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Construction of a Chiral Quaternary Carbon Center by Enantioselective Deprotonation: Application to the Formal Synthesis of (+)-α-Cuparenone

Toshio Honda,* Nobuaki Kimura and Masayoshi Tsubuki

Institute of Medicinal Chemistry, Hoshi University, Ebara 2-4-41, Shinagawa-ku, Tokyo 142, Japan

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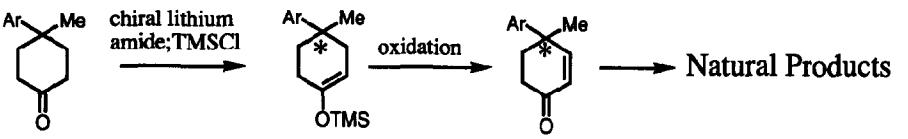
Abstract: Construction of a chiral quaternary carbon center was achieved by employing an enantioselective deprotonation with chiral bases and this strategy was applied to the formal synthesis of (+)-α-cuparenone.

The recent development of the enantioselective deprotonation of meso or prochiral compounds having a σ-plane using chiral lithium amide bases has opened an efficient and simple route for the preparation of the various types of chiral compounds including natural products.[1] Application of this methodology to 4,4-disubstituted cyclohexanone aimed at the construction of a chiral quaternary carbon center, however, seems to be lacking prior to our study. We would like to report here the construction of a chiral quaternary carbon center by employing enantioselective deprotonation methodology and its application to the synthesis of (+)-α-cuparenone.[2] (Scheme 1)

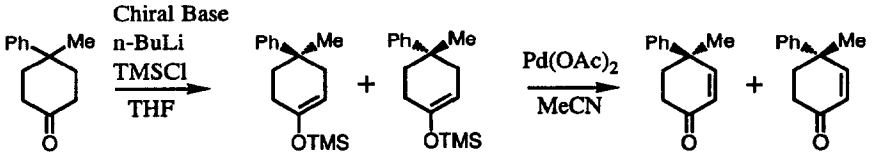


Scheme 1

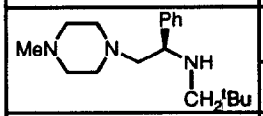
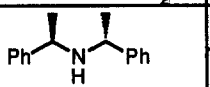
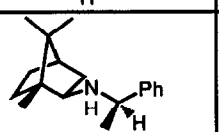
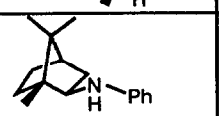
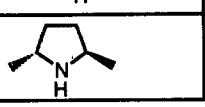
We choose 4-phenyl-4-methylcyclohexanone (**1**)[3] as a starting material to investigate a possibility of chiral induction with several kinds of chiral lithium amide bases, since a benzylic quaternary carbon center is often observed in a variety of natural products. Thus, the treatment of **1** with lithium (*R*)-2-(4-methyl-piperazin-1-yl)-*N*-neopentyl-1-phenylethylamide in tetrahydrofuran at -78°C in the presence of trimethylsilyl chloride afforded the silyl enol ether (**2**) in 73% yield. The enantioselectivity of the product after its conversion into the known enone (**3**)[4] by oxidation with palladium acetate[5] was determined to be 56% e.e. based on the HPLC analysis using the chiral column, CHIRALCEL OJ (Daicel Chemical Industries, Ltd.) and the absolute configuration was also confirmed by comparison of its optical rotation with that of the literature.[4] When this reaction was carried out at -100°C, the enantioselectivity was increased to be 66% e.e. The highest enantiomeric excess (71% e.e.) was obtained from the reaction of **1** with lithium (*R*, *R'*)-α, α'-dimethyl-

dibenzylamide at -100°C in 81% conversion yield. The results for the enantioselective deprotonations of **1** using other chiral bases were listed in the Table. It is noteworthy that (2*R*, 5*R*)-2,5-dimethylpyrrolidine having C_2 symmetry was not effective for this purpose, although the mechanistic rationale is not clear at the present time. (Table)

Table. Enantioselective Deprotonation of 4,4-Disubstituted Cyclohexanone with Chiral Bases



1 (*R*)-**2** (*S*)-**2** (*R*)-**3** (*S*)-**3**

Chiral Base	Temp.(°C)	Silyl Enol Ether (2)		Enone (3)			
		Yield (%)	$[\alpha]_D$ [a]	Yield (%)	$[\alpha]_D$ [a]	Configuration	e.e. (%)[b]
	-78	73	-53.9	98	+60.5	R	56
	-100	66	-63.8	80	+72.3	R	66
	-78	80	+56.6	81	-63.7	S	60
	-100	81	+67.7	80	-76.5	S	71
	-100	21	+18.0	97	-21.6	S	19
	-78	80	+37.1	85	-42.1	S	38
	r.t.	10	+2.0	60	-2.5	S	2

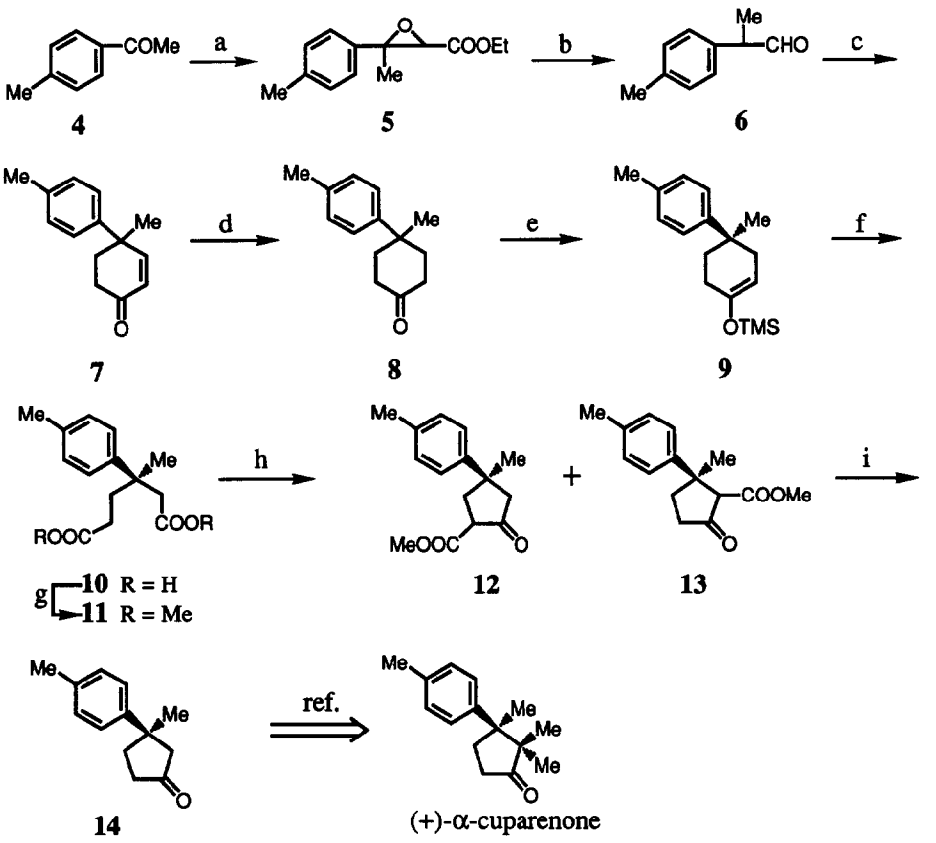
a) Measured in EtOH at 25 ± 1°C

b) Determined based on HPLC analysis using the chiral column CHIRALCEL OJ (Daicel Chemical Industries, Ltd.).

Using this strategy, the chiral synthesis of (+)-α-cuparenone was investigated as follows.

4'-Methylacetophenone (**4**) was converted into the glycidic ester (**5**) under the Darzens condensation reaction conditions using ethyl chloroacetate and potassium *tert*-butoxide in *tert*-butyl alcohol in 82% yield. Hydrolysis of the ester (**5**) with sodium ethoxide in aqueous ethanol, followed by acidification with 2N hydrochloric acid afforded the aldehyde (**6**), in 62% yield, which was treated with methyl vinyl ketone in the presence of a catalytic amount of ethanolic potassium hydroxide in ether to give the cyclohexenone (**7**) in 65%

yield. Catalytic reduction of **7** over 10% palladium on carbon in acetic acid under 3 atm of hydrogen provided the cyclohexanone (**8**) in 91% yield. Enantioselective deprotonation of the cyclohexanone (**8**) employing the chiral lithium amide, prepared from (*S*, *S*')-α, α'-dimethyldibenzylamine with *n*-butyllithium, in tetrahydrofuran at -100°C for 10 min in the presence of trimethylsilyl chloride afforded the silyl enol ether (**9**) {$[\alpha]_D$ -57.1 (c=1.0, EtOH)}in 94% conversion yield with 70% e.e. Oxidative bond cleavage reaction of the silyl enol ether (**9**) using molybdenyl acetylacetonate and *tert*-butyl hydroperoxide in dry benzene[6] furnished the diacid (**10**) in 82% yield. After esterification of the acid (**10**) with methyl iodide and potassium carbonate



Scheme 2: (a) $ClCH_2CO_2Et$, *t*-BuOK, *t*-BuOH, r.t.; (b) EtONa, EtOH, then 2N HCl; (c) MVK, cat. KOH in EtOH, Et_2O, 0°C to r.t.; (d) Pd-C, AcOH, 3 atm H_2; (e) (*S*,*S*')-α,α'-dimethyldibenzylamine *n*-BuLi, TMSCl, THF, -100°C, 10 min; (f) $MoO_2(acac)_2$, *t*-BuOOH, benzene, 60°C, 2 days; (g) MeI, K_2CO_3, DMF, 1 h; (h) MeONa, THF, r.t.; (i) NaCl, H_2O-DMSO, reflux.

in *N*,*N*-dimethylformamide, the resulting diester (**11**) {$[\alpha]_D$ -20.0 (c=1.3, $CHCl_3$)} was subjected to the Dieckmann condensation to provide the cyclization products (**12** and **13**), which, without separation, were

decarboxylated with sodium chloride in aqueous dimethyl sulfoxide at refluxing temperature to give the known cyclopentanone (**14**),[2g] mp 42-43°C (lit.,[2g] mp 45.0-45.5°C){$[\alpha]_D$ +10.3 (c=0.8, $CHCl_3$), lit.,[2g] $[\alpha]_D$ +13.3 ($CHCl_3$)}. Since the cyclopentanone (**14**) has already been transformed into (+)-α-cuparenone,[2g] this synthesis constitutes its formal synthesis. (Scheme 2)

Thus, we could disclose the construction of the chiral benzylic quaternary carbon center by enantioselective deprotonation of 4,4-disubstituted cyclohexanones with chiral bases, and its application to the formal synthesis of (+)-α-cuparenone. This strategy should be applicable to the synthesis of other types of natural products having a quaternary carbon center.

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