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Novel Steroidal Chiral Auxiliaries: Enantioselective Synthesis of Chiral α-Hydroxy Acids

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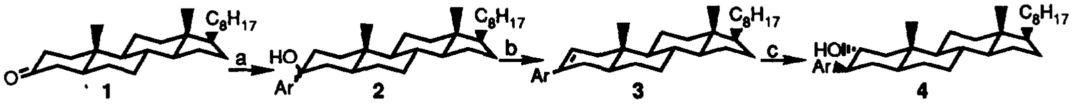
Abstract: The synthesis is reported of three novel steroidal chiral auxiliaries (4) which were used to generate an α-hydroxy acid in high optical purity (90-98% ee).

Chiral auxiliaries for enantioselective syntheses are of current interest.[1-3] Cyclohexyl based chiral auxiliaries, such as menthol, 8-phenylmenthol, and *trans*-2-phenylcyclohexanol, have been used for various asymmetric inductions.[1-2] Herein we report the synthesis and application of three novel steroidal chiral auxiliaries (4) for enantioselective synthesis. The steroidal chiral auxiliaries are readily derived from natural sources, are highly crystalline and easily recovered. Furthermore, their preparation requires no enzymatic resolution.[1d,e]

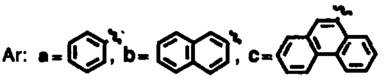
The steroidal chiral auxiliaries (4) were synthesized in three steps (Scheme 1).[3] 5α-Cholestan-3-one (1) was arylated and transformed, either by Grignard or by lithium reactions, into the tertiary alcohols (2) which were then dehydrated to the olefins (3) with thionyl chloride or phosphorous oxychloride in pyridine at room temperature. Hydroboration of the olefins (3) with borane-methyl sulfide complex gave the desired chiral auxiliaries (4). The overall yields for the three steps synthesis were 20-45%.[4]

The enantioselective synthesis of 2-hydroxy-2-phenylbutanoic acid (7) using the new steroidal chiral auxiliaries (4) was explored, to examine their effectiveness. The synthesis of 7 was chosen to allow a direct comparison of the new auxiliaries with (1R, 2S)-2-phenylcyclohexan-1-ol (8)[2b] and (1R, 2R)-2-phenoxylcyclohexan-1-ol (9)[2a] which have been reported recently.

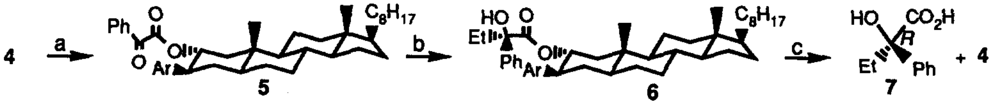
Reaction of the steroidal chiral auxiliaries 4 and benzoylformic acid in the presence of a catalytic amount of *p*-toluenesulfonic acid (PTSA) in benzene with azeotropic removal of water afforded the glyoxalates 5.[2,4] Treatment with ethylzinc chloride [obtained from ethylmagnesium bromide and $ZnCl_2$ (1:1)] yielded the α-hydroxy esters 6[2,4] which on hydrolysis gave the desired 2-hydroxy-2-phenylbutanoic acid (7) and the



Conditions[3]: (a) ArMgBr, THF; or ArLi, Et_2O or THF. (b) $SOCl_2$ or $POCl_3$, pyridine. (c) (1) BH_3-Me_2S, THF, reflux; (2) H_2O_2, NaOH, reflux



Scheme 1



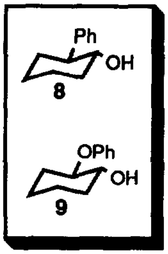
Conditions[2]: (a) PhCOCOOH, PTSA, PhH. (b) EtZnCl, THF. (c) KOH, MeOH, THF.

Scheme 2

Table 1. Enantioselective Synthesis of 2-Hydroxy-2-phenylbutanoic Acid (7) with Chiral Auxiliaries 4

Ar in 4	Rotation $[\alpha]_D^{25}$ (c, EtOH)	ee %[a]	Abs. Conf.
Phenyl (**4a**)	-30.1 (1.0)[b]	90	*R*
2-Naphthyl (**4b**)	-32.6 (1.0)	98	*R*
9-Phenanthryl (**4c**)	-31.6 (1.0)[c]	95	*R*

[a] 84% ee with auxiliary **8** and 80-82% with **9**.[2] [b] T=27°. [c] T=26°.



recovered steroidal chiral auxiliaries **4** (Scheme 2).[2] The overall yields of **7** were 60-70% (after recrystallization from petroleum ether). The optical purities of the 2-hydroxy-2-phenylbutanoic acid (**7**) were measured by optical rotation {lit.[5] $[\alpha]_D^{25}$ +33.3 (c 0.87, EtOH) conf. *S*, ee >99% } and the data are shown in Table 1.

As anticipated, higher ee's were obtained with the more rigid steroidal chiral auxiliaries **4** than with the cyclohexyl based chiral auxiliaries **8** and **9**.[2] Also, the longer 2-naphthyl auxiliary (**4b**) led to a higher ee than the phenyl auxiliary (**4a**). Preparation of 2α-arylated cholestan-3β-ols, which presumably will lead to the opposite enantiomer, is under investigation. Application of the steroidal chiral auxiliaries **4** to other enantioselective syntheses is in progress.

References and Notes

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4. All new compounds were purified by silica gel column chromatography and were characterized by NMR and MS spectra. Analysis of **4b** is given as an example: ^{1}H NMR (CDCl3, 300 MHz): δ 0.75 (s, 3H), 0.94 (d, *J* = 5.6 Hz, 6H), 0.99 (d, *J* = 6.6 Hz, 3H), 0.85-1.97 (m, 28H), 2.02-2.15 (m, 1H), 2.26 (dd, *J* = 12.3 and 7.9 Hz, 1H), 2.726 (ddd, *J* = 9.8, 9.8 and 4.4 Hz, 1H), 4.09 (ddd, *J* = 10.7, 10.7 and 4.3 Hz, 1H), 7.45-7.60 (m, 3H), 7.78 (s, 1H), 7.82-7.95 (m, 3H); MS (FAB) *m/z* 514 (M^+).
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