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## Synthesis of Butenolides via Enantioselective Deprotonation of Protected 4-Hydroxycyclohexanone

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Abstract: Enantioselective synthesis of two butenolides (4S, 6R)-2,3-Dihydroaquilegiolide and (4S, 6S)-2,3-Dihydromenisdaurilide based on deprotonation of 4-*tert*-butyldimethylsiloxy-cyclohexanone with a chiral lithium amide base is described.

A current topic of interest in organic synthesis is the deprotonation of cyclic ketones with chiral lithium amide bases.<sup>1</sup> Cyclohexanone derivatives that were deprotonated enantioselectively with these bases include several 4-alkylcyclohexanones<sup>2a-c</sup> as well as 2,6-dimethyl- and 3,5-dimethylcyclohexanone.<sup>2d,3</sup> To increase the synthetic appeal of enantioselective deprotonation of cyclic ketones, we have conducted a study involving the enolisation of cyclohexanone derivatives bearing a functional group containing oxygen at the 4-position. A number of protected 4-hydroxycyclohexanones 4 were deprotonated with chiral, optically pure, lithium amides and the resulting enolates were trapped as enol acetates or silyl enol ethers.<sup>4</sup> Below, we describe how the results of this study were used to approach the synthesis of two naturally occurring chiral butenolides which have been recently isolated in minute quantities from the rhizome and caulis of *Sinomenium acutum*: 2,3-Dihydroaquilegiolide **1a** and 2,3-Dihydromenisdaurilide **1b**.<sup>5</sup>

Enantioselective synthesis of other butenolides was briefly explored before.<sup>6</sup> Our retrosynthetic analysis of 1a and 1b is shown in Scheme 1. Compounds 1a and 1b can be disconnected to give protected 4-hydroxycyclohexanone 4. Both the enantio- and the diastereoselectivity of the hydroxylation transform (3 --> 4) must be considered in this strategy.



Lithium amides derived from readily available<sup>7</sup> chiral isomers of  $\alpha$ -methyl-N-(1phenylethyl)benzenemethanamine (5a) were used successfully for enantioselective deprotonation of several ketones.<sup>1,2d,3</sup> In our initial study we reported low enantioselectivity (36% ee) of deprotonation of 4 with the chiral lithium amide derived from the C<sub>2</sub> symmetrical amine 5a, and much higher selectivity (74% ee) with the analogous bis-naphthyl Li-amide derived from 5b, which we developed for this purpose.<sup>4</sup>

Recently, we, and others, have established that addition of LiCl to the reaction mixture often results in a significant improvement of enantioselectivity of deprotonation.<sup>3,8</sup> This LiCl effect varies with the amine, the ketone and the reaction conditions.<sup>9</sup> Interestingly, the *in situ* generation of the lithiated **5a**-LiCl complex from the amine hydrochloride proved especially beneficial.<sup>9</sup> In agreement with these observations, when enantioselective deprotonation<sup>10</sup> of compound **4** was performed with the chiral lithium amide generated at  $-78 \, ^{\circ}$ C from the amine hydrochloride **5a**-HCl and two equivalents of n-BuLi in THF, the resulting enolate was trapped as the silyl enol ether **6** in 91% yield and an ee of 70% (Scheme 2), a significant improvement over 36% observed before in this system.<sup>4</sup> Analogous experiments with the bis-naphthylethylamine hydrochloride (**5b**-HCl) initially offered little promise for improvement and yielded **6** having 77% ee. After some experimentation we determined that two factors were important for maximum selectivity: lowering deprotonation of the lithium amide - LiCl complex resulted in formation of the silyl enol ether **6** in high yield (90%) and of high optical purity (90% ee).

Thus the use of the *in situ* generated LiCl additive and carefully controlling the reaction conditions offered a much improved protocol for enantioselective synthesis of **6** and set the stage for construction of the butenolide skeleton.



Oxidation of the silyl enol ether 6 with m-CPBA afforded two diasteroisomeric  $\alpha$ -hydroxyketones 7 and 8 in a ratio of 1 : 3 (93% combined yield). When OsO<sub>4</sub> was used instead of m-CPBA the reaction proceeded with opposite selectivity and gave a 2 : 1 mixture of 7 and 8 (88% combined yield). The diastereoselectivity in these reactions was low, which seems to be a general trend in hydroxylation of enolates of cyclic ketones.<sup>11</sup> However, compounds 7 and 8 could be easily separated by chromatography and, with pure samples of these compounds at hand, the synthesis of butenolides 1 could be approached.

The (4*S*, 6*R*) isomer of 2,3-Dihydroaquilegiolide 11 was synthesized as follows: the  $\alpha$ -hydroxy group was first protected as a TBDMS ether using standard procedures (TBDMSCl, imidazole, CH<sub>2</sub>Cl<sub>2</sub>) to give 9 in 97% yield (Scheme 3). Selective formation of the Z-isomer of 10 was achieved using Peterson olefination involving the lithiated species produced from LDA and TMSCH<sub>2</sub>CO<sub>2</sub>Et<sup>12</sup> at -78 °C, which gave compound 10 as a mixture of the Z and E isomers (13 : 1 ratio of Z : E isomers was determined by GLC; 87% yield). Due

to difficulties in separation of the Z and E isomers of 10 the crude mixture was subjected to deprotection. Using standard conditions (TBAF, Dowex H<sup>+</sup>, aqueous HCl, or NaOH<sup>13</sup>) only the silyl group in the 4-position could be removed. The use of 40% HF in CH<sub>3</sub>CN<sup>13</sup> caused deprotection at the 4-position to occur after only 15 minutes, but the silyl group at the  $\alpha$ -position remained intact. However, with prolonged exposure to 40% HF (room temperature, overnight) removal of both silyl groups was achieved, with concomitant lactonization forming Dihydroaquilegiolide 1a in 86% yield (the dextrarotatory isomer [ $\alpha$ ]D<sup>24</sup> +113 c, 1.0; MeOH). A small amount of the diol 12, which clearly resulted from the deprotection of the two silyl groups in the E isomer of 10, was also obtained.



Reagents: a. TBDMS-CI, imidazole; b. TMSCH2COOEt, LDA; c. 40% HF, MeCN.

To confirm the enantiomeric purity (90% ee) of the final butenolide 11, the OH group at C-6 (butenolide numbering) was converted into the Mosher's ester. The % ee established from the NMR data of this derivative was consistent with the GLC data obtained on the Mosher's ester derived from the  $\alpha$ -hydroxy ketone 7. Butenolide 11 was isolated as a solid (previously reported to be an oil<sup>5</sup>) which prompted us to try fractional crystallization as the means to obtain the enantiomerically pure compound. However, the optical purity of 11 was not enhanced by recrystallization and the optical rotation remained constant.

The cis hydroxyketone **8** was converted into the cis isomer of **11** i.e., into (4S, 6S)-Dihydromenisdaurilide *via* an identical sequence of reactions: protection using TBDMS-Cl (82%), Peterson olefination (88%; cis : trans = 6 : 1), hydrolysis with concomitant lactonization (83% yield,  $[\alpha]_D^{26}$  -112 c, 2.0, MeOH).

In summary, two novel butenolides were made from a common starting material 4-tertbutyldimethylsiloxycyclohexanone 4 via enantioselective deprotonation strategy. Stereoselectivity in two out of three critical steps was reasonably high: deprotonation of the cyclohexanone derivative 4 proceeded with 90% ee and Peterson olefination of 9 gave predominantly the required Z isomer. Both diastereoisomeric  $\alpha$ hydroxyketones 7 and 8, produced in the step of low diastereoselectivity, were utilized in this divergent synthesis. The synthetic sequences involved were short and reasonably efficient (30-38% yield from 4).

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