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# An allylation-metathesis sequence as a convergent strategy towards enantiopure equivalents of highly functionalized cyclic dienes

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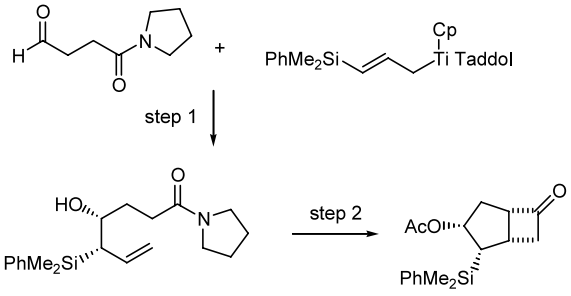
Dedicated to Professor Georges Hoornaert on the occasion of his retirement from the KUL.

**Abstract**—Highly enantioenriched equivalents of cyclic dienes have been readily prepared by asymmetric allylation of unsaturated aldehydes using a chiral allyltitanium reagent, followed by a ring-closing metathesis. The resulting β-hydroxy allylsilanes react stereoselectively with a wide variety of electrophilic reagents.

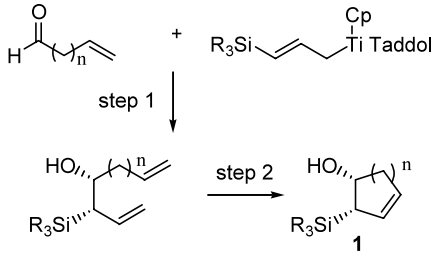

We have previously reported a two-step reaction sequence consisting of an asymmetric allylation of an aldehyde followed by a diastereoselective silicon-directed [2+2] cycloaddition (Scheme 1).[1] This illustrated a convergent strategy for the enantioselective synthesis of polycyclic compounds.

More recently we became interested in a variation of this strategy which combines an asymmetric metallation (step 1) with a ring-closing metathesis (RCM) as a general route to enantiomerically pure β-hydroxy-allylsilanes **1** which can be looked upon as *chiral equivalents* of cyclic conjugated dienes (Scheme 2). The dense functionality of these products make them prone to undergo useful transformations into a wide range of enantiomerically enriched mono- and polycyclic molecules.

Examples of sequential asymmetric allylation-RCM have been reported, but in these cases the olefinic partners for the RCM were linked by a heteroatom which became part of the newly formed ring.[2] The sequence of Scheme 2 has been very recently investigated by Roush et al. who showed that it could be elegantly applied to the synthesis of conduritols and inositols of high enantiomeric purity.[3] This report prompts us to quickly describe our own studies on the enantioselective synthesis of β-hydroxy allylsilanes **1** and their transformation into a wide variety of enantioenriched synthetic intermediates.




**Scheme 1.**




**Scheme 2.**

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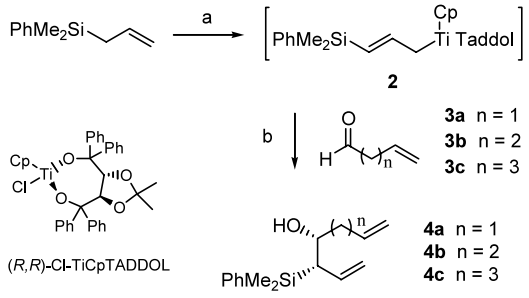
In our studies, the allylmetallation (step 1 of Scheme 2) of the unsaturated aldehydes **3a**–**c**[4] was effected with the (*E*)-γ-dimethylphenylsilyl substituted titanium reagent **2** generated from allyldimethylphenylsilane, *n*-BuLi and (*R*,*R*)-Cl-TiCpTADDOL (Table 1).[5]

The reaction gave only the *anti*-β-hydroxyallylsilanes **4a**–**c** in good yields and high enantiomeric purities. Silylation of **4a**–**c** yielded the corresponding silyl ethers **5a**–**c** which were submitted to the ring-closing metathesis (Table 2). The configurations of the two new stereogenic centers (3*S*, 4*R*) of **4a** were assigned by X-ray diffraction analysis.[1] The absolute configurations of **5a**–**c** were assigned by analogy. *t*-Butyldimethylsilyl ethers **5a**,**b** underwent an extremely fast RCM reaction in the presence of the first generation Grubbs'catalyst **8** (entries 1 and 2). Thus, with **5b**, the RCM was completed in one hour in refluxing dichloromethane with *as little as 0.05 mol% catalyst* (entry 3). The reaction was much slower with the free alcohol **4b** which is a better coordinating group than the corresponding TBS ether and could therefore deactivate the catalyst (entry 4).[2a] The RCM of the homologous diene **5c** was much slower, requiring higher temperatures and more catalyst (entry 5). However the use of 2 mol% of the new generation Grubbs' catalyst **9** enabled the reaction to take place at room temperature in 2 hours (entry 6).

**Table 1.** Asymmetric allylmetallation of 3-butenal, 4-pentenal and 5-hexenal with **2**



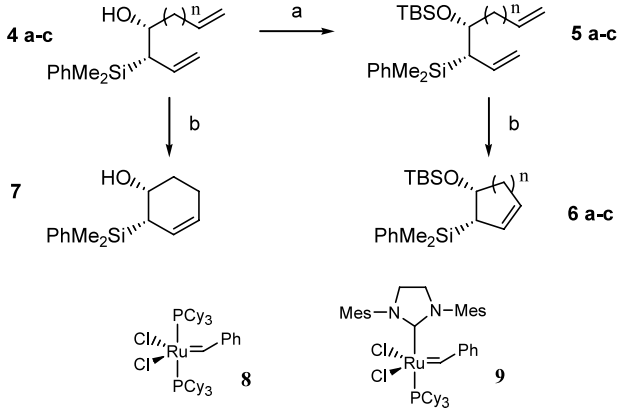

| Entry | Product | *n* | Yield | de (%) | ee (%) |
|---|---|---|---|---|---|
| 1 | **4a** | 1 | 68 | >98 | 96 |
| 2 | **4b** | 2 | 68 | >98 | 92 |
| 3 | **4c** | 3 | 75 | >98 | 90 |

*Reagents and conditions*: (a) *n*-BuLi (1.1 equiv.) in THF, 20 min, rt then (*R*,*R*)-Cl-TiCpTADDOL (1.15 equiv.), 30 min, −78°C to give a solution of **2**; (b) aldehyde **3** (1 equiv.), 3 h, −78°C, 40% aqueous $NH_4F$, 15 h, rt, flash chromatography (100% $CH_2Cl_2$), ee determined by HPLC on a Chiralcel AS or OD column.

Compounds **6a**–**c** contain a unique combination of an allyl- and a β-silyloxysilane which should be prone to undergo interesting transformations leading to a wide variety of enantioenriched, highly functionnalized synthetic building blocks. Scheme 3 shows a selection of diastereoselective transformations illustrating the synthetic utility of **6a**–**c**. In these transformations, the silyl group acts as stereodirecting group favouring the attack on the opposite face. The enantiomeric purity of all compounds described in Scheme 3 were identical to those of *anti*-β-hydroxyallylsilanes **4a**–**c**.

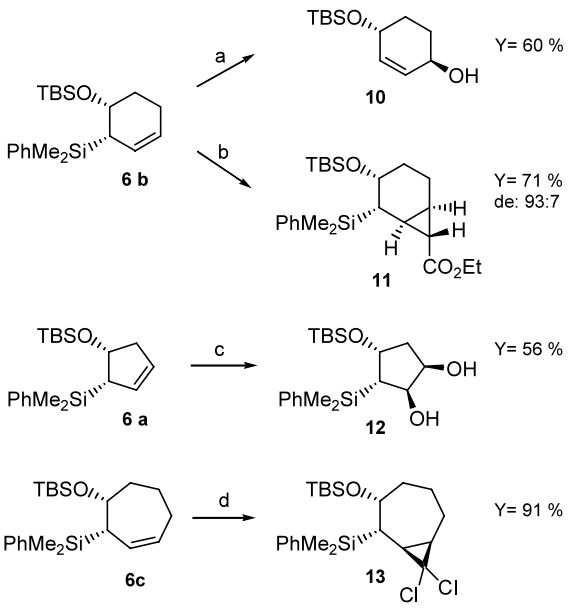
Clearly the synthetic utility of this asymmetric allylmetallation-RCM sequence would be greatly enhanced if it could be successfully applied to substituted aldehydes (Scheme 4). We have examined the silyl allyltitanation of the acetonide-protected aldehyde **14** which

**Table 2.** Ring-closing metathesis of **4b** and **5a**,**c**

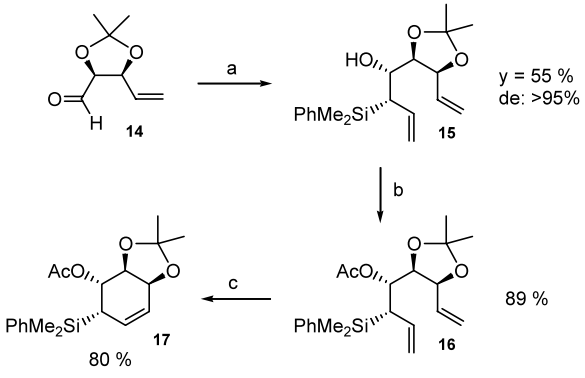



| Entry | Diene | *n* | Cat. (mol%) | Conditions for (b) | Prod. | Yield (%) |
|---|---|---|---|---|---|---|
| 1 | **5a** | 1 | **8** (2) | DCM, rt, 5 min | **6a** | 98 |
| 2 | **5b** | 2 | **8** (1.6) | DCM, rt, 2 min | **6b** | 99 |
| 3 | **5b** | 2 | **8** (0.05) | DCM, reflux, 1 h | **6b** | 99 |
| 4 | **4b** | 2 | **8** (5) | DCM, rt, 3 h | **7** | 86 |
| 5 | **5c** | 3 | **8** (7.5) | Toluene, 60°C, 2 h | **6c** | 93 |
| 6 | **5c** | 3 | **9** (2) | DCM, rt, 2 h | **6c** | 82 |

*Reagents*: (a) TBSCl (1.5 equiv.), imidazole (3 equiv.), 36 h, 50°C, DMF; (b) Mes = 2,4,6-trimethylphenyl and Cy = cyclohexyl.




**Scheme 3.** *Reagents and conditions*: (a) *N*-methyl-1,2-oxido-1,2,3,4-tetrahydroiso-quinoleine tetrafluoroborate (1 equiv.), $CH_2Cl_2$, rt, 30 min; (b) Ethyl diazoacetate (1.2 equiv.), $Cu(acac)_2$ (2 mol%), toluene, 90°C, 3 h; (c) $K_2OsO_4{\cdot}2H_2O$ (2 mol%), NMO.$H_2O$ (1.7 equiv.), $H_2O$/THF, rt, 48 h; (d) $Et_3BnNCl$ (0.1 equiv.), NaOH 50%, $CHCl_3$, rt, 15 h.




**Scheme 4.** *Reagents and conditions*: (a) *n*-BuLi (1.1 equiv.) in THF, 20 min, rt then (*R*,*R*)-Cl-TiCpTADDOL (1.15 equiv.), 30 min, −78°C then **14** (1 equiv.), 3 h, −78°C, 40% aqueous $NH_4F$, 15 h, rt; (b) pyridine (3.5 equiv.), $CH_3COCl$ (2.5 equiv.), DCM, 4 h, rt; (c) Grubbs'catalyst **9** (8 mol%), boiling DCM, 2 h.

proceeded indeed with high diastereoselectivity to give the corresponding *anti*-β-hydroxyallylsilane **15**. The corresponding acetate **16** was subjected to RCM in the presence of the second generation Grubbs'catalyst to give 80% yield of the polysubstituted cylohexene **17** in high enantiomeric purity (ee>95%).

$^1$H NMR analysis and molecular modeling (Monte Carlo exploration of conformational space with MM3 force field)[6] of **17** suggested a half-chair conformation with a pseudoaxial silyl substituent (Fig. 1). This should allow an interaction (β-effect) with the olefinic bond and favor electrophilic attack on the face opposite to

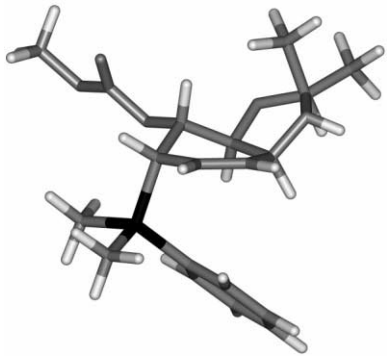


**Figure 1.** Lowest energy conformation of **17**.

the one occupied by the silyl substituent. However, the dichlorocyclopropanation reaction under the classical conditions (PTC or *t*-BuOK+$CHCl_3$) did not take place, probably as a result of the steric hindrance on both faces of the double bond. It is interesting to note that the dihydroxylation of the double bond was possible when the two oxygen atoms were not part of a ring.[3b]

## Acknowledgements

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6. We thank Dr M. Laguerre for his help.