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DIASTEREOSELECTIVE REDUCTION OF AN α-KETO-ESTER DERIVED FROM (-)-8-PHENYLMENTHOL: A 4-step synthesis of R-Halostachine analogue.

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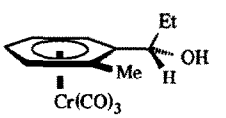
Abstract: *An efficient (80% total yield) 4-step synthesis of a 94% e.e. R-(-)-Halostachine analogue is described. The method offers the possibility to introduce various substituents onto the aromatic ring and various alkyl groups on the amine. A one-step and high yield (≈100%) conversion of esters into amides is presented.*

Introduction

Diastereoselective reduction of chiral phenylglyoxylate has been extensively studied but diastereoselectivities equal or superior to 90% have been reported in only two cases: with L-Selectride (at -78°C) when the chiral auxiliary was the complexed benzylic alcohol **1**[1] and with K- or L-Selectride(at -70°C) when the chiral auxiliary was the L-Quebrachitol **2**[2].



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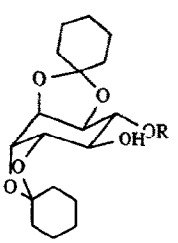

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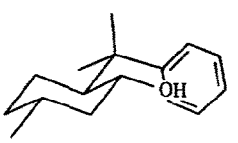

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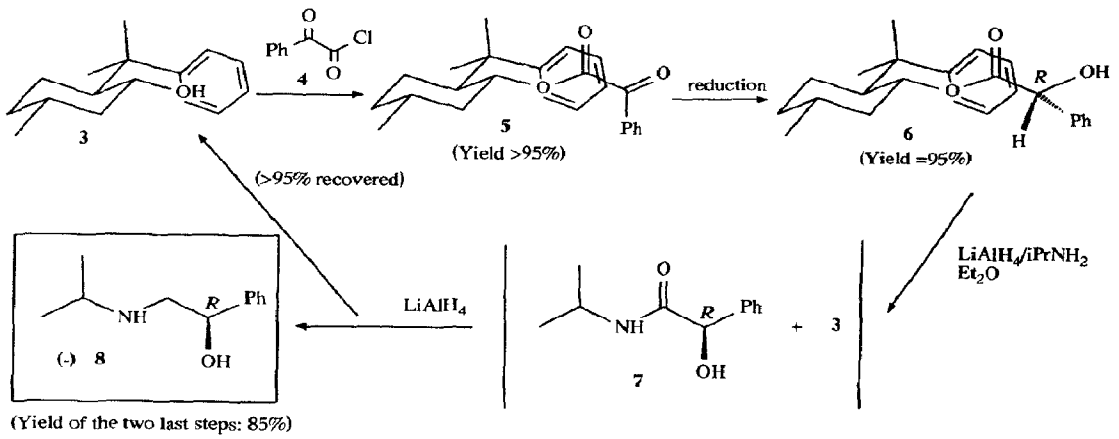
In the course of our study on asymmetric synthesis of halostachine type amino-alcohol[3a-c] we became interested in the use of 8-phenylmenthol **3** as an easily recoverable chiral auxiliary and decided to investigate the reduction of 8-phenylmenthyl phenylglyoxylate **5** as a route to these amino-alcohols[4].

Results and Discussion

As shown on the Scheme, the key step of the synthesis is the diastereoselective reduction of 8-phenylmenthyl phenylglyoxylate **5** which was obtained in almost quantitative yield (>95%) from (-)-8-phenylmenthol **3** and phenylglyoxylic chloride **4**.

Scheme:



(Yield of the two last steps: 85%)

The reduction-step was studied using various hydrides and the results are shown in the Table.

Table: Reductions of α-keto-ester **5**.

Hydride	Solvent	Added salt	Yield	I/II
$(iBu)_2AlH$/hexane	THF		>95%	87/13
	THF	$MgCl_2$	70%	87/13
	THF	$MgBr_2$	>95%	88/12
	THF	$ZnCl_2$	92%	80/20
$sBu(iBu)_2AlHLi/Et_2O$/ hex./cyclohex.	THF		>95%	92/8
$(Et(Me)CH)_3BHLi$/THF	THF		89%	68/32
$(iPrO)_3BHK$/THF	THF		93%	69/31
Bu_3BHK/THF	THF		>95%	97/3

The diastereomeric ratios were determined on crude products[5] using the 200 MHz ^1H NMR signals of the methylene and of the hydroxyl protons[6].

In contrast with the reduction of ß-keto-sulfoxides[7,8], reduction of **5** with DIBAL or DIBAL/added salt (lines 1-4) lead to no inversion of configuration at the asymmetric carbon created and to no change in diastereoselectivity, 87-88/13-12,[9] which might be consistent with the fact that such complexation involving two carbonyls and leading to a strained five-membered ring ought to have but little efficiency.

In an attempt to replace DIBAL by a monohydride of lithium and aluminium the lithium sec-buthyl-diisobuthyl aluminium hydride was synthesized[10] but only a small increase of the diastereoselectivity was observed: 91/9 (line 5).

When L-Selectride was employed (line 6) a low diastereoselectivity was observed, 68/32, in contradiction with literature results[1,2].

On the assumption that this low diastereoselectivity could be due to a mismatch between the chirality of the optically pure keto-ester **5** and the racemic L-Selectride, achiral borohydrides were synthesized. Potassium tri-isopropoxy-borohydride was thus prepared using Brown's procedure[11] but lead to a 70/30 mixture (line 7) in agreement with the 75/25 mixture obtained by Whitesell[12].

However potassium tri-butyl-borohydride, prepared following the same procedure[11], happened to lead to the desired diastereoselectivity: 97/3 (line 8).

Then the displacement of the 8-phenylmenthoxy group to give the hydroxy-amide **7** was carried out in 95% yield using an old method adapted to primary amines[13a,b].

Subsequent reduction of the thus obtained mixture of 8-phenylmenthol **3** and hydroxy-amide **7** with $LiAlH_4$ lead to a mixture of 8-phenylmenthol **3** and amino-alcohol **8** from which the desired amino-alcohol **8** was easily obtained in 85% yield by acidic extraction.

The sign of the optical rotation of the amino-alcohol **8** being minus ($[\alpha]_D$= -58.7) and by analogy with the fact that the (-)-Halostachine has the *R*-configuration it is concluded that the absolute configuration of the asymmetric carbon created is *R*[14], which is also consistent with Whitesell's results[12].

In summary this constitutes an efficient (80% total yield) 4-step synthesis of a 94% e.e. R-(-)-Halostachine analogue, with the possibility of introducing various substituents onto the aromatic ring and various alkyl groups on the amine.

Experimental part

^1H and ^{13}C NMR spectra were recorded on a Bruker AC 200 ($CDCl_3$/TMS, δ ppm, J Hz). IR spectra were recorded on a Perkin-Elmer 457 (√ cm-1). Specific rotations were measured on a Perkin-Elmer 141 polarimeter.

1R,2S,5R-(-)-8-phenylmenthol **3** has been prepared following the procedure described in the literature[15], however instead of the KOH/EtOH saponification we prefered to perform an $LiAlH_4$ reduction of the 8-phenylmenthyl chloroacetate which allowed us to isolate without distillation and in 95% yield the (-)-8-phenylmenthol pure on the NMR scale ($[\alpha]^{25}_D$= -26 ; c, 2; EtOH).

Phenylglyoxylic chloride **4** was prepared by exchange between phenylglyoxylic acid and oxalyl chloride: yield= 90%; IR (neat) $\sqrt{}_{CO}$(acid chloride)= 1770, $\sqrt{}_{CO}$(conjugated ketone)= 1690.

Preparation of 8-phenylmenthyl phenylglyoxylate **5**

To 0.7g (3mmol) of *1R,2S,5R*-(-)-8-phenylmenthol **3** in 20ml of benzene were successively added at 25°C: 0.2ml (1 equiv.) of anhydrous pyridine and 0.51g (1 equiv.) of chloride **4**. The mixture was stirred at this temperature untill no alcohol **3** remained (as shown by TLC, ether/hexane 2/8). Then the pyridinium hydrochloride formed was filtrated out, the benzenic phase was washed with water (4 x 5ml) untill pH=6 and dried over $MgSO_4$. After concentration under vacuum, 0.98g of keto-ester **5** were obtained: yield >95%.

1R,2S,5R-8-phenylmenthyl phenylglyoxylate **5**

White solid, mp= 89-90°C (crystallized in ether/hexane 2/8)
R_f= 0.67 (ether/hexane 2/8)
$[\alpha]^{25}_D$= +0.8 , $[\alpha]^{25}_{500}$= -1.2 , $[\alpha]^{25}_{450}$= -9.1 , $[\alpha]^{25}_{425}$= -27.1 , (c, 3; CCl_4).
IR (CCl_4): $\sqrt{}_{CO}$(ester)= 1720, $\sqrt{}_{CO}$(conjugated ketone)= 1690
^1H NMR: 0.85 (d, 3H, CH_3); 1.20 (s, 3H, CH_3); 1.30 (s, 3H, CH_3); 1-1.4 (m, 4H, overlapped with the two singlets); 1.5 (m, 2H); 2 (m, 2H); 5.0 (t.d, 1H, J= 11Hz, J= 4Hz, O-CH); 6.95 (t, 1H, arom. ring A); 7.01 (t, 2H, arom.); 7.15 (d, 2H, arom.); 7.45 (t, 2H, arom., Ph-CO); 7.75 (t, 1H, arom., Ph-CO); 7.85 (d, 2H, arom., Ph-CO).
^{13}C NMR: 21.8 (CH_3); 26.3 (CH_3); 27.0 (CH_2); 27.5 (CH_3); 31.5 (CH); 34.4 (CH_2); 40.1 (C); 41.5 (CH_2); 50.6 (CH); 77.6 (O-CH); 125.4 (arom. p-CH); 125.6, 128.1, 128.8 and 130.2 (arom. o- and m-CH); 132.7 (arom. C,Ph-CO); 134.7 (arom. p-CH, Ph-CO); 150.4 (arom. C); 162.8 (C ester); 185.8 (C ketone).
Anal. Calcd for $C_{24}H_{28}O_3$: C, 79.08; H, 7.74. Found: C, 79.29; H, 7.88.

Preparation of a 0.1M solution of lithium sec-butyl-diisobutyl aluminium hydride in ether/hexane/cyclohexane (5/6.5/1) according to ref. 10.

To a 1.3ml (1.3mmol) of DIBAL (1M in hexane) were added successively at 25°C: 1ml (1.3mmol) of sec-BuLi (1.3M in cyclohexane), 5.2ml of hexane and 5ml of anhydrous ether.

Preparation of a 2.5M solution of potassium tri-isopropoxy-borohydride in THF according to ref. 11.

To 0.6g (15mmol) of KH (rinced with hexane) in 4ml of anhydrous THF was added 2.3ml (10mmol) of $(iPrO)_3B$. The mixture was heated at 50°C for 24h. Then the temperature was allowed to reach ambiant and the precipitate to decant.

Preparation of a 0.5M solution of potassium tri-butyl-borohydride in THF.

To 1.2g (30mmol) of KH (rinced with hexane) in 10ml of anhydrous THF was added dropwise 20ml (20mmol) of nBu_3B (1M in THF). The mixture was heated at 50°C for 24h. Then 10ml of anhydrous THF were added, the temperature was allowed to reach ambiant and the precipitate to decant.

Reduction of 8-phenylmenthyl phenylglyoxylate **5**

With Aluminium hydrides:

To 0.36g (1mmol) of **5** in 20ml of anhydrous THF was added 1.2 equiv. of the desired salt if necessary, after stirring for 15mn the temperature was lowered to -78°C and 1.1 equiv. of the desired reducing agent was added dropwise. The mixture was stirred at -78°C untill no keto-ester remained (as shown by TLC, ether/hexane 2/8). Then were successively added (at -78°C): 1ml of MeOH, 15ml of AcOEt and 5ml of a saturated sodium tartrate solution. The temperature was allowed to reach ambiant, 15ml of H_2O were added, the organic phase was separated and the aquous phase extracted with AcOEt (3 x 10ml). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated under vacuum. The crude compound (a yellowish oil) was weighted and analyzed by ^1H NMR before purification.

With borohydrides:

The procedure differs only by the work up: when no starting keto-ester **5** remained, were added successively (at -78°C): 1ml of MeOH, 1.5ml of NaOH 10% and 1.5ml of H_2O_2 30%; then the temperature is allowed to reach ambiant (1h) and the THF was evaporated under vacuum. After addition of 30ml of water the aquous phase was extracted with ether (5 x 10ml). The organic phases were combined, dried over $MgSO_4$ and concentrated under vacuum. The crude product (a yellowish oil) was weighted, analyzed by ^1H NMR and used for the following step without further purification in the case of reduction with potassium tri-butylborohydride (Table, line 8).

1R,2S,5R,R-(-)-8-phenylmenthyl mandelate **6**

Description of the 97/3 mixture:
White solid; mp 83-84°
$[\alpha]^{25}_D$= -57.6 (c, 5.7; CCl_4).
IR (CCl_4) ν_{OH}= 3580, 3520; ν_{CO}(ester)= 1720.
^1H NMR: *Diastereomer I* (major): 0.80 (d, 3H, CH_3); 0.90 (s, 3H, CH_3); the other ring protons give multiplets between 1 and 2; 2.35 (d, 1H, OH, J= 4Hz); 4.72 ([d, 1H, O-CH chain] + [t.d, 1H, O-CH ring]); 7.3 (m, 10H, arom.). *Diastereomer II* (minor): all proton-signals overlap with those of diastereomer I but: 3.14 (d, 1H, OH, J= 5Hz) and 3.95 (d, 1H, O-CH chain, J= 5Hz).
^{13}C NMR: *Diastereomer I* (major): 21.8 (CH_3); 26.2 (CH_3); 26.6 (CH_3); 26.9 (CH_2); 31.4 (CH); 34.4 (CH_2); 39.8 (C); 41.5 (CH_2); 50.3 (CH); 73.9 (O-CH); 77.0 (O-CH); 125.6, 127.0, 128.0 and 128.5 (6 CH arom.); 137.8 (C arom. Ph-CO); 151.1 (C arom.); 172.0 (C ester). *Diastereomer II* (minor): 8 signals only lead to non-equivalence: 22.7 (CH_3); 40.7 (CH_2); 50.6 (CH); 72.2 (O-CH); 76.2 (O-CH); 138.5 (C arom. Ph-CO); 151.8 (C arom.); 173.0 (C ester).
Anal. Calcd for $C_{24}H_{30}O_3$: C, 78.65; H, 8.25. Found: C, 78.43; H, 8.21.

Obtention of amino-alcohol **8**

1g (26.4mmol) of $LiAlH_4$ in 100ml of anhydrous ether was refluxed for 90mn, then the temperature was allowed to return to ambiant and 12ml (5 equiv.) of isopropylamine disolved in 50ml of anhydrous ether were added dropwise. A precipitate was formed, the mixture is stirred for 30mn after the end of the addition. Then 0.4g (1.1mmol) of the hydroxyester **6** disolved in 10ml of anhydrous ether were added dropwise and the mixture was stirred for 4 hours at room temperature. The work-up was done by carefull successive addition of: 1ml of H_2O, 1ml 10% NaOH and 3ml of H_2O. The mixture was stirred untill the precipitate became white and powdered. The precipitate was then filtered out and carefully extracted in refluxing ether (three times). The ether phases were combined and concentrated under vacuum. The crude product (O.434gr) was used for the next step without further purification.

1g (26.4mmol) of $LiAlH_4$ in 50ml of anhydrous THF was refluxed for 90mn, then the temperature was allowed to return to ambiant and 0.434g of the above product in 10ml of anhydrous THF were added dropwise. The mixture was stirred under reflux for 16h. The work-up and the isolation of the crude product were done as above. The residu thus obtained was dissolved in 3ml of HCl 10% and the (-)-8-phenylmenthol **3** is extracted with ether (3 x 10ml). The combined ether phases were dried over $MgSO_4$, after evaporation of the solvent, 0.25g (≈95%) of the starting chiral auxiliary **3** were recovered. 5ml of a saturated solution of $NaHCO_3$ were added to the aquous phase which was then extracted with CH_2Cl_2 (5 x 10ml). The organic phases were combined, dried over $MgSO_4$ and concentrated: 0.166g (85% yield) of amino-alcohol **8**.

R(-)-2-([N-isopropyl]-amino)-1-hydroxy-1-phenyl-ethane **8**

94% e.e.
Pale yellow solid, mp= 84°-85°
$[\alpha]^{25}_D$= -58.7 (c, 5.96; EtOH)
^{1}H NMR: 1.05 (d, 6H, $2CH_3$); 2.65 (d.d, 1H, A part of an ABX, CH_2, J_{AB}= 12Hz, J_{AX}= 9Hz); 2.82 (Sept., 1H, CH-iPr); 2.95 (d.d, 1H, B part of the ABX, CH_2, J_{AB}= 12Hz, J_{BX}= 3.5Hz); 4.67 (d.d, 1H, X part of the ABX, O-CH); 7.32 (m, 5H arom.).
^{13}C NMR: 19.1 ($2CH_3$); 51.5 and 52.7 (CH_2, CH); 69.1 (O-CH); 125.9 (2CH arom. meta); 128.1 (CH arom. para); 128.7 (2CH arom. ortho); 140.3 (C arom.).

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b: Solladié-Cavallo A., Dreyfus A.C., Sanch F., Klein A., *Chem. Lett.*, **1987**, *8*, 1583.
c: Solladié-Cavallo A., Bencheqroun M., *J. Organomet. Chem.*, **1991**, *406*, C15.
4) It must be noticed that highly diastereoselective reductions of chiral phenylglyoxamides have been reported (Kawanami Y., Fujita I., Taniguchi Y., Katsuki T., Yamaguchi M., *Chem. Lett.*, **1987**, 2021. Solodin I., Goldberg Y., Zelcans G., Lukevics E., J. *Chem. Soc. Chem. Commun.*, **1990**, 1321), however hydrolysis is more difficult and partial racemisation takes place.
5) The diastereoselectivity is determined on crude products to avoid enrichment during purification.
6) In $CDCl_3$/TMS, (ppm), diastereomer I (major): 2.35 (d, OH, J= 4Hz), 4.72 (d, O-CH, J= 4Hz); diastereomer II (minor): 3.14 (d, OH, J= 5Hz), 3.95 (d, O-CH, J= 5Hz).
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