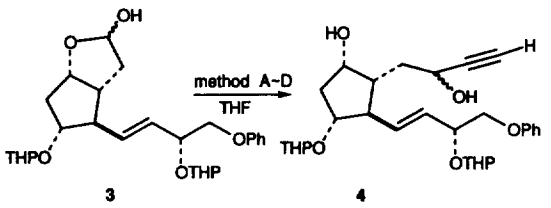
Table 1. Preparation of Propargyl alcohl **4**



Method	Conditions	Yield (%)
A	i. H−≡−$SnBu_3$/n-BuLi, −78℃ ~*rt.* ii. n-BuLi, −78℃ ~*rt.*	82
B	i. H−≡−$SiMe_3$/n-BuLi, −78℃ ~*rt.* ii. TBAF, *rt.*	93
C	H−≡−H/n-BuLi, −78℃ ~*rt.*	82
D	H−≡−MgBr, 0℃ ~*rt.*	91

We describe herein a convenient synthesis of **1** *via* facile introduction of protonated allenyl group starting with the known lactone **2**.[6]

The basic strategy of this synthesis involves efficient ring opening of lactol **3** with metal acetylides, subsequent acetylation and facile introduction of three-carbon unit with formation of allenyl group (Scheme 1).

We intended to develop a simple synthetic route to fenprostalene (**1**) by the direct reaction of lactol with metal acetylide and acetylation of the resulting diol since our synthetic strategy need not differentiate two hydroxy groups in C-6 and C-9 (PG numbering) positions. The lactone **2** was reduced with DIBALH in toluene at −78 ℃ to the lactol **3**, which was sufficiently pure to be used without purification.

Firstly, the reaction of the lactol **3** was examined with several metal acetylides (Table 1). When the lactol **3** was treated with lithium acetylide-ethylendiamine complex in THF or DMF as the solvent, the reaction did not completed due to the low reactivity of lithium acetylide-ethylenediamine complex. But, the reactions of the lactol **3** with lithium anion of 5 equivalents of ethynyltri-*n*-butyltin or trimethylsilylacetylene in tetrahydrofuran (−78 ℃ ~*r.t.*) proceeded smoothly to afford the propargylic alcohol **4** in 82% and 93% yield, respectively (method A and B). The propargylic alcohol **4** was also obtained by the reaction of the lactol with **5** equivalents of lithium acetylide or ethynylmagnesium bromide (method C and D). The reaction of lactol with ethynylmagnesium bromide (method D) seems to be appropriate and efficient since the reaction with lithium tri-*n*-butylstannanylacetylide or lithium trimethylsilylacetylide necessitate additional deprotecting step. The resulting propargylic alcohol **4** was transformed to the propargylic acetate **5** with an excess amount of acetic anhydride and triethylamine in the presence of a catalytic amount of 4-dimethylaminopyridine (DMAP) in 91% yield.

The propargylic acetate was further converted to the protonated allene with concomitant three-carbon homologation through cuprate-based Grignard reaction. The reaction of propargylic acetate **5** with 3-*t*-butyldimethylsilyloxypropylmagnesium bromide and catalytic amount of $CuI \cdot P(OEt)_3$ at −40 ℃ in THF afforded cleanly the allenic acetate **6** in 76% yield. The fenprostalene (**1**)[2] was formed from the allenic acetate **6** by the following sequential reactions; deprotection of silyl group with *tetra-n*-butylammonium fluoride (TBAF) (98%), consecutive oxidation with pyridinium dichromate (PDC)/CH_2Cl_2 and PDC/MeOH/DMF (84%), deprotection of acetyl group in **8** with methanolic potassium carbonate (89%), and deprotection of tetrahydrofuranyl group with acetic acid/H_2O/THF (19 : 11 : 3) (65%). The spectroscopic properties of **1** were in accord with those described in the literature.[2]

In conclusion, the synthesis of luteolytic prostaglandin fenprostalene (**1**) has been achieved in 8 steps and ~30% overall yield starting from lactone **2**. The efficacy of our synthesis relies on the facile introduction of allenic moiety with concomitant three-carbon homologation. The synthetic steps were also shortened by direct reaction of the lactol **3** with ethynylmagnesium bromide followed by acetylation.

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Nucleophilic Additions to 5-Hydroxymethyl-2-pyrrolidinone: Synthesis of Chiral 2,5-Disubstituted Pyrrolidines

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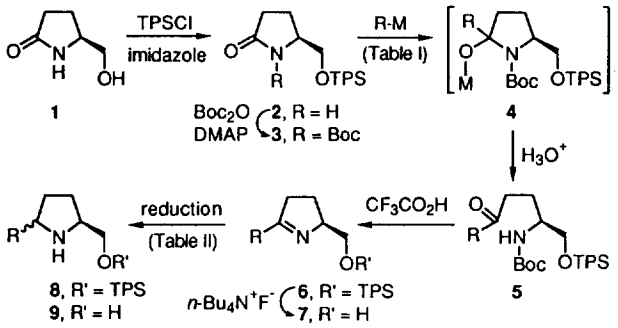
2,5-Disubstituted pyrrolidines occur as many bioactive natural products,[1] and C_2 symmetric 2,5-disubstituted pyrrolidi-



Scheme 1.

nes are useful ligands in asymmetric synthesis.[2] Ample examples of stereoselective synthesis of these compounds have been appeared in the literature.[3] We have been interested in the stereoselective synthesis of 5-substituted-2-hydroxymethylpyrrolidines, with substituents of different steric bulkiness, as possible chiral bidentate ligands and also as useful synthetic intermediates. Herein, we wish to report a general and efficient synthetic route to chiral 5-substituted-2-hydroxymethylpyrrolidines. (*S*)-5-Hydroxymethyl-2-pyrrolidinone, which is readily available from L-glutamic acid,[4] was chosen as the starting material. The introduction of carbon nucleophiles of different steric bulkiness to the lactam carbonyl group and the stereoselective reduction of 2,5-disubstituted five-membered cyclic imines are the subjects of this paper (Scheme 1).

The examples of nucleophilic addition of organometallic reagents to lactams are limited because lactam carbonyl groups have inherently poor electrophilicity. Only very reactive organolithiums are known to undergo addition to tertiary amides.[5] This problem was solved by activating the lactam carbonyl group: that is, protection of lactam nitrogen with an electron-withdrawing group such as Boc or Cbz. This approach, the nucleophilic addition to an activated lactam, has been originally reported by S. Nozoe.[6] We have studied this approach with sterically hindered nucleophiles such as *sec*- and *tert*-carbon-based nucleophiles as well as *pri*-carbon nucleophiles. Typical *pri*-carbon nucleophiles such as RMgX reacted readily with the activated lactam **3** to give the mono-addition product **5** in high yields as already reported in the literature.[6] In the case of *sec*-carbon nucleophiles, for example, *i*-PrMgBr also gave the adduct in high yield. However, *s*-BuLi gave a much lower yield and a considerable amount of starting material was recovered after quenching the reaction; this indicates that deprotonation was a competing reaction. Deprotonation was also significant for *t*-BuMgCl as well as *t*-BuLi and a significant amount of the starting material was recovered in each case. It is well known that organocerium reagents show negligible basicity compared to the corresponding RMgX or RLi but have comparable nucleophilicity.[7] Thus, when organocerium reagents of *sec*-and *tert*-carbon nucleophiles were employed in the addition reaction, the deprotonation problem was largely solved and high yields of adducts were obtained (Table 1).

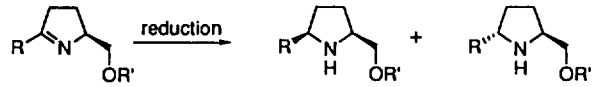
In no case, the second addition of the nucleophile was observed in the above reactions, which indicates that the mono-adduct was stable in the form of tetrahedral intermediate **4** before hydrolysis. When the R is *tert*-butyl group in **4**, it was necessary to hydrolyze the adduct in acidic condition (20% AcOH in CH_2Cl_2) for several hours to generate the acyclic adduct **5**. Treatment of the adduct **5** with CF_3CO_2H at 0 ℃ and subsequent basic work-up readily afforded the corresponding cyclic imine **6** in high yields (90-97%).[8]

Table 1. Nucleophilic Addition of R-M to the Lactam **3**

entry	R-M	Condition (℃ ; h)	**5**, % Yield[a]
1	PhMgBr	−40; 1	92
2	MeMgCl	−40; 1	94
3	*n*-BuMgBr	−40; 1	96
4	*i*-PrMgBr	25; 1	87
5	*s*-BuLi	−78; 0.5	54(25)
6	*i*-PrMgBr-$CeCl_3$	0; 0.2	92
7	*t*-BuMgCl	25; 24	53(35)
8	*t*-BuLi	−78; 0.5	74 (15)
9	*t*-BuLi-$CeCl_3$	−78; 0.5	78

[a] Isolated yields after column chromatography on SiO_2: values in parenthesis are those of the recovered starting material.

Table 2. Stereoselective Reduction of the Imine **6** and **7**



Entry	Imine	Reduction condition	*Cis* : *Trans*[a]	% Yield[b]
1	**6** (R=*n*-Bu)	H_2-Pd/C	≤95 : 5	85
2		DIBALH	≤95 : 5	70
3		Me_3Al-$LiAlH_4$	70 : 30	–
4	**7** (R=*n*-Bu)	$NaBH(OAc)_3$	45 : 55	(60)[c]
5		PtO_2	75 : 25	88

[a] The ratio was determined by ^1H NMR spectrum analysis for **8**: in the case of **9**, it was converted to **8**. [b] Isolated yield. [c] Yield in parenthesis is that of the N-Cbz-protected **8**.

The stereoselective reduction of the cyclic imine bond was studied for both **6** (R=*n*-Bu) and **7** (R=*n*-Bu). The catalytic hydrogenation of **6** with Pd/C (50 psi H_2, 25 ℃) was *cis*-selective: the *cis/trans* ratio was ≥95 : 5,[9] which was determined by ^1H NMR spectrum analysis for the amine **8** (R=*n*-Bu). The *cis* and *trans* product mixture[10] were separately synthesized for the NMR analysis by adopting the Nozoe's procedure. The methylene protons at *C*-2′ (-CH_2OTPS) exhibit different splitting patterns for each isomers: two doubled-doublets for the *cis*-**8** [δ 3.64 (1H, *J*=16.1, 10.1 Hz), 3.72 (1H, *J*=10.0, 10.1 Hz)] and a doublet for the *trans*-**8** [δ 3.55 (2H, *J*=6.6 Hz)]. The major product of the hydrogenation reaction was assigned as *cis*,[11] which could be explained by the conformational change of the five-membered ring including the nitrogen inversion.[12] The reduction of **6** (R=*n*-Bu) with DIBALH (2-4 molar equiv., −78 ℃) also gave *cis*-isomer with selectivity comparable to that of the hydrogenation.[9] Interestingly, even with the Me_3Al-$LiAlH_4$ system that was proven to be *trans*-selective in the case of six-membered cyclic

imines by H. Yamamoto,[13] *cis*-isomer was obtained as major product.

We turned our attention to other *trans*-selective reduction approach for the hydroxy-imine **7**. The reduction of the imine **7** with $NaBH(OAc)_3$, which is useful for the "directed reduction",[14] however, gave almost an equal amount of both isomers. Hydrogenation of the imine **7** with PtO_2 as catalyst also gave the *cis*-isomer as major product[15] (Table 2).

In conclusion, nucleophilic additions of sterically hindered carbon nucleophiles to the activated lactam **3** can be efficiently carried out through organocerium complexes. Also, the stereoselective reduction of five-membered cyclic imine **6** and **7** has been done with several reagents. Although a further study is necessary to develop an efficient *trans*-selective reduction method, our results will be useful for the preparation of *cis*-2,5-disubstituted pyrrolidine derivatives. A synthetic application of this work is in progress.

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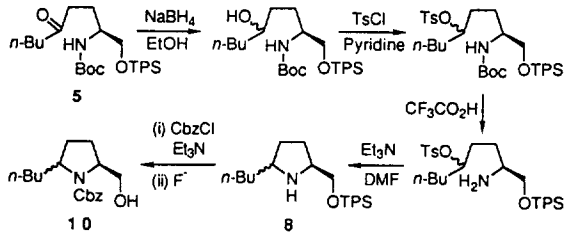
9. In the case of **6** (R=*i*-Pr), a similar selectivity was observed.
10. It was difficult to separate *cis*-**8** and *trans*-**8** mixture by column chromatography; however, almost 1 : 1 ratio of *cis/trans* could be determined by ^1H NMR spectrum analysis. If desired, each isomer can be separated at the stage of **10** by careful column chromatography on SiO_2.



11. It has been assumed that the catalytic reductions of 2,5-disubstituted cyclic imines produce the major *cis*-pyrrolidines: see the paper of D. Bacos *et al.* in reference 1.
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Stabilizing Effect of Tributyltin Group on Adjacent Carbon Radicals

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In connection with radical cyclization of N-aziridinylimines,[1,2] we have reported that the radical cyclization of **1** afforded only **3** in high yields without the formation of **4** (eq. 1), while **5** gave a 87 : 13 mixture of **6** and **7** under the similar radical conditions due to the formation of an intermediate allylic radical (eq. 2). Further studies with **8** gave the similar results and only **9a** and **9b** were isolated in 82% and 89% yield, respectively (eq. 3).[3,4] It is also noteworthy that 1,5-hydrogen transfer did not take place prior to radical cyclization. Since the reaction should proceed via an intermediacy of **2**, the sole formation of **3** and **9** was quite surprising to us. We assumed that the reason for this observation could