Stereogenic Reactions of the α-Carbon Radicals of 8-Phenylmenthyl Esters

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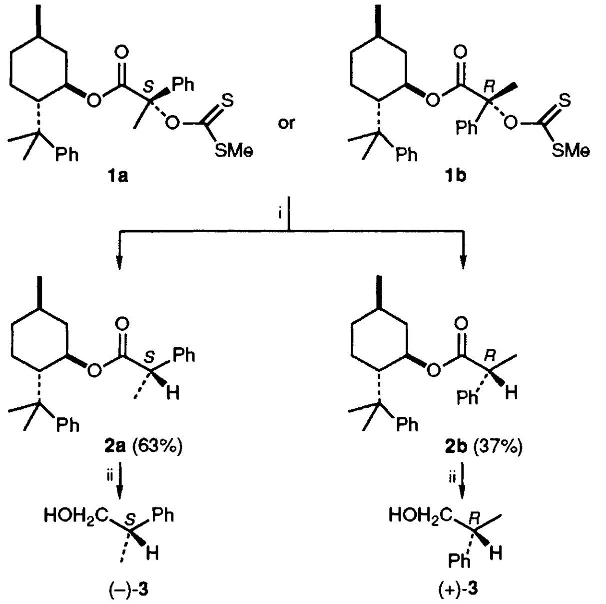
The stereoselective free-radical type reduction and cyclisation of 8-phenylmenthyl esters is described; the predominant products are considered to be derived from the transition states with conformations having the larger substituent *anti* to the alkoxy group of the ester.

Acyclic stereocontrol in the reactions of α-carbon radicals of amides has been recently reported by several research groups,[1] but stereochemistry in the related radical reactions of esters is not yet defined. Guindon *et al.* have advanced the stereocontrol by the β-substituents, especially with polar substituents such as a fluorine atom or a methoxy group.[2] The stereogenic selectivity of acyclic ester-substituted radicals has been inferred by Crich and Davies in the addition reactions of the *O*-propionyl thiohydroxamate to chiral acrylates.[3] The ester having the 8-phenylmenthol auxiliary appears to exert better stereocontrol than other tested esters with auxiliaries of menthol or camphorsulphonamide. Very recently, Hamon *et al.* have also observed highly stereoselective radical reactions of the 8-phenylmenthyl ester of *N*-Boc-glycine.[4] These reports prompt us to disclose our study on stereogenic selectivity of α-radicals of the esters **1**, **4** and **8–11**.



Scheme 1 *Reagents and conditions*: i, Bu_3SnH, azoisobutyronitrile (AIBN), PhH, 80 °C, 0.5 h, 72% yield; ii, $LiAlH_4$, tetrahydrofuran (THF), room temp., 5 h, 76% yield

As shown in Scheme 1, xanthate **1a** having the (2*S*)-configuration† was treated with tributylstannane in refluxing benzene to give two epimeric compounds **2a** and **b** (63:37), which have respectively, the (2*S*)- and (2*R*)-configurations by correlation to the alcohols **3** *via* reduction.[5] The free-radical type reduction of xanthate **1b** having the (2*R*)-configuration† under similar conditions also afforded **2a** and **b** in a ratio of 63:37. These results indicated that the reactions probably proceeded through common intermediates. We then studied the reductive cyclisation of 8-phenylmenthyl 2-phenylthiohept-6-enoate **4** (Scheme 2).‡ The stereochemistry of the four products **5a-d** was determined by transformation into the corresponding 2-methylcyclopentyl methanols **6** and **7**, for which absolute configurations have been established.[6] Thus, the major cyclisation product **5a** (*cis*) was assigned to have the (1*S*,2*R*)-configuration, and **5b** (*trans*), **5c** (*cis*) and **5d** (*trans*) are, respectively the (1*S*,2*S*)-, (1*R*,2*S*)- and (1*R*,2*R*)-isomers.

The stereochemical outcome observed in both the radical reactions of **1** and **4** suggests a working hypothesis for the transition states. The α-radical appears to be planar as it is conjugated with carboxylic ester,[7] the conformation **Ta** (*Z*-form) with the larger phenyl group being *anti* to the alkoxy group seems to be favourable over the one (**Tb**, *E*-form) having the phenyl group *syn* to the alkoxy group. By analogy to the stereoselectivity found in those reactions of 8-phenyl-

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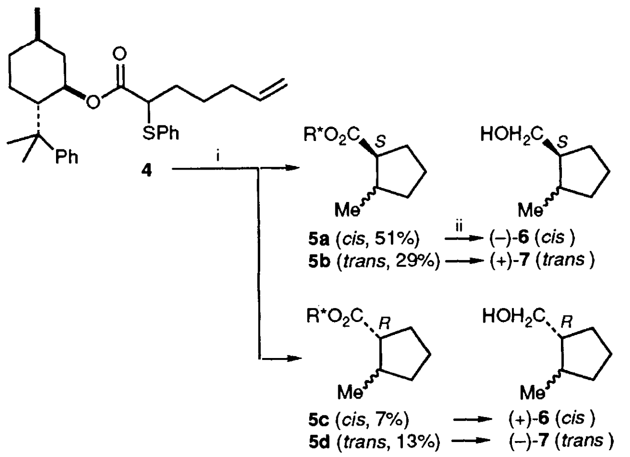
† The predominant alcohol (2*S*-configuration, 95%) obtained by addition of PhLi to (−)-phenylmenthyl pyruvate was separated and subsequently converted to the xanthate **1a** (NaH, CS_2, then MeI). Alternatively, addition of MeMgCl to 8-phenylmenthyl 2-oxo-2-phenylacetate gave an alcohol which was subsequently transformed into xanthate **1b** having the 2*R*-configuration. All new compounds reported in this article are characterised by the spectral methods (IR, mass, ^1H and ^{13}C NMR) along with combustion analysis or high resolution mass spectra.

‡ Sulphide **4** was prepared from dimethyl malonate *via* sequential alkylation (NaOMe, 5-bromopent-1-ene, 62%), sulphenylation (NaH, *N*-phenylthiosuccinimide, 67%), hydrolysis (KOH), decarboxylation (H_3O^+), and esterification [(−)-8-phenylmenthol, 1,3-dicyclohexylcarbodiimide, 79%]. Sulphide **4** consisted of two C-2 epimers and was used as such.

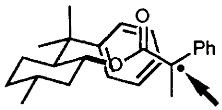


Scheme 2 *Reagents and conditions*: i, Bu_3SnH, AIBN, PhH, 80 °C, 6 h, 90% yield; ii, $LiAlH_4$, Et_2O, 0 °C to room temp., 1 h; R* represents the 8-phenylmenthyl group

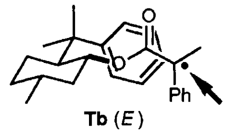
Table 1 The radical reduction and allylation of xanthates with the 8-phenylmenthoxycarbonyl group as substituent

Entry	Xanthate, R =	Reaction condition[a] (T/°C)	Products, isomeric ratio	Total yield(%)
1	**1a**, Ph	A (80)	**2a,b**, 63 : 37	72
2	**1a**, Ph	B (25)	**2a,b**, 71 : 29	67
3	**1a**, Ph	B (−78)	**2a,b**, 75 : 25	65
4	**1a**, Ph	C (−78)	**12**, >99 : 1	36
5	**8**, Pr^i	A (80)	**13**, 72 : 28	68
6	**8**, Pr^i	B (−78)	**13**, >95 : 5	53
7	**9**, $CH_2CMe{=}CH_2$	A (80)	**14**, 65 : 35	70
8	**10**, $(CH_2)_2CH{=}CH_2$	A (80)	**15**, 68 : 32	66
9	**11**, $CMe_2(CO_2Me)$	A (80)	**16**, 90 : 10	75

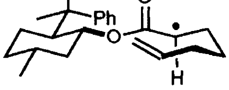
[a] Condition A: the reaction was carried out at a concentration of 0.01 mol dm^{-3} in refluxing benzene by using 2.0 equiv. of $Bu^n{}_3SnH$ and a catalytic amount of AIBN (0.02 equiv.). Condition B: the reaction was performed as in condition A except in toluene solution and by photoinitiation (300 nm). Condition C: all conditions were similar to condition B except that $Bu^n{}_3SnCH_2CH{=}CH_2$ was used instead of $Bu^n{}_3SnH$.



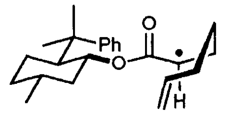
Ta (*Z*)



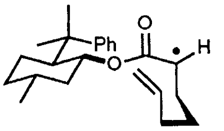
Tb (*E*)



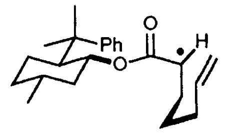
A (*Z-cis*)



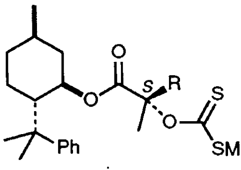
B (*Z-trans*)



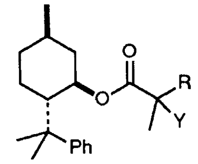
C (*E-cis*)



D (*E-trans*)



8; R = Pr^i
9; R = $CH_2CMe{=}CH_2$
10; R = $(CH_2)_2CH{=}CH_2$
11; R = $CMe_2(CO_2Me)$



12; R = Ph, Y = $CH_2CH{=}CH_2$
13; R = Pr^i, Y = H
14; R = $CH_2CMe{=}CH_2$, Y = H
15; R = $(CH_2)_2CH{=}CH_2$, Y = H
16; R = $CMe_2(CO_2Me)$, Y = H

menthyl esters,[4,8] we assume the hydrogen abstraction occurs exclusively from the *Re*-face of **Ta** to give **2a** and from the *Si*-face of **Tb** to give **2b**. The predominant products **5a** and **b** (80% in total) from the reaction of **4** can also be explained by the models **A** and **B** having the larger methylene group *anti* to the alkoxy group and the double bond approaching the radical centre from the *Re*-face. Alternatively, **5c** and **d** derived from the transition states **C** and **D** having the methylene group *syn* to the alkoxy group are less favourable.

Table 1 lists other examples of the radical reactions of xanthates **8–11** having the 8-phenylmenthyl groups as the chiral auxiliary. The reduction at −78 °C tended to give better diastereoselectivity, but one reaction in refluxing benzene (entry 9) was still highly selective. When the xanthate **1a** was treated with allyl tributylstannane at −78 °C, only a single allylation product **12** was obtained. Although the absolute configurations of the products **12–16** are not yet assigned, the present study shows that even abstraction of a hydrogen atom by an ester-substituted radical centre of acyclic systems reaches modest to high diastereoselectivity providing an appropriate chiral auxiliary is annexed. Furthermore, we have indicated the preferred conformations in transition state for the ester radicals generated from **1** and **4** by investigation of the final trapped products. Since previous physical methods, such as the ESR technique and muon spin experiment along with computer calculations,[9] have difficulty in prediction of the stereochemistry of ester-substituted radicals, the studies by Hamon's and our groups have shed light on solving this long-standing problem at least in the cases with the auxiliary of 8-phenylmenthol.

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