Pergamon

Tetrahedron Letters, Vol. 37, No. 11, pp. 1863-1866, 1996

0040-4039/96 $15.00 + 0.00

S0040-4039(96)00137-2

5(N-Methylbenzoylamino)-2, 2, 6, 6-tetramethylheptan-3-ol as a New Class of Recoverable Chiral Auxiliary

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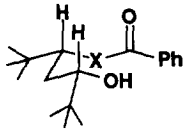
Abstract: Reduction of α-ketoesters bearing 5(N-methylbenzoylamino)-2, 2, 6, 6-tetramethylheptan-3-ol as a chiral auxiliary proceeds with high diastereoselectivity by using DIBAL as a reducing agent. The chiral auxiliary is recovered upon treatment with base, and α-hydroxy carboxylic acids are obtained in good chemical yields with high enantioselectivity.

We previously developed a 2, 2, 6, 6-tetramethyl-3,5-heptanediol (TMHDiol) derivative **1** as a new class of chiral auxiliaries.[1] This chiral auxiliary is an acyclic, but strongly conformationally biased, molecule. Conjugate addition of lithium N-benzyl-N-(trimethylsilyl)amide to the enoates bearing TMHD auxiliary proceeded with high diastereoselectivities to give β-amino esters in high yields.[1] Organocopper conjugate addition to TMHD enoates produced high diastereoselectivities,[1] and Diels-Alder reaction of TMHD acrylate with cyclopentadiene in the presence of $TiCl_4$ afforded an endo adduct exclusively with high diastereoselectivity.[1,2]

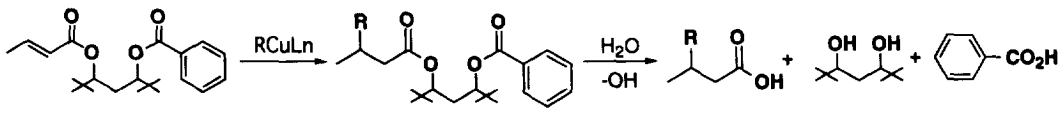


1; X=O, 5(benzoyloxy)-2,2,6,6-tetramethylheptan-3-ol
TMHDiol derivative

2; X=NH, 5(benzolyamino)-2,2,6,6-tetramethylheptan-3-ol

3; X=NMe, 5(N-methylbenzolyamino)-2,2,6,6-tetramethylheptan-3-ol

Only the problem in the reactions of TMHDiol derivatives was that the chiral auxiliary could not be recovered; for example, conjugate addition of organocopper reagents to the enoates bearing 5(benzoyloxy) 2, 2, 6, 6-tetramethylheptane-3-ol chiral auxiliary produced the corresponding diesters **4**, and the hydrolysis of **4** gave a mixture of benzoic acid, TMHDiol, and the desired conjugate adduct (carboxylic acid). It occurred to us that, if amide chiral auxiliaries such as **2** and **3** are utilized instead of **1**, the ester group may be hydrolyzed selectively without destroying the amide bond and thus the chiral auxiliary may be recovered. We wish to report that in fact **3** acts as a recoverable chiral auxiliary.



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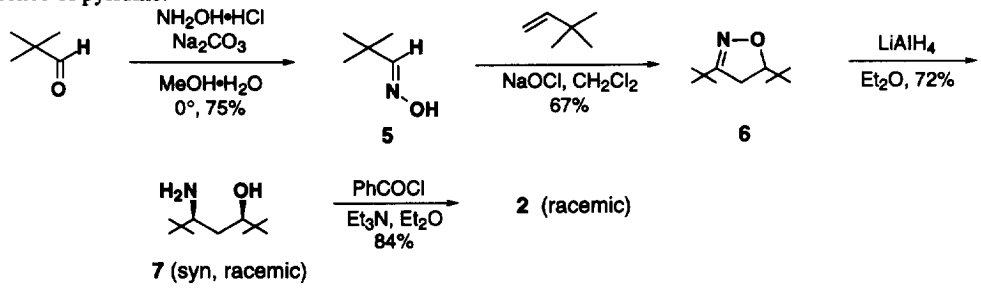
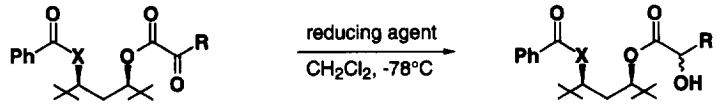
We first studied the reduction of ketoesters bearing **1** and **2** as a chiral auxiliary. Synthesis of the benzoylamino auxiliary **2** is shown in Scheme 1. Pivaladehyde was converted to the corresponding oxime **5**. Treatment of **5** with 3.3-dimethyl-1-butene/CH_2Cl_2/Et_3N/aqueous sodium hypochlorite solution gave isoxazoline **6** in 67% yield.[3] Reduction with $LiAlH_4$ afforded the corresponding syn-amino alcohol **7** in 72% yield.[4] Treatment of **7** with 1 eq benzoyl chloride in the presence of Et_3N gave **2** (racemic) in 84% yield.[5] Ketoesters (**8** or **9**) were prepared by the reaction of RCOCOCl with either **1** or **2**, respectively, in the presence of pyridine.



Scheme 1. Synthesis of **2** (racemic).



8; X=O
9; X=NH
16; X=NMe

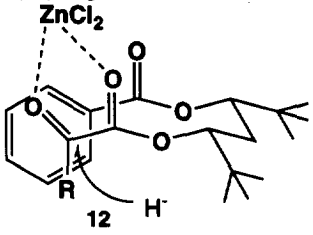
10; X=O
11; X=NH
17; X=NMe

Table 1. Reduction of **8** and **9**

entry	**8** or **9** R	X	Reducing Agent	diastereomer ratio	**10** or **11** yield, %
1	Me	O	DIBAL (1.2 eq)	60 : 40	45
2	Ph	O	DIBAL (1.2 eq)	70 : 30	41
3	Me	O	L-Selectride (1.0 eq)	64 : 36	57
4	Me	O	$LiAl(OtBu)_3H$ (1.2 eq)	53 : 47	70
5	Me	O	DIBAL (1.2 eq) / $ZnCl_2$ (1.5 eq)	94 : 6	78
6	Me	O	DIBAL (1.2 eq) / $MgBr_2•OEt_2$ (1.5 eq)	89 : 11	88
7	Ph	O	DIBAL (1.2 eq) / $ZnCl_2$ (1.5 eq)	93 : 7	78
8	Ph	O	L-Selectride (1.0) / $ZnCl_2$ (1.5 eq)	76 : 24	85
9	Ph	NH	DIBAL (1.2 eq)	50 : 50	89
10	Ph	NH	DIBAL (1.2 eq) / $ZnCl_2$ (1.5 eq)	60 : 40	60

Reduction of **8** and **9** with DIBAL, L-Selectride, and $LiAlH(OtBu)_3$ is summarized in Table 1.

Reduction of **8** without an additive gave low diastereoselectivities (entries 1-3). In the presence of chelating agents such as $ZnCl_2$ and $MgBr_2 \cdot OEt_2$, reduction of **8** proceeded with high diastereoselectivities in good yields (entries 5-7). However, reduction of **9** produced very low diastereoselectivities regardless of the presence or absence of $ZnCl_2$ (entries 9-10). Highly diastereoselective reduction of **8** using DIBAL / $ZnCl_2$ is presumably due to chelating effect of $ZnCl_2$ as shown in **12**. On the other hand, low diastereoselectivity via **9** may be ascribed to hydrogen bonding between NH and ester oxygen atom (**13**), which puts benzoyl group far away from acyl group and therefore the blocking effect of the aromatic ring is lost.



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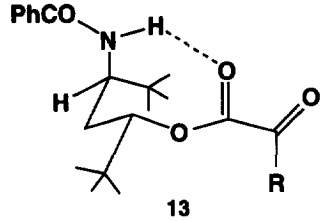

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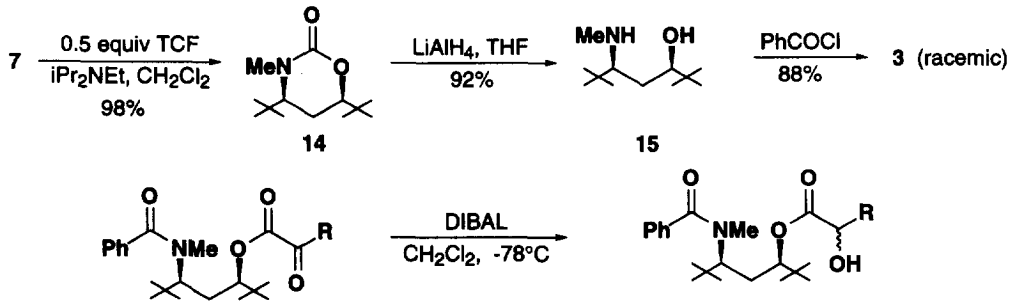
Accordingly, N-methylbenzoylamine auxiliary **3** was synthesized to avoid an unfavorable hydrogen bonding. Treatment of **7** with 0.5 equiv trichloromethylchloroformate / 2 equiv iPr_2NEt gave the cyclic carbamate **14** in 98% yield. Reduction with $LiAlH_4$ produced **15** in 92% yield.[6] The usual benzoylation afforded **3** (racemic) in 88% yield. The corresponding ketoesters **16** were prepared by the reaction of RCOCOCl with **3** in the presence of pyridine in CH_2Cl_2; **16a** was obtained in 82% yield, **16b** in 87% yield, and **16c** in 96% yield. The reduction of **16a** with 1.2 equiv DIBAL gave an 80 : 20 diastereomer mixture of **17a** in 67% yield. The reduction of **16b** afforded an 88: 12 isomeric mixture of **17b** in 65% yield, and that of **16c** produced a 94 : 6 mixture of **17c** in 66% yield. As expected, removal of the effect of hydrogen bonding enhanced diastereoselectivity of reduction of the ketoesters. However, the use of $ZnCl_2$ as a chelating agent decreased the diastereoselectivity; the reduction of **16a** with DIBAL / $ZnCl_2$ gave a 67 : 33 diastereomer mixture of **17a**. A reason for this ineffectiveness of the chelating agent is not clear.

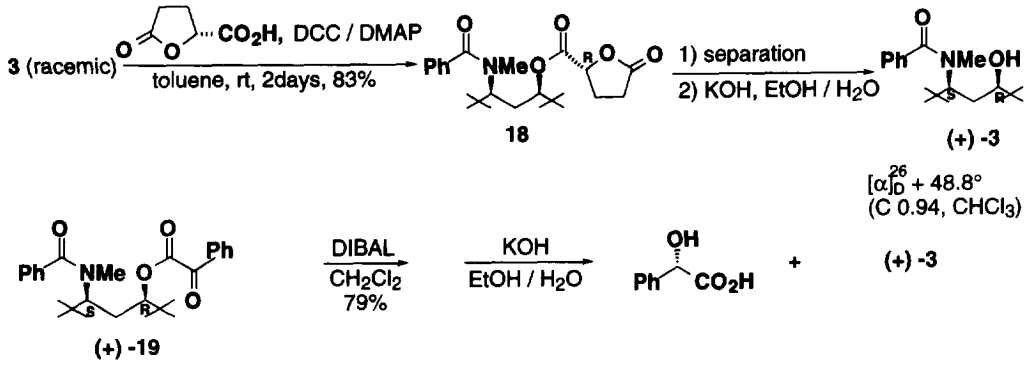


16a; R=Me
b; R=Et
c; R=Ph

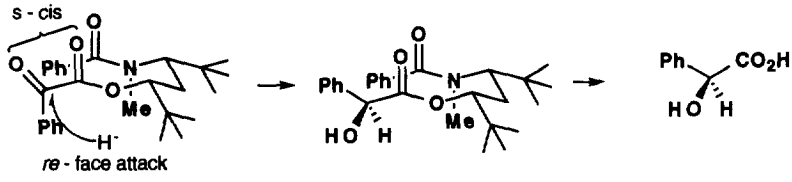
17a; R=Me
b; R=Et
c; R=Ph

Since high to good diastereoselectivity was obtained via **3** (racemic), we next investigated reduction using optically active **3** and tested recovery of the chiral auxiliary. Treatment of **3** (racemic) with (R)-5-oxo-2-tetrahydrofurancarboxylic acid[7] in the presence of DCC / DMAP[8] gave a diastereomeric mixture of **18** in

83% yield.[9] Two diastereomers were separated by HPLC using YMC D-SIL-5-06 column; **18a** with 18.7 min retention time and **18b** with 20.1 min retention time. Hydrolysis of **18a** with KOH / EtOH-H_2O gave **3** (non-racemic); $[\alpha]^{26}$+48.8° (C 0.94, $CHCl_3$). No epimerization took place in this hydrolysis step. Absolute configuration of (+)-**3** was determined as such from X-ray analysis of **18a**.



Optical active ketoester (+)-**19** was synthesized by the standard method. Reduction of (+)-**19** with DIBAL gave a 94 : 6 mixture of the corresponding hydroxy ester in 79% yield. Subsequent hydrolysis afforded (+)-**3** in 93% yield and (S)-(+) mandelic acid in 98% yield. No epimerization of the recovered (+)-**3** was observed. Since (S)-(+)mandelic acid was obtained, the reduction of (+)-**19** would proceed as shown in **20**.



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(*Received in UK* 24 *November* 1995; *revised* 23 *January* 1996; *accepted* 26 *January* 1996)