



Diastereoselective alkylation of 8-phenylmenthyl 2-methylacetoacetate. Preparation of enantiomerically pure 4,4-disubstituted 2-pyrazolin-5-ones

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Abstract: Alkylation of (1*R*,3*R*,4*S*)-8-phenylmenthyl 2-methylacetoacetate with alkyl halides affords 2-alkyl-2-methylacetoacetates in diastereomeric ratios 72:28 to 85:15. The major *R* (at C- α) diastereoisomers are converted into enantiopure 4,4-disubstituted 2-pyrazolin-5-ones with recovery of the chiral inductor. © 1997 Elsevier Science Ltd

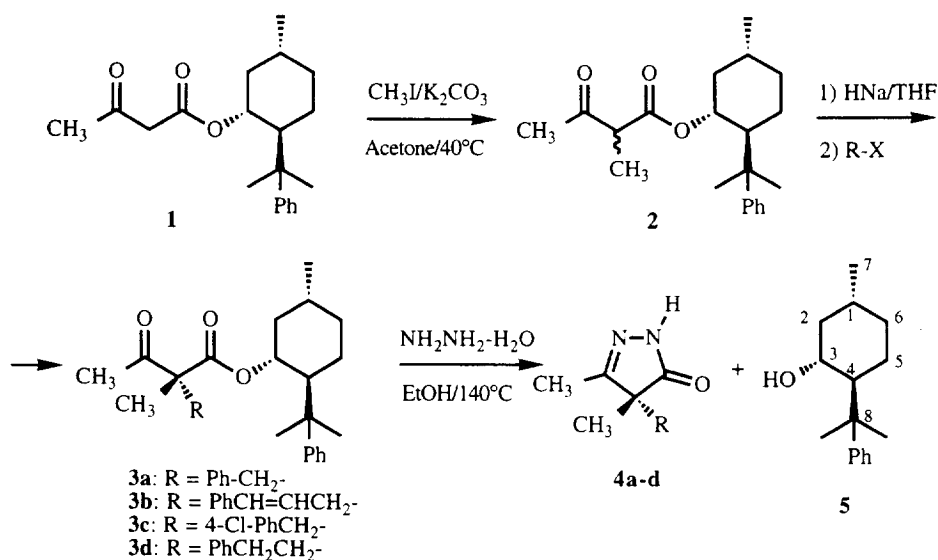
4,4-Disubstituted 2-pyrazolin-5-ones are prepared by reaction of hydrazine with α,α -disubstituted β -ketoesters.¹ Alternatively, 4-unsubstituted pyrazolones are selectively allylated at C-4 under Pd(0)-catalysis.² However, to the best of our knowledge methods to prepare enantiomerically pure 4,4-disubstituted 2-pyrazolin-5-ones have not been described. Their preparation requires either cyclization of enantiomerically pure α,α -disubstituted β -ketoesters featuring different substituents at C- α or the enantioselective alkylation of a pyrazolinone already monosubstituted at C-4. We present here a solution based on the first strategy.

Diastereoselective monoalkylations of chiral acetoacetyl derivatives ($\text{CH}_3\text{COCH}_2\text{CO-X}_c$) are known in spite of the lability of the stereogenic center formed at C- α .³ Diastereoselective dialkylations in open chain β -ketoesters or ketoamides present a more difficult problem. However, diastereoselective dialkylations of the relatively unencumbered α -cyanoacetamides ($\text{NC-CH}_2\text{-CO-X}_c$) have been reported.⁴ Concerning open-chain β -ketoesters the most general approach consists of the alkylation of chiral enamines formed from monoalkylated β -ketoesters and *t*-butyl ester of (*S*)-valine,^{5,6} each enantiomer (after hydrolysis) of the final product being predominantly produced depending on the solvent. However, the enantiomeric purity of the final product depends only on the diastereoselectivity of the alkylation step, since no diastereoisomers are isolated, direct hydrolysis of the initially formed imines being carried out.

Since we are interested in enantiomerically pure 2-pyrazolin-5-ones, we looked for methods providing separable diastereoisomers before the cyclization step. Experiments with menthyl acetoacetate showed low diastereoselectivity. Much better results were obtained using (1*R*,3*R*,4*S*)-8-phenylmenthyl acetoacetate, **1**,^{7,8} (Scheme 1). Methylation of **1** afforded **2** (92%, oil, bp 130°C/0.2 mmHg) as a diastereoisomeric mixture (69:31). Alkylation of **2** as indicated furnished compounds **3a–d** (see Table 1) in reasonable diastereoisomeric excesses. The major diastereoisomers were isolated in pure form. X-Ray diffraction of **3a** and **3c** showed their configurations at C- α to be *R* and we assume this is the case for the major diastereoisomers **3b** and **3d**.

Reaction of **3a–d** with hydrazine hydrate affords (4*R*)-4-alkyl-3,4-dimethyl-2-pyrazolin-5-ones, **4a–d**, the recovery of the chiral inductor **5** by column chromatography being nearly quantitative.

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Scheme 1.

Table 1. Compounds 3 and 4

	Yield (%) (a)	dr (R:S) (b)	mp (°C)	[α] ₅₈₉ (c)		Yield (%)	mp (°C)	[α] ₅₈₉ (c)
3a	62 (27)	83:17	91-93	ca. 0 (d)	4a	95	99-101	- 186
3b	57 (24)	82:18	70-72	+ 14	4b	70 (f)	127-128	- 201
3c	--- (29)	72:28	112-113	ca. 0 (e)	4c	88	87-88	- 87
3d	41 (35)	85:15	oil	- 13	4d	80	71-72	- 95

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7. Oil, bp 165–175°C/0.2–0.3 mmHg, $[\alpha]_{589}^{20} = +16$ (in HCCl_3) prepared by reaction of (1*R*,3*R*,4*S*)-8-phenylmenthol, **5**, with 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (diketene–acetone adduct) according to a general method, see Clemens, R. J.; Hyatt, J. *J. Org. Chem.* **1985**, *50*, 2431–2435.
8. We use the stereochemical descriptor (1*R*,3*R*,4*S*) for 8-phenylmenthol according to the IUPAC authorized trivial names nomenclature and contrary to the numbering found in some catalogues

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