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Synthesis of Butenolides via Enantioselective Deprotonation of Protected 4-Hydroxycyclohexanone

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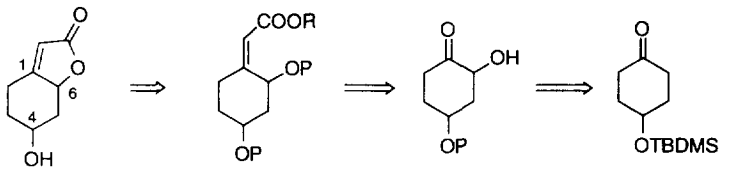
Abstract: Enantioselective synthesis of two butenolides (4*S*, 6*R*)-2,3-Dihydroaquilegiolide and (4*S*, 6*S*)-2,3-Dihydromenisdaurilide based on deprotonation of 4-*tert*-butyldimethylsiloxy-cyclohexanone with a chiral lithium amide base is described.

A current topic of interest in organic synthesis is the deprotonation of cyclic ketones with chiral lithium amide bases.[1] Cyclohexanone derivatives that were deprotonated enantioselectively with these bases include several 4-alkylcyclohexanones[2a-c] as well as 2,6-dimethyl- and 3,5-dimethylcyclohexanone.[2d,3] 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.[4] 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**.[5]

Enantioselective synthesis of other butenolides was briefly explored before.[6] 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.

Scheme 1.



1a trans
1b cis

2a **3** **4**

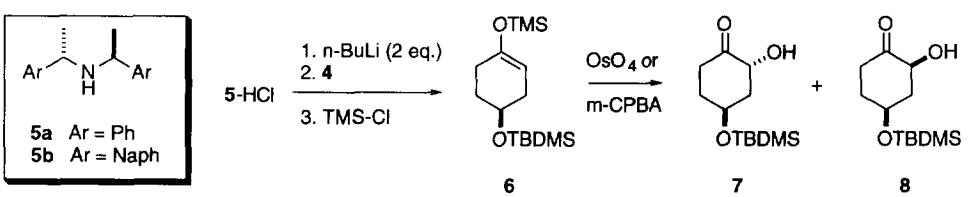
Lithium amides derived from readily available[7] chiral isomers of α-methyl-N-(1-phenylethyl)benzenemethanamine (**5a**) were used successfully for enantioselective deprotonation of several

ketones.[1,2d,3] In our initial study we reported low enantioselectivity (36% ee) of deprotonation of **4** with the chiral lithium amide derived from the C_2 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.[4]

Recently, we, and others, have established that addition of LiCl to the reaction mixture often results in a significant improvement of enantioselectivity of deprotonation.[3,8] This LiCl effect varies with the amine, the ketone and the reaction conditions.[9] Interestingly, the *in situ* generation of the lithiated **5a**-LiCl complex from the amine hydrochloride proved especially beneficial.[9] In agreement with these observations, when enantioselective deprotonation[10] of compound **4** was performed with the chiral lithium amide generated at –78 °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.[4] 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 temperature to –100 °C (ether - liquid nitrogen bath) and adding the ketone slowly (over 30 min.) to the solution 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.

Scheme 2.

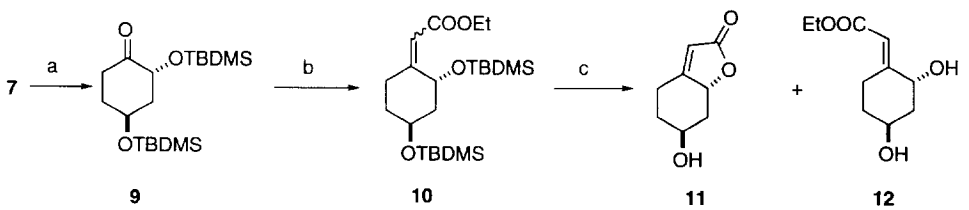


Oxidation of the silyl enol ether **6** with m-CPBA afforded two diasteroisomeric α-hydroxyketones **7** and **8** in a ratio of 1 : 3 (93% combined yield). When OsO_4 was used instead of m-CPBA the reaction proceeded with opposite selectivity and gave a 2 : 1 mixture of **7** and **8** (88% combined yield). The diastereoselectivity in these reactions was low, which seems to be a general trend in hydroxylation of enolates of cyclic ketones.[11] 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 α-hydroxy group was first protected as a TBDMS ether using standard procedures (TBDMSCl, imidazole, CH_2Cl_2) 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 $TMSCH_2CO_2Et$[12] 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^+, aqueous HCl, or NaOH[13]) only the silyl group in the 4-position could be removed. The use of 40% HF in CH_3CN[13] caused deprotection at the 4-position to occur after only 15 minutes, but the silyl group at the α-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 $[\alpha]_D^{24}$ +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.

Scheme 3.



9 **10** **11** **12**

Reagents: a. TBDMS-Cl, imidazole; b. $TMSCH_2COOEt$, 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 α-hydroxy ketone **7**. Butenolide **11** was isolated as a solid (previously reported to be an oil[5]) 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 (4*S*, 6*S*)-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-*tert*-butyldimethylsiloxycyclohexanone **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 α-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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10. In a typical deprotonation experiment n-BuLi (1.96 mL of a 2.5 M solution in hexane, 4.91 mmol) was added to a suspension of the amine hydrochloride salt **5b**-HCl (0.89 g, 2.46 mmol) in THF (20 mL) at 0°C under argon and the mixture was stirred for 1 hour. The resulting solution was cooled to –100 °C whereupon a premixed solution of freshly distilled Et_3N (1.14 mL, 8.19 mmol) and TMSCl (0.83 mL, 6.55 mmol) was added. After 2 minutes, freshly distilled **4** (0.38 g, 1.64 mmol) in THF (6 mL) was added dropwise over a period of 30 minutes and the mixture was stirred for another 30 minutes. The reaction mixture was then quenched by the addition of saturated aqueous NH_4Cl (10 mL). Water (20 mL) was added and the mixture was extracted with Et_2O (3 x 30 mL). The combined organic layers were then washed with saturated aqueous $NaHCO_3$ (2 x 10 mL), brine (1 x 10 mL) and were dried ($MgSO_4$). The solvent was removed *in vacuo* and the product was purified by flash column chromatography (hexane : ethyl acetate, 20 : 1) to provide the enol silane **6** (0.45 g, 90%). We were unable to find a method for direct measurement of the ee of **6**. However, the Mosher's esters of the α-hydroxy ketones **7** and **8** indicated (GLC on an HP-1 silicone gum column) the ee of 90 %. The absolute stereochemistry was assumed to be the same as in other cyclic ketones deprotonated with the same base, c.f., ref. 3. Compounds **7**-**12** (and the analogous substances on the pathway to (4*S*, 6*S*)-Dihydromenisdaurilide) have been fully characterized by NMR, IR, MS, $[\alpha]_D$ and elemental analysis.
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