Tetrahedron Letters,Vol.26,No.16,pp 2021-2024,1985
Printed in Great Britain

0040-4039/85 $3.00 + .00

HIGHLY STEREOCONTROLLED SUBSTITUTION OF PHENOLS WITH PYRUVIC ESTERS. A VIABLE ROUTE TO *ortho*-HYDROXYATROLACTIC ESTERS OF (2R)- AND (2S)-CONFIGURATION

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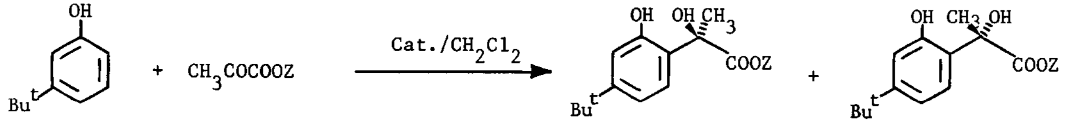
Abstract : Treatment of phenols with optically active (+)- and (-)-menthyl pyruvate assisted by Al(III)- or Ti(IV)-based promoters leads to the formation of *ortho*-hydroxyatrolactic esters of (2R)- and (2S)-configuration. The use of suitable menthol-based promoters augments markedly (up to 96% d.e.) the intrinsic stereochemical bias of the chiral pyruvate.

In spite of numerous studies on the stereoselective carbon-carbon bond constructions,[1] the asymmetric version of the electrophilic aromatic substitution remains unexplored. Only recently, in connection with our studies on the regiospecific functionalization of phenols with electrophilic reactants by metal promoters,[2] good levels of enantiodifferentiation (up to 80% e.e.) have been reported in the *ortho*-specific hydroxyalkylation of phenols with trichloroacetaldehyde by using chirally modified aluminium chlorides.[3]

It was therefore of interest to expand the scope of this approach which allow the preparation of optically active hydroxylated aromatics. This communication deals with highly stereocontrolled synthesis of *ortho*-hydroxyatrolactic esters **3** whose racemic version has been recently reported by us[4] and others.[5]

The reaction of 3-*tert*-butylphenol **1a** with pyruvic esters **2** giving 2-hydroxy-4-*tert*-butylatrolactic esters **3a** was firstly investigated in order to search conditions for optimum stereocontrol.



1a 2 (2R)-3a (2S)-3a

The crucial results are illustrated in Table 1. The following trends emerged. (i) Starting with achiral ethyl pyruvate **2A**, simple induction with (-)-menthoxy(ethyl)aluminium chloride

Table 1. Auxiliary-Catalyst Interactivity[a]

Run	Pyruvate	Auxiliary (Z)	Products[b] (2S)and(2R)	Catalyst	Yield%[c]	Ratio[d] (2S)-**3a**:(2R)-**3a**
1	**2A**	Ethyl	**3aA**	(-)-MenthylO(Et)AlCl	41	29:71
2	**2A**	Ethyl	**3aA**	(-)-MenthylOTiCl$_3$	62	59:41
3	**2B**	(-)-Menthyl	**3aB**	EtO(Et)AlCl	50	67:33
4	**2B**	(-)-Menthyl	**3aB**	EtOTiCl$_3$	67	83:17
5	**2C**	(+)-Menthyl	**3aC**	EtOTiCl$_3$	66	14:86
6	**2B**	(-)-Menthyl	**3aB**	(+)-MenthylO(Et)AlCl	71	81:19
7	**2C**	(+)-Menthyl	**3aC**	(-)-MenthylO(Et)AlCl	70	17:83
8	**2B**	(-)-Menthyl	**3aB**	(-)-MenthylOTiCl$_3$	74	91:9
9	**2B**	(-)-Menthyl	**3aB**	(-)-MenthylO(Et)AlCl	68	42:58
10	**2B**	(-)-Menthyl	**3aB**	(+)-MenthylOTiCl$_3$	71	71:29

[a] Experimental conditions, see the Text. [b] All new compounds gave spectroscopic and analytical data consistent with their structure. [c] Overall yield. [d] Diastereomeric ratios were determined by HPLC and/or ^{1}H NMR; enantiomeric ratios were determined by ^{1}H NMR by using Eu(hfc)$_3$ chiral shift reagent.

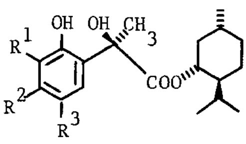
gave moderate preference of levorotatory (2R)-**3aA**[6] (run 1) while induction with (-)-menthoxytitanium trichloride gave only very modest preference of dextrorotatory (2S)-**3aA**[6] (run 2); (ii) starting with (-)-menthylpyruvate **2B**, reaction with achiral aluminium promoters gave moderate preference of (2S)-**3aB** (run 3) while the use of achiral titanium promoters gave good preference of (2S)-**3aB** (run 4); (iii) equal and opposite biases were observed by using the (+)-menthol-based pyruvate **2C** (run 5); (iv) the matched pairs **2B** in tandem with (+)-menthoxy(ethyl)aluminium chloride and **2B** in tandem with (-)-menthoxytitanium trichloride (runs 6 and 8) augmented markedly the intrinsic preference of **2B** in the (2S)-direction; (v) permuting the matched pair chirality (run 7) resulted in reversal of stereochemistry; and (vi) the mismatched pairs (runs 9 and 10) gave only modest results reverting or lowering the intrinsic stereochemical bias of the chiral pyruvate.

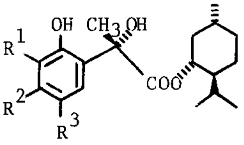
In particular, the data reveal that multiplicativity of the inherent stereochemical biases of the chiral pyruvate and the chiral organometallic promoter is roughly realized[7] by simply using menthol as a chiral adjuvant. Thus, since both the optical antipodes of menthol are commercially available, this asymmetric route, especially in the double induction version, permits real preparative access to *o*-hydroxyatrolactic esters **3** in either enantiomeric series.

We therefore exploited the synthetic potential of this approach by using variously substituted phenols. Selected synthetic results are collected in Table 2.

As can be seen in Table 2, the matched pairs **2B** in tandem with (+)-menthoxy(ethyl)aluminium chloride or with (-)-menthoxytitanium trichloride (entries 1 and 4) ensured pronounched diastereofacial bias during the bond construction favoring the enantiomers of (2S)-configuration, while the "reverse" pairs involving **2C** (entries 2,3, and 5) gave an opposite bias in favour of (2R)-compounds. On the other hand, the mismatched pairs **2B**/(-)-menthoxy(ethyl)aluminium chloride (entry 6) and **2C**/(+)-menthoxy(ethyl)aluminium chloride (entry 7), in which resident catalyst

Table 2. Double Stereodifferentiating Synthesis of (2R)- and (2S)-atrolactic esters **3**[a]


(2R)-**3B**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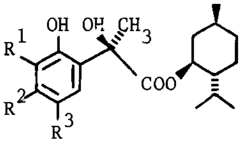
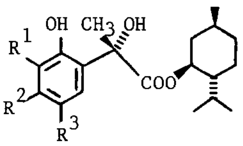

(2R)-**3C**


(2S)-**3C**

Entry	Phenol	Pyruvate	Catalyst	Compd[b]	R^1	R^2	R^3	Yield[c] (%)	$[\alpha]^{20d}_{546}$ (deg)	M.p. (°C)
1	3-Bu^t-phenol	**2B**	(+)-MenthylO(Et)AlCl	(2S)-**3aB**	H	Bu^t	H	58(62)	-80.7	150-151
2	3-Bu^t-phenol	**2C**	(-)-MenthylO(Et)AlCl	(2R)-**3aC**	H	Bu^t	H	58(66)	+77.6	146-147
3	3-Bu^t-phenol	**2C**	(+)-MenthylOTiCl_3	(2R)-**3aC**	H	Bu^t	H	67(82)	+77.6	146-147
4	1-Naphtol	**2B**	(-)-MenthylOTiCl_3	(2S)-**3bB**	-$(CH{=}CH)_2$-		H	88(96)	-241.5[e]	oil
5	Sesamol	**2C**	(+)-MenthylOTiCl_3	(2R)-**3cC**	H	-OCH_2O-		84(91)	+44.8	100-101
6	3-Bu^t-phenol	**2B**	(-)-MenthylO(Et)AlCl	(2R)-**3aB**	H	Bu^t	H	40(17)	-56.9	133-134
7	3-Bu^t-phenol	**2C**	(+)-MenthylO(Et)AlCl	(2S)-**3aC**	H	Bu^t	H	39(16)	+54.9	134-135

[a] Experimental conditions, see the Text. [b] The configuration of (-)-(2S)-**3aB** was stabilished by X-ray analysis (see the Text); the configuration of the other products was judged as such on the basis of optical or empirical correlation (NMR, HPLC) with (-)-(2S)-**3aB**. [c] Yield of pure isolated major diastereomer. Values in parentheses refer to d.e. [d] C = 0.5 - 1.0 in absolute ethanol. [e] Lit.[8], $[\alpha]^{20}_{D}$ = -196.769 (C = 2.043, EtOH).

chirality overrides chirality in the pyruvate, permitted the second enantiomeric pair (2R)-**3aB** and (2S)-**3aC** to be synthesized, though less efficiently than did the corresponding matched pairs in constructing (2S)-**3aB** and (2R)-**3aC** enantiomers.

In closing, this double asymmetric method for the synthesis of o-hydroxyatrolactic esters seems to be of great value since the stereochemistry of the aromatic substitution is controlled by only permuting the menthol chiralities and therefore (2R)- and (2S)-stereoisomers are obtainable with high optical purity. This approach will undoubtedly be suited to introduce ortho-specifically other chiral hydroxylated functionalities into phenols too, and will be elaborated on further.

Menthyl (-)-(2S)-(2-hydroxy-4-tert-butylphenyl)lactate (2S)-**3aB** (Typical Al-based Procedure): A solution of (+)-menthol (1.56 g, 10 mmol) in dry CH_2Cl_2 (10 ml) was added to Et_2AlCl (1.0 M in hexane, 10 ml, 10 mmol) in 10 ml of CH_2Cl_2 at -20 °C under nitrogen. After 20 min at -20 °C, 3-tert-butylphenol (1.50 g, 10 mmol) was added dropwise as a solution in 10 ml of CH_2Cl_2. After an additional 2 hr at -20 °C, (-)-mentyl pyruvate (2.26 g, 10 mmol) was added and the reaction was stirred at -20 °C for 24 hr. The reaction was then quenched with saturated NH_4Cl and extracted twice with CH_2Cl_2. The combined organic phases were dried (Na_2SO_4) and condensed under vacuum to yield a white solid. Crystallization from hexane then gave pure (2S)-**3aB** as colorless needles; 2.20 g, yield 58%, m.p. 150-151 °C, $[\alpha]^{20}_{546}$ = -80.7 (c, 0.5 in EtOH).

Menthyl (+)-(2R)-(2-hydroxy-4-tert-butylphenyl)lactate (2R)-**3aC** (Typical Ti-based Procedure): A solution of (+)-menthol (1.56 g, 10 mmol) in dry CH_2Cl_2 (10 ml) was added to $TiCl_4$ (1.90 g, 10 mmol) in 10 ml of CH_2Cl_2 at -60 °C under nitrogen. After 20 min at -60 °C, 3-tert-butylphenol (1.50 g, 10 mmol) was added as a solution in 10 ml of CH_2Cl_2. After and additional 2 hr at -60 °C (+)-mentyl pyruvate (2.26 g, 10 mmol) was added and the reaction was stirred at -60 °C for 3 hr. Work-up as above gave 2.50 g of (2R)-**3aC** (yield 67 %), colorless needles, m.p. 146-147 °C, $[\alpha]^{20}_{546}$ = +79.6 (c, 0.6 in EtOH).

X-ray Analysis: X-ray quality crystals of (-)-(2S)-**3aB** were obtained from 3:1 hexane/benzene solution. Crystal data: $C_{23}H_{36}O_4$, *M* = 376.5, orthorhombic, space group $P2_12_12_1$, *a* = 23.121(3), *b* = 15.077(2), *c* = 6.587(1) Å, *U* = 2296.2 Å^3, *Z* = 4, *Dc* = 1.09 g cm^{-3}, *F*(000) = 824, Cu-*K*α radiation, $\bar{\lambda}$= 1.54178 Å, μ (Cu-*K* α) = 5.5 cm^{-1}, crystal size 0.11 x 0.11 x 0.33 mm. Data were measured to 2 Θ_{max} = 120°; in this way 2010 reflections were measured, of which 1220 with $I > 2\sigma$ (*I*) were considered as observed and 1067 with $I > 3\sigma$ (*I*) were used in the subsequent analysis. No absorption correction was applied. The structure was solved by direct methods using the program SHELX and refined by full matrix least-squares to *R* = 0.0689 and Rw = 0.0744 (observed reflections only; with unrefined isotropic hydrogen atoms).[9] The atomic scattering factors used in the calculations take into account the anomalous scattering effects.

A view of the molecule is shown in Figure 1. Since the (R,S,R)-stereochemistry of the (-)-menthol moiety is well estabilished, the absolute configuration at C(11) (C-2 elsewere) is S.

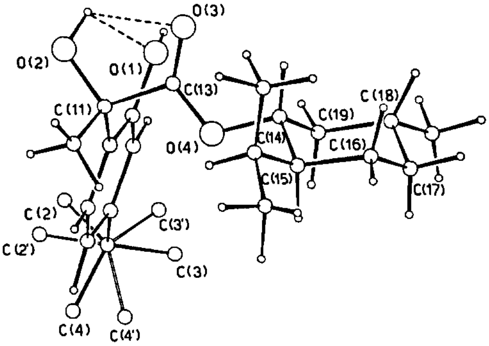


Figure 1. Projection of a molecule of (-)-(2S)-**3aB**

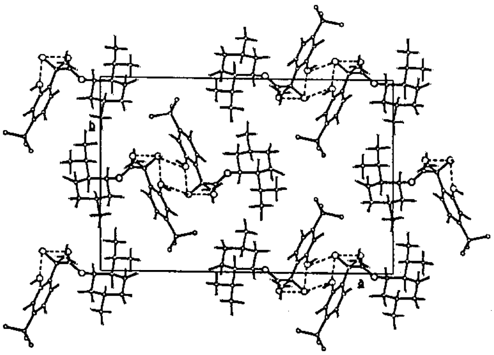


Figure 2. Crystal packing seen along [001]

The O(2) atom forms a three-center (bifurcated) intramolecular H-bond [O(2)H(2 O)...O(3) = 2.68(1), O(2)H(2 O)...O(1) = 2.80(1) Å]. An intermolecular H-bond [O(1)H(1 O)...O(2) (1/2-x, 1-y, 1/2+z) = 2.76(1) Å] determines the formation of helicoidal chains (Figure 2) running around the screw axis parellel to [001]. Some selected distances are: C(11)-O(2) = 1.44(1), C(11)-C(13) = 1.57(1), C(13)-O(3) = 1.20(1), C(13)-O(4) = 1.32(1), O(4)-C(14) = 1.48(1) Å.

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6. The (2S)-configuration of (+)-**3aA** [and hence the (2R)-configuration of (-)-**3aA**] was determined by chemical correlation with (-)-(2S)-**3aB** via convergent $LiAlH_4$ reduction to (-)-(2S)-(2-hydroxy-4-*tert*-butylphenyl)-1,2-dihydroxypropane.
7. The observed stereochemistry in the matched pair of run 6 in Table 1 (62% d.e.) is lower than that calculated from the intrinsic stereoselectivity of each reactant (42% + 34% = 76%) (runs 1 and 3). This fact is quite usual in multiple asymmetric induction: S. Masamune, Heterocycles, **1984**, 21, 107-136.
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9. The atomic co-ordinates and bond lengths (with standard deviations) for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

(Received in UK 11 February 1985)