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SILACYCLES AS TEMPLATES FOR ACYCLIC DIASTEREOSELECTION

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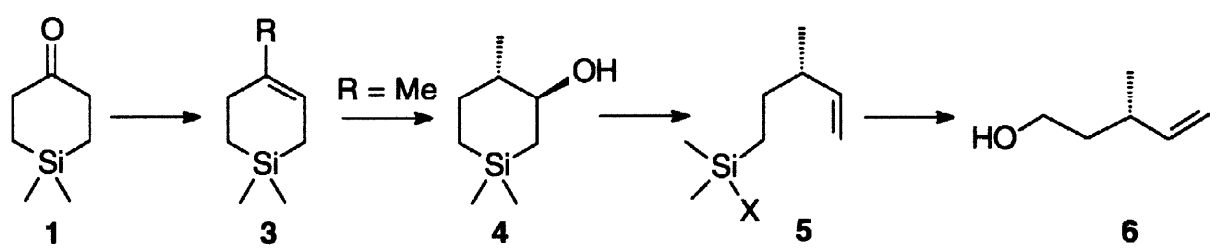
Abstract: *The 4-substituted silacyclohex-3-enes (**3**) prepared from the vinyl triflate (**9**) derived from 1,1-dimethyl-1-silacyclohexan-4-one (**1**) and higher-order organocuprates provides a versatile template for the construction of non-racemic 3-methyl-4-penten-1-ol (**6**). Through asymmetric hydroboration, **3** affords the requisite β-hydroxysilane (**4**) with the ideal geometry to undergo elimination to the chiral acyclic silane (**5**) which is oxidatively converted to **6**.*

Functionalized silacycles are potentially versatile intermediates for the construction of chiral acyclic synthons because they can undergo a variety of highly selective Si-C bond-cleaving processes. Among these, the well-known stereospecific elimination of β-hydroxysilanes (Hudrlick elimination)[2] and the Tamao oxidation[3] of organosilanes are representative, producing alkenes and alcohols, respectively. Unsymmetrical chiral synthons are of particular interest because they can be further elaborated two-dimensionally taking advantage of the non-equivalence of differing terminal functionalities. These simple chiral synthons often provide the basic building block from which a plethora of chiral centers are assembled sequentially through a series of stereoselective conversions. The Kishi synthesis of lasalocid A (X537A) represents but one example of this, with (+)-(3*S*)-methyl-4-penten-1-ol (**6**) being systematically elaborated to the non-racemic antibiotic.[4a] Because **6** has also been used similarly for the total syntheses of monensin,[5a] (+)-aplidiasphingosine,[5b] ambruticin,[5c] compactin[5d] and mevilovin,[5d] it is clearly an important synthetic intermediate whose multi-step syntheses from (*R*)-(-)-citronellene, D-(+)-ribonic acid γ-lactone, or chiral oxazolidones as well as from a microbial reduction of *E*-3-methyl-2,4-pentadien-1-ol are, themselves, non-trivial processes.[4-6] The preparation of both enantiomeric forms of **6**, when possible, involves several additional steps with the existing methodology, and none are easily amenable to changes in the substitution pattern. Easy access to either enantiomeric form of such synthons clearly provides enhanced value for such intermediates in synthetic applications (*c.f.* patchouli alcohol).[7] We envisaged **1**[8] as a novel divinyl ketone equivalent and precursor to **3**, an efficient template for the introduction of a chiral center which is retained after the silacycle is unraveled to the unsymmetrical functionalized acyclic five-carbon unit (*i.e.* **6**).



1 **3** **4** **5** **6**

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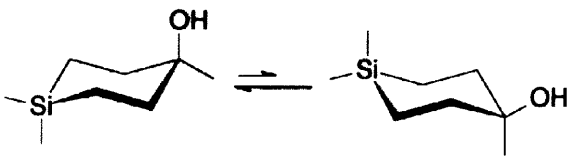


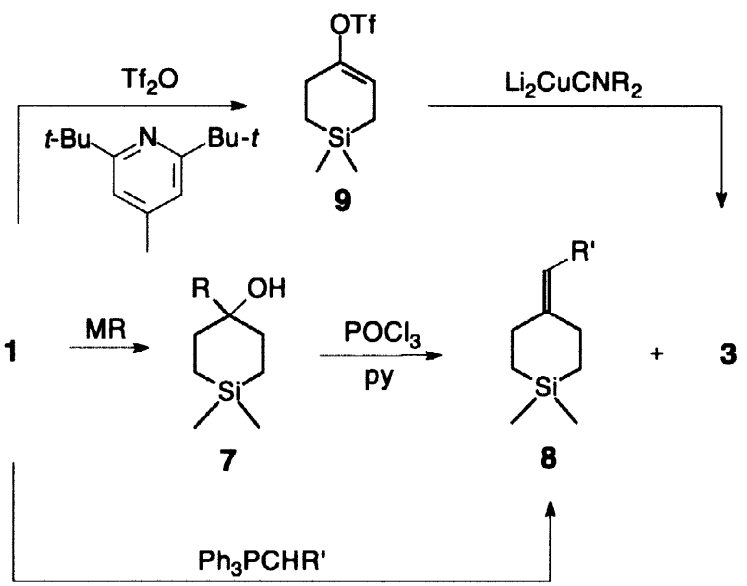
7a

We examined several methods for the **1** → **3** conversion, including the addition of several organometallic reagents which produce the corresponding carbinols (**7**) efficiently (Table 1). For the R = Me example, the chair conformation of **7a** is preferred both in the solid state ($[OH]_{ax}$ /$[OH]_{eq}$ = 2) and in solution, a conclusion which is also supported by MMX calculations which are wholly consistent with the X-ray and NMR data.[9] Whereas the dehydration of **7d** (R = Ph) with $POCl_3$ /py produces **3** (76%), this process for **7a** and **7b** leads to **3** together with minor amounts of their exocyclic counterparts **8**, which were independently prepared through standard Wittig procedures. To circumvent these regioisomeric problems, we employed a modified version of the McMurry approach[10] finding that the vinyl triflate (**9**) was easily prepared through the Stang protocol (70%)[11] and reacts cleanly with a variety of Lipshutz reagents[12] to produce **3** free of **8**. Importantly, we noted that, in contrast to their higher-order counterparts, lower-order organocuprates (*e.g.* $LiCuMe_2$), while equally effective, *result in organocopper by-products which can detonate upon chromatographic product purification!*[13] Therefore, we substituted the safer cyanocuprates for the preparation of **3**.

Table 1. Substituted silacyclohex-3-enes (**3**) from **7** and **9**.

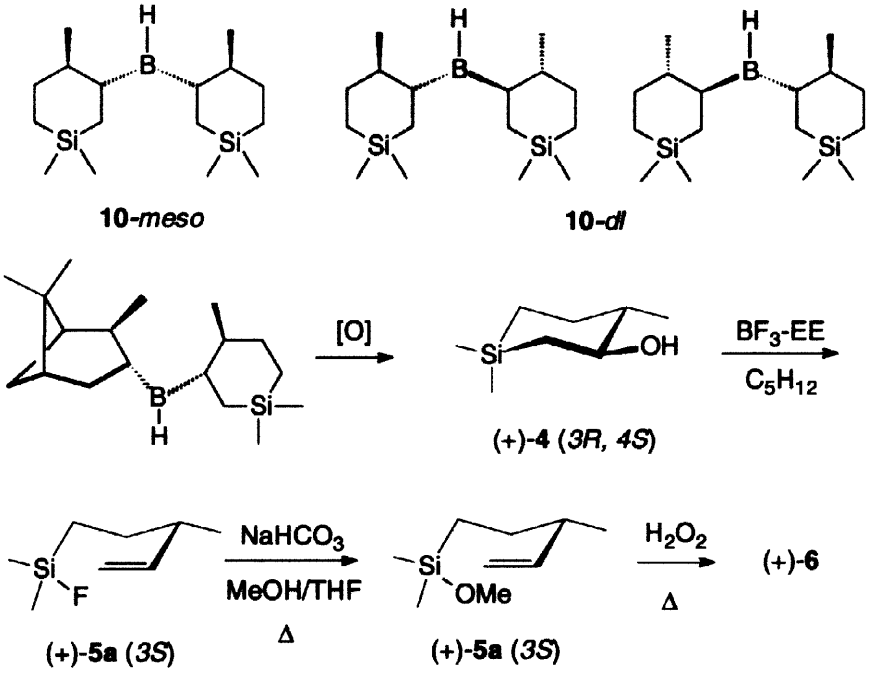
Precursor[a]	R	3/8	Series	Yield (%)[b]
7a	Me	95/5	**a**	44
9[c]		100/0	**a**	100[b] (67)[d]
7b	Bu	79/21	**b**	60
9[c]		100/0	**b**	95[b]
7c	AMV	- - -	**c**	- -
9[c]		100/0	**c**	100[b]
7d	Ph	100	**d**	76
9[c]	*t*-Bu	100/0	**e**	74
9[c,e]	$SnBu_3$	100/0	**f**	77

[a] Starting carbinols (**7**) were prepared from **1** and LiMe (**a**, 84%, bp 58-60 °C (0.5 Torr)), LiBu (**b**, 72%, bp 86-90 °C (0.75 Torr)), α-methoxyvinyllithium (LiAMV)[23] (**c**, 78%, bp 80-82 °C (0.65 Torr), and PhMgBr (**d**, 73%, mp 77-80 °C). [b] GC yield. [c] In each case, the Li_2CuCNR_2 reagent was prepared in THF by the addition of LiR to CuCN at -78 °C.[22] [d] $LiCuMe_2$ (from LiMe/CuI in EE). [e] $LiSnBu_3$ from LDA/$HSnBu_3$.

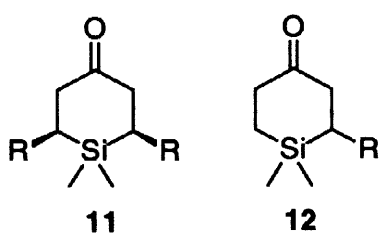


For the conversion of **3** to **4**, we initially carried out the hydroboration of **3a** with borane-methyl sulfide (BMS) which gives the dialkylboranes regioselectively as a 60:40 mixture of *meso* and *dl* dialkylboranes (**10**) which were analyzed as their methyl borinates (^{13}C NMR (OMe) δ 52.8 and 52.9, respectively (confirmed by transesterification with (-)-*cis*-myrtanol which produces separate ^{13}C NMR signals (C-10) for the *meso, d* and

l components of the resulting borinates at 67.7, 68.0 and 70.0 ppm)).[14] The alkaline hydrogen peroxide oxidation of **10** gives racemic **4** (80%). Employing monoisopinocampheylborane (100% ee), the hydroboration of **3a** (1:1, -20 °C) produces, after oxidation of the 1:1 adduct, the non-racemic (+)-**4** (70%, 68% ee ($Eu(tfc)_3$ method, Me(C-4)), a value which compares well to that achieved for 1-methylcyclohexene (72% ee) with this reagent.[15] Since both enantiomeric forms of $IpcBH_2$ are readily available, either enantiomeric form of **4** should be available by this asymmetric hydroboration approach. While potentially better optical purity is achievable (*e.g.* Masamune's borolane[16]), for the purposes of the present study, the selectivity resulting from the readily available $IpcBH_2$ reagent permitted us to establish that **4** could be effectively converted to **6** without loss of optical purity. Toward this end, we found that the slow addition of BF_3-EE (0.33 equiv) to **4** in C_5H_{12} (or HOAc) at 25 °C gives **5** (**a**, X = F), quantitatively (100% GC yield).[2,17] The small-scale isolation of this volatile intermediate (53% , bp 66-70 °C , 45 Torr) was carried out to obtain analytical and spectroscopic data and repeated for (+)-**4** ($[\alpha]_D^{29}$ = +5.3 (*c* 0.114, $CDCl_3$). We also converted (+)-**5a** to its methoxy counterpart ((+)-**5b**, X = OMe) with heating at reflux (2 h) in THF/MeOH/$NaHCO_3$ (100% GC yield, $[\alpha]_D^{30}$ = +3.5 (*c* 0.086, $CDCl_3$)).The oxidation of **5a** can be accomplished with anhydrous trimethylamine *N*-oxide (TMANO) in refluxing DMF to give (±)-**6** cleanly (69%).[18] However, **6** was most effectively produced by a one-pot procedure from (+)-**4a** through **5a** and **5b** followed by oxidation with H_2O_2 (100% GC yield).[3] The product formed from (+)-**4a** (66% ee) gave (+)-**6** (66% ee, $[\alpha]_D^{25}$ = +19.4 (*c* 0.031, $CDCl_3$, lit[4b] $[\alpha]_D^{25}$ = +29.2 (*c* 1.54, $CHCl_3$) which demonstrates that no loss of optical purity occurs through this sequence.



The methodology demonstrates that **1** can provide a cyclic template for the introduction of chiral centers and that these derivatives can be selectively elaborated to acyclic synthons of importance. With more substituted derivatives of **1** also available[19] (*cf.* **11**, **12**), variations on the above theme are currently being investigated to extend the generally of this novel approach to acyclic diastereoselection.



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