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An efficient synthesis of optically active (2*R*,3*R*)-2-methyl-3-[(1*R*)-1-methylprop-2-enyl]cyclopentanone, a useful chiral building block for synthesis of vitamin D and steroids

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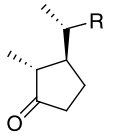
Abstract—An efficient synthesis of optically active (2*R*,3*R*)-2-methyl-3-[(1*R*)-1-methylprop-2-enyl]cyclopentanone, a useful chiral building block for synthesis of vitamin D and steroids, has been developed starting from readily accessible optically active secondary propargyl phosphate (*R*)-**2**, where the asymmetric Michael addition of a chiral allenyltitanium to alkylidenemalonate **3** is a key reaction.

3-Substituted-2-methylcyclopentanones of the type **1** shown in Figure 1, which have a stereodefined side-chain at the 3-position, or their acetal derivatives have been accepted as useful CD ring synthons of vitamin D, steroids and their derivatives. Among these compounds, those having a functionalized side-chain, such as **1b** and **1c**, have been considered to be versatile since the functionality could be derivatized to a variety of side-chains.[1] Therefore, much effort has been paid to develop new efficient methodology to synthesize these cyclopentanones. However, to date, only a limited number of methods have been reported which allow access to these cyclopentanones with high optical purity due to the difficulty in asymmetric construction of the relative and the absolute stereochemistries with respect to the side-chain, which correspond to the C-17 and C-20 of steroids, respectively. These synthetic methods include selective cleavage of bicyclic compounds,[2] asymmetric conjugated addition to cyclopentenones,[3] and other processes.[4] Thus, new efficient methodology to prepare such cyclopentanones is still highly desirable.



1a: R = $CH_2CH_2CH_2CH(CH_3)_2$, for synthesis, see ref. 2b, 2c, 3, and 4c

1b: R = CH_2CH_2OR', for synthesis, see ref. 2b

1c: R = $CH{=}CH_2$, while synthesis has not been reported, see ref. 3 for synthesis of its acetal derivative.

Figure 1.

In line with our continuing interest in vitamin D synthesis,[5] we report herein an efficient and practical synthesis of optically active (2*R*,3*R*)-2-methyl-3-[(1*R*)-1-methylprop-2-enyl]cyclopentanone (**1c**) from an acyclic compound.

Recently, we have reported that the Michael addition of chiral allenyltitaniums, generated from readily accessible optically active secondary propargyl phosphates and a Ti(O-*i*-Pr)$_4$/2*i*-PrMgCl reagent,[6,7] to alkylidenemalonates proceeds with excellent diastereo- and enantioselectivity.[6a] With these results, we expected that the reaction could be used to synthesize cyclopentanone **1c** efficiently, as shown in Scheme 1 by a retrosynthetic way.

The allenyltitanium, prepared from (*R*)-1-methyl-3-trimethylsilylprop-2-ynyl phosphate (**2**) with 98.0% e.e.[8] and Ti(O-*i*-Pr)$_4$/2*i*-PrMgCl, reacted smoothly with diethyl 3-(*tert*-butyldimethylsilyloxy)propylidenemalo-

Keywords: Michael addition; chiral allenyltitanium; vitamin D; steroids.

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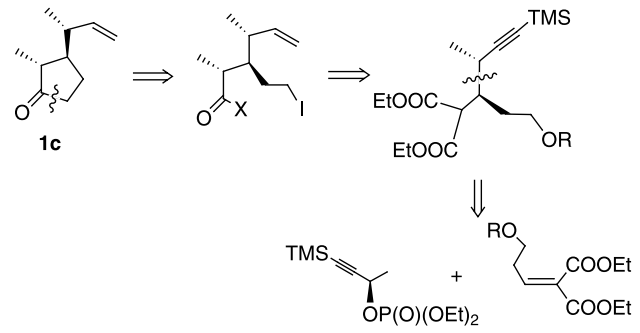
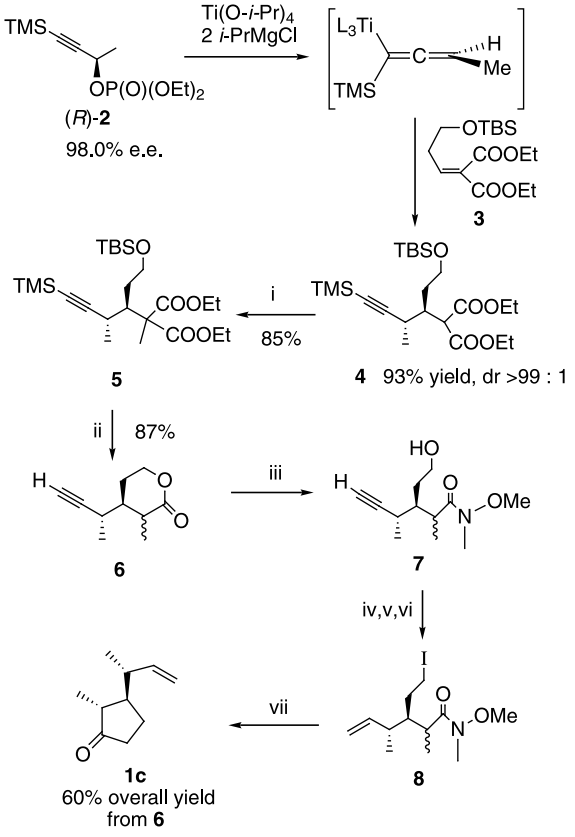
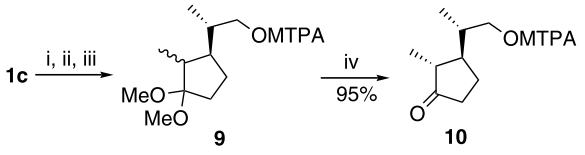


Scheme 1.



Scheme 2. *Reagents and conditions*: (i) NaH, MeI, THF; (ii) LiCl, H_2O, DMSO, reflux, 8 h, then 1N HCl; (iii) $AlMe_3$ (3 equiv.), Me(OMe)NH·HCl (3 equiv.), THF–CH_2Cl_2; (iv) Lindlar's cat., H_2; (v) MsCl, NEt_3, THF; (vi) NaI, acetone; (vii) *t*-BuLi (2.4 equiv.), −78°C, THF, then 1N NaOH.

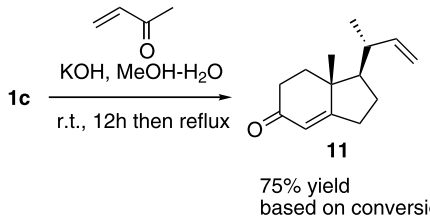


Scheme 3. *Reagents and conditions*: (i) PTS, $HC(OMe)_3$, MeOH, 90%; (ii) O_3, MeOH, then $NaBH_4$, 86%; (iii) (*R*)-/(*S*)-MTPACl, py., 84%; (iv) TFA, CH_2Cl_2, H_2O.

nate (**3**)[9] to afford the expected product *anti*-**4** as the only detectable isomer in 93% yield, as shown in Scheme 2. Compound **4** was methylated with NaH and MeI to give **5** in high yield, which was subsequently subjected to the decarbethoxylation reaction. To our satisfaction, in addition to removal of one of the ester groups, both silyl protective groups of **5** were simultaneously removed to afford δ-lactone **6** as a diastereomeric mixture with respect to the α-stereogenic center of the carbonyl group in 87% yield. Lactone **6** was then treated with *N*,*O*-dimethylhydroxyamine hydrochloride/$AlMe_3$ reagent[10] to give amide **7**, which was successively subjected to partial hydrogenation of the terminal triple bond and conversion of the hydroxy to an iodo group by conventional reactions to furnish iodoamide **8**. Compound **8** was smoothly cyclized by treatment with 2.4 equiv. of *tert*-butyllithium at −78°C to afford, after epimerization, the title compound **1c** in 60% overall yield from **6**.

The enantiomeric excess (e.e.) of cyclopentanone **1c** thus obtained was determined to be 97.5% by ^1H NMR analysis after derivatization to 2-methoxy-2-trifluoromethyl-2-phenylacetyl (MTPA) ester **9**, as shown in Scheme 3, indicating the overall enantiospecificity from **2** to **4** is >99%. Meanwhile, the absolute configuration of **1c** was determined after derivatization to a pair of diastereomeric MTPA ester **10**, as shown in Scheme 3, among which **10** with the (*R*)-MTPA moiety displayed identical NMR spectra to those of its known enantiomer, (*S*)-MTPA ester of (2*S*,3*S*)-2-methyl-3-[(1*R*)-1-methyl-2-hydroxyethyl]cyclopentanone.[11]

Cyclopentanones **1a** and **1b** have been converted to hydrindenone, the CD ring portion of vitamin D, steroids, and their derivatives, by Robinson annulation. However, the corresponding Robinson annulation of **1c** has not been reported, and thus, we carried out this transformation. Treatment of **1c** with methyl vinyl ketone in the presence of KOH furnished hydrindenone **11** in 62% yield with 17% recovery of **1c**, as shown in Eq. (1). Compound **11** might serve as a key intermediate for synthesizing vitamin D derivatives having a variety of side-chains,[12] thanks to the versatility of the vinyl moiety present in **11**.[13]



(1)

In conclusion, an efficient entry to optically active (2*R*,3*R*)-2-methyl-3-[(1*R*)-1-methylprop-2-enyl]cyclopentanone, a useful chiral building block for synthesis of vitamin D and steroids, has been developed starting from readily accessible propargyl phosphate (*R*)-**2**. Further applications of this compound for the synthesis of novel vitamin D analogs are currently being carried out in this laboratory.

Acknowledgements

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