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Synthesis of 5-Substituted-3,3-Dimethyl-2-Pyrrolidinones: "Quat" Chiral Auxiliaries

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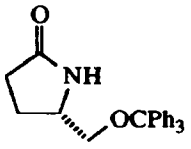
Abstract: The synthesis of a series of chiral auxiliaries, 5-substituted-3,3-dimethyl-2-pyrrolidinones, "quats", from L-glutamic acid is described. Efficient regeneration of the chiral auxiliaries from their *N*-pivaloyl derivatives is readily achieved with LiOH in THF-water at 20°C.

Chiral auxiliary methodology is proving to be increasingly useful for the asymmetric synthesis of many classes of compound. The most versatile chiral auxiliaries function by controlling the stereoselectivity of reactions of attached acyl fragments. Ideally the three stages involved in the use of such a chiral auxiliary, attachment of the acyl fragment, the stereoselective reaction and removal of the acyl fragment should all proceed easily and efficiently. Koga and Tomioka have developed the O-trityl-5-hydroxymethyl-2-pyrrolidinone **1** as a chiral auxiliary for use in stereoselective conjugate additions and Diels-Alder reactions of attached α,β-unsaturated *N*-acyl fragments.[1] This auxiliary is unsuitable for controlling the reactions of attached acyl enolates because of competing C-3 deprotonation of the 2-pyrrolidinone. Such problems do not exist in the oxazolidin-2-one chiral auxiliaries **2** developed by Evans, which have proved effective for inducing stereoselectivity in alkylation,[2] acylation,[3] bromination,[4] amination,[5] hydroxylation,[6] and aldol reactions[7] of attached *N*-acyl enolates.



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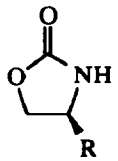
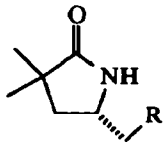


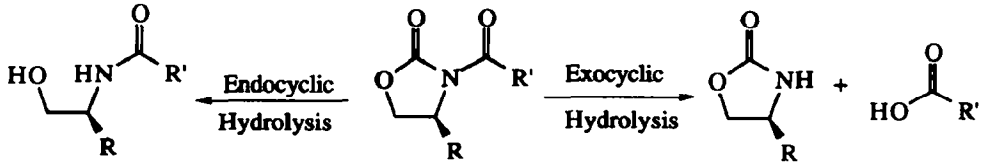
2a R = iPr,
2b R = Bn



Quats:
3a, R = $OSiMe_2{}^tBu$; **3c**, R = Me
3b, R = $OCPh_3$; **3d**, R = Et

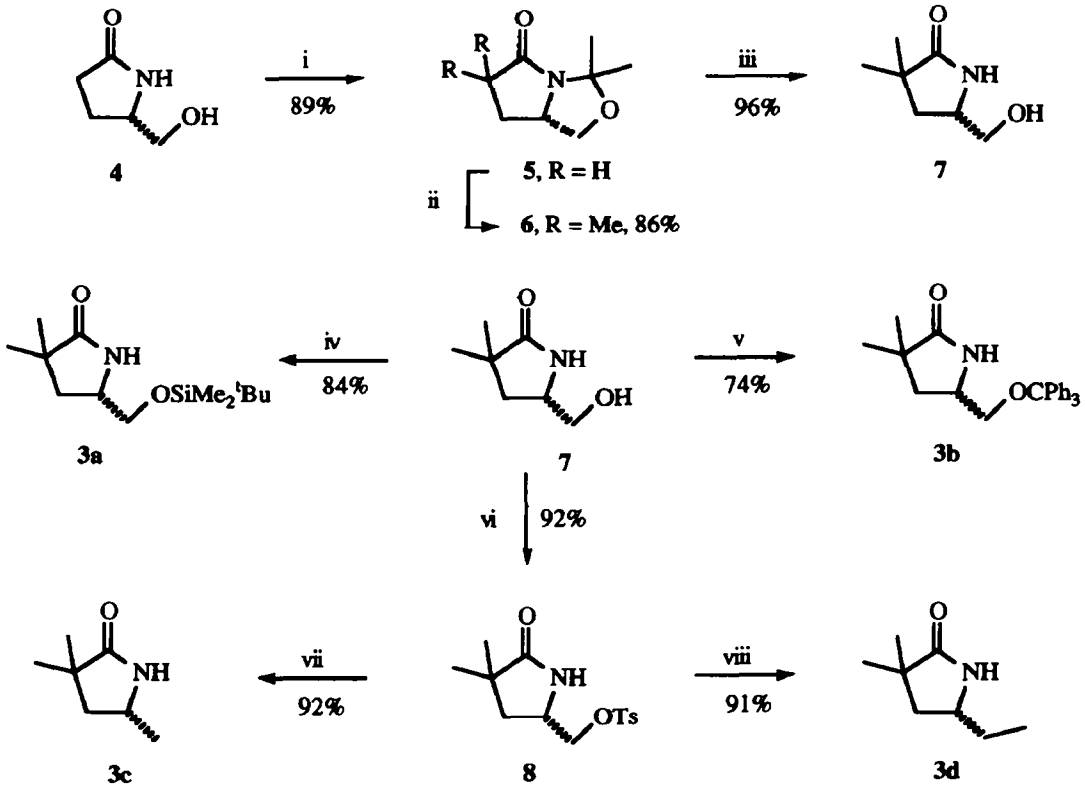
A crucial factor for the utility of a chiral auxiliary in any synthetic strategy is the mild and selective removal of the auxiliary without compromisation of the stereogenic centres in the system. The position of nucleophilic cleavage in *N*-acyloxazolidinones is dependent upon steric and electronic requirements (Scheme 1).[8] The nucleophilic cleavage of unhindered *N*-acyl derivatives is subject to electronic factors and exocyclic cleavage occurs to give the required products. However, when the group R' is large or α-branched, steric factors render the unwanted endocyclic cleavage of the oxazolidinone ring more favourable. This problem can

be overcome by using, for example, lithium hydroperoxide as the nucleophile, which is apparently less susceptable to steric hindrance.[8] The use of this reagent on a large scale may however prove hazardous.



Scheme 1

We report herein the synthesis of "Quat" chiral auxiliaries, 5-substituted-3,3-dimethyl-2-pyrrolidinones **3** designed to be efficient and highly practical chiral auxiliaries. We envisaged that a large increase in steric bulk adjacent to the endocyclic carbonyl should favour exocyclic cleavage, and for this purpose, we have synthesised the compounds **3a-d** in which a gem-dimethyl group is situated adjacent to the ring carbonyl. Compounds **3a-d** were prepared according to Scheme 2.

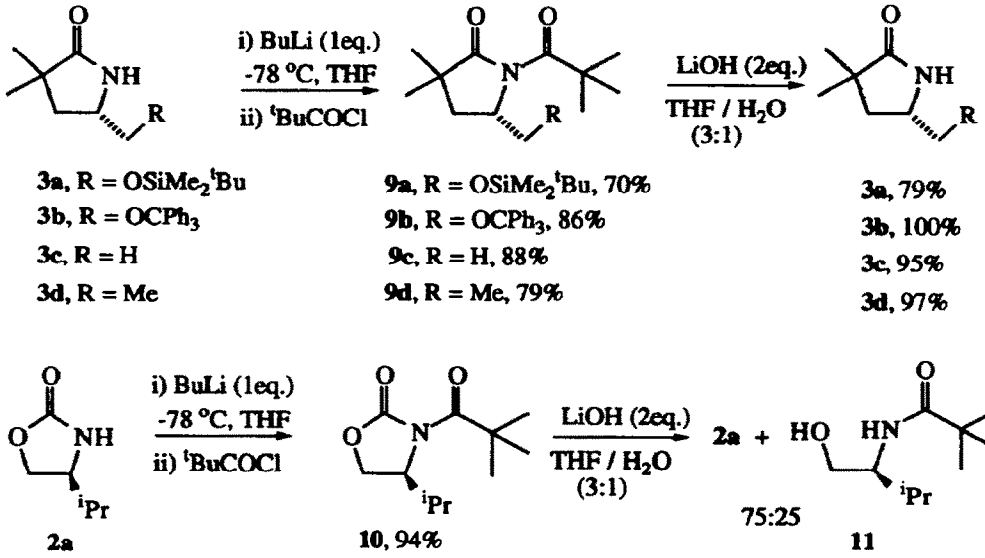


Scheme 2. ***Reagents and conditions*** : i, 2-methoxypropene, PTS (cat.), toluene at reflux; ii, LDA (1.2eq.), -78°C ; MeI, -78°C to rt; LDA (1.3eq.), -78°C ; MeI, -78°C to rt; iii, methanol, PTSA (cat.), reflux; iv, TBDMSCl, imidazole, DMF; v, Ph_3CCl, DMAP, NEt_3, CH_2Cl_2; vi, TsCl, Py, CH_2Cl_2; vii, $NaBH_4$ (2eq.), DMSO, 85°C; viii, Me_2CuLi (3eq.), THF, -20°C.

(S)-(+)-5-Hydroxymethyl-2-pyrrolidinone **4** was prepared in 56% yield from natural L-glutamic acid using the method of Levy and Silverman.[9] The hydroxyl and amido protons in compound **4** were protected as the oxazolidine **5** in high yield, by treatment of **4** with 2-methoxypropene in toluene containing a catalytic amount of pyridinium tosylate (PTS). Dimethylation of **5** was achieved in 78% yield utilising a one-pot procedure involving sequential addition of LDA followed by iodomethane. The oxazolidine protecting group was easily removed in nearly quantitative yield by heating to reflux a solution in methanol containing a catalytic amount of p-toluenesulphonic acid (PTSA) to give the alcohol **7**. Treatment of **7** with t-butyldimethylsilylchloride (TBDMSCl) and imidazole in dimethylformamide, or trityl chloride / 4-dimethylaminopyridine (DMAP) / NEt_3 in dichloromethane gave the auxiliaries **3a** and **3b** in 84% and 74% yield respectively (**3a**, $[\alpha]_D^{22}$ +46.7 (c 1.0, $CHCl_3$), **3b**, $[\alpha]_D^{24}$ +10.6 (c 0.5, $CHCl_3$)). Reaction of the alcohol **7** with tosyl chloride in a mixture of pyridine and dichloromethane (1:5) furnished the compound **8** in 92% yield. Reduction of **8** was achieved using $NaBH_4$ (2eq.) in dimethylsulphoxide and furnished the auxiliary **3c** in 92% yield (**3c**, $[\alpha]_D^{22}$ -22.5 (c 2.0, $CHCl_3$)). Reaction of **8** with Me_2CuLi (3eq.) in THF at -20°C furnished the auxiliary **3d** in 91% yield (**3d**, $[\alpha]_D^{22}$ -28 (c 2.0, $CHCl_3$)).

All new compounds in Scheme 1 were subject to full characterisation, including elemental analysis. Compound **1c** was shown to be homochiral by ^1H NMR spectroscopic analysis in the presence of O-acetyl mandelic acid using racemic **1c** for comparison.

With these four new auxiliaries in hand, it was important to ascertain whether the presence of the gem-dimethyl group resulted in the predicted greater selectivity for the cleavage of hindered *N*-acyl derivatives. We envisaged that cleavage of the *N*-pivaloyl substrates with LiOH would provide a good model. The *N*-pivaloyl derivatives **9a-d** were easily prepared in high yield by reaction of auxiliaries **3a-d** with butyllithium in tetrahydrofuran at -78°C, followed by quenching with excess of pivaloyl chloride (Scheme



Scheme 3.

3). The non-crystalline *N*-pivaloyl substrates were purified by flash column chromatography on silica gel. The *N*-pivaloyloxazolidinone **10** was prepared from oxazolidinone **2a**, as a white solid in 94% yield using a similar procedure (Scheme 3).

The *N*-pivaloyl quats **9a-d**, and the *N*-pivaloyl oxazolidinone analogue **10**, were treated with two equivalents of lithium hydroxide in a 3:1 mixture of tetrahydrofuran and water at 20°C. The reactions were monitored by thin layer chromatography until all the starting material had been consumed, and worked up by treatment with saturated aqueous sodium bicarbonate solution and extraction with diethyl ether. As shown in Scheme 4, the hydrolysis of the *N*-acyl derivatives **9a-d**, furnished the recovered auxiliaries **3a-d** in excellent yields. As expected, no products from endocyclic cleavage were observed in any of these reactions, the lower yield for **9a** being due to partial desilylation of the auxiliary **3a**. In contrast, hydrolysis of the *N*-pivaloyl oxazolidinone **10** under similar conditions, gave a mixture of products (**2a**+**11**) resulting from both *endo* and *exo*cyclic cleavage. The ratio **2a**: **11** measured by ^{1}H NMR spectroscopy (300 MHz) was 75:25. It is apparent from this study that an increase in steric bulk adjacent to the endocyclic amide bond does indeed favour exocyclic cleavage of *N*-acyl groups using lithium hydroxide as the nucleophile.

Stereoselective reactions of the Quat auxiliary **3c** and its application to asymmetric synthesis are described in the following paper.

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