# Asymmetric synthesis of 2,3-disubstituted oxepanes *via* acetalization–cyclization of an enantioenriched functionalized allylsilane with aldehydes

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**According to the protocol for the acetalization–intramolecular allylsilane cyclization, a new enantioenriched allylsilane, (*R*)-(*E*)-7-(dimethylphenylsilyl)undec-5-en-1-ol, in the presence of a variety of aldehydes provided enantioenriched *trans*-2,3-disubstituted oxepanes stereoselectively.**

Allylsilanes bearing hydroxylated alkyl groups have been utilized for the efficient synthesis of cyclic ethers *via* an acetal formation with aldehydes, followed by an intramolecular cyclization of the allylsilane with an oxonium ion generated from the acetal in the presence of an acid catalyst.[1,2] Moreover, an asymmetric version of the acetalization–intramolecular allylsilane cyclization (AIAC) protocol was recently established by us with use of enantioenriched allylsilanes, which were synthesized *via* a highly stereoselective intramolecular bis-silylation of enantioenriched allylic alcohols.[3] Although the AIAC protocol was successfully applied to the stereoselective synthesis of five- and six-membered cyclic ethers, attempt at the seven-membered ring formation has never been reported. In the light of the synthetic importance of the oxepane derivatives, it is highly desirable to develop a new methodology for the stereoselective construction of oxepanes. Herein, we report stereoselective synthesis of enantioenriched seven-membered cyclic ethers through the AIAC protocol by use of a new enantioenriched allylsilane **1**, which was readily available from δ-valerolactone in a multigram scale.[4]

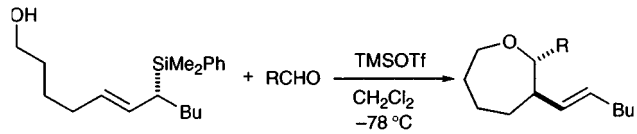
Reaction of δ-valerolactone with 1-lithiohex-1-yne followed by THP protection (THP = tetrahydropyranyl) of the resulting hydroxy group provided the ynone **2** (Scheme 1). Ruthenium-catalyzed enantioselective reduction of the carbonyl group afforded the propargyl alcohol **3** with high optical purity.[5] After the conversion of **3** to the corresponding allylic alcohol **4**, the enantiomeric excess was determined to be 97.1%. Compound **4** was then subjected to our protocol for the synthesis of enantioenriched allylsilanes.[6] The palladium-catalyzed intramolecular bis-silylation of the disilanyl ether **5** and subsequent treatment with BuLi followed by THP deprotection with PPTS afforded the enantioenriched allylsilane (*R*)-**1** with a hydroxybutyl chain.[7] The enantiomeric purity of 96.3% ee was confirmed by chiral HPLC analysis after the appropriate derivatization.[3] Note that the procedure was efficient enough to enable us to prepare (*R*)-**1** on a 10 g scale without difficulty.

With the enantioenriched allylsilane (*R*)-**1** in hand, the AIAC reaction with acetaldehyde was examined in the presence of TMSOTf (2 equiv.). Under essentially the same conditions that we reported previously for the six-membered ring formation, the cyclization took place to give the seven-membered cyclic ether **6a** in 63% yield (Table 1, entry 1).

It is noteworthy that only the *trans*-2,3-disubstituted seven-membered ring ether with *E* olefin geometry was selectively produced.[8] The enantiomeric excess of **6a** was determined to be not less than 92%; finding the chiral GC or HPLC conditions for the complete separation of the enantiomers **6a** proved difficult. Also, the cyclizations with some aliphatic aldehydes proceeded with a good level of chirality transfer ( > 96%) (entries 2–4).[9,10] As observed for the reaction of acetaldehyde, only the *trans*-*E*-oxepanes **6b**–**d** were selectively obtained in the cyclization. The amount of the TMSOTf could be reduced to 1.1 equiv. without a decrease in the yield or stereoselectivity (entry 3).

Reaction with benzaldehyde also proceeded in good yield with high stereoselectivity (entry 5). A trace amount (2%) of *cis*-oxepane was detected by $^1$H NMR, however, the enantiomeric excess of the *trans*-oxepane **6e** was found to be 95.6%. This high stereoselectivity in the seven-membered ring formation with benzaldehyde is in sharp contrast with the correspond-

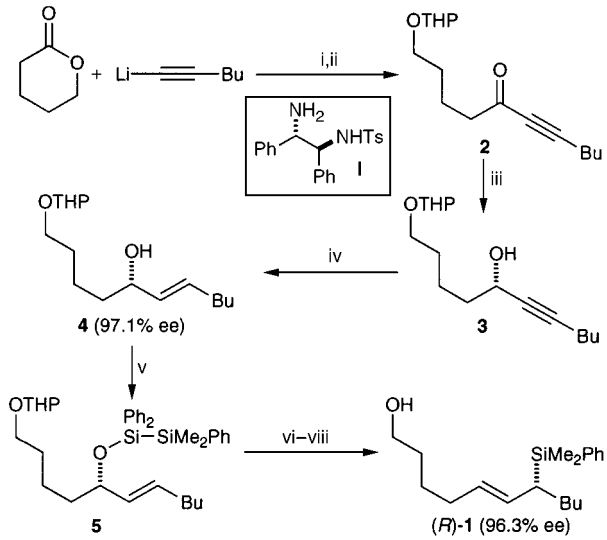
**Table 1** Synthesis of enantioenriched 2,3-disubstituted oxepanes through cyclization of (*R*)-**1** (96.3% ee) with aldehydes[a]




(*R*)-**1** (96.3% ee) **6**

| Entry | R | Product (% yield)[b] | *trans*:*cis*[c] | *E*:*Z*[c] | Ee (%)[d] | Stereo conservation (%)[e] |
|---|---|---|---|---|---|---|
| 1 | Me | **6a** (63) | > 99:1 | > 99:1 | 92[f] | 96 |
| 2 | *n*-Hex | **6b** (71) | > 99:1 | > 99:1 | 93.6 | 97 |
| 3[g] | Pr$^i$ | **6c** (94) | > 99:1 | > 99:1 | 92.5 | 96 |
| 4 | Bu$^t$ | **6d** (71) | > 99:1 | > 99:1 | 93.9 | 98 |
| 5 | Ph | **6e** (82) | 50:1 | > 99:1 | 95.6 | 99 |
| 6 | *p*-MeC$_6$H$_4$ | **6f** (70) | 40:1 | > 99:1 | 93.3 | 97 |
| 7 | *p*-NO$_2$C$_6$H$_4$ | **6g** (74) | 20:1 | > 99:1 | 90.9 | 94 |

[a] The reactions were carried out at −78 °C in $CH_2Cl_2$ for 2 h in the presence of TMSOTf (2.0 equiv.) unless otherwise noted. [b] Isolated yields. [c] Determined by $^1$H NMR. [d] Determined by chiral HPLC unless otherwise noted (ref. 9). [e] (Ee of the product **6**)/[ee of (*R*)-**1**]. [f] Determined by chiral GC (Chrompack Cyclodextrine-β-236M-19) with incomplete separation of signals for enantiomers. [g] Use of 1.1 equiv. of TMSOTf.




**Scheme 1** *Reagents and conditions*: i, THF, 0 °C; ii, DHP, TsOH, $CH_2Cl_2$, room temp.; iii, **I**, $[RuCl_2(p\text{-cymene})]_2$ (cat), KOH, $Pr^iOH$, room temp., 41% for 3 steps; iv, Red-Al, THF, 0 °C to reflux, 95%; v, $ClPh_2SiSiMe_2Ph$, $Et_3N$, DMAP (cat), THF, room temp., 87%; vi, $Pd(acac)_2$, $Bu^tCH_2CMe_2NC$, toluene, reflux; vii, BuLi, THF, 0 °C; viii, PPTS, EtOH, 60 °C, 72% for 3 steps.

ing non-stereoselective six-membered ring formation, where all four possible diastereomers were formed. Reaction of **1** with *p*-tolualdehyde also gave *trans*-*E*-oxepane **6f** stereoselectively (entry 6). Interestingly, benzaldehydes bearing electron-donating or -withdrawing substituents at the *p*-positions presented contrasting results in the reactions with **1**. Thus, *p*-nitrobenzaldehyde successfully afforded the corresponding oxepane **6g** of 91% ee with slightly lower diastereoselectivity (entry 7), while no reaction occurred with *p*-anisaldehyde.

In summary, a new and highly stereoselective synthesis of oxepanes has been developed on the basis of the stereoselective preparation of the enantioenriched allylsilane. The success in the practical synthesis of **1** may lead to the synthesis of related functionalized allylsilanes, which can be used as enantioenriched building blocks in organic synthesis.

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## Notes and references

1 For the five-membered ring formation, see: P. Mohr, *Tetrahedron Lett.*, 1993, **34**, 6251; T. Oriyama, A. Ishiwata, T. Sano, T. Matsuda, M. Takahashi and K. Koga, *Tetrahedron Lett.*, 1995, **36**, 5581; T. Sano and T. Oriyama, *Synlett*, 1997, 716.

2 For the six-membered ring formation, see: I. E. Markó and A. Mekhalfia, *Tetrahedron Lett.*, 1992, **33**, 1799; I. E. Markó and D. J. Bayston, *Tetrahedron*, 1994, **50**, 7141; I. E. Markó, M. Bailey, F. Murphy, J. P. Declercq, B. Tinant, J. Feneau-Dupont, A. Krief and W. Dumont, *Synlett*, 1995, 123.

3 M. Suginome, T. Iwanami and Y. Ito, *J. Org. Chem.*, 1998, **63**, 6096.

4 For a review of the reactions of chiral allylsilanes, see: C. E. Masse and J. S. Panek, *Chem. Rev.*, 1995, **95**, 1293.

5 K. Matsumura, S. Hashiguchi, T. Ikariya and R. Noyori, *J. Am. Chem. Soc.*, 1997, **119**, 8738; K.-J. Haack, S. Hashiguchi, A. Fujii, T. Ikariya and R. Noyori, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 285. The absolute configuration (*S*) of **3** was assigned by an analogy with these reports.

6 M. Suginome, A. Matsumoto and Y. Ito, *J. Am. Chem. Soc.*, 1996, **118**, 3061; M. Suginome, T. Iwanami, A. Matsumoto and Y. Ito, *Tetrahedron: Asymmetry*, 1997, **8**, 859.

7 The absolute configuration (*R*) was assigned by analogy with previous reports. See ref. 5 and 6. *Selected data* for (*R*)-**1**: $\delta_H(CDCl_3)$ 0.24 (s, 3H), 0.25 (s, 3H), 0.82 (t, *J* 6.9, 3H), 1.04–1.68 (m, 13H), 1.97–2.05 (m, 2H), 3.62 (t, *J* 6.6, 2H), 5.10–5.25 (m, 2H), 7.31–7.37 (m, 3H), 7.43–7.51 (m, 2H); $\delta_C(CDCl_3)$ −5.1, −4.5, 13.9, 22.3, 26.0, 28.5, 31.4, 32.4, 32.5, 62.9, 127.6, 128.5, 128.8, 131.5, 134.1, 138.4; $\nu_{max}$(neat)/$cm^{-1}$ 3356, 2968, 2940, 2864, 1432, 1250, 1114 (calc. for $C_{19}H_{32}OSi$ 304.2222, found 304.2221); $[\alpha]_D^{20}$ −8.38 (*c* 3.1, benzene).

8 The *trans* stereochemistry in the seven-membered ring was determined on the basis of the $^1H$ NMR coupling constant between the 2- and 3-protons in the ring. Compound **6a** exhibited a coupling constant of 9.6 Hz, whereas that for *trans*- and *cis*-2-(phenylsulfonylmethyl)-3-(phenylmethyl)oxepane were reported as 8.5 and 2.6 Hz, respectively. See: P. L. López-Tudanca, K. Jones and P. Brownbridge, *Tetrahedron Lett.*, 1991, **32**, 2261.

9 The enantiomeric excesses of **6**, except for **6a**, were determined after derivatization to the corresponding 2-substituted 3-oxepanecarboxylic acid by $RuO_2$-catalyzed oxidative C=C bond cleavage in the presence of $NaIO_4$ ($CCl_4$, MeCN, $H_2O$). The 3,5-dinitrophenylanilides were subjected to chiral HPLC with Sumichiral OA columns indicated below [compound, column, solvent (a ratio of hexanes–1,2-dichloroethane–ethanol)]: (**6b**, OA-4400, 50:15:1); (**6c**, OA-4500 × 3, 15:15:1); (**6d**, OA-4400, 15:5:1); (**6e**, OA-4900, 15:5:1); (**6f**, OA-4500, 15:5:1); (**6g**, OA-4600, 15:5:1). The absolute configurations were assigned by analogy with the stereochemical outcome for the six-membered ring formation reported previously. See ref. 3.

10 The slight decrease in the enantiomeric excesses may be attributed to a minor contribution of '*syn* attack' of the electrophiles on the allylsilane moieties during the cyclization in addition to the normal '*anti* attack'. For a discussion on the '*anti*' *vs.* '*syn*' attack in the reaction of allylsilanes with electrohiles, see: M. J. C. Bucke, I. Fleming and S. Gil, *Tetrahedron Lett.*, 1992, **33**, 4479.

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