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ENANTIOSELECTIVE ROUTES TO 2,5-DISUBSTITUTED- AND 4-SUBSTITUTED-2-CYCLOHEXENONES

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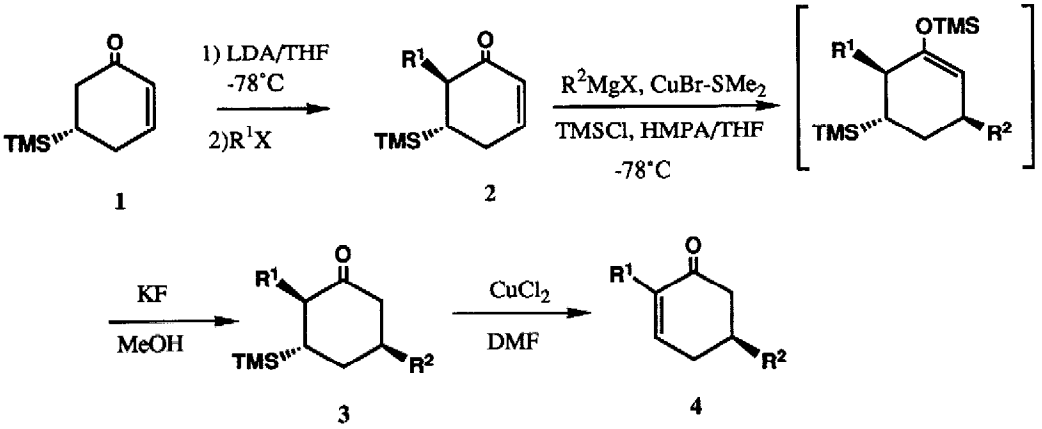
Summary: Starting with 5-trimethylsilyl-2-cyclohexenone, widely applicable enantioselective routes to the title compounds are established.

Although 2-cyclohexenone derivatives have been used as useful starting materials of a wide variety of natural products,[1] only a limited number of enantioselective syntheses of substituted 2-cyclohexenones are known. Therefore, new and efficient methods for the preparation of optically active 2-cyclohexenones are desirable. In the preceding paper we reported an efficient enantioselective preparation of 5-substituted 2-cyclohexenones from a newly developed chiral building block, 5-trimethylsilyl-2-cyclohexenone (**1**).[2] In this paper we will describe the enantioselective preparation of 2,5-disubstituted and 4-substituted-2-cyclohexenones.[3]

The synthesis of 2,5-disubstituted 2-cyclohexenones was carried out by the three step sequence as outlined in Scheme 1. Treatment of the enone (**1**) with LDA at -78°C for 1 h followed by alkylation with alkyl halides (-78 -25°C, 3 h) gave the corresponding 6-alkylated derivatives in good yields. Estimation of diastereomeric purity of the alkylated products by ^{13}C NMR revealed that single isomer was obtained when methallyl iodide was used as an alkylating agent, whereas about 10 to 1 mixture of diastereoisomers were obtained with methyl iodide. Subsequent 1,4-addition of Grignard reagents to **2** in the presence of TMSCl, HMPA, and a catalytic amount of CuBr-Me_2S[4] proceeded smoothly to give the adducts **3a-d** in high yields. The ^{13}C NMR of the adduct showed the diastereoisomeric homogeneity of **3d**, and in the cases of **3a-c** the ratios of the diastereomers were proved to be unchanged (10 to 1). Considering the fact that generally in the 1,4-addition of Grignard reagents to 2-cyclohexenone derivatives the effect of substituent in position 5 is greater than that in position 6, it is assumed that the substituent at 3 position is exclusively introduced from the top side of **2a,b**. This assumption was confirmed afterward by the highly enantioselective synthesis of (S)-(+)-carvone and (R)-(-)-carvotanacetone. Oxidative desilylation of **3** with $CuCl_2$ in DMF[2] proceeded smoothly to give the corresponding 2,5-disubstituted 2-cyclohexanones in good yields. Since both enantiomers of **1** can be obtained in

enantiomerically pure form, the above conversion offers the enantiomeric access to 2,5-disubstituted 2-cyclohexenones. Actually, the efficiency of this route was proved by the demonstrational synthesis of (S)-(+)-carvone [(+)-**4b**: $[\alpha]_D^{15}$+58.3°(neat), lit.[5a] $[\alpha]_D^{20}$+61.2°(neat)] and (R)-(-)-carvotanacetone [(-)-**4c**: $[\alpha]_D^{22}$-56.4°(neat), lit.[5b] $[\alpha]_D^{22}$-56.7°(neat)] starting with (S)-(+)-**1** and (R)-(-)-**1**. These results are listed in Table 1.



1 **2** **3** **4**

Scheme 1

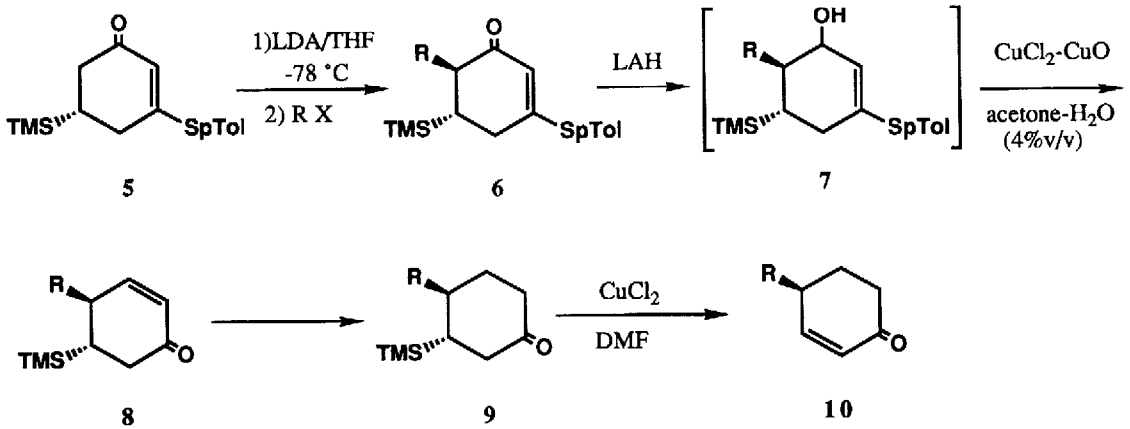
Table 1 Synthesis of 2,5-Disubstituted-2-cyclohexenones[a]

entry	1	R^1	yield(%) 2	R^2	yield(%) 3	yield(%) 4
1	rac-**1**	Me	**2a** 67	Ph	**3a** 92	**4a** 70
2	rac-**1**	Me		isopropenyl	**3b** 89	**4b** 76
3	rac-**1**	Me		isopropyl	**3c** 83	**4c** 74
4	rac-**1**	methallyl	**2b** 80	isopropyl	**3d** 97	**4d**[b] 70
5	(S)-(+)-**1**	Me	(+)-**2a** 48	isopropenyl	(-)-**3b** 88	(+)-**4b** 75
6	(R)-(-)-**1**	Me	(-)-**2a** 61	isopropyl	(+)-**3c** 90	(-)-**4c** 84

a) The structures were confirmed by spectral (IR and NMR) data and elemental analysis or by comparison with authentic sample.
b) **4d**: 2-(2-methylpropyl)-5-isopropyl-2-cyclohexenone. Oxidative desilylation was carried out after hydrogenation (92%) of **3d**. A constituent of Roman camomile.[3a]

As depicted below, the enantioselective synthesis of 4-substituted 2-cyclohexenones was started with 3-tolylthio-5-trimethylsilyl-2-cyclohexenone (**5**) which can be obtained easily in racemic and enantiomeric form.[6] Lithium enolate formation of **5** and alkylation were carried out under similar reaction conditions as mentioned for **1**. As long as checked by ^{13}C NMR, none of the alkylated compounds **6** were contaminated with diastereoisomer. The high yields of the alkylated products **6** comparing with those of **2** are presumably

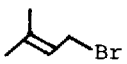
attributed by the greater stability of lithium enolate by the contribution of the arylthio group.[7] 1,3-Carbonyl transposition was carried out by reduction with lithium aluminium hydride followed by hydrolysis with $CuCl_2$-CuO in wet acetone.[8] ^{13}C NMR analysis of the enones **8** indicated their diastereoisomeric homogeneity. Hydrogenation in the presence of Pd or Pt catalyst or 1,4-conjugate reduction of the cyclohexenone **8a-c** and subsequent oxidative desilylation furnished 4-substituted 2-cyclohexenones **10**. The inferior yield of **10a** is presumably due to the volatility of the product. Though the high level of stereocontroll by trimethylsilyl group in this sequential transformation was confirmed by ^{13}C NMR estimation, epimerization in the last step is still in question. To confirm the viability of this route, synthesis of (-)-4-methyl-2-cyclohexenone was carried out from R-(+)-**5** and the product was proved to have high optical purity.[9] These results are listed in Table 2.



5 **6** **7** **8** **9** **10**

Scheme 2

Table 2 Synthesis of 4-Substituted-2-cyclohexenones[a]

entry	5	RX	yield(%) 6		yield(%) 8		method[b]	yield(%) 9		yield(%) 10	
1	rac-5	MeI	**6a**	82	**8a**	61	A	**9a**	96	**10a**	45
2	rac-5	BnBr	**6b**	95	**8b**	65	B	**9b**	87	**10b**	70
3	rac-5		**6c**	93	**8c**	74	C	**9c**	74	**10c**	74
4	(R)-(+)-5	MeI	(+)-**6a**	80	(+)-**8a**	67	A	(+)-**9a**	89	(-)-**10a**	44
5	(S)-(-)-5	BnBr	(+)-**6b**	88	(-)-**8b**	55	A	(-)-**9b**	97	(+)-**10b**	76

a) The structures were confirmed by spectral (IR and NMR) data and elemental analyses.
b) Method A: Pd-C/H_2, AcOEt; method B: PtO_2/H_2, AcOEt; method C: MeCu-DIBAH/HMPA-THF, at -50°C.

In conclusion, the ready access to both enantiomers of these types of 2-cyclohexenones provides the necessary pool of synthons for optimum chiral choice in the planning of synthesis.

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9) (5S,6S)-**6a**: $[\alpha]_D^{21}$+98.1°(c 1.02, $CHCl_3$), (4S,5S)-**8a**: $[\alpha]_D^{21}$+130.4°(c, $CHCl_3$), (3S,4S)-**9a**: $[\alpha]_D^{18.5}$+154.3°(c, $CHCl_3$), (4S)-**10a**: $[\alpha]_D^{22}$-114.3°(c 9.46, $CHCl_3$) [(4R)-**10a**: lit.[3d] $[\alpha]_D^{22}$+105°(c 9.2, $CHCl_3$)]. (5R,6R)-**6b**: $[\alpha]_D^{22}$+82.1°(1.01, $CHCl_3$), (4R,5R)-**8b**: $[\alpha]_D^{24}$-122.8°(c 1.05, $CHCl_3$), (3R,4S)-**9b**: $[\alpha]_D^{24}$-102.8°(c 1.02, $CHCl_3$), (4S)-**10b**: $[\alpha]_D^{26}$+80.3°(c 1.01, $CHCl_3$).

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