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Efficient and Practical Synthesis of Optically Active 5-*t*-Butyldimethylsiloxy-2-cyclohexenone as a Convenient Chiral 2,5-Cyclohexadienone Synthon

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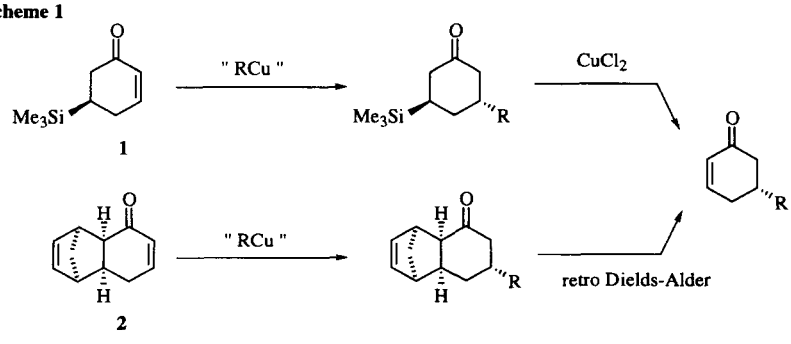
Abstract: An efficient and practical method for the preparation of optically active 5-*t*-butyldimethylsiloxy-2-cyclohexenone (**3**), a convenient chiral 2,5-cyclohexadienone synthon, from readily available ethyl 4-chloro-3-hydroxy-butyrate (**7**) has been developed where Ti(II)-mediated intramolecular nucleophilic acyl substitution and $FeCl_3$-mediated ring expansion are the key reactions. The synthesis of racemic 6-*t*-butyldimethylsiloxy-2-cycloheptenone (**10**), a potential 2,6-cycloheptadienone synthon, is also described. © 1997 Elsevier Science Ltd.

In relation to the synthesis of chiral compounds containing cyclohexane ring systems, the preparation of chiral 2,5-cyclohexadienone synthons has attracted considerable interest. Asaoka and Takei have introduced optically active 5-trimethylsilyl-2-cyclohexenone (**1**)[1], and Takano and Ogasawara have developed optically active tricyclic dienone (**2**)[2]. These compounds **1** and **2** can be prepared in excellent optical purity and allow highly stereoselective reactions such as nucleophilic 1,4-addition and Diels-Alder reactions. The resulting products are then converted into the corresponding cyclohexenones by removal of the group masking the double bond as exemplified by the reactions shown in Scheme 1. However, these steps sometimes afforded rather low yields for **1** or required severe reaction conditions for **2**.

Scheme 1

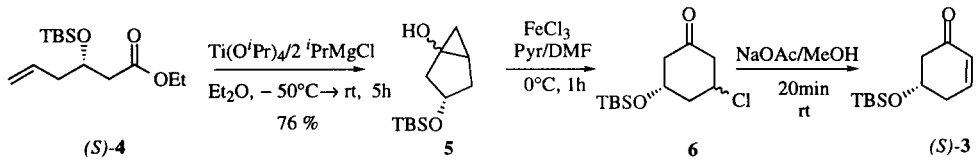


Optically active 5-alkoxy-2-cyclohexenone seems to be an attractive candidate as the synthon, since the generation of the double bond after stereoselective synthetic elaboration must be easy. Two research groups, independently, synthesized optically active 5-benzyloxy-2-cyclohexenone according to porcine liver esterase-

catalyzed asymmetric hydrolysis of *meso*-1,3-*cis*, 3,5-*cis*-1,3-diacetoxy-5-benzyloxy-cyclohexane and oxidation of the resulting monoacetate[3,4]. However, the enantiomeric excess of the compound thus obtained was 85-87% and the method only allows access to the enantiomer with *(S)*-configuration. To the best of our knowledge, no report on its utilization as a chiral 2,5-cyclohexadienone synthon has appeared. Herein, we report an efficient and practical method for synthesizing optically active 5-*t*-butyldimethylsiloxy-2-cyclohexenone (**3**) which works as a versatile chiral 2,5-cyclohexadienone synthon.

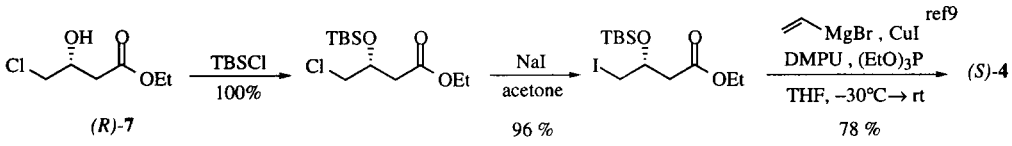
The synthesis of *(S)*-**3** starting from *(S)*-**4** is summarized in Scheme 2. Thus, the reaction of *(S)*-**4** with a $Ti(O^iPr)_4/2\ ^iPrMgCl$ reagent resulted in a tandem intramolecular nucleophilic acyl substitution and intramolecular carbonyl addition reaction to afford **5** in 76% yield[5,6]. The reaction of **5** with $FeCl_3$ in the presence of pyridine resulted in the ring expansion product **6**, which was treated in turn, without purification, with NaOAc in CH_3OH to furnish *(S)*-**3**[7] in 90% overall yield from **5**[8]. The requisite starting material *(S)*-**4** can be synthesized from *(R)*-**7** (98.3% e.e.) in 75% overall yield *via* the conventional reaction sequence shown

Scheme 2



(S)-**4** **5** **6** *(S)*-**3**

Scheme 3



(R)-**7** 96 % 78 %

in Scheme 3. It should be noted that both enantiomers of **7** having excellent optical purity are commercially available or can be readily prepared in large quantity[10,11]; thus, the present method allows the preparation of both enantiomers of **3**. The synthetic development of chiral **3** is practical: the reagents used for the reactions shown in Schemes 2 and 3 are nontoxic and inexpensive, the reaction procedure is operationally simple and the overall yield is good.

With highly practical access to **3** in hand, our next concern was its utility as a chiral 2,5-cyclohexadienone synthon. Compound *(S)*-**3** reacted with Bu_2CuLi or $Bu_2Cu(CN)Li_2$ to afford the 1,4-addition product **8** (R = Bu) in excellent yield. The diastereomeric ratio of **8** was dependent on the organocopper compound used, and the use of $Bu_2Cu(CN)Li_2$ resulted in an excellent ratio of 98:2 (Scheme 4). It is noteworthy that the two diastereomers can be easily separated by column chromatography, and the pure *trans*-isomer could be isolated in excellent yield. The generation of the double bond from the 1,4-addition product thus obtained can be smoothly achieved: treatment of *trans*-**8** (R = Bu) with DBU (DMF, rt, 3h) or *cat.* TsOH (THF/H_2O = 4/1, reflux, 15h) furnished the 2-cyclohexenone **9** (R = Bu) with 98.3% e.e. (checked by GC using a CHROMPACK chiral column - Chirasil-DEX CB column-0.25mm X 25m, DF = 0.25: 100% calculated e.e. in respect of **7**) (Scheme 4). Similarly, $Me_2Cu(CN)Li_2$ and $Ph_2Cu(CN)Li_2$ reacted with

excellent diastereoselectivity to afford the corresponding *trans*-**8** which, in turn, was converted into **9**; the results are summarized in Table 1.

Scheme 4

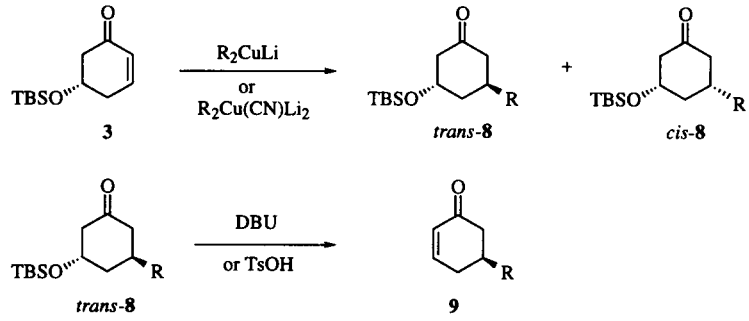
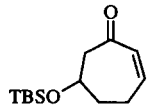


Table1: *Conversion of* **3** *into* **8** *and then into* **9**.

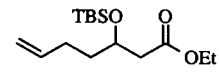
Organocopper [a] Reagent	R	Product **8**			Product **9** [e]		
		trans : *cis* [b]	total yield (%)[c]	isolated *trans*-**8** (%)	yield (%) [d]	$[\alpha]_D$ [f]	Ref
R_2CuLi	Bu	89 : 11	98	87	—	—	
$R_2Cu(CN)Li_2$	Bu	98.4 : 1.6	94	92	93 (90[g])	+49.6 (c 0.5)	12
$R_2Cu(CN)Li_2$	Me	97 : 3	86	83	92	+88.1 (c 0.5)	13
$R_2Cu(CN)Li_2$	Ph	93 : 7	86	80	94	+43.5 (c 0.5)	14

a: All 1,4-additions were carried out in THF except the reaction with $Ph_2Cu(CN)Li_2$ which occurred in Et_2O – *b:* Measured by GC – *c:* From **3** – *d:* From **8** – *e:* Obtained after treatment with DBU in DMF – *f:* In $CHCl_3$ at 23°C – *g:* By treatment with *cat.* TsOH in THF (reflux).

The present methodology also enables access to 6-*t*-butyldimethylsiloxy-2-cycloheptenone (**10**), a potential 2,6-cycloheptadienone synthon. Thus, starting from *(±)*-**11**, the compound **10**[15] was obtained in 58% overall yield. The preparation of chiral **10** and its utility as a chiral 2,6-cycloheptenone synthon is under investigation in our laboratoty.



10



11

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6. *(S)*-**5**: To a stirred solution of *(S)*-**4** (2.82g; 10 mmol) in dry ether (50 mL) was added, under argon, neat $Ti(O^iPr)_4$ (5.68g; 20 mmol). The resulting colourless mixture was cooled to –45°C and ^{i}PrMgCl (1.48M in Et_2O; 27.0 mL; 40 mmol) was added dropwise. The clear, yellow solution, which turned slowly to dark orange, was stirred for 1 h between –45 and –40°C before allowing the temperature to rise to r.t. over a period of 90 min; stirring was then continued for another 2 h and the reaction was hydrolysed at 0°C with sat. NH_4Cl (10 mL). The resulting heterogeneous grey mixture was vigorously stirred for 30 min at r.t. whereupon a white suspension appeared. Extraction with ether (3 X 50 mL) and drying over $MgSO_4$ gave, after evaporation of the solvent, a pale yellow oil which was purified by flash-chromatography (SiO_2; hexanes-ether) to give the title compound (1.73g; 76%) as a colorless oil.
7. Compound*(S)*-**3**: ^{1}H 300MHz NMR (δ, $CDCl_3$): 6.88 (1H, ddd, *J* = 10.2, 5.1 and 3.1Hz); 6.06 (1H, br d; *J* = 10.2Hz), 4.23 (1H, dddd, *J* = 9.7, 7.6, 4.5 and 4.5Hz); 2.66 (1H, dd, *J* = 15.9, and 4.5Hz); 2.65-2.54 (1H, m); 2.48 (1H, dd, *J* = 15.9 and 9.7Hz); 2.38 (1H, dddd, *J* = 18.3, 7.6, 3.1 and 3.1Hz); 0.88 (9H, s); 0.07 (6H, s). ^{13}C 75MHz NMR (δ, $CDCl_3$): 198.3 (4); 146.7 (3); 129.8 (3); 67.3 (3); 47.6 (2); 35.2 (2); 25.3 (1); 17.5 (4); -5.2 (1); -5.3 (1). $[\alpha]_D$= +9.82 (c 1.0, $CHCl_3$).
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15. Compound(±)-**10**: ^{1}H 300MHz NMR (δ, $CDCl_3$): 6.65 (1H, ddd, *J* = 12.0, 6.5 and 4.2Hz); 6.01 (1H, br d, *J* = 12.0Hz); 4.22 (1H, dddd, *J* = 6.5, 5.3, 5.3 and 3.9Hz); 2.84 (1H, dd, *J* = 14.3 and 6.5Hz); 2.78 (1H, dd, *J* = 14.3 and 5.2Hz); 2.66 (1H, ddddd, *J* = 18.7, 8.9, 4.2, 4.2 and 2.4Hz); 2.37 (1H, ddddd, *J* = 18.7, 6.5, 6.5, 3.5 and 1.0Hz); 2.05-1.86 (2H, m); 0.87 (9H, s); 0.06 (6H, s). ^{13}C 75MHz NMR (δ, $CDCl_3$): 200.7 (4); 147.3 (3); 132.8 (3); 66.4 (3); 52.8 (2); 36.2 (2); 25.6 (2); 25.6 (1); 17.8 (4); -5.0 (1); -5.1 (1).

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