The Absolute Stereochemistry of Wieland–Miescher Ketone Analogues bearing an Angular Protected Hydroxymethyl Group

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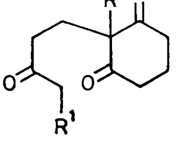
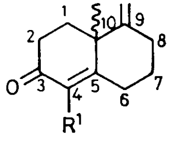
The Wieland–Miescher ketone analogues (**3**) and (**4**), each bearing an angular protected hydroxymethyl group, have been prepared by the amino-acid catalysed cyclisation of their cyclohexane-1,3-dione derivatives (**1**) and (**2**); the optical purities and absolute configurations of (**3**) and (**4**) have been determined by applying the methoxy(trifluoromethyl)phenylacetate method and the c.d. exciton chirality method, respectively, to their mono-9-ol derivatives.

In a previous paper, we reported that cyclisation of the cyclohexane-1,3-dione derivatives (**1**) and (**2a**) proceeded smoothly, by the use of an optically active amino-acid catalyst, to give the optically active Wieland–Miescher ketone analogues (**3**) and (**4a**), bearing an angular protected hydroxymethyl group.[1,2] We report here the results of the determination of the optical purities and absolute configurations of compounds (**3**) and (**4**).

After a large number of experiments under various conditions, compounds (**3**) and (**4**) were obtained with satisfactory chemical and optical yields by the use of the following reagents: L-proline (1 equiv.)–dimethyl sulphoxide (room temp., 24 h) for (**3**), D-β-phenylalanine (1 equiv.)–D-camphor-10-sulphonic acid (0.5 equiv.)–dimethylformamide (room temp. to *ca.* 60 °C, 210 h) for (**4a**), and D-β-phenylalanine (1 equiv.)–$HClO_4$ (0.5 equiv.)–MeCN (80 °C, 96 h) for (**4b**). The results are summarized in Table 1. Treatment of these optically active bicyclic diketones with sodium borohydride in ethanol [0 °C for (**3**), −60 °C for (**4a**), and 0 °C for (**4b**)] caused the regio- and stereo-selective reduction of the saturated ketone function at C-9 (steroidal numbering) to give the corresponding hydroxyenones, quantitatively, {(**5a**), $[\alpha]_D^{20}$ + 116.8° (c 0.30, $CHCl_3$), (**6a**), $[\alpha]_D^{20}$ −175.2° (c 0.21, $CHCl_3$), and



(1) R^1 = H, R^2 = $MEMOCH_2$
(2)a; R^1 = Me, R^2 = $AcOCH_2$
b; R^1 = Me, R^2 = $MeOCH_2$



(3) R^1 = H, R^2 = $MEMOCH_2$ ►
(4) a; R^1 = Me, R^2 = $AcOCH_2$ ---
b; R^1 = Me, R^2 = $MeOCH_2$ ---

MEM = $MeOCH_2CH_2OCH_2$

Table 1. Chemical and optical yields of the Wieland–Miescher ketone analogues.

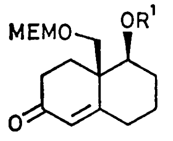
Compound	Yield/%[a]	$[\alpha]_D^{20}$/°(c)[b]	Optical purity[c] % e.e.
(**3**)	70	+76.6 (0.14)	75
(**4a**)	77	−74.9 (0.20)	90
(**4b**)	86	−128.8 (0.10)	86

[a] Yield of total material isolated by t.l.c. Catalysts and conditions are described in the text. [b] Measured in $CHCl_3$. [c] Estimated by the MTPA method.

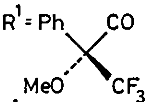
Table 2. C.d. data for the enone–benzoates.

		C.d. data[b]		
Compound	Chirality[a]	First Cotton effect λ_{ext}/nm ($\Delta\epsilon$)	Second Cotton effect λ_{ext}/nm ($\Delta\epsilon$)	Absolute configuration
(**5c**)[c]	+	248 (+28.6)	230 (−11.6)	(9*S*, 10*S*)
(**6c**)[d]	−	261 (−27.4)	241 (+13.2)	(9*R*, 10*R*)
(**7c**)[e]	−	260 (−21.5)	242 (+10.4)	(9*R*, 10*R*)
(**8c**)[f]	+	247 (+27.6)	228 (−10.9)	(9*S*, 10*S*)

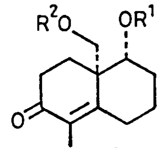
[a] Between the long axes of enone and benzoate chromophores. [b] Measured in EtOH. [c] For 75% e.e. material. [d] For 90% e.e. material. [e] For 86% e.e. material. [f] For 68% e.e. material.



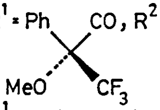
(5)a; R^1=H

b; R^1= 

c; R^1=p-ClC_6H_4CO

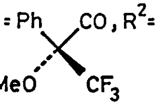


(6)a; R^1=H, R^2=Ac

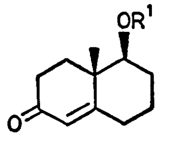
b; R^1=  , R^2=Ac

c; R^1=p-$MeOC_6H_4CO$, R^2=Ac

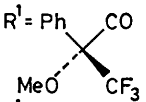
(7)a; R^1=H, R^2=Me

b; R^1=  , R^2=Me

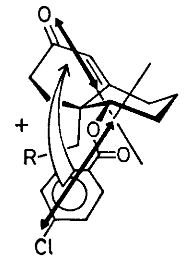
c; R^1=p-$MeOC_6H_4CO$, R^2=Me



(8)a; R^1=H

b; R^1= 

c; R^1=p-ClC_6H_4CO



(5c); R=MEMO

(8c); R=H

(7a), $[\alpha]_D^{20}$ −174.5° (*c* 0.20, $CHCl_3$)} as the only product. The relative configuration (*cis* to the angular substituent, equatorial) of the newly produced hydroxy-group in each compound was established unambiguously by the n.m.r. coupling pattern of the hydrogen at C-9 (axial) of the corresponding benzoate derivative: δ ($CDCl_3$) 5.00 (dd, *J* 10 and 6 Hz) in (**5c**), 5.08 (dd, *J* 10 and 6 Hz) in (**6c**), and 5.00 (dd, *J* 11 and 5.5 Hz) in (**7c**).

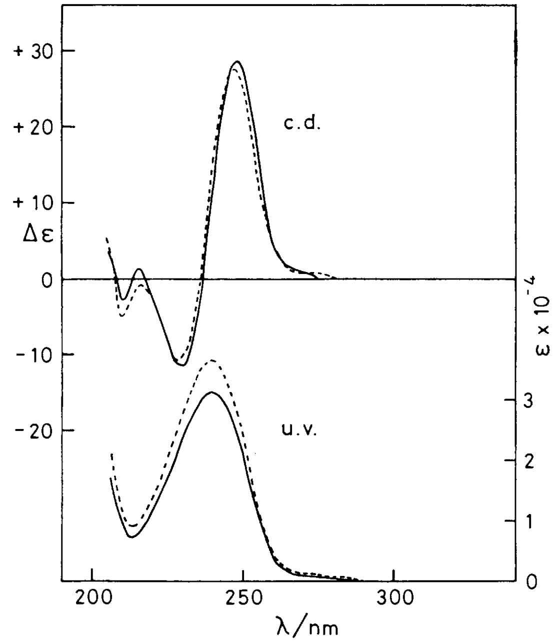


Figure 1. The c.d. and u.v. spectra of *p*-chlorobenzoyloxyenones (9*S*, 10*S*)-(**5c**) (75% e.e.) (solid line) and (9*S*, 10*S*)-(**8c**) (68% e.e.) (dashed line) in ethanol.

The optical purity of the hydroxyenones was determined by applying the methoxy(trifluoromethyl)phenylacetate (MTPA) method.[3] Thus, treatment of compounds (**5a**), (**6a**), and (**7a**) with (+)-α-methoxy-(α-trifluoromethyl)phenylacetyl chloride (p-dimethylaminopyridine–pyridine–CCl_4) gave the corresponding (+)-MTPA esters (**5b**), (**6b**), and (**7b**), quantitatively. The optical purity of compounds (**5b**), (**6b**), and (**7b**), [*i.e.* (**3**), (**4a**), and (**4b**)] was estimated from the ratio of the areas under the two CF_3 peaks in the ^{19}F n.m.r. spectrum for each compound and the results are given in Table 1.†

The absolute configurations of the hydroxyenones was determined simply and unambiguously by application of the c.d. exciton chirality method to their benzoate derivatives.[4,5] The known (9*S*, 10*S*)-hydroxyenone (**8a**) (68% e.e.)[2a] was also used for c.d. measurement to confirm the nonempirical applicability of this method to a bicyclic enone–benzoate chromophore system consisting of two independent absorbing groups. In order to enhance the exciton coupling between enone and benzoate chromophores, the *p*-chlorobenzoates (**5c**) and (**8c**) (p-$ClC_6H_4CO_2$: λ_{max} *ca.* 239 nm) in the 4-demethylenone compounds (**5a**) and (**8a**) (enone: λ_{max} *ca.* 240 nm),

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† The (+)-MTPA ester of each racemate clearly shows two CF_3 singlets of equal intensity due to two diastereoisomers.

and the *p*-methoxybenzoates (**6c**) and (**7c**) (p-MeOC$_6$H$_4$CO$_2$: λ_{max} *ca.* 254 nm) in the 4-methyl-enones (**6a**) and (**7a**) (enone: λ_{max} *ca.* 250 nm) were chosen for c.d. measurements.‡ These benzoates were prepared in the usual manner. As expected, in all the benzoates strong exciton split c.d. Cotton effects were observed in the region of the allowed enone and benzoate $\pi \rightarrow \pi^*$ transitions. The results are summarized in Table 2, and the spectra of compounds (**5c**) and (**8c**) are given in Figure 1. As shown in Figure 1, the c.d. spectrum of compound (**8c**) clearly exhibits the first positive Cotton effect at longer wavelength, in agreement with the positive exciton chirality between the two long axes of enone and benzoate chromophores,[5] *i.e.*, a right-handed screw, derived from the known (9*S*, 10*S*) configuration. On the other hand, the c.d. spectra of both compounds (**6c**) and (**7c**) exhibit exciton split Cotton effects of negative exciton chirality, which leads to a left-handed screw between the two chromophores, *i.e.*, the (9*R*, 10*R*) absolute configuration. The absolute configuration of the original Wieland–Miescher ketone analogues (+)-(**3**), (−)-(**4a**), and (−)-(**4b**) were thus determined to be (*S*), (*R*), and (*R*) respectively as formulated.

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‡ When the u.v. λ_{max} values of two different chromophores in such nondegenerate systems are similar, the exciton coupling becomes more effective (a large $\Delta\epsilon$ value).[5]

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