Asymmetric Synthesis of β-Alkoxycyclic Ethers *via* the Intramolecular Cyclization of Group 14 Allyls containing Chiral Acetals

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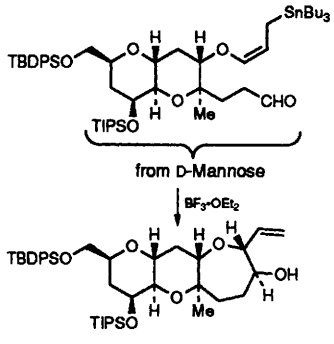
Treatment of an allylic tin-bearing chiral acetal **1a** with $TiCl_4$–PPh_3 gives the (2*S*, 3*R*) isomer **2** with high diastereoselectivity (**2** : **3** = 93 : 7), whereas the reaction of an allylic silane derivative **1f** affords predominantly the (2*R*,3*S*) isomer **3** (**2** : **3** = 37 : 63).

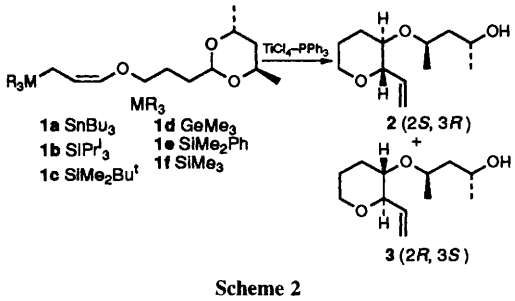
We have recently accomplished a stereocontrolled synthesis of the 7,7,6,6-tetracyclic ether skeleton of hemibrevetoxin *via* intramolecular allylic tin–aldehyde (or ketone) condensation.[1] A key step for this methodology is shown in Scheme 1, in which asymmetric centres in the starting material are derived from D-mannose. Although this asymmetric cyclization was very suitable for the synthesis of hemibrevetoxin skeleton, we needed more flexible and widely applicable methods for asymmetric synthesis of β-alkoxycyclic ethers because cyclic ether frameworks having slightly different structures are frequently found in marine natural products.

We wish to report that the treatment of the allyltributyltin-bearing chiral acetal **1a** with $TiCl_4$–PPh_3 gives the (2*S*, 3*R*) cyclic ether **2** with high diastereoselectivity (Scheme 2, Table 1, entry 1).[2] The cyclization proceeded very rapidly at −78 °C by the use of a Lewis acid–Lewis base combination[2b] to give the *trans* products **2** and **3** in a ratio of 93 : 7; *cis* isomers were not detected.† Use of $TiCl_4$ alone or $TiCl_n(OPr)_{4-n}$ (n = 0, 2) gave poor results. Allylsilane and germane derivatives **1b–f** also underwent cyclization by the use of $TiCl_4$–PPh_3 (entries 2–6). Very interestingly, the cyclization of triisopropylsilyl (**1b**) and *tert*-butyldimethylsilyl (**1c**) derivatives gave predominantly the (2*S*, 3*R*) isomer **2**, whereas cyclization of trimethylgermyl (**1d**), dimethylphenylsilyl (**1e**), and trimethylsilyl (**1f**) derivatives afforded preferentially the (2*R*, 3*S*) isomer **3**. Here also, no *cis* products were detected.

The absolute configuration of **3** was determined unambiguously by converting it to **4** (Scheme 3). The oxidation of a 63 : 37 mixture of **3** and **2** (obtained from the reaction of **1f**) with PCC and subsequent treatment with potassium carbonate in methanol gave the corresponding β-hydroxy cyclic ethers.



Scheme 1 TBDPS = *tert*-butyldiphenylsilyl; TIPS = triisopropylsilyl

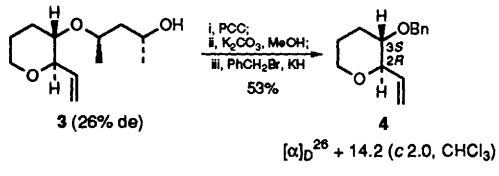


Scheme 2

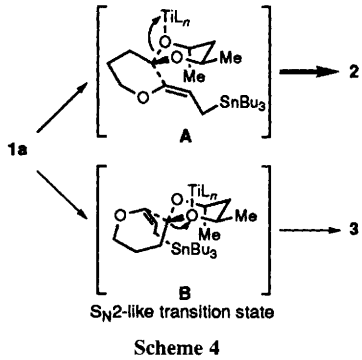
Benzyl protection of the resulting ethers with benzyl bromide–KH afforded a mixture of **4** and its enantiomer in 53% yield. The specific rotation of this mixture was +14.2 (*c* 2.0, CH_2Cl_2, 26 °C). The reported $[\alpha]_D$ value for the (2*S*, 3*R*) enantiomer of **4** is −52.2 (*c* 3.6, CH_2Cl_2, 20 °C).[3] Accordingly, it is clear that the major enantiomer of **4** formed by the reaction of **1f** possesses the (2*R*, 3*S*) configuration; the $[\alpha]_D^{20}$ value of +14.2 corresponds to *ca.* 27% de, which is in good agreement with the diastereoisomer ratio of the cyclic ethers obtained from the reaction of **1f**.

A mechanistic rationale which accounts for predominant formation of **2** from **1a** is shown in Scheme 4. As we previously reported in the enantiodivergent synthesis of steroidal side chains,[4] the reactive allylic tin reagent **1a** would react in a S_N2 like manner; breaking of a C–O bond of the acetal would take place simultaneously with C–C bond formation between the γ-allylic carbon and acetal carbon (**A** and **B**). The transition state **B** is less stable than **A** owing to unfavourable steric repulsion between TiL_n and an equatorial Me group. Therefore, the cyclization takes place predominantly through **A**, giving **2** in high diastereoselectivity. On the other hand, the less reactive allylic trimethylsilane **1f** would react in a S_N1 manner (Scheme 5).[4] Cleavage of a C–O bond of the acetal would occur prior to C–C bond formation. It is obvious that transition state **D** is less stable than **C** because of an unfavourable steric interaction between a methyl group and the attacking allylic reagent. This is further emphasized, if we consider the transition state geometries using Newman type projections **C**′ and **D**′; the attack of the allylic reagent shown in **D**′ has to proceed through an *anti*-Cram manner. Therefore, the cyclization of **1f** proceeds predominantly through the transition state **C** to give **3** preferentially.

Upon changing the Group 14 fragment of the allyl substrate the diastereoisomeric ratios of **2** : **3** changed from 93 : 7 to 37 : 63, as shown in Table 1. The diastereoselectivity sequence



Scheme 3

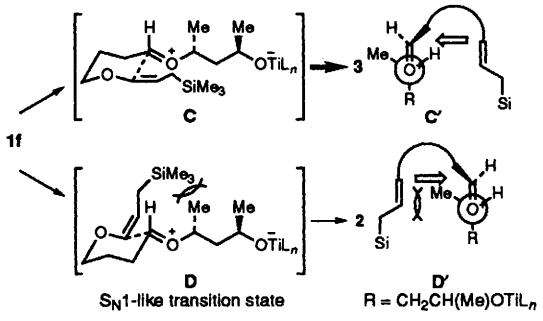


Scheme 4

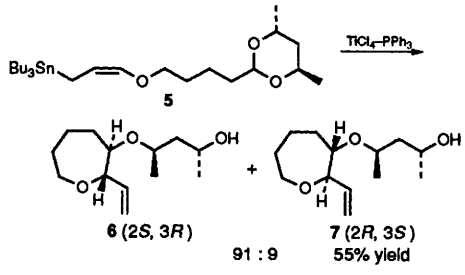
Table 1 Asymmetric cyclization of **1**[a]

Entry	MR_3	Ratio (**2**:**3**)[b]	Yield (%)[c]
1 **1a**	$SnBu^n_3$	93:7	51
2 **1b**	$SiPr_3$	77:23	41
3 **1c**	$SiMe_2Bu^t$	58:42	39
4 **1d**	$GeMe_3$	44:56	52
5 **1e**	$SiMe_2Ph$	41:59	52
6 **1f**	$SiMe_3$	37:63	38

[a] To a CH_2Cl_2 solution (5 ml) of $TiCl_4$–PPh_3 (1 mmol) cooled at −78 °C was added dropwise a CH_2Cl_2 solution (8 ml) of **1** (0.5 mmol), and the mixture was stirred at that temperature. Complete consumption of the starting material was confirmed by monitoring the reaction with TLC. The reaction was quenched with saturated $NaHCO_3$ and extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography on silicagel (eluent: hexane–AcOEt) to give a diastereomeric mixture of products. [b] Ratio determined by capillary GC analysis. [c] Isolated yield.

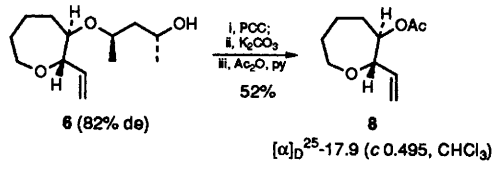


Scheme 5



Scheme 6

for the formation of **2** is $SnBu_3$ > $SiPr^i_3$ > $SiMe_2Bu^t$ > $GeMe_3$ > $SiMe_2Ph$ > $SiMe_3$. It is known that relative reactivities of Group 14 allyls toward diarylcarbenium ions are in the following order;[5] $SnBu_3$ ≫ $SiPr^i_3$ > $SiMe_2Bu^t$ > $SiMe_3$ > $SiMe_2Ph$, $GeMe_3$. This reactivity order is in good agreement with the present diastereoselectivity order, except for $SiMe_3$. The very reactive tin compound **1a** would react in a S_N2 manner, whereas the less reactive trimethylgermyl, dimethylphenylsilyl and trimethylsilyl compounds **1d–f** would react in a S_N1 manner. Another interesting point is that reversed diastereoselectivity was observed for **1d–f**. Previous results[6] on the S_N2/S_N1 problem of acetal ring cleavage indicate that the diastereoselectivities decrease with shifting of the mechanism from S_N2 to S_N1 type cleavage, but diastereoselectivity reversal has never been observed.[4] Perhaps, memory of the chirality of the acetal disappears completely in the present case, and that diastereoselectivity is dictated primarily by the stereochemistry of the asymmetric centre at the α-carbon (see modified Cram models **C'** and **D'**), whereas the memory



Scheme 7

remains to some extent in the previously studied reactions. The disappearance of chirality memory of the acetal may result from the use of $TiCl_4$–PPh_3.

Irrespective of the precise mechanism, the cyclization seemed to be promising for asymmetric synthesis of β-alkoxy cyclic ethers. We extended the method employing tin to seven-membered cyclization (Scheme 6). The reaction of **5** with $TiCl_4$–PPh_3 in CH_2Cl_2 gave a 91:9 mixture of (2*S*, 3*R*) **6** and (2*R*, 3*S*) **7** in 55% yield. Here again, no *cis* products were detected. The absolute configuration of **6** was determined by converting it to the corresponding acetyl derivative **8** (Scheme 7). Oxidation of **6** (82% de) with PCC followed by treatment with K_2CO_3 gave the corresponding β-hydroxy cyclic ether. Subsequent treatment with acetic anhydride–pyridine afforded **8** in 52% overall yield. Comparison of $[\alpha]_D^{25}$ −17.9 (*c* 0.0495, $CHCl_3$) with the literature value[7] for the (2*S*, 3*R*) enantiomer, $[\alpha]_D^{21}$ −21.1 (*c* 1.1, $CHCl_3$), indicated (2*S*, 3*R*) configuration.

We are now in a position to carry out asymmetric cyclization of ω-organometallic ether acetals with higher flexibility in comparison with the reaction shown in Scheme 1. Further, the reversal of the diastereoselectivity is mechanistically interesting. We are applying the present method to the synthesis of certain natural products.

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Footnote

† The $TiCl_4$–PPh_3 mediated cyclization of allyltrimethylsilane derivative bearing a simple acetal gave a 98:2 mixture of *trans* and *cis* products [ref. 2(*b*)].

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