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SYNTHESIS OF OPTICALLY ACTIVE AMINO KETONES FROM (S)-SERINE

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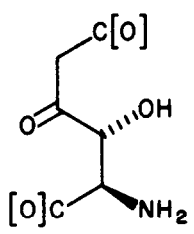
Summary: The oxazoline-protected (S)-serine methyl ester **2** can be coupled with various organolithio compounds to give the corresponding ketones **4a-d** in good yield without racemisation.

A chiral amino ketone of type **1** is required for a biomimetic total synthesis of the antitumor antibiotic mitomycin C.[2] The addition of a substituted lithio dithiane to a suitably protected (S)-serine derivative was considered a direct entry to the carbon chain **1**, which in the antibiotic itself is biosynthetically derived from D-glucosamine.

The preparation of unsymmetrical ketones by reaction of carboxylic acid derivatives with organometallic reagents is well known,[3] but is often complicated by the formation of tertiary alcohols as undesired side products. One method of avoiding this side reaction employs the reaction of Grignard reagents with activated esters.[4] All such esters contain an unsaturated nitrogen functionality in the potential leaving group, which might chelate with the Grignard reagent and promote its addition to the ester carbonyl group. A second approach[5] involves the conversion of an isoxazole alkyl ester into a ketone using an excess of Grignard reagent in the presence of triethylamine, the resulting carbonyl functionality being protected as its magnesium enolate.

We wish to report that one equivalent of various lithio dithianes **3a-c** or even n-butyllithium itself reacts rapidly with the oxazoline-protected (S)-serine methyl ester **2** to form the corresponding ketones **4a-d** (Table). The formation of tertiary alcohols was not observed except for a trace amount (<3%) in the case of n-butyllithium.

In contrast, when the N-benzyloxycarbonyl-O-benzyl-protected serine ester **5**[6] was treated with the lithio dithiane **3a** under the same conditions, only β-elimination of benzyl alcohol took place, reflecting the much higher acidity of the proton α to the ester in the carbamate **5** compared to that in the oxazoline **2**.



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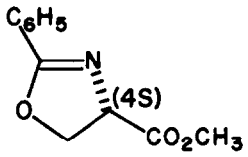

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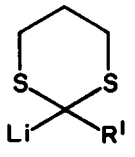

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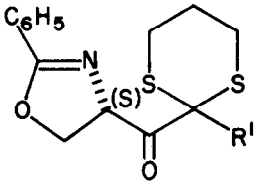
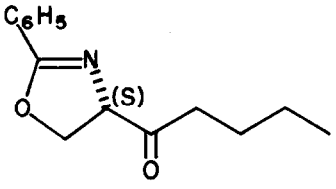
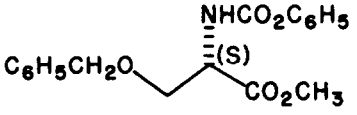


4a-c



4d



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3, 4, 6a: R^1 = H; b: R^1 = $CH_2CH_2OCH_2C_6H_5$; c: R^1 = $CH_2CH(OC_2H_5)_2$

Table: Synthesis of Ketones 4 from ester 2.

R-Li	reaction temperature [°C]	ketone 4[a]	yield[b]	mp.	$[\alpha]_D$ (c, in $CHCl_3$)
3a	-78°	4a	79%	58-61°	+18.6° (2.95)
3b	-78°	4b	48%[c]	oil	+48.2° (0.55)
3c	-78°	4c	59%[d]	148-150°	+180.0° (4.20)
n-Buli	-100°	4d	78%	oil[e]	+56.6° (1.00)

[a] For all compounds satisfactory spectroscopic (IR, ^{1}H-NMR, ^{13}C-NMR, MS) and analytical (microanalysis, high resolution MS) data were obtained.

[b] All yields are calculated for purified material (flash-chromatography on Florisil® or medium pressure liquid chromatography on a silicagel column).

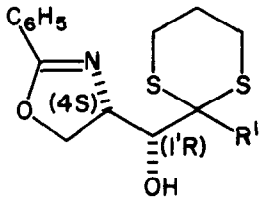
[c] 25% of 3b and 2 were recovered, together with 5% of an elimination product corresponding to 4b with R^1: $CH{=}CH_2$.

[d] 26% of 3c and 2 were recovered.

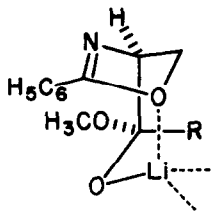
[e] decomposes during storage at r.t.

In a general procedure, an 0.1 M solution of the lithio dithiane 3 or n-butyllithium (0.1-6 mmole) was prepared[7] in THF or diethyl ether under argon, cooled to the required reaction temperature and added rapidly with vigorous stirring to a cooled 0.1 M solution of the ester 3[8] in THF. The reaction was quenched after 10 min. with methanol and allowed to reach room temperature, after adjustment of the pH to 7.5 with dilute hydrochloric acid. Partition between chloroform and water gave after purification by chromatography the ketones **4a-d**.

The optical purity of the ketones **4a-d** is better than 95%: ^{1}H NMR spectra in the presence of the chiral solvent (S)-phenyl-trifluoromethyl-carbinol[9] of the corresponding alcohols (4S,1'R)-**6a-c** (obtained after carbonyl reduction of the ketones **4a-c**[10]) showed no enantiomeric impurities, whereas the signals of the two enantiomers of the deliberately racemised alcohol (threo)-**6a**[11] were clearly separated under the same experimental conditions.



6a-c



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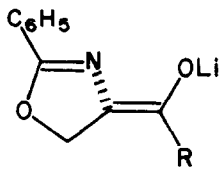

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To explain these highly selective conversions of the ester 2 into amino ketones in the absence of any specific ester activation by a special leaving group (compare[4]), we suggest the intermediacy of a lithio complex such as 7. Such a complex, stabilised by interaction of the oxazoline with the lithium cation, would protect the potential carbonyl group in the form of a tetrahedral intermediate against further reaction to a tertiary alcohol. Formation of an enolate 8, as postulated for the reaction of the isoxazole alkyl ester with Grignard reagents,[5] does not occur, since the resulting ketones **4a-d** would then be optically inactive.

This type of amino ketone preparation with reactive organolithium reagents might be applicable to the synthesis of certain other natural products, for example sphingosines.

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References and Notes

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7. **4a**: A. Beck and D. Seebach, Org. Synth. **51**, 76 (1971); **4b,c**: see reference 3b; **4b**: The anion was prepared in diethyl ether at 0°C under argon. Deuteration (D_2O) and ^{1}H-NMR showed deprotonation to be complete after 2 hrs (recovery 89% of dithiane). The inhomogenous solution was diluted with THF (20% w/v) before reaction with the ester **3**.

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10. L-Selectride® in THF at -78°C reduces **4a** with very high diastereoselectivity to the alcohol (4S, 1'R)-**6a**. The absolute configuration of **6a** was assigned by ^{1}H NMR and NOE measurements after conversion of **6a** into a corresponding 1,3-dioxolane. Superhydride in THF at -100°C reduces **4b** to a 4:1 diastereomeric mixture of **6b**, whereas $NaBH_4$ in ethanol at 0°C gives 1:1 diastereomeric mixtures of the alcohols **6a-c**.

11. Obtained by treatment of **4a** with LDA in THF at -78°C and subsequent reduction with L-Selectride®.

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