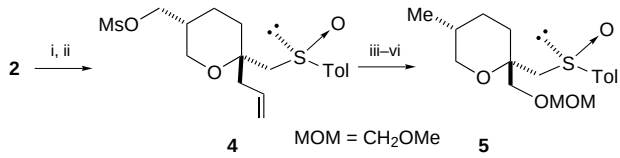


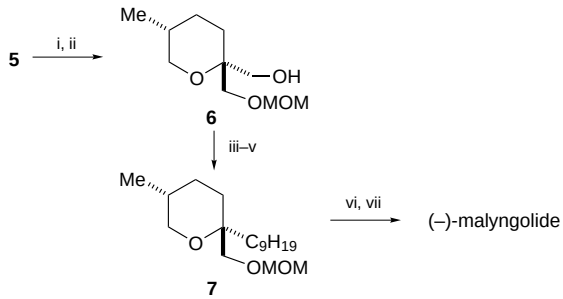
Fig. 1



Scheme 2 *Reagents and conditions*: i, $TiCl_4$, allyltrimethylsilane, CH_2Cl_2, −100 °C; ii, MsCl, DMAP, CH_2Cl_2, 0 °C (73% in 2 steps); iii, $LiBEt_3H$, THF, room temp. (97%); iv, $PdCl_2(PhCN)_2$, benzene, 80 °C (60%, 90% based on recovery of material); v, O_3, MeOH, −78 °C then $NaBH_4$, room temp. (93%); vi, MOMCl, Pr^i_2NEt, CH_2Cl_2, room temp. (77%)

ses of malyngolide have been reported,[9] most of synthetic routes lack stereocontrol at the C_2 methyl group. A few methods overcome this problem by constructing the two chiralities one by one.[9a,c,e,f] After the nucleophilic acetal cleavage reaction of **2**, the major diastereomeric isomer **3a**, which possesses three appropriately installed side-chains for the synthesis of (−)-malyngolide, was isolated as a mesylate **4** (73% yield from **2**). After reduction of the mesylate moiety with Super Hydride®, a catalytic amount of $PdCl_2(PhCN)_2$ was used to isomerise the allyl group to a prop-1-enyl group.[10] Ozonisation was followed by a reductive work-up, and protection as a methoxymethyl (MOM) ether was undertaken to yield **5** (Scheme 2).

The *p*-tolylsulfinyl group was converted into the alcohol **6** *via* Pummerer rearrangement followed by reduction with $LiBH_4$. After Dess–Martin oxidation,[11] eight carbon elongation at the hindered position was successfully accomplished with a Wittig reagent followed by hydrogenation of the olefin to produce compound **7** in good yield. Finally, the tetrahydropyran ring was oxidised to the δ-lactone with RuO_4, and the MOM ether was removed with Me_3SiBr to give (−)-malyngolide without epimerisation at the methyl group (Scheme 3). The spectroscopic data and specific rotation [$[\alpha]_D$ −12.5 ($CHCl_3$)] were consistent with the reported data [$[\alpha]_D$ −13.0 ($CHCl_3$)].[6]



Scheme 3 *Reagents and conditions*: i, Ac_2O, AcONa, 130 °C (90%; 2 : 1 diastereomeric ratio); ii, $LiBH_4$, THF, room temp. (97%); iii, Dess–Martin periodinate, CH_2Cl_2, 0 °C (88%); iv, $Ph_3P^+(C_8H_{17})Br^-$, KHMDS, THF, 0 °C (94%); v, H_2, 10% Pd–C, MeOH, room temp. (86%); vi, $RuCl_3{\cdot}3H_2O$, $NaIO_4$, CCl_4–MeCN–H_2O (57%, 80% based on recovery of material); vii, Me_3SiBr, CH_2Cl_2, −30 °C (85%)

In summary, we have synthesised 2,2,5-trisubstituted tetrahydropyran **1** as a multifunctional chiral synthon based on facial and group selective acetal cleavage reactions, in which highly diastereoselective 1,3- and 1,6-asymmetric induction was observed. The utility of this chiral synthon was demonstrated by its application to the total synthesis of (−)-malyngolide.

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Footnotes and References

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† Relative and absolute configurations at the C_2 and the C_5 positions in the chiral synthon **1** can be controlled by the sulfinyl chirality. Furthermore, inversion of the stereochemistry at the C_2 position in **1** (R′ = allyl) is also possible, since both allyl and sulfinyl groups can be converted into variety of functional groups.

‡ The absolute configurations of **3b**–**d** were determined as (2*S*,5*R*), (2*R*,5*S*), and (2*R*,5*R*), respectively. Structural determination of these compounds will be reported elsewhere.

§ The X-ray crystal structure of compound **3a** confirms the relative configuration at C_2 and C_5 although the quality of the data is not adequate for publication. These assignments are supported by the conversion of **3a** into (−)-malyngolide.

¶ The absolute configuration of the sulfoxide moiety in **3a** was based on the optical rotation of the known methyl *p*-tolyl sulfoxide (ref. 12), from which **3a** was derived (ref. 2). Since all synthetic intermediates after introduction of the sulfinyl group (including **2** and **3a**) possess positve optical rotations, their absolute configurations on sulfur are assumed to be retained during the transformations [by the empirical rule (ref. 13)].

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