1-(*NN*-Dimethylaminomethyl)-2-formylcymantrene as a Reagent for the Asymmetric Synthesis and Retroracemisation of Amino Acids

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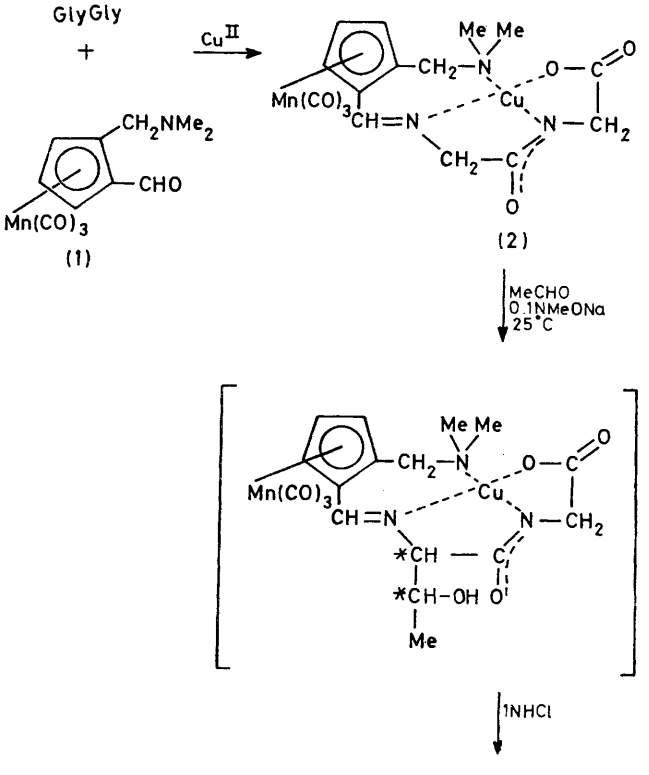
Summary 1-(*NN*-Dimethylaminomethyl)-2-formylcymantrene (AFCMT) has been resolved into enantiomers which gave copper complexes with GlyGly which were alkylated with acetaldehyde; hydrolysis of the resulting dipeptides gave threonine with an asymmetric yield of 92—98% and chiral AFCMT in the presence of copper ions partially retroracemises (*R*,*S*)-Ala-(*R*,*S*)-Nva.

THE pyridoxal-dependent enzyme serine transhydroxymethylase[1] may be regarded as a chiral carbonyl-containing reagent which effects the synthesis of β-hydroxy-α-amino acids through the intermediate formation of a Schiff base of an aromatic aldehyde (pyridoxal) and glycine. It has been shown that the chiral environment of such a Schiff base on the active centre of the enzyme can be imitated in stereochemically inert complexes of Co^{III}.[2] For the free amino acid to be isolated after the asymmetric transformation, the Co^{III} complex must be destroyed, and its chirality, governed by the spatial arrangement of the ligands about the Co^{III} ion, is irrevocably lost. Replacement of salicylaldehyde with a chiral analogue would allow the chiral fragment of the complex to be preserved after the isolation of the amino acid. We here report on the asymmetric synthesis of threonine and resolution of amino acids using the chiral carbonyl-containing compound 1-(*NN*-dimethylaminomethyl)-2-formylcymantrene (**1**) which can be repeatedly employed for this purpose.

To resolve (**1**) into enantiomers, we utilized the ability of aromatic aldehydes (*e.g.* salicylaldehyde) to form stable copper complexes with chiral dipeptides.[3] In the case of (**1**) the formation of copper complexes with chiral dipeptides is enantiospecific. (*S*)-Ala-(*S*)-Ala and (*S*)-Ala-Gly form mixed copper complexes preferentially with $(-)_{436}$-(**1**). The unchanged $(+)_{436}$-(**1**) is extracted from the reaction mixture with benzene. The enantiomers $(-)_{436}$-(**1**) and $(+)_{436}$-(**1**) gave enantiomeric copper complexes with diglycine [(**2a**) and (**2b**), respectively] in 60% yield (Scheme) as shown by the electronic spectrum and o.r.d. of the complexes.



SCHEME

The interaction of (**2a**) or (**2b**) with a 50-fold excess of acetaldehyde at 25 °C leads to a mixture of diastereomeric complexes from which, after mild hydrolysis with 1N HCl, a mixture of dipeptides containing threonine and *allo*-threonine was obtained (Scheme). Under these experimental conditions the condensation of acetaldehyde with the copper complex of diglycine does not proceed.

In the interaction of (**2a**) and (**2b**) with acetaldehyde only the *N*-terminal fragment of glycylglycine is alkylated, as shown chromatographically by comparing the dipeptides separated from the reaction mixture with standard dipeptides (GlyGly, ThrGly, GlyThr).

After hydrolysis of the isolated dipeptides (6N HCl, 105 °C, 24 h) the quantitative and enantiomeric composition of the mixture of amino acids obtained was determined by g.l.c.[4] (Table 1).

Using the enantiomers of (**1**) we have succeeded in retroracemising the dipeptide (*R,S*)-Ala–(*R,S*)-Nva. This was conducted in 0·5N MeONa in MeOH at room temperature under argon in the presence of stoicheiometric quantities of copper acetate and the corresponding enantiomer of (**1**). After decomposition of the reaction mixture with 1N HCl, a mixture of dipeptides was isolated, which, after hydrolysis (6N HCl, 105 °C, 24 h) was analysed by g.l.c. (Table 2).

The dipeptides were separated from the reaction mixture

TABLE 1

Enantiomeric composition of the mixture of threonines obtained in the alkylation of complexes (**2a**) and (**2b**) (c 3·5 × 10^{-3} mol l^{-1}) with acetaldehyde in 0·1 N MeONa in MeOH at 25 °C under argon; complex–acetaldehyde ratio 1 : 50.

Complex	Reaction Time/h	Thr/*allo*-Thr	Gly/Thr+*allo*-Thr	Asymmetric yield, %	
				Threonine	*allo*-Threonine
(**2a**)	1	2·42	1·9	92—98 *S*	95—100 *S*
(**2a**)	4	2·15	1·2	92 *S*	95—100 *S*
(**2b**)	1	2·30	1·5	93 *R*	100 *R*
(**2b**)	4	2·30	1·2	96 *R*	100 *R*

The chemical yield of threonines is practically unchanged within the time interval of 1—4 h and is 80% for the *N*-terminal glycine. The asymmetric yield of threonine does not change in the course of the reaction and is 92—98% (Table 1). The alkylation of complex (**2a**) containing $(-)_{436}$-(**1**), after the decomposition of the mixture, gives a dipeptide containing (*S*)-threonine and (*S*)-*allo*-threonine, while the dipeptide obtained in the alkylation of complex (**2b**) contains (*R*)-threonine and (*R*)-*allo*-threonine, the asymmetric yields for (**2a**) and (**2b**) being the same. In addition to the dipeptides, a corresponding enantiomer of (**1**) can also be removed from the mixture by extraction with $CHCl_3$, in 85% yield. The ^1H n.m.r., i.r., and electronic spectra of (**1**) obtained from the reaction mixture were identical to those of the starting (**1**). The separated $(-)_{436}$-(**1**) interacts again with GlyGly and copper ions, giving (**2a**). Alkylation of this complex with acetaldehyde gives (*S*)-threonine and (*S*)-*allo*-threonine, as before, with the same asymmetric yield.

Thus, the enantiomers of (**1**) can be recycled for the asymmetric synthesis of threonine and threonine-containing dipeptides from glycylglycine.

quantitatively. As can be seen from Table 2, both the *N*-terminal and *C*-terminal amino acids are retroracemised. The rigorous conditions under which the experiment is conducted lead to the α-proton of the *C*-terminal amino acid becoming labile.[5] Evidently, copper complexes of $(-)_{436}$-(**1**) with chiral dipeptides are most stable when the configuration of the *N*-terminal amino acid is *S* and that of the *C*-terminal amino acid is *R*.

After decomposition of the reaction mixture with 1N HCl and extraction with $CHCl_3$ a corresponding enantiomer of (**1**), having the same specific rotation in $CHCl_3$ as the initial (**1**), was obtained in 65% yield. Consequently, by using enantiomers of (**1**), it is possible to effect retroracemisation of the dipeptides. It is important to note that the enantiomers of (**1**) are not liable to racemisation in the course of the threonine synthesis and retroracemisation of the dipeptides.

TABLE 2

Enantiomeric composition of amino acids obtained after the retroracemisation of (*R,S*)-Ala–(*R,S*)-Nva in 0·5N MeONa and MeOH in the presence of stoicheiometric quantities of $(-)_{436}$-(**1**) or $(+)_{436}$-(**1**) and copper acetate at room temperature under argon.

(**1**)	Reaction time/h	% of enantiomers			
		(*S*)-Ala	(*R*)-Ala	(*S*)-Nva	(*R*)-Nva
$(-)_{436}$	1	78·31	21·69	39·43	60·57
$(-)_{436}$	3	76·85	23·15	26·20	73·80
$(+)_{436}$	1	26·80	73·20	57·88	42·12

We thank S. V. Vitt and M. B. Saporovskaya for performing quantitative and enantiomeric g.l.c. analyses.

(*Received, 27th March* 1979; *Com.* 316.)

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