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1,4-Remote Stereocontrol via Asymmetric [2,3]-Wittig Rearrangements

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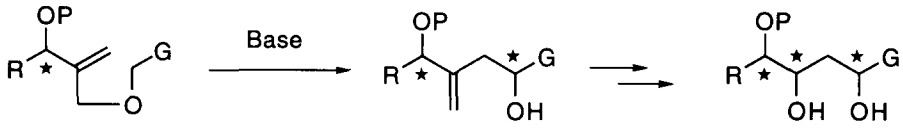
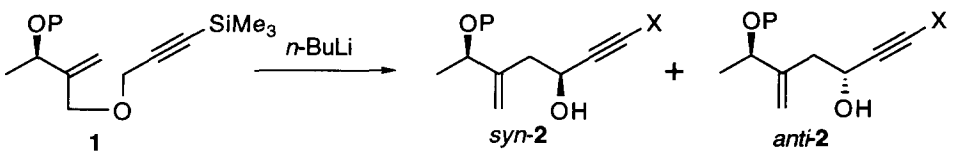
Abstract: *The carbanion rearrangement of the propargylic ether of the β-(1-alkoxyethyl) allyl alcohol was found to proceed with a high degree of either 1,4-syn or 1,4-anti selection by virtue of the proper choice of the combination of the alkoxy group with the solvent used.*

Remote stereocontrol in acyclic systems is a challenging problem in organic synthesis.[1] While the [2,3]-Wittig rearrangements have currently enjoyed wide application for stereocontrol over adjacent and contiguous chiral centers,[2] little attention has been paid to the carbanion rearrangement as a method for remote stereocontrol. In an effort to further enhance the synthetic utility of the asymmetric [2,3]-Wittig technology, we became interested in 1,4-remote stereocontrol via the novel type of [2,3]-Wittig variation depicted by eq 1, wherein the key to success is the proper choice of the G group on the carbanion terminus and the P group.



(1)

In fact, Brückner et al. have reported that the use of G=CO_2CH_3 or C≡C-$SiMe_3$ with P=MOM (CH_2OCH_3) does not provide any appreciable level of 1,4-stereocontrol.[3] Herein we disclose the [2,3]-Wittig variants (G=C≡C-$SiMe_3$ or Ph) which provide a relatively high level of 1,4-asymmetric induction in either the *syn* or *anti* fashion by virtue of the proper choice of the P group, and demonstrate the utility of this method in the stereocontrolled synthesis of the 1,2,4-triol systems (see eq 1) which occur in some biologically important compounds. First, we prepared the propargyl ethers **1a-c** from commercially available (*R*)-methyl-β-(α-hydroxyethyl)acrylate via the standard reaction sequence[4] and examined their rearrangements with *n*-BuLi (eq 2). Table 1 summarizes the stereochemical outcomes thus observed.



1 *syn*-**2** *anti*-**2**

(2)

a ; P=TBS, **b** ; P=TIPS, **c** ; P=H (Li) X=$SiMe_3$ or H

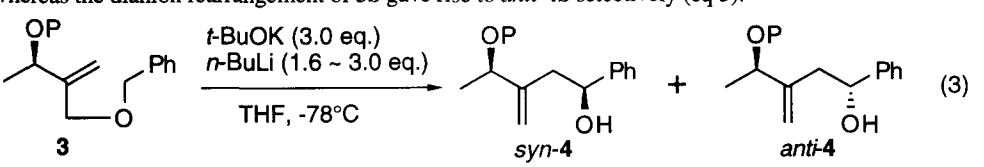
The rearrangement of **1a** was found to afford an 81:19 diastereomeric mixture favoring the *syn* isomer (entry 1),[5] whereas the use of a lower reaction temperature (entry 2) and a bulkier silyl group as the P group (entry 4) led to a slightly higher selectivity. The *syn* configuration of the major isomer was assigned by its conversion to the known derivative of (*S*)-4-pentyn-1,3-diol.[6] In contrast, the dianion rearrangement of **1c** (P=Li) was found to exhibit the opposite sense of stereoselection to afford *anti*-**2c'** (X=H)[5] as the major isomer apparently via desilylation during the workup. Interestingly, the *anti* selectivity was enhanced by using a mixture of THF and *N,N'*-dimethylpropyleneurea (DMPU) as the solvent (entries 3, 6 and 7).

Table 1. [2,3]-Wittig rearrangement of (*R*)-**1**[a]

Entry	Substrate	Solvent	*syn* : *anti*[b]	Yield (%)
1	**1a**, P=TBS	THF	81 : 19	92
2[c]		THF-Et_2O-Hex = 4 : 1 : 1	84 : 16	82
3		THF-DMPU = 1 : 1	68 : 32	43
4	**1b**, P=TIPS	THF	85 : 15	88
5[d]	**1c**, P=H (Li)	THF	29 : 71	77[e]
6[d]		THF-DMPU = 3 : 1	14 : 86	62[e]
7[d]		THF-DMPU = 1 : 1	11 : 89	86[e]

a) Unless otherwise noted, the rearrangement was run with 1.2 equiv of *n*-BuLi at -78°C. b) Determined by ^{1}H NMR analysis (ref. 5). c) Run at -110°C. d) Run with 4.0 equiv of *n*-BuLi. e) Refers to the yield of the desilylated product **2c'** (X=H).

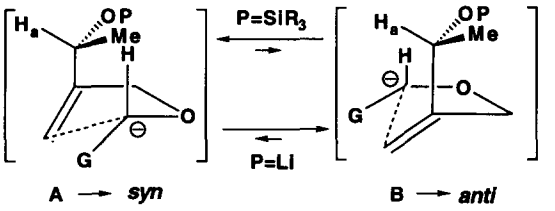
Next, we studied the rearrangement of the benzylic ethers **3a,b** using LIC-KOR (*n*-BuLi / *t*-BuOK).[7,8] Again, the rearrangement of the silyl-protected substrate **3a** was found to afford *syn*-**4a** as the major isomer, whereas the dianion rearrangement of **3b** gave rise to *anti*-**4b** selectively (eq 3).[9]



3 — *syn*-**4** + *anti*-**4** (3)

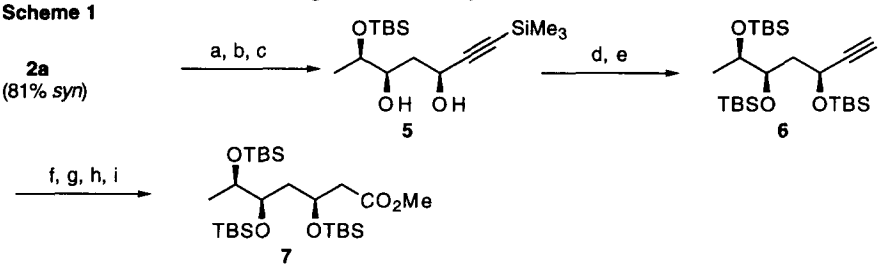
a ; P=TBS — **a** ; 79 : 21 (48 %)
b ; P=H (Li) — **b** ; 20 : 80 (90 %)

The stereochemical trends observed in the rearrangement of **1** and **3** can be rationalized in terms of the transition states **A** vs. **B**, where the allylic hydrogen (H_a) is located on the π-plane so as to minimize the allylic 1,3-strain and where the G group occupies the pseudo-equatorial position to avoid 1,3-diaxial interaction. Of the two possible conformers, **A** should be sterically favored when P=SiR_3, thus leading to *syn* selection as actually observed. By contrast, **B** should be favored when P=Li, thus resulting in *anti* selection as actually observed. This argument can be extended to explain the increased *anti* selection by addition of DMPU; the strong ability of DMPU to coordinate with Li^+ might reduce the inert volume[10] of the alkoxy anion involved, thus making conformer **B** more favorable. In this dianion case, the preference for conformer **B** might be strengthened by the so-called "complex induced proximity effect".[11]



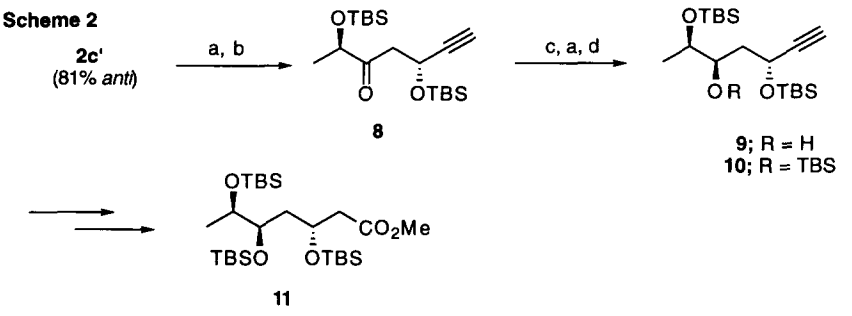
The [2,3]-Wittig rearrangement of **2** is of synthetic value because it attains a relatively high level of either 1,4-*syn* or 1,4-*anti* selection through the proper choice of the P group and the rearrangement product possesses a unique multifunctionality which readily allows a variety of further transformations. To demonstrate its synthetic utility, we carried out the stereocontrolled syntheses of the C_7-C_{13} fragment (**7**) of amphotericin B[12] from **2a** (scheme 1) and the C_{21}-C_{27} fragment (**11**) of bryostatins[13] from **2c'** (scheme 2).

Scheme 1



(a) O_3, MeOH / Me_2S, -78 °C; (b) $LiBEt_3H$, THF, -78 °C (two steps 61 %); (c) SiO_2 chromatography; (d) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, -10 °C; (e) MeONa, MeOH-THF, rt (two steps 83 %); (f) H_2, P-$_2$Ni, EtOH-THF, rt; (g) 9-BBN, THF, rt / NaO_2H; (h) PDC, DMF, 50~60 °C; (i) CH_2N_2, MeOH, rt (four steps 36 %).

Scheme 2



(a) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, -10 °C; (b) O_3, MeOH / Me_2S, -78 °C (two steps 70 %); (c) $LiBEt_3H$, THF, -78 °C; (d) SiO_2 chromatography (three steps 49 %).

Ozonolysis of **2a** (84% *syn*) followed by reduction with $LiBEt_3H$ gave the diol **5** as a 78:22 diastereomeric mixture. These diastereomers are easily separable by silica gel chromatography (5:1 hexane:EtOAc). The purified major diastereomer of **5**[14] was treated with TBSOTf followed by selective removal of TMS by NaOMe to give **6**, which was then converted to the C_7-C_{13} fragment of Amphotericin B (**7**) by the standard sequence: partial hydrogenation, hydroboration, oxidation, and esterification. Likewise, **10** was synthesized from **2c'** (81% *anti*) as a single diastereomer[14], which can be similarly transformed to the C_{21}-C_{27} fragment of bryostatins (**11**).

In summary, we have shown that the [2,3]-Wittig rearrangement of **1** and **3** provide a high level of 1,4-remote stereocontrol either in the *syn* or *anti* fashion by the judicious choice of the P group. Furthermore, we have demonstrated its synthetic utility through the syntheses of chiral fragments of amphotericin B and bryostatins.

Acknowledgment: We thank Professor Yutaka Nishigaichi (Shimane University) for providing the spectral data of the methyl ether of **4**. We also thank Fujisawa Pharmaceutical Co., Ltd. for supplying the chiral starting material.

References and Notes

1. Selected recent examples on remote stereocontrol: (a) Roush, W.R.; Wada, C. K. *J. Am. Chem.Soc.* **1994**, *116*, 2151. (b) Molander, G. A.; Bobbitt, K. L. *J. Am. Chem.Soc.* **1993**, *115*, 7517. (c) Carey, J. S.; Thomas, E. J. *Tetrahedron Lett.* **1993**, *34*, 3935.
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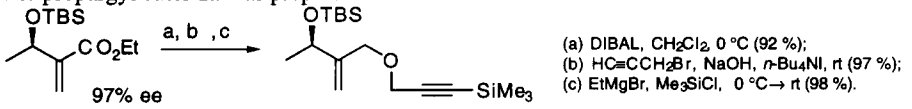
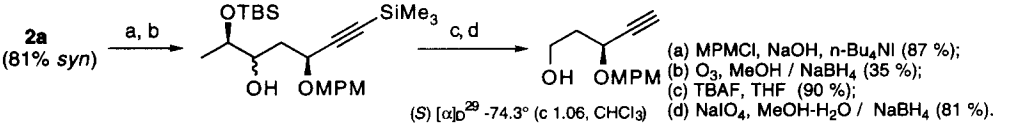
3. However it should be noted that a high degree of 1,3-stereocontrol in the [2,3]-Wittig rearrangement systems has been achieved: Scheuplein, S. W.; Kusche, A.; Brückner, R.; Harms, K. *Chem. Ber.* **1990**, *123*, 917.
4. The propargyl ether **1a** was prepared as shown below.



5. Diastereomers of **2a-c'** are easily distinguishable by ^{1}H NMR ($CDCl_3$, ppm): the δ value for CH_2, 2.37, 2.66 for *syn*-**2a** and 2.49, 2.59 for *anti* -**2a**; δ value for CH_2, 2.41, 2.64 for *syn*-**2b** and 2.52, 2.60 for *anti* -**2b**; δ value for the propargylic proton, 4.58 for *syn*-**2c'** and 4.49 for *anti* -**2c'**.
6. The stereochemistry of **2** was assigned by comparing its specific optical rotation with that of the known MPM ether as depicted below. The value for the (*R*)-isomer (>95% ee): $[\alpha]_D^{23}$ +120.0° (c 1.00, $CHCl_3$): Tomooka, K.; Nakamura, Y.; Nakai, T. Unpublished result.



7. Schlosser, M. *Pure Appl. Chem.* **1988**, *60*, 1627
8. We have also examined the rearrangement of **3** using *n*-BuLi. However, these reactions resulted in complex mixtures.
9. The stereochemistry and diastereomeric ratio of **4** was assigned by comparing its ^{1}H NMR spectrum with that of the known methyl ether derivative: Nishigaichi, Y.; Takuwa, A.; Jodai, A. *Tetrahedron Lett.* **1991**, 21, 2383.
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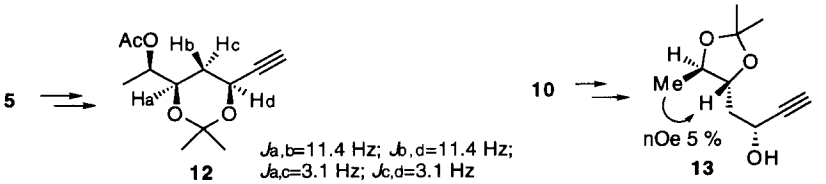
14. The stereochemistry of **5** and **10** were assigned as shown below.



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