Alkaloid-catalysed Asymmetric Addition of Thiocarboxylic *S*-Acids to Cyclohex-2-en-1-ones. Absolute Configuration of the Adducts by *O,S*-Dibenzoate Cotton Effect

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Summary The cinchona alkaloid-catalysed 1,4-addition of thiocarboxylic *S*-acids to cyclohex-2-en-1-ones gives optically active keto-thioesters; the signs of the Cotton effects of the *O,S*-dibenzoates were used as a basis for the assignment of their absolute configurations.

ALKALOID-CATALYSED conjugate addition of benzene thiols[1] and benzene selenols[2] to cyclohex-2-en-1-ones, and of thiols to other conjugated systems,[3,4] has received considerable attention in the past few years, including extensive mechanistic studies.[5] The chiral sulphides, although

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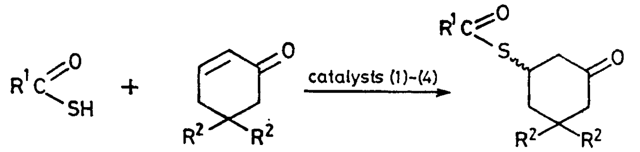
valuable synthetic products *per se*, cannot be easily transformed into other thiol derivatives. We have found that the versatile chiral thiol derivatives can readily be obtained by asymmetric addition of thiocarboxylic *S*-acids to cyclohex-2-en-1-ones in the presence of catalytic amounts of cinchona alkaloids.

TABLE. Asymmetric additions of thiocarboxylic *S*-acids to cyclohex-2-en-1-ones.[a]

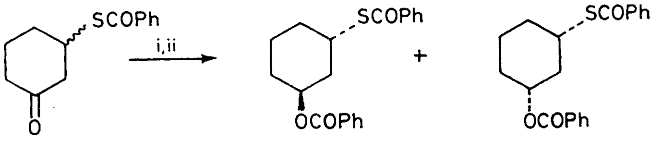
R^1	R^2	Catalyst (abs. config.)	$[\alpha]_{578}(CCl_4)$ /°	Adduct[b] enant. excess /%[c]	Abs. config.
Me	H	Cinchonine (8*R*,9*S*) (**1**)	−55·0	54	*S*
		Quinidine (8*R*,9*S*) (**2**)	−55·0	54	*S*
		Cinchonidine (8*S*,9*R*) (**3**)	+52·0	51	*R*
		Quinine (8*S*,9*R*) (**4**)	+46·4	45	*R*
Ph	H	(**1**)	−33·0	53	*S*
		(**2**)	−27·7	45	*S*
		(**3**)	+27·1	44	*R*
		(**4**)	+25·9	42	*R*
Me	Me	(**1**)	−15·6	48	*S*
Ph	Me	(**1**)	− 8·5	49	*S*

[a] Reaction conditions: thioacid 0·6 M, cyclohexenone 0·52 M, catalyst 0·005 M in benzene, room temp., *ca.* 4 h, chemical yield *ca.* 100%. [b] All new compounds have been fully characterized by spectral and elemental analyses. [c] Determined by ^{13}C n.m.r. spectroscopy of diastereomeric acetals of (−)-(2*R*,3*R*)-butane-2,3-diol: H. Hiemstra and H. Wynberg, *Tetrahedron Lett.*, 1977, 2183.

Our results (Table) show that the reaction proceeds in benzene at room temperature at a convenient rate with essentially quantitative chemical yield and *ca.* 50% enantiomeric excess. Under these conditions the non-catalysed reaction (leading to racemic product) is at least one order of magnitude slower. As in the case of other asymmetrically catalysed additions,[1,2,4,5] the stereochemistry of the product is controlled by the absolute configuration of the (alkaloid) β-amino-alcohol catalyst. The keto-thioester product is an obvious entry into numerous other chiral derivatives.



In order to establish the absolute configuration of the adduct (**5**), $[\alpha]_{578}(CCl_4)$ −33·0°, it was reduced to a mixture of *trans* and *cis* (1 : 4) hydroxy-thiobenzoates, separated by column chromatography as the 1,3-*O*,*S*-dibenzoates (**6**) and (**7**). The *trans*-*O*(a),*S*(e)-dibenzoate (**6**) and *cis*-*O*(e),*S*(e)-dibenzoate (**7**) were easily distinguished by ^1H n.m.r. spectroscopy. The *trans*-isomer (**6**) shows a positive exciton-split Cotton effect[6] for the benzoate intramolecular charge-transfer transition between 250 and 220 nm (Figure).



(**5**) (**6**) (**7**)

Reagents and conditions: i, $NaBH_4$–EtOH, room temp.; ii, PhCOCl–pyridine.

If we assume that the sign of the Cotton effect of the *O*,*S*-dibenzoate obeys the same rules as those applicable to the *O*,*O*-dibenzoate,[7] positive chirality between the C–O and C–S bonds is established. Since the chirality is conformation-independent, the absolute configuration of the adduct (**5**) is *S*.

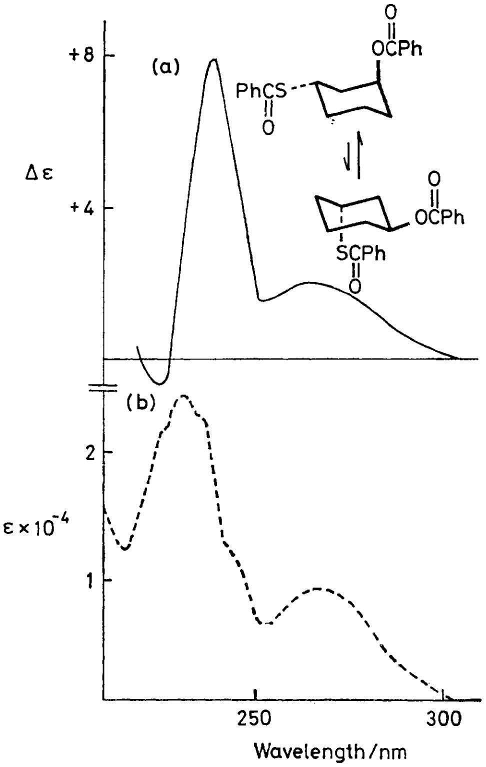


FIGURE. C.d. (a) and u.v. (b) curves of (1*S*, 3*S*)-(**6**), corrected to 100% e.e., solvent cyclohexane.

Additional support for the absolute configuration of the adducts comes from their strong n–π* transition Cotton effect, originating from the consignate (octant-like) contribution of the β-equatorial thioester substituent.

(*Received*, 18*th November* 1980; *Com.* 1234.)

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