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ASYMMETRIC OXIDATION OF β-KETOESTERS WITH BENZOYL PEROXIDE; ENANTIOSELECTIVE FORMATION OF PROTECTED TERTIARY ALCOHOLS

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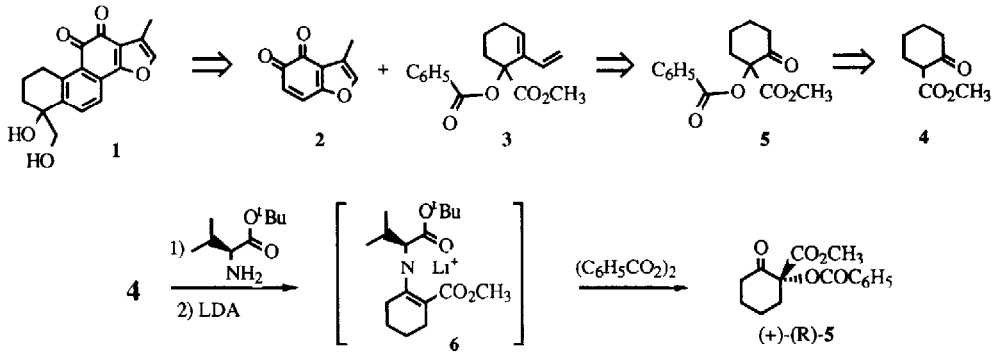
Key Words β-ketoester oxidation, asymmetric enolate oxidation, benzoyl peroxide, lithioenamine

Abstract Asymmetric oxidation of β-ketoesters by the benzoyl peroxide quench of their lithioenamines formed with (S)-valine t-butyl esters has been accomplished with good enantioselectivity for the formation of tertiary benzoate esters This procedure thus enables generation of tertiary alcohols in protected form

In the course of the synthesis of tanshindiol A [**1**], an ultrasound promoted cycloaddition between o-quinone **2** and diene **3** was used to construct the abietane skeleton (Scheme 1) [1] Diene **3** was prepared via the benzoyl peroxide (BPO) quench of the enolate of methyl cyclohexanone-2-carboxylate [**4**] giving the tertiary alcohol protected as the benzoate ester **5** Since the chirality in diene **3** was generated by the peroxide quench of the enolate of **4**, this step had to be accomplished with high enantioselectivity for the asymmetric synthesis of **1** Several methods have been reported for the asymmetric oxidation using chiral auxiliaries[2] or chiral oxidizing agents[3] of otherwise achiral enolates to produce α-hydroxycarbonyl compounds with excellent optical purity However, these procedures were not applicable to our particular problem due to the subsequent steps in our synthetic route to tanshindiol A which required the tertiary alcohol in protected form [4] Koga had reported that the lithioenamine **6** derived from **4** and (S)-valine t-butyl ester could be alkylated with high diastereoselectivity [5] Indeed, we had previously used this procedure in the asymmetric preparation of methyl tanshinonate and tanshinone IIB [6] We now report that the reaction of lithioenamine **6** with BPO produces the benzoate ester (+)-(R)-**5** in good yield and with excellent selectivity (92% e e), thereby generating the protected tertiary alcohol Reactions with other β-ketoesters have been similarly successful

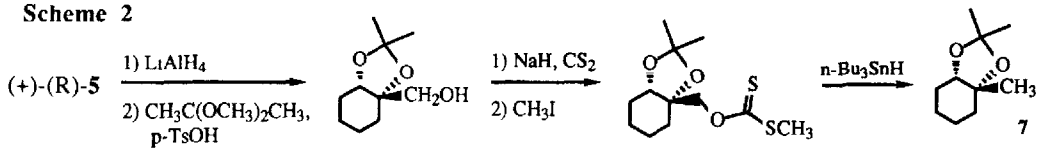
Scheme 1



Koga had reported that the stereoselectivity of the alkylation of **6** in toluene was dependent upon the added lithium ligand, in the presence of THF (2 0 eq), methylation of **6** produced the S-enantiomer in 92% e e, while the selectivity was reversed in the presence of HMPA (1 0 eq), as the added lithium ligand, producing the R-enantiomer in 99% e e [5,7] When the same procedures were employed for the BPO oxidation, benzoate (+)-(R)-**5** was obtained in 60% yield, 71% e e when THF was the ligand Using HMPA as the ligand reduced the yield to only 34%, and the e e was only 30%, but still the (R)-enantiomer was dominant In the absence of any added ligand, (+)-(R)-**5** was obtained in 51% yield, 50% e e Thus, the diastereoselectivity of the BPO quench of **6** with THF as the added ligand is enhanced relative to no added ligand, and the facial selectivity is the same as observed by Koga in the alkylations of **6** But with HMPA, the selectivity was not reversed, only lowered (Table, Items 1 - 3) Both the yield and selectivity were optimized using THF as the solvent, producing (+)-(R)-**5** in 69% yield with 92% e e (Table, Item 4) This contrasts with the alkylations in which excess THF as the added lithium ligand reduced the diastereofacial selectivity [7]

Subsequently, the dialkylaluminoenamines formed with $AlMe_3$ and $AlEt_3$ were examined (Table, Items 5 and 6) Under these conditions, (-)-(S)-**5** was the dominant product, though in only 30% and 26% e e for $AlMe_3$ and $AlEt_3$, respectively Production of (-)-(S)-**5** therefore was best accomplished using (R)-valine t-butyl ester as the auxiliary (Item 11) Decreasing the steric bulk of the valine ester group (Items 7 - 10) greatly decreased the facial selectivity of the BPO quench of the dialkylaluminoenamines, though much less so for the lithioenamines The valine esters could be recovered without any racemization (typically >90% recovery) following work-up The absolute stereochemistry of (+)-(R)-**5** was assigned by conversion to the known (1R,2S)-methylcyclohexane-1,2-diol acetonide [**7**] (Scheme 2) [1]

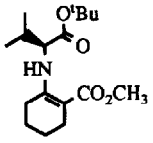
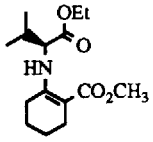
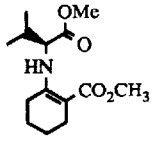
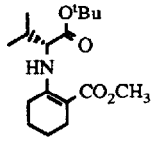
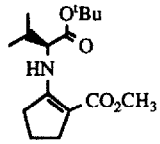
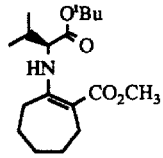
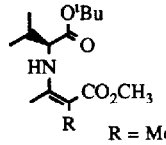
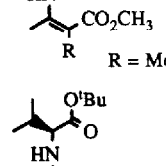
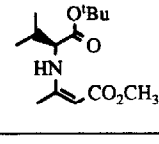
Scheme 2



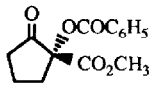
Application of the procedure to other β-ketoesters was also briefly examined, with good success (Items 12 - 19) Thus, the enolates were oxidized to the benzoate esters, thereby generating a tertiary alcohol in protected form with good enantioselectivity In each case, the selectivity could be reversed, though with only poor selectivity (≤ 50% e e) using $AlMe_3$ as the deprotonating base and chelating metal for the enamine The absolute stereochemistry of **10** and **11** were assigned by hydrolysis, producing the known 2-acetolactic and 2-aceto-2-hydroxybutanoic acids, respectively [8] The absolute stereochemistry for benzoates **8** and **9** was tenatively assigned by the established facial selectivity for electrophile addition to the lithioenamine using the (S)-valine t-butyl ester as the chiral auxiliary, both in this work and in that previously reported by Koga

Oxidation of methyl acetoacetate via the (S)-valine t-butyl ester enamine under the same conditions produced the corresponding racemic α-benzoate **12** in 53% yield (Item 19) Presumably rapid tautomerization to the enol eliminates any selectivity achieved in the oxidation Indeed, in Koga's alkylation of β-ketoesters, only the generation of quaternary centers were reported By comparison, the alkylation of ketone α-methylene positions via their lithioenamines derived from (S)-valine t-butyl esters was not subject to racemization [9]

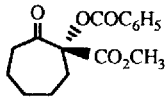
Table Oxidation of β-Ketoester with Benzoyl Peroxide via Their Metallo-Enamines

Item	Enamine	Conditions[a]	Yield (%)[b]	Product	E.E (%)[c]
1		LDA, toluene/THF (1 eq)	60	(+)-(R)-**5**	71
2		LDA, toluene/HMPA (1 eq)	34	(+)-(R)-**5**	30
3		LDA, toluene	51	(+)-(R)-**5**	50
4		LDA, THF	69	(+)-(R)-**5**	92
5		$AlMe_3$, CH_2Cl_2	65	(-)-(S)-**5**	30
6		$AlEt_3$, CH_2Cl_2	56	(-)-(S)-**5**	26
7		LDA, THF	63	(+)-(R)-**5**	85
8		$AlMe_3$, CH_2Cl_2	66	(-)-(S)-**5**	12
9		LDA, THF	50	(+)-(R)-**5**	70
10		$AlMe_3$, CH_2Cl_2	40	(±)-**5**	0
11		LDA, THF	60	(-)-(S)-**5**	90
12		LDA, THF	57	(-)-(R)-**8**	78
13		$AlMe_3$, CH_2Cl_2	30	(+)-(S)-**8**	5
14		LDA, THF	58	(+)-(R)-**9**	80
15		$AlMe_3$, CH_2Cl_2	52	(-)-(S)-**9**	50
16		R = Me LDA, THF	50	(-)-(R)-**10**	85
17		R = Me $AlMe_3$, CH_2Cl_2	51	(+)-(S)-**10**	25
18	 R = Me, Et	R = Et LDA, THF	70	(-)-(R)-**11**	78
		R = Et $AlMe_3$, CH_2CH_2	46	(+)-(S)-**11**	38
19		LDA, THF	53	**12**	0

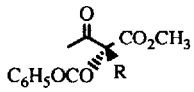
a) All reactions were run at -78 °C for 72 h b) Isolated yields c) Optical purities were determined by CLIS in the ^1H NMR spectra using (+)-Eu(hfc)$_3$



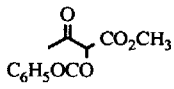
(-)-(R)-**8**



(+)-(R)-**9**



(-)-(R)-**10** R = Me
(-)-(R)-**11** R = Et



12

The preparation of **10** and **11**, protected forms of 2-acetolactic acid and 2-aceto-2-hydroxybutanoic acid, represent very routine procedures for obtaining these key intermediates in the biosynthesis of valine and leucine, respectively, with high optical purity [10] While the parent α-hydroxyacids are not stable, **10** and **11** can be stored indefinitely (or at least for a year which is the length of time we've now stored these compounds!)

In a typical procedure, the freshly prepared and distilled (S)-valine t-butyl ester enamine (10 5 mmol) was slowly added as a THF solution (10 mL) with stirring to a solution of LDA (11 0 mmol) in THF (10 mL) previously cooled to -78 °C, producing the red color of the lithioenamine The mixture was stirred at -78 °C for 1 h, then a solution of BPO (23 mmol) in THF (10 mL) was added, and stirring continued for 72 h at -78 °C The temperature was then allowed to rise to 0 °C, and the reaction was quenched by slowly adding 2N HCl (50 mL) The reaction mixture was then thoroughly extracted with diethyl ether, the ether layer dried, and then the solvent removed in vacuo The residue was purified by flash chromatography on silica gel [11] The ^{1}H and ^{13}C NMR spectra and HRMS of the products were in accord with the assigned structures The ^{1}H NMR spectra of the enamines were also recorded prior to use and were in complete agreement with the assigned structures Work on the structure of the lithioenamine and aluminoenamine intermediates is in progress in order to gain a better understanding of the basis of the facial selectivity of the electrophile addition

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