Cite this paper: Vietnam J. Chem., **2021**, *59(1)*, 42-46 Article
DOI: 10.1002/vjch.202000095

A New Approach for the Synthesis of Sotolon in Racemic and Enantioenriched Forms

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Submitted June 9, 2020; Accepted August 2, 2020

Abstract

Sotolon (3-hydroxy-4,5-dimethyl-2(5H)-furanone) has been synthezised both in racemic and enantioenriched forms by a short sequence involving intramolecular tandem isomerization-aldolisation and tandem izomerization/Mannich reactions as key steps. Optically active Sotolon has been obtained by using (*S*)-*N*-*tert*-butane sulfinimine as a chiral starting material.

Keywords. Sotolon, isomerization-Mannich, catalysis, nickel, α-aminoester.

1. INTRODUCTION

3-Hydroxy-4,5-dimethyl-2(5H)-furanone (Sotolon) is a powerful flavor compound found in various foods and spices, as well as in beverages including aged beers, wines and sake. It has an extremely powerful aroma with a typical smell of fenugreek, maple syrup, caramel and burnt sugar at low concentration.[1,2] Both the olfactory properties and the odour intensity are very different for the two enantiomers: in dry white wines for instance, the perception threshold of (*R*)-sotolon was determined to be 89 μg/l, whereas the threshold of (*S*)-sotolon was significantly 100 times lower with 0.8 μg/l.[3] It has been proposed that, in wine, Sotolon was produced by the oxidative degradation of ascorbic acid,[4] whereas in aged sake, this molecule was formed by condensation of α-ketobutyrate and acetaldehyde, both being acid decomposition products of threonine.[5] Blank *et al.* have formulated a pathway for the formation of Sotolon *via* thermally induced oxidation of 4-hydroxy isoleucine and its lactones with *α*-dicarbonyl.[6] The results showed that methylglyoxal was the best dicarbonyl compound at a 1:10 molar ratio and aminolactone was a better precursor than its aminoacid 4-hydroxyl *iso*leucine. Very recently, Lanfermann *et al*. gave support for this pathway in cultures of *Laetiporus sulphureus* by using labelled derivatives as precursors.[7] To date, several syntheses of Sotolon and its derivatives have been reported but there are only few procedures to obtain the final product in optically active form.[8] In this paper, we describe a novel strategy toward the synthesis of Sotolon either in racemic form or as optically active derivatives based on a tandem isomerization-aldolisation reaction from the but-3-en-2-ol allylic alcohol.

2. MATERIALS AND METHODS

Reagents were obtained from commercial suppliers and used without further purification. All reactions have been carried out under a nitrogen atmosphere and dry conditions. The used solvents were freshly distilled under anhydrous conditions. The reaction mixtures have been magnetically stirred with teflon stirring bars, and the temperatures were measured externally. For sensitive reactions, glassware was dried at 120 °C for at least 24 h by using a drying oven. Yields refer to chromatographically and spectroscopically (^{1}H- and ^{13}C-NMR) homogeneous materials. The reactions have been monitored by thin layer chromatography (TLC) and carried out on silica gel plates (60 F254) purchased from Merck. The mixtures of *n*-pentane and ethyl acetate (EtOAc)

were used as eluents, with detection by UV light (254 nm), or a *p*-anisaldehyde or $KMnO_4$ stains. Flash column chromatography was carried out using silica gel from Acros with particle size of 0.040-0.063 mm. Nuclear magnetic resonance (NMR) spectra have been recorded with Bruker Avance 500 spectrometers. NMR chemical shifts are reported δ in ppm relative to tetramethylsilane as an internal reference $\delta(C\boldsymbol{H}Cl_3)$ = 7.26 ppm for ^1H and δ ($\boldsymbol{C}DCl_3$) = 77.0 ppm for ^{13}C. Multiplicities were designated: s = singlet, d = doublet, t = triplet, m = multiplet, br = broad, etc. IR spectra have been measured on a 16PC IR-FT Perkin Elmer spectrometer. Mass spectra were obtained using electron spray ionization at the Centre Régional de Mesures Physiques de l'Ouest in Rennes (France). The optical rotation values have been measured with a Perkin-Elmer 141 Polarimeter, at 589 nm. The concentration was reported in gram per milliliter (c, g. ml^{-1}).

Tandem isomerization - aldolization reaction from allylic alcohol with ethylglyoxalate using $Fe(CO)_5$ as the catalyst. Synthesis of 3 and 4. A solution of alcohol **2** (200 mg, 2.78 mmol); ethyl glyoxalate (238 mg, 2.78 mmol) and $Fe(CO)_5$ (37 µL, 0.278 mMol) in THF (15 mL) was irradiated with a Philip HPK125 lamp during 1h. Solvent was removed under reduced pressure and residue was filtered on silica gel with Et_2O as eluent to afford a diasteroisomeric mixture of aldols (2 diastereoisomers: 75/25 by ^1H NMR). These products were separated by column chromatography on silica gel with Pent/EtOAc (70/30) as eluent. The two diastereoisomers **3** and **4** were isolated as colorless solids with 98 % overall yield (474.6 mg).

Isomer *syn*-3: Rf (*syn*-**3**) = 0.35; Mp = 116-118 °C. IR ν_{max} cm^{-1}: 3400 (br, m), 1700 (s), 1620 (m), 1420 (m), 1380 (m), 1220 (s), 1160 (s), 930 (m), 860 (m), 780 (m). ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 4.59 (dd, *J* = 4.0 Hz, *J* = 7.4 Hz, 1H (*CH*OH)); 4.27 (q, *J* = 7.1 Hz, 2H (CH_2CH_3)); 2.96 (dq, *J* = 4.0 Hz, *J* = 7.4 Hz, 1H ($CHCH_3$)); 2.24 (s, 3H ($CO\boldsymbol{CH_3}$)); 1.31 (t, *J* = 7.1 Hz, 3H ($CH_2\boldsymbol{CH_3}$)); 1.23 (d, *J* = 7.1 Hz, 3H ($CH\boldsymbol{CH_3}$)); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 208.9, 172.9, 70.6, 61.5, 49.6, 27.6, 13.7, 9.9.

Isomer *anti*-4: Rf (*anti*-**4**) = 0.30; Mp = 122-124 °C. IR ν_{max} cm^{-1}: 3400 (br, m), 1760 (s), 1620 (m), 1430 (m), 1380 (m), 1210 (s), 1150 (s), 930 (m), 860 (m), 780 (m). ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 4.29 (dd, *J* = 5.1 Hz, *J* = 7.2 Hz, 1H (*CH*OH), 4.23 (q, *J* = 7.1Hz, 2H (CH_2CH_3)); 3.03 (dq, *J* = 5.1 Hz, *J* = 7.2 Hz, 1H ($CHCH_3$)); 2.20 (s, 3H ($CO\boldsymbol{CH_3}$)), 1.28 (d, *J* = 7.2 Hz, 3H ($CH_2\boldsymbol{CH_3}$)); 1.13 (d, *J* = 7.2 Hz, 3H ($CH\boldsymbol{CH_3}$)); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 209.7, 172.9, 72.1, 61.2, 49.8, 28.4, 13.7 and 12.2.

Tandem cyclisation and reduction of the mixture *syn*-3 and *anti*-4 using $NaBH_4$ and BnBr. $NaBH_4$ (456 mg, 12 mmol) was added in 3 portions, under nitrogen at 0 °C, to a solution of the mixture of α-hidroxy ester *syn*-**3** and *anti*-**4** (1.03 g, 6.0 mMol) and BnBr (2.85 mL, 24 mmol), in MeOH (30 mL). The reaction mixture was kept under magnetic stirring at 0 °C until the starting material disappeared (TLC monitoring, about 1 h). After addition of water (15 mL) and extraction with EtOAc (3x15 mL), the organic phases were combined, washed with a saturated solution aqueous of NaCl, dried (Na_2SO_4), and concentrated under vacuum. The crude product was purified by chromatography on SiO_2 by using a 4:6 mixture of *n*-pentane and EtOAc as the eluent. The **5**, mixture of more than 3 diastereoisomers, was collected with 90 % overall yield (702 mg).

Synthesis of Sotolon in racemic form: A solution of oxalyl chloride (152 mg, 1.2 mMol) in 10 mL of freshly distilled CH_2Cl_2 was cooled to -78 °C, and DMSO (187 mg, 2.4 mmol) was carefully added under nitrogen atmosphere. After stirring for 15 min, a solution of hydroxylactone **5** (78 mg, 0.6 mmol) in CH_2Cl_2 (5 mL) and Et_3N (7.0 mL) was added successively. The cooling bath was removed and the reaction mixture was allowed to warm to room temperature and stirred for 2.5 h. The solvent was removed under reduced pressure and the residue was extracted with ethyl acetate. The extract was washed with saturated aqueous Na_2CO_3 solution, brine and dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, the crude product was purified by silica gel chromatography by using as eluent a 4:6 mixture of *n*-pentane and EtOAc, Sotolon was isolated in 90 % yield (69.1 mg). IR ν_{max} cm^{-1}: 3350 (br, m), 1750 (s), 1710 (s), 1680 (m), 1335 (m), 1220 (s), 1160 (s), 1065 (m), 1025 (m), 920 (m), 780 (m). ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 5.43 (s, br, 1H (CH*OH*)); 4.45 (dq, *J* = 7.1 Hz, *J* = 1.5 Hz, 1H (*CH*CO)); 1.95 (d, *J* = 1.5 Hz, 3H ($C\boldsymbol{CH_3}$)); 1.40 (d, *J* = 7.1 Hz, 3H ($CH\boldsymbol{CH_3}$)). ^{13}C NMR (125 MHz, $CDCl_3$) δ(ppm) 178.6, 140.8, 123.8, 60.5, 29.7, 14.2.

(*S*)-Sotolon: Aminolactone **8**[11] (45 mg, 0.27 mmol) was dissolved in a phosphate buffer (20 mL, 0.1 mol/L, pH 5.0) at room temperature, then methylglyoxal (20 mg, 2.7 mmol) was added. The solution was boiled for 1 h. After cooling down,

water (20 mL) were added. The mixture was saturated with NaCl, then the pH was adjusted to 4 with HCl (1 mol/L) and extracted with Et_2O. The extract was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel chromatography by using as eluent a 4:6 mixture of *n*-pentane and EtOAc, (*S*)-sotolon was isolated in 32 % yield (11 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 6.0 (s, br, 1H (CH*OH*)); 4.83 (dq, *J* = 6.8 Hz, *J* = 1.5 Hz, 1H(*CH*CO)); 1.95 (d, *J* = 1.5 Hz, 3H (CH*CH*$_3$)); 1.40 (d, *J* = 6.8 Hz, 3H (CH*CH*$_3$)). ^{13}C NMR (75 MHz, $CDCl_3$) δ(ppm) 173.1, 139.5, 118.5, 76.4, 17.8, 12.2. HRMS: Calcd. for $C_6H_{12}NO_2$ $[M+H]^+$ 129.0868; found $[M+H]^+$ 129.0867. $[\alpha]_D^{20} = +7.2$ (c 0.02, Et_2O). By using the most recent data on (*S*)-Sotolon (+15.2),[12] this translates into 47% ee.

(*R*)-Sotolon: The same proceduce that used for the synthesis of *(S)*-Sotolon was applied. Lactone **9**[11] (56 mg, 0.34 mmol), methylglyoxal (244 mg, 3.4 mmol), 30 ml phosphate buffer, (*R*)-Sotolon was obtained in 33 % yield (14.4 mg). ^{1}H and ^{13}C NMR was the same of (*S*)-Sotolon. HRMS: Calcd. for $C_6H_{12}NO_2$ $[M+H]^+$ 129.0868; found $[M+H]^+$ 129.0870. $[\alpha]_D^{20} = -6.6$ (c = 0.18, Et_2O). By using the most recent data on (*R*)-Sotolon (-23.1),[12] this translates into 29 % ee.

3. RESULTS AND DISCUSSION

Firstly, the racemic synthesis involves a tandem isomerization-aldolisation reaction from an allylic alcohol with ethyl glyoxylate to produce *α*-hydroxyesters (A), followed by a reduction/cyclization step to afford *α*-hydroxylactones (B). Finally, Swern oxidation of these lactones should afford the desired racemic Sotolon (figure 1).

The second pathway involves a tandem isomerization-Mannich reaction with a chiral sulfinylimine as the electrophilic component, to produce a *N*-protected α-aminoester (C), followed by a reduction/cyclization to afford an aminolactone. Then, cleavage of *N*-protecting group can give aminolactone (D). Finally, reaction of the primary amine with an *α*-dicarbonyl compound should result in a Schiff base which, after double bond shift and subsequent hydrolysis, will give rise to Sotolon (figure 1).[6,7]

Thus, for the synthesis of racemic Sotolon, the tandem isomerization-aldolisation reaction of allylic alcohol **2** with ethylglyoxylate, and using $Fe(CO)_5$ at 10 mol % as catalyst, afforded in excellent yield the *α*-hydroxy esters **3** and **4** in a 75/25 diastereoisomeric ratio (scheme 1). The separation of these aldol products was performed easily by chromatography on silica gel. In agreement with previous results,[9] the stereochemistry of these *α*-hydroxyesters was established by ^{1}H NMR: the *anti*-diastereoisomer J_{12} (scheme 1) coupling constants were larger (5.1 Hz) than the *syn* one (4.0 Hz). However, the separation of these derivatives was not absolutely required since the two diastereoisomers could be used together directly for the next transformation.

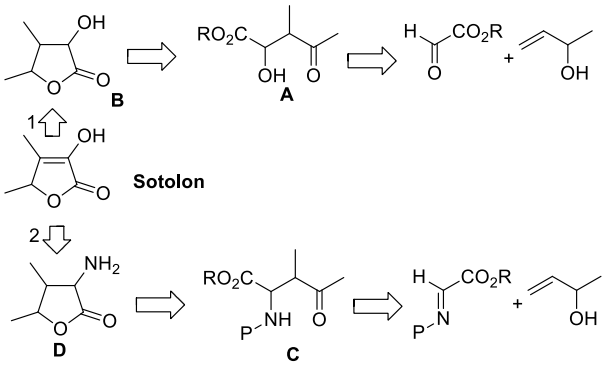
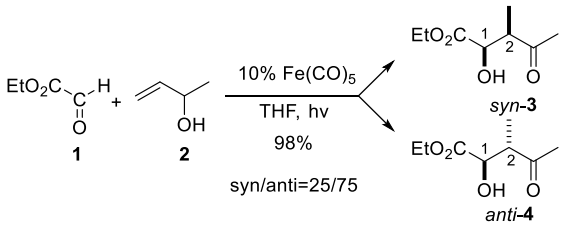


Figure 1: Retrosynthetic analysis for the preparation of racemic (**1**) and optically active Sotolon (**2**)

The next step was the reduction of ketone to the corresponding hydroxyl group. Several agents were tried for the reaction, such as $LiAlH_4$, $NaBH_4$, L-selectride, Super-hydride, etc. In every case, the reaction was not selective and afforded the desired product **5** as a complex mixture with several byproducts, such as the opened form derivatives and over reduction products of lactone **5**. This result has been also observed recently by Wagner *et al*.[10]

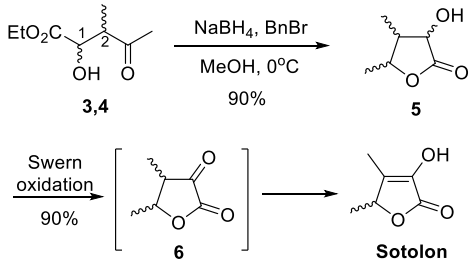


Scheme 1: Tandem isomerization- aldolisation starting from allylic alcohol **2** and preparation of intermediates **3** and **4**

The combination of $NaBH_4$ and BnBr was found to be the most effective agent for this reduction. The tandem reduction-cyclization of the mixture of **3** and **4** with $NaBH_4$ in presence of BnBr in MeOH at 0 °C afforded in 90 % overall yield the mixture of lactones **5** (scheme 2). Finally, the transformation of

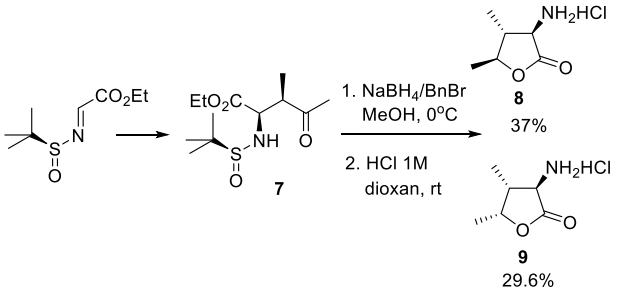
lactones **5** to Sotolon was carried out by Swern oxidation in CH_2Cl_2 at -78 °C. This reaction afforded first an unstable intermediate **6**, which isomerized immediately to racemic Sotolon (scheme 2). The ^1H, ^{13}C NMR data of this product were in complete agreement with those reported in the literature.[6]

For the synthesis of optically active Sotolon, (*S*)-*N*-*tert*-butane sulfinimine was used as an excellent chiral auxilliary. We have already reported the tandem isomerization-Mannich reaction from glyoxylate sulfinimine and allylic alcohol **2** by using the NiHCl(DPPE)/$MgBr_2$ catalytic system, affording in excellent yield the protected β-aminoketones **7** (74 %, 75/25 diastereoisomeric ratio). Separation of major *syn* product, followed by the reduction of this amino ketone by the $NaBH_4$/BnBr combination, and cleavage of the sulfinyl group gave the two optically pure (ee > 99 %) aminolactones **8** and **9** with 37 % and 29.6% yield respectively (scheme 3).[11]



Scheme 2: Synthesis of racemic Sotolon

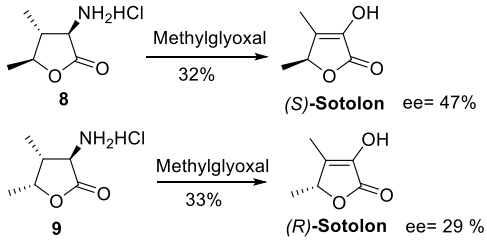
The transformation of these lactones amino hydrochlorides **8** and **9** to optically active (*S*)- and (*R*)-Sotolon was carried out with methylglyoxal in a phosphate buffer solution, following a procedure reported in the literature.[7]



Scheme 3: Preparation of the aminolactones **8** and **9**

Reaction between each aminolactone and the dicarbonyl compound produced first the corresponding Schiff base. This was followed by migration of the double bond, and a final hydrolysis of this regioisomeric imine generated (*S*)- and (*R*)-Sotolon in 32 % and 33 % yields respectively (scheme 4).

Spectral data of these derivatives were identical to previous racemic compound. Comparison of the $[\alpha]^D$ values with the most recent datas,[12] indicated that these derivatives were obtained in 47 % et 29 % ee's only. Since this process has been performed earlier only with racemic compounds,[7] we demonstrate here that some racemization is occurring during this step. It is interesting to remark that a slow racemization of Sotolon has been already demonstrated also in wine model solutions.[3]



Scheme 4: Synthesis of (*S*)- and (*R*)-Sotolon

4. CONCLUSIONS

In conclusion, we reported herein the synthesis of Sotolon in both racemic and enantiomerically enriched forms by using tandem isomerization-aldolisation and isomerization-Mannich reactions starting from cheap and commercially available raw materials. This method can be extented to analogues of Sotolon, even in larger scale. Moreover, this strategy offers an efficient strategy towards new α-hydroxyesters and α-aminoesters, as well as amino lactones, which can be considered as interesting building blocks for organic and medicinal chemistry.

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