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Stereoselective Synthesis of (±)-Cedranediol *via* Intramolecular Double Michael Reaction

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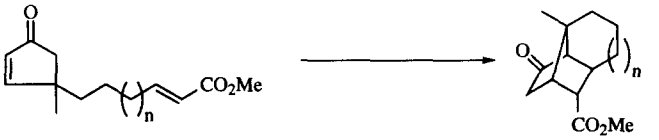
Abstract. Total synthesis of (±)-cedranediol (**7**) was achieved using intramolecular double Michael reaction. Heating the enone **10** together with $ZnCl_2$, Et_3N, and TMSCl gave the tricyclo[5.2.1.$0^{1,5}$]decane **9** as a single diastereomer, which was converted into (±)-cedranediol (**7**).

Domino (cascade) reaction is one of the most promising methods for stereoselective construction of polycyclic compounds.[1,2] We previously reported the synthesis of tricyclo[5.3.0.$0^{3,8}$]decane **3** and tricyclo[6.3.0.$0^{3,9}$]undecane **4** by the intramolecular double Michael reaction of cyclopenten-1-ones **1** and **2** bearing the α,β-unsaturated ester at the 4-position.[3] We now describe the stereoselective synthesis of tricyclo[5.2.1.$0^{1,5}$]decanes from 5-substituted cyclopenten-1-one derivatives using the intramolecular double Michael reaction, and the synthesis of an oxygenated cedrane derivative, (±)-cedranediol, by the application of this methodology.



1 n = 1
2 n = 2

3 n = 1
4 n = 2

We first examined the assembly of **6** by the intramolecular double Michael reaction of **5**.[4] Treatment of **5** with lithium hexamethyldisilazide (LHMDS) in Et_2O at -78 °C (method A) gave the desired tricyclic compound **6** as a single diastereomer in 42% yield. Stereochemistry of the ester group of **6** was determined by NMR spectroscopy; W-shaped long range coupling (2.2 Hz) was observed between the methylene hydrogen at the α-position of keto carbonyl group and the methine hydrogen at the α-position of ester group. The fact suggests that the ester group orients to endo. Furthermore, reaction of **5** with $ZnCl_2$, Et_3N and TMSCl in toluene in a sealed tube at 160 °C (method B)[5] gave **6** in 58% yield as a sole product.

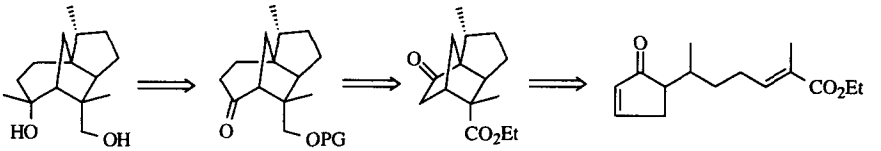
On the other hand, reaction with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) and Et_3N

(method C) afforded a disappointed result, and treatment with TMSI or $^{n}Bu_2BOTf$ in the presence of hexamethyldisilazane (HMDS)[3] (methods D and E) produced no cyclized product, although **4** was obtained in good yields by both methods D and E. Thus, it has been made clear that the method B is proper for construction of tricyclo[5.2.1.$0^{1,5}$]decane.

5 **6**

Conditions	Yield (%)
(Method A) LHMDS	42
(Method B) $ZnCl_2$, Et_3N, TMSCl, heat	58
(Method C) TBSOTf, Et_3N	7
(Method D) TMSI, HMDS	0
(Method E) $^{n}Bu_2BOTf$, HMDS	0

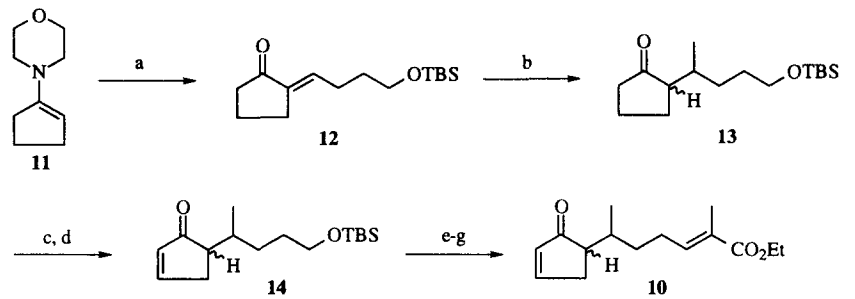
Next, we investigated the synthesis of (±)-cedranediol (**7**) utilizing this strategy. Cedranediol, the oxygenated cedrane derivative, was isolated in 1968 from *Juniperus fortidissima* by Norin *et al.*[6] Stereoselective construction of three methyl groups is the most difficult problem for the synthesis.[7] Our retrosynthetic analysis is outlined as below. The methyl group neighbouring the tertiary hydroxy group can be introduced from the convex face of **8**, which can be earned from **9**. The tricyclic compound **9** could be stereoselectively synthesized from **10** employing the intramolecular double Michael reaction.



(±)-cedranediol (**7**) **8** **9** **10**

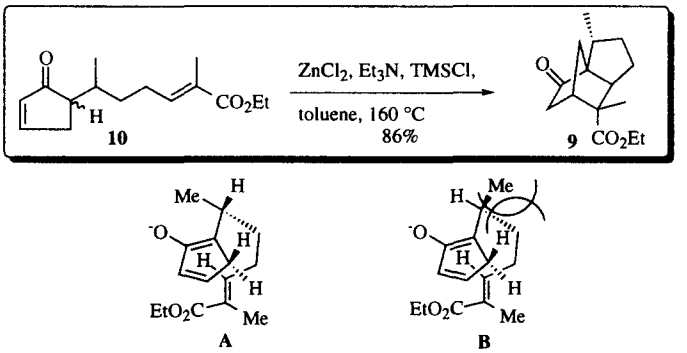
The key intermediate **10** was prepared as follows. Aldol reaction of 4-(1-cyclopenten-1-yl)morpholine with 4-(*tert*-butyldimethylsiloxy)-1-butanal,[8] followed by dehydration, gave the enone **12** as a single isomer, in 60% yield. After the conjugate addition of the Gilman reagent[9] (92% yield), transformation of the resulting 1:1 diastereoisomeric mixture **13** into **14** was performed in 83% yield using catalytic Saegusa reaction[10] under Larock's reaction conditions.[11] Deprotection (97% yield), followed by oxidation with PDC, gave the crude aldehyde, which was treated with Wittig reagent to furnish the substrate **10** of the key reaction in 71% yield for two steps.

Treatment of **10** with $ZnCl_2$, Et_3N and TMSCl in toluene at 160 °C in the sealed tube caused the



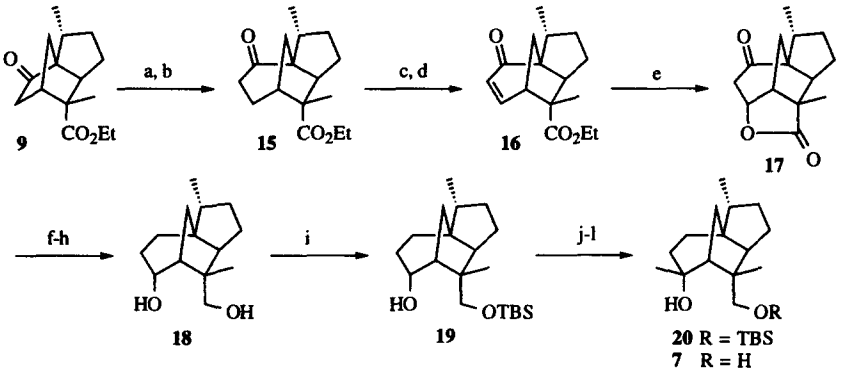
a) 4-(*tert*-butyldimethylsiloxy)-1-butanal, MeCN, reflux; aq. NH_4Cl, 60%; b) Me_2CuLi, 92%; c) LDA; TMSCl, Et_3N; d) $Pd(OAc)_2$, O_2, DMSO, 83%; e) $^nBu_4NF$, 97%; f) PDC;g) $Ph_3P{=}C(Me)CO_2Et$, 71% for two steps.

intramolecular double Michael reaction to afford the tricyclo[5.2.1.$0^{1,5}$]decane **9** as a single stereoisomer in 86% yield. Two conformations **A** and **B** were considered as transition states during the cyclization, and the latter **B** would suffer from the steric interaction between the methyl group and the hydrogen at the sp^3 carbon on the five-membered ring. Therefore, the conformation **A**, which leads to **9** having the required stereochemistry, would be the preferred one. The stereostructure of **9** was eventually established by the following transformation into (±)-cedranediol (**7**).



Treatment of **9** with ethyl diazoacetate in the presence of $BF_3{\cdot}OEt_2$,[12] followed by deethoxycarbonylation using $MgCl_2$ in hot DMSO,[13] gave **15** surprisingly as a sole rearranged product in 74% yield for two steps. After conversion of **15** into **16** (76% yield for two steps), hydrolysis of **16** with aqueous NaOH in MeOH, followed by acidic treatment, underwent the smooth intramolecular lactonization to provide **17** in 85% yield. Decarbonylation of the keto carbonyl group was accomplished in two steps (dithioketalization and Raney Ni reduction). The diol **18** (53% yield for three steps) was obtained by reduction of the resulting crude product with DIBALH. Selective silylation of the primary hydroxy group was carried out in 94% yield using TBSCl in the presence of DMAP in DMF. Oxidation of the resulting secondary hydroxyl group with $^nPr_4NRuO_4$ and *N*-

methylmorpholine-*N*-oxide (NMO),[14] and the subsequent addition of MeLi produced **20** in 85% yield as a single diastereoisomer. Finally, deprotection of the TBS group of **20** with tetrabutylammonium fluoride (TBAF) gave (±)-cedranediol (**7**). The spectral data of the synthetic compound **7** were consistent with reported ones[6,7a] in all respects.



a) N_2CHCO_2Et, $BF_3{\cdot}OEt_2$; b) $MgCl_2{\cdot}6H_2O$, DMSO, heat, 74% for two steps; c) TMSOTf, Et_3N; d) $Pd(OAc)_2$, O_2, DMSO, 76% for two steps; e) 10% NaOH, MeOH, reflux then dil. HCl, 85%; f) $HS(CH_2)_2SH$, $BF_3{\cdot}OEt_2$; g) Raney Ni(W2); h) DIBAH, toluene, reflux, 53% for three steps; i) TBSCl, DMAP, DMF, 94%; j) $^nPr_4NRuO_4$, NMO, 4AMS, 78%; k) MeLi, Et_2O, 85%; l) $^nBu_4NF$, quant.

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4. Compound **5** was prepared as follows; i) alkylation of *N*-(cyclopentylidene)cyclohexylamine with 4-(*tert*-butyldimethylsiloxy)-1-bromobutane in the presence of LDA and HMPA, and then treatment with aq. NH_4Cl (94%), ii) phenylselenylation with LDA and PhSeCl followed by oxidative elimination with H_2O_2 and pyridine (55% for two steps), iii) desilylation with AcOH-THF-H_2O, (1:1:1 v/v) (93%), iv) oxidation with $^nPr_4NRuO_4$ in the presence of NMO and 4A molecular sieves; v) Wittig reaction using $Ph_3P{=}CHCO_2Me$, (79% for two steps).
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