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Synthesis of Optically Active 6-Amino-2-Cycloheptenone as a Convenient Chiral Building Block for the Preparation of 6-Alkyl-2-Cycloheptenone

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Abstract: Optically active 6-amino-2-cycloheptenone **5** has been prepared from ethyl 2*(E)*,6-heptadienoate where the Michael addition of a chiral amine, Ti(II)-mediated intramolecular nucleophilic acyl substitution reaction and $FeCl_3$-mediated ring expansion are the key steps. The compound **5** undergoes highly diastereoselective conjugate addition of a Grignard reagent in the presence of a catalytic amount of $Li_2Cu(CN)Cl_2$ to provide the corresponding *cis*-adducts which, in turn, are converted into 6-alkyl substituted 2-cycloheptenones by treatment with *p*-TSA. © 1999 Elsevier Science Ltd. All rights reserved.

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Optically active seven-membered ring carbocycles occur frequently in nature and many of them exhibit interesting biological activities. Therefore, a variety of asymmetric synthetic methods and strategies aiming at seven-membered rings have been reported [1]. We report here the synthesis of optically active 6-amino-2-cycloheptenone and its utilization as a chiral building block for preparing substituted seven-membered carbocyclic frameworks.

Recently, we have developed an efficient and practical method for preparation of optically active 5-*tert*-butyldimethylsiloxy-2-cyclohexenone (**2**) and have shown that it works as a 2,5-cyclohexadienone synthon. As shown in Scheme 1, the Ti(II)-mediated cyclization of the optically active ethyl 3-*tert*-butyldimethylsiloxy-5-hexenoate (**1**) [2] and the successive $FeCl_3$-mediated ring expansion [3] provided **2** in excellent overall yield. The reaction of **2** with organocuprates gave highly selectively the corresponding 1,4-addition products which, in turn, could be converted into optically active 5-alkyl-2-cyclohexenone **3** by treatment with a base or acid [4]. With these results in hand, we became interested in the synthesis of chiral 2-cycloheptenone **5** having a proper leaving group X at the 6-position starting from optically active **4**, aiming to see whether **5** can work as an effective chiral 2,6-cycloheptadienone synthon, *i.e.*, the feasibility for its stereoselective conversion into **6** (Scheme 1).

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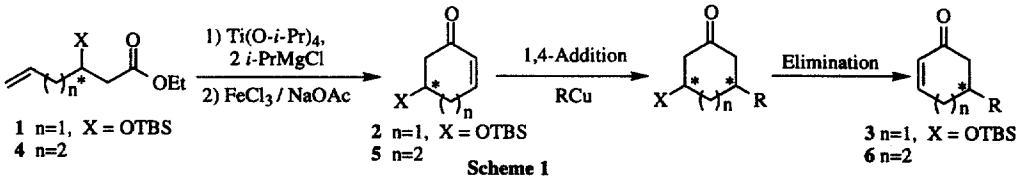
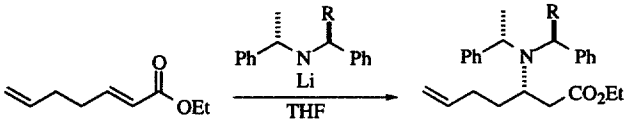


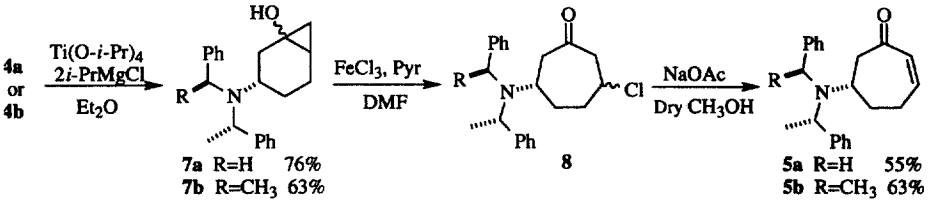
Scheme 1

As the starting **4**, we selected a 3-amino-6-heptenoate derivative since both enantiomers are easily accessible according to the Davies protocol. Thus, **4a** and **4b** were synthesized highly selectively from ethyl 2*(E)*,6-heptadienoate and *(S)*-(−)-benzyl-α-phenylethylamine or *(S)*-(−)-bis(α-phenylethyl)amine, respectively, as shown in eq. 1 [5].



(1)

The reaction of **4a** or **4b** with a Ti(O-*i*-Pr)$_4$/ 2 *i*-PrMgCl reagent afforded, as expected, the corresponding bicyclic compound **7** in 76% and 63% yield, respectively. The reaction of the resulting **7** with $FeCl_3$ afforded **8** which was treated in turn, without purification, with NaOAc in anhydrous CH_3OH [6] to provide **5a** and **5b** in 55 and 63% overall yield from the corresponding **7**, respectively (eq. 2). Needless to say, the antipode of **5a,b** can be prepared starting with *ent*-**4a,b** which can be prepared by using the amine with *(R)*-configuration in eq 1.



(2)

With an efficient and practical access to **5a** and **5b** in hand, our research interest was then directed to the 1,4-addition reaction of an organometallic compound. The results of the reaction of several *n*-butyl organometallic compounds under various reaction conditions are summarized in Table 1. It can be seen that organocuprates such as Bu_2CuLi and $Bu_2Cu(CN)Li_2$ showed almost no diastereoselectivity (entries 1 and 2). However, the reaction of the *n*-butyl Grignard reagent in the presence of a catalytic amount of CuI or $Li_2Cu(CN)Cl_2$ gave a synthetically useful level of selectivity to afford a *syn*-addition product irrespectively to **5a** and **5b** [7]. The use of $Li_2Cu(CN)Cl_2$ as catalyst gave better yield and slightly better selectivity than CuI (entry 3 *vs* 4). The selectivity was improved from 90:10 to 95:5 by decreasing the temperature from −78 to

−100°C (entry 5), and the presence of Me_3SiCl [8] in the reaction mixture lowered the selectivity (entry 6).

Table 1: 1,4-Addition of organocopper reagents onto **5a** and **5b**.

Entry	RCu	Conditions[a]	1,4-Adducts from **5a**		1,4-Adducts from **5b**	
			Cis : Trans[b]	Yield (%)[c]	Cis : Trans[b]	Yield (%)[c]
1	Bu_2CuLi	− 78°C	50 : 50	75	55 : 45	60
2	$Bu_2Cu(CN)Li_2$	"	50 : 50	88	55 : 45	95
3	BuMgBr, CuI (10 mol%)	"	80 : 20	67	90 : 10	82
4	BuMgBr, $Li_2Cu(CN)Cl_2$ (10 mol%)	"	**90 : 10**	**92**[d]	**90 : 10**	**85**[d]
5	"	− 100°C	**95 : 5**	**86**		
6	"	− 78°C + TMSCl (3eq)	65 : 35	93		

a: All reactions were run in THF for 1h. *b:* NMR measurement. *c:* NMR yield unless otherwise noted.
d: Isolated yield

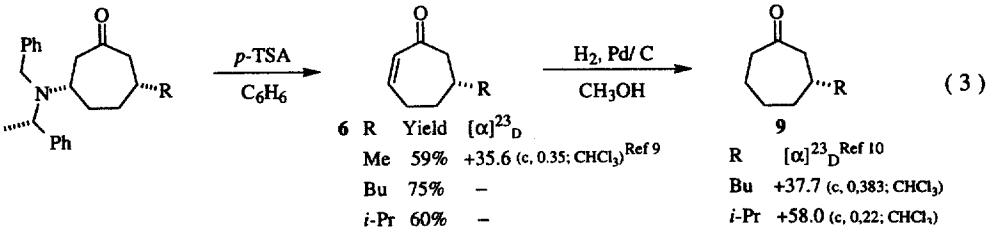
With the results shown in Table 1, we carried out the 1,4-addition of a variety of RMgX onto **5a** and/or **5b** in the presence of $Li_2Cu(CN)Cl_2$ (10 mol%). As shown in Table 2, in addition to a primary alkyl Grignard reagent (*i.e.*, BuMgBr) and except for a tertiary alkyl Grignard reagent (entry 6), the reaction proceeded with good to excellent selectivity with secondary alkyl (entry 4), phenyl (entry 7) and vinyl Grignard reagents (entry 8). Meanwhile, the stereoselectivity with the methyl Grignard reagent was low, presumably due to its low steric requirement; however, interestingly, the presence of Me_3SiCl improved the selectivity to a synthetically useful level (entries 2 and 3).

Table 2: $Li_2Cu(CN)Cl_2$- catalyzed 1,4-addition of Grignard reagents onto **5a** and **5b**.

Entry	RMgBr (Cl)	Conditions[a]	1,4-Adducts from **5a**		1,4-Adducts from **5b**	
			Cis / Trans[b]	Yield[c] (%)	Cis / Trans[b]	Yield[c] (%)
1	MeMgBr	− 78°C	45 : 55	95[d]	62 : 38	84[d]
2	"	− 78°C + TMSCl (3eq)	84 : 16	79	87 : 13	83[d]
3	"	− 100°C + TMSCl (3eq)			**94 : 6**	**82**[d]
4	*i*-PrMgCl	− 78°C	80 : 20	95	**85 : 15**	**87**
5	"	− 100°C	80 : 20	73[d]		
6	*t*-BuMgCl[e]	− 78°C → 0°C	55 : 45	71	60 : 40	61[d]
7	PhMgBr	− 78°C	>90 : <10	71	**>95 : <5**	**70**
8	CH_2=CHMgBr	"	80 : 20	75	**85 : 15**	**91**

a: All reactions were run in THF for 1h. *b:* NMR measurement.
c: Isolated combined yield otherwise noted; cis and trans-products were not separable. *d:* NMR yield
e: CuI was used as the catalyst; when $Li_2Cu(CN)Cl_2$ was used, the yield was very low.

The resulting 1,4-addition products can be easily converted into the corresponding 6-substituted 2-cycloheptenones **6** by treatment with *p*-toluenesulfonic acid as exemplified by eq 3. The absolute configuration of **6** was verified by comparison of its $[\alpha]_D$ value with the reported one for R=Me or after hydrogenation to **9** for R=Bu and *i*-Pr which, in turn, confirmed the *syn*-selective 1,4-addition onto **5**.



(3)

6 R	Yield	$[\alpha]^{23}_D$
Me	59%	+35.6 (c, 0.35; $CHCl_3$)[Ref 9]
Bu	75%	–
i-Pr	60%	–

9 R	$[\alpha]^{23}_D$[Ref 10]
Bu	+37.7 (c, 0,383; $CHCl_3$)
i-Pr	+58.0 (c, 0,22; $CHCl_3$)

Optically active 6-substituted 2-cycloheptenones thus prepared can be further manipulated by using the enone functionality. Thus, the compound **5** may find wide utility as a chiral building block for preparing optically active seven-membered carbocyclic frameworks as well as those with other than the seven-membered entity. From the viewpoint of the synthetic methodology, it is noteworthy that, although optically active β-amino esters obtained by the Davies protocol have widely been used for synthesizing optically active N-containing compounds, to the best of our knowledge, use of these products for preparing optically active nitrogen-free compounds has not been seen in the literature.

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[8] For the effect of Me_3SiCl on the 1,4-addition reaction, see Nakamura, E. in Organocopper Reagents: A Practical Approach (Taylor, R. J. K. Ed.) Oxford University Press 1994.

[9] 84:16 diastereomeric mixture (entry 2 in Table 2) was used. (R)-(+)-6-methyl-2-cycloheptenone with >98%e.e. has $[\alpha]_D$=+64.6 (c,1.09; $CHCl_3$); see, McWilliams JC, Clardy J. J. Am. Chem. Soc. 1994;116:8378-8379.

[10] It has been reported that the $[\alpha]_D$ has (+)-sign for **9** (R=Bu and *i*-Pr) with the structure depicted in eq.3; however, the value was not given. Zhou Q-L, Pfaltz A. Tetrahedron, 1994;50:4467-4478.