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Exo-10,10-Diphenyl-2,10-Camphanediol as a New Chiral Auxiliary in Asymmetric Reduction

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Abstract: Stereoselective reduction of α-keto ester derived from *exo*-10,10-diphenyl-2,10-camphanediol with various hydrides proceeded with high diastereoselectivities (≥ 96% de) to afford the corresponding α-hydroxy ester with excellent yields. Change of reducing reagents and molar ratio modifications leading to dramatic changes in diastereofacial selectivity were examined. The auxiliary can be recovered from the asymmetric reaction products without loss of chirality.

The synthesis of homochiral α-hydroxy acid derivatives has attracted considerable attention since such compounds are a versatile class of molecules in the preparation of biologically active products.[2] Substantial efforts have been devoted to developing practical methods toward the preparation of these structural arrays.[3] Among these methods, the diastereoselective reduction of chiral α-keto esters which bear an appropriate chiral auxiliary is a conventional strategy.[3a,h,i,k] For example, the use of α-(arylsulfonamido)borneols as auxiliaries to effect stereoselective reduction has been reported.[3k] In the course of our studies of new camphor-based chiral auxiliaries and their synthetic applications, we found that chiral α-keto ester **4** can be efficiently reduced to α-hydroxy ester with high stereoselectivities under conventional conditions.

Due to the advantages of conformational rigidity and steric congestion, camphor-derived systems have been employed as highly efficient chiral inducers for a wide variety of asymmetric reactions.[4] The versatility of camphorsulforamides as a practical facial discrimination in many reactions of their *N*-enoyl derivatives have been documented.[5] To gain a deeper understanding of this stereoface-differentiating bias, we have designed and synthesized related auxiliaries **3**, and the structural features of **3** merit comment. Unlike most of the camphor-derived auxiliaries, the two protons at C-10 (camphor numbering) were replaced with two phenyl groups in the presence of a tertiary hydroxy functionality. The free rotation between C-1 and C-10 is expected to be minimized which should reduce the number of possible conformations. Further, the three contiguous quaternary carbon centers would enhance the rigidity of the system and may simplify the complexity due to the mobilities of the single bonds of the derived α-keto ester.

The compound *exo*-10, 10-diphenyl-2,10-camphanediol **3a** can be easily prepared from the ketopinic acid methyl ester **1**.[6] Treatment of **1**, ($[\alpha]_D$+39.1° (*c* 1.0 in $CHCl_3$)), with phenylmagnesium bromide (4.0 equiv, THF, 0 °C) afforded hydroxy ketone **2** in 89% yield. LAH reduction (THF, -78 °C) provided the desired products in 95% yield with the *exo* alcohol **3a** dominated (*exo*:*endo*/95:5). The ^{1}H NMR spectra of the methine proton on C-2 of **3a** appeared at δ 4.26 ppm, while the corresponding proton of **3b** shifted downfield

0040-4039/99/$ - see front matter
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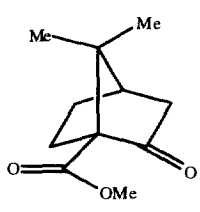
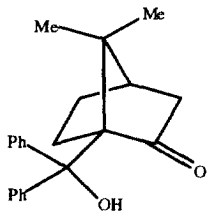
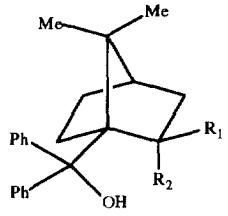
to δ 4.94 ppm. The structure of the latter was further confirmed by single crystal X-ray analysis. Reaction of **3a** with benzoformic acid chloride,[7] prepared from the corresponding benzoformic acid ($SOCl_2$, 60 °C), in THF at 0 °C afforded α-keto ester **4** in excellent yield. The structure of **4** was established unequivocally by X-ray crystallographic analysis.



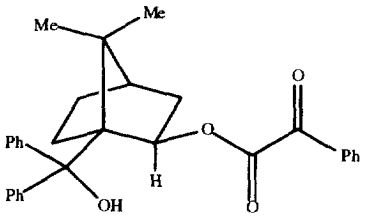
1



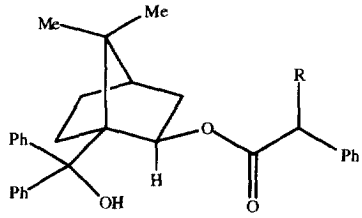
2



3a: R_1=OH; R_2=H
3b: R_1=H; R_2=OH



4



5a: R=α-OH
5b: R=β-OH

Reduction of α-keto ester **4** with sodium borohydride gave two inseparable diastereomers **5** in 78% yield with a disappointingly low diastereomeric excess (de), while reduction with DIBAL-H resulted in no reaction. Reduction of **4** with L-Selectride® at 0 °C in THF afforded **5** with enhanced selectivity in 94% yield (entry 3). High diastereoselectivity (92% de) with excellent chemical yield was obtained when the reaction was carried out at -78 °C (entry 4). The diastereomeric ratios were determined based on the intensities of relevant 200 MHz ^{1}H NMR signals. The newly generated stereogenic center was determined to be *(S)* chirality by correlating the sign of the specific rotation of the cleaved acid, *(S)*-mandelic acid. A slightly improvement in stereoselectivity was obtained when 2.0 equiv of L-Selectride® was employed (entry 5). The use of K-Selectride® as a reductant led only to 32% de, indicating that the complexation of the counter metal ion with the Lewis base atoms of the substrate might play a crucial role in the control of the stereochemistry (entry 8). Of particular note is the fact that opposite chirality was obtained when $LiAlH(OCEt_3)_3$ was used. Thus, when 1.0 equiv of $LiAlH(OCEt_3)_3$ was used, moderate stereoselectivity ((*S*)-form) was observed (entry 10). However, treatment of **4** with 1.2 equiv of $LiAlH(OCEt_3)_3$ in THF at -78 °C lead to inversion of configuration at the asymmetric carbon center created (entry 11). The stereoselectivities increased with increased amount of reducing agent. When 2.0 equiv of $LiAlH(OCEt_3)_3$ was used, a very high level of selectivity was obtained (entry 13). Even more interestingly, when the same reaction was carried out at 0 °C, the reaction was complete within 10 min (vs 2 hr at -78 °C) with selectivity greater than 96% de (entry 14). This result is comparable with

the best results achieved when reduction of analogous chiral α-keto esters.[3k] A brief survey of solvent effects showed that the diastereoselectivities were highly dependent on the solvent used (entries 4, 6, and 7; 10, 15, and 16). Thus, it is likely that the change of solvent results in a difference of aggregation and/or a different extent of aptitude to complexation of the counter cation(s) to the oxygen atoms. The stereoselection decreased sharply when less ligating ability of solvent was used (entries 7 and 16). The addition of 1.0 equiv of Lewis acid lead to decrease in stereoselectivities (entries 17, 18 and 19).

Table: Reduction of α-Keto Ester **4**

Entry	Hydride	Equiv	Additive	Solvent	Temp(°C)	Yield[a] (%)	%de[b]	Config.[c]
1	$NaBH_4$	1.0	--	THF	0 °C	78	33	R
2	DIBAL-H	1.2	--	THF	-78 °C	nr[d]	--	--
3	L-Selectride	1.0	--	THF	0 °C	94	63	S
4	L-Selectride	1.0	--	THF	-78 °C	98	92	S
5	L-Selectride	2.0	--	THF	-78 °C	94	≥ 96	S
6	L-Selectride	1.0	--	CH_2Cl_2	-78 °C	91	88	S
7	L-Selectride	1.0	--	toluene	-78 °C	77	38	S
8	K-Selectride	1.0	--	THF	-78 °C	87	32	S
9	$LiAlH(OCEt_3)_3$	0.8	--	THF	-78 °C	60	33	S
10	$LiAlH(OCEt_3)_3$	1.0	--	THF	-78 °C	91	55	S
11	$LiAlH(OCEt_3)_3$	1.2	--	THF	-78 °C	94	55	R
12	$LiAlH(OCEt_3)_3$	1.5	--	THF	-78 °C	95	84	R
13	$LiAlH(OCEt_3)_3$	2.0	--	THF	-78 °C	95	92	R
14	$LiAlH(OCEt_3)_3$	2.0	--	THF	0 °C	96	≥ 96	R
15	$LiAlH(OCEt_3)_3$	1.0	--	CH_2Cl_2	-78 °C	98	54	R
16	$LiAlH(OCEt_3)_3$	1.0	--	toluene	-78 °C	99	6	R
17	$LiAlH(OCEt_3)_3$	1.0	LiI	THF	-78 °C	91	59	R
18	$LiAlH(OCEt_3)_3$	1.0	$ZnCl_2$	THF	-78 °C	83	71	R
19	$LiAlH(OCEt_3)_3$	1.0	$MgBr_2$	THF	-78 °C	45	25	R
20	$LiAlH(OCEt_3)_3$[e]	1.0	--	THF	-78 °C			
	+ L-Selectride	1.0	--	THF	-78 °C	95	71	S
21	L-Selectride[f]	1.0	--	THF	-78 °C			
	+ $LiAlH(OCEt_3)_3$	1.0	--	THF	-78 °C	94	83	S

[a]Isolated yield. [b]Ratios determined by 200 MHz ^1H NMR analysis of relevant signals. [c]The absolute stereochemistry was determined by comparison of the sign of optical rotations of the cleaved acid, (*S*)-mandelic acid. [d]nr: no reaction. [e]One equiv of $LiAlH(OCEt_3)_3$ was added followed by the addition of 1.0 equiv of L-Selectride. [f]One equiv of L-Selectride was added followed by the addition of 1.0 equiv of $LiAlH(OCEt_3)_3$.

It has been proposed that the *s*-cis conformation of α-keto ester is formed during the reduction through the coordination of a metal cation with the carbonyl moieties.[3k] The hydride anion then selectively approached from the less hindered side of the α-carbonyl carbon. There have also been reported of other systems such as the changeover in diastereofacial selectivity via the addition of Lewis acids[8] or crown ethers.[3i] In our case, the origin of the reversal of facial selectivity with $LiAlH(OCEt_3)_3$ remained uncertain. However, the use of more than equimolar amount of $LiAlH(OCEt_3)_3$ that led to inversion of configuration may be rationalized as follows: the first equiv of the counter cations coordinated to the oxygen atoms and the hydride was delivered to the α-carbonyl carbon atom intramolecularly. On the other hand, in the presence of more equiv of reducing agent, the hydride from the "free" reagent attacked faster intermolecularly from the opposite face of the α-carbonyl carbon

center of the complexed conformation. More information is needed before the exact mechanism can be fully realized and the role that the tertiary hydroxy group plays remains unclear.[9]

The auxiliary can be easily removed from the reduction product by saponification (NaOH, THF, H_2O; 88% yield) at room temperature and recovered by the usual workup. No racemization of compound **3a** was observed.[10]

In conclusion, an efficient method for the preparation of high optical purity of chiral α-hydroxy ester has been developed. Compound **3a** has proved to be an effective chiral auxiliary. *High optical purity of either of the two diastereomers of α-hydroxy ester can be prepared easily from a single enantiomer of the chiral auxiliary and the yields were generally excellent.* More applications are currently under investigation.

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10. Recovered compound **3a**: $[\alpha]_D$+164.8° (*c* 1.0 in $CHCl_3$); original compound **3a**: $[\alpha]_D$+166.1° (*c* 1.0 in $CHCl_3$).